

Cutaneous Involvement as the First Manifestation in a Case of T-Cell Prolymphocytic Leukaemia

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Mature T-cell malignancies of extracutaneous origin are rare disorders. T-cell prolymphocytic leukaemia (T-PLL) is the most common form of all mature T-cell leukaemias in adults. Secondary skin involvement by T-PLL has been reported in 25% of patients. A case of T-PLL which presented with cutaneous infiltration mimicking a cellulitis-like lesion resistant to antibiotic therapy is described. The diagnosis of T-PLL was subsequently fully supported by the clinical, laboratory and cytological findings, as well as by the immunophenotypic study of the skin biopsy. The present case stresses the importance of accurate evaluation of skin lesions in the diagnosis of some haematological conditions and gives additional information about T-PLL such as a previously non-reported cytogenetic abnormality [t(6;6)] and lack of cutaneous lymphocytic-associated antigen expression. Key words: Cutaneous lymphocytic-associated (CLA) antigen; immunophenotyping; skin biopsy; T-cell leukaemia.

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Prolymphocytic leukaemia (PLL) is a rare chronic lymphoproliferative disease that originates in B-lymphocytes in more than 80% of cases and in T-lymphocytes in about 20% of cases (1, 2). The clinical course of the disease is usually aggressive, with little or no response to therapy (2). T-cell PLL (T-PLL) is the most common of all mature T-cell leukaemias in adults, accounting for over 30% (2). Other mature T-cell malignancies include large granular lymphocytic leukaemia and leukaemia/lymphoma syndromes such as adult T-cell leukaemia/lymphoma (ATLL), cutaneous T-cell lymphoma and peripheral non-cutaneous T-cell non-Hodgkin's lymphoma. In contrast to B-cell lymphoproliferative disorders, T-cell malignancies show a tendency to specific cutaneous involvement. Thus, whereas skin infiltration is seen in less than 5% of B-cell malignancies, in T-cell disorders it ranges from 10% to 100% (3). We report a case of T-PLL with skin lesion as the first manifestation.

CASE REPORT

A 73-year-old woman was referred to the Dermatology Department in March 1995 with a 1-month history of a cellulitis-like lesion on the right leg (Fig. 1). Resistant to antibiotic therapy, the lesion rapidly enlarged to an erythematous plaque 20 × 10 cm in size with multiple indurated nodules on its surface. Lymphoedema of the involved leg was also observed. General physical examination revealed hepatomegaly, splenomegaly and generalized lymphadenopathy. The WBC count was $188 \times 10^9/l$ with 99% prolymphocytes. The platelet count was $117 \times 10^9/l$ and the Hb concentration was normal. Serum lactate dehydrogenase was 709 IU/l (normal values: 250–450 IU/l). The bone marrow showed increased cellularity with a 70% infiltration by pro-

lymphocytic cells (Fig. 2). Cytochemistry of atypical cells showed acid phosphatase positivity in the centrosomes. Genomic studies of the C β and J γ regions by Southern blot analysis were consistent with monoclonality. FACS immunophenotypic studies of peripheral blood confirmed the diagnosis of CD4+ CD8- T-PLL (*vide infra*). Cytogenetic study of peripheral blood showed a t(6;6)(q23;q36). A skin biopsy demonstrated the infiltration by prolymphocytes with a T-cell immunophenotype (*vide infra*).

The patient was treated with deoxycoformicin (4 mg/sqm every 2 weeks × 7) with a reduction in the WBC count, but no changes in the skin lesions. Disease progression occurred within a few days, with the appearance of peripheral lymph node enlargement, facial peripheral paralysis and claudication of upper and lower extremities, which was considered as consistent with central nervous system involvement by the disease. Cytospin of the cerebrospinal fluid was normal. Electromyography detected mixed axonal and radicular polyneuropathy, and a sural nerve biopsy showed infiltration by prolymphocytes. The patient was subsequently given CHOP (cyclophosphamide,



Fig. 1. Macroscopic appearance of the skin lesion.

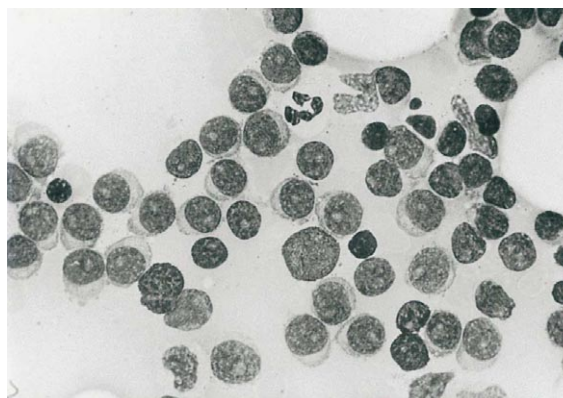


Fig. 2. Typical prolymphocytes from bone marrow of patient (May-Grünwald-Giemsa × 1000).

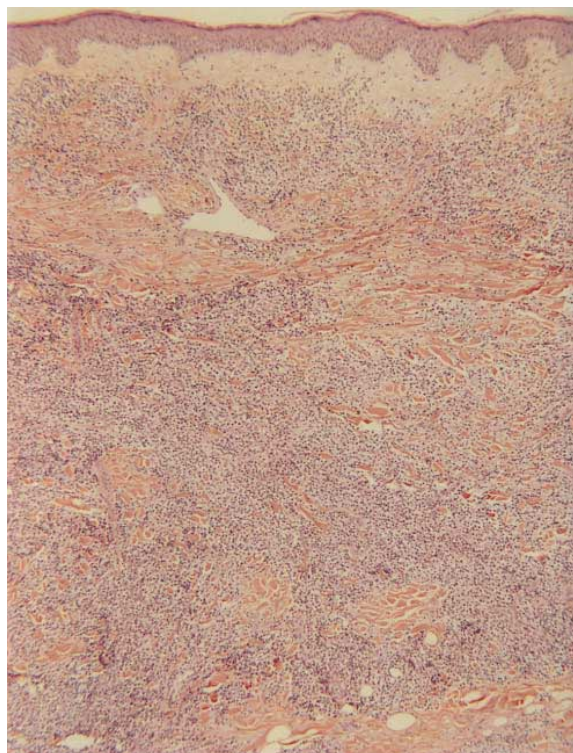


Fig. 3. Non-epidermotropic dermal and hipodermal infiltration by medium-size T-PLL cells (Hematoxylin-eosin $\times 100$).

doxorubicin, vincristine, prednisone) as well as intrathecal methotrexate and cytarabine, but she did not improve. She eventually died a few weeks later, 10 months after presentation.

Cutaneous light microscopy

Histopathological examination of a skin biopsy showed a normal epidermis and a preserved Grenz zone. A dense and diffuse lymphoid infiltrate was present in the upper and lower dermis, extending to the subcutaneous tissue. It was composed of small- and medium-sized lymphoid cells with rounded nucleus without cerebriform features and with a prominent nucleolus (Fig. 3).

Cutaneous immunohistochemistry

Immunohistochemical studies made on both paraffin-embedded and frozen skin tissue revealed that the infiltrate had a mature helper T-cell phenotype (CD2+, CD3+, CD4+, CD7+, CD43+, CD45Ro+). These T-cells were negative for activation antigens such as HLA-DR, CD25 and CD30. The neoplastic population did not show the cutaneous lymphocyte-associated antigen (CLA), whereas a high percentage of vessels were positive for E-selectin, the endothelial CLA ligand. Few (10%) CD8+ lymphocytes and HLA-DR+ dendritic cells and very few (<1%) B-cells (CD19+, CD20+, CD22+) and CLA+ dendritic cells were diffusely scattered throughout the infiltrate. Immunohistochemistry methods employed were avidin-biotin-alkaline phosphatase for antigens investigated on paraffin-embedded tissue and avidin-biotin-peroxidase for antigens investigated on frozen tissue, with the exception of the CLA antigen which was studied by an indirect peroxidase method using a goat anti-rat IgM as secondary antibody (Table 1).

Peripheral blood immunophenotyping

The immunophenotype of circulating leukaemic cells was studied with a three-channel fluorescence cytometer (FACScan, Becton Dickinson)

Table 1. Immunophenotype of the T-cell prolymphocytic leukaemia cells on skin and peripheral blood

| Antigen | Skin | Blood |
|---------------------|------|-----------|
| CD1 | ND | - |
| CD2 | +++ | +++ |
| CD3 | +++ | cyt+++ s- |
| CD4 | +++ | +++ |
| CD5 | ND | + |
| CD7 | +++ | +++ |
| CD8 | - | - |
| CD16 | ND | - |
| CD19 | - | - |
| CD20 | - | - |
| CD22 | - | - |
| CD25 | - | - |
| CD30 | - | - |
| CD43 | +++ | ND |
| CD45Ro | + | ND |
| CD56 | ND | - |
| CD57 | ND | - |
| TCR α/β | ND | - |
| TCR γ/δ | ND | - |
| TdT | ND | - |
| HLA-DR | - | - |
| CLA | - | - |

+++ >75%; ++ 50-75%; + 25-50%.

ND: not done.

by direct immunofluorescence, with the exception of cytoplasmic detection of CD3 and TCR α/β , which was carried out using the alkaline phosphatase antialkaline phosphatase method (APAAP), and CLA antigen, which was investigated by immunohistochemistry (indirect immunoperoxidase method) on peripheral blood smears. The results were: CD2+, CD4+, CD7+, CD5+, CD3_{cyt}+(100%), but CD3_s-(2%), CD8-, TdT-, CD1-, CD16-, CD56-, CD57-, TCR α/β -(surface and cytoplasmic), TCR γ/δ -, CD19-, HLA-DR-, CD25-, CD30-. CLA antigen was also negative (Table 1).

DISCUSSION

T-PLL is characterized by a high tumour mass with marked leukocytosis, hepatosplenomegaly and lymphadenopathy. Cutaneous involvement, which occurs in about a quarter of patients (3), is usually present at the time of diagnosis (e.g. 88% in the series reported by Matutes et al. (2)), and may be the first manifestation of the disease, as happened in our patient. A slight female predominance in cases with cutaneous involvement has been observed. The most commonly reported skin lesion is a diffuse infiltrated erythema. Other clinical patterns include erythematous papules, nodules or plaques, erythroderma and bullous lesions. The face and ears are typical localizations for specific skin infiltration of mature T-cell leukaemias (3).

Skin biopsies of T-PLL cutaneous involvement show a normal epidermis and a dermal infiltrate concentrated around blood vessels and appendages without involving them. In some cases the infiltrate extends to subcutaneous fat, as it did in our case. Epidermotropism has never been described (2, 3). The lymphoid cells which compose the infiltrate have a prominent nucleolus similar to the cells in peripheral blood.

Regarding the immunophenotype of T-PLL in 65-70% of the cases is CD4+ CD8-, and in 15-20% CD4+ and CD8+ (2, 3). Expression of CD7 is a consistent feature. But this

marker is often negative in ATLL, Sézary syndrome and lymphocyte leukaemia (2). The membrane expression of CD3 is negative in only 19% of cases (2, 4). As expected, in the case reported here, peripheral blood prolymphocytes has an immunophenotype identical to that found in the skin infiltrate. To the best of our knowledge, CLA expression by T-PLL cells has not been previously investigated. Although positivity for CLA seems to be variable in non-cutaneous T-cell lymphoproliferative disorders (5), the absence of this skin-related adhesion molecule could be a useful feature in the study of a T-cell leukemia/lymphoma involving skin, which could be of help by excluding the diagnosis of Sézary syndrome, which is typically CLA+ (6).

The cytogenetic abnormality most frequently found in T-PLL involves chromosome 14 (2, 4), with breakpoints at bands q11 and q12, and it is often associated with less specific rearrangements, more frequently trisomy 8q (7, 8). A deletion or interstitial deletion of chromosome 6 is another finding observed in about 30% of T-PLL with cytogenetic abnormalities. The proto-oncogene *c-myc*, which may play a role in T-lymphocyte differentiation, has been mapped to 6 q22-24 (4, 7). The cytogenetic abnormalities in the present case involved chromosome 6, but to our knowledge a translocation (6;6) has not been previously described in T-PLL.

The clinical course of T-PLL is progressive because of the disease's resistance to conventional chemotherapy. The introduction of purine analogues such as fludarabine, deoxycoformycin and 2-chlorodeoxyadenosine has brought new therapeutical expectations. Although treatment results are highly variable from one study to the next (9-11), it has been reported that deoxycoformycin could be an effective treatment (2, 10). In our patient, 2-deoxycoformycin initially induced a response with a marked reduction in the number of peripheral blood prolymphocytes, but the skin infiltrate did not disappear and the patient eventually died. Since the choice of treatment depends on the correct diagnosis, this case emphasizes the significance that a complete and systematic study of skin lesions may have in the diagnosis of lymphoproliferative disorders.

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