*Case report*

**Primary Evans Syndrome with Concurrent Autoimmune Hemolytic Anemia and Immune Thrombocytopenia: A Rare Autoimmune Hematological Challenge**

.

**ABSTRACT**

Evans syndrome exists as a rare autoimmune condition that combines autoimmune hemolytic anemia with immune thrombocytopenia which can occur simultaneously or in sequence. A 43-year-old female with multiple comorbidities received successful Evans syndrome management which added valuable information to diagnostic methods and treatment results in the literature. The patient exhibited severe shortness of breath together with palpitations, syncope and jaundice which presented classical features of both hemolytic anemia and thrombocytopenia. Medical professionals diagnosed primary Evans syndrome through systematic investigation which excluded secondary causes and treated it successfully with corticosteroids leading to improved hematological results. The treatment of Evans syndrome requires systematic diagnostic procedures followed by immediate appropriate therapy according to this case.

*Keywords: Evans syndrome, autoimmune hemolytic anaemia, immune thrombocytopenia, corticosteroid therapy, case report*

**1. INTRODUCTION**

The rare autoimmune disorder Evans syndrome exists when patients experience autoimmune hemolytic anemia together with immune thrombocytopenia. Medical experts have not determined the exact cause of this condition but multiple genetic and environmental and immunological factors seem to trigger self-tolerance failures that produce autoantibodies against blood cells [1,2]. Patients who suffer from Evans Syndrome might develop additional autoimmune conditions such as autoimmune neutropenia and autoimmune hepatitis and systemic lupus erythematosus.

Evans syndrome can be classified as either primary (idiopathic) or secondary to underlying conditions. Primary Evans syndrome represents a diagnosis of exclusion after ruling out secondary causes including systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), common variable immunodeficiency (CVID), lymphoproliferative disorders, and certain viral infections [2,3]. This distinction is crucial as treatment approaches and prognosis may differ significantly between primary and secondary forms of the disease.

A diagnosis of Evans Syndrome requires testing blood samples alongside performing bone marrow aspiration along with potential genetic testing. Management strategies for Evans Syndrome focus on immunomodulatory drugs with corticosteroids and rituximab together with splenectomy for controlling the autoimmune process along with its clinical manifestations [3]. Evans Syndrome represents an essential case for multiple essential reasons. Medical professionals encounter difficulties in Evans Syndrome diagnosis because the condition is rare and shows multiple clinical features thus leading to delayed treatment that worsens patient outcomes. Evans Syndrome lacks effective treatment methods because scientists have not determined its origins and additional research is needed to identify the autoimmune disease mechanisms [3,4,5].

The treatment of Evans syndrome becomes challenging because patients may require numerous treatment options due to disease refractoriness and relapses. Additional research must focus on disease development understanding while developing better treatment options that address Evans Syndrome specifically.

Research indicates that Evans Syndrome exists with other autoimmune diseases and myelodysplastic syndromes based on descriptions found in literature which demonstrates these diseases share a molecular connection [2]. This potential link might enable research teams to discover new information about diseases that fall under the autoimmune and hematological categories and potentially help develop better diagnostic and therapeutic approaches.

**2. Case Presentation**

A 43-year-old female housewife visited Medical College & Hospital Kolkata because she experienced severe shortness of breath together with palpitations and syncope and dizziness when standing. She described similar events two previous times when her skin turned yellowish together with these symptoms. The patient has diabetes mellitus and hypothyroidism combined with hypercholesterolemia and hypertension which she manages through levothyroxine and metformin treatment alongside aspirin and atorvastatin medications. Her menstrual cycle included heavy bleeding which exceeded normal amounts and was painless. Diabetes and hypertension affected both parents in her family history. The patient did not show any recorded drug sensitivities or history of surgical procedures.

The patient showed signs of being conscious and cooperative yet suffered from extreme fatigue. The patient displayed severe pallor together with jaundice as important physical symptoms. Vital signs showed blood pressure measured at 129/71 mm Hg and random blood sugar level of 199 mg/dl as well as oxygen saturation at 85% and pulse rate of 123 bpm. The physician found no enlargement of liver or spleen during the examination of the patient's abdomen.

Laboratory tests at the beginning revealed substantial abnormalities in blood cell counts. Patient blood results indicated low erythrocytes and platelets along with 5 gm% hemoglobin. Peripheral blood examination showed macrocytes together with faget cells and enlarged platelets as the main findings. The Direct Coombs Test results showed positive findings which established that the patient's hemolysis had an autoimmune basis. The coagulation test results displayed elevated prothrombin time combined with elevated D-Dimer measurements. The liver tests showed increased total and direct bilirubin but all tests for HIV, HBsAg and HCV came back negative. Systemic lupus erythematosus was ruled out by the negative results from the ANA profile test.

| **Parameter** | **Result** | **Reference Range** |
| --- | --- | --- |
| **Hemoglobin** | 5.0 g/dL | 12-15.5 g/dL |
| **RBC Count** | 1.5 × 10⁶/µL | 4.2-5.4 × 10⁶/µL |
| **Platelet Count** | 45,000/µL | 150,000-450,000/µL |
| **Reticulocyte Count** | 20% | 0.5-2.5% |
| **Direct Bilirubin** | 1.5 mg/dL | 0.0-0.3 mg/dL |
| **Direct Coombs Test** | Positive | Negative |

**Table 1: Patient's  Initial Hematological and Biochemical Parameters**

The significant hemoglobin drop (5 g/dL) and platelet count decline (45,000/µL) in our patient initially raised consideration of splenic sequestration syndrome. However, the absence of splenomegaly on physical examination, along with the positive Direct Coombs test and markedly elevated reticulocyte count (20%) clearly indicated an active hemolytic process rather than sequestration. These findings, combined with the exclusion of secondary causes, confirmed the diagnosis of primary Evans syndrome

Our patient was put on methylprednisolone 1 gram intravenous daily, which was continued for the duration shown in Table 2 (approximately 11 days). From day 4 onwards, treatment was continued with high-dose methylprednisolone, with a plan to transition to oral prednisolone 1mg/kg/day for 4 weeks following discharge. The patient's haemoglobin increased from 5 gm% to 9.8 gm% on day 11 of therapy. Her platelet count rose to 30,000/mm3 on day 11 of therapy after its nadir between days 6 and 8 of therapy. Bilirubin level also decreased significantly to near normal on day 11 of treatment. These results show her good response to steroid therapy.

The patient showed remarkable improvement during hospitalization.

| **Day** | **Major Interventions** | **Medications** | **Clinical Events** |
| --- | --- | --- | --- |
| **Day 1** | Hospital admission, Initial assessment | — | Severe anemia (Hb 5.0 g/dL) and thrombocytopenia (Platelet count 45,000/µL) diagnosed. Oxygen saturation 85% on room air. |
| **Day 4** | Started methylprednisolone IV | Methylprednisolone 1g IV daily | — |
| **Day 6** | Continued therapy | Methylprednisolone 1g IV daily | Platelet count nadir of **12,500/µL**. |
| **Day 8** | Continued therapy | Methylprednisolone 1g IV daily | Platelet count **12,500/µL**. |
| **Day 11** | Treatment response assessment | Methylprednisolone 1g IV daily | Significant improvement: **RBC count (3.0 × 10**⁶**/µL), Platelet count (30,000/µL), Hemoglobin (9.8 g/dL).** Bilirubin decreasing (**0.5 mg/dL**). |
| **Day 13** | Discharge planning | — | Patient discharged with **follow-up plan**. |

**Table 2: Treatment Timeline and Interventions**

Serial monitoring of blood parameters demonstrated progressive improvement, with hemoglobin increasing from 5 gm% to 9.8 gm% by day 11. The RBC count improved from 1.5 million to 3 million, while platelet count, after reaching a nadir of 12,500 between days 6-8, recovered to 30,000 by day 11. Direct bilirubin levels decreased from 1.5 mg/dl to 0.5 mg/dl, indicating reduced hemolysis. The patient was discharged on day 13 with a plan for follow-up after one month.

| **Parameter** | **Day 1** | **Day 6** | **Day 8** | **Day 11** |
| --- | --- | --- | --- | --- |
| **RBC Count (× 10⁶/µL)** | 1.5 | 2.0 | 2.5 | 3.0 |
| **Platelet Count (/µL)** | 45,000 | 12,500 | 12,500 | 30,000 |
| **Hemoglobin (g/dL)** | 5.0 | 7.5 | 9.0 | 9.8 |
| **Direct Bilirubin (mg/dL)** | 1.5 | 1.2 | 0.8 | 0.5 |

**Table 3: Treatment Response Monitoring**

**3. discussion**

Evans syndrome was first described in 1951 by Robert Evans when a patient presented with autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura [6]. In a few cases, it is also accompanied by autoimmune neutropenia in about 15%. Cytopenias at disease onset occur concurrently (in 31% of cases) or sequentially [7]. Both AIHA and ITP occur simultaneously in 55% of cases at onset. Although Evans syndrome is commonly seen in children, the mean age at disease onset in adults is reported to be 52 years. Evans syndrome has gender predilection to females (60%). Primary Evans syndrome which is idiopathic and a diagnosis of exclusion, is observed in half of the cases. Research shows that autoimmune diseases such as SLE along with immunodeficiencies and lymphoproliferative disorders and marrow dysplastic syndromes and viral infections among other conditions are linked to the other half of patients [8,9,10].

Patients who have Evans syndrome experience symptoms of hemolysis and anemia with reticulocytosis as a bone marrow response together with thrombocytopenia signs following other cause elimination [9]. Our patient experienced severe shortness of breath combined with palpitations, syncope, dizziness, fatigue, pallor and jaundice because of her warm autoimmune hemolytic anemia. Menstruation bleeding was excessive due to the likely presence of immune thrombocytopenia.

Multiple diagnostic tests revealed decreased hemoglobin levels along with reduced platelets and an elevated reticulocyte percentage reaching 20% and higher total and indirect bilirubin together with increased lactate dehydrogenase values. The collected data points towards AIHA being the cause of hemolytic anemia along with idiopathic thrombocytopenia.

The PBS also revealed macrocytes, faget cells, and large platelets. The fact that the presence of a positive Direct Coomb’s Test in addition to the above investigation results further confirmed Evans syndrome [10].

Conditions associated with secondary Evans syndrome are excluded due to the patient's extensive workup. HIV antibodies, HCV antibodies, HBsAg, and HBcAb are all negative, ruling out HIV, HCV, and HBV infections. Our patient had no known history of relevant drugs to Evans syndrome. Few drugs such as ACE Inhibitors and NSAIDs are reported to be associated with Evans syndrome [12]. The fact that ANA and Anti-ds DNA antibodies are negative essentially rules out SLE.

Corticosteroids remain the first-line therapy for Evans syndrome. The immediate response rate of these patients to steroids is fairly high even though remission for longer periods is maintained in about one-third of the patients. This coincides with the disease’s chronic relapsing nature in the majority of the patients [12]. Hence first-line treatments are not sufficient in most patients. IVIGs are also important adjuncts to steroids when the latter are not considered sufficient to induce and maintain remission or are contraindicated. However, IVIGs have little to do with the natural course of the disease. Due to the high relapse rate in steroid therapy alone, more than half of patients require second-line therapy. Rituximab is the preferred second-line drug for refractory Evans syndrome with a rate of achieving remission in two-thirds of patients at 1-year follow-up and almost one-third of patients never relapsed. The majority of patients need to undergo treatment with at least three different approaches. Medical treatment options also include splenectomy as well as immunosuppressants and stem cell transplantation. The medical procedure of splenectomy shows high success rates for Evans syndrome patients because it produces sustained results in 50% of cases along with no recurrence in 31% of patients. Modern medical practice uses immunosuppressive drugs cyclosporine, cyclophosphamide, mycophenolate mofetil and azathioprine and sirolimus mainly for unresponsive patients or those requiring chemotherapy for hematologic malignancies. Despite the popular belief that hematopoietic stem cell transplantations as a long-lasting solution to Evans syndrome, strong pieces of evidence are lacking on their outcomes. People do not generally recommend them except for patients who have run out of other treatment options [9,11].

For patients with refractory disease or those who experience frequent relapses despite corticosteroid therapy, surgical interventions may be considered. Splenectomy has shown efficacy in approximately 50% of Evans syndrome cases with sustained results and no recurrence in about 31% of patients [13]. The procedure works by removing a major site of antibody production and destruction of antibody-coated blood cells. However, the risk of post-splenectomy infections and thromboembolic complications must be carefully weighed against potential benefits. Hematopoietic stem cell transplantation (HSCT) represents a more aggressive approach reserved for severe, refractory cases that have failed multiple lines of therapy. While HSCT offers the potential for long-term remission by replacing the dysfunctional immune system, its significant morbidity and mortality risks limit its use to the most severe cases under specialist care [14].

Our patient was put on methylprednisolone 1 gram intravenous daily for 3 days. From day 4 onwards, she was started on prednisolone 1mg/kg/day for 4 weeks. The patient’s hemoglobin increased from 5 gm% to 9.8 gm% on day 11 of therapy. Her platelet count rose to 30,000/mm3 on day 11 of therapy after its nadir between days 6 and 8 of therapy. Bilirubin level also decreased significantly to near normal on day 11 of treatment. These results show her good response to steroid therapy.

Evans syndrome, though it is a rare disorder, should always be considered in patients presenting with symptom complexes of anemia and low platelet count. Furthermore, these patients should be investigated extensively to rule out secondary causes. Our patient was just put on the first line of treatment during her hospital course and was discharged from the hospital being on prednisolone. Because of the disease’s nature of high relapse rate and risk of development of other autoimmune and hematologic disorders, it is necessary to have a strict follow-up in such patients.

**4. Conclusion**

This case demonstrates the successful management of primary Evans syndrome in a 43-year-old female with multiple comorbidities. The patient's positive response to corticosteroid therapy highlights the efficacy of this first-line treatment approach, with significant improvements in hemoglobin levels and platelet counts within days of initiation. However, given the chronic relapsing nature of Evans syndrome, long-term follow-up is essential to monitor for disease recurrence and potential treatment-related complications. For patients who fail to respond adequately to corticosteroids or experience frequent relapses, escalation to second-line therapies such as rituximab, immunosuppressants, splenectomy, or in severe refractory cases, hematopoietic stem cell transplantation may be warranted. A multidisciplinary approach involving hematologists, immunologists, and surgeons is crucial for optimizing outcomes in this rare but challenging autoimmune disorder.

**Consent (where ever applicable)**

Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

**Ethical approval (where ever applicable)**

As per international standards or university standards written ethical approval has been collected and preserved by the author(s).

**Disclaimer (Artificial intelligence)**

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

Option 2:

Author(s) hereby declare that generative AI technologies such as Large Language Models, etc. have been used during the writing or editing of manuscripts. This explanation will include the name, version, model, and source of the generative AI technology and as well as all input prompts provided to the generative AI technology

Details of the AI usage are given below:

1.

2.

3.

**References**

1.Grimes, A. B., Kim, T. O., Kirk, S. E., Flanagan, J. M., Lambert, M. P., Grace, R. F., & Despotovic, J. M. (2021). Refractory autoimmune cytopenias in pediatric Evans syndrome with underlying systemic immune dysregulation. In European Journal Of Haematology (Vol. 106, Issue 6, p. 783). Wiley. <https://doi.org/10.1111/ejh.13600>

2.Hochman, M. J., & DeZern, A. E. (2022). Myelodysplastic syndrome and autoimmune disorders: two sides of the same coin? [Review of Myelodysplastic syndrome and autoimmune disorders: two sides of the same coin?]. The Lancet Haematology, 9(7). Elsevier BV. https://doi.org/10.1016/s2352-3026(22)00138-7

3.Koster, M. J., Lasho, T. L., Olteanu, H., Reichard, K. K., Mangaonkar, A. A., Warrington, K. J., & Patnaik, M. M. (2023). VEXAS syndrome: Clinical, hematologic features and a practical approach to diagnosis and management [Review of VEXAS syndrome: Clinical, hematologic features and a practical approach to diagnosis and management]. American Journal of Hematology, 99(2), 284. Wiley. https://doi.org/10.1002/ajh.27156

4.Austestad, J., Madland, T. M., Sandnes, M., Haslerud, T., Benneche, A., & Reikvam, H. (2023). VEXAS Syndrome in a Patient with Myeloproliferative Neoplasia. In Case Reports in Hematology (Vol. 2023, p. 1). Hindawi Publishing Corporation. <https://doi.org/10.1155/2023/6551544>

5.Staels, F., Betrains, A., Woei‐A‐Jin, F. J. S. H., Boeckx, N., Beckers, M., Bervoets, A., Willemsen, M., Neerinckx, B., Humblet‐Baron, S., Blockmans, D., Vanderschueren, S., & Schrijvers, R. (2021). Case Report: VEXAS Syndrome: From Mild Symptoms to Life-Threatening Macrophage Activation Syndrome. In Frontiers in Immunology (Vol. 12). Frontiers Media. https://doi.org/10.3389/fimmu.2021.678927

6.Michel M, Chanet V, Dechartres A, Morin AS, Piette JC, Cirasino L, Emilia G, Zaja F, Ruggeri M, Andrès E, Bierling P, Godeau B, Rodeghiero F. The spectrum of Evans syndrome in adults: new insight into the disease based on the analysis of 68 cases. Blood. 2009 Oct 8;114(15):3167-72. doi: 10.1182/blood-2009-04-215368. Epub 2009 Jul 28. PMID: 19638626.

7.Dhingra KK, Jain D, Mandal S, Khurana N, Singh T, Gupta N. Evans syndrome: a study of six cases with review of literature. Hematology. 2008 Dec;13(6):356-60. doi: 10.1179/102453308X343518. PMID: 19055865.

8.Wang WC. Evans syndrome in childhood: pathophysiology, clinical course, and treatment. Am J Pediatr Hematol Oncol. 1988 Winter;10(4):330-8. doi: 10.1097/00043426-198824000-00013. PMID: 3071168.

9.Audia S, Grienay N, Mounier M, Michel M, Bonnotte B. Evans' Syndrome: From Diagnosis to Treatment. J Clin Med. 2020 Nov 27;9(12):3851. doi: 10.3390/jcm9123851. PMID: 33260979; PMCID: PMC7759819.

10.Jäger U, Barcellini W, Broome CM, Gertz MA, Hill A, Hill QA, Jilma B, Kuter DJ, Michel M, Montillo M, Röth A, Zeerleder SS, Berentsen S. Diagnosis and treatment of autoimmune hemolytic anemia in adults: Recommendations from the First International Consensus Meeting. Blood Rev. 2020 May;41:100648. doi: 10.1016/j.blre.2019.100648. Epub 2019 Dec 5. PMID: 31839434.

11.Fattizzo B, Michel M, Giannotta JA, Hansen DL, Arguello M, Sutto E, Bianchetti N, Patriarca A, Cantoni S, Mingot-Castellano ME, McDonald V, Capecchi M, Zaninoni A, Consonni D, Vos JM, Vianelli N, Chen F, Glenthøj A, Frederiksen H, González-López TJ, Barcellini W. Evans syndrome in adults: an observational multicenter study. Blood Adv. 2021 Dec 28;5(24):5468-5478. doi: 10.1182/bloodadvances.2021005610. PMID: 34592758; PMCID: PMC8714709.

12.Ahoussougbemey Mele A, Chew C, Ruiz Vega R, Mahmood R, AlRubaye R. Naproxen-Induced Evans Syndrome. Cureus. 2023 Feb 13;15(2):e34910. doi: 10.7759/cureus.34910. PMID: 36938179; PMCID: PMC10016752.

13. Giudice V, Rosamilio R, Ferrara I, Seneca E, Serio B, Selleri C. Efficacy and safety of splenectomy in adult autoimmune hemolytic anemia. Hematology. 2020;25(1):19-24.

14. Rabuñal Martínez MJ, Ríos Herranz E. Hematopoietic stem cell transplantation in Evans syndrome. Med Clin (Barc). 2019;153(10):418-423.