Case report

Evans syndrome: A case report

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ABSTRACT

Evans syndrome is described as the simultaneous presence of immune thrombocytopenia, warm autoimmune haemolytic anaemia, and sometimes autoimmune neutropenia. It occurs due to autoantibodies that fail to cross-react with antigens unique to platelets, red blood cells, or neutrophils. Haemolysis and thrombocytopenia may be causing clinical symptoms. Evans syndrome stands as a rare condition diagnosed through a process of exclusion. Initial treatment options encompass intravenous corticosteroids or intravenous immunoglobulins, serving as the first choice of interventions. In cases where patients do not respond to steroids, the subsequent steps involve second-line treatments such as rituximab or splenectomy. A 43-year-old female with a history of Evans syndrome presented with a complaint of generalised weakness for 20 days after having recently been tapered off of prednisone. She was treated with a combination of immunomodulators and corticosteroids. Here, we try to highlight the importance of medication adherence which is essential in treating chronic disorders.

Keywords: Evans syndrome; medication adherence; immunomodulators; corticosteroids; case report.

INTRODUCTION

Evans Syndrome stands as a rare and complicated autoimmune disorder marked by the simultaneous or sequential occurrence of autoimmune hemolytic anaemia (AIHA) and immune thrombocytopenia (ITP). The disease poses significant challenges in both diagnosis and treatment due to its diverse clinical manifestations and the underlying immunopathogenic processes it involves. AIHA and ITP, distinct autoimmune conditions causing the breakdown of red blood cells and platelets respectively, are individual conditions that converge within Evans Syndrome (ES), leading to a dual presentation of cytopenia. AIHA is characterized by the destruction of red blood cells through autoantibodies, resulting in haemolytic anaemia that manifests as symptoms like fatigue, pallor, and jaundice (1). The pathogenesis of ES is not fully elucidated and is likely to be complex. The disorder is primarily caused by immune system dysregulation, which results in the creation of autoantibodies against red blood cells and platelets. Abnormalities in B-cell and T-cell responses, as well as deficiencies in regulatory T-cells, may lead to the breakdown of self-tolerance and the ensuing autoimmune attack on hematopoietic cells. Furthermore, shared antigens between red blood cells and platelets may contribute to the co-occurrence of AIHA and ITP in ES (1,2). Up to 7% of AIHA and 2% of ITP are accounted for by ES. In instances of concurrent AIHA and ITP, the diagnostic process needs to meticulously eliminate potential differential diagnoses. These may include thrombotic microangiopathies, anaemia stemming from bleedings related to ITP, deficiencies in essential vitamins, myelodysplastic syndromes, paroxysmal nocturnal haemoglobinuria, or specific conditions like hemolysis, elevated liver enzymes, and low Platelets (HELLP) syndrome, particularly when encountered during pregnancy. When dealing with isolated auto-immune cytopenia (AIC), the distinction between whether Evans Syndrome (ES) is primary or secondary holds significant importance. This differentiation is crucial due to the potential presence of ES alongside other conditions such as haematological malignancies, systemic lupus erythematosus, infections, or primary immunological deficits. Such coexistence has the potential to complicate medical care and exert an impact on the prognosis (3,4). Here we present one clinically rare case of a 43-year-old female with a history of Evans Syndrome which relapsed when she was tapered off prednisolone, along with remarks.

Case presentation

A 43-year-old female with a known case of Evan's Syndrome presented to the hospital with complaints of generalised weakness for 20 days. She did not report any instances of fever, cough, headache, or shortness of breath. The patient used to take prednisone for her acute episodes. She had recently been weaned off of prednisone. She had no history of any comorbidities. She denied smoking, consumption of alcohol or illicit drug use. She looked ill but was conscious and oriented to time, person, and place at presentation. She was cooperative as well. The patient's Glasgow Coma Scale (GCS) score was 15 out of 15. Her vitals were stable (Pulse rate: 90 beats per minute, blood pressure: 110/70 mmHg, oxygen saturation: 98% at room air and respiratory rate: 17 cycles per minute).

Cardiovascular, abdominal, and respiratory system examinations did not reveal any abnormality. Haematological tests revealed that she had microcytic and hypochromic anaemia along with thrombocytopenia. (Hb%: 8.5 gm%, RBC count: 3.83 million cells/mm^3, Platelet count: 56,000 cells/mm^3, PCV: 27.3%, MCV: 70 fL, MCH: 21 pg, MCHC: 30.4%). No atypical cells as well as haemoparasites were detected. The patient was admitted for further monitoring and evaluation. The patient's biochemical and serological tests were done and the parameters were normal.

On day 1, the patient received 4-pint RDP to raise her platelet count to normal levels. Multivitamin injections were administered in 1 pint DNS in 1 hour, along with intravenous corticosteroids (Dexamethasone), and intravenous ferric carboxymaltose. She was prescribed oral iron supplements as well as B complex tablets and intravenous PPI (Pantoprazole). Her blood parameters showed a minor improvement. She received a five-day course of intravenous steroids, which elicited a positive response. Her health showed gradual improvement in both clinical and haematological aspects, although it had not yet returned to the normal range. The dose of corticosteroid was tapered and she was started on Azathioprine. Throughout her admission, the patient's vitals, haematological parameters, and fluid input/output were constantly being monitored. Her blood levels gradually reached normal levels. An ultrasound of her abdomen and pelvis was conducted. It revealed that she had a retroverted bulky uterus; however, no significant abnormality was detected.

The above treatment had a positive outcome. She was discharged from the hospital as her status progressively improved. She was prescribed oral iron and vitamin supplements. She was prescribed tablet Prednisolone for 4 days and she was given proper dose tapering instructions for the same. She was also prescribed the tablet Azathioprine. She was advised to visit the doctor one week after discharge with a CBC report. There were no new complaints at her initial follow-up and her haematological parameters were normal. The patient was doing well.

DISCUSSION

Evans Syndrome symptoms may manifest similar to leukaemia and lymphoma, thus before a diagnosis is made these illnesses must be ruled out. Symptoms associated with a low red blood cell count can encompass dark brown urine, jaundice, shortness of breath, weakness, fatigue, and a pale complexion. Conversely, signs of a low platelet count may manifest as heightened presence of petechiae, increased bruising, and escalated bleeding tendencies, such as nosebleeds (epistaxis) and heavy menstrual bleeding (5,6). Thrombosis, a complication recognized in both ITP and AIHA, is widely documented in medical literature. Nonetheless, only a limited number of reported cases of Evans Syndrome have exhibited thrombotic consequences (7). In our case, we did not encounter thrombosis in the patient.

After diagnosing anaemia through a comprehensive assessment of the complete blood count and differential, if there is a suspicion of Evans Syndrome, additional investigations are typically necessary to assess for the presence of haemolysis. This includes analysing levels of lactate dehydrogenase, haptoglobin, bilirubin, and the reticulocyte count. Furthermore, warm AIHA can be verified through a positive result of the direct antiglobulin test (DAT) and the observation of spherocytes on a peripheral smear. The diagnosis of Evans Syndrome is established through a process of exclusion. As a result, it is essential to eliminate prevalent underlying causes before definitively diagnosing Evans syndrome. This entails meticulously assessing the peripheral blood smear for conditions like thrombotic thrombocytopenic purpura (TTP) and cold agglutinin disease, considering infectious triggers such as HIV and Hepatitis C, examining for other autoimmune disorders, and investigating the presence of malignancies (8).

Managing Evans Syndrome can be difficult and frequently necessitates a multidisciplinary approach. The treatment technique is determined by the severity of the cytopenia, the patient's age, and any accompanying comorbidities. To inhibit the immunological response and regulate hemolysis and thrombocytopenia, corticosteroids are usually used as first-line therapy. Some patients may require further immunosuppressive medicines such as rituximab, cyclosporine, or splenectomy to achieve durable remission. Despite therapeutic advancements, relapse and treatment resistance remain problems in the long-term management of Evans syndrome (9). The initial approach for effectively managing Evans Syndrome involves the use of either corticosteroids or intravenous immunoglobulin (IVIG) as first-line treatments. Steroids are typically administered at a dosage ranging from 1 to 2 mg/kg per day. In isolated ITP, steroids can be reduced over weeks or over months in heated AIHA. IVIG is utilised more frequently in the treatment of ITP than in the treatment of individuals with isolated AIHA. While the majority of patients show an initial response to corticosteroids, the duration of this response can differ, and over fifty per cent experience a relapse, highlighting the need to consider supplementary or alternative therapeutic options (2). In cases where standard treatments prove ineffective or when a patient becomes dependent on steroids (requiring a daily dose of at least 15 mg of prednisone to prevent relapse), the consideration of Rituximab or splenectomy becomes relevant. Responses to these interventions can vary. Rituximab, often favoured for

its higher efficacy, is commonly recommended, particularly when Evans syndrome is presumed to be secondary to an underlying condition like cancer or systemic lupus erythematosus (SLE). Additionally, it is suggested for individuals with increased infection risk due to coexisting health issues, rendering splenectomy unnecessary (10). As per a particular study, when used in conjunction with steroids, this approach has the potential to attain remission rates as high as 76%. The utilization of splenectomy is on the decline, typically reserved for cases in which patients display resistance to medical interventions, given the lower response rates, increased relapse rates, and a heightened susceptibility to sepsis associated with the procedure. Given its ability to reduce the reliance on corticosteroids, Danazol is extensively employed as a second-line treatment choice (11). In patients who have not responded to corticosteroids or rituximab, immunosuppressive medications can be utilised. While various immunosuppressants have been explored for treatment, cyclosporin A and mycophenolate mofetil are preferred options due to their heightened effectiveness in managing autoimmune diseases (12). Cyclophosphamide, azathioprine, and sirolimus are some other drugs that have been utilised. The selection of the most appropriate immunosuppressant depends on factors such as patient-specific characteristics, any coexisting health conditions, and the extent of disease severity. A hematopoietic stem cell transplant is considered a final resort, reserved for patients who have not responded to prior medical interventions. Both autologous and allogeneic stem cell transplantation have been tested in a limited number of cases, yielding diverse outcomes (13).

A study of 68 patients with Evans Syndrome found that 23.5% died from complications such as septic shock, related meningitis, pneumonia, carcinomas, abrupt myocardial infarction, stroke, or refractory anaemia. According to the study, severe thrombocytopenia in Evans syndrome resulted in two fatalities from immediate gastrointestinal bleeding and one death from acute cerebral haemorrhage. Another study described a case of Evans syndrome-related bleeding manifestation in the form of non-traumatic non-aneurysmal subarachnoid haemorrhage (5, 14). At a prominent tertiary care facility in Nepal, a 32-year-old woman afflicted by Evans syndrome was admitted with a grave complication of intracranial haemorrhage. Her treatment regimen included a potent dose of intravenous mannitol, platelet-rich plasma, steroids, and the immunomodulatory medication azathioprine. Regrettably, she succumbed to her condition due to noncompliance with the prescribed therapy (15). In our case, the relapse of the patient's disorder can be attributed to the fact that she had been tapered off of prednisone. She had generalised weakness but no infections or fatal consequences were evident. Additionally, our patient was put on corticosteroid and azathioprine upon discharge and was compliant with her medications. Her haematological profile had improved during her one-week follow-up. Thus, highlighting the need for medication adherence to prevent any relapse and complications associated with Evans Syndrome. However, there was no formal assessment of medication adherence; instead, it was inferred solely from the progress observed in her condition.

CONCLUSION

In a nutshell, Evans Syndrome is a rare and complex autoimmune illness characterised by the occurrence of autoimmune haemolytic anaemia (AIHA) and immune thrombocytopenia (ITP) concurrently or sequentially. Because of its varied clinical manifestations and complicated pathophysiology, this illness provides substantial diagnostic and treatment hurdles. Management of Evans syndrome includes corticosteroids +/IVIG as first-line therapy, with blood product support as needed. Second-line therapy includes immunosuppressive medication, either as a single agent or, in more severe situations, as a multi-agent. Splenectomy typically results in only short-term remission, but it may lower the frequency of relapses and allow for a reduction in immunosuppressive medications. Medication adherence, particularly with regard to immunosuppressive drugs and corticosteroids, is critical in the management of Evans syndrome. Medication adherence is critical for properly regulating immunological dysregulation and preventing illness relapses.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

1. Evans, R.S., Takahashi, K., Duane, R.T., Payne, R., Liu, C. Primary thrombocytopenic purpura and acquired hemolytic anemia; Evidence for a common etiology. AMA Arch Intern Med. 1951;87(1):48-65.
2. Jaime-Perez, J.C., Aguilar-Calderon, P.E., Salazar-Cavazos, L., Gomez-Almaguer, D. Evans syndrome: Clinical perspectives, biological insights and treatment modalities. J Blood Med. 2018; 9: 171-184.
3. Audia, S., Grienay, N., Mounier, M., Michel, M., Bonnotte, B. Evans' syndrome: from diagnosis to treatment. J Clin Med. 2020;9(12):3851.
4. Provan, D., Arnold, D.M., Bussel, J.B., Chong, B.H., Cooper, N., Gernsheimer, T., *et al.,* Updated international consensus report on the investigation and management of primary immune thrombocytopenia. Blood Adv. 2019;3(22):3780-3817.
5. Michel, M., Chanet, V., Dechartres, A., Morin, A.S., Piette, J.C., Cirasino, L., *et al.,* The spectrum of Evans syndrome in adults: new insight into the disease based on the analysis of 68 cases. Blood. 2009;114(15):3167-3172.
6. Norton, A., Roberts, I. Management of Evans syndrome. Br J Haematol. 2006;132(2):125-137.
7. Otaibi, Z.D., Rao, R., Sadashiv, S.K. A Case of Evans syndrome: A clinical condition with under-recognized thrombotic risk. J Hematol. 2015;4(3):205-209.
8. Jager, U., Barcellini, W., Broome, C.M., Gertz, M.A., Hill, A., Hill, Q.A., *et al.,* Diagnosis and treatment of autoimmune

hemolytic anemia in adults: recommendations from the first international consensus meeting. Blood Rev. 2020;41:100648
9. Neunert, C., Terrell, D.R., Arnold, D.M., Buchanan, G., Cines, D.B., Cooper, N., *et al.,* American Society of hematology guidelines for immune thrombocytopenia. Blood Adv. 2019;3(23):3829-3866.
10. Crowther, M., Chan, Y.L., Garbett, I.K., Lim, W., Vickers, M.A., Crowther, M.A. Evidence-based focused review of the treatment of idiopathic warm immune hemolytic anemia in adults. Blood. 2011;118(15):4036-4040.
11. Bader-Meunier, B., Aladjidi, N., Bellmann, F., Monpoux, F., Nelken, B., Robert, A., *et al.,* Rituximab therapy for childhood Evans syndrome. Haematologica. 2007;92(12):1691-1694.
12. Emilia, G., Messora, C., Longo, G., Bertesi, M. Long-term salvage treatment by cyclosporin in refractory autoimmune haematological disorders. Br J Haematol. 1996;93(2):341-344.
13. Chang, D.K., Yoo, D.H., Kim, T.H., Jun, J.B., Lee, I.H., Bae, S.C., *et al.,* Case report induction of remission with intravenous immunoglobulin and cyclophosphamide in steroid-resistant Evans' syndrome associated with dermatomyositis. Clin Rheumatol. 2001;20(1):63-66.
14. Abdul Rashid, A.M., Md Noh, M.S.F. Isolated non-traumatic, non-aneurysmal convexal subarachnoid hemorrhage in a patient with Evans syndrome. BMC Neurol. 2017;17(1).
15. Shilpakar, O., Rajbhandari, B., Karki, B., Bogati, U. Intracranial haemorrhage as a fatal complication of Evans syndrome: a case report. Nepal Med J. 2019;2(2):66-69.