Mycosis Fungoides. Differencial Diagnosis

MD. Daniela NAKUCI
Anatomic- Pathologist.
Department of Pathology, Regional Hospital of Vlora
danielanakuci@yahoo.com

MD. Erisa KOLA
Anatomic-Pathologist
Department of Pathology, Regional Hospital of Gjirokaster
erisa_k87@yahoo.com

PhD. Leart BERDICA
Anatomic-Pathologist
QSUT, Nene Teresa Hospital
leartberdica@ymail.com

Prof.Dr. Mehdi ALIMEHMETI
European University of Tirana
mehdi.alimehmeti@uet.edu.al

Abstract

Background: *Mycosis funguides (MF) is a rare malignant skin neoplasms, and one of the most common primary cutaneous T cell lymphomas. MF have the appearance of many skin lesions, particularly in its early clinical course, creating diagnostic challenges, especially in our country (growing countries) as it requires tissue biopsy, histological diagnosis with hematoxylin & eosin, immunohistochemistry and molecular diagnostic elements.*

Materials and Methods: *This is a differencial diagnosis based on retro and pro spective study, about 6638 articles published in Pubmed for Cutaneous Lymphoma (CL) with focus MF,33 articles of Primary Cutaneous CD 30+,WHO-EORTC classification for CL and recently updated articles about MF. All these evidence of the MF were reviewed and analyzed.*

Results: *In this study was reviewed, the importance of bioptic examination for the diagnosis of MF and other examinations such as immunohistochemistry, and the histopathological finding of MF were again reviewed and definied. And it was given a panel of the differential diagnosis of this pathology that mimics many inflammatory pathologies in particular Spongiform Dermatitis, and neoplasmic skin lesions like Sezary Syndrome and Primary Cutaneous CD 30+- T cell Lymphoma, to warn clinicians of the wide spectrum of this difficult disease.*

Conclusion: *The classification of cutaneous lymphomas is multidisciplinary and needs the correlation between clinical, histopathological, immunohistochemical, and molecular diagnostic elements. It is important to be suspected of MF when an erythematosus process has long-lasting progression, poor responses to medications for other inflammatory pathologies, and most importantly during histopathological examination to detect atypical lymphocytes in the epidermis.*

Key words: *Mycosis fungoides, differencial diagnosis,Primary Cutaneous Lymphoma, inflammatory skin diseases*

Introduction

Primary cutaneous lymphomas are classified in the group of extranodal non-Hodgkin Lymphomas.

Primary cutaneous lymphomas have a different clinical attitude and prognosis from systemic lymphomas involving the skin secondly, and for this reason require different types of therapies.

Hence, recent classification systems such as the EORTC classification for primary cutaneous lymphomas and the WHO classification for tumours of haematopoieticand lymphoid tissues considered primary cutaneous lymphomas as separate entities.

They may be: T cell, B cell, or NK cell origin.[6,7]

Cutaneous T Cell lymphomas (CTCL) include a group of lymphomas in which:*Mycosis fungoides* is the most primary, common type of CTCL.

It is a cutaneous lymphoma that originates in the memory T-cells (CD45RO+), which express the T-cell receptor (TCR) and CD4+ immunophenotype.[1]

The etiology and risk factors of the disease are unclear.

Clinical Variants are (as report in the WHO-EORTC Classification for Cutaneous Lymphomas)

- Follicular or folliculotropic mycosis fungoides
- Pagetoidreticulosis or Woringer- Kolopp type
- Granulomatous slack skin[6,7]

Histopathology of mycosis fungoides varies in stages of the disease.

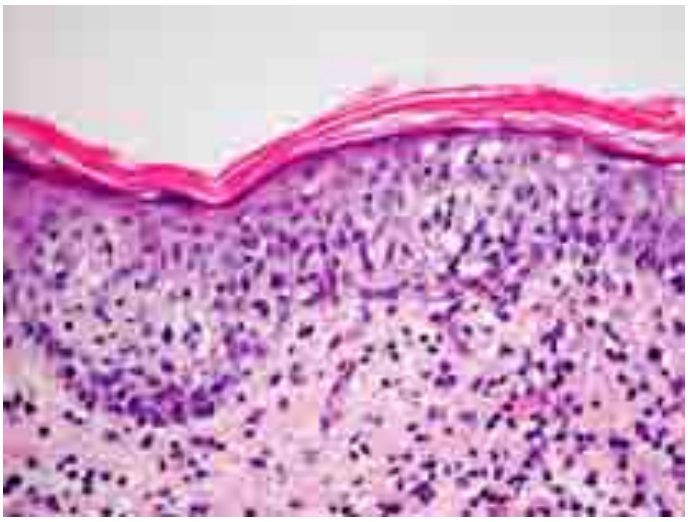
Epidermal lymphoid infiltrate, (epidermotropism) with absent or rare spongiosis, and lymphoid atypia (cerebriformcells, which are the diagnostic cells) are the main features.

Patch stage

The histological diagnosis of MF in its early stages is difficult, as the disease resemble as an inflammatory skin diseases

Patchy lichenoid infiltrate of lymphocytes in thickened papillary dermis and in small collection within a minimally spongiotic epidermis (Atypical lymphocytes cerebriform cell circumscribed to the epidermis (epidermotropism)).

Epidermis may show psoriasisform hyperplasia



Plaque stage

Findings are similar to those seen in patch stage, but the infiltrate is denser.

The epidermotropism is more noticeable and the presence of intraepidermal collections of atypical cells (Pautriermicroabscesses) is a real feature close to diagnose. Lymphocytes may be cytologically atypical.

Tumor stage

In this stage the epidermotropism is lost and the tumor cells (atypical lymphocytes) increase in number and size.In this part of the disease are present medium to large lymphoid cell (blast cells with large nuclei and prominent nucleoli)[1,2]

Immunohistochemistry

Tumour cells have a mature CD3+, CD4+, CD45RO+ memory T-cell phenotype. In same cases is documented a CD4– /CD8+ mature T-cell phenotype (MF, cytotoxic immunophenotype variant). Similar cases have the same clinical feature and prognosis as CD4+ cases. With the progression of the disease loss of CD2, CD5, and CD7 may be seen. When large blast stage take place, cells can express the CD30 molecule and/or a cytotoxic phenotype.[2,5] *An image of MF in early stage..*[22]

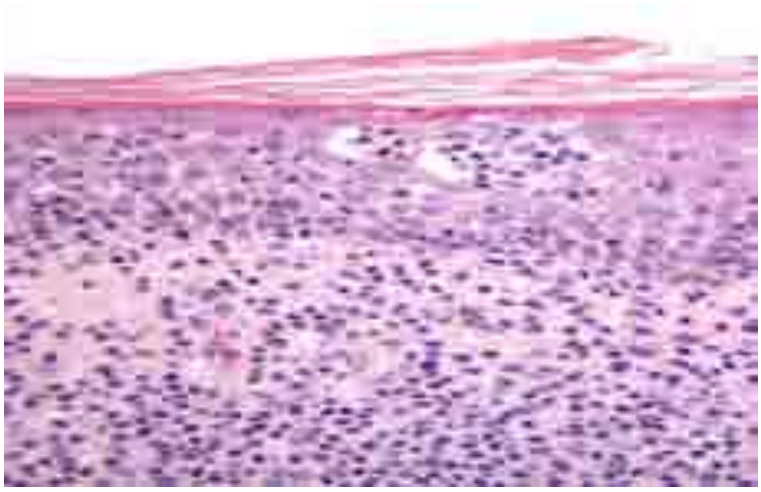


Image of Pautrier microabcesses

Primary cutaneous CD30+ T-cell lymphoproliferative diseases are the second most common category of CTCLs. CD30-positive CTCLs include: lymphomatoidpapulosis (LP), anaplastic large cell lymphoma (ALCL), and some cases of mycosis fungoides with large cell transformation (MFLCT).[7] *Images og plaque-stage, when are seen the Pautrier microabcesses*[22]

Materials and Methods

This is a concentric, factual, and descriptive retro- and prospective analysis of MF. Our study is supported in detailed review of more articles about MF, published in

Pubmed, or Free article and our little experience in diagnosis this entity through clinical, histopathological, immunohistochemical elements.

Some of these articles are updated lately.

In practice, the diagnosis of MF in an early stage can be very challenging because clinicopathologic features overlap with various inflammatory dermatitis and conflict with clinical presentations and pathologic features.[10]

Results

Inflammatory process, not mycosis fungoides
Explanation

Different histopathologic findings are nearly related to skin diseases, more than 40 different benign dermatitis – most of them inflammatory dermatoses such as eczema, psoriasis, nonspecific dermatitis, lichen, lupus, pseudolymphoma, parapsoriasis, and toxidermia have been interpreted as being clinically and pathologic imitated by mycosis fungoides.

In the first place need to be specified the histological data about MF. [11,13]

Many studies confirmed that the characteristic histopathologic features of MF in **an early stage** include enlarged epidermal lymphocytes with cerebriform nuclei in the epidermis and epidermotropism, and others features which are mention above.Despite this, none of these features are entirely specific for MF.After all the pattern may vary, epidermotropism is considered an emblem of MF.

Pautrier microabsces are atypical lymphocytes tend to become aggregation in round collections in the epidermis, named

wrong for Pautrier (it was Darier who described them first) is considered more specific for MF but is only seen in a few lesions.A variety of inflammatory and neoplastic diseases may look-alike MF if only changes in the epidermis alone are taken into account.[14]During histopatological examination, the doctor see neutrophils in the dermis or in the epidermis, extravasation in number of erythrocytes in the papillary dermis and sometimes in the epidermis, marked spongiosis and/or ballooning of the epidermis, and mounds of parakeratosis staggered between zones of orthokeratosis in a cornified layer.[9,12] When one or more of the signs are presented, an supposition justified that the process is inflammatory and evolving, and not neoplastic.

However, an epidermis that have changes that look closely those of mycosis fungoides and edema is prominent in the papillary dermis, a pathologist can conclude, perfectly, that the disease is not mycosis fungoides, but an inflammatory one.[9,12]

According to Differencial Diagnosis in Surgical Pathology ‘s book Spongiotic Dermatitis is one of the most closely related disease, that have the same findings as MF in an early stage.[3]

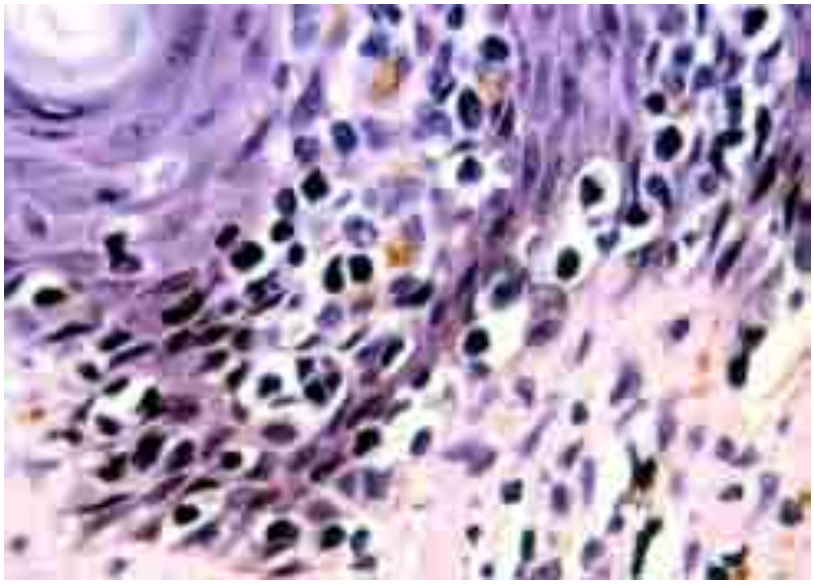
The difficulty arises because collections of mononuclear cells are present in discrete foci in the epidermis of both conditions.

But, when a histopathologist sees no pure population of lymphocytes, numerous cells that have prominent stellate cytoplasm (keratocytes)mixed with Langerhans cell,there is no doubt for a manifestation of spongiotic dermatitis.

Also we mention the importance of Pautrier ‘ s collections.

The red blood cells tend to be extravasated in the upper part of the dermis of some spongioticdermatitides, but none in mycosis fungoides.

In short, the findings in mycosis fungoides are the antagonistic of those in spongioticdermatitides.[11]



An image of a Halo Lymphocites [22]

Sezary ‘s sindrom vs mycosis fungoides

Explanation

Sezary’s Sindrom (SS) is a variant of Mycosis Fungoides represent an erythrodermic form of it with neoplastic cells (Sezary cells) populating the peripheral blood.

The characteristics between those pathologies are very difficult. The histopathologicalfinding and the immunostaining are exactly like MF.[16]The immunohistochemical pattern of Sezary syndrome is CD3+, CD4+, CD7-, and CD8- cells,same as MF.To differentiate those pathologies is used immunostaining

for MUM-1 (multiple myeloma oncogene) because it is positive in Sezary syndrome and negative in mycosis fungoides.

MF and SS may be distinguished by identification of certain molecules, including Programmed-Death-1.[15]

Primary cutaneus cd30+ t-cell lymphomas vs mycosis fungoides

Explanation

As MF progresses **to the tumor stage**, the infiltration of atypical lymphocytes shares a nodular pattern in the dermis with loss of epidermotropism, and others situations(the formation of a large atypical lymphocytes –the blasts) mention above in tumor stage. The important thing during this phase is the expression of the atypical lymphocytesof CD30 molecule, complicating the differential diagnosis with others limphoproliferativ disorders like Primary Cutaneus CD30+ TcellLymphoma.It is needed to point out, even in this case when MF express CD 30+, that the definitive diagnosis of MFLCT requires the clinical history(clinical assessment) and cutaneous infiltration by large atypical lymphocytes.[17] The difference diagnosis is made between MF and CD30-positive CTCLs include: lymphomatoidpapulosis (LP), anaplastic large cell lymphoma (ALCL).

LP is classified as a low-grade CTCL, in the spectrum of cutaneous CD30-positive lymphoproliferative disorders.[3,20]Histopathologically, LP can present itself in four different patterns type A,B,C and D.

LP type B is characterized by small to medium CD4-positive lymphocytes and are often CD30-negative, with cerebriform nuclei with epidermotropism. These findings are identical as in MF. [1,18]

But, the definitive diagnosis of LP requires close clinical-pathological correlation, especially when it comes to the last common histologic subtypes (B, C, and D).[20]

ALCL is a CD30-positive non-Hodgkin's lymphoma, classified by the World Health Organization .

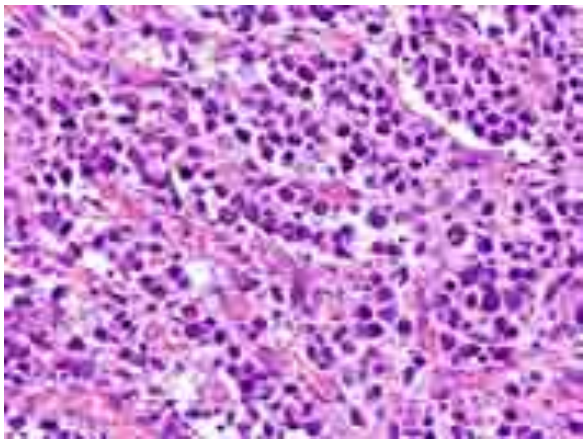
Microcsopically ALCLs shows evidence of diffuse dermal infiltrate of lymphoid cells containing large, round, oval, or irregular vesicular nuclei, with prominent and eosinophilic nucleoli and abundant cytoplasm. The epidermotropism is absent.

The large lymphoid cells show strong positivity for CD 30+ molecule in the form of diffuse membrane staining, as well as a paranuclear dot-like reaction in the Golgi area.[19]

According to genetic level, this tumor is characterized by the chromosomal translocation t(2;5), which generates the chimeric NPM-ALK transcript.

This can be detected by immunohistochemistry, RT-PCR and in situ hybridization in the lesional tissue.

In contrast of systemic CD30+ lymphomas, most C-ALCs express the cutaneous lymphocyte antigen (CLA), but do not express the epithelial membrane antigen (EMA) and the anaplastic lymphoma kinase (ALK; indicative of the t2;5 chromosomal translocation or its variants).[21]



Anaplastic large cell lymphoma

-CD30 positive,diffuse, uniform staining in all tumor cells (membrane and Golgi zone pattern)[22]

Conclusion

Mycosis fungoides is the most frequent primary cutaneous lymphoma and various differential diagnoses can be made especially in the early phases of the disease. Sometimes it can be difficult to suspect and diagnose from the clinical presentation to histopathological and immunohistochemical findings. Hence it requires good knowledge of the disease from both clinicians and pathologists.

The aim of this article is to highlight the importance of close clinico-pathological correlation for an accurate diagnosis.

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