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CLINICAL VIGNETTE

An Unusual Complication of a Commonly Prescribed Antibiotic – Drug Induced Hemolytic Anemia

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Case Presentation

The patient is a 48-year-old male with a history of multiple sclerosis on a stable drug regimen of glatiramer and interferon beta who was being treated for acute prostatitis. He was initially started on Ciprofloxacin but had persistent fevers, chills, and sweats and was changed to high dose cefpodoxime and doxycycline. While on day 7 of his antibiotics, he developed brownish colored urine and exertional tachycardia with dyspnea.

On physical examination, he was afebrile with a blood pressure of 116/65 mm Hg and a heart rate of 59 bpm. His 02 saturation was normal at 99%. His head and neck exam revealed anicteric sclerae and no retinal lesions. He had a normal cardiac exam and his lungs were clear. His abdominal exam revealed no distention, masses, or splenomegaly. He had no lymphadenopathy and his extremities revealed no petechiae or purpura.

His laboratory evaluation included a hemoglobin of 10.9 g/dL (baseline hemoglobin 14.0 g/dL) with a mean corpuscular volume of 94 fL and a reticulocytosis to 8%, uncorrected. In addition, while his LDH was 190 and in normal range, he did have an elevated indirect bilirubin and a haptoglobin level of less than 8 ug/dL (reference range 21 – 210 mg/dL). Finally, a direct antiglobulin test (DAT, Coombs Test) was positive with a negative test for C3 DAT but positive test for IgG in the eluate. His cold agglutinin titer was negative. Of note, his iron saturation and ferritin were in normal range.

His cefpodoxime was discontinued 10 days after the start of his symptoms, his hemoglobin had increased to 12.1 and his tachycardia and dyspnea both resolved.

Discussion

Hemolytic anemia is defined as the shortening of red blood cell survival to less than 100 days (normal range is 110 – 120 days). In the presence of hemolysis, the degree of anemia is mitigated by a compensatory increase in erythropoietin and red blood cell production by the bone marrow. Therefore, a major clue for the diagnosis of hemolytic anemia is an increase in the reticulocyte percentage and reticulocyte count. This case represents one of the most common causes of acquired hemolytic anemia. Autoantibodies directed against antigens on the red blood cell can cause immunologic destruction. There are two major types of antibodies produced in autoimmune hemolytic anemia. IgG antibodies also called "warm agglutinins" react with protein antigens on the RBC surface at body temperature. IgM antibodies on the other hand interact with polysaccharide antigens only at temperatures below core body temperatures and are called "cold agglutinins".

The fixation of these antibodies can result in phagocytosis in which the red blood cell is entirely engulfed or the ingestion is incomplete and the surface to volume ratio is decreased resulting in spherocytic red blood cells. As a result, these spherocytes are unable to pass through the narrow slits of the splenic sinuses and are destroyed. Red blood cell destruction can also be caused by complement fixation on the surface of the red blood cells by the antibodies. IgM antibodies are more likely to cause this, as only one molecule is required while IgG requires two. Other methods of destruction include IgG mediated adherence to monocytes and physical red blood cell membrane changes induced by the antibodies to the Pr component of glycoproteins.

In our case, a drug was the likely precipitant of the patient's autoimmune hemolytic anemia. Fortunately, drug induced hemolytic anemias (DIHA) are rare but may be underestimated or misdiagnosed. The typical history is significant for an abrupt onset of hemolytic anemia in association with starting a drug. There are two major mechanism for DIHA. The most common mechanism is the production of antibodies that bind to the red blood cells only in the presence of the drug or its metabolite. In this case, the drug is part of the antigen to which the antibody reacts i.e. the drug is a hapten. Of note, the drug may be firmly or loosely bound. This can lead to mixed results on direct Coombs testing as detailed below.[1,2]

The other mechanism is that the drug essentially alters antigens on the red cell membrane thereby evoking an immune response and production of antibodies that cross-react with a component of the surface Rh complex. This leads to Fc-mediated partial phagocytosis resulting from non-complement activating antibodies that react with the red blood cell in the presence as well as absence of the drug. Historically, the prime example of this was alpha-methyldopa.[3]

In addition to the sudden decrease in hemoglobin and increase in reticulocyte count, the diagnosis of DIHA is usually made by the direct antiglobulin test (DAT) first described by Coombs.

The test is performed by washing the red blood cells free of adherent proteins and reacted with antibodies prepared against various immunoglobulins (the most common of which is IgG) and a fragment of the third component of complement. If IgG is present, then this is likely the cause of the red blood cell destruction. While there are about 40,000 copies of the Rh complex on the red cell surface, they are anchored to the underlying cytoskeleton and are immovable. The distance that separates them does not allow two IgG molecules to be close enough to initiate complement activation. Therefore, the direct Coombs test is often negative or weakly positive for C3. If C3 is also present, then complement-mediated destruction may play a role as well. If C3 but not IgG is present then the antibody may be to IgM or rarely IgA or the IgG was weakly fixated and washed off in the eluate process. In summary, the direct Coombs test for drug-induced hemolytic anemia can give variable results for IgG and C3 and is dependent on the implicated drug and mechanism for hemolysis.

In an expert opinion review article from 2009, the drugs most frequently implicated in causing DIHA were third generation cephalosporins, diclofenac, alpha-methyldopa, high dose penicillin therapy for greater than 10 days, oxaliplatin, rifampicin, fludarabine, levodopa, quinidine, and mefenamic acid.[4]

A subsequent review article in 2010 cited cefotetan, ceftriaxone, piperacillin, and other beta-lactamase inhibitors as the most common drugs associated with DIHA over a previous 10-year period. The authors note that antibiotics are the most common medications to cause drug dependent hemolytic anemia in which the antibiotic serves as a hapten. This is in contrast to fludarabine, which is now the most common drug to cause drug independent hemolytic anemia.[5]

In a case control study investigating the possibility of drug induced immune hemolytic anemia, 124 patients with new onset immune hemolytic anemia were compared with 731 controls. Significantly increased odds ratios were observed for beta-lactam antibiotics, cotrimoxazole, ciprofloxacin, fludarabine, and lorazepam as well as diclofenac.[6]

More recently a German study reviewed, two decades of DIHA cases and identified 73 patients. By far the most commonly associated drug was diclofenac, followed by piperacillin, ceftriaxone, and oxaliplatin. These four drugs accounted for more than 80% of all cases of DIHA. All the patients had evidence of acute intravascular hemolysis, which was fatal in 17 patients (23%).[7]

In summary, this clinical vignette highlights a rare complication of a commonly prescribed medication, cefpodoxime. The likely mechanism is that the cefpodoxime served as a hapten for antibody production. The drugs most commonly associated with drug-induced hemolytic anemia has changed over the years as our prescribing practices have changed and it is helpful to know the most common suspects.

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