

SINDROMUL SEZARY. URMĂRIREA TIMP DE ȘAPTE ANI A UNUI PACIENT CU ERITRODERMIE, ALOPECIE DIFUZĂ, KERATODERMIE PALMO-PLANTARĂ ȘI IMPLICAREA GANGLIONILOR

SEZARY SYNDROME. SEVEN YEARS FOLLOW UP OF A PATIENT WITH ERYTHRODERMA, DIFFUSE ALOPECIA, PALMO-PLANTAR KERATODERMA, AND LIMPH NODES INVOLVEMENT

MIHAIL-ALEXANDRU BADEA*, ELENA-GABRIELA STRETE**,***,
MARIA-RALUCA TOPLICEANU****, LAURA BANIAS*****, EMOKE HORVATH*****,
SIMONA GURZU*****, DORIANA IANCU*****,
RAUL GHERASIM*****, LAURIAN STEFAN MAXIM*****

Rezumat

Sindromul Sezary (SS) reprezintă varianta leucemică a limfomului cu celule T cutanate (CTCL). Este cea mai agresivă formă cu limfom cutanat cu un anual de 1/10.000 și cuprinde 3% din toate cazurile de CTCL. Debutul bolii apare deseori cu apariția rapidă a plăcilor eritemato-scuamoase însoțite de mâncărimi severe care imită eczele, psoriazisul sau reacțiile cutanate la medicamente. Prezentăm evoluția clinică a unui pacient de 65 de ani

Summary

Sezary Syndrome (SS) represents the leukemic variant of the cutaneous T-cell lymphoma (CTCL). It is the most aggressive form of cutaneous lymphoma with an annual incidence of 1/10,000 and comprises 3% of all cases of CTCL. The onset of the disease often occurs with rapid onset of erythematous-squamous plaques accompanied by severe itching that mimic eczema, psoriasis or drug skin reactions. We present the clinical course of a 65-year-old patient diagnosed with

* Private Practice Târgu-Mureș, Mureș, Romania

** Psychiatry Department, University of Medicine, Pharmacy, Sciences and, Technology "George Emil Palade" of Târgu-Mureș, Mureș, Romania

*** Clinic of Psychiatry II Târgu-Mureş, County Hospital, Mureş, Romania

**** University of Medicine, Pharmacy, Sciences and, Technology “George Emil Palade” of Târgu-Mureș, Mureș, Romania

**** Pathology Department, University of Medicine, Pharmacy, Sciences and, Technology “George Emil Palade” of Târgu-Mureș,
Mureș, Romania

***** Department of Pathology, Emergency County Hospital Târgu-Mureș, Mureș, Romania

***** Research Center of Oncopathology and Translational Research, Târgu-Mureș, Mureș, Romania

***** Romanian Academy of Medical Sciences, Bucharest, Romania

***** ENT Department, "Sfântul Andrei" Emergency Hospital of Galați, Galați, Romania

***** Faculty of Medicine and Pharmacy, Dunarea de Jos University of Galati, Galati, Romania

***** Urology Department, University of Medicine, Pharmacy, Sciences and, Technology “George Emil Palade” of Târgu-Mureș,
Mureș, Romania

***** Clinic of Urology Târgu-Mureş, County Hospital, Mureş, Romania

***** Faculty of Medicine, Transilvania University of Braşov, Braşov, Romania

***** Emergency County Hospital Brasov, Romania

diagnosticat cu sindrom Sezary și urmărit timp de șapte ani. A fost internat pentru o erupție cutanată compusă din plăci mari eritematoase cu scuamă fină, foarte pruriginoasă care a implicat capul, trunchiul și rădăcina membrilor. Am observat, de asemenea, plăci fisurate ale palmelor și tălpilor asociate, onicholiză, poliadenopatie axilară și inghinală, astenie fizică și inapetență. Biopsiile anterioare repetate au raportat modificări histopatologice nespecifice. O nouă biopsie cutanată a evidențiat un infiltrat limfohistiocitar inflamator în dermul papilar și reticular dispus în agregate perivascularare dense cu limfocite solitare ascendente în stratul bazal și formarea unor cuiburi intraepidermice rare. Limfocitele observate la nivel interstițial au fost de dimensiuni mici și mijlocii, cu nuclee lărgite, poliedrice și conturate neregulate. A fost efectuată o citometrie în flux sanguin periferic care a detectat prezența unei clone de limfocite cu fenotip identic cu cel găsit în biopsiile cutanate. O biopsie a ganglionilor limfatici a evidențiat o arhitectură microscopică perturbată, topici, UVB nb și PUVA. Din cauza implicării multiple de organe, pacientul a murit la șapte ani după ce a fost pus diagnosticul de SS. Acest aspect este deosebit pentru acest caz, conform datelor din literatura de specialitate, speranța medie de viață după diagnosticul de SS este de aproximativ 2 ani.

Cuvinte cheie: sindrom Sézary, eritrodermie, citometrie în flux, examen histopatologic.

Sézary syndrome and followed for seven years. He was admitted for a skin eruption composed of large erythematous plaques with fine scale, highly pruritic that involved the head, the trunk and the root of the limbs. We noted also associated fissured plaques of the palms and soles, onycholysis, axillar and inguinal polyadenopathy, physical asthenia and inappetence. Repeated previous biopsies reported nonspecific histopathological changes. A new cutaneous biopsy revealed an inflammatory lymphohistiocytic infiltrate in the papillary and the reticular dermis disposed in dense perivascular aggregations with ascending solitary lymphocytes in the basal layer and the formation of rare intraepidermic nests. Lymphocytes observed at the interstitial level were small and medium in size, with enlarged, polyhedral and irregularly contoured nuclei. A peripheral blood flow cytometry was performed which detected the presence of a lymphocyte clone with identical phenotype to that found in the cutaneous biopsies. A lymph node biopsy, revealed a disrupted microscopic architecture, proliferation of medium to large-sized cells with irregular nuclear contours, hyperchromatic or vesicular nuclei, prominent nucleoli, and atypical mitoses. However, residual lymphoid follicles could be occasionally observed. After the diagnosis, the patient was treated with different agents according to the status like chemotherapy, adjuvant treatment, retinoids. Local treatment consisted in topical steroids, UVB nb and PUVA. Due to multiple organ involvement, the patient died seven years after the diagnosis of SS was performed. This aspect is highly particular for this case, according to the literature data the medium life expectancy after the diagnosis of SS is about 2 years.

Key words: Sézary syndrome, erythroderma, flow cytometry, histopathological examination.

Intrat în redacție: 25.04.2025

Acceptat: 27.05.2025

Received: 25.04.2025

Accepted: 27.05.2025

Introduction

Sézary Syndrome (SS) represents the leukemic variant of the cutaneous T-cell lymphoma (CTCL). It is the most aggressive form of cutaneous lymphoma with an annual incidence of 1/10,000 and comprises 3% of all cases of CTCL. The onset of the disease often occurs with rapid onset of erythematous-squamous plaques accompanied by severe itching that mimic eczema, psoriasis or drug skin reactions. In evolution, patients can develop asymptomatic polyadenopathy, infiltrated skin plaques, alopecia, onycholysis and keratoderma of the palms and soles [1-2]. Diagnosis criteria according to the most recent

guideline are erythroderma, generalized lymphadenopathy and the presence of clonally related neoplastic T cells with cerebriform nuclei (Sézary cells) in skin, lymph nodes and peripheral blood [3].

Case presentation

A 65-year-old patient that was admitted for a cutaneous eruption composed of large erythematous plaques with fine scale, highly pruritic that involved the head, the trunk and the root of the limbs. The patient also associated fissured plaques of the palms and soles, onycholysis, axillar and inguinal polyadenopathy, physical

asthenia and inappetence. Repeated previous biopsies reported nonspecific histopathological changes. Under systemic corticotherapy with prednisone 0.5 mg/kg/day, topical corticotherapy with methylprednisolone and NB-UVB phototherapy, the patient had a partial response and rapid relapses when corticotherapy and phototherapy were tapered. A new cutaneous biopsy revealed an inflammatory lymphohistiocytic infiltrate in the papillary and the reticular dermis disposed in dense perivascular aggregations with ascending solitary lymphocytes in the basal layer and the formation of rare intraepidermic nests. Lymphocytes observed at the interstitial level were small and medium in size, with enlarged, polyhedral and irregularly contoured nuclei. The immunophenotypic dermal and epidermal lymphoid infiltrate had a mature T helper cell profile with CD3 +, CD5 +, CD4 +, CD8- and CD20-. CD8 stains small dermal lymphocytes and few epidermal lymphocytes with the CD4 / CD8 ratio being net in favour of CD4. CD4 and CD5 reveal the lymphocyte group as dense aggregations around the superficial vascular plexus as well as the predominant interstitial cells among the collagen fibers, as aggregations in the dermal papillae and as numerous epidermal ascended lymphocytes. Thus, the histopathological aspect was highly suggestive for the SS motivation for which a peripheral blood flow cytometry was performed which detected the presence of a lymphocyte clone with identical phenotype to that found in the cutaneous biopsies.

Patients was referred to Haematology Department for further treatment. To differentiate between Sézary syndrome and HTLV-associated adult T-cell leukaemia/lymphoma (ATLL), serological testing for HTLV was carried out, indicating a negative result. CT scan showed multiple lymphadenopathies involving the mediastinum, abdomen and inguinal regions, with the largest nodes located in the retrohilar segment (2,2/1 cm), along with the right inguinal region (2.1/1.1 cm).

A further evaluation of lymphadenopathy included a right inguinal lymph node biopsy, revealing a disrupted microscopic architecture, proliferation of medium to large-sized cells with irregular nuclear contours, hyperchromatic or

vesicular nuclei, prominent nucleoli, and atypical mitoses. However, residual lymphoid follicles could be occasionally observed.

Immunohistochemical staining showed a positive reaction for CD45, CD3, and CD4, while CD20 and CD8 were negative, with few positive CD68 cells, and a 10% Ki-67 proliferation index.

Besides his underlying hematologic condition, patient has a history of chronic ischemic heart disease with premature ventricular beat arrhythmia, COPD, chronic hepatitis and mixed dyslipidaemia. Treatment included trimetazidine 35mg daily, metoprolol 25mg twice a day and fluticasone propionate inhaler.

After the diagnosis of peripheral T-cell lymphoma was confirmed, the patient initiated chemotherapy in October 2016. Since then, he completed five cycles of polychemotherapy (PCT) following the MTX-CHOP (Methotrexate-Cyclophosphamide, Hydroxydaunorubicin, Oncovin, Prednisone) regimen associated with tretinoin, but with slowly clinical improvement.

In addition, immunomodulatory therapy with interferon was initiated in September 2016 and continued through the five chemotherapy cycles. Also, patient received supportive medication consisting of gastroprotective therapy, antiemetics, and prophylactic antibiotics, while maintaining cardiac and bronchodilator treatment.

Chemotherapy-induced anaemia was noted, presenting with low haemoglobin and serum iron levels. It was managed with folic acid supplements and iron supplements. Moreover, in February 2017, the patient was administered 10 sessions of adjuvant photochemotherapy (PUVA), but the treatment failed to produce any therapeutic benefit. In 2019, the patient developed a depressive episode and was treated with paroxetine 20 mg daily with improvement of the symptoms after two months, however the agent was continued for other six months. In 2021, the patient developed multiple episodes of urinary infections and was treated in Urology Department. However, a complete urological examination, ultrasound and urography do not revealed a organic issue.

Due to multiple organ involvement, the patient died in June 2023, seven years after the diagnosis of SS was performed. This aspect is

highly particular for this case, according to the literature data the medium life expectancy after the diagnosis of SS is about 2 years.

Discussions

Sézary syndrome (SS) is a rare and aggressive form of cutaneous T-cell lymphoma characterized by the triad of pruritic erythroderma, lymphadenopathy and atypical malignant Sézary cells in the skin, blood and lymph nodes. [4] These cells, originally termed *cellules monstreuses* and observed in the setting of generalized red skin (*l'homme rouge*), were first described by Sézary and Bouvraïn in 1938. The typical Sézary cells are medium-sized to large and show the characteristic convoluted to cerebriform nucleus. [5]

Sézary syndrome presents a diagnostic challenge even for experienced clinicians due to its overlapping features with benign inflammatory dermatosis and nonspecific histopathological changes. Given the heterogeneity and indolent nature of the disease, a high degree of suspicion is required for early diagnosis. [5]

SS typically presents with erythroderma, defined as diffuse erythema affecting at least 80% of the body surface area. The differential diagnosis is extremely difficult at this stage and includes erythroderma secondary to psoriasis, atopic dermatitis, pityriasis rubra pilaris and drug reactions as well as erythrodermic mycosis fungoides (eMF). Other clinical findings often associated with Sézary syndrome include generalized lymph nodes enlargement, intense and debilitating pruritus, palmoplantar keratoderma, non-scarring alopecia, nail dystrophies, ectropion. [5, 6]

Nonetheless, erythroderma may be absent at the onset of the disease which further delays the diagnosis. Jabran-Maanaoui S et al. reported a case presenting with generalized morbilliform erythematopapular eruption and Abdul Samad K et al. reported the presence of multiple asymptomatic erythematous and skin coloured papules, plaques and nodules. According to a study conducted at Mayo Clinic, the most common cutaneous findings were erythematous patches and plaques. Patients may or may not develop

erythroderma following these skin eruptions [7-9].

Skin biopsy, preferably deep punch biopsies or an excisional or incisional biopsy from the most representative skin lesions, should be performed for histopathology and immunohistochemical analysis as a next step to confirm the diagnosis of SS. Even if an appropriate biopsy specimen is obtained, a definitive diagnosis is not always possible. In up to one-third of skin biopsies from patients with otherwise classic SS, the histopathological findings may be nonspecific (spongiotic or psoriasiform dermatitis) and can also be found in many benign inflammatory dermatoses or in reactive conditions such as lymphomatoid drug eruption. Regarding the evolution of our patient, when there is high clinical suspicion of CTCL it is justified to perform repeated skin biopsies. [10, 11]

The most commonly noted histopathologic features in SS include the presence of a dermal perivascular to bandlike or interface lymphoid infiltrate at the dermoepidermal junction, with lymphocytic cytologic atypia and reactive epidermal changes, such as mild spongiosis, acanthosis and parakeratosis, but these changes are also described in benign conditions. [12] Many cases will lack epidermotropism or Pautrier microabscesses, usually seen in MF. The neoplastic T cells have CD3+, CD4+, CD8-phenotype, characteristically lack CD7 and CD26 expression. Immunohistochemical studies showing a CD4 predominance and the expression of programmed death-1 (PD-1; CD279) is also helpful for diagnosis [5, 10].

Taking into consideration that both clinical presentation and histopathological findings may be nonspecific, evidence of peripheral blood involvement is imperative for the diagnosis of Sézary syndrome. Therefore, flow cytometry of peripheral blood is of great value as it can detect neoplastic cells. Peripheral blood findings such as CD3+, CD4+, CD8-, CD45RO+ and abnormalities including elevated CD4/CD8 ratio, aberrant CD26, CD27 and CD7 expression and T-cell clonality along with clues such as eosinophilia are evocative of Sézary syndrome. The loss of CD7 or CD26 is sensitive and highly specific for SS. [11,12]

The neoplastic CD4+ T cells have the ability of circulating between skin, lymph nodes and peripheral blood in SS [13]. For a positive diagnosis it is mandatory to identify clonally related T-cells in the peripheral blood and in the lymph nodes, by performing blood flow cytometry as mentioned above, and lymph node excision, respectively. Ultrasound, computer tomography, positron emission tomography or MRI scans can be used for visualization and confirmation of lymphadenopathy before the biopsy is performed. Histopathological examination of involved lymph nodes showed a dense,

monotonous infiltrate of Sézary cells with complete effacement of the normal lymph node architecture. [6, 10]

The diagnosis of Sézary syndrome raises difficulties, but integration of a thorough physical examination alongside histology and peripheral blood findings is crucial for the diagnosis and treatment. Increasing awareness of this diagnosis for early detection and multidisciplinary approach between dermatologists, pathologists and hematologists, are key factors in the management of the disease.



Figure 1. Clinical aspect: a) Erythema, scales and diffuse alopecia of the scalp and eyebrows; b) Diffuse erythroderma; c) Palmar keratoderma with fissures

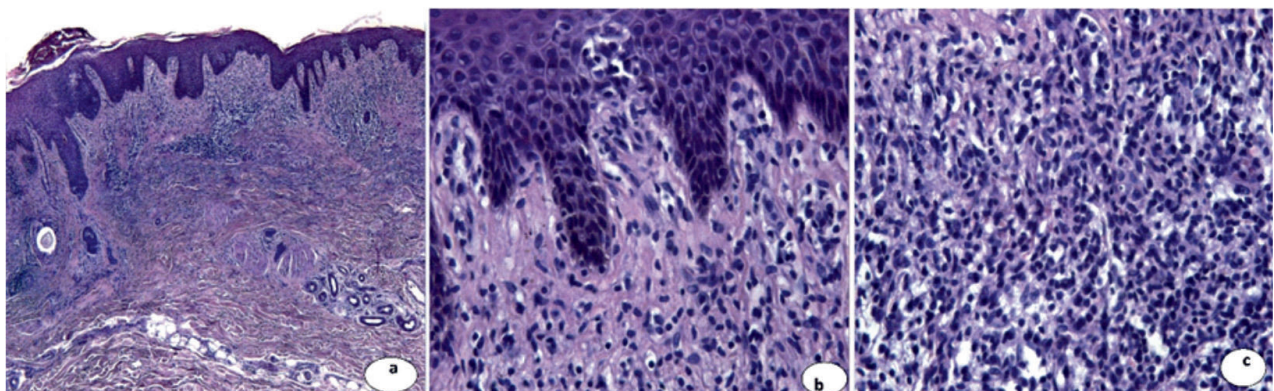


Figure 2. Skin biopsy: a, b, c) inflammatory lymphohistiocytic infiltrate in the papillary and the reticular dermis disposed in dense perivascular aggregations with ascending solitary lymphocytes in the basal layer and the formation of rare intraepidermic nests. Lymphocytes observed at the interstitial level were small and medium in size, with enlarged, polyhedral and irregularly contoured nuclei

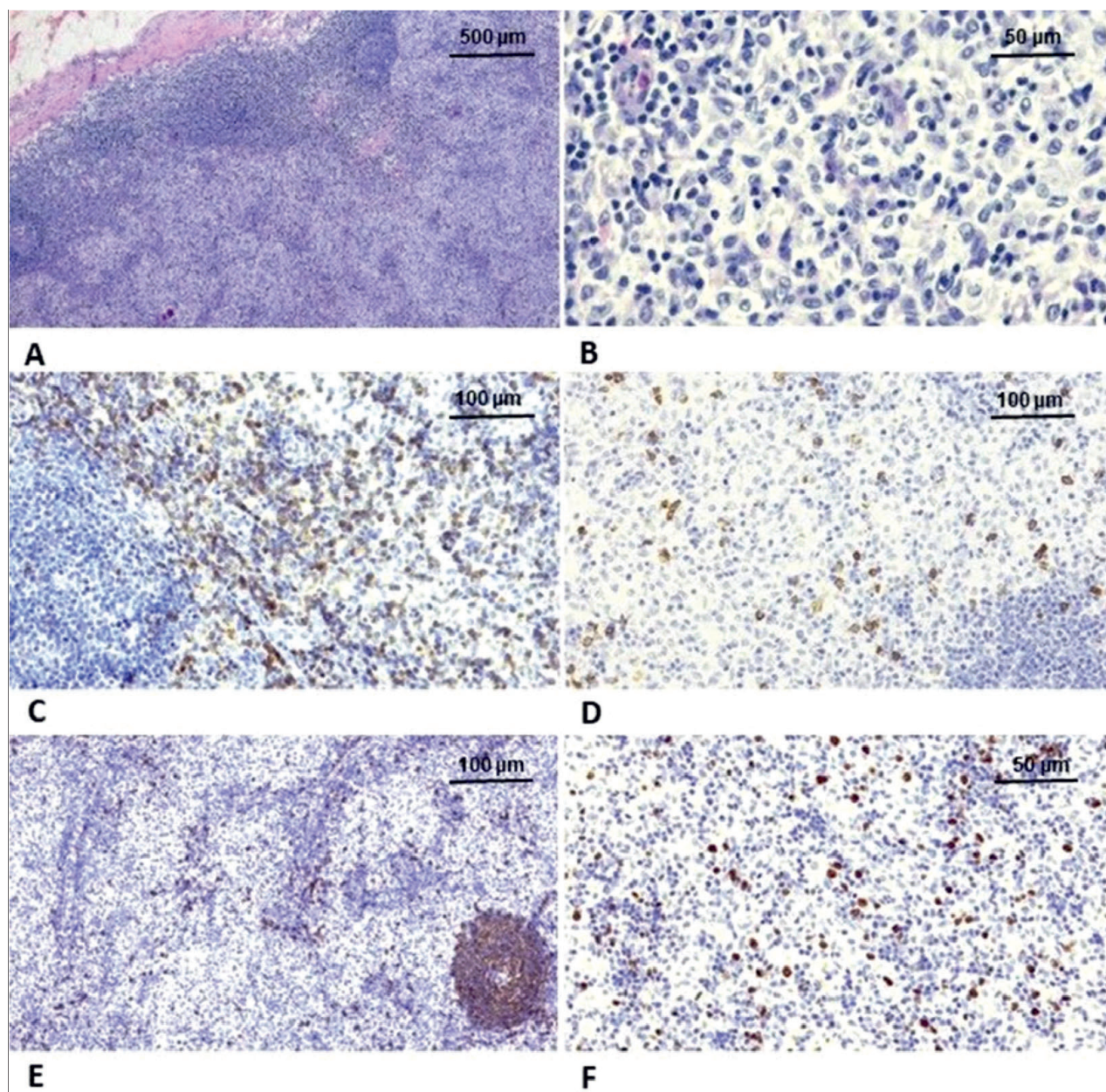


Figure 3. Lymph node biopsy.

The examined lymph node shows an effaced structure (A), replaced by a proliferation of medium- and large-sized cells with marked nuclear pleomorphism, characterized by hyperchromatic or vesicular nuclei, irregular contours, prominent nucleoli, and atypical mitoses (B). The tumor cells express the immunohistochemical marker CD4 (C) and are negative for CD8 (D) and CD20 (E), with a proliferation index Ki-67 of approximately 10% (F).

Conclusion

SS may evolve for a period of time with uncharacteristic clinical and histopathological changes. A clinical suspicion of SS may require

multiple cutaneous biopsies as well as confirmation of the leukemic determination by peripheral blood flow cytometry.

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Conflict de interese
NEDECLARATE

Conflict of interest
NONE DECLARED

Adresa de corespondență: Elena-Gabriela Strete
Departamentul de Psihiatrie, Universitatea de Medicină, Farmacie, Științe și Tehnologie „George Emil Palade” din Târgu-Mureș, Mureș, România
e-mail: elena.buicu@umfst.ro

Correspondance address: Elena-Gabriela Strete
Psychiatry Department, University of Medicine, Pharmacy, Sciences and, Technology “George Emil Palade” of Târgu-Mureș, Mureș, Romania
e-mail: elena.buicu@umfst.ro