STAGE II MYCOSIS FUNGOIDES ASSOCIATED WITH MYELODYSPLASTIC SYNDROME – CASE REPORT

MICOZIS FUNGOID STADIUL II ASOCIAT CU SINDROM MIELODISPLAZIC – CAZ CLINIC

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Abstract

Keywords:

mycosis fungoides, myelodysplasitc syndrome, immunosuppression

Cutaneous T cell lymphomas (CTCL) represent 65% of all cutaneous lymphomas. Mycosis fungoides is the most common form of CTCL, consisting in a clonal proliferation of T CD4+ and CD45Ro+ cells. It can coexist with a series of malignant hemopathies. Myelodysplastic syndromes (MDS) are clonal disorders of the hematopoietic stem cell with cytopenia and hyper-/normocellular bone marrow and signs of dyshematopoiesis, evolving into acute leukemia in a significant number of cases. We report a case of stage II MF associated with myelodysplastic syndrome.

Rezumat

Cuvinte-cheie:

micozis fungoid, sindrom mielodisplazic, imunosupresie

Limfoamele cutanate cu celule T (CTCL) reprezintă 65% din totalul limfoamelor cutanate. Micozisul fungoid (MF) este cea mai frecventă formă de CTCL și reprezintă o proliferare clonală a celulelor T CD4+, CD45Ro+. Acesta poate coexista cu o serie de hemopatii maligne. Sindroamele mielodisplazice (SMD) sunt afecțiuni clonale ale celulei stem hematopoietice, caracterizate prin citopenii cu măduvă hiper/normocelulară, cu semne de dishematopoieză multiliniară și, într-un procent semnificativ din cazuri, progresie către leucemii acute.
Noi prezentăm un caz de MF stadiul II asociat cu sindrom mielodisplazic.

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Introduction

Cutaneous lymphomas represent a heterogeneous group of malignant hemopathies originating in the immune system, undergoing various phases of differentiation (1). The etiopathogenesis of these conditions remains unknown, as it is currently considered that multiple factors are involved, with an important role for the genetic, infectious, physical and chemical factors. Mycosis fungoides (MF) affects mostly adults between 55 and 60 years of age, with a male/female ratio of 2/1. The incidence of this condition varies between 6.4–9.6/1000000 population in the USA (2). It represents a form of CTCL with a favorable outcome and a slow evolution. MDS has a prevalence of 2-10/100000 population, increasing with age and therefore reaching 50/100000 population after 70 years old. The male-to-female ratio is in favor of males (3).

Clinical case

A 67-year-old patient from the rural area requested a dermatologic consult for a rash consisting of purple-erythematous plaques and placard, slightly scaly, infiltrated clearly defined, outline circinate, intensely itchy, disseminated on the limbs and trunk, that had appeared three weeks before (Figures 1 and 2). The patient had been diagnosed with MDS five years ago, being monitored in the Hematology Department where he was receiving supportive treatment consisting in blood products, antibiotics, iron chelation therapy and hematopoietic growth factors

Past medical history: myelodysplastic syndrome; severe secondary anemia; secondary hemochromatosis; chronic hepatitis B; stage 2 essential hypertension. All conditions had been diagnosed in 2010.

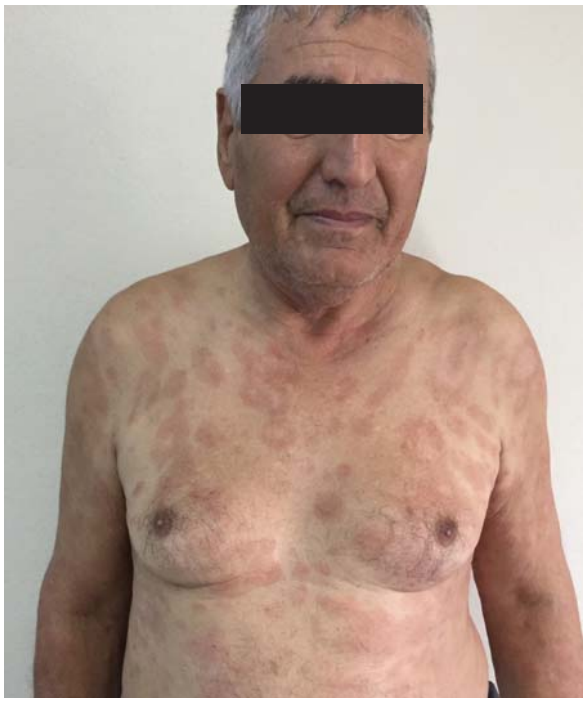

Figure 1. Clinical aspect at admission

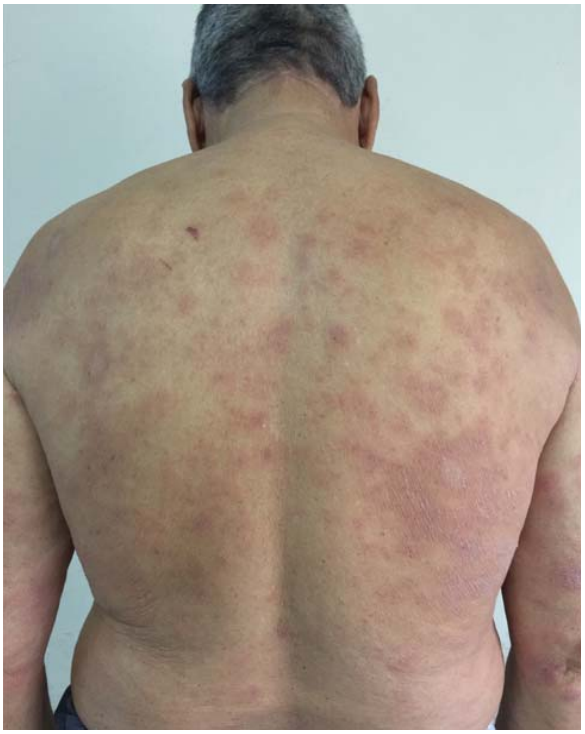

Figure 2. Clinical aspect at admission

Physical examination: fair general condition; class 1 obesity (BMI = 31 kg/m^2); bilateral, mobile, non-tender, non-painful axillary lymph nodes of about 1cm in diameter; inferior liver edge 3 cm below the costal margin; slightly distended, non-painful abdomen; inappetence; physical fatigue.

Laboratory tests: Red blood cell count 2.78 mil/mm^3, hemoglobin 7.57 g/dL, white blood cell count 2800/mm^3, platelet count 96500/mm^3, neutrophils 48.2%, lymphocytes 35%, monocytes 9.32%, eosinophils 6.21%, basophils 1.27%; MCV 80.9 fL, hematocrit 22.5%, MCH 27.3 pg, MCHC 33.7 g/dL, ferritin 4009 ng/mL (N = 28-365 ng/mL), ESR 85 mm/h, 130 mm/2 h, urea 69 mg/dL, blood glucose level 112 mg/dL, serum creatinine 1.0 mg/dL, γ-GT 40 U/L, GOT 32 U/L, GPT 73 U/L, ALP 61 U/L, total protein 6.9 g/dL; urinalysis: frequent mucus, yeasts, rare calcium oxalate.

Histopathological examination revealed parakeratosis and areas of spongiosis in the epidermis with the tendency to form intraepidermal microvesicles. The underlying dermis is infiltrated with mostly perivascular lymphoid cells with moderate nuclear atypia. Rare mitosis was present with an epidermotropism aspect. The histological aspect suggested mycosis fungoides (Figures 3 and 4).

Based on the clinical aspect, lab investigations, and histological and immunohistochemical examinations, we established the following diagnosis: stage II Mycosis fungoides; myelodysplastic syndrome; secondary severe anemia; secondary hemochromatosis; chronic hepatitis B; stage 2 essential hypertension.

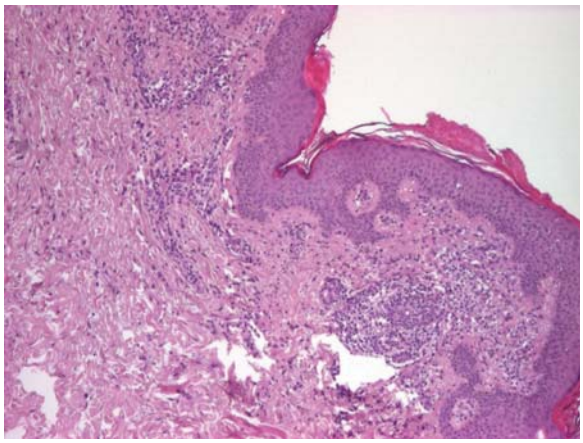

Figure 3. Col HEx40. Parakeratosis, spongiosis and lymphocytic infiltrate in the dermis

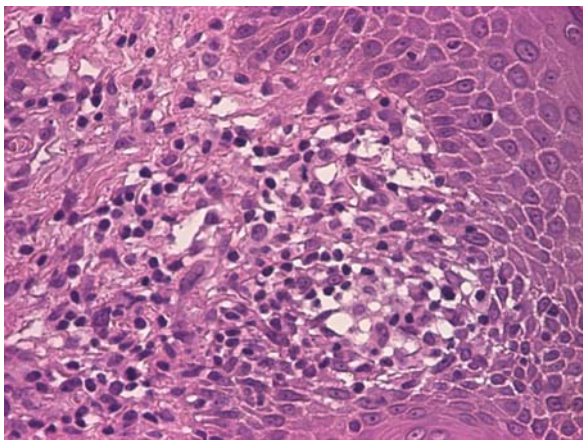

Figure 4. Col HE x200. Moderate nuclear atypia, epidermotropism

At discharge, the patient received systemic antihistaminic treatment (levocetirizine 1 tablet od) and local treatment with ichthyol and nystatin with class III dermatocorticoids once daily. The outcome was positive after three weeks. The patient was referred to the Hematology Department.

Discussion

Cutaneous lymphomas represent a heterogeneous group of malignant hemopathies originating in the immune system, undergoing various phases of differentiation. These conditions can be primitive, representing malignant lymphoproliferative disorders originating in the skin, or secondary, consisting in a cutaneous involvement of another type of lymphoma (1). The incidence is 1:100000 population and the male-to-female ratio is in favor of males (2).

The etiopathogenesis of these conditions remains unknown, as it is currently considered that multiple factors are involved, with an important role for the genetic, infectious, physical and chemical factors.

After a long debate regarding a classification system, in 2005, WHO-EORTC classified cutaneous lymphomas based on the biological profile, the clinical aspect and the outcome. This classification was updated in 2008 (4, 5).

The 2008 WHO classification of primitive cutaneous lymphomas:

Indolent
- mycosis fungoides
- MF variants:
    - folliculotropic MF
    - pagetoid reticulosis
    - granulomatous slack skin
- primary cutaneous anaplastic large cell lymphoma (CD30+)
- lymphomatoid papulosis (CD30+)
- subcutaneous panniculitis-like T-cell lymphoma
- primary cutaneous CD4+ small/medium-sized pleomorphic T-cell lymphoma

Aggressive
- Sézary syndrome
- primary cutaneous NK/T-cell lymphoma
- primary cutaneous γ/δ T-cell lymphoma
- primary cutaneous peripheral T-cell lymphoma, other

In 1975, Lutzner and Edelson introduced the term cutaneous T-cell lymphoma (CTCL), including mycosis fungoides and Sézary syndrome in this category. MF represents 40% of all cutaneous lymphomas (6-8).

MF was first described in 1806 by Jean L Alibert. It is the most common subtype of CTCL. It consists in a clonal proliferation of T CD4+ and CD45Ro+ cells. The clinical aspect varies from single lesion MF and Woringer-Kolopp syndrome to generalized subtypes with extended tumors and erythrodermia (2).

MF's etiopathogenesis is little-known. Although many theories have been formulated regarding the involvement in MF's pathogenesis of solvents, chemical substances and infectious agents, such as human T-lymphotropic virus type 1 (HTLV-1) that was found in peripheral blood and in cutaneous lesions in a large number of patients, none have been confirmed (7). It was also suggested that some cytokines are essential in MF's pathogenesis (cytokines released by Th1 and Th2: INFγ, IL-2, IL-4, IL-5 and IL-10). In the plaque stage of MF, mRNA of cytokines released by Th1 and Th2 was detected, while during the progression towards the tumor stage, mRNA of cytokines released by Th2, IL-4 and IL-5, appears to be increased (9, 10).

MF can occur in patients that underwent organ transplantation without being related to opportunistic infections or immunosuppression (11). Other lymphoproliferative cutaneous disorders, such as lymphomatoid papulosis, can precede or succeed MF. It can also coexist with a series of lymphoid B-cell malignant disorders, like chronic lymphocytic leukemia (CLL) and monoclonal gammopathy. Finally, it was suggested that this condition is caused by malignant transformation of T cells secondary to persistent antigenic stimulation or chronic inflammation (2).

MF usually affects adults aged between 55 and 60, with a male-to-female ratio of 2/1. In the USA, the incidence of this condition varies between 6.4 and 9.6/1000000 population/year. It is a subtype

of CTCL with a favorable outcome and a slow evolution (2).

The diagnosis in early stages is often difficult, with a mean period between the condition's debut and the diagnosis of approximately 48 months (12).

The differential diagnosis in our case included: large plaque parapsoriasis, psoriasis, contact allergic eczema, tinea corporis, drug-induced rash.

In the early stages, MF has a favorable prognosis, with an overall five-year survival rate of 87-89% and 75% at 10 years (2).

Medical literature states multiple factors that are associated with a poor prognosis: male gender, old age, late disease stage, increased lactate dehydrogenase, presence of follicular mucinosis, moderate/severe lymphocytic atypia, Pautrier's microabscesses consisting in more than 10 atypical lymphocytes, a decrease of CD7 and CD8 lymphocytes (1).

Our patient's evolution six months after discharge was favorable, with a decreased pruritus and a significantly reduced rash (Figure 5). Regarding MF's therapy, there are multiple options for each stage of the disease, but none of these is well-defined and the treatment failure rate is high.

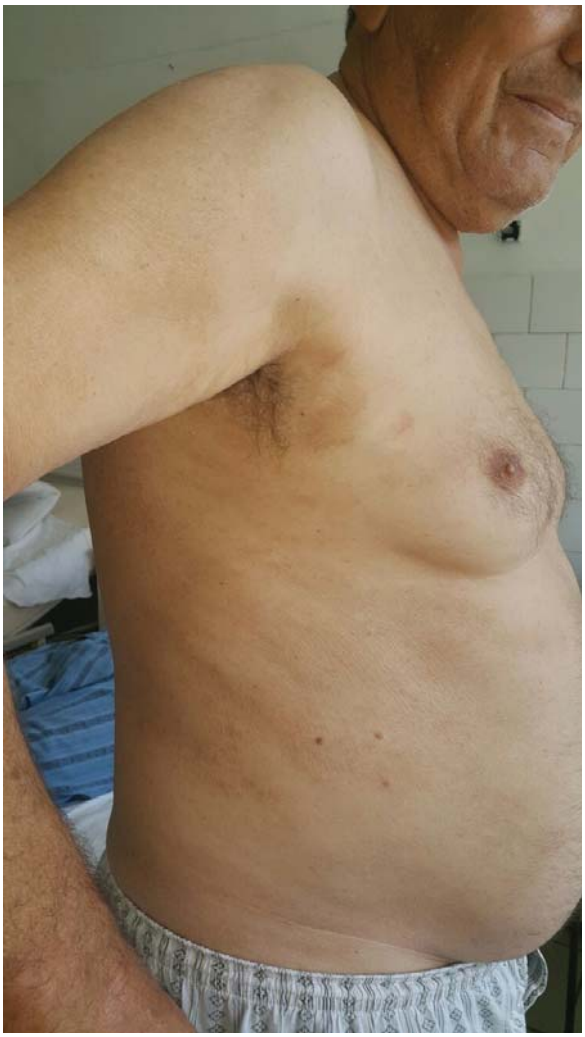

Figure 5. Clinical aspect six month after discharge

Topical treatment includes dermatosteroids, local chemotherapy (Nitrogen Mustard – Mechlorethamine, Carmustine), bexarotene (1% targretin gel); PUVA therapy (3 times/week, followed by maintenance therapy), with a possible association of systemic interferon or retinoids.

Radiotherapy is the most effective therapy in cutaneous lymphomas. Conventional radiotherapy or superficial electron beam radiation can be used (14).

Systemic chemotherapy is used only in MF with extracutaneous involvement. Monochemotherapy (fludarabine, methrotrexate 5-50 mg/week, pentostatin: 5 mg/m2 for 3 days, every 28 days) or polychemotherapy in various regimens can be used: CHOP (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone), COP (Cyclophosphamide, Vincristine, Prednisone). Other therapy options include: corporal electrotherapy, leukapheresis, photopheresis, interferon, systemic retinoids and monoclonal antibodies: Alemtuzumab, Mogamulizumab, Brentuximab vedotin (Adcetris).

Myelodysplastic syndromes (MDS) are clonal disorders of the hematopoietic stem cell, consisting in cytopenia with hyper-/normocellular bone marrow and signs of dyshematopoiesis, evolving into acute leukemia in a significant number of cases. MDS do not present specific signs or symptoms and approximately 50% of all patients are asymptomatic when diagnosed. In the later stages, the following signs can occur: anemia, various recurrent infections, hemorrhagic disorders, splenomegaly, adenopathies, dermatological conditions (Sweet syndrome, pyoderma gangrenosum, etc.) (16).

Many individual biological disorders are involved in the MDS physiopathology, leading to ineffective hematopoiesis and medullar apoptosis.

When a harmful genetic event affecting the hematopoietic stem cell is associated with an excessive inflammatory response it determines an increased growth and, eventually, a clonal hematopoiesis. An important pathogenic mechanism involved in MDS is represented by premature marrow cellular death, explaining the hypercellular marrow associated with peripheral cytopenia (15).

Cytogenetic abnormalities can be detected in about 50% of primary MDS patients and 80% of secondary MDS patients (15).

The condition's etiology remains unknown, but in about 20% of the cases it results following exposure to medicine, industrial toxic substances or in the context of genetic disorders, such as Down syndrome, Fanconi syndrome, Schwachman-Diamond syndrome and neurofibromatosis. Many factors were associated with the progression of MDS, including smoking, alcohol, infections, autoimmune disorders, benzene, aromatic hydrocarbons, organic solvents, radiation and previous chemotherapy (15, 16).

The medullar microenvironment is involved in MDS's development and progression, as it consists

in an environment of cytokines and T-cell-mediated myelosuppression (13).

Non-mediated immunity appears to be involved in the development of all cancers, including MDS, but clear evidence is difficult to find. Successful use of immunosuppressive therapy, the potential curative role of allotransplantation and recent data reporting peripheral cytopenia and the elimination of cytogenetic abnormalities using immunomodulatory agents underline the role of non-mediated immunity in the development of MDS.

Although we could not find any association between MF and MDS in medical literature, we consider that a common etiology (solvents, chemical substances, HTLV1) and physiopathology, represented by immunologic abnormalities caused by the dysplastic process affecting the lymphoid cell line, should not be ruled out.

Over 30 cases of MF in patients with HIV infections have been reported. It was also reported in patients with organ transplantation and in association with malignant hemopathies (chronic l lymphocytic leukemia, monoclonal gammopathy, B-cell lymphoma, non-Hodgkin's lymphoma) or Merkel cell carcinoma and thymoma. About 1% of all MF patients present non-Hodgkin's lymphoma (17, 18). It appears that the association between MDS and other lymphoid neoplasms is common, the two conditions being usually diagnosed simultaneously (15).

It is obvious that cytokines are involved in the physiopathology of both MF and MDS, suggesting a possible common physiopathology of the two conditions.

Conclusion

The coexistence of both MF and MDS in our patient represents a poor outcome factor, requiring thorough clinical and biological monitoring.

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