Síndrome febril indeterminado y paniculitis – un caso raro de linfoma T subcutáneo paniculitis-like

Undetermined febrile syndrome and panniculitis - a rare case of subcutaneous panniculitis-like T-cell lymphoma

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ABSTRACT

Subcutaneous panniculitis-like T-cell lymphoma (SPTCL) is an extremely rare form of skin lymphoma that primarily involves subcutaneous adipose tissue. SPTCL diagnosis is demanding because of its nonspecific systemic features, such as fever or weight loss, that usually mimic other more common conditions. Further complicating diagnosis, lesion biopsies are often inconclusive. For this matter, patients are frequently seen by different clinicians and may be submitted to various cutaneous biopsies before a definitive diagnosis is reached.

We present the case of a 64-year-old man with a two-month history of fever and subcutaneous nodular lesions scattered by the lower limbs and torso, whose final diagnosis of SPTCL illustrates the main features of the disease as well as the challenge of its identification.

Keywords: cutaneous T-cell lymphoma, panniculitis, diagnosis, biopsy.

INTRODUCTION

Subcutaneous panniculitis like T-cell lymphoma (SPTCL) is a rare cytotoxic T-cell lymphoma characterized by the infiltration of the subcutaneous tissue by neoplastic cytotoxic T cells simulating panniculitis.[1] First described in 1991, only in 2001 the World Health Organization defined it as a distinct nosological entity.[2] It affects women slightly more often than men and can occur at any age.[2,3] We report the case of a patient with a prolonged febrile syndrome associated with panniculitis-type subcutaneous nodules, whose final diagnosis of SPTCL was a challenge.

CASE REPORT

A 64-year-old man was admitted for febrile syndrome associated with subcutaneous nodular lesions on the legs, abdomen and back for the last two months. The patient had a personal history of myelodysplastic syndrome, diagnosed one year before, due to weight loss and moderate thrombocytopenia, classified as low risk according to the International Prognostic Scoring System. For this purpose, he was medicated with prednisolone 5mg id for 9 months and weekly darbopoetin 500mcg for 4 months, due to the subsequent onset of anemia.

Two months before admission, he referred the appearance of papulonodular cutaneous lesions, hard and nontender, scattered over the lower limbs and torso. One of the right leg nodules had been biopsied, revealing small lymphoid cells with nuclear polymorphism, histiocytic cells and necrosis. The lymphocytic infiltrate was CD4>CD8, CD56 - and granzyme – and had no evidence of lobular rimming of lymphocytes. This result was first interpreted as a nonspecific lymphocytic panniculitis, of probable reactive nature and the patient was told to increase the dose of prednisolone to 20mg a day, without clinical improvement. A few weeks later, he started fever, a peak per day. For that matter he was given antibiotic therapy with cefuroxime and clindamycin for a week, maintaing symptoms. About one month after the onset of fever, the patient was hospitalized.

On examination at admission, he had mild cutaneous pallor and multiple subcutaneous nodules on both legs and thighs, abdomen, thorax and dorsal region. He had also a palpable hard, adherent and painless mass on the left maxillar region, confounded with the parotid gland. The remaining examination was unremarkable.

Laboratory exams were performed and are described in Table 1.

A chest-abdomen-pelvis computed tomography was done, but did not reveal any nodules, masses or organ enlargements, although the subcutaneous tissue of thorax and abdomen showed diffuse edematous infiltration (Fig. 1).

Due to the presence of a left maxillary mass, he performed an ultrasound that revealed a solid, heterogeneous formation of 30x17mm, with nonspecific features, likely to be a lipomatous mass.

During hospitalization, the patient maintained fever and new subcutaneous nodules developed. We decided to perform a simultaneous biopsy of the left maxillary mass and one of the left thigh subcutaneous nodules. The maxillary tissue biopsy (Fig. 2) showed diffuse but moderate infiltration of small CD8+/CD4- lymphocytes, and prominent presence of CD68+ histiocytic cells that conferred a pattern of panniculitis. Histiocytes surrounded vacuoles and outlined granulomas. There was also rimming of vacuoles by CD8+ lymphocytes. The biopsy of the subcutaneous nodule of the leg would be identical. Based on pathology results, a diagnosis of SPTCL involving extranodal adipose tissue was made.

The study of bone marrow revealed dysplastic alterations of the erythroid line, with 3.8% of blasts and 7% of ringed si-

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Table 1: Relevant laboratory tests performed during febrile panniculitis differential diagnosis

Laboratory study	Result	Reference range
Hemoglobin	8.5	13 – 17.5 g/dL
Mean corpuscular volume	99.5	80 – 100 fL
Leucocyte count	2380	4 – 10 x 103/µL
Neutrophils	1330	2 – 7 x 103/µL
Linfocytes	760	1 – 3 x 103/µL
Platelets	52	150 – 400 x 103/µL
ESR	57	<20 mm/1st hour
C reactive protein	6.75	<0.8 mg/dL
Creatinine	61.6	64 – 104 mmol/L
Total protein count	60	66 – 83 g/L
Albumin	34	35 – 52 g/L
Total bilirrubin	34.2	5.1 – 20.5 mmol/L
Alanine transaminase	7	< 45 U/L
Aspartate transaminase	31	< 35 U/L
Alkaline phosphatase	42	42 – 150 U/L
Lactate dehydrogenase	489	125 – 220 U/L
Creatine kinase	21	< 171 U/L
Antinuclear antibody	Negative	-
Anti-dsDNA	0.60	Negative < 10 IU/mL
C3	152	88 – 252 mg/dL
C4	43	12 – 72 mg/dL
p-ANCA	Negative	-
c-ANCA	Negative	-
ECA	36	8 – 52 U/L
Blood cultures	Two negative sets	-
Rose bengal reaction	Negative	-
Borrelia antibodies	IgG and IgM negative	-
Leptospira antibodies	IgG and IgM negative	-
Syphilis screening	Negative	-
IGRA	Negative	-
HIV screening	Negative	-
Hepatitis B	Negative	-
Hepatitis C	Negative	-
Parvovírus	IgG positive, IgM negative	-
Cytomegalovirus	IgG positive, IgM negative	-
Epstein Barr virus	IgG positive, IgM negative	-
SPE	No relevant abnormalities	-
Imunoglobulin count	Normal	-
Serum immunofixation	No relevant abnormalities	-
Urinalysis	No relevant abnormalities	-

Legend: ESR: erythrocyte sedimentation rate; Anti-dsDNA: anti-double stranded DNA antibody; C3/C4: complement component 3/4; p/c-ANCA: perinuclear/cytoplasmatic anti-neutrophil cytoplasmic antibodies; ECA: angiotensin conversor enzyme; IGRA: Interferon gamma release assay; HIV: human imunodeficiency virus; SPE: serum protein electrophoresis

Fig. 1. Chest-abdomen-pelvis computed tommography showing diffuse subcutaneous nodular formations and subcutaneous edema (A), resolved 9 months after initiating treatment (B)

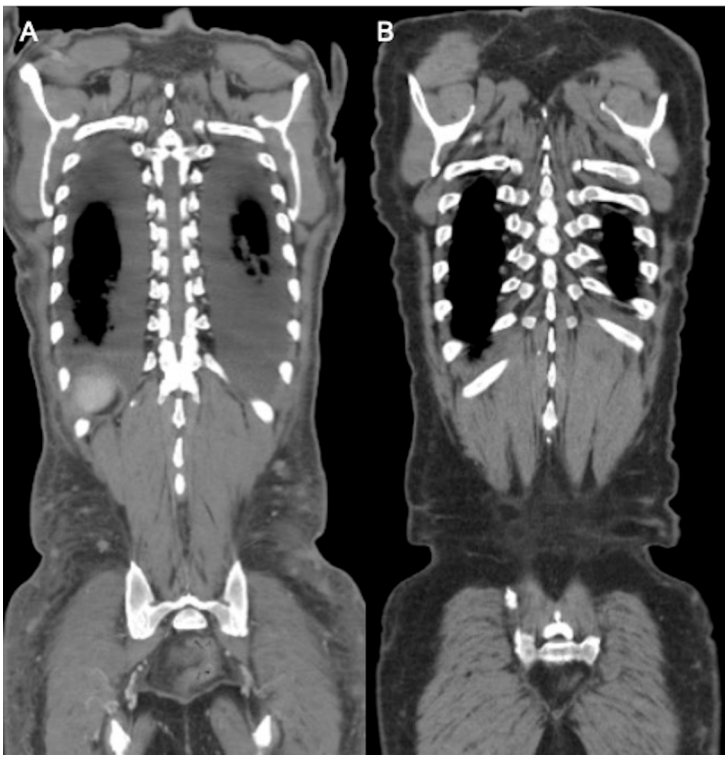
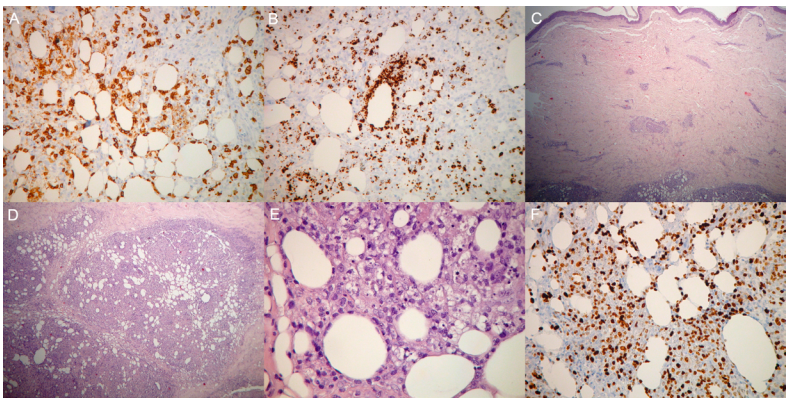


Fig. 2. Biopsy of maxillary subcutaneous nodule. (A) CD8 staining the atypical cells rimming fat space, ×100. (B) Tumour cells have a cytotoxic phenotype and express granzyme. (C) Infiltrate is confined to the subcutaneous tissue with no involvement of the overlying dermis or epidermis, Hematoxylin-Eosin, x40. (D) Predominant involvement of fat lobule by the infiltrate, Hematoxylin-Eosin, x100. (E) Neoplastic cells rim fat cells, Hematoxylin-Eosin, x200. (F) Ki67 expression, x100.



deroblasts, compatible with the diagnosis of myelodysplastic syndrome, but excluded organ involvement by the lymphoma.

The patient started treatment with prednisolone 1mg/kg/day (30mg bid) and cyclosporine 2.5mg/kg/day (75mg bid) with resolution of fever and disappearance of the subcutaneous nodules, as well as recovery of blood cell counts to normal values.

Eighteen months after diagnosis, he is asymptomatic, there is no relapse of subcutaneous nodules neither systemic symptoms related to lymphoma. The dose of prednisolone has been slowly tapered to the current dose of 15mg id, as well cyclosporin that has also been reduced to 50mg bid.

DISCUSSION

SPTCL was initially defined as a cytotoxic T-cell lymphoma with either an αβ or a γδ T-cell phenotype, since both types share a panniculitic presentation.[2] However, a more in-depth knowledge of these diseases showed clinical, histological and immunophenotypical differences. The αβ T-cell phenotype is typically CD4-, CD8+, CD56- and carries a more favorable prognosis. The γδ phenotype is CD4-, CD8- with co-expression of CD56 and is associated with a poor prognosis and much more frequent complications, namely hemophagocytic syndrome.[3] Today, the term SPTCL is applied only to the αβ type.

Patients report the appearance of multiple subcutaneous nodules of varying diameter (1 to 20 cm)[1], more often distributed in limbs and trunk. These are generally painless and rarely ulcerate, a feature most commonly associated with γδ subtype. In early stages, the nodules may disappear spontaneously, leaving areas of lipoatrophy, appearing later elsewhere in the body.[1] Systemic symptoms such as fever, weight loss, sweating and myalgias are common, but only a minority of patients have lymphadenopathies or organomegalies. Evidence of lymphoproliferative disease outside the subcutaneous tissue is rare in SPTCL.[1] Bone marrow involvement is rare but should be excluded.[4,5] In our case, even though bone marrow involvement by T cell lymphoma was excluded, we hypothesize that the myelodisplastic syndrome could be a paraneoplastic manifestion of the lymphoproliferative disease, considering the recovery of platelet count, hemoglobin and leukocytes to normal values when immunosuppressive treatment was initiated.

Differential diagnosis of panniculitis and fever includes autoimmune, infectious diseases and differentiation from other types of cutaneous or subcutaneous lymphomas.

About 20% of patients with SPTCL have an associated autoimmune disease, mostly systemic lupus erythematosus[2,6], although there are reports of association with juvenile rheumatoid arthritis, Sjogren's syndrome or rheumatoid arthritis.

In many cases, patients with SPTCL have a delayed diagnosis due to its presentation with nonspecific symptoms and signs. Additionally, identification of its histological findings requires experience and strong clinical suspicion. Patients are often seen several times by different clinicians and may be submitted to various cycles of empiric antibiotic therapy or cutaneous biopsies of inconclusive result, before a definitive diagnosis is reached.[9]

Due to rarity of this disease, there is no standardized therapy for SPTCL.[7,8] Cyclosporine may be a good option as a first-line therapy even in patients with disseminated disease due to favorable safety profile and ease of administration.[7] Similarly, monotherapy with systemic corticosteroids has achieved complete remission of SPTCL in various case reports.[8] For this matter, recent studies suggest that immunosuppressive drugs should be used as primary therapies for SPTCL patients.[9] Standard chemotherapy remains an option for refractory or relapsed patients. Generally, SPTCL carries a good prognosis, with a 5-year overall survival of 80%.[3]

Awareness of SPTCL is essential in a differential diagnosis of panniculitis, even if features of a different disease are present.

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