Mefenamic acid induced autoimmune hemolytic anemia- A case report

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Abstract

Immune hemolytic anemia (IHA) is an uncommon adverse effect of a wide variety of drugs. The incidence is on the rise due to the extensive use of nonsteroidal anti-inflammatory drugs (NSAID). Mefenamic acid is the most common among NSAIDs causing AIHA by an autoimmune mechanism. We are presenting a case of three years old child presented with history dark colored urine, severe anemia, and jaundice after taking mefenamic acid for fever. Investigations revealed leucocytosis, hyperbilirubinemia, raised reticulocyte count, and negative direct Coombs test. The urinalysis demonstrated proteinuria, hematuria, and pus cell of 18-20/HPF. The urine for free hemoglobin was positive. As all the clinical, as well as investigation reports, were suggestive of the autoimmune hemolytic anemia except for the negative cooms test, the child was diagnosed to be a case of Coombs-negative autoimmune hemolytic anemia (Mefenamic induced) with urosepsis. He was managed conservatively by withdrawing the offending drug, and the latter steroid was added. The child became asymptomatic after a week. While investigating for hemolysis, Coombs-negative autoimmune hemolytic anemia should always be kept in the differentials. Self-remission has been described, especially in children. Withdrawing the offending medication and instituting steroids usually suffice in alleviating the condition.

Keywords: Immune hemolytic anemia, Mefenamic acid, Nonsteroidal anti-inflammatory drug.

INTRODUCTION

Drug-induced immune hemolytic anemia was first described by Snapper (1953) following the development of pancytopenia and hemolysis with positive direct antiglobulin test (DCT) after the ingestion of mephenytoin [1]. It is a life-threatening condition, with a prevalence of 1 per 100000. In children, it often presents as an acute, self-limiting illness. Patients in the age group of two to twelve years show an excellent response to short-term steroid therapy [2-4]. However, the response in children with chronic AIHA, on either side of this age group, is variable, requiring other modalities of treatments and have a mortality of 25% [5].

The incidence of AIHA is on the rise due to the extensive use of nonsteroidal anti-inflammatory drugs (NSAID) like Mefenamic acid, ibuprofen, sulindac, naproxen, and aspirin, etc. Mefenamic acid is most frequently implicated.

We are presenting a case of a 3-year-old child with autoimmune hemolytic anemia after taking Mefenamic acid. Here we will analyze the etiopathogenesis, clinical, and hematological profile and efficacy of the treatment.

CASE REPORT

A three years old male child was admitted with a history of intermittent fever with chills and rigor for two days. There were no other complaints. He was treated with mefenamic acid and paracetamol combination at a local hospital. The fever subsided the following day, but he developed dark colored urine. The remaining history was unremarkable except for the treatment of urinary tract infection at the age of two. There was no history of any immunological or hematological illnesses running in his family. The child had a mild fever on examination, with moderate pallor and icterus. The vitals were normal. The liver was enlarged 3cm below the right costal margin, and the spleen was not palpable. The other systemic examinations were normal. Investigation revealed a high TLC count (27300 with neutrophils of 70% and lymphocyte 7%), Hb-5.5, PCV-17.2%. The MCV, MCH, and MCHC were within normal limits. The total platelet count was 1.51 lakh, and the reticulocyte count was 13%. The comment on peripheral smear showed dimorphic anemia, leukocytosis, absolute neutrophilia, occasional spherocytes present.

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CRP -23.25mg/L (raised), LFT- Serum bilirubin- total-5.46, direct-1.27, indirect-4.19, SGOT-200, SGPT-27. The total protein and serum albumin were normal. The DCT was negative, and the G-6-PD activity was normal. The urinalysis demonstrated proteinuria, hematuria, and pus cell of 18-20/HPF. The urine for free hemoglobin was positive.

The patient was admitted with the diagnosis of Coombs-negative autoimmune hemolytic anemia (Mefenamic induced) with urosepsis and was managed conservatively by withdrawing the offending drug. Injectable ceftriaxone, amikacin was given to treat the urosepsis and trenaxamic acid to control the bleeding. As the hematuria was persisting, prednisolone was started on day fourth of admission. After seven days of starting the predinisolone, the child became asymptomatic, and he was discharged with prednisolone for six weeks along with folic acid.

DISCUSSION

Immune hemolytic anemia (IHA) is uncommon, though a significant adverse effect of a variety of drugs. Its incidence is on the rise. Garratty *et al*; in 2007 updated the drug list, and there 125 drugs responsible for autoimmune hemolytic anemia (AIHA) [6]. Several recent case reports have implicated the nonsteroidal anti-inflammatory drugs (NSAIDs) including Mefenamic acid, ibuprofen, sulindac, naproxen, tolmetin, feprazone, and aspirin. Mefenamic acid was the most common cause of hemolytic anemia among NSAIDs, which was caused by an autoimmune mechanism.

AIHA in children is predominantly an acute onset disease lasting for 3–6 months in 70–80% of cases. Chronic hemolysis develops in a quarter of patients with an underlying secondary cause [7]. There are three mechanisms of drug-induced hemolytic anemia, autoimmune, drug adsorption, and immune complex [8].

In autoimmune immune hemolytic anemia, the drug stimulates the production of antibodies against intrinsic RBC antigens. It is further subdivided according to their maximal binding temperature. Warm hemolysis is where maximum bind to red blood cells occurs in body temperature (37°C), referred to as IgG autoantibodies. Methyldopa is the prototype drug of this warm hemolysis. In cold hemolysis, IgM autoantibodies (cold agglutinins) bind red blood cells at lower temperatures (0° to 4°C). When warm autoantibodies attach to red blood cell surface antigens, these IgG-coated red blood cells are deformed, forming spherocytes. These spherocytes are hemolysed extravascularly in the RE system, the spleen, liver, and bone marrow. Degradation of hemoglobin releases bilirubin exceeding the liver capacity to conjugate, thus leading to unconjugated bilirubinemia and bilirubin degradation products in urine. The appearance of jaundice and abnormally dark urine along with anemia is suggestive of hemolysis, but it presents only in 60% of patients. It is always important to first rule out other causes of hemolysis such as microangiopathy, hereditary conditions (i.e., spherocytosis or G6PD), or sickle cell anemia. A positive direct antiglobulin test (DAT), which demonstrates the presence of antibodies or complement on the surface of RBCs, an elevated reticulocyte count in thebackground of hemolysis are the cornerstones of the diagnosis [9,10].

The Coombs' test, however, has a false-negative and false-positive rate in about 2–4% and 8% of all cases, respectively [11]. In our case, all clinical features were all correlating to AIHA, but DCT was negative. In a study by CP Engelfriet and *et al.*, out of 79 patients aged between 2 months and 66 years, DCT was negative in six patients, out of which two children were having all the features of hemolysis. Another case series reported by Rahul Naithani and et al. taking 26 children, 3 (11.5%) patients were DCT negative [12]. A negative DCT in patients with the clinical pictures of AIHA could be due to a low level of antibodies in the red blood cells or lower sensitivity to DCT [13]. Recently, flow cytometry has demonstrated increased sensitivity for the detection of RBC-bound immunoglobulin. The use of flow cytometry can also be employed to confirm clinical suspicion that indicates AIHA in DCT negative cases [14, 15]. Our patient responded to prednisone at 2mg per kg body weight. Hematuria decreased after seven days of starting the treatment, and a gradual increase in the hemoglobin was also marked. The mechanism of action of steroids is probably down-regulation of Fc receptors on phagocytes and reduced IL-2 production [14]. In a series of 79 cases by CP Engelfriet *et al.*, relapse was seen in six patients. Relapse correlated with an increased duration between the onset of symptoms and treatment [6]. Transfusions are rarely effective and should be reserved for patients who clinically deteriorate due to the severity of anemia. In our case, blood transfusion was required as there was a gradual fall of hemoglobin, and hematuria was persisting. Rituximab, IVIG, splenectomy, or plasma exchange is the other modalities of treatment in case of non-responsive to steroids or there is remission of the disease.

CONCLUSION

Immune hemolytic anemia (IHA) is an uncommon disease but is a significant adverse effect of a variety of drugs. Mefenamic is one of the most common drugs among NSAIDs. Early diagnosis and early treatment is the key to a better outcome of the disease. Although the clinical features of hemolysis including pallor, and dark-colored urine along with a positive DAT is tell tale, presence of a Coombs-negative autoimmune hemolytic anemia should always be kept in the differentials. Self-remission has been described, especially in children. Withdrawing the offending medication and instituting steroids usually suffice in alleviating the condition. Transfusions are rarely effective and should be reserved for patients who clinically deteriorate due to the severity of anemia.

Conflict of interest

There is no conflict of interest.

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