Caso clínico

Linfoma paniculítico y síndrome hemofagocítico

Subcutaneous panniculitis-like T-cell lymphoma and haemophagocytic syndrome

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Resumen

Se presenta el caso de un hombre de 57 años con una historia de tres meses de evolución caracterizada por la aparición de varios nódulos subcutáneos localizados en una pequeña área del abdomen y de la región inguinal, acompañados de ulceración, pancitopenia y fiebre. El examen patológico revelo un infiltrado atípico de células linfoides localizado en la región subcutánea. Estas células fueron identificadas por inmunohistoquímica como linfocitos T, descritos con importante cariorrexis, angioinvasión y necrosis grasa, compatible con un linfoma T subcutáneo. Esta rara entidad pertenece al subgrupo de los linfomas T periféricos y se acompaña ocasionalmente del síndrome hemofagocítico. El paciente presentó pobre respuesta a la quimioterapia y múltiples complicaciones infecciosas durante su hospitalización.

Palabras clave: paniculitis, Histiociotosis de células No Langerhans, linfoma de células T cutáneo.

Abstract

We report the case of a 57-year-old Colombian male with a 3-month history of subcutaneous nodular eruption confined to a small area located in the abdomen and inguinal area accompanied by secondary ulceration, pancytopenia and fever. Histopathological examination revealed an atypical lymphoid cell localized localised to the panniculus. These cells were identified as T-cells by immunohistochemistry; there was associated karyorrhexis, angiocentric infiltration and fat necrosis consistent with a subcutaneous T-cell lymphoma, a rare subset of peripheral T-cell lymphoma accompanied by haemophagocytic syndrome. Haemophagocytosis was present in the panniculus and bone marrow, no tumor being evident outside the subcutaneous tissue. The patient presented a poor response to chemotherapeutical treatment and multiple infectious complications during his hospitalization.

Key words: panniculitis, lymphoma, T-cell, cutaneous, histiocytosis.

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Recibido: 6/04/05; aceptado: 12/08/05

Introduction

Haemophagocytic syndrome (HS) represents a rare immune regulation disorder. Clinical features consist of fever, pancytopenia, hepatosplenomegaly, lymph nodes enlargement, hypertriglyceridaemia and coagulopathy. Haemopoietic cells are actively ingested by monocytes and macrophages in lymph nodes, bone marrow, liver and spleen. Systemic findings may also include pulmonary infiltrate, renal failure, a high predisposition to infection and inappropriate antidiureçtic state (1).

It has been described as being associated with many diseases (such as lymphomas); most of them are T-cell lymphomas which must be distinguished from other causes by immunophenotypic analysis (2). Subcutaneous panniculitis-like T-cell lymphoma is a rare primary cutaneous tumour, representing less than 1% of all non-Hodgkin's lymphomas, often initially mistaken as being a benign panniculitis manifesting an aggressive, fulminant presentation in approximately 50% of patients; the remainder acquire a high degree of malignancy after evolving for months or years. A frequent complication of this lymphoma, responsible for its poor prognosis, is haemophagocytic syndrome (though to be a cytokine-mediated reactive T-cell process) (3-5).

It is difficult to treat HS associated with cutaneous lymphoma, requiring intensive supportive therapy, treatment of coagulopathy disorders, applying high-dose corticosteroids and undergoing polychemotherapy treatment; however, there is no response in most cases and evolution becomes fatal.

The case of a 57-year-old Colombian male having subcutaneous peripheral T-cell lymphoma is reported. This was clinically presented as panniculitis associated with HS and multiple infectious complications during the hospitalisation period and following chemotherapeutic treatment.

Case report

The case concerned a 57-year-old male patient from Chiscas (Boyacá, Colombia) who was admitted to the Instituto Nacional de Cancerología after being referred from a regional third-level hospital presenting a clinical picture of 3 months' evolution consisting of predominant vesperal fever associated with asthenia, adinamia, the loss of 16 kg of weight and the appearance of three ulcerated, scabrous lesions in the left-hand side periumbilical and inguinal region **(figure 1)**. Extra-institutional evaluation revealed pancytopenia (Hb, 9 g/dl; haemogram: 1,600 leucocytes, 63.000 platelets and 411 absolute neutrophils) plus skin infection and soft tissues on the inner front region of the left thigh which was being treated with ceftriaxone and amikacine following a diagnosis of febrile neutropenia associated with abscessed cellulitis. He had been sent to receive integral haematological treatment in line with supposed medullar aplasia.

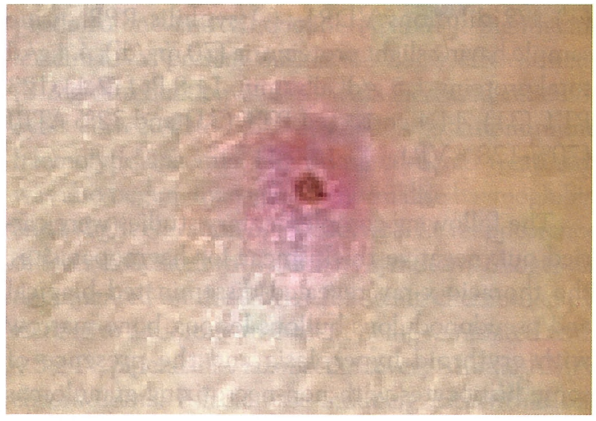


Figure 1. Pseudonodules localised in the periumbilical region.

The following were documented as being important antecedents: the presence of type 2 diabetes mellitus diagnosed 4 years before during treatment for irregular diet, heavy alcohol consumption and a hemorrhagic disorder during the 6 months prior to the appearance of gingivorrhagia, self-limiting alternating epistaxis and bleeding during programmed exodontia.

After being admitted, it was found that the patient was in regular physical condition, he was afebrile and hydrated, with a pulse of 89 per minute, respiratory frequency, 18, and blood pressure, 100/60; without any evidence of lesions in the oral mucosa suggesting recent bleeding, no cardiopulmonary alterations, soft abdomen, depressible, without lumps, and palpable splenomegaly 6 cm below the left-hand side rib rebound and a 4 cm hepatomegaly. There were ulcerated lesions of 3 cm and 1.5 cm covered by a whitish scab located in

the left-hand side of the periumbilical and inguinal region without infection signs. Paraclinical tests revealed the following: a haemogram showing 1,000 leucocytes, 404 neutrophils, 529 lymphocytes; 10.7 g/dl Hb (haemoglobin), 31.1% (hematocrit), 17,700 platelet count, 1.8% reticulocyte count, 287 mg/dl fibrinogen (325 mg/dl control), negative D dimer (0.8 mg/dl), 233 U/L aspartate aminotransferase (AST), 86 U/L alanine aminotransferase, 146 U/L alkaline fosfatase, 1.34 mg/dl total bilirrubin, 137.1 mmol/L Na, 4.68 mmol/l K, 103.2 mmol/L Cl, 11 mg/dl BUN (blood urea nitrogen), 0.8 mg/dl creatinine, 8.6 mg/dl corrected calcium, 2250 U/L LDH (lactate dehydrogenase), (-) serology for hepatitis C virus, (-) AgS hepatitis B virus, (-) ELISA for HIV, (+) 1/8 dilutions VDRL, (-) syphilis RPR, urine sample having slight proteinuria (70 mg/dl), 4.4 g/dl total proteins, 1.5 g/dl albumin, 14.8 Pt (12.1), 123 PTT (31), 44.4 corrected PTT (31) and 32% ATIII (70%-128% VR).

The following complementary studies were carried out: negative thick smear for haemoparasites, the thoracic x-ray revealed disseminated biapical and pseudonodulous bullous lesions, bone marrow with erythroid hyperplasia and the presence of some histiocytes with non-necrotizing granulomas and 70% cellularity which was negative for tumour infiltration, suggestive of haemophagocytosis, and negative myelocultures for fungi and acid alcohol resistant bacilli (AARB). The following results were also obtained: (+) direct Coombs, 43.2 UI/ml (+) for *Toxoplasma* IgG, 0.2 UI/ml (-) *Toxoplasma* IgM, 0.7 UI/ml (-) CMV IgM, (-) EBV IgM and IgG, positive 1:640 antinuclear antibodies (ANAS) (IFI on Hep2 cells), 1:320 mottled and nucleolus pattern, (-) anti-DNA and (-) ENAS.

A biopsy was also carried out of the cutaneous lesions under the impression of possible cutaneous tuberculosis *cf* actinomycosis or cutaneous lymphoma. Pathological evaluation revealed subcutaneous tumour infiltration by septal and lobular panniculitis, with frequent large interstitial atypical cells having karyorrhexis, histiocytes having haemophagocytosis, perivascular invasion and fatty necrosis **(figure 2)**. Immunohistochemistry revealed 80% Ki 67, (+) CD3, (-) CD 20 and few cells positive for CD8, CD68 and CD56. Immunophenotyping was used in a fresh study of the marrow, T predomination being identified in the lymphocyte population, having 0.3% CD34 cells and haemophagocytic syndrome morphology biopsy revealing abundant histiocyte foci **(figure 3)**.

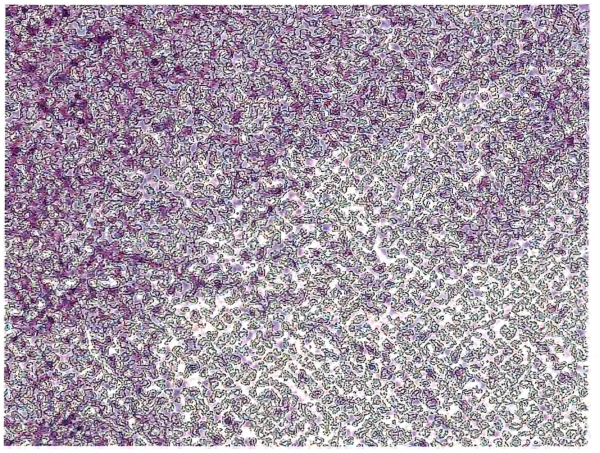


Figure 2. Skin biopsy compatible with panniculitic cutaneous T-lymphoma.

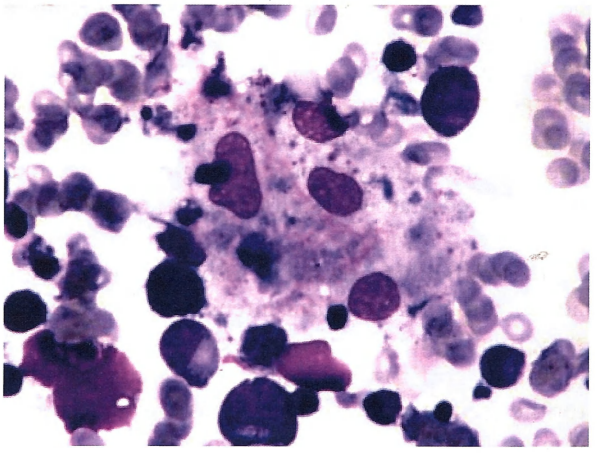
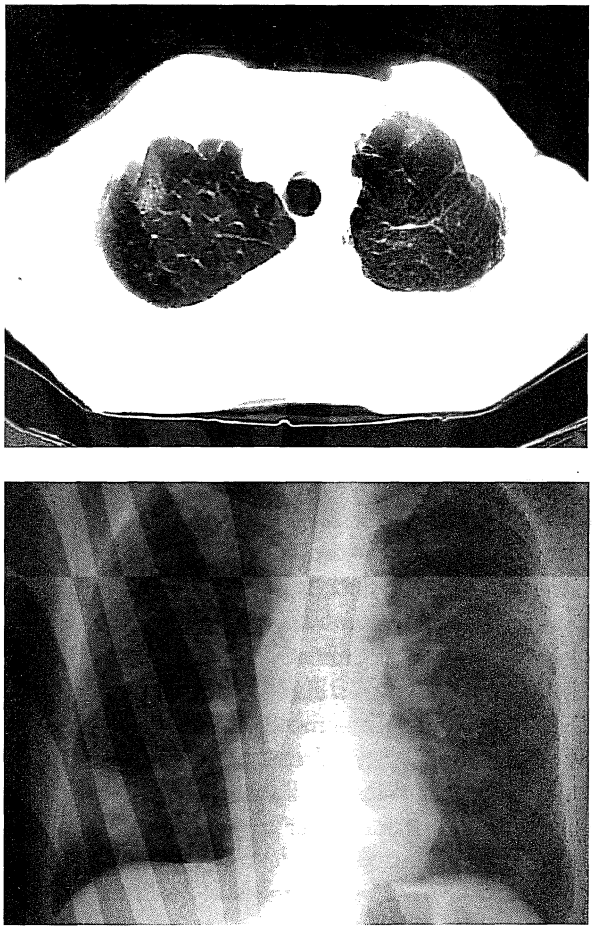


Figure 3. Haemophagocytosis in bone marrow.

On the sixth day after being admitted, the patient presented progressive dyspnoea associated with productive cough accompanied by abundant mucoid, purulent expectoration. Changes in x-rays suggested the presence of right-hand basal nosocomial pneumonia following late appearance in an immunocompromised patient, leading to broad spectrum antimicrobial treatment with 1g cefepime, IV, every 8 hours. Formal studies presented serial haemocultures and negative uroculture after a 5-day incubation period. Abdominal and pelvic thoracic tomography (to ascertain tumour state) revealed the presence of hepatomegaly with

superficial and peripheral nodular lesions of the parenchyma, splenomegaly and right-hand basal consolidation, with scarce non-inflammatory pleural seepage in cytochemical and bacteriological study of the pleural liquid, plus the presence of multiple bilateral bulbous pesudonodules in the upper left-hand lobe with no tumour adenopathy at mediastinum or retroperitoneum level (figures 4 and 5).



Figures 4 and 5. Tomography and x-ray of the thorax showing bilateral bulbous pulmonary pesudonodules in the upper left-hand lobe.

It was decided to carry out complementary diagnostic fibrobronchoscopy which revealed (+) BAL (bronchoalveolar lavage) with granulocytes, few Gram negative bacilli, KOH with no fungal elements, ZN (Ziel-Nielsen test) with no acid alcohol resistant bacterias and negative cultures for common germs and fungi. Transbronchial biopsy revealed no evidence of mycotic lesions or tumour infiltration.

Hepatic biopsy revealed alteration to the structure due to the presence of thin fibrotic bands accompanied by chronic inflammation rich in non-atypical T-lymphocytes ((+) CD3, (-) CD20) and lobular and confluent necrosis (PAS, PASD, TM and (+) reticulum) compatible with sinusoidal fibrosis with occasional megamitochondria. No abnormal deposits of histiocytes or tumour forms were observed, leading to the study being suggestive of hepatitis grade 6/18, stage 5/6, probably arising from alcohol poisoning.

It was decided to begin chemotherapeutical treatment for the pulmonary infection with a satisfactory clinical evolution with cyclophosphamide, etoposide, prednisolone and vincristine (CHOP). Significant anaemia was present during the 2 day of treatment (3.2 g/dl reduction of Hb) with increased reticulocytes corrected to 5.5% in relation to autoimmune haemolytic anaemia. High dose corticoid treatment was also begun, managing to normalise haemoglobin and a slight elevation of leucocytes. The reappearance of fever associated with a urinary symptomatology was documented on the 9th day following chemotherapy, leading to antibiotic treatment being reinitiated with 4.5 g, IV, piperacillin/tazobactam every 8 hours; AMPc chromosomal B-lactamase-inducing *Escherichia coli* and extended spectrum B-lactamase (ESBL) were isolated in uroculture, requiring 500 mg, IV, meropenem to be taken every 4 hours until remission of the fever was achieved 3 days later. The patient was discharged from the haematology service in acceptable general conditions, without significant changes in his marrow control study or the dimensions of his nodular skin lesions.

The second polychemotherapy cycle was administered as an outpatient 15 days later; feverish neutropenia was presented on the 7th day as a pulmonary complication arising from left-hand basal consolidation and increased nodular lesions documented during the previous stay. A fresh fibrobronchoscopy revealed negative results in the microbiological study and transbronchial biopsies, leading to an open pulmonary biopsy. The pathology report confirmed the presence of aspergillosis and the tissue culture was positive for *Aspergilus niger* leading to treatment with amphotericin B until 1.2 g/kg had been completed. A poor clinical result was obtained which is why a change was then made to caspofungin which also

elicited no response. The patient died on the 17th day of the second treatment cycle without having achieved haematological recuperation, accompanied by multiple organic dysfunction mediated by uncontrolled fungemia.

Discussion

Primary cutaneous T-cell lymphomas account for 80% of all primary cutaneous lymphomas, comprising a group of heterogeneous lymphoproliferative disorders characterised by clonal accumulation of neoplastic T-lymphocytes in the skin. Mycosis fungoids and Sézary syndrome are the most common (4).

Subcutaneous panniculitic T-cell lymphoma is a very rare malignancy which was described in 1991, mainly affecting women during their fourth and fifth decades of life. The disease typically follows a distinctive, indolent course of recurrent, self-healing subcutaneous nodules ranging from 0.5 cm to several centimetres in diameter; larger nodules may occasionally become necrotic (6). These lesions clinically mimic lipomas whilst histologically resembling a panniculitis. Alternatively, a rapidly progressive course might be observed, accompanied by constitutional symptoms and, in some cases, the development of a potentially fatal haemophagocytic syndrome with significant cytopenia (7). Clinical conditions were initially interpreted in our case as being a prolonged fever syndrome, probably related to infectious or rheumatological disease.

We report a patient having primary subcutaneous malignant disease presented with 1.5-3 cm diameter subcutaneous nodules, preferentially involving the abdomen and inguinal area. Histologically, the lesions were reminiscent of panniculitis and were composed of a mixture of small and large atypical lymphoid cells infiltrating between adipocytes. Sheets of tumour cells were found to be associated with fat necrosis; benign histiocytes were present as well as small blood vessels being involved with minimal angiocentric infiltrates not accompanied by angiodestruction.

As noted above, subcutaneous panniculitis-like T-cell lymphoma cytological composition is extremely variable. There is usually a predominance of small atypical lymphoid cells in the lesions accompanied by large transformed cells having hyperchromatic nuclei or a mixture of several different cell types. Mixed reactive histiocytes are frequently present, particularly in areas where fat has been infiltrated and destroyed; histiocytes are frequently vacuolated, due to ingested lipid material. Vascular invasion may be seen in some cases, necrosis and karyorrhexis being common. However, infiltrates are usually confined to the subcutaneous tissue, sparingly occurring in the dermis; this feature is helpful in differential diagnosis with other skin lymphomas (8).

Immunophenotypic analysis revealed a T-cell phenotype for atypical cells in our case having a positive reaction for natural killer-associated antigen CD56 and CD3, CD8 and CD68. Staining was negative for microorganisms including PAS-D, Gram-stain, GMS and Fite. This neoplasm is widely regarded as being a CD8+ cytotoxic T cell tumour accompanied by cytotoxic proteins, T-cell-restricted intracellular antigen; granzyme B is commonly demonstrated (8,9).

Subcutaneous panniculitic T-cell lymphoma has two distinct clinical presentations. The first is characterised by an indolent, protracted course and the second by rapid clinical deterioration, secondary to haemophagocytosis. Haemophagocytic syndrome is the cause of death in most patients suffering from subcutaneous panniculitis-like T-cell lymphoma; patients could occasionally present dissemination in lymph nodes and other organs occurring late in the clinical course (8).

Haemophagocytic syndrome is characterised by histiocyte proliferation and phagocytosis of blood elements, hepatosplenomegaly and coagulopathy associated with immune system derangement accompanied by defective T-cell function, T-cell and monocyte hyperactivation and hypercytokinaemia. Selective cellular cytotoxicity deficiency has also been reported. The following elements have been reported as being commonly elevated in this condition: interleukin (IL)-1 receptor antagonist, soluble IL-2 receptor (slL-2r), IL-6, interferon- (IFN-g), tumour necrosis factor- (TNF) and neopterin. (10) Our case presented multiple infection (mainly regarding the lungs), mediated by cellular and humoral immunity alteration. The patient died after the second treatment cycle suffering from multiple

organic dysfunction, secondary to A. niger-mediated mycotic disease.

Guidelines have recently been developed to facilitate diagnosing haemophagocytic syndrome; according to these, five criteria must be fulfilled: fever, cytopenia (two of three lineages), splenomegaly, hypertriglyceridemia and/or hypofibrinogemia and haemophagocytosis. Other conditions such as cytophagic histiocytic panniculitis (HCP), first described by Winklemann, could also be associated with haemophagocytosis. A relationship between subcutaneous T-cell lymphoma and HCP has been raised; whereas some authors believe that HCP and subcutaneous T-cell lymphoma are separate benign and malignant entities, others have suggested that they represent a clinical spectrum involving natural disease progression from benign panniculitis to malignant lymphoma (1).

Recent developments have produced evidence of concomitant Epstein-Barr virus (EBV) infection in both conditions. EBV-encoded RNAs have been found in infiltrating T-cells in both HCP and panniculitic T-cell lymphoma. For unknown reasons, EBV involvement seems to occur more commonly in Asiatic cases than in the United States. Cases in the USA have mostly been EBV negative, except for those in which there were angiodestructive foci in which medium-sized blood vessels were infiltrated and destroyed by atypical lymphocytes. A patient should be evaluated for EBV infection if there is a suggestion of recent viral or infectious illness and, in the event of being demonstrated, it will be considered to be a sign of a poor outcome (11-14).

Some authors have suggested that subcutaneous T-cell lymphoma may be treated with chemotherapy (CHOP or CHOP-based regimens) in the absence the haemophagocytic syndrome. The Histiocyte Society developed a common treatment protocol (HLH-94) in 1994 primarily designed for inherited haemophagocytic syndrome (primary disease); however, this may be extrapolated to secondary disease in special circumstances. Cyclosporine A immunotherapy is combined with steroids and VP-16 in the HLH-94 protocol; intrathecal methotrexate is added in the case of selected patients and high-dose chemotherapy should be considered with autologous peripheral stem-cell transplantation if relapse occurs following chemotherapy (1). The patient described here received systemic treatment with anthracyclines based on the above recommendation, a marginal response being obtained. This was followed by severe infectious consequences due to deterioration of his immune system which had already become altered by base illness.

A systematic review concerning published cases of subcutaneous panniculitis-like T-cell lymphoma has recently reported that prednisone has been frequently used as initial therapy in patients who have presented less aggressive disease when first seen. However, durable complete remission was infrequent. Anthracycline-based chemotherapy treatment was most commonly used and was the most effective systemic treatment option, producing long-term complete remission in approximately 30% of patients. It was found that 92% of patients receiving high-dose chemotherapy and stem cell transplant for refractory or recurrent disease achieved complete remission, mean response lasting nearly 14 months; 48% of patients died of disease (27-month mean survival) during a mean 24-month follow-up period (15).

Our patient presented a marginal response to chemotherapy and died shortly thereafter with uncontrolled haemophagocytic syndrome and systemic fungal infection. Patients having subcutaneous T-cell lymphoma have a poor prognosis with or without therapy.

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