Evans Syndrome with Acute Kidney Injury

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Abstract
Evans syndrome is a rare syndrome associated with the simultaneous or sequential development of autoimmune hemolytic anemia (AIHA) and idiopathic thrombocytopenic purpura (ITP). Furthermore, acute kidney injury (AKI) is a syndrome characterized by the rapid loss of kidney excretory function and is most often secondary to extrarenal events. However, AKI has rarely been recorded in Evans syndrome without systemic autoimmune disease and malignant tumors of the blood and lymphatic system. Herein, we report the case of a patient who exhibited Evans syndrome presenting with AKI.

A 73-year-old woman presented with diarrhea, anuria, low platelet count, and a progressive increase in blood urea nitrogen and serum creatinine as well as anemia with a positive direct Coombs test. We excluded hemolytic uremic syndrome, ITP, and leukemia. Treatment with antibiotics, rehydration therapy, and hemodialysis resulted in partial remission. Thus, we diagnosed the patient with Evans syndrome presenting with AKI. The patient was successfully treated by the addition of steroid treatment. When AKI presents with hemolysis and thrombocytopenia, physicians should consider Evans syndrome, which can be appropriately treated when detected early.

Keywords: Acute kidney injury, Evans syndrome


Introduction
Evans syndrome, which was first described by Evan and Duane in 1951, is a rare syndrome associated with the simultaneous or sequential development of autoimmune hemolytic anemia (AIHA) and idiopathic thrombocytopenic purpura (ITP).1 In this syndrome, antibodies and/or complement cause lysis of red blood cell membranes, leading to progressive red blood cell damage and hemolytic anemia. Antiplatelet autoantibodies are produced simultaneously; thus, reduced platelet count is observed in patients with AIHA or ITP.2 Evans syndrome may occur simultaneously with or as a subsequent complication of many diseases, including systemic lupus erythematosus, Hashimoto’s thyroiditis, scleroderma, dermatomyositis, rheumatoid arthritis, primary hyperthyroidism, malignant tumors of the blood and lymphatic system, other malignant diseases (e.g., thymoma, some solid tumors), and immunodeficiencies. The primary clinical manifestations of Evans syndrome include anemia, bleeding, jaundice, hepatosplenomegaly, and hemoglobinuria. Furthermore, it is a poor prognostic factor in autoimmune cytopenias.3,4

Acute kidney injury (AKI) is a syndrome characterized by the rapid loss of kidney excretory function and is most often secondary to extrarenal events.5 AKI secondary to Evans syndrome has rarely been recorded. Here, we report a case of Evans syndrome presenting with AKI, which was successfully treated by steroid administration.

Case Report
A 73-year-old woman presented with complaints of diarrhea, vomiting, and increased serum creatinine for 2 days in August 2015, after developing the symptoms of a cold. On that day, she had passed watery stool three times, totaling approximately 1000 g. She had also vomited three times, totaling approximately 200 g, and exhibited tea-colored urine output of approximately 50 mL daily. She had no prior history of fever, cough, abdominal cramps, or urinary irritation symptoms. She was treated in our hospital emergency department. Peripheral blood count and a renal function test showed the following: white blood cell count (WBC) of 14.27 × 10^9/L, hemoglobin (Hb) of 104 g/L, platelet count (PLT) of 70 × 10^9/L, and serum creatinine (SCr) of 734 μmol/L (Table 1). She reported a history of AIHA and urticaria 4 years prior. Two years prior, she had exhibited anemia, thrombocytopenia, and renal injury after acute gastroenteritis. She was treated in our hospital emergency department. Peripheral blood count and a renal function test showed the following: white blood cell count (WBC) of 14.27 × 10^9/L, hemoglobin (Hb) of 104 g/L, platelet count (PLT) of 70 × 10^9/L, and serum creatinine (SCr) of 734 μmol/L (Table 1). She reported a history of AIHA and urticaria 4 years prior. Two years prior, she had exhibited anemia, thrombocytopenia, and renal injury after acute gastroenteritis. She was diagnosed with acute renal injury, acute gastroenteritis, and AIHA in both January 2014 and July 2014 (Table 1).

Physical examination revealed a temperature of 36.5°C, breathing rate of 18 breaths/min, blood pressure of 88/56 mm Hg, and weight of 50 kg. The patient exhibited no eruption or purpura on the skin. Her chest examination was normal. Her heart rate was 95 bpm, regular and
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Table 1. The Results of the Auxiliary Examination

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<tr>
<td>Complete blood count</td>
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<td></td>
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<tr>
<td>White blood cells (×10^6)</td>
<td>↑ 13.87×10^6</td>
<td>↑ 9.49×10^6</td>
<td>↑ 12.04×10^6</td>
<td>↑ 8.39×10^6</td>
<td>↑ 14.27×10^6</td>
<td>↑ 12.29×10^6</td>
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<tr>
<td>Neutrophils (%)</td>
<td>↑ 80.59</td>
<td>↑ 55.87</td>
<td>↑ 79.48</td>
<td>↑ 55.06</td>
<td>↑ 84.43</td>
<td>↑ 63.96</td>
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<tr>
<td>Hemoglobin (g/L)</td>
<td>↓ 88</td>
<td>↓ 124</td>
<td>↓ 109</td>
<td>↓ 97</td>
<td>↓ 104</td>
<td>↓ 91</td>
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<tr>
<td>Platelets (×10^9)</td>
<td>↓ 87×10^9</td>
<td>↓ 340×10^9</td>
<td>↓ 65×10^9</td>
<td>↓ 254×10^9</td>
<td>↓ 70×10^9</td>
<td>↓ 203</td>
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<td>Biochemistry</td>
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<td>Albumin (g/L)</td>
<td>↓ 31.20</td>
<td>↓ 32.80</td>
<td>↓ 36.00</td>
<td>↓ 34.80</td>
<td>↓ 34.60</td>
<td>↓ 34.00</td>
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<tr>
<td>BUN (mmol/L)</td>
<td>↑ 31.88</td>
<td>↑ 9.87</td>
<td>↑ 26.65</td>
<td>↑ 12.13</td>
<td>↑ 23.67</td>
<td>↑ 13.31</td>
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<td>Creatinine (μmol/L)</td>
<td>↑ 785</td>
<td>↑ 145</td>
<td>↑ 585</td>
<td>↑ 188</td>
<td>↑ 734</td>
<td>↑ 179</td>
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<td>CRP (mg/L)</td>
<td>↑ 103</td>
<td>↑ 6</td>
<td>↑ 110</td>
<td>↑ 12</td>
<td>↑ 130</td>
<td>↑ 10</td>
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<td>Immune-serological findings</td>
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<td>Direct Coombs test</td>
<td>Positive</td>
<td>Negative</td>
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<td>Negative</td>
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Abbreviations: BUN, blood urea nitrogen; CRP, C-reactive protein; APTT, activated partial thromboplastin; FDP, fibrin fibrinogen degradation. Abnormal values are shown by arrows: ↑, higher than normal range; ↓, lower than normal range.

Discussion

The patient presented with diarrhea, vomiting, and oliguria with AKI, concurrent with AIHA and thrombocytopenia, resulting in a differential diagnosis of Evans syndrome presenting with AKI. Combined with her past history of AIHA, the patient had diarrhea gastroenteritis, high WBC, and elevated inflammation, based on increased C-reactive protein; she also exhibited reduced blood pressure and dehydration, suggesting intestinal infection. Examination revealed anemia, thrombocytopenia, a positive Coombs test, and elevated SCr. The most likely diagnosis was Evans syndrome and intestinal infection that had developed into AKI. However, with prior antibiotic therapy, rehydration therapy, and hemodialysis, the patient had shown partial remission in April 2014 and September 2014 (Table 1). Thus, intestinal infection was not likely to be the primary cause of AKI. Due to morbidity in this case, steroids were added to the therapeutic protocol to control symptoms of Evans syndrome; the patient’s renal function and anemia gradually improved and had returned to normal at 1 year of follow-up. Evans syndrome presenting with AKI is a
Figure 1. (a) Light microscopy showed there was diffuse interstitial edema with an interstitial infiltrate of inflammatory cells. (b) Electron microscopy showed that vacuoles were present in glomerular capillary endothelial cells, and red blood cells were evident in glomerular capillary lumens.

rare case to be recorded.

Other differential diagnoses in this case included hemolytic uremic syndrome (HUS)/ITP. Presentation with AKI, hemolytic anemia, and thrombocytopenia as the main symptoms can also be indicative of HUS/ITP. The clinical features of HUS/ITP are hemolytic anemia in microvessels, thrombocytopenia, kidney and central nervous system damage, peripheral blood smears exhibiting broken red blood cells, and a significant increase in blood pressure. However, the patient showed normal peripheral blood erythrocyte fragments and her blood pressure was low, reducing the likelihood of HUS/ITP. Finally, leukemia was a possible diagnosis: elderly women who present with anemia and thrombocytopenia should be checked for the presence of leukemia. However, bone marrow analysis did not support a diagnosis of leukemia.

The precise etiology and pathogenesis of Evans syndrome has not been fully elucidated; Evans syndrome has a chronic course with periods of exacerbation and remission. Our case of a patient with Evans syndrome presents another etiologic avenue: AKI. Bone marrow examination was within normal limits and did not show infiltration of immature lymphoid cells. There were no clinical features of lymphadenopathy; however, diagnostic renal biopsy showed massive lymphocyte infiltration and some immunologic tests were positive, which was consistent with the prior literature regarding Evans syndrome as a disorder of immune regulation. Recent observations have confirmed an increased level of T cell activation and apoptosis, with dramatic reduction in the number of naïve CD4+ T cells and an imbalance in Th1/Th2 responses in Evans syndrome. In acute renal failure, nonspecific immunity and specific acquired immunity, inflammatory factors, T and B lymphocytes play an important role, especially in the balance of Th1/Th2 responses. T lymphocytes have been implicated in a mouse renal ischemia-reperfusion model and play an important role in the resulting injury. The balance of Th1/Th2 responses has been confirmed to play an important role in renal ischemia-reperfusion injury. Therefore, in this case we could not rule out Evans syndrome caused by a reduction in the number of naïve CD4+ T cells and an imbalance in Th1/Th2 responses, which promotes the occurrence of AKI.

In our case, the patient had been previously hospitalized three times: once, she was diagnosed with AIHA, while the other instances resulted in diagnoses of AKI after acute gastroenteritis. With antibiotic therapy, rehydration therapy, and hemodialysis, she experienced partial remission; however, this response was lost upon dose reduction and/or during acute infections, since there was no diagnosis of Evans syndrome and prednisolone was not used. Treatment of Evans syndrome is largely empirical. The first-line therapy for Evans syndrome is usually steroids and/or intravenous immunoglobulins; options for second-line therapy include immunosuppressive drugs, especially mycophenolate mofetil, vincristine, cyclophosphamide, and rituximab. A large majority (80%) of Evans syndrome patients respond to corticosteroids. Typically, corticosteroids are administered at an initial dose of 1–4 mg/kg/d. In our case, renal function and anemia gradually improved with prednisolone treatment combined with rehydration, along with blood component support. After 1 year of follow-up, the patient’s renal function and routine blood tests were normal and her prognosis continues to be favorable.

A patient with Evans syndrome presenting with AKI is rare. The symptoms of AIHA and ITP meet the strict inclusion criteria for Evans syndrome without secondary factors. Renal function can be gradually restored to normal levels by treatment with steroid hormones and immunosuppressive drugs. This case was presented to illustrate that when AKI presents with hemolysis and thrombocytopenia, physicians should consider Evans syndrome, which can be appropriately treated when detected early.

Authors’ Contribution
HL and KW conceived and drafted the manuscript. WZ and GL collected and collated data. CC reviewed and finally approved the manuscript.

Conflict of Interest Disclosures
The authors have no conflicts of interest.

Ethical Statement
The Helsinki Declaration was followed in this study.

References
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