Early-onset Evans Syndrome in a 4-Month-Old Infant: A Case Report and Review of Literature

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ABSTRACT

Evans syndrome (ES) is a rare autoimmune disorder characterized by autoimmune hemolytic anemia (AIHA) and immune thrombocytopenic purpura (ITP). We report a case of a 4-month old infant who presented with a history of acute pallor and jaundice. She had no family history of any hematological or autoimmune disorders. Her laboratory investigations revealed a positive direct Coombs test with immunoglobulin G autoantibodies, anemia and thrombocytopenia. She was managed initially by blood transfusion and started on high-dose steroid therapy with marked improvement. Very few cases of ES in infants have been reported in the literature. We concluded that this case report may support the possibility of an early-onset ES among infants <6 months of age.

Key words: Autoimmune hemolytic anemia, corticosteroids, Evans syndrome, immune thrombocytopenic purpura, infants, rare diseases

INTRODUCTION

Evans syndrome (ES) is a rare autoimmune hematologic disorder characterized by simultaneous or sequential presence of a positive antiglobulin test, autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP).[1] ES was first described in 1951 in 24 patients aged 3–78 years by Robert Evans.[2] The precise incidence of ES has not yet been determined with the related literature of scant isolated case reports and limited retrospective or questionnaire-based series.[3-6] It is recognized as a poor prognostic factor in autoimmune cytopenias.[7] ES has been reported in only ten infants <12 months of age.[3-8] Due to the rarity and lack of comprehensive background of such diagnosis in pediatric age group, our aim is to raise the possibility of early-onset presentation of ES.

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CASE REPORT

A female Saudi infant presented to our hospital at the age of 4 months with a history of acute pallor, jaundice and poor feeding of 7 days’ duration. The full-term infant was delivered after an uneventful pregnancy via an elective cesarean section with a birth weight of 2850 g. The infant’s mother had no history of chronic illness.

The infant had neither history of bleeding tendencies nor a family history of hematologic or autoimmune disorders. She also had neither history of recent infections nor contact with ill patients. Apart from her vitamin D supplement, the infant had not been prescribed any other medication. Her growth parameters were appropriate for age. Her abdominal examination did not reveal any abdominal distention or organomegaly, and the rest of her systemic examination was within normal range.

The infant’s initial laboratory results revealed the following values: hemoglobin (Hgb) was 5.4 g/dl, red blood cell (RBC) was 1.62 Mil/ul, mean corpuscular volume was 111.4 fL, mean corpuscular hemoglobin was 33.5 pg and 18.7% reticulocytes and platelets were in clumps for the first two readings, then it was 72 k/ul and decreased to 62 k/ul. White blood cells count was 20 k/ul with a normal differential count. Liver chemistry showed an increased total bilirubin of 6.1 mg/dl, with normal direct bilirubin level and elevated levels of lactate dehydrogenase reaching 1477 U/L. Her direct Coombs test (DCT) was positive only for immunoglobulin G (IgG) autoantibodies. The blood smear did not show evidence of RBC fragmentation [Figure 1]. Both the infant’s and the mother’s blood groups (A, Rh+) were compatible. Hgb electrophoresis showed normal values for age without evidence of Hgb-opathies. Folate and vitamin B12 levels were within normal ranges. Antinuclear antibodies test was negative.

As a result of the low level of Hgb, the patient was immediately transfused with packed RBCs. A bone marrow examination revealed normal cellularity with a normal level of megakaryocytes and brisk hyperplasia of erythroid series representing 76% of bone marrow mononuclear cells. In addition, there was an increment of abnormal blasts and hemophagocytes. However, no dysplastic cells were found on bone marrow film [Figure 2]. IgM-antibodies against cytomegalovirus, Epstein–Barr virus and human immunodeficiency virus antibody were not detected. During her hospital stay, the patient’s Hgb declined gradually after she received her initial transfusion upon admission, with a major decrease from 9.4 g/dl to 6.8 g/dl within a 4-day period, for which she received another blood transfusion. Her platelets count also gradually decreased until it reached 64,000/ul. The patient’s complete blood count values trend is shown in Table 1.

On the 5th day of admission, high-dose steroid (methylprednisolone: 10 mg/kg/day) was started; accordingly, after the bone marrow aspiration, not only her Hgb improved significantly, but also the platelets count increased (from 64 to 136 k/ul) in association with decrement in reticulocytes (from 18.7% to 11.6%) [Figure 3]. The steroid dose was tapered over 4 days until it was 4 mg/kg/day. The Hgb level ranged between 10.4 and 11.5 g/dl without transfusion. Accordingly, the patient was prescribed prednisolone (4 mg/kg/day) and discharged from the hospital in a stable condition. Due to the presence of positive DCT of IgG-autoantibodies, anemia and thrombocytopenia, we diagnosed the infant with ES.

DISCUSSION

In 1951, Robert Evans identified the association between immune thrombocytopenic purpura (ITP) and AIHA, both mediated by autoantibodies.[2] ES is currently defined as autoimmune destruction of at least two hematologic cell types after exclusion of other diagnoses;[3-7] however, in our case, only anemia and thrombocytopenia have been described. In children, autoimmune cytopenia may indicate the presence of an underlying primitive immunodeficiency (PID). These conditions have an unknown etiology. However, there

| Day | WBC (k/ul) | Hgb (g/dl) | Platelets count (k/ul) | Neutrophils (%) | Reticulocytes (%) |
|-----|------------|------------|------------------------|----------------|-----------------|
| 1   | 13.8       | 5.4        | In clumps              | 39             | 18.7            |
| 2   | 17.8       | 9.4        | In clumps              | 43             | -               |
| 3   | 10.6       | 8.5        | 72                     | 42             | 14.9            |
| 4   | 16.8       | 8.2        | 62                     | 30             | 11.7            |
| 5   | 14.6       | 7.5        | In clumps              | 28             | 15.3            |
| 5   | 12.1       | 6.8        | 64                     | 23             | -               |
| (repeated) | | | | | |
| 6   | 6.5        | 11.7       | 136                    | 70.5           | 11.6            |
| 7   | 15.2       | 10.7       | 136                    | 84             | -               |
| 8   | 14.3       | 11.5       | 202                    | 76.5           | -               |
| 9   | 7.8        | 10.5       | 223                    | 71.9           | 12.2            |
| 11  | 9          | 10.4       | 277                    | 70.9           | 7.8             |

Abnormal values are in bold. WBC – White blood cell count, Hgb: Hemoglobin
are a number of mechanisms that have been proposed for such an alteration in immune regulation.\[8\]

The exact incidence of ES remains unknown. However, the largest reported series of pediatric ES included 164 cases of ITP and 15 of AIHA; only 7 (4.1%) children were diagnosed with the syndrome.\[4\] In the adult series of Michel et al., which included 68 ES patients, no PID was reported and eight cases were associated with hematologic malignant conditions while in another study of pediatric series, 3/156 PIDs were identified and no cases of cancer occurred despite significant follow-up and an adequate survey.\[1,8\]

The differential diagnoses for ES include ITP, chronic cold agglutinin disease, other causes of acquired or hereditary hemolytic anemia, drug-induced hemolytic anemia and/or thrombocytopenia. It is important to mention that our patient had been excluded from having any of the other differential diagnoses of ES by means of laboratory investigations and bone marrow examination.

A review of the literature revealed that fewer than 100 heterogeneous cases of ES have been published. In addition, it has been reported in only ten infants <12 months of age.\[3-8\] This observation indicated that our patient was one of the youngest to develop such a syndrome and this should raise the possibility of an early-onset presentation of ES.

In our patient, bone marrow aspiration was done before prescribing steroid therapy to confirm the active megakaryopoiesis, which points to immune destruction of the platelets and rules out hyporegenerative thrombocytopenia that is caused by expansion of the erythroid series.\[9\] Regarding the macrocytosis that was found in our patient, it can be explained by reticulocytosis (18.7%), which may give a false, spurious macrocytosis. It also can be explained by the agglutination that may occur in autoimmune hemolysis.\[9\]

In former study series, the reported mortality rates for childhood ES were 7% (3/42),\[3\] 30% (3/10)\[6\] and 36% (4/11).\[3,5,6\] The disease is characterized by frequent exacerbations and remissions within a chronic course and response to treatment varies even for the same individual. It is apposite to highlight that there are neither management guidelines nor standardized response criteria for ES.\[7\] Norton and Roberts reported that indications for treatment have not been established by any other evidence-based study. However, it is reasonable and usual to treat symptomatic patients
with low blood counts; not all asymptomatic patients with low counts require treatment and the decision to treat or not should be considered according to each individual case.\[10\] Moreover, one of the crucial elements of management criteria is the patient’s age upon diagnosis of ES, especially when the patient is an infant. Delaying the management of patients in this age group, even with an asymptomatic low blood count, could lead to a catastrophic event with subsequent presentations.

Corticosteroids remain the cornerstone of therapy of the acute symptomatic cytopenias, with good initial results, despite lack of controlled trials proving their efficacy.\[10\] Pui et al. found that prednisolone at a daily dose of 1–2 mg/kg resulted in remission. However, there was no remission on dose reduction and/or acute viral infections.\[4\] Our patient did respond well to the initial exclusive management of steroids (methylprednisolone: 10 mg/kg/day) within 24 h during which time her Hgb and platelets levels normalized. In case of ineffective or unacceptably high doses of steroids are required to maintain remission or if toxicity occurs, the most commonly used treatment is IVIG. The second-line treatment includes immunosuppressive agents (e.g., cyclosporine), chemotherapy (e.g., cyclophosphamide), danazol and monoclonal antibodies (e.g., rituximab).\[10\]

A treatment observation was reported by Norton and Roberts regarding the role of splenectomy in ES, which was traditionally used as the initial second-line therapy in patients with autoimmune cytopenia (ITP or AIHA) who did not respond to or relapsed after standard therapy with steroids with or without IVIG. However, the role of splenectomy in the treatment of ES is not clearly established.\[10\] Unfortunately, the majority of patients relapse as therapy is tapered down and a second-line therapy will be required.

**CONCLUSION**

We conclude that ES can be presented acutely in infants of <6 months of age. The acquisition of a DCT in infants presenting with acute pallor and jaundice should be considered as a routine test to exclude autoimmune causes. AIHA and thrombocytopenia in association with positive DCT confirm the diagnosis of ES. Bone marrow examination prior to initiation of steroid therapy will help exclude malignancy and will confirm the original diagnosis.

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**Conflicts of interest**
There are no conflicts of interest.

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