Case Report

Early-Onset Antibiotic-induced Autoimmune Hemolytic Anemia

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Abstract

Drug-induced immune hemolytic anemia (DIIHA) is a rare adverse reaction that causes secondary autoimmune hemolytic anemia in susceptible patients. Drug-induced antibodies and nonimmunological protein absorption are the known mechanisms associated with DIIHA. The two most common reported antibiotics to cause drug dependent antibodies are cephalosporin and penicillin. The author reports two rare cases of DIIHA. The first case is a middle-aged woman clinically diagnosed with community-acquired pneumonia, which develops hemolytic anemia secondary to ceftriaxone. The second case is an elderly gentleman who developed DIIHA secondary to piperacillin–tazobactam that started managing gastrostomy site infection. Both patients had hypoxemia and shortness of breath secondary to drop in hemoglobin, but the outcome was uneventful. Antibiotic-induced hemolytic anemia can develop as early as 2 days after starting the antibiotic. Therefore, early diagnosis and discontinuation of the offending agent can prevent poor prognosis.

Keywords: Autoimmune hemolytic anemia, ceftriaxone, direct antiglobulin test, hemolytic anemia, piperacillin–tazobactam

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) is the destruction of red blood cells due to autoantibodies formation secondary to immune system malfunction. It has an estimated incidence in adults of 1–3/100,000/year and a mortality rate of 11%.[1-3] It can be idiopathic (primary) or acquired (secondary). The acquired form of AIHA has several etiologies, including drugs, infections, autoimmune diseases, and lymphoproliferative disorders.

Drug-induced immune hemolytic anemia (DIIHA) is rare, occurring in about 1 per million of the population.[1] More than 130 drugs have been reported to induce antibody formation, causing hemolysis.[3-6] They are classified into drug-dependent antibodies and drug-independent antibodies. The most common antibiotics reported

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to be associated with drug-dependent antibodies are cephalosporin and penicillin.[3,5,7-10]

The author reports two rare cases of DIIHA secondary to ceftriaxone and piperacillin–tazobactam used in patients diagnosed with community-acquired pneumonia and percutaneous endoscopic gastrostomy site infection, respectively.

CASE REPORTS

Case 1

A 59-year-old female with a medical history of hypertension presented to the hospital with a history of high-grade fever for 4 days duration associated with chills, fatigue, dry cough, and shortness of breath (SOB) on mild exertion. There was no history of wheezes. Normal bowel and bladder function. Surgical history included appendectomy and lower cesarean section. Medication history included bisoprolol. There was no history of allergies, recent travel, sick contact, or smoking. Her vital signs on initial presentation: Heart rate was 68 beats/min, blood pressure 115/67 mmHg, temperature 38.7°C, and respiratory rate was 18 breaths/min. In the general examination, the patient was in stable general condition. On chest examination, there was decreased air entry in the right lower lobe with dullness to percussion and increased vocal fremitus. Other systemic examinations were within normal limits.

The initial blood test showed a white blood count of 10.08×10/ccm with a left neutrophilic shift, hemoglobin 101 g/L, platelets of 285×10/cmm, and C-reactive protein 639 mg/L. Blood film on admission was reported to be normal. Chest X-ray showed patchy consolidation in the right lower lobe. The patient was managed as a case of community-acquired pneumonia and started on ceftriaxone and azithromycin. On day 2, the patient developed worsening SOB requiring 3 L oxygen via nasal cannula to maintain oxygen saturation above 92%. Her arterial blood gas analysis showed hypoxemia, and her electrocardiogram (ECG) revealed a normal sinus rhythm. Serum D dimer level was abnormally high at 2.25 ug/mL; however, a normal computed tomography angiography excluded pulmonary embolism. The coagulation profile and fibrinogen level were normal. Repeat

laboratory investigations did not show any significant abnormalities, but improvement in inflammatory markers. Mycoplasma IgM and Legionella urine antigen were negative. Blood and sputum cultures were negative. On day 5, hemoglobin dropped to 71 g/L, and platelets result was 402×10/cmm.

No evidence of any active bleeding was observed. On day 6, anemia workup showed elevated lactate dehydrogenase (LDH), low haptoglobin, elevated reticulocyte counts, and a peripheral blood smear was suggestive of hemolytic anemia. The direct antiglobulin test was positive for IgM, IgG, and C3d. Mycoplasma pneumonia associated hemolytic anemia was ruled out by a negative mycoplasma IgM test. Patient had normal levels of Glucoose-6-phophate dehydrogenase. Ceftriaxone was stopped on day 7. Following hematology consultation, the patient was initiated on low-dose steroids. The patient did well afterward and was weaned off oxygen. Her renal function was normal, and there was no evidence of acute cardiac events. Repeat lab tests showed that hemoglobin was stable at 76 g/L. The patient did not require a blood transfusion. She was discharged on day 9 of the hospital stay. Patient was followed-up 3 weeks from day of discharge. Repeated laboratory investigations showed normal levels of inflammatory markers and hemoglobin of 93 g/L [Figure 1]. Also, the peripheral blood smear did not show any evidence of hemolysis. The patient was in stable general condition with no active complaints.

Case 2

A 97-year-old male presented to the hospital with a high-grade fever for 1-day duration associated with pus discharge from the gastrostomy feeding tube
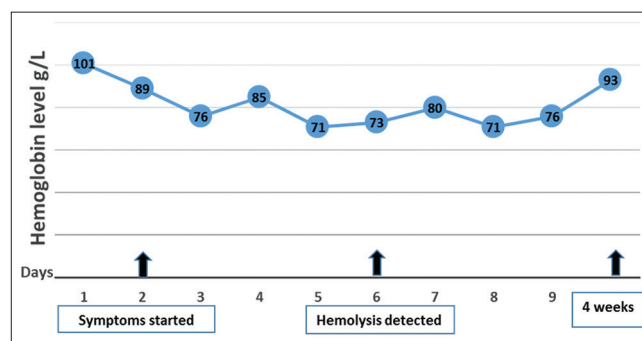

Figure 1: Hemoglobin level during the hospital stay and 1-month postdischarge. The onset of symptoms, hemolysis, and recovery are highlighted

site, cloudy urine, and reduced physical activity. The review of other systems was negative. He had a medical history of hypertension, ischemic heart disease, atrial fibrillation, mechanical mitral valve, cerebrovascular accident, chronic kidney disease, and iron-deficiency anemia. His medication history includes warfarin, aspirin, bisoprolol, ferrous fumarate, levothyroxine, omeprazole, rosuvastatin, and tamsulosin.

His vital signs on initial presentation: Heart rate was 71 beats/min, blood pressure 103/55 mmHg, temperature 38.6°C, and the respiratory rate was 20 breaths/min; on examination, nothing significant apart from erythema around the gastrostomy tube site with pus discharges. His laboratory investigations showed normal white blood cell (WBC) count with a left neutrophilic shift, C-reactive protein (CRP) 138 mg/L, hemoglobin 9 g/L, and international normalized ratio of 2.68. His most recent blood film was reported normal with no evidence of dysplastic changes or leukemic cells. The patient had mild renal impairment secondary to dehydration. The patient was empirically started on piperacillin–tazobactam and received intravenous hydration. The patient responded well to treatment, the renal function returned to baseline, and his inflammatory markers were trending down. However, on day 5 of hospital stay, the patient required 1 L oxygen therapy for mild SOB, but no evidence of a drop in oxygen saturation. Furthermore, his urine was dark and black. Repeat laboratory investigations showed WBC 11.48 × 10/cmm, hemoglobin 86 g/L, platelets of 285 × 10/cmm, increased reticulocytes count, mild renal impairment, and and CRP 35 mg/L. His coagulation profile showed an INR 2.68, PTT 55s, PT 32s, and Fibrinogen 6g/L. Patient is on warfarin for underlying atrial fibrillation. ECG and chest X-ray did not show any new acute pathology. Anemia workup showed elevated LDH, low haptoglobin, indirect hyperbilirubinemia, and direct antiglobulin test (DAT) positive for IgG. His Glucoose-6-phophate dehydrogenase level was normal. Peripheral blood smear was suggestive of hemolytic anemia. The antibiotic therapy was stopped as it was only drug newly started that can be associated with hemolytic anemia. The patient

was managed conservatively; he did not require blood transfusion or other treatments. The patient was observed in the hospital for 2 weeks. He was weaned off oxygen entirely, and all other associated symptoms subsided. His renal function returned to normal baseline, and inflammatory markers resolved. Hemolytic workup showed gradual improvement with first marker to normalize was the indirect bilirubin. The patient did well after discharge, and a repeat hemoglobin level after three weeks showed a result of 90 g/L [Table 1].

DISCUSSION

DIIHA is a relatively uncommon disorder reported in several case reports in both children and adults.[9] It can be unnoticed, asymptomatic, or mild in severity. Other cases have been reported to have poor outcomes associated with multiple organ failure and even death.[3,10] Acute renal failure has been reported as a common complication associated with DIIHA,[9,10] Multiple drugs have been mentioned in the literature to cause immune hemolysis, and the most common antibiotics are cephalosporin and penicillin.[3,5,6,8-10] These are widely used antibiotics for various medical conditions. The time of onset of symptoms in people prone to develop DIIHA secondary to antibiotics varies. It was reported that the time to onset of symptoms from penicillin-induced hemolytic anemia could range from 1 to 2 weeks, and it can also extend up to 1 month.[5] In our case reports, hemolysis was identified after 2 days in the first case secondary to ceftriaxone and after 5 days in the second case report secondary to piperacillin-tazobactam.

Different mechanisms have been mentioned in the literature to be involved in DIIHA; they are drug-induced antibodies and nonimmunological protein absorption.[6,10,11] Ceftriaxone and piperacillin–tazobactam lead to immune hemolytic anemia by forming drug-dependent antibodies. The presence of the drug in vulnerable people leads to the production of antibodies that bind to erythrocytes and causes hemolysis. Drug-dependent antibodies can be further classified into penicillin-type reaction and immune complex-type reaction. Penicillin combines covalently with erythrocyte membrane

Table 1: Results of the hematological investigations of case 2

	Days (from admission)							
	1	5*	6	8	10	15	18	39**
Hemoglobin (g/L)	90	86	82	88	78	76	81	90
Reticulocytes count (%)	-	-	4.11	-	5.26	3.56	3.71	-
Indirect bilirubin (micomol/L)	-	-	6.4	7	4	1.8		-
LDH (IU/L)	-	-	547	608	559	471	510	-
Haptoglobin (g/L)	-	-	<0.1	<0.1	<0.1	<0.1	<0.1	-

*Onset of symptoms. **Postdischarge clinic follow up. LDH: Lactate dehydrogenase

proteins forming a penicillin coated red blood cells (RBC). In the presence of IgG penicillin antibody, the antibody will attach to the penicillin coated-RBC which will be cleared up by macrophages and lead to hemolysis. In our case report, the second patient DAT result was positive for IgG. Ceftriaxone causes immune-complex type reaction by the formation of mostly IgM-type antibodies that lead to complement-mediated intravascular hemolysis. DAT in ceftriaxone induced immune hemolytic anemia is usually positive for C3, IgM, and in some cases also for IgG.[3,6,9-12] This was identified in the first patient in our case report.

Laboratory tests that can aid in the diagnosis include complete blood count, lactate dehydrogenase, haptoglobin, indirect bilirubin, urine dipstick, reticulocyte count, peripheral blood smear, and DAT. Serological tests can be performed to confirm the diagnosis, but this requires a specialized laboratory, and it may take a week to have the result back.[6,12] However, in all cases, discontinuation of the antibiotic and maintaining close monitoring of the clinical status is the mainstay of treatment. Blood transfusion can be considered if the patient is symptomatic and hemoglobin drops below 7 g/L. Other treatment methods include steroids, intravenous immunoglobulin, and plasmapheresis.[1,6,8,12]

In both the cases reported here, the onset of symptoms was within the 1st week of initiating antibiotics. The main symptom observed in both patients was SOB, which can be attributed to symptomatic anemia. One of the patients had acute renal impairment, which is commonly associated with DIIHA. The mainstay of treatment once DIIHA is highly suspected is to hold the culprit drug and to have Hematology team on board. The duration

of monitoring in hospitals may differ among people as it will depend on the clinical status and other associated medical conditions. The main factors determining the severity are the patient's clinical status, hemoglobin level, and associated complications secondary to hypoperfusion. It is crucial to report the side effect on the patient's chart to avoid re-exposure. Moreover, patients should be educated about the associated complication and be followed within a month with routine labs and general checkups.

CONCLUSIONS

Antibiotic-induced hemolytic anemia is a rare adverse reaction that can develop within 48 h of starting antimicrobial treatment. Hemolytic workup should be considered in all patients with new-onset SOB or change in urine color immediately after the initiation of antibiotics. Physicians should be vigilant, and early diagnosis is crucial to prevent severe outcomes.

Author's contribution
Single author.

Conflicts of interest
There are no conflicts of interest.

Compliance with ethical principles
Ethical approval was obtained from Research Ethics Committee at Sheikh Shakhbout Medical City. The reported information cannot lead to the identification of the involved individuals.

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