

CLINICAL REPORT

T-cell Large Granular Lymphocytic Leukaemia with an Uncommon Clinical and Immunological Phenotype

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A 39-year-old man presented with a rapidly growing unilateral painless nodule on the right cheek. Histopathological examination and peripheral blood analysis both showed a population of T-cell large granular lymphocytes, which were CD1⁺, CD2⁺, CD5⁺, CD7⁺ and CD16⁺, with expression of cutaneous lymphocyte-associated antigen. Further laboratory examination revealed severe neutropaenia, relative lymphocytosis and a clonally rearranged T-cell receptor. The cutaneous manifestation of T-cell large granular lymphocytic leukaemia is very rare. In this particular patient, however, it was instrumental in establishing the diagnosis and may have been enabled by the expression of cutaneous lymphocyte-associated antigen on the cell surface. Key words: large granular lymphocyte leukaemia; skin; methotrexate; cyclosporine.

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T-cell large granular lymphocyte (T-LGL) leukaemia is a rare, mostly indolent, malignancy that is usually characterized by CD3⁺, TCRαβ⁺, CD4⁺, and CD8⁺ T lymphocytes, a profound neutropenia and/or pure red cell aplasia. The diagnosis is either made by coincidence or because of clinical symptoms that are associated with the cytopenia and can consist of anaemia-related signs or infections due to neutropenia. Sometimes, however, skin symptoms such as lobular panniculitis can be the first clinical sign of the disorder (1).

We report here on a patient with the unusual and hitherto unique clinical manifestation of T-LGL as a unilateral cheek tumour in association with an uncommon immunophenotype.

CASE REPORT

A 39-year-old, previously healthy, Dutch man, was referred to the department of dermatology for evalua-

tion of erosions on the oral mucosa. These lesions had manifested several weeks earlier and had already been biopsied by an oral surgeon. Histology was reportedly unspecific, showing superficial erosions with granulation tissue and a mixed inflammatory infiltrate only.

Clinical examination revealed a firm, relatively sharply demarcated red-to-purple nodule with a diameter of approximately 3 cm on the right cheek (Fig. 1A). His medical history revealed that he had not been feeling well for several weeks, had experienced significant weight loss (15 kg in 3 weeks), recurrent upper airway infections within the last few months and night-sweats. The nodule had been present for approximately 2 months. Additional physical examination did not show other abnormalities except for splenomegaly. Since the cutaneous lesion and the history raised the suspicion of a malignancy, a skin biopsy and laboratory screening were performed.

Histopathological examination showed an interadnexal infiltrate of atypical lymphoid cells without epidermotropism or angiotropism (Fig. 2A). The nuclei were small and hyperchromatic. Upon immunohistochemical examination the cells stained positive for CD5 and, to a lesser extent, for CD3. CD8 staining showed more positive cells than CD4 staining, but both were positive in only a small percentage of the lymphoid cells. CD56 and CD57 were negative. The same atypical cells, staining positive for CD5, were also found in a biopsy taken from the ipsilateral oral mucosa 2 weeks prior to the initial presentation in our department.

Biochemical evaluation showed an increase in total protein to 75.7 g/l (normal 60–80) with oligoclonal hypergammaglobulinaemia (20.4 g/l). The haemoglobin concentration was 8.9 mmol/l (normal 8.2–11.0). Testing for antinuclear antibodies was negative. There was a complete agranulocytosis with an absolute leukocyte count of $8.1 \times 10^9/l$ and a relative lymphocytosis (76%) that consisted predominantly of large granular-type lymphocytes. Immunophenotyping of this lymphoid population by FACS analysis demonstrated that the cells expressed CD1, CD2, CD7, CD16 and CD38. Only 22% of these cells showed cytoplasmic CD3 positivity. The cells were negative for CD4, CD5, CD8, cytoplasmic terminal deoxynucleotidyl transferase, CD56, CD57 and CD34. TCRαβ and γδ rearrangements could not

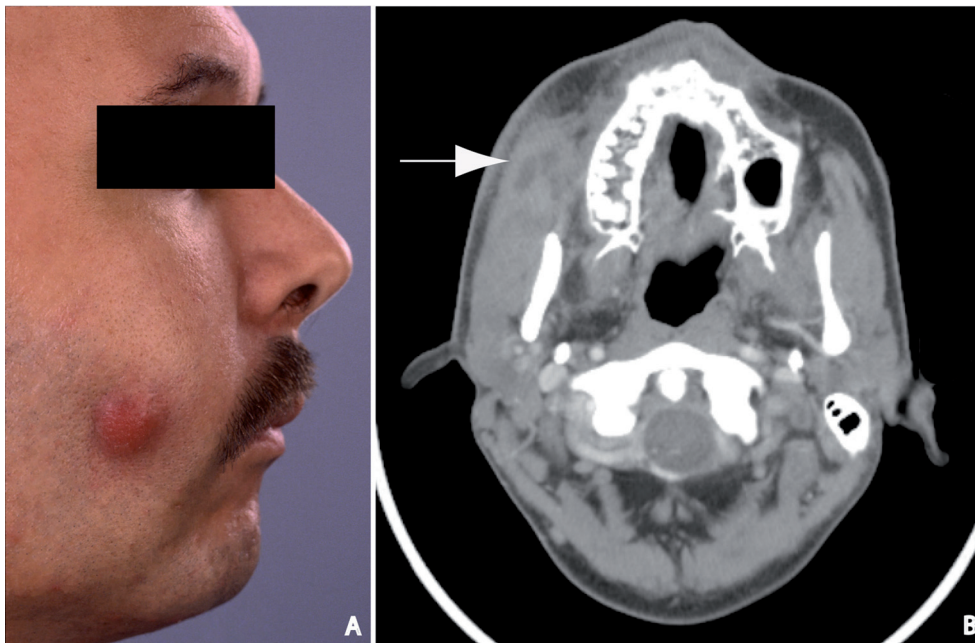


Fig. 1. (A) Clinical presentation with a prominent red-to-purple skin nodule on the right cheek. (B) Cranial computed tomography (CT) scan showing a tumour over the right masseter muscle (arrow).

be demonstrated in the skin biopsies. Amplification of the gamma-TCR gene from peripheral blood leukocytes demonstrated the presence of a monoclonal T-cell population; the α -, β - and δ -chains were not tested.

Epstein-Barr virus (EBV) infection was ruled out by real-time quantitative polymerase chain reaction (PCR) on patient serum. EBV could not be cultured from the mucosal lesions, nor could it be demonstrated by *in situ* hybridization on biopsy specimens. As the cells were obviously capable of skin infiltration, we examined them immunohistochemically for expression of cutaneous lymphocyte-associated antigen (CLA) (2, 3) and found that most of them stained strongly positive (Fig. 2B).

Computed tomography of the skull, thorax and abdomen showed a tumour over the right masseter muscle (Fig. 1B). The spleen was enlarged but enlarged lymph nodes or thymus were not seen. There were no other abnormalities.

Based on the clinical presentation, histopathological examination, and the results of immunophenotyping,

we made the diagnosis of T-LGL with an aberrant immunophenotype, CD1⁺, CD2⁺, CD5⁺, CD7⁺, CD16⁺.

Initially, we treated the patient with methotrexate in doses of up to 20 mg/week. However, 3 months of treatment did not result in haematological improvement. During treatment, he experienced several episodes of infection of the biopsy site on the cheek as well as oral candidiasis. These were successfully treated with broad-spectrum antibiotics and fluconazole, respectively. We then started cyclosporine 5 mg/kg twice daily with a favourable response within a few weeks. His neutrophil count increased to $0.8 \times 10^9/l$ and the oral complaints resolved completely. Novel skin lesions have not developed since. The patient is currently doing well on cyclosporine 5 mg/kg twice daily.

DISCUSSION

T-LGL leukaemia is mostly a disease of the elderly, with a median age at diagnosis of 60 years (4). Symp-

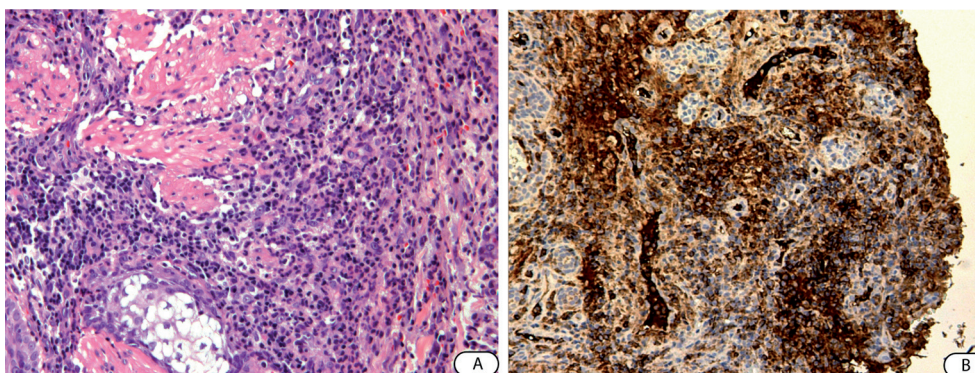


Fig. 2. (A) Histology showing a prominent dermal infiltrate composed of atypical lymphocytes with small, hyperchromatic nuclei (Haematoxylin-Eosin $\times 200$). (B) Strong cutaneous lymphocyte-associated antigen (CLA) expression within the infiltrate ($\times 50$).

tomatic patients present with recurrent infections or fatigue due to immune-mediated neutropenia and anaemia, respectively; thrombopenia is a rare feature. Serological abnormalities such as antinuclear antibodies and hypergammaglobulinaemia are frequent.

Enlarged lymph nodes are rarely found, but splenomegaly is often present. To the best of our knowledge, a cutaneous presentation as observed in our patient is uncommon.

T-LGL leukaemia is usually a clonal proliferation of suppressor T cells. The most common immunophenotype associated with the disease is CD3⁺, CD4⁻, CD8⁺, CD16⁺, CD27⁻, CD45RO⁻, CD57⁺, CD94⁺ (4). Several variations have been reported, but the particular immunophenotype found in our patient, with cytoplasmic CD3 positivity and negative staining for CD8, CD56 and CD57, has not been described previously. The presence of CD1, CD2, CD3 (22%), CD7, CD16 and a γ -TCR gene rearrangement marks the LGL-type lymphoid cells in our patient as T-LGL with an aberrant immunophenotype. The small number of CD3-positive cells probably reflects marker loss. We could not demonstrate clonality in the skin biopsy, probably because the number of malignant cells was too low to generate a monoclonal peak above background.

The aetiology of LGL leukaemia is unknown, but the phenotype of autoimmune lymphoproliferative syndrome, caused by mutations in, for example, Fas and Fas ligand, is quite similar to that of LGL leukaemia, including the immunophenotype of the malignant cells (5). It was shown in previous reports that leukaemic LGLs express high levels of Fas and Fas ligand, whereas the cells themselves are resistant to Fas/Fas ligand induced apoptosis (6). It is possible that the cytopenia results from expression of Fas by the LGLs. Interestingly, EBV has been detected in the LGLs of some patients (7), suggesting a viral origin. However, our patient was EBV-negative. Finally, B-cell malignancies can be associated with T-LGL leukaemia. The frequent presence of serological abnormalities such as hypergammaglobulinaemia and positive ANF are suggestive of B-cell dysfunction in the presence of T-LGL (8). It is tempting to speculate from these observations that both malignancies share a common trigger.

When indicated, treatment of the leukaemia is by drugs that suppress the function of the malignant T cells. Various agents have been successfully used, including methotrexate, cyclophosphamide and cyclosporine (4). The latter drug has been successfully applied in several studies, which prompted us to start cyclosporine when the initial therapy with methotrexate failed. In one study, 14 out of 25 patients with LGL leukaemia and cytopenia responded favourably, most patients requiring maintenance therapy after induction with cyclosporine 10 mg/kg/day (9).

The more frequent types of leukaemia and lymphoma can occur in the skin as fast growing, sometimes ulcerating nodules, but the present case shows that indolent

haematological malignancies can also manifest with a cutaneous lesion as initial symptom. Our patient showed loss of many T-cell markers but expression of CLA. Quite possibly, this allowed the cells to invade the skin, as Sézary cells have a similar expression of CLA (11). What this means for the prognosis of this particular LGL leukaemia compared with non-epidermotropic ones is currently unclear. For some forms of natural killer-cell lymphoma though, such as the nasal type, CLA expression is suggestive of an unfavourable prognosis (12).

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