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The Other Side of Ceftriaxone: Cephalosporin Induced Immune Mediated Hemolytic Anemia

Medical Science

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ABSTRACT

Ceftriaxone ,a 3rd generation cephalosporin and the most commonly used broad spectrum antibiotic today, can lead to a rare but devastating adverse effect in form of immune-mediated hemolytic anemia. It can turn lethal if high degree of suspicion isn't maintained. Here we describe a case of overwhelming postsplenectomy infection due to Streptococcus pneumonia for which drug of choice is ceftriaxone where the patient developed a catastrophic drop of haemoglobin within five days of initiating the drug. Early recognition and initiation of desperate measures were taken and the patient survived.

CASE REPORT-

A 25 year old male was admitted with complaints of continuous fever since over 15 days. A significant past history revealed, evidence of splenectomy done three months back because of blunt abdomen injury. Given the urgency of surgery he could not have been vaccinated but this was also not carried out post-op. Nor was he put on any oral penicillin prophylaxis post surgery. He was not allergic to any known drugs nor was there any exposure to beta lactam antibiotics in the past. On presentation he was running a high fever of 102 deg F and his other parameters were stable. A clinical suspicion of OPSI [overwhelming post-splenectomy infection] was high on the cards, given the clinical scenario. Other infections like malaria weren't far behind, given the Indian epidemiology. Three sets of blood cultures were ordered, which revealed a growth of *Streptococcus pneumoniae* sensitive to ceftriaxone, aminoglycosides, cotrimoxazole, vancomycin and carbapenems. The malarial antigen was negative and the urine was bland. Ultrasonography of the abdomen was negative except of the post-splenectomy status. A high WBC count with a left-ward shift was seen. Chest roentenogenogram was unremarkable. Other blood work was normal. He was started on a double dose of ceftriaxone.

His fever resolved over five days but he developed pallor and high colored urine. Mild scleral icterus was seen. The blood work showed hemoglobin dropped from 12.2 on presentation to 4.8gm%. Total bilirubin was 3.5 mg% with the indirect component being 2.5. His direct Coombs' test was positive, LDH- 3120 U/L [very high], hemoglobinuria, hemosiderinuria were present and serum haptoglobin was decreased. Peripheral smear showed many normoblasts with auto-agglutination over the RBCs. The reticulocyte production index was 6.51 [>2.5].

Given the clinical scenario, a drug induced hemolytic anemia was suspected and ceftriaxone was withheld. Two cross matched packed cell volumes were transfused but the patients hemoglobin dropped further to 2.4gm%. Then a decision was taken to start the patient on high dose steroids given the progressive nature of the immune mediated reaction. Intravenous methyprednisone was given upto 1gm daily for three days followed by oral predisone at a dose of 1mg/kg. This regime was covered by intravenous meropenem and vancomycin for the ongoing infection. Daily counts were done which showed rising trend of hemoglobin in the next seven days.. LDH decreased to 1246 U/L over the next seven days. Fever did not recur nor was there any derangement in hemodynamic status.

The repeat cultures were negative after 10 days of antibiotics and was discharged with erythromycin 500mg BID and necessary vaccinations. On follow-up patient was weaned of his steroids over two weeks post his stabilization of hemoglobin and decreasing LDH.

DISCUSSION

Drugs cause at least 18% of all cases of acquired hemolytic anemia. [1] It requires a high index of suspicion and managing it can be challenging with high mortality.

Drug induced hemolysis can be immune mediated or non-immune mediated. Non-immune mediated hemolysis could be because of the drugs direct effects as in case of ribavarin which has a dose dependent hemolytic anemia or because or of oxidative damage as in use of primaquine in case of glucose-6-phosphate deficiency. These reactions are expected to occur and their presence can be modified, by either decreasing the dose or using an alternative. Drug induced immunue mediated hemolytic anemia [DIIHA] is rare and requires a battery of tests to be diagnosed but a sharp accumen to be suspected. [2]

Second and third generation cephalosporins have been attributed to the causative agents for this adverse effects in many patients, making them the most common antibiotics associated with this complication.[3] These antibiotics are the cornerstone of managing many infections but they do have their share of complications and DIIHA, although rare, is one of them. There a few mechanisms by which the drug can cause an immune mediated hemolysis-

a. A drug can induce antibody formation by behaving as an hapten. Penicillin is known to behave like this.

b. A drug can trigger antibody formation, probably through molecular mimicry against potential red cell antigens. [4]

Other mechanism include membrane modification and immune complex formation .[5] Antibodies can be either IgM or IgG.

Though not completely understood, it is theorized that ceftriaxone bind loosely to RBCs, probably acting as an hapten and inducing an antibody production that leads to immune complex formation and subsequent intravascular hemolysis. Antibodies to ceftriaxone are present in 68% of patients. [6,7]

OPSI [overwhelming post-splenectomy infection] is a major complication occurring in splenectomized individuals, more so in patients who are not vaccinated against capsulated organisms. First drug therapy is ceftriaxone for this medical emergency, and that too in high dose of 2grams 12 hourly. Until 2014 atleast 37 case reports had been identified in medical literature of ceftriaxone induced hemolytic

anemia out of which 70% were children.[6] One in three patients affected by this condition died thus showing the disease to be having high mortality. Immediate stopping of drug and packed cell transfusion are all that is necessary but steroids may be warranted in severe cases, although there is limited data on this. [8] Massive intravascular hemolysis can lead to acute kidney injury.

Our case is unique for few reasons. First, it adds to the limited data of literature available to this topic. A differential could have been *Streptococcus pneumoniae* induced hemolytic uremic syndrome but absence of thrombocytopenia and renal involvement and presence of a positive Coombs' test and response to steroids ruled it out. Second, given the high mortality of ceftriaxone induced hemolytic anemia developing in a patient with OPSI meant severe morbidity and apparently high chances of mortality. But timely detection of the condition and immediate withdrawing of the drug saved the patient's life. Thirdly, for prophylaxis against OPSI, he was started on erythromycin 500mg BID as there is evidence of cross reactivity among beta lactams with necessary vaccinations. [9]

A limitation of our case was that we couldn't do ceftriaxone antibody levels, they being not commonly available in India.

CONCLUSION-

A high index of suspicion is warranted for adverse drug events, even when using a common drug like ceftriaxone to prevent catastrophic events like DIIHA.

CONSENT-

Written informed consent was obtained from the patient for publication of this case report. A copy of the written consent is submitted to the Editor-in-Chief of this journal.

DECLARATIONS

OPEN ACCESS

COMPETING INTERESTS

The authors declare that they have no competing interests.

AUTHORS' CONTRIBUTIONS

All authors read and approved the final manuscript.

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