Case report

Respiratory failure in a patient with Sézary syndrome

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Abstract

Case presentation. A 44 year old female patient, with no preexisting underlying disease, with a history of approximately ten months of presenting pruritic erythematous-desquamative lesions initially localized in the lower extremities and later generalized throughout the body, associated with weight loss of 15 kg. **Treatment.** Initial management consisted of topical corticosteroids and oral antihistamines with little clinical response. A dermatology work-up was initiated, and the initial diagnosis of malignant T-cell neoplasm was confirmed. A bone marrow smear was performed, in which "cerebriform" cells were identified, confirming the diagnosis of Sézary syndrome. The patient received cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone chemotherapy. **Outcome.** The initial response was favorable, with hospital discharge and outpatient follow-up. After three months of treatment, the patient consulted for a febrile episode, productive cough plus respiratory distress associated with bilateral basal rales, presented respiratory failure, and during induction of mechanical ventilation suffered cardiorespiratory arrest and died.

Keywords

Lymphoma, Sezary Syndrome, Mycosis Fungoides, Dermatitis Exfoliative.

Resumen

Presentación del caso. Paciente de 44 años de sexo femenino, sin ninguna enfermedad de base preexistente, con una historia de aproximadamente de diez meses de presentar lesiones eritemato-descamativas pruriginosas inicialmente localizadas en extremidades inferiores y que luego se generalizaron en todo el cuerpo, asociándose a la pérdida de peso de aproximadamente 15 kg. **Intervención terapéutica.** El manejo inicial consistió en corticoides tópicos y antihistamínicos orales con poca respuesta clínica. Se inició el estudio por dermatología y se confirmó el diagnóstico inicial de neoplasia cutánea maligna de células T. Luego se realizó el frotis de médula ósea, en el que se identificaron células «cerebriformes» que confirmaron el diagnóstico de síndrome de Sézary. La paciente recibió esquema de quimioterapia ciclofosfamida, doxorrubicina, vincristina, etopósido y prednisona. **Evolución clínica.** La respuesta inicial fue favorable, con alta hospitalaria y seguimiento en la consulta externa. Transcurridos tres meses de tratamiento, la paciente consultó por episodio febril, tos productiva más distrés respiratorio asociado a estertores basales bilaterales, presentó insuficiencia respiratoria y durante la inducción a la ventilación mecánica sufrió un paro cardiorrespiratorio y falleció.

Palabras clave

Linfoma, Síndrome de Sézary, Micosis Fungoide, Dermatitis Exfoliativa.

Insuficiencia respiratoria en una paciente con síndrome de Sézary

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Introduction

Cutaneous T-cell lymphoma is a general term to identify non-Hodgkin's T-cell lymphomas that primarily affect the skin. There are many subtypes of cutaneous T-cell lymphoma, the most common of which are mycosis fungoides and Sézary syndrome (SS). They can simulate benign skin disorders, making them a diagnostic challenge for dermatologists[1,2].

SS and mycosis fungoides are closely related entities, with mycosis fungoides being considered the indolent form and SS its aggressive leukemic phase. Therefore, it is hypothesized that SS may evolve gradually from mycosis fungoides or occur spontaneously, although some authors now consider them to be different entities[2].

SS is a malignant neoplasm originating from T lymphocytes, which involves the skin and can extend to the bone marrow, blood lymphocytes, lymph nodes, and various organs, characterized by erythroderma, superficial adenopathy, and atypical cells in the blood[1].

Regarding the epidemiological distribution of this syndrome, it predominates in men with a 2:1 ratio between 60 and 70 years of age[1,3] and has an annual incidence rate of one every ten millions, representing 3 % of all cutaneous lymphomas[4]. This syndrome affects the white population more than African-Americans and does not present a genetic predisposition[2].

The prevalence of primary cutaneous lymphomas recorded between 1986 and 2002 in the Netherlands and Austria was 3 %[5], which represents similar data to those reported by the World Health Organisation, Organisation for Research and Treatment of Cancer (WHO/EORTC)[6]. In Argentina, a prevalence of 0.13 % was reported in a specialized dermatological center from 2006 to 2016[7].

Case presentation

A 44 year old female patient and a teacher; with no preexisting underlying disease, neither family nor surgical history. She consulted with a ten-month history of generalized pruritus, without visible skin lesions, accompanied by unquantified febrile episodes, fatigue, and decreased appetite, with a weight loss of 15 kg, which led to multiple consultations in which she had been prescribed laboratory tests and had received treatment with oral antihistamines. In addition, she had two months of onset with scaly, pruritic, progressive and generalized skin lesions (Figure 1 and 2), and was treated with oral antihistamines and topical steroids without improvement. Physical examination revealed marked xerosis, signs of grattage, intense generalized erythema and palpable cervical and inguinal lymphadenopathy.

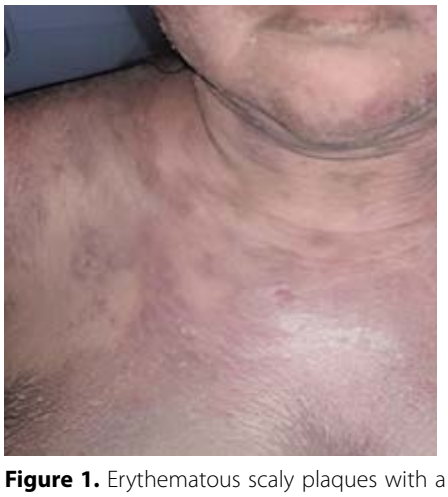
She was evaluated by a dermatologist in private practice who decided to perform a skin biopsy of the dorsal and anterior chest region. The results of the skin biopsy with immunohistochemical (IHC) assessment revealed: CD20 negative, CD3 positive, CD5 positive, CD7 negative, CD8 positive in 10 % with a diagnosis of malignant cutaneous T-cell neoplasm (Sézary Syndrome).

Due to the persistence of the febrile process and the worsening of the patient's general condition, it was decided to transfer her to the Medical-Surgical Hospital of the Salvadoran Social Security Institute (ISSS), where laboratory tests reported marked leukocytosis (leukemoid reaction), in peripheral blood smear: Decreased erythrocyte line with moderate anemia, normocytic, normochromic, immature cells from 8 % to 10 % with characteristics of large lymphocyte-like cells with abundant cytoplasm and irregular nuclei (Table 1).

Chest X-ray showed mediastinal widening without evidence of consolidating lesions in both lung fields (Figure 2). In addition, palpable cervical and inguinal adenopathies were identified on physical examination. As a result, inpatient management was decided to complete the study.

Computed tomography of the neck, thorax, abdomen and pelvis highlighted the presence of conglomerate lymphadenopathy in both jugular chains, posterior neck, supraclavicular and inguinal triangles without areas of necrosis or calcifications. These findings led to the suspicion of lymphoproliferative syndrome (Figure 3).

Upon admission to the hospitalization service, she was evaluated by the hematology unit where a bone marrow aspirate was indicated for smear processing and biopsy (Figure 4), which showed the presence of hypercellularity with the presence of megakaryocytes, myeloid series with 60 % predominance of adult forms,



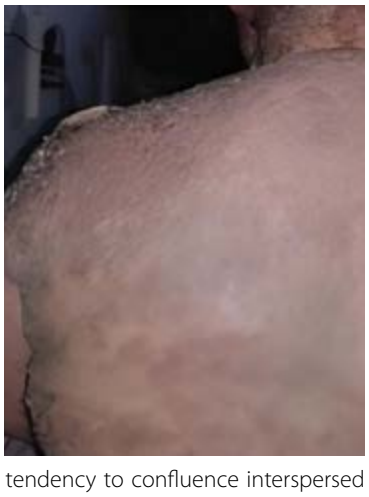


Figure 1. Erythematous scaly plaques with a tendency to confluence interspersed with areas of healthy skin, involving extensive areas of the anterior and dorsal region of the thorax.

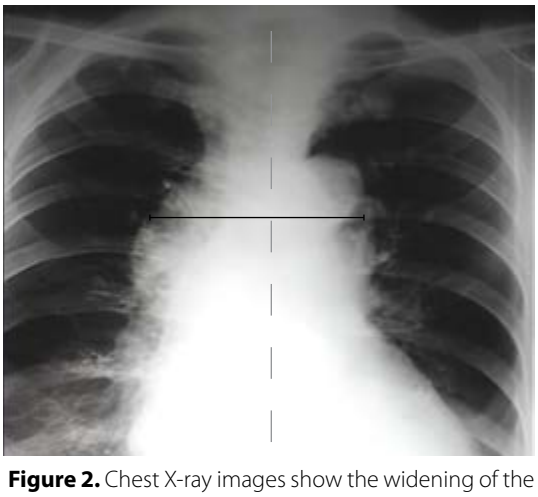


Figure 2. Chest X-ray images show the widening of the mediastinum related to a possible lymphoproliferative hematopoietic neoplasm

Table 1. Laboratory test results on admission

Hemogram	
White cells	54,0 x 10^6/mm^3
Neutrophils	33,6 %
Lymphocytes	43,2 %
Monocytes	20,7 %
Hemoglobin	9,9 g/dL
Hematocrit	30,3 %
Platelets	362x10^3
Blood Chemistry	
Glucose	84,5 mg/dL
Creatinine	0,59 mg/dL
Urea nitrogen	9,3 mg/dL
Urea	20 mg/dL
Sodium	133 mEq/L
Potassium	4,1 mEq/L
C-reactive protein	20,2
Erythrocyte sedimentation rate	53 mm/h
Tiempos de coagulación	
Partial Thromboplastin time	38,6 segundos
Prothrombin time	13,3 segundos
International normalized ratio (INR)	1,2

EUrine test: yellow, density: 1020 pH: 6; protein: 0 mg/dl; leukocytes 10-15 per field; leukocyte esterase and urine sediment: negative
Blood and urine cultures: negative
Electrocardiogram: no abnormalities.

although with a slight increase of juvenile forms and toxic granulation. The erythroid series with normal shape and size but decreased in 20 %; lymphoid series with 20 % presented irregular nuclei, some with condensed chromatin and "cerebriform" appearance, a pathognomonic finding in this disease. The bone marrow biopsy was negative for lymphoma.

Flow cytometry reported that 76 % of all events are lymphocytes, 97 % of T lymphocytes are CD4 and express CD3, CD4, CD5, CD2, CD25 heterogeneous and CD7 negative, CD34, CD10, and CD56 negative with immunophenotype reading of adult T-cell lymphoma-leukemia or anaplastic lymphoma.

Therapeutic intervention

The initiation of the chemotherapy regimen available at the institutional level was indicated, with cyclophosphamide, doxorubicin, vincristine, etoposide and prednisone (CHOEP).

Five days after the start of chemotherapy, she presented febrile peaks of 38. 5°C, documented leukopenia/neutropenia associated with chemotherapy, so reverse isolation was implemented, a prophylactic antibiotic regimen was started with: 2 g of ceftriaxone, intravenously every day, plus 900 mg of clindamycin, orally every eight hours. The febrile peaks persisted, and *Acinetobacter baumannii*, with sensitivity to carbapenems, was preliminarily identified in blood cultures (Table 2). This data was confirmed in the definitive report. The patient consulted with the infectious disease specialist, who indicated treatment with 500 mg of imipenem intrave-

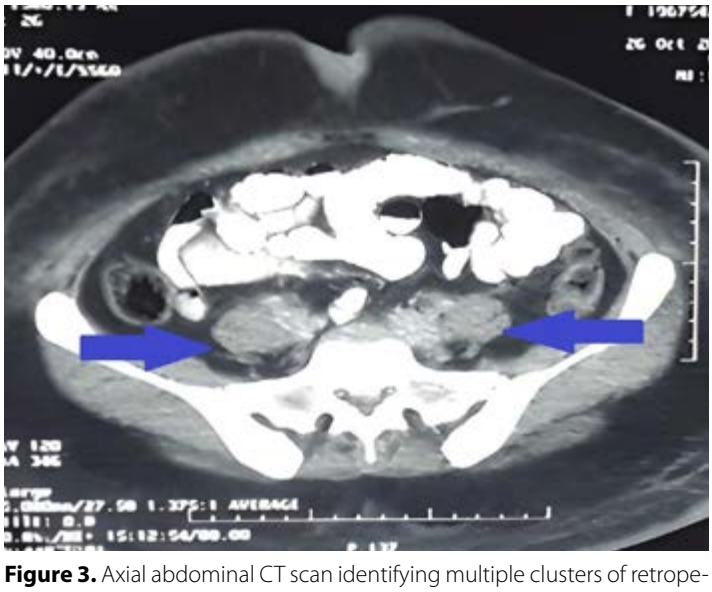


Figure 3. Axial abdominal CT scan identifying multiple clusters of retroperitoneal para-aortic adenopathy (arrows)

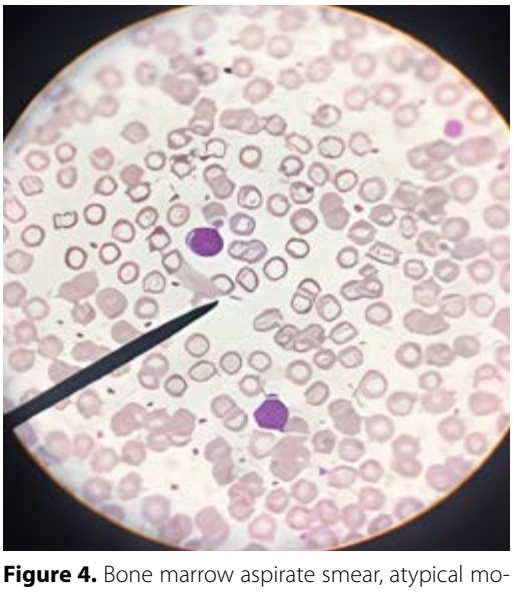


Figure 4. Bone marrow aspirate smear, atypical mononuclear cells (lymphocytes) with "cerebriform" nuclei, also called Sézary cells

nously every six hours for 14 days. The fever subsided on the second day of treatment.

Clinical evolution

The patient was discharged from the hospital due to clinical improvement with an increase in the number of white blood cells (Table 2). In addition, the outpatient follow-up plan by the hematology specialty was indicated.

After three months of oncological treatment, the patient consulted due to a week of unquantified febrile episodes, productive cough and dyspnea. The physical examination revealed bilateral basal rales and subcostal tension. As such, the patient management was in the area of maximum urgency, where she presented episodes of desaturation and frank respiratory distress. Therefore, starting mechanical ventilation was decided. During induction, the patient presented a cardiorespiratory arrest that was not reversed with resuscitation maneuvers, so she died.

Clinical diagnosis

The presence of cutaneous lesions associated with Sézary cells in bone marrow aspirate smears and the aberrant expression of markers in T lymphocytes by flow cytometry confirmed the diagnosis of Sézary syndrome as a variant of cutaneous T-cell lymphoma, eventually complicated by respiratory failure.

Discussion

SS was first described in 1938 by Sézary and Bouvrian, who described the Sézary syndrome triad, characterized by erythroderma, generalized lymphadenopathy, and the presence of neoplastic T-cells in the skin, lymph nodes, and peripheral blood[6,8].

SS corresponds to stages IVA2 and IVB of cutaneous T-cell lymphoma (T 1-4, N 0-3, M 0-1, B 0-2) according to the specific staging and classification TNMB (Table 3) proposed since 2007 by the consensus between the International Cutaneous Lymphoma Society and the Cutaneous Lymphoma Working Group of the European Organization for Research and Treatment of Cancer (ISCL/EORTC)[9-11].

SS patients present extensive and infiltrative erythroderma often manifesting with leonine facies and intense pruritus, and may also present alopecia, ectropion, mild palmo-plantar keratoderma and nail onychodystrophy[2,9]. Adenopathy, hepatosplenomegaly, associated with more than 1000/mm^3 (or >10 %) atypical mononuclear cells circulating in the bloodstream with "cerebriform" nuclei (Sézary cells), these cells can be: CD4+, CD7-, CD26- with a CD4+/CD8+ T-cell ratio >10[7,9].

Genetic factors have been implicated in its etiopathogenesis, in particular, rearrangements in the 6q23-27 region that lead to alterations in the MYB proto-oncogene and in the gene of interleukin-22 receptor subunit alpha-2 (IL22RA2)[4]; infectious factors such as human T-cell lymphotropic virus type 1, Epstein-Barr virus, cytomegalovirus and human herpesvirus type 8; immunological factors, including the lack of cytokine regulation, which influences tumor cells, where CD4 (Th2) T cells and their clones produce IL-4, IL-5, IL-6, and IL-10; and environmental factors, although their etiology remains unclear[7].

The diagnostic criteria for SS are: 80 % of erythroderma over of the body surface, abnormal lymphocyte count, presence of Sézary cells >1000 cells/mm^3, increased CD4+ cells in peripheral blood, and a CD4/CD8 ratio >10.5 % to 35 %[7,11]. A skin biopsy may be inconclusive in slightly more than half of the cases (60 %)[12]. Evidence of clonal expansion of CD4+/CD7- ≥ 40 % or CD4+/CD26- ≥30 % is also considered sufficient for diagnosis[9].

The differential diagnosis of SS includes mycosis fungoides, psoriasis, pityriasis rubra pilaris, dermatitis, hypereosinophilic syndrome and adult T-cell leukemia, primary skin disorders such as scabies, adverse drug reactions and graft-versus-host disease[2,7,13]. It is frequently delayed in diagnosis (up to six years from initial presentation) as it can mimic benign inflammatory diseases[6].

Initial evaluation of these patients includes CBC, renal function, liver function tests, lactate dehydrogenase (LDH),

Table 2. Laboratory test results for febrile process

	Febrile process	Hospital discharge
White blood cells	3,28 x 10^6/mm^3	4,08 x ,10^6/mm^3
Neutrophils	13,6 %	63,6 %
Lymphocytes	23,1 %	27,2 %
Monocytes	10,2 %	7,7 %
Hemoglobin	9,8 g/dl	10,4 g/dL
Hematocrit	30,3 %	32,3 %
Platelets	368x10^3	211x10^3

Urine test and negative urine cultures
Chest X-rays, without alveolar occupancy evidence
Blood cultures: isolated Acinetobacter baumannii sensitive to carbapenems..

chest X-ray, CT, MRI and PET-CT scans, and initial lymph node biopsy[6].

The treatment depends on the stage of the disease; those with stage IA-IIA are initiated with skin-directed therapies, such as topical steroids or phototherapy (psoralen-UV-A [PUVA] or narrow-band UVB). In stage IIB patients, localized radiotherapy can be used if they are single lesions, or gemcitabine or doxorubicin in monotherapy in multiple lesions[2,7,9]. In patients with advanced stages, chemotherapy with liposomal doxorubicin, gemcitabine or alemtuzumab can be considered. If the patients are young, consider hematopoietic stem cell transplantation or therapy with mogamulizumab, a monoclonal antibody directed against the C-C chemokine receptor 4 (CCR4), a transmembrane cell surface receptor for the chemokines CCL17 and CCL22, which play a role in cell migration and trafficking of various lymphocyte subpopulations to the skin[12,14,15].

The prognosis is poor, with an approximate five year survival of no more than 30-40 % reported[9,11].

Ethical aspects

This case report was conducted by the principles of the Declaration of Helsinki. Patient confidentiality and nonmaleficence were considered.

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