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CASE REPORT

An Unusual Presentation of Systemic Lupus Erythematosus as Evan Syndrome: A Case Report and Review Literature

Evans Syndrome Associated with Systemic Lupus Erythematosus in an Adult: A Case Report and Literature Review

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Evans syndrome is a rare autoimmune disorder with an unknown etiology. In this paper, we report the case of a 32-year-old Saudi woman living with Evans syndrome for more than 8 years (post-splenectomy) who was also diagnosed with systemic lupus erythematosus (SLE). She was admitted to our Hospital with severe headache and confusion due to cerebral venous thrombosis. The major hematologic manifestations of SLE were pancytopenia and the antiphospholipid syndrome, which are indicators of disease activity when all other possible causes are excluded. The patient was treated with anticoagulation and immunosuppressive therapy and subsequently showed significant improvements in thrombosis, thrombocytopenia, and anemia. This case report provides an overview of the association between Evan syndrome and SLE.

Keywords: Evans syndrome; hemolytic anemia; systemic lupus erythematosus; thrombosis

Introduction

Evans syndrome (ES), which was first described in 1951, is an autoimmune disorder characterized by the simultaneous or sequent development of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) sometimes accompanied by immune neutropenia in the absence of any underlying cause (Evans et al, 1951), (Barcellini W and Zanella, 2014; Gupta et al, 2011). ES is a rare disease that is diagnosed in only 0.8% to 3.7% of all patients with either ITP or AIHA (Jorfen et al, 1998), (Norton A and Robert I, 2005). Although ES is considered an idiopathic condition and is mainly diagnosed based on exclusion of other disease, ES may be associated with or present as other diseases or conditions such as systemic lupus erythematosus (SLE), lymphoproliferative disorders, or primary immunodeficiency. Whereas ES relies on antibody-mediated AIHA and ITP, the combination of AIHA and ITP can also be observed in patients with SLE, suggesting a link to other inflammatory mechanisms (Costallat, 2012). In childhood, ES may also present as autoimmune lymphoproliferative syndrome (ALPS), a disorder of disrupted lymphocyte homeostasis related to some mutations in the Fas apoptotic pathway (Teachey et al, 2005; Copelovitch et al, 2008). However, relatively little data on ES among adults are available in the literature, and the characteristics and outcomes related to ES among adults remains relatively unexamined. Moreover, because there have been no prospective or randomized controlled trials, the management of ES is based on empirical data and on indirect evidence extrapolated from the primary standard of care for ITP and AIHA Therefore, we report the successful treatment of a case of ES in an adult woman associated with SLE.

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Case Presentation

A 32-year-old Saudi woman being treated for ES (post-splenectomy) was admitted to our hospital l because of severe headache and blurred vision lasting for 2 days. She had noticed small reddish spots on her arms and legs during the 2 weeks prior to her admission and had a remote history of malar rash and polyarthralgia. At the same time, she started having shortness of breath upon exertion. These symptoms progressively deteriorated, prompting her hospital visit. Physical examination of the patient indicated that she was vitally stable and afebrile but mildly confused. She was dehydrated with pallor, mild jaundice, and a bilateral extensor plantar reflex but was able to move all four limbs and had bilaterally reactive pupils. Her fundus examination showed papilledema. Small purpuric rash was scattered over her arms and legs. There was no lymphadenopathy. The chest and cardiovascular examinations were unremarkable. The abdominal examination showed no hepatomegaly and an ultrasound examination proved no accessory spleen.

The patient was admitted to the intensive care unit with APACHE II score of 9 points for close monitoring.

Brain computed tomography (CT) with contrast was performed and showed evidence of cerebral venous thrombosis (**Figure 1**). Laboratory investigations revealed moderate bicytopenia in the form of moderate microcytic, hypochromic anemia (hemoglobin [Hb] 8.5 g/dL, reference range [RR]: 12.0–16.0 g/dL) and moderate thrombocytopenia (platelet count: 79 × 10^3/μL, RR: 150–400 × 10^3/μL) with a high mean platelet volume (MPV)15 fl and platelets distribution width (PDW)17 fl. The total and differential leukocyte counts were within the RR as was the routine coagulation screen. Fibrinogen degradation products and D-dimers were normal (3.2 μg/dL, RR: less than 5.0 μg/dL and 1.1 μg/dL, RR: less than 2.0 μg/dL, respectively). The total serum bilirubin level was elevated (2.9 mg/dL, RR: 0.2–1.3 mg/dL) with dominant elevation of indirect bilirubin. Serum lactate dehydrogenase (LDH) was also elevated (550 IU/L, RR: 119–219 IU/L), but the blood urea nitrogen, creatinine, and serum electrolyte levels were all within the RR and the urinalysis did not show any abnormal findings. The serum haptoglobin level was low (10 mg/dL, RR: 43–180 mg/dL), suggesting hemolytic anemia. Examination of the peripheral blood smear (PBS) clearly showed schistocytes, polychromasia (i.e., reticulocytosis), and giant platelets. The patient's bone marrow aspiration report revealed active marrow with erythroid hyperplasia and a mild increase in megakaryocytes while all other bone marrow series were normal. Immunological investigations showed a positive antinuclear antibody (ANA) titer (1:360) together with positivity for anti-dsDNA and anticardiolipin antibodies. Both the direct and indirect Coombs tests were positive, and the serum complement levels were low (CH50: 21 U/mL, RR: 32–49 U/mL; C3: 51 mg/dL, RR: 65–135 mg/dL; C4: 8 mg/dL, RR: 13–35 mg/dL). Hepatitis and human immunodeficiency virus (HIV) serology were negative.

Thus, according to the collective clinical and laboratory findings, the patient fulfilled the criteria for SLE (i.e., malar rash and polyarthritis together with thrombocytopenia and positivity for ANAs, anti-dsDNA antibodies, and anticardiolipin antibodies). The patient was treated with dexamethasone intravenously (4 mg/day for 3 days) followed by oral prednisolone (50 mg/day). She was started on oral warfarin and subcutaneous fondaparinux (7.5 mg/day) with a target International Normalized Ratio INR of 2–3. She started azathioprine (100 mg once daily [OD]) and hydroxychloroquine (400 mg OD). After 5 consecutive days, her symptoms and abnormal laboratory tests, especially the non-hematological findings, had reasonably improved (i.e., a complete response [CR]). A CR for AIHA was defined by a normal Hb level (12.0–16.0 g/dL) with no history of transfusion and the disappearance of hemolysis (i.e., normal bilirubin and LDH levels). For ITP, a CR was defined by a normal platelet count (150–400 × 10^3/μL). A follow up CT scan of her brain showed resolution of the transverse sinus clot (**Figure 2**). unfortunately, we lost the follow up with the patient to see what was the disease progression.

Discussion

Since its first description in the early 1950s, ES has long been considered as a rather incidental and anecdotal combination of ITP and AIHA possibly accompanied by autoimmune neutropenia in the absence of any underlying cause. More recently, the spectrum of the disease has broadened, especially in children, and there is increasing evidence to suggest that ES reflects a state of profound immune dysregulation as opposed to a coincidental combination of immune cytopenias (Musa et al, 2000; Wang W et al 1983; Ridolfi RL and Bell WR, 1981). Currently, ES refers to the combination of Coombs-positive warm AIHA and ITP; however, less commonly, some patients will also have autoimmune neutropenia (15% in one case series).

ES is a heterogeneous disorder with significant morbidity and mortality. A high incidence of quantitative serum immunoglobulin abnormalities, lymphoid hyperplasia, and associated systemic manifestations suggests that ES may represent a stage of a broader spectrum, generalized immune dysregulation (Savaşan et al, 1997). Although many cases of ES are idiopathic in origin, approximately one-half of the cases are associated with a number of other conditions, including infections, SLE, lymphoproliferative disorders (LPD), common variable immunodeficiency, and ALPS, and may occur following allogeneic hematopoietic cell transplantation (Jorfen et al, 1998).

ALPS is also a rare disorder and disrupts lymphocyte homeostasis. Clinical manifestations of ALPS vary but typically include autoimmune cytopenias, organomegaly, lymphadenopathy, and an increased risk of malignancies.

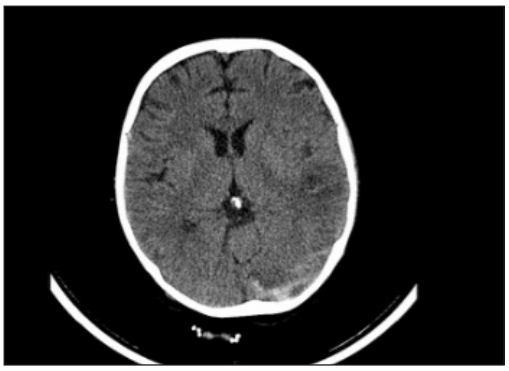

Figure 1: Picture of the left transverse sinus thrombosis associated with left temporal lobe venous haemorrhagic infarction.

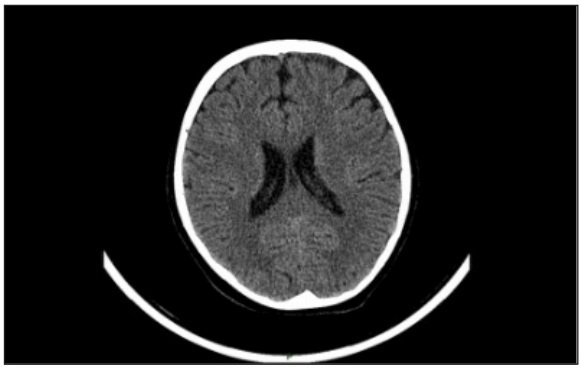

Figure 2: Picture of the left transverse sinus thrombosis resolution after 10 days of treatment.

A similar spectrum of symptoms may be seen in some patients with ES. Therefore, some studies have hypothesized that a subset of patients diagnosed with ES may have ALPS and have suggested that an analysis of double-negative T-cells (i.e., CD4-CD8-) might be a sensitive first-line screening test serving as a marker of patients who should undergo definitive testing for ALPS. a number of patients with ES might have ALPS, a novel finding with important therapeutic implications (Teachey et al, 2005).

Furthermore, the antibodies that cause hemolysis are different from those that cause platelet destruction. For example, those causing red blood cell destruction are directed against base protein portions of the Rh blood group system, while those destroying platelets are frequently directed against platelet GpIIb/IIIa (Musa et al, 2000). Therefore, the following proposals were suggested as the minimal work-up in adults with newly diagnosed ES: a complete blood count; PBS; serum protein electrophoresis; serum immunoelectrophoresis (immunofixation); measurement of serum immunoglobulin concentrations; immunophenotyping of circulating B lymphocytes; an antinuclear, anti-dsDNA, anticardiolipin antibody titer; a lupus anticoagulant assay; HIV, HCV, and HBV tests; a CT scan of the chest, abdomen and pelvis; and a bone marrow aspiration/biopsy. An HBV test is indicated to prevent viral reactivation in HBV carriers prior to corticosteroid therapy, especially if rituximab is considered (Michel et al, 2009).

In this case, a patient with ES was subsequently diagnosed with SLE based on her physical and laboratory findings: a malar rash, polyarthralgia, increased levels of several autoantibodies, and decreased serum complement concentrations.

Finally, steroid preparations may be used because they lessen the damaging effect of cerebral edema, increased intracranial pressure, and a disturbed blood-brain barrier as well as to counteract the stress factor associated with acute cerebral infarction, hemorrhage, or trauma (Tellez and Bauer, 1973). One of the rare manifestations of SLE following ES is lupus cystitis. Some of the reported cases have been successfully treated with bolus methylprednisolone therapy (1,000 mg over 3 days) (Matsuhashi et al, 2002).

ES is a rare manifestation in SLE-identified in 2.7% of cases. It occurs in patients with severe multisystemic manifestations of SLE. Treatment strategies frequently used for SLE contribute to longer disease remission and less frequent exacerbation than observed in the general population with ES [15]. In addition, SLE patients with initial hematological manifestations have a more benign course, not worsened by splenectomy (Lavalle et al, 1983).

Platelets indices (mean platelets volume MPV, platelets distribution width PDW) are simple easily obtained parameters that can point toward immune thrombocytopenia when compared to hypo productive types of thrombocytopenia with very decent sensitivity and specificity (Negash et al, 2016). MPV and PDW were thought to be a predictor of non-favorable outcome especially in critically ill patients as they found to be in high values in non-survivors in intensive care units admissions than survivors. and Platelet distribution width greater than 17% and MPV greater than 11.3 fL were independent risk factors for mortality (Zhang et al, 2014), (Tajarernmuang et al, 2016).

Conclusion

In cases of ES among adults, investigations for any associated conditions, with special consideration of SLE, LPD, and autoimmune disorders are needed. The diagnosis of associated conditions will help better manage the case resulting in a more favorable prognosis. However, further research is needed to help clarify the pathophysiology and obtain better therapeutic strategies for ES associated with or complicated by SLE in adults.

Competing Interests

The authors have no competing interests to declare.

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