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A Patient with Mixed Type Evans Syndrome: Efficacy of Rituximab Treatment

Mixed type Evans syndrome is a very rare hematologic disease. Although mixed type Evans syndrome may initially respond well to steroids, this disease usually runs a chronic course with intermittent exacerbations. We describe here a 46-yr-old female with the steroid-refractory, mixed type Evans syndrome, and she had a prompt response to rituximab. She was diagnosed as having the mixed type Evans syndrome with the clinical features of symptomatic anemia, jaundice and thrombocytopenia. Prednisone therapy was commenced and her hemoglobin and platelet level returned to the normal. However, after 15 weeks, she relapsed with hemolytic anemia and thrombocytopenia. We started rituximab at the dose of 375 mg/m^2 once weekly for a total of 4 doses, which was well-tolerated and this induced the normalization of hemoglobin, bilirubin and lactic dehydrogenase, and there was also a significant increase of the platelet count.

Key Words : *Mixed Type Evans Syndrome; Anemia, Hemolytic; Thrombocytopenia; Steroids; rituximab*

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INTRODUCTION

Patients with mixed type Evans syndrome are very rarely seen and it is difficult to manage them. Although mixed type Evans syndrome may initially respond well to steroids, it usually runs a chronic course with intermittent exacerbations (1, 2). Rituximab, a chimaeric monoclonal antibody against CD20 that depletes B cells in the circulation and in lymphoid tissues, has shown efficacy for the treatment of CD20-positive lymphoproliferative disorders. The pathogenetic mechanism of autoimmune cytopenias is complex and B cells play a crucial role in the pathogenesis of these disorders so that this agent Rituximab has also been used with good success for patients with autoimmune disease, including immune thrombocytopenic purpura, autoimmune hemolytic anemia and the other types of immune disease (3-6). We report here on a patient with the mixed type Evans syndrome who had a prompt response to rituximab.

CASE REPORT

In July 2004, a 46-yr-old Korean woman was diagnosed with mixed type Evans syndrome following her hospital admission because of the symptomatic anemia, jaundice and thrombocytopenia. The laboratory tests showed: Hemoglobin, 4.1 g/dL; reticulocytes, 12.6%; WBC, 3,030/μL; platelets, 89,000/μL; and elevated levels of indirect bilirubin (2.53 mg/dL) and lactic dehydrogenase (LDH; 1,499 IU/L). Her initial direct antiglobulin test was positive for complement (C3d) and IgG. In addition, the patient's serum contained a cold hemagglutinin that had high thermal amplitude. The serologies for HIV, EBV, CMV, hepatitis B and C viruses, and *Mycoplasma pneumoniae* were all negative. Rheumatoid factor, antinuclear antibodies, anti-double stranded DNA antibodies and lupus anticoagulant were undetectable. Prednisone therapy was started at a dose of 1 mg/kg/day. The hemoglobin level and platelet count rose to 11.7 g/dL and 356,000/μL, respectively. Fifteen weeks later (December 2004), the prednisone was tapered to a maintenance dose of 10 mg daily. She relapsed with hemolytic anemia (5.9 g/dL) and thrombocytopenia (9,000/μL). Despite retreatment of high dose steroid, she never achieved any response. Rituximab was started at the dose of 375 mg/m^2 once a week for a total of 4 doses, and this was well-tolerated and it induced a normalization of hemoglobin, bilirubin and LDH, as well as inducing a significant platelet count increase. The hemoglobin increased to 13.2 g/dL on day 56 and the platelet count increased to 30,000/μL by day 12 after the first rituximab infusion. She subsequently entered a durable remission with her hemoglobin level in the range of 13.2-14.7 g/dL and her platelet count in the range of 32,000-42,000/μL; she has maintained this remission now for 6 months (Fig. 1).

DISCUSSION

Mixed type Evans syndrome is a very rare hematologic dis-

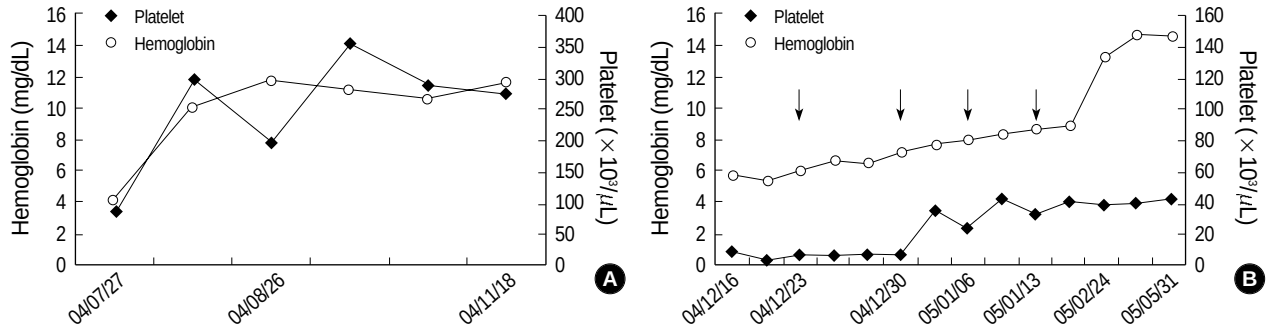

Fig. 1. Schematic representation of the platelet and hemoglobin level in the period from July 2004 until May 2005 (At December 16, 2004 the patient was relapsed). (A) Mixed Evans syndrome was diagnosed and successfully treated with prednisone. (B) After relapse, intravenous infusions of rituximab (375 mg/m²) were given once weekly for 4 consecutive weeks. Until 6 months of rituximab therapy, the patient was stable. Black arrows represent rituximab infusions.

ease. Steroid is the standard treatment for mixed type Evans syndrome. Additional treatment modalities, including splenectomy, intravenous immunoglobulin, vincristine or azathioprine, are used for the steroid-resistant or relapsing cases. However, these treatment options are often unsuccessful and they may be associated with serious side effects (1, 2). Rituximab was approved for the treatment of B-cell lymphomas, and this drug has emerged as a promising treatment for idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia (AIHA), including Evans syndrome and mixed AIHA. The response rates have ranged from 25% to 100% (3). The administration of rituximab causes depletion of B cells expressing the surface antigen CD20. The mechanism of cellular killing is thought to be secondary to the antibody-dependent cellular toxicity and complement activation. Suppression of autoreactive B cells may explain the sustained response attained when using rituximab for the treatment of lymphomas and autoimmune diseases (3). In the three previous reports on rituximab treatment for the mixed type AIHA, including one case of mixed type Evans syndrome, all the patients had successful resolution of their hemolytic anemia (4-6). Our patient responded promptly and had a sustained response, and any rituximab related side effects were not observed.

In conclusion, a decision to initiate rituximab early in the course of mixed AIHA with/without immune thrombocytopenia is a reasonable treatment option if the syndrome is refractory to steroid treatment.

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