Clonality in sarcoidosis, granuloma annulare, and granulomatous mycosis fungoides

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Abstract: The histological discrimination of granulomatous cutaneous T-cell lymphomas (CTCLs) from reactive granulomatous disorders such as sarcoidosis and granuloma annulare (GA) may be difficult due to overlapping histological features. We analyzed the T-cell receptor gene rearrangement in sarcoidosis and GA to investigate the value of the detection of clonal T cells as an adjunctive diagnostic marker in the differentiation between sarcoidosis and GA versus granulomatous CTCLs. Rearrangement of T-cell receptor genes was examined by the use of automated high-resolution polymerase chain reaction fragment analysis in 35 cases of sarcoidosis and 15 cases of GA and compared with a series of 19 cases of granulomatous CTCLs. A monoclonal T-cell population was found in none of the cases of sarcoidosis and in 2 of 15 cases of GA (13%). In granulomatous CTCLs, a neoplastic T-cell clone was detected in 94%. Presence of clonal T cells argues in favour of a granulomatous CTCL, while a polyclonal T-cell population makes the presence of a sarcoidosis or a GA more likely. The analysis of T-cell clonality is a useful diagnostic adjunct in the differentiation between sarcoidosis and GA from granulomatous CTCLs.

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Title: Granulomatous mycosis fungoides and granulomatous slack skin: a multicenter study of the Cutaneous Lymphoma Histopathology Task Force Group of the European Organization for Research and Treatment of Cancer (EORTC)

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Abbreviations:

GMF: Granulomatous mycosis fungoides
GSS: Granulomatous slack skin
CTCL: Cutaneous T-cell lymphoma
EORTC: European Organisation for Research and Treatment of Cancer
Abstract:

**Background:** Granulomatous cutaneous T-cell lymphomas (CTCLs) are rare and represent a diagnostic challenge. Only limited data on the clinicopathological and prognostic features of granulomatous CTCLs are available. We describe 19 patients with granulomatous CTCLs to further characterize the clinicopathological, therapeutic and prognostic features.

**Observations:** The group included granulomatous mycosis fungoides (GMF; n=15) and granulomatous slack skin (GSS; n=4) defined according to WHO-EORTC classification for cutaneous lymphomas. GMF and GSS displayed overlapping histological features and differed only clinically by the development of bulky skin folds in GSS. Histologically, epidermotropism of lymphocytes was not a prominent feature and was absent in 9 of 19 (48%) cases. Stable or progressive disease was observed in the most patients despite various treatment modalities. Extracutaneous spread occurred in 5 of 19 (26%) patients. Second lymphoid neoplasms developed in 4 of 19 (21%) patients. Six of 19 (32%) patients died due to their disease. Disease-specific 5-year-survival rate in GMF was 66%.

**Conclusions:** GMF and GSS differ clinically, but can histologically not be discriminated. Development of hanging skin folds is restricted to the intertriginous body regions. Granulomatous CTCLs show a therapy-resistant slowly progressive course. Nevertheless, the prognosis in GMF appears worse than in classic non-granulomatous MF.
Introduction

The occurrence of sarcoid-like granulomas is a well known phenomenon in malignant lymphoma and is most commonly observed in patients with Hodgkin’s disease (HD)\(^1,2\). In contrast, granulomatous features are rarely found in primary cutaneous lymphomas (CL) with approximately 2% of all CL displaying granulomatous features\(^3,4\).

Granuloma formation was reported in a broad variety of primary CL\(^5,6\) such as Sézary syndrome\(^7\), primary cutaneous anaplastic large T-cell lymphoma\(^8\), subcutaneous panniculitis like T-cell lymphoma as well as in primary cutaneous B-cell lymphomas (CBCL)\(^4\).

Granulomatous MF is the most common form of granulomatous cutaneous T-cell lymphoma (CTCLs). In contrast granulomatous slack skin (GSS) is a very rare form of CTCLs and to date only approximately 50 cases have been reported in the literature\(^9,10\). In the WHO-EORTC classification for cutaneous lymphomas, GSS is considered as a distinct subtype of mycosis fungoides (MF) with characteristic clinical and histological features\(^11,12\).

So far, there are only a limited number of studies on granulomatous CTCLs, particularly granulomatous MF (GMF). The clinicopathological features and the course of granulomatous CTCLs are still poorly characterized. The granuloma formation can be very extensive so that the histologic diagnosis of lymphoma may be delayed and not rarely the findings are initially misdiagnosed as granulomatous dermatitis\(^4\). There is a controversy whether the presence of granulomas in CL correlates with a better prognosis\(^5,13\). Thus, a multicenter study was conducted to analyze the clinical, histopathological, immunophenotypic and genotypic features of granulomatous reactions in CTCLs, particularly GMF and GSS, as well as the course and prognosis of these granulomatous CTCLs.

In this study, we demonstrate that GMF and GSS differ in regard to their clinical presentation, but show overlapping histological features. This finding has implications on the future classification of GSS. Our data demonstrate that GMF and GSS exhibit often a slowly progressive course with only limited response to a broad variety of therapeutic approaches.
Nevertheless, the prognosis of GMF is worse than in classic, non-granulomatous MF.

Methods

Patients and biopsies

Twenty-three skin biopsies from 23 well-documented patients from a total of 18 European Centers were submitted as „granulomatous cutaneous T-cell lymphoma“ by the members of the EORTC Cutaneous Lymphoma Histopathology Task Force (EORTC CLTF). Cases to be included and further analyzed had to show prominent granuloma formation or numerous histiocytic giant cells or a histiocyte-rich infiltrate defined by histiocytes accounting for >25% of the entire infiltrate. The following clinical data were recorded: sex, age at diagnosis, biopsy site, clinical manifestation including localization and distribution of skin lesions, TNM stage at diagnosis according to TNM classification of malignant tumors, age at first symptoms (if available) and age at first biopsy displaying granulomatous features, the results of staging investigations, treatment, response to treatment and outcome.

Inclusion criteria included H&E and immunohistochemical stainings of diagnostic quality, written detailed data or photographies of clinical presentation and informations on therapeutic interventions as well as follow-up on course and outcome.

All biopsy specimens were formalin-fixed and paraffin-embedded. Hematoxylin and eosin (HE) as well as stainings for elastic fibers were performed. Immunohistochemical stainings for lymphocytic (CD3, CD4, CD8, CD30) and histiocytic antigens (CD68) were visualized by Streptavidin-biotin or APAAP method according to standard protocols. Rearrangement of T-cell receptor gamma genes was assessed by PCR as previously described.

Statistical analysis was performed using SPSS version 15.0 (SPSS Chicago IL).
Results

According to the WHO-EORTC classification for cutaneous lymphomas\textsuperscript{11,12}, 19 CTCL\textsubscript{s} cases could be identified and classified as GMF (n=15) or granulomatous slack skin (n=4). Two cases originally submitted as GSS were reclassified as granulomatous MF, since the skin lesions did not evolve to hanging skin folds during follow-up period. Four additional cases were classified as primary cutaneous peripheral T-cell lymphoma, unspecified (PTL, NOS) (n=4) which were excluded from further analysis since the presented study focused on GMF and GSS. In addition to the 23 CTCL\textsubscript{s} cases, secondary cutaneous involvement by systemic T-cell NHL (n=3) including nodal Lennert’s lymphoma (as a variant of nodal peripheral T-cell lymphoma), angioimmunoblastic T-cell lymphoma and one case of nodal CD4\textsuperscript{+} T-cell NHL NOS had been submitted, but were excluded from this study due to their primary extracutaneous origin.

The clinical data, therapy and outcome are presented in Table 1. Table 2 displays the histopathological, immunophenotypical and genotypic features.

**Group 1: Granulomatous mycosis fungoides (GMF)**

Clinical features: This group consisted of 15 patients, 9 males and 6 females resulting in a male to female ratio of 1.5:1. Median age at diagnosis was 48 years of age with a broad range (20 to 72 years). In two patients, the disease had started in childhood before age of 10 years. All patients in this group exhibited patches and plaques (Fig. 1), some of them with atrophy of the skin, but lack of cutis laxa-like features (Fig. 1). In one patient, the disease was restricted to a solitary plaque representing unilesional MF. In 5 of 15 (33\%) patients, skin lesions were hyperpigmented (Fig. 2). At the time of diagnosis, 13 of 15 (87\%) were in stage I or II according to TNM staging system\textsuperscript{14}. First symptoms of the disease had been reported to be present years or decades (median value: 11 years; range: 1-15 years) before diagnosis of GMF was established. Four patients had experienced suffered from other types of lymphoid or
myeloid neoplasms before or after the occurrence of GMF: Two patients had suffered from nodal Hodgkin lymphoma (HL), nodular sclerosing type, 20 years before and 4 years after the occurrence of granulomatous MF. In the third patient nodal CD30-positive anaplastic large-cell lymphoma (ALCL) developed 4 years before the diagnosis of GMF and the fourth patient had myeloid leukemia in childhood 21 years before the diagnosis of GMF. In all four patients complete remission (CR) from those second neoplasias, nodal non Hodgkin lymphomas or myeloid leukemia, respectively, was observed.

Treatment of GMF was heterogeneous involving combined treatment with psoralen-UVA (PUVA) and interferon-alpha in 7 patients. Three patients received chemotherapy with CHOP regimen, whereas two patients were treated with monoagent chemotherapy. Radiation was applied in 7 of 15 patients. Other treatment modalities included topical corticosteroids, imiquimod, and systemic retinoids. Complete tumor regression was observed in only 3 of 15 (20%) patients, but recurrence occurred within a period of two years in two-one patients. In both patients with complete remission, complete remission followed treatment with interferon-alpha. Progression of the disease was observed in 6 of 15 (40%) patients and extracutaneous spread was observed in 5 of 15 (33%) patients with involvement of lymph nodes, liver and bone marrow (Table 1). In 3 of 15 (20%) patients transformation into CD30+ large-cell lymphoma phenotype was observed. Six of 15 (40%) patients including the three patients with transformation into a CD30+ large-cell phenotype died due to lymphoma after a median follow-up of 5.3 years (median value; range 1-20 yrs) after diagnosis and 16 years (median value; range 2 to 54 years) after onset of the disease, i.e. the appearance of first symptoms. Disease-specific 5-year-survival rate in GMF was 66%.

Histological features: The infiltrate was diffuse (6/15; 40%), nodular (4/15; 27%) (Fig. 3) or perivascular or periannexal (5/15; 33%) and extended throughout the entire dermis (8/15; 53%) and into the subcutis in 5 of these cases (33%). Epidermotropism of lymphocytes was a
prominent feature in only 4 of 15 (27%) and subtle with only a few lymphocytes in another 4 of 15 (27%) cases. In the remaining 7/15 (47%) biopsies epidermotropism of lymphocytes could not be detected (Fig. 3). The lymphocytic compartment of the infiltrate consisted of small lymphocytes without significant nuclear atypia in 4 of 15 (27%) cases, whereas small lymphocytes with cerebriform nuclei were found in 5 of 15 (33%). In 6/15 (40%) cases, tumor cells were small to medium-sized with pleomorphic nuclei and in one case large pleomorphic lymphocytes were intermingled with the predominant small to medium-sized tumor cells. Eosinophils were present and readily identifiable in 9 of 15 (60%) (Fig. 4). Remarkably, clusters of plasma cells, which were not related to overlying ulceration, were observed in 2 (13%) of the biopsies. Granuloma formation with aggregations of histiocytes was found in 13 of 15 (87%) cases and multinucleated histiocytic giant cells were present in 8 of 15 (53%) biopsies (Fig. 4 and 5). In all cases with granuloma formation, there was a sarcoid-like pattern of granulomas (Fig. 4), whereas a granuloma annulare-like pattern could not be found in any of the biopsies. Granulomas were absent in two biopsies, but numerous multinucleated giant cells were scattered in a diffuse lymphocytic infiltrate in those two cases (Fig. 6 and 7). In 4 of 15 (27%) cases, infiltration of dermal or subcutaneous vessels by lymphocytes was found and in two of these 4 cases numerous multinucleated giant cells were observed around and within the walls of large veins in the subcutis (Fig. 8). Elastica staining was available in 12 cases. Loss of elastic fibers throughout the infiltrated areas was found in all 12 biopsies, but elastophagocytosis was only found in 1 of 12 (8%) biopsies.

Immunophenotype and Genotype:

The lymphocytes expressed a CD3+ CD4+ CD8- phenotype in 12 of 15 (80%) cases. One case showed expression of TIA-1 by CD4+ lymphocytes. Three of 15 (20%) cases exhibited a CD3+ CD4- CD8+ cytotoxic phenotype. Clonal rearrangement of TCR gamma genes was detected by PCR in 13 of 15 (87%) biopsies.
Group 2: Granulomatous slack skin (GSS)

Clinical features: The group included 2 males and 2 females. Median age at diagnosis was 46 years (range: 22 to 71 years). All four patients showed poikilodermatous patches and plaques in the intertriginous areas (axillae, groins) with the development of characteristic bulky skin folds (Fig. 9). In one patient with additional skin lesions on non-intertriginous areas of the trunk, only the lesions in the axillae and groins underwent cutis laxa-like changes, whereas skin lesions at other sites did not evolve in a similar way. All patients experienced an indolent slowly progressive course without extracutaneous spread and were alive with disease after a median follow-up of 17 years. One patient developed a second lymphoid neoplasia (CD30+ lymphoproliferative disorder of the skin) after the occurrence of GSS. Partial remission could be achieved in two patients by PUVA or topical carmustine. However, none of the other therapies including surgical excision, topical steroids, nitrogen mustard or systemic therapies such as IFN-alpha in combination with retinoids were effective and in none of the patients complete tumor regression was observed. All patients were alive after a median follow-up of 17 years (range 10 to 28 years) resulting in a 5-year-survival rate of 100%.

Histological features: Five biopsies of the 4 patients were available for histological evaluation. In 4 of 5 biopsies there was a diffuse lymphocytic infiltrate throughout the entire dermis and the upper parts of the subcutis were found with numerous scattered multinucleated giant cells displaying more than 10 nuclei per cell (Fig. 10 and 11). In addition, granuloma formation was identified in 2 of 4 cases. One biopsy exhibited a lichenoid infiltrate of small to medium-sized lymphocytes mostly in the upper and mid dermis with sarcoid-like granuloma and a few giant cells. This pattern was not related to initial disease manifestation, since this biopsy was performed from established lesions with hanging skin folds. Epidermotropism of lymphocytes was present in only one case, but absent or very subtle with only a few scattered
intarepidermal lymphocytes in the remaining three cases. The lymphocytes were small without nuclear atypia in two cases and small to medium-sized pleomorphic in the remaining two cases. Eosinophils could be found in all biopsies and mostly scattered plasma cells were present in 3 of 4 cases. In two cases, infiltration of large veins in the subcutis by multinucleated giant cells and lymphocytes was observed. Elastica staining revealed loss of elastic fibers in the infiltrated area in all cases. Elastophagocytosis was subtle and only found in 2 of 4 cases.

Immunophenotype and genotype:

In three of four patients, lymphocytes displayed a CD3+ CD4+ CD8- phenotype. In contrast, one case showed a CD3+ CD4- CD8+ phenotype. Monoclonal rearrangement of TCR gamma genes could be demonstrated by PCR in all cases. In addition, monoclonal rearrangement of T-cell receptor beta genes was demonstrated by Southern blot technique in one of the cases.

Comment

In our series GMF was the most common disorder accounting for 79% of the analyzed cases. Patients affected by GMF and GSS were at diagnosis in their 5th decade with a male predominance in the GMF. In both disorders, GMF and GSS, the disease extent and distribution of skin lesions at diagnosis corresponded to TNM stage Ia in the majority of patients (11 of 19; 58%) with the trunk representing the predilection site (Fig. 1). The clinical presentation of skin lesions in GMF was not indicative for the histologically detected granulomatous features (Fig. 1). GMF manifested with hyperpigmented skin lesions in a third of the patients (Fig. 2). Hyperpigmented MF had been reported as a common feature in CD8+ MF, but none of the cases with hyperpigmented skin lesions in our series displayed a CD8+ cytotoxic T-cell phenotype.
PUVA and/or IFN-alpha as well as radiotherapy were the most commonly employed treatment modalities. Complete tumor regression could be achieved in only 3 of 15 (20%) patients with GMF. In half of the patients, the disease showed a slowly progressive course. Extracutaneous spread was observed in a third of GMF patients and was associated with transformation into CD30+ anaplastic large-cell lymphoma (ALCL) in 20% of the patients.

Six of 15 (40%) patients with GMF, including the three patients with large-cell transformation, died due to the disease. The percentage of patients with unfavourable outcome is identical to the study by Chen et al. who reported death due to the disease in 40% of GMF patients. Whereas the occurrence of granulomas in MF has been considered to be associated with a favorable prognosis by some authors, other investigators could not confirm this observation. These findings demonstrate that GMF is not associated with a better prognosis compared to classic, non-granulomatous MF. In fact, 5-year-survival of GMF (66%; Figure 12) is worse than in classic MF and similar to folliculotropic MF.

In contrast, all patients with GSS were still alive after a median follow-up of 17 years despite GSS being therapy-resistant and CR could not be achieved in any of the patients. Recently, response of GSS to topical nitrogen mustard was observed in two patients, but definitive therapy of GSS has yet to be established. Extracutaneous spread is exceedingly rare in GSS and did not occur in our series of GSS patients.

Patients suffering from GMF and GSS are known to be at risk for the development of second lymphoid neoplasias. In our series, 4 of 19 (21%) patients with GMF or GSS had experienced a second lymphoma before or after occurrence of granulomatous CTCLs and an additional patient had had myeloid leukemia. This prevalence is lower than reported in the literature with 48% of the GSS patients with second lymphoid neoplasia. These patients may be overrepresented in the literature due to the development of a second lymphoma and eventually misinterpretation of large-cell transformation as development of a second ALCL unrelated to GSS. Hodgkin lymphoma is the most common second neoplasm in patients with
granulomatous CTCLs in the literature as well as in our series\textsuperscript{10,25,26}. The time interval between lymphoid neoplasias and GMF or GSS may be years or even decades as seen in one patient of our series who developed nodal Hodgkin lymphoma 20 years before onset of GMF. Thus, life-long observation of patients with GMF and GSS is required.

Histologically, a diffuse infiltrate of lymphocytes extending throughout the entire dermis and the subcutis was the most common growth pattern (Fig. 4). Granulomas were sarcoid-like in all biopsies (Fig. 6). Other patterns of granulomatous reactions such as granuloma annulare-like, palisaded or necrobiotic granuloma as reported in the literature\textsuperscript{27-30} were not found in our series. In 70\% of the CTCLs cases, the infiltrates contained histiocytic giant cells displaying 10 or more nuclei (Fig. 11). Remarkably, infiltration of the vessel walls of large veins by small lymphocytes and even by large multinucleated histiocytic giant cells was observed in a third of the cases (Fig. 8). This is far more common than reported in the literature\textsuperscript{4,5}. The lymphocytic compartment in GMF and GSS was composed of small lymphocytes, which showed nuclear atypia in half of the cases (Fig. 6). Medium-sized pleomorphic lymphocytes were admixed in almost half of GMF and GSS cases (Fig. 5).

Epidermotropism of lymphocytes was previously reported as a common finding in granulomatous CTCLs and considered to be a useful histological feature for discrimination of granulomatous CTCLs from reactive granulomatous disorders\textsuperscript{5}. In our series, however, epidermotropism was absent in almost half of the cases limiting its value as a diagnostic marker in GMF and GSS. Although classic MF commonly displays epidermotropism, this histological feature is not a prerequisite for MF according to WHO-EORTC classification. Thus, lack of epidermotropism does not exclude the diagnosis of MF. In those cases, diagnosis of MF relies on the characteristic clinical presentation with patches and plaques. Diagnosis in granulomatous CTCLs is often delayed with a latency of years to decades after onset of first symptoms. Diagnosis is particularly challenging in cases with predominant granuloma formation in the absence of nuclear atypia or epidermotropism of tumor cells.
Detection of a neoplastic T-cell clone, which was present in nearly all cases may thus be a useful diagnostic adjunct in granulomatous CTCLs.

The histological features of GSS have been reported as pathognomonic with a diffuse lymphocytic infiltrate harbouring numerous scattered multinucleated giant cells\(^5,\text{31}\) (Fig. 6 and 7), but identical histological features can also be observed in GMF\(^32\). Remarkably, this pattern was in our series also found in two of the 15 GMF cases in our series (Fig. 6-7) and is therefore not pathognomonic for GSS. These observations demonstrate that GMF and GSS differ clinically but show overlapping histological findings and therefore can not be discriminated by histology alone. In fact, it should be recalled that both diseases represent merely are considered variants of a single disease\(^33\). It implies that GSS may be listed in future classifications for cutaneous lymphomas as another variant and not a subtype of MF. As emphasized by Scarabello and coworkers, diagnosis of GSS should rest on clinical grounds and be restricted to those patients presenting clinically with characteristic bulky skin lesions\(^4\).

The classic pathogenetic concept links the development of hanging skin folds in GSS to destruction of elastic fibers due to elastophagocytosis by histiocytic giant cells. However, loss of elastic fibers was found in all examined cases. The extent of loss of elastic fibers correlated with the extent of the granulomatous infiltrate, but was not restricted to GSS. Moreover, only skin lesions in skin folds such as the axillae and the groins underwent cutis laxa-like changes, whereas skin lesions present at other body sites did not evolve in a similar way. These observations suggest that development of hanging skin folds is merely a location-related phenomenon and not solely the result of the destruction of elastic fibers. Hypothetically, the continuous stretching of elastic fibers in the intertriginous body areas during physiological movements may facilitate the loss of their function when these regions become affected by lymphomatous infiltrates.
The pathogenetic mechanisms of granuloma formation in lymphoid neoplasms is poorly understood. Granulomatous reaction has been regarded by some authors as a local tissue response to the infiltrating malignant cells or their antigens, but this hypothesis has been criticized by others based on the occurrence of granulomas in histologically lymphoma-free tissues. In addition, treatment with IFN alpha or bexarotene may induce sarcoid-like reactions. However, granuloma formation in our series was not related to previous therapy.

In sarcoidosis, granuloma formation is preceded by a hyperactive T-helper 1-biased CD4+ T-cell response. Recent data indicate that the absence or deficiency of CD1d-restricted natural killer T-cells could contribute to the persistent T-cell activity leading to granuloma formation. On the other hand, granuloma formation was also found in GMF with tumor cells expressing both Th1 and Th2 chemokine receptors. To our knowledge, the presence and functional status of this subset of T-cells has not been investigated in granulomatous forms of CL. Recently, genetic alterations with t(3;9)(q12;p24) have been reported in a case of GSS which may indicate genetic predisposition to granuloma formation. The pathogenetic processes underlying granuloma formation in granulomatous CTCL remain to be elucidated.
References


### Tables

#### Table 1:

Clinical and therapeutic data of a series of 19 patients with granulomatous cutaneous T-cell lymphomas.

**Legend:**

- ALCL: anaplastic large cell lymphoma
- ACR: alive with complete remission
- AWD: alive with disease
- BM-TPL: bone marrow transplantation
- Chth: chemotherapy
- CR: complete tumor regression
- CS: topical corticosteroids
- Distrib: Number of skin lesions
- DOD: death due to disease
- Extr: extremities
- GMF: granulomatous mycosis fungoides
- GSS: granulomatous slack skin
- HL: Hodgkin lymphoma
- HN2: nitrogen mustard
- IFN: interferon-alpha
- Imiq: imiquimod
- LPD: lymphoproliferative disorders
- LN: lymph nodes
- MC: mechlorethamine
- Mult: multiple
- Nod: nodule(s)
- Pat: patches
- Phago: phagocytosis
- Pigm: hyperpigmented
- Plaq: plaques
- PD: progressive disease
- PR: partial tumor regression
- Predn: prednisone orally
- PUVA: psoralen-Ultraviolet A light therapy
- Resp: response to treatment
- Ret: retinoids
- RT: Radiation therapy
- SD: stable disease
- S: small
- S-M: small to medium-sized
- Sol: solitary

#### Table 2:

Histological, immunophenotypic and genotypic data of a series of 19 patients with granulomatous cutaneous T-cell lymphomas.

**Legend:**

- Angio: angiocentric growth
- El: Elastica-staining
- Eos: eosinophilic granulocytes
- M: medium-sized
- Perivasc: perivascular
- Pleo: pleomorphic
- TCR: T-cell receptor

rearrangement (+: monoclonal, -: polyclonal).
Figures

Fig. 1: Granulomatous mycosis fungoides: Erythematous patches and plaques. Note: Clinical features are not suggestive for granulomatous histology (left side) and atrophic skin lesions without bulky skin folds (right side).

Fig. 2: Granulomatous mycosis fungoides: Hyperpigmented patches in granulomatous MF.

Fig. 3: Granulomatous mycosis fungoides: Dense nodular lymphocytic infiltrates throughout the entire dermis. Note the grenz zone and the absence of epidermotropism. H&E, scanning magnification.

Fig. 4: Granulomatous mycosis fungoides: Infiltrate of small lymphocytes with granuloma formation (H&E, original magnification 40X) (left side). The lymphocytes exhibit nuclear atypia. Note admixed eosinophils (H&E, original magnification 200X) (right side).

Fig. 5: Granulomatous mycosis fungoides: Infiltrate with histiocytic multinucleated giant cells. H&E, original magnification 100X.

Fig. 6: Granulomatous mycosis fungoides: Diffuse lymphocytic infiltrate covering all dermal layers. H&E, scanning magnification.

Fig. 7: Granulomatous mycosis fungoides: Scattered multinucleated giant cells. Absence of granuloma formation (H&E, original magnification 20X). Note scattered multinucleated giant cells with phagocytosis of small lymphocytes (H&E, original magnification 100X) (inlay).
Fig. 8: Infiltration of large subcutaneous vein by the infiltrate containing multinucleated giant cells. H&E, original magnification 20X.

Fig. 9: Granulomatous slack skin: Bulky skin folds in the right axilla.

Fig. 10: Granulomatous slack skin: Dense lymphocytic infiltrate throughout the entire dermis. H&E, scanning magnification.

Fig. 11: Granulomatous slack skin: Numerous multinucleated giant cells, but lack of granuloma formation. H&E, original magnification 100X.

Figure 12: Survival curves in granulomatous mycosis fungoides and granulomatous slack skin.
Authors contributions:
Study concept and design: Kempf, Burg, Willemze
Acquisition of data: All authors.
Analysis and interpretation of data: Kempf, Ostheeren-Michaelis, Burg, Willemze
Drafting of the manuscript: Kempf
Critical revision of the manuscript for important intellectual content: All authors
Statistical analysis: Kempf, Golling
Study supervision: Kempf, Burg, Willemze, Cerroni

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