New insights into granulomatous mycosis fungoides (GMF): A single-center experience

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Introduction

- Granulomatous mycosis fungoides (GMF) is a rare variant of MF/cutaneous T-cell lymphoma (CTCL) characterized by epidermotropism and granulomatous infiltrates.
- Although an enhanced immune response associated with granulomatous formation may indicate a good prognosis in MF patients, cases with an aggressive course have also been reported.
- Skin manifestations of GMF could be variable and occasionally not typical of classic patch/plaque MF.

Objective

- We aimed to perform a clinical analysis of GMF patients focusing attention on clinical features and impact on prognosis.

Materials & Methods

- In this single-center, observational retrospective study, medical charts of all GMF cases registered in our database over a period of 10 years, from January 2011 to December 2020, were reviewed with regard to demographics, clinical-pathological features, treatment modalities, follow-up, and outcomes.
- Moreover, three cases of GMF presenting with atypical MF lesions are demarcated in more detail.

Results (I) - Summary

Table 1 Summary of clinical-pathological features, treatment modalities, and outcome of GMF patients

Case no.	Sex/age (yrs)	TNMB stage at diagnosis	Clinical presentation	Sites affected	Histologic findings	Therapy	Follow-Up (mon)	Clinical course/Outcome
1	M/80	T2aN0M0B0	Classic MF plaques	Trunk, limbs	Moderately dense perivascular, diffuse and interstitial LIs of atypical CD8+ T cells in lower dermis with epidermotropism. Macrophages and giant cells scattered throughout dermis in a granuloma annulare-like pattern.	TCS, PUVA, NB-UVB	79	- CR after PUVA - Two minor relapses alleviated with phototherapy
2	M/53	T1aN0M0B0	Classic MF plaques	Trunk	Dermal perivascular and periadnexal LIs of atypical CD4+ T cells with epidermotropism. Dermal granulomas composed of epithelioid and giant cells.	TCS	48	CR with TCS
3	F/46	T1aN0M0B0	Classic MF patches with dermatofibroma-like lesions	Left upper limb	- 1st biopsy: Epidermotropism with dense LIs in dermis. Multiple giant cells surrounded by atypical CD3+CD4+CD8- T cells. - 2nd biopsy: Typical dermatofibroma in mid-dermis surrounded by a halo of atypical CD3+CD4+CD8- T cells with single lymphocytes infiltrating among the spindle fibrous cells.	TCS	45	Stable disease
4	F/75	T2bN0M0B1	Granuloma annulare-like lesions	Trunk, limbs	Dermal perivascular, periadnexal and interstitial LIs of small CD4+ T cells with folliculotropism and epidermotropism. Histiocytes and giant cells dispersed in entire dermis.	PUVA, Ac, MTX, BXT, TSEBT, RT	22	- No response to PUVA plus BXT - CR after TSEBT plus BXT - Relapse 12 months after TSEBT with new T3 lesions and B2 blood class treated with MTX plus regional RT - LCT limited to skin
5	M/69	T2bN0M0B0	- Psoriasiform plaques - Rosacea-like lesions	Face, trunk, limbs	Dense LIs of atypical CD8+ T cells in reticular dermis with folliculotropic and epidermotropic features. Granuloma annulare-like formation comprising Touton giant cells and histiocytes.	PUVA, Ac, MTX, RT	82	- Initial PR after PUVA - CR after Re-PUVA - Relapse after 5 years – PR after MTX plus regional RT - Very severe pruritus
6	M/71	T1bN0M0B0	- Sarcoid-like plaques - Bluish-purple papules - Ulcerative lesions on genitals and oral mucosa	Trunk, limbs, oral mucosa, genitals	Dense epidermotropic LIs expanding in entire dermis with variable numbers of sarcoid or granuloma annulare-like granulomas composed of histiocytes and giant cells.	Ac, PUVA, OCS plus MTX , BV	27	- Progressive skin lesions - LCT - Systemic (nodal + CNS) involvement - Death of lymphoma

Abbr.: Ac, Acitretin; BXT, Bexarotene; BV, Brentuximab vedotin; CNS, Central nervous system; CR, Complete remission; F, Female; GMF, Granulomatous mycosis fungoides; LCT, Large cell transformation; LI, Lymphocytic infiltrates; M, Male; MF, Mycosis fungoides; mon, Months; MTX, Methotrexate; NB-UVB, Narrow-band ultraviolet B phototherapy; OCS, Oral corticosteroids; PR, Partial remission; PUVA, Psoralen plus ultraviolet A photochemotherapy; Re-PUVA, Retinoid plus PUVA; RT, Radiotherapy; TCS, Topical corticosteroids; TNMB, Tumor-node-metastasis-blood; TSEBT, Total skin electron beam therapy; yrs, Years.

Summary of Results

A total of 6 GMF cases (4 males, 2 females; mean age 65.6 years) were studied, representing 0.8% of all MF patients (n = 728) in our registry. Three distinct clinical patterns were recorded: (i) cases with typical of classic MF lesions, consisting of erythematous, scaly, infiltrated plaques (n = 2); (ii) patients with typical and atypical MF lesions (n = 1), consisting of flat, red, scaly patches combined with dermatofibroma-like lesions (n = 1); and (iii) cases with exclusively atypical lesions (n = 3), mostly mimicking granulomatous disorders. The following atypical presentations were observed: granuloma annulare-like lesions (annular smooth papules and plaques with central clearing; n = 1); sarcoid-like plaques with bluish-purple papules and oral/genital ulcerative lesions (n = 1); and psoriasiform plaques with rosacea-like lesions. Contrary to "classic" MF cases, all "atypical" cases showed a trend towards a more rapid disease progression, thus poor prognosis, including two cases of CD30+ large cell transformation in either skin or extracutaneous (both nodal and central nervous system) sites and ultimately lymphoma-related death (n = 1).

Table 1 provides a summary of the clinical-pathological features, treatment modalities, and outcome of GMF patients.

Results (II) - Case Presentations

Patient #3 – Classic MF patches with dermatofibroma-like lesions

A 46-year-old female was referred for evaluation of scaly, erythematous non-indurated plaques grouped over her left arm. The lesions appeared 3 months prior to presentation and progressively expanded showing no response to topical corticosteroids (TCS). On physical examination, no other skin findings were detected, while general and systemic examination were found to be unremarkable. Initial pathological and immunophenotypical analyses showed epidermotropism with dense dermal lymphoid infiltrates, as well as multiple giant cells surrounded by atypical CD3+CD4+CD8- T-cells, which led to the diagnosis of GMF. After 1 month, new nodular lesions similar to dermatofibromas were noted in the same area. Subsequent skin biopsies revealed the presence of a typical dermatofibroma in mid-dermis surrounded by a halo of atypical CD3+CD4+CD8- lymphocytes with single T-cells infiltrating among the spindle fibrous cells. PCR analysis demonstrated clonal TCRγ gene rearrangements. These findings confirmed the diagnosis of MF with a prominent granulomatous component. The patient was initiated on TCS maintaining a stable disease status.

Patient #4 – Granuloma annulare-like lesions

A 75-year-old female presented with a 1-year history of annular plaques with central clearing on her trunk and limbs mimicking granuloma annulare (Fig. xx). At presentation, no lymph nodes were palpated, while all laboratory tests were within normal limits. Histological examination of skin lesions showed perivascular, periadnexal, and interstitial infiltrates of small CD4+ T cells with epidermotropic and folliculotropic features. Scattered histiocytes with giant cells were also noted throughout the dermis. Based on clinicopathological findings, the diagnosis of GMF was established. Initial combination therapies of psoralen plus ultraviolet A radiation (PUVA) with retinoids (acitretin, bexarotene) achieved no response. Due to disease progression, treatment intensification with total skin electron beam therapy (TSEBT) and oral retinoids (bexarotene) was required leading to complete regression of skin lesions. However, 12 months after completion of TSEBT, her course deteriorated with onset of new tumor-type (T3) skin lesions with concomitant large cell transformation (LCT) and B2 blood class requiring methotrexate (MTX)-based regimens plus regional radiotherapy (RT).

Patient #6 – Sarcoid-like plaques + Bluish-purple papules + Oral/Genital Ulcerations

A 71-year-old male presented with palmoplantar psoriasiform lesions initially treated as psoriasis with TCS and oral retinoids (acitretin) (Fig. 1a). Due to lack of response, a skin biopsy performed after 8 months was compatible with plaque-stage MF (Fig. 1b) and PUVA was added to the regimen. After 1 month, ulcerated lesions appeared on the genital skin and oral mucosa (Fig. 1 c, d) combined with bluish-purple papules on the trunk. Subsequent skin biopsies showed dense epidermotropic infiltrates of atypical CD4+ lymphocytes expanding in the entire dermis with variable numbers of sarcoid or granuloma annulare-like granulomas composed of histiocytes and giant cells (Fig. 1 e, f). Combination systemic regimens (MTX plus prednisolone) led to a gradual clinical improvement. After 18 months, the patient presented with relapsed skin rash and cervical lymph node enlargement. Histopathology of biopsied lymph nodes demonstrated extracutaneous infiltration of lymph nodes by CD30+ T cells (Fig. 1 g, h). Although brentuximab vedotin was introduced achieving improvement of skin disease, his course was further complicated by central nervous system involvement ultimately leading to lymphoma-related death.

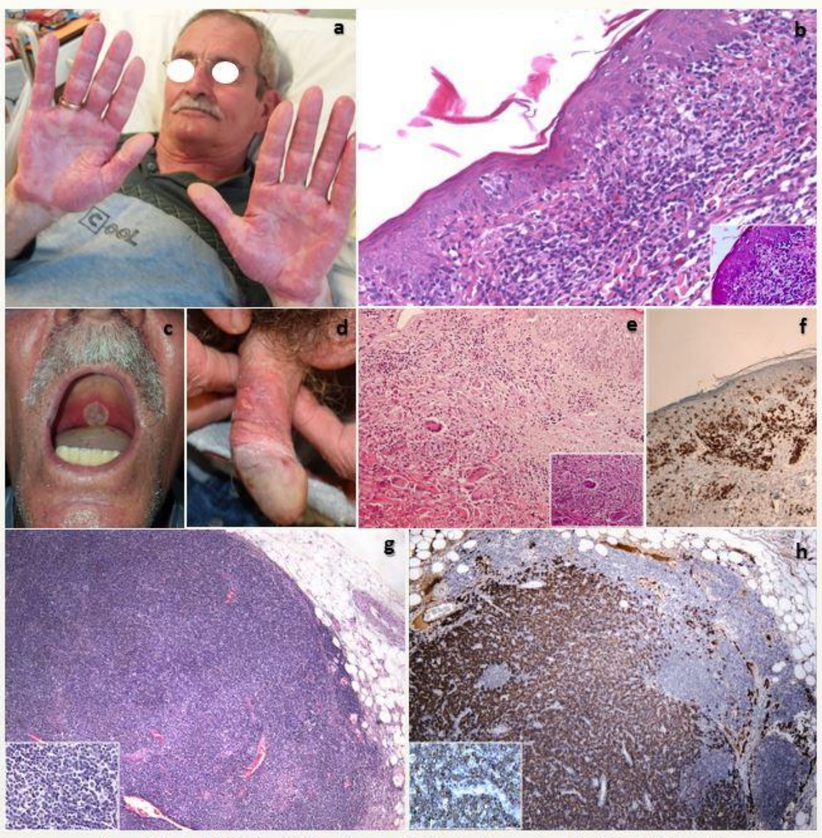

Figure 1. Patient #6 – Sarcoid-like plaques + Bluish-purple papules + Oral/Genital Ulcerations

Conclusions

- This case series indicates that GMF can be associated with a range of skin lesions, both typical and atypical of "classic" MF.
- Among GMF cases, patients presenting with atypical lesions seemed to have a distinct, but usually worse, prognosis compared to patients with classic-type MF lesions, possibly reflecting the potential biologic differences of GMF.
- These findings could serve as a basis for further research into whether or not certain presentations may carry different prognostic implications, opening new perspectives for accurate disease classification.

References

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