

# B-cell lymphofollicular infiltrates in mycosis fungoides

Gerardo Ferrara<sup>1</sup>, Concetta Chiarelli<sup>2</sup>, and Stefano Simonetti<sup>3</sup>

<sup>1</sup>Pathologic Anatomy Unit, Gaetano Rummo General Hospital, Benevento; <sup>2</sup>Pathologic Anatomy Unit, San Martino Hospital, Belluno; <sup>3</sup>Department of Dermatology, University of Perugia, Perugia, Italy

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## ABSTRACT

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**Aims and background.** The histopathological picture of mycosis fungoides can be characterized by heavy reactive infiltrates. These are rarely composed of B lymphocytes with formation of reactive follicles.

**Methods and study design.** We collected three cases of mycosis fungoides with a reactive B-cell lymphofollicular reaction at the bottom of the epidermotropic infiltrate.

**Results.** Case 1 showed flat lesions (patches) with a CD4<sup>+</sup> neoplastic phenotype; case 2 presented infiltrated lesions (plaques) with a CD8<sup>+</sup> immunophenotype; case 3 was characterized by nodular lesions (tumors) with a CD4<sup>+</sup> neoplastic component. In all three cases, no clonal gene rearrangement was found with the polymerase chain reaction technique.

**Conclusions.** Among the protean clinicopathological features which mycosis fungoides can show, we underline that a B-cell lymphofollicular component can be encountered at the base of the epidermotropic infiltrate even in clinically flat ("patchy") lesions. Free full text available at [www.tumorionline.it](http://www.tumorionline.it)

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## Introduction

Granulomatous mycosis fungoides<sup>1</sup> and granulomatous slack skin<sup>2</sup> are well-recognized clinicopathological subtypes of mycosis fungoides (MF) that may harbor a reactive infiltrate mainly composed of epithelioid histiocytes with or without giant cells. Interstitial mycosis fungoides may also show a histiocytic component accounting for up to 30% of the dermal infiltrate<sup>3</sup>. Folliculotropic mycosis fungoides may be associated with marked eosinophilic and/or plasmacellular infiltration<sup>4</sup>. Cutaneous lymphomas other than MF may also show a reactive granulomatous infiltrate<sup>5</sup>; other cutaneous lymphoproliferative disorders including type A lymphomatoid papulosis<sup>6</sup>, marginal zone B-cell lymphoma<sup>7</sup>, and T-cell-rich B-cell lymphoma<sup>8</sup> are characterized by a more or less heavy reactive infiltrate within which only a minority of neoplastic cells are found.

In 1999 van der Putte *et al.*<sup>9</sup> reported an unusual variant of MF characterized by a heavy B-cell infiltrate, even with immunohistochemical evidence of immunoglobulin light chain restriction. Since then, this unusual accompanying feature of MF has been rarely investigated<sup>10,11</sup>.

We describe 3 additional such cases, which point to the possibility that even "patchy" (non-infiltrated) lesions of MF can host a heavy reactive B-cell lymphofollicular infiltrate.

## Case reports

### Case 1

A 59-year-old woman was seen for flat, erythematous and scaling lesions of the trunk and limbs involving less than 10% of the skin surface (Figure 1, A-B). A biopsy

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Conflict of interest: none

Correspondence to: Dr Gerardo Ferrara, Pathologic Anatomy Unit, Gaetano Rummo General Hospital, Via dell'Angelo 1, 82100 Benevento, Italy. Tel +39-0824-57315 ; fax +39-0824-57332; e-mail [gerardo.ferrara@libero.it](mailto:gerardo.ferrara@libero.it)

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specimen from the axilla revealed a superficial and deep infiltrate with marked formation of follicles with pale centers (Figure 1C). Within the superficial dermis, the infiltrate showed a perivascular and interstitial distribution, with a tendency to fill the dermal papillae and align along the basal layer of the epidermis (Figure 1D). The deep infiltrate showed reactive-appearing germinal centers and some mono- and multinucleated histiocytes (Figure 1D), even with ill-formed epithelioid granulomas. No elastophagic giant cells were found. Immunohistochemically, CD3<sup>+</sup>, CD4<sup>+</sup> (Figure 1E), CD5<sup>+</sup>, CD7<sup>+</sup>, CD8<sup>+</sup>, and CD56<sup>-</sup> T lymphocytes were the prevailing cell population within the superficial dermis, as well as within the epidermis, whereas CD20<sup>+</sup> and CD79 $\alpha$ <sup>+</sup> B lymphocytes with some bcl6-positive aggregates prevailed within the deep dermis; the cell cycle-related protein Ki67 was prevalently expressed within the germinal centers with evidence of polarization (Figure 1F) (see Table 1 for the list of the antibodies used in the present study). The anti-kappa and the anti-lambda antibodies showed few positive cells. Only sparse cells stained with the anti-CD30 antibody. No clonal IgH and TCR gene rearrangements were found with the polymerase chain reaction performed on the paraffin-embedded tissue sample according to the previously described technique<sup>12</sup>.

Staging procedures performed according to a standard protocol<sup>13</sup> proved negative for extracutaneous involvement (Stage IA; T1 N0 M0).

#### Case 2

A 68-year-old man was seen for long-standing plaques of the trunk involving 20% of the skin surface (Figure 2, A-B). Histology showed an extremely thinned epidermis with a heavy subepidermal infiltrate (Figure 2C) of small to medium-sized atypical lymphocytes (Figure 2D) admixed with a few large cells. The deep portion of the infiltrate was mainly composed of variously sized lymphoid cells with well formed germinal centers (Figure 2, C-D). Immunohistochemically, most subepidermal lymphocytes were CD3<sup>+</sup>, CD4<sup>+</sup>, CD5<sup>+</sup>, CD7<sup>+</sup>, CD8<sup>+</sup> (Figure 2E), and CD56<sup>-</sup>; conversely, the majority of the deep lymphocytes were CD20<sup>+</sup> (Figure 2F) and CD79 $\alpha$ <sup>+</sup> with nodular aggregates which were highly proliferating as shown by the anti-Ki67 antibody. Only occasional cells were found to be CD30<sup>+</sup>. No appreciable plasma-cell component was detected with the anti-kappa and anti-lambda antibodies. No clonal gene rearrangement was found with the PCR technique. Staging procedures were negative for extracutaneous involvement (Stage IB; T2 N0 M0).

#### Case 3

A 55-year-old man had a 3-year history of infiltrated plaques and nodules on the buttocks and thighs (Figure 3, A-B). Histopathologically, there was a dense lym-

phoid infiltrate involving the entire dermis (Figure 3C). The superficial portion of the infiltrate was predominantly composed of small lymphocytes with irregular nuclear contours; some collections of lymphocytes were also seen within the epidermis (Figure 3D). The deeper portion of the infiltrate mainly showed well formed germinal centers with a reactive architecture. Sparse histiocytic giant cells were seen as well. Immunohistochemistry showed that the subepidermal, intraepidermal, and some of the deep dermal component was mostly composed of CD3<sup>+</sup>, CD4<sup>+</sup> (Figure 3E), CD5<sup>+</sup>, CD7<sup>+</sup>, CD8<sup>+</sup>, and CD56<sup>-</sup> cells, while the B-cell antigens CD20 and CD79 $\alpha$  were prevailing within the cell population of the reticular dermis. The anti-bcl6 antibody highlighted the germinal center component (Figure 3F) with no appreciable staining of cells in the diffuse areas; the germinal centers showed a large fraction of Ki67<sup>+</sup> cells. Only sparse CD30<sup>+</sup> blasts were found within the dermis. The anti-kappa and anti-lambda antibodies stained a small population of plasma cells with no evidence of clonal restriction. T-cell receptor and IgH genes were not clonally rearranged. The inguinal nodes were enlarged, but histopathologically negative (Stage IIB; T3 N1 M0).

#### Discussion

The present cases draw the attention to an unusual histopathological pitfall of MF, namely, the presence of a heavy B-cell lymphofollicular reaction at the bottom of the epidermotropic infiltrate. We interpret this finding as a peculiar host response to the tumor; its prognostic significance is still unknown due to the limited number of cases reported so far. Interestingly, we found that this feature can be present even at an early ("patch") stage of MF, which is quite unexpected on clinical grounds. The cases we have described above show an undoubtedly intriguing histopathological picture that leaves space for numerous differential diagnoses. In short, we think that the main diagnostic clues of our cases are i) the clinical picture; ii) the striking compartmental distribution of the infiltrate; iii) the more or less pronounced epidermotropism.

Clinicopathological correlation is crucial for the diagnosis of MF in each of its stages and each of its diverse clinicopathological presentations. Several inflammatory dermatoses, such as psoriasis, dermatophytosis, chronic eczema, erythema multiforme, pityriasis rubra pilaris, drug eruption, secondary syphilis, scleroderma, etc.<sup>14,15</sup>, are notoriously hard to be differentiated from MF, particularly in its early or "patch" stage. Our cases 2 and 3 showed long-standing infiltrated lesions involving large areas of the body, a picture which was not consistent with an inflammatory dermatosis. Only case 1 could clinically recall an inflammatory dermatosis, but its histopathological picture, albeit highly unusual, al-

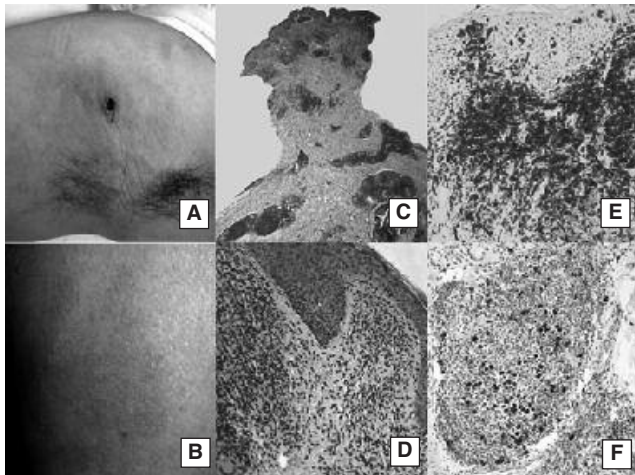


Figure 1 - Case 1: erythematous and scaly lesions of the axilla (A) and thigh (B). Histopathologically, there is a mononuclear infiltrate which expands the papillary dermis and features follicles with pale centers in the deeper portion (C; hematoxylin-eosin,  $\times 25$ ). The superficial infiltrate fills the papillae and shows some alignment along the basal layer of the epidermis (D; hematoxylin-eosin,  $\times 200$ ); it is mainly composed of CD4<sup>+</sup> lymphocytes (E;  $\times 200$ ). The deep lymphoid follicles show germinal centers with a high proliferation rate (F;  $\times 200$ ) as expected in a reactive condition.

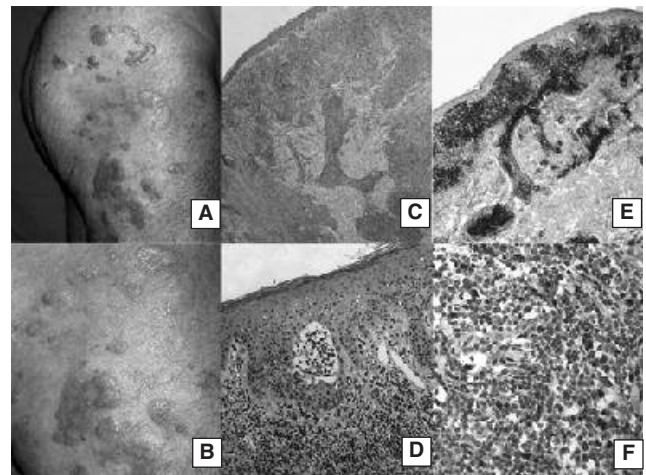


Figure 3 - Case 3: plaques and nodules of the thigh (A, B). Histopathologically there is a dense, superficial and deep lymphoid infiltrate (C; hematoxylin-eosin,  $\times 40$ ) with involvement of the epidermis and formation of Pautrier's microabscesses (D; hematoxylin-eosin,  $\times 200$ ). Immunohistochemically, most superficial cells expanding the papillary dermis are CD4<sup>+</sup> lymphocytes (E;  $\times 25$ ), whereas the deeply located B lymphocytes aggregate into bcl6-positive follicular structures (F;  $\times 400$ ).

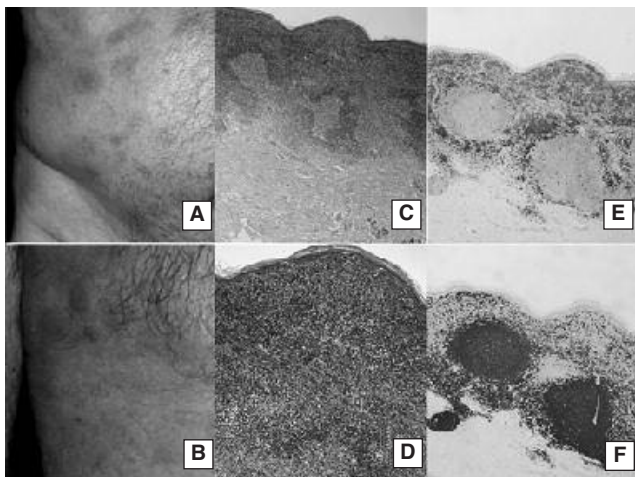


Figure 2 - Case 2: erythematous patches (A) and plaques (B). Histopathology shows a thick band-like infiltrate with lymphoid follicles at its base (C; hematoxylin-eosin,  $\times 40$ ); the epidermis is eroded by small atypical lymphocytes (D; hematoxylin-eosin,  $\times 100$ ). Immunohistochemically, most of the cells close to the epidermis are CD8<sup>+</sup> lymphocytes (E;  $\times 40$ ), whereas the nodules at the base of the infiltrate are composed of CD20<sup>+</sup> lymphocytes (F;  $\times 40$ ).

lowed us to exclude virtually all the inflammatory dermatoses that enter the classical differential diagnosis of patch-stage MF<sup>14,15</sup>.

The term cutaneous pseudolymphoma is a “working clinicopathological diagnosis” which – from time to time – is applied to benign mimickers of lymphoma, low-grade lymphomas, and/or lymphoid infiltrates with a favorable prognosis. The clinical picture is highly vari-

Table 1 - List of primary antibodies used in the present study

Target cell antigen	Clone	Source
CD3 $\epsilon$	F7.2.38	DakoCytomation, Glostrup, DK
CD4	4B12	LabVision, Fremont, CA, USA
CD5	CD5/54/F6	DakoCytomation, Glostrup, DK
CD7	DK24	DakoCytomation, Glostrup, DK
CD8	4B12	LabVision, Fremont, CA, USA
CD20	L26	DakoCytomation, Glostrup, DK
CD30	BerH2	DakoCytomation, Glostrup, DK
CD56/NCAM	1B6	Novocastra Labs, Newcastle-upon-Tyne, UK
CD79 $\alpha$	JCB117	DakoCytomation, Glostrup, DK
Ki67	MIB1	DakoCytomation, Glostrup, DK
bcl6	P1F6 + PG-B6p	LabVision, Fremont, CA, USA
kappa light chains	Polyclonal	DakoCytomation, Glostrup, DK
lambda light chains	Polyclonal	DakoCytomation, Glostrup, DK

able, depending on the etiology. Histopathologically, a pseudolymphoma can be either band-like (e.g., lymphomatoid allergic contact dermatitis, lymphomatoid drug eruption) or nodular/diffuse (e.g., insect bite)<sup>16-18</sup>, with the latter more typically showing an admixture of T and B lymphocytes. Histopathological clues for nodular/diffuse pseudolymphoma are the prevalingly superficial (“top-heavy”) distribution of the infiltrate; the preservation of epidermal and adnexal structures; the lack of involvement of the subcutis; the presence of reactive components (eosinophils, polyclonal plasma cells, highly proliferating polarized germinal centers, vertically oriented thick-walled vessels, edematous and fibrotic areas)<sup>16-18</sup>. With the remarkable exception of the germinal center cell component, virtually none of these

features of pseudolymphomas was present in our cases. Moreover, the striking compartmental distribution of the infiltrate, with most T lymphocytes close to the epidermis and most B lymphocytes in the deeper portion, also argued against a pseudolymphoma, whose lymphocytic components are classically intermingled.

Cutaneous follicle center cell lymphoma<sup>19</sup> and cutaneous marginal zone lymphoma<sup>7</sup> are low-grade B-cell malignancies which can harbor more or less well-formed germinal centers as well as a more or less conspicuous reactive T-cell component. Clinically, these neoplasms are characterized by sparse or grouped papulonodular lesions; the flat (patchy) erythematous areas found in our cases 1 and 2 are usually not found in these B-cell malignancies. Histopathologically, the differential diagnosis of these B-cell lymphomas from a nodular/diffuse pseudolymphoma can prove difficult; in follicle center cell lymphoma, germinal centers are neoplastic, and this can be documented by the absence of tingible-body macrophages, the absence of polarization, and the low proliferation rate<sup>19</sup>; in marginal zone lymphoma, the germinal centers are reactive but they are surrounded by sheets of small to medium-sized lymphocytes with irregular nuclei and relatively abundant, pale cytoplasm, often associated with monotypic plasma cells<sup>7</sup>. None of these entities commonly show epidermotropic T lymphocytes, as found in our cases.

Epidermotropic T lymphocytes are also found in primary cutaneous aggressive epidermotropic CD8-positive lymphoma, in cutaneous/subcutaneous gamma/delta T-cell lymphoma, and in nasal-type extranodal NK/T-cell lymphoma<sup>20</sup>. These malignancies are clinically very aggressive and rapidly progressive; histopathologically, they never show an appreciable reactive B-cell infiltrate; immunohistochemically, neoplastic lymphocytes express one or more cytotoxic antigens, namely, CD56, TIA1, and perforin<sup>20</sup>. We suggest the use of at least one of these cytotoxic markers when typing cutaneous lymphoid infiltrates, with the caveat that even primarily non-cytotoxic lymphomas, including classical MF, can express cytotoxic molecules<sup>15,20</sup>.

All the above-described entities can be differentiated also by means of biomolecular techniques, the most popular being PCR-DGGE on paraffin-embedded tissues for the rearrangement of the IgH and TCR genes. However, it must be underlined that a clonal rearrangement is found in roughly 75% of lymphomas and that cases of "clonal dermatitis" have been reported as well<sup>21,22</sup>.

In conclusion, the cases we have described are a good example of the polymorphic clinicopathological features MF may show. A B-cell lymphofollicular infiltrate can be present even in clinically flat (patchy) lesions of MF, a finding that is quite surprising from a clinicopathological point of view. The need for a continuing dialogue between clinicians and histopathologists must

be underlined to make sure deceptive cases of MF with a polymorphic morphology and immunopathology will not be missed.

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