CASE REPORT

T-cell prolymphocytic leukaemia (T-PLL): a rare disease with a grave prognosis

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SUMMARY

T-cell prolymphocytic leukaemia (T-PLL) is an extremely uncommon haematological malignancy that has an aggressive course and a grave prognosis. We describe a patient who presented with lymphocytosis, scalp erythema, ascites and splenomegaly and was diagnosed with T-PLL. He was treated with alemtuzumab with a good response and was referred for allogeneic stem cell transplantation.

BACKGROUND

T-cell prolymphocytic leukaemia (T-PLL) is a rare type of mature T-cell leukaemia that presents at an advanced age and carries a dismal prognosis. Most cases of T-PLL will harbour chromosomal abnormalities involving 14q11.2 (T-cell receptor α/δ (TCR α/δ)), 14q32 (TCL1) or Xq28 (MTCP-1), abnormalities of chromosome 8, 12p and deletions of the long arm of chromosomes 5, 6, 11 and 13.[1–3] Despite the advances in the understanding of the biology of this disease, the prognosis still remains poor with a short survival and no curative therapy. The advent of monoclonal antibodies has given haematologists some hope in treating this extremely rare leukaemia. Intravenous alemtuzumab, a monoclonal antibody directed against CD 52, is the best available current treatment for T-PLL. It has resulted in very high response rates of more than 90% when given as first-line treatment and has resulted in a significant improvement in survival. Consolidation of remissions with autologous or allogeneic stem cell transplantation further prolongs survival, and the latter may offer potential cure.[4] In this case report, we describe a man who presents with fatigue, weakness, elevated white blood cell count, splenomegaly, mature large lymphocytes on peripheral blood smear and was eventually diagnosed with T-PLL by peripheral blood flow cytometry and bone marrow studies. Prompt recognition of this rare diagnosis is of uttermost importance to prevent morbidity and mortality.

CASE PRESENTATION

A 57-year-old man with diabetes mellitus on oral hypoglycemics, presented to the hospital with fatigue, weakness, change in mental status and decreased oral intake for a few weeks. On admission, he was afebrile and vital signs were stable. Physical exams were significant for scalp erythema, ascites, splenomegaly and there was no evidence of lymphadenopathy. Neurological examination was normal.

INVESTIGATIONS

Laboratory studies revealed: white blood cell count 173 000/μl (95% lymphocytes), haemoglobin of 10.2 g/dl, platelets of 22 000/μl, albumin of 2.5 g/dl, total bilirubin of 4.5 mg/dl and alkaline phosphatase of 218 units/l. Rest of the liver function tests and basic metabolic profile were normal. Peripheral blood smear revealed mature, large atypical lymphocytes and a few smudge cells. CT scan of the abdomen and pelvis with intravenous contrast revealed splenomegaly measuring up to 19 cm, multiple hypodense regions in the spleen consistent with splenic infarcts, and significant ascites. There was no evidence of lymphadenopathy. Iron studies, ferritin, B_{12} and folate levels were normal. Lactate dehydrogenase was 315 units/l, haptoglobin was 2 mg/dl, reticulocyte count was 4.56% and Direct Coombs test was negative. Fibrinogen was 118 mg/dl and the patient was transfused cryoprecipitate. Hepatitis panel, HIV serology and human T lymphotropic virus (HTLV)-1 serology were negative. Diagnostic and therapeutic paracentesis was performed. The cytology revealed lymphocytes expressing T-cell markers CD2, CD3, CD4, CD5, CD7 and CD8, which was consistent with a diagnosis of T-PLL. T-cell receptor rearrangement was positive for γ rearrangement. Peripheral blood flow cytometry was positive for an abnormal T-cell population expressing CD2, CD3, CD4, CD5, CD7, CD8, and TCR α/β. Staining for CD52 was strongly positive. The cells did not express CD25, CD56 and CD57. Blasts were not identified. Bone marrow biopsy revealed T-cells that strongly expressed CD52, coexpression of CD4 and CD8. These results were consistent with T-PLL. Cytogenetics revealed 14q translocation.

TREATMENT

After the confirmation of the diagnosis of T-PLL, cytomegalovirus (CMV) serology was ordered. Allopurinol and intravenous fluids were started. Prophylactic antibiotics including levofloxacin, valcyclovir, fluconazole and trimethoprim sulfamethaxazole were initiated. Intravenous alemtuzumab (anti-CD52) was initiated at a dose of 3 mg on day 1, 10 mg on day 2 and 30 mg on day 3. The white blood cell (WBC) started decreasing and was 65 000/μl at the time of discharge. He was discharged home on prophylactic antibiotics, antivirals, antifungals and allopurinol. On the outpatient basis, alemtuzumab was continued at a dose of 30 mg three times a week for a maximum of 18 weeks.

OUTCOME AND FOLLOW-UP

CMV PCR was monitored once a week and the patient was admitted to the hospital once during

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his treatment course to receive intravenous ganciclovir for a positive CMV PCR. Pegfilgrastrim was started when there was evidence of neutropenia. After 18 weeks of alemtuzumab treatment the blood counts revealed WBC of 2.28/µl, haemoglobin of 12.1 g/dl and platelet count of 67000. His treatment was stopped given the good response to alemtuzumab and he was referred to a tertiary bone marrow transplantation centre for an evaluation for bone marrow transplant. Scalp erythema improved and the splenomegaly and ascites resolved clinically.

DISCUSSION

T-PLL is an aggressive malignancy with a median survival of 7 months with conventional chemotherapy.[5] It is an uncommon lymphoproliferative disorder of mature post-thymic T cells. It represents approximately 33% of all mature T-lymphocyte disorders with a leukaemic presentation.[6] Clinicians diagnose one case every 5–10 years, which makes recognition of this disorder extremely difficult. In previous reports in the literature, it was recognised that approximately 95% of chronic lymphocytic leukaemia (CLL) patients exhibit a B phenotype and 5% exhibit a T phenotype.[7] Shortly thereafter, a subset of CLL cells, called prolymphocytes was identified based on cytological examination and the presence of significant splenomegaly. Both T-CLL and cytologically defined prolymphocytic leukaemia had a poorer prognosis than the more prevalent typical B-CLL. Most patients with phenotypically defined T-CLL have prolymphocytic cell morphology, whereas a small lymphocyte variant also exists.[8] Most experts now agree that the term CLL should apply to B-CLL only. T-PLL should be considered a specific entity, regardless of the cytological features, and that the diagnosis of T-CLL should be discarded.[9] Matutes *et al*[5] has reported a series of 78 patients. The diagnosis of T-PLL in the 76 patients was confirmed on the presence of a monoclonal T-cell population in the peripheral blood with positivity for CD2, CD 3, CD 5 and CD 7 and either CD4/CD8$^-$ (54%), CD4/CD8 (25%) or CD4$^-$/CD8$^+$ (22%). The clinical course is usually rapid with a small minority of patients who remain indolent for a brief time. The median age of diagnosis is 65 with a predilection for men (male:female=2 : 1 ratio). Signs and symptoms include a high leucocyte count (median, 74.8×10^9/l), massive splenomegaly in 64%, haepatomegaly in 40%, lymphadenopathy in 54% and skin involvement (maculopapular rash, skin nodules, erythroderma) in 18% of the patients. Some patients can also have pleuroperitoneal and central nervous system (CNS) involvement. There may be presence of anaemia and thrombocytopenia in half the cases. LDH may be elevated. Serology for HTLV-1 and HTLV-2, found in association with adult T-cell/leukaemia, is consistently negative in these patients.

Examination of the peripheral blood smear is essential to the diagnosis of T-PLL. Prolymphocytes are medium-sized cells with a high nuclear–cytoplasmic ratio. The nuclei have a single prominent nucleolus and intensely basophilic agranular cytoplasm with cytoplasmic protrusions. Diagnosis can be made on peripheral blood flow cytometry where a monoclonal lymphocyte population will show positivity for T-cell markers including CD 2, CD 3, CD 5, CD 7 and CD52. CD4 and CD 8 expressions are variable. More than two-thirds of cases express CD3 and T-cell receptor-β (TCR-β) in the cell membrane, whereas the remainder is negative with either one or both markers. In the patients lacking the surface expression of CD3 and TCR-β, these T cell-specific molecules are consistently expressed in the cytoplasm and the TCR-β and/or γ chain genes are rearranged in all cases.[4] T-prolymphocytes express strong positivity to CD7 unlike the other mature T-cell leukaemias. Cytogenetic studies are usually positive for t(14;14), in V.14, t(X;14), iso8q and complex cytogenetics. Chromosomal abnormalities involving chromosome 14 is present in 75% of the cases of T-PLL, with inV.14 being the most common abnormality detected. Infiltration of the marrow with prolymphocytes is with a mixed pattern (diffuse and interstitial) and reticulin fibrosis is present.

Differential diagnosis for T-PLL includes T cell large granular lymphocytic leukaemia, adult T-cell leukaemia/lymphoma, sézary syndrome and peripheral T-cell lymphoma. To discriminate between T-PLL and these other T-cell malignancies, it is crucial to integrate all the clinical and laboratory information (PB morphology, histology, immunological and genetic markers). T-PLL can be distinguished from B-PLL based on immunohistochemistry studies and the presence of lymphadenopathy and skin involvement.

The first-line treatment for T-PLL is alemtuzumab. Intravenous alemtuzumab (Campath), used either alone or in combination with a purine analogue, is an effective and well-tolerated treatment, with overall response rates ranging between 51% and 95%,[10 11] and a median survival of 15 to 19 months in patients achieving a complete response,[12] increasing to 48 months after consolidation with autologous or allogeneic stem cell transplantation (SCT). Skin involvement responds well to alemtuzumab. In patients who have CNS involvement, CNS-directed therapy including methotrexate, hydrocortisone, cytarabine or high dose methotrexate should be implemented. Routine CNS prophylaxis is not recommended. Infection prophylaxis for Pneumocystis jerovicci and herpes viruses together with regular monitoring for CMV reactivation should be done. Despite the long-term disease-free survival with alemtuzumab, this disease is still considered incurable. There have been several reports of long-term remission and potential cure in T-PLL patients treated with allogeneic SCT,[13 14] the majority of who underwent matched-sibling transplantation. Therefore, after the attainment of maximal response with alemtuzumab, all patients should be referred for bone marrow transplantation. Purine analogues such as pentostatin, fludarabine and cladribine do not offer substantial benefit but rather add significant toxicities. Therefore these alkylating agents should be reserved for patients who do not respond to alemtuzumab.

T-PLL is a rare disease and careful attention should be given to correctly diagnosing this T-cell leukaemia. Owing to its aggressive and rapid clinical course, delay in making the diagnosis may lead to a fatal outcome. With the advent of alemtuzumab, although much progress has been made in the treatment of this disease, haematopoietic SCT still remains the only hope for cure. Thus, once patients are treated with alemtuzumab in the first-line setting, they should be immediately sent for an evaluation for haematopoietic SCT.

Learning points

- Prompt diagnosis and treatment is important to prevent serious morbidity and mortality associated with this rare and aggressive haematological malignancy.
- Diagnosis is made by T cells strongly expressing CD52 on peripheral blood flow cytometry.
- First-line treatment includes alemtuzumab (anti-CD52).
- Long-term remissions and cure can only be achieved with allogeneic stem cell transplantation.

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