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Interstitial mycosis fungoides, a variant of mycosis fungoides resembling granuloma annulare and inflammatory morphea*

Background: Interstitial mycosis fungoides (IMF) is a rare variant of mycosis fungoides that resembles the interstitial form of granuloma annulare and inflammatory morphea. IMF has received little attention in the literature.
Methods: Clinical, histological, immunophenotypical, and genotypical findings of five cases of IMF were reviewed. The histological and immunophenotypical findings were compared with those of eight cases of interstitial granuloma annulare and six cases of inflammatory morphea.
Results: Five patients with IMF presented with non-indurated, erythematous macules; ill-defined erythematous plaques with slight scale; and nodules on the trunk and proximal limbs. Two of five patients had a prior diagnosis of mycosis fungoides. Skin biopsies revealed a striking dermal interstitial infiltrate of lymphocytes with rare histiocytes that resembled the interstitial form of granuloma annulare or inflammatory morphea. Epidermotropic lymphocytes were present at least focally in all cases. A band-like lymphocytic infiltrate was observed in two of five cases. In contrast, many plasma cells and histiocytes were observed in cases of inflammatory morphea and interstitial granuloma annulare, respectively. With Movat-pentachrome stains, increased dermal mucin deposition was observed in two of five IMF cases, in all cases of interstitial granuloma annulare, and in one of six cases of inflammatory morphea. There was focal loss of elastic fibers in all cases of inflammatory morphea. Immunohistochemical studies of IMF highlighted a dominant population of T cells (CD3+) in the dermis and epidermis. In contrast, moderate numbers of B cells (CD20+) were admixed with T cells and plasma cells in inflammatory morphea. Almost equal numbers of histiocytes (CD68+) and T cells comprised the infiltrate of interstitial granuloma annulare. In two of five IMF cases, a clonal T-cell population was detected by PCR T-cell gamma gene rearrangement analysis.
Conclusion: Mycosis fungoides occasionally presents as an interstitial lymphocytic infiltrate that mimics granuloma annulare and inflammatory morphea. Hematoxylin & eosin (H&E) findings alone can sometimes distinguish the three disorders. Immunophenotyping and genotyping may be helpful in difficult cases.

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Mycosis fungoides is a cutaneous lymphoma of helper T-cell phenotype exhibiting varied clinical and histological appearances. Patients usually present with patches, plaques, tumors and/or erythroderma.[1] Occasionally, less typical lesions are encountered. Verrucous lesions,[2] plaques resembling acanthosis nigricans,[3] and perioral dermatitis-like lesions[4] are among them. While almost any histological pattern can be seen on biopsy, the most common is a superficial perivascular lymphoid infiltrate in a somewhat lichenoid distribution accompanied by epidermotropic lymphoid cells.[5] Unusual histological presentations, such as a vasculitis, panniculitis, bullae or an interstitial infiltrate resembling granuloma annulare or inflammatory morphea, have been reported.[5–7] The latter pattern, termed interstitial mycosis fungoides (IMF), is not well studied in the literature and is only briefly mentioned in an editorial,[8,9] a study[5] and some texts.[6,10] While the histological findings of IMF are known, the clinical appearance, immunophenotype, and clonality are not well documented in the literature.

We recently identified five patients with IMF. The clinical presentation, pathological findings and differential diagnoses were reviewed. We also compared the histological and immunophenotypical findings with eight cases of interstitial granuloma annulare and six cases of inflammatory morphea to identify features that distinguish the three disorders.

Materials and methods

Five cases of IMF were identified from the pathology databases of Stanford Medical Center, University of Michigan and University of California, San Francisco. Clinical histories, pathology reports, hematoxylin & eosin (H&E)-stained slides and immunoperoxidase preparations were retrieved and reviewed. For immunostained sections, formalin-fixed, paraffin-embedded tissues were sectioned, heated to boiling in a microwave oven for 12 min in 10 mmol/l citrate buffer (antigen retrieval) and stained with antibodies to CD3 (1:50), CD20 (1:500), CD68 (1:1600) (BerH2, Dako, Carpinteria, CA). Antibody binding was detected by means of the ABC method with DAB as the chromogen. Sections were also stained with Movat-pentachrome connective tissue stain following standard procedures.[11]

We assayed for clonal T-cell receptor (TCR) γ gene rearrangement on the remaining formalin-fixed tissues using a polymerase chain reaction (PCR)-based method followed by heteroduplex analysis, as described previously.[12,13]

Eight recent cases of interstitial granuloma annulare and six cases of inflammatory morphea were selected consecutively from the pathology database of University of Michigan hospitals. H&E-stained sections were reviewed. Additional sections obtained from the paraffin-embedded, formalin-fixed tissue blocks were stained with Movat-pentachrome and with antibodies to CD3, CD20 and CD68. Percentages of cells expressing CD3, CD20 and CD68 were counted in all cases.

Results

Table 1 summarizes the clinical, histological and genotypical information from our five IMF patients, four women and one man aged between 60 and 77 years. Two of the five (patients 2 and 3) had a prior history of mycosis fungoides confirmed by biopsy. The patients presented with erythematous macules (Fig. 1), nodules (Fig. 2), and/or scaly patches (Fig. 3) at various sites. Symptom duration was 8 months to 28 years. Clinical stage ranged from 1a to 2b. Drug reaction was clinically excluded: two patients were not on any medication, and no new medications were started that temporally corresponded to the onset of the rash in the remaining three patients.

Lesional biopsies from IMF patients demonstrated a prominent infiltrate of small- to medium-sized lymphoid cells between collagen bundles and around some adnexa and blood vessels in the papillary and reticular dermis. Interstitial dermal mucin deposition was observed in two of the five cases (Fig. 4). The histological pattern simulated an interstitial presentation of granuloma annulare. In the remaining three cases, there was no significant increase in interstitial dermal mucins, which resulted in a histological pattern simulating inflammatory morphea (Fig. 5). Focally, lymphocytes with pericytoplasmic haloes were arrayed as single units and sometimes present as Pautrier's collections in the lower portions of non-spongiotic epidermis (Figs. 4 and 5). Lymphocyte nuclei were slightly hyperchromatic and displayed slightly convoluted outlines. In two of five cases, papillary dermis was altered by a band-like infiltrate of lymphocytes, some entrapped in wiry collagen (Fig. 5, inset). Rare interspersed histiocytes were observed. Dermal collagen and elastic fibers appeared unaltered in Movat-pentachrome stains. In immunostained sections (Fig. 4, inset), there was a dominant population of T cells (CD3+) in the epidermis and dermal interstitium (70–85% of mononuclear cells). Sections stained with antibody to CD68 and CD20 showed few histiocytes (10–30%) and rare B cells (0–5%) in the dermal infiltrate of IMF. Analysis of formalin-fixed tissues for clonal TCR γ gene rearrangement by heteroduplex PCR demonstrated a clonal T-cell population in two of five cases. No clonal T-cell population was detected in two other cases. The remaining

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Table 1. Summary of clinical, histopathological and genotypical findings for interstitial mycosis fungoides (IMF) patients

Patient	Age and sex	Symptom duration	Lesion type	Lesion distribution	Clinical stage	Therapy	Follow-up duration	Current status	Epidermotropism	Band-like lymphoid infiltrate	T-cell PCR studies for clonality
1	72F	8 months	Pruritic erythem. macules	Trunk, thighs, butocks	1B	Mustargen ointment	34 months	Clinical remission with 10% Mustagen ointment	Focally present	None	Negative
2	68M	2 years	Patches and plaques	Trunks, thighs, arms, buttocks	1B	Mustagen ointment, UVB	30 months	Resolution with 30% Mustargen ointment Relapsed. Treated with UVB and now in clinical remission for 5 months	Focally present	None	Negative
3	60F	28 years	Patches, plaques, nodules	Scalp, back, trunks, thighs	2B	E-beam, PUVA, Ontak, Targretin	22 months	Has baseline persistent patches and plaques despite E-beam and PUVA. Nodules did not respond to Ontak but are responding to Targretin	Focally present	None	Positive
4	77F	3 years	Pruritic scaly patches	Proximal limbs, abdomen, buttocks	1A	Mustargen ointment	9 months	Persistent patches that partially responded to 10% Mustargen. Near-clinical remission with 20% Mustargen	Brisk	Present	Indeterminate due to inhibitor
5	77F	8 months	Pruritic erythem. macules	Proximal limbs, abdomen, axilla	1A	Starting PUVA	2 months	Starting PUVA, otherwise well	Brisk	Present	Positive

erythem., erythematous.

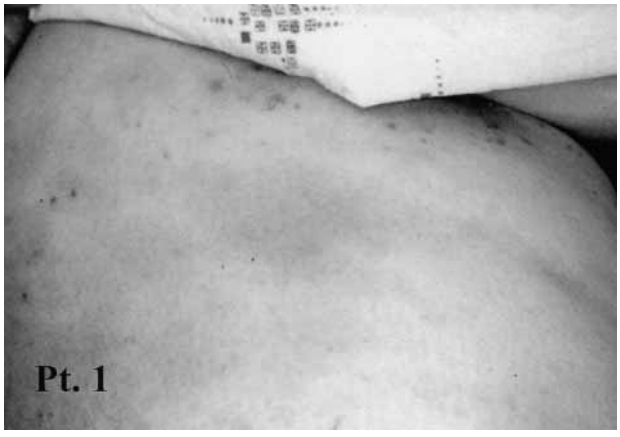

Fig. 1. Interstitial mycosis fungoides (IMF) presented as erythematous, ill-defined, non-scaly patches in patient 1.

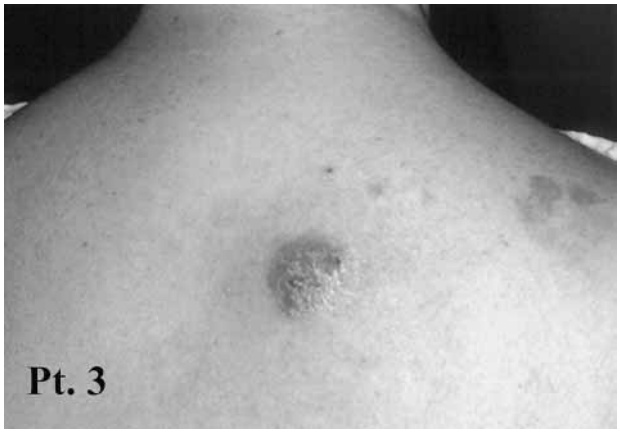

Fig. 2. Patient 3 had a 28-year history of mycosis fungoides and presented with violaceous nodules on the scalp and back. A patch lesion was also present on the right shoulder.

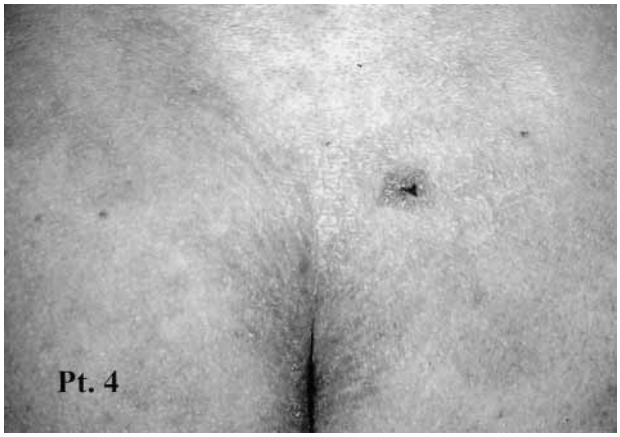

Fig. 3. Patient 4 had large and irregularly bordered, scaly erythematous plaques on the buttocks.

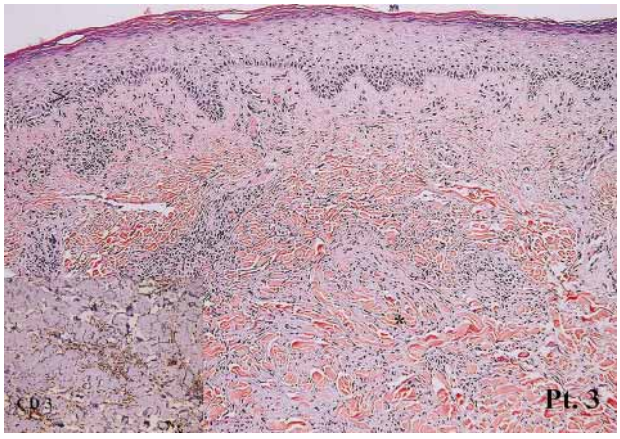

Fig. 4. Biopsy of a nodule from the back of patient 3 with interstitial mycosis fungoides (IMF). At scanning magnification, mononuclear cells course between dermal collagen accompanied by increased interstitial dermal mucin (*), a pattern resembling interstitial granuloma annulare. Epidermotropic foci are present (arrowhead). In immunostains (inset), the interstitial infiltrate of IMF consists predominantly of T lymphocytes (CD3+). PCR genotypic studies detected a clonal population of T cells in this biopsy.

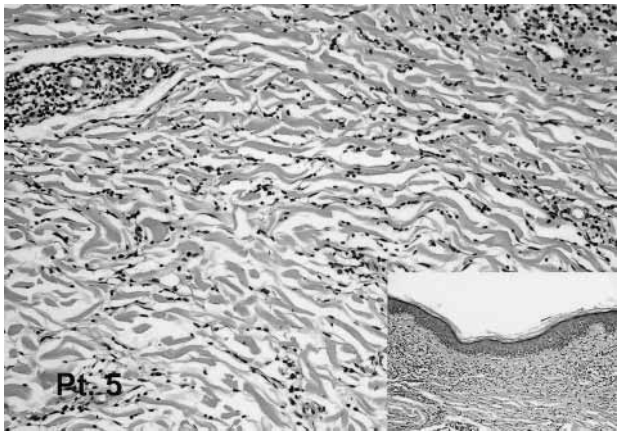

Fig. 5. Biopsy of an erythematous macular lesion on the thigh of patient 5. Interstitial infiltration by lymphocytes in deeper dermis without dermal mucin deposition simulated inflammatory morphea. As in mycosis fungoides, haloed lymphoid cells are usually present focally along the lower half of epidermis, sometimes accompanied by lymphoid cells in a lichenoid array entrapped in wiry collagen in the papillary dermis (inset). A clonal T-cell population was detected in this biopsy.

case was indeterminate for a clonal T-cell population due to the presence of a PCR inhibitor in the tissue sample.

Superficial and sometimes deep infiltrates of T lymphocytes (50–60%) were admixed with noticeably more CD68+ histiocytes (35–50%) in interstitial granuloma annulare (Fig. 6). None to a few B cells (0–5%) were present. The mononuclear cells coursed between collagen bundles that were slightly splayed apart by dermal mucinous deposits. Increased dermal

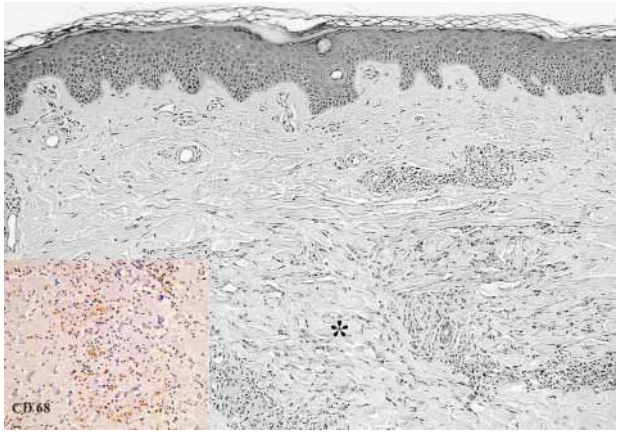

Fig. 6. In granuloma annulare, the interstitial dermal infiltrate (*) consists of many histiocytes (CD68+, inset) intermingled with T lymphocytes, usually accompanied by increased dermal mucins. The epidermis is unremarkable.

mucins were noted in all cases in Movat-pentachrome stains. A few multinucleated histiocytes were observed. Epidermis appeared unremarkable.

Our six cases of inflammatory morphea showed superficial and deep, moderately dense interstitial, periadnexal and perivascular infiltrates of lymphocytes between dermal collagen (Fig. 7). Many plasma cells were observed in all cases, some with lymphocytes along the dermal subcutaneous junction. Moderate numbers of B cells (10–40%) admixed with T cells (50–70%) were seen in immunoperoxidase preparations, but histiocytes were few in number (10–20%). There was slight eosinophilia and thickening of collagen in one case and a slight increase in dermal mucins in another case. In all cases, Movat-pentachrome sections showed areas devoid of elastin in intensely inflamed foci. Epidermis was generally unremarkable except in one case where there was slight vacuolar interface alteration and effacement of the rete ridges. Table 2 contrasts the histological and immunophenotypical findings for the three disorders.

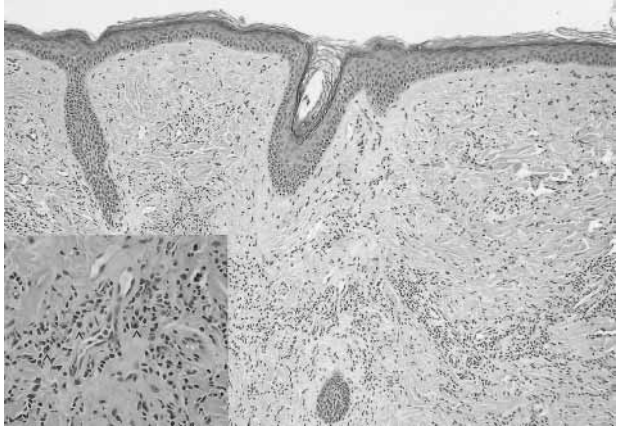

Fig. 7. Inflammatory morphea also displays an interstitial dermal infiltrate. Unlike interstitial mycosis fungoides (IMF), variable but noticeable numbers of plasma cells comprise the infiltrate (inset with arrowhead). Collagen bundles also appear slightly swollen and coarse. Epidermis is unremarkable.

Discussion

The concept of an interstitial form of MF is generally credited to A. Bernard Ackerman (PEL, unpublished observations), although it was first mentioned in a study of MF by Shapiro and Pinto.[5] Subsequently, IMF was described as a histological simulant of granuloma annulare[8–10] and inflammatory morphea.[6]

Several observations in this study support the concept that IMF is a form of mycosis fungoides. Firstly, IMF is seen in patients with mycosis fungoides. Two of our patients had a prior history of mycosis fungoides documented by biopsy. Moreover, the clinical appearances of the IMF lesions are consistent with various stages of mycosis fungoides. Secondly, histological changes of mycosis fungoides are observed in IMF. Epidermotropism with small Pautrier's collections, the hallmark of mycosis fungoides, was present focally in our examples of IMF. The band-like papillary dermal infiltrate often seen in mycosis fungoides was observed in two cases. Thirdly, in keeping with mycosis fungoides, a clonal T-cell proliferation is sometimes demonstrable, as seen in two of our five cases. PCR heteroduplex analysis for TCRγ gene rearrangement could not confirm a clonal T-cell population in three IMF cases. However, one case was indeterminate due to a PCR inhibitor. Since this molecular diagnostic technique has a sensitivity of approximately 70% for detecting T-cell clonality in MF,[12, '13] a neoplastic process could not be excluded in the two PCR-negative cases.

IMF manifests as an interstitial dermal infiltrate composed predominantly of lymphocytes with few histiocytes. The relationship of IMF to granulomatous MF,[14] which also simulates granuloma annulare, is unclear. IMF and granulomatous MF might exemplify the ends of a spectrum of host immune response to the dermal component of mycosis fungoides. In granulomatous MF, histiocytes are arranged in a palisaded and interstitial pattern admixed with neoplastic lymphocytes in the dermis.[10, '14] Unlike granuloma annulare, there is usually some epidermotropism and a lichenoid component to the infiltrate.[6, '14]

Several disorders should be considered in the differential diagnosis of IMF. Among them are inflammatory morphea, granuloma annulare, and the recently described interstitial granulomatous drug reaction.[15] Several histological findings distinguish inflammatory morphea from IMF. While both inflammatory morphea and IMF display interstitial infiltrates of lymphoid cells, plasma cells are common

Table 2. Summary of histological and immunophenotypical findings

	Epidermotropism	Band-like lympoid infiltrate	Plasma cells	Increased dermal mucins	Loss of elastic fibers	%CD3+ cells (range)	%CD20+ cells (range)	%CD68+ cells (range)
IMF	Focal in 3/5 Brisk in 2/5	2/5	Rare	2/5	0/5	70–85%	0–5%	10–30%
IMORPH	0/6	0/6	Many	1/6 (slight)	6/6	50–70%	10–40%	10–20%
IGA	0/8	0/8	Rare	8/8	0/8	50–60%	0–5%	35–50%

IMF, interstitial mycosis fungoides; IMORPH, interstitial/inflammatory morphea; IGA, interstitial granuloma annulare.

in the former but usually not the latter. Infiltrates of lymphocytes, plasma cells and histiocytes may be seen aggregating along the dermal–subcutaneous junction in inflammatory morphea,[16] but show no such propensity in IMF. Lymphocytes may be seen along the dermal–epidermal interface in both conditions, but slight vacuolar interface alteration, slight squamotization of basal keratinocytes, and effacement of the rete ridge pattern favor inflammatory morphea. Our studies found areas devoid of elastic fibers in Movat-pentachrome-stained sections of inflammatory morphea, while the elastic fibers were not significantly altered in IMF. The presence of moderate numbers of B cells and some plasma cells with T cells in inflammatory morphea contrasts sharply with the predominant population of T cells seen in IMF. While occasional plasma cells, B cells and eosinophils are sometimes seen in mycosis fungoides that present with a conventional histology, very few were present in our five examples of this unusual MF variant.

An interstitial expression of granuloma annulare[17,18] can sometimes be confused with IMF, as both share an interstitial dermal mononuclear infiltrate,[6,8–10] sometimes accompanied by increased interstitial dermal mucins. The clinical appearances may be similar when granuloma annulare presents as a macule or patch without a well-developed papular or raised border. However, histologically, granuloma annulare lacks the epidermotropism and Pautrier's collections seen focally in IMF. A wiry pattern of fibrosis to the papillary dermis with a lichenoid infiltrate may also be seen in IMF but not in granuloma annulare. In our study, as well as in one other,[14] CD68 + histiocytes and T cells comprised a significant proportion of the dermal infiltrate in interstitial granuloma annulare, while T cells predominated in IMF. (Curiously, this finding of CD68 positivity in granuloma annulare contradicts those of Mullens and Helms,[19] possibly because we examined interstitial rather than regular granuloma annulare).

Recently, Magro et al.[15] described 20 patients who often developed annular plaques, mostly on the limbs, shortly after sustained ingestion of various medicines. Designated as 'interstitial granulomatous drug reaction', this disorder clinically resembled cutaneous T-cell lymphoma, granuloma annulare, lupus erythematosus and erythema annulare centrifugum. The defining histomorphology was an interstitial infiltrate of lymphocytes and histiocytes associated with elastolysis, collagenolysis, and vacuolar interface inflammation. Transformed lymphocytes with convoluted nuclear membranes were seen interstitially and along the dermoepidermal junction in half of the cases. Because the lesions resolved when the implicated drug was discontinued, this curable disorder should be given serious consideration before a diagnosis of IMF is rendered. A confounding clinical observation was the weak temporal association between initiation of the drug and onset of lesions, ranging from 4 weeks to 25 years. While there are some histological features in common with IMF, interstitial granulomatous drug reaction has a prominent histiocytic infiltrate, fragmentation of elastic and collagen fibers, and interface dermatitis not seen in IMF. Furthermore, a clonal population of T cells is not observed in interstitial granulomatous drug reaction.

The clinical behavior, prognosis and treatment appropriate for IMF are not established. In our series, four patients manifested an early clinical stage of mycosis fungoides, while one patient had relatively advance mycosis fungoides. Hence, IMF might represent an interstitial presentation of mycosis fungoides that can occur at any stage of the disease, and the prognosis might be determined ultimately by the overall clinical stage. Larger studies, particularly with long-term follow up, will be required to better understand this disease.

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