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Case Report

Cracking of enigma of Evans: a rare association with Sjogren and systemic lupus erythematosus

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ABSTRACT

Evans syndrome (ES) is characterized by the simultaneous or consecutive occurrence of warm autoimmune hemolytic anemia (AIHA) along with immune thrombocytopenia (ITP), and less commonly, autoimmune neutropenia. It may manifest spontaneously or as a result of autoimmune, malignancy or lymphoproliferative disease. Clinical manifestations may be associated with hemolysis and thrombocytopenia, potentially leading to life-threatening outcomes. ES is a rare diagnosis of exclusion. Due to its infrequency, the treatment is typically empirical, relying largely on intravenous corticosteroids or immunoglobulins. We are presenting case of a 46-year-old- female with bleeding from the mouth and gums and rashes all over the body with no prior diagnosis of rheumatological disorder. This case is pivotal as it highlights a key factor contributing to ES and presents a pragmatic method for addressing the condition.

Keywords: ES, Hematology, Immunoglobulins, Neutropenia, Thrombocytopenia

INTRODUCTION

Evans syndrome (ES) is characterized by the simultaneous or consecutive occurrence of warm AIHA along with ITP, and less commonly, autoimmune neutropenia.[1] While ES has traditionally been labelled as "idiopathic," implying that it is primarily a diagnosis reached by excluding other conditions, it can also be linked to or manifest in conjunction with other diseases or conditions such as systemic lupus erythematosus (SLE), lymphoproliferative disorders, or primary immunodeficiencies.[2,3] ES is a rare disorder, occurring in approximately 7% of cases of AIHA and about 2% of ITP.[4] A higher incidence has been documented in the female gender, with rates ranging from 60% to 70%. While ES has been traditionally viewed as an incidental discovery associated with ITP and AIHA, recent studies indicate a more intricate immune dysregulation involving both humoral and cellular systems.[5] Due to its uncommon occurrence, there is a lack of evidence-based treatment for ES. Here, we present a case of ES in the context of SLE and Sjogren syndrome.

CASE REPORT

A 46-year-old female, with no prior co-morbidity presented in medical emergency with complaints of bleeding from mouth and gums and rashes all over the body for 12 days. Upon further questioning, she reported experiencing dry mouth, dry eyes, fatigue, and occasional joint pain over the last three years. No history of hair loss, photosensitivity, or malar rash was noted. The patient had previously been admitted to a local hospital where she received 19 units of RDP (Random Donor platelets) and given intravenous methyl prednisone 1g for 3 days. Despite this treatment, her platelet count remained below 10,000/micro-L. Two months prior, she

had a similar episode, for which she received 4 units of RDP along with other medications. She had a history of taking anti-tubercular treatment (ATT) for two months and a 10-day course of oral steroids. Upon examination, she appeared in poor health, displaying a Glasgow coma scale (GCS) score of 15/15. A thorough assessment uncovered petechiae throughout her body, accompanied by pallor. Other system examinations revealed no significant findings, and her vital signs were stable.

Initial blood workup of the patient showed hemoglobin of 7.9 gm% with an MCV of 86.6 fL, platelet count of 10,000, and WBC count of 3690/cumm. KFT and LFT were grossly within normal limits. Serum LDH levels were 258IU/L and peripheral blood smear revealed normocytic normochromic anemia decreased WBC count, neutrophil/ lymphocyte %- 48/40%, and markedly decreased platelets. Further workup showed ANA by IFA was positive, with 1:100 titre, mixed homogeneous speckled pattern, and her ANA profile showed SS-A/Ro60 +++, SS-A/ Ro 52 +++, SS-B/La +++, SmD1 +, U1-SnRNP +++ and her Direct Coomb's Test (DCT) was positive. Other laboratory results revealed normal coagulation parameters, normal urine analysis, normal B12, and folate levels, and a negative viral panel of hepatitis B, Hepatitis C, and HIV.

Considering the previous experience of steroid ineffectiveness, she received a five-day course of intravenous immunoglobulin (IVIG). She positively responded to the IVIG treatment, and there was a gradual improvement in both her clinical and hematological conditions. Following the IVIG therapy, her hemoglobin, white blood cell (WBC) count, and platelet count showed improvement.

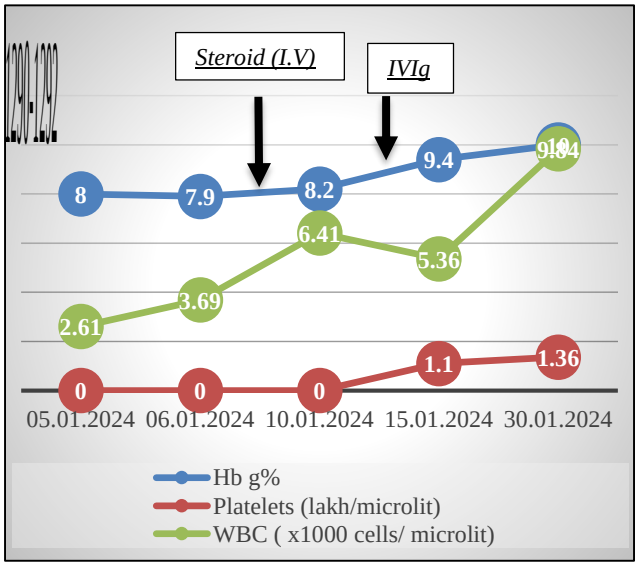

Figure 1: Blood parameters.

On her discharge, she was prescribed a gradually decreasing dosage of steroids. Two weeks post-discharge, a full blood count was conducted for monitoring purposes, revealing an improvement in her blood counts compared to the time of discharge. She is currently in good health.

DISCUSSION

ES typically involves the simultaneous presence of two or more immune cytopenias, with AIHA and thrombocytopenia being the most prevalent. Coined by Robert Evans in 1951, ES has historically been regarded as a somewhat coincidental and "anecdotal" association of ITP and AIHA and/or autoimmune neutropenia, without any discernible underlying cause, since its initial description.[6] Although the cause of the condition is still unknown, researchers believe that immunological dysregulation may be a key factor in its development. While these immune response deficiencies are found in other autoimmune disorders, the continuous production of IL-10 and INF might trigger autoreactive responses. Recent studies suggest that immunization may trigger disease in susceptible individuals. Genetic mutations associated with ES are identified in autoimmune lymphoproliferative syndrome (ALPS)-FAS gene, cytotoxic T lymphocyte antigen-4 (CTLA-4), and lipopolysaccharide-responsive vesicle trafficking beige-like and anchor protein (LRBA).[7]

The clinical manifestations vary and are contingent on the specific blood cell lines affected. Patients often exhibit fatigue, dyspnea, and dizziness, indicative of hemolytic anemia, along with bleeding symptoms associated with thrombocytopenia.[8] The initial assessment of a patient suspected of having ES should encompass a thorough examination, including a complete blood count, hemolysis parameters, Coombs test, platelet antibody measurement, and a peripheral blood smear[9]. It is essential to exclude infiltrative processes in patients with pancytopenia, especially before initiating corticosteroid therapy.

ES can manifest as either primary (idiopathic) or secondary, with associations to autoimmune disorders such as SLE, Sjögren's syndrome, antiphospholipid syndrome, and autoimmune lymphoproliferative syndrome. A 2009 study revealed that in 34 individuals (50%), ES was identified as "primary," while in 50% of cases, it was linked to an underlying condition, predominantly systemic lupus, lymphoproliferative diseases, and common variable immunodeficiency.[10]

There are no clinical trials available for ES treatment and indications for starting therapy have not been established by evidence-based studies. Managing ES continues to be a challenging task. The syndrome is characterized by periods of remission and exacerbation corticosteroids and IVIG represent the cornerstone of treatment for patients experiencing ITP or AIHA.[11] Steroids are administered at a dosage of 1 to 2 mg/kg per day, with gradual tapering over weeks in cases of isolated ITP or over months in instances of warm AIHA. Second-line therapy options

include immunosuppressive medications such as ciclosporin or mycophenolate mofetil, as well as vincristine, danazol, or a combination thereof. In cases refractory to standard treatment or those dependent on steroids (defined as requiring at least 15 mg of prednisone daily to prevent relapse), rituximab or splenectomy may be considered.[12]

CONCLUSION

ES, characterized by the simultaneous presence of AIHA and ITP, poses significant challenges in management, particularly when standard treatments such as corticosteroids fail to achieve adequate control. The management of ES coexisting with SLE and Sjogren's syndrome presents a complex clinical challenge. IVIG therapy emerges as a promising treatment option, offering immunomodulatory effects that can address the underlying autoimmune dysregulation. Further research and clinical studies are warranted to elucidate the optimal dosing regimens and long-term efficacy of IVIG in this multifaceted clinical scenario.

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