

The challenge of managing Mycosis Fungoides: a case report

O desafio do manejo da Micose Fungoide: um relato de caso

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Amanda Pereira Quintaes

Graduate in Medicine

Institution: Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória
(EMESCAM)

Address: Av. Nossa Sra. da Penha, 2190, Santa Luíza, Vitória - ES, CEP: 29045-402
E-mail: quintaesamanda@gmail.com

Bárbara Sarnaglia Colnaghi

Graduate in Medicine

Institution: Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória
(EMESCAM)

Address: Av. Nossa Sra. da Penha, 2190, Santa Luíza, Vitória - ES, CEP: 29045-402
E-mail: bárbara.colnaghi@emescam.br

Ana Paula Pontes Jacques

Graduate in Medicine

Institution: Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória
(EMESCAM)

Address: Av. Nossa Sra. da Penha, 2190, Santa Luíza, Vitória - ES, CEP: 29045-402
E-mail: ana.jacques@emescam.br

Maria Clara Gomes Emerick Padilha

Graduate in Medicine

Institution: Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória
(EMESCAM)

Address: Av. Nossa Sra. da Penha, 2190, Santa Luíza, Vitória - ES, CEP: 29045-402
E-mail: maria.padilha@emescam.br

Matheus Dias Caprini

Graduate in Medicine

Institution: Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória
(EMESCAM)

Address: Av. Nossa Sra. da Penha, 2190, Santa Luíza, Vitória - ES, CEP: 29045-402
E-mail: matheus.caprini@emescam.br

Alessandra Barbosa Cazeli

Graduate in Medicine

Institution: Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória
(EMESCAM)

Address: Av. Nossa Sra. da Penha, 2190, Santa Luíza, Vitória - ES, CEP: 29045-402
E-mail: alessandra.cazeli@emescam.br

Ivie Moura de Moura

Graduate in Medicine

Institution: Hospital Santa Casa de Misericórdia de Vitória

Address: R. Dr. João dos Santos Neves, 143, Vila Rubim, Vitória - ES, CEP: 29025-023

E-mail: ivie.moura@emescam.br

Vitória Sampaio Cunha

Graduate in Medicine

Institution: Hospital Santa Rita

Address: Av. Mal. Campos, 1579, Santa Cecília, Vitória - ES, CEP: 29043-260

E-mail: vitóriacunha@gmail.com

ABSTRACT

Objective: To report a case of mycosis fungoides in a patient monitored by the Santa Casa de Misericórdia de Vitória Hospital (HSCMV) who died. **Method:** after approval by the Research Ethics Committee, we retrieved the patient's records from the HSCMV information system and reviewed the document retrospectively for the case description.. **Case report:** Male, 60 years old, attended an appointment in 2017 with the complaint of xerosis, pruritus, and pain. He underwent a biopsy of skin lesions on the dorsum and abdomen that diagnosed mycosis fungoides. Despite treatment with phototherapy and methotrexate, the disease progressed. In 2021, he was admitted to the HSCMV and started chemotherapy without complete remission. He evolved to death by septic shock in February 2022. **Final considerations:** Mycosis fungoides presents itself in a nonspecific form, making the diagnosis a challenge. Thereby, it could delay the establishment of effective treatment, worsening the prognosis.

Keywords: Mycosis Fungoides, lymphoma T-cell cutaneous, lymphoma non-hodgkin.

RESUMO

Objetivo: Relatar um caso de micose fungoide em um paciente monitorado pelo Hospital da Santa Casa de Misericórdia de Vitória (HSCMV) que morreu. **Método:** após aprovação pelo Comitê de Ética em Pesquisa, recuperamos os registros do paciente do sistema de informações HSCMV e revisamos o documento retrospectivamente para a descrição do caso. **Relato do caso:** Masculino, 60 anos, participou de uma consulta em 2017 com a queixa de xerose, prurido e dor. Ele foi submetido a uma biópsia de lesões cutâneas no dorso e no abdômen que diagnosticaram micose fungoide. Apesar do tratamento com fototerapia e metotrexato, a doença progrediu. Em 2021, ele foi admitido no HSCMV e começou a quimioterapia sem remissão completa. Ele evoluiu até a morte por choque séptico em fevereiro de 2022. **Considerações finais:** A micose fungoide apresenta-se de forma inespecífica, tornando o diagnóstico um desafio. Assim, pode atrasar o estabelecimento de tratamento eficaz, piorando o prognóstico.

Palavras-chave: Micose Fungoides, linfoma cutâneo de células T, linfoma não-hodgkin.

1 INTRODUCTION

Mycosis fungoides (MF) is part of the group of cutaneous T-cell lymphomas (CCTL)¹. The term refers to T-cell neoplasms of primary cutaneous origin, classified as non-Hodgkin

lymphomas, comprising several clinical forms, including mycosis fungoides - responsible for approximately 60% of CCTL - Sézary syndrome, among others^{1, 2, 3}.

Generally, the clinical presentation of MF includes persistent, slowly progressive skin lesions of varying size and shape. They can be associated with pruritus, opportunistic infections, alopecia, and, more rarely, visceral involvement⁴.

This case report seeks to highlight the impact of difficult diagnosis and refractory treatment of mycosis fungoides on the patients' prognosis and to discuss its clinical presentation, diagnostic methods, and therapeutic options. Thus, the aim is to contribute to the scientific community to broaden the knowledge about the management of mycosis fungoides.

2 CASE REPORT

I.A., a 60-year-old black male patient, came to the Dermatology Department of the HSCMV in June 2017, presenting xerosis, pruritus, and pain for one year and two months, starting in the calf and knee regions, with subsequent dissemination to the rest of the body. On that occasion, he reported using itraconazole, ketoconazole, metronidazole, hydroxyzine, and topical moisturizer. In addition, he also used betamethasone dipropionate, which was the only treatment that improved the symptoms. Physical examination revealed hypochromic patches on the trunk, besides erythematous and slightly scaling patches on the trunk and limb. The lesions spared elbows, knees, and fingernails. A skin biopsy of the right lumbar region and abdomen showed atypical (epidermotropic) lymphomononuclear infiltrate with psoriasiform hyperplasia of the epidermis, besides focal exocytosis of lymphocytes with focal clusters (Pautrier microabscesses), which raised suspicion of mycosis fungoides. The lesions progressed throughout the year and phototherapy was started in August, followed by methotrexate (MTX), but there was no improvement. A new biopsy of the back region revealed discrete superficial and interface chronic dermatitis with pigmentary effusion with the absence of epidermotropism.

In January 2019, the patient returned to the Dermatology outpatient clinic after missing follow-up for approximately one year, reporting the reappearance of pruritic and painful lesions on hands, feet, and face. The hyperchromic psoriasiform plaques progressed to the trunk and lower limbs. Therefore, MTX was prescribed again in addition to topical clobetasol on hands and feet. After, the patient was also referred to Hematology.

Despite the disease progression, the patient continued with irregular treatment. Erythematous-exudative plaques appeared in the interdigital region of the left foot toes, and three infiltrated violet nodular lesions (the largest measuring about 5 cm in diameter) developed on the left forehead, all of them hardened and with no fluctuating points (Figure 1). Given the

context, the doctor responsible performed an incisional biopsy of the forehead lesion, which showed infiltration of histiocytoid mononuclear cells in the dermis, with frequent intermingled eosinophils, associated with follicular mucinosis. The immunohistochemical study suggested mycosis fungoides with follicular mucinosis and associated dermal eosinophilia.

Figure 1 - Hardened and infiltrated nodular lesion located on the left forehead, well-defined, erythematous, interspersed with hypochromic and hyperchromic areas and alopecia in the left frontal region.



Source: Image taken during hospitalization at HSCMV with permission of the patient (2022).

In August 2021, the patient came to the emergency room of the HSCMV complaining of intense and generalized pain. The physical examination showed myiasis on the left toes and worsening of the other skin lesions (figures 2, 3, and 4). Thus, the Hematology Department admitted the patient and initiated antibiotic therapy.

Figures 2 - Hyperkeratotic erythematous scaly palmoplantar plaques with skin infiltration. Presence of unguinal dystrophy in the first and third left digits.



Source: Images taken during hospitalization at HSCMV with permission of the patient (2022).

Figures 3 - Hyperkeratotic erythematous scaly palmoplantar plaques with skin infiltration. Presence of unguinal dystrophy in the first and third left digits.



Source: Images taken during hospitalization at HSCMV with permission of the patient (2022).

Figura 4 - Presence of large confluent infiltrated and desquamative plaques associated with ulcerative lesions with a dirty bottom on the first and fourth left toes.



Source: Image taken during hospitalization at HSCMV with permission of the patient (2022).

During his hospitalization, the patient was staged as T4 (erythroderma), M0 (no visceral involvement), and B0 (no atypical circulating cells). Despite imaging confirmation of lymph node involvement, the biopsy lacked information for N staging.

As the disease progressed, chemotherapy (CTX) was started with a regimen of cyclophosphamide, vincristine, and prednisone (CVP), aiming for cytoreduction until the patient stabilized. After, the regimen was changed to cyclophosphamide, doxorubicin, vincristine, etoposide, and prednisone (CHOEP) in September 2021. However, due to the partial response to the established treatment, it was decided to switch to etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin in continuous infusion (EPOCH).

Figures 5 and 6 show the partial regression of the nodular lesion on the lip after the proposed treatment.

Figure 5 - Large erythematous nodular lesion on the upper lip, without fluctuation points



Source: Image taken during hospitalization at HSCMV with permission of the patient (2022).

Figure 6 - Lip nodular lesion in partial regression



Source: Image taken during hospitalization at HSCMV with permission of the patient (2022).

Later, the lesions on the left toes worsened, and amputation was indicated, with evidence of osteomyelitis in the culture collected during the procedure.

Even during chemotherapy, the patient presented progression of lymph node involvement and increased labial infiltration, and radiotherapy was initiated, with a total of 12 sessions.

Despite the proposed treatment and intensive clinical support offered, the patient developed febrile neutropenia and septic shock of refractory pulmonary focus, which caused his death in February 2022.

3 DISCUSSION

As already mentioned, MF is one of the primary cutaneous lymphomas, presenting with multiple clinicopathological variations⁵.

The initial cutaneous involvement of MF presents with erythematous patches or plaques with a scaly surface, mainly located in areas protected from sunlight, which may manifest variable degrees of atrophy^{4,6}. This nonspecific aspect of the lesions resembles inflammatory dermatoses such as chronic eczema, indeterminate leprosy, and pityriasis alba⁵. As the disease progresses, it may develop into infiltrated and generalized plaques and later ulcerated and exophytic tumors, as well as papules, poikiloderma, cutaneous hypopigmentation⁴. In cases of advanced disease, generalized erythroderma may be seen, accompanied by atrophy or lichenification of the skin, intense pruritus, desquamation, and lymphadenopathy⁴. The advanced clinical condition is compatible with that of the patient in this study; however, the great majority of patients remain in the initial stage, presenting non-specific and non-infiltrated lesions for years, without the evolution to plaques and tumors⁵.

Furthermore, pruritus is one of the most common and debilitating symptoms of MF, and it is related to the degree of severity of the disease, which is corroborated by this case report, since pruritus was one of the patient's initial complaints and persisted throughout the course of the disease⁴. Extracutaneous manifestations include regional lymph node involvement and visceral involvement, which correlate with the extent of cutaneous involvement⁴. Despite the exuberant cutaneous picture presented by the patient in question, there was not evident visceral involvement.

Another important topic about MF concerns its epidemiology since it affects mostly black males (2:1) between 55 and 60 years of age, a fact observed in this study since the patient described is a 60-year-old black man^{3,4}. All patients with clinical signs suggestive of MF should undergo biopsy and immunohistochemistry of the skin lesion, which characteristically shows atypical mononuclear cells infiltrating the upper dermis and epidermal keratinocytes - thus revealing an epidermotropism^{4,2}. These cells may also form intra-epidermal aggregates, known as Pautrier's microabscesses⁴, as was found in the first biopsy of the patient, contributing to the diagnostic suspicion of MF. However, it is pertinent to note that in the early stages of the disease, the histological appearance is sometimes nonspecific^{4,5}. Thus, distinguishing between benign inflammatory skin diseases is not always possible, requiring repeated biopsies of different lesions during the investigation, explaining the frequent delay in initial diagnosis². In this report, the patient went through several biopsies throughout follow-up; however, it should be pointed out that treatment with topical corticosteroids, phototherapy, and systemic

immunosuppressants may eliminate neoplastic T cells and other typical histopathological findings, acting as a confounding factor in diagnosis⁷. This fact can be observed in the patient's clinical history since the first histopathological study showed MF, and the second, performed after the prescription of MTX, revealed only nonspecific inflammatory findings.

The treatment of MF relies on the evolutive phase in which the disease is found and is related to the individual response of each patient. Thus, skin-targeted therapies (ultraviolet light, topical corticotherapy, and nitrogen mustard) are the main strategies for early-stage MF, and systemic therapies (retinoids, chemotherapy, targeted therapy) are directed toward advanced disease⁸. The treatment with topical corticosteroid and ultraviolet light results in complete clinical response in up to 60% and 80%-90% of patients, respectively². In patients with relapsed or refractory course to therapy and plaque development, skin-targeted treatment and systemic treatment are combined, including retinoids and their analogs (acitretin, bexarotene) or low-dose MTX². In this report, phototherapy did not have therapeutic success, and MTX use was discontinued by the patient several times due to gastrointestinal intolerance caused by the drug, highlighting the difficulty in follow-up, which may have negatively influenced disease progression.

In advanced disease, with thick plaques and cutaneous tumor stage, monochemotherapy with gemcitabine or doxorubicin is effective². Chemotherapy regimens based on cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) should be restricted to patients with extracutaneous dissemination and usually result in a short-lived response². Moreover, allogeneic hematopoietic stem cell transplantation is an option for advanced MF and Sézary syndrome, but its limitation regards high relapse and mortality rates⁸. In the present case, the CHOEP regimen followed by EPOCH was chosen due to the extremely advanced stage of the disease, but it did not respond.

Regarding staging, it includes the assessment of skin lesions (T), lymph nodes (N), visceral involvement (M), and blood (B), making up the TNMB system, as shown in Table 1.

Table 1 - TNMB system for staging mycosis fungoides

Skin (T)	Definition
T1	Patches, papules, and/or plaques covering <10 percent of the skin surface
T2	Patches, papules, or plaques covering ≥10 percent of the skin surface
T3	One or more tumorsΔ (≥1 cm diameter)
T4	Confluence of erythema covering ≥80 percent body surface area

Node (N)	
N0	No clinically abnormal lymph nodes*
N1	Clinically abnormal lymph nodes; histopathology Dutch grade 1 or NCI LN0-2. N1a: clone negative; N1b: clone positive
N2	Clinically abnormal lymph nodes; histopathology Dutch grade 2 or NCI LN3. N2a: clone negative; N2b: clone positive
N3	Clinically abnormal lymph nodes; histopathology Dutch grades 3-4 or NCI LN4; clone positive or negative
NX	Clinically abnormal lymph nodes; no histologic confirmation
Visceral (M)	
M0	No visceral organ involvement
M1	Visceral involvement with pathology confirmation
Blood (B)	
B0	No significant blood involvement: ≤ 5 percent of atypical cells (Sézary cells)
B1	Does not meet the criteria of B0 or B2
B2	Positive clone‡ plus one of the following: $\geq 1000/\text{microL}$ Sézary cells; $CD4/CD8 \geq 10$; $CD4+CD7^-$ cells ≥ 40 percent; or $CD4+CD26^-$ cells ≥ 30 percent.

*Abnormal lymph node(s) indicates any lymph node that on physical examination is firm, irregular, clustered, fixed, or 1.5 cm or larger in diameter
Source: Modified from HOPPE; KIM, 2021b.

Regarding the prognosis of MF, the International Prognostic Index for Cutaneous Lymphomas (CLIPi) identified male gender, age over 60 years, visceral involvement, and stages B1/B2 and N2/N3 as the leading adverse factors associated with advanced stages⁹. The reported patient presented some of them, such as male gender and age over 60 years, but, as already mentioned, information for the classification of N staging is lacking.

Moreover, in this case, complications common to oncology patients were observed, such as febrile neutropenia during chemotherapy regimens, a condition that contributes to poor prognosis and was present in the context of his death.

4 FINAL CONSIDERATIONS

As discussed above, MF manifests itself through several clinical features and, more than that, it presents itself, most of the time, in an extremely nonspecific way. Most patients present the disease in an indolent form, with slow progression, and cases in which the disease evolves to severe and disseminated skin lesions, with tumors and/or erythroderma, are rare. Thus, diagnosis becomes a challenge since there is a large intersection with benign inflammatory

dermatoses that present similarly. Even histopathological studies may present nonspecific results during the early stages of MF, which makes it even more difficult to establish a diagnosis and effective treatment. This situation can lead, in rare cases, to dissemination, exacerbation of the lesions, and extracutaneous involvement, with a significantly poor prognosis.

The present case report sought to highlight precisely this evolution of MF, going through the nonspecificity of the condition, the great challenge of diagnosis, the worsening of the disease, the presence of complications, and refractoriness of treatment, culminating in the deterioration of the prognosis and death. It is, therefore, of extreme scientific importance since knowledge about the negative impacts on the evolution of the condition can prevent such an outcome from being repeated in new cases.

5 METHODOLOGY

The study is observational and descriptive, based on data obtained from medical records provided by the Hospital Santa Casa da Misericórdia de Vitória (HSCMV). In addition, we used images of the patient's skin lesions, obtained from photographic records of the period of his hospitalization at the HSCMV, which were taken with his permission and preserved his identity.

Moreover, articles from PubMed, UpToDate, and Scielo supported the description and discussion of the case. For that, the researchers used a search strategy elaborated with terms from the Medical Subjects Headings (MeSH) from PubMed.

The Human Research Ethics Committee (HREC) of the Escola Superior de Ciências da Santa Casa de Misericórdia de Vitória (EMESCAM) approved the present study with the substantiated opinion granted by number 5.372.386. By request of the researchers, the HREC waived the informed consent since the patient died during his hospitalization at the HSCMV and therefore could not sign it.

It is important to emphasize that the researchers involved in the study are committed to using the data obtained exclusively for scientific purposes, assuring confidentiality and privacy during all the procedures employed.

The coordinator of the Clinical Research Center of the HSCMV signed the consent letter, which allowed the researchers to access the information. The letter of consent and the waiver of the informed consent comply with the requirements of the National Health Council, Resolution 466/2012, which establishes the Regulatory Guidelines and Standards for Research Involving Human Beings.

After the HREC approved the project, we retrieved the patient's records from the HSCMV information system and reviewed the document retrospectively for the case description.

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