

Cutaneous T-cell lymphoma of the mycosis fungoides type: report of case series

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Abstract: Cutaneous T-cell lymphomas represent a heterogeneous group of lymphoproliferative diseases characterized by skin infiltration by mature malignant T cells. More than 40% of cutaneous T-cell lymphomas are represented by mycosis fungoides. As they present non-specific cutaneous manifestations, they are often underdiagnosed. This article reports four cases of mycosis fungoides with different subtypes treated by a multidisciplinary team, highlighting aspects related to clinical heterogeneity and diagnostic, therapeutic and differential diagnostic challenges, followed by a brief review of the literature. The cases described demonstrate the heterogeneity of cutaneous and systemic clinical signs, with presentations that present a significant diagnostic challenge due to other diseases with similar manifestations, especially for non-specialist physicians in basic healthcare units. Mycosis fungoides continues to be a problematic diagnosis, as the cases described had varied presentations and numerous inconclusive biopsies. Low clinical suspicion and technical limitations in the analysis of biopsies of skin lesions were the main factors implicated. It is hoped that this series of cases will bring a better understanding of the diagnostic aspects of this disease.

Keywords: Mycosis fungoides; Cutaneous T-cell lymphoma; Cutaneous lymphoma.

1. Introduction

Mycosis fungoides (MF) is a subtype of cutaneous T-cell lymphoma (CTCL) that accounts for more than 40% of cutaneous lymphomas and 50-60% of CTCL. It has heterogeneous features and is insidious. It mainly affects non-photo exposed areas of the skin and presents as papules, spots, tumors and erythroderma [1, 2]. It is a disease with very different clinical, pathological, genetic, therapeutic, and prognostic features [1,3]. Its incidence has increased in recent decades due to a better understanding of the disease and greater diagnostic capacity [3]. A recent study has shown that the incidence of MF in the United States has increased from 3.0 per million person-years in the 1970s to 5.9 in the 2010s, which has been associated with an improved ability for early diagnosis, with overall survival rates improving significantly over the decades [2]. In Brazil, 727 patients were

identified in a recent cohort between 1989-2018. MF was diagnosed in 92.6% (673) and Sezary syndrome (SS) in 7.4% (54) [4].

Despite significant advances in the histopathological, immunohistochemical, and molecular characterization of the disease, the definitive diagnosis of mycosis fungoides (MF) remains challenging. Diagnosis is often preceded by a “pre-mycotic” period that can range from months to decades. The patient may present with pruritus, non-specific skin lesions, and inconclusive biopsies [1]. These features make MF a complex diagnosis that requires an integration of clinical data, pathologic evaluations, and molecular studies in combination with a high degree of clinical suspicion on the part of the physician [5]

This manuscript presents four cases of different subtypes of mycosis fungoides (MF) with heterogeneous clinical characteristics. The aim is to highlight the mimicking aspect of MF, which often simulates other diseases, resulting in significant diagnostic challenges and, consequently, delays in diagnosis and therapeutic limitations. The study also emphasizes diagnostic aspects, evolution, and treatment.

2. Case Report

2.1 Case Report 1

Male, 63 years old, phototype 2, diabetic and hypertensive, complained in 2019 of erythematous spots on the trunk that had appeared two years earlier and spread rapidly to the upper and lower limbs, without symptoms. She had previously undergone various tests, including two biopsies, one from the skin and the other from the bone marrow, with inconclusive results. Physical examination revealed an erythrodermic rash on 80% of the body surface, sparing the palmoplantar region, and no adenomegaly (Figure 1A). Pharmacoderma was suspected. A new biopsy was performed, the pathology of which showed atypical epidermal and folliculotropic lymphoid proliferation, suggestive of MF. At this point, the erythrodermic condition was maintained and phototherapy with UVB-NB (FT-UVB-NB) was indicated. Nevertheless, she developed erythematous-infiltrated plaques. The immunohistochemical (IHC) profile (Table 1), imaging tests and immunophenotyping of peripheral blood confirmed the suspicion of AP with staging T4N0M0B0 when chemotherapy was then started. In 2021, an erythematous plaque in the infra-axillary region became heavily infiltrated and developed into a tumor (Figure 1B). As the disease was unresponsive, bone marrow infiltration and death occurred in 2022, 5 years after the first lesions appeared, as described in similar cases in the literature [6].

2.2 Case Report 2

In 2021, a 35-year-old woman without concomitant diseases reported hypochromic and severely itchy spots that had been present for five years and developed cranio-caudally. She reported that she had consulted several specialists and underwent tests, including two biopsies, the results of which indicated cutaneous amyloidosis and lichen simplex chronicus. On physical examination, he had hypochromic, xerotic, scaly, and extensive patches of varying sizes on his trunk, hands, and feet. Suspecting atopic dermatitis or MF, a new biopsy was performed, the AP of which indicated spongiotic dermatitis. After discontinuing follow-up for about ten months, the patient returned to the office, and a new biopsy was performed with AP suggestive of cutaneous T-cell lymphoma (CTCL) (Figure 2A), which was confirmed by IHC (Table 1). UVB-NB phototherapy (FT-UVB-NB) and oral chemotherapy with methotrexate (MTX) were prescribed, which resulted in transient improvement but with persistent pruritus. A few months later, the lesions spread, and desquamation of the palmoplantar regions occurred when venous systemic chemotherapy was started. Six months later, he developed a tumor in the posterior region of his trunk. The oncology department is still treating it.

Figure 1. Clinical presentation of case 01, MF with atypical epidermal and folliculotropic lymphoid proliferation.



Legend: MF in different stages, erythrodermic rash evident on the abdomen and chest in 2019 (A), tumor evolution of erythematous plaque in the infra-axillary region in 2022 (B).

Table 1. Summary of reported cases, including histopathology and immunohistochemistry results.

	DX ^a	MDD ^b	CLINICAL ^c	AP	IHC ^d	THERAPY ^e
Case 01	2	Farmacodermia	Patch developing into a tumor	2018: inconclusive	2018: CD3 +, CD4 +/-, CD5 +, CD8 +/-, CD20 -/+	UVB-NB phototherapy
			Erythroderma	2019: atypical epidermal and folliculotropic lymphoid proliferation		Methotrexate
Case 02	6	Cutaneous amyloidosis	Hypochromic, xerotic, desquamative patches and plaques evolving into a tumor	2016: Cutaneous amyloidosis and lichen simplex chronicus	2022: CD3 and CD4 +; CD7, CD8 and CD20 +/-; CD30 -. CD4:CD8 slightly increased	Antihistamine

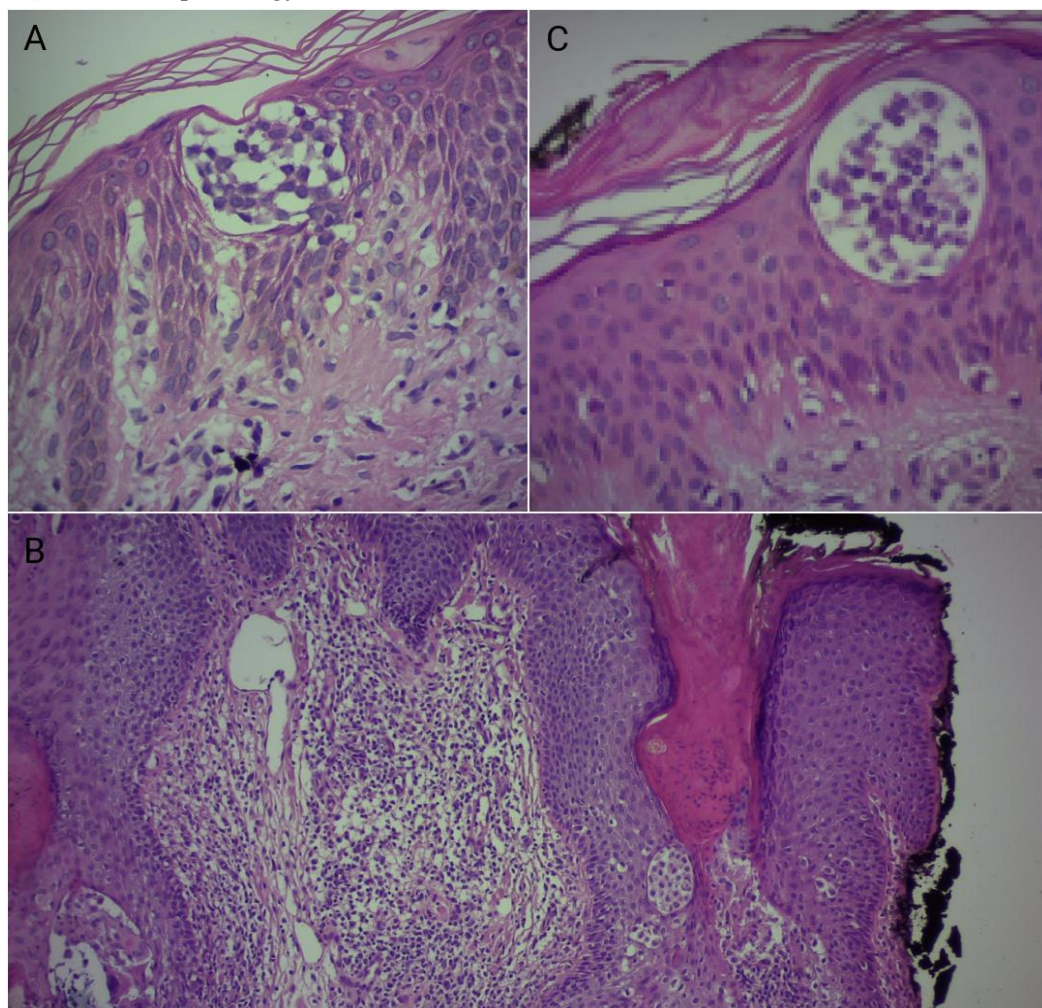
		Chronic lichen simplex		2021: Spongiotic dermatitis		Prednisolone
		Atopic dermatitis		2022: Lymphocytic infiltrate with epidermotropism		UVB-NB phototherapy
Case 03	6	Syphilis	Erythematous-infiltrated plaques	2013: Lymphoplasmacytic dermatitis	2019: CD3 +, CD4 +, CD5 +, CD8 -/+ , CD20 -, CD30 - (compatible with folliculotropic MF)	UVB-NB phototherapy
		Leprosy		2016: Seborrheic dermatitis		Interferon-gamma
		Nummular eczema		2019: Epidermal and folliculotropic atypical lymphocytic infiltrate		Methotrexat and
Case 04	1	Leprosy	Patch and erythematous-infiltrated plaques	2019: Epidermotropic atypical lymphocytic infiltrate	2019: CD3, CD4 and CD5 +; CD8, CD20 and CD30 -/+; CD4:CD8 > 10:1 (compatible with MF)	Folic acid

Legend: ^a Time (in years) from onset of clinical presentation to diagnosis; ^b MDD main differential diagnoses; ^c Initial clinical presentation; ^d + positive, +/- focally positive, -/+ in rare lymphocytes, - negative; ^e Treatments instituted throughout evolution, not necessarily together.

2.3 Case Reports 3 and 4

Patients 3 and 4, male and female, 41 and 51 years old, respectively, without comorbidities, visited the dermatologist consecutively in 2013 and 2019 with skin lesions that had started about 12 months earlier. The man had erythematous patches in the forehead/labela area, on the bridge of the nose, and a patch on the buttocks. The woman had erythematous patches on her thighs, abdomen, and lower back. The initial suspicions were seborrheic dermatitis, contact dermatitis in case 3, and leprosy in case 4. The first biopsy of patient 3 in 2013 revealed a diagnosis of non-specific lymphoplasmacytic dermatitis. He was not followed up for three years. During this time, he was treated in another institution under the hypothesis of multibacillary leprosy and seborrheic dermatitis. In 2019, on the third biopsy (case 3), the AP was consistent with folliculotropic lymphocytic infiltrate (Figure 2B).

Similarly, in patient 4, who had erythematous lesions on the thigh, abdomen, and lower back, a biopsy was performed on more than one site, which showed that it was the folliculotropic variant of MF (Figure 2C). Treatment with FT-UVB-NB and interferon-gamma was initiated, which was later replaced with MTX and folic acid (FA) due to inadequate response to the first therapy and inadequate control of the lesions. A summary of the four cases can be found in Table 1.

Figure 2. Histopathology of lesions in cases 2, 3 and 4.

Legend: AP shows superficial lymphocytic infiltrates irregularly distributed in the superficial dermis of patients 02 (A), 03 (B) and 04 (C). In A and C, permeation of the epidermis by lymphocytes with enlarged nuclei and irregular contours (hematoxylin-eosin, original magnification 40x). In B, the atypical infiltrate is epidermal and folliculotropic (hematoxylin-eosin, original magnification 10x).

3. Discussion

CTCL has a worldwide incidence of 10.2/million people. MF is the most common subtype, accounting for half of the cases in some series (5.6/million) [7,8]. Diagnosis, staging, and treatment follow the recommendations of the European Organization for Research and Treatment of Cancer (WHO-EORTC) in a document updated in 2018 [7].

In most patients, the disease is at an early stage, and progression between stages is generally slow. It is estimated that more than 90% of patients with early forms do not progress to the tumor stage or with extracutaneous manifestations, and the risk of this progression correlates with the extent and nature of the lesions. Although rare, erythroderma can occur in MF and must be distinguished from Sézary syndrome (SS), another form of CTCL. In the initial macular and patch stages, microscopic findings are nonspecific and overlap with those of other inflammatory or neoplastic diseases [5], as in cases 3 and 4, and frequently in tumor stages (8%) and erythrodermic conditions (30-42%) [6], which occurred in cases 1 and 2 where there was marrow infiltration and rapid progression of the disease.

In patients with a higher phototype (darker skin), the MF patches and plaques may be hypochromic and extensive, which is more common in young people and children, or

they may represent the hypopigmented variant, as was the case in patient 2 [7], which makes the differential diagnosis with atopic dermatitis important, not least because the AP of patient 2 concluded that it was a spongiotic dermatitis, which is common in eczema, making the differential diagnosis between these two pathologies even more difficult to begin with.

Therefore, the diagnosis of MF is challenging and requires careful clinical and laboratory correlation, taking, on average, 4 to 6 years to establish [9,10]. Biopsies of lesions, immunophenotyping of peripheral blood, imaging studies, and biopsies of affected organs are essential for propaedeutics [9]. Differential diagnoses include benign inflammatory dermatoses such as contact dermatitis, atopic dermatitis, leprosy, psoriasis, and other conical eczema [11]. Histopathologic features may also be absent after multiple biopsies, as in cases 1, 2, and 3, where analyses were inconclusive or suggestive of benign dermatoses, referred to as the “pre-mycotic” period [12]. In this context, immunophenotyping is necessary to complement the histopathology, especially in the T2 stages where the neoplastic lymphocytes have a memory TCD4+ phenotype and express markers at different intensities, with a decrease in TCD8+ cells (values below 600/mL are a sign of poor prognosis) [13].

It is not uncommon for MF to be diagnosed late, years after the onset of the clinical picture and after exhaustive treatment attempts for other conditions [9]. This was also the case in the cases described: leprosy is an endemic disease in this region and was considered a possible diagnosis in cases 3 and 4. This is a challenge for the clinician who, despite its rarity, must consider MF in the repertoire of differential diagnoses of the most common pathologies. In case 1, as the disease progressed, more complex tests such as CT scans and bone marrow biopsies were required to detect disease progression. Cases 2 and 3 were examples of the diagnostic difficulty as the first biopsy suggestive of MF was six years after onset. Various algorithms have been proposed to facilitate this, but they are not always well known or easy to interpret [14]. Population studies have shown that early diagnosis has an impact on overall survival and brings significant gains in quality of life [3].

In this context, clinical staging is crucial for MF's treatment and prognosis. The TNMB classification (tumor, lymph nodes, metastases, blood) is used, which takes into account the extent of skin lesions (T1-T4), lymph node involvement (N0-N3), visceral involvement (M0-M1) and blood spread (B0-B2) [12]. In parallel, the development of new diagnostic technologies such as 18F-fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET) imaging and the detection of a clonal TCR gene rearrangement by PCR have been incorporated into the revised guidelines of the International Society for Cutaneous Lymphoma (ISCL) and the cutaneous lymphoma task force of the European Organization of Research and Treatment of Cancer (ISCL/EORTC) and have improved the stratification of prognosis and treatment [15].

In 2023, the EORTC updated its consensus on the treatment of MF. In the early stages, treatment in the expectant phase is an option due to the low risk of disease progression. For stages above IA, treatment begins with skin-targeted therapies such as topical medications (corticosteroids, clomipramine, retinoids, and calcineurin inhibitors), UV phototherapy, photodynamic therapy, electron beam therapy of the skin, and radiotherapy [15]. UVB-NB phototherapy was chosen in all cases based on the experience of the treating oncologist.

In stages above IIB, systemic therapies with retinoids, interferon- α , chemotherapy, and immunotherapy [15]. Radiotherapy is also an alternative to reduce the tumor burden in patients with generalized lesions [16]. In the cases described, the predominant systemic treatment was methotrexate and interferon-gamma, with acceptable response and remission of lesions in cases 3 and 4, partially in case 2. Case 1 progressed to T4 involvement and ended in death five years after diagnosis. This confirms the data in the literature on the average survival time of 5 to 10 years, especially in folliculotropic MF, a variant associated with a higher risk of progression [6]

Currently, there is still no curative therapy for CTCL, including MF, except allogeneic stem cell transplantation, which is limited to more severe cases in which there has been little response to previous therapies due to high complication and mortality rates [15]. More recently, studies have investigated the potential of immune checkpoint inhibitors in these diseases. They are based on the interaction between the receptor for programmed cell death 1 (PD-1) and its ligands (PD-L1 and PD-L2), expressed on the cell membranes. This binding has been shown to prevent the activation and proliferation of T-cells by weakening the immune response, which occurs in T-cell tumors that express more PD-L1 and escape the immune system [14]. Anti-PD-1 antibodies have already been tested in clinical trials and translational research to restore T-cell function [17, 18].

This study has significant limitations. In most cases, it was not possible to make a detailed diagnosis by immunophenotyping and FDG-PET, which limits clinical staging. As it is a retrospective case report, there are gaps in clinical and sociodemographic information. Nevertheless, it highlights clinical and chronological aspects that are fundamental to a better understanding of the behavior of this rare but important pathology.

4. Conclusion

Although MF is a well-known disease in the medical literature, its diagnosis and treatment are still difficult and associated with limitations, especially in unfavorable cases, such as when it develops into a tumor. Descriptions of case series reporting experiences in diagnosis and treatment, and especially cohort studies, are essential for a better understanding of this important pathology and the development of public health strategies for early detection and health promotion.

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References

1. Larocca C, Kupper T. Mycosis Fungoides and Sézary Syndrome: An Update. *Hematol Oncol Clin North Am.* 2019 Feb;33(1):103-120. doi: 10.1016/j.hoc.2018.09.001. PMID: 30497668; PMCID: PMC7147244.
2. Hodak E, Geskin L, Guenova E, Ortiz-Romero PL, Willemze R, Zheng J, Cowan R, Foss F, Mangas C, Querfeld C. Real-Life Barriers to Diagnosis of Early Mycosis Fungoides: An International Expert Panel Discussion. *Am J Clin Dermatol.* 2023 Jan;24(1):5-14. doi: 10.1007/s40257-022-00732-w. Epub 2022 Nov 18. Erratum in: *Am J Clin Dermatol.* 2023 May;24(3):493. PMID: 36399227; PMCID: PMC9673193.
3. Kaufman AE, Patel K, Goyal K, O'Leary D, Rubin N, Pearson D, Bohjanen K, Goyal A. Mycosis fungoides: developments in incidence, treatment and survival. *J Eur Acad Dermatol Venereol.* 2020 Oct;34(10):2288-2294. doi: 10.1111/jdv.16325. Epub 2020 May 24. PMID: 32141115; PMCID: PMC7733543.
4. Miyashiro D, Sanches JA. Characteristics and outcomes of 727 patients with mycosis fungoides and Sézary syndrome from a Brazilian cohort. *Int J Dermatol.* 2022 Apr;61(4):442-454. doi: 10.1111/ijd.15865. Epub 2021 Aug 26. PMID: 34435672.
5. Hodak E, Amitay-Laish I. Mycosis fungoides: A great imitator. *Clin Dermatol.* 2019 May-Jun;37(3):255-267. doi: 10.1016/j.clin-dermatol.2019.01.004. Epub 2019 Jan 11. PMID: 31178107.
6. Kempf W, Mitteldorf C. Cutaneous T-cell lymphomas-An update 2021. *Hematol Oncol.* 2021 Jun;39 Suppl 1:46-51. doi: 10.1002/hon.2850. PMID: 34105822.
7. Willemze R, Cerroni L, Kempf W, Berti E, Facchetti F, Swerdlow SH, Jaffe ES. The 2018 update of the WHO-EORTC classification for primary cutaneous lymphomas. *Blood.* 2019 Apr 18;133(16):1703-1714. doi: 10.1182/blood-2018-11-881268. Epub 2019 Jan 11. Erratum in: *Blood.* 2019 Sep 26;134(13):1112. PMID: 30635287; PMCID: PMC6473500.
8. Korgavkar K, Xiong M, Weinstock M. Changing incidence trends of cutaneous T-cell lymphoma. *JAMA Dermatol.* 2013 Nov;149(11):1295-9. doi: 10.1001/jamadermatol.2013.5526. PMID: 24005876.

9. Cerroni L. Mycosis fungoides-clinical and histopathologic features, differential diagnosis, and treatment. *Semin Cutan Med Surg*. 2018 Mar;37(1):2-10. doi: 10.12788/j.sder.2018.002. PMID: 29719014.
10. Lee H. Mycosis fungoides and Sézary syndrome. *Blood Res*. 2023 Apr 30;58(S1):66-82. doi: 10.5045/br.2023.2023023. PMID: 37105561; PMCID: PMC10133849.
11. Zic JA. Diagnosis and Management of Cutaneous Lymphomas Including Cutaneous T-cell Lymphoma. *Med Clin North Am*. 2021 Jul;105(4):737-755. doi: 10.1016/j.mcna.2021.04.010. PMID: 34059248.
12. Valente M, Ribeiro K, Cruz T, Silva L, Ferreira A, Mayrink G, Silva D, Barbosa C, Drumond V, Utsch P. O desafio do diagnóstico clínico e histopatológico da micose fungoide. *Hematol Transfus Cell Ther*. 2021 Oct;43(1)
13. Pulitzer MP, Horna P, Almeida J. Sézary syndrome and mycosis fungoides: An overview, including the role of immunophenotyping. *Cytometry B Clin Cytom*. 2021 Mar;100(2):132-138. doi: 10.1002/cyto.b.21888. Epub 2020 Jun 9. PMID: 32516521; PMCID: PMC9306215.
14. Ryu HJ, Kim SI, Jang HO, Kim SH, Oh SH, Park S, Kim SK. Evaluation of the International Society for Cutaneous Lymphoma Algorithm for the Diagnosis of Early Mycosis Fungoides. *Cells*. 2021 Oct 15;10(10):2758. doi: 10.3390/cells10102758. PMID: 34685738; PMCID: PMC8534563.
15. Latzka J, Assaf C, Bagot M, Cozzio A, Dummer R, Guenova E, Gniadecki R, Hodak E, Jonak C, Klemke CD, Knobler R, Morris 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. Epub 2023 Sep 18. PMID: 37890355.
16. Thomas TO, Agrawal P, Guitart J, Rosen ST, Rademaker AW, Querfeld C, Hayes JP, Kuzel TM, Mittal BB. Outcome of patients treated with a single-fraction dose of palliative radiation for cutaneous T-cell lymphoma. *Int J Radiat Oncol Biol Phys*. 2013 Mar 1;85(3):747-53. doi: 10.1016/j.ijrobp.2012.05.034. Epub 2012 Jul 17. PMID: 22818412.
17. Dobos G, Lazaridou I, de Masson A. Mycosis Fungoides and Sézary Syndrome: Microenvironment and Cancer Progression. *Cancers (Basel)*. 2023 Jan 25;15(3):746. doi: 10.3390/cancers15030746. PMID: 36765704; PMCID: PMC9913729.
18. Ryu HJ, Kim SI, Jang HO, Kim SH, Oh SH, Park S, Kim SK. Evaluation of the International Society for Cutaneous Lymphoma Algorithm for the Diagnosis of Early Mycosis Fungoides. *Cells*. 2021 Oct 15;10(10):2758. doi: 10.3390/cells10102758. PMID: 34685738; PMCID: PMC8534563.