Revista médica del
Hospital General de México

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CLINICAL CASE

Evans syndrome: A purpose of a case

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Abstract

Evans syndrome is a very rare disorder in medical practice that can be both idiopathic and secondary to another underlying pathology. It is a clinical manifestation of autoimmune hemolytic anemia (AIHA) that can be simultaneous or subsequent to autoimmune thrombocytopenia (AITP). Sometimes, it can be accompanied by autoimmune neutropenia. It is estimated that 0.8-4% of patients with ITP or AIHA suffer from this syndrome. The case of a 32-year-old female patient with a history of systemic lupus erythematosus is described, who was admitted at the emergency unit of our hospital, presenting symptoms of asthenia, adynamia, and hyporexia.

Key words: *Evans syndrome. Autoimmune hemolytic anemia. Autoimmune thrombocytopenia. Systemic lupus erythematosus.*

Introduction

Evans syndrome is a very rare disorder that is defined as the simultaneous or sequential presentation of autoimmune hemolytic anemia (AIHA) plus autoimmune thrombocytopenia (AITP) and/or autoimmune neutropenia, with a positive direct Coombs test, in case of a unknown underlying etiology[1]. Some patients may present symptoms of hemolytic anemia and later develop cytopenias within months or years

3 after the initial onset. It is estimated that approx. 15-30% of AIHAs that occur in children are due to Evans syndrome[2,3]. Compared to the onset of AIHA alone, Evans syndrome is more difficult to treat, tending to chronicity and relapses. In 50% of cases, it is associated with autoimmune systemic disease such as systemic lupus erythematosus (SLE), lymphoproliferative disease, or primary immunodeficiency[4]. The median age of presentation ranges from 55 to 77 years; however, there is no predominant sex ratio and it has been reported in all age groups.

A variety of immunoregulatory abnormalities has been described. Although, no specific abnormality has been identified. The generation of autoantibodies directed against specific antigens in each of the bloodlines with cross-reaction mechanisms seems to be the main pathophysiology mechanism[5]. Premature immunosenescence is a pathological mechanism that has been associated and may occur due to chronic immune stimulation, such as persistent viral infections[6]. In addition, genetic factors that favor premature differentiation and/or persistence of senescent immune cells could be a predisposing factor for autoimmunity, even in the absence of persistent infections. However, despite our greater molecular understanding, the question of whether genetic predisposition contributes to autoimmune cytopenia remains unresolved for most patients[7].

This is usually a chronic condition, which is characterized by frequent exacerbations and remissions. The clinical presentation includes the usual characteristics of hemolytic anemia: paleness, lethargy, jaundice, and heart failure in severe cases and thrombocytopenia: petechiae, bruises, and mucocutaneous hemorrhage[8]. Tests may reveal lymphadenopathy, hepatomegaly, and/

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Date of reception: 12-09-2019
Date of acceptance: 16-12-2019
DOI: 10.24875/HGMX.19000073

Available online: 21-04-2020
Rev Med Hosp Gen Mex. 2020;83(2):66-69
www.hospitalgeneral.mx

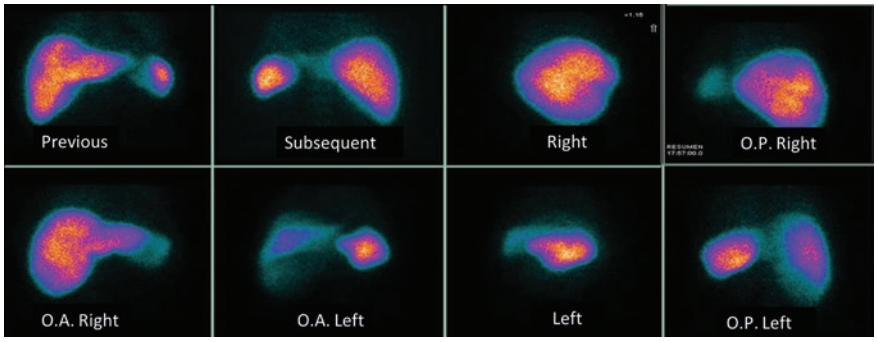

Figure 1. Liver and spleen scan (gammagraphy) with 99-mTc colloidal sulfide, which reported splenomegaly without focal lesions suggesting hypersplenism.

or splenomegaly. First-line therapy usually consists of corticosteroids and/or intravenous immunoglobulin (IVIg), to which most patients respond; however, relapse is frequent[9]. Options for second-line therapy include immunosuppressive drugs, especially cyclosporine or mycophenolate mofetil; vincristine; danazol; or a combination of these agents[10]. More recently, a small number of patients have been treated with rituximab, which induces remission in most cases, although such responses are often maintained for < 12 months and the long-term effects in children are unclear[11,12]. Splenectomy can also be considered, although long-term remissions are less frequent than in uncomplicated ITP[13]. For very severe and refractory cases, stem cell transplantation (SCT) offers the only possibility of long-term cure. The limited data available suggest that allogeneic SCT may be superior to autologous SCT, but both carry risks of severe morbidity and transplant-related mortality[14].

Clinical case

A 32-year-old female patient without a significant heredofamilial history and a medical history of SLE diagnosed in 2018 with the following serological profile: antinuclear antibodies by immunofluorescence: 1:1000, centromere pattern +; anti-SSA positive antibodies; antimitochondrial antibodies: positive; and anti-double stranded DNA antibodies: 48.4 UI/ml in treatment with azathioprine 50 mg orally every 12 h.

Clinical onset characterized by the presence of asthenia, adynamia, and hyporexia.

On admission to the emergency unit, the patient presented the following vital signs: blood pressure 110/60 mmHg, heart rate 90 beats/min, respiratory rate 18 breaths/min, and oxygen saturation rate (SpO_2) of 94%. During the physical examination, the patient was dehydrated and with pale teguments and mucous membranes.

Paraclinical exams were requested. They presented the following results: hemoglobin 8.9 g/dL, hematocrit 24.5%, mean corpuscular volume 103 fL, mean corpuscular hemoglobin 36 pg, platelets 8 103/mL, total bilirubin 2.15 mg/dL, direct bilirubin 0.3 mg/dL, indirect bilirubin 1.85 mg/dL, and lactic dehydrogenase 445 U/L. As part of the anemic syndrome approach, Vitamin B12, folic acid, and iron kinetics, that did not show any alterations, corrected reticulocytes count 3.4% and a direct positive Coombs test was also performed.

Regarding medical imaging exams, a liver and spleen scan (gammagraphy) with 99-mTc colloidal sulfide was performed, which reported splenomegaly without focal lesions suggesting hypersplenism (Fig. 1).

Disease management was initiated with 1-g methylprednisolone intravenous (IV) every 24 h for 3 days. After completion of the treatment, platelet control was requested, which reported 10 103/mL. Thus, treatment continued with 6-g IV immunoglobulin (IVIg) by infusion pump and hydrocortisone 150 mg-75 mg-75 mg for 2 days, with a subsequent platelet count of 6×10^3/mL. This was the reason for adjusting corticosteroid administration to 12 mg dexamethasone IV. Given the inadequate response to such management, splenectomy was performed 3 days later. Hematic control biometrics was requested 2 weeks after the surgery, which reported the following: hemoglobin 13.4 g/dL, hematocrit 40.9%, mean corpuscular volume 96.7 fL, mean corpuscular hemoglobin 31.7 pg, and platelets 76×10^3/mL. With a final diagnosis of Evans syndrome, the patient was discharged with 12 mg dexamethasone-based management orally every 24 h, 50 mg azathioprine every 24 h, and 5 mg Folic acid every 24 h.

Discussion and conclusions

AITP and AIHA usually occur as distinct clinical entities. In the year 1951, Evans described a syndrome characterized by the combination of AITP and AIHA[1,2]. This association led him to postulate similar immune pathogenesis for both hemolytic anemia and thrombocytopenia. Even both entities usually occur in association with other autoimmune disorders, particularly SLE[3,4].

Three to sixteen percent of patients with SLE present with AITP as an initial manifestation of the disease and 20-25% of patients with AIHA develop AITP, while the evolution toward Evans syndrome is relatively uncommon in patients with AITP[5,6]. In different series, all patients presented with thrombocytopenia (100%) and only two of them (18%) had clinical evidence of autoimmune hemolysis during the initial onset[7]. This emphasizes the importance of performing a Coombs test in all patients who are diagnosed with AITP and during follow-up[8].

Evans syndrome is the manifestation of AIHA that can be simultaneous or subsequent to AITP and can sometimes be accompanied by autoimmune neutropenia[7,8]. According to its origin, it can be an idiopathic or secondary event; approximately 50% is of the first type and of the secondary group, 41% is associated with autoimmune diseases (more frequently with SLE), and 17% is associated with immunodeficiencies (usually due to common variable immunodeficiency) and lymphomas. Clinical manifestations include data on AIHA and AITP: paleness, lethargy, jaundice, heart failure (in severe cases), petechiae, bruises, and mucocutaneous hemorrhage, among others. Lymphadenopathy, hepatomegaly, and splenomegaly may also be reported. In addition, laboratory tests can detect polychromasia, spherocytes, reticulocytosis, unconjugated hyperbilirubinemia, and a decrease in haptoglobin and a positive direct Coombs test[9].

Although Evans syndrome is a blood disorder, which is related to several diseases of immunological origin, it is very common to find patients that present an onset of autoimmune disease with this syndrome, without any other clinical presentation that may suggest the diagnosis of SLE. Hence, we believe it is necessary to look for laboratory criteria for SLE, in those patients who have Evans syndrome[10].

Those patients who present with Evans syndrome associated with SLE generally have a chronic and relapsing clinical course, with a higher number of admissions. Hence, it is recommended that once this association is found, laboratory tests have to be performed more frequently than in those patients with SLE, solely to treat relapses, as soon as possible[11].

First-line therapy is with corticosteroids; prednisone at a dose of 1-2 mg/kg/day or methylprednisolone, at a dose of 30 mg/kg/day, for 3 days, and then 20 mg/kg/day, for 4 days, following a dose of 10, 5, 2, and 1 mg/kg/day, 1 week each. A range of medications can be used in second-line therapy such as cyclosporine, cyclophosphamide, danazol, rituximab, among other immunosuppressants, as well as chemotherapeutic agents, therapy antibodies, infrequently administered drugs, splenectomy, and plasmapheresis[12].

Evans syndrome has a favorable prognosis with the appropriate treatment. However, it is associated with other autoimmune conditions involved in severe conditions. It is shown that patients over 60 years of age are at greater risk of cardiovascular complications related to AIHA and infections after splenectomy[13,14].

Therefore, we can conclude that Evans syndrome is an entity that is potentially underrecognized in adult patients. The existence of hemolytic anemia with positive Coombs test, as well as thrombocytopenia, obliges the clinician to rule out the possibility of the presence of this syndrome, as the impact on the prognosis depends on its recognition and early management because the latter is generally refractory to treatment with corticosteroids, IVIg, and splenectomy. For the early treatment of this condition, a direct Coombs test must be performed and interpreted together with other laboratory tests and clinical exams to avoid false negatives.

Acknowledgments

The authors would like to thank the Internal Medicine and Rheumatology Divisions of the General Hospital “Dr. Manuel Gea González” Mexico City, Mexico.

Conflicts of interest

The authors declare that they have no conflicts of interest.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

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