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Evan's syndrome, primary or secondary? Navigating the diagnostic puzzle

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Evans syndrome (ES) is a rare autoimmune disorder characterized by the simultaneous or sequential occurrence of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP). Distinguishing between primary and secondary forms is crucial for management. This report presents a 69-year-old male with bleeding gums, anemia, and thrombocytopenia, who was diagnosed with ES following an extensive workup. Multiple potential triggers, including recent vaccinations, antibiotic use, past tuberculosis, and skin malignancies, were identified, highlighting the multifactorial nature of ES. The patient was treated with glucocorticoids, intravenous immunoglobulin (IVIG), Rituximab, and Romiplostim resulting in improved hematologic parameters. This case underscores the diagnostic challenges and importance of individualized therapeutic approaches in managing ES. Understanding the potential triggers and underlying immune dysregulation is pivotal for accurate diagnosis and effective treatment.

INTRODUCTION

Evans syndrome (ES) is a rare and complex autoimmune disorder first described by Robert Evans in 1951. While individual occurrences of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP) are more commonly encountered in clinical settings, their simultaneous or sequential manifestation within a single patient, as observed in ES, is decidedly uncommon. The true prevalence of ES remains somewhat elusive, largely due to its rare nature and the potential for misdiagnosis. Estimates suggest that ES accounts for about 5- 10% of all chronic ITP cases and approximately 2-3% of all AIHA cases. This rarity can pose diagnostic challenges, particularly when clinicians are faced with differentiating between primary and secondary forms of the syndrome.

AIHA and ITP, when considered individually, have been extensively studied and are recognized as autoimmune disorders targeting specific blood cells. However, when they converge as ES, it signifies a profound disturbance within the immune system. Primary ES manifests without an identifiable underlying cause, whereas secondary ES can be linked to various conditions, from systemic lupus erythematosus (SLE) and other autoimmune diseases to lymphoproliferative disorders, infections, and even certain medications. Therefore, accurate diagnosis, timely management, and an appreciation of potential triggers and secondary causes can significantly impact patient outcomes.

This report aims to delve deeper into a case of Evans Syndrome, exploring its potential etiologies and shedding light on the nuances of its management.

CASE DESCRIPTION

A 69-year-old man presented to the hospital with bleeding gums and symptomatic anemia for the past month. History goes back to 1 month before admission when the patient started experiencing symptoms of anemia, including exertional dyspnea, lightheadedness, and generalized fatigue. Since then, he also noted petechiae on his arms and legs that gradually resolved. He also mentioned remote episodes of dark stools. He noted that his gums have started bleeding with minimal pressure, sometimes waking up from sleep with clotted blood in his mouth. He reports that the bleeding lasted up to 30 minutes.

A review of systems was negative for any infections, significant weight loss, night sweats, fevers, bleeding into joints, any family history of bleeding disorders, or similar prior episodes. He denied sick contacts and recent travel. The patient reports finishing a course of Amoxicillin prescribed by the dentist for a right molar abscess 5 weeks before admission. He also endorses receiving his third COVID-19 vaccine (Pfizer) concurrently with the Influenza vaccine 2 weeks before the symptoms started. His past medical history is significant for basal and squamous cell carcinoma resected 4 and 8 months before presentation, respectively. He also had a history of pulmonary tuberculosis treated at the age of 35.

Table 1. Relevant results of patient's laboratory analyses.

Pertinent Lab Findings	Value
• White blood cell count	2.76 K/uL
• Hemoglobin	5.6 g/dL
• Platelet count	28 K/uL
• Absolute neutrophil count	990 K/uL
• MCV	87 fL
• Reticulocyte count index	0.6%
• Total Bilirubin	1.4 mg/dL
• Lactate	3.1 mmol/L
• PT/INR	13.5/1.18
• PTT	25.5 sec
• LDH	630 U/L
• Coombs test	Positive
• Urine urobilinogen	Positive

At the time of admission, he was hemodynamically stable. On physical examination, he had streaks of dried blood on his tongue and had pallor. Petechiae on the legs was noted. No lymphadenopathies were palpated. Abdominal examination and chest auscultation were unremarkable. The patient had anemia and thrombocytopenia on laboratory testing with elevated Lactate dehydrogenase and low haptoglobin (Table 1). Coombs antibodies were positive for IgG, and the peripheral smear showed low platelets and no schistocytes, spherocytes, or clumping. D- Dimer, B12, Folate, and iron panel were all normal. An autoimmune workup including ANA, Rh- Factor, C3, and C4 were negative. An infectious workup, including HIV and Hepatitis panel, was negative. Fluorescence in situ hybridization (FISH) and Flow cytometry studies were also negative.

Bone marrow biopsy demonstrated hypercellular bone marrow (60-70%) with maturing trilineage hematopoiesis with megakaryocytic and erythroid hyperplasia with left shift, mild dyserythropoiesis with no significant increase in blasts nor signs of dysplasia. As for radiographic imaging, CT of the chest, abdomen, and pelvis was significant for left upper lobe scarring with a calcified hilar lymph node and a 2 cm left adrenal nodule. The tests mentioned above helped rule out paroxysmal nocturnal hemoglobinuria, vitamin deficiencies, and the presence of a myelodysplastic process. Due to the presence of a positive Coombs test, evidence of hemolysis, and thrombocytopenia, the patient was diagnosed with Evans Syndrome and was subsequently treated for it. He received a unit of packed red blood cells and a unit of single donor platelets and was started on Dexamethasone 40 mg daily for 4 days, then switched to Prednisone 100mg (1mg/kg) daily for two weeks, followed by slow taper. He also received IVIG 500 mg/kg for 4 days, in addition to Rituximab, which was started as a weekly regimen. Romiplostim was also administered.

Ultimately, the patient's anemia and thrombocytopenia improved (Table 2), and he was discharged with close outpatient follow-up and age-appropriate malignancy screening.

DISCUSSION

Evans syndrome was once considered a random occurrence of AIHA and ITP. However, it is now understood as a deep-seated immune imbalance that can cause various immune-related cytopenias, either simultaneously or consecutively. Many factors, ranging from blood cancers and immune deficiencies to viruses, pregnancy, vaccinations, and autoimmune conditions, have been linked to Evans syndrome. In the case at hand, the patient exhibited several of these potential triggers. We aim to sift through the evidence and pinpoint the most probable cause for this patient's Evans syndrome. One of the hypotheses that might contribute to the development of ES in our patient is the history of administered vaccines. Gil Z. Shlamovitz, have documented a unique case where Evans Syndrome developed secondary to an influenza vaccine, with symptoms manifesting just four days post-vaccination.[1] Our patient's concurrent administration of two vaccines complicates pinpointing a sole trigger. Moreover, multiple separate cases of AIHA and ITP were described with influenza and COVID-19 vaccines.[2] Thus, it is conceivable that the combined effect of both vaccines could have amplified the immune response, potentially leading to the development of ES. Furthermore, the symptoms appearing within a month post-vaccination fall within the generally accepted window for vaccine-induced reactions. Therefore, the temporal proximity underscores the potential causality between the vaccines and ES.

A pivotal mechanism underpinning the pathophysiology of Evans Syndrome is the interaction between CTLA-4 (or CD 152) and the CD80/CD86 molecules found on Antigen Presenting Cells (APCs). This interaction plays a critical role in maintaining immune homeostasis. Any disruptions to this balance could predispose individuals to autoimmune disorders like ES.[3] Notably, similar disruptions in this interaction have been identified as contributing factors to the autoimmune side effects observed with some COVID-19 vaccines.

One potential cause of isolated AIHA or ITP and rarely ES is antibiotics such as Amoxicillin, which has been associated with the formation of drug-dependent antibodies. In the context of drug- induced immune reactions, these antibodies are typically of the IgG type, like the ones seen in our patient. Once these antibodies are produced, they target the drug molecule attached to the membrane of red blood cells (RBCs) or platelets. This binding action initiates a cascade where macrophages recognize these antibody-coated cells, resulting in Fc-mediated extravascular hemolysis, where the blood cells are destroyed outside the blood vessels. However, a distinguishing feature of drug-induced hemolytic anemia is that the hemolysis and related symptoms typically resolve upon discontinuing the offending

Table 2. Comparison of the patient's complete blood count on day 1, day 7, and day 14.

Complete blood count	Day 1	Day 7	Day 14
• WBC count (K/uL)	2.76	5.82	6.90
• Hemoglobin (g/dL)	5.6	7.7	9.3
• Hematocrit (%)	16	24.4	28.6
• MCV (fL)	87.9	103.4	101.8
• Platelets (K/uL)	28	3	85
• Absolute Neutrophil count (K/uL)	990	3120	4570

drug. In this patient's case, the persistence and worsening of symptoms, even after weeks of cessation of amoxicillin use, raises questions about its role as the primary culprit. While Amoxicillin might have acted as a trigger or a contributing factor, the continued disease progression suggests that there might be other underlying mechanisms or factors at play in the development and persistence of Evans syndrome in this patient.

Another potential trigger for ES is a history of previously treated TB.[4] This association is supported by various reports, including a notable case presented by Sharma et al., which described ES likely secondary to TB infection.[5] The proposed mechanism involves the production of autoantibodies against blood cells by lymphocytes, triggered in response to the tubercular pathogen.[6] This phenomenon can be attributed to molecular mimicry, where antigens of the tubercular bacilli resemble platelet surface antigens, leading to an autoimmune attack on these cells and resulting in thrombocytopenia, a hallmark of ES.[5] In addition to the direct immune response to the TB pathogen, there are documented cases where ES developed secondary to TB infection, potentially due to the impaired cellular immunity caused by TB itself or the immunosuppressive effects of its treatment.[6] This dual influence of TB—both as an infection and through its treatment—highlights a complex interplay between infectious agents and autoimmune disorders. The long-term immunological repercussions of TB are also significant. Studies have demonstrated that patients with a history of TB exhibit a higher incidence of autoimmune diseases, likely due to lasting alterations in their immune systems.[6] These alterations might include chronic immune activation or a shift in immune regulation, which can create a predisposition to autoimmune conditions like ES. Despite the compelling connections, the direct causality between TB and ES in our patient is less certain due to the considerable time gap of 20 years since the TB treatment and the onset of ES. However, the long-term immunological changes resulting from the past TB infection cannot be entirely dismissed. Such changes may have subtly altered the patient's immune response, making it more susceptible to autoimmune triggers encountered later in life.

While there is a well-known association between ES and hematologic malignancies, limited evidence suggests the possibility of ES as paraneoplastic syndrome. The presence of treated squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) in our patient's medical history necessitates carefully evaluating their potential influence on the onset of Evans syndrome. These skin malignancies, while not typically associated with systemic autoimmunity, can significantly impact the immune milieu of the individual. These malignancies are associated with complex immune evasion strategies, such as modulation in antigen presentation, which can increase the propensity of autoimmunity. However, most autoimmune paraneoplastic syndromes resolve after treating primary cancer, making this hypothesis less likely unless there is another undiagnosed malignancy. Thus, the importance of age-appropriate cancer screening in patients with ES is at risk.

ES presents a therapeutic challenge, often displaying reduced responsiveness to conventional treatments, leading to more recurrent relapses and an elevated mortality rate than isolated warm AIHA or ITP. A study involving 68 ES patients showed that while over 80% displayed short-term responses to treatment, only about 32% remained in remission without any treatment after an average follow-up period of 4.8 years, and 24% had passed away the condition. General recommendations include the combined administration of glucocorticoids, Rituximab, and mycophenolate mofetil,[7] supplemented with intravenous immunoglobulin (IVIG) if the platelet count dips below 20,000/microL. Glucocorticoids are most used, especially in resource-limited settings, with or without IVIG. Given that ES patients often exhibit concurrent ITP, the deployment of IVIG in their treatment is more frequent than in patients with isolated AIHA. The employment of Thrombopoietin receptor agonists remains a subject of discussion, generally assessed on an individual patient basis. Their use is often approached with caution, especially in thrombophilic conditions. In our case, thrombophilic conditions were confidently excluded prior to administering Romiplostim, and subsequent observations indicated a significant rise in the platelet count, aligning with findings from other clinical studies.

CONCLUSION

In conclusion, this case illustrates the complexity of Evans syndrome, emphasizing its multifactorial etiology, deep-rooted immune dysregulation, and association with various potential triggers. While our patient's medical history

showcases several potential instigators, ranging from vaccinations and antibiotic use to prior tuberculosis and skin malignancies, discerning the principal cause remains challenging. This reinforces the importance of a comprehensive clinical assessment, tailored therapeutic approaches, and continuous monitoring.

LEARNING POINTS

1. The cause of Evan’s syndrome is multifactorial, and there may be a potential link between vaccination and the development of the syndrome.
2. Accurate diagnosis, timely treatment, and identification of potential triggers and underlying causes are crucial in managing Evan’s syndrome.
3. When dealing with hematologic diseases, it is important to consider various factors beyond the obvious. Medication usage and previous health conditions can act as triggers for many conditions, including Evan’s syndrome.

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