Life-threatening piperacillin-induced immune haemolysis in a patient with cystic fibrosis

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SUMMARY

We present a 24-year-old man with a history significant for cystic fibrosis and insulin-dependent diabetes mellitus who developed anaemia in the setting of piperacillin-induced immune haemolysis. This case provided a diagnostic challenge, a rare association of piperacillin-induced haemolysis in those suffering from cystic fibrosis.

BACKGROUND

Patients with cystic fibrosis are routinely treated with intravenous piperacillin-tazobactam for pulmonary exacerbations given its activity against *Pseudomonas aeruginosa*. The patient developed a life-threatening haemolytic process while receiving piperacillin-tazobactam. A Naranjo Adverse Drug Reaction probability score of 7 indicates a probable association of piperacillin-tazobactam-induced drug-induced immune haemolytic anaemia (DIIHA).[1] Further work-up revealed a positive direct antiglobulin test and peripheral smear consistent with extravascular haemolysis. Immediate intervention with corticosteroids and intravenous immunoglobulin (IVIG) preceding packed red blood cell transfusions allowed for a slow, gradual increase in haemoglobin with a full recovery. This case illustrates the importance of early detection of DIIHA, particularly in patients with underlying cystic fibrosis.

CASE PRESENTATION

The patient is a 24-year-old man with a medical history significant for cystic fibrosis and insulin-dependent diabetes mellitus who initially presented to a local emergency department (ED) with fever, chills and generalised malaise and was treated with intravenous piperacillin-tazobactam and tobramycin for 10 days as an inpatient and subsequently discharged with a peripherally inserted central catheter (PICC) line and instructed to complete an additional 11 days of intravenous antibiotic therapy. In the middle of his outpatient therapy he began to experience progressive fever, malaise, nausea and vomiting. The symptoms progressed over 3 days when the patient presented back to the local ED. In the ED he was found to be profoundly anaemic with haemoglobin of 4 g/dl with accompanying leucocytosis and tachycardia raising concern of sepsis and he was subsequently transferred to a tertiary care facility. On arrival at our hospital the patient was febrile, tachycardic, hypotensive and profoundly anaemic. He was admitted to the intensive care unit and started on broad-spectrum intravenous antibiotics (doripenem and vancomycin) and given several boluses of fluids, which reversed his hypotension. He was ordered several units of packed red blood cells; however, he was only able to tolerate part of the first transfused unit when he developed dark urine, worsening respiratory symptoms and fatigue. The transfusion was stopped and the blood bank called for suspicion of acute autoimmune haemolytic anaemia, supported by elevated lactate dehydrogenase, low haptoglobin levels and ultimately a positive direct antiglobulin test (DAT) (IgG Coomb's autoantibody) and the presence of spherocytes without schistocytes on peripheral smear consistent with predominantly extravascular haemolysis.

TREATMENT

Haematology/oncology physician was consulted and recommended solumedrol 125 mg and IVIG 1 g/kg prior to any further transfusions. Over the next 24 h, the patient's symptoms improved and he tolerated blood transfusions with gradual improvement in his haemoglobin. The patient's cultures were positive for gram-positive cocci and maintained on broad-spectrum antibiotics (coagulase negative *Staphylococcal* species). Subsequently, the patient was transferred to the general medicine floor with continuation of corticosteroids and broad-spectrum antibiotics. He was ultimately discharged on prednisone 60 mg daily with appropriate follow-up.

OUTCOME AND FOLLOW-UP

The patient made a full recovery without any complications. The patient remained on insulin infusion during his hospitalisation as a result of the combination of corticosteroids and his underlying insulin-dependent diabetes mellitus. The patient was discharged home on prednisone 60 mg daily to follow up with his primary care provider and the haematology/oncology physician.

DISCUSSION

Intravascular haemolysis refers to the destruction of red blood cells in circulation as a result of mechanical trauma, compliment fixation and activation on the cell surface or an infectious aetiology. In contrast, extravascular haemolysis refers to the removal of red blood cells from circulation and destruction by macrophages of the spleen and liver.[2] DIIHA is a form of extravascular haemolysis that is considered to be a rare, life-threatening, complication of antibiotic therapy. Cephalosporins, in particular cefotetan and ceftriaxone, and piperacillin are the most common culprits of antibiotic-related DIIHA.[3] There are three mechanisms resulting in DIIHA: hapten-induced, immune complex or autoantibody-mediated.[2] Piperacillin, a semi-synthetic antibiotic related to penicillin with

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extended spectrum activity against *P aeruginosa*, has been implicated in several cases of immune haemolysis particularly in patients with underlying cystic fibrosis.[4] Patients suffering from cystic fibrosis often suffer from chronic infection with bacteria such as *P aeruginosa*. As a result, aggressive treatment with intravenous antibiotics, in particular piperacillin-tazobactam, results in better outcome in susceptible individuals. Haemolysis resulting from piperacillin-tazobactam is an example of hapten-induced haemolytic anaemia. An abundance of antibiotics present on the red blood cell membrane is thought to stimulate IgG antibody production, which in turn binds to the cell membrane ultimately resulting in extravascular haemolysis.[2]

It is thought that nitrous oxide plays a crucial role in the increased susceptibility of DIIHA in patients with cystic fibrosis. In reaction to stress, nitrous oxide acts as a potent vasodilator facilitating red blood cell flow through vasculature. In times of mechanical stress, endothelial cells synthesise nitrous oxide in response to ATP expressed by red blood cells.[5] Red cells produce significantly reduced levels of ATP under the same mechanical stress in patients with cystic fibrosis. Thought to be a result of the CFTR (cystic fibrosis transmembrane regulator) gene, this ultimately leads to decreased nitrous oxide production. The resulting impairment in vasodilatation combined with haemolytic anaemia may be one reason why patients with cystic fibrosis are prone to severe, life-threatening DIHHA as compared with the general population.[6 7]

Mayer *et al* recently analysed sera from eight patients suffering from severe, acute haemolytic anaemia with positive direct antiglobulin test. Three of the eight patients suffered from cystic fibrosis. In their study, sera from four patients reacted with red blood cells in the presence of piperacillin as well as ex vivo antigens, sera from three patients showed positive reactivity with untreated red blood cells in the presence of piperacillin, and the remaining patients' sera was reactive only in the presence of piperacillin ex vivo antigens.[4]

In conclusion, patients suffering from cystic fibrosis are at an increased risk of piperacillin-induced DIIHA. It is important to recognise susceptible patients, terminate treatment with haemolysis, pretreat with corticosteroids steroids (with/without IVIG) prior to blood transfusion and advise them against any further piperacillin exposure.

Learning points

- Patients with cystic fibrosis appear to be more susceptible to drug-induced immune haemolytic anaemia (DIIHA).
- DIIHA should be considered in any patient exposed to an offending agent with worsening anaemia, particularly following a blood transfusion.
- While our patient improved with corticosteroids and intravenous immunoglobulin, it is not clear whether these drugs produce improvement over immediate suspension of the offending agent alone.

Competing interests None.

Patient consent Obtained.

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