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Enterococco y sonda urinaria: un binomio peligroso

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La complicación más frecuente del sondaje urinario es la infección del tracto urinario (ITU): casi 4 de cada 10 infecciones de adquisición nosocomial son infecciones urinarias asociadas al catéter (ITUAC), por lo que se considera una de las infecciones más frecuente de las relacionadas con los cuidados sanitarios[1].

El riesgo de desarrollar una ITU tras la inserción de un catéter se relaciona con la duración del sondaje y ocurre diariamente en el 3% - 7% de los pacientes sondados, con cifras que oscilan de 3.2 ITUAC por 1.000 catéter día en residencias socio-sanitarias a 7,78 ITUAC por 1000 catéter-día en las unidades de cuidados críticos[1,2].

Las manifestaciones clínicas de las ITUAC varían desde la bacteriuria asintomática hasta cuadros más graves como pielonefritis aguda, bacteriemia, urosepsis y muerte. Sin embargo, a veces resulta muy difícil diferenciar entre la bacteriuria asintomática de la ITUAC, ya que la presencia de neutrófilos en la orina, un buen predictor de ITU no complicada, no es un buen indicador de diagnóstico de ITUAC, como tampoco lo es la presencia de nitritos. En el diagnóstico de la ITUAC se exige la presencia de síntomas o signos compatibles en ausencia de otro foco, junto a piuria y un recuento > 1.000 UFC/ml de una única especie bacteriana. El hallazgo en el urocultivo de más de un microorganismo debe ser interpretado con cautela, ya que en el paciente sondado la infección a menudo es polimicrobiana[3-5].

El proceso clave en las ITUAC es la formación del *biofilm*. El paso inicial es la adhesión y colonización bacteriana de la superficie interna del catéter, proceso que se ve favorecido por la respuesta inflamatoria local tanto por el traumatismo durante la inserción como por la presencia de un cuerpo extraño en la vejiga. Debido a ello se produce una disrupción del uroepitelio con pérdida de la capa de mucopolisacáridos y secreción de fibrinógeno y otras sustancias que favorecen la adhesión, el anclaje y la proliferación de las bacterias que acaban formando microcolonias que posteriormente se unen y extienden. De esta manera se forma el *biofilm*, constituido por bacterias y una matriz extracelular compuesta por diferentes componentes derivados tanto del huésped como de productos secretados por las bacterias. El *biofilm* supone una ventaja de supervivencia para los microorganismos ya que no pueden ser eliminados por la fuerza de arrastre del flujo urinario, son poco accesibles a la fagocitosis y adoptan formas vegetativas que son resistentes a los antibióticos comúnmente utilizados[6-9].

A diferencia de las ITU no asociadas a catéter adquiridas en la comunidad donde el principal microorganismo implicado es el *Escherichia coli uropatógeno*, en las ITUAC la diversidad de especies aisladas es mayor. En este sentido, los enterococos, que suelen aparecer muy abajo en la lista de microorganismos aislados en las ITU comunitarias, se sitúan en la segunda o tercera posición de los aislamientos bacterianos de las ITUAC. Conjuntamente las especies E*nterococcus faecalis* y *Enterococcus faecium* son responsables del 15% al 30% de las ITUAC.

Asimismo, *E faecalis* y *E faecium* se encuentran entre los patógenos predominantemente aislados en las colonizaciones polimicrobianas de las superficies de catéteres urinarios permanentes. En este sentido los enterococos, pueden establecer una relación de comensalismo con otras bacterias, como *Pseudomonas spp* y *E coli*, tanto en las ITUAC como en las infecciones del pie diabético o de las úlceras de decúbito[8-9].

Las causas que favorecen este cambio epidemiológico de las ITUAC con una cada vez mayor frecuencia del enterococo como agente causal implicado son múltiples:

1. Es un comensal habitual de la flora intestinal del ser humano, principal fuente de entrada de la ITUAC.
2. Debido a que los enterococos son altamente resistentes a circunstancias ambientales muy adversas de pH, temperatura, humedad y concentraciones de sal, puede ser trasmitido también por el personal sanitario cuando la higiene de manos no es la adecuada y se ha tenido contacto previo con otro paciente institucionalizado que esté colonizado.
3. Cada vez hay una mayor evidencia de la potencial transmisión vía contaminación de alimentos, sobre todo procedentes de granjas de animales que usan antibióticos como en su día

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lo fue la avoparcina que genera cepas de enterococos resistentes a vancomicina[10,11].

4. El enterococo produce diversas moléculas que favorecen la adhesión, colonización y persistencia sobre determinadas superficies, ya sea un catéter urinario o biliar o las válvulas cardíacas nativas o protésicas. Entre estas moléculas destacan aquéllas que se adhieren o favorecen el anclaje a determinadas moléculas como el colágeno (adhesina Ace), la fibronectina (EfbA), o el fibrinógeno y otras proteínas de la matriz extracelular o las plaquetas, como el pilus asociado al biofilm y a la endocarditis (EbpA) o las sortasas A y C[6].

5. El enterococo tiene resistencia intrínseca de bajo nivel a aminoglicósidos y a ciertos betalactámicos, especialmente *E faecium*, lo que puede provocar su selección en los pacientes que han sido sometidos a tratamientos antibióticos previos[12].

6. El enterococo puede adquirir a través de elementos móviles (traspones, plásmidos…) de otras bacterias que condicionan resistencia adquirida a múltiples antibióticos. Este hecho tiene especial relevancia en aquellos pacientes que han recibido múltiples antibióticos especialmente cuando son prolongados en el tiempo[13].

El artículo de González Hidalgo y col publicado en este número de Galicia Clínica pone de manifiesto la relevancia que tanto *E faecalis* como *E faecium* tienen en las ITUAC adquiridas en un hospital de tercer nivel y en los factores del huésped que las favorecen: edad, permanencia de la sonda > de 5 días, sexo femenino, demencia y uso previo de antibióticos, similar a los descritos por otros autores del entorno[14].

El otro aspecto reseñable del artículo pone el foco sobre el problema de las resistencias antibióticas. Conviene recordar que, en el año 2017, la Organización Mundial de la Salud (OMS) publicó una lista de las bacterias que más preocupación e impacto podían tener en el ámbito de la salud humana mundial por los patrones de resistencia antibiótica, a veces a múltiples familias, y que, por lo tanto, deberían ser una prioridad en la investigación de nuevos fármacos. En esta lista de microorganismos, conocida con el acrónimo ESKAPE, el *E faecium* resistente a la vancomicina figuraba dentro del grupo prioritario 2.

El enterococo es intrínsecamente resistente a las cefalosporinas y presenta una susceptibilidad reducida a las penicilinas. Esto se debe a la expresión de proteínas de unión a penicilina con baja afinidad (PBP-5) que se unen débilmente a los antibióticos betalactámicos y que les confieren resistencia de bajo nivel a penicilinas semisintéticas. *E. faecium* presentan valores de CIM para las penicilinas mucho más elevados que *E faecalis*, debido a una mayor producción de PBP5.

En el caso de los aminoglicósidos (AG), la resistencia suele ser intrínseca y de bajo nivel, relacionándose con modificaciones enzimáticas que en algunos casos son codificadas cromosómicamente e inducidles en la presencia del fármaco. La resistencia de alto nivel a AG puede ser ribosómica o mediante enzimas modificadoras[11-13].

La primera noticia tranquilizadora es que *E faecalis* sigue mostrando un patrón de sensibilidad próximo al 90% frente a ampicilina y próximo al 100% para glicopéptidos. Por el contrario, la situación es preocupante en *E faecium*, donde la ampicilina carece de actividad y, además, se detecta una elevada y creciente tasa de resistencia a glicopéptidos.

La mayoría de las resistencias del enterococo a la vancomicina (ERV) son adquiridas y mediadas por ocho operones v*an (vanA, vanB, vanD, vanE, vanG, vanL, vanM, and vanN)*, y un operon intrínseco (*vanC*). Los operones suelen estar asociados a transposones, el más conocido TN1546 asociado a *vanA*. Los ERV con genotipo vanA emergieron a finales de los 80 y principios de los 90 en los animales de granja, humanos sanos, productos alimenticios y muestras ambientales, ligándose por un lado al uso del glicopéptido avoparcina y, en países donde este antibiótico no se utilizó como EEUU al incremento en el consumo de vancomicina en las unidades de críticos. La diferencia entre vancomicina y teicoplanina se justifica porque la teicoplanina suele seguir manteniendo activa frente al enterococo en las mutaciones debidas al ERV genotipo *VanB*[11-13].

También es preocupante la resistencia al linezolid mediante genes transferibles, en su mayoría

optrA, en enterococos de animales productores de alimentos y alimentos de origen animal.

Por último, pero no por ello menos importante, hay que hacer una doble reflexión: la primera relacionada con el uso, y probablemente abuso, de la cateterización urinaria: la indicación de debe ser críticamente sopesada, valorando la ratio riesgo-beneficio, y el catéter debe permanecer colocado el menor tiempo posible. Además, es aconsejable establecer los paquetes de medidas (*bundles*) respecto a protocolizar todos los pasos a considerar y seguir cada vez que se realiza el sondaje, ya sea por personal médico o de enfermería, para mantener el riesgo de ITUAC lo más bajo posible. La segunda tiene que ver con la uso inapropiado de antibióticos, tanto en espectro como en duración, que condicionan por una parte la selección de bacterias resistentes en la microbiota intestinal, cutánea y genitourinaria que pueden provocar la trasferencia de material genético asociado a la aparición de multirresistencias y que cuando condicionan una infección clínica, como la ITUAC, suponen un reto terapéutico.

BIBLIOGRAFÍA

1. Maki DG, Tambyah PA. Engineering out the risk for infection with urinary catheters. Emerg Infect Dis. 2001; 7:342–347.
2. Kline KA, Lewis AL. Gram-Positive Uropathogens, Polymicrobial Urinary Tract Infection, and the Emerging Microbiota of the Urinary Tract. Microbiol Spectr. 2016;4(2):10.1128/microbiolspec.UTI-0012-2012.
3. Chant C, Smith OM, Marshall JC, Friedrich JO. Relationship of catheter-associated urinary tract infection to mortality and length of stay in critically ill patients: a systematic review and meta-analysis of observational studies. Crit Care Med. 2011;39(5):1167–1173.
4. Macià MD, Del Pozo JL, Díez-Aguilar M, Guinea J. Microbiological diagnosis of biofilm-related infections. Enferm Infecc Microbiol Clin (Engl Ed). 2018;36(6):375-381.
5. Kranz J, Schmidt S, Wagenlehner F, Schneidewind L. Catheter-Associated Urinary Tract Infections in Adult Patients. Dtsch Arztebl Int. 2020;117(6):83-88.
6. Ch'ng JH, Chong KKL, Lam LN, Wong JJ, Kline KA. Biofilm-associated infection by enterococci. Nat Rev Microbiol. 2019;17(2):82-94.
7. Tien BYQ, Goh HMS, Chong KKL, Bhaduri-Tagore S, Holec S, Dress R, Ginhoux F, Ingersoll MA, Williams RBH, Kline KA. Enterococcus faecalis Promotes Innate Immune Suppression and Polymicrobial Catheter-Associated Urinary Tract Infection. Infect Immun. 2017;85(12):e00378-17.
8. Gaston JR, Andersen MJ, Johnson AO, Bair KL, Sullivan CM, Guterman LB, White AN, Brauer AL, Learman BS, Flores-Mireles AL, Armbruster CE. Enterococcus faecalis Polymicrobial Interactions Facilitate Biofilm Formation, Antibiotic Recalcitrance, and Persistent Colonization of the Catheterized Urinary Tract. Pathogens. 2020;9(10):835.
9. Trautner BW, Darouiche RO. Role of biofilm in catheter-associated urinary tract infection. Am J Infect Control. 2004;32(3):177-83.
10. Brito-Zerón P, Nicolás-Ocejo D, Jordán A, Retamozo S, López-Soto A, Bosch X. Diagnosing unexplained fever: can quick diagnosis units replace inpatient hospitalization? Eur J Clin Invest. 2014; 44:707-718.
11. Trautner BW, Darouiche RO. Role of biofilm in catheter-associated urinary tract infection. Am J Infect Control. 2004;32(3):177-83.
12. Abat C, Huart M, Garcia V, Dubourg G, Raoult D, Enterococcus faecalis urinary-tract infections: do they have a zoonotic origin?, J Infect. 2016; 73 (4):305-313.
13. Torres C, Alonso CA, Ruiz-Ripa L, León-Sampedro R, Del Campo R, Coque TM. Antimicrobial Resistance in Enterococcus spp. of animal origin. Microbiol Spectr. 2018;6(4).
14. Flores-Mireles A, Hreha TN, Hunstad DA. Pathophysiology, Treatment, and Prevention of Catheter-Associated Urinary Tract Infection. Top Spinal Cord Inj Rehabil. 2019;25(3):228-240.
15. Werneburg GT. Catheter-Associated Urinary Tract Infections: Current Challenges and Future Prospects. Res Rep Urol. 2022;14:109-133.
16. Turjeman A, Babich T, Pujol M, Carratalà J, Shaw E, Gomila-Grange A, Vuong C, Addy I, Wiegand I, Grier S, MacGowan A, Vank C, Cuperus N, van den Heuvel L, Leibovici L, Eliakim-Raz N; COMBACTE MAGNET WP5 RESCUING Study Group and Study Sites. Risk factors for enterococcal urinary tract infections: a multinational, retrospective cohort study. Eur J Clin Microbiol Infect Dis. 2021;40(9):2005-2010.

PULSE PARA VOLVER AL ÍNDICE

HPV infection in people living with HIV

Infección por VPH en personas que viven con VIH

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En el artículo "Prevalencia de infección orogenital por VPH en una población no vacunada de hombres que tienen sexo con hombres VIH+ (HSH-VIH) en el Noroeste de España), el Dr Pérez-González y colaboradores presentan interesantes datos que ayudan a conocer la prevalencia y características de la infección por VPH en una población de alto riesgo, como son los HSH-VIH.
El VPH es la infección de transmisión sexual más frecuente en el mundo, se considera que más del 90% de las personas adultas sexualmente activas han estado expuestas en alguna ocasión al VPH[1]. Afortunadamente la mayoría de estas infecciones se aclaran de manera espontánea, sin producir daño tisular relevante. Pero, en algunos casos (y más frecuentemente en personas inmunosuprimidas), la persistencia de genotipos de alto riesgo provoca cambios en la mucosa que, de no regresar, puede conllevar al desarrollo de tumores.
En los últimos años hay un interés creciente en el campo del VPH, fundamentalmente por esta vinculación al desarrollo de distintos tipos de cáncer, como son los tumores del canal cervicovaginal, canal anal, pene y los de cabeza y cuello. En HSH-VIH la incidencia de cáncer de canal anal es más de 100 veces superior a la población general, de ahí la necesidad de programas de cribado de displasia de canal anal e infección por VPH[2, 3]. En esta población específica, los cánceres de canal anal son más frecuentes que los de pulmón, o colon y tanto como los de próstata[4].
En este sentido, el Dr Palefsky et al han publicado recientemente en NEJM, el ensayo clínico ANCHOR, que demuestra que el tratamiento de la displasia de alto grado de canal anal en HSH-VIH disminuye la incidencia de cáncer de canal anal en un 57% (IC95% 6-80), tras 25,8 meses de seguimiento, este beneficio provocó la finalización temprana del ensayo clínico, al no considerarse ético continuar aleatorizando pacientes al brazo de seguimiento observado[5]. Estos resultados, aunque esperables, muestran la necesidad del abordaje terapéutico de las lesiones de alto grado, al menos en pacientes similares a los incluidos en el estudio ANCHOR. Las organizaciones sanitarias deben implementar programas de cribado y tratamiento de displasia de canal anal.
Pérez-González et al, en una serie de 107 HSH-VIH presentan datos transversales, con una prevalencia de infección por VPH en cualquier localización de 47,7%, el 34,6% tienen infección genital, el 24,3% oral, con un alto porcentaje de casos con infección en ambas localizaciones. Además, como ya es conocido en la literatura, es muy frecuente la infección por múltiples genotipos de VPH[6]. Hay que destacar la alta prevalencia de los genotipos 16 y 18, considerados de muy alto riesgo oncogénico, entre otros. La cohorte presentada no está vacunada frente a VPH, por lo que es esperable un impacto favorable de la vacunación en esta población específica (HSH-VIH).
En Galicia, se recomienda y financia la vacunación de determinadas poblaciones adultas de alto riesgo hasta los 45 años, como son las personas que viven con VIH. Este avance, junto con la reciente comunicación de la extensión de vacunación juvenil a los varones en esta comunidad autónoma, con seguridad tendrán un impacto muy favorable en reducir la incidencia de tumores asociados al VPH en distintas localizaciones, tanto en mujeres como en hombres, como han documentado aquellos países que incorporaron esta recomendación hace ya 15 años[7].
En los datos de Pérez-González es llamativa la presencia de determinados genotipos de alto riesgo, no contenidos en la vacuna recomendada en Galicia (Gardasil 9), especialmente los genotipos 51 y 68 en muestras genitales. Aunque hay que tomar estos resultados con cautela por la naturaleza del estudio, como reconocen los autores, datos longitudinales y un aumento del tamaño muestral ayudarán en el futuro a esclarecer el papel de dichos genotipos en la población estudiada.
Sin lugar a dudas, la infección por VPH es un problema de interés creciente para el Sistema de Salud, no solo en la población en estudio (HSH-VIH) sino en personas con cualquier tipo de inmunosupresión, con especial atención a la inmunosupresión celular, como en el trasplante de órgano sólido. Quizás no tardemos mucho en

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incluir la vacunación frente al VPH entre las inmunizaciones habituales en personas en situación de pretrasplante.

En el momento actual, el papel de la vacunación y de los programas de vigilancia, cribado y tratamiento precoz, es fundamental y lo será aún más en los próximos años, para el adecuado control de la infección por VPH y la patología asociada.

BIBLIOGRAFÍA

1. McQuillan G, Kruszon-Moran D, Markowitz LE, Unger ER, Paulose-Ram R. Prevalence of HPV in adults aged 18-69: United States, 2011-2014. NCHS Data Brief. 2017; 280: 1–8.
2. Clifford GM, Georges D, Shiels MS, Engels EA, Albuquerque A, Poynten IM, et al. A meta-analysis of anal cancer incidence by risk group: toward a unified anal cancer risk scale. Int J Cancer. 2021;148:38-47.
3. Belzer M, Lee J, Gaur AH, Mayer K, et al. High Prevalence of Anal High-Grade Squamous Intraepithelial Lesions, and Prevention Through Human Papillomavirus Vaccination, in Young Men Who Have Sex With Men Living With Human Immunodeficiency Virus. Clin Infect Dis. 2021;73(8):1388-1396.
4. Yuan T, Hu Y, Zhou X, Yang L, Wang H, Li L, et al. Incidence and mortality of non-AIDS-defining cancers among people living with HIV: A systematic review and meta-analysis. E Clinical Medicine. 2022;52:101613.
5. Palefsky JM, Lee JY, Jay N, Goldstone SE, Darragh TM, Dunlevy HA et al. Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer. N Engl J Med. 2022;386(24):2273-2282.
6. Wei F, Gaisa MM, D'Souza G, et al. Epidemiology of anal human papillomavirus infection and high-grade squamous intraepithelial lesions in 29900 men according to HIV status, sexuality, and age: a collaborative pooled analysis of 64 studies. Lancet HIV. 2021;8(9):e531-e543.
7. Patel C, Brotherton J, Pillsbury A, Jayasinghe S, Donovan B, Macartney C, et al. The impact of 10 years of human papillomavirus vaccination in Australia: what additional disease burden will a nonavalent vaccine prevent? Euro Surveill. 2018;23(41):1700737.

Infección urinaria producida por enterococo faecalis y enterococo faecium asociada a sonda vesical: factores de riesgo y evaluación de los patrones de resistencia

Urinary infection produced by enterococcus faecalis and enterococcus faecium associated with bladder catheterization: risk factors and evaluation of resistance patterns

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ABSTRACT

Background and objectives: Urinary tract infection (UTI) is one of the most common infections in hospitalized and outpatients. Bladder catheterization is an important risk factor. The increase in antibiotic resistance can make the treatment of these infections a challenge. The main objective of this study is to analize the resistance and sensitivity rates of UTIs in catheterized patients caused by Enterococcus (E.faecium and E.faecalis). Associated risk factors were also studied.

Materials and methods: Retrospective observational study of patients with urinary infection associated to catheterization caused by E.faecium and E.faecalis during 2020 in al Internal Medicina Unit.

Results: Ampicillin was the antibiotic with the highest resistance rate in the case of E.faecium (94.4%), while 93.05% of E.faecalis presented resistance to Gentamicin. Teicoplanin and Vancomycin were the ones with the lowest rates. Regarding risk factors, dementia, catheterization > 5 days, previous antibiotic therapy, immunosuppresion, and institutionalized patients were statistically significant.

Conclusions: It is important to know the epidemiology of UTIs in each area, as well as the raties of resistance and risk factors in order to provide the most adequate treatment possible, and to avoid the increase in resistance.

Keywords: Bladder catheterization, UTI, resistence, E.faecalis, E.faecium.

RESUMEN

Introducción y objetivos: La infección urinaria es una de las infecciones intra y extrahospitalarias más frecuentes, siendo el sondaje vesical uno de los principales factores de riesgo. El aumento de resistencias antibióticas al que estamos asistiendo hace que su tratamiento a veces suponga un reto. El objetivo principal del estudio pretende analizar las tasas de resistencia y sensibilidad de las principales infecciones urinarias producidas por Enterococos (E.faecium y E.faecalis) en pacientes sondados. También se estudiaron los factores de riesgo asociados.

Material y métodos: Estudio retrospectivo observacional de pacientes con infección urinaria asociada a sondaje por E.faecium y E.faecalis durante el año 2020 en un servicio de Medicina Interna.

Resultados: La ampicilina fue el antibiótico que mayor tasa de resistencia obtuvo en el caso de E.faecium (94.4%), mientras que el 93.05% de casos por E.faecalis presentó resistencias a gentamicina. Teicoplanina y vancomicina fueron los que menores tasas tuvieron. En cuanto a los factores de riesgo, la demencia, el sondaje > 5 días, la antibioterapia previa, la inmunodepresión y los pacientes institucionalizados fueron estadísticamente significativos.

Conclusiones: Es importante conocer la epidemiología de las infecciones urinarias de la zona por áreas geográficas, así como las tasas de resistencias y los factores de riesgo con el fin de un tratamiento lo más adecuado posible, y evitar el aumento de resistencias.

Palabras clave: Sonda vesical, ITU, resistencia, E.faecalis, E.faecium.

INTRODUCCIÓN

La infección del tracto urinario (ITU) es una de las infecciones bacterianas más frecuentes. Es la segunda causa de infección extrahospitalaria y la tercera de origen nosocomial[1,2,3] La ITU nosocomial está relacionada en la mayoría de los casos al sondaje vesical, la cual se define como aquella que acontece en sujetos durante el sondaje o en las 72 horas posteriores a su retirada[2,4]. El microorganismo más frecuentemente aislado tanto en las ITU ambulatorias como nosocomiales es Escherichia coli. Sin embargo, dado el aumento de resistencias antibióticas que se está experimentando, están adquiriendo importancia patógenos como Pseudomona aeruginosa o bacterias grampositivas como los Enterococos, entre los que destacan Enterococo faecalis (E. faecalis) y Enterococo faecium (E.faecium)[2,3]. El objetivo principal de este estudio es evaluar las tasas de resistencia y sensibilidad de E. faecalis y E.faecium a diversos antibióticos en pacientes portadores de sonda vesical. El objetivo secundario es analizar los principales factores de riesgo para su desarrollo.

MATERIAL Y MÉTODOS

De los 258 casos de ITU asociadas a pacientes sondados, 126 cumplieron los criterios de inclusión. Se realizó un estudio observacional retrospectivo en pacientes ingresados en el Servicio de Medicina Interna con diagnóstico de infección del tracto urinario (ITU) asociada a sonda vesical durante el año 2020 en un hospital de tercer nivel. La ITU asociada a catéter se definió como la presencia de por más 1000 unidades formadoras de colonias (UFC) en una muestra de orina de catéter, o en muestra de orina obtenida 72h después de retirado el catéter[5,6]. Los criterios de inclusión fueron: a) pacientes con edades comprendidas entre 18 y 84 años, b) portadores de sondaje vesical al menos durante 72 horas, c) ausencia de datos de ITU al momento del ingreso y d) aislamiento microbiológico de E. faecalis y E. faecium en urocultivos además de clínica compatible con ITU. Los datos de sensibilidades y resistencias antimicrobianas se extrajeron de los antibiogramas de los urocultivos. Para realizar el análisis estadístico se usó SPSS versión 23. Se realizó un estudio descriptivo para evaluar los patrones de sensibilidad y resistencia. Para analizar los factores de riesgo se realizó un análisis bivariante, para lo que se empleó la prueba de chi-cuadrado.

Para la realización del presente trabajo se han cumplido las normas éticas del Comité de Investigación y de la Declaración de Helsinki de 1975.

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RESULTADOS

De los 126 pacientes que cumplieron los criterios de inclusión, 89 pacientes eran mujeres y 37 hombres, lo que correspondía al 70,6% y al 19,4% respectivamente. La media de edad fue de 68 años. E. faecium produjo el 42,86% de los casos de ITU (54 casos) y el 57,14 % (72 casos) lo ocasionó E.faecalis.

Cuando se analizaron las tasas de sensibilidad y resistencia de los principales antibióticos empleados en E faecium, la mayor tasa de resistencia se obtuvo para ampicilina (94.4%), seguida de fosfomicina (53.7%). Les siguió en frecuencia linezolid, vancomicina y teicoplanina con unas resistencias del 24.07%, 16.67% y 11.1% respectivamente. Tan solo dos de los antibióticos incluidos en el estudio mostraron resistencias inferiores al 10%, que fueron ciprofloxacino (9.27%) y daptomicina (0%). Al estudiar los patrones de resistencia y sensibilidad en el caso de E. faecalis, el antibiótico que mayor resistencia presentó fue gentamicina con un 93.05%, seguido de linezolid (37.5%), rifampicina (26.38%) y ampicilina (12.5%). Vancomicina y teicoplanina fueron los que menores tasas de resistencias presentaron (4.2% y 0% respectivamente) (Tabla 1).

Tabla 1. Tasas de sensibilidad y resistencia antimicrobianas de las infecciones urinarias producidas por E.faecium y E. faecalis

ANTIBIÓTICO	E. faecium Sensibilidad	E. faecium Resistencia
Ampicilina	3 (5,6%)	51 (94,4%)
Teicoplanina	48 (88,9%)	6 (11,1%)
Vancomicina	45 (83,33%)	9 (16,67%)
Ciprofloxacino	49 (90,75%)	5 (9,25%)
Fosfomicina	25 (46,3%)	29 (53,7%)
Daptomicina	54 (100%)	0 (0%)
Linezolid	41 (75,93%)	13 (24,07%)
ANTIBIÓTICO	**E.faecalis Sensibilidad**	**E.faecalis Resistencia**
Ampicilina	63 (87,5%)	9 (12,5%)
Teicoplanina	72 (100%)	0 (0%)
Vancomicina	69 (95,8%)	3 (4,2%)
Linezolid	45 (62,5%)	28 (37,5%)
Gentamicina	5 (6,95%)	67 (93,05%)
Rifampicina	53 (73,61%)	19 (26,38%)

Se examinó la frecuencia de algunos factores de riesgo en los pacientes con infección producida por E.faecalis y E.faecium, así como la significación estadística. Para su cálculo se comparó el grupo de pacientes sondados con ITU por E.faecalis y E.faecium respecto a un grupo control con asilamiento microbiológico diferente. Ambos grupos eran comparables en sexo, edad, lugar de residencia y características basales.

En nuestro estudio el factor de riesgo más frecuente fue la institucionalización de los pacientes en centros sociosanitarios, que se presentó en un 72.22% de todos los casos. Al analizar la duración del sondaje vesical, dividiendo a los pacientes en dos grupos, aquellos que la tuvieron menos de 5 días, y aquellos que la tuvieron durante un tiempo mayor, este último grupo correspondió al segundo factor de riesgo en frecuencia (69%). Les siguieron en frecuencia la demencia y la toma de antibióticos previa (58.7% y 54.8%). En el caso de E. faecalis, el factor más frecuente, al igual que en análisis global, fue el sondaje vesical mayor de 5 días (44.41%), sin embargo, en el caso de E. faecium fue la institucionalización. Respecto a los factores menos presentes, cabe destacar la hospitalización los 15 días previos, la inmunodepresión y el sexo masculino, para ambos grupos por separado y en conjunto (Tabla 2).

Se evaluó cuáles de estos factores de riesgo tenían relación estadísticamente significativa con las ITU producidas por Enterococos, para lo que se comparó con aquellos pacientes con ITU asociada a sondaje vesical producidas por otros microorganismos (n: 132). Los parámetros que obtuvieron un resultado significativo fueron la demencia (p=0.04), sondaje vesical durante más de 5 días (p=0.032), uso de antibioterapia los tres meses previos (p=0.02), la inmunodepresión (p=0.049) y los pacientes residentes de centros sociosanitarios (p= 0.0125) (Tabla 3).

DISCUSIÓN

Son pocos los estudios científicos recientes que se centran en los patrones de resistencias antibióticas de enterococo. En ellos destaca como especie más usualmente aislada E. faecalis, con una frecuencia que oscila entre el 50% y el 80%, según la serie, de todas las ITU nosocomiales producidas por enterococo[7-12]. Lo mismo ocurre en nuestro estudio, en el que este microorganismo representó el 57.14 % de la muestra.

Así mismo, los antibióticos cuyas resistencias y sensibilidades se estudian no presentan uniformidad, por lo que es difícil establecer una comparativa entre ellas. En el caso de E.faecium, en el estudio de Rodriguez *et al*[12] se obtuvo un 95% de resistencias a ampicilina, cifra muy similar a la obtenida en nuestro grupo, cuya tasa de resistencia fue del 94.4%. En otro estudio se analizó la resistencia de varios antibióticos, entre ellos ciprofloxacino, con una resistencia en torno al 40%, valor muy diferente al nuestro, en que la tasa de resistencia no llega al 10%. Otro antibiótico evaluado tanto en este trabajo como en el nuestro fue vancomicina, siendo en nuestro caso la tasa de resistencia del 16.67% frente al 0%, lo que puede ser reflejo del aumento de resistencias que está experimentando este grupo antibiótico a enterococos en los últimos años[13]. Algo más estudiado ha sido E. faecium, del que se han examinado tanto tasas de sensibilidad como de resistencia. Estas últimas obtuvieron en el estudio de Yasufuku *et al* [14] un 1% para el caso de ampicilina, cifra muy similar a la que nosotros obtuvimos (12.5%). Sin embargo estos examinaron antimicrobianos diferentes a los analizados por nuestra parte. En el caso de Casal *et al* [15], realizado sobre una muestra de 1937 casos de ITU intrahospitalaria, al examinar la sensibilidad se obtuvieron cifras del 67.9% para la gentamicina, 97.1% para linezolid y 100% para vancomicina. Si comparamos estos datos con los aportados en el presente estudio, se observa que gentamicina presenta una sensibilidad bastante menor en nuestros aportes (6.95%), al igual que linezolid (62.3%). Sin embargo, el porcentaje de vancomicina son similares (95.8%). Todo esto puede justificarse por el aumento de resistencias de los últimos años, la variabilidad epidemiológica en patrones de resistencias y en el tamaño muestral de los diferentes estudios.

Los factores de riesgo han sido un aspecto más ampliamente estudiado. En la mayoría de los estudios el sexo masculino ha

Tabla 2. Frecuencia de los factores de riesgo estudiados. La segunda columna corresponde a ambos géneros de enterococo en conjunto. Las dos siguientes cada una de las especies por separado.

	Enterococos (n: 126)	E.faecalis (n: 72)	E.faecium (n: 54)
Sexo masculino	37 (14,4%)	21 (11,01%)	16 (8,39%)
Edad >70 años	48 (38,1%)	20 (15,86%)	28 (22,24%)
Demencia	74 (58,7%)	49 (38,87%)	26 (19,83%)
Diabetes	44 (34,9%)	21 (16,66%)	23 (18,34%)
Sondaje vesical < 5 días	39 (31%)	18 (14,31%)	21 (16,69%)
Sondaje vesical > 5 días	87 (69%)	56 (44,41%)	31 (24,56%)
Antibioterapia los 3 meses previos	69 (54,8%)	43 (34,15%)	20 (20,65%)
Hospitalización los 15 días previos	21 (16,7%)	10 (7,95%)	11 (8,75%)
Inmunodepresión	25 (19,84%)	12 (9,52%)	13 (10,32%)
Institucionalizado	91 (72,22%)	51 (40,47%)	20 (31,75%)

Tabla 3. Relación estadística de los principales factores de riesgo analizados para el desarrollo de infección urinaria asociada al sondaje vesical producidas por Enterococo.

	Enterococos (n: 126)	No enterococos (n: 132)	p
Sexo masculino	37 (14,4%)	26 (19,69%)	0.06
Edad >70 años	48 (38,1%)	55 (41,67%)	0.053
Demencia	74 (58,7%)	51 (28,64%)	**0.04**
Diabetes	44 (34,9%)	61 (46,21%)	0.125
Sondaje vesical < 5 días	39 (31%)	53 (41,12%)	0.055
Sondaje vesical > 5 días	87 (69%)	79 (58,82%)	**0.032**
Antibioterapia los 3 meses previos	69 (54,8%)	47 (35,6%)	**0.02**
Hospitalización los 15 días previos	21 (16,7%)	23 (17,42%)	0.325
Inmunodepresión	25 (19,84%)	15 (11,36%)	**0.049**
Institucionalizado	91 (72,22%)	71 (53,79%)	**0.0125**

sido el predominante en cuanto a las infecciones por enterococo, representando más del 50% de los casos, obteniendo un valor estadísticamente significativo, al contrario de lo que ocurre con nuestro grupo, donde los hombres representaron apenas el 19.4% de los casos de ITU por enterococo (p>0.06)[16,17,18,19].

Algunos de los que se han incluido en la mayoría de estudios para analizar una posible relación y que no han obtenido significación han sido la diabetes en el caso de Madrazo *et al* (p=0.458)[16], Álvarez-Artero *et al* (p=0.909)[17] o Kajihara *et al* (p=0.748)[20], todo ello compatible con nuestros resultados (p=0.125). Algo más controvertidos han sido los resultados obtenidos en el caso de la demencia en el que Madrazo *et al*[16] no obtuvieron asociación (p=0.325) mientras que nuestro estudio y el de Billington *et al* [21] sí (p<0.001). La inmunodepresión, un factor de riesgo bien conocido como predisponente para el aumento de riesgo de infecciones, no obtuvo significación estadística en el caso de los análisis de Uda *et al*[19] o Álvarez-Artero *et al*[17], mientras que en nuestro caso sí que se obtuvo, si bien con una p muy cercana a la no significación estadística (p=0.49).

No obstante, sí que han sido unánimes los resultados respecto a la toma de antibioterapia previa o la historia de hospitalización reciente como factor de riesgo para el desarrollo de estas infecciones[16,17]. El antecedente de toma de antibiótico sí que resultó significativo en nuestro caso (p=0.02), sin embargo, la hospitalización reciente no (p=0.325).

Existen otros factores de riesgo para el desarrollo que han sido descritos en la literatura, pero que no han sido incluidos en los estudios más recientes acerca del tema. Entre ellos destacamos

el papel de aquellos pacientes residentes en instituciones socio-sanitarias, los cuales en nuestro grupo presentaron el 72.22% de casos de ITU asociada a sondaje vesical (p = 0.0125); o el tiempo medio de sondaje vesical, concluyéndose de nuestros resultados que el grupo que tuvo una media de tiempo mayor presentó mayor frecuencia de estas infecciones (portadores de sonda < 5 días: 31% vs portadores de sonda > 5 días: 69%, presentando este último una p= 0.032).

CONCLUSIONES

Las ITU asociada a sondaje vesical se producen con frecuencia, observándose que existen algunos factores de riesgo modificables por el clínico. Así misma, la resistencia de estos patógenos es variable dependiente de la zona geográfica que se estudie. Por ello, junto al escaso número de estudios científicos que se centran ello, sería importante la realización de más estudios regionales para poder conocer estos patrones y factores y con ello intentar establecer una conducta lo más dirigida y adecuada posible.

CONFLICTO DE INTERESES

Los autores declaramos que no existe ningún conflicto de intereses.

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CONSIDERACIONES ÉTICAS

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BIBLIOGRAFÍA

1. Álvarez Artero E, Campo Nuñez A, García Bravo A, Cores Calvo O, Belhassen G, Pardo Lledias J. Infección urinaria en el anciano. Rev Clin Esp. 2019 (4): 189-93.
2. De Toro-Peinado I, Mediavilla-Gradolph MC, Tormo-Palop N, Palop-Borrás B. Diagnóstico microbiológico de las infecciones urinarias. Enferm Infecc Microbiol Clin.2015; 33(Supl 2): 34-9.
3. Echevarría-Zarate J, Sarmiento Aguilar E, Osores-Plenge F. Infección del tracto urinario y manejo antibiótico. Acta Med Per. 2006; 23(1): 26-31
4. Pigrau C. Infecciones del tracto urinario nosocomial. Enferm Infecc Microbiol Clin. 2013; 31(9): 614-24.
5. Delgado Mallen P. Infecciones del Tracto Urinario. En: Lorenzo V, López Gómez JM (Eds) . Nefrología al día. Infecciones Urinarias. Disponible en: https://www.nefrologiaaldia.org/255. Consultado 28 Jul 2021.
6. Flores Siccha MK, Perez Bazán LM, Trelles Guzmán MG, Málaga Rodríguez G, Loza Munariz C, Tapia Egoavil E. Infección urinaria intrahospitalaria en los servicios de hospitalización de Medicina de un hospital general. Rev Med Hered. 2008; 19 (2): 46-52.
7. Mensa J, Gatell JM, García-Sánchez JE, Letang E, López-Suñé E, Marco R. Guía de terapéutica antimicrobiana. Editorial Antares. 2020. Página 399.
8. Fiore E, Van Tyne D, Gilmore M. Pathogenicity of Enterococci. Microbiol Spectr. 2019; 7 (4): 10.1128/microbiolspec.GPP3-0053-2018.
9. Braïek OB, Smaoui S. Enterococci: Between Emerging Pathogens and Potential Probiotics. Biomed Res Int. 2019;2019:5938210.
10. Cercenado E. Enterococcus: resistencias fenotípicas y genotípicas y epidemiología en España. Enferm Infecc Microbiol Clin. 2011; 29 (Supl 5): 59-65.
11. Weiner LM, Webb AK, Limbago B, Dudeck MA, Patel J, Kallen AJ, Edwards JR, Sievert DM. 2016. Antimicrobial-Resistant Pathogens Associated With HealthcareAssociated Infections: Summary of Data Reported to the National Healthcare Safety Network at the Centers for Disease Control and Prevention, 2011–2014. Infect Control Hosp Epidemiol. 37(11):1288–301.
12. Rodríguez CH, García S, Barberis C, Saposnik E, Weyland B, Nastro M et al. Enterococcus spp: Resistencia antimicrobiana en infecciones intrahospitalarias. 2013; 47 (1): 155-60.
13. Silva J, Asserella L, Bolados N, Herrera N, Leyton J. Resistencia a antimicrobianos en cepas de Enterococcus sp aisladas en hospitales del norte de Chile. Rev Chil Infect. 2006; 23 (3): 226-31.
14. Yasufuku T, Shigemura K, Shirakawa T et al. Mechanisms of and risk factors for fluoroquinolone resistance in clinical Enterococcus faecalis isolates from patients with urinary tract infections. J Clin Microbiol. 2011; 49: 3912–16.
15. Casal MM, Causse M, Solis F, Rodríguez F, Casal M. Investigación de las resistencias a antimicrobianos en Enterococcus faecalis. Rev Esp Quimioter.2009; 22(3): 117-19.
16. Madrazo M, Esparcia A, Alberola J, Ferrer A, Eiros JM, Artero A. Predictive factors for Enterococcus faecalis in complicated community-acquired urinary tract infections in older patients. Geriatr Gerontol Int. 2020; 20 (3): 183-86.
17. Alvarez-Artero E, Campo-Nuñez A, García-García I, García-Bravo M, Cores-Calvo O, Galindo-Pérez I et al. Infección urinaria por enterococos: Factores de riesgo y mortalidad. Estudio observacional. Revista Clínica Española. 2021; 221 (7): 375-83.
18. Hansen K, Hertz F, Rasmussen S, Fimodt-Moller N. Urinary tract infection-related Bacteremia due to Enterococcus faecalis: a retrospective case control study of potential risk factors. Epidemiology. 2015; 05: 1–4.
19. Uda A, Shigemura K, Kitagawa K, Osawa K, Onuma K, Yan Y et al. Risk factors for the acquisition of Enterococcus faecium infection and mortality in patients with Enterococcal Bacteremia: A 5-years retrospective analysis in Tertiary Care University Hospital. Antibiotics.2021; 10 (64): 1-10.
20. Kajihara T, Nakamura S, Iwagana N, Oshima K, Takatono T, Miyazaki T et al. Clinical characteristics and risk factors of enterococcal in Nagasaki, Japan: a restrospective study. BMC Infect Dis. 2015; 15: 426.
21. Billington E, Phang S, Gregson D, Pitout JD, Ross J, Church D et al. Incidence, Risk factors and outcomes for Enterococcus spp. Blood stream Infections. A population-Based Study. International Journal of Infectious Disease. 2014; 26: 76-28.

Prevalence of HPV genitalia and oral infection in an unvaccinated population of MSM-HIV in Northwest Spain

Prevalencia de la infección genital y oral por VPH en población no vacunada de HSH-VIH en el noroeste de España

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ABSTRACT

Introduction: Human papillomavirus (HPV) infection is the most common sexually transmitted infection (STI), and it is a major risk factor for penile, oropharyngeal and anal cancer. HPV anal infection is common in men-who-have-sex-with-men (MSM), especially in patients living with HIV (MSM-HIV). HPV can also be detected in genitalia and oral tissues. The objective of this cross-sectional study is to analyze the prevalence of HPV genital and oral infection in a HIV-MSM cohort.

Methods: This cross-sectional study of HPV infection included 107 HIV-MSM subjects recruited in a HIV follow-up unit of Northwest Spain.
HPV-vaccinated subjects were excluded. HPV-DNA was detected with Anyplex™ II HPV28 method. Participants completed a questionnaire on lifestyle and sexual behavior.

Results: Median age was 43 years (range 35-54 years); 97 patients received antiretroviral treatment (ART); 81 (75.7%) had undetectable HIV-RNA; median CD4-lymphocyte count was 746 cell/mm^3; 70 (65.4%) participants had a previous STI. Genitalia HPV-DNA was detected in n=37 (34.6%) subjects and oral HPV-DNA was detected in 26 (24.3%). In 12 (11.2%) patients, HPV-DNA was detected in both locations. High risk HPV (hrHPV) genotypes were detected in 24 (22.4%) and 15 (14%) patients in genitalia and oral samples respectively. Genitalia HPV-DNA isolation was more common in HIV virologically non-suppressed patients (65.4% vs 24.7%; p<0.001).

Conclusions: HPV genitalia and oral infection is common in unvaccinated HIV-MSM patients. Detectable HIV-RNA was associated with higher HPV prevalence in genitalia. High oncogenic risk HPV genotypes were more common in genitalia than in oral cavity.

Keywords: HPV, HIV, papillomavirus, prevalence, men who have sex with men.

RESUMEN

Introducción: La infección por el virus del papiloma humano (VPH) es la infección de transmisión sexual (ITS) más común; y es factor de riesgo para el desarrollo de cáncer de pene, orofaringe y ano. La infección por VPH es frecuente en hombres-que-tienen-sexo-con-hombres (HSH), especialmente en pacientes infectados por VIH (HSH-VIH). Asimismo, el VPH puede infectar genitales y cavidad oral. El objetivo de este estudio transversal es estimar la prevalencia de la infección orogenital por VPH en una cohorte HSH-VIH.

Métodos: se incluyeron 107 pacientes de una Unidad de VIH del noroeste de España. Los pacientes vacunados fueron excluidos. El material genético del VPH (ADN-VPH) fue detectado mediante Anyplex™-II HPV-28. Los participantes completaron un cuestionario sobre hábitos sexuales.

Resultados: la mediana de edad fue 43 años (rango 35-54); 97 pacientes recibían tratamiento antirretroviral (TAR); 81 (75,7%) presentaban carga viral del VIH suprimida, la mediana de linfocitos-CD4 era de 746 células/mm^3, 70 (65,4%) habían padecido una ITS. Se detectó VPH en los genitales de 37 (34.6%) sujetos, en la cavidad oral de 26 (24.3%) y en 12 (11,2%) en ambas localizaciones. Se detectaron genotipos de alto riesgo oncogénico (AR-VPH) en 24 (22,4%) y 15 (14%) sujetos en genitales y cavidad oral respectivamente. El aislamiento del VPH fue más común en pacientes virológicamente no-suprimidos (65.4% vs 24.7%).

Conclusiones: la infección orogenital por VPH es frecuente en pacientes HSH-VIH no vacunados. La no-supresión virológica del VIH se asoció con mayor prevalencia de infección genital por VPH. La detección de genotipos AR-VPH fue más común en genitales que cavidad oral.

Palabras clave: VPH, VIH, papilomavirus, prevalencia, HSH

INTRODUCTION

Human papillomavirus (HPV) infection is the most common sexually transmitted infection (STI) in many countries, including United States[1] and some South European regions[2]. HPV is the main cause of cervical cancer in woman[3] and anal cancer in HIV-MSM([4]). Moreover, HPV is a major cause of penile cancer[5] and oropharyngeal carcinoma[6]. HPV genotypes are classified in four categories based on their oncogenic risk: high oncogenic risk (i.e., HPV-16, HPV-18), probably high-risk (i.e., HPV-53), low risk (i.e., HPV-6, HPV-11) and indeterminate risk (i.e., HPV-25)[7]. Prior studies have reported an incidence of HPV anal infection in MSM-HIV patients between 24 and 33/100 person-years, higher than MSM HIV negative subjects[8]. On the other hand, previous studies reported an HPV penile incidence around 11/100 persons-year in people living with HIV (PLWH)[9]. Incidence is also higher in HIV-MSM individuals compared to men-who-have-sex-with-women (MSW). In regard of oral HPV infection, our research group reported a prevalence of 13.4% in a MSM-HIV cohort[10]. HPV-16 and HPV-18 are the most detected HPV genotypes in anal and genitalia samples. However, several cross-sectional studies did not fin concordance between HPV genotypes across anatomic locations[11]. Sexual behavior plays a key role in the acquisition of HPV infection. In addition, specific sexual practices (i.e., oral sex, multiple sexual partners) may increase the risk of HPV infection in genitalia or oral cavity[9]. Also, a great number of sexual partners and a younger age of first sexual intercourse increase the risk of HPV infection[9].

Currently, the interaction between HPV and HIV is not yet fully understood but several studies have found a higher risk of HPV related carcinomas in PLWH[7]. This may be attributed to several mechanisms, such as the immunosuppression state induced by HIV, disruptions of the mucosal epithelial barrier and low clearance of HPV[12].

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Coinfection of HPV, HIV and other STIs is also frequent[13]. Indeed, *Chlamydia trachomatis* coinfection may increase HPV-related cancer in males[14] and infertility[15]. Furthermore, *Ureaplasma* and other bacterial STIs could increase the HPV carcinogenity[13].
To date, few studies have analyzed concurrent infection in the genitalia and the oral cavity. We performed a cross-sectional hospital-based study to evaluate the prevalence of HPV DNA in a HIV-MSM cohort from Northwest Spain.

METHODS

Study design

This cross-sectional study was performed in Vigo, Spain, from January 2019 to December 2019. Patients were recruited in the HIV follow-up Unit of Alvaro Cunqueiro Hospital, in Northwest Spain (population area around 540,000 inhabitants). HPV-vaccinated subjects were excluded. HIV virological suppression was defined as a HIV viral load under 50 copies per milliliter. The study was approved by Ethics Committee of Pontevedra-Vigo-Ourense (reference 217/2019). Written informed consent was obtained from each participant.

Data collection

Subjects were recruited during their follow-up at HIV unit. A questionnaire was used to collect sexual behavior data, including condom usage, age of sexual intercourse and number of sexual partners. Demographical and clinical data were obtained from the medical records.

Sample collection and laboratory test

Samples were collected in the HIV follow-up unit. Genitalia samples were obtained with a cytologic brush (Endobrush®, Covaca S.A., Madrid, Spain) from glans, coronal sulcus and scrotum, and stored in TrisEDTA pH8 molecular grade at 4 ºC. Oral samples were taken after one hour fast. Patients were asked to make two rinses with 5 mL of sodium chloride. First rinse was safely disposed while the second was sent to laboratory in a sterile bottle at ambient temperature.

In addition, anal, oral and genitalia swabs were obtained for bacterial STI detection and stored in PCR media (Roche Diagnostics®, Basel, Switzerland). Samples were tested for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Serum was obtained for *Treponema pallidum* study (enzyme immunoassay, LIAISON®, Diasorin; rapid plasma reagin, Biomerieux®, France).

HPV-DNA was extracted from genitalia and oral samples employing the QIAcube automated extraction system (Qiagen, Hilden, Germany). The HPV genotypes were identified by applying the Anyplex™ II HPV28 detection method (Seegene, Seoul, South Korea), following the manufacturer's recommendations. This test simultaneously detects 19 types of high-risk HPV (HPV-16, HPV-18, HPV-26, HPV-31, HPV-33, HPV-35, HPV-39, HPV-45, HPV-51, HPV-52, HPV-53, HPV-56, HPV-58, HPV-59, HPV-66, HPV-68, HPV-69, HPV-73, HPV-82) and 9 types of low-risk HPV (HPV-6, HPV-11, HPV-40, HPV-42, HPV 43, HPV-44, HPV-54, HPV-61, HPV-70). The system performs 3 real-time multiplex polymerase chain reactions per sample using DPO™ Technology and the TOCETM technology melting curve analysis method.

Statistical analyses

Quantitative variables are expressed as median and interquartile range. Qualitative variables are shown as absolute value and percentages. Categorical variables were compared with χ-square test or Fischer exact test as appropriate. For quantitative variables comparison we used U Man Whitney test. A p value less than 0.05 was considered significant. Statistical analysis was performed with Statistical Package for Social Sciences (SPSS), IBM, version 22.

Ethics

All patients signed an informed consent form. Study was approved by Ethics Committee of Pontevedra-Vigo-Ourense (reference 217/2019).

RESULTS

A total of 107 HIV-MSM subjects were recruited. The median age was 43 years (IQR, 35-54) and most of them were Spanish (n=80, 74.8%). Demographic and clinical characteristics are shown in Table 1.

Table 1. Baseline characteristics of study population

Ethnicity, n (%)	
Spanish	80 (74.8%)
Latin-American	25 (23.4%)
Other	2 (1.8%)
Age in years, median (range)	43 (35 – 54)
Subjects receiving ART	97 (90.7%)
Naive to ART	10 (9.3%)
Nadir CD4 lymphocyte (cell/mm3; median and range)	326 (197 – 456)
CD4 nadir less than 200 (cell/mm3), n (%)	25 (23.4%)
CDC C stage, n (%)	21 (19.6%)
CD4 lymphocyte at recruitment (cell/mm3; median and range	746 (447 – 966)
HIV RNA < 50 copies/mL	81 (75.7%)
Time since HIV diagnosis (years; median and interquartile range)	8 (4 – 13)
Circumcision, n (%)	22 (20.6%)
Anogenital condylomata acuminata	17 (15.9%)
Prior HPV anal infection, high risk genotype	68 (63.6%)
Tobacco consumption	
Current smoker, n (%)	34 (31.8%)
Former smoker, n (%)	19 (17.8%)
Never smoker, n (%)	53 (49.5%)
Previous sexually transmitted infection, n (%)	70 (65.4%)
Syphilis, n (%)	64 (59.8%)
Gonorrhea, n (%)	21 (19.6%)
Chlamydia trachomatis infection, n (%)	10 (9.3%)

HIV: human immunodeficiency virus; ART: anti-retroviral treatment, CDC: Centers for Disease Control and Prevention, HIV-RNA: human immunodeficiency viral load; HPV: human papillomavirus

Sexual behavior questionnaire

Consistent use of condom in penetration was reported by 55 patients (51.4%), but only 5 (4.7%) used condom in oral sex. The median number of lifetime sexual partners was 100 (IQR,40-300) and 4 in the past year (IQR, 1-10). The median age of first sexual intercourse was 17 years (IQR, 15-18) (Table 2). The sexual behavior questionnaire is attached as supplementary material.

Table 2. Results of sexual behavior questionnaire

Age of first sexual intercourse, median (range)	17 (15 – 18)
Lifetime number of sexual partners, median (range)	100 (40 - 300)
Sexual partners last year, median (range)	4 (1 - 10)
Consistent condom use (penetration), n (%)	55 (51.4%)
Consistent condom use (oral sex), n (%)	5 (4.7%)

Bacterial STI samples

A total of 24 patients tested positive for another STI excluding HPV infection. The most frequent bacterial STI was *Chlamydia trachomatis* infection with 12 cases (11.2%), followed by *Neisseria gonorrhoeae* (9 cases, 8.4%) and *Haemophilus parainfluenzae* (2 subjects, 1.9%). *Chlamydia* spp. and gonococcus spp. coinfection was detected in 2 subjects (1.9%). Ten subjects (9.3%) tested positive for anal infection, followed by oral cavity (5 cases, 4.7%) and urethra (4 cases, 3.7%). One subject (0.9%) tested positive in two locations: anal conduct and oral cavity. Ten patients (9.3%) tested positive for active syphilis. HPV infection prevalence did not vary between patients who tested positive for a concurrent bacterial STI (27.5% vs. 17.9% respectively).

HPV prevalence and distribution

HPV prevalence results are shown in Table 3, Table 4 and Figure 1. A total of 51 subjects (47.7%) tested positive for HPV-DNA in one or both locations. HPV DNA was detected in 37 genitalia samples (34.6%). HPV DNA was isolated from oral samples of 26 participants (24.3%).

The distribution of HPV genotypes was different between genitalia and oral samples. HPV-51 was the most common in genitalia samples (n=9; 8.4%), followed by HPV-16 (n=7, 6.5%) and HPV-68 (n=6, 5.6%). However, HPV-66 was the most frequent strain in oral samples, reaching 6 cases (5.6%) tied with HPV-16 (6 cases, 5.6%). HPV-51 and HPV-68 were not detected in oral samples. Coinfection of more than one HPV genotype was more common in genitalia than oral cavity (52.8% vs 30.8% respectively).

Overall, prevalence of HPV-DNA detection was higher in non-virologically suppressed patients. However, after stratification by anatomical site, only genitalia infection was associated with detectable HIV RNA (65.4% vs 24.7%; p<0.001). No difference was observed in HPV oral infection between virologically suppressed and non-suppressed patients (24.9% and 23.1%, respectively). Age, number of sexual partners and age of first sexual intercourse did not differ between HPV positive and HPV negative patients.

HPV genitalia infection did not vary between smokers and non-smokers. Regarding oral cavity, there was no significant differences in HPV prevalence in smokers and ex-smokers vs. never smokers (30.2% and 20.5%, respectively). HPV oral infection pre-

Table 3. Study population characteristics stratified by HPV infection status

	HPV negative (n=56)	HPV positive (n=51)	*p value*
Demographic characteristics			
Age, median (range), years	49 (16)	43 (28)	*p=0.512*
Spanish origin, n (%)	43 (76.8%)	37 (72.5%)	*p=0.461*
Clinic and HIV characteristics			
Time of known HIV, median (range), years	9 (8.3)	7 (10.0)	*p=0.154*
CDC stage C, n (%)	8 (13.3%)	13 (25.5%)	*p=0.223*
HIV viral load < 50 copies/mL, n (%)	48 (85.7%)	33 (64.7%)	*p=0.014*
CD4 nadir less than 200 (cell/mm3), n (%)	10 (17.9%)	15 (29.4%)	*p=0.258*
CD4 lymphocyte at recruitment (cell/mm3; median and interquartile range)	747 (473)	746 (632)	*p=0.772*
Naive to ART, n (%)	2 (3.6%)	8 (15.7%)	*p=0.045*
Current smoker, n (%)	22 (39.3%)	12 (23.5%)	*p=0.098*
Circumcision, n (%)	9 (16.1%)	13 (25.5%)	*p=0.261*
Sexual questionnaire			
Age of first sex intercourse, median (range), years	17 (3)	17 (4)	*p=0.260*
Lifetime number of sexual partners, n (%)	100 (227)	150 (413)	*p=0.752*
Sexual partners last year, median (range)	3 (8)	4 (11)	*p=0.534*
Consistent condom use (penetration), n (%)	31 (59.6%)	24 (57.1%)	*p=0.836*
Consistent condom use (oral sex), n (%)	3 (5.8%)	2 (4.8%)	*p=1.000*
History of sexually transmitted infection, n (%)	39 (69.6%)	31 (60.8%)	*p=0.417*
Current sexually transmitted infection, n (%)	10 (17.9%)	14 (27.5%)	*p=0.255*

valence did not differ between patients with a history of a previous STI. In both locations, prevalence was not related with HIV stage C nor a CD4 cell count less than 200 cell/mm^3. Age, circumcision status, number of lifetime sexual partners, consistent condom use, age of first sexual intercourse, CD4 lymphocyte count, nadir CD4 lymphocyte count and tobacco consumption did not differ between HPV positive and HPV negative subjects.

Table 4. HPV results stratified by anatomical site

Location	Genitalia	Oral Cavity
Coinfection of more than one genotypes	19 (17.8%)	8 (7.5%)
At least one high-risk genotype	24 (22.4%)	15 (14.0%)
High-risk genotypes		
HPV-16	7 (6.5%)	6 (5.6%)
HPV-18	5 (4.7%)	1 (0.9%)
HPV-26	2 (1.9%)	0
HPV-31	2 (1.9%)	3 (2.8%)
HPV-33	4 (3.7%)	1 (0.9%)
HPV-35	1 (0.9%)	0
HPV-45	2 (1.9%)	0
HPV-51	9 (8.4%)	0
HPV-52	3 (2.8%)	0
HPV-56	1 (0.9%)	3 (2.8%)
HPV-58	2 (1.9%)	2 (1.9%)
HPV-59	3 (2.8%)	0
HPV-66	2 (1.9%)	6 (5.6%)
HPV-68	6 (5.6%)	0
HPV-69	0	2 (1.9%)
HPV-73	3 (2.8%)	1 (0.9%)
HPV-83	0	1 (0.9%)
HPV-84	1 (0.9%)	0
HPV-89	1 (0.9%)	0
Probably high-risk genotypes		
HPV-53	2 (1.9%)	0
Indeterminate risk genotypes		
HPV-25	0	1 (0.9%)
Low-risk genotypes		
HPV-6	3 (2.8%)	1 (0.9%)
HPV-11	2 (1.9%)	0
HPV-40	1 (0.9%)	0
HPV-42	3 (2.8%)	2 (1.9%)
HPV-43	5 (4.7%)	0
HPV-44	4 (3.7%)	1 (0.9%)
HPV-61	2 (1.9%)	2 (1.9%)
HPV-62	1 (0.9%)	1 (0.9%)
HPV-70	4 (3.7%)	0
HPV-72	0	1 (0.9%)
HPV-81	0	1 (0.9%)

DISCUSSION

In this cross-sectional study we analyzed the prevalence of HPV-DNA in genitalia and oral samples in a Spanish HIV-MSM cohort. The study results are similar to previous research in another European countries (between 20% and 31%.) ([11,16]). However, the estimated incidence of HPV genital and oral infection varies widely across different studies, due to several reasons. Firstly, the study population may vary between studies. For example, studies focused in PLWH reveal a higher prevalence of HPV-DNA detection than HIV negative populations. In addition, there is not a clear consensus about how to collect genitalia and oral samples. The lack of a standard criteria may over or underestimate the real prevalence of HPV infection. Thirdly, vaccination programs may reduce the prevalence rate of some HPV genotypes (i.e., HPV-16, HPV-18). In our study, we excluded HPV vaccinated subjects. Therefore, our study could report a higher prevalence compared to studies including vaccinated patients. Finally, geographical and regional variations may influence the results of unicentric studies.

Overall prevalence of HPV infection was higher in genitalia than oral cavity, including hrHPV, similar to previous research[17]. We could not find any studies in Spanish population that compared HPV infection prevalence between genitalia and oral samples.

Distribution of genotypes also varied between both locations, maybe signaling different tropism based on the genotype. The cause of this variability remains unknown, but the interactions between HPV and mucosal surface, microbiome and local immunity could play a significant role[12].

HPV-16 was the only genotype detected in a similar rate in both locations (6.5% vs. 5.6%). The prevalence in our study is slightly higher than previous research[18].

On the other hand, HPV-66 was the most detected genotype in oral samples, tied with HPV-16. HPV-66 is classified as probable high risk oncogenic strain with an estimated prevalence in woman around 16%[19]. The prevalence and relevance of this genotype in HIV-MSM is still unknown.

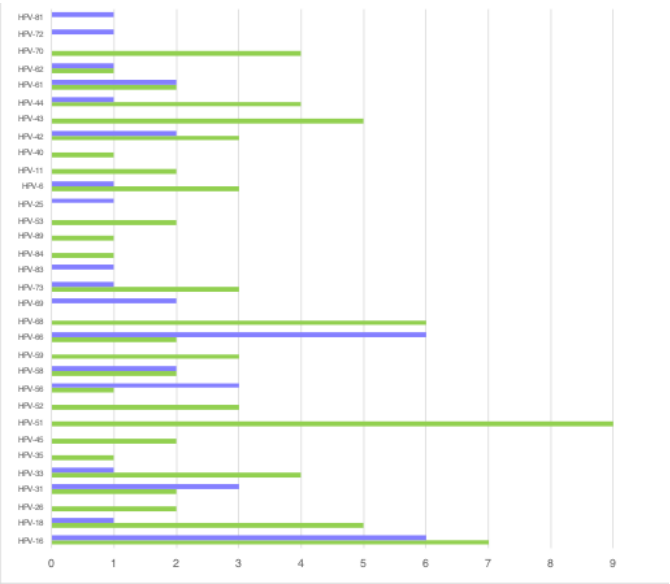
HPV-51 was the most common genotype isolated from genital samples; however, it was not detected in any oral sample. HPV-51 is a hrHPV, which anal prevalence in a nationwide Spanish cohort was around 20%[20].

HPV-18, HPV-33, HPV-52 and HPV-68 were also more commonly detected in genitalia than oral samples. All of them are considered hrHPV. Most of the previous studies have been focused on anal samples[20], while real prevalence and incidence of these genotypes outside anal conduct remains unknown.

Coinfection of multiple genotypes was also more common in genitalia than in oral cavity. HPV coinfection is frequent in HIV-MSM[21]. HIV enhance individual susceptibility to HPV infection through various mechanisms. Firstly, HIV decrease the number of CD4 lymphocytes, which increases the risk of HPV infection. Secondly, cells exposed to HIV produce many inflammatory substances, damaging epithelial barriers and other defensive mechanisms. Finally, HIV infection lowers the rate of HPV clearance[12].

We found no correlation between HPV genotypes in genitalia and oral cavity. Our previous research showed no concordance between anal and oral HPV genotypes[10]. The lack of concordance between locations have been reported in several previous cross-sec-

Figure 1. HPV distribution stratified by anatomical site



tional studies[22]. The absence of concordance between genital and oral samples may be due to different interactions between HPV and both tissues. Furthermore, anatomic alterations in oral or genitalia mucosa may increase or diminish de risk of HPV infection. For example, a cross-sectional study in Denmark found a lower risk of HPV genitalia infection in circumcised males[9]. In our study, we did not found difference in circumcised and uncircumcised patients, but this could be due to a lower sample size compared to previous research.

Consistent use of condom was similar to a previous study of Tao et al in Chinese MSM-HIV population[23]. Consistent use of condom during penetration was not associated with a lower HPV infection prevalence. This could be attributed to two factors. Firstly, HPV can be transmitted by direct contact with unprotected areas, such as scrotum, perineum and lips[24]. Secondly, low sample size may limit the statistical analysis. Moreover, use of condom during oral sex was very low. We did not find any study regarding the use of condom in oral sex in HIV-MSM. However, Hollway *et al*. found a rate use around 9% in males[25].

Previous research showed an increased risk of HPV anal and genitalia infection in patients with detectable HIV-RNA or low CD4 lymphocyte count[22]. However, in our study, CD4 lymphocyte count was not associated with an increased HPV prevalence. On the other hand, a detectable HIV-RNA was associated with a higher prevalence of genitalia infection, but not within the oral cavity. In addition, age, number of sexual partners and age of initial sexual intercourse were not associated with a higher HPV infection prevalence. Although the interactions between HIV and HPV are not yet fully understood, several studies showed an increase of HPV incidence in PLWH[26,27]. Multiple reasons for this have emerged in the recent years. Firstly, the immunosuppresed state induced by HIV impairs the host defense against HPV and another virus. Secondly, epithelial damage caused by HIV-related inflammation could facilitate the infection of some HPV genotypes.

CONCLUSIONS

Genital and oral HPV infection is frequent in HIV-MSM, including hrHPV. HPV 16 was the most common genotype in the study population. Prevalence and distribution of genotypes varied based on anatomic location, but no correlation was found between genitalia and oral samples. A detectable HIV-RNA was associated with a higher HPV genital prevalence but not with HPV oral infection rate. CD4 lymphocyte count, circumcision status, age and number of sexual partners were not associated with a higher prevalence of HPV infection.

Our study has several limitations. Firstly, the study of HPV infection prevalence outside anal conduct is challenging due to lack of commercial validated kits and a clear standard of sample collection. Moreover, management of this specimens in the Microbiology Department does not follow well established indications. Each laboratory uses a customized routine in order to detect HPV-DNA. We used the most common technique for each location (triple sample collection in genitalia and rinse in oral cavity) but both procedures are not validated. These two elements could explain the great variability of results between different research studies. Our research group has used these two techniques in previous studies, increasing our experience in HPV-DNA detection outside anal conduct[10,28,29]. Secondly, sample size is relatively small, so many comparisons could not be accurate (e.g., condom usage). Finally, only 10 patients were naïve to ART, so comparisons between naive and treated subjects may not be significant due to low sample size.

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CONFLICT OF INTEREST

The Author(s) declare(s) that there is no conflict of interest.

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ETHICAL ASPECTS

The study was approved by Ethics Committee of Pontevedra-Vigo-Ourense (reference 217/2019). Written informed consent was obtained from each participant.

REFERENCES

1. Satterwhite CL, Torrone E, Meites E, Dunne EF, Mahajan R, Ocfemia MCB, et al. Sexually transmitted infections among US women and men: prevalence and incidence estimates, 2008. Sex Transm Dis. 2013;40(3):187–93.
2. Schettino MT, De Franciscis P, Schiattarella A, La Manna V, Della Gala A, Caprio F, et al. Prevalence of HPV Genotypes in South Europe: Comparisons between an Italian and a Turkish Unvaccinated Population. J Environ Public Health. 2019;2019:1–7.
3. Burd EM. Human Papillomavirus and Cervical Cancer. Clin Microbiol Rev. 2003;16(1):1–17.
4. Nelson VM, Benson AB. Epidemiology of Anal Canal Cancer. Surg Oncol Clin N Am. 2017;26(1):9–15.
5. Stratton KL, Culkin DJ. A Contemporary Review of HPV and Penile Cancer. Oncology (Williston Park). 2016;30(3):245–9.
6. Wierzbicka M, Klussmann JP, San Giorgi MR, Wuerdemann N, Dikkers FG. Oral and laryngeal HPV infection: Incidence, prevalence and risk factors, with special regard to concurrent infection in head, neck and genitals. Vaccine. 2021;39(17):2344–50.
7. Gage JC, Schiffman M, Solomon D, Wheeler CM, Gravitt PE, Castle PE, et al. Risk of precancer determined by HPV genotype combinations in women with minor cytologic abnormalities. Cancer Epidemiol Biomarkers Prev. 2013;22(6):1095–101.
8. Wei F, Gaisa MM, D'Souza G, Xia N, Giuliano AR, Hawes SE, et al. Epidemiology of anal human papillomavirus infection and high-grade squamous intraepithelial lesions in 29 900 men according to HIV status, sexuality, and age: a collaborative pooled analysis of 64 studies. Lancet HIV. 2021;531–43.
9. Hebnes JB, Munk C, Frederiksen K, Joergensen HO, Iftner T, Kjaer SK. The role of circumcision, tobacco, and alcohol use in genital human papillomavirus infection among men from Denmark. Int J STD AIDS. 2021;
10. Ocampo Cancelas A, Diniz Freitas M, Pérez González A, Pérez Castro S, Carballo Fernández R, Iribarren Díaz M, et al. Concordance between oral and anal human papillomavirus infection in HIV-infected men who have sex with men. Oral Dis. 2020;26(1):224–7.
11. Parisi SG, Cruciani M, Scaggiante R, Boldrin C, Andreis S, Bello FD, et al. Anal and oral human papillomavirus (HPV) infection in HIV-infected subjects in northern Italy: a longitudinal cohort study among men who have sex with men. BMC Infect Dis. 2011;11(1):150.
12. Dreyer G. Clinical implications of the interaction between HPV and HIV infections. Best Pract Res Clin Obstet Gynaecol. 2018;47:95–106.
13. Xie L, Li Q, Dong X, Kong Q, Duan Y, Chen X, et al. Investigation of the association between ten pathogens causing sexually transmitted diseases and high-risk human papilloma virus infection in shanghai. Mol Clin Oncol. 2021;15(1):1–7.
14. Masiá M, Fernández-González M, García JA, Padilla S, García-Payá E, Gutiérrez A, et al. Infection With Chlamydia trachomatis Increases the Risk of High-grade Anal Intraepithelial Neoplasia in People Living With Human Immunodeficiency Virus. Clin Infect Dis. 2020;70(10):2161–7.
15. Goulart ACX, Farnezi HCM, França JPBM, Santos A dos, Ramos MG, Penna MLF. HIV, HPV and Chlamydia trachomatis: impacts on male fertility. JBRA Assist Reprod. 2020;
16 King EM, Oomeer S, Gilson R, Copas A, Beddows S, Soldan K, et al. Oral Human Papillomavirus Infection in Men Who Have Sex with Men: A Systematic Review and Meta-Analysis. Lama JR, editor. PLoS One. 2016;11(7):e0157976.
17. van Rijn VM, Mooij SH, Mollers M, Snijders PJF, Speksnijder AGCL, King AJ, et al. Anal, Penile, and Oral High-Risk HPV Infections and HPV Seropositivity in HIV-Positive and HIV-Negative Men Who Have Sex with Men. Zhang L, editor. PLoS One. 2014;9(3):e92208.
18. Rollo F, Latini A, Pichi B, Colafigli M, Benevolo M, Sinopoli I, et al. Prevalence and determinants of oral infection by Human Papillomavirus in HIV-infected and uninfected men who have sex with men. Tornesello ML, editor. PLoS One. 2017;12(9):e0184623.
19. Molina-Pineda A, López-Cardona MG, Limón-Toledo LP, Cantón-Romero JC, Martínez-Silva MG, Ramos-Sánchez HV, et al. High frequency of HPV genotypes 59, 66, 52, 51, 39 and 56 in women from Western Mexico. BMC Infect Dis. 2020;20(1):889.
20. Torres M, González C, del Romero J, Viciana P, Ocampo A, Rodríguez-Fortúnez P, et al. Anal Human Papillomavirus Genotype Distribution in HIV-Infected Men Who Have Sex with Men by Geographical Origin, Age, and Cytological Status in a Spanish Cohort. J Clin Microbiol. 2013;51(11):3512–20.
21. Del Amo J, Gonzalez C, Geskus RB, Torres M, Del Romero J, Viciana P, et al. What Drives the Number of High-Risk Human Papillomavirus Types in the Anal Canal in HIV-Positive Men Who Have Sex With Men? J Infect Dis. 2013;207(8):1235–41.
22. Vergori A, Garbuglia AR, Piselli P, Del Nonno F, Sias C, Lupi F, et al. Oral human Papillomavirus DNA detection in HIV-positive men: prevalence, predictors, and co-occurrence at anal site. BMC Infect Dis. 2018;18(1):25.
23. Tao L, Liu M, Li S, Liu J, Wang N. Condom use in combination with ART can reduce HIV incidence and mortality of PLWHA among MSM: a study from Beijing, China. BMC Infect Dis. 2018;18(1):124.
24. Christensen ND. HPV disease transmission protection and control. Microb Cell. 2016;3(9):475–89.
25. Holway GV, Hernandez SM. Oral Sex and Condom Use in a U.S. National Sample of Adolescents and Young Adults. J Adolesc Heal. 2018;62(4):402–10.
26. Lin C, Franceschi S, Clifford GM. Human papillomavirus types from infection to cancer in the anus, according to sex and HIV status: a systematic review and meta-analysis. Lancet Infect Dis. 2018;18(2):198–206.
27. Camargo M, Del Río-Ospina L, Soto-De León SC, Sánchez R, Pineda-Peña AC, Sussmann O, et al. Association of HIV status with infection by multiple HPV types. Trop Med Int Heal. 2018;23(11):1259–68.
28. López Diez E, Pérez S, Iñarrea A, de la Orden A, Castro M, Almuster S, et al. Prevalence and concordance of high-risk papillomavirus infection in male sexual partners of women diagnosed with high grade cervical lesions. Enferm Infecc Microbiol Clin. 2017;35(5):273–7.
29. Lopez-Diez E, Perez S, Carballo M, Iñarrea A, de la Orden A, Castro M, et al. Lifestyle factors and oncogenic papillomavirus infection in a high-risk male population. Grce M, editor. PLoS One. 2017;12(9):e0184492.

Comorbilidades asociadas a mortalidad o enfermedad severa en pacientes hospitalizados con COVID-19

Comorbidities associated with mortality or severe disease in hospitalized patients with COVID-19

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ABSTRACT

Objective: To evaluate the comorbidities in hospitalized patients with COVID-19 and identify which ones are associated with severe COVID-19 disease and/or in-hospital mortality.

Methods: Unicenter retrospective cohort study was performed. All patients admitted with confirmed COVID-19 from March 1 to May 31, 2020 were included consecutively. A descriptive analysis of comorbidities at admission was made. We evaluated what comorbidities are associated with in-hospital mortality and/or severe COVID-19 disease using a binary logistic regression model.

Results: A total of 336 patients were included in the study: 284 (84,5%) were discharged and 52 (15,5%) died during hospitalization. The diagnosis of COVID-19 was made by SARS-CoV-2 polymerase chain reaction in 317 patients (94%). Mean age was 66 + 14 years, 58% were men and Charlson Comorbidity Index was 1. In multivariate analysis, age >65 years (OR 2,65; 95%CI 1,15 to 6,10; p 0,021), male sex (OR 3,26; 95%CI 1,47 to 7,24; p 0,004), atherosclerotic cardiovascular disease (OR 2,11; 95%CI 1,03 to 4,29; p 0,040), non-atherosclerotic cardiovascular disease (OR 6,40; 95%CI 2,25 to 18,21, p<0,001) and malignancy (OR 5,09; 95%CI 2,28 to 11,34; p< 0,001), were identified as comorbidities associated with in hospital-mortality. Age >65 years (OR 1,87; 95%CI 1,05 to 3,34; p 0,033), male sex (OR 2,86; 95%CI 1,58 to 5,17; p<0,001), obesity (OR 1,82; 95%CI 1,04 to 3,18; p 0,034) and obstructive sleep apnea (OR 5,26; 95%CI 1,60 to 17,25; p 0,006) were associated with severe COVID-19 disease.

Conclusions: Previous cardiovascular disease and malignancy are risk factors of in-hospital mortality while obesity and obstructive sleep apnea are associated with severe COVID-19 disease in hospitalized patients. Age >65 years and male sex are associated with both.

Keywords: Comorbidity; COVID-19; mortality: severe disease.

RESUMEN

Objetivo: Conocer las comorbilidades de los pacientes hospitalizados con COVID-19 e identificar cuales se asocian a mayor severidad y/o mortalidad intrahospitalaria.

Métodos: Estudio de cohortes retrospectivo unicéntrico en el que se incluyeron todos los pacientes ingresados con COVID-19 desde marzo del 2020 hasta mayo de 2020. Se realizó un análisis descriptivo de las comorbilidades al ingreso y se vio cuales se asocian a una mayor mortalidad intrahospitalaria y/o mayor severidad de la enfermedad mediante un modelo de regresión logística binaria.

Resultados: Un total de 336 pacientes fueron incluidos en el estudio de los cuales 284 (84,5%) fueron dados de alta y 52 (15,5%) fallecieron durante el ingreso. El diagnóstico de COVID-19 fue realizado por reacción en cadena de la polimerasa a SARS-CoV-2 en 317 pacientes (94%). Un 58% eran varones, la edad media fue 66 años y el índice Charlson fue de 1. En el análisis multivariante se identificaron como comorbilidades asociadas a mortalidad la edad > 65 años (OR 2,65; IC95% 1,15-6,10; p 0,021), el sexo masculino (OR 3,26; IC95% 1,47-7,24; p 0,004), la enfermedad cardiovascular ateroesclerótica (OR 2,11; IC95% 1,03-4.29; p<0,040) y no ateroesclerótica (OR 6,40; IC95% 2,25-18,21; p<0,001) y la neoplasia activa (OR 5,09; IC95% 2,28-11,34; p<0,001). Se asociaron a mayor severidad de la COVID-19 la edad> 65 años (OR 1,87; IC95% 1,05-3,34; p 0,033), el sexo masculino (OR 2,86; IC95% 1,58-5,17; p <0,001), la obesidad (OR 1,82; IC95% 1,04-3,18; p 0,034) y (OR 5,26; IC95% 1,60-17,25; p 0,006).

Conclusiones: La enfermedad cardiovascular previa y la neoplasia se asocian a mortalidad intrahospitalaria mientras que la obesidad y el SAOS se asocian a mayor severidad de la enfermedad en pacientes hospitalizados con COVID-19. La edad >65 años y el sexo masculino se asocian a una mayor severidad y mortalidad intrahospitalaria.

Palabras clave: Comorbilidad; COVID-19; mortalidad: severidad.

INTRODUCCIÓN

Tras la aparición de los primeros casos de infección por una nueva cepa de coronavirus (Severe Acute Respiratory Syndrome Coronavirus 2 ó SARS-CoV-2) en diciembre 2019 en Wuhan-China, el número de casos ha ido en aumento en todo el mundo declarándose pandemia mundial el 11 de marzo 2020. España es uno de los países más afectados por la infección por SARS-CoV-2, notificándose a 1 diciembre de 2021, unos 5.174.720 casos con 88.080 fallecidos[1]. Las manifestaciones clínicas más frecuentes son comunes a otros virus respiratorios (fiebre, tos, disnea, mialgias, fatiga, diarrea y anosmia/ageusia); también se han confirmado casos asintomáticos[2]. Una de las principales complicaciones potencialmente mortales de la enfermedad es el síndrome de distrés respiratorio agudo (SDRA) debido a la afectación pulmonar bilateral extensa[3]. La tasa de mortalidad global en pacientes hospitalizados en la primera ola se sitúa entre 20-30% según estudios, pudiendo algunos factores como la edad o las comorbilidades explicar estas diferencias de mortalidad[4,5]. Se han descrito algunos factores de riesgo clínicos asociados a un mal pronóstico en pacientes con COVID-19: la edad avanzada, el sexo masculino y la presencia de comorbilidades como la hipertensión, la diabetes, la enfermedad cardiovascular (ECV), enfermedades respiratorias crónicas, enfermedad renal crónica (ERC) y neoplasia maligna[5-7].

En la actualidad, el número creciente de nuevas infecciones junto con la alta prevalencia de comorbilidades condicionan una sobrecarga para el sistema sanitario sin precedentes[8]. Profundizar en el conocimiento de esta infección es importante para poder mejorar el manejo de estos pacientes. Identificar aquellos que pueden tener una peor evolución o mayor mortalidad podría ayudarnos en la toma de decisiones, optimizar las medidas de soporte e iniciar los tratamientos recomendados de forma precoz.

El objetivo de nuestro estudio es conocer la prevalencia de las

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principales comorbilidades entre las personas hospitalizadas con COVID-19 en nuestra área sanitaria durante la primera ola (previa a la aparición de vacunas y tratamientos específicos), así como identificar cuales se asocian a una mayor mortalidad intrahospitalaria y/o severidad de la enfermedad.

MATERIAL Y MÉTODOS

2.1. Tipo de estudio

Estudio de cohortes retrospectivo observacional realizado en el Complejo Hospitalario Universitario de Santiago de Compostela (A Coruña, España), un hospital de aproximadamente 1395 camas que cuenta con unidad de cuidados intensivos (UCI) y trasplantes, con una población de referencia de 384.852 habitantes. Se incluyeron de forma consecutiva pacientes ingresados con diagnóstico de infección por SARS-CoV-2 desde el 01 de marzo de 2020 hasta el 31 de mayo de 2020. A todos los pacientes se les hizo seguimiento hasta la fecha de fin del estudio o fallecimiento. Criterios de inclusión: todos los pacientes >18 años ingresados en nuestro centro con infección por SARS-CoV-2 confirmada. La COVID-19 se confirmó mediante un test positivo de la reacción en cadena de la polimerasa en tiempo real (RT-PCR) en una muestra de exudado faríngeo, esputo o lavado broncoalveolar o bien por un resultado positivo de un test serológico con un cuadro clínico compatible. Criterios de exclusión: ingresos posteriores del mismo paciente, ausencia de consentimiento informado o pacientes asintomáticos con COVID-19 ingresados por otro motivo.

2.3. Recogida de información

Se revisaron las historias clínicas de dichos pacientes tras obtener su consentimiento. Se recogieron las variables agrupadas por: 1) datos epidemiológicos 2) datos relacionados con RT-PCR y serología 3) hábitos tóxicos como tabaco y alcohol 4) situación funcional 5) índice de Charlson y comorbilidades que incluyen hipertensión, diabetes mellitus, obesidad, cardiopatías, enfermedad pulmonar obstructiva crónica (EPOC), otras enfermedades pulmonares, enfermedad renal crónica (ERC), enfermedad vascular periférica, enfermedad cerebrovascular, neoplasia activa, enfermedades sistémicas 6) medicación previa como inhibidores de la enzima conversora de angiotensina (IECA), antagonistas de los receptores de angiotensina 2 (ARA-2), estatinas, diuréticos, beta bloqueantes, antagonistas de los canales del calcio (ACC), corticoides sistémicos e inhalados, inmunosupresores, terapias biológicas, antiagregantes, anticoagulantes 7) síntomas, hallazgos en la exploración física al ingreso y tiempo de evolución desde el inicio de los síntomas hasta su ingreso 8) datos de laboratorio y radiológicos al ingreso 9) necesidad de ingreso en unidad de cuidados intensivos (UCI), necesidad de ventilación mecánica invasiva (VMI) y no invasiva (VMNI) 10) evolución del paciente (alta, reingreso, fallecimiento).

Para la valoración del grado de comorbilidad se utilizó el índice de comorbilidad de Charlson[9] y para valorar el estado funcional previo al ingreso el índice de Barthel (independiente o dependencia leve: 91-100; dependencia moderada: 61-90; y dependencia severa: <60)[10]. Definimos enfermedad cardiovascular ateroesclerótica como historia previa de cardiopatía isquémica (incluye infarto de miocardio, angor, síndrome coronario agudo o revascularización coronaria), enfermedad cerebrovascular (ictus isquémico o hemorrágico, accidente isquémico transitorio) o enfermedad arterial periférica (claudicación intermitente, revascularización, amputación extremidades o aneurisma aorta abdominal). Enfermedad cardiovascular no ateroesclerótica incluye fibrilación auricular e insuficiencia cardiaca congestiva. Se define obesidad cuando el índice masa corporal fue >30 Kg/m^2. Se consideró que el paciente presentaba hipertensión, diabetes mellitus o dislipemia cuando estaban diagnosticados al ingreso o tomaban medicación para ello. El diagnóstico de neoplasia activa incluye tumores sólidos y/o hematológicos activos o diagnosticados en los últimos 5 años, excluyendo el melanoma. ERC fue definida como un filtrado glomerular <45 mL/1.73 m2 según CKD-EPI[11]. El SDRA fue valorado según la clasificación de Berlín[12]. Se define infección grave o severa por SARS-CoV-2 aquellos pacientes que fallecen, precisan VMI o VMNI, atención en UCI o presentan SDRA severo definido como presión parcial oxígeno arterial/fracción de oxígeno inspirado (PaO2/FiO2) <200 mmHg durante el ingreso. Consideramos mortalidad intrahospitalaria al fallecimiento del paciente durante la hospitalización por cualquier causa.

2.4. Análisis estadístico

Se calcularon frecuencias y porcentajes para las variables cualitativas. Las variables cuantitativas se expresaron como media + desviación típica (mediana). La prueba de Kolmogorov-Smirnov se utilizó para analizar la normalidad de la distribución de parámetros. La comparación de variables cuantitativas se realizó mediante el test de T-student (para variables con distribución normal) y test de U de Mann-Whitney (para variables con distribución no normal). La comparación de variables cualitativas se realizó mediante el test de Chi-cuadrado o el test exacto de Fisher. El grado de asociación se estimó mediante la odds ratio (OR) con un intervalo de confianza del 95% (IC95%).

Para identificar aquellas comorbilidades que se asocian de forma independiente a mortalidad intrahospitalaria o a mayor severidad se realizó un análisis de regresión logística binaria (procedimiento hacia delante según Wald). Se asigna como variable dependiente la muerte intrahospitalaria o la infección grave y como variable independiente aquellas que presentaron diferencias significativas ($p<0,05$) en el análisis univariante. Se confirma la ausencia de colinealidad significativa a través del factor de inflación de la varianza entre las variables incluidas en el modelo.

El análisis estadístico se realiza mediante el programa Statistical Package for the Social Sciences (SPSS) para Windows versión 18.0 (SPSS Inc., an IBM Co. Chicago, Illinois, EE.UU.).

2.5. Aspectos éticos y legales

Los datos personales se tratan cumpliendo con la Ley 14/2007 de 3 de julio, de Investigación Biomédica, así como con el Reglamento (UE) 2016/679, del Parlamento Europeo y del Consejo, de 27 de abril de 2016, Reglamento general de protección de Datos y la Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y Garantía de los Derechos Digitales. Este estudio forma parte del Registro SEMI-COVID-19 que tiene la aprobación del Comité de Ética e Investigación de la provincia de Málaga, además del comité de ética de nuestro centro.

Se solicitó a los pacientes el consentimiento informado. Cuando no fue posible obtenerlo por escrito por razones de bioseguridad o por encontrarse el paciente ya de alta hospitalaria, se recogió de forma verbal, dejando constancia en su historia clínica.

RESULTADOS

Se incluyeron un total de 336 pacientes. El 94,3% se diagnosticaron mediante PCR-RT en exudado nasofaríngeo, siendo negativa la primera muestra en un 17% de los casos. El resto fueron diagnosticados por serología positiva con un cuadro clínico compatible. En un 12,5% de los casos la adquisición fue nosocomial y sólo un 5,4% era personal sanitario. El 55% de los pacientes referían un contacto estrecho previo. La edad media fue de 66 + 14 años, un 58% eran varones y el índice de comorbilidad de Charlson fue de 1. La mayoría no tenían hábitos tóxicos y hasta un 12,5% de los pacientes tenían una dependencia moderada-severa para sus actividades habituales. El 83,6% de los casos presentaban alguna comorbilidad siendo las más frecuentes hipertensión (48,5%), dislipemia (46,4%), diabetes mellitus (25,3%), obesidad (38,4%), enfermedad cardiovascular previa (31%, siendo la más frecuente la cardiopatía isquémica), neumopatía crónica (15,8% destacando la EPOC y el asma) y neoplasias (11,9%). Al ingreso la duración media de los síntomas era de 7 días siendo los más frecuentes febrícula-fiebre, tos, astenia y disnea, esta última presente en la mitad de los casos. Al ingreso, el grado de severidad SDRA fue: leve en el 28% de los casos, moderado en el 8,6% y severo en 1 paciente. Durante el ingreso 44 pacientes (13,1%) necesitaron ingreso en UCI, 18 pacientes (5,4%) oxigenoterapia de alto flujo, 5 pacientes VMNI y 33 pacientes (10%) VMI con una duración media de estancia en UCI de 13 días y estancia hospitalaria de 10 días. De los 336 pacientes el 15,5% (52 pacientes) fallecieron durante el ingreso, la mayoría debido a COVID-19; sólo 5 fallecieron por otras causas

3.2. Factores asociados a mortalidad intrahospitalaria.

La tabla 1 muestra los datos epidemiológicos y comorbilidades de los pacientes del estudio. La edad media (76 vs 65 años), así como edad >65 años (83 vs 54%) y sexo masculino (81 vs 54%) fueron mayores en los pacientes fallecidos. El consumo de alcohol fue también mayor en el grupo de fallecidos, sin diferencias significativas en relación al hábito tabáquico. La media de tiempo transcurrido entre la aparición de los síntomas y el ingreso hospitalario fue mayor en el grupo de vivos (7 vs 5 días) siendo los síntomas similares en ambos grupos. En cuanto a las comorbilidades analizadas, se observaron diferencias significativas siendo más frecuentes en los pacientes fallecidos: diabetes mellitus, obesidad, enfermedad cardiovascular previa, SAOS, enfermedad neurológica degenerativa y neoplasia. Cuando analizamos por separado enfermedad cardiovascular (ECV) ateroesclerótica y no ateroesclerótica ambas se asocian a una mayor mortalidad siendo más marcada en la ECV-no ateroesclerótica. Sin embargo no hubo diferencias significativas en hipertensión, dislipemia, EPOC, enfermedad cerebrovascular ERC.

Se analizaron las diferencias en los tratamientos médicos previos al ingreso observándose que los pacientes tratados con diuréticos, beta bloqueantes, anticoagulantes, IDPP-4 e insulina presentaban una mayor mortalidad. No hubo diferencias en cuanto al tratamiento previo con IECAS, ARA-2, estatinas ni ácido acetilsalicílico (AAS).

Cuando realizamos el análisis multivariante con las variables que resultaron significativas en el univariante, sólo 5 de ellas se asocian de forma independiente con mortalidad intrahospitalaria: la edad > 65 años (OR 2,65; IC95% 1,15-6,10; p 0,021), el sexo masculino (OR 3,26; IC95% 1,47-7,24; p 0,004), la enfermedad cardiovascular ateroesclerótica (OR 2,11; IC95% 1,03-4.29; p<0,040) y no ateroesclerótica (OR 6,40; IC95% 2,25-18,21; p<0,001) y la neoplasia activa (OR 5,09; IC95% 2,28-11,34; p<0,001) (tabla 2).

3-Factores asociados a severidad de la COVID-19.

En la tabla 3 se muestra la distribución de los pacientes en función de si tenían enfermedad severa o no. La edad media (71 vs 65 años), así como edad >65 años (73.5 vs 54%) y sexo masculino (76 vs 52%) fueron mayores en los pacientes con infección grave por SARS-CoV-2 sin observarse diferencias significativas en relación a los hábitos tóxicos ni al grado de dependencia. La media de tiempo transcurrido entre la aparición de los síntomas y el ingreso hospitalario fue similar en ambos grupos (7 días) siendo la disnea el síntoma más frecuente en infección grave y los síntomas gastrointestinales en los casos de infección no grave. En cuanto a las comorbilidades analizadas, la diabetes mellitus, obesidad, enfermedad cardiovascular previa, SAOS y neoplasia presentaban con mayor frecuencia enfermedad grave. En cuanto a la medicación previa al ingreso se observó una mayor severidad de la COVID-19 en pacientes tratados con diuréticos, beta bloqueantes, ACC, anticoagulantes e IDPP-4. No se encontraron diferencias con IECAS, ARA-2, estatinas ni AAS.

Se realizó un análisis multivariante usando como variable dependiente la presencia de COVID severo y como variables independientes aquellas que mostraron mayor significación estadística (p<0,05) en el análisis univariante previo. En nuestro estudio hemos encontrado que la edad> 65 años (OR 1,87; IC95% 1,05-3,34; p 0,033), el sexo masculino (OR 2,86; IC95% 1,58-5,17; p <0,001), la obesidad (OR 1,82; IC95% 1,04-3,18; p 0,034) y (OR 5,26; IC95% 1,60-17,25; p 0,006) se asocian a una mayor severidad de la COVID-19 (tabla 4)

Tabla 1. Datos epidemiológicos y comorbilidades de los pacientes incluidos en el estudio según mortalidad

Variables	Total	Vivos	Fallecidos	Análisis univariante		
	n (%)	n (%)	n (%)	OR	IC 95%	p
Varón	195 (58,0)	153 (53,9)	42 (80,8)	3,59	1,73-7,44	**<0,001**
Edad (media + DE)	76 + 14 (68)	65 +13 (67)	76+11 (77)	1,09	1,05-1,12	**<0,001**
Edad >65 años	197 (58,6)	154 (54,2)	43 (82,7)	4,03	1,89-8,58	**<0,001**
Alcohol	25 (7,4)	17 (6)	8 (15,4)	2,85	1,16-7,01	**0,025**
Tabaco -no -exfumador -fumador activo	 210 (98,8) 111 (33,0) 15 (4,5)	 186 (65,5) 83 (29,2) 15 (5,3)	 24 (46,2) 28 (53,8) 0			 0,107
Estado funcional						
independiente o leve	295 (87,8)	259 (91,2)	26 (69,2)			**<0,001**
dependencia moderada	17 (5,1)	8 (2,8)	9 (17,3)			
dependencia severa	24 (7,1)	17 (13,5)	7 (13,5)			
Comorbilidad						
Charlson (media + DE)	1,5+ 2,1 (1)	1+ 1,5 (0)	2,4+ 2 (2)	1,37	1,21-1,56	**<0,001**
Hipertensión	163 (48,5)	132 (46,5)	31 (59,6)	1,70	0,93-3,10	0,081
Dislipemia	156 (46,4)	131 (46,1)	25 (48,1)	1,08	0,59-1,95	0,795
Diabetes	85 (25,3)	61 (21,5)	24 (46,2)	3,13	1,69-5,79	**<0,001**
Obesidad	129 (38,4)	100 (35,2)	29 (55,8)	2,32	1,27-4,22	**0,005**
Depresión/Ansiedad	50 (14,9)	41 (14,4)	8 (15,4)	1,07	0,47-2,45	0,859
Enf. NRL degenerativa	23 (6,8)	16 (5,6)	7 (13,5)	2,60	1,01-6,68	**0,047**
ECV ateroesclerótica	88 (26,2)	62 (21,8)	26 (50,0)	3,58	1,94-6,60	**<0,001**
ECV no-ateroesclerótica	21 (6,3)	12 (4,2)	9 (17,3)	4,74	1,88-11,93	**<0,001**
Neumopatía crónica	53 (15,8)	42 (14,8)	11 (21,2)	1,54	0,73-3,24	0,247
Hepatopatía crónica	13 (3,9)	11 (3,9)	2 (3,8)	0,99	0,21-4,61	0,675
ERC	15 (4,5)	11 (3,9)	4 (7,7)	2,06	0,63-6,76	0,188
Neoplasias	40 (11,9)	23 (8,1)	17 (32,7)	5,51	2,68-11,31	**<0,001**
Conectivopatías	17 (5,1)	12 (4,2)	5 (9,6)	2,41	0,81-7,15	0,104
Enfermedad cardiovascular ateroesclerótica						
Cardiopatía isquémica	36 (10,7)	26 (9,2)	10 (19,2)	2,36	1,06-5,25	**0,031**
Enf. cerebrovascular	20 (6,0)	15 (5,3)	5 (9,6)	1,90	0,66-5,49	0,181
Enf. Vascular periférica	24 (7,1)	15 (5,3)	9 (17,3)	3,75	1,54-9,11	**0,005**

Enfermedad cardiovascular NO ateroesclerótica						
ICC	20 (6,0)	8 (2,8)	12 (23,1)	10,35	3,98-26,87	**<0,001**
Fibrilación auricular	34 (10,1)	19 (6,7)	15 (28,8)	5,65	2,64-12,08	**<0,001**
Neumopatía crónica						
EPOC	20 (6,0)	15 (5,3)	5 (9,6)	1,90	0,66-5,49	0,181
Asma	25 (7,4)	24 (8,5)	1 (1,9)	0,21	0,02-1,60	0,075
SAOS	16 (4,8)	10 (3,5)	6 (11,5)	3,57	1,23-10,30	**0,024**
Tratamientos						
Estatinas	141 (42,0)	119 (41,9)	22 (42,3)	1,01	0,55-1,85	0,956
IECA	45 (13,4)	37 (13,0)	8 (15,4)	1,21	0,53-2,78	0,646
ARA-2	87 (25,9)	73 (25,7)	14 (26,9)	1,06	0,54-2,07	0,854
Diuréticos	83 (24,7)	63 (22,2)	20 (38,5)	2,19	1,17-4,09	**0,012**
Beta bloqueantes	49 (14,6)	35 (12,3)	14 (26,9)	2,62	1,29-5,31	**0,006**
Antagonistas del calcio	52 (15,5)	36 (12,7)	16 (30,8)	3,06	1,54-6,07	0,001
AAS	47 (14,0)	36 (12,7)	11 (21,2)	1,84	0,87-3,92	0,105
Anticoagulantes	31 (9,2)	19 (6,7)	12 (23,1)	4,18	1,88-9,27	**0,001**
Metformina	53 (15,8)	42 (14,8)	11 (21,2)	1,54	0,73-3,24	0,247
IDPP-4	36 (10,7)	25 (8,8)	11 (21,2)	2,78	1,27-6,07	**0,008**
GLP-1	5 (1,5)	4 (1,4)	1 (1,9)	1,37	0,15-12,53	0,571
SGLT-2	9 (2,7)	7 (2,5)	2 (3,8)	1,58	0,32-7,84	0,418
Insulina	25 (7,4)	16 (5,6)	9 (17,3)	3,50	1,45-8,43	**0,007**
Corticoides sistémicos	30 (8,9)	22 (7,7)	8 (15,4)	2,16	0,90-5,16	0,071
Corticoides inhalados	26 (7,7)	20 (7,0)	6 (11,5)	1,72	0,65-4,51	0,197
Inmunosupresores	16 (4,8)	15 (5,3)	1 (1,9)	0,35	0,04-2,72	0,260
Terapias biológicas	7 (2,1)	7 (2,5)	0	0,84	0,80-0,88	0,305
TARGA	2 (0,6)	2 (0,7)	0	0,84	0,80-0,88	0,714
Total	**336**	**284**	**5**			

Tabla 2. Variables incluidas en el análisis multivariante para predecir mortalidad intrahospitalaria

	Análisis univariante			Análisis multivariante		
Variables	OR	IC 95%	p	OR	IC 95%	p
Alcohol	2,85	1,16-7,01	0,025			
Obesidad	2,32	1,27-4,22	0,005			
Enfermedad neurológica degenerativa	2,60	1,01-6,68	0,047			
Neoplasia activa	5,51	2,68-11,31	<0,001	5,09	2,28-11,34	**<0,001**
ECV ateroesclerótica	3,58	1,94-6,60	<0,001	2,11	1,03-4,29	**0,040**
ECV *no-ateroesclerótica*	4,74	1,88-11,93	<0,001	6,40	2,25-18,21	**<0,001**
Diabetes mellitus	3,13	1,69-5,79	<0,001			
SAOS	3,57	1,23-10,30	0,024			
Sexo	3,59	1,73-7,44	<0,001	3,26	1,47-7,24	0,004
Edad >65 años	4,03	1,89-8,58	<0,001	2,65	1,15-6,10	**0,021**

Abreviaturas: OR, odds ratio; IC, intervalo de confianza; DE, desviación estándar; ECV, enfermedad cardiovascular; SAOS, síndrome apnea obstructiva del sueño.

Tabla 3. Datos epidemiológicos y comorbilidades de los pacientes incluidos en el estudio según gravedad de la COVID-19.

Variables	Total	Vivos	Fallecidos	Análisis univariante		
	n (%)	n (%)	n (%)	OR	IC 95%	p
Varón	195 (58,0)	132 (52,2)	63 (75,9)	2,88	1,64-5,05	**<0,001**
Edad (media + DE)	76 + 14 (68)	65 +13 (67)	71+12 (73)	1,03	1,01-1,05	**<0,001**
Edad >65 años	197 (58,6)	136 (53,8)	61 (73,5)	2,38	1,38-4,12	**0,002**
Alcohol	25 (7,4)	15 (5,9)	10 (12,0)	2,17	0,93-5,04	**0,065**
Tabaco	15 (4,5)	14 (5,5)	1 (1,2)	0,54	0,11-2,50	0,532

Comorbilidad						
Charlson (media + DE)	1,5+ 2,1 (1)	1,1+ 1,7 (0)	1,7+ 1,8 (1)	1,22	1,10-1,37	**<0,001**
Hipertensión	163 (48,5)	115 (45,5)	48 (57,8)	1,64	0,99-2,71	0,050
Dislipemia	156 (46,4)	114 (45,1)	42 (50,6)	1,24	0,76-2,05	0,380
Diabetes	85 (25,3)	50 (19,8)	35 (42,2)	2,96	1,73-5,05	**<0,001**
Obesidad	129 (38,4)	83 (32,8)	46 (55,4)	2,54	1,53-4,22	**<0,001**
Depresión/Ansiedad	50 (14,9)	36 (14,2)	14 (16,9)	1,22	0,62-2,40	0,558
Enf. NRL degenerativa	23 (6,8)	16 (6,3)	7 (8,4)	1,36	0,54-3,44	0,509
ECV ateroesclerótica	88 (26,2)	57 (22,5)	31 (37,3)	2,05	1,20-3,49	**0,008**
ECV no-ateroesclerótica	21 (6,3)	11 (4,3)	10 (12,0)	3,01	1,23-7,37	**0,012**
Neumopatía crónica	53 (15,8)	37 (14,6)	16 (19,3)	1,39	0,73-2,66	0,313
Hepatopatía crónica	13 (3,9)	9 (3,6)	4 (4,8)	1,37	0,41-4,58	0,743
ERC	15 (4,5)	10 (4,0)	5 (6,0)	1,55	0,51-4,69	0,539
Neoplasias	40 (11,9)	23 (9,1)	17 (20,5)	2,57	1,30-5,10	**0,005**
Conectivopatías	17 (5,1)	11 (4,3)	6 (7,2)	1,71	0,61-4,78	0,384
Enfermedad cardiovascular ateroesclerótica						
Cardiopatía isquémica	36 (10,7)	25 (9,9)	11 (13,3)	1,39	0,65-2,97	**0,389**
Enf. cerebrovascular	20 (6,0)	13 (5,1)	7 (8,4)	1,70	0,65-4,41	0,288
Enf. Vascular periférica	24 (7,1)	15 (5,9)	9 (10,8)	1,93	0,81-4,59	**0,131**
Enfermedad cardiovascular NO ateroesclerótica						
ICC	20 (6,0)	8 (3,2)	12 (14,5)	5,17	2,03-13,15	**0,001**
Fibrilación auricular	34 (10,1)	17 (6,7)	17 (20,5)	3,57	1,73-7,38	**<0,001**
Neumopatía crónica						
EPOC	20 (6,0)	13 (5,1)	7 (8,4)	1,70	0,65-4,41	0,288
Asma	25 (7,4)	20 (7,9)	5 (6,0)	0,74	0,27-2,05	0,571
SAOS	16 (4,8)	5 (2,0)	11 (13,3)	7,57	2,55-22,52	**<0,001**

Tratamientos						
Estatinas	141 (42,0)	104 (41,1)	37 (44,6)	1,15	0,69-1,90	0,578
IECA	45 (13,4)	33 (13,0)	12 (14,5)	1,12	0,55-2,29	0,743
ARA-II	87 (25,9)	61 (24,1)	26 (31,3)	1,43	0,83-2,47	0,193
Diuréticos	83 (24,7)	54 (21,3)	29 (34,9)	1,97	1,15-3,40	**0,013**
Beta bloqueantes	49 (14,6)	30 (11,9)	19 (22,9)	2,20	1,16-4,17	**0,013**
Antagonistas del calcio	52 (15,5)	32 (12,6)	20 (24,1)	2,19	1,17-4,09	**0,014**
AAS	47 (14,0)	34 (13,4)	13 (15,7)	1,19	0,59-2,39	0,161
Anticoagulantes	31 (9,2)	17 (6,7)	14 (16,9)	2,81	1,32-6,00	**0,006**
Metformina	53 (15,8)	34 (13,4)	19 (22,9)	1,91	1,02-3,57	**0,040**
IDPP-4	36 (10,7)	19 (7,5)	17 (20,5)	3,17	1,56-6,44	**0,001**
Insulina	25 (7,4)	15 (5,9)	10 (12,0)	2,17	0,93-5,04	**0,065**
Corticoides sistémicos	30 (8,9)	21 (8,3)	9 (10,8)	1,34	0,59-3,06	0,481
Total	**336**	**253**	**83**			

Abreviaturas: n, número; OR, odds ratio; IC, intervalo de confianza; DE, desviación estándar; Enf, enfermedad; NRL, neurológica; ECV, enfermedad cardiovascular; ERC, enfermedad renal crónica; ICC, insuficiencia cardiaca congestiva; EPOC, enfermedad pulmonar obstructiva crónica; SAOS, síndrome apnea obstructiva del sueño; IECA, inhibidores de la enzima conversora de angiotensina; ARA-2, antagonistas del receptor de la aldosterona 2; AAS, acido acetil salicílico; IDPP-4, inhibidores de la dipeptidil peptidasa 4.

Tabla 4. Variables incluidas en el análisis multivariante para predecir COVID severo

	Análisis univariante			Análisis multivariante		
Variables	OR	IC 95%	p	OR	IC 95%	p
Obesidad	2,54	1,53-4,22	<0,001	1,82	1,04-3,18	**0,034**
Neoplasia activa	2,57	1,30-5,10	0,005	2,06	1,01-4,29	**0,049**
ECV ateroesclerótica	2,05	1,20-3,49	0,008			
ECV no-ateroesclerótica	3,01	1,23-7,37	0,012			
Diabetes mellitus	2,96	1,73-5,05	<0,001			
SAOS	7,57	2,55-22,52	<0,001	5,26	1,60-17,25	**0,006**
Sexo	2,88	1,64-5,05	<0,001	2,86	1.58-5,17	**<0,001**
Edad >65 años	2,38	1,38-4,12	0,002	1,87	1,05-3,34	**0,033**

Abreviaturas: OR, odds ratio; IC, intervalo de confianza; DE, desviación estándar; ECV, enfermedad cardiovascular; SAOS, síndrome apnea obstructiva del sueño.

DISCUSIÓN

La infección por SARS-CoV-2 ha provocado en todo el mundo una sobrecarga sanitaria sin precedentes. Esto junto con el envejecimiento y la alta prevalencia de comorbilidades en la población nos obliga a optimizar los recursos disponibles. Por ello es importante conocer que pacientes podrían tener un peor pronóstico, ya sea por mortalidad o gravedad de la infección. Nuestra serie son pacientes predominantemente varones, de edad avanzada y con una alta comorbilidad (84%), superior a la descrita en algunas series chinas[6,13]. La hipertensión, diabetes, dislipemia y obesidad son las comorbilidades más frecuentes, hallazgos similares a otras series[13-15]. La mortalidad intrahospitalaria en el presente estudio (15,5%) es similar a otras series españolas pero inferiores a las descritas en Wuhan[13-15].

La edad avanzada, el sexo masculino y las neoplasias son factores de riesgo de mortalidad descritos en algunas series[7,16-17]. En nuestra cohorte casi el 60% eran mayores de 65 años observándose diferencias de mortalidad y severidad partir de los 80 años. Además hemos encontrado que el sexo masculino es un factor de riesgo independiente de mortalidad y de enfermedad grave, con un riesgo 3,5 veces mayor de morir que las mujeres. Estas diferencias se explican parcialmente en base a una mayor incidencia de enfermedades preexistentes en los varones y en la edad avanzada. En nuestro estudio los varones presentaban más ECV ateroesclerótica y ERC mientras que los pacientes de edad avanzada tenían mayor frecuencia de todas las comorbilidades excepto las neumopatías y ERC. Se ha descrito en la literatura que los varones presentan comportamientos de mayor riesgo, exposición ocupacional y altos niveles de andrógenos que aumentan la expresión de una proteína, la transmembrana proteasa serina 2 (TMPRSS2), que permitiría la entrada de SARS-CoV-2 en receptores de enzima conversora de angiotensina 2 (ACE2)[18]. Respeto a la edad pasaría algo similar: los receptores ACE2 y CD26, sobreexpresados en células senescentes, favorecerían la entrada del SARS-CoV-2 en la célula explicando una mayor severidad y mortalidad[19].

También hemos observado que, en nuestros pacientes, la neoplasia y la ECV previa son factores de riesgo independientes de mortalidad. En cuanto a la ECV, hemos analizado por separado ECV ateroesclerótica y no ateroesclerótica y en ambas se mantiene esta diferencia en el análisis multivariante con un riesgo de 2 y 6 veces respectivamente de fallecer. Sin embargo esta diferencia no se mantiene cuando analizamos severidad de la enfermedad. Creemos que ello puede estar relacionado con el hecho de que muchos pacientes con neoplasias activas y ECV sobretodo no ateroesclerótica, se limita el esfuerzo terapéutico; es decir, habrá pocos pacientes con estas características no fallecidos que hayan recibido cuidados en UCI. Nuestros resultados contrastan con los resultados de un metaanálisis previo de 3 estudios, que no encontraron correlación entre la historia de la ECV y la mortalidad, pero revelaron una asociación con mayor gravedad de la enfermedad[20]. Otros estudios sin embargo han revelado una asociación entre ECV preexistente y mortalidad[21,22]. Se piensa que la tormenta de citoquinas que tiene lugar en el SARS-CoV-2 agrava la insuficiencia cardíaca preexistente, causando depresión de la actividad miocárdica, hipercoagulabilidad y mayor disfunción endotelial[23].

Hay publicaciones que relacionan la obesidad con una mayor mortalidad[15,24]. Se cree que puede tener relación con una mayor expresión de los receptores ACE2[25]. Además los pacientes con obesidad suelen asociar otras comorbilidades como enfermedades cardíacas y cerebrovasculares[26,27]. En nuestra serie no hemos observado esta asociación en el análisis multivariante pero encontramos que la obesidad es un factor de riesgo independiente de presentar enfermedad severa con un riesgo 1,8 veces mayor que los que no tienen obesidad.

El SAOS se asocia con las principales comorbilidades que a su vez se asocian a mayor severidad de la COVID-19, entre ellas la obesidad. Se cree que el empeoramiento de la hipoxemia por el SAOS asociado a la tormenta de citoquinas que presentan los pacientes con obesidad podrían explicar una peor evolución en este grupo de pacientes. Dos estudios de pacientes con neumonía COVID-19 muestran que una cuarta parte de los pacientes tenían SAOS[28,29]. En nuestro estudio los pacientes con SAOS tienen un riesgo 5 veces mayor que los que no lo tienen de presentar enfermedad severa. No hemos encontrado diferencias en la mortalidad.

Otras comorbilidades como la hipertensión, la diabetes, la ERC o la cirrosis se han descrito como factores pronósticos de mortalidad[4,24,30]. Sin embargo en muestra serie no hemos confirmado estos hallazgos salvo la diabetes que ha mostrado diferencias en el análisis univariante pero no se mantiene en el multivariante. En el caso de la cirrosis y de la ERC creemos que es debido al pequeño tamaño de la muestra.

En cuanto a las diferencias encontradas en los pacientes tratados con diuréticos, betabloqueantes, ACC, anticoagulantes e IDPP-4, éstas son un fiel reflejo de las comorbilidades que presentan.

FORTALEZAS Y LIMITACIONES

Nuestro estudio presenta las limitaciones propias de un estudio retrospectivo donde los resultados dependen de la calidad de los datos recogidos por distintas personas. Además el estudio es unicéntrico y los resultados son menos extrapolables a la población general ya que puede haber sesgos locales. Hay que tener en cuenta que se realizó antes de la aparición de las vacunas por lo que habría que valorar si estos resultados se mantienen en pacientes vacunados. Quizás una de las limitaciones más importantes sea la diversidad de tratamientos empleados, consecuencia de los cambios frecuentes en los protocolos: esto hace complicado poder identificar factores de riesgo de mortalidad en relación con los tratamientos empleados, ya que crea sesgos. Además el escaso número de eventos en algunas de las variables de comorbilidad podría limitar los resultados habiéndose excluido potenciales variables pronósticas al ser muestras pequeñas. Quizás esto se podría resolver haciendo subanálisis de distintas poblaciones en estudios multicéntricos. Otros factores pronósticos como variables genéticas, niveles de vitamina D, etc no se han podido incluir por ausencia de estos datos.

Como fortalezas cabe destacar que el tamaño de la serie es considerable y sus características son similares a la mayoría de las series europeas. Además los factores que se exploran son comorbilidades, fáciles de obtener por la historia clínica sin necesidad de realizar procedimientos invasivos.

CONCLUSIONES

Es importante conocer las características de los pacientes con COVID-19 que presentan peor evolución para así poder mejorar su atención. En pacientes hospitalizados con infección por SARS-CoV-2, la edad >65 años y el sexo masculino se asocian a mayor riesgo de mortalidad y gravedad de la COVID. La enfermedad cardiovascular ateroesclerótica y sobretodo la no-ateroesclerótica además de la neoplasia activa se asocian a mayor mortalidad a diferencia de la obesidad o SAOS que tienen un mayor riesgo de enfermedad severa pero no de mortalidad. Por lo tanto es en estos grupos de pacientes donde debemos hacer hincapié en optimizar las medidas de soporte y los tratamientos recomendados en ese momento.

CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

FINANCIACIÓN

La presente investigación no ha recibido ayudas específicas provenientes de agencias del sector público, sector comercial o entidades sin ánimo de lucro.

ASPECTOS ÉTICOS

Los investigadores han seguido las normas éticas vigentes y la Declaración de Helsinki. Los participantes en el estudio han firmado un consentimiento informado para participar.

BIBLIOGRAFÍA

1. Update n.515. Coronavirus disease (COVID-19). 01.12.2021 (consolidated data at 19:00 p.m. on 01.12.2021). Internet. Ministry of Health, Government of Spain; 2021 December (see also do 1 Dic 2021). Available at: https://www.mscbs.gob.es/profesionales/saludPublica/ ncayes/alertsActual/nCov/documents / Update_515 _COVID-19.pdf .
2. McIntosh K. COVID-19: Epidemiology, virology and prevention. In: UpToDate. 2021.
3. Wang X, Fang X, Cai Z, Wu X, Gao X, Min J et al. Comorbid chronic diseases and acute organ injuries are strongly correlated with disease severity and mortality among COVID-19 patients: a systemic review and meta-analysis. Research. 2020 Apr 19;220:2402961.
4. Yang J, Zheng Y, Gou X, Pu K, Chen Z, Guo Q et al. Prevalence of comorbidities and its effects in coronavirus disease 2019 patients: a systematic review and meta-analysis. Int J Infect Dis. 2020;94:91-95.
5. Sheng-Qun Deng, Hong-Juan Peng. Characteristics of and Public Health Responses to the Coronavirus Disease 2019. Outbreak in China. J Clin Med. 2020;9(2):575.
6. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020b;395(10223):497-506.
7. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA. 2020;323(11):1061-1069.
8. Emanuel EJ, Persad G, Upshur R, Thome B, Parker M, Glickman A et al. Fair Allocation of Scarce Medical Resources in the Time of Covid-19. N Engl J Med. 2020;382:2049-2055.
9. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis. 1987;40(5):373-83.
10. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. Md State Med J. 1965;14:61-5.
11. Levey A, Stevens L, Schmid CH, Zhang YL, Castro AF, Feldman HI et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604-612.
12. Definition Task Force ARDS, Ranieri VM, Rubenfeld GD, Thompson BT, Ferguson ND, Caldwell E et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA. 2012;307(23):2526-2533.
13. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020;395(10229):1054-62.
14. Casas-Rojo JM, Antón-Santos JM, Millán-Núñez-Cortés J, Lumbreras-Bermejo C, Ramos-Rincón JM, Roy-Vallejo E et al. Clinical characteristics of patients hospitalized with COVID-19 in Spain: Results from the SEMI-COVID-19 Registry. Rev Clin Esp. 2020;220(8):480-94.
15. Gil-Rodrigo A, Miró Ò, Piñera P, Burillo-Putze G, Jiménez S, Martín A et al. Evaluation of the clinical characteristics and evolution of patients with COVID-19 from a series of 1000 patients treated in Spanish emergency services. Emergencies 2020;233-41.
16. Zhou Y, Yang Q, Chi J, Dong B, Lv W, Shen L et al. Comorbidities and the risk of severe or fatal outcomes associated with coronavirus disease 2019: A systematic review and meta-analysis. Int J Infect Dis. 2020;99:47-56.
17. Moula AI, Micali LR, Matteucci F, Lucà F, Rao CM, Parise O et al. Quantification of Death Risk in Relation to Sex, Pre-Existing Cardiovascular Diseases and Risk Factors in COVID-19 Patients: Let's Take Stock and See Where We Are. J Clin Med. 2020;9(9):2685.
18. Gebhard C , Regitz-Zagrosek V, Neuhauser HK, Morgan R , Klein SL. Impact of sex and gender on COVID-19 outcomes in Europe. Biol Sex Differ. 2020;11:29.
19. Gheblawi M, Wang K, Viveiros A, Nguyen Q, Zhong JC, Turner AJ et al. Angiotensin-Converting Enzyme 2: SARS-CoV-2 Receptor and Regulator of the Renin-Angiotensin System. Circ Res. 2020;126(10):1456-1474.
20. Aggarwal G, Cheruiyot I, Aggarwal S, Wong J, Lippi G, Lavie CJ et al. Association of Cardiovascular Disease With Coronavirus Disease 2019 (COVID-19) Severity: A Meta-Analysis. Curr Probl Cardiol 2020;45(8):100617.
21. Martos Pérez F, Luque Del Pino J, Jiménez García N, Mora Ruiz E, Asencio Méndez C, García Jiménez JM, et al. Comorbidity and prognostic factors on admission in a COVID-19 cohort of a general hospital. Rev Clin Esp (Barc). 2021; 221(9):529-535.
22. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. BMJ. 2020;368: m1091.
23. Wang K, Gh eblawi M, Oudit GY. Angiotensin Converting Enzyme 2: A Double-Edged Sword. Circulation 2020;142:426-428.
24. Richardson S, MD, Hirsch JS, Narasimhan M. Presenting characteristics, comorbidities and outcomes among 5700 patients hospitalized with COVID-19 in the New York City Area. JAMA. 2020;323(20):2052-2059.
25. Li MY, Li L, Zhang Y, Wang XS. Expression of the SARS-CoV-2 cell receptor gene ACE2 in a wide variety of human tissues. Infect Dis Poverty. 2020;9(1):45.
26. Huang JF, Wang XB, Zheng KI, Liu WY, Chen JJ, George J et al. Letter to the Editor: Obesity hypoventilation syndrome and severe COVID-19. Metabolism. 2020;108:154249.
27. Sattar N, McInnes IB, McMurray JJV. Obesity is a risk factor for severe COVID-19 infection: multiple potential mechanisms. Circulation. 2020;142(1):4-6.
28. Arentz M, Yim E, Klaff L, Lokhandwala S, Riedo FX, Chong M et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. JAMA. 2020;323(16):1612-4.
29. Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK et al. Covid-19 in critically ill patients in the Seattle Region-Case Series. N Engl J Med. 2020;382(21):2012-22.
30. Motta JC, Novoa DJ, Gómez CC, Moreno JM, Vargas L, Pérez J et al. Prognostic factors in hospitalized patients diagnosed with SARS-CoV-2 infection, Bogotá, Colombia. Biomedical. 2020;40(Suppl 2):116-30.

Impacto de un cribado oportunista de hipercolesterolemia familiar (estudio CRIBACOL) en el area sanitaria de Vigo

Impact of an Opportunist Screening for Family Hypercholesterolemia (CRIBACOL study) in the sanitary area of Vigo

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ABSTRACT

Objective: To assess the effectiveness of the diagnosis of Familial Hypercholesterolemia (FH) through opportunistic screening in the health area of Vigo.
Material and Methods: An opportunistic screening was carried out retrospectively on all patients in the Vigo Health Area who had been requested to determine their LDLc during 2018. The inclusion criterion was LDL>250 mg/dL, and the exclusion criteria (TSH >4 mIU/L, A1C>6.5%, fasting glucose>126 mg/dL, Triglycerides>150 mg/dL, GGT>55 IU/L and/or alkaline phosphatase>135 IU/L, proteinuria>3g/ L and serum albumin <30g/L).
Opportunistic screening was performed using the Modulab Gold (IZASA) program.
Results: The total number of LDL determinations was 236,528 out of 185,095 patients. 233 patients met the inclusion criteria. 162 were discarded due to the exclusion criteria. 71 patients with a possible diagnosis of HF were obtained. These patients underwent a clinical interview applying the criteria of the Dutch Lipid Clinics Network (DLCN). The results were: men (21.12%) and women (78.87%); the mean age was 58 years; had hypertension (22.53%), diabetes (1.4%), smoker (23.49%), received statins (63.38%). The results of applying the DLCN criteria were diagnosis possible (53.52%), probable (32.39%) and certain (14.08%).
Conclusion: HF is an underdiagnosed and undertreated disease. The application of an opportunistic screening method with an alarm system for health professionals who request lipid profiles can make an early diagnosis of this disease with high cardiovascular risk.

Keywords: Cholesterol, Hypercholesterolemia, Heterozygous Familial Hypercholesterolemia, Opportunistic Screening, Dutch Lipid Clinic Network.

INTRODUCCIÓN

La hipercolesterolemia familiar (HF) es el trastorno hereditario más frecuente. Se caracteriza por un aumento de los niveles de LDLc y un elevado riesgo de enfermedad cardiovascular precoz. Su prevalencia es 1:500 y 1:1.000.000 para heterocigoticos y homocigoticos respectivamente[1-3].
A pesar del elevado riesgo cardiovascular (RCV), la mayoría de los pacientes están sin diagnosticar ni tratar. Su diagnóstico precoz permite utilizar medidas preventivas, entre ellas, el tratamiento crónico con estatinas. Este ha demostrado en los pacientes con HF ,sin enfermedad coronaria previa, una marcada reducción del RCV similar al de la población general[4].
La detección de la HF cumple los criterios de la Organización Mundial de la Salud (OMS) para el cribado sistemático de una enfermedad y es costo-efectiva para detectar nuevos casos de HF [5-8].

OBJETIVO

Valorar la efectividad del diagnostico de HF mediante un cribado oportunista en el área sanitaria de Vigo.

MATERIAL Y METODOS

Realizamos de manera retrospectiva un cribado oportunista a todos los pacientes del Área Sanitaria de Vigo a los que se les había solicitado determinación de LDLc durante el periodo de enero a diciembre de 2018. Los criterios de inclusión y exclusión aplicados para el cribado se exponen en la tabla 1.

Tabla 1

CRITERIOS DE INCLUSIÓN	CRITERIOS DE EXCLUSIÓN
	TSH >4 mUI/L
	A1C >6,5%
LDL >250 mg/dL	Glucosa en ayunas >126 mg/dL
	Triglicéridos>150 mg/dL.
	GGT>55 UI/L y/o Fosfatasa alcalina >135 UI/L
	Proteinuria>3g/L y albumina sérica <30g/L

Se tuvieron en cuenta los valores de las variables de exclusión determinadas en el periodo comprendido entre los 30 días antes y después de un resultado de LDL>250.
El cribado oportunista se realizó mediante el programa Modulab Gold (IZASA) empleado como sistema de información de laboratorio (LIS) para la gestión de los análisis clínicos del CHUVI. Este está basado en las últimas tecnologías disponibles para los sistemas IT (tecnology information).

Aspectos éticos y legales:
El estudio fue aprobado por el Comité de Ética e Investigación de Galicia bajo el Código de Registro 2019/209 con fecha 25/04/2019. Los investigadores han seguido las normas éticas y legales aplicables. Se obtuvo el consentimiento informado por escrito de todos los participantes incluidos en el estudio.

Análisis estadístico:
Mediante el programa estadístico SPSS 19.0 se realizó un análisis descriptivo de los datos recogidos.

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RESULTADOS

El número total de determinaciones de LDL fue de 236.528 sobre 185.095 pacientes (varios pacientes tenían más de una determinación de LDLc en el periodo de estudio). Un total de 233 pacientes cumplieron el criterio de inclusión. Fueron descartados 162 tras la aplicación de los criterios de exclusión, cuyo objetivo era descartar pacientes con hiperlipemia familiar comibinada y otras causas de hipercolesterolemia secundaria distintas de la HF: Hipertrigliceridemia (45,06%), TSH (22,2%), Glucosa basal y A1C (16,04%), GGT y Fosfatasa Alcalina (16,04%), Proteinuria e hipoalbulinemia (2,46%).

Como resultado del cribado se obtuvieron 71 pacientes con diagnostico posible de HF. Estos paciente fueron invitados a participar en el estudio y tras su aceptación de colaboración fueron citados en consultas externas de Endocrinología del CHUVI. Se realizó entrevista clínica aplicando los criterios de la Red de Clínicas de Lípidos Holandesas (RCLH) y se inició seguimiento por el Servicio de Endocrinología.

Los resultados fueron: 15 hombres (21,12%) y 56 mujeres (78,87%); la edad media era 58 años; tenían HTA 16 (22,53%), Diabetes I (1,4%), tabaquismo 27 (23,49%), recibían estatinas 45 (63,38%). Los resultados de aplicar los criterios de la Red de Lípidos Holandesas fueron diagnostico posible en 38 (53,52%), diagnostico probable 23 (32,39%) y diagnostico cierto 10 (14,08%).

Se solicitó estudio genético de HF a 8 pacientes: 4 con resultado negativo para HF, y 4 con estudio genético positivo (3 con mutaciones en LDRL y 1 con mutación apoE3/apoE4 compatible con HF poligénica).

A todos los pacientes se les dio consejos sobre dieta, ejercicio y cese de habito tabáquico. A todos los pacientes se les inició o intensificó el tratamiento hipolipemiante con estatinas de alta potencia, adición de ezetimiba o tratamiento con inhibidores de la PCSK9 en aquellos que cumplían criterios para su uso. También se intensificó el control del peso, HTA y prediabetes/diabetes. La mayoría de los pacientes pudieron ser dados de alta del Servicio de Endocrinología , en un breve periodo de tiempo, por gran mejoría de los niveles de LDcL y de los otros factores de riesgo cardiovascular con las medidas implantadas.

A los pacientes con diagnostico cierto de HF se les ofreció la posibilidad de realizar un diagnostico en cascada a familiares de primer grado.

DISCUSION

En este estudio decidimos utilizar un punto de corte de LDLc>250 mg/dL basándonos en los criterios de la RCLH y en experiencias previas publicadas de otros cribados oportunistas de HF.

El laboratorio de análisis clínico del Área Saitaria de Vigo ofrece servicio a una población potencial de 500.000 personas. Se realizó determinación de LDLc al 37% de la población en un periodo de tiempo de 1 año. Extrapolando los resultados obtenidos en nuestro estudio, la prevalencia de HF en nuestra Área Sanitaria es de 1/794, es decir se espera una prevalencia cercana al 0,42%, lo que representa 2100 pacientes con HF en nuestra Área Sanitaria. Nuestro trabajo muestra que dado el elevado número de determinaciones de LDLc realizadas en el Área Sanitaria de Vigo, queda constatado que las aplicaciones informáticas del Servicio de Análisis Clínicos son el método mas adecuado para el diagnostico de HF potencial.

Los software de informática de laboratorio son una herramienta útil y predecible para el cribado poblacional de HF, debido a su capacidad de manejo de un gran volumen de datos con precisión, de forma eficaz y con bajo coste.

La principal limitación de este estudio viene determinada por que un porcentaje elevado de pacientes recibían tratamientos con estatinas. Esto hace que sus concentraciones de LDLc fuesen menores y por tanto al aplicar los criterios RCLH, solo un pequeño número de pacientes alcaza la puntuación suficiente para establecer el diagnostico cierto de HF. Esta limitación es inevitable ya que por motivos éticos y lógicos no se puede suspender el tratamiento con estatinas.

Cabe destacar el elevado porcentaje de pacientes con HF posible que no recibían tratamiento con estatinas (36,62%) la mayoría por abandono de tratamiento, pero otros por tratarse de pacientes que no poseían diagnóstico de la enfermedad y por tanto tampoco tratamiento.

La mayor prevalencia de HF detectada en nuestro estudio respeto al artículo más prominente en este campo publicado por Bell et. al y haciendo referencia a la población Australiana puede explicarse en parte debido a la herencia autosómica dominante de la enfermedad. Este componente genético puede determinar que en diferentes poblaciones geográficas la prevalencia de la enfermedad sea variable.

CONCLUSIÓN

La HF es un enfermedad infradiagnosticada e infratratada. La aplicación de un método de cribado oportunista con un sistema de alarmas para los profesionales de la salud que solicitan perfiles lipídicos puede permitir diagnosticar de forma precoz esta enfermedad. De este modo se puede tratar más precoz y eficazmente a esta población de pacientes con elevado riesgo cardiovascular.

CONFLICTO DE INTERESES

Los autores refieren no presentar conflictos de interés.

FINANCIACIÓN

Este estudio no ha recibido financiación externa.

ASPECTOS ÉTICOS

El estudio fue aprobado por el Comité de Ética e Investigación de Galicia bajo el Código de Registro 2019/209 con fecha 25/04/2019. Los investigadores han seguido las normas éticas y legales aplicables. Se obtuvo el consentimiento informado por escrito de todos los participantes incluidos en el estudio.

BIBLIOGRAFÍA

1. Singh S, Bittner V. Familial hypercholesterolemia—epidemiology, diagnosis, and screening. Curr Atheroscler Rep. 2015;17(2):3.
2. Santos RD. Screening and management of familial hypercholesterolemia. Curr Opin Cardiol. 2019;34(5):526-530.
3. Benito-Vicente A, Uribe KB, Jebari S, Galicia-Garcia U, Ostolaza H, Martin C. Familial hypercholesterolemia: the most frequent cholesterol metabolism disorder caused disease. International journal of molecular sciences. 2018;19(11):3426.
4. Versmissen J, Oosterveer DM, Yazdanpanah M, Defesche JC, Basart DC, Liem AH, et al. Efficacy of statins in familial hypercholesterolaemia: a long term cohort study. BMJ. 2008; 337.
5. Ned RM, Sijbrands EJ. Cascade screening for familial hypercholesterolemia (FH). PLoS currents. 2011;3.
6. Oliva J, López-Bastida J, Moreno SG, Mata P, Alonso R. Cost-effectiveness analysis of a genetic screening program in the close relatives of Spanish patients with familial hypercholesterolemia. Revista Española de Cardiología (English Edition). 2009;62(1):57-65.
7. Defesche JC. Defining the challenges of FH screening for familial hypercholesterolemia. Journal of clinical lipidology. 2010; 4(5):338-341.
8. Bell DA, Hooper AJ, Bender R, McMahon J, Edwards G, van Bockxmeer FM, et al. Opportunistic screening for familial hypercholesterolaemia via a community laboratory. Ann Clin Biochem. 2012;49(6):534-537.

Basic principles of Palliative Care on Pediatrics: A narrative review

Principios básicos de cuidados paliativos en pediatría: una revisión narrativa

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ABSTRACT

Palliative care is a topic that is gaining more and more relevance. This therapy benefits the patient throughout their illness, for that reason, the scientific community is becoming aware of the importance of including such treatments in basic health services. Unfortunately, only some of the developed countries manage to have decent assistance in this type of care, and that is why governments and world organizations are taking more ambitious objectives in order to improve health quality even more.

The evidence presented in this article shows the future possibilities of PC, focusing its attention on pediatric patients and their families, as well as the guidelines to be followed by the professional team to guarantee a complete and satisfactory approach.

Keywords: palliative care, pediatrics, end of life care, pain relief, hospice.

RESUMEN

Los cuidados paliativos son un tema cada vez más de actualidad. Esta terapéutica beneficia al paciente a lo largo de toda su enfermedad, por lo que se empieza a tomar conciencia de la importancia de incluirlos en los servicios básicos de salud. Por desgracia sólo algunos de los países desarrollados consiguen tener una asistencia digna en este tipo de cuidados, y es por ello que gobiernos y organizaciones mundiales toman objetivos más ambiciosos con el fin de mejorar todavía más la calidad sanitaria.

La evidencia presentada en el presente artículo muestra las posibilidades futuras de los cuidados paliativos, centrando su atención en los pacientes pediátricos y sus familias, así como las directrices a seguir por parte del equipo profesional para garantizar un abordaje completo y satisfactorio.

Palabras clave: cuidados paliativos, pediatría, cuidados al final de la vida, alivio del dolor, hospicio.

INTRODUCTION

Palliative medicine is a largely unknown field, and it is even more so when it is limited to the pediatric age. Currently it is thought to be restricted to agony, to keep the patient sedate at the time of death. Nothing is further from reality, Palliative Care (PC) provides well-being and support to the patient and their families, and they ensure that the patient is conscious, free of pain and in the event of death, to help dying with dignity. They don't speed up or stop the dying process; they just give the patient a better quality of life.

Palliative Care can be given at the same time as treatments intended to cure or treat disease. PC can start when the disease is diagnosed, throughout treatment, follow-up, and at the end of life. They may accompany the patient throughout his illness, without neglecting any aspect (physical, psychological, social and spiritual), being all equally important.

Children are special patients, they do not understand death and pain in the same way as adults. To this fact adds the ethical problems that arise about who should make such tough decisions. Therefore it is important to adequately inform the family and the patient to avoid suffering and uncertainty, and also accompanying them properly.

For all these reasons, the authors have tried to gather information relevant to palliative care in children, given that it is a subject of great ignorance and where health professionals require a great deal of specialized training.

MATERIALS AND METHODS

A bibliographic search was carried out to date in PubMed. The search strategy used the following keywords: *palliative care, pediatrics, and their combination, end of life care, hospice, pain relief, terminal care, agony, pediatric oncology, quality life, acute and chronic pain*. Only articles available in English or Spanish were included. The search has focused on the last 10 years, and if publications of interest do not appear in that period, an attempt has been made to find the most recent and best quality experiences. Articles containing information exclusively on adults or whose results could not be extrapolated were excluded.

Children from 0 to 19 years of age have been taken as a reference for pediatric patients, which is the classification that the WHO follows in palliative care.

RESULTS

PALLIATIVE CARE IN PEDIATRICS

Definition

Palliative care helps people with serious illnesses feel better by preventing or treating symptoms and side effects of illness and treatment.

The WHO defines palliative care in children as "active total care of the body, mind and spirit that also implies giving support to the family". This same organization in 1999 marks a milestone in palliative medicine, urging that palliative treatment should begin when the child is diagnosed for the first time, and continue throughout the course of the disease[1].

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Health personnel must assess and alleviate the physical, psychological, social, emotional and spiritual problems of the child. This requires a broad multidisciplinary approach not restricted only to the hospital setting, they must also take place in the child's home. All this makes the child have a better quality of life[2].

Epidemiology

The following data were extracted from the Global Atlas of Palliative Care 2020[3]:

More than 97% of children aged 0-19 who need palliative care live in low- and middle-income countries. Children with HIV / AIDS and congenital malformations are 46%, followed by birth trauma (18%) and injuries (16%). Cancer lags far behind all of these (4.1%).

In 2017, 45.3% of deaths in the world required palliative care. 40% were 70 years or older and only 7% were children (0-19 years). In this same year it was estimated that almost 4 million children needed palliative care.

Reality and barriers

A study was carried out to find out when the PC started. 54.4% of oncopediatric patients had received palliative services before death[4].

The mean time from cancer diagnosis to palliative consultation was 509.6 days. Therefore, it did not occur at the time of diagnosis as recommended by the WHO.

In part it is due to the fear of the professionals themselves; starting palliative care so early may provoke a feeling of hopelessness both in the child and the family[5].

Related to this, a study of 1.2 million subjects revealed that between 33% to 38% of patients received treatment with curative intent, but with no beneficial effects, in the last 6 months of life[6]. It is better to alleviate and not be stubborn in these cases. Finding the best comfort conditions for the patient.

In addition to the above, there are numerous barriers to the effective implementation of Palliative Care: policy (many countries do not include the need for this care in their legislation), education (professionals around the world are poorly trained in these subjects), availability of medicines (many countries have limited access to opioids. Developed countries consume 90% of painkillers3. If this is added that more than 97% of the children who need PC are in the latter countries), implementation, need for health personnel, psychological, social and cultural (people tend to avoid everything associated with the word death), financial...

Common Symptoms

Pain is the most common symptom. Another frequent symptom in the last phase is dyspnea[7].

There are also constitutional symptoms (anorexia and asthenia), digestive (vomiting and constipation), neurological (seizures, agitation and insomnia), dermatological (pruritus) and urological (urinary tract infection and incontinence).

Palliative Treatments

PCs can and should coexist with treatment and are important from diagnosis.

Many palliativists follow the SPIKES8 method:

1. S (*set up*)	set up the conversation.
2. P (*perceptions*)	to evaluate the patient's perceptions.
3. I (*invitation*)	obtain patient consent.
4. K (*knowledge*)	to give information to the patient.
5. E (*emotions*)	addressing the patient's emotions with an empathetic response.
6. S (*strategize and summarize*)	establish a strategy and summarize.

RESULTS

Ethics And Autonomy

There is a question we must ask ourselves: who should decide? The decision should be a joint one between the patient, the relatives and the healthcare personnel. The child, if he/she is somewhat older, has the right to know the situation and to be well informed[9]. The child, regardless of age, must be adequately informed and adapted to his or her age.

Spirituality

A fundamental theme in PC is spirituality. Caregivers should bring peace to the patient and family members. Findings suggest that spiritual care has positive effects[10].

Death Awareness

Seriously ill children who know that death is irreversible are afraid of not leaving a legacy, of being forgotten. They also tend to think about death, even if they do not communicate it[11].

From 18 months to 5 years of age, children do not understand the concept of the future, they live only in the present and associate death with sleep and immobility. From 5 to 10 years of age, they begin to be curious about death, and it implies separation not only from parents but also from friends and school. The irreversible nature of death is acquired around the age of 9 years, especially the fear of the death of parents appears[12].

Family Experience And Bereavement

Anxiety is a frequent symptom in the family in the last stage of the children's illness, because of the severe suffering they see their children going through[13].

In Sweden, a study was conducted of parents who experienced the death of a child between 1992 and 1997 and were asked a questionnaire about whether they had talked to their children about the death. Of 449 families, none of the 147 who talked to their children about the death had regrets. However, 69 of the 258 parents who did not talk to their children about it regretted it[14].

Grief begins long before the death (*anticipatory grief*); when the idea that your relative is going to die irremediably becomes conscious. This process is exacerbated in the moments closest to the patient's death (acute grief) and can last up to 2 years (more in cases of *complicated grief*).

It should be explained to the family members about this reality and give them support and recommendations to overcome this process[15].

The problem occurs when this grief becomes complicated. It is essential to see the risk factors by which a normal bereavement can become a pathological bereavement[16]: death of children or adolescents, unexpected or sudden death, being even worse traumatic (accidents) or stigmatized (suicide, AIDS...), prolonged and painful illness, history of previous unresolved losses, simultaneous stressors (low economic level, family problems...), lonely or distant people, insufficient social support, families with insufficient levels of communication and ability to express their feelings, belief that more could have been done for the patient...

One study states that 94% of mothers, 87% of fathers and 69% of siblings reported substantial changes in their lives and priorities. They also report a higher prevalence of sadness and depression[17].

Another study, which took data between 1999 and 2000 in children with cancer, reports that 36% of the families did not receive any conversation about PC[13].

ONCOPEDIATRICS

Pediatric cancer and its treatment have improved substantially in recent decades, increasing survival and improving prognosis. Despite all this progress and as a consequence of the search to improve the quality of life of these patients, preventing and treating their symptoms, a strong integration of palliative care in oncopediatrics has emerged[18].

Evidence confirms that good palliative treatment from early stages of the disease helps these patients, as well as their families, considerably[5].

One of the main recommendations is doctor-patient communication, as well as focusing on the family[19], talking and explaining everything they need, as this increases patients' wishes for their families to make appropriate decisions as needed, improves patients' understanding of end-of- life options, increases the likelihood of limiting futile treatment, and increases the family's ability to carry out their children's wishes.

PAIN IN PEDIATRICS

The International Association for the Study of Pain defined pain as "an unpleasant sensory and emotional experience, associated with actual or potential tissue damage." It is a multidimensional, subjective phenomenon that requires comprehensive care.

Pain in pediatrics is not evaluated and treated efficiently[20]. Good pain control in pediatric patients is vitally important so as not to create future trauma.

Types Of Pain

Pain can be acute, chronic, or a combination of acute over chronic. Furthermore, it was found that pain increases with age and is more common in girls20.

Chronic pain is defined as any prolonged pain that lasts longer than expected; usually the benchmark is set at 3 months[21]. It can also be any recurring pain that occurs at least 3 times over a 3-month period. King et al. report that the most frequent recurrent chronic pain in children is headache, followed by abdominal pain[22].

Pain Assessment

A correct evaluation of pain facilitates the diagnosis and follow-up of the disease. It must be continuous since the pathological process is a continuum and they vary. To make a correct anamnesis the following points should be touched[1]: evaluate (children can experience pain and not transmit it in the same way as adults), locate (complete examination, noting grimaces or contractions), contextualize (take into account social and family factors of the child), document (use pain scales based on cultural context), assess the effectiveness of the treatment and modify the treatment plan if necessary.
Therefore, information comes in 3 ways: self-report, behavior of the patient and physiological indicators[20].

Pediatrics covers a very wide age range; It is not the same to evaluate a newborn as an adolescent, therefore, you have to look at different details[12]:

In premature infants, infants and in early childhood children will not speak, therefore it is vitally important to look at their behavior and their physiological indicators.

In schoolchildren and preschoolers it can be seen that they are already capable of expressing pain, although with limitations.

Crying is more typical when the pain is brief, however, when the pain is persistent, motor disorders, disinterest in the environment, less ability to concentrate and sleep disorders are often seen[1].

Children over 6/7 years of age are already able to correctly verbalize the presence of pain, its location and define its intensity, in a similar way to adults.

There is no single scale that evaluates intensity for all ages and all types of pain: Numeric Rating Scale (NRS), Visual Analogue Scale (VAS), VAS pictorial adaptations, Faces Pain Scale-Revised (FPS-R)[23]. All of these scales can be used to see the evolution of the child's pain and illness over time.

Pain Control

Pain control brings a series of benefits to the child such as: improved satisfaction, increased trust in healthcare personnel, improved quality of life, improved sleep, protects against depression and reduces the cost of overall treatment.

For pain control there are non-pharmacological guidelines and pharmacological guidelines.

Non-pharmacological guidelines

These measures should complement the pharmacological treatment but not replace it. The first thing would be the support methods: provide good psycho-emotional assistance to children. Reinforce empathy and give them participation in the decisions that are made.

There are also cognitive methods that try to influence the child's thoughts, the more distracted in an activity he is, the less pain he will feel.

Finally, there are physical methods, which are of vital importance in childhood, such as caressing, cradling, taking in arms.

Pharmacological guidelines

The WHO Analgesic Ladder is followed. The first rung is a non-opioid analgesic, the second rung is a minor opioid along with NSAIDs, and the third will be a major opioid along with NSAIDs.

Doses should be given at set times and not only when there is pain, unless the painful episodes are with a very wide frequency range. In addition, rescue doses are added in case of breakthrough pain. Patient Controlled Analgesia (PCA) is useful in children over 7 years of age for rescue pain relievers; after each use there is a lockout period. This way, the child is protected as much as possible from pain.

In pediatrics it is of vital importance to choose a good route of administration. It has to be the simplest, most effective and least painful way.

TREATMENT IN THE LAST DAYS. AGONY

This section represents an important multidisciplinary challenge[24]. Given the nature of this phase, it is essential to recognize and diagnose this process, understand the characteristics of the suffering of the patient, provide the best care and support the family and, as well as differentiate the terminal phase with a relapse.

To complete the care of the patient and his family, it is essential to take care of 3 sections[16]: physical, psychological and social care.

CHILD EUTHANASIA

The debate on infant euthanasia goes back a long way, with a major precedent being the case of the newborn Bente Hindriks in 2001. Born with a rare and fatal skin disease, both relatives and professionals made the decision to perform active euthanasia. This caused an international uproar due to the legal consequences of the acts, establishing as a legal basis the Groningen Protocol, the purpose of which was to establish the criteria under which legal action could not be taken against the team responsible[25]: the diagnosis and prognosis must be confirmed, there must be unbearable and hopeless suffering, there must be confirmation by a second opinion from an independent physician, both parents must give informed consent and the procedure must be carried out carefully and in accordance with medical standards.

The Spanish Organic Law regulating euthanasia defines euthanasia as the deliberate act of ending the life of a person, produced by the express will of the person him/herself and with the aim of avoiding suffering. However, in Spain this law requires the applicant to be of legal age as an indispensable requirement[26].
There are very few countries that have regularized this process, but only Belgium contemplates child euthanasia since the amendment of its law in 2014.

This is a precedent that reinforces the idea that the minor is competent in his or her condition and decision to die.

DISCUSSION

It is observed that the vast majority of children in need of PC live in low- and middle-income countries (>97%), so it can be considered that living in such a country is a risk factor for needing palliative care.

Another problem we found is late referral to palliative care due to the reluctance of the health care providers themselves and the "hopelessness" that this could provoke in the families. The evidence shows that early treatment in palliative care, from the moment of diagnosis, increases the quality of life of the child and the satisfaction of the family considerably.

There is a great need to educate healthcare personnel and patients about the need for PCs. Myths must be debunked and taught to be compatible with the different cultures and religions that exist throughout the world. All people have the right not to suffer, to have a good quality of life even when ill, and in the event of illness, to have a dignified and comfortable death.

One of the most debated ethical issues is the autonomy and competence of the child's choice. How much weight should be given to the child's opinion? How should the child's maturity be assessed?

These are undoubtedly big questions that are frequently asked in this area. It should be better regulated and not value so much the numerical age, but the maturity of each child.

In terms of pain, health care workers should be better trained to recognize the suffering of the child in each age range, use scales and treat appropriately. Old myths such as addiction should be dismantled and the patient's pain should be adequately controlled to improve their quality of life.

Non-pharmacological therapies such as games, visits from superheroes, visits from school friends... help the child to escape from pain and illness and to enjoy as much as possible. These types of therapies acquire special value in childhood, helping the child to develop properly.

CONCLUSIONS

Despite medical advances, pediatric palliative patients still continue to suffer significantly.

One of the most important goals of PCs focuses on the need to initiate this aspect of care as soon as possible, as well as to work in a multidisciplinary manner, delving into the latest quality information in order to improve the health care of our patients.
A fundamental point is the doctor-patient relationship and the doctor-family relationship, in order to achieve a global approach to the patient's problems. To this end, it is essential to work on the psychosocial, emotional and spiritual aspects, as well as to provide the necessary and fair information to both the patient and the family members in order to facilitate the assimilation of the process.

Another very influential aspect is the international inequality in terms of recognition of this right and the material and drug availability of the countries. Governments must cooperate and help less wealthy countries to achieve the objectives proposed by the WHO.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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REFERENCES

1. WHO. Cancer pain relief and palliative care in children. Geneva, Switzerland: World Health Organization. 1998.
2. Marcus KL, Santos G, Ciapponi A, Comandé D, Bilodeau M, Wolfe J, et al. Impact of Specialized Pediatric Palliative Care: A Systematic Review. J Pain Symptom Manage. 2020;59(2):339-364.
3. WHO. Global Atlas of Palliative Care 2ed. Geneva, Switzerland: World Health Organization. 2020.
4. Cheng BT, Rost M, De Clercq E, Arnold L, Elger BS, Wangmo T. Palliative care initiation in pediatric oncology patients: A systematic review. Cancer Med. 2019;8(1):3-12.
5. Weaver MS, Heinze KE, Kelly KP, Wiener L, Casey RL, Bell CJ, et al. Palliative Care as a Standard of Care in Pediatric Oncology. Pediatr Blood Cancer. 2015;62 Suppl 5(Suppl 5):S829-33.
6. Cardona-Morrell M, Kim J, Turner RM, Anstey M, Mitchell IA, Hillman K. Non-beneficial treatments in hospital at the end of life: a systematic review on extent of the problem. Int J Qual Health Care. 2016;28(4):456-69.
7. Chan KS. Palliative care: the need of the modern era. Hong Kong Med J. 2018;24(4):391-399.
8. Akard TF, Hendricks-Ferguson VL, Gilmer MJ. Pediatric palliative care nursing. Ann Palliat Med. 2019;8(Suppl 1):S39-S48.
9. Weaver MS, Mooney-Doyle K, Kelly KP, Montgomery K, Newman AR, Fortney CA, et al. The Benefits and Burdens of Pediatric Palliative Care and End-of-Life Research: A Systematic Review. J Palliat Med. 2019;22(8):915-926.
10. Gijsberts MHE, Liefbroer AI, Otten R, Olsman E. Spiritual Care in Palliative Care: A Systematic Review of the Recent European Literature. Med Sci (Basel). 2019 7;7(2):25.
11. Foster TL, Gilmer MJ, Davies B, Barrera M, Fairclough D, Vannatta K, et al. Bereaved parents' and siblings' reports of legacies created by children with cancer. J Pediatr Oncol Nurs. 2009;26(6):369-76.
12. Martín Rodrigo J., "Paciente Pediátrico y Cuidados Paliativos", SECPAL.
13. Hechler T, Blankenburg M, Friedrichsdorf SJ, Garske D, Hübner B, Menke A, et al. Parents' perspective on symptoms, quality of life, characteristics of death and end-of-life decisions for children dying from cancer. Klin Padiatr. 2008;220(3):166-74.
14. Kreicbergs U, Valdimarsdóttir U, Onelöv E, Henter JI, Steineck G. Talking about death with children who have severe malignant disease. N Engl J Med. 2004 16;351(12):1175-86.
15. Iasevoli M, Giantin V, Voci A, Valentini E, Zurlo A, Maggi S, et al. Discussing end-of-life care issues with terminally ill patients and their relatives: comparisons among physicians, nurses and psychologists. Aging Clin Exp Res. 2012;24(3 Suppl):35-42.
16. Grupo de Trabajo de la Guía de Práctica Clínica sobre Cuidados Paliativos. Guía de Práctica Clínica sobre Cuidados Paliativos. Madrid: Plan Nacional para el SNS del MSC. Agencia de Evaluación de Tecnologías Sanitarias del País Vasco; 2008. Guías de Práctica Clínica en el SNS: OSTEBA Nº 2006/08
17. Gilmer MJ, Foster TL, Vannatta K, Barrera M, Davies B, Dietrich MS, et al. Changes in parents after the death of a child from cancer. J Pain Symptom Manage. 2012;44(4):572-82.
18. Mack JW. Pediatric Palliative Care-A Shared Priority. JAMA Oncol. 2017 1;3(9):1220-1221.
19. Levine DR, Mandrell BN, Sykes A, Pritchard M, Gibson D, Symons HJ, et al. Patients' and Parents' Needs, Attitudes, and Perceptions About Early Palliative Care Integration in Pediatric Oncology. JAMA Oncol. 2017 1;3(9):1214-1220.
20. Manworren RC, Stinson J. Pediatric Pain Measurement, Assessment, and Evaluation. Semin Pediatr Neurol. 2016;23(3):189-200.
21. WHO. Guideline for the management of chronic pain in children. Geneva, Switzerland: World Health Organization. 2020.
22. King S, Chambers CT, Huguet A, MacNevin RC, McGrath PJ, Parker L, et al. The epidemiology of chronic pain in children and adolescents revisited: a systematic review. Pain. 2011;152(12):2729-2738.
23. Tomlinson D, von Baeyer CL, Stinson JN, Sung L. A systematic review of faces scales for the self-report of pain intensity in children. Pediatrics. 2010;126(5):e1168-98.
24. Leuter C, Petrucci C, La Cerra C, Dante A, Franconi I, Caponnetto V, et al. Nurses' and physicians' opinions on end-of-life: a secondary analysis from an Italian cross-sectional study. Ann Ig. 2020;32(3):274-284.
25. Verhagen AA. The Groningen Protocol for newborn euthanasia; which way did the slippery slope tilt? J Med Ethics. 2013;39(5):293-5.
26. Congreso de los Diputados, Ley Orgánica 3/2021, de 24 de marzo, de regulación de la eutanasia, BOE, 2021.

No todo es lo que parece amigo

Everything is not what it seems

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ABSTRACT

We present the case of a female patient with Crohn's disease who consults because of gastrointestinal symptoms and fever. In the initial studies we found peritoneal implants, ascites and pleural effusion. It's suggested as differential diagnosis a tumoral etiology or an infectious/inflammatory disease.

Keywords: Croh's disease; tuberculosis; ascites

RESUMEN

Presentamos el caso de una mujer con enfermedad de Crohn que consulta por clínica gastrointestinal y fiebre. En los estudios iniciales se evidenciaron implantes peritoneales, ascitis y derrame pleural. Se plantea el diagnóstico diferencial entre patología tumoral o infecciosa/inflamatoria

Palabras clave: Enfermedad de Crohn; tuberculosis; ascitis

CASO CLÍNICO

Mujer de 24 años que acude al servicio de Urgencias en abril 2022 por clínica de 2-3 semanas de evolución de dolor abdominal, náuseas, vómitos y aumento del número de deposiciones de hasta 4-5 deposiciones líquidas diarias sin sangre ni otros productos patológicos.

Es natural de Ecuador, aunque reside en España desde los 4 años. Ha sido diagnosticada de enfermedad de Crohn A2L2B1 en 2018 y tratada con adalimumab. En mayo de 2020 inició tratamiento con isoniazida por infección tuberculosa latente hasta febrero 2021. En febrero de 2022 desarrolló clínica compatible con eritema nodoso en cara anterior de ambas piernas; la histología fue compatible con paniculitis septal crónica con granulomas, con baciloscopia y cultivo de mycobacterias negativo. Mejoró tras la modificación de tratamiento biológico por infliximab.

En la exploración física se encontraba febril (38ºC), taquicárdica (112 lpm) y normotensa, con una saturación de oxígeno respirando aire ambiente de 90%. La auscultación cardiopulmonar era normal y el abdomen era blando, doloroso a la palpación de forma difusa de predominio en epigastrio y con signo de Murphy positivo. No tenía peritonismo ni se palpaban masas o megalias.

En análisis se observaron como alteraciones anemia microcítica hipocrómica (Hb 11.1 g/dL) similar a previas, linfopenia de 800 células/mm3 con leucocitos totales normales, y colestasis disociada (GGT 138 U/L y FA 146 U/L). El resto de los parámetros no demostró alteraciones significativas.

Ante la alteración oximétrica se realiza una radiografía de tórax, en la que se aprecia un derrame pleural izquierdo de pequeña cuantía. En la ecografía de abdomen se demuestra discreta ascitis. Se completa evaluación mediante TC de abdomen, que refleja ascitis moderada, micronodularidad y trabeculación de la grasa de predominio en omento mayor y noduralidad de las fascias sugestiva de carcinomatosis peritoneal.

DIAGNÓSTICO DIFERENCIAL

Se trata de una paciente inmunosuprimida con un cuadro subagudo de fiebre, vómitos y diarrea, con el hallazgo de ascitis, derrame pleural unilateral e implantes peritoneales. Podemos dividir el diagnóstico diferencial en tres grandes grupos: causa tumoral, infecciosa-inflamatoria y síndromes autoinflamatorios (tabla 1).

Tabla 1

TUMORAL	INFECCIOSA	AUTOINFLAMATORIA
Ovario	Apendicitis	Paniculitis mesentérica
Colorrectal	Diverticulitis	Lipodistrofia mesentérica
Pseudomixoma pritoneal	Enterocolitis	Mesenteritis retráctil o mesenteritis esclerosante crónica
Leiomiosarcoma	Pancreatitis	Pseudotumor inflamatorio
Estómago	Tuberculosis	

Dentro de las etiologías tumorales se puede tratar de un origen primario, como pseudomixoma o leiomiosarcoma, o representar una diseminación secundaria de un cáncer de ovario o gástrico[1]. Debemos tener en cuenta que se trata de una paciente sin antecedentes familiares conocidos de mutaciones genéticas predisponentes a cánceres ginecológicos o colorrectales, además de corta edad (24 años) por lo que la etiología tumoral la consideramos menos probable. Además, la fiebre no sería un signo esperable, salvo que de forma intercurrente presentara un brote de su enfermedad inflamatoria intestinal.

Los implantes peritoneales secundarios a causas infecciosas/inflamatorias se presentan más frecuentemente de forma reactiva y por contigüidad. Pueden además producir cierta cantidad de líquido ascítico. En un brote de enterocolitis por enfermedad de Crohn se puede detectar mínima ascitis; no obstante, cantidades clínicamente detectables no debidas a hipertensión portal son excepcionales[2]. La ascitis franca es una complicación rara de la enfermedad de Crohn y, cuando está presente, suele ser debida a un síndrome de Budd-Chiari o a una trombosis del eje esplenoportal en el contexto de un estado de hipercoagubilidad[3], ambos procesos razonablemente descartados mediante técnicas de imagen. Tampoco se vislumbraban signos de otros procesos

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inflamatorios abdominales ni se elevaron las enzimas pancreáticas en los análisis.

Otras entidades que se pueden presentar como nódulos peritoneales o aumento de densidad y necrosis de la grasa peritoneal son los procesos autoinflamatorios/fibróticos. La etiopatogenia muchas veces permanece incierta (se describen factores traumáticos, isquémicos, autoinmunes, autoinflamatorios, quirúrgicos, procesos malignos como linfomas...)[1]. Este tipo de entidades suele afectar más a hombres en la edad media (entre 50-60 años)[4]. La mayoría son asintomáticos inicialmente y se diagnostican como hallazgo incidental en una prueba de imagen. Pueden provocar dolor abdominal, síntomas sistémicos y/o masa abdominal palpable, pero en todo caso, suelen tener un comportamiento lentamente progresivo[5], al contrario que en nuestra paciente.

Por último, teniendo en cuenta la inmunosupresión y el antecedente epidemiológico de tuberculosis latente, nos planteamos como etiología más probable una tuberculosis con diseminación peritoneal y pleural.

RESOLUCIÓN DEL CASO

Una paracentesis diagnóstica demuestra un líquido inflamatorio no indicativo de hipertensión portal (gradiente de albúmina 0.2, 3.180 leucocitos con >70% linfocitos, ADA 70 U/L, baciloscopia negativa y citología negativa para malignidad).

Se realiza exploración y ecografía ginecológicas, que no demostraron alteraciones.

Se completó el estudio con una TC de tórax, en la que se evidenció una consolidación alveolar en la língula, signos de relleno de la vía aérea distal bilateral, derrame pleural bilateral con signos inflamatorios pleurales, sugestivo todo ello de una tuberculosis activa. Además, presenta un granuloma calcificado en el lóbulo superior derecho, así como numerosas adenopatías hilio-mediastínicas de pequeño tamaño.

Para completar el proceso diagnóstico se decidió realizar una broncoscopia. Tanto la PCR de mycobacterias como la baciloscopia fueron positivas. Se obtuvo posteriormente crecimiento de Mycobacterium tuberculosis. Se pautó tratamiento con fármacos antituberculosos. La evolución ha sido favorable, con resolución de la sintomatología.

El tratamiento con agentes biológicos, en particular inhibidores de TNF-alfa, está asociado con un aumento del riesgo de tuberculosis, por lo que el diagnóstico precoz de infección latente tuberculosa en los pacientes que vayan a iniciar estos fármacos está indicado[4]. El riesgo de tuberculosis varía entre los diferentes fármacos biológicos, siendo los de mayor riesgo adalimumab e infliximab (riesgo relativo 29.3 y 18.6 respectivamente). Si se desarrolla tuberculosis durante un tratamiento con anti-TNF-α, es más probable que se trate de una tuberculosis diseminada y extrapulmonar[6].

CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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ASPECTOS ÉTICOS

Los participantes del estudio han dado su consentimiento para participar en el mismo.

BIBLIOGRAFÍA

1. Corwin MT, Smith AJ, Karam AR, Sheiman RG. Incidentally detected misty mesentery on CT:risk of malignancy correlates with mesenteric lymph node size. J Comput Assist Tomogr. 2012;36(1):26–9.
2. Aparicio Tormo JR, Laveda R, Gómez Andrés A. Enfermedad de Crohn y ascitis. Gastroenterol Hepatol. 2000;23:394-388.
3. Paspatis GA, Kissamitaki V, Kyriakakis E, et al. Ascites associated with the initial presentation of Crohn's disease. Am J Gastroenterol. 1999;94:1974-1976.
4. Cortés P, Ghoz HM, Mzaik O, et al. Colchicine as and alternative first-line treatment of sclerosing mesenteritis: A retrospective study. Dig Dis Sci. 2022; 67:2403-2412.
5. Dobler CC. Biologic Agents and Tuberculosis. Microbiol Spectr. 2016;4.
6. Colombel JF, Sands BE, Rutgeerts P, et al. The safety of vedolizumab for ulcerative colitis and Crohn's disease. Gut. 2017;66:839-851.

Autoimmune Hepatitis after AstraZeneca Coronavirus Disease 2019 (COVID-19) vaccine: need for epidemiological study

Hepatitis Autoinmune tras vacunación con la vacuna AstraZeneca contra la COVID-19: necesidad de un estudio epidemiologico

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ABSTRACT

This case-report and brief review of literature were written concerning autoimmune hepatitis potentially triggered by virus vaccines. Soon after the Astrazeneca COVID-19 vaccine, a 70-year-old women presented with jaundice and nausea, with significant hepatic injury (aspartate aminotransferase (AST) 746 U/L; hyperbilirubinemia 9,30 mg/dL (conjugated bilirubin 7,14 mg/dL), elevated immunoglobulin (Ig)G and antinuclear, anti-smooth muscle and anti-actin F antibodies were detected. Considering autoimmune hepatitis (AIH) as a possible cause, a liver biopsy was performed and compatible with AIH. Prednisolone therapy was initiated, with optimal response. This report suggests that immunization against COVID-19 might precipitate or induce AIH. Further data regarding confirmed cases of AIH are mandatory in order to establish a causal link. Therefore, long-term pharmacovigilance surveillance of large cohorts of patients is needed.

Keywords: autoimmune hepatits, SARS-CoV-2, COVID-19 vaccines.

INTRODUCTION

Autoimmune hepatitis (AIH) is a persistent inflammatory disorder which directly affects the liver[1–3]. Clinical presentation is highly variable[3] and the diagnosis is based on clinical, laboratory and histological features[1–3], by using score-systems, such as revised International Autoimmune Hepatitis Group (IAIHG) criteria[4]. The prompt improvement after initiation of corticotherapy confirms the diagnosis of AIH.

No diagnostic criteria or treatment strategy for AIH induced by vaccination have been established, thus diagnosis must be based on the existent state-of-art evidence as in the presented case.

CASE DESCRIPTION

A 70-year-old woman presented to the emergency room of a tertiary-care hospital with jaundice, anorexia and nausea beginning within 72h, without other symptoms, history of drug intake or recent medication changes. She received the first dose of AstraZeneca COVID-19 vaccine 5 days prior to hospital admission. Her physical exam was unremarkable, except for jaundice and tenderness in the upper abdominal regions. Complete blood count was unremarkable, but serum biochemistry revealed aspartate aminotransferase 746 U/L (reference range (RR): 10-30 U/L), alanine aminotransferase (ALT) 682 U/L (RR: 10-36 U/L), gamma-glutamyl transpeptidase 473 U/L (RR: 6-39 U/L), and alkaline phosphatase (ALP) 353 U/L (RR: 35-104 U/L); also total hyperbilirubinemia 9,30 mg/dL (RR: 0.20-1.00mg/dl), conjugated bilirubin 7,14 mg/dL (RR: 0.00-0.30mg/dl) and prolonged partial thromboplastin time (47,2 seconds). An abdominal ultrasound showed no signs of acute disease and computed tomography showed hepatic steatosis, but no stricture nor dilation of the biliary tracts. A predominant hepatocellular hepatitis was assumed and she was admitted to a general medical ward for further investigation: serologic tests for hepatitis A, B, C, D and E, Epstein Barr virus (EBV), Cytomegalovirus were negative; Wilson's disease and toxoplasmosis were also ruled out. Immunology tests revealed elevated immunoglobulin (Ig) G (2486,0 mg/dL; RR: 793,0-1590,0) and positive antinuclear (1:320; RR < 1:160), anti-smooth muscle (1:640; RR < 1:40) and anti-actin F (47,8U/mL; RR > 20U/mL) antibodies. In the first 48h, she developed acute liver failure, with a maximum Model for End-Stage Liver Disease score of 20. Considering AIH as a possible cause, a liver biopsy was performed and the histopathology revealed cholestatic hepatitis with intralobular canalicular cholestasis, interface hepatitis with necroinflammatory activity and ductular reaction, and expansion of portal tracts by a polymorphic inflammatory infiltrate with abundant neutrophils. Based on the revised IAIHG criteria[1], the pre-treatment score was 18 points, which correlates with definite AIH (ALP:ALT ratio < 1.5; IgG 1.56 times above upper limit of normality, high titres of antinuclear antibodies and negative anti-mitochondrial antibodies; no hepatitis viral markers nor use of hepatotoxic drugs, liver histology with interface hepatitis and no other specific changes).

An immune-mediated hepatitis possibly secondary to the first dose of AstraZeneca vaccine was assumed and prednisolone (0.5 mg/kg/day) therapy was initiated; afterwards, clinical and laboratory findings improved significantly and she was discharged, under close follow-up. Prednisolone was gradually tapered, without clinical nor laboratory relapse until the present day.

DISCUSSION

This case-report describes a woman who developed AIH after AstraZeneca COVID-19 vaccination. AIH is a persistent inflammatory disorder which directly affects the liver, more commonly in women[1–3]. Due to clinical heterogeneity, diagnosis also relies on laboratory and histological features[1–3]. Laboratory tests were highly suggestive of AIH, revealing elevated IgG and aminotransferase levels and presence of antinuclear antibodies. The histopathological pattern of cholestatic hepatitis has several etiologies (in

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Table 1. Laboratory tests at hospital admission and discharge and in ambulatory re-evaluation after hospitalization. Abbreviations: Alb, serum albumin; ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; DBil, direct bilirubin; GGT, gamma-glutamil transferase; INR, international normalized ratio; TBil, total bilirubin.

Laboratory test	Admission	Before Discharge	Ambulatory Revaluation
AST (U/L)	746	82	21
ALT (U/L)	682	120	21
ALP (U/L)	353	289	141
GGT (U/L)	473	257	65
TBil (mg/dl)	9,30	6,41	1,07
DBil (mg/dl)	7,14	3,37	0,37
INR	1,41	1,42	1,35
Alb (g/dl)	2,81	3,20	4,61

this case scoring 3 points, according to IAIHG score-system). The sample was immunohistochemically negative for Hepatitis B and C viruses, EBV and Cytomegalovirus; rodanin coloration did not show alterations, excluding Wilson's disease. The prompt improvement in liver parameters following initiation of corticotherapy confirmed the diagnosis of AIH.

Multiple factors contribute to the development of AIH, from infections to an impaired immunoregulatory system[3]. According to previous reports, several pathogens, including EBV, Hepatitis A, B and C viruses can induce AIH[2,3]. There are also reports of AIH induced by Hepatitis A and Influenza virus vaccination[2,3,5]. Molecular mimicry and bystander activation of dormant autoreactive T-helper cells have been nominated as potential mechanisms[6]. COVID-19 has also been associated with the development of autoimmune disorders[6], with at least one case of AIH described by Hong J. et al ([7]). To our knowledge, most of the reported cases of AIH induced by COVID-19 vaccination are related to mRNA-1273 vaccines, such as Pfizer or Moderna vaccines[8,9]. This case-report suggests that COVID-19 immunization based on viral vector may also precipitate or induce AIH.

In our patient, AIH was not triggered by a hepatotoxic virus infection nor drug-induced liver injury. Symptoms started 72h after the first inoculation with the AstraZeneca COVID-19 vaccine. Previous publications stated that the lag-time between vaccination and the onset of symptoms can range from a week to a month after vaccination[2,3]. Our observation is not in agreement with those reports because the latency period was relatively brief, which might question the association between the potential trigger and the autoimmune process. However, brief latency periods after vaccination have been previously described[8,9]. Moreover, and until the present time, as all of COVID-19 vaccines are recent, it is yet not feasible to perform an in-vitro provocation test, to establish a causal link between AstraZeneca vaccine and the development of AIH. Therefore, remains the question whether the vaccine was a direct trigger of an immune injury process or if it awakened a dormant pre-existent and undiagnosed AIH.

CONCLUSIONS

As immunization might be a possible cause of other autoimmune diseases, it is acceptable to hypothesize that COVID-19 vaccine could trigger the development of AIH/hepatotoxic phenomena. COVID-19 vaccination is considered safe and effective[10] and whether there is a causal association with the development of AIH remains to be determined. We have no intention of discouraging the prescription of COVID-19 vaccination, but to shed light over potential serious side effects. Further data regarding confirmed cases of AIH are mandatory in order to establish a causal link. Therefore, long-term pharmacovigilance of large cohorts of patients is needed to detect autoimmune and other rare adverse events of vaccination[5].

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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ETHICAL ASPECTS

All participants submitted a consent form to be included in this study.

REFERENCES

1. Corte C Della, Carlucci A, Francalanci P, Alisi A, Nobili V. Autoimmune hepatitis type 2 following anti-papillomavirus vaccination in a 11-year-old girl. Vaccine [Internet]. 2011;29(29–30):4654–6.
2. Sasaki T, Suzuki Y, Ishida K, Kakisaka K, Abe H, Sugai T, et al. Autoimmune hepatitis following in fl uenza virus vaccination. 2018;0(June):27–30.
3. Perumalswami P, Peng L, Odin JA. Vaccination as a triggering event for autoimmune hepatitis. Semin Liver Dis. 2009;29(3):331–4.
4. Alvarez F, Berg PA, Bianchi FB, Bianchi L, Burroughs AK, Cancado EL, et al. International Autoimmune Hepatitis Group Report: Review of criteria for diagnosis of autoimmune hepatitis. J Hepatol. 1999;31(5):929–38.
5. Vadalà M, Poddighe D, Laurino C, Palmieri B. Vaccination and autoimmune diseases: is prevention of adverse health effects on the horizon? EPMA J. 2017;8(3):295–311.
6. Capecchi PL, Lazzerini PE, Brillanti S. Comment on "Autoimmune hepatitis developing after coronavirus disease 2019 (COVID-19) vaccine: Causality or casualty?" J Hepatol [Internet]. 2021;2019.
7. Hong JK, Chopra S, Kahn JA, Kim B, Khemichian S. Autoimmune hepatitis triggered by COVID-19. Intern Med J. 2021;51(7):1182–3.
8. Zin Tun GS, Gleeson D, Al-Joudeh A, Dube A. Immune-mediated hepatitis with the Moderna vaccine, no longer a coincidence but confirmed. J Hepatol. 2022;76(3):747–9.
9. Suzuki Y, Kakisaka K, Takikawa Y. Letter to the editor: Autoimmune hepatitis after COVID-19 vaccination: Need for population-based epidemiological study. Hepatology. 2022;75(3):759–60.
10. Union E, Management R, Union E, Management R, Substance D, Number V. EUROPEAN UNION RISK MANAGEMENT PLAN (EU RMP) FOR VAXZEVRIA (ChAdOx1-S [RECOMBINANT]). 2021;1(101).

Acquired Haemophilia associated with SARS-CoV2 infection

Hemofilia Adquirida asociada a infección por SARS-CoV2

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ABSTRACT

We present the case of a 73-year-old man, with a history of SARS-CoV2 infection (January 2021), who came to the emergency department three months post infection, with complaints of left hip and knee pain, that turned out to be a substantial thigh hematoma. Analysis showed a normocytic/ normochromic anaemia (9,0 g/dL), prolonged aPTT (63.2 seconds; normal range 24.7–39.0 sec.), with normal prothrombin time. We arrived at a diagnosis of Acquired Haemophilia A. Treatment was promptly started, with clinical and laboratory improvement. After the vaccination to SARS-CoV2, a relapse was observed.

Acquired Haemophilia A is a rare, autoimmune disease, distinguished by the presence of inhibitors against factor VIII. It's characterised by subcutaneous hematomas and muscle bleeding, with prolonged aPTT. SARS-CoV2 infection has already been mentioned as a possible cause.

Keywords: Acquired Haemophilia A, SARS-CoV2.

CASE REPORT

We reported the case of a 73-year-old man that was admitted to the emergency department (ED) in April 2021 with left knee and hip pain with one week of progression. No history of trauma was present. His past medical history included a stroke (1994), high blood pressure, chronic renal disease and SARS-CoV2 infection that didn't need hospitalisation (January 2021). Medicated with acetylsalicylic acid 150 mg once a day, enalapril 20 mg plus lercanidipine 10 mg once a day, sertraline 50 mg once a day, donepezil 5 mg once a day, nebivolol 2.5 mg once a day, olodaterol 2,5 mcg plus tiotropium bromide 2.5 mcg 2 puffs a day and pantoprazole 20 mg once a day. Upon Orthopaedics' examination, he had oedema from his left hip and knee, with pain in active and passive mobilisation. Laboratory analysis showed normocytic/ normochromic anaemia (9,0 g/dL), with leukocytosis (23.1 G/L), normal platelets count, prolonged activated partial thromboplastin time (63.2 seconds; normal range 24.7 – 39.0 sec.), with normal prothrombin time. An ultrasound performed on the left thigh, indicated possible quadriceps tendon rupture; this diagnosis was established, and the patient was admitted to the Orthopaedic ward. After 8 days with no improvement, he went into surgery so an evaluation could be made of his quadriceps tendon. They found a large thigh hematoma, without tendon rupture. In the recovery room he started to bleed from puncture sites. He remained under the Orthopaedics' department care for almost one month, in constant need of blood transfusions (14 red cell concentrates and 8 fresh frozen plasma in total). After this time, Internal Medicine was consulted, because the patient presented fever and cough. Analysis showed leukocytosis (23.07 g/L), normocytic/ normochromic anaemia (7.8 g/dL), thrombocytosis (639 G/L), an indomitable aPTT and an increase of C-reactive protein (17.08 mg/dL). The thorax x-ray showed multiple bilateral infiltrates. The diagnosis of nosocomial pneumonia was assumed, and the patient started piperacillin plus tazobactam. He was then transferred to the Internal Medicine department.

We started the study of his prolonged activated partial thromboplastin time. The mix test failed to correct aPTT (initial aPTT 140 seconds and after mix test 107 seconds), suggesting the presence of an inhibitor. The dosage of factor VIIIc was <1%, Lupus anticoagulant was negative, the dosing of specific inhibitors of factor VIII showed a residual activity of 29% and 719 Bethesda Units/ mL. IgG SARS-CoV2 antibody was positive. Thorax CT-scan suggested the presence of alveolar haemorrhage. The diagnosis of Acquired Haemophilia A (AHA) was subsequently made, due to the presentation of the thigh hematoma and alveolar haemorrhage. Treatment with activated factor VII, corticoid (prednisolone 1 mg/Kg/day) and rituximab (4 cycles) was performed. A clinical improvement and reduction of aPTT was documented. Causes of AHA such as haematological malignancies, solid malignancies and immunological disorders were excluded.

At discharge, in June 2021, he maintained previous medication and continued treatment with prednisolone 1 mg/kg/day. It was recommended that the patient should not be vaccinated against SARS-CoV2 because he had been treated with rituximab. Unfortunately, he was vaccinated two weeks after discharge, and one week later he was admitted to the ED with a new thigh hematoma and hemarthrosis. Blood tests revealed normocytic/ normochromic anaemia (9.4 g/dL) and prolonged aPTT (91.8 sec.). The patient passed away due to a complication from infection.

DISCUSSION AND CONCLUSION

Acquired haemophilia A is a rare disorder, characterised by the presence of inhibitors against factor VIII[1]. It frequently occurs in elderly patients[2]. Laboratory findings revealed an isolated, prolonged aPTT, reduced FVIII activity and presence of autoantibodies (Bethesda assay or enzyme-linked immunosorbent assay)[1]. Commonly, the patient presents large subcutaneous hematomas and muscle bleeding, but gastrointestinal, genitourinary and retroperitoneal bleeding can also occur[1,2]. In the case study we report, the patient presented a thigh hematoma, but also an alveolar haemorrhage. Until now, alveolar haemorrhage has not been described as a presentation of AHA.

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In the majority of cases, no etiological factor is found[2], but AHA can be associated with cancer (haematological and solid), autoimmune diseases and infections[2].

The treatment strategy is to control the haemorrhage, eradicate the inhibitor, investigate and treat the cause[1,2]. To control haemorrhage, factor VIII bypassing agents should be used such as activated prothrombin complex concentrate or recombinant activated factor VII[1,2]. To eradicate the inhibitor, immunosuppressive therapy is mandatory[1]. The 2020 recommendations[1] state that immunosuppressive therapy is dependent on factor VIII activity. So if factor VIII is ≥1% and ≤20 BU/mL, proceed with a treatment of only steroids for 3 - 4 weeks, if factor VIII is <1% or >20 BU/mL, then double immunosuppressive therapy is necessary, with steroids plus cyclophosphamide or rituximab for 3 - 4 weeks[1]. These patients should be monitored frequently until they are in remission[7]. Complete remission can be achieved in 50% of patients with first-line immunosuppressive treatment[8]. With AHA mortality ranging between 30 and 40%[2].

Recently, SARS-CoV2 has been linked to AHA[3–5]. SARS-CoV2 infection has caused systemic alterations, and thromboembolic and coagulopathy has been reported[1]. *Franchini et al.*(2020) presented the case of a 66-year-old man who had a past history of AHA, that presented a relapse, after 9 years of normal blood tests, during the SARS-CoV2 infection[4]. *Hfzah* et al. (2021) references the case of a 73-year-old man who presented with AHA four months after having a SARS-CoV2 infection that did not need hospitalisation[5]. *Wang* et al. (2021) reported one case of a 65-year-old man, with a distant history of autoimmune thyroid disease, that was diagnosed with AHA, and was positive for SARS-CoV2 antibodies, probably the result of a previous asymptomatic infection[3].

This case shows the importance of being alerted to coagulation alteration in patients with SARS-CoV2 active infection or history of infection. After analysing the case study, we have concluded that the SARS-CoV2 infection, that occurred three months earlier, was the most likely trigger for this AHA case, and the relapse after receiving the SARS-CoV2 vaccine was one more point that supported the diagnosis. Until this paper was written, only three cases of AHA induced by SARS-CoV2 infection had been reported, and no relation with the SARS-CoV2 vaccination has been noted.

SARS-CoV2 is a multisystemic infection. Every day a new related manifestation, complication or association is being reported. The impact of the infection in the coagulation has been proven, and many thrombotic events have been reported. Autoimmunity appears to have an important role in many of the complications associated with the SARS-CoV2 infection. AHA is a rare autoimmune disease that requires a high index of suspicion to identify. Being recognized, diagnosed, and treated correctly has an impact on the prognosis. Our report describes one case of AHA, probably related to a SARS-CoV2 infection, that relapsed after the injection of the SARS-CoV2 vaccine, up until now the only reported.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

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All participants submitted a consent form to be included in this study.

REFERENCES

1. Tiede A, Collins P, Knoebl P, Teitel J, Kessler C, Shima M, et al. International recommendations on the diagnosis and treatment of acquired hemophilia A. Haematologica. 2020;105(7):1791–801.
2. Leebeek FWG. New Developments in Diagnosis and Management of Acquired Hemophilia and Acquired von Willebrand Syndrome. HemaSphere. 2021;5(6):e586.
3. Wang KY, Shah P, Roarke DT, Shakil SA. Severe acquired haemophilia associated with asymptomatic SARS-CoV-2 infection. BMJ Case Rep. 2021;14(7):e242884.
4. Franchini M, Glingani C, De Donno G, Casari S, Caruso B, Terenziani I, et al. The first case of acquired hemophilia A associated with SARS-CoV -2 infection. Am J Hematol [Internet]. 2020.
5. Hafzah H, McGuire C, Hamad A. A Case of Acquired Hemophilia A Following SARS-CoV-2 Infection. Cureus [Internet]. 2021 [citado 30 de novembro de 2021]; Disponível em: https://www.cureus.com/articles/64168-a-case-of-acquired-hemophilia-a-following-sars-cov-2-infection
6. Kapur S, Levin MB. Precursor T-Cell Lymphoblastic Lymphoma Presenting as Cardiac Tamponade in a 25-Year-Old Male: A Case Report and Review of Literature. World J Oncol. 2014;5(3):129-134.
7. Ozdemir R, Meşe T, Karadeniz C, Doksöz Ö. Unusual Presentation of Pre-T Cell Acute Lymphoblastic Leukemia: Massive Pericardial Effusion Only. Pediatr Emerg Care. 2015;31(10):711-2
8. Alimi H, Poorzand H, Jafarian AH. Malignant lymphoma with diffuse cardiac involvement and pulmonary stenosis. J Cardiol Cases. 2020;23(5):198-201.
9. Sablak CH, Dudley RM, Youngdahl A, Roth KR. Point-of-Care Ultrasound Assists in Rapid Diagnosis of T-cell Lymphoblastic Lymphoma in a Young Boy. Cureus. 2021;13(5):14978.
10. Gupta P, Pandey T, Gautam U, Rajwanshi A, Srinivasan R, Gupta N et al. Lymphoreticular malignancies in serous effusions: Cytomorphologic, flow cytometric and immunocytochemical analysis. Diagn Cytopathol. 2021;49(5):647-656.

Pleural AA amyloidosis preceding the diagnosis of inflammatory bowel disease

Amioloidosis AA pleural que precede el diagnóstico de una enfermedad inflamatoria intestinal

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ABSTRACT

Pleural amyloidosis constitutes a rare presentation of a rare disease. We report a case of amyloidotic pleural effusion that preceded the diagnosis of inflammatory bowel disease by six months. The patient had a paucisymptomatic gastrointestinal disease but an exuberant AA amyloidosis that progressed to involve multiple organs, including lung, kidney and heart. Despite immunomodulatory treatment with corticosteroids and infliximab with good gastrointestinal response, the patient eventually passed away 2 years after diagnosis.

Keywords: AA amyloidosis, pleural amyloidosis, inflammatory bowel disease.

INTRODUCTION

Amyloidosis is characterized by the extracellular deposition of insoluble proteins in the form of amyloid fibrils. These insoluble proteins are the result of the misfolding of several different precursor proteins. The origin of the precursor protein defines the type of amyloidosis. AA amyloidosis (AAA) results from the misfolding of serum amyloid A (SAA), an acute phase protein produced mainly by hepatocytes.

CASE REPORT

A 62-year-old woman with a remote history of breast cancer presented to our Emergency Department with 5 days of dyspnea. She also reported 5 months of anorexia and intermittent diarrhea for several years, with up to 4 bowel movements per day, without mucus or blood and without abdominal pain. She had undergone a colonoscopy the previous year which had been normal. Physical exam was remarkable for absent breath sounds on the left hemithorax, low extremity edema and macroglossia.

Initial workup showed acute kidney injury with an elevated creatinine (1.2 mg/dL from baseline 0.8 mg/dL), elevated erythrocyte sedimentation rate (107 mm/1h) and C-reactive protein (147 mg/L), decreased levels of hemoglobin (7.9 g/dl, normocytic, normochromic) and serum albumin (2.8 g/dl). Urinalysis revealed non-nephrotic proteinuria. A computed tomography scan of the chest, abdomen and pelvis showed bilateral pleural effusions (Figure 1). A thoracentesis was performed, and pleural fluid studies demonstrated a non-purulent exudative effusion (per Light's Criteria), lymphocyte predominance (80%) and normal pH. There were no structural or functional heart changes on transthoracic echocardiogram. Pleural biopsy was performed, identifying AA type amyloid infiltration. The same type of amyloid was identified in a rectal biopsy taken during a sigmoidoscopy which did not identify any macroscopic abnormalities. *Mycobacterium tuberculosis* was not identified in either pleural or colon biopsies. Serum amyloid A protein level was 12.0 mg/dL (normal <6.0). A diagnosis of systemic inflammatory amyloidosis was established, with pleural and intestinal deposition and presumed renal involvement. The patient was treated with furosemide and was discharged with resolution of the pleural effusions and no dyspnea.

In the three months following her discharge, the patient underwent extensive investigation of the cause of her amyloidosis. Work-up included normal immunoglobulin and light chain levels, normal serum and urine electrophoresis and immunoelectrophoresis, and normal bone marrow biopsy. Whole-body scans did now show any evidence of malignancy, including focused breast studies (mammography, breast echography and magnetic resonance), which were not suggestive of cancer recurrence. HIV serology, tuberculin skin test and IGRA studies were negative. An upper endoscopy was done and the duodenal biopsy did not show signs of infection by *Tropheryma whipplei*. Cytomegalovirus DNA was not isolated from a colon biopsy. Auto-immunity work-up revealed a positive IgA anti-ASCA. A repeat colonoscopy 6 months later showed multiple new deep ulcers between the transverse colon and rectum with areas of uninvolved mucosa (Fig. 2). Histological analysis suggested inflammatory bowel disease, with glandular architecture distortion and inflammatory infiltrate extending to the *muscularis mucosa*e.

Figure 1. CT scan of Thorax showing left pleural effusion (arrow).

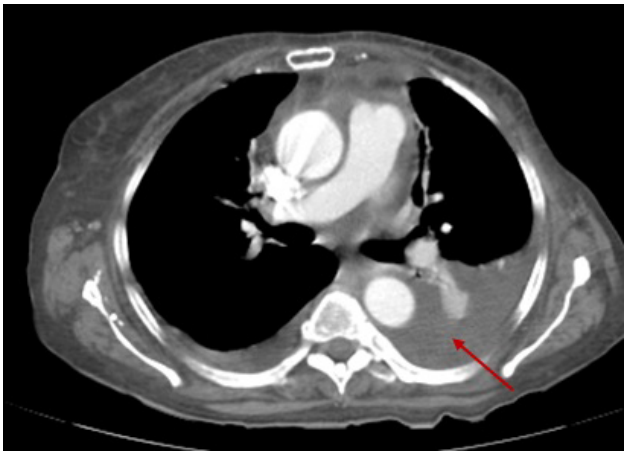

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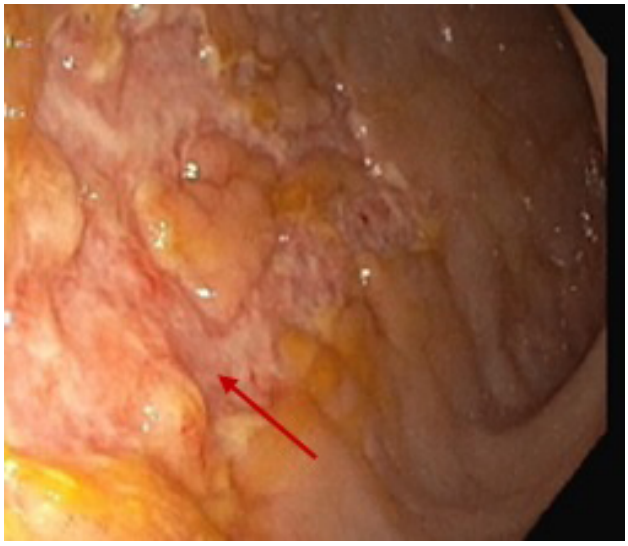
Figure 2. Colonoscopy showing colonic ulcers (arrow).



Immunomodulatory therapy was started with prednisolone 40 mg/day and mesalamine 3 g/day. Following treatment, calprotectin remained elevated and colonoscopy showed persistent colonic ulcers, prompting initiation of infliximab (5 mg/kg at weeks 0, 2 and 6, followed by 5 mg/kg every 8 weeks).

Early into immunomodulatory therapy, the patient experienced clinical deterioration with anasarca secondary to hypoalbuminemia and fulminant heart failure requiring diuretics. Following immunomodulators, albumin levels and fluid distribution stabilized, erythrocyte sedimentation rate normalized, and there was resolution of the colonic ulcerative lesions on repeat endoscopy.

Two years after the diagnosis the patient was admitted to our Emergency Department with acute heart failure. Transthoracic echocardiogram now showed signs of cardiac involvement by amyloidosis, with left ventricular hypertrophy with diastolic dysfunction and normal systolic function. A week into hospitalization she went into cardiac arrest. A do not resuscitate request was followed.

DISCUSSION

Chronic inflammation is associated with elevated levels of SAA. Different diseases can lead to chronic inflammation and subsequent AAA, notably chronic inflammatory arthritides, periodic fevers, vasculitides, chronic infections, neoplasia and inflammatory bowel disease[1]. Despite the long list of possible causes of AAA, this is a rare entity, and the majority of patients with these inflammatory syndromes do not develop AAA. It is not known why some patients develop AAA while others do not. One theory is that patients with poorly controlled inflammation are more likely to develop AAA[2]. Usually a diagnosis of AAA is made years after the primary disorder is diagnosed[2], and the symptoms result from dysfunction of the organs affected by amyloid deposition[1]. Virtually any organ can be affected by amyloidosis, but in AAA the kidney is most frequently involved, with nephrotic syndrome being the most common presentation. Diagnosis of AAA requires biopsy of the affected organ and relies on the appearance of an apple-green birefringence with polarized light and positive Congo red staining of the amyloid fibrils[1]. The management of AAA relies on the treatment of the primary inflammatory disorder. In the case of inflammatory bowel disease, anti-TNF drugs have shown positive results[1].

Our case is remarkable because the diagnosis of AAA preceded that of the paucisymptomatic inflammatory bowel disease by several months, and the initial presentation was characterized primarily by respiratory symptoms secondary to pleural involvement. Pleural amyloidosis is rarely reported. When present it is normally a sign of AL amyloidosis, another type of amyloidosis associated with plasma cell dyscrasia[3]. AAA with pleural involvement has been reported before[4], but there are no previous descriptions of inflammatory bowel disease associated with pleural amyloidosis. AAA diagnosis before of the causing disease is well described and, recently, investigation protocols were proposed[5]. The clinical significance of pleural amyloidosis is debatable. It is often difficult to discern whether it is the sole cause of pleural effusion, as the same patient can have concomitant heart failure and nephrotic syndrome secondary to amyloid deposition in the heart and kidneys[3]. In our case, the pleural effusion can be attributed to at least two factors: hypoalbuminemia with resulting lower plasma oncotic pressure and pleural deposition of amyloid with subsequent impairment of pleural fluid reabsorption.

CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors

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ETHICAL ASPECTS

All participants submitted a consent form to be included in this study.

REFERENCES

1. Real de Asúa D, Costa R, Galván JM, Filigheddu MT, Trujillo D, Cadiñanos J. Systemic AA amyloidosis: epidemiology, diagnosis, and management. Clin Epidemiol. 2014, 29;6:369-77.
2. Tosca Cuquerella J, Bosca-Watts MM, Anton Ausejo R, Tejedor Alonso S, Mora De Miguel F, Minguez Perez M. Amyloidosis in Inflammatory Bowel Disease: A Systematic Review of Epidemiology, Clinical Features, and Treatment. J Crohns Colitis. 2016;10(10):1245-53.
3. Berk JL. Pleural effusions in systemic amyloidosis. Curr Opin Pulm Med. 2005;11(4):324-8.
4. Dias C, Tavares I, Magalhães A, Melo N. Pleural effusion in AA amyloidosis - A rare involvement of a rare disease. Rev Port Pneumol (2006). 2017;23(4):234-236.
5. Brunger AF, Nienhuis HLA, Bijzet J, Hazenberg BPC. Causes of AA amyloidosis: a systematic review. Amyloid. 2020;27(1):1-12.

Fahr's Syndrome – A Case Report

Síndrome de Fahr: un caso clínico

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ABSTRACT

Fahr's syndrome is an uncommon neurodegenerative disorder, characterized by bilateral and extensive deposition of calcium in the basal ganglia.
We present the case of a 66-year-old female presented to the Emergency Department with (a sudden and) intense holocranial headache accompanied by nausea. She also reported paresthesias of the hands and feet with several years of evolution, mnesic changes and periods of uninhibited behavior. Head CT revealed extensive and bilateral calcifications of the basal ganglia, cerebellum and frontal region and the analytical findings showed a severe hypocalcemia. She begun replacement with intravenous and oral calcium. An improvement of signs and symptoms were observed during the hospitalization.
Although rare, Fahr's syndrome must be kept in mind and appropriate treatment should be aplied in order to stop it's progression and improve the clinic symptoms and signs.

Keywords: Fahr's syndrome; basal ganglia; hypoparathyroidism; hypocalcemia; neuropsychiatric.

INTRODUCTION

Fahr's syndrome is a rare and chronic disease characterized by bilateral and extensive deposition of calcium in the basal ganglia, thalamus, cerebral cortex, cerebellum and hippocampus[1,2,3]. The most common presenting signs and symptoms are neuropsychiatric manifestations like seizures, cognitive impairment and can also be associated with parestesias due to hypocalcemia. Fahr's syndrome usually appear in the fourth or fifth decade of life[2,3].
The most common metabolic cause of Fahr's syndrome is hypoparathyroidism[4,5].
Hypoparathyroidism is an endocrine disease, that can be idiopathic or secondary. Idiopathic form is characterized by deficient secretion of parathyroid hormone (PTH) without a definitive cause.

CASE REPORT

We report a case of a 66-year-old woman with history of hypertension and dyslipidemia and with no significant family history, presented to the Emergency Department (ED) with (a sudden and) intense holocranial headache accompanied by nausea. She also reported paresthesias of the hands and feet with several years of evolution, mnesic changes and periods of uninhibited behavior. In the ED, the patient had a generalized tonic-clonic seizure, that ceased after the administration of 5 mg of diazepam. She was afebrile and euglycemic. No nuchal rigidity or focal neurologic signs were observed.
Head CT revealed extensive and bilateral calcifications of the basal ganglia, cerebellum and frontal region (Figure 1). Analytical findings showed a severe hypocalcemia of 5.7 mg/dL (N: 8.6 –

Figure 1

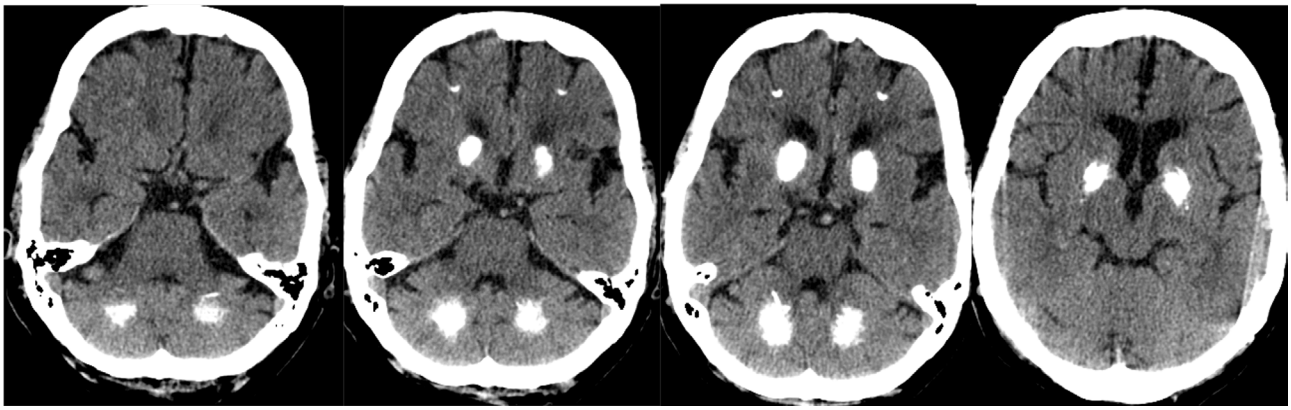

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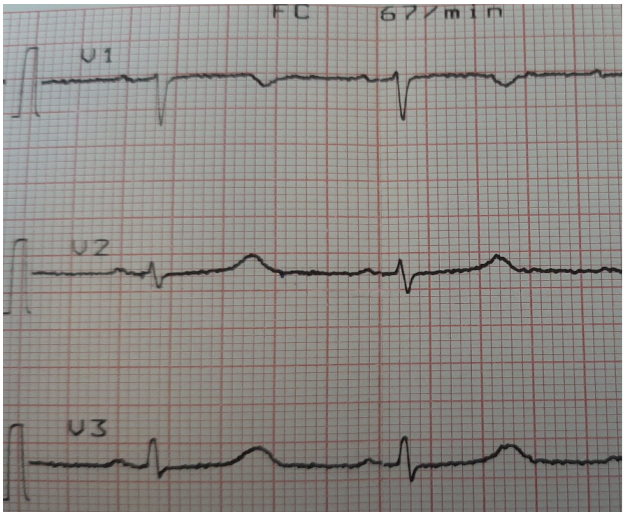
Figure 2



10.3 mg/dL) with an ionized calcium level of 0.60 mmol/L (N: 1.13 – 1.31 mmol/L). Other analytical findings showed a PTH of 11.08 pg/mL (N: 15-65 pg/mL), phosphorus of 6.4 mg/dL (N: 2,5 – 4,9 mg/dL), magnesium of 1,26 mg/dL (N: 1,6 – 2.6 mg/dL) and a vitamin D of 30 ng/mL (N: 6,2 – 53,2 ng/mL). An electrocardiogram was performed and revealed a prolongation of the QT interval (Figure 2).

The electroencephalogram confirmed the diagnosis of epilepsy. Thyroid and parathyroid ultrasonography were normal and parathyroid antibodies were also negative.

Based in all these findings the diagnosis of Fahr's syndrome due idiopathic primary hypoparathyroidism was made.

The patient began immediate replacement with intravenous calcium gluconate, until there was normalization of the electrocardiographic changes, followed by oral supplemental calcium and calcitriol. She also started replacement for the hypomagnesemia with intravenous magnesium until the levels were normalized.

Levetiracetam 250 mg twice daily was prescribed to prevent any seizures.

During hospitalization, the symptoms of the patient improved as the levels of calcium were normalized. She remained stable, without any more seizures.

The patient was discharged and referred to an Internal Medicine and Endocrinology consult.

DISCUSSION

Fahr's syndrome is due to calcification of the basal ganglia and other regions of the brain, that are bilateral and symmetric[1,2,4,6]. The most common reported metabolic disorder are hypoparathiroidism and pseudo-parathiroidism.

Hypoparathyroidism is an endocrine disorder that can be iatrogenic, due the surgical removal or radiotherapy, or idiopathic. The idiopathic form is uncommon and of unknown etiology[4,6]. It refers to the deficient PTH secretion, with the presentation of levels of PTH and calcium that are low. In pseudo-parathiroidism PTH levels will be high with hypocalcemia.

There is no clear explanation for the mechanism that cause these calcifications. It is suggested that the increased calcium-phosphorus complex plays an important role 6, by deposition in the vessel wall and eventually extending to the neuron.

The most common clinical manifestations of this syndrome are neuropsychiatric like seizures, headache, cognitive decline and parkinsonism[1,2].

The alterations found in the electrocardiogram are a well-known impact of the low levels of the calcium.

To the date there's is no specific treatment for Fahr's syndrome[2,4,6]. The management of the clinical manifestations is limited to supportive care, using anxiolytics, anticonvulsant and a hemodynamic balance. If the Fahr' syndrome is due to the hypoparathyroidism, like in our case, the symptoms usually improve with the normalization of the calcium and phosphorus levels.

The patient was treated with IV and oral calcium and anti-convulsant, but no other medications were needed once that the neuropsyquiatric symptoms resolved after the normalization of the plasmatic calcium level. She maintained treatment with oral calcium and calcitriol to prevent symptomatic hypocalcemia.

CONCLUSION

Fahr's syndrome, although rare, should incorporate the list of differential diagnoses of neuropsychiatric disorders and epileptic seizures. The calcifications of the basal ganglia, despite being a suggestive finding of an evolved disease, may be a finding of enormous value since they can immediately guide the diagnosis and allow rapid treatment of hypocalcemia and hypoparathyroidism.

CONFLICTS OF INTEREST

The authors declare that there is no potential conflict of interest relevant to this article.

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AUTHORS' CONTRIBUTION

Costa, Raquel and Mendes, Tiago wrote de paper; Fontes, Joana, Sousa, Barbara and Silva, Joana reviewed the paper.

REFERENCES

1. Saleem S, Aslam HM, Anwar M, et al. Fahr's syndrome: literature review of current evidence. Orphanet J Rare Dis. 2013; 8:156.
2. Manyam BV, Walters AS, Narla KR, et al. Bilateral striopallidodentate calcinosis: clinical characteristics of patients seen in a registry. Mov Disord. 2001;16(2):258-64.
3. Nicolas G, Pottier C, Charbonnier C, et al. Phenotypic spectrum of probable and genetically-confirmed idiopathic basal ganglia calcification. Brain. 2013;136(Pt 11):3395-3407.
4. Basak R. A case report of basal ganglia calcification – a rare finding of hypoparathyroidism. Oman Medical Journal. 2009; 24: 220-222.
5. Schupper A, Chen M. A unique presentation of Fahr syndrome secondary to chronic hypoparathyroidim: a case report. Imaging Med. 2018; 10(5).
6. Marinkovic D, Dragovic T, Kikovic S, Jankovic S, Djuran Z, Hajdukovic Z, et al. Fahr's syndrome and idiophatic hypoparathyroidism – a case report. Vojnosanitetski pregled. 2017; 74(2): 184-188.

Pulmonary and cutaneous sarcoidosis in a patient with selective immunoglobulin M deficiency

Sarcidosis pulmonar y cutánea en un paciente con déficit selectivo de inmunoglobulina M

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ABSTRACT

Selective immunoglobulin M deficiency (SIgMD) is a rare primary immunodeficiency characterized by decreased serum levels of immunoglobulin M. The pathogenesis of SIgMD is unclear, as well as its association with various immunopathological disorders. We describe a case of sarcoidosis associated with SIgMD. To our knowledge, such association has not been reported previously.

Keywords: Sarcoidosis; Selective immunoglobulin M deficiency

INTRODUCTION

Sarcoidosis is a multisystemic granulomatous disease whose etiology remains unknown. It usually develops before the age of 50 years, with the incidence peaking at 20 to 39 years. Diagnosis implies compatible clinical and radiological findings, histologic evidence of non-caseating granulomas in one or more organs and exclusion of all other causes of granulomas[1].

Primary selective immunoglobulin M deficiency (SIgMD), previously known as type V dysgammaglobulinemia, is a rare disorder defined as serum immunoglobulin M (IgM) levels two standard deviations below the mean for healthy controls and normal IgG and IgA levels[2,3,4]. Its pathogenesis is unclear and there are few published case reports[3]. Patients with SIgMD may be asymptomatic or present with infections, allergic or autoimmune diseases and malignancies[5,6].

To the best of our knowledge, this is the first case report of sarcoidosis associated with SIgMD.

CASE REPORT

A 45-year-old man with a history of renal lithiasis was admitted to the emergency department for presenting exertional dyspnea, chills and night sweats in the last month. One week before admission, he presented to another hospital for worsening dyspnea, orthopnea, and fever. Based on the clinical features, a presumptive diagnosis of respiratory infection was made and empirical treatment with levofloxacin was started. He had no history of recent travel, immunosuppressive therapy, weight loss, or exposure to persons with similar symptoms or known pulmonary tuberculosis. There was no family history of any immunodeficiency.

On examination, the temperature was 38.5ºC, the pulse 89 beats per minute, the blood pressure 142/75 mm Hg, peripheral oxygen saturation 99% (FiO2 21%), and there were no abnormalities in pulmonary auscultation. Arterial blood gas analysis revealed hypoxemia (PaO2 76 mm Hg). On laboratory testing, total white cell count was 7.84x10^9/L and C reactive protein level was 3.49 mg/dL. Chest radiography revealed bilateral hilar adenopathy and small infiltrates in the left upper lobe. Empirical antimicrobial therapy with ceftriaxone was initiated and admission for etiological investigation and inpatient care was proposed.

Computed tomography (CT) of the chest showed bilateral mediastinal and hilar adenopathies, some with central necrosis, and pulmonary parenchyma with discrete bilateral infiltrates and nodular opacities. Blood tests revealed negative antinuclear and antineutrophil cytoplasmic antibodies, angiotensin converting enzyme level of 49.2 U/L (normal range 8-55U/L), and IgM serum level of 26 mg/dl (normal range 40-230 mg/dL) with normal serum IgG (991 mg/dL) and IgA (358 mg/dL). Immunophenotypic lymphocyte analysis was unremarkable. Blood cultures and serologies for human immunodeficiency virus, cytomegalovirus, Epstein-Barr virus, and syphilis were negative.

Bronchofibroscopy was performed and cytological, bacteriological, mycological, and mycobacteriological direct and cultural examination of the bronchial aspirate was negative. Histopathologic examination of specimens obtained by transbronchial biopsy was inconclusive, as well as that of the samples obtained by endobronchial ultrasound-guided fine-needle aspiration of intrathoracic lymph nodes.

On physical examination on the tenth day of hospitalization, multiple tender, erythematous subcutaneous nodules were observed in the patient's legs, compatible with erythema nodosum.

Biopsy of intrathoracic lymph nodes by means of mediastinoscopy revealed non-necrotizing granulomatous lymphadenopathy. Thus, the patient was diagnosed with SIgMD complicated by sarcoidosis.

Pulmonary function tests, including spirometry, lung volumes and diffusing capacity for carbon monoxide were unremarkable, as well as transthoracic echocardiography.

The patient did not require oral glucocorticoid therapy because he had spontaneous remission of symptoms. After a one-year follow-up, he maintained clinical remission of sarcoidosis and had no infectious complications. However, IgM serum levels remained low and no modifications over the other Ig classes were observed.

DISCUSSION

The presence of mediastinal and hilar adenopathies with central necrosis on CT made the differential diagnosis challenging, requiring multiple hypotheses, from the non-rare pulmonary tuberculosis to the rare necrotizing sarcoid granulomatosis. The case became even more interesting by the finding of SIgMD.

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Although SIgMD was first described more than 5 decades ago[2,7], only in 2017 was incorporated in the International Union of Immunological Societies classification of primary immunodeficiency diseases[5,8].

SIgMD is associated with various immunopathological disorders. However, the pathogenic mechanisms involved are unclear and it is difficult to elucidate how strong these associations are[3]. IgM plays an important role in immune tolerance[5] and there are studies suggesting that the deficiency of serum IgM may impact the clearance of self-antigens and induce secondary autoimmune disease[6]. Mice genetically generated to be deficient in secreted IgM showed a tendency towards spontaneous development of autoantibodies and autoimmune diseases[2,5]. However, high IgM levels can also be associated with autoimmune diseases, which make it more difficult to clarify the relationship between low serum IgM levels and increased susceptibility to autoimmune conditions[2,3]. It might be a compensatory mechanism for inhibiting inflammation[2].

Further research on the effect of IgM on B-cell development and prevention from autoantibody formation is needed in order to elucidate the precise mechanism of IgM-mediated regulation of tolerance and so, the role of IgM in autoimmunity[6].

Although patients who present with recurrent infections and specific antibody deficiency responses may benefit from current immunoglobulin treatment, given to the possible immunomodulatory and antimicrobial effects of IgM, highly enriched IgM preparations could reveal to be a more desirable option, either for these patients or for those with autoimmune diseases[2,7]. In cases of secondary SIgMD, treatment for associated diseases may lead to an improvement in immunodeficiency. However, when it is primary, even if remission of autoimmune disease occurs, as in the case we present, the IgM deficit persists.

Patients with decreased serum IgM levels should undergo regular immunological evaluation for any recovery (to exclude secondary causes) or for progression to common variable immunodeficiency[2,3].

CONCLUSION

Patients with recurrent infections, atopic or autoimmune diseases should be investigated for IgM deficiency. On the other hand, since SIgMD can be complicated by sarcoidosis, this disease should be considered in the differential diagnosis of patients with SIgMD who present with cough, dyspnea, fatigue, fever and/or weight loss.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this work.

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ETHICAL ASPECTS

All participants submitted a consent form to be included in this study.

REFERENCES

1. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med. 2007; 357:2153-65.
2. Gupta S, Gupta A. Selective IgM Deficiency-An Underestimated Primary Immunodeficiency. Front Immunol. 2017; 8:1056.
3. Chovancova Z, Kralickova P, Pejchalova A, Bloomfield M, Nechvatalova J, Vlkova M, Litzman J. Selective IgM Deficiency: Clinical and Laboratory Features of 17 Patients and a Review of the Literature. J Clin Immunol. 2017; 37(6):559-574.
4. Gupta S, Gupta A. Defining primary selective IgM deficiency. J Clin Immunol. 2019; 39(4):350-352.
5. Lucuab-Fegurgur DL, Gupta S. Comprehensive clinical and immunological features of 62 adult patients with selective primary IgM deficiency. Am J Clin Exp Immunol. 2019; 8(6):55-67.
6. Campochiaro C, Atay S, Clark KEN, Ong V, Denton CP. Autoimmunity and immunodeficiency at the crossroad: autoimmune disorders as the presenting feature of selective IgM deficiency. BMJ Case Rep. 2019; 12(1):e223180.
7. Ni J, Zhang J, Chen Q, Chen Y, Liu J. The epidemiology and clinical features of selective immunoglobulin M deficiency: A single-center study in China. J Clin Lab Anal. 2020; 34(7):e23289.
8. Picard C, Bobby Gaspar H, Al-Herz W, Bousfiha A, Casanova JL, Chatila T, Crow YJ, Cunningham-Rundles C, Etzioni A, Franco JL, Holland SM, Klein C, Morio T, Ochs HD, Oksenhendler E, Puck J, Tang MLK, Tangye SG, Torgerson TR, Sullivan KE. International Union of Immunological Societies: 2017 Primary Immunodeficiency Diseases Committee Report on Inborn Errors of Immunity. J Clin Immunol. 2018; 38(1):96-128.

Atypical and severe presentation of autoimmune polyglandular syndrome type 2

Presentación grave y atípica de un síndrome autoinmune poliglandular tipo 2

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ABSTRACT

Background: Recurrent pericarditis has been described as an unusual manifestation of autoimmune polyglandular syndrome type 2 (APS 2). Case report: We describe a case of a 44-year-old woman who was admitted to hospital due to 5 pericarditis, 3 of them with cardiac tamponade, and in the etiological study of this pathology she was diagnosed with an APS 2. Conclusion: The association of serositis with APS 2 is exceptional with less than 10 cases reported in the literature. The presence of recurrent pericarditis of unknown cause should make us consider APS 2 in the differential diagnosis.

Keywords: autoimmune polyglandular syndrome, pericarditis, cardiac tamponade, recurrent polyserositis, case report.

RESUMEN

Introducción: La pericarditis recidivante se ha descrito como una manifestación poco frecuente del síndrome poliglandular autoinmune tipo 2 (APS 2). Caso clínico: Presentamos el caso de una mujer de 44 años que ingresa en el hospital debido a 5 pericarditis, 3 de ellas con taponamiento cardiaco, y en el estudio etiológico de dicha patología se diagnostica un APS 2. Conclusión: La asociación de serositis con el APS 2 es excepcional, con menos de 10 casos publicados en la literatura. La presencia de pericarditis de casusa desconocida debe hacernos considerar el APS 2 en el diagnóstico diferencial.

Palabras clave: syndrome poliglandular autoimmune, pericarditis, taponamiento cardiac, poliserositis recidivante, caso clínico

INTRODUCTION

Autoimmune Polyglandular Syndrome type 2 (APS 2) is characterized by the combination of Addison's disease (the defining component), type 1 diabetes mellitus, and/or autoimmune primary hypothyroidism. A variety of organ-specific autoimmune associated conditions, such as vitiligo, hypogonadotropic hypogonadism, autoimmune hepatitis, alopecia, pernicious anemia, seronegative arthritis, or myasthenia, have also been described[1]. Since the association of serositis with APS 2 is exceptional, we consider that the following clinical case report is of special interest.

CASE REPORT

A 44-year-old woman, with no relevant medical history, presented to the emergency room with fever of several days of evolution, associating pleuritic chest pain and bilious vomiting. She also referred frequent vomiting in the last month, and one-year history of asthenia and a 15 kg weight loss. On physical examination, she had a blood pressure of 88/66 mmHg, generalized skin hyperpigmentation and an axillary temperature of 38ºC were observed. Blood test were performed, showing 13.3 x 10^9 leucocytes, which 45% neutrophils, C-reactive protein (CRP) of 12 mg /dl, creatinine level of 3.9 mg / dl, a Glomerular Filtration Rate (MDRD4) of 13 ml / min, a sodium level of 125 mmol /L and a potassium level of 4.5 mmol / L. The electrocardiogram showed no alterations except for low voltages, and the chest X-ray evidenced an enlarged cardiac silhouette and minimal bilateral pleural effusion.

She was admitted with the diagnosis of acute pericarditis, suspicion of adrenal insufficiency and probable prerenal renal failure in the setting of volume depletion from continuous vomiting. Treatment with fluid therapy, corticosteroids, acetylsalicylic acid (ASA) and colchicine was initiated. During hospital admission, she was diagnosed with autoimmune hypothyroidism, with high serum thyroid-stimulating hormone (TSH) values (13 µU/ml) and both anti-thyroid peroxidase antibodies and anti-thyroglobulin antibodies positive. An autoimmune adrenal insufficiency was diagnosed too, with a morning serum cortisol of 2 µg/dl, a serum corticotropin (ACTH) of 352 pg/ml and positive anti-adrenal antibodies. With these data, the presumptive diagnosis of APS 2 was made, and hormone replacement therapy with levothyroxine 75 µg and hydrocortisone 30 mg daily was initiated, with favorable evolution. Serum antinuclear antibodies, cardiotrope virus serologies and Mantoux test were performed to establish the cause of pericarditis but were negative. Finally, the patient was discharged, with chronic hormone replacement therapy.

After 9 months, the patient presented again to the emergency department with a cardiac tamponade due to a new episode of acute pericarditis, with bilateral pleural effusion and hemodynamic instability, although without requiring pericardiocentesis. She clinically improved with treatment with corticosteroid, ASA and colchicine, and finally she was discharged again.

One month later, she came back to the emergency department with a new episode of cardiac tamponade due to another episode of acute pericarditis, with hemodynamic instability. A positron emission tomography-computed tomography (PET-CT) was made, with no significant findings. The determination of antibodies against several viruses (Coxsackie B, Epstein Barr, cytomegalovirus, herpes simplex 1 and 2, adenovirus, influenza), as well as against *Chlamydia pneumoniae, Borrelia burgdorferi, Brucella Spp., Salmonella Spp. and Mycoplasma pneumoniae*, was negative. Antinuclear anti-deoxyribonucleic acid (DNA) and anti-extractable nuclear antigens (ENAs) antibodies were also negative. Prednisone

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60mg daily was prescribed in a tapering regimen.
After 4 months, the patient was admitted again for cardiac tamponade, coinciding with a decrease in prednisone daily dose from 10 mg to 5 mg. Pericardiocentesis and pericardial fluid analysis were performed, obtaining exudative material with nonspecific inflammatory cytology. To complete the aetiological study of recidivant pericardial effusion a genetic study was performed to rule out autoinflammatory syndromes, with no findings.
Due to development of corticosteroid dependence, immunosuppressive therapy with azathioprine 200 mg and prednisone 7.5 mg daily was initiated. Twelve months after treatment with azathioprine the patient has not had any new pericarditis.

DISCUSSION

APS 2 is the most frequent endocrine autoimmune syndrome, although it continues to be a rare disease, approximately 1:20.000[1]. Addison's disease (AD) is present in 100% of the cases, autoimmune thyroid diseases (AITD) in 69–82% and type 1 diabetes mellitus (T1DM) in 30–52% of the patients[2]. Dual combinations are more common than the classical triad of AD, AITDs and T1DM, which appears only for 7.5% of cases, according to a meta-analysis published in 2020[3]. The mean age at the time of diagnosis is 34.7 years[3]. It has a polygenic inheritance pattern,and has been found to be strongly associated with HLA haplotypes with DR3/DQ2 and DR4/DQ8 and with DRB1*0404[4]. A series of minor clinical manifestations have been described that have also been associated with APS 2, such as: vitiligo, hypogonadotropic hypogonadism, autoimmune hepatitis, alopecia, pernicious anemia, seronegative arthritis, myasthenia, multiple sclerosis or coeliac disease.

Recurrent polyserositis has been described as an unusual manifestation of APS 2. To the best of our knowledge, less than 10 cases have been reported in the literature[5-10] (table 1). Although theoretically it is more frequent in women , half of the published cases are men. Endocrinopathy can be diagnosed before serositis, coincidental, or later; as in the present case, among the reported cases, the most common presentation is the sinchronic diagnosis of adrenal crisis together with acute pericarditis. Pericardial involvement has been found more common than pleural[5-10].

CONCLUSION

The presence of recurrent pericarditis of unknown cause should make us consider APS 2 in the differential diagnosis. In addition, we must be aware of the clinical manifestations suggestive of polyserositis in patients with APS 2. Effusive-constrictive pericarditis in the setting of autoimmune diseases and endocrine dysregulation can produce profound hemodynamic instability and cardiac tamponade. In fact, early recognition can prevent cardiac tamponade and be life-saving.

Table 1. Published cases of serositis and autoimmune polyglandular syndrome type 2

	Medical History	Clinical presentation	Physical exploration	Blood tests	Positive antibodies at diagnosis	Complications
Torfoss et al. [5], 1997, Case 1	Man, 42 years. No relevant pain medical history.	Pleuritic chest pain	Hyperpigmentation, hypotension	MSC <1µg/dl, hypertransa minasemia	TPO, AA	Recurrent pericarditis with tapering corticosteroids therapy
Torfoss et al. [5], 1997, Case 2	Man 36 years. No relevant medical history.	Pleuritic chest pain	Man 36 years. No relevant medical history.	MSC <1 µg/dl	TPO, AA	Cardiac tamponade and pericarditis
Fernández et al. [6], 2006, Case 1	Man 43 years. Graves disease	Chest pain and dyspnea	Hyperpigmentation, hypotension	MSC <1 µg/dl	AA	2 pericarditis
Alkaabi et al. [7], 2008, Case 1	Woman, 34 years. Autoinmune hypothyroidism	Chest pain and dyspnea	Hyperpigmentation, hypotension	MSC <1 µg/dl	TPO y AA	7 pericarditis
Alkaabi et al. [7], 1997, Case 2	Woman, 35 years. Autoinmune hypothyroidism	Dyspnea	Hyperpigmentation, hypotension	MSC 2 µg/dl	TPO, TGA, EA	2 hospitalizations for pleural effusion, celiac disease
Alkaabi et al. [7], 1997, Case 3	Man, 58 y.ears No relevant medical history.	Chest pain and dyspnea	Hyperpigmentation	MSC <1µg/dl	TPO	Autoinmune Hypogonadism, 1 pleuritis, 5 pericarditis
Palmer et al. [8], 2014, Case 1	Man 54 years. APS 2 (stop Prednisone 6 months before)	Chest pain	Hyperpigmentation, hypotension, weak peripheral pulses	MSC <1 µg/dl	No	Recurrent pericarditis in the same admission
Khalid et al [9], 2015, Case 1	Woman 48 years. APS 2.	Pleuritic chest pain and dyspnea	Hypotension, tachycardia	-	-	Cardiac tamponade and adrenal crisis
Mcnamara et al [10], 2017, Case 1	Man 29 years. Hypothyroidism	Chest pain	Hypotension, tachycardia	MSC <1 µg/dl	TPO y AA	Cardiac tamponade and pericarditis
Current case	Woman 44 years. No relevant medical history.	Chest pain and dyspnea	Hyperpigmentation, fever, vomiting	MSC 2 µg/dl	TPO, AA, TgAB	5 pericarditis, adrenal crisis

MSC: Morning Serum Cortisol. TPO: anti-thyroid peroxidase antibodies; TgAB: antithyroglobulin antibodies; AA: anti-adrenal antibodies; TGA: Anti-tissue transglutaminase antibodies; EA: antibodies against endomysium

LIST OF ABBREVIATIONS

APS 2: autoimmune polyglandular syndrome type 2
AD: Addison disease
AITD: Autoinmune thyroid disease
T1DM: Type 1 Diabetes mellitus
MSC: Morning serum cortisol.
TPO: anti-thyroid peroxidase antibodies;
TgAB: antithyroglobulin antibodies;
AA: anti-adrenal antibodies;
TGA: Anti-tissue transglutaminase antibodies;
EA: antibodies against endomysium

CONFLICT OF INTEREST

None

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ETHICAL APPROVAL

Ethical approval is not required at our institution for publishing a case report in a medical journal.

CONSENT FOR PUBLICATION

Informed consent was obtained from the patients to publish this case.

REFERENCES

1. Frommer L, Kahaly GJ. Autoimmune polyendocrinopathy. J Clin Endocrinol Metab. 2019; 104, 4769–4782
2. Schneller C, Finkel L, Wise M, Hageman JR, Littlejohn E. Autoimmune polyendocrine syndrome: a case-based review. Pediatr Ann. 2013; 42(5):203–208
3. Pham-Dobor, G., Hanák, L., Hegyi, P., Márta K., Párniczky A.,Gergics M., et al. Prevalence of other autoimmune diseases in polyglandular autoimmune syndromes type II and III. J Endocrinol Invest. 2020; 43, 1–9
4. Hansen MP, Matheis N, Kahaly GJ. Type 1 diabetes and polyglandular autoimmune syndrome: a review. World J Diabetes. 2015; 6(1):67–79
5. Torfoss D, Lippe E, Jacobsen D. Cardiac tamponade preceding adrenal insufficiency - an unusual presentation of Addisons's disease: a report of two cases. J Intern Med. 2007;241(6):525-528
6. Fernández Fernández F, de la Fuente Aguado J, Pérez Fernández S, Hervás Abad E, Páramo Fernández C. Serositis recidivante como manifestación de síndrome poliglandular autoinmune tipo 2. Rev Clin Esp. 2006;206(8):410
7. Alkaabi J, Chik C, Lewanczuk R. Pericarditis with Cardiac Tamponade and Addisonian Crisis as the Presenting Features of Autoimmune Polyglandular Syndrome type II: a Case Series. Endocr Pract. 2008;14(4):474-478
8. Palmer W, Kurklinsky A, Lane G, Ussavarungsi K, Blackshear J. Cardiac tamponade due to low-volume effusive constrictive pericarditis in a patient with uncontrolled type II autoimmune polyglandular syndrome. Acute Card Care. 2014;16(1):23-2
9. Khalid N, Chhabra L, Ahmad S, Umer A, Spodick D. Autoimmune Polyglandular Syndrome Type 2 Complicated by Acute Adrenal Crisis and Pericardial Tamponade in the Setting of Normal Thyroid Function. Methodist Debakey Cardiovasc J. 2015;11(4):250-252
10. McNamara D, Yamamoto H, Sarode V, Zaha V. Effusive Constrictive Pericarditis in Autoimmune Polyglandular Syndrome Type II. Am J Med. 2017;130(5):e213-e21

Non-HIV Associated Kaposi's Sarcoma: A case report

Sarcoma de Kaposi no asociado a VIH: un caso clínico

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ABSTRACT

Kaposi sarcoma (KS), first described in 1872, is an angioproliferative neoplasm that often presents with red-purple macules in the skin. This report is of a case of classic/iatrogenic form of KS in a 79-year-old male, that had a prolonged hospitalization due to surgical complications. After discharge, he presented a red-purple macule. A biopsy was made and KS was confirmed. He was HIV negative. The patient did not require any other treatment asides from the total removal of the lesion. Kaposi's sarcoma is an uncommon disease, still very associated with HIV. This case demonstrates the importance of recognition of KS in non-HIV patients. There are four types of Kaposi's sarcoma and the importance of its recognition in non-HIV patients.

Keywords: Kaposi sarcoma; HIV-negative; classic; macule; biopsy.

INTRODUCTION

Kaposi's sarcoma (KS) was first described by a Hungarian dermatologist, Moritz Kaposi, in 1872[1,2]. KS is an angioproliferative neoplasm that often presents with red-purple macules in the skin. There are four types of categories that these patients can be divided into Classic KS, epidemic KS, iatrogenic KS and endemic KS[3]. The classic KS is often associated with elderly men, normally with a Mediterranean and Eastern European heritage. The epidemic KS is related to HIV-positive patients. The endemic is also called de African endemic form and usually occurs in children and adults of sub-Saharan Africa[4]. Iatrogenic KS is seen in immunosuppressive drug therapy, including transplant patients. Since 1981 the majority of KS has been seen in HIV-positive patients[4], but with the evolution of medical therapies, like immunosuppression drugs, physicians must be mindful that this rare neoplasm can appear more often in non-HIV patients. The classic variant normally has an indolent course and presents with skin lesions that affect more often the lower limbs and feet (85-98%)[5]. We present a case of a 79-year-old man with a classic/iatrogenic KS.

CASE DESCRIPTION

We report the case of a 79-year-old man, that was referred to an Internal Medicine consult by his surgeon, for treatment of oesophagal candidiasis. The patient had a medical history of partial gastrectomy over 25 years. He wasn't medicated for any other conditions. When asked, he admitted that he had extra-conjugal relations until 1999, when he was abroad in France and Mozambique. Four months before the consult, the patient was submitted to a laparoscopy cholecystectomy that was complicated by a sub-hepatic and peri-hepatic hemoperitoneum. He had a prolonged hospitalization and received multiple courses of antibiotics. A month after being discharged, he went to his surgeon complaining of odynophagia. At the time, he was submitted to an upper digestive endoscopy that showed white mucosal plaques adherent to the mucosa of the oesophagus. A biopsy was performed and confirmed the diagnosis of candidiasis. Around this time, the patient was already being followed in the Internal Medicine consult and was medicated with fluconazole 400 mg per day for 14 days. At the physical examination, he mentioned a small purple macula in his right knee. There were no lymphadenopathies or other changes in the physical exam.

A biopsy of the knee lesion was made and confirmed the diagnosis of Kaposi's sarcoma. The neoplasm was fully removed at the time of the biopsy. For the investigation of Kaposi's sarcoma and oesophagal candidiasis, an HIV test was ordered and came back negative. Considering these clinical features another test was made, at the same time other entities that could cause an immunosuppression state were sought.

The second serologic test for HIV also came negative. All other laboratory findings were in the normal range. The CD4 count was within the normal range with a CD4/CD8 ratio of 1.08. A pan-tomography was performed and showed no enlarged lymph nodes or other images suggestive of cancer. The patient underwent another upper and total colonoscopy, to obtain biopsies of the intestinal mucosa, looking specifically for Kaposi sarcoma. No signs of KS were found either through direct visualization or in the biopsies made. The oesophagal candidiasis was much better.

The patient didn't need any other treatment, apart from the removal of the single lesion of the KS.

At 3-month and 6-month follow up, no more skin lesions were noted. He remains asymptomatic up to today, with his scans and analytical studies within normal ranges.

DISCUSSION

Kaposi's sarcoma can be classified into four categories: classic, endemic, iatrogenic and AIDS-associated. Non-AIDS KS is considered a very rare disease[3]. The classic form is more frequent in an elderly male with Mediterranean heritage. A male-to-female ratio of 15:1 has been reported[3].

KS classically presents with red-purple macules in the skin, which affects more the lower limbs with the classic form and rarely presents a visceral involvement[2]. The iatrogenic form presentation is very similar to the classic form[8]. The definitive diagnosis is made with a skin biopsy and histopathology.

The course of the classic form is indolent[3,6] and has a good prognosis with no significant impact on the survival rate. In case of recurrence, local cryotherapy usually resolves the isolated lesions.

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Other therapies are available, when the KS manifest with multiple lesions, like intralesional chemotherapy with vincristine[7].

The iatrogenic form normally resolves when the immunosuppressive medications are stopped or decreased. In this case, these risks/benefits have to be balanced.

Management of KS depends on primary aetiology. Nowadays with active antiretroviral therapy (HAART), HIV patients have decrease rates of KS[6].

In our case, the patient had two simultaneous diseases that are often considered opportunistic. Extensive etiologic exams were performed, including two HIV tests and CD-cell count. The patient remained asymptomatic and didn't need any other treatment, apart from the anti-fungic and the removal of the KS. The local recurrence is rare after a complete excision[2].

Considering that the patient had a long-term hospitalization due to surgical complications with multiple courses of antibiotics, this was considered to be the cause for his immunocompromised state and the cause for both esophagi candidiasis and KS. He also fitted the classic form, according to age, heritage and site of the lesion.

Kaposi's sarcoma is an uncommon disease, still very associated with HIV. It is a very important differential diagnosis in skin lesions of HIV patients. With this case, we reinforced the idea, that there are four types of KS and the importance of its recognition in non-HIV patients. The skin biopsy is very important for the diagnosis and accurate treatment.

CONFLICT OF INTEREST

The authors declare that there is no potential conflict of interest relevant to this article.

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AUTHORS' CONTRIBUTION

Costa, Raquel and Mendes, Tiago wrote de paper; Fontes, Joana, Sousa, Barbara and Silva, Joana reviewed the paper.

ETHICAL ASPECTS

All participants submitted a consent form to be included in this study.

REFERENCES

1. Florek AG, Eilers D, Armstrong AW. A Case of Kaposi sarcoma in an immunocompetent, heterosexual Irish man: a discussion of etiology and viral transmission. Dermatol. Online J. 2015;21 (10).
2. Seleit I, Attia A, Maraee A, Samake R, Bakry O, Eid E. Isolated Kaposi Sarcoma in two HIV negative patients. Journal of Dermatological Case Reports. 2011;5(2):24-6
3. Jakob L, Metzler G, Chen K-M, Garbe C (2011): Non-AIDS Associat ed Kaposi's Sarcoma: Clinical Features and Treatment Outcomes. PLoS ONE. 2011; 6(4): e18397
4. Gupta K, Tun A, Gupta A, Berkowitz L, Anwar R, Liu Y, Guevara E. A case of classic Kaposi Sarcoma in an immunocompetent human immunodeficiency virus-negative Dominica man. SAGE Open Medical Case Reports. Volume 8: 1-4
5. Mohanna S, Ferrufino JC, Sanchez J, Bravo F, Gotuzzo E. Epidemiological and clinical characteristics of Classic Kaposi's sarcoma in Peru. J. AM. Acad. Dermatol. 2005;53(3):435-41.
6. Curtiss P, Strazzulla LC, Kien AE. An update on Kaposi's sarcoma: epidemiology, pathogenies and treatment. Dermatol Ther 2016; 6(4): 465-470.
7. Bramdilla L, et al. Intralesional vincristine as first-line therapy for nodular lesions in classic Kaposi sarcoma: a prospective study in 151 patients. Br J Dermatol. 2010; 162(4):854-9
8. Wang J, Reid H, Klimas N, Koshelev M. Na unususal series of pat ients with Kapo -si sarcoma. JAAD Case Reports. 2019;5:646-9.

Hepatojugular reflux at the bedside

Reflujo Hepatoyugular a pie de cama

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ABSTRACT

Keywords: HIV infection; pulmonary hypertension; heart failure

CASE REPORT

A 65-year-old and smoker man with HIV infection on virological suppression under antiretroviral therapy (ART) and severe chronic obstructive pulmonary disease, was admitted to the hospital due to orthopnea, as well as paroxysmal nocturnal dyspnea episodes, since one week before.

A physical examination revealed normal heart sounds without murmurs and crackles in the lower lung lobes. There was no pedal edema. Venous pressure was normal, as determined by observing the vertical height of jugular venous column. When applying firm and sustained pressure over the upper right abdomen while the patient was breathing quietly, jugular venous pressure increased transiently (hepatojugular reflux, as showed in video). Echocardiogram disclosed severe pulmonary hypertension (> 60 mmHg), right cavities dilatation and right ventricular dysfunction. *Cor pulmonale*, that is, pulmonary hypertension and right-sided heart failure, was diagnosed.

Treatment with loop diuretics was initiated. Aldosterone antagonist diuretics were added as blockers of renin-angiotensin-aldosterone axis. The patient´s condition and functional performance improved.

DISCUSSION

Heart failure in persons living with HIV receiving ART and achieving virological suppression is increasing with improved survival. The most frequent underlying causes are coronary artery disease and left ventricular hypertrophy[1]. However, pulmonary hypertension due to obstructive lung disease appears as a quite common cause of chronic right-sided heart failure in long-term smokers[2].

EXTERNAL VIDEO FILE

https://vimeo.com/735391610

CONFLICT OF INTEREST

The authors declare no relevant conflicts of interest to the content of the manuscript.

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ETHICAL ASPECTS

The patient provided written consent for publication of his audiovisual material.

REFERENCES

1. Hsue PY, Waters DD. Heart failure in persons living with HIV infection. Curr Opin HIV AIDS. 2017;12(6):534-539.
2. Basyal B, Jarrett H, Barnett C. Pulmonary Hypertension in HIV. Can J Cardiol. 2019;35(3):288-298.

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Oral Kaposi Sarcoma

Sarcoma de Kaposi oral

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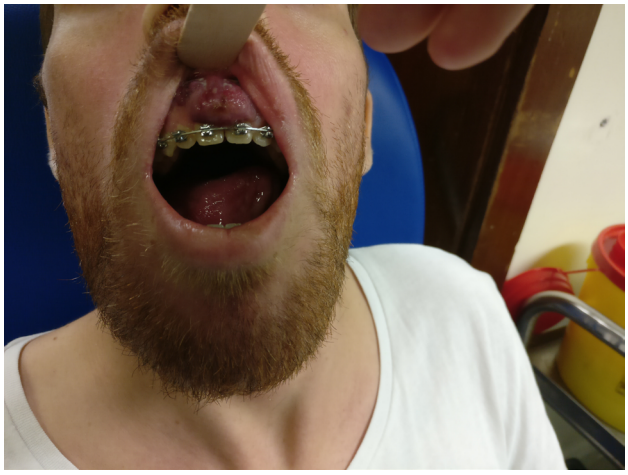
CASE REPORT

A 28-year-old autonomous male presented with asthenia and a painless lesion in the upper labial frenulum region, with progressive growth for 3 months. In the last 5 days he also developed high fever. He revealed one unprotected heterosexual anal contact a year ago. No relevant past medical history or usual medication was found.

Physical examination revealed a temperature of 40.5°C, a sessile swelling of about 2cm in the superior alveolar arch and ecchymotic infiltration of the remaining alveolar arch, and bilaterally palpable cervical adenomegaly of area II, with reactive features. Labs showed anemia, lymphopenia, thrombocytopenia, positive HIV test, CD4+ count of 11, viral load 799363 units. A diagnosis of HIV disease in AIDS stage was made. Lesion biopsy confirmed Kaposi's Sarcoma (KS). He started antiretroviral therapy with Darunavir, Cobicistat, Tenofovir Alafenamide and Emtricitabine, as well as doxorubicin, with an undetectable viral load and with only a residual lesion on superior alveolar arch 6 months later.

KS is a widely known vascular tumor etiologically associated with human herpesvirus 8[(1)]. There are four variants, being AIDS-related KS the most common tumor arising in HIV-infected persons. It is most common in homosexual or bisexual men, unlike our patient[(2)]. Extracutaneous disease is rare at presentation and biopsy is mandatory for diagnosis[(3)]. Oral cavity involvement occurs in up to 35% of patients[(1)]. For patients with symptomatic visceral involvement, it is indicated systemic chemotherapy in combination with highly active antiretroviral therapy[(1)].

Figure 1.



CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this work.

SOURCE OF FUNDING

This research had no funding sources.

ETHICAL ASPECTS

All participants submitted a consent form to be included in this study.

REFERENCES

1. Facciolà A, Venanzi Rullo E, Ceccarelli M, D'Aleo F, Di Rosa M, Pinzone MR, Condorelli F, Visalli G, Picerno I, Fisichella R, Nunnari G, Pellicanò GF. Kaposi's sarcoma in HIV-infected patients in the era of new antiretrovirals. Eur Rev Med Pharmacol Sci. 2017;21(24):5868-5869.
2. Nichols CM, Flaitz CM, Hicks MJ. Treating Kaposi's lesions in the HIV-infected patient. J Am Dent Assoc. 1993;124(11):78-84.
3. Beral V, Peterman TA, Berkelman RL, Jaffe HW. Kaposi's sarcoma among persons with AIDS: a sexually transmitted infection? Lancet. 1990;335(8682):123-8.

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Addison's Disease In Schmidt Syndrome

Enfermedad de Addison en el Síndrome de Schmidt

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ABSTRACT

Autoimmune polyglandular syndromes are rare conditions distinguished by the coexistence of at least two autoimmune glandular diseases. Autoimmune polyendocrine syndrome type II, also known as Schmidt syndrome is characterized by Addison's disease, autoimmune thyroid disease, or type 1 diabetes mellitus that can be associated with other autoimmune disorders. We present the case of 26 year-old male that was admitted by asthenia and palpitations and who had a new hyperpigmentation on his lips and forehead.

Keywords: Addison's disease; Hyperpigmentation; Hyperkalemia; Hyponatremia; Polyglandular autoimmune syndrome.

CASE REPORT

26 year-old male was admitted by asthenia and palpitations. The young man had a past history of type 1 diabetes mellitus at age 12 and celiac disease at 16. He had a new hyperpigmentation on his lips (Figure 1) and forehead (Figure 2). Blood workup revealed hyperkalemia and hyponatremia. Additional tests revealed: decrease secretion of cortisol and aldosterone, and an increase in rennin. 21-hydroxylase antibody was negative. He started fludrocortisone 0,1mg/day[1], considering the hypothesis of Addison's disease. Autoimmune polyendocrine syndrome type II, also known as Schmidt syndrome [2], is a rare autoimmune disorder in which there is a steep decrease in production of several essential hormones. This syndrome occurs in adults with a peak incidence at age 30 in females and it consists of Addison's disease[3], autoimmune thyroid disease and type 1 diabetes[3,4]. Addisons disease is a rare endocrine condition related to adrenal insufficiency. When first described, this disorder was thought to manifest by adrenal (Addison's disease) and thyroid insufficiency (Hashimoto's thyroiditis) alone. However, as more patients were studied, the scope of the syndrome was expanded to include other autoimmunes disorders.

Figure 1.

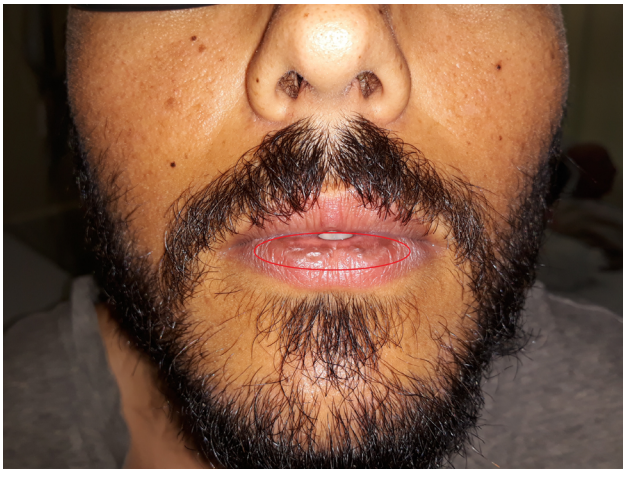
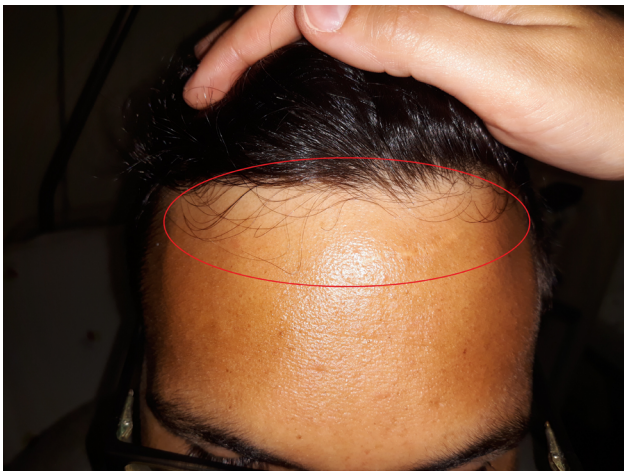


Figure 2.



CONFLICT OF INTEREST

The authors declare that there is no conflict of interest in this work.

SOURCE OF FUNDING

This research had no funding sources.

ETHICAL ASPECTS

All participants submitted a consent form to be included in this study.

REFERENCES

1. Choudhury S, Meeran K. Glucocorticoid replacement in Addison disease. Nat Rev Endocrinol. 2018; 14:562-5
2. Bain A, Stewart M, Mwamure P, et al. Addison's disease in a patient with hypothyroidism: autoimmune polyglandular syndrome type 2. BMJ Case Rep. 2015
3. Kirkgoz T, Guran T. Primary adrenal insufficiency in children: Diagnosis and management. Best Pract Res Clin Endocrinol Metab. 2018; 32:397-424
4. Kahaly GJ, Förster G, Otto E, Hansen C, Schulz G. Type 1 diabetes as part of the polyglandular autoimmune syndrome. In German. Diabetes Stoffwechsel. 1997; (6):19–27.

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La frambuesa insular del cerebro

The insular raspberry of the brain

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RESUMEN

La patogenia de las mal formaciones vasculares (MAV) cerebrales aun no está totalmente definida. La mayoría son congénitas y esporádicas. Su tamaño varía ampliamente y algunas experimentan crecimiento, remodelación o regresión con el tiempo. La cirugía de cavernomas solo está indicada cuando existen síntomas y signos de sangrado. La escisión radical tiene como objetivo eliminar el riesgo de sangrado adicional y, finalmente, eliminar el efecto de masa. En cuanto al pronóstico, depende principalmente de la ubicación de la lesión.

Keywords: Cavernoma; Malformación vascular; Neurocirurgía; Parestesias

IMÁGENES MÉDICAS

Los carvernomas son malformaciones vasculares del sistema nervioso central, consideradas benignas, que representan alrededor del 5% al 13%[1] de todas las malformaciones vasculares en el SNC (sistema nervioso central). La mayoría se localizan en la región supratentorial y son lesiones circunscritas que varían en tamaño: desde milímetros hasta centímetros. La clínica no es específica[2], existe una correlación entre su tamaño y los síntomas. Los síntomas se deben al efecto de masa[3].

Los autores presentan el caso de un paciente de 37 años que acude al servicio de urgencias por parestesias en miembro superior derecho y cefalea sin aura, con una evolución desde hace 4 años. El paciente no tenía antecedentes de relevancia, ni ninguna otra clínica acompañante. Al ingreso, estaba en una escala de Glasgow 15, fuerza muscular 4/5 y disminución de la motricidad fina. No hay más cambios en el examen neurológico y objetivo restante. Se realizó tomografía craneal (TC) sin contraste: "se observa una lesión neoestriatal-insular izquierda intraaxial expansiva, espontáneamente hiperdensa, sin edema asociado y con efecto masa proporcional a su volumen". En la resonancia magnética nuclear (RMN) "se observa una lesión intraaxial centrada en la región lentículo-insular de la izquierda, dimensiones 44x28x46mm compatible con un cavernoma gigante con signos de sangrado reciente, con efecto masa con moldeado ventricular y desviación de la línea media" Figura 1 y 2 . El paciente fue sometido a craneotomía, con posterior inicio de rehabilitación física.

Figure 1. Left upper limb lesion, with suture dehiscence and active hemorrhage.

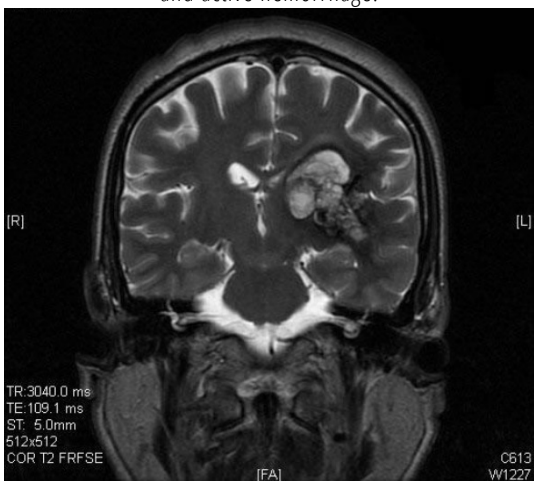
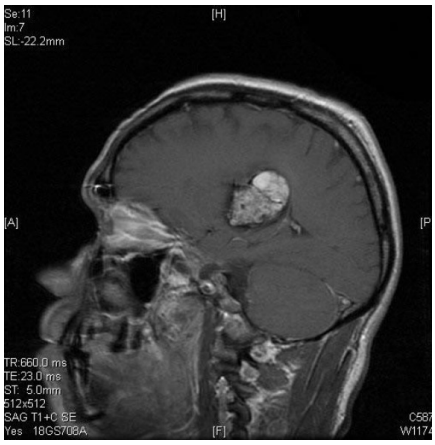


Figure 2.



CONFLICTOS DE INTERÉS

Los autores declaran no tener conflictos de interés.

FINANCIACIÓN

Esta investigación no ha precisado financiación externa.

ASPECTOS ÉTICOS

El paciente firmó un consentimiento informado consintiendo la publicación del caso clínico.

BIBLIOGRAFÍA

1. Scimone C, Donato L, Marino S, et al. Vis-à-vis: a focus on genetic features of cerebral cavernous malformations and brain arteriovenous malformations pathogenesis. Neurol Sci. 2019; 40:243.
2. Pabaney AH, Rammo RA, Tahir RA, Seyfried D. Development of De Novo Arteriovenous Malformation Following Ischemic Stroke: Case Report and Review of Current Literature. World Neurosurg. 2016; 96:608.e5.
3. Flemming KD, Lanzino G. Management of Unruptured Intracranial Aneurysms and Cerebrovascular Malformations. Continuum (Minneap Minn). 2017; 23:181.

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Gastrointestinal Kaposi's sarcoma without cutaneous involvement

Sarcoma de Kaposi gastrointestinal sin lesiones cutáneas

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2. Internal Medicine Assistant, Hospital Beatriz Ângelo

CASE REPORT

Kaposi's sarcoma (KS) is a low-grade tumor of the vascular endothelium that affects skin, vasculature, lymphatics, and viscera. It can be classified into four types, organized by the clinical context in which it develops: classic, endemic, iatrogenic, and AIDS associated

A 56-year-old healthy caucasian woman was admitted to investigate a history of several months of weight loss and anorexia. She had anemia and thrombocytopenia without other analytic alterations. A diagnosis of acquired immunodeficiency syndrome (AIDS) was made (CD4+ lymphocytes 8cells/mm3; RNA VIH1 102000 copies/ml). Oral candidiasis was objectivated although she was asymptomatic, so she went under an upper gastrointestinal endoscopy. It demonstrated lesions positive for CD31 and human herpesvirus 8, consistent with Kaposi's Sarcoma (Images 1 and 2). She didn't have any cutaneous lesions. She started highly active antiretroviral therapy (HAART) with slow regression of the lesions. The most common type of Kaposi's sarcoma is AIDS associated, and in the last years has decreased since the introduction of highly active antiretroviral therapy (HAART), being currently 6 per million. Despite that, it remains the most common malignancy among patients with AIDS. Visceral involvement of AIDS-related KS is frequent (50-70% of patients), but the existence of isolated visceral involvement is rare. There is a worst prognosis when there is visceral involvement.

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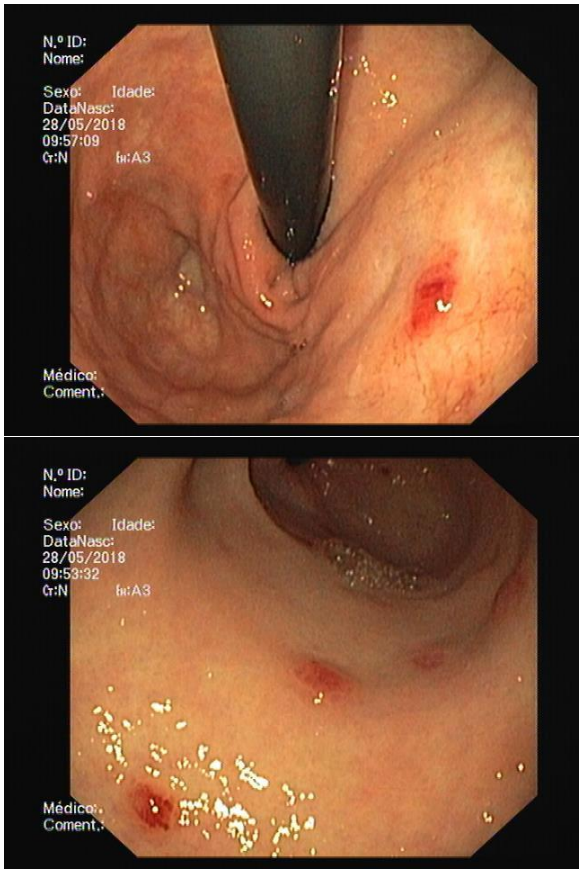

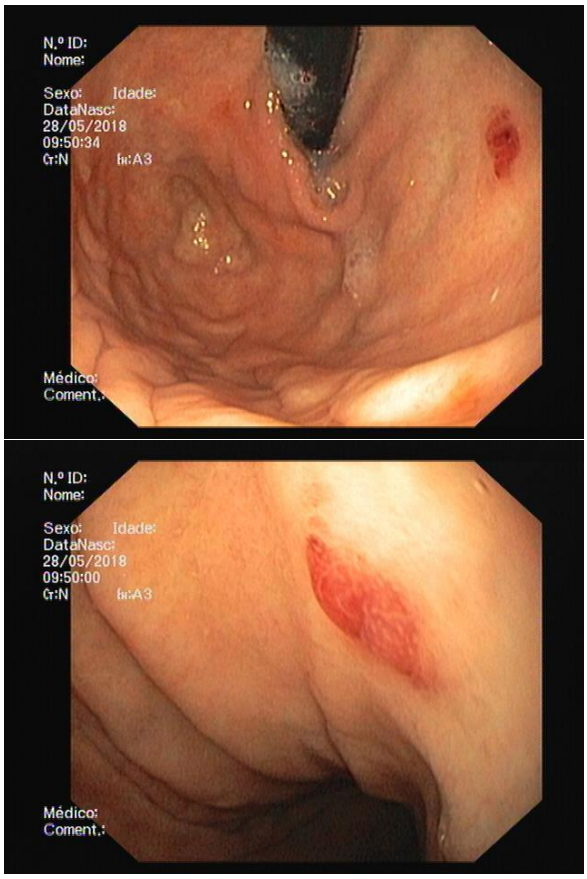

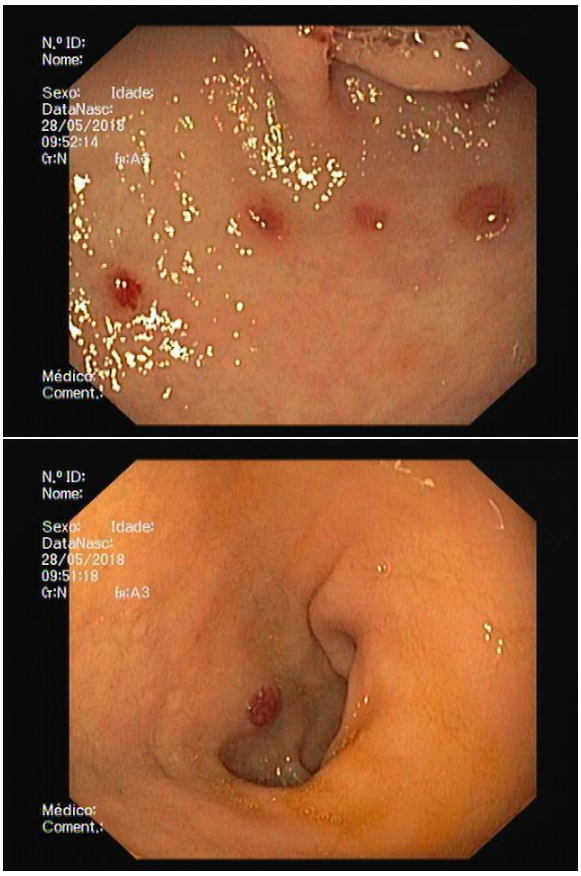

CONFLICT OF INTEREST

None.

FUNDING

None.

ETHICAL APPROVAL

Ethical approval is not required at our institution for publishing a case report in a medical journal.

CONSENT FOR PUBLICATION

Informed consent was obtained from the patients to publish this case.

BIBLIOGRAFÍA

1. Alluhaybi AF, Hatatah NM. HIV-Associated Cutaneous Kaposi's Sarcoma. Cureus. 2021;13(2): e13544.
2. Mocroft A, Kirk O, Clumeck N, Gargalianos-Kakolyris P, Trocha H, Chentsova N, et al. The changing pattern of Kaposi sarcoma in patients with HIV, 1994–2003: the EuroSIDA Study. Cancer. 2004;100(12):2644-54.
3. Radu O, Pantanowitz L. Kaposi sarcoma. Arch Pathol Lab Med. 2013;137(2):289-94.

Síndrome de titono o el problema la inmortalidad

Tithonos Syndrome or the problem of immortality

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Señor director:

Skolnik[1] describió por primera en 2016 vez en JAMA el síndrome de Tithonus o Titono, que hace referencia a la situación que se da cuando los familiares demandan mantener con vida y medios desproporcionados a su ser querido, en situación clínica ya muy deteriorada e irreversible, y que surge como fruto de su cariño, dependencia afectiva y quizás por algo de egoísmo.

En la mitología griega, Eos o Aurora, diosa del amanecer e hija de Zeus, se enamoró de Tithonus o Titono y quiso casarse con él. Sin embargo, Titono era un hombre, y como tal mortal. Aurora pidió a Zeus, su padre y rey de los dioses, que hiciera a Titono inmortal como ella, cosa que Zeus hizo. Por desgracia, Aurora no pidió que no envejeciera y, como consecuencia de ello, Titono no pudo morir[2]. Finalmente, envejecido e incapaz de moverse, Titono terminó convirtiéndose en un grillo, reclamando una muerte que nunca le llegó.

El aumento de la esperanza de vida, así como la mejora de los recursos sanitarios, han llevado a una población cada vez más envejecida, lo cual se refleja en los hospitales donde se ven con mayor frecuencia ancianos con deterioro cognitivo en la fase final de su enfermedad. Recientemente hemos asistido a pacientes nonagenarios con afectación grave de sus funciones cognitivas e ingresos repetidos por infecciones o por dificultad para su alimentación por vía oral, que recibían cuidados minuciosos por parte de sus familiares en sus domicilios. Durante las hospitalizaciones los familiares exigían mantener los cuidados, excesivos para su situación clínica de acuerdo con nuestros criterios médicos, reclamando instaurar o mantener sueroterapias, alimentación artificial, antibióticos y rechazando desprescripciones.

Este deseo de los familiares de preservar a cualquier precio la vida de los pacientes, condena a sus seres queridos a prolongadas agonías con cuidados desproporcionados y se podría encuadrar dentro de lo que se ha denominado un síndrome de Titono. Además, crea conflictos y deteriora la relación con la familia.

Como médicos, sabemos que estamos obligados a preservar la vida de todos los pacientes, y que limitar el esfuerzo terapéutico no significa tratarlos peor[5]. En estas situaciones que podemos denominar como síndrome de Titono, el criterio médico choca con las expectativas de los familiares que encuentran en nuestros planteamientos médicos de "no hacer", un abandono del cuidado de su ser querido. Gruenberg[4] ya hacia referencia a "el fracaso del éxito", en el que alentados por servir a nuestro fin último de preservar y prolongar la vida, condenamos a nuestros pacientes a una elevada morbilidad, enfermedades crónicas e ingresos repetidos.

Pese a que creemos que el Síndrome de Titono no es algo excepcional, no hemos encontrado publicaciones sobre él en nuestro país. Para su diagnóstico no disponemos de criterios diagnósticos y tampoco sabemos como manejarlo. Otro aspecto que debería plantearse es si debería reflejarse en los informes clínicos como diagnóstico.

Recordando a Miller[3], los médicos nos encontramos a menudo con Titono, teniendo ante él poderes similares a los de Zeus para determinar su destino y condenarle a la búsqueda de la inmortalidad tras un camino de penurias y sufrimiento. Quizá haya llegado el momento, de identificar a Titono, y por fin dejarle morir y darle el descanso que merece.

CONFLICTO DE INTERESES

Ninguno

FINANCIACIÓN

Ninguna

CONSIDERACIONES ÉTICAS

Ninguna

BIBLIOGRAFÍA

1. Skolnik N. Tithonus Syndrome. JAMA Intern Med. 2016;176(9):1247. doi: 10.1001/jamainternmed.2016.3079.
2. Young P, Demuria M, C Finn B, Bruetman JE. Síndrome de Titono [Tithonus syndrome]. Rev Med Chil. 2017;145(9):1222-1223.
3. Miller WT. Tithonus. Semin Roentgenol. 1994;29(4):317.
4. Gruenberg EM. The failures of success. Milbank Mem Fund Q Health Soc. 1977 Winter;55(1):3-24.
5. Al-Rawi Y. When Tithonus met corona: the COVID-19 pandemic and acute illness in the elderly. BMJ Support Palliat Care. 2020;10(4):372-373.

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En el número de Galicia Clínica de Abril-Mayo-Junio 2022 Volumen 83 (2), en la sesión de Comunicaciones orales aparecen tres "fe de erratas" que se detallan a continuación:

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