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)

Werner Kempf, MD; Sonja Ostheeren-Michaelis, MD; Marco Paulli, MD; Marco Lucioni, MD; Janine Wechsler, MD; Heike Audring, MD; Chalid Assaf, MD; Thomas Rüdiger, MD; Rein Willemze, MD; Chris J. L. M. Meijer, MD; Emilio Berti, MD; Lorenzo Cerroni, MD; Marco Santucci, MD; Christian Hallermann, MD; Mark Berneburg, MD; Sergio Chimenti, MD; Alistair Robson, MBBS; Martà Marschalko, MD; Dmitry V. Kazakov, MD, PhD; Tony Petrella, MD; Sylvie Fraitag, MD; Agnes Carlotti, MD; Philippe Courville, MD; Hubert Laeng, MD; Robert Knobler, MD; Philippa Golling, MD; Reinhard Dummer, MD; Günter Burg, MD

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 studied 19 patients with granulomatous CTCLs to further characterize the clinicopathological, therapeutic, and prognostic features.

Observations: The group included 15 patients with granulomatous mycosis fungoides (GMF) and 4 with granulomatous slack skin (GSS) defined according to the World Health Organization–European Organization for Research and Treatment of Cancer classification for cutaneous lymphomas. Patients with GMF and GSS displayed overlapping histologic 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 cases (47%). Stable or progressive disease was observed in most patients despite various treatment modalities. Extracutaneous spread occurred in 5 of 19 patients (26%), second lymphoid neoplasms developed in 4 of 19 patients (21%), and 6 of 19 patients (32%) died of their disease. Disease-specific 5-year survival rate in GMF was 66%.

Conclusions: There are clinical differences between GMF and GSS, but they show overlapping histologic findings and therefore cannot be discriminated by histologic examination alone. Development of hanging skin folds is restricted to the intertriginous body regions. Granulomatous CTCLs show a therapy-resistant, slowly progressive course. The prognosis of GMF appears worse than that of classic nongranulomatous mycosis fungoides.

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

Granuloma formation was reported in a broad variety of primary CLs such as Sézary syndrome, primary cutaneous anaplastic large T-cell lymphoma, subcutaneous panniculitis-like T-cell lymphoma, and primary cutaneous B-cell lymphomas. Granulomatous mycosis fungoides (MF) is the most common form of granulomatous cutaneous T-cell lymphoma (CTCL). In contrast, granulomatous slack skin (GSS) is a very rare form of CTCL and to date only approximately 50 cases have been reported in the literature. In the World Health Organization–European Organization for Research and Treatment of Cancer (WHO-EORTC) classification for cutaneous lymphomas, GSS is considered a distinct subtype of MF with characteristic clinical and histologic features.

There have been 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 the findings are often initially misdiagnosed as granulomatous dermatitis. There is controversy over whether the presence of granulomas in CLs correlates with a better prognosis. Thus, a multicenter study was conducted to analyze the clinical, histopathological, immunophenotypic, and ge-
notypic features of granulomatous reactions in CTCLs, particularly GMF and GSS, as well as the course and prognosis of these granulomatous CTCLs.

### METHODS

#### PATIENTS AND BIOPSIES

Twenty-three skin biopsy specimens from 23 patients with well-documented disease from a total of 18 European centers were submitted as “granulomatous CTCL” by the members of the EORTC Cutaneous Lymphoma Histopathology Task Force. Cases to be included and further analyzed had to show prominent granuloma formation or numerous histiocytic giant cells or a histiocytic-rich infiltrate defined by histiocytes accounting for more than 25% of the entire infiltrate. The following clinical data were recorded: sex, age at diagnosis, biopsy site, clinical manifestation including location and distribution of skin lesions, TNM stage at diagnosis according to TNM classification of malignant tumors, age at first symptoms (if available), age at first biopsy specimen during the follow-up period. Four additional cases were originally submitted as GSS were reclassified as GMF because the skin lesions did not evolve to hanging skin folds during the follow-up period.

### RESULTS

According to the WHO-EORTC classification for cutaneous lymphomas, 19 cases of CTCL could be identified and classified as GMF (n = 15) or GSS (n = 4). Two cases originally submitted as GSS were reclassified as GMF because the skin lesions did not evolve to hanging skin folds during the follow-up period. Four additional cases were classified as primary cutaneous peripheral T-cell lymphoma, unspecified, and were excluded from further analysis because this study focused on GMF and GSS. In addi-
to the 23 cases of CTCL, 3 cases of secondary cutaneous involvement by systemic T-cell non-Hodgkin lymphoma—including 1 case of nodal Lennert lymphoma (as a variant of nodal peripheral T-cell lymphoma), 1 case of angioimmunoblastic T-cell lymphoma, and 1 case of nodal CD4+ T-cell non-Hodgkin lymphoma not otherwise specified—had been submitted but were excluded from this study because of 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: GMF**

**Clinical Features**

This group consisted of 15 patients, 9 men and 6 women, resulting in a male to female ratio of 1.5:1. Median age at diagnosis was 48 years, with a broad range (20-72 years). In 2 patients, the disease had started in childhood before age 10 years. All patients in this group exhibited patches and plaques (**Figure 1**), some of them with atrophy of the skin but without cutis laxa–like features. In 1 patient, the disease was restricted to a solitary plaque representing unilesional MF. In 5 of 15 patients (33%), skin lesions were hyperpigmented (**Figure 2**). At the time of diagnosis, 13 of 15 (87%) were in stage I or II according to the TNM staging system.14 First symptoms of the disease had been reported to be present years or decades (median 11 years; range 1-15 years) before the diagnosis of GMF was established. Four patients had developed other types of lymphoid or myeloid neoplasms before or after the occurrence of GMF. Two patients had had nodal Hodgkin lymphoma, nodular sclerosing type, 20 years before and 4 years after the occurrence of GMF. In the third patient, nodal CD30+ anaplastic large-cell lymphoma develop-
oped 4 years before the diagnosis of GMF, and the fourth patient had had myeloid leukemia in childhood 21 years before the diagnosis of GMF. In all 4 patients, complete remission from nodal non-Hodgkin lymphomas or myeloid leukemia was observed.

Treatment of GMF was heterogeneous, involving combined treatment with psoralen–UV-A and interferon alfa in 7 patients. Three patients received chemotherapy with the CHOP regimen (cyclophosphamide, doxorubicin, vincristine sulfate, and prednisolone acetate), whereas 2 patients were treated with single-agent 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 patients (20%), but recurrence developed within 2 years in 1 patient. In both patients with complete remission, the remission followed treatment with interferon alfa. Progression of the disease was observed in 6 of 15 patients (40%), and extracutaneous spread was observed in 5 (33%) with involvement of lymph nodes, liver, and bone marrow (Table 1). In 3 of 15 patients (20%), transformation into CD30⁺ large-cell phenotype was observed. Six of 15 patients (40%), including the 3 patients with transformation into a CD30⁺ large-cell phenotype, died of lymphoma after a median follow-up of 5.3 years (range, 1-20 years) after diagnosis and 16 years (range, 2-54 years) after onset of the disease, ie, the appearance of first symptoms. Disease-specific 5-year survival rate in GMF was 66%.

**Histologic Features**

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

Immunophenotype and Genotype

The lymphocytes expressed a CD3⁺, CD4⁺, CD8⁻ phenotype in 12 of 15 cases (80%). One of those cases showed expression of TIA-1 by CD4⁺ lymphocytes. Three cases (20%) exhibited a CD3⁺, CD4⁻, CD8⁺ cytotoxic phenotype. Clonal rearrangement of T-cell receptor γ genes was detected by polymerase chain reaction in 13 (87%) of the biopsy specimens.

GROUP 2: GSS

Clinical Features

The GSS group included 2 men and 2 women. Median age at diagnosis was 46 years (range, 22-71 years). All 4 pa-
Patients showed poikilodermatous patches and plaques in the intertriginous areas (axillae and groins) with the development of characteristic bulky skin folds (Figure 9). In 1 patient who had additional skin lesions on nonintertriginous areas of the trunk, only the lesions in the axillae and groin 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 was achieved in 2 patients by psoralen–UV-A or topical carmustine. However, none of the other therapies, including surgical excision, topical corticosteroid, and mechlorethamine hydrochloride, or systemic therapies such as interferon alfa, in combination with retinoids, was effective, and in none of the patients was complete tumor regression observed. All patients were alive after a median follow-up of 17 years (range, 10-28 years), resulting in a 5-year survival rate of 100%.

**Histologic Features**

Five biopsy specimens of the 4 patients were available for histologic evaluation. In 4 of the 5 specimens there was a diffuse lymphocytic infiltrate throughout the entire dermis and the upper parts of the subcutis with numerous scattered multinucleated giant cells displaying more than 10 nuclei per cell (Figure 10 and Figure 11). In addition, granuloma formation was identified in 1 of 4 cases. One biopsy specimen 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 because this biopsy specimen was obtained from established lesions with hanging skin folds. Epidermotropism of lymphocytes was present in
only 1 case, but absent or very subtle with only a few scattered intraepidermal lymphocytes in the remaining 3 cases. The lymphocytes were small without nuclear atypia in 2 cases and small to medium-sized pleomorphic cells in the remaining 2 cases. Eosinophils could be found in all specimens, and mostly scattered plasma cells were present in 3 of 4 cases. In 2 cases, infiltration of large veins in the subcutis by multinucleated giant cells and lymphocytes was observed. Elastica staining demonstrated loss of elastic fibers in the infiltrated area in all cases. Elastophagocytosis was subtle and found in only 2 of 4 cases.

**Immunophenotype and Genotype**

In 3 of 4 patients, lymphocytes displayed a CD3⁺ CD4⁺ CD8⁻ phenotype. In contrast, 1 case showed a CD3⁺ CD4⁺ CD8⁺ phenotype. Monoclonal rearrangement of T-cell receptor γ genes could be demonstrated by polymerase chain reaction in all cases. In addition, monoclonal rearrangement of T-cell receptor β genes was demonstrated by Southern blot technique in 1 of the cases.

In our series, GMF was the most common disorder, accounting for 79% of the analyzed cases. Patients affected by GMF and GSS were on average diagnosed in their fifth decade of life, with a male predominance in GMF. In both disorders, 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 (Figure 1). The clinical presentation of skin lesions in GMF was not indicative of the histologically detected granulomatous features (Figure 1). One-third of the patients with GMF manifested hyperpigmented skin lesions (Figure 2). Hyperpigmented MF has been reported in the literature as well as in our series.10,25,26 The interval between lymphoid neoplasias and GMF or GSS may be years or even decades, as seen in 1 patient in our series who developed nodal Hodgkin lymphoma 20 years before onset of GMF. Thus, lifelong 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 (Figure 4). Granulomas were sarcoid-like in all biopsy specimens (Figure 6). Other patterns of granulomatous reactions, such as granuloma annulare–like, palisaded, or necrobiotic granuloma, as reported in the literature,27-30 were not found in our series. In 70% of the CTCL cases, the infiltrates contained histiocytic giant cells displaying 10 or more nuclei (Figure 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 (Figure 8). This is more common than reported in the literature.15 Epidermotropism of lymphocytes was previously reported as a common finding in granulomatous CTCLs and considered to be a useful histologic feature for discrimination of granulomatous CTCLs from reactive granulomatous disorders.3 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 histologic feature is not a prerequisite for MF according to the 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 the onset of initial 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.

In contrast, all patients with GSS were still alive after a median follow-up of 17 years despite the fact that GSS was therapy resistant and complete remission could not be achieved in any of the patients. Recently, response of GSS to topical mechlorethamine was observed in 2 patients,24 but definitive therapy for GSS has yet to be established. Extracutaneous spread is exceedingly rare in GSS and did not occur in our series of patients with GSS.

Patients with GMF and GSS are known to be at risk for the development of second lymphoid neoplasias. In our series, 4 of 19 patients (21%) 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 that reported in the literature, with 48% of the patients with GSS having second lymphoid neoplasias.10,25,26 These patients may be overrepresented in the literature because of the development of a second lymphoma and, eventually, misinterpretation of large-cell transformation as development of a second anaplastic large-cell lymphoma unrelated to GSS. Hodgkin lymphoma is the most common second neoplasia in patients with granulomatous CTCLs in the literature as well as in our series.10,25,26 The interval between lymphoid neoplasias and GMF or GSS may be years or even decades, as seen in 1 patient in our series who developed nodal Hodgkin lymphoma 20 years before onset of GMF. Thus, lifelong observation of patients with GMF and GSS is required.

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The histologic features of GSS have been reported as pathognomonic, with a diffuse lymphocytic infiltrate harboring numerous scattered multinucleated giant cells,\(^3\) (Figures 6 and 7), but identical histologic features can also be observed in GMF.\(^2\) Remarkably, this pattern was also found in 2 of the 15 GMF cases in our series (Figures 6 and 7) and is therefore not pathognomonic for GSS. These observations demonstrate that GMF and GSS differ clinically but show overlapping histologic findings and therefore cannot be discriminated by histologic examination alone. It should be recalled that both diseases are considered variants of a single disease,\(^3\) which 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,\(^1\) diagnosis of GSS should rest on clinical grounds and be restricted to patients presenting clinically with characteristic bulky skin lesions.

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 axilla and the groin 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 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 physiologic 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 are poorly understood. Granulomatous reaction has been regarded by some authors as a local tissue response to the infiltrating malignant cells or their antigens,\(^34\) but this hypothesis has been criticized by others on the basis of the occurrence of granulomas in histologically lymphoma-free tissues.\(^35\) In addition, treatment with interferon alfa or bexarotene\(^36\) may induce sarcoid-like reactions. However, granuloma formation in our series was not related to previous therapy.

Recently, genetic alterations with t(3:9)(q12;p24) have been reported in a case of GSS,\(^37\) which may indicate genetic predisposition to granuloma formation. The pathogenetic processes underlying granuloma formation in granulomatous CTCLs remain to be elucidated.

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Author Affiliations: Departments of Dermatology, University Hospital, Zurich, Switzerland (Dr Kempf, Os-theeren-Michaelis, Golling, Dummer, and Burg), Hospital Henri Mondor, Creteil, France (Dr Wechsler), Charité, Berlin, Germany (Drs Audring and Assaf), Leiden University, Medical Center, Leiden, the Netherlands (Dr Willemze), University Milan-Bicocca, Milan, Italy (Dr Berti), Medical University of Graz, Graz, Austria (Dr Cerroni), University Hospital Tubingen, Tubingen, Germany (Dr Berneburg), University of Rome, Rome, Italy (Dr Chimenti), Semmelweis Medical School, Budapest, Hungary (Dr Marschalko), Neckers-Enfants Malades Hospital, Paris, France (Dr Fraïtage), and Hospital Tarnier Cochin, Paris, France (Dr Carlotti); Departments of Pathology, University of Pavia, Pavia, Italy (Drs Paulli and Lucioni), Hôpital Henri Mondor, Creteil, France (Dr Wechsler), Luitpold Hospital, Würzburg, Germany (Dr Rudiger), Vrije Universiteit Medical Center, Amsterdam, the Netherlands (Dr Meijer), University Hospital, Dijon, France (Drs Petrella and Courville), and Cantonal Hospital, Aarau, Switzerland (Dr Laeng); Department of Human Pathology and Oncology, University of Florence Medical School, Florence, Italy (Dr Santucci); Hautklinik Linden, Hannover, Germany (Dr Hallermann); Skin Tumour Unit, St John's Institute of Dermatology, St Thomas' Hospital, London, England (Dr Robson); Sikl's Department of Pathology, Charles University, Medical Faculty Hospital, Pilsen, Czech Republic (Dr Kazakov); and Division of Special and Environmental Dermatology, Department of Dermatology, Vienna, Austria (Dr Knobler).

Correspondence: Werner Kempf, MD, Department of Dermatology, University Hospital Zurich, Gloriastrasse 31, CH-8091 Zurich, Switzerland (kempf@derm.unizh.ch).

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