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Acquired Pure Megakaryocytic Aplasia Report of Two Cases With Long-Term Responses to Antithymocyte Globulin and Cyclosporine

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Acquired pure megakaryocytic aplasia is a rare disorder defined by severe thrombocytopenia with no other hematologic abnormalities and absent, or severely decreased marrow megakaryocytes. The etiology may be immune suppression of megakaryocyte development. Two patients are described who both responded rapidly to a combination of antithymocyte globulin and cyclosporine and who remain in remission 13–20 months after discontinuation of cyclosporine. This regimen is well described for treatment of aplastic anemia and may also be effective for acquired pure megakaryocytic aplasia. Am. J. Hematol. 62:115–117, 1999. © 1999 Wiley-Liss, Inc.

Key words: amegakaryocytic thrombocytopenia; megakaryocytic aplasia; antithymocyte globulin; cyclosporine

INTRODUCTION

Acquired pure megakaryocytic aplasia (APMA) is a rare disorder characterized by severe thrombocytopenia with no other hematologic abnormalities and the absence, or marked decrease, of marrow megakaryocytes. More commonly, patients with acquired amegakaryocytic thrombocytopenia have additional hematologic abnormalities such as macrocytosis or dyserythropoiesis, abnormalities which may predict progression to aplastic anemia or myelodysplasia [1–3]. APMA can be caused by a variety of pathogenetic mechanisms: acquired clonal cytogenetic abnormalities, viral infection, toxin exposure, drug sensitivity, or immune cytotoxicity caused by either antibodies or cell-mediated mechanisms [1]. Data suggesting an immune-mediated process [4] are supported by clinical observations of efficacy of immunosuppressive treatments, comparable to efficacy in patients with aplastic anemia or pure red cell aplasia. In aplastic anemia, intensive immunosuppression by using cyclosporine combined with antithymocyte globulin (ATG) or antilymphocyte globulin (ALG) has been shown to be more effective than either agent alone and is the standard treatment for patients who are not candidates for allogeneic bone marrow transplantation [5–7]. Since this regimen has not previously been described for the treatment of APMA and since mortality in case series is high [2,3], we now report two patients who have had dramatic responses and sustained remissions after treatment with cyclosporine and ATG.

CASE REPORTS

Case 1

LH is a 25-year-old previously healthy Native American male who presented on February 13, 1997 with generalized petechiae and gingival bleeding for 3 weeks. His platelet count was <5,000/μl; white blood cell count, hemoglobin concentration, and red cell mean corpuscular volume (MCV) were normal. Peripheral blood smear demonstrated no abnormalities of white cells or red cells. Physical examination was normal except for purpura. Bone marrow aspirate and biopsy obtained on February 14 demonstrated absent megakaryocytes with no other abnormalities. Laboratory evaluations were normal or negative, including serum chemistries, vitamin B_{12}, folic

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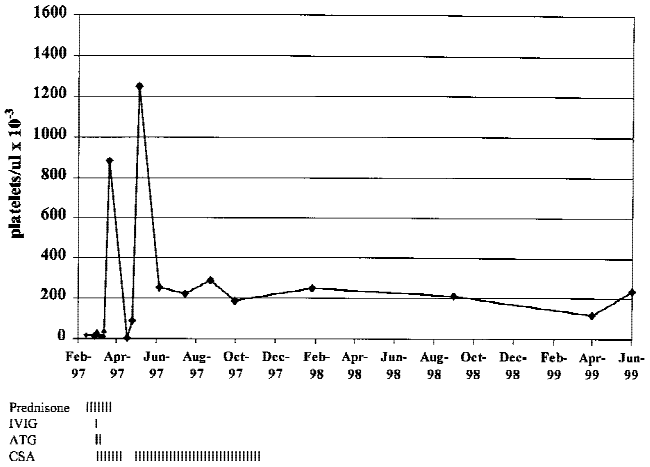

Fig. 1. Clinical course of Case 1, LH, a 25-year-old man with APMA. Prednisone, 1 mg/kg/day, was begun at diagnosis on February 13, 1997. IV Ig, 1 gm/kg for 2 days was given on February 27 and 28. ATG and cyclosporine A (CSA) were begun on March 4: ATG, 37.5 mg/kg/day for 8 days; CSA, 6 mg/kg twice daily. CSA was stopped in October, 1997. The most recent evaluation was June 21, 1999.

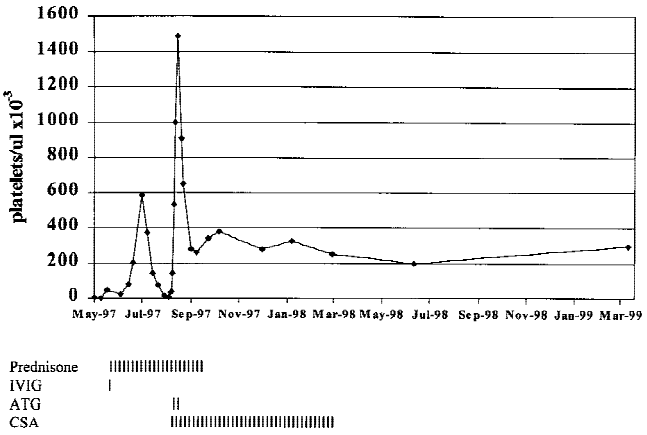

Fig. 2. Clinical course of Case 2, LA, a 47-year-old woman with APMA. Prednisone, 1 mg/kg/day, was begun at diagnosis on May 15, 1997, and IV Ig, 1 g/kg, was also given on May 15. ATG and CSA were begun on August 15, 1997: ATG, 37.5 mg/kg/day for 8 days; CSA, 6 mg/kg twice daily. CSA was stopped in March 1998. The most recent evaluation was March 24, 1999.

acid, HIV, ANA, heavy metal screen, and an acid hemolysis test. He was treated initially with prednisone, 1 mg/kg daily, with no improvement of his thrombocytopenia after 2 weeks (Fig. 1). Karyotype was normal on a repeat bone marrow aspirate done on February 27. IV Ig was administered at 1 g/kg/day on February 27 and 28 without response. Beginning March 4 he was treated with ATG, 37.5 mg/kg IV for 8 days, and cyclosporine A, 6 mg/kg orally twice daily [5]. He also received methylprednisolone, 5 mg/kg, before each dose of ATG for prevention of serum sickness [5]. Thrombocytosis occurred within 2 weeks. He did well until April 15, 1997 when he returned with 2 days of gross hematuria and was found to have a platelet count of 2,000/μl after having been off cyclosporine for 2 weeks. His cyclosporine was resumed with platelet recovery in 6 days, reaching a platelet count over 1,200,000/μl in 2 weeks. Cyclosporine was continued for 6 months and discontinued in October, 1997, after being tapered for 1 month. His platelet count remained normal off all therapy for 12 months after cyclosporine was stopped. His most recent platelet count, on June 21, 1999 was 238,000/μl with otherwise normal blood counts, normal MCV, and normal peripheral blood smear.

Case 2

LA is a 47-year-old Native American female who presented on May 15, 1997 with excessive bleeding following a tooth extraction. She was discovered to have a platelet count of 6,000/μl; white blood cell count, hemoglobin concentration, and MCV were normal. Peripheral blood smear demonstrated no abnormalities of white cells or red cells. Her medical history was remarkable for asthma for which she used theophylline, aerosolized albuterol, and aerosolized steroids. Physical examination was normal except for purpura. Bone marrow aspirate and biopsy demonstrated absent megakaryocytes with no other abnormalities. Laboratory data were normal or negative, including serum chemistries, vitamin B_{12}, folic acid, ANA, and thyroid function studies. She was treated with prednisone, 1 mg/kg daily, and IV Ig 1 g/kg on May 15, with return of her platelet count to normal. However, in August 1997 her thrombocytopenia relapsed when prednisone was tapered with symptoms of epistaxis and petechiae. Repeat bone marrow aspirate and biopsy again demonstrated absent megakaryocytes on the aspirate (one megakaryocyte was seen on the biopsy) with no other abnormalities. On August 15 she was treated with ATG and cyclosporine (same regimen as Case 1 [5]) with a rapid increase in her platelet count. Her therapy was complicated by cyclosporine-induced hepatitis requiring discontinuation for 1 week, but no further elevation in liver enzymes was noted following reintroduction of cyclosporine. Cyclosporine was tapered over 6 months and discontinued in March 1998. Her platelet count has remained normal off all therapy for 13 months after cyclosporine was stopped.

DISCUSSION

Amegakaryocytic thrombocytopenia is rare and its clinical course is variable. In some patients it is a prodrome to aplastic anemia or myelodysplasia; most of these patients present with other hematologic abnormalities, such as macrocytosis or dyserythropoiesis [1–3].

Patients who present without other hematologic abnormalities, described as acquired pure megakaryocytic aplasia, are even less common; these patients may have immune suppression of megakaryocyte development and platelet production [4] and may therefore respond to immunosuppressive treatment. Standard immunosuppressive therapies for immune thrombocytopenic purpura, such as steroids, IV Ig, and splenectomy, are often unsuccessful in patients with APMA [2]. More intensive immunosuppression with ATG and cyclosporine is effective in patients with aplastic anemia [5–7]. ATG and cyclosporine have both been reported to be effective in APMA as single agents in four and two patients, respectively [1–3], but failures of ATG [3,8] and cyclosporine [1,9] have also been reported. With these previous treatments, mortality in amegakaryocytic thrombocytopenia remains high [2,3].

Our two patients demonstrate that treatment of APMA with a combination of cyclosporine and ATG can induce rapid and long-term remissions. A remarkable observation in both patients was the rapid development of extreme thrombocytosis following initiation of treatment. This is reminiscent of the dramatic reticulocytosis that may occur after successful immunosuppressive treatment of pure red cell aplasia. [10].

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