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Short communication

Long term remission with 6-Mercaptopurine in refractory Evan's syndrome

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The management of Evan's syndrome remains a challenge and innovative approaches are needed. Initial therapeutic failure, relapses after initial response and refractoriness to treatments are typical. Options for second-line therapy include immunosuppressive drugs, especially cyclosporin or mycophenolate mofetil; vincristine; danazol or a combination of these agents. We report here a long-term remission of Evan's syndrome obtained with 6-mercaptopurine in a 35-year-old female patient.

Key words: 6-Mercaptopurine, Evan's syndrome, remission.

INTRODUCTION

Evan's syndrome (ES) is a rare and severe hematological disease although the exact frequency is unknown. ES is defined by the simultaneous presentation of autoimmune haemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP) in the absence of known etiology. These conditions may appear concomitantly or one may precede the other by several months (Norton and Roberts, 2006). The management of ES therefore remains a challenge and innovative approaches are needed. Many approaches exist, and because all have some efficacy, treatments tend to be physician or center specific. Choices for severe and refractory disease include combination strategies, vincristine, cyclosporine, splenectomy, cyclophosphamide and rituximab (Bennett et al., 2006). We report a case of long-term remission of ES obtained with 6-mercaptopurine.

CASE REPORT

A 35-year-old Moroccan female was referred to department of Hematology, Ibn Tofail Hospital, in Marrakech because of symptomatic anemia and thrombocytopenia in May, 2010. She had been in her usual good health until four months prior to her hospitalization when she started to suffer from fatigue and progressive loss of 3 kg of two months duration. She denied any alcohol or tobacco use. There was no family history of haematological disease. Physical examination revealed that the patient was moderately nourished. The temperature was 36.5°C, the pulse was 96/min, the blood pressure was 120 /80 mmHg, and respirations were 22 /min. No icterus, skin rashes, or petechiae were present. She had no jugular vein distension. Peripheral lymphadenopathy was not observed. She had no thoracic malformations or tenderness and her heart examination was normal. The abdominal examination was normal. No hepatosplenomegaly was noted. The vertebral column and joints of the extremities were normal. No positive nervous system signs were found.

Laboratory investigations showed haemoglobin of 8 (normal range 12 to 16) g/dl, mean cell corpuscular volume (MCV) of 83 (80 to 98) fl, white cell count of 3,900 /L (4,000 to 10,000 /L) and platelets of 13,000 /L (150,000 to 300,000 /L). The bleeding time and coagulation time were normal. Erythrocyte sedimentation rate was 20 (0 to 16) mm/h and C-reactive protein was 6 (0 to 5) mg/L. The lactate dehydrogenase was 400 U/L (200 to 400) and reticulocytes 280 G/L. Ferritin level were low. The direct Coombs' test was negative, but the antibody screening test for the RBC was positive and the total bilirubin was increased. Peripheral blood film examination to determine red blood cells morphology (polychromatosia, spherocytes) and to exclude other underlying diagnoses (malignancies, microangiopathic hemolytic anemia) was normal. A bone marrow examination revealed an increased number of megakaryocytes, without any evidence of dysplastic changes in hematopoietic components or pathologic medullary infiltration, which was consistent with the bone marrow

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characteristics of ITP. The serologies for human immunodeficiency virus (HIV), hepatitis B and C viruses were all negative. Rheumatoid factor, antinuclear antibodies, anti-double stranded DNA antibodies and lupus anticoagulant were undetectable. Chest-X ray, abdominal and pelvic ultrasound scans were normal.

Prednisone therapy was started at a dose of 1 mg/kg/day in order to control the acute, symptomatic cytopenias. The haemoglobin level and platelet count increased to 10.8 g/dL and 256,000 /L, respectively. Two months later, the prednisone was tapered to a maintenance dose of 10 mg daily. She relapsed with hemolytic anemia (6.1 g/dl) and thrombocytopenia (5,000 /L). A direct Coombs test proved positive. Thus, we diagnosed her with Evans syndrome. Although treatment with high dose of steroids was initiated, her platelet counts remained extremely low, and her hemorrhagic diathesis was getting worse. Transfusions of platelet concentrate produced only transient and minimal responses. 6-Mercaptopurine (6MP) was started at the dose of 100 mg per day and this was well-tolerated and it induced a normalization of LDH, bilurubin and hemoglobin, as well as inducing a significant platelet count increase: The hemoglobin increased to 11.9 g/dl on day 28 and the platelet count increased to 50,000 /L. She subsequently entered a remission with her hemoglobin level in the range of 12.6 to 14 g/dL and her platelet count in the range of 70,000 to 150,000 /L. Her physical and hematological recovery was normal and she was discharged from hospital in a state of very good partial response. The dosage of 6MP was successfully reduced (to 50 mg/day). After 8 months of further medical treatment, this patient is currently in remission.

DISCUSSION

First-line therapy in ES is usually corticosteroids and/or intravenous immunoglobulin, to which most patients respond; however, relapse is frequent. The syndrome is characterised by periods of remission and exacerbation and response to treatment varies even within the same individual. There have been no randomised-controlled trials in ES and the few trials of treatment regimens contain small numbers of patients. Options for second-line therapy include immunosuppressive drugs, especially cyclosporin or mycophenolate mofetil; vincristine; danazol or a combination of these agents. The choice of which second-line agent to use depends upon clinical criteria, particularly the age of the patient, severity of the disease and its natural history because all of these treatments have significant short- and long-term side effects. To the best of our knowledge, long-term treatment of Evan's syndrome with 6-mercaptopurine (6MP) has been reported only in few cases (Lyu et al., 1986).

The pathophysiology of ES is also elusive, partially owing to the overlap of clinical characteristics with other autoimmune disorders. Nevertheless, current improvement in cytogenetic testing and molecular biology promises to shed light on the diagnostic criteria for ES. There is a suspected alteration in cellular and humoral immune function in patients with ES. A decreased number of T-lymphocytes have been described, as well as abnormal CD4/CD8 ratios, even after therapeutic interventions (Avcin et al., 2003). 6MP, a purine anti-metabolite, was developed in the 1950s as a chemotherapy agent along with thioguanine and the anti-folate metabolites. Because of its immunosuppressant effects, as a suppressor of both B and T lymphocytes, it was tried in the 1960s as a treatment for AIHA and ITP, and found to have activity (Schwartz and Dameshek, 1962).

A potential challenge to our interpretation of this case is that in disorders such as ES, which wax and wane spontaneously, it is difficult to confirm that an improvement in hematologic parameters is due to any specific treatment and is not a coincidental spontaneous remission.

Our case, along with those of other studies (Sobota et al., 2009), suggests that 6MP deserves early consideration as salvage therapy for immune cytopenias that are refractory to corticosteroid treatment. Sobota et al reviewed retrospectively 29 children with ITP, AIHA or ES treated with 6MP from 2000 to 2007. The authors found an overall response rate of 83% among all patients. Fourteen percent of patients stopped drug because of side effects (Sobota et al., 2009).

Given the rarity of this syndrome, further prospective trials in larger series of patients are needed to confirm the efficiency of this treatment, to assess its long-term safety, and to identify predictive factors of response to 6MP.

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