

Diffuse and Aggressive Cutaneous Granulomatosis Revealing a Cytotoxic Cell Systemic Lymphoma

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Sir,

Systemic lymphomas may give rise to a variety of non-specific skin manifestations, such as pigmentation, urticaria, erythroderma, ichthyosis, erythema multiforme, erythema nodosa (1) and, rarely, cutaneous granulomas. The development of non-infectious granulomas in involved and non-involved organs, such as spleen, liver, bone marrow or lymph nodes, is a classical occurrence in systemic lymphomas, even though skin involvement is less frequently reported (2–4). We report here a patient with diffuse sarcoidosis-like granulomatous skin lesions associated with and revealing a Hodgkin's-like T-cell systemic lymphoma.

CASE REPORT

A 56-year-old man with no significant medical history was referred for evaluation of multiple papulonodular elements on the back, face (Fig. 1a and 1b) and scalp of 2 months' duration, associated with diffuse acquired follicular keratosis, marked cough, multiple superficial lymphadenopathies, hepatosplenomegaly and degradation of general health. Scalp nodules resulted in patchy alopecia (Fig. 1c), whereas some back lesions evolved toward ulcerations. Standard blood tests showed a major inflammatory syndrome and an elevated rate of lactate dehydrogenase

of 496 IU/l (normal 220–450 IU/l). A three-stage computed tomography (CT) scan displayed multiple pulmonary nodules with enlarged mediastinal lymph nodes along with hypodense nodules in liver, pancreas and spleen. Skin biopsies repeatedly showed epithelioid granulomas without necrosis, consistent with sarcoidosis, without any atypical cells but featuring an aggressive behaviour for collagen fibres, which were separated and infiltrated by granulomas (Fig. 2). Polymerase chain reaction analysis of skin lesions showed two major clonal rearrangements of the T-cell receptor γ -chain (TCR γ) gene. Bone marrow biopsy and smear were both normal, but a mediastinal lymph node biopsy displayed a diffuse atypical CD5+ CD8+ CD56– lymphoid proliferation associated with large Epstein-Barr virus (EBV)-encoded RNA (EBER)+ Reed-Sternberg-like cells and numerous histiocytes, often also organized in granulomas. Molecular analysis of this lymph node could not be adequately performed. A final diagnosis of systemic cytotoxic peripheral T-cell lymphoma (U-PTL according to the World Health Organization (WHO) classification) was then established, revealed by diffuse and aggressive, although non-specific, nodular granulomatous skin lesions. Clinical outcome was marked by rapid enlargement and multiplication of skin elements, resulting in extension of alopecia and ulcerations. After numerous courses of chemotherapy, including two courses of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone), three courses of VIP (vepeside, ifosfamide and cisplatin) and three courses of CYM (methotrexate and cytarabine), the cutaneous and systemic lesions slowly subsided and the patient has now been in complete remission for 22 months.



Fig. 1. Prominent papulo-nodules of (a) the trunk and (b) the head, of sudden onset and (c) patchy alopecia of the scalp.

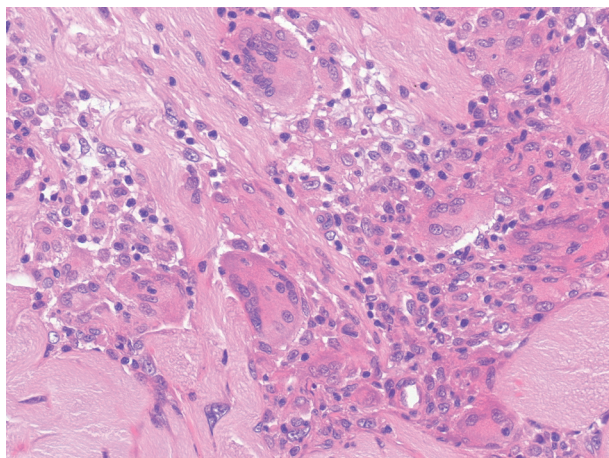


Fig. 2. Epithelioid granulomas in skin lesions with aggressive behaviour toward collagen fibres.

DISCUSSION

Patients with systemic lymphoma may display granulomas of varied histological patterns in different organs, such as liver, spleen, bone marrow and lymph nodes, and the relatively high frequency of this association has led to the concept of a sarcoidosis-lymphoma syndrome (2). The skin is less frequently involved by a similar process and two types of skin granulomas have been reported in association with systemic lymphomas (3, 4). The first type is associated with specific lymphomatous lesions, a situation reminiscent of some subsets of cutaneous T-cell lymphoma, which may show a granulomatous pattern with or without the particular slack skin clinical picture (5); in this setting, neoplastic cells are admixed with histiocytes and the occurrence of a granuloma might represent a reactive pattern against tumoural cells. The second type is a non-specific granulomatous reaction without any neoplastic cells, and different histological patterns have been described, such as sarcoidosis-like, granuloma annulare-like and tuberculoid granuloma (6, 7). The dominant histological picture seems to be the sarcoidosis-like pattern, more particularly reported in association with Hodgkin's disease in a significant number of cases. The skin lesions may develop before or after the diagnosis of systemic lymphoma, sometimes during chemotherapy or radiotherapy of the related condition (4). Our patient seems to fit more closely with the second subset, since no neoplastic cell were present on repeated cutaneous biopsies; however, the presence of one or two dominant TCR γ gene rearrangement(s) in skin lesions according to molecular biology analysis precluded us from ruling out the possibility of very scarce neoplastic cells intertwined with granulomas although no direct comparison with the true tumoural, lymph node-related clone could be performed. In some cases, as in our patient, the underlying lymphoma is di-

agnosed when investigating the granulomatous disease. This possibility must be kept in mind when evaluating patients featuring multiple skin granulomas of recent occurrence without any triggering factor, perhaps especially when the skin lesions are unusually aggressive, with ulcerations and follicular involvement leading to a rapidly worsening hair loss, and aggression of collagen fibres by granulomas. Conversely, general health status can be unaltered at this early stage of evolution of the underlying disease, but some clinical abnormalities, such as organomegaly or transient general symptoms, may already be present.

The patho-mechanisms of systemic lymphoma-associated granulomas are still unknown; although some theories have been constructed, none are supported by experimental data. Accordingly, this granulomatous reaction might represent a cytokine-mediated systemic host-response to the tumour (8) with non-specific stimulation of the immune system including histiocytes; this could explain the possible relationship between the aggressivity of the lymphoma and the importance of the cutaneous lesions. Another hypothesis is that granulomas represent a hypersensitivity reaction against tumoural cells or viral antigens such as HTLV1 (9, 10). A triggering role of chemotherapy (11) can be discussed in some cases through the massive release of tumoural antigens.

In conclusion, in a situation of clinically and histologically aggressive and/or profuse cutaneous granulomas, whatever their histological pattern, a systemic lymphoma must always be considered and searched by appropriate means even in the absence of atypical cells in skin lesions.

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