

T-cell large granular lymphocytic leukaemia: successful response to 2-deoxycoformycin

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ABSTRACT

We report a 25-year-old woman with T-cell large granular lymphocytic leukaemia presenting with severe neutropenia, anaemia and recurrent infections with a chronic disease course. Immunophenotyping showed an expansion of CD3⁺, TCRγδ⁺, CD4⁻, CD5⁺, CD7⁺, CD8⁺, CD57⁺ large granular lymphocytes. Clonality was demonstrated with T-gamma polymerase chain reaction analysis which revealed clonal rearrangement of the TCRγ chain gene. Cyclosporine, granulocyte colony-stimulating factor, methotrexate and a combination of cyclophosphamide, vincristine and prednisolone failed to correct the neutropenia and the anaemia. Finally, treatment with 2-deoxycoformycin resulted in both clinical and haematological complete responses, despite molecular evidence of the persistence of the abnormal T-cell clone.

KEYWORDS

2-deoxycoformycin, anaemia, CD8⁺, neutropenia, T-cell large granular lymphocyte

INTRODUCTION

T-cell large granular lymphocytic leukaemia (LGL) is an indolent leukaemia characterised by the clonal proliferation of morphologically distinct lymphocytes named for their typical large azurophilic cytoplasmic granules.¹ The majority of cases are of T-cell origin, mainly with a CD3⁺, TCRαβ⁺, CD8⁺ immunophenotype, and a minority derived from CD3⁻ NK cells. Leukaemic LGL may also be CD3⁺, TCRγδ⁺, being CD4⁻, CD8⁺ or CD4⁻, CD8⁻.² Clinically, T-LGL leukaemia is characterised by chronic neutropenia or other manifestations including rheumatoid arthritis and anaemia. Splenomegaly and lymphadenopathy is

extremely rare. Although the natural history of T-LGL is relatively benign, its clinical course may be complicated by recurrent neutropenic infections and severe anaemia.²⁻⁴ Unlike B-cell malignancies, there is no standard treatment for patients with T-LGL leukaemia. Treatment approaches have included growth factor, splenectomy, cytotoxic therapy (alkylating agents, purine analogues) immunosuppressive drugs (cyclosporin A (CSA), methotrexate (MTX) and monoclonal antibodies (alemtuzumab).²⁻¹³

Here we describe a patient with T-LGL leukaemia who remained refractory to various treatments with CSA, granulocyte colony-stimulating factor (G-CSF), MTX and a combination of cyclophosphamide, vincristine and prednisolone, respectively. Finally, a trial with 2-deoxycoformycin (2-DCF) resulted in both clinical and haematological complete responses, despite the molecular evidence for the persistence of the abnormal T-cell clone.

CASE REPORT

A 25-year-old woman was referred to the Department of Haematology in May 2000 for the evaluation of neutropenia and anaemia. She had a previous one-year history of fatigue and arthralgias. Physical examination showed splenomegaly 2 cm below the costal margin. CT scans of the chest, abdomen and pelvis showed only splenomegaly, but no evidence of hepatomegaly or lymphadenopathy. Peripheral blood counts at diagnosis were: white blood cells (WBC) $2 \times 10^9/l$, neutrophils $0.4 \times 10^9/l$, lymphocytes $1.6 \times 10^9/l$, platelets $221 \times 10^9/l$, haemoglobin (Hb) 9.2g/dl, and haematocrit (Hct) 29%. Seventy percent of lymphocytes exhibited LGL morphology. Immunophenotyping of the peripheral blood lymphocytes by flow cytometry demonstrated CD3⁺ (89%), CD4⁻ (11%), CD5⁺ (85%), CD7⁺ (89%), CD8⁺ (79%), CD11c⁻ (3.2%), CD19⁻

(2.6%), CD79a⁺ (0.3%), TCR $\gamma\delta$ ⁺ (59%), TCR $\alpha\beta$ ⁺ (7.9%). Monoclonal rearrangement of T-cell receptor γ gene was detected on both the peripheral blood and bone marrow mononuclear cells, using polymerase chain reaction and heteroduplex temperature gradient gel electrophoresis. The bone marrow aspirate showed an infiltration (56%) by LGL, and a bone marrow trephine biopsy revealed a slightly hypocellular marrow with normal megakaryocytes, an interstitial and micronodular lymphocytic infiltration, but rare granulocytic precursors. Serum immunoglobulin levels were normal. Antinuclear antibodies and antineutrophil antibodies were negative. Rheumatoid factor level was elevated (13,000 IU/ml; normal 35 IU/ml) but the radiographic examination of the joints did not show any soft tissue swelling, joint effusion and/or any bony erosion. Cytogenetics on bone marrow metaphases was normal. Based on these findings, the diagnosis of T-LGL leukaemia was made in our patient. Although the clinical course was satisfactory for six years, sudden drops in her already decreased neutrophils caused concomitant recurrent bacterial infections such as cellulitis, pharyngitis, sinusitis, respiratory tract infections and perirectal abscesses. She had no compatible sibling donor for bone marrow transplantation; in view of her young age, she was given the following treatment schedule from May 2000 to April 2006: CSA 5 mg/kg/day for six months which increased the WBC count to $3 \times 10^9/l$, neutrophils to $1.5 \times 10^9/l$, Hb to 10.9 g/dl and Hct to 33%. Six months later, CSA was withdrawn because of significant renal function impairment. Readministration of CSA at a dose of 3 mg/kg/day was without effect. She was also unresponsive to G-CSF 5 $\mu\text{g}/\text{kg}/\text{day}$ for nine months and to MTX 10 mg/m²/week orally for six months respectively. She therefore received six cycles of a combination of cyclophosphamide (750 mg/m² iv day 1), vincristine (1.4 mg/m² iv day 1), and prednisolone (100 mg/day x 5 orally). Cycles were repeated every 28 days. The patient had only minor and transient benefit from this treatment. In March 2006, she was scheduled to receive six cycles of 2-DCF (6 mg/m² iv every two weeks, six doses). Before the initiation of the treatment the patient's peripheral blood values were as follows: WBC $1.4 \times 10^9/l$, neutrophils $0.3 \times 10^9/l$, lymphocytes $1.1 \times 10^9/l$, platelets $312 \times 10^9/l$, Hb 8.2 g/dl, and Hct 25%. Bone marrow trephine biopsy showed interstitial and micronodular lymphocytic infiltration with LGL. After the start of the treatment a slight increase in the neutrophil count was observed, and after the completion of the third cycle of DCF, the patient had a normal absolute neutrophil count ($2.3 \times 10^9/l$), and a physical examination was normal with no splenomegaly. On the last follow-up on April 2007, the patient was very well. A complete blood count showed: WBC $4.7 \times 10^9/l$, neutrophils $3.3 \times 10^9/l$, lymphocytes $1.4 \times 10^9/l$, Hb 14.1 g/dl, Hct 41.5% and platelets $330 \times 10^9/l$. Rheumatoid factor level was within normal limits (20 IU/ml). After this treatment T-LGL clonality was still persisting.

DISCUSSION

We describe a case of T-LGL leukaemia (CD3⁺, TCR $\gamma\delta$ ⁺, CD4⁻, CD5⁺, CD7⁺, CD8⁺, CD57⁺ phenotype) associated with neutropenia, anaemia, and recurrent infections during the course of the disease. Most patients with T-LGL leukaemia have CD3⁺, TCR $\alpha\beta$ ⁺, CD4⁻, CD8⁺ phenotype. Very rarely leukaemic LGL may also have CD3⁺, TCR $\gamma\delta$ ⁺, CD4⁻, or CD8⁺. These TCR $\gamma\delta$ ⁺ cases seem to have similar clinical presentations to TCR $\alpha\beta$ ⁺ cases, including neutropenia and arthritis.¹⁴⁻¹⁸

Immunomodulation is the mainstay of T-LGL leukaemia treatment with recurrent infections and symptomatic anaemia as the most common indication for therapy. But symptomatic thrombocytopenia, progressive lymphocytosis and splenomegaly are also indications for treatment. An optimal therapy for T-LGL leukaemia patients has not yet been defined. Because of the rarity of T-LGL leukaemia, no prospective clinical trials have been reported and current treatment strategies are based on anecdotal case reports and small retrospective studies.⁴⁻¹³

Agents such as CSA, MTX, and prednisolone have been used with varying success rates.^{4-7,9,10} First-line, single agent therapy with CSA is effective for correcting cytopenia in some patients, but its nephrotoxicity remains a problem for long-term treatment. Furthermore, CSA does not affect the abnormal LGL even in responding patients.^{7,9} Our patient initially responded favourably to CSA treatment, but renal toxicity led to its withdrawal. Reinstitution of CSA at a lower dose was ineffective. The benefit of haematopoietic growth factor such as G-CSF, granulocyte-macrophage colony-stimulating factor (GM-CSF) or erythropoietin is controversial.⁵⁻⁷ In our patient G-CSF administration was ineffective. More encouraging results in the treatment of patients with T-LGL leukaemia have been reported with the use of low-dose MTX with or without prednisolone. The majority of patients treated with this immunosuppressive drug entered complete clinical remission.^{4,8,10} Unfortunately, our patient failed to respond to MTX.

Low-dose oral cyclophosphamide and/or prednisolone therapy is an effective treatment for some patients with T-LGL leukaemia. In our case, combined cyclophosphamide, vincristine and prednisolone resulted in minimal and transient responses in anaemia, neutropenia and splenomegaly.

Some studies continue to support the utility of purine analogues.^{4,7,11-13} There have been a few cases of T-LGL leukaemia achieving a long-term clinical and haematological remission with DCF, despite molecular evidence of the persistence of the abnormal T-cell clone.¹¹⁻¹³ Our patient responded both clinically and haematologically to DCF treatment, with the persistence of the abnormal T-cell clone.

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