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Granulomatous Slack Skin

Report of Three Patients with an Updated Review of the Literature

Abstract

Purpose: Granulomatous slack skin (GSS) is a rare cutaneous disorder characterized clinically by the evolution of circumscribed erythematous lax skin masses, especially in the body folds, and histologically by a granulomatous T-cell infiltrate and loss of elastic fibers. GSS is often associated with preceding or subsequent lymphoproliferative malignancies, especially mycosis fungoides (MF) and Hodgkin's disease (HD). No effective treatment is known yet. Whether this entity is a benign disorder, a peculiar host reaction to a malignant lymphoma, a precursor of malignant lymphoma or an indolent cutaneous T-cell lymphoma (CTCL) in itself is still a matter of debate. **Patients and Methods:** The results of the patients with GSS from the Netherlands are compared with the cases reported in the world literature. **Results:** A female patient had had GSS for 8 years without developing a secondary malignancy. In a second female patient with a histologically confirmed diagnosis of MF, GSS developed 18 years later in the axillary and inguinal folds which had previously been affected by plaque-stage MF lesions. A third male patient with a 6-year history of erythemasquamous skin disease diagnosed as CTCL developed GSS. Moreover, granuloma formation was also found in a facial basal cell carcinoma, in a cervical lymph node and the spleen. Clonal rearrangements of the T-cell receptor β genes were found in the 2 female patients; the male patient could not be tested. **Conclusion:** GSS is a rare clinicopathological entity. Only 34 patients have been described so far. The development of GSS within plaque MF lesions has not been reported before. Our third case developed very extensive skin lesions and showed a strong propensity to develop granulomas as compared to cases reported before. The presence of a clonal T-cell population was demonstrated in all cases tested. Our cases support the idea that GSS is a very rare and rather indolent type of CTCL. Apparently, the disease is associated with a peculiar immune response, characterized by granuloma formation and disappearance of elastic fibers resulting in the lax skin. The relationship between GSS and other preexisting or subsequent lymphoproliferative diseases (diagnosed in approximately 50% of the cases) warrants a life-long follow-up.

Key Words

Granulomatous slack skin
Mycosis fungoides
Hodgkin's disease

Introduction

Granulomatous slack skin (GSS) is a rare cutaneous disorder, characterized by slowly progressive indurated plaques which evolve into erythematous pendulous skin

folds, predominantly in the flexural areas and especially in the inguinal and axillary region. In long-standing disease, other skin areas can also become involved. Histological examination of early lesions shows a dense dermal infiltrate consisting of small- to medium-sized normochromatic

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T lymphocytes and monocyte-derived nonneoplastic macrophages intermingled with eosinophils, and sometimes plasma cells and B lymphocytes. Fully developed lesions also show cells with larger hyperchromatic cerebriform nuclei among tumor-infiltrating lymphocytes. As the most conspicuous feature, numerous epithelioid and giant cell granulomas occur in which phagocytized elastic fibers can be found [1–3]. The disappearance of elastic fibers results in lax skin. Follow-up data from all reported patients with GSS reveal a relationship between GSS and a preexistent or subsequent lymphoproliferative malignancy in about half of the cases [3–11].

Molecular clonality studies of skin samples have been reported in 8 patients [3, 8–13]. These studies revealed clonal rearrangement of the T-cell receptor TCR β or TCR γ gene. Genotypic studies in 2 cases revealed trisomy 8 in both of them [13, 14]. Therefore most authors suggest that GSS in fact is an indolent cutaneous T-cell lymphoma (CTCL) [3, 8–15].

We present 3 patients with GSS in the context of an updated review of the literature. The purpose of this study is to define a place for GSS among the known lymphoproliferative disorders and to contribute to the discussion on the pathobiology of GSS.

Case Reports

Case I

A 35-year-old Caucasian female patient presented in 1988 with circumscribed nonitching, slightly scaling, slowly progressive skin lesions in the right inguinal fold and on the right medial thigh. The lesions had been present for 7 years and the skin showed a tendency to hang in loose folds (fig. 1a). Further physical examination revealed no abnormalities. A skin biopsy specimen showed acanthosis, slight parakeratosis and a dense dermal lymphocytic infiltrate with scattered multinucleated giant cells. The lymphocytes had normal-sized, normochromatic, slightly irregular nuclei. Occasionally scattered eosinophils were seen. Almost complete absence of elastic fibers was confirmed by Verhoeff-Van Gieson staining. Some giant cells contained fragments of elastic fibers (fig. 2).

The lymphocytes had the T-cell phenotype without loss of T-cell markers [CD2 (TII)+, CD3 (leu-4)+ and CD5 (leu-1)+]. T cells with the helper phenotype, CD4 (leu-3a), predominated over cells with the suppressor phenotype, CD8 (leu-2a; CD2, Central Laboratory of the Netherlands Blood Transfusion Service, Amsterdam, the Netherlands, all other antibodies from Becton-Dickinson, Mountain View, Calif., USA).

Molecular clonality studies on a skin specimen revealed clonal TCR β and TCR γ gene rearrangements in about 25% of the nucleated cells in the biopsy; this corresponded with the relative size of the T-cell infiltrate [16]. Also a clonal immunoglobulin heavy-chain (IgH) gene rearrangement was found. This was interpreted as a cross-lineage immunoglobulin gene rearrangement in the clonal T cells because the biopsy did not contain sufficient B lymphocytes to explain the detection of a clonal IgH gene rearrangement [17].

A chest X-ray and a CT scan of the abdomen revealed no signs of lymphoproliferative disease. Laboratory investigations were within normal limits.

A diagnosis of GSS was made, based on the clinical and histological data. The diseased skin in the groin was excised, but the skin lesions recurred. Lesions were treated topically with steroids of different strengths and topical nitrogen mustard without success.

Treatment with psoralen-ultraviolet A resulted in partial remission of early lesions on the buttocks and hips but had no effect on the lesions in the groins. During the 8-year follow-up period after the initial GSS diagnosis the lesions slowly progressed. During the last half year she was treated with intralesional interferon α which was not effective. However, no clinical or histological signs for the development of a malignant lymphoproliferative disease were observed, in spite of the clonal T cells in the skin infiltrate.

Case II

A 22-year-old Caucasian female patient with a history of psoriasis vulgaris presented in 1975 with several red infiltrated well-demarcated scaling skin lesions which were diagnosed as mycosis fungoides (MF). No enlarged lymph nodes were found.

The patient was treated with total skin electron beam irradiation (4 MeV, 3,500 rad). This resulted in remission of all lesions except for a lesion on the dorsum of the left foot.

From 1983, recurrences were treated with topical application of nitrogen mustard which resulted in partial remission.

In 1993, MF lesions involved the axillary and inguinal folds, the lower quadrants of the abdomen, the mammae and flexural areas (fig. 1b). Sometimes papules and nodi were noticed within the lesions during an exacerbation. Hanging lax skin folds developed in the right axilla and both inguinal folds within the preexisting MF lesions. A skin biopsy specimen showed a granulomatous infiltrate (fig. 3) with small lymphocytes revealing epidermotropism and a dermal infiltrate of lymphocytes with medium-sized irregular and hyperchromatic nuclei, histiocytes and scattered multinucleated giant cells, some of which contained fragments of elastic fibers. The size of the lymphocytes was invariably much smaller than the MF cells found in earlier biopsies (fig. 4). Absence of elastin was confirmed by Verhoeff-Van Gieson staining. Occasional eosinophils were seen.

All lesional lymphocytic cells had the T-cell phenotype (CD2+, 3+) with CD4+ cells predominating over CD8+ cells. The atypical lymphocytes were CD5–.

Molecular clonality studies of a representative skin specimen from the axilla revealed that approximately 20% of the nucleated cells in the biopsy specimen contained a clonal TCR β gene rearrangement which is consistent with the presence of 20–30% of atypical T lymphocytes. A diagnosis of GSS was made. For cosmetic reasons, a lesion of 3×5 cm was excised from the right axilla. The lesions in the axillae have continued to progress, and on the abdomen GSS lesions have appeared in areas which had previously been affected by MF. Treatment with topical carmustine resulted in partial remission.

Case III

A 49-year-old Caucasian man developed slowly progressive infiltrated erythematous plaques on the lower half of the abdomen and in the left axilla in 1962.

A skin biopsy specimen revealed atypical lymphocytes, histiocytes, eosinophils and some multinucleated giant cells of the Langerhans type. A diagnosis of eosinophilic granuloma was considered. Therapy with prednisone and procarbazine was started but discontin-

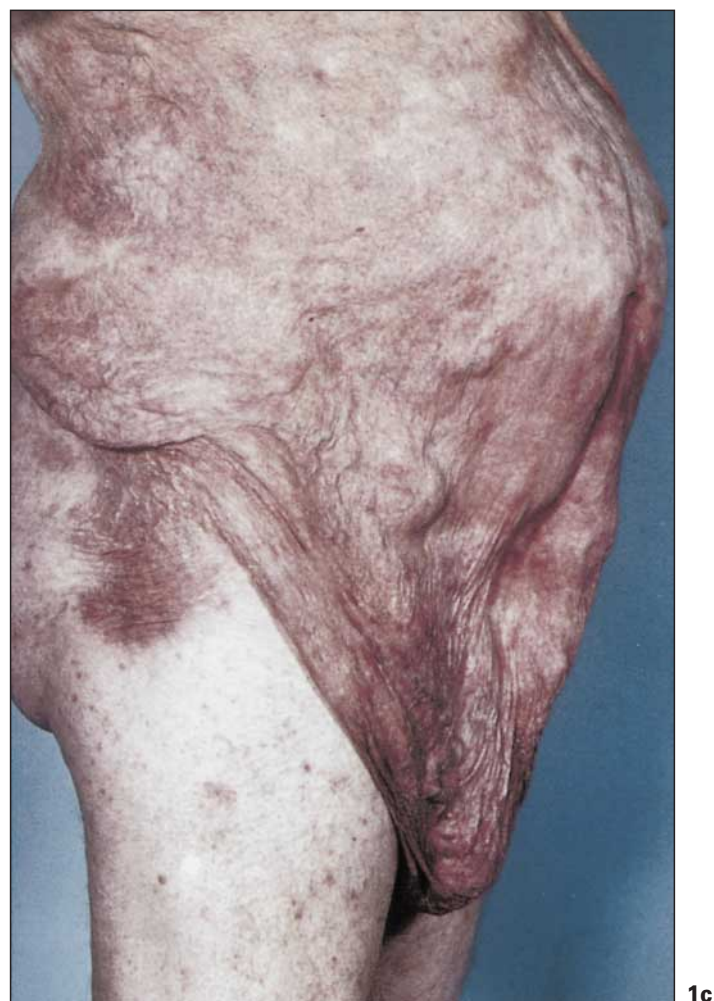
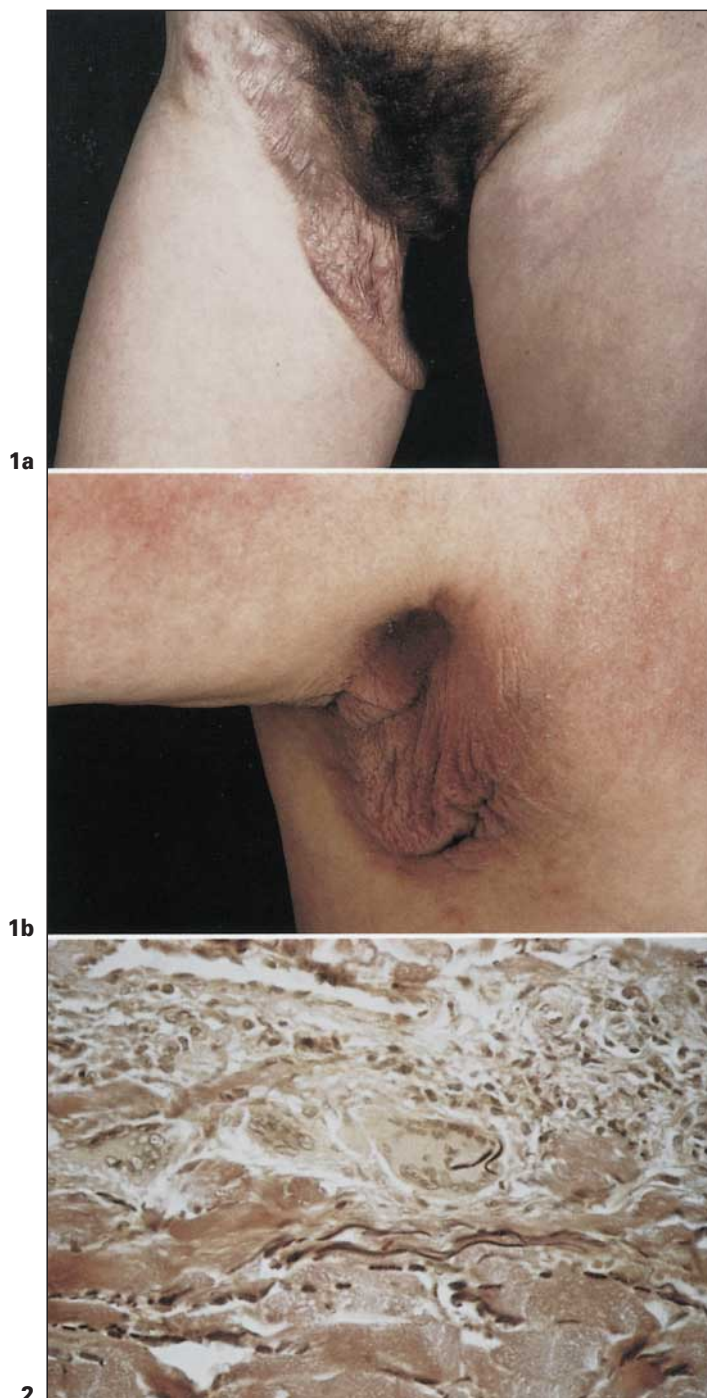


Fig. 1. **a** Right inguinal area with sharply demarcated red-brown atrophic lax skin lesion in patient I. **b** Right axilla with a pendulous fold of erythematous skin in previous mycosis fungoides plaque in patient II. **c** Extensive lax skin formation on the trunk in patient III.

Fig. 2. Elastin Verhoeff-van Gieson staining showing a multinucleated giant cell with phagocytized elastic fibers in patient I. Original magnification $\times 400$.

ued because of leukopenia. Treatment with busulfan and prednisone resulted in partial remission. Three years later, the skin lesions had progressed to paper-thin lax skin folds. Several firm palpable lymph nodes were present inguinally.

A punch skin biopsy revealed a diffuse dermal infiltrate composed of small, normal T lymphocytes, histiocytes and eosinophilic granulocytes with scattered multinucleated giant cells and granuloma formation. The giant cells contained fragments of elastin fibers.

The diagnosis of GSS was made. Treatment with prednisone 15 mg/day was started which slowed down the disease progress; lowering of the dosage resulted in fever and/or worsening of the skin condition. One year later, an adenocarcinoma of the colon was diagnosed and during surgery a grossly enlarged spleen was found. The spleen, 800 g, was removed and upon histological examination showed non-caseating granulomas, comparable to those found in the skin. Liver biopsies revealed no abnormalities.

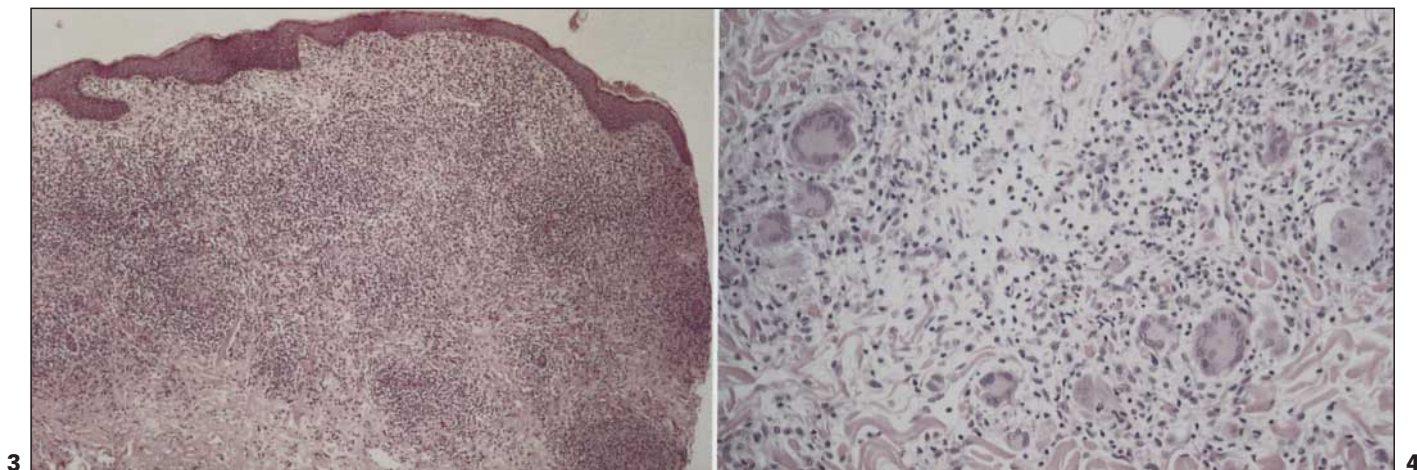


Fig. 3. Dense dermal granulomatous infiltrate in patient II. Original magnification $\times 40$.

Fig. 4. Detail of infiltrate showing multiple Langhans giant cells, eosinophils and small lymphocytes in patient II. Original magnification $\times 200$.

In the following years, several basal cell carcinomas and a squamous cell carcinoma developed in the face. An enlarged lymph node was found on the right side of his neck.

One of the basal cell carcinomas and the cervical lymph node showed granuloma formation. Four years later in 1976, the patient died at the age of 63 years of an unknown cause. At this time, his trunk was covered with extremely sagged atrophic skin and several varicose veins (fig. 1c). On the extremities, many small infiltrated plaques were present and in his neck firm lymph nodes were noticed. Permission for autopsy was not granted.

Unfortunately, there was no material available for TCR gene clonality studies.

Discussion

The three case histories contribute to the still ongoing debate concerning the pathobiology of 'GSS' and the relationship between GSS and other lymphoproliferative diseases, especially MF and Hodgkin's disease (HD). The first patient presented with classical GSS without MF cells in the infiltrate and no association with a lymphoproliferative malignancy was found after 8 years follow-up. Molecular clonality studies in this patient however showed clonal TCR β and TCR γ gene rearrangements in the T-cell infiltrate of the skin.

In the second female patient with a histologically confirmed diagnosis of MF, GSS developed in the preexisting plaque-stage MF lesions in the axillary and inguinal folds. Molecular clonality studies showed clonal rearrangement of the TCR β genes, but we cannot officially exclude that the finding of these clonal rearrangements was due to the preexistent MF cells.

The third patient developed very extensive lax skin lesions over many years. In addition granulomas were found in a basal cell carcinoma, in the enlarged spleen and in a cervical lymph node.

History

Before Ackerman [1] in 1978 proposed the term granulomatous slack skin (GSS), some cases have been reported under other denominations.

In 1968, Bazex et al. [18] reported on a patient with a skin and lymph node disorder characterized by hanging skin masses in the body folds some of which had an ulcerative course. On histology granulomas were found. The case report was entitled 'Maladie de Besnier-Boeck-Schaumann chalazodermique?', but we have the opinion that this case report represents the first case of GSS.

In 1973, Convit et al. [4] reported on a patient with a 'progressive atrophying chronic granulomatous dermohypodermatitis'. The onset of the disease in this particular case started after the successive injection of Mitsuda antigen (used for assessment of the cell-mediated response to *Mycobacterium leprae*) and BCG vaccine. The patient developed papular lesions coalescing into plaques that showed a tendency to hang in loose folds. One of the initial lesions appeared at the site where the Mitsuda antigen had been injected.

Histologically, in the lesions granulomas with lymphocytes, epithelioid cells, giant cells and histiocytes were found [4, 18]. In 1978, the disease was further defined by Ackerman [1] who proposed the term GSS, based on the

histological and clinical features [19]. In the French literature, the term 'chalazodermie granulomateuse' is used [6, 18, 20].

Since the report of Convit et al. [4] on GSS, 34 patients (including the 3 patients in this report) have been described.

Sex and Age Distribution

The age of onset of GSS ranges from late childhood to mid-adult life (range 14–69 years; mean age 37 years). The time span between the start of the disease and the GSS diagnosis may vary significantly. First biopsy specimens were often taken when a patient presented with lax skin formation, but in some reports CTCL/MF-like lesions had been present for more than 10 years [20]. The male:female ratio is about 2.3:1.

Only Caucasian patients with GSS have been described so far.

Clinical Features

The features of 34 patients with GSS are summarized in table 1.

At the onset, indurated plaques with swollen subcutaneous tissue are usually found, but papules and nonitching erythematous scaling patches with poikiloderma vasculare atrophicans have also been described [4, 6, 20, 33]. The lesions evolve into areas of hanging bulky skin masses. At this stage, the skin surface starts to wrinkle and softens [34]. In some patients ulceration may occur [10, 11, 13, 18]. When lesions become more atrophic, subcutaneous blood vessels may become visible [34]. The inguinal and axillary folds are most often affected, but in long-standing disease other skin areas can also be involved. Unusual sites of involvement include the back, hands and eyelids [3, 14, 34].

Histological Features

Early GSS lesions show a lymphohistiocytic band-like infiltrate mainly confined to the upper dermis. The lymphocytes are small- to medium-sized with less convoluted and less hyperchromatic nuclei than usually observed in classic MF [6]. There is a loss of both papillary and reticular dermal elastic tissue (Verhoeff-Van Gieson staining).

Multinucleated giant cells with phagocytized elastic fibers are the most conspicuous feature [8]. The granulomas are noncaseating [34].

Fully developed lesions show small- to medium-sized lymphoid cells permeating the entire dermis and also the subcutis. The lymphoid cells have larger hyperchromatic cerebriform nuclei comparable with classical MF cells [8, 34]. Atypical lymphoid cells with a tendency to epidermotropism may be detected. Pautrier's microabscesses have

been reported [3, 34] but are usually absent [3, 8, 33]. Mild spongiosis (i.e. mild intra- and extracellular edema in the epidermis) may occur [8, 13, 34].

The multinucleated giant cells in fully developed GSS lesions are evenly distributed within the infiltrate [3]. The nuclei of the giant cells are arranged randomly within the cytoplasm (foreign-body giant cells), but arrangement along the periphery of the cells has also been observed (Langhans giant cells; case I) [8, 15, 34]. Eosinophils, B lymphocytes and plasma cells may also be observed [15] and were seen in cases I and II of the present study. Indications for the presence of apoptotic lymphocytes and lymphophagocytosis have been demonstrated by electron microscopy [3, 8, 11].

In the case presented by Le Boit [34], granulomatous arteritis with both lymphocytes and giant cells within the intima of an artery was observed.

In 1 patient with disseminated disease, infiltrates similar to those in the skin were present in the submucosa of the bronchi [34]. In case III, the GSS patient showed granuloma formation in a basal cell carcinoma and a cervical lymph node, and lymph node involvement has also been described in the case reported by Bazex et al. [18].

Immunohistochemistry

Immunophenotypic studies show that the lymphocytic infiltrates mainly consist of CD4+/CD45RO+ T lymphocytes. Loss of T-cell markers (CD3, CD5, CD7) has been reported [35]. Occasionally CD30 (ki-1)-positive cells have been found [14].

The granulomatous component appears to be derived from the monocyte-macrophage lineage as the multinucleated giant cells express the monocytic CD14 antigen and the macrophage CD68 antigen [3, 8, 12, 14, 32–34].

Rearrangement and Genotypic Studies

Southern blot analysis of the TCR β and TCR γ genes in GSS skin lesions has been carried out in 10 patients (table 1: patients No. 3, 8, 9, 10, 13, 22, 29, 32, 33). The presence of a clonal T-cell population was demonstrated in all cases tested [8, 10, 34]. In cases 3 and 8, mononuclear cell fractions tested in peripheral blood revealed no rearrangements [8, 13]. In addition to clonal rearrangement of the TCR β and TCR γ genes in skin lesions a clonally rearranged IgH gene was found in case I of this report; this has not been reported in GSS so far. We concluded the presence of a single T clone with both TCR and cross-lineage IgH gene rearrangements [16, 17].

This is in line with the observation that after 8 years follow-up no secondary B-cell malignancy has developed. Tri-

Table 1. Summary of all reported patients with granulomatous slack skin (n=34)

Case No.	Ref.	Sex/age at diagnosis	Follow-up years after diagnosis	Associated LPD	Additional remarks
1	18	m/24	1	none	granulomatous lymphadenitis
2	4	m/15	22	HD after GSS	onset after Mitsuda test, died of HD
3	2, 13	m/39	15	none	ulceration of lesions, trisomy 8, clonal rearrangement
4	5	m/21	?	HD after GSS	died of HD
5	21	m/27	2	none	
6	6	m/55	10	HD and GSS	CR of HD with polychemotherapy, alive with GSS, HD and GSS
7	20	f/23	12	none	
8	8	f/14	>10	none	clonal rearrangement, dermatopathic lymphadenitis
9	8, 22	m/46	?	HD after GSS	cutaneous HD within GSS lesion, clonal rearrangement
10	3, 8	m/42	?	NHL after GSS	granulomatous infiltrates in lungs, died of NHL after relapse, clonal rearrangement
11	7	m/41	>5	NHL before GSS	PR of GSS following chemotherapy, CR of NHL
12	23, 24	f/25	>8	none	gallium-67 uptake in lung lesions
13	12	m/20	>7	HD after GSS	relapse of HD following chemotherapy, clonal rearrangement
14	12	m/30		small lymphocytic NHL after GSS	RD of NHL after excision/RT/topical nitrogen mustard
15	12	m/51	>8	none	
16	25	m/24		mixed cellularity HD after GSS	RD of GSS after excision
17	26	f/56	?	none	diabetes
18	27	m/30	15	nodular acclerosing HD after GSS, myelocytic leukemia	died of leukemia, PR of GSS and HD due to polychemotherapy
19	28	f/22	2	none	
20	29	m/69	10	none	
21	30	f/43	7	LCH after GSS	PR of LCH after prednisone
22	9	m/66	4	none	clonal rearrangement
23	19	m/33	?	none	
24	31	f/31	>5	GMF and GSS	
25	32	m/29	>4	NHL after GSS	chemotherapy: CR of NHL, PR of GSS
26	14	m/57	>7	none	
27	14	m/53	>7	none	
28	33	m/54	7	HD before GSS	granulomatous lymphadenitis
29	10	m/49	>3	none	clonal rearrangement, trisomy 8
30	15	m/38	>11	HD after GSS	
31	11	m/24	5	GSS and MF	alive with GSS and MF, clonal rearrangement
32	I	f/28	8	none	clonal rearrangement
33	II	f/40	2	GSS after MF	GSS within MF lesions, clonal rearrangement
34	III	m/49	14	none	adenocarcinoma of colon, granulomas in spleen and lymph node, variety of skin malignancies, died with extensive GSS

LPD=Lymphoproliferative disease; NHL=non-Hodgkin's lymphoma (nodal); LCH=Langerhans cell histiocytosis; CR=complete remission; PR=partial remission; RD=relapsing disease (after initial remission); RT=radiotherapy; I, II, III=presented case reports.

somy of chromosome 8 which is known to play a role in the pathogenesis of HD, non-Hodgkin's lymphomas, some leukemias and Ewing's sarcoma has been observed in a skin cell culture obtained from 2 patients with GSS [10, 13].

Comparative cytogenetic studies of GSS and associated preexistent and subsequent lymphoproliferative disorders have not been reported yet.

Extracutaneous Involvement

Extracutaneous involvement of GSS rarely occurs. Granulomatous lymphadenitis has been reported in 3 patients [18, 33]. Case III of this report showed granuloma formation in an enlarged cervical lymph node and in the enlarged spleen.

In one patient with disseminated GSS, infiltrates similar to those in the skin were present in the submucosa of bronchial tissue as proven by transbronchial biopsy [34].

Clinical and Histological Differential Diagnosis

The clinical differential diagnosis of GSS is constituted by diseases with localized acquired lax skin due to localized defects in elastic tissue [34]. Generalized cutis laxa differs from GSS in that there is no tendency to involve flexural areas while there is often involvement of the facial skin and elastin tissue in other organs [34].

Anetoderma refers to an area of circumscribed slack skin evolving to flaccid folds. This disorder may occur associated with granulomatous inflammatory disease and BCG vaccination [38]. In anetoderma, lesions are usually smaller, the distribution of the lesions is at random and there is no association with systemic elastolysis [34]. Jubert et al. [35] reported on a patient with Sjögren's syndrome who developed numerous areas of slack skin and small plaques on the trunk. The diagnosis anetoderma was made and the patient appeared to have a multifocal cutaneous plasmacytoma and a malignant B-cell lymphoma of the parotid gland [35].

Mid-dermal elastolysis (MDE) is characterized by idiopathic wrinkling or wrinkling associated with clinical evidence of inflammation. The wrinkling is circumscribed and of the crinkle type, involving the entire skin surface in otherwise healthy young or middle-aged women. There is however no tendency to develop pendulous skin folds [39].

Kuramoto et al. [40] reported on a patient who developed an 'elastolytic granuloma' secondary to adult T-cell leukemia. The dorsa of both hands, the face, the neck and one thigh were affected. Laboratory data in this patient revealed the presence of antibody to human T-cell leukemia/lymphoma virus I. The cutaneous changes developed

in preexisting lymphomatous lesions but did not result in bulky hanging skin lesions [40]. Finally, early lesions of GSS may mimic MF and patches with poikiloderma have been described in GSS [20].

Granulomatous inflammation has been noted in the cutaneous infiltrates of MF and Sézary syndrome of which granulomatous MF (GMF) appears to be the most prevailing [34]. In both diseases dermal band-like lymphocytic infiltrates can be found.

Epidermotropic MF cells and/or Pautrier's microabscesses are rare in GSS. Fully developed GSS and GMF can be discriminated by permeation of the dermis and the subcutis by a granulomatous infiltrate and a complete loss of elastic fibers in GSS, while in GMF a variable loss of elastin is seen with low numbers and a different distribution of granulomas and multinucleated giant cells.

In GSS the giant cells may contain up to 40 nuclei per cell even in one section [32] in contrast to GMF where up to 5–10 nuclei per cell can be present [3]. In GSS lymphophagocytosis is far more common than in GMF [13]. The atypia of lymphocyte nuclei in GSS is usually less pronounced as compared to GMF and MF [3, 13, 25, 32–34].

The histology of MDE with inflammation is characterized by a perivascular inflammatory infiltrate, phagocytosis of elastin by multinucleated giant cells (foreign-body type) and mid-dermal loss of elastin, thus showing close resemblance to GSS apart from the lack of atypical lymphoid cells in MDE [39].

Course and Prognosis

It appears that the skin lesions in GSS follow an indolent course over more than 10 years with slow progression from flexural areas to other skin sites. The disease itself is not life-threatening. The prognosis is mainly determined by the presence of a concomitant malignant lymphoproliferative disease.

Associated Lymphoproliferative Diseases

The disease course of GSS may be complicated by the development of a lymphoproliferative disease in both cutaneous and in extracutaneous sites or vice versa (table 2).

In 7 cases (21%), GSS was followed by HD [4–6, 8, 12, 15, 27, 33]. GSS was preceded by HD in 1 case [33]. GSS and HD may present simultaneously [6], or HD may present several years after the diagnosis of GSS has been made [5, 12]. Even 11 years after the GSS diagnosis, the occurrence of HD has been described [15]. HD developed within a GSS lesion in 1 case [8]. Other secondary malignant diseases in GSS patients included Langerhans cell histiocyto-

Table 2. Relationship between GSS and preexisting, accompanying or subsequent lymphoproliferative malignancies (n=34)

Presenting disease	2nd disease	Cases, n
GSS	HD	7 ¹
GSS	NHL	3
GSS	LCH	1
GSS	not known/none	17
HD	GSS	1 ²
NHL	GSS	1
GSS and MF simultaneously		2
MF	GSS	1 ³
HD and GSS simultaneously		1
Total		34

NHL=Non-Hodgkin's lymphoma (nodal); LCH=Langerhans cell histiocytosis.

¹ GSS within HD lesion. One patient died of myelogenous leukemia after a first diagnosis of GSS and a second diagnosis of HD.

² HD within GSS lesion.

³ GSS within MF lesion.

Table 3. Response to treatment for GSS in 34 cases

Treatment(s)	Response
PUVA	PR (32)
Topical steroids	PD (1, 32)
Excision	RD (2, 3, 16, 33), CR (5)
(Poly)chemotherapy	PR (11, 18, 25), RD (10, 13), PD (28)
Systemic steroids	PR (34), PR (21)
Nitrogen mustard	PD (32)
Carmustine	AD (33)
Radiotherapy	AD (1, 8)
Azathioprine	PR (2)
Interferon α	PR (28)
Etretinate + interferon α	PR (27)
Interferon α + clofazimine	PR (26)
Surgery + radiotherapy + nitrogen mustard	AD (14)
Polychemotherapy + radiotherapy	RD (22)

Only the treatments that were given after the diagnosis of GSS was made are represented. When more than one therapy was administered to one patient, not as a combination, separate results are given. Figures in parentheses indicate patient No. CR=Complete remission; PR=partial remission; AD=arrest or slowing down of disease; PD=progressive disease; RD=relapsing disease (after initial remission); PUVA=ultraviolet A plus psoralen.

sis [30] and noncutaneous non-Hodgkin's lymphomas [3, 7, 8, 12, 32]. GSS and MF presented simultaneously [11, 31] or GSS developed in the axillary and inguinal folds that had previously been affected by plaque-stage MF lesions (patient II of this study).

Treatment

To date, no treatment has resulted in complete remission. This is summarized in table 3.

Excision of diseased skin has been performed for cosmetic or functional reasons [12, 25]. However, even when diseased skin was totally excised, lesions recurred within months. The only exception appears to be case 5 (table 3) in whom no recurrence appeared after excision of a lesion during a 2-year follow-up period [21]. Although reports concerning treatment results and follow-up data in GSS are scarce, it seems that in a proportion of the patients the same treatment options, such as topical nitrogen mustard, PUVA and UVB, that are given to patients with MF can also induce remission in GSS [8, 14, 33, 34].

Pathobiology

Based on TCR gene rearrangement studies [2, 3, 8–10, 12, 13] and cytogenetic [10, 13] studies, it is suggested that GSS results in fact from a clonal T-cell proliferation presenting as an indolent granulomatous CTCL.

The pathobiology of GSS and notably its association with lymphoproliferative malignancies, the cause of the granuloma formation and its elastolysis, remains elusive.

GSS can be associated with preceding, concomitant and subsequent lymphoproliferative disease in both cutaneous and in extracutaneous sites in about 50% of the cases. These are HD [4–6, 8, 12, 15, 27, 33], non-Hodgkin's lymphoma [3, 7, 8, 12, 32], Langerhans cell histiocytosis [30] and MF [11, 31] (table 2). It has been suggested that GSS and HD represent cytogenetically related lymphoproliferative disorders. The finding of trisomy 8 in 2 patients with GSS but without HD supports this hypothesis because this numerical aberration has also been found in HD [13]. Involvement of chromosome 8 is uncommon in MF and Sézary syndrome but has been reported in myeloid disorders such as myelodysplastic syndrome, non-Hodgkin's lymphoma and acute myeloid leukemia [10].

It has also been suggested that in some cases GSS and HD may potentially derive from one single T-cell clone [15], a mechanism only proved in few patients with HD, lymphomatoid papulosis and MF-type CTCL without GSS [41, 42]. The case described by Le Boit (patient 9) [8] who reported the occurrence of a nodule with histological features of HD in a preexistent GSS lesion (no extracutaneous

HD was reported in this particular case) and case II presented by us with the development of GSS within preexistent MF lesions stress the close relationship of GSS and both HD and MF. The occurrence of two different lymphomas at one location is consistent with the definition of a composite lymphoma [43], but this phenomenon is rare. More insight into the relationship between GSS and the other above-mentioned diseases can be obtained by TCR gene clonality studies. However, these genotypic studies on lymphoproliferative diseases in patients who also have GSS have not yet been performed, so it is not yet known whether GSS and associated disorders represent the same disease with a rare clinical presentation in the skin or are separate diseases.

Granuloma formation is a second characteristic phenomenon in GSS. Other granulomatous skin diseases which show marked elastolysis include elastolytic giant cell granuloma [36, 40] and MDE [39]. Granulomatous inflammation in association with malignant lymphoma may represent an aberrant immunological response in patients with a disordered immune system either resulting from or perhaps predisposing to lymphoma. This hypothesis is supported by the presence of granuloma annulare in patients with malignant lymphoma [37].

Alternatively the granulomatous inflammation might represent a peculiar host reaction to the lymphoid tumor cells as part of the disease. Hermes et al. [36] hypothesized that the granuloma formation in GSS may be the result of the antigenic status of the atypical lymphocytes and/or elastic fibers. In addition, granulomatous lymphadenitis has been reported [33] in a patient with nodal HD and subsequent GSS. This phenomenon may indicate immunological control.

However, there are reports of tumor progression in patients with GMF repudiating the claim that granulomatous inflammation might be protective in CTCL [3, 45].

Our case III contributes to this discussion, because granuloma formation was found in epithelial skin cancer, a skin site which was clinically not involved by GSS. This suggests that the granulomatous infiltrate in this patient represented a peculiar, nonspecific host reaction to tumor cells or inflammation.

Another characteristic feature of GSS is complete loss of dermal elastic fibers leading to lax skin formation. GSS may be classified under the general heading 'cutis laxa' (dermatochalasia), a group of elastolysis syndromes [39, 44]. The pathophysiology of most of these syndromes remains unknown. In acquired cutis laxa syndromes infiltrates in the skin may directly or indirectly affect the structure of elastic fibers [44].

This elastic fiber phagocytosis may be a bystander phenomenon of cytokine production involved in the activation of histiocytic cells resulting in aspecific degradation and phagocytosis of elastin [14].

A third explanation is given by Hwang et al. [44] who postulated that acquired cutis laxa in general and possibly syndromes such as MDE may be caused, at least in part, by α_1 -antitrypsin deficiency leading to a localized (or generalized) increase in granulocyte elastase activity. However, in GSS the presence of this enzyme has not yet been investigated.

Conclusions

Based on the characteristics of GSS and in analogy with other syndromes with granuloma formation and elastolysis it can be hypothesized that GSS is a rare variant of CTCL of low-grade malignancy [46]. Therefore, pathologists should look for the presence of atypical lymphoid cells in punch biopsies from GSS lesions, and eventually TCR gene clonality studies should be performed. GSS can be distinguished clinically and histologically from other CTCL by the lax skin formation and granulomas with nearly complete destruction of elastic fibers. It is a slowly progressive disease presenting in the skin, but extracutaneous granulomas may develop as well.

The association of GSS with preexisting or subsequent lymphoproliferative diseases, especially HD, is an important feature that warrants a long-term follow-up of patients with GSS.

Surgery should be reserved only for cosmetically or functionally disturbing lesions. Topical therapy may slow down disease progression. Polychemotherapy should be reserved for severe skin lesions that do not respond to topical therapy or for treatment of extracutaneous manifestations.

Longitudinal comparative TCR gene clonality studies or comparative retrospective analysis of skin biopsies in GSS patients might provide more insight into the precise relationship between GSS and other preexisting or subsequent lymphoproliferative diseases. This is especially important for understanding whether GSS, MF and HD are directly related or represent separate diseases which develop in a susceptible patient.

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