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Case Report

MELANODERMA AS AN EARLY CLINICAL MANIFESTATION OF SÉZARY SYNDROME

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Abstract

Primary cutaneous lymphomas are a heterogeneous group of hematologic malignancies originating from the T-cells or B-cells residing within the human skin. More than two-thirds (70-85%) of cases are diagnosed as cutaneous T-cell lymphomas (CTCL), with Mycosis fungoides and Sézary syndrome being the most notable. CTCL have an annual incidence of 10 cases per 1 million, with a predominance to males over the age of 50 (male-to-female ratio of 2:1).

Here, we report a case of a 54-year-old female who presented with persistent and generalized hyperpigmentation, later evolving into Sézary syndrome. Initially, the patient was referred to the University Clinic for Dermatology in Skopje, due to a five-month medical history of persistent pruritus and hyperpigmentation. Based on the clinical presentation and skin biopsy findings consistent with non-specific dermatitis, she was diagnosed as having atopic dermatitis and underwent treatment with topical steroids and emollients. However, the clinical presentation got worse in the following six months, and evolved into generalized melanodermia with ulcerated tumor growths. In order to conclude the final diagnosis, a biopsy of the skin lesions was performed with histopathological findings consistent with Sézary syndrome. Following this diagnosis, the patient was referred to the University Clinic for Hematology in Skopje for further treatment.

Keywords: primary cutaneous lymphomas, cutaneous T-cell lymphomas, Sézary syndrome, melanodermia

Introduction

The human skin comes after the gastrointestinal tract, as the most common "birthplace" of the primary extranodal non-Hodgkin lymphomas[1]. In most cases (70-85%), primary cutaneous lymphomas arise from the T-cell line (CTCL), whereas primary cutaneous B-cell lymphomas (CBCL) represent a minority [1-3]. CTCLs are heterogeneous group of T-cell malignancies originating from the memory T-lymphocytes residing in the human skin. Notably, two distinctive clinical entities - Mycosis fungoides (MF) and Sézary syndrome (SS) stand out, as they constitute more than 50% of all primary cutaneous lymphomas [1]. Majority of patients diagnosed with a CTCL are males over the age of 50 with a male-to-female ratio of 2:1, i.e. the incidence of CTCLs tend to increase with advanced age [3,4]. Epidemiological studies show that the incidence of CTCL has tripled since the early 1980s, now exceeding 10 cases per million annually [1].

The diagnosis of CTCLs relies on combination of clinical presentation, histopathology, immunophenotyping with flow cytometry and molecular tests (e.g. PCR, Southern blot technique, next-generation sequencing) looking for T-cell receptor (TCR) rearrangements. Once the diagnosis is confirmed, the disease must be staged using the TNMB classification. T1-T4 stands for skin lesions, N0-N3 for lymph nodes involvement, M0-M1 for visceral involvement, and B0-B2 for peripheral blood involvement [1]. Despite advancements in chemotherapy protocols and personalized treatment approach, the prognosis of Sézary syndrome remains poor. The five-year survival is estimated to be 40-50%, with septicemia being the leading cause for death among patients with SS [5,6].

Case report

We report the case of a 54-year-old female with persistent melanodermia for 2 years that ultimately progressed into Sézary syndrome. The patient was first referred to the University Clinic for Dermatology in Skopje back in January, 2020. She reported a history of mild itchiness and pigmentation that had begun on her back two years earlier, which had progressed to generalized itch five months prior to consultation. At the time, she was diagnosed with atopic dermatitis and treated with topical steroids and emollients.

However, in May 2021, the patient returned with complaints of mild pruritus and diffuse hyperpigmentation (Fig.1). An initial skin biopsy showed a superficial perivascular lymphocytic infiltrate and mild spongiosis, findings consistent with atopic dermatitis. Additional findings included melanocytic hyperpigmentation of the basal layer of the epidermis and melanophages in the upper dermis.

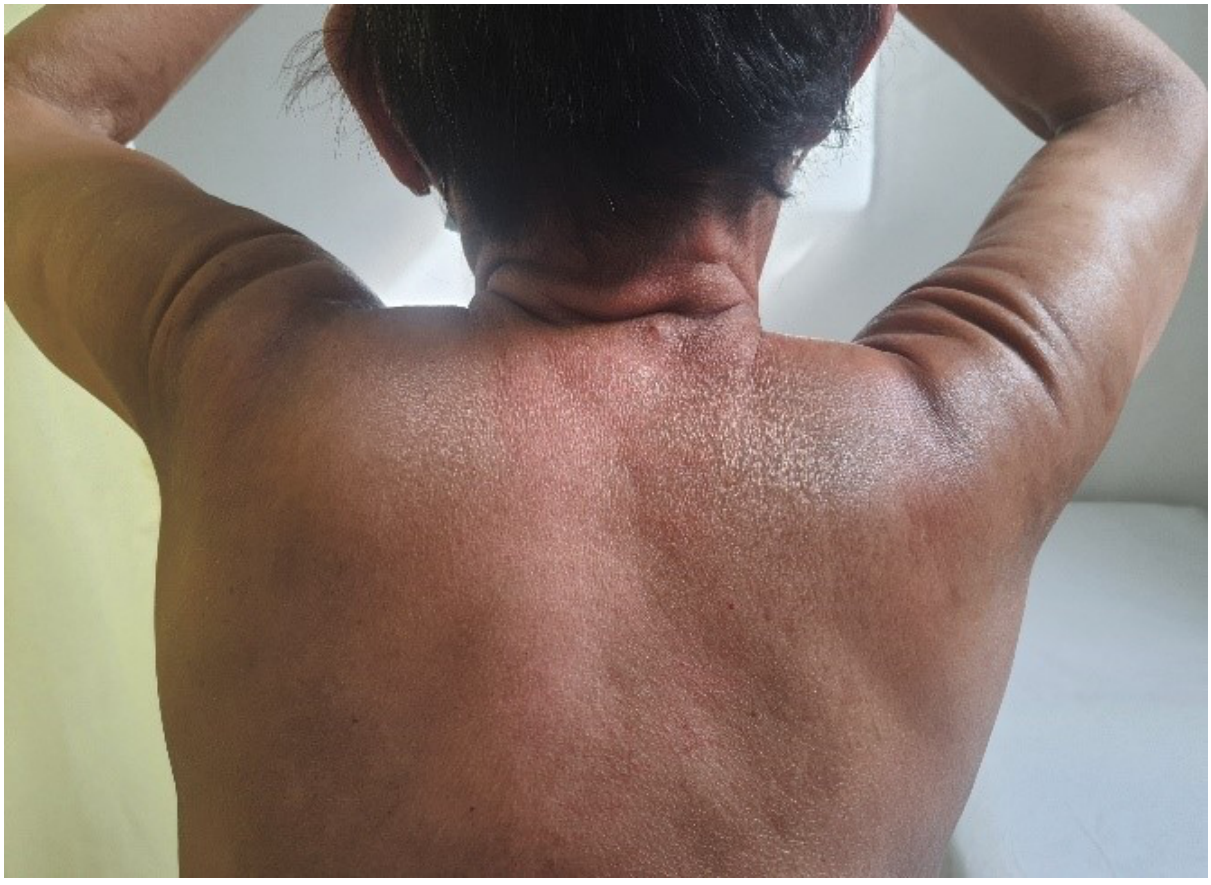

Fig.1. Melanodermia

Within a few months, the patient's skin condition progressed to generalized darkening, affecting more than 90% of the body surface area. A rebiopsy of the skin was performed, which revealed features consistent with the diagnosis of Sézary syndrome: a dense band of lymphoid cells beneath the epidermis, intermediate in size with irregular nuclear contours and occasional larger cells with prominent nuclei. Epidermotropism was not prominent. Skin biopsy showed the presence of Sézary cells with cerebriform nuclei without signs of epidermal lymphocytic infiltrate. Flow cytometry report showed immunophenotype of T-lymphocytes consistent with Sézary syndrome. During the ongoing diagnostic procedures, the patient experienced rapid development of nodular and tumor growths (Fig.2 and Fig.3) with subsequent ulcerations (Fig. 3 and Fig.4).

Further imaging evaluation was initiated to assess the disease extension. A computed tomography (CT) scan of the thorax, abdomen and pelvis showed no evidence of lymphadenopathy or hepatosplenomegaly. Based on the clinical, histopathological, and radiological findings, the patient was diagnosed to have Sézary syndrome and was transferred to the University Clinic for Hematology for specialized treatment.

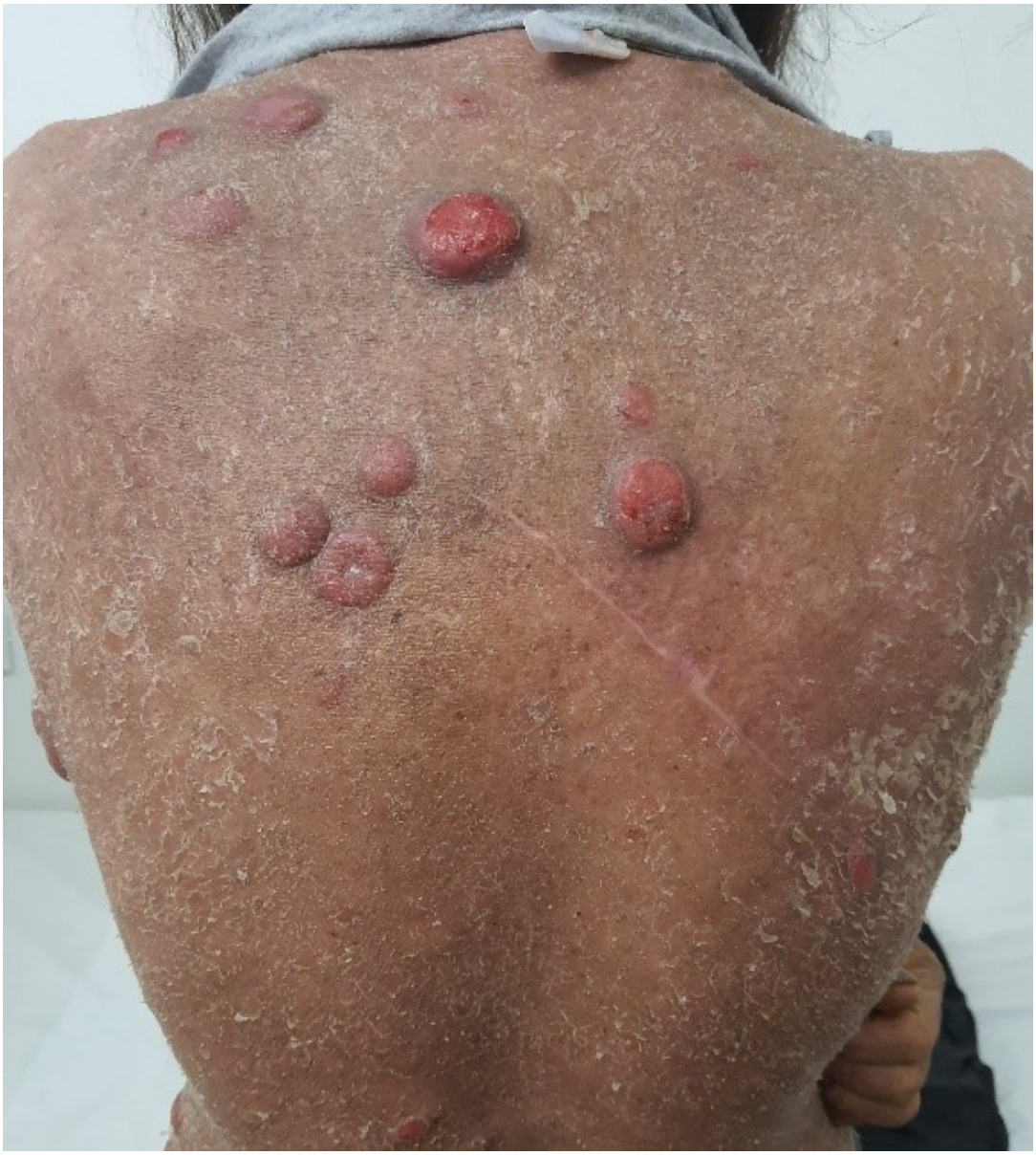

Fig. 2. Generalized melanodermia with ulcerated tumor growths

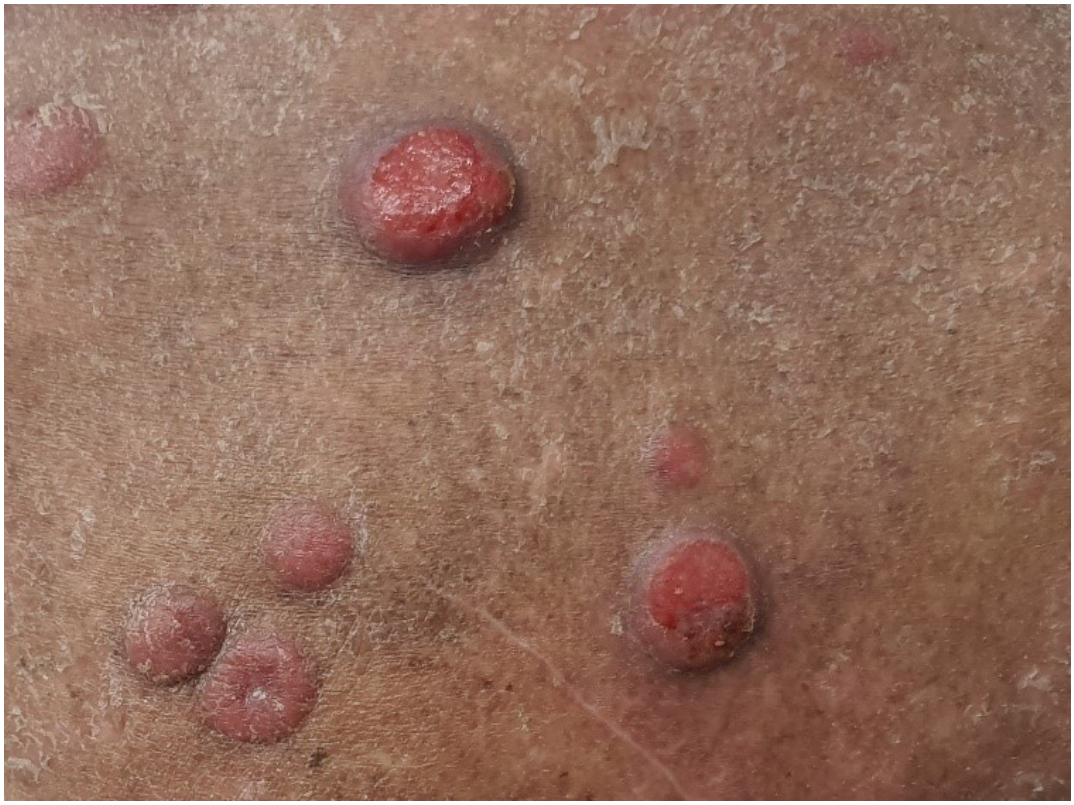

Fig. 3 Advanced stages with ulcerated tumors

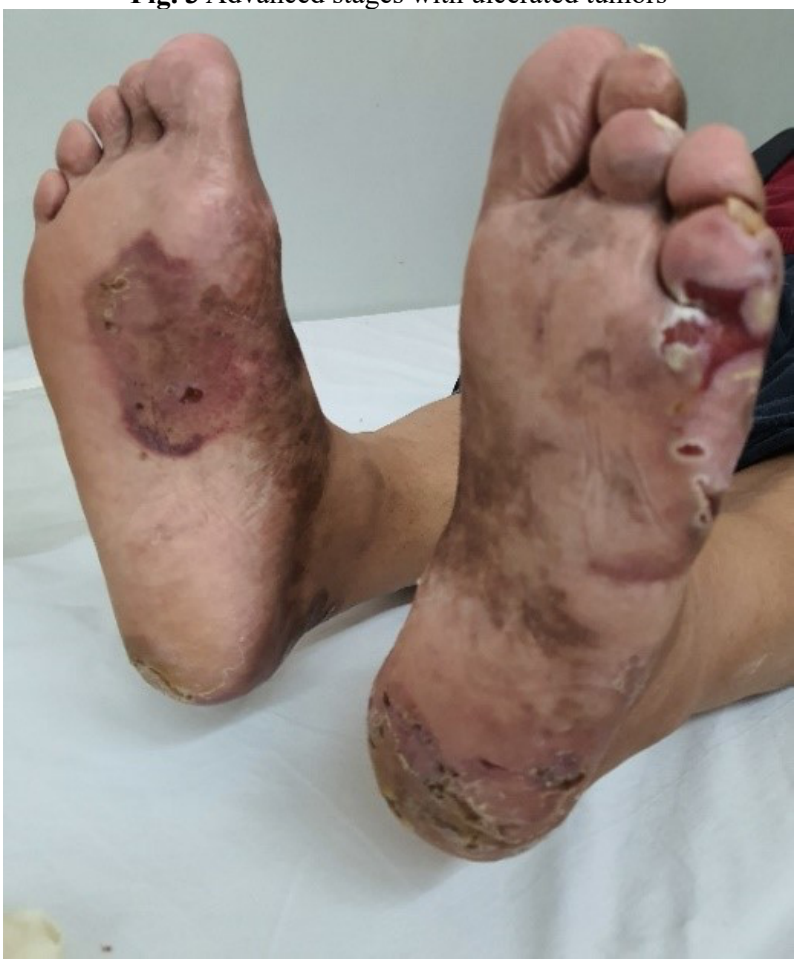

Fig.4 Neoplastic ulcerations on feet

Discussion

The pathogenesis of skin lymphomas remains an enigmatic puzzle, posing a challenge that continues to elude scientific understanding. One proposed theory suggests that different endogenous and/or environmental factors can chronically trigger T-cells via antigen presenting cells leading to accumulation of mutations in tumor suppressor genes and/or oncogenes [1,5].

The majority of patients with skin lymphomas are diagnosed with either Mycosis fungoides or Sézary syndrome. According to the World Health Organization and European Organization for Research and Treatment of Cancer (EORTC) classification of Mycosis fungoides, clinicians recognize the classic Albert-Bazin form named after the physicians Jean-Louis-Marc Alibert and Pierre-Antoine-Ernest Bazin, who first described MF in 1806, as well as three variants: folliculotropic MF, pagetoid reticulosis, and granulomatous slack skin. Each form of MF has specific clinical presentation, dermatopathological findings, and clinical behavior [1]. However, clinicians should be aware of certain rare subtypes of MF, such as: granulomatous, hyperpigmented, ichthyosiform, syringotropic, papular, purpuric, interstitial, pustular, bullous, verrucous, and psoriasiform MF [1].

Sézary syndrome (SS) is a leukemic form of CTCL described by Albert Sézary and Yves Bouvrain in 1938 [5]. The median age of diagnosis for SS is 60-65, indicating that it primarily affects the elderly. The clinical triad of erythroderma, lymphadenopathy, and circulating Sézary cells > 1000μL with prominent cerebriform nuclei distinguishes SS from other CTCLs [1,5]. Additionally, patients present with pruritus, onychodystrophy, palmoplantar keratoderma, facies leonine, and non-scaring alopecia [1,5]. Among these symptoms, intense pruritus is the most common, affecting 80% of MF patients and all SS patients. The severe itchiness can lead to skin destruction and significantly reduce the quality of life. Regarding systemic symptoms, a literature review conducted by Morris *et al.* found they are infrequently present among SS patients. Out of 505 SS patients included in the study, only 8 (1.6%) reported B symptoms, such as fever, night sweats, and weight loss [1]. SS erythrodermic patients are classified into three distinct clinical morphological phenotypes: erythrodermic, infiltrative, and melanodermic [7].

The histopathological report on Sézary cells presented in the skin, enlarged lymph nodes, and peripheral blood is fundamental for diagnosing the Sézary syndrome. Beside the histopathology, further immunophenotyping of malignant T-cells and molecular tests on T-cell receptor (TCR) rearrangements are necessary for making the diagnosis conclusive [1,5,6]. Flow cytometry findings consistent with Sezary syndrome include: CD3+ CD4+ T-lymphocytes, with CD4/CD8 ratio of ≥10; increased CD4+ cells with abnormal phenotype (CD4+CD7- ratio of 40% or more and/or CD4+CD26- ratio of 30% or more). Staging follows the TNMB system. More detailed overview on Sézary cell's immunophenotype in Sézary syndrome as a diagnostic criterion is presented in Table 1.

Table 1. Immunophenotype of malignant T-cells in Sézary syndrome [1]

Immunophenotype diagnostic criteria in Sézary syndrome	
Immunophenotype of Sézary cells ≥1000 cells/μL	**CD4/CD8 ratio ≥ 10** **CD4 + CD7- ≥ 40%** **CD4 + CD26- ≥ 30%**
Additional immunophenotyping markers	CCR7+, L-selectin+, CD27+, CCR4+, skin-homing receptors + (CCR6, CCR10, CLA), CD3+, CD4+, CD45RO+, CD8-

Legend. + (positive), - (negative); CCR4 and CLA (confer tropism to the skin); CCR7 and L-selectin (confer tropism to the lymph nodes); CD3+, CD4+, CD45RO+, CD8- (memory T-cells antigens)

The term "melanoerythroderma" refers to a generalized erythrodermic skin condition with diffuse brownish-red discoloration of the skin, rather than representing a distinct diagnosis. Hyperpigmented mycosis fungoides is a rare clinical phenotype, with only eight cases reported to date. This clinical variant is characterized by hyperpigmented macules or patches without poikilodermatous changes and has a higher incidence among younger patients with dark complexions. Hyperpigmented mycosis fungoides is predominantly associated with a CD8+ phenotype [8].

A multimodal treatment approach is necessary for Mycosis fungoides and Sézary syndrome. This includes skin-directed therapies (e.g. topical treatments, ultraviolet phototherapy, and radiotherapy) and systemic therapies (e.g. retinoides, interferon α, chemotherapy, and biological response modifiers). For patients with more advanced stages of MF/SS, allogenic bone marrow transplant (alloSCT) and extracorporeal photopheresis are the therapies of choice. Although alloSCT can provide prolonged remissions, it is associated with risks such as graft-versus-host disease, increased susceptibility to infections, and procedure-associated morbidities [9,10].

Conclusion

In this article, we report a rare case of a patient with Sézary syndrome presenting with melanoderma and pruritus as the initial clinical signs, ultimately followed by ulcerative tumor growth eruptions. Primary skin lymphomas are rare malignancies that are often overlooked by clinicians or misdiagnosed as atopic dermatitis. Furthermore, epidemiological data indicate an increased incidence over the past few decades, underscoring the importance of heightened awareness of skin lymphomas, particularly among the elderly.

Conflict of interest statement. None declared.

References:

1. Miyashiro D, Sanches JA. Mycosis fungoides and Sézary syndrome: clinical presentation, diagnosis, staging, and therapeutic management. *Front Oncol*. 2023 Apr 14;13:1141108. doi: 10.3389/fonc.2023.1141108.
2. Hristov AC, Tejasvi T, Wilcox RA. Mycosis fungoides and Sézary syndrome: 2019 update on diagnosis, risk-stratification, and management. *Am J Hematol*. 2019 Sep;94(9):1027-1041. doi: 10.1002/ajh.25577.
3. Lee H. Mycosis fungoides and Sézary syndrome. *Blood Res*. 2023 Apr 30;58(S1):66-82. doi: 10.5045/br.2023.2023023.
4. Latzka J, Trautinger F. Mycosis fungoides and Sézary syndrome - Review and outlook. *J Dtsch Dermatol Ges*. 2023 Apr;21(4):386-391. doi: 10.1111/ddg.15051. Epub 2023 Mar 27.
5. Miyashiro D, Souza BCE, Torrealba MP, Manfrere KCG, Sato MN, Sanches JA. The Role of Tumor Microenvironment in the Pathogenesis of Sézary Syndrome. *Int J Mol Sci*. 2022 Jan 15;23(2):936. doi: 10.3390/ijms23020936.
6. García-Díaz N, Piris MÁ, Ortiz-Romero PL, Vaqué JP. Mycosis Fungoides and Sézary Syndrome: An Integrative Review of the Pathophysiology, Molecular Drivers, and Targeted Therapy. *Cancers*. 2021;13(8):1931. doi: 10.3390/cancers13081931.
7. Roccuzzo G, Giordano S, Avallone G, Rubatto M, Canonico S, Funaro A, Ortolan E, Senetta R, Fava P, Fierro MT, Ribero S, Quaglino P. Sézary Syndrome: Different Erythroderma Morphological Features with Proposal for a Clinical Score System. *Cells*. 2022 Jan 20;11(3):333. doi: 10.3390/cells11030333.

8. Lu YY, Wu CH, Lu CC, Hong CH. Hyperpigmentation as a peculiar presentation of mycosis fungoides. *An Bras Dermatol*. 2017;92(5 Suppl 1):92-94. doi: 10.1590/abd1806-4841.20175544.
9. Quaglino P, Pimpinelli N, Berti E, Calzavara-Pinton P, Alfonso Lombardo G, Rupoli S, Alaibac M, Bottoni U, Carbone A, Fava P, Fimiani M, Mamusa AM, Titli S, Zinzani PL, Bernengo MG; Gruppo Italiano Linfomi Cutanei. Time course, clinical pathways, and long-term hazards risk trends of disease progression in patients with classic mycosis fungoides: a multicenter, retrospective follow-up study from the Italian Group of Cutaneous Lymphomas. *Cancer*. 2012;118(23):5830-9. doi: 10.1002/cncr.27627.
10. Latzka J, Assaf C, Bagot M, Cozzio A, Dummer R, Guenova E, Gniadecki R, Hodak E, Jonak C, Klemke CD, Knobler R, Morrris S, Nicolay JP, Ortiz-Romero PL, Papadavid E, Pimpinelli N, Quaglino P, Ranki A, Scarisbrick J, Stadler R, Väkevä L, Vermeer MH, Wehkamp U, Whittaker S, Willemze R, Trautinger F. EORTC consensus recommendations for the treatment of mycosis fungoides/Sézary syndrome - Update 2023. *Eur J Cancer*. 2023 Dec;195:113343. doi: 10.1016/j.ejca.2023.113343.