American Journal of Case Reports

e-ISSN 1941-5923
© Am J Case Rep, 2020; 21: e920760
DOI: 10.12659/AJCR.920760

Received: 2019.10.16
Accepted: 2019.12.03
Available online: 2020.01.24
Published: 2020.02.07

A Case of Evans Syndrome with Acute Hemolysis and Hemoglobin Cast Nephropathy

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Data Collection B
Statistical Analysis C
Data Interpretation D
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Conflict of interest: None declared

Patient: Male, 60-year-old
Final Diagnosis: Evans syndrome
Symptoms: Back pain
Medication: —
Clinical Procedure: —
Specialty: Hematology

Objective: Rare disease

Background: Evans syndrome is characterized by 'warm' autoimmune hemolytic anemia and autoimmune thrombocytopenia, and is more common in the pediatric population than in adults. Evans syndrome is often associated with underlying autoimmune disease, connective tissue disease, immune deficiency disorders, lymphoproliferative disorders, or malignancy of the immune system. A case is presented of acute kidney injury due to hemoglobin cast nephropathy in an adult man with Evans syndrome.

Case Report: A 60-year-old man was diagnosed with Evans syndrome, which was complicated by acute renal failure that required treatment with hemodialysis. Laboratory tests and renal histology confirmed a diagnosis of hemolysis-associated hemoglobin cast nephropathy.

Conclusions: The diagnosis of Evans syndrome is important as it may be associated with underlying hematological and immunological disorders. Although rare, hemoglobin cast nephropathy due to hemolysis can be a cause of acute kidney injury in patients with Evans syndrome.

MeSH Keywords: Acute Kidney Injury • Anemia, Hemolytic • Anemia, Hemolytic, Autoimmune • Purpura, Thrombocytopenic, Idiopathic • Thrombocytopenia

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/920760

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Background

Evans syndrome is a rare disorder characterized by 'warm' autoimmune hemolytic anemia, autoimmune thrombocytopenia, and autoimmune neutropenia. Evan and Duane first described the syndrome in 1951 [1]. Evans syndrome is more common in the pediatric population than in adults and is often associated with underlying autoimmune disease, connective tissue disease, immune deficiency disorders, lymphoproliferative disorders, or malignancy of the immune system. Evans syndrome is classified as either primary or secondary, depending on the presence of underlying autoimmune disease or connective tissue disease. Associated diseases include systemic lupus erythematosus (SLE), autoimmune lymphoproliferative syndrome (ALPS), and immune deficiency disorders such as common variable immunodeficiency (CVID), or lymphoid malignancy, including non-Hodgkin's lymphoma (NHL), and chronic lymphocytic leukemia (CLL) [1]. The degree of intravascular hemolysis in Evans syndrome often results in hemoglobinemia, which may lead to hemoglobin cast nephropathy, acute tubular necrosis (ATN), and acute kidney injury [2].

Case Report

A 60-year-old man with a history of hypertension and obstructive sleep apnea presented to an external hospital with sudden onset of severe low back pain and hematuria. He was anemic with initial investigations indicating a hemolytic process. He had acute kidney injury (AKI) and low to normal platelet levels. Due to concerns for the presence of thrombotic thrombocytopenic purpura (TTP), he was treated with high-dose steroids (methylprednisolone 1 g) and underwent plasma exchange (PLEX). During his hospitalization, he developed acute renal failure with an acute rise in creatinine from 1.5 mg/dL to 7 mg/dL and a low urine output that required treatment with hemodialysis.

He was transferred to our hospital for further management. His recent medical history included a sore throat and body aches two weeks previously, recent use of ibuprofen, and jaundice that developed during the previous week. He reported a similar history more than one year previously, which had been associated with low blood counts. At that time, he was told that he had a viral illness that spontaneously resolved. He was also diagnosed with deep vein thrombosis (DVT) at the time and was treated with rivaroxaban for three months.

On admission, physical examination showed that he was mildly jaundiced with scleral icterus and generalized peripheral edema. There was no evidence of petechiae, skin rash, or oral ulcers. His hemoglobin level had fallen to 6.0 g/dL, with a low haptoglobin of <8 mg/dL, increased serum levels of low-density lipoprotein (LDL) of >3000 U/L, increased unconjugated total bilirubin of 4.1 mg/dL, and thrombocytopenia with platelet levels of 122×10^3/mcL. Renal failure was identified with the findings of serum creatinine (Cr) of 6.27 mg/dL and urinalysis that showed protein (2+), and blood (3+). An initial peripheral blood smear showed spherocytes with no schistocytes. Serum ferritin levels were >40,000 ng/ml, and the white blood cell (WBC) count was 27×10^3/mcL, indicating a severe inflammatory response. Given his significant hematological changes and laboratory findings of renal failure, the differential diagnosis included thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), systemic rheumatic disease, paroxysmal nocturnal hemoglobinuria (PNH), Evans syndrome, sepsis with disseminated intravascular coagulation (DIC), and hemophagocytic lymphohistiocytosis (HLH).

Treatment continued with 250 mg and methylprednisolone, and he was referred to the Departments of Hematology and Nephrology. Hematology investigations showed a positive direct Coombs test for autoimmune hemolytic anemia with 'warm' IgG and C3d antibodies, and antiplatelet antibodies to glycoproteins GPIIb/IIIa, GPIb/IX, and GPIa/IIa. He had low ADAMTS-13 activity (39%), which was believed to be low secondary to high levels of free hemoglobin. The patient underwent tests for secondary Evans syndrome and was found to have negative results for antinuclear antibody (ANA), antineutrophil cytoplasmic antibody (ANCA), extractable nuclear antigen (ENA), anticardiolipin antibody, but had no antibodies to lupus anticoagulant, and human immunodeficiency virus (HIV). Tests for paroxysmal nocturnal hemoglobinuria (PNH), the Donath–Landsteiner test for paroxysmal cold hemoglobinuria, cold agglutinins, and serum protein electrophoresis (SPEP) tests were all negative.

Treatment was commenced with prednisone 1 mg/kg for a total of 30 days and intravenous rituximab 100 mg each week for four weeks. He underwent renal biopsy and histology, which showed hemoglobin cast nephropathy, and immunohistochemistry showed that the casts were positive for hemoglobin, but there were with histological findings of microangiopathy (Figure 1).

Treatment with high-dose steroids and intravenous rituximab reduced hemolysis, improved renal function, and improved urine output. He was discharged from hospital on high-dose prednisone with plans to continue intravenous rituximab and intermittent hemodialysis. Following discharge from hospital, he underwent bone marrow biopsy, which showed mild hypocellularity and reduced hematopoiesis with no significant dysplasia or increased blasts with no evidence of metastatic carcinoma, lymphoma, or granulomas. Flow cytometry showed no evidence of lymphoproliferative disorder or myeloid neoplasm.

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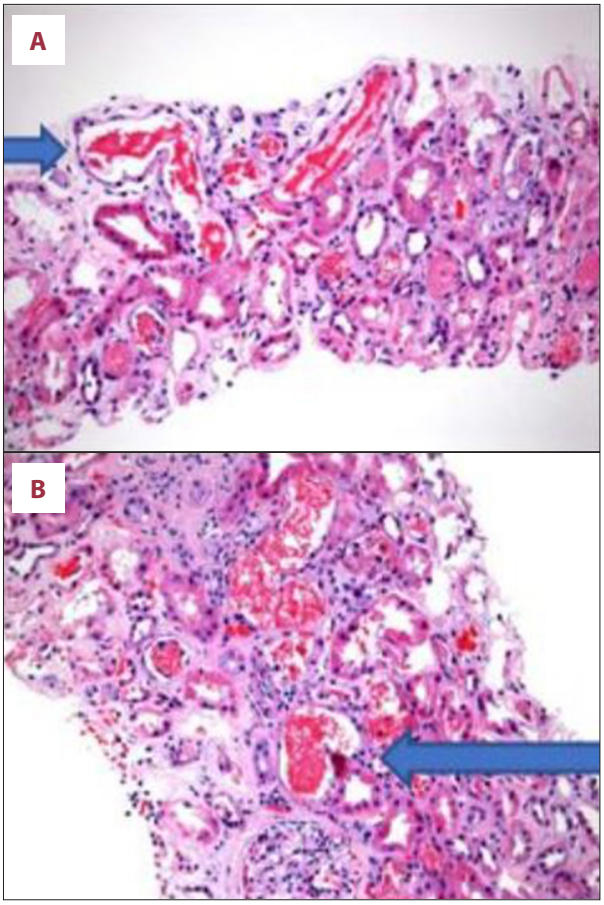

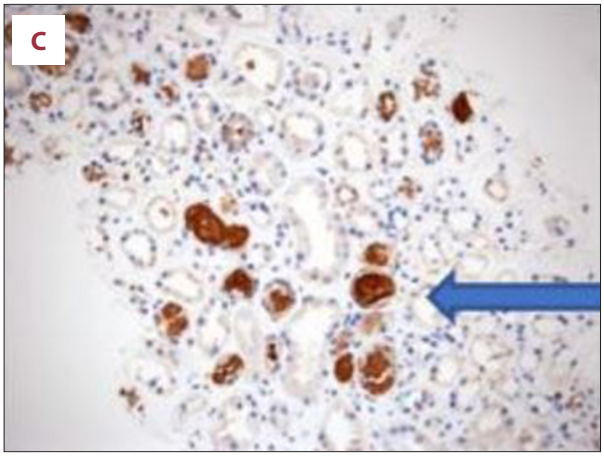

Figure 1. Photomicrographs of the histology and immunohistochemistry of the renal biopsy from a 60-year-old man with Evans syndrome and acute hemoglobin cast nephropathy. (**A**) Histology of the renal biopsy shows that the renal tubules contain pigmented casts. Hematoxylin and eosin (H&E). (**B**) Histology of the renal biopsy shows that the renal tubules contain pigmented casts. Hematoxylin and eosin (H&E). (**C**) Immunohistochemistry shows that the renal tubule casts stain positively with antibodies to hemoglobin.

Discussion

Evans syndrome includes 'warm' autoimmune hemolytic anemia and autoimmune thrombocytopenia and is caused by autoantibodies that result in both platelet dysfunction and red blood cell damage. Evans syndrome occurs more commonly in children but can present in adults, with a mean age of >50 years [3]. Evans syndrome is diagnosed in less than 5% of patients with idiopathic thrombocytopenic purpura (ITP) or autoimmune hemolytic anemia (AIHA). Evans syndrome is often more challenging to treat than AIHA alone, treatment often requires the use of steroids, and Evans syndrome has a higher mortality rate than AIHA [4].

The pathophysiology of Evans syndrome remains unknown, but it is recognized as a condition of immune dysregulation [3]. Recent molecular theories include deficiencies of cytotoxic T-lymphocyte antigen 4 (CTLA-4), lipopolysaccharide responsive beige-like anchor protein (LRBA), tripeptidyl peptidase 2 (TPP2), and a reduced CD4/CD8 ratio [5]. Many cases are idiopathic, as was the case with this patient. To determine whether Evans syndrome is primary or idiopathic, underlying causes or secondary causes of Evans syndrome should be excluded. There is an association between Evans syndrome and underlying autoimmune and lymphoproliferative disorders, infections that include human immunodeficiency virus (HIV), hepatitis C virus (HCV), and thrombotic events [3]. In a study reported by Michel et al., up to 50% of cases of Evans syndrome were associated with an underlying disorder, predominantly SLE [3]. Common variable immunodeficiency was also seen in patients younger than 45 years [3]. Non-Hodgkin's lymphoma was the most commonly associated disease in patients >50 years [3]. Although cases may be initially classified as idiopathic, with no underlying cause or association, as in this case, patients may still develop one of the main associated conditions later in life. Therefore, patients diagnosed with Evans syndrome require close hematologic monitoring and follow-up.

Although there is no standard diagnostic approach to laboratory tests for Evans syndrome, a systematic approach should be taken to screen patients for underlying or associated diseases. There is an association between Evans syndrome and underlying systemic lupus erythematosus (SLE), and investigations for the presence of antinuclear antibodies (ANAs) and anti-double-stranded DNA should be undertaken [6]. Given that patients with Evans syndrome are at increased risk of thrombotic events, tests for anticardiolipin antibodies and a lupus anticoagulant test should also be considered. Also, an infection screen should be performed to exclude infections with human immunodeficiency virus (HIV), hepatitis B virus (HBV), and hepatitis C virus (HCV). In the adult age group of patients with Evans syndrome, serum protein electrophoresis (SPEP),

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and computed tomography (CT) imaging of the chest, abdomen, and pelvis should be considered to exclude underlying malignancy, and cancer screening appropriate for age and gender should be performed [3].

First-line treatment consists of high-dose glucocorticoids, such as prednisone, at a dose of 1 to 2 mg/kg per day. Azathioprine, cyclophosphamide, danazol, and intravenous rituximab are often second-line treatment agents. In previous decades, the classic preferred second-line treatment was splenectomy, but the use of agents such as intravenous rituximab has become the preferred second-line treatments [4].

In this case, the severity of hemolysis resulted in acute renal failure secondary to heme pigment nephropathy (Figure 1). The degree of hemolysis saturates haptoglobin leaving free hemoglobin to damage the renal tubules. Patients will often have abnormal laboratory findings of anemia, increased levels of lactate dehydrogenase (LDH), reduced haptoglobin, and increased serum creatinine. Urine dipstick testing may be positive for blood in the absence of erythrocytes. Other urine tests include pigmented granular casts and hemoglobinuria.

Hemolysis-associated hemoglobin cast nephropathy results from direct damage to the renal tubule from heme pigment through several mechanisms [2]. Damage occurs via renal vasoconstriction, direct tubular damage by the inflammatory effect of hemoglobin, and intraluminal cast formation, which plugs the tubules and damages the cells [7]. Hemoglobin pigment nephropathy caused by myoglobin is often seen and best described as a complication of rhabdomyolysis. Rarely, hemoglobin cast nephropathy occurs following intravascular hemolysis due to sepsis, paroxysmal nocturnal hemoglobinuria (PNH), valvular heart disease, and malaria [8]. It is rarely seen in association with Evans syndrome alone but has been reported in a pediatric case, diagnosed postmortem [9]. Hemoglobin cast nephropathy has also been reported in an adult woman who was later diagnosed with lupus nephritis, in a case of secondary Evans syndrome [6]. The association between Evans syndrome and acute kidney injury with autoimmune disease or lymphoproliferative disorder can result in renal damage due to mechanisms other than hemoglobin pigment nephropathy [10]. In addition to hemoglobin pigment nephropathy, other uncommon complications associated with Evans syndrome have been reported, including non-traumatic subarachnoid hemorrhage [11].

Although rare, Evans syndrome in the adult population should be recognized and patients should be investigated for the presence of underlying hematological and immunological disorders. Patients with Evans syndrome are at increased risk of thromboembolic events, autoimmune and connective tissue disorders, and malignancy of the immune system at the time of diagnosis or even years later. Having a systematic diagnostic approach and undertaking basic laboratory investigations will help to identify causes and associations, if present, and improve the management of this condition and its complications. Although exceeding rare, hemoglobin pigment nephropathy can be a cause of acute kidney injury in Evans syndrome and should be considered in the appropriate clinical context.

Conclusions

This case report has highlighted the importance of the recognition and diagnosis of Evans syndrome, as patients are at increased risk of underlying hematological and immunological disorders. In Evans syndrome, autoimmune hemolysis may result in hemoglobin pigment nephropathy and acute kidney injury. Prompt diagnosis and treatment is important to reduce patient morbidity. A systematic diagnostic approach is helpful, given that Evans syndrome is rare in the adult population and can be challenging to diagnose. Increased awareness of the rare complications associated with Evan syndrome should be considered in the correct clinical context.

Conflict of interest

None.

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