Revista Brasileira de Hematologia e Hemoterapia
Brazilian Journal of Hematology and Hemotherapy
www.rbhh.org

Original article

Experience with Evans syndrome in an academic referral center

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ARTICLE INFO

Article history:
Received 9 December 2014
Accepted 14 February 2015
Available online 28 March 2015

Keywords:
Autoimmune hemolytic anemia
Thrombocytopenia
Neutropenia
Evans syndrome
Rituximab

ABSTRACT

Objective: To document the experience of one referral service with patients diagnosed with Evans syndrome, the treatment and response and to briefly review current treatment strategies and results.

Methods: Patients enrolled in this study fulfilled criteria for Evans syndrome. Data were retrieved from the clinical files and electronic databases of the Department of Hematology, Hospital Universitario "Dr. José Eleuterio González". Treatment modalities and response and the use of additional therapies were evaluated. The literature was reviewed in the context of the clinical course of the studied patients.

Results: Six patients were diagnosed with Evans syndrome in the study period. Patient 1 was treated with steroids, relapsed twice and was again treated with steroids. Patient 2 treated initially with steroids plus intravenous immunoglobulin was subsequently lost to follow-up. A good response was achieved in Patients 3 and 4, who were treated with steroids plus rituximab; patient 4 also received danazol as a second-line therapy. However both relapsed and subsequently underwent splenectomy at ten and nine months, respectively. One patient, number 5, treated with steroids, danazol and rituximab did not relapse within four years of follow-up and Patient 6, who received steroids plus danazol did not relapse within three years of follow-up.

Conclusion: Evans syndrome is an uncommon hematologic condition rarely diagnosed and not widely studied. Clinicians must have it in mind when evaluating a patient with a positive direct antiglobulin test, anemia and thrombocytopenia, since prognosis depends on its early recognition and opportune therapy, but even this leads to variable results.

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http://dx.doi.org/10.1016/j.bjhh.2015.03.002

Introduction

Evans syndrome is a rare autoimmune disorder characterized by simultaneous or sequential presence of a positive anti-globulin test, autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP).[1] It is characterized by frequent exacerbations and remissions within a chronic course. Evans syndrome was first described in 1951[2] and it is recognized as a poor prognostic factor in autoimmune cytopenias.[3] It is a rare disorder diagnosed in 0.8% to 3.7% of all AIHA or ITP cases.[1] Its etiology and cause are unknown, but alterations in immune regulation mechanisms are documented.

This syndrome can be classified as primary or idiopathic when there is no associated disease, and secondary when it is associated with other autoimmune diseases, such as systemic lupus erythematosus (SLE), primary antiphospholipid syndrome, Sjögren syndrome, IgA deficiency, Hodgkin's disease and chronic lymphocytic leukemia.[4] The diagnosis is made by exclusion of other pathologies, including infectious processes and malignant and autoimmune diseases. It presents with bicytopenia, which can coincide or occur separately or sequentially. After the appearance of the first cytopenia, the second may occur months to years later, which can delay diagnosis.[5,6]

Management of Evans syndrome remains a challenge. Response to treatment varies even within the same individual. Indications for treatment have not been established by evidence-based studies,[5] in part due to the low frequency and heterogeneous nature of the disease. The first-line treatment for Evans syndrome is corticosteroids with or without intravenous immunoglobulin (IVIG).[7] The range of options for second-line treatment includes immunosuppressive agents, the monoclonal antibody rituximab, chemotherapy or a combination of these agents. However, only a small percentage of patients achieve complete remission and these drugs have numerous side effects.[8] Splenectomy may also be considered a second-line treatment. The majority of patients will respond to first or second-line therapy modalities, sometimes for several years. However, for patients with severe relapsing disease despite second-line therapy, other options have to be considered. The main third-line options are cyclophosphamide, alemtuzumab or stem cell transplantation.[5]

There is very limited information available in the literature regarding this infrequent syndrome; therefore we decided to present and discuss six cases diagnosed in our hospital over six years in order to call the attention of the physician to the importance of considering this disease when confronted with a patient exhibiting clinical and laboratory features compatible with Evans syndrome.

Methods

This study was performed in accordance with the ethical standards of the Helsinki Declaration, including the provisions for patient informed consent. The Review and Ethics Committee of the institution approved the study.

The six patients included in this report were diagnosed between 2007 and 2012. All patients presented with AIHA and a positive direct antiglobulin test plus ITP. Clinical presentation included the usual features of hemolytic anemia: pallor, lethargy, jaundice, thrombocytopenia, petechiae, bruising and mucocutaneous bleeding.

There are no guidelines established for management of Evans syndrome, thus, for the purpose of this report, response was defined as resolution of all clinical symptoms and increase or no further decrease in both, platelet count and hemoglobin concentration. Relapse was considered to exist when patients presented with the same or similar clinical symptoms and laboratory data, including a positive direct antiglobulin test.

Results

Patient characteristics

Data of six patients, four women (66.64%) and two men (33.32%), fulfilling the diagnostic criteria of Evans Syndrome were retrieved from the clinical files and electronic databases (Table 1). Median age at diagnosis was 24 years. Both cytopenias occurred simultaneously in all cases. No cases of autoimmune neutropenia at diagnosis or during the clinical course were observed. Evans syndrome was considered idiopathic in one patient (16.6%) and was associated with one or more underlying diseases in the other five patients (83.4%; Table 1).

The complete blood count at diagnosis showed remarkable alterations (Table 2), including platelet counts ranging from 2.33 to 13.1 $\times$ 10^9/L (median: 5.8 $\times$ 10^9/L); hemoglobin concentration at presentation varied from 6.1 to 10.7 g/dL (median: 6.9 g/dL), the Mean corpuscular volume was within the normal range (76.2 to 101 fL), but the red cell distribution width varied widely from 17.1 to 25.6% (median: 20%) reflecting the abundant presence of reticulocytes which ranged from 6.8 to 23.1% (median: 9.8%). Accordingly, indirect bilirubin concentration was increased in almost every case (median: 1.5 mg/dL), and lactate dehydrogenase (LDH) values varied between 295 and 554 U/L (median: 426.5 U/L), reflecting the ongoing active hemolysis. The presence of anemia at variable degrees with hemolytic characteristics, including a high level of LDH and/or indirect bilirubin, with a repeatedly positive direct antiglobulin test and thrombocytopenia led to the diagnosis of Evans syndrome in all six patients.

Detailed information regarding clinical presentation, treatment and evolution, as well as relapses and their therapy is shown in Table 3. Patient 1 was the only case in which steroids were successfully used as both first-line treatment and during relapses without additional medications; in all the remaining five cases a combination of therapies was needed to achieve response. Response times, as days needed for the increase in hemoglobin concentration and platelet count to take place, are shown in Table 3. Patients were discharged at a median of nine days (range: 3–12 days).

Follow-up and relapses

Relapse was diagnosed when patients presented with same or similar symptoms as baseline and the simultaneous or sequential presence of a positive anti-globulin test,