# Nodal Peripheral T-cell Lymphoma with Secondary Granulomatous Cutaneous Involvement

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*Sir,*

The presence of a granulomatous pattern has rarely been described in cutaneous lymphomas, mycosis fungoides (MF) being the variant more frequently reported (1–4). The aetiology of granulomatous reactions remains unclear and its prognostic value is still disputed, although a favourable influence on outcome has been hypothesized (5). We report here the case of an 87-year-old man with nodal peripheral T-cell lymphoma (PTL) with secondary cutaneous involvement, who clinically presented with multiple eruptive papular and nodular skin lesions on the upper part of the body and histologically showed a strong granulomatous reaction in the skin.

## CASE REPORT

An 87-year-old man was referred to our department because of the presence of 1 month duration of multiple papular and nodular cutaneous lesions, accompanied by an indolent, palpable axillary and inguinal lymphadenopathy. The skin lesions, initially confined to the trunk, rapidly extended to involve the neck, upper extremities and head. The patient also complained of severe weight loss, weakness and nocturnal sweating. His medical history was unremarkable.



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Examination revealed multiple, hard, itching erythematous-violaceous nodular lesions, variously sized, localized on the neck, head, trunk and upper arms (Fig. 1). On the chest nodules coalesced into an infiltrated plaque, $5 \times 6$ cm in size. During hospitalization, new crops of lesions occurred, showing a tendency to enlarge within a few days, and the patient also had fever (38.5°C). Repeated blood cultures were negative. Routine laboratory tests, demonstrated slightly increased ESR (40 mm/h, normal 0–15) and C-reactive protein (1.2 mg/dl, normal $<1$), and moderate anaemia (haemoglobin 9.4 g/dl, normal 12–16), neutrophilic leukocytosis (87%, normal 40–60%) and lymphopenia (5%, normal 20–30%).

Autoimmune screening (IgG, IgA, IgM, C3 and C4 serum levels and ANA) gave normal or negative results. Serum β2-microglobulin and lactate dehydrogenase levels were increased (10 μg/ml, normal 0.6–2.6 and 730 UI, normal 230–460, respectively). Peripheral blood was negative for Sezary cells. Serology for Epstein–Barr virus, cytomegalovirus, hepatitis B and C, Coxsackiae B, parvovirus, Echo viruses and *Borrelia burgdorferi* were negative or consistent with previous infection. Histopathological examination of a cutaneous nodule disclosed a dense infiltrate of small medium sized pleomorphic lymphocytes throughout the dermis, associated with a prominent granulomatous reaction (exceeding 25% of the dermal infiltrate) characterized by patchy epithelioid granulomas with many giant cells, some of them with elastophagocytosis and leukocytophagocytosis (Fig. 2). Immunohistochemistry, performed both on formalin-fixed and frozen material with commercially available kits using a broad panel of monoclonal and polyclonal antibodies, documented a mature T-helper phenotype of the infiltrating lymphoid cells (CD3+, CD4+ CD8–); the cells also expressed T-helper memory subset antigen CD45RO. The giant cells showed reactivity with histocytic marker CD68. Analysis of T-cell receptor γ (TCRγ) gene re-arrangement, using a PCR technique as described by McCarthy et al. (6), showed a monoclonal pattern.

A biopsy from an enlarged axillary lymph node showed a diffuse proliferation of medium- to large-sized pleomorphic lymphocytes without a granulomatous response. On immunohistochemistry, the lymphocytes exhibited the same phenotype as observed in the skin. The TCRγ gene, analysed by PCR (7), showed the same monoclonal re-arrangement as in the skin. In contrast, peripheral blood mononuclear cells revealed a polyclonal pattern. Bone marrow aspirate and biopsy failed to show pathological findings and no other organ involvement could be found by imaging procedures, except for a diffuse lymphadenomegaly. A CT scan documented mild cerebral atrophy without focal parenchymal alterations, while thoraco-abdominal CT showed diffuse lymphadenomegaly. Based on the clinical, immunocytological and molecular genetic features, a diagnosis was made of nodal PTL unspecified, according to WHO classification, with secondary cutaneous involvement. The patient, who was suffering from severe itching and burning, was given oral prednisone 37.5 mg once daily, at progressively tapered dosage. A specific polychemotherapy regimen was not instituted because of the age and poor general condition of the patient. The treatment induced a marked clinical improvement within 2 weeks: the fever abated and the cutaneous manifestations stopped developing and progressing. One month after therapy, the nodular skin lesions were completely resolved. The patient is alive without systemic disease 6 months after the onset of skin lesions.

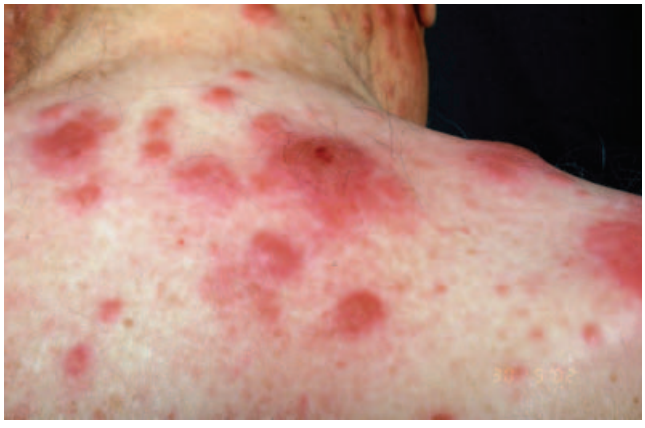

*Fig. 1.* Skin lesions involving the back.

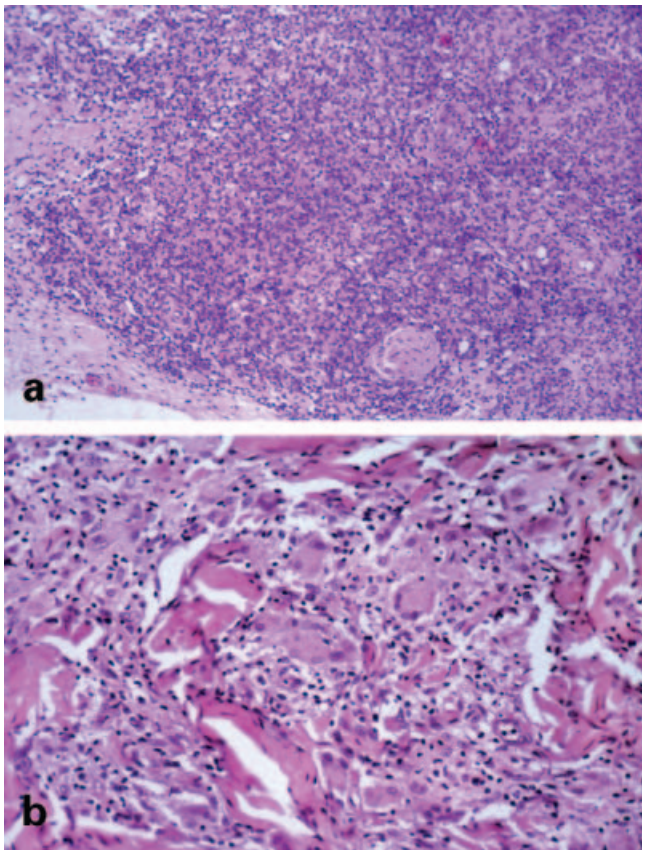


*Fig. 2.* a) Skin histology showing a dense cellular infiltrate throughout the whole dermis (haematoxylin-eosin, ×100). b) The dermal infiltrate is mainly composed of small- to medium-sized pleomorphic lymphocytes; many giant cells, some with leukocytophagocytosis, are also evident (×250).

## DISCUSSION

The phenomenon of granuloma formation has rarely been described within the framework of haematological diseases, particularly in Hodgkin's disease (4) and chronic lymphatic leukaemia (8). In addition to lymphoproliferative disorders, development of granulomatous reaction has been observed in lung and breast carcinoma (7), as well as in malignant melanoma (9). In the skin, both formation of granulomas representing a non-specific reaction pattern and true sarcoidosis – cutaneous or extracutaneous – have been rarely reported in association with Hodgkin's disease and non-Hodgkin extracutaneous lymphomas (10). The presence of a granulomatous reaction has been described in skin lesions of various cutaneous lymphomas, most notably including MF (3, 4), Sezary

syndrome (1) and subcutaneous 'panniculitis-like' T-cell lymphoma (2). A 'granulomatous' variant of MF has been well characterized by Ackerman & Flaxman (3). Although it has been suggested that the granulomatous reaction may be associated with a good prognosis, patients with granulomatous MF showing an aggressive clinical course have been reported (4, 11). Granulomatous slack skin (GSS) is a rare form of cutaneous T-cell lymphoma of unclear aetiology, clinically characterized by the presence of bulky, pendulous skin folds (4). Indeed, many authors have suggested that granulomatous MF and GSS are only variants within the broad clinicopathological spectrum of MF (12). A recent systematic study showed (5) a prominent granulomatous reaction in only 1.8% (30 of 1706) of patients with different cutaneous lymphomas. One of these patients, diagnosed as having nodal PTL with secondary cutaneous involvement, was both clinically and histopathologically similar to our patient. Interestingly, in our case, a granulomatous pattern was not observed in the lymph nodes (no information on this in ref. 5). It is possible that a strong granulomatous reaction confers a favourable prognosis; however, other parameters, including clinical features, cytological aspects and immunohistochemical markers, may influence the outcome. Prognosis is poor in cases of secondary involvement of the skin by nodal lymphoma. Immunocytologically, CD30 expression is considered a relatively favourable prognostic marker (13), whereas CD8 and TCR-δ1 are usually related to more aggressive course among the cutaneous lymphomas (14, 15).

Our case is peculiar for the prominent dermic granulomatous reaction to the neoplastic lymphocytic infiltrate in the skin and for the good response of widespread cutaneous lesions to systemic corticosteroids.

## REFERENCES


1. Gregg PJ, Kantor GR, Telang GH, Lessin SR, Nowell PC, Wonderheid EC. Sarcoidal tissue reaction in Sezary syndrome. J Am Acad Dermatol 2000; 43: 372 – 376.
2. Salhany KE, Macon WR, Choi JK, Elenitsas R, Lessin SR, Felgar RE, et al. Subcutaneous panniculitis-like T-cell lymphoma: clinicopathologic, immunophenotypic, and genotyping analysis of alpha/beta and gamma/delta subtypes. Am J Surg Pathol 2000; 22: 881 – 893.
3. Ackerman AB, Flaxman BA. Granulomatous mycosis fungoides. Br J Dermatol 1970; 82: 397 – 401.
4. LeBoit PE, Zackheim HS, White CR Jr. Granulomatous variants of cutaneous T-cell lymphoma: the histopathology of granulomatous mycosis fungoides and granulomatous slack skin. Am J Surg Pathol 1988; 12: 83 – 95.
5. Scarabello A, Leinweber B, Ardigò M, Rütten A, Feller AC, Kerl H, et al. Cutaneous lymphomas with prominent granulomatous reaction. Am J Surg Pathol 2002; 26: 1259 – 1268.
6. McCarthy KP, Sloane JP, Kabarowsky JHS, Matutes E, Wiedemann LM. A simplified method of detection of clonal rearrangements of the T-cell receptor-gamma chain gene. Diagn Mol Pathol 1992; 1: 173 – 179.
7. Brincker H. Sarcoid reactions in malignant tumours. Cancer Treat Rev 1986; 13: 147 – 156.
8. Cerroni L, Zenahlik P, Kerl H. Specific cutaneous infiltrates of B-cell chronic lymphocytic leukemia arising at the site of herpes zoster and herpes simplex scars. Cancer 1995; 76: 26 – 31.
9. Robert C, Schoenlaub P, Avril MF, Lok C, Grosshans E, Valeyre D, et al. Malignant melanoma and granulomatosis. Br J Dermatol 1997; 137: 787 – 792.
10. Brincker H. Sarcoid reactions and sarcoidosis in Hodgkin's disease and other malignant lymphomata. Br J Cancer 1972; 26: 120 – 123.
11. Gomez de la Fuente E, Ortiz PL, Vanaclocha F, Rodriguez-Peralto JL, Iglesias L. Aggressive granulomatous mycosis fungoides with clinical pulmonary and thyroid involvement. Br J Dermatol 2000; 142: 1026 – 1029.
12. Topar G, Zelger B, Schmuth M, Romani N, Thaler J, Sepp N. Granulomatous slack skin: a distinct disorder or a variant of mycosis fungoides? Acta Derm Venereol 2001; 81: 42 – 44.
13. Marzano AV, Alessi E, Berti E. CD-30-Positive multilobated peripheral T-cell lymphoma primary involving the subcutaneous tissue. Am J Dermatopathol 1997; 19: 284 – 288.
14. Avinoach I, Halevy S, Argov S, Sacks M. Gamma/delta T-cell lymphoma involving the subcutaneous tissue and associated with a hemophagocytic syndrome. Am J Dermatopathol 1994; 16: 426 – 433.
15. Urrutia S, Piris MA, Orradre JL, Martinez B, Cruz MA, Garcia-Almagro D. Cytotoxic/suppressor (CD8+, CD4–) cutaneous T-cell lymphoma with aggressive course. Am J Dermatopathol 1990; 12: 603 – 606.