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CORRESPONDENCE

Autoimmune Hemolytic Anemia, Erythrophagocytosis and Liver Dysfunction After Cefixime Use for Urinary Tract Infection in a Child

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Dear editor,

Drug-induced hemolytic anemia and hepatitis associated with ceftriaxone administration have been reported previously; however, these have rarely been described in association with erythrophagocytosis [1–3]. We present a case of 3-year-old boy who developed severe autoimmune hemolytic anemia (AIHA) and liver dysfunction in the first week of cefixime use at a dose of 8 mg/kg/day orally in single daily dose for urinary tract infection. On examination, he was found to have mental and behavioral changes and, jaundice. At that time, testing indicated platelet count 151,000/mm^3, leukocyte count 17.900/mm^3, hemoglobin (Hb) concentration 5.1 g/dL and reticulocytes 8.5%. Peripheral blood smear and bone marrow findings were consistent with erythrophagocytosis (Fig. 1). Biochemical investigations revealed elevated AST (259 IU/dL), ALT (316 IU/dL), bilurubin (7.4 mg/dL) and lactate dehydrogenase (1750 IU/L) and low haptoglobin as 10 mg/dL (normal range, 30–200 mg/dL). The serum levels of ferritin and ammonia were high as 4031 mg/dL and 130 umol/L, respectively. The patient's prothrombin time was 4 s longer than the upper limit of our laboratory's normal range and a direct Coombs test was positive with reactive anti-C3. None of the viral (Epstein–Barr virus, Cytomegalovirus, Hepatitis A, B, C virus, HIV, Rubella and Parvovirus B19) serological markers were positive. Altered consciousness, acute liver failure and AIHA did not respond to 10–15 cc/kg fresh frozen plasma infusion and methylprednisolone at a dose of 2 mg/kg/day administration for 2 days. Therapeutic plasma exchange (TPE) and intravenous immunoglobulin were administered for 2 consecutive days, after which clinical and laboratory assessments revealed a dramatic response. Over the following 5 days, his Hb level gradually increased and his abnormal liver function tests returned to normal range. Complete resolution of AIHA and liver failure was achieved within 3 weeks after TPE and IVIG administration. The patient remained well with no signs of disease recurrence in the next 6 months after diagnosis.

The World Health Organization classifies drug-induced adverse reactions as certain, probable, possible or unlikely in the WHO Program for International Drug Monitoring (www.who-umc.org). The clinical and laboratory findings in our case were consistent with the descriptions of possible drug-induced adverse reactions. Our report describes an uncommon complication of an oral third-generation cephalosporin (cefixime) in a pediatric case. In previously reported cases, AIHA developed on average 5 days after cephalosporin use in children [4]. If AIHA develops in patients with fever, particularly in childhood, it is mostly considered to be of viral origin. In the case presented, AIHA was considered to be most likely induced by cefixime because the drug was administered 7 days before the anemia occurred, and viral screening was negative, and fever was absent on admission. Drug-induced anemia usually develops due to immunologic or toxic effects [4]. Drug-induced antibodies were not analyzed in our patient; however, a positive Coombs test with reactive anti-C3,

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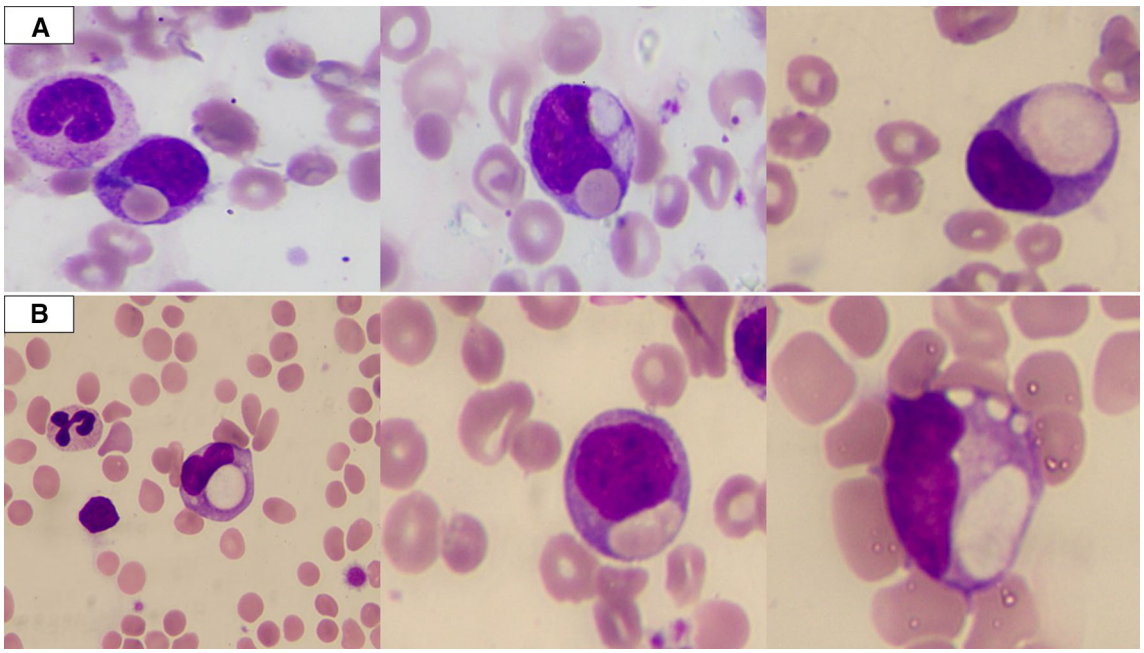

Fig. 1 **a** Bone marrow smear showing erythrophagocytosis by macrophage, **b** peripheral blood smear showing erythrophagocytosis by monocytes

monocytosis and erythrophagocytosis suggest that an immunologic mechanism was responsible for the anemia as opposed to a direct toxic effect of cefixime on erythropoiesis. Despite the widespread use of cefixime, this triad of side effects has not previously been reported in connection with this drug. Rapid recovery after IVIG and TPE further supports immune-mediated hemolysis. Similarly, it has been reported that erythrophagocytosis is increased in peripheral blood and bone marrow as a reaction to an excessive immune response induced by virus and cold agglutinin disease, and that such increase is accompanied by reactive monocytes [2, 3, 5]. To the best of our knowledge, ours is the first case description of cefixime-induced erythrophagocytosis, AIHA and liver failure.

Compliance with Ethical Standards

Conflict of interests The authors have no conflict of interests.

Human and Animal Rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Informed consent was obtained from parents.

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