

Correspondence

JA Garcia Vela, Department of Hematology, Hospital Universitario de Getafe, Carretera de Toledo km 12,500, Madrid 28905, Spain. Phone: international +34-91-6839360, ext 2049 • E-mail: javela@ran.es

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Effect of cyclosporin-A on anemia in idiopathic myelofibrosis

ANTONIETTA FALCONE, PELLEGRINO MUSTO,
MARIO CAROTENUTO

Division of Hematology, IRCCS "Casa Sollievo della Sofferenza",
San Giovanni Rotondo, Italy

The recent report of Pietrasanta *et al.*,¹ described an improvement of anemia in a case of idiopathic myelofibrosis (IMF) treated with cyclosporin-A (CyA) for psoriatic skin lesions.

We have also used CyA in four IMF patients, all with transfusion dependent anemia. We report briefly the clinical aspects, hematological parameters and responses to the treatment for every patient.

Case #1. A 61-year-old female with diagnosis of IMF, pathologic stage III, low risk according to the

LILLE scoring system, became transfusion dependent 62 months after diagnosis. Before use of CyA blood test results were: median levels Hb 7.9 g/dL (range 7.1-8.7), WBC $15 \times 10^9/L$, Plt $624 \times 10^9/L$, reticulocytes 3.7%, sEPO 8.2 mIU/mL (vn 4-25), Coombs D/I negative, ratio CD4/CD8 1.1. The patient was treated with hydroxyurea (HU) and had received splenic irradiation 6 months previously. A median of 2 packaged red blood cell units was needed monthly. The treatment with CyA (200 mg/day) was performed for 4 weeks: no response was observed.

Case #2. A 65-year-old male with IMF, pathologic stage III, intermediate risk, needed 7 packaged red blood cell units monthly, he became transfusion dependent 29 months after diagnosis. Median levels Hb 5.4 g/dL (range 4.6-6.7), WBC $13 \times 10^9/L$, Plts $26 \times 10^9/L$, reticulocytes 4.7%, sEPO 13.4 mIU/mL, ratio CD4/CD8 0.6. The patient received hydroxyurea (HU). The treatment with CyA (200 mg/day) was performed for 12 weeks, but the hemoglobin level and the transfusional support remained invariable.

Case #3. A 57-year-old female afflicted by IMF, pathologic stage II, intermediate risk, was treated with recombinant human erythropoietin (4000 U/ three times weekly) and HU for 2 years, with improvement of Hb levels (Hb > 10 g/dL). After the loss of response to EPO, the Hb was 6.7 g/dL, reticulocytes 1.9%, sEPO 1496 mIU/mL, and transfusional support was need. CyA (200 mg/day) was administered for 6 weeks, without any effect.

Case #4. A 66-year-old male, 2 months after diagnosis of IMF (pathologic stage I) developed a pure red cell aplasia (PRCA). Blood test results were Hb 4.5 g/dL, WBC $21 \times 10^9/L$, Plt $342 \times 10^9/L$, reticulocytes 0.5%, sEPO 15 mIU/mL, Coombs D/I negative, ratio CD4/CD8 0.9. The treatment with CyA was performed for 12 weeks, without response. Considering the level of sEPO inadequate for the degree of anemia, r-EPO (10,000 U/three times weekly) was associated to CyA for another 10 weeks. Again the treatment failed.

In all our cases, the use of CyA was ineffective. The report by Centenara *et al.*² described a reduction of transfusional support in 4 out of the 7 IMF patients available for evaluation. No other reports on the efficacy of CyA in IMF have been published. Immunologic abnormalities described in IMF^{3,4} and the positive action of CyA on certain types of anemia (PRCA during lymphoproliferative disorders) could justify the use of CyA. Nevertheless, the need to clarify the role of immune mechanisms in the pathogenesis of IMF and then perform further investigations about the use of immunosuppressive agents in selected patients are essential.

Correspondence

Antonietta Falcone, MD, Divisione di Ematologia IRCCS "Casa Sollievo della Sofferenza", 71013 San Giovanni Rotondo, Italy. Phone: international +39-0882-410539 • Fax: international +39-0882-411705.

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Splenic peliosis with spontaneous splenic rupture in a patient with immune thrombocytopenia treated with danazol

F. JAVIER PEÑALVER, NIEVES SOMOLINOS, CONCEPCIÓN VILLANUEVA,* JORGE SÁNCHEZ, DOLORES MONTEAGUDO, RICARDO GALLEGO

*Department of Hematology and *Department of Pathology, Hospital de Móstoles, Madrid, Spain*

We present a 79-year-old man diagnosed with immune thrombocytopenia (ITP), treated with danazol, who died as a result of a spontaneously ruptured spleen. The histopathological diagnosis was splenic peliosis. This patient presents a chronological association between the treatment with danazol and the development of peliosis, which suggests a clear cause-effect relationship. Facing an individual patient with ITP, clinicians should weigh the potential benefits of danazol with the possible development of serious complications, such as hepatic failure or splenic rupture due to peliosis.

Peliosis is an ectasial vascular process, characterized by the presence of blood-filled cavities in the parenchyma of the liver or spleen.^{1,2} Isolated splenic peliosis is rare.³ The liver is the most frequently affected organ, and most of the reported cases have been incidentally discovered in autopsies³ relating to tuberculosis⁴ and hematological malignancies.^{3,5} Recently, cases of patients treated with anabolic corticosteroids, with or without steroids, as well as Rickettsia-like organisms in HIV-infected patients have been reported. Peliosis may be asymptomatic, or may be responsible for hepatic failure or life-threatening intraperitoneal bleeding.^{4,5}

Danazol is a synthetic androgen used in the treatment of ITP.⁶ The response rate of ITP to danazol is variable.⁷ It may exhibit synergic action with steroids, which are considered standard initial treatment of ITP, reduces the need for steroids and may even replace them once remission has set in. Danazol is a

well-tolerated drug. However, some unfavorable effects have been described.^{6,7} More significantly, danazol is regarded as a potential cause of hepatic injury, including cholestatic hepatitis, peliosis and neoplasia.^{4-6,8}

We present a 79-year-old male patient diagnosed with ITP in July of 1994 (8×10^9 platelets/L). Initially, he was treated with non-specific gammaglobulins (25 g/day, 5 days) with a favorable response (239×10^9 platelets/L). Later he developed a new episode of severe thrombocytopenia (19×10^9 platelets/L), and treatment with prednisone (1 mg/kg/day) was started, with response after three weeks of treatment (160×10^9 platelets/L). Steroid-related effects developed thereafter (diffuse osteoporosis, vertebral collapse, myopathy and behavior disorders) and the dose was therefore reduced (0.1 mg/Kg/day). In January, 1995, danazol was added to the treatment (400 mg/day) with gradual normalization of platelet count. This allowed the gradual tapering of steroids, which were discontinued in July, 1995 (214×10^9 platelets/L). Two months later the patient was admitted to hospital with acute abdomen. Ultrasonography showed evidence of hemoperitoneum and spleen rupture. An emergency splenectomy was performed. The patient developed multi-organ failure, dying 11 days after surgery. The histopathologic findings showed a ruptured spleen with extensive splenic peliosis. No liver biopsies were obtained.

Peliosis appears to be the general histopathologic expression of a wide range of agents capable of damaging viscera, particularly the liver and spleen. How peliosis develops is unclear. One hypothesis relates its appearance to sinusoidal barrier damage.⁴ In HIV patients with peliosis, treatment of the rickettsial infection resolved both the hepatosplenomegaly and also liver function test abnormalities, which suggests the possible reversibility of the injury.^{9,10}

Danazol has been said to play an etiologic role in peliosis development. Nesher⁵ and Makdisi⁴ have published two cases of patients with hepatosplenic peliosis who received danazol as treatment for ITP. Because the exposure to danazol in both patients was brief; these reports did not clearly demonstrate that danazol was the causal agent. However, it is probable that danazol could have had an additive or synergistic effect with other potential causes of peliosis like steroid therapy. The patient we present developed splenic rupture while being exposed to this drug, steroid treatment having been stopped three months before.

We feel that this report strongly suggests that danazol plays a main casual role in the development of splenic peliosis. It is tempting to speculate that the effects of steroids and danazol on endothelial function could converge not only in their therapeutic effect but also in the development of peliosis.

We think that the clinician must weigh the potential benefits of danazol with the possible development of serious complications, such as hepatic failure or