

Diagnostic Approach of Mycosis Fungoides and Unusual Benign Mimickers

Fatma EL-Zahraa Salah El-Deen Yassin*¹, Reham Ezz Eldawla², Sheren Farrag Mahmoud Ahmed¹

Departments of ¹Pathology and ²Dermatology, Venereology, and Andrology,

Faculty of Medicine, Sohag University, Sohag, Egypt

*Corresponding author: Fatma El-Zahraa Salah El-Deen Yassin, Mobile: (+20)01007970144,

Email: fatmaf2002@yahoo.com

ABSTRACT

Background: Diagnosis of mycosis fungoides (MF) and its mimickers is a major diagnostic challenge in era of Dermatopathology. **Objective:** To draw a diagnostic stepwise approach to minimize this challenge focusing on the benign (unusual) mimickers of infectious etiology.

Patients/methods: This retrospective study included 94 paraffin blocks of patients with clinical suspicious of MF or its mimickers, during the period from Jan 2019-July 2021. The hematoxylin and eosin (H&E) stained sections and their associated clinical presentations were reviewed. Ancillary studies were performed upon the preliminary clinical diagnosis of each case. Deeper serial sections with selected special stains were done for benign mimickers. Primary (CD3/CD4/CD7/CD68) and secondary (CD20/CD8/CD30) panels of immunohistochemistry (IHC) markers were performed for most of the cases.

Results: A wide spectrum of MF mimickers was identified, our cases were categorized into 3 groups: the first is classic MF (24) and its variants (5), the second is benign mimickers [subgrouped into infectious (31) & non infectious (21)] and the third is heterogeneous group; (other lymphomas/parapsoriasis) (13). A suggested stepwise diagnostic approach with selected IHC panels characterizes each group.

Conclusion: A constellation of diagnostic clinical data, diagnostic histopathological clues and the suggested stepwise approach minimize the misdiagnosis of classic MF and conclusively identify the infectious mimickers.

Keywords: Histopathology, Mycosis Fungoides, Mimickers.

INTRODUCTION

Cutaneous lymphoproliferative lesions are a common diagnostic challenge; they include typical versus atypical infiltrates. Mycosis fungoides (MF) is the most common diagnosis for atypical infiltrate. The international classification of cutaneous lymphoma published by World Health Organization (WHO) new variants of MF: folliculotropic and granulomatous MF (1, 2).

The straightforward clinical diagnosis is usually associated with typical histopathological features of the same lesion. However, the ambiguous clinical presentation is reflected histopathologically and creates diagnostic challenges. Mycosis fungoides is characterized by indolent progression through three stages: patch, plaque and tumor, characteristic progression of histopathological features through different stages was illustrated in (Figure 1).

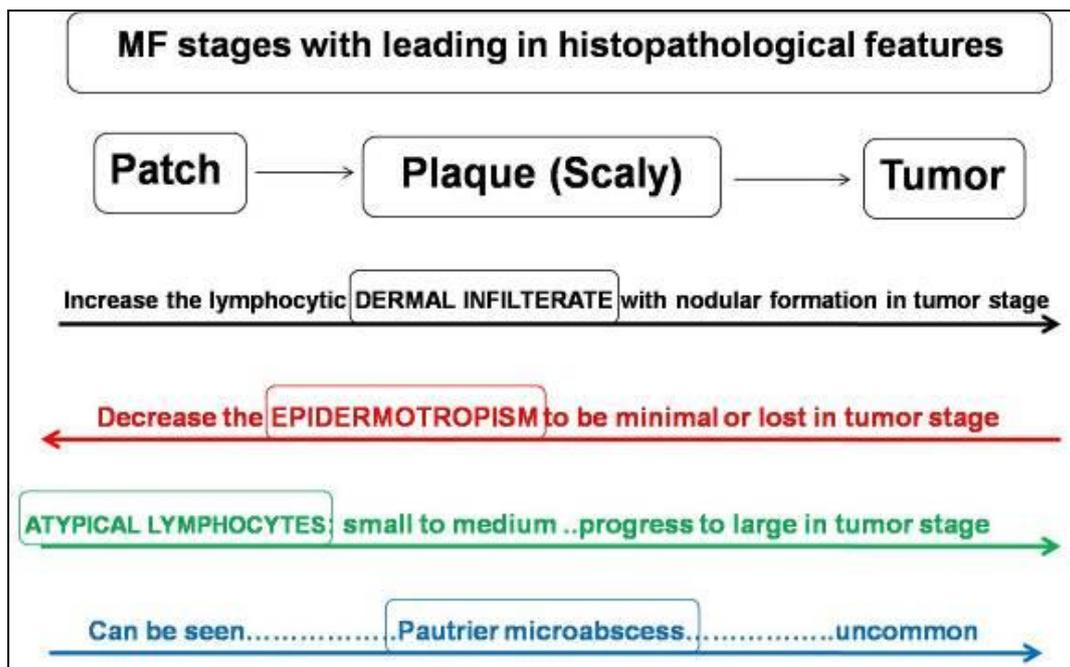


Figure (1): MF stages with progression of histopathological features, direction of the arrows from the minimum to the maximum.

Clinical and histopathological variations of MF create a wide spectrum of mimickers: some of them are common (usual) and others are considered uncommon (unusual). The most common MF mimickers are benign dermatosis: psoriasis, eczema, hypertrophic lichen.....etc⁽³⁾.

Diagnosis of MF is not an easy task especially in the presence of a wide spectrum of mimickers so **we aimed** to draw a diagnostic stepwise approach with major diagnostic histopathological criteria of classic MF to minimize the diagnostic challenge of MF and its mimickers especially benign dermatosis.

PATIENTS AND METHODS

Patients and samples:

This is a retrospective study carried out in a tertiary care center, during the period from Jan 2019-July 2021. Ninety-four paraffin blocks were obtained as their clinical suspicious of MF. All mimickers were mentioned as one of the differential diagnosis in the clinical reports.

The hematoxylin and eosin (H&E) stained sections and their associated clinical presentations

were reviewed by two pathologists (Fatma El-Zahraa & Sheren). Ancillary studies were performed upon the preliminary clinical diagnosis of each case: Deeper serial sections with selected special stains (PAS/Ziehl Neelsen (ZN)/Modified Ziehl Neelsen (MZN)/Masson trichrome) were done for benign mimickers. Primary and secondary panels of immunohistochemistry markers were performed for most of cases.

Dewar and his colleagues⁽⁴⁾ described important steps for optimal histopathological evaluation of cutaneous lymphoproliferative lesions under microscope: low power examination to assess the architecture of the infiltrate (superficial, superficial and deep, deep and subcutaneous), presence of epidermotropism/pilotropism/syringotropism. Followed by mid power examination to assess the nature of the infiltrate (monomorphic versus mixed). Lastly, high power examination is done to assess the degree of cellular atypia. All above morphological clues will help us to select the appropriate second step in our approach (Figure 2).

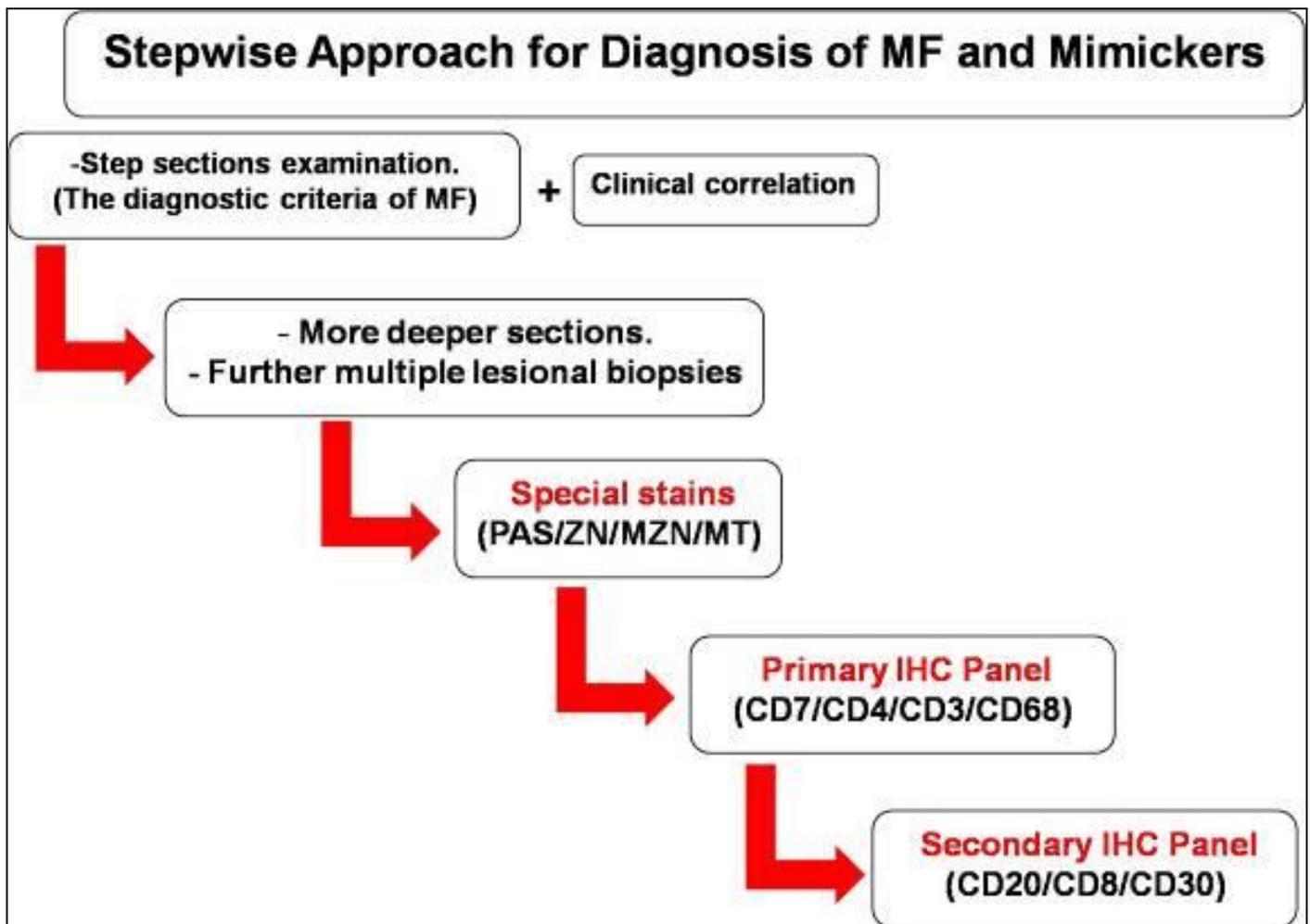


Figure (2): Stepwise approach of MF diagnosis and its mimickers.

Immunohistochemistry:

The primary panel was (CD3/CD4/CD7 ± CD68). The secondary confirmatory panel was (CD20/CD8/CD30) (Figure 3). The used panel is determined according to the clinical and provisional diagnosis of each case.

Representative formalin-fixed, paraffin-embedded, routinely processed tissue sections from each specimen were stained with optimal concentration of the selected primary antibodies (CD3/CD4/CD7/CD68/CD20, CD8/CD30), mouse monoclonal antibodies (LABVISION Corporation, Fremont, USA) were used according to the associated protocols: Tissue sections were deparaffinized and rehydrated, antigens were retrieved by incubating sections in sodium citrate buffer (pH 6.0) in an 800w microwave for 10 min. After blocking nonspecific reactions by endogenous hydrogen peroxidase, sections were incubated at suitable temperature with specific antibody. Visualization of staining was conducted using streptavidin–biotin; ABC staining kit (Catalog # TA-015-HP, Lab-Vision Corporation Fremont, USA), according to manufacturer’s instructions. Immunohistochemical reactions were developed with 3,3- diaminobenzidine; chromogen peroxidase substrate (DAB).

Counterstaining of tissue sections was done using Myer’s Hematoxylin and mounted using DPX and cover slipped. Both positive and negative controls were consistently immunoreactive and lacking reactivity respectively. This confirms the validity of the staining results.

Immunohistochemical evaluation: the expression of each marker was assessed according to the recommended cut-off values⁽⁵⁾ in the epidermis and dermis of suspected cases.

Statistical analysis

The collected data were coded, processed and analyzed using the SPSS (Statistical Package for Social Sciences) version 22 for Windows® (IBM SPSS Inc, Chicago, IL, USA).

RESULTS

According to the clinical, provisional histopathological diagnoses and immunohistochemical features of the selected panel (Figure 3), we categorized our cases into 3 groups: the first is classical MF and its variants, the second is benign mimickers and the third is heterogeneous group (other lymphomas/parapsoriasis) (Table 1).

Tables: Table (1): MF and mimickers in the current study.

| Diagnosis | | No. of cases | Ancillary studies | | | | | | | |
|------------------------|-------------------------|----------------------------------|------------------------------------|-------------|------|------|------|------|-------|------|
| | | | Special stain | CD4 | CD3 | CD7 | CD8 | CD20 | CD68 | |
| MF & Variants | Classical MF: | 24 | ---- | + | + | -ve | ± | ---- | ----- | |
| | Folliculotropic variant | 3 | MZN (-ve) PAS (+mucin) | + | + | -ve | -ve | -ve | -ve | |
| | Hypo pigmented variant | 2 | -----MT (direction of collagen) | + | + | -ve | -ve | -ve | -ve | |
| Benign mimickers of MF | Infectious N=31 | 1-Scabies | 6 | ----- | --- | ---- | ---- | ---- | ----- | |
| | | 2- Secondary syphilis | 3 | Gimsa (+ve) | -ve | -ve | +ve | ---- | ---- | +ve |
| | | 3- Leprosy | 8 | MZN(±) | -ve | -ve | +ve | ---- | ---- | +ve |
| | | 4-Fungal infection | 14 | PAS (±) | ---- | ---- | ---- | ---- | ---- | ---- |
| | Non- infectious N=21 | 1-Eczema (spongiotic dermatitis) | 12 | (±) | -ve | -ve | +ve | ---- | ---- | --- |
| | | 2- Lichen planus | 4 | (±) | -ve | -ve | +ve | ---- | ---- | --- |
| | | 3-DLE | 3 | PAS (mucin) | -ve | -ve | +ve | ---- | ---- | --- |
| | | 4- Lymphocytoma cutis | 2 | (±) | ±ve | ±ve | ±ve | ---- | +ve | +ve |
| Miscellaneous | 1-B cell lymphoma | 4 | ----- | -ve | -ve | -ve | -ve | +ve | ---- | |
| | 2- Parapsoriasis | 9 | (±) | -ve | -ve | +ve | ---- | ---- | +ve | |
| Total= | | | 94 | | | | | | | |

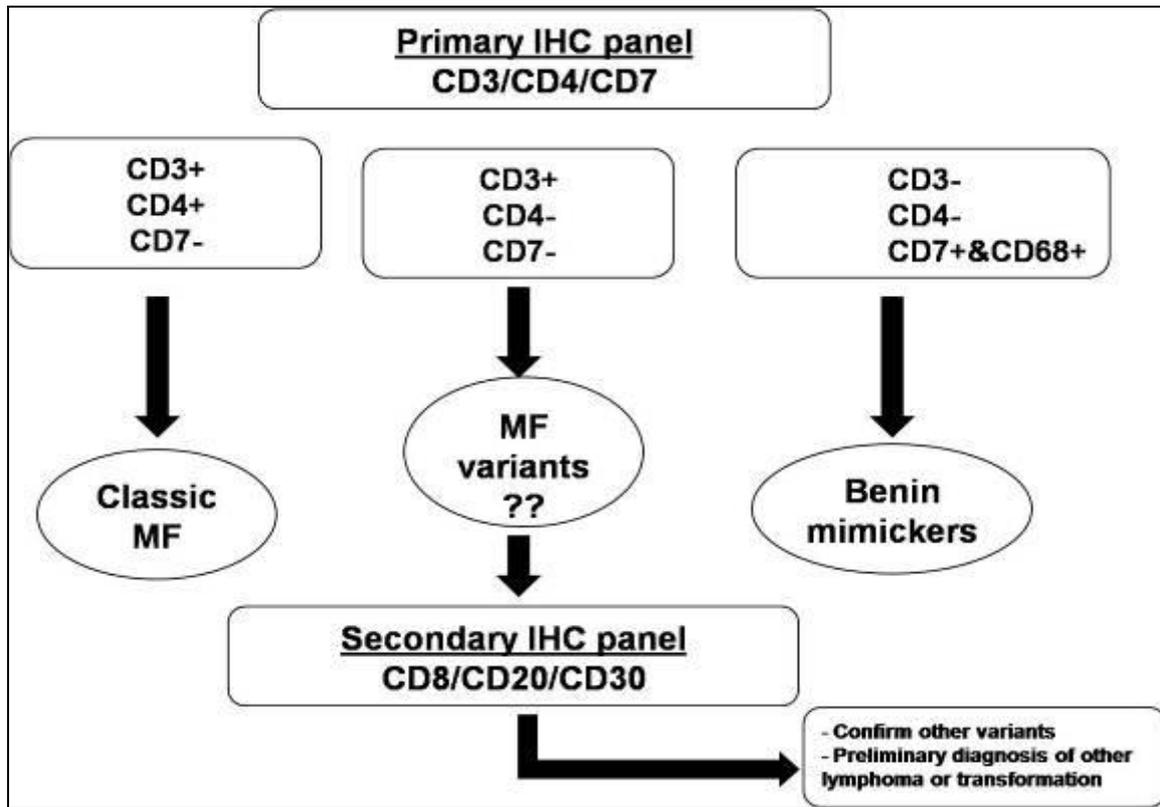


Figure (3): The suggested IHC panels in the current study.

1. The first group (Classical MF & its variants) (N=29): included 24 classic MF, 3 folliculotropic MF and 2 hypo-pigmented variants.

The classical MF showed unique histopathological features according to the corresponding clinical stages (Figure 1).

- 1- **Lining up** of haloed lymphocytes along the dermo-epidermal junctions.
- 2- **Epidermotropism**: small to medium sized atypical lymphocytes are attacking the epidermis with cerebriform nuclei, arranged either singly or in small collections.
- 3- **Pautrier microabscess**: sharply margined discrete clusters of lymphocytes in close apposition with one another, within the epidermis.
- 4- **Superficial dermal atypical lymphocyte infiltrate**: band like or lichenoid pattern.
- 5- **Subepidermal fibrosis** (Table 2 & Figures 4 & 5).

Table (2): Histopathological Diagnostic Clues of MF.

Diagnostic Histopathological criteria (Clues) of MF

- **Haloed cerebriform lymphocytes** aligned along the slightly expanded papillary dermis, then they confined along the basal layer (single or groups).
- **Epidermotropism**: epidermal lymphocytes are larger than those in the dermis and may equal the size of nucleus of an epithelial cell, progress from patch to plaque and absent in tumor stage.
- **Pautrier microabscess**: is a characteristic, could be seen easily in plaque stage and absent in tumor stage.

(Epidermotropism should be isolated from collections of Pautrier microabscess)

- **Dermal infiltrate**:

- Small to medium size lymphocytes (patch to plaque stage)
- Superficial +/- folliculotropism or syringotropism.
- A few eosinophils and/or plasma cells.
- Deeper dense larger lymphocytes with more atypia and mitosis in tumor stage (deep dermis and subcutaneous tissue may be involved).

- **Epidermis**: may be mild acanthosis or atrophic (poikiloderma).

- Minimal to absent spongiosis

- **Sub epidermal fibrosis**: Especially in chronic stages (perpendicular on basement membrane or haphazardly arranged).

- **Other findings(-/+)**:

- Melanin pigment incontinence (more in hypo pigmented MF).
- Vesicle/bullae.
- Telangiectatic vessels/vasculitis.

Alert signs for revision your diagnosis as MF

- Excessive eosinophils/plasma cells.
- Excessive dermal edema.
- Marked spongiosis.
- Disproportionate between the histopathological findings and corresponding clinical stage.

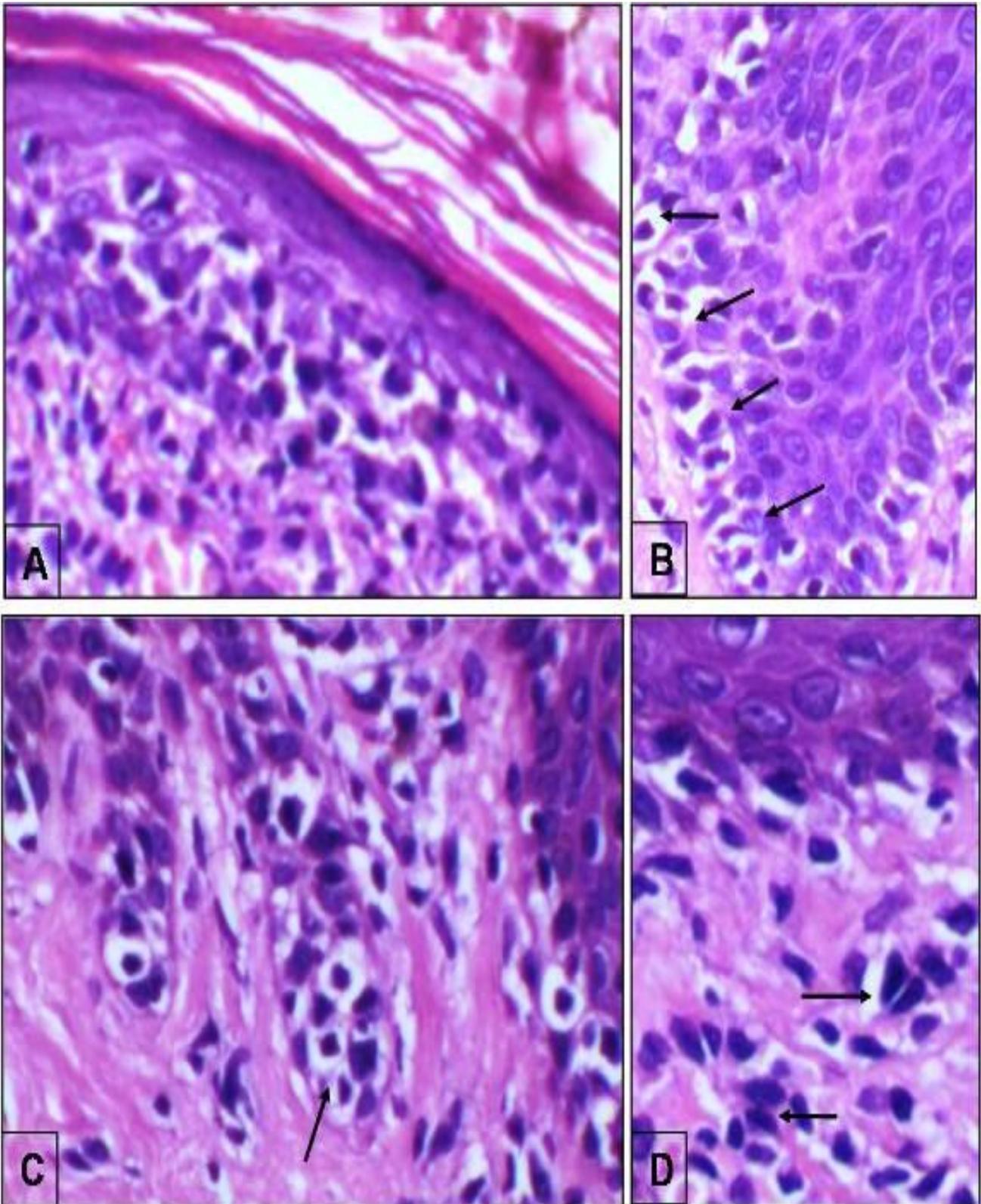


Figure (4): A-D: One of the important histopathological diagnostic clues is the atypical haloed lymphocyte attacking the dermo-epidermal junction and the papillary dermis. They are also infiltrating the dermis. (HE; x400 for all, original).

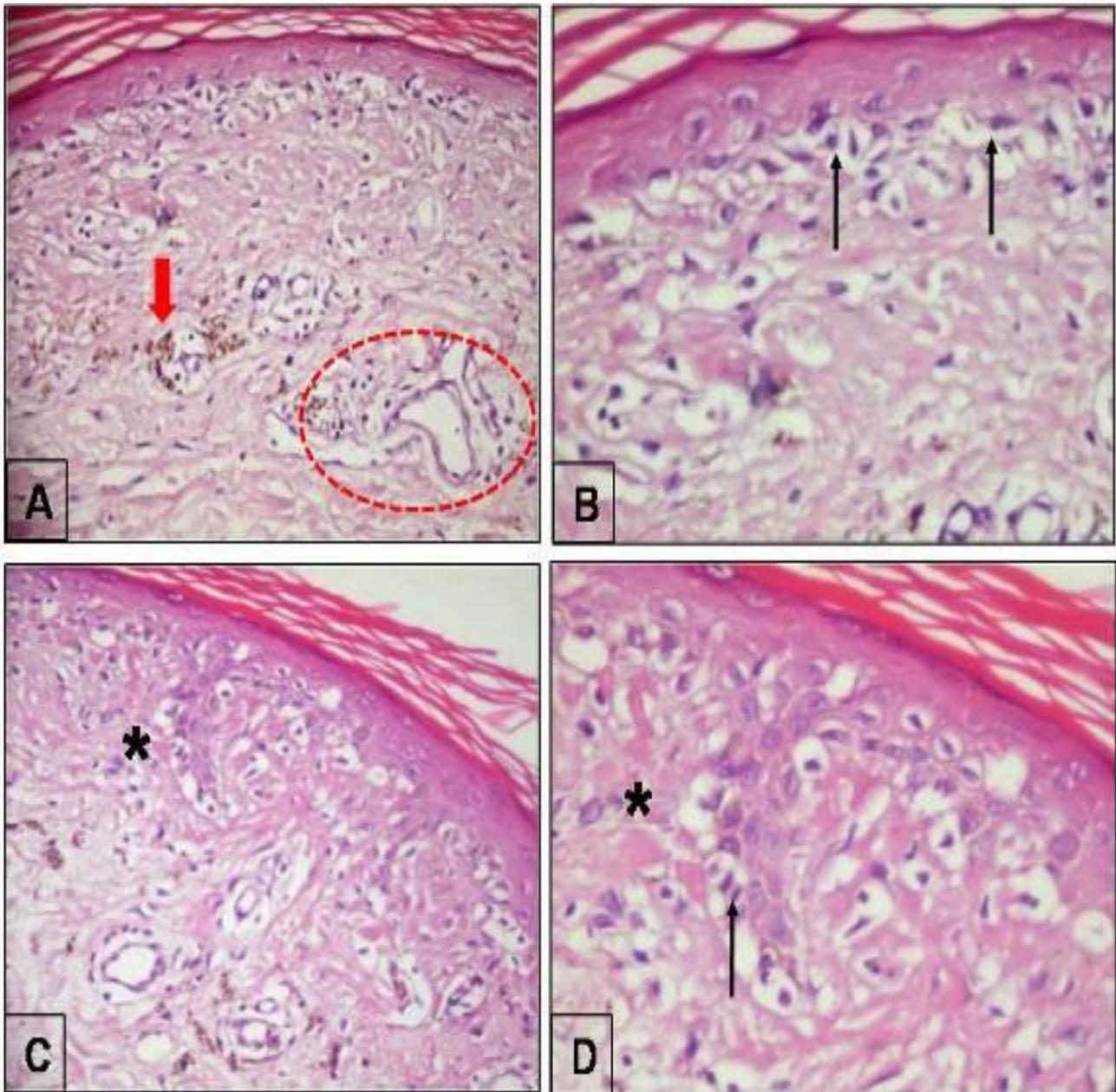


Figure (5): A-D: Another case of classic MF. The atypical haloed Lymphocytes (black arrows) attacking the dermo-epidermal junction & the papillary dermis, dermal fibrosis (astrix), ectatic blood vessels (dotted red circle) and melanin pigment incontinence (red arrow). (HE; x200,400,200, 400, original).

Some histopathological features could be noticed in MF: minimal to mild spongiosis, tissue crackling, and melanin pigment incontinence.

Folliculotropic MF (Figure 6) is clinically presented by grouped follicular papules and plaques associated with alopecia. Histopathologically: a dense mixture of atypical lympho-plasmocytic infiltrates encircling the hair follicles with variable degrees of epidermotropism.

Hypopigmented MF: showed marked epidermotropism with extension of the lymphocytic infiltrate around the adnexa. Melanin incontinence could be noticed.

Immunophenotyping: classic MF revealed positive CD 4/CD8 with ratio more than 2.5 (Within the epidermis) (Figure 7). Some cases showed negative CD8 expression. Positive CD3 expression and negative staining of CD7 were encountered in all MF cases (Figures 6 & 7). Immunophenotyping of MF variants revealed CD 4+ /CD8-, CD20-ve and CD68-ve (Figure 6).

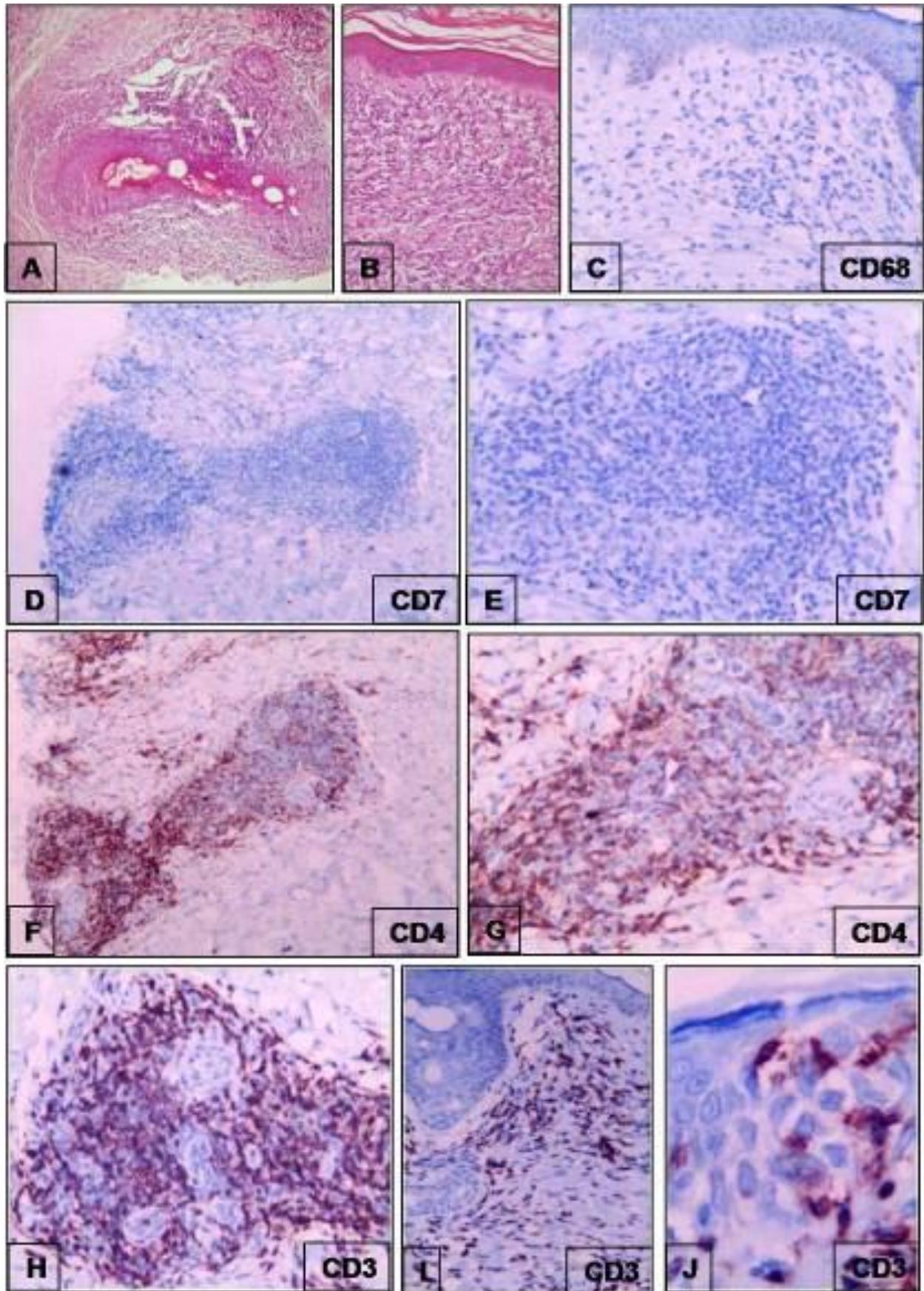


Figure (6): A case of folliculotropic MF mimics leprosy. A-B: A dense dermal lymphocytic infiltrate with folliculotroism. C-E: The infiltrate showed negative staining of both CD68&CD7 excluding the inflammatory nature. F-J: Positive expression of CD3&CD4 confirming MF. J:CD3 can pick up the atypical lymphocytes within the epidermis. (Original; HEx200,400-CD68x100- CD4x100,400-CD3x200,100,400).

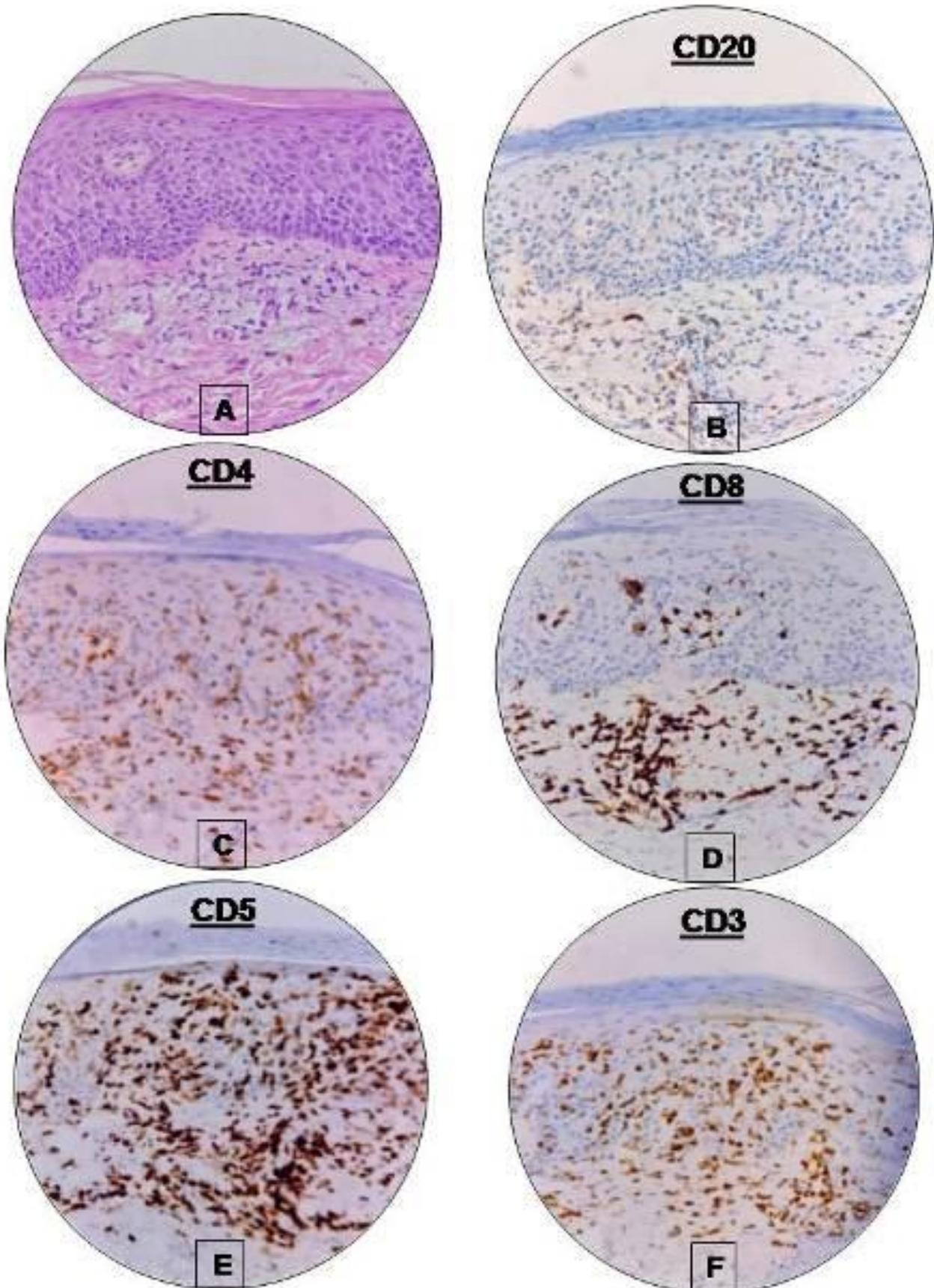


Figure (7): A case of classic MF with typical immunoprofile A; epidermotropism with focal parakeratosis. B; negative expression of CD20. C-D; Positive expression of CD4 & CD8 with ratio 2.5:1 intra epidermally. E-F; Positive expression of pan T cell markers (CD5&CD3) (Original, X200 all).

2. The second group (Benign MF mimickers) (N= 52):

Include wide spectrum of lesions: subgrouped into infectious (N=31) and none infectious (N=21) (Table 1).

The infectious groups include the following clinical diagnoses: scabies, syphilis, leprosy and fungal infections.

Scabies (figure 8): clinically nodular or crusted types not responding to usual treatment. Histopathological examination revealed dense dermal lymphocytic infiltrates (nodules) with numerous eosinophils, Pautrier like microabscess, fibrin thrombi within small dermal vessels and obvious dermal edema. Definite evidence of diagnosis depends mainly on fragmented mite/egg/eggshell and scybala within the epidermis.

Secondary Syphilis: a dense mixture of inflammatory infiltrate with plasma cell predominance obscuring the dermo epidermal junction, epidermal hyperplasia and

end arteritis obliterans were observed. Step sections examination and deeper ones confirm the diagnosis.

Leprosy: a mixed lympho- histocytic infiltrate occupying the superficial dermis with encroachment of pilo- sebaceous units and eccrine sweat glands are confusing features with MF. Immunophenotyping highlighted the histocytic nature (CD68+ve) and (CD7+ve) of dermal lymphocytic infiltrate. Cases with paucicellular organisms give negative Modified ZN stain.

Fungal infection: considerable spongiosis with dense mixture of inflammatory infiltrate characterizes the specimen. Numerous eosinophils and presence of sandwich sign (neutrophils between the parakeratotic and orthokeratotic layers of the epidermis) can confirm the diagnosis. PAS usually solves the diagnostic challenge. The possibility of concomitant MF and fungal is sometime suspected.

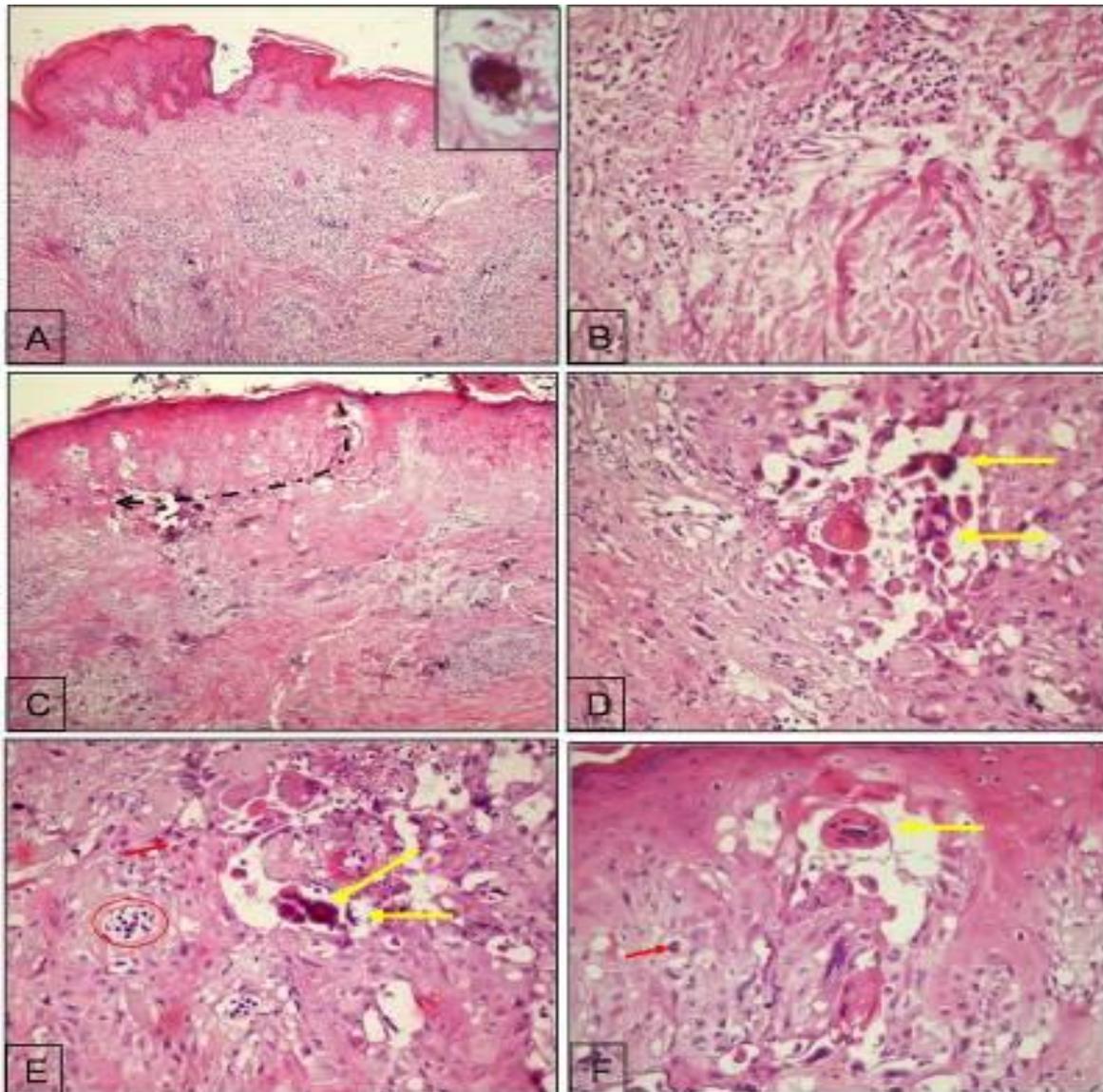


Figure (8): A case of nodular scabies with clinical suspicion of MF: A-B; Nodular inflammatory infiltrate (Scybala inset) mainly perivascular with eosinophils. C; Coiled arrow represent the burrow within the epidermis. D; Yellow arrows referred to multiple degenerated eggs. E-F; Red arrows referred to esinophilic exocytosis and Pautrier microabscess (red circle). (HE X100x200, x100,400,400,400 original).

None infectious groups include the following clinical diagnoses: Eczema, pityriasis Rosea (spongiotic dermatitis), lichen planus, DLE and Lymphocytoma cutis.

Lymphocytoma cutis: is considered a reactive process of benign cutaneous lymphoid hyperplasia, usually secondary to drugs or infections or insect bites. It showed pandermal infiltrate encircling the adnexa (folliculotropic and eccrinotropic) with sparing of grenz zone, moderate to dense admixture of small lymphocytes, immunoblasts like cells, eosinophils and plasma cells. Follicles with active germinal center could be seen. Triggering factors like mite or arthropod infections could be highlighted as in (**Figure 9**).

Contact/ allergic dermatitis: Significant spongiosis which is propionate to the degree of inflammatory infiltrate, upper dermal edema, Langerhans cell collections within the epidermis (pale cytoplasm and more vesicular nuclei) highlighted these cases. Positive expression of CD7 and negative CD3&CD4 confirm the diagnosis.

Lichen planus (LP): wedge shaped hypergranulosis, necrotic keratinocytes and saw tooth appearance of rete ridges characterized LP. Misleading features: presence of epidermotropism, Pautrier microabscess and presence of atypical lymphocytic infiltrate.

Discoid Lupus Erythematous (DLE): a dense atypical epidermotropic or folliculotropic lymphocytic infiltrate is one confusing feature in DLE, positive serology solves the challenge.

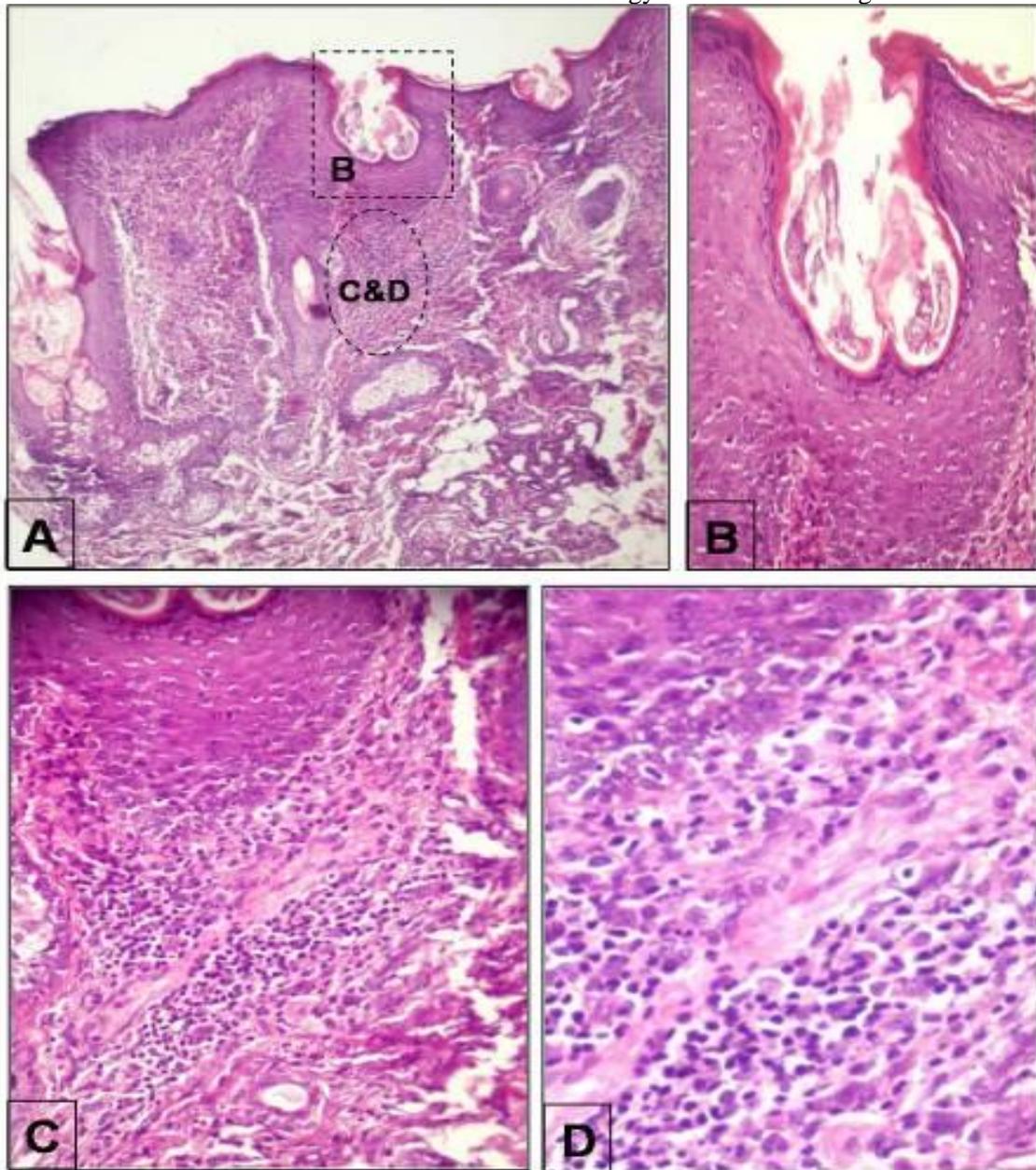


Figure (9): A case of Lymphocytoma cutis mimic MF. A; scanning view with dense infiltrate around the adnexa. B; The organism can be seen inside the ostium of follicle (triggering agent). C-D; Folliculotroism with Lymphoplasmocytic infiltrate could be observed. (HE; x100,400,400,400, original).

3. The third group (Miscellaneous mimickers: other lymphomas and Parapsoriasis) (N=13):

Parapsoriasis: characterized by moderate to dense inflammatory infiltrate with minimal epidermotropism (non haloed lymphocytes), mild acanthosis and focal parakeratosis with papillary dermal fibrosis.

B cell lymphoma: admixture of infiltrate with folliculotropism and dense atypical dermal infiltrate and immunophenotyping by positive expression of monoclonal B cells confirm the diagnosis. The applied and selected immunohistochemical panel was illustrated in (Figure 10).

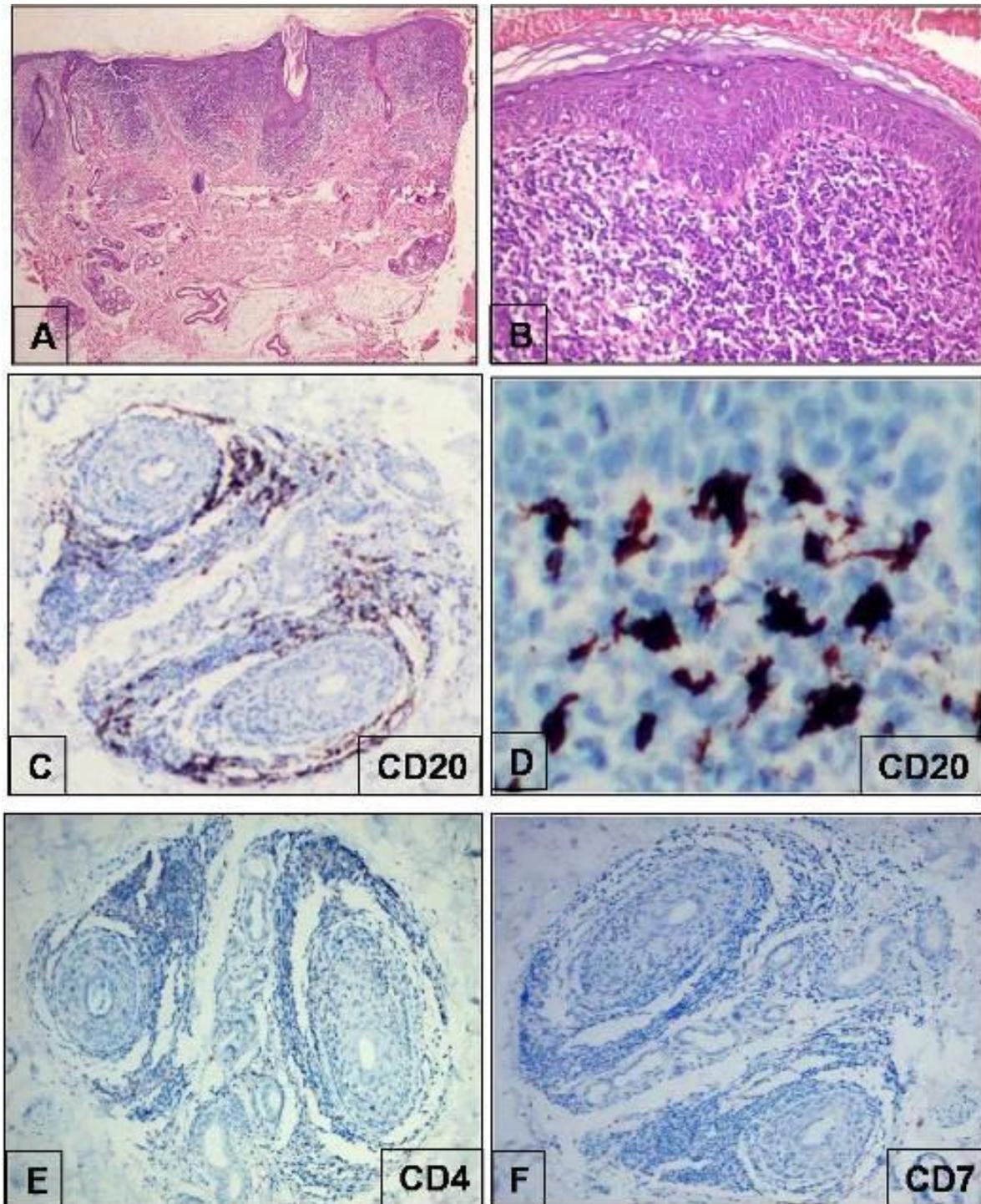


Figure (10): A case of B cell lymphoma mimics folliculotropic MF. A-B; A dense atypical infiltrate surrounds the adnexa. C; Positive Expression of the infiltrate around hair follicles could be detected. E-F; Negative expression of both CD4&CD7 could be observed. (HE;x40,400, CD20;x200, 400. CD4&CD7; x200,200, original)

DISCUSSION

The clinical and histopathological variation of MF created a wide spectrum of mimickers; some of them are common (usual) while others are relatively uncommon (unusual). **Kelati *et al.*** ⁽⁶⁾ recommended that there is variability of MF mimickers between different countries and populations. Developed countries reported psoriasis, spongiotic dermatitis and drug eruption at the top of MF mimickers list, while ours found that the infectious group of MF mimickers is the most common (60% of cases).

Benign mimickers of infectious etiology were very common in our locality; we considered them a major diagnostic challenge with MF as self medical treatment and late medical advice create overlap between the clinical and histopathological features. Therefore, we will focus on these lesions and will discuss them in detail.

Many clinical and histopathological difficulties are facing both clinicians and dermatopathologists and lead to false negative and false positive diagnoses. Clinical obstacles are: lack of specific symptoms, variable clinical stages which differ from one person to another, remission and progression nature of the disease (wax and wane) which lead to absence of diagnostic clinical criteria of MF ⁽⁷⁾.

Presence of a wide spectrum of dermatosis and dermatosis like conditions sharing the same histopathological features with MF lead to inconclusive reports of skin biopsies.

However, histopathological examination is still the golden rule for more accurate diagnosis in MF cases. **Kelati *et al.*** ⁽⁶⁾ reported that 84.5% of clinically diagnosed lymphoma was subsequently excluded by histopathological examination. More accurate diagnosis of MF initiates early treatment with more favorable prognosis of the patients.

Several researchers ^(6, 8, 9) put forth helpful diagnostic criteria for MF. However, none of them was entirely specific. We stated reliable diagnostic criteria for more accurate diagnosis of MF and to distinguish it from infectious dermatosis, according to the previous literatures (Table 2) ⁽⁷⁾.

Epidermotropism: is considered a hallmark of MF. Variable percentages were reported within different populations ⁽⁶⁾, some authors ^(1,2) mentioned its absence in 4% of MF cases. However, it is one of most common findings in several benign dermatoses. Intra epidermal lymphocytes are generally larger and more cerebriform than dermal lymphocytes and usually surrounded by halo (haloed lymphocytes).

We want to specify the epidermotropism for lymphocytes and not for other inflammatory cells. We mean that presence of neutrophils, histocytes and eosinophils in addition to lymphocytes in the epidermis favors the diagnosis of benign dermatosis

over MF. However, admixture of dermal infiltrate of any of the previous cells could be detected in MF and dermatosis. Another confirmatory tool is CD3 immunophenotyping which can pick up the epidermotropic atypical lymphocytes.

Pautrier microabscess is considered a more specific and characteristic of MF. **Muñoz-González *et al.*** ⁽²⁾ declared its presence in less than 25% of early patch stage, step sections examination in plaque stage raising the percentage to 50% of biopsies. Both **Pautrier microabscess** and **Epidermotropism** are normally absent in tumor stage of MF.

Spongiotic dermatitis showed what is called **pseudo Pautrier micro abscess** which is collections of histocytes (with more pale cytoplasm and vesicular nuclei). It is common in allergic dermatitis and pityriasis rosea. CD3 can pick up atypical lymphocytes within true Pautrier microabscess in MF while CD68 highlight the pseudo Pautrier microabscess in spongiotic dermatitis.

Disproportionate epidermotropism; a feature described to a lesser degree of spongiosis in relation to the degree of epidermal infiltrate of lymphocytes, favoring the diagnosis of MF. Marked spongiosis whatever the degree of infiltrate is not mentioned in MF and we should revise our diagnosis as dermatosis ⁽⁶⁾.

Atypical dermal lymphocytes: **Muñoz-González *et al.*** ⁽²⁾ reported this finding in less than 10% of early cases of MF so its presence raises the score toward MF with subsequent confirmatory immunohistochemical panels.

Other histopathological features are less specific and we considered them minor criteria: Sub epidermal fibrosis, reactive epidermal changes (acanthosis or atrophy or focal parakeratosis), folliculotropism /syringotropism, Melanin pigment incontinence....etc.

Revision of diagnosis should be done if one of the following is found: Marked spongiosis, excessive dermal edema and overwhelming eosinophilic, plasmocytic or histocytic infiltrates (whatever the clonality).

Several variants of MF were published by the World Health Organization (WHO) ⁽¹⁾, some of them with worse prognosis and others with better prognosis than classical MF. In the current work, we were faced with two variants: folliculotropic MF of worse prognosis and hypo pigmented MF with a better prognosis than the classical MF. We will discuss the unusual infectious group of dermatitis (Scabies, secondary syphilis, leprosy and fungal infections) versus corresponding variant of MF followed by None infectious group. **We used the suggested stepwise approach for the diagnosis of MF and its mimickers (Figure 2)**

1-Folliculotropic variant of MF versus leprosy:

Leprosy is not uncommon in our locality; we found the variability of clinical stages of leprosy from flat macules to elevated nodules that mimic MF in its variable clinical stages, leading to overlapping features especially in borderline leprosy. The clinicians wrote the diagnosis of leprosy in their differential diagnosis of MF cases. Application of step sections examinations, use of modified Z.N. and positive serology help in solving the diagnostic puzzle. Primary panel of IHC: positive CD7/ negative CD4 of dermal infiltrate with highlight of histocytes by CD68 expression confirm our diagnosis as leprosy.

Folliculotropic MF showed aggregates of atypical lymphocytes in the outer root sheath of the hair follicle (folliculotropism), perivascularly and periadnexially with follicular mucinosis, eosinophils and plasma cells. Three out of 29 MF cases were diagnosed as Folliculotropic MF in the current study with double positivity of CD3&CD4 and double negativity of CD7&CD68. **Gunawan et al.**⁽¹⁰⁾ reported a similar case of psoriasiform lesion of borderline lepromatous leprosy mimicking MF.

2-Hypopigmented variant of MF versus post inflammatory hypo pigmentation:

Hypo pigmented MF is characterized by marked epidermotropism, psoriasiform hyperplasia of the epidermis⁽²⁾. IHC revealed CD4+/CD8+ and negative expression of CD7. A confusing finding is the presence of CD1a Langerhans cells in the epidermis which is more common in dermatosis. Hence CD3 immunophenotyping can pick up atypical lymphocytes within the epidermis.

The post inflammatory hypo pigmented lesions lacked the previous immunoprofile and had severe dermal fibrosis (parallel to the basement membrane of dermo epidermal junction). Hypopigmented MF can imitate leprosy.

3-MF versus nodular scabies:

Unusual mimicker of MF which could be seen in the current study is scabies. It is characterized by a dense dermal infiltrate, mainly lymphocytes admixed with eosinophils, considerable degree of spongiosis with epidermotropism and Pautrier microabscess. One of the alarming signs is presence of numerous epidermal and dermal eosinophils which favors the diagnosis of infectious dermatosis over MF. Meticulous examination of serial sections can highlight the presence of mite, eggs or eggshells within the epidermis. A study **Reddy and Bhawan**⁽¹¹⁾ mentioned scabies as MF mimicker.

4-MF versus secondary syphilis:

A dense lymphocytic infiltrate with cerebriform nuclei, epidermotropism, folliculotropism and follicular mucinosis create confusion between MF and

secondary syphilis diagnoses. However, numerous plasma cells within the infiltrate with mixture of polyclonal T and B cells shift the diagnosis towards the infectious dermatosis. Deeper sections with further biopsy and positive serological tests confirm the diagnosis of syphilis. **Reddy and Bhawan**⁽¹¹⁾ mentioned secondary syphilis as a great imitator of MF.

5-MF versus fungal dermatitis:

Fungal dermatosis represents a broad category of our cases (45% of infectious dermatosis) similar to others⁽¹²⁾. Considerable spongiosis, a mixture of acute and chronic inflammatory infiltrate with numerous eosinophils characterize this era. PAS examination can highlight the hyphae or spores. Presence of dense dermal atypical lymphocyte infiltrate with epidermotropism creates confusion with MF. However, concomitant fungal infection with MF is possible.

6-MF versus spongiotic dermatitis:

Eczema, allergic or contact dermatitis represents more than half of cases in non infectious dermatitis. Significant spongiosis, Langerhans cell collections (pseudo Pautrier microabscess) and upper dermal edema are suggestive features of dermatosis over MF. Good clinical history, positive patch test and confirmatory panel of immunophenotyping are usually conclusive. Positivity of CD1a highlights Langerhans cell within the epidermis while positive expression of CD7 assures the inflammatory nature of the dermal infiltrate.

7- MF versus Parapsoriasis:

Wobser et al.⁽¹²⁾ and **Sarveswari and Yesudian**⁽¹³⁾ considered large plaque parapsoriasis an inflammatory process while others considered it a part of spectrum of MF stages. Our cases could be diagnosed histopathologically: minimal epidermotropism (with small lymphocytes), associated epidermal changes (acanthosis and parakeratosis) and absent spongiosis. Immunophenotyping is not conclusive in these cases.

8- MF versus Lymphocytoma cutis:

Lymphocytoma cutis is considered a reactive process of benign cutaneous lymphoid hyperplasia, usually secondary to drugs or infections or insect bites^(6, 11). Presence of eosinophils, plasma cells and germinal centers enables distinction from lymphoma. Identification of underlying triggering factor such as infections or insect bite is a helpful tool in diagnosis. IHC is confirmatory by negative panel of lymphoma, and positive CD7 & CD68.

Some entities will not discuss: DLE, drug eruption, psoriasis as they need more and more details and they are extensively mentioned by **Wobser et al.**⁽¹²⁾.

We recommended certain guidelines to minimize the diagnostic challenge of MF and its mimickers: step examination of all serial sections, followed by another lesional biopsy if could not reach preliminary diagnosis. Bear in your mind the infectious group of mimickers and the variability of MF from one person to another even at the same clinical stage, the important role of ancillary studies: beginning with special stains followed by primary and secondary panels of IHC and lastly the molecular studies if they are available (Figure 3).

A constellation of history, clinical, histopathological and histochemical features with immunohistochemistry is complementary tools for more accurate diagnosis of MF.

Disproportionate epidermotropism, picking up the intra epidermal lymphocytes by CD3 and negativity of CD7 are clues for conclusive diagnosis of MF while single criterion as isolated negativity of CD7 is not sufficient for MF diagnosis.

CONCLUSION

Distinguishing MF and its mimickers is a major diagnostic challenge in era of Dermatopathology. A constellation of diagnostic clinical data, diagnostic histopathological clues and the suggested stepwise approach minimize the misdiagnosis of classic MF and conclusively diagnose the infectious mimickers.

Financial support and sponsorship: Nil.

Conflict of interest: Nil.

REFERENCES

1. Swerdlow S, Campo E, Harris N *et al.* (2017): World Health Organization Classification of Tumours of Hematopoietic and Lymphoid Tissue. Revised 4th edition. Lyon: IARC Press. <https://publications.iarc.fr/Book-And-Report-Series/Who-Classification-Of-Tumours/WHO-Classification-Of-Tumours-Of-Haematopoietic-And-Lymphoid-Tissues-2017>
2. Muñoz-González H, Molina-Ruiz A, Requena L (2017): Clinicopathologic Variants of Mycosis Fungoides. *Actas Dermosifiliogr.*, 108(3):192-208.
3. Wobser M, Geissinger E, Rosenwald A *et al.* (2015): Mycosis fungoides: A mimicker of benign dermatoses. *World J Dermatol.*, 4(4): 135-144.
4. Dewar R, Andea A, Guitart J *et al.* (2015): Best practices in diagnostic immunohistochemistry. Workup of cutaneous lymphoid lesions in the diagnosis of primary cutaneous lymphoma. *Arch Pathol Lab Med.*, 139: 338-350.
5. Ryu H, Kim S, Jang H *et al.* (2021): Evaluation of the international society for cutaneous lymphoma algorithm for the diagnosis of early mycosis fungoides. *Cells*, 10: 2758-63.
6. Kelati A, Gallouj S, Tahiri L *et al.* (2017): Defining the mimics and clinico-histological diagnosis criteria for mycosis fungoides to minimize misdiagnosis. *International Journal of Women's Dermatology*, 3: 100–106.
7. Lebas E, Collins P, Somja J *et al.* (2021): A Comprehensive Update of the Atypical, Rare and Mimicking Presentations of Mycosis Fungoides. *Dermatol Ther.*, 11:1931–1951.
8. Pimpinelli N, Olsen E, Santucci M *et al.* (2005): Defining early mycosis fungoides. *J Am Acad Dermatol.*, 53:1053–63.
9. Vandergriff T, Nezafati K, Susa J *et al.* (2015): Defining early mycosis fungoides: Validation of a diagnostic algorithm proposed by the International Society for Cutaneous Lymphomas. *J Cutan Pathol.*, 42:318–28.
10. Gunawan H, Utami F, Achdiat P *et al.* (2019): A unique case of borderline lepromatous leprosy with psoriasis-like lesions all over the body and mycosis fungoides-like lesions on the face. *J Clin Tuberc Other Mycobact Dis.*, 17: 1-5.
11. Reddy K, Bhawan J (2007): Histologic mimickers of mycosis Fungoides: A review. *J Cutan Pathol.*, 34: 519–525.
12. Wobser M, Geissinger E, Rosenwald A *et al.* (2015): Mycosis fungoides: A mimicker of benign dermatoses. *World J Dermatol.*, 4(4): 135-144.
13. Sarveswari K, Yesudian P (2009): The conundrum of parapsoriasis versus patch stage of mycosis fungoides. *Indian J Dermatol Venereol Leprol.*, 75(3): 229-235.