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Solitary Small- to Medium-Sized Pleomorphic T-Cell Nodules of Undetermined Significance: Clinical, Histopathological, Immunohistochemical and Molecular Analysis of 26 Cases

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Key Words
Small- to medium-sized pleomorphic T-cell lymphoma · Cutaneous T-cell lymphoma · T-cell pseudolymphoma

Abstract
Background: Solitary skin nodules composed of pleomorphic T lymphocytes are often the source of diagnostic problems. ***Objective:*** To characterize the clinicopathological features, prognosis and optimal treatment modalities of patients with solitary lymphoid nodules of small- to medium-sized pleomorphic T lymphocytes. ***Methods:*** Twenty-six patients were analysed for clinical, histopathological, immunophenotypical, molecular and follow-up data. ***Results:*** Lesions were located mainly on the head and neck (n = 16; 61.5%) or trunk (n = 8; 30.8%). Histopathology showed non-epidermotropic nodular or diffuse infiltrates of small- to medium-sized pleomorphic T lymphocytes. Monoclonality was found by PCR in 54.2% of cases (n = 13/24). After a mean follow-up of 79.7 months, a local recurrence could be observed only in 1 patient. ***Conclusions:*** Our patients have a specific cutaneous lymphoproliferative disorder characterized by reproducible clinicopathological features. The incongruity between the indolent clinical course and the worrying histopathological features poses difficulties in classifying these cases unambiguously as benign or malignant. We suggest to describe these lesions as 'solitary small- to medium-sized pleomorphic T-cell nodules of undetermined significance'. Irrespective of the name given to these equivocal cutaneous lymphoid proliferations, follow-up data support a non-aggressive therapeutic strategy.

Introduction

In the recent World Health Organization-European Organization for the Research and Treatment of Cancer (WHO-EORTC) classification of cutaneous lymphomas, primary cutaneous CD4+ small- to medium-sized pleomorphic T-cell lymphoma (SMPTCL) is included as a provisional entity [1]. SMPTCL is characterized histopathologically by dense infiltrates of small- to medium-sized CD4+ pleomorphic T lymphocytes with a small proportion (up to 30%) of large pleomorphic cells. Immunohistochemically these lymphomas have by definition a CD3+/CD4+/CD8–/CD30– phenotype, although CD8+ cases have been described [1, 2]. The clinical outcome is usually favourable with estimated 5-year survival rates of 60–80% [1]. To date only small case series of

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patients with this type of lymphoma have been published, and optimal treatment modalities have still to be defined [3–8]. Moreover, these series probably included heterogeneous groups of patients, as in the past cases with similar clinical and histopathological features have been published under different names, and cases with different clinicopathological features have been included in this group.

We reviewed the clinicopathological features of 26 cases that histopathologically and phenotypically could be classified as SMPTCL according to current diagnostic criteria but that were characterized by invariably good prognoses.

Methods

Biopsy specimens from 26 patients (M:F = 13:13; mean age: 47.7 years; median age: 49; age range: 6–80) were included in the study. These cases represented all patients with this diagnosis seen at the Department of Dermatology, Medical University of Graz, in the period of 1993–2005. All patients had a histopathological diagnosis suggestive of SMPTCL as currently defined in the WHO-EORTC classification. Biopsies of 12 other patients with similar lesions were excluded because of lack of sufficient follow-up time (less than 24 months from the date of first diagnosis). During the available follow-up time, none of these 12 patients developed progressive cutaneous disease and/or extracutaneous involvement. All diagnoses were reviewed by at least 3 independent dermatopathologists (B.L., H.B., L.C.). Diagnoses were made according to the WHO-EORTC classification of cutaneous lymphomas [1] and were based on clinical, histological, immunohistochemical and molecular data. We included only cases that, based on clinical, histological, immunohistochemical and molecular data, were considered histopathologically consistent with the definition of SMPTCL as reported in the WHO-EORTC classification of cutaneous lymphomas [1].

Histology

All biopsy specimens were fixed in 10% buffered formalin, routinely processed and subsequently embedded in paraffin. For routine histopathological analysis, sections were stained with haematoxylin and eosin.

Immunohistology

All cases were studied immunohistochemically on routinely fixed, paraffin-embedded tissue sections according to a previously described 3-step immunoperoxidase technique [9]. Sections were immunostained with monoclonal antibodies against CD3, CD4 (Novocastra, Newcastle upon Tyne, UK), CD8, CD20, CD30 and MIB-1 (Dako Cytomation, Glostrup, Denmark) and TIA-1 (Immunotech, Marseilles, France). Second and third antibodies were obtained from Dako. Biopsy specimens of normal skin structures and tonsil tissues served as external positive controls. Negative controls were obtained by omitting the primary antibody or replacing it with normal human serum. Heat-induced antigen retrieval was performed for all of the antibodies.

Molecular Biology

PCR analysis of the T-cell receptor γ gene was performed in 24 cases according to standard procedures as described previously with minor modifications [10].

Results

Clinical Findings

Clinical data of the patients are summarized in table 1. All patients presented clinically with an asymptomatic, solitary, red to purplish plaque or tumour (fig. 1–3). None of the patients showed concomitant lesions or had a previous history of mycosis fungoides or of eczematous and/or psoriasiform skin lesions. There was no history of local trauma or arthropod bite either. None of the patients had previously been treated with anticonvulsants or with other drugs known to be involved in cutaneous pseudolymphomatous eruptions.

In all 26 patients, a complete physical examination did not reveal other skin lesions or lymphadenopathy. Lesions were located on the head and neck in 16 patients (61.5%) and on the trunk in 8 (30.8%). In 1 case each, lesions were located on the upper arm and the upper leg, respectively. Superficial erosion or ulceration could be observed in 2 cases (patients No. 2 and 22). Routine laboratory tests in all patients including complete blood cell count, chemistry panel, liver and renal function, chest X-ray, and lymph node and abdominal ultrasound did not show evidence of extracutaneous involvement.

Twenty patients (76.9%) were treated by complete surgical excision (with minimal margins). Two patients (7.7%) underwent deep shavings and electrocoagulation. In 2 patients with lesions on the face, the nodules spontaneously regressed after incisional (punch) biopsies. Radiotherapy was performed in 1 patient (No. 26). Another one (patient No. 22) presented clinically with a large ulcerated lesion on the upper leg persistent for several years. The lesion resolved completely after local radiotherapy.

The mean follow-up was 79.7 months (median: 65 months, range: 24–215 months). Twenty-five patients did not experience any recurrence and are in complete remission (mean follow-up: 77.8 months). In 1 patient (No. 23), a recurrent lesion developed after 12 years at a site near the primary tumour. Both the recurrent and the initial lesions were treated by complete surgical excision. The patient did not develop any further recurrences during a follow-up of 357 months. One patient in complete remission died of an unrelated cause after a follow-up of 127 months.

Table 1. Clinical features, therapy and follow-up data

Case No.	Age years	Gender	Clinical presentation	Location	Therapy	Status	Follow-up months
1	62	M	tumour	nose	no treatment after punch biopsy	A	61
2	80	M	erosive plaque	shoulder	surgical excision	A	24
3	71	F	tumour	shoulder	surgical excision	A	55
4	51	F	tumour	shoulder	surgical excision	A	168
5	52	M	tumour	nose	surgical excision (deep shaving and cauterization)	A	65
6	53	M	tumour	temporal	surgical excision	A	67
7	43	F	tumour	forehead	surgical excision	A	65
8	40	F	tumour	throat	surgical excision	A	66
9	6	M	tumour	cheek	surgical excision	A	90
10	29	F	plaque	cheek	surgical excision (deep shaving and cauterization)	A	162
11	44	F	plaque	forehead	surgical excision	A	49
12	28	F	plaque	cheek	surgical excision	A	42
13	61	M	tumour	back	surgical excision	A	36
14	41	F	tumour	cheek	no treatment after punch biopsy	A	138
15	56	M	tumour	chest	surgical excision	A	64
16	51	F	tumour	mamma	surgical excision	A	25
17	71	M	tumour	capillitium	surgical excision	A	44
18	68	M	tumour	nose	surgical excision	D	127
19	47	M	tumour	arm	surgical excision	A	78
20	20	F	plaque	chin	surgical excision	A	82
21	25	F	tumour	temporal	surgical excision	A	52
22	61	F	ulcerated tumour	upper leg	radiotherapy	A	115
23	28	M	tumour	chin	surgical excision	A	357
24	40	M	tumour	thorax	surgical excision	A	70
25	39	M	tumour	shoulder	surgical excision	A	62
26	73	F	tumour	cheek	radiotherapy	A	50

M = Male; F = female; A = alive, disease free; D = dead, disease free.

Histological Findings

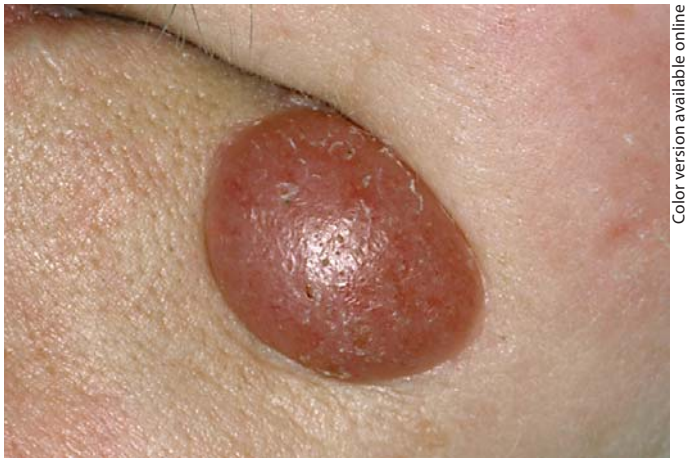
In all cases biopsy specimens showed dense, nodular or diffuse lymphoid infiltrates in the entire dermis with common extension to the subcutaneous fat. Although a mild exocytosis of single lymphoid cells could be observed in 2 specimens, epidermotropism was never found. In all cases, the infiltrate was predominantly composed of small- to medium-sized pleomorphic lymphocytes with few large pleomorphic cells (not exceeding 30% of the infiltrate). Small numbers of plasma cells and eosinophils could also be observed. Tiny collections of histiocytes with occasional multinucleated giant cells were found in 9 cases (34.6%). Adnexal structures were obliterated, at least in part, in all specimens. Angiocentricity was observed in 6 cases (23%), without any evidence of angiodestruction. No necrosis was seen in any of the cases.

Immunohistochemical Findings

Immunohistochemistry showed in all cases a T-cell phenotype (CD3+) with variable proportion of B cells (CD20+). The cells expressed a T-helper phenotype (CD4+) admixed with CD8+/TIA-1+ cells in 23 cases (61.5%). In 3 cases staining for CD4 was not evaluable (1 of these 3 cases showed a strong CD8 expression; in the other 2 only a minority of the cells were positive for CD8). Scattered CD30+ cells (<1% of the infiltrate) were found in 14 cases. The proliferation rate (estimated by Ki-67 staining) was never exceeding 20%.

Molecular Studies

Presence of a monoclonal rearrangement of the T-cell receptor γ gene was found in 13/24 cases (54.2%), whereas in the other 11 cases a polyclonal smear was observed.



Color version available online

Fig. 1. Large erythematous nodule on the chin.

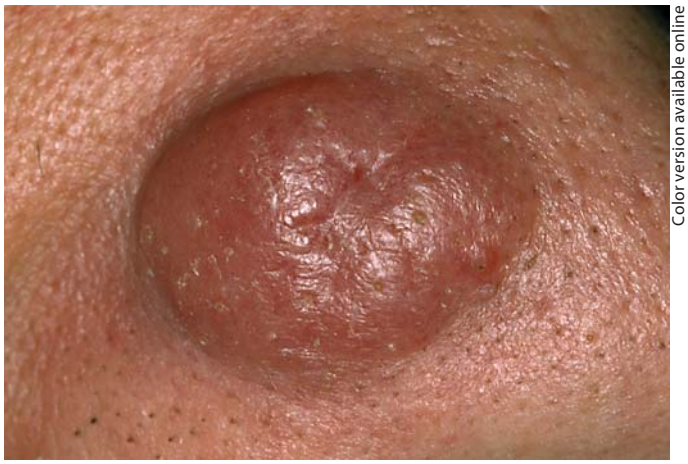


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Fig. 2. Reddish nodule on the nose; note small scar of a previous punch biopsy.

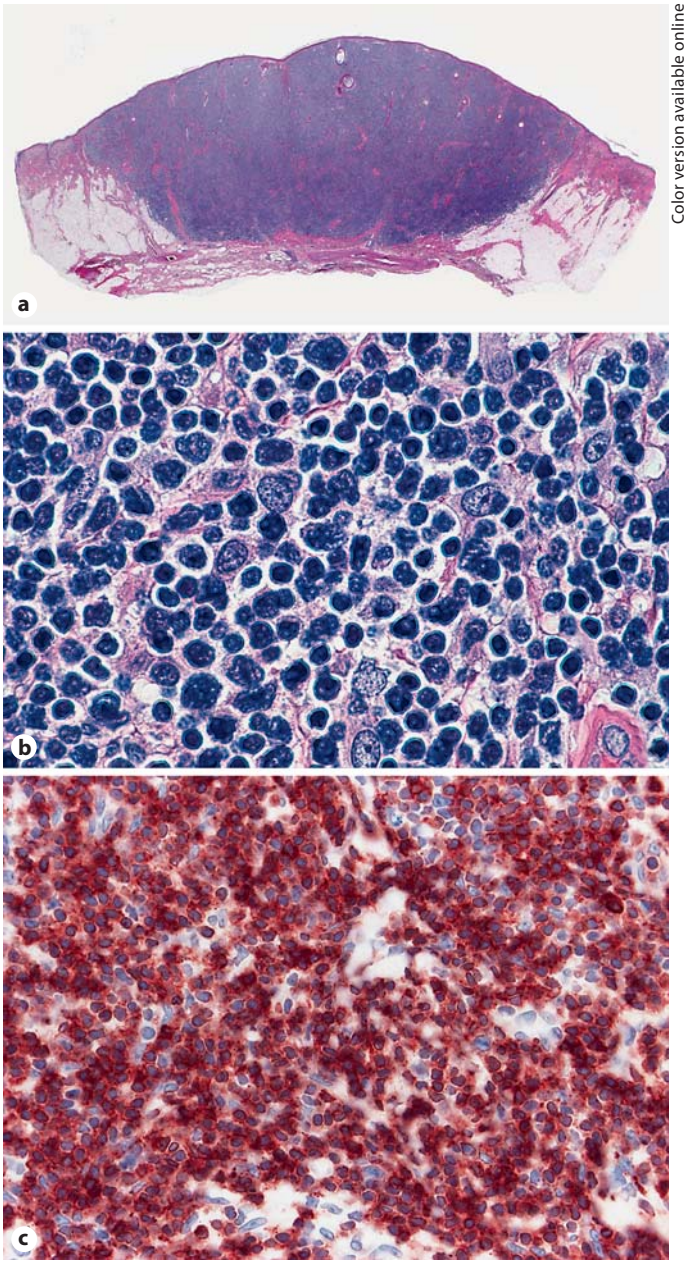

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Fig. 3. a Histological features showing dense lymphoid infiltrates within the entire dermis. Haematoxylin-eosin. Original magnification ×4. **b** Predominance of small- to medium-sized lymphocytes. Haematoxylin-eosin. Original magnification ×1,000. **c** These lymphocytes are positive for CD3. Anti-CD3 antibody. Original magnification ×400.

Discussion

SMPTCL is listed as a provisional entity in the WHO-EORTC classification of cutaneous lymphomas and is considered as a type of cutaneous T-cell lymphoma with a relatively favourable prognosis (estimated 5-year survival rate of 60–80%) [1, 3–6, 11]. Patients present typically with solitary plaques or tumours, mainly in the head and neck area or on the trunk. Less commonly, multiple lesions have been described [3–8, 12]. Histopathologically, SMPTCLs are characterized by dense infiltrates of small- to medium-sized pleomorphic T lymphocytes with a small proportion (not exceeding 30%) of large pleomorphic cells and a CD3+/CD4+/CD8–/CD30– phenotype. To date, only a few, small, heterogeneous series of cases of SMPTCL have been published [3–8]; thus, clinical features, prognosis and optimal treatment modalities are not well characterized. In this context, it should be underlined that precise diagnostic criteria for the differ-

entiation of SMPTCL from benign lesions (pseudolymphomas) are lacking, and cases with clinicopathological features overlapping with those of SMPTCL have been reported under different names, including 'solitary lymphomatous papule, nodule or tumour' [13], 'cutaneous lymphoid hyperplasia' [14], 'solitary non-epidermotropic T-cell pseudolymphoma' [15], 'pseudolymphomatous folliculitis' [16, 17] and 'unilesional mycosis fungoides' [18]. Cases reported recently as 'indolent CD8+ lymphoid proliferation of the ear' [19] or 'pleomorphic CD8+ small/medium size cutaneous T-cell lymphoma' [20] may represent a phenotypic variant of the same pathological process, too. Finally, bringing more confusion to an already confused field, mycosis fungoides and Sézary syndrome represent well-defined entities of cutaneous T-cell lymphoma with a predominance of small- to medium-sized pleomorphic T cells. It was therefore recommended that the diagnosis of SMPTCL should be restricted to cases without a history of mycosis fungoides or Sézary syndrome, without lesions clinically suggestive of these entities, and without distinct epidermotropism seen histopathologically [1, 2].

In the present study, we described a homogeneous group of 26 patients with solitary skin tumours that showed histopathologically features indistinguishable from those of SMPTCL as classified according to current diagnostic criteria. All patients had an indolent clinical course in spite of non-aggressive treatment modalities, without evidence of extracutaneous disease after a long follow-up period. Our cases, just as those previously published in the literature under many different names, are characterized by conflicting diagnostic criteria, some pointing at a benign process, while others are consistent with a low-grade malignant lymphoma. The worrisome features are represented by the presence of dense, diffuse infiltrates of pleomorphic lymphocytes and by the finding of a monoclonal T-cell population in over half of the lesions. Cases with similar histopathological and molecular features have recently been classified unequivocally as SMPTCL [7, 8]. On the other hand, the indolent nature of these lesions was demonstrated by follow-up data. A similar benign course has already been reported [3, 4, 6, 12], including a case showing spontaneous resolution after incomplete surgical excision as observed in 2 of our patients [4]. It should be underlined, however, that most published series included both patients with solitary and with multiple lesions, and that a better prognosis was observed usually in those presenting with solitary tumours, particularly those of small dimensions [4, 7, 8].

It has been suggested that between the groups of cutaneous lymphomas on one end and cutaneous pseudolymphomas on the other, a category designated as 'clonal cutaneous lymphoid hyperplasia' or 'cutaneous lymphoid dyscrasia' can be identified [21, 22]. This cutaneous lymphoproliferative disorder is described as a 'borderline' condition with some potential for evolution into malignant lymphoma. However, it must be underlined that cases included in this borderline group are probably heterogeneous, as some patients eventually developed a cutaneous B-cell lymphoma rather than a cutaneous T-cell lymphoma [21]. On the other hand, clonal proliferations of lymphoid cells with undetermined prognostic significance are well known among systemic lymphoproliferative disorders, monoclonal gammopathy of undetermined significance representing probably the best example [23]. In this context, it may be hypothesized that our patients as well as those described in the literature presenting with similar clinicopathological features have a cutaneous condition conceptually comparable to monoclonal gammopathy of undetermined significance. As skin lesions are often completely excised in early stages, though, the true potential of this cutaneous disorder for evolution into overt malignant lymphoma, if any, is yet unclear. It remains unclear whether the patients described in the literature having multiple lesions at different body sites or large tumours and with a bad prognosis belong to the same group or to a different group of lymphoproliferative disorder altogether.

In summary, we presented a group of patients with a specific cutaneous lymphoproliferative disorder characterized by reproducible clinicopathological features. These include presence of solitary lesions characterized by dense, diffuse lymphoid infiltrates, small- to medium-sized cytomorphology, predominance of T lymphocytes with a CD4+ or CD4+/CD8+ and CD30– phenotype, frequent monoclonal T-cell receptor gene rearrangement and excellent prognosis. The incongruity between the indolent clinical course and the histopathological and molecular features poses difficulties in classifying these cases precisely as benign or malignant [24, 25]. We suggest to describe these lesions as 'small-to-medium pleomorphic T-cell nodules of undetermined significance'. An alternative possibility may be to use the acronym PLYNUS (pleomorphic lymphocytic nodules of undetermined significance). On the other hand, irrespective of the name given to these equivocal cutaneous lymphoid proliferations, our follow-up data support a non-aggressive therapeutic strategy, and we suggest treating these patients with complete surgical excision followed by regular follow-up controls.

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