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Mycosis Fungoides in the Setting of T-cell Large Granular Lymphocyte Proliferative Disorder

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Large granular lymphocytes (LGLs) are medium-to-large cells, of either T- or natural killer (NK)-cell lineage, characterized by eccentric nuclei, condensed chromatin, and abundant pale cytoplasm containing coarse azurophilic granules (1, 2). Proliferative conditions of T- and NK-LGLs represent a complex spectrum of different clinico-pathological entities, ranging from benign reactive lymphocytosis to overt malignant leukaemia. Although patients with mycosis fungoides (MF) are known to be at increased risk of additional haematological neoplasms (occurring either before or following the appearance of MF lesions) (3, 4), no association with LGL proliferative disorders has been described. We report here a patient who developed MF in the setting of T-LGL proliferative disorder, and discuss the possible pathogenetic implications of this previously unreported association.

CASE REPORT

In April 2010, a 62-year-old man presented to our department with a widespread erythemato-squamous dermatosis of 5 years' duration. He reported persistent pruritus, with partial improvement of cutaneous lesions following sun-exposure. Ten years previously he had been diagnosed at a different institution with indolent T-LGL leukaemia; treatment with cyclosporine (CyA) (5 mg/kg/day) had been administered since February 2000, virtually without interruption.

Physical examination revealed a sub-erythrodermic status, characterized by the presence of several erythematous, mildly scaling macules and patches, at times exhibiting a finely wrinkled appearance, widely scattered over the trunk and proximal limbs (Fig. 1A); diffuse xerosis and skin changes secondary to scratching were also evident. The physical examination was otherwise unremarkable. Histopathological evaluation of two 4-mm punch biopsy specimens taken from representative patches on both arms revealed features consistent with early-stage MF: mild epidermal hyperplasia, disproportionate epidermotropism of atypical lymphocytes in areas with only scant spongiosis, and an expanded, slightly fibrotic superficial dermis harbouring a patchy-lichenoid mononuclear cell infiltrate. Several solitary lymphocytes exhibiting pleomorphic and hyperchromatic nuclei were also observed aligned along the dermo-epidermal junction (Fig. 1B). Immunohistochemical stains revealed that intraepidermal lymphocytes, as well as 65–75% of dermal lymphocytes, were $CD3^+$, $CD4^+$, $CD8^-$, $CD20^-$, $CD30^-$, $CD56^-$ cells. Polymerase chain reaction (PCR) analysis of gamma T-cell receptor (TCR) gene rearrangement in the skin failed to detect any clonal population of T cells; a result still compatible with patch-stage MF (3).

In-depth staging studies, including total body computed tomography (CT) scan, human T-cell lymphotropic virus-1/2 serology (assessed by enzyme-linked immunosorbent assay (ELISA)), peripheral blood smear and flow cytometry (FC) analysis, and FC assay for Vbeta TCR repertoire, failed to produce any abnormal result. Bone marrow (BM) biopsy, however, revealed an abnormal, interstitial infiltrate of $CD3^+$ $CD8^+$ mononuclear cells, replicating the picture observed in previous BM studies. Accordingly, a diagnosis of patch-stage MF (Stage IB; TII, N0, M0), together with subclinical T-LGL proliferative disorder, was made. Oral CyA was interrupted; the patient was started on treatment with narrowband ultraviolet B (UVB) along with close haematological monitoring. At the time of last follow-up (January 2010) the patient's skin lesions and reported itching had significantly improved, while his haematological status was stable.

DISCUSSION

With the exception of muco-cutaneous pyogenic infections secondary to chronic neutropaenia, reports of dermatological manifestations associated with chronic LGL proliferative disorders have been scarce and fragmentary, with significant overlap between diseases of T- and NK-cell origin. The overwhelming majority of such cutaneous features can be classified schematically within three major clinico-pathological categories: (*i*) cutaneous small- or medium-sized vessel vasculitis, usually presenting as palpable purpura, necrotic pustules, urticaria vasculitis, or polyarteritis nodosa-like ulcers (5, 6); (*ii*) vasculopathy without histological evidence of true vasculitis, manifesting as livedoid vasculopathy and/or eruptive telangiectatic lesions (5, 7, 8); (*iii*) persistent ulcerations with histological demonstration of intravascular LGL, often localized to the lower limbs

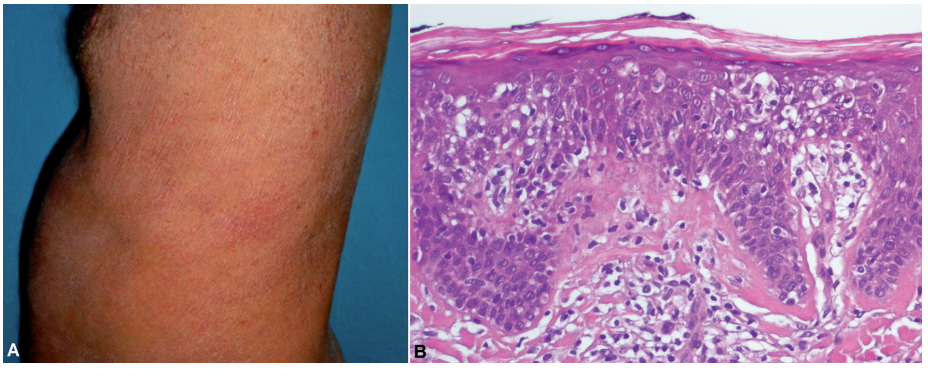

Fig. 1. (A) Multiple erythematous scaling macules and patches on the trunk in a pattern reminiscent of parapsoriasis. (B) Biopsy specimen showing sparse lymphoid infiltrate in the papillary dermis and intraepidermal aggregates of lymphocytes without significant spongiosis (haematoxylin and eosin × 200).

(7, 9). Interestingly, Mallo et al. (10) reported a case of indolent T-LGL leukaemia with persistent generalized pruritus as the only alleged manifestation. There are striking similarities between this case and the one we report; indeed, the clinico-pathological picture described by Mallo et al. would perfectly fit with the so-called "invisible dermatosis" presentation of MF, which is an uncommon, but well-known, scenario (3).

Patients with either T-LGL proliferative disorders or MF appear to be subjected to heightened risk of developing discordant lymphomas (1, 4, 11), defined as second, histologically distinguishable lymphoid neoplasms involving different anatomical sites (12). In this regard, Assaf et al. (13) described a case of indolent T-cell-prolymphocytic leukemia (T-PLL) with subsequent development of MF, lymphomatoid papulosis, and primary cutaneous $CD30^+$ anaplastic large cell lymphoma; molecular studies revealed identical monoclonal TCR genes rearrangements as well as cytogenetic abnormalities in T-PLL and cutaneous T-cell lymphoma (CTCL) cells, indicating that leukaemic and cutaneous malignant T lymphocytes derived from the same clone. According to the authors, T-PLL and CTCL might have arisen concomitantly from the same progenitor cell, or, more likely, T-PLL might have evolved linearly to generate the three cutaneous disorders. We could not employ a similar investigative approach, as cytogenetic aberrations are not a common feature of either T-LGL disorders or MF, and no monoclonal TCR gene rearrangements could be detected in either peripheral blood or skin. Nonetheless, malignant $CD8^+$ T-LGL are thought to be antigen-activated T cells arising, at least in most cases, out of oligoclonal proliferations of a physiological subset of post-thymic $CD8^+$ cytotoxic T cells; this view has also been supported by analysis of V-beta receptor transcripts. Malignant transformation could stem from insensitivity to apoptosis, acquired through constitutive, activating phosphorylation of Stat3 (14). Interestingly, similar Jak3/Stat3 signalling aberrations may play a key role in the pathogenesis of MF (15). Speculative, is it, in our case, a common stem cell/lymphoid precursor, having undergone one or more somatic events predisposing to cytokine-independent activation of the Jak3/Stat3 pathway, generated, through divergent differentiation, two distinct aberrant populations of T lymphocytes (i.e., $CD8^+$ LGL and $CD4^+$ cells, respectively).

Secondly, loss of immune competence resulting from long-standing CyA treatment may have favoured development and/or progression of MF in our case (4, 11): cases have been reported where treatment with low-dose CyA (< 5 mg/kg/day) following a misdiagnosis of inflammatory dermatoses led to clinical worsening and aggressive transformation of MF (16, 17). Of note, in our patient the effect of continuous CyA administration may have been compounded by the relative immunosuppression which is known to be inherent in patients with lymphoproliferative conditions, including T-LGL disorders.

Lastly, although no proven risk factor seems to be shared by T-LGL disorders and MF (1, 3, 11), an independent transformation of distinct lineages of lymphocytes secondary to common exposure to environmental carcinogens or oncogenic viruses cannot be ruled out.

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