

Refractory pure red-cell aplasia associated with B chronic lymphocytic leukemia successfully treated by fludarabine

Sir,

Pure red cell aplasia (PRCA) is a rare hematologic disorder characterized by a selective erythroid hypoplasia, probably as the result of inhibition of erythropoiesis by T-cells. More than half of the cases remain idiopathic. However, approximately one third are associated with lymphoproliferative disorders. A variety of treatments including prednisolone, cyclosporin A, and cytotoxic chemotherapy are sometimes effective in inducing and maintaining remission of PRCA in patients with chronic lymphocytic leukemia (CLL), but refractory cases are often observed.¹

We describe the case of a patient with CLL-associated PRCA refractory to cyclosporin A and alkylating agents, successfully treated with fludarabine.

A 56-year old man had CLL stage C in August 1997 with a lymphocyte count of $5,700 \times 10^6/L$ (mature CD5⁺ CD19⁺ lymphocytes), hemoglobin 5.9 g/dL, reticulocyte count 0% and platelet count $159 \times 10^9/L$. He had disseminated lymphadenopathy but not hepatosplenomegaly. Bone marrow examination showed interstitial infiltration by small lymphocytes and a total absence of red cell precursors despite adequate myelopoiesis. He had no evidence of parvovirus infection, and an autoantibody screen was negative. He was given, without success, the following therapy: alkylating agents (chlorambucil); 2 courses of CVP (cyclophosphamide, vincristine and prednisone); 3 courses of CHOP (cyclophosphamide, doxorubicin, vincristine and prednisone); and cyclosporin A (5 mg/kg) with prednisone (Figure 1). Since diagnosis, he had been dependent on red blood cell transfusions, two units every 2 weeks. Fludarabine was started in May, 1998, and was given intravenously 5 days every month (25 mg/m² per day) for 5 months (Figure 1). The last transfusion was given after the first cycle of fludarabine on May 11, 1998. The reticulocyte count increased progressively and reached normal values after the second course of fludarabine. Hemoglobin increased to 10 g/dL and 14.9 g/dL after the third and fourth courses, respectively (Figure 1). Seven months after the last course of fludarabine, the patient is in remission from PRCA and has no manifestations of CLL.

The purine-nucleoside analog fludarabine is the most effective chemotherapeutic agent for CLL, whether used as a first-line or second-line therapy. The most common fludarabine toxicities are myelosuppression and immunodeficiency with depression of CD4⁺ lymphocyte counts and consequent development of opportunistic infections. Other rare, life-threatening, and even fatal toxicities associated with fludarabine therapy are hemolytic anemia and PRCA.^{2,3} Surprisingly, our case clearly illustrates that

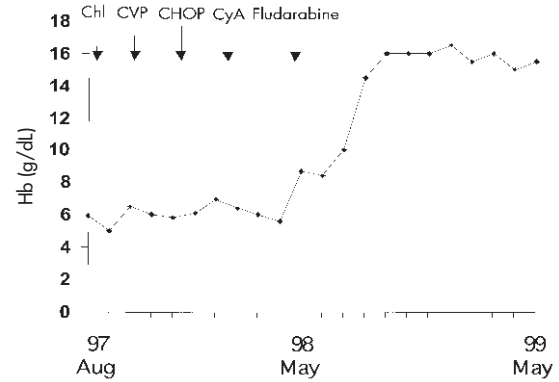


Figure 1. Clinical course of PRCA case treated by fludarabine therapy. Chl, chlorambucil; CVP, cyclophosphamide, vincristine, prednisone; CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; CyA, cyclosporin A.

fludarabine can be an effective and safe therapy for the induction of remission from refractory PRCA in patients with CLL. As far as we know, there has been only one other case report of a patient with CLL in whom refractory PRCA resolved after fludarabine treatment.⁴ It is unclear by what mechanism fludarabine might induce remission from PRCA in these patients with CLL. T-cell-mediated suppression of erythropoiesis appears to be the usual explanation for PRCA in patients with lymphoproliferative disorders.⁵ The fact that immunosuppressive therapies are sometimes effective provides support for the speculation that a reduction in cell-mediated immunity would be essential for inducing responses. Fludarabine can cause severe and prolonged immunosuppression. It produces a long-lasting depression of CD4⁺ lymphocyte counts.⁶ In addition, fludarabine but not cyclosporin A inhibits the cytokine-induced activation of STAT pathways (signal transducers and activators of transcription).⁷ We believe this profound cell-mediated immunosuppression is the best explanation for the response to fludarabine in our case of CLL and PRCA. Further studies are needed to confirm this hypothesis. Our experience suggests that it would be reasonable to use fludarabine to induce remission of PRCA for patients with CLL, at least in refractory cases. Additional reports of fludarabine in CLL-associated PRCA will be needed to be compiled to assess the safety of this treatment strategy further.

Sandra Serra, Esperanza Real, Emilio Pastor, Enric Grau

Department of Hematology, Hospital Lluís Alcanyis, Xativa, Spain

Key words

Fludarabine, chronic lymphocytic leukemia, pure red-cell aplasia

Correspondence

Enric Grau, M.D., Department of Hematology, Hospital Lluís Alcanyis, Ctra. Xativa-Silla, km 2, 46800 Xativa, Spain. Phone: international +34-96-2289595 – Fax: international +34-96-2289572 – E-mail: egrau@san.gva.es

References

1. Charles RJ, Sabo KM, Kidd PG, Abkowitz JL. The pathophysiology of pure red cell aplasia: implications for therapy. *Blood* 1996; 87:4831-8.
2. Weiss RB, Freiman J, Kweder SL, Diehl LF, Byrd JC. Hemolytic anemia after fludarabine therapy for chronic lymphocytic leukemia. *J Clin Oncol* 1998; 16:1885-9.
3. Leporrier M, Reman O, Troussard X. Pure red-cell aplasia with fludarabine for chronic lymphocytic leukemia. *Lancet* 1993; 342:555.
4. Jaccard A, Oksenhendler E, Clauvel J-P. Cytopenia and fludarabine. *Lancet* 1993; 342:1049.
5. Maung Z-T, Norden J, Middleton PG, Jack FR, Chandler JE. Pure red cell aplasia: further evidence of T cell clonal disorder. *Br J Haematol* 1994; 87:189-92.
6. Wijermans PW, Gerrits WBJ, Haak HL. Severe immunodeficiency in patients treated with fludarabine monophosphate. *Eur J Haematol* 1993; 50:292-6.
7. Frank DA, Mahajan S, Ritz J. Fludarabine-induced immunosuppression is associated with inhibition of STAT1 signaling. *Nature Med* 1999; 5:444-7.

Inappropriate secretion of antidiuretic hormone as the initial sign of central nervous system progression of nocardiosis in a patient with chronic lymphocytic leukemia

Sir,

Nocardiosis is a relatively rare infection caused by aerobic actinomycetes of the genus *Nocardia*. Nocardiosis occurs mainly in immunocompromised hosts as an opportunistic infection; pulmonary infection is the general form of presentation.¹ The infection, however, frequently disseminates to distant sites, especially the central nervous system (CNS) but the onset of CNS invasion can be silent for months or even years.^{1,2}

A 52-year old woman was diagnosed in early 1993 as having Binet stage II classic B-cell chronic lymphocytic leukemia (CLL). She was treated with chlorambucil and prednisone for six months. CLL progressed very slowly, but she refused further therapy. In July 1998 she was admitted to hospital because of a four-day history of dyspnea and fever. Physical examinations and chest X-rays revealed a massive right pleural effusion with bilateral alveolar condensation. An aerobic actinomycetes later identified as *N. asteroides* was isolated from her sputum. No antimicrobial susceptibility tests were performed and treatment with imipenem (500 mg every 6 hours) plus amikacin (500 mg every 12 hours) was started. A thoracic CT scan showed a solid alveolar condensation in the right upper lobe of the lung with signs of extensive central cavitation (Figure 1). Within five days her clinical condition dramatically improved. However, twenty-five days later the patient developed drowsiness, a change in character and visual hallucinations. Her blood chemistry showed plasma sodium of 120 meq/L (normal >138 meq/L); plasma osmolality

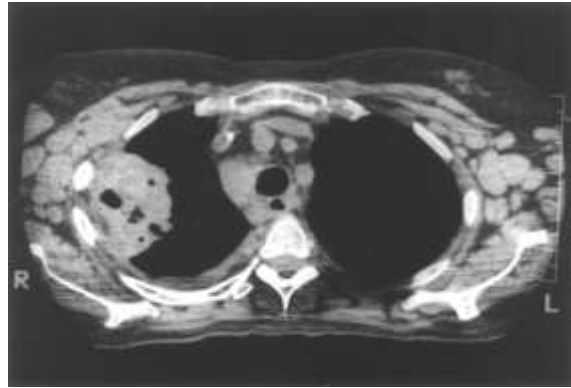


Figure 1. Thoracic CT scan shows an alveolar infiltrate in the right upper lobe with various areas of cavitation.

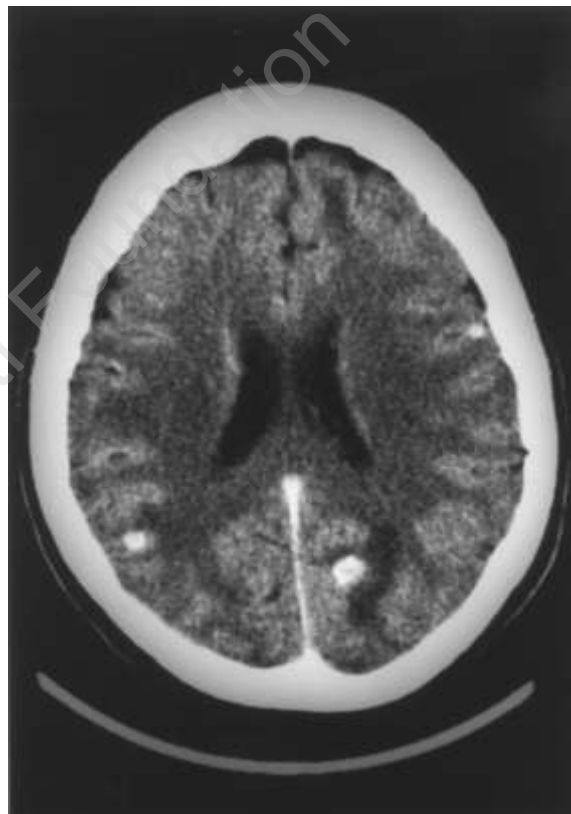


Figure 2. Brain CT scan shows several nodular lesions suggestive of brain abscesses.

was 259 mosm/L (normal >300 mosm/L) with concomitant high urinary osmolality of 347 mosm/L. These findings were consistent with the diagnosis of inappropriate secretion of antidiuretic hormone (SIADH); pharmacological causes of this syndrome were excluded. A cranial CT scan showed multiple bilateral hypodense lesions with ring-shaped enhancement following the administration of intravenous contrast (Figure 2) highly suggestive of intracranial abscesses. The antibiotic treatment was changed to meropenem