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# Hiperparatireoidismo primário na gravidez tratado com bisfosfonatos

## *Primary hyperparathyroidism in pregnancy treated with bisphosphonates*

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### Introduction

The diagnosis of primary hyperparathyroidism (PHPT) is made when hypercalcemia and elevated parathormone (PTH) levels are present and most of cases are due to single parathyroid adenomas<sup>1</sup>.

It is the third most common endocrine disorder after diabetes mellitus and thyroid disease, but is much less common during pregnancy<sup>2,3</sup>.

PHPT mainly affects women in older age groups, with only 5–10% of cases diagnosed in women of reproductive age. In the general population, the prevalence is about 0.1–0.4% but in pregnant women the precise incidence is unknown<sup>4</sup>.

Maternal and fetal complications of moderate/severe PHPT during pregnancy are recognized (around 67% and 89% respectively) but the diagnosis may be missed, misleading or masked by physiological changes and overlapping clinical symptoms associated to this period of life<sup>1</sup>.

Recent studies show that PHPT during pregnancy with serum calcium levels only mildly elevated is generally not associated with an increased risk of obstetrical and fetal complications<sup>2,3</sup>. It is now recognized that PHPT has a large spectrum presentation and it is highly expected that severe symptomatic disease has different maternal and fetal effects compared with mild disease<sup>3</sup>. For that reason, the distinction between mild disease, which may be observed, and the clinically significant one, which should be treated, is crucial.

The surgical treatment is recommended mostly in second trimester<sup>1</sup> but there are no guidelines indicating the exact medical treatment when the surgical approach is not possible. We describe a case of PHPT during pregnancy treated with furosemide and pamidronate.

**Palabras clave:** Hipercalcemia. Embarazo. Bisfosfonatos. Pamidronato. Hiperparatireoidismo primario.

**Keywords:** Hypercalcemia. Pregnancy. Bisphosphonates. Pamidronate. Primary hyperparathyroidism

### Case presentation

A 31-year-old Caucasian woman with a history of renal lithiasis since she was 18 years old was referred to an endocrine consultation. She presented with high PTH 171.4 pg/mL (15.0–65.0), hypercalcemia 11.3 mg/dL (8.8–10.2), hypophosphatemia 1.9 mg/dL (2.7–4.5) and normal vitamin D levels. The cervical ultrasound did not show parathyroid localization.

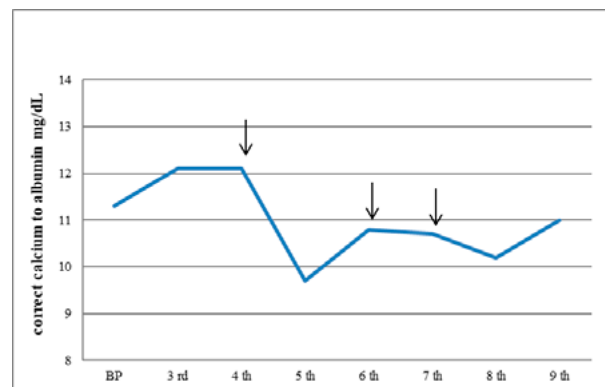
Bone densitometry and Tc99m-sestamibi scintigraphy were requested. Unexpectedly the patient did not perform these exams

because she had unintentionally become pregnant (gestation of 12 weeks). A diet with calcium restriction and strict oral hydration was instituted but, despite that, the patient experienced worsening of nausea and vomiting, with marked hypercalcemia (correct calcium to albumin 12.1 mg/dL). She started furosemide 20 mg/day at 15 weeks of gestation to a maximum dose of 120 mg/day.

A cervical ultrasound was repeated but, for the second time, no parathyroid gland was identified. Exploratory surgery was proposed in her second trimester of pregnancy, but she refused and postponed it to the postpartum period. Options for medical management were therefore explored.

Despite the measures described above, serum calcium levels remained elevated and symptoms became worse. Treatment with a bisphosphonate was decided and the patient underwent the first treatment with pamidronate 60 mg IV at 21 weeks of gestation. At that time the calculated calcium for albumin was 12.3 mg/dL. After the first infusion of pamidronate, there was a subsequent decline of the calcium concentration levels. However, due to clinical and analytical exacerbation, she repeated pamidronate infusion at 25 and 30 weeks of gestation, with a decline of serum calcium between doses (Fig 1).

Figure 1. Calcium levels during pregnancy, arrows – pamidronate treatments



Legend: arrows: pamidronate treatments; BP: before pregnancy, numbers: Pregnancy month

Prior to the administration of the drug the side effects in the short term and the lack of knowledge of long-term side effects were explained to the patient and she signed a written consent to this therapy.

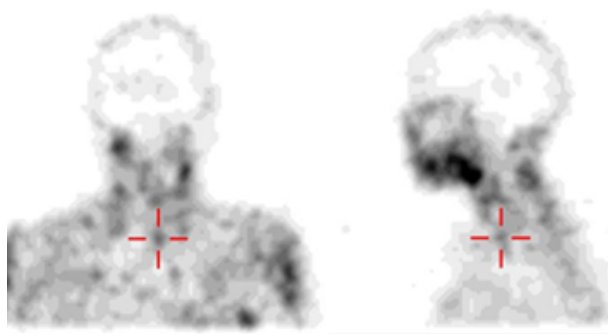
Fetal ultrasound examination was normal, and biometry showed normal fetal development.

The delivery was anticipated due to clinical manifestations, mainly the persistent nausea and vomiting. An elective caesarean delivery was performed at 37 weeks of gestation without complications. A female of 2800g was born, with Apgar 9/10 and no episodes of hypocalcemia in the neonatal period.

The sestamibi scintigraphy performed in postpartum period showed a hyperfixation focus inferiorly to the left lobe of the thyroid gland (Fig 2). The patient was submitted to a left inferior radioguided parathyroidectomy with intraoperative PTH evaluation that enabled the correct identification and removal of the enlarged gland with consequent normalization of PTH and hypercalcemia. The pathological exam confirmed a 15x5 mm parathyroid adenoma.

The child, now a two years old girl, is healthy, and has normal motor, cognitive and psychosocial development.

Figure 2. Sestamibi scintigraphy



## Discussion

### Maternal-fetal complications

In the final weeks of gestation, the foetus needs 25 to 30 g of calcium for bone mineralization<sup>5</sup>. In order to meet those fetal needs, intestinal calcium absorption doubles under mediation by calcitriol, prolactin, and placental lactogen<sup>6</sup>. This calcium is actively transported across the placenta resulting in suppression of fetal PTH secretion until after delivery. In maternal PHPT, this gradient is further elevated, resulting in a state of fetal PTH suppression and in a potential hypocalcaemic state and tetany in the new-born due to parathyroid hypoplasia<sup>7</sup>. Additional neonatal complications include neonatal hypoparathyroidism (manifested in only 12% of neonates), mental retardation and low birth weight<sup>2</sup>.

Reported maternal complications include hyperemesis, nephrolithiasis, muscular weakness, mental symptoms, skeletal pain, fatigue, pre-eclampsia, pancreatitis and hypercalcaemic crisis (reported for calcium levels >14 mg/dL)<sup>2,5</sup>.

It is reported that about 48% of pregnant women with untreated PHPT suffer miscarriages. Most of these cases occurred in the late first trimester or early second trimester and were related to the serum calcium levels. Miscarriage is more common as calcium levels exceed 11.4 mg/dl. Normal et al reported that 72% of all pregnancy losses occurred in women with serum calcium levels of 11.4 mg/dl or higher. Once the mean serum calcium levels exceed 12 mg/dl, a full term pregnancy is even more unlikely<sup>8</sup>.

Even though many pregnant women with PHPT reach a state of normocalcemia (explained by the specific physiology of pregnancy such as hemodilution, hypoalbuminemia and maternal hypercalciuria), our patient presented with a progressive increase in the calcium levels, with a maximum of 12.3 mg/dL despite the initial measures of hydration reinforcement and forced diuresis.

In addition to the risk of spontaneous abortion, pancreatitis and pre-eclampsia may also occur, even with lower calcium levels compared to those of our patient<sup>9</sup>.

Even with calcium levels superior to those associated with adverse maternal and fetal outcomes, treatment prevented further calcium elevations, therefore minimizing the risk of these complications.

### Location techniques

Sestamibi scintigraphy, the usual technique used for detecting parathyroid adenomas or diffuse parathyroid hyperplasia, is not recommended in pregnancy due to the risk of ionizing radiation for the foetus. Neck ultrasound is the first-line exam for locating abnormal parathyroid during pregnancy (sensitivity of 69%, specificity of 94%)<sup>1</sup>. In patients with calcium levels higher than 12 mg/dL, such as our case, it is unusual for imaging studies to be unsuccessful.

Magnetic resonance imaging (MRI) has relatively low sensitivity detecting normally located or ectopic parathyroid adenomas<sup>5</sup> and was not performed.

### Surgery

There are no current guidelines for the treatment of hyperparathyroidism in pregnancy. The options are either a conservative attitude or surgery. The approach selected depends on the presence and severity of symptoms, the gestational age and the patient's preference.

Mild PHPT with mild elevation in maternal calcium levels can be monitored, but clinically significant disease should be operated<sup>7,8</sup>.

The timing of surgical treatment of PHPT is a central finding. Since the majority of pregnancies are lost between weeks 10 and 15, it may be appropriate to operate early in the second trimester, especially in patients with calcium levels exceeding 11.4 mg/dL and in those with a previous history of pregnancy loss<sup>8</sup>.

Several studies have considered that surgery in the second trimester is safe for both mother and fetus but their results are based on a small number of patients<sup>3</sup>.

Another study reported that third trimester parathyroidectomy is much safer than previously assumed, with reported fetal complications as low as 5.9%. Consequently, a widening of the recommended window for surgery has been proposed<sup>10</sup>. Minimally invasive approaches have gained progressive acceptance over the past two decades as a safe and effective alternative technique, owing to the use of preoperative imaging either with neck ultrasound or sestamibi scintigraphy to suggest or mark, respectively, the position of the parathyroid glands. The negative imaging prior to the surgery is not an absolute contraindication for neck exploration surgery, even in pregnancy<sup>5</sup>.

Our patient chose to delay neck surgery to after the delivery. Options for medical management were therefore explored.

### Medical treatment

The efficacy and safety of medical management for PHPT in pregnancy are unknown. Hydration and calcitonin have emerged as safe treatments but are considered ineffective for long-term serum calcium control<sup>6</sup>. Intravenously or orally administered hydration (with or without forced diuresis) is the first line of treatment<sup>8</sup>. Furosemide crosses the placenta and adverse events have been observed in animal reproduction studies<sup>11</sup>. Calcitonin may cause prompt reduction in calcium levels when administered intravenously or intramuscularly, but it is not a viable option for prolonged treatment, since tachyphylaxis rapidly develops<sup>4</sup>. For that reason, calcitonin was not administered in this patient.

The use of cinacalcet during pregnancy is debated<sup>6</sup>. Cinacalcet is a calcimimetic agent that binds to the calcium-sensing receptor (CaSR), activating CaSR to react to the extracellular calcium concentration and decrease PTH secretion. It is effective in all forms of hyperparathyroidism but is mainly used for the treatment of secondary hyperparathyroidism and parathyroid carcinoma<sup>12</sup>. As CaSRs are present in the placenta, cinacalcet may alter placental function and potentially induce fetal and neonatal hypocalcemia. Its use is limited by the lack of data on the fetus and new-born but animal studies did not show embryonal or fetal toxicity<sup>13</sup>.

The use of cinacalcet for treatment of PHPT in pregnancy was reported<sup>6,13</sup>. No adverse fetal effects were reported but in one case the benefit of cinacalcet was weak<sup>6</sup>.

Bisphosphonates are commonly used in the treatment of osteoporosis, hypercalcemia, and other conditions characterized by excessive bone resorption. They are incorporated into active bone remodelling sites and suppress bone turnover by inhibiting bone mineral breakdown. Consequently, there is a decrease in calcium release and levels of serum calcium, an increase in bone mineral density, and an improvement in bone quality<sup>12</sup>.

Bisphosphonates cross the placenta. Studies on animals have associated gestational exposure to bisphosphonates to decreased fetal bone growth, decreased fetal survival and decreased birth weight. Nonetheless, there is a lack of data on its use in pregnant women or in women of childbearing age. In addition, the bisphosphonate doses used in animal studies are generally much higher than those used in humans<sup>14</sup>.

There are a few published data on women exposed to bisphosphonates during pregnancy. Stathopoulos et al. identified 78 foetus whose mothers took bisphosphonates before or during the pregnancy. Sixty-nine gestations resulted in live births while 9 abortions were reported. All of those were attributed to maternal concomitant disease and medications. There were at least 33 cases of women that received treatment with bisphosphonates during the first 3 months of pregnancy and four cases of women who received bisphosphonates after 28 weeks' gestation. Two neonates had transient hypocalcemia after delivery. None of the new-borns presented with serious adverse events<sup>14</sup>.

Green et al found 9 published cases of women taking pamidronate prior to pregnancy and 5 cases during pregnancy. Of the latter, 4 were in the 2<sup>nd</sup> and 3<sup>rd</sup> trimesters of pregnancy and the neonatal adverse events described were transient hypercalcaemia and hypocalcemia (1 case each)<sup>15</sup>.

In our case, we chose to use bisphosphonates (pamidronate) because of its superior efficiency compared to cinacalcet and its previous use in pregnant women to treat hypercalcemia.

### Conclusion

our case of primary hyperparathyroidism during pregnancy highlights the difficulty in locating anomalous parathyroid(s). After the surgical option was refused by the patient, the choice of medical treatment was challenging, and deciding on the most balanced medical treatment to control maternal calcium levels without fetal harm was essential. The use of loop diuretics and bisphosphonates proved to be effective in controlling hypercalcemia until the end of pregnancy without fetal or neonatal complications.

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# Solitary plasmacytoma extramedullary to duodenal level: an unusual case of intestinal occlusion

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## Abstract

Plasma cell neoplasms represent only 1-2% of hematological malignancies and intestinal plasmocytoma represents only 3%. Extramedullary plasmocytomas most commonly are located in upper airway and oral cavity; the gastrointestinal plasmocytoma only represents 12%, the most frequent being the gastric one. We present a brief report about an extramedullary solitary plasmocytoma at the intestinal level (duodenum).

**Palabras clave:** plasmocitoma extramedular. Oclusión intestinal. Neoplasia de células plasmáticas.

**Keywords:** Extramedullary plasmocytoma, intestinal occlusion, plasma cell neoplasms.

## Introduction

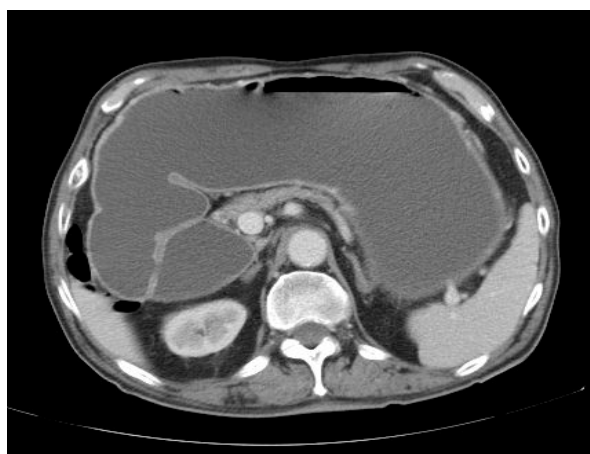
The plasma cell neoplasms represent only 1-2% of hematological malignancies and intestinal plasmocytoma represents only 3%. Extramedullary plasmocytomas are most frequently located in the upper airway and oral cavity. The gastrointestinal plasmocytoma only represents 12% and the most frequent is the gastric one. We present a brief report about a solitary plasmocytoma extramedullary at the intestinal level (duodenum).

## Clinical case

An 85-year-old patient, with a personal history of bladder and prostate neoplasia in complete remission who went to the emergency room presenting abdominal pain, nausea and vomiting of bilious content, with anorexia and weight loss of 10 kilograms in the last two months. In the physical exam, anorexia was highlighted. The analysis presents leukocytosis with neutrophilia, acute renal failure and hyperchloremic acidosis; interpreted in the context of diges-

tive losses. Abdominal ultrasound was performed, which caused thickening in the pylorus, and upper digestive endoscopy with biopsy extraction; they were informed anatomopathologically as chronic gastritis. The patient improved after hydration, tested tolerance to oral diet and was discharged with high doses of proton pump inhibitors. After four days, the patient returned to the emergency room due to digestive and abdominal aggravation. Abdominal computed axial tomography (CT) was performed (Fig 1, A. Upper panel: abdominal CT show signs of obstruction at the duodenum level), which showed signs of obstruction at the duodenal level, due to circumferential growth, and digestive echoendoscopy, showing stenosis at the level of the second portion of the duodenum (Fig 1, B. Lower panel: Digestive echoendoscopy confirm the stenosis at the second portion of the duodenum). Biopsies were performed at this level. The anatomopathological examination showed infiltration of post-positive plasma cells for CD138, CD79, CD43, BCL2, EMA and vimentin, with restriction for Kappa chains. Diagnosis of duodenal plasmocytoma was confirmed. The patient was referred to hema-

Fig. 1. A. Upper panel: abdominal CT show signs of obstruction at the duodenum level. B. Lower panel: Digestive echoendoscopy confirm the stenosis at the second portion of the duodenum



tology where a pteinogram was made in blood and urine, without evidence of monoclonal peak and extension study without evidence of other lesions. In view of the local extension of the tumor and the age of the patient, systemic treatment with bortezomib, melphalan and prednisone was decided upon with a good response until now.

## Discussion

The intestinal extramedullary plasmacytoma is a rare entity; the first case was published in 1947.<sup>1</sup> In the cases described in the literature it usually occurs in people older than 50 years, and with certain predominance in males<sup>2,3</sup>. The most common symptoms are dyspepsia, vomiting, abdominal pain and weight loss. There is a case that debuted as melenas<sup>3</sup>. The diagnosis is established by the association of clinical, laboratory and radiological examination in cases in which multiple myeloma can be excluded biopsy of the lesion. Definitive diagnosis is established by biopsy of the lesion, with markers positive for CD138 and light chains. The biopsy is more profitable if it is performed through surgery or endoscopic ultrasound. The treatment of choice is surgical resection and radiotherapy<sup>5</sup>. Radiation therapy is accepted as the standard treatment, even without a standardized dose and period, in

addition to the need for irradiation of regional lymph nodes. Surgery is first-line treatment and adjuvant chemotherapy can be used to prevent progression to multiple myeloma. In the present case chemotherapy was applied due to the tumor presentations. The prognosis is better than solitary bone plasmacytoma with a survival rate of 70% at 10 years. Despite the rarity of its location, the extramedullary plasmacytoma should be considered in the differential diagnosis of abdominal tumors.

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# Síndrome poliglandular autoinmune tipo 2 presentándose como emergencia endócrina – a propósito de un caso

*Autoimmune Polyglandular Syndrome type 2 presenting as an endocrine emergency: a case report*

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## Resumen

Los síndromes poliglandulares autoinmunes son un grupo raro de endocrinopatías caracterizadas por la disfunción auto-inmune de una o más glándulas endócrinas, pudiendo afectar a otros órganos. Los dos tipos más comunes, tipo 1 y 2, tienen la Enfermedad de Addison (EA) como principal componente, pero la disfunción de la glándula suprarrenal puede no ser la primera manifestación. Las disfunciones auto-inmunes de las glándulas endócrinas son consideradas muchas veces como la “punta del iceberg”, ya que, en la mayoría de las veces coexisten otras patologías auto-inmunes. Los autores relatan el caso de una mujer de 56 años, admitida en el servicio de urgencias por un cuadro de náuseas, vómitos, dolor abdominal, hiponatremia y hiperpotasemia, y cuya investigación etiológica llevó al diagnóstico de síndrome poliglandular autoinmune tipo 2.

**Palabras clave:** síndrome poliglandular autoinmune, anemia perniciosa, insuficiencia de la suprarrenal, tiroiditis autoinmune.

## Abstract

Polyglandular autoimmune syndromes are a rare and heterogeneous group of endocrine diseases characterized by autoimmune dysfunction of one or more endocrine glands, even though non-endocrine organs can also be affected. The two major autoimmune polyendocrine syndromes, type 1 and type 2, present Addison's Disease as a prominent component, although adrenal gland dysfunction is not usually the first manifestation. Autoimmune disorders of the endocrine glands are often regarded as the “tip of the iceberg” since they most often coexist with other autoimmune diseases, which may not be apparent at first sight. The authors report the clinical case of a 56 year old woman admitted to the emergency department with nausea, vomiting, abdominal pain, hyponatremia and hyperkalemia, whose etiological investigation led to the diagnosis of Polyglandular autoimmune syndrome type 2.

**Keywords:** polyglandular autoimmune syndromes, pernicious anemia, adrenal insufficiency, autoimmune thyroiditis.

## Introducción

Los Síndromes Poliglandulares Autoinmunes (SPGA) son un grupo raro de poliendocrinopatías que resultan de una destrucción inmune-mediada y que cursan con la insuficiencia de múltiples glándulas endócrinas<sup>1</sup>. Se caracterizan por la asociación de dos o más alteraciones funcionales/disfunciones autoinmunes específicos de órgano<sup>2</sup>, y pueden ser clasificados en 4 tipos, descritos por *Neufeld* y *Blizzard*<sup>3</sup>.

El SPGA tipo 2 obliga a la presencia de la enfermedad de Addison (EA), verificándose insuficiencia aguda de la glándula suprarrenal (IAS), que ocurre por procesos humorales y mediados por células que llevan a la destrucción del córtex de la suprarrenal<sup>4</sup>. Cuando se asocia a Diabetes Mellitus tipo 1 (DM1) se denomina Síndrome de Carpenter, y cuando se asocia a Tiroiditis Autoinmune, Síndrome de Schmidt. El tipo 2 es el más prevalente, con una prevalencia estimada de 1.4 a 5.4 casos/100.000 habitantes<sup>5</sup>, con predisposición genética, ocurriendo entre los 30 e 40 años. Más frecuente en sexo femenino, con una ratio 3:1. La IAS es su manifestación principal, y muchas veces se presenta como emergencia endócrina, con alta tasa de mortalidad asociada.

La edad de presentación de este caso es poco frecuente, lo que puede hacer que el diagnóstico sea más difícil y con-

secuentemente retrasar el inicio del tratamiento, cursando con un *outcome* desfavorable. Además, existen pocos casos reportados debido a una gran variedad de presentaciones, por que los autores pretenden alertar de la posibilidad de este diagnóstico cuando un paciente se presente con una o más endocrinopatías.

## Caso

Mujer de 56 años, autónoma para las actividades de vida diaria, con antecedentes de gastritis crónica, dislipidemia, e hipotiroidismo de etiología no conocida tratada con levotiroxina. Acude al Servicio de Urgencias (SU) por un cuadro de dolor abdominal, náuseas, vómitos y diarrea (5-6 deposiciones/día, sin productos patológicos), astenia, anorexia y pérdida ponderal de 13.9% de su masa corporal, en 3 meses. Se destacaba la realización de una salpingo-ooforectomía bilateral por laparoscopia antes del inicio del cuadro.

Con una historia clínica más detallada se destacaba además “*salt craving*” (avidez por la sal), con dos semanas de evolución, y consumo apenas de legumbres y fruta, y mayor intolerancia al frío. Los antecedentes familiares eran importantes ya que ambas sus hijas (de 26 y 30 años) tenían hipotiroidismo, también de etiología desconocida, y una de ellas, padecía además de vitíligo.

Al examen clínico presentaba mucosas pálidas y deshidratadas, apirética y perfil tensional bajo con **nadir** de 75-50mmHg. Se des-

tacaban áreas de hiperpigmentación de la piel, sobre todo a nivel de los pliegues cutáneos. La analítica general revelaba hiperpotasemia de 6.38mmol/L e hiponatremia de 125 mmol/L.

En los análisis destacaba anemia macrocítica normocrómica (con hemoglobina 10.2g/dL), sin otras alteraciones. Se inició de inmediato sueroterapia intensiva, y corrección de la hiperpotasemia. Dado haber alta sospecha de IAS, se procedió a **la coleta** de la Hormona Adrenocorticotrófica (ACTH) y cortisol, y se hizo la primera toma de hidrocortisona en dosis de *stress*. Los resultados del estudio de la ACTH y cortisol confirmaron la sospecha de IAS – Enfermedad de Addison.

Se realizó tomografía computarizada (TC) abdominal para evaluación de las suprarrenales, endoscopia digestiva alta (EDA) por sospecha de gastritis autoinmune, y ecografía tiroidea, además de un estudio analítico más amplio con las restantes hormonas.

Los resultados del estudio esclarecieron la etiología del Hipotiroidismo como un síndrome auto-inmune, con títulos elevados de Anticuerpos (Ac) anti-tiroideos y una ecografía sugestiva de tiroiditis; la etiología de la anemia, aunque tenía un déficit de vitamina B12, mostró también la positividad de los Ac anti-célula parietal y anti-factor intrínseco a favor de un cuadro de anemia perniciososa. Los resultados analíticos, de imagen y anatomo-patológicos más relevantes están descritos en la Tabla 1.

Así, y teniendo en cuenta la presencia de dos endocrinopatías (enfermedad de Addison y Tiroiditis autoinmune) se hizo el diagnóstico de Síndrome de Schmidt. El estudio de los Ac anti-carboxilasa y anti-21-OH, que confirmarían el diagnóstico, no fue efectuado por no estar disponible en nuestro laboratorio. Sin embargo, la clínica de la paciente, junto con las otras enfermedades auto-inmunes, hace altamente probable la hipótesis diagnóstica de SPA2 y son suficientes para firmar el diagnóstico, ya que la evaluación de estos Ac sería más académica y no cambiaría la actitud terapéutica. El estudio de los AC anti-suprarrenal en las hijas de la paciente sí que pueden tener interés dado la alta susceptibilidad genética a esta condición, y sabiendo además que padecían ambas de hipotiroidismo de etiología no esclarecida, y una de ellas también de vitíligo.

La paciente presentó una evolución favorable y fue dada de alta con tratamiento con hidrocortisona 20mg/día, fludrocortisona 100microg/día y levotiroxina sódica 0.1mg/día. Fue derivada a la consulta de Endocrinología y sesiones de grupo sobre la EA y sus emergencias asociadas.

## Discusión

Las disfunciones auto-inmunes de las glándulas endócrinas son consideradas muchas veces como la “punta del iceberg”, ya que, la mayoría de las veces coexisten con otras enfermedades auto-inmunes, que pueden no ser aparentes a una primera instancia.

En 1980, Neufeld e Blizzard<sup>4,6</sup> organizaron y clasificaron estas condiciones clínicas, denominándolas de SPGA. El SPGA-2 es la forma más común, poligénica, y no tiene un patrón claro de herencia. Afecta sobre todo mujeres adultas y tiene formas de presentación clínica extraordinariamente heterogéneas<sup>2</sup>. Para que el diagnóstico sea establecido es necesario la presencia de EA asociada a tiroiditis y/o DM1, pudiendo aún existir otras manifestaciones auto-inmunes *minor*, del foro endocrinológico o no<sup>6</sup> (Tabla 2).

La asociación entre el Síndrome de Schmidt y la DM1 fue confirmada por *Carpenter* en una revisión de 142 pacientes con ese síndrome, que se diagnostica por la Tríada completa

Tabla 1. Resultados del estudio analítico e imagenológico

Estudio analítico		
Parametro	Resultado	Intervalo de referencia
Cortisol 8h (µd/dL)	4.3	6.2-19.4
ACTH 8h (pg/mL)	>1250	0-46
TSH (uUI/mL)	0.60	0.27-4.2
T4 libre (ng/dL)	1.47	0.93-1.7
Ac anti-Tiroglobulina (UI/mL)	143.1	<1
Ac anti-Peroxidase Tiroide UI/mL	513,9	<9
Anti-Célula Parietal (UI)	60.1	<25
Ac anti-Factor Intrínseco (RU/mL)	162	<10
Vitamina B12 (pg/mL)	55,9	197-771
Ácido Fólico (ng/mL)	16.1	4.6-18.7
Exámenes de imagen		
Ecografía tiroidea	Contorno glandular regular y textura difusamente heterogénea, micronodular difusa, predominantemente hipoecogénica, sugestiva de tiroiditis.	
TC abdominal	Glándulas suprarrenales de normal configuración y pequeñas dimensiones, con brazos y región del cuerpo filiformes. No se identifican lesiones nodulares.	
EDA con biopsia gástrica	Gastropatía eritematosa. El examen anatomo-patológico fue compatible con gastritis crónica moderada a intensa, sin evidencia de actividad, y atrofia moderada a marcada	

con EA, DM1 y tiroiditis. Desde entonces se denomina Síndrome de Carpenter<sup>8</sup>.

En el caso de la paciente se presentó con la combinación más común: EA y tiroiditis, aunque sea rara en la 5ª década de la vida. Además, se sabe que el SPGA-2 ocurre, en general, en una secuencia particular, en que la DM1 ocurre antes de la Enfermedad de Addison. La tiroiditis es más variable pudiendo ocurrir antes, mientras o después<sup>2</sup>.

*Bettlere et al.*<sup>10</sup> describieron la prevalencia de los componentes del SPGA-2: EA y tiroiditis ocurren en 56% de los casos;



Tabla 2. Clasificación de los SPGA segundo Neufeld y Blizzard<sup>6</sup>

Tipo	Edad de inicio	Características clínicas
SPA-1	Infancia	Candidiasis mucocutánea crónica, hipoparatiroidismo crónico, EA (por lo menos 2 presentes).
SPA-2	Después de la 3ª década	EA (siempre presente), tiroiditis y/o DM1.
SPA-3	Después de la 3ª década	Tiroiditis asociada a otra enfermedad autoinmune (excluido - EA y/o hipoparatiroidismo).
SPA-3	Después de la 3ª década	Combinaciones que no incluyen los grupos previos.

EA y Enfermedad de Graves (EG) en 21%; EA y DM1 en 11%; EA, tiroiditis y DM1 en 9.6%; EA, EG y DM tipo1 en 2%.

La EA es la causa auto-inmune más frecuente de IAS, responsable del 60-90% de los casos<sup>9</sup>. Para la confirmación diagnóstica es necesario el estudio con Ac anti-célula del córtex de la supra-renal y Ac anti-21-OH, que deberán ser positivos. En nuestro caso no se buscaron por los motivos arriba mencionados.

La actuación de factores ambientales desencadenantes (infecciones virales, drogas, tabaco, alimentos) en individuos genéticamente predispuestos resulta generalmente en una ruptura de la tolerancia inmunológica, resultando en una IAS<sup>9</sup>. En este caso la intervención quirúrgica, y el estrés fisiológico asociado, podría haber sido el *trigger*, dado la relación temporero-causal.

Se estima que un cuarto de los pacientes con una única disfunción endócrina puede llegar a desarrollar otras enfermedades auto-inmunes<sup>7</sup>. Así, en estos casos, los clínicos tienen que estar más alerta, ya que se observa una alta tasa de mortalidad cuando no hay un diagnóstico y tratamiento precoz.

Estos enfermos necesitarán un tratamiento de sustitución hormonal "*ad eternum*" y vigilancia, ya que siempre existirá la posibilidad de desarrollar una otra enfermedad auto-inmune<sup>7</sup>. La tasa de supervivencia y calidad de vida, están frecuentemente reducidas en comparación con la población general<sup>9</sup>, lo que es mayoritariamente atribuible a la EA.

Recurrir a marcadores de auto-inmunidad puede ayudar a predecir el riesgo de otras enfermedades auto-inmunes y establecer de forma más precoz el diagnóstico de otros componentes del SPGA, incluso antes de que el déficit sea total. Esto puede condicionar un abordaje terapéutico de estos enfermos más individualizado, traducándose en un mejor pronóstico<sup>9</sup>.

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# Migraine aura without headache – a challengecase of clitoris parestesia

*Aura de migraña sin dolor de cabeza:  
un caso de desafío de parestesias del clítoris*

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Palabras clave: Aura. Migraña. Clítoris

Keywords: Aura. Migraine. Clitoris

The term “aura” denotes recurrent attacks of neurologic symptoms that can include visual, sensory, speech, motor or other central nervous symptoms. The neurologic symptoms generally last some minutes and are fully reversible. The aura is generally followed by a headache but in some migraine attacks there is aura without headache, previously called “silent migraine” or “acephalgic migraine” and can become more common as people get older.<sup>1</sup>

Our clinical report is about a 25-year-old woman. She has a boyfriend for 5 year and she is sexually active. No medical history of relevance except migraine and asthma, having only as chronic medication the contraceptive pill and analgesics as needed for headache (ibuprofen 600mg). The frequency of migraines ranged from 2 to 3 times a month. She identifies the fact of sleeping less as a trigger and describe her migraines as a pulsating, severe pain, associated with phonophobia and photophobia. She denies a history of falls with trauma to the brain or any type of surgical intervention.

She presented worried, at a medical appointment, with complaints of clitoral paresthesia episodes with two weeks of evolution. She explains that events occur one to three times a day, on non-consequential days, and have a duration of 10 to 45 minutes. She denies a traumatic event and does not associate the onset of symptoms with any particular situation. She mentions that the first time it occurred to her, was on a morning when she was driving after work. Maintains libido and the ability to achieve orgasm. When asked, she confirmed that in two of these episodes she had associated migraine after 5 minutes of that clitoris aura and the headache was similar to her previous migrainous headaches.

She denied other symptoms/signs. Neurological examination and control analysis were normal. Cranial computed tomography and electroencephalogram were also normal.

About five years ago, this patient had already had two episodes of migraine with aura, but on those occasions, it was a visual aura where she saw the images as if they were hexagons. Except for these cases, her migraines never had an aura before.

The episodes of clitoral paresthesia occurred with and without associated headache in this patient, the last ones can

be classified as migraine aura without headache in which aura is neither accompanied nor followed by headache of any sort. The lack of knowledge of this disease led the patient to become worried and think that she could have a sexual problem, which led her to see a doctor. She was medicated with sumatriptan 50mg and paracetamol 100mg prn for the migraine, one of the treatment options of NICE guidelines. These aura symptoms completely disappeared and the frequency of migraines was reduced to one or two times a month so no prophylactic treatment was offered.

Clinical and preclinical studies suggest that migraine aura is caused by cortical spreading depression (CSD), a slowly propagating wave of depolarization/excitation followed by hyperpolarization/inhibition in cortical neurons and glia. While specific processes that initiate CSD in humans are not known, mechanisms that invoke inflammatory molecules as a result of emotional or physiological stress, such as lack of sleep, may play a role.<sup>2</sup> Sensory aura is the second most frequent kind of aura after the visual aura (31% versus 99%).<sup>3</sup> It may appear in form of paresthesia, hypoesthesia, or both and the sensory symptoms classically begin in one hand, spread to the arm and reach the perioral region. In the absence of headache fulfilling criteria for migraine without aura, the precise diagnosis of aura and its distinction from its imitators that may signal serious disease becomes more difficult and requires additional investigation. When aura occurs for the first time after the age of 40, when symptoms are exclusively negative or when aura is prolonged / very short, other causes, for example transient ischemic events, should be excluded.

<sup>1</sup> Migraine aura without headache should be diagnosed only when transient ischemic attack and seizure disorders have been ruled out.<sup>4</sup>

We only found in the literature two patients (a male and a female patient) who experienced prominent sensory symptoms in the genital region during their migraine auras. The male had paresthesia clearly localized in his testicles, more evident on the left and the female patient presented with headache preceded by right hemianopia, which was consistently followed by intense paresthesia in both the right half of her mouth and the ipsilateral vulva.<sup>5</sup> We have not found in the available

literature any description of sensory aura involving the clitoris. Genital disturbances as migraine aura have not been described in many patients, but other neurological disorders are known to produce this kind of symptoms. Seizures have genital symptoms well characterized: orgasms may trigger reflex epileptic seizures and genital symptoms may represent true epileptic manifestations<sup>6</sup>, sexual auras presenting as erotic pleasant feelings or thoughts with or without sexual arousal and orgasm are associated with temporal lobe epilepsy.<sup>7</sup>

The reasons for a low incidence of sensory symptoms in the genital region during migraine aura are partially unknown. Some authors suggest that the cortical neurons representing the genital area can have a higher threshold to be activated during the CSD.<sup>8</sup> Feelings of embarrassment can also explain the fact that patients don't always confess this sort of symptoms, so they may have been under-recognized.

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## Eritrodermia generalizada

*Generalized erythrodermia*

Mujer de 56 años que presenta una erupción cutánea muy pruriginosa, sugestiva de eritrodermia exfoliativa o eritema polimorfo relacionado con administración de nitrendipina (antagonista del calcio). Es un hecho descrito con diltiazem, pero muy infrecuente. Se presentó con fiebre, leucocitosis e neutrofilia, PCR elevada. Pústulas estériles, con rubor y calor local. Resolución clínica con descamación en guante, sin complicaciones. El diagnóstico de certeza se realiza con la readministración o demostrado mediante Prick Test, que no fue realizado.

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Diagnóstico:

### Eritrodermia exfoliativa o eritema polimorfo relacionado con administración de nitrendipina

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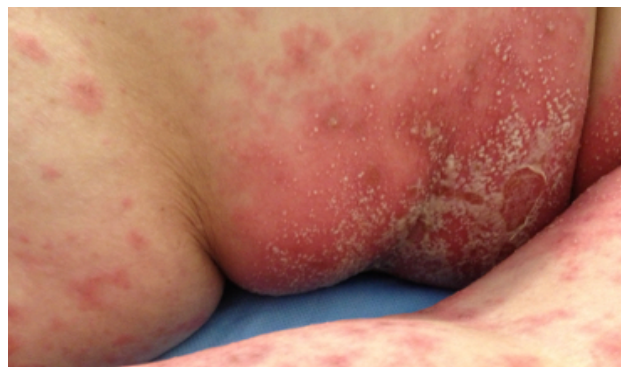
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Figuras 1-4. Erupción cutánea sugestiva de eritrodermia exfoliativa o eritema polimorfo relacionado con administración de nitrendipina (antagonista del calcio)



# Estomatite Ulcerosa - O Desafio Diagnóstico

## *Ulcerative Stomatitis - A Diagnostic Challenge*

Methotrexate (MTX) is an immunomodulating agent used in many autoimmune diseases. Its toxicity is dose-dependent and affects rapidly dividing tissues such as gastrointestinal tract and bone marrow<sup>1</sup>. Oral ulcerative stomatitis can be found in up to 14% of patients but its wide histopathologic spectrum, which ranges from non-specific ulceration to lichenoid reactions, represents a diagnostic challenge<sup>2</sup>. A 65-year-old woman with rheumatic arthritis, stop attending medical care since 2012 but kept a daily dose of 10 mg of methotrexate associated with 5mg/day of folic acid. In 2015, she was admitted in the Medicine Department after developing multiple shallow areas of ulceration in the floor of the mouth, buccal and labial mucosa and soft palate (Figure 1). Extra-oral observation showed lip ulceration. The other physical examination was irrelevant. She had bicytopenia (27000 leukocytes and 82000 platelets), C-Reactive protein of 143 mg/L (normal <7.5mg/L) and creatinine of 1.6 mg/dL (normal<1.3 mg/dL). Liver function test and chest x-ray were normal. Serology for Human Immunodeficiency Virus 1 and 2 was negative. MTX was discontinued with resolution of the oral ulceration and analytical abnormalities. She was dismissed to her rheumatologist and restarted MTX therapy (10mg/weekly) 2 years later without recurrence of adverse events. In conclusion, adherence to methotrexate is the key to attaining disease remission/low disease activity and low toxicity profile<sup>3</sup>. A careful medical and pharmacological history is mandatory and clinicians should be aware of this drug possible side effects<sup>3</sup>.

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Figure 1. Ulcerative Stomatitis



Diagnosis:

### Ulcerative Stomatitis: Oral effect of methotrexate

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## Large gouty tophi

*Tofos gotosos de gran tamaño*

Gout results from the deposition of uric acid crystals at various locations (preferably joints, subcutaneous tissue, and kidney). About seven percent of the adult population develop hyperuricemia, but only about one percent progress to gout. We report the case of a 57 year old patient with a history of hyperuricemia with 30 years of evolution, hypertension and obesity. Medicated previously with colchicine, indomethacin and lisinopril and hydrochlorothiazide. Admitted by complaints of dysarthria and hypertensive crisis. In the objective examination, blood pressure 160/95 mmHg, left central facial paresis, without other neurological signs, xanthelasma, multiple massive gouty tophi, at the level of the joints of the hands, feet, and at the elbows, conditioning marked joint deformation and functional impotence, motivating inability to walk. It also presented deposition of crystals at the subcutaneous level, even with ulcerated wounds in the right lower limb, giving rise to crystals of uric acid. Laboratory tests without leukocytosis, urea 146 mg / dl, creatinine 2.15mg / dl, uricemia 10.3mg / dl. The renal function prior to this hospitalization was unknown. He performed a cranial CT scan that showed only chronic vascular leukoencephalopathy.

The radiograph of the hands showed destruction of the distal phalanges, with peri-articular erosions and exuberant inflammation of the soft parts involving crystals of uric acid. Renal echography showed areas of diffuse atrophy of the renal parenchyma, with loss of parenchymal-sinusal differentiation, compatible with a diagnosis of chronic renal disease; contributed to this, most likely, both hypertension and hyperuricemia. The patient was discharged with allopurinol and prednisolone; his glomerular filtration rate was greater than 50mL/min, not requiring any adjusting of the dose of allopurinol. He was observed two months later, already clinically improved, with gait without imbalance and with significant weight loss.

We assumed that this disorder made part of a metabolic syndrome, the patient was obese, had hypertension and dyslipidemia. Hyperuricemia was not an isolated disorder, so no hereditary cause was suspected despite the early onset.

The severity and size of the gouty tophi conditioned over the years, a degree of disability that ended with some regression after the institution of adequate therapy.

Diagnosis:

### Multiple massive gouty tophi

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Fig. 1. Multiple gouty tophi of the hands



Fig. 2. Peri-articular erosions and exuberant inflammation of the soft parts



Fig. 3. Multiple gouty tophi of the elbow



# A treatable cause of heart failure

## *Una causa tratable de insuficiencia cardíaca*

Primary cardiac tumors are extremely rare, and myxomas are the most common primary cardiac neoplasm. Approximately 80% of myxomas originate in the left atrium, and they may be symptomatic or found incidentally. The cardiovascular manifestations depend on the anatomic location of the tumor. Tumors involving the heart may cause symptoms by obstruction of circulation (producing symptoms of heart failure), interference with heart valves, embolization, direct invasion of the myocardium, invasion of adjacent lung, or by the production of constitutional symptoms. If a cardiac tumor is suspected, imaging procedures are used to determine if a mass is present and where it is located within the heart. The echocardiography is the simplest technique for assessment. Usually myxomas are managed by surgical resection because of the risk of embolization and other cardiovascular complications.<sup>1,2,3</sup>

The authors report the case of a 72-year-old woman with history of type 2 DM, HT and dyslipidaemia, that was asymptomatic until 3 months earlier, when she reported a 15-kg weight loss. Also, she had been feeling progressively worsening effort dyspnoea for a month and dyspnoea at rest, orthopnoea and paroxysmal nocturnal dyspnoea for 8 days. An outpatient echocardiogram revealed a bulky mass in her left atrium (LA). She was referred to the emergency room, being subfebrile with polypnea, tachycardia and a peripheral saturation of 81%. A new echocardiogram showed a bulky mass with irregular contours (78x30mm) in her LA, which had its pedicle at the level of the lower fossa ovalis, was mobile with a protrusion to the left ventricle (LV) going past the ventricular middle region and was obstructing the LV entry tract, with an estimated pulmonary artery systolic pressure of 86 mmHg. She underwent a myxoma excision and an interatrial septoplasty. Afterwards, she was asymptomatic.

This case highlights that cardiac myxomas, although being benign tumours, may be potentially severe; if diagnosed promptly they are also a treatable and reversible cause of heart failure. The challenge is to ponder the possibility of a cardiac tumor so that the appropriate diagnostic tests can be conducted, since symptoms may mimic other cardiac conditions.

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Diagnosis:

### Cardiac myxoma

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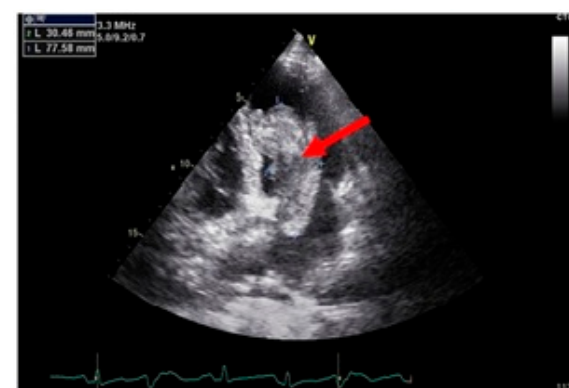
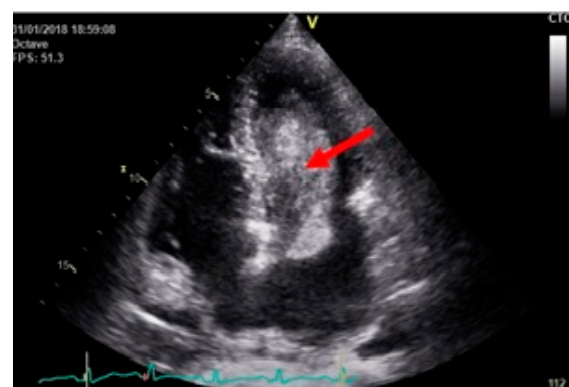
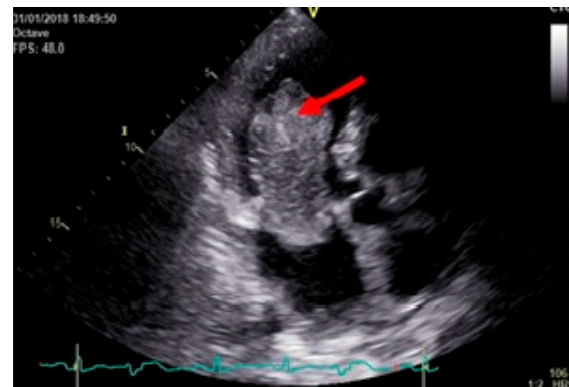
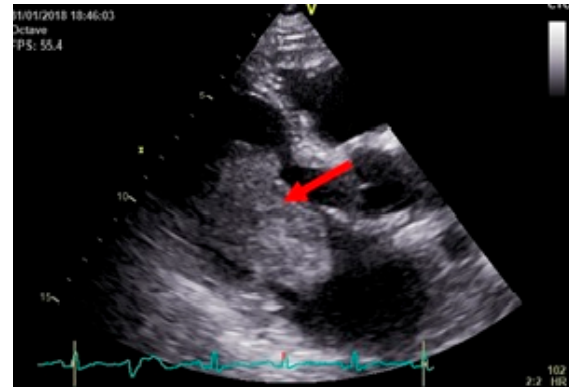
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Figure. 1. Bulky mass with irregular contours (78x30mm) in the left atrium, with pedicle at the level of the lower fossa ovalis, mobile, with a protrusion to the left ventricle going past the ventricular middle region and obstructing the left ventricle entry tract



## Low back pain: it is not always osteoarticular pathology

*Lumbalgia: ni siempre es patologia osteoarticular*

A 84-year-old man, with excess weight and a previous history of hypertension, dyslipidemia, chronic obstructive pulmonary disease (COPD), osteoarticular disease and renal lithiasis, went to the emergency department with low back pain radiating to the front of the abdomen with a day of evolution, unresponsive to pain therapy. At admission, the patient was hypotensive and normocardial. Abdomen was distended, with bowel sounds diminished, little depressible, without palpable masses. Femoral pulses were little wide and symmetrical. During the evaluation the patient started precordial pain described as tightness, without irradiation, without relief or worsening factors, followed by syncope. Electrocardiogram in sinus rhythm, with ST segment depression in anterior leads. Analytically with anemia (not known), slight elevation of myocardial necrosis markers, d-dimers 4200ng / mL. Urinalysis without changes. Computed tomography pulmonary angiography did not show signs of pulmonary thromboembolism. Upper abdominal and renal-bladder ultrasonography revealed abdominal aortic aneurysm. Contrast-enhanced computed tomography scan of the abdomen and pelvis (Figure 1 and Figure 2) showed fusiform abdominal aortic aneurysm, with a maximum aneurysm diameter of 7.5 cm, from the infrarenal abdominal aorta to the left common iliac artery, with signs of rupture (retrohemoperitoneum). The patient was submitted to emergent surgery with fatal outcome.

Low back pain is one of the symptoms that motivates more access to health care.<sup>1,2</sup> It is estimated that 80% of the population, at any time, will present this symptomatology.<sup>1-3</sup> There are multiple possible etiologies.<sup>2,3</sup> Mostly they have multifactorial origin.<sup>3</sup>

The abdominal aortic aneurysms have a prevalence of 2-5% in the general population, with a mortality rate of 80% in case of rupture.<sup>1,4</sup> In 91% of the cases it is accompanied by low back pain.<sup>1,4</sup> It is crucial to include abdominal aortic aneurysm in the differential diagnosis of low back pain,<sup>1,4</sup> especially in the presence of risk factors for developing it (male gender, age over 65, vascular risk factors, family history, chronic obstructive pulmonary disease, peripheral arteriopathy, among others),<sup>1,4</sup> in order to diagnose early a pathology with high morbidity and mortality. The Point-of-care ultrasound, a widely used tool in emergency medicine, can contribute to this goal, since it detects the presence of abdominal aortic aneurysms in symptomatic individuals with high sensitivity and specificity.<sup>5</sup> Therefore, the use of Point-of-care ultrasound in all patients admitted to the emergency room with abdominal pain or low back pain who present factors for the development of abdominal aortic aneurysms will be of added value.

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Figure 1. Contrast-enhanced computed tomography scan of the abdomen and pelvis (axial section): abdominal aortic aneurysm.



Figure 2. Contrast-enhanced computed tomography scan of the abdomen and pelvis (axial section): abdominal aortic aneurysm from the infrarenal abdominal aorta to the left common iliac artery.



Diagnosis:

**Aneurysm from the infrarenal abdominal aorta with signs of rupture**

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# Aortic dissection: an atypical presentation

## *Diseción aórtica: una presentación atípica*

Male, 48 years old, caucasian, smoker. Personal history: hypertension, costal trauma 3 months ago; chest pain after effort, compatible with unstable angina, having performed catheterization (without intercurrents) that did not reveal alterations, 1 month ago; respiratory infection treated with levofloxacin 2 weeks ago.

He went to the emergency department due to asthenia, edema of the lower limbs (lls) – more predominant in the right –, nocturnal sweating over the last 3 weeks, non-painful violaceous macular lesions, poorly delimited, variable-sized, and paresthesias in the toes which started recently. Medical examination: exophthalmia, cutaneous pallor, slowed speech, cardiac auscultation with aortic systolic murmur III/VI, lls already described; radial, femoral and popliteal pulses present and symmetrical; stable and normal vital signs.

Analytically: macrocytic anemia, thrombocytopenia, acute renal injury, negative infection parameters. A biopsy of the cutaneous lesions was performed, showing histology compatible with lesions secondary to vascular disorders. Venous and arterial Doppler echocardiography of the lls did not present alterations. The computed axial tomography (CT) of the thorax disclosed pleural effusion and hepatomegaly. The echocardiogram showed enlargement of the cardiac, aortic root and ascending aorta; left ventricle with depressed systolic function, ejection fraction of 41%; aortic valve of tricuspid morphology without coaptation of the cusps, conditioning severe insufficiency. After aortic insufficiency diagnosis, the patient did AngioTC, which revealed aortic dissection Type A (AAD), involving the abdominal aorta until slightly below the renal vessels, without involvement of the iliac artery, supraortic trunks or abdominal aortic derivatives. The patient was transferred to a center with cardiothoracic surgery for aortic replacement and valvular repair.

The incidence of aortic dissection is 3 to 6 per 100,000 person-years<sup>1-3</sup>, it's more common in males between 40 and 70 years old. Stanford's AAD is characterized by involvement of the ascending aorta.<sup>1</sup> Typically, the symptoms presented are intense retrosternal pain, arterial hypertension and asymmetry of the peripheral arterial pulses, however other signs and symptoms may be present: syncope, dyspnea, hemoptysis, hemiplegia. Murmur of aortic insufficiency is common in AAD.

In the case presented, the absence of typical symptoms delayed the diagnosis. Symptoms as fatigue, lls edema, cutaneous lesions, aortic murmur and comorbidities of the patient were important for the diagnosis.

The treatment of AAD is surgical. Mortality is about 90%, being higher than 50% in the first 48 hours. In the postoperative period, mortality in the first month decreases to about 30 %.<sup>2,3</sup>

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Fig. 1. Violaceous macular lesions not painful in the lower limbs



Fig. 2. Computed angiotomography: aortic dissection Type A, involving the abdominal aorta until slightly below the renal vessels



Diagnosis:

## An atypical presentation of Aortic dissection

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