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DRUG INDUCED IMMUNE HEMOLYSIS IN A THALASSEMIA PATIENT

Transfusion Medicine

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ABSTRACT

Drug induced immune hemolytic anemia (DIIHA) is a rare condition that results due to drug induced antibodies, either drug dependent or drug independent result from the administration of an antibiotic, most notably the cephalosporin class, commonly used in both adult & paediatric population. A delay in recognition by a provider may lead to continuation of the offending agent and possibly result in fatal outcomes. The exact incidence of DIIHA is not known, but as per data published by Garratty, the incidence of DIIHA is estimated to be one in million population. We report the case of 10 year old child, known case of Beta thalassemia major admitted with fever, palpitations, pain in the left side of the abdomen & bilateral knee joint pains since 2 days. Patient was suddenly deteriorated after two doses of intravenous ceftriaxone, with increase in pallor, fatigue, decreased oral intake and foul smelling frank hematuria. Laboratory investigations showed signs of hemolysis, presence of schistocytes, tear drop cells & target cells, raised lactic dehydrogenase & indirect bilirubin. Reticulocyte count was 8.5% . Direct antiglobulin test was strong positive (4+) with IgG and C3d positive. Eluate came negative. Suspecting DIIHA drug was stopped immediately. Child was started on oral prednisolone and subseuent transfusions planned in small alliquots and 80 ml leukodepleted, phenotypically matched PRBC with pre transfusion iv hydrocartisone, avil, paracetamol were given As child is having continuous fever spikes antibiotic shifted to iv doxycycline. Patient general condition improved 5 days after stopping the drug. Till day 8 of admission total around 40 ml/kg PRBC transfusion done, however Hb showed no improvement, hence on 9th day of admission IVIG at 1gm/kg transfused and LD-PRBC at 8ml/kg transfused and repeat Hb showed improvement from 4.8 to 5.9 g/dl. Although rare, drug induced immune hemolytic anemia caused by ceftriaxone may be a potentially fatal condition, especially in thalassemia major patients. But with early recognition and withdrawal of the offending agent, successful treatment may ensue. Serological tests should be utilized to obtain definitive diagnosis.

KEYWORDS

Autoimmune hemolytic anemia, drug-induced hemolytic anemia, ceftriaxone

INTRODUCTION:

The hemolytic anemia is caused either due to the intrinsic abnormalities arising from within the red blood cell (RBC) and/or its membrane (intracorpuscular defects) or extrinsic abnormalities in the environment of the RBC. Extrinsic abnormalities are mainly because of the autoimmune mechanisms as in warm and cold hemolytic anemia. Drugs are also responsible for hemolytic anemia called as drug-induced immune hemolytic anemia (DIIHA). It is a rare condition that results primarily due to drug-induced antibodies, either drug dependent or drug independent. The exact incidence of DIIHA is not known, but as per data published by Garratty, the incidence of DIIHA is estimated to be one in million population.[1] There are many drugs which are implicated in causing DIIHA ranging from antimicrobials, antineoplastics to anti-inflammatory drugs. Among antimicrobials, cephalosporins are commonly reported to cause hemolytic anemia.[2] We hereby report a life-threatening hemolytic reaction to cephalosporin (ceftriaxone) in a 10-year-old child.

Case Report:

A 10 year old female child, known Beta thalassemia major presented with fever, palpitations, pain in the left side of the abdomen & bilateral knee joint pains since 2 days. She was started i.v. ceftriaxone. After 2 days of treatment her general condition got deteriorated. Her CBC revealed pancytopenia (Hb-4.1, TLC-2700, Platelet -1,39,000) with peripheral smear showing microcytic hypochromic RBC, anisopoikilocytosis, tear drop cells, target cells, schistocytes. Urine examination showed microscopic hematuria (blood 2+, RBC – 6-8 cells/Hpf) One unit PRBC at 10 ml/kg transfused. At the end of her transfusion, she developed fever spike and gross hematuria, with pancytopenia, Normal PT, INR, aPTT. elevated Serum LDH(>1500 U/L), urine for hemoglobinuria was positive Negative ANA by IF. IV vitamin K stat was given along with stoppage of offending drug, conversion to a different antiobiotic, addition of steroid and IV Ig. The patients laboratory reports improved over time spontaneously.

Immunohaematological Workup:

Blood grouping was 'A' positive with no discrepancy in forward and reverse typing. DAT was 4+ positive. Antibody screen was pan 3+ positive while Auto control was negative. All the tests were performed on anti human globulin (AHG) column agglutination card. (Tulip, India).

Direct Antiglobulin Test (Monospecific):

DAT was repeated using monospecific DAT card (IgG, IgM, IgA, C3c, C3d and control I Bio-Rad laboratories, Mumbai, Maharashtra, India) to identify the type of antibody sensitisation. Results showed DAT positivity due to IgG and complement (C3d 3+ & C3c 1+ positive). Control was negative which validated the results.

Elution:

Heat elution was performed [Waterbath at 57°C (S.M. Scientific P. Limited, Jindal) & 6% albumin was used] to free the IgG antibody and recover it in usable form. Positive and negative controls were used in parallel to validate the results. Eluate showed no reactivity with three reagent cell screening panel (Tulip diagnostics (P) Ltd. Goa, India). Eluate was also negative with the three different A cells and B cells. Last wash was negative which validated the elution and wash process.

With the hemolytic clinical picture, DAT positivity and negative eluate, possibility of DIIHA was considered. Offending drug (ceftriaxone) was suspected in causing hemolysis and DAT positivity, drug was stopped immediately. A further testing of the eluate with the offending drug was performed which showed DAT positivity mildly

confirming the diagnosis of DIIHA.

Suggested Mechanisms Involved In DIIHA:

There are two types of drug-related antibodies. Drug-independent antibodies are those antibodies that can be detected in vitro without adding any drug; thus, in vitro and in vivo characteristics are identical to red blood cell (RBC) autoantibodies. Drug-dependent antibodies are those antibodies that will only react in vitro in the presence of drug (eg, bound to RBCs or added to the patient's serum in test systems to detect drug antibodies); these are antibodies directed at epitopes on the drug and/or its metabolites, or a combination of drug plus RBC membrane protein. The mechanisms involved in the serological and clinical findings are controversial.[1]

DISCUSSION:

Cephalosporins are well known for causing DIIHA. Specially ceftriaxone which accounts for > 20% cases[3] As per published reports, children are more susceptible to ceftriaxone induced hemolytic anemia causing severe cardiovascular compromise with renal failure leading even to mortality.[4] In our case also, a 10 yr old female child was diagnosed with ceftriaxone induced hemolytic anemia presented with acute renal failure and hemolysis. Tasch & Gonzalez-Zayaz[5] reported a case of 65 yr old woman on ceftriaxone infusions after being diagnosed with acute mitral valve endocarditis, presented with severe anemia & bilateral transient vision loss. The patient being Jehovah's witness refused blood transfusions and was managed with alternative therapies like prednisone taper was initiated, starting at 40 mg daily (day 2 of hospital stay and Epoetin alfa was initiated on day 2 and dose gradually increased upto day 10 of hospital stay. The patient's Hb eventually plateued at 5.7 and slowly improved with cessation of ceftriaxone. In our case also drug was stopped child was started on oral prednisolone at 1 mg/kg/day and subsequent transfusions were planned in small alliauots with leukodepleted, phenotypically matched, cross match compatible PRBC. Till day 8 of admission Hb plateued at around 4.2 g/dl, hence on day 9th IVIG at 1gm/kg transfused & LD-PRBC at 8ml/kg transfused and repeat Hb showed improvement from 4.8 to 5.9 g/dl, from then onwards, it gradually increased. Dara et.al[6] also reported a case of 15 year old male child stated that after 3 days of ceftriaxone treatment, fever was persistent and his general condition got deteriorated and showed signs of hemolysis with strong positive DAT & eluate negative. They have done the workup for DIHA & identified drug dependent antibodies. Ceftriaxone was stopped patient was kept under observation on supportive care with oxygen and nutritional support. IV immunoglobulin & packed red cells were given without any antibiotic support. There was a rapid improvement in patients general condition after discontinuation of drug.[6] Sandeep Kumar et al[7] also reported a case of ceftriaxone induced hemolytic anemia in a 62 year old woman with a diagnosis of diabetic ketoacidosis with a urinary tract infection. Five days after the initiation of ceftriaxone therapy, her Hb level dropped from 10.5g/dl to 6.4 g/dl, fall in hematocrit, increased indirect bilirubin, serum lactic acid dehydrogenase and increased reticulocyte count to 7.1%. Seven days after discontinuation of ceftriaxone therapy her hemoglobin level improved to 7.5 g/dl. On day 40 her Hb level was 11.5 g/dl & patient returned to her routine life.[7] De Wilde et.al[8] reported life-threatening ceftriaxone-induced immune hemolytic anemia with an acute kidney injury in a 76-year-old woman,[8] while Mulkens et.al[9] reported ceftriaxone-induced severe hemolytic anemia in a 57-year-old female who was diagnosed with neuroborreliosis and treated with ceftriaxone. The patient developed severe massive intravascular hemolysis led to shock and acute renal failure, necessitating mechanical ventilation, and dialysis.[9] In a sudy of Garratty[1] , ceftriaxone was the second most common drug to cause DIIHA after cefotetan. It has also been noticed that ceftriaxone causes more severe clinical course and more outcomes that was fatal than do other drugs responsible for DIIHA[10,1]

Diagnosing or suspecting DIIHA, without available drug-dependent antibody testing, is one of the main challenges that restrict proper management of these patients. This case highlights the importance of availability of proper immunohematological services which at present are lacking in various regions of country.

In this case report, we have used an approach to diagnose DIIHA given by AABB technical manual Dara et al and Leger et.al[11]

CONCLUSION:

The presented case highlights the importance of close vigilance while prescribing drugs known to cause hemolytic anemia. Although rare, drug induced immune hemolytic anemia caused by ceftriaxone may be a potentially fatal condition, especially in thalassemia major patients. But with early recognition and withdrawal of the offending agent, successful treatment may ensue. Serological tests should be utilized to obtain definitive diagnosis.

Declaration Of Patient Consent:

The authors certify that they have obtained all appropriate patient & guardian consent forms regarding their clinical information to be reported in the journal, understand that their names & initials will not be published & due efforts will be made to conceal their identity.

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