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Case Report

Successfully Treated Sulphasalazine-Induced Fulminant Hepatic Failure, Thrombocytopenia and Erythroid Hypoplasia with Intravenous Immunoglobulin

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Abstract: We report the simultaneous development of fulminant hepatic failure, thrombocytopenia and erythroid hypoplasia in a child treated with sulphasalazine. A 12-year-old girl with juvenile rheumatoid arthritis developed fulminant hepatic failure, thrombocytopenia and erythroid hypoplasia, which was confirmed by liver histology and bone marrow examination, 2 weeks after initiation of sulphasalazine therapy. The patient recovered after administration of high doses of intravenous immunoglobulin. This is the first reported case of the concurrent development of these complications associated with sulphasalazine hypersensitivity. The use of intravenous immunoglobulin may have helped in the treatment of this rare adverse effect of sulphasalazine.

Keywords :Erythroid hypoplasia; Hepatic failure; Juvenile rheumatoid arthritis; Sulphasalazine

Introduction

Sulphasalazine (SSE) has been widely used as a second-line agent for the treatment of seronegative and seropositive rheumatoid arthritis (RA) in adults [1,2] and in children with juvenile rheumatoid arthritis (JRA) [3–5]. Several reports [3–6] revealed that 40–80% of patients with JRA had significant improvement after SSE therapy. Adverse reactions to SSE, as well as to the general sulphonamide class of drugs, involve widespread organ systems [7]. Idiosyncratic reactions have been widely reported which included skin rashes, fever, agranulocytosis, polyarteritis and neurotoxicity [7,8]. Hepatic toxicity to SSE is not common and was once reported to occur in 2.5% of 200 adult patients with RA [9]. Erythroid hypoplasia is a syndrome characterised by severe normochromic, hypochromic anaemia, reticulocytopenia, and the absence of erythroblasts in otherwise normal bone marrow. Its acute self-limiting form is usually associated with drugs or infection. Concomitant adverse hepatic reactions, thrombocytopenia and erythroid hypoplasia to SSE in patients with RA or JRA has not been reported in the English literature. We describe the clinical and pathological features of a patient with fulminant hepatic failure and red cell aplasia that developed 2 weeks after starting SSE treatment.

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Case Report

A 12-year-old girl with systemic JRA was admitted to our hospital because of a 3-day history of fever, abdominal pain, jaundice and progressive pallor. She had had several remissions and exacerbations within a 3-year history of chronic arthritis, and her joint symptoms were only treated by non-steroidal anti-inflammatory drugs (NSAIDs). Two weeks before admission, she was given SSE, at a starting dose of 500 mg once daily, when a gradual increase in the number of affected joints (knees, ankles and several finger joints) was noticed. On

physical examination she was ill-looking and febrile with jaundice. The liver and spleen were 3 and 2 cms below the right and left costal margin respectively, with a smooth, non-tender edge. She had no skin rash.

Initial laboratory investigations showed total bilirubin 5.5 mg%, direct bilirubin 2.7 mg%, alanine aminotransferase (ALT) 20802 IU/l, aspartate aminotransferase (AST) 6380 IU/l, alkaline phosphatase (ALP) 404 IU/l, γ-glutamyl transpeptidase (γ-GT) 46 IU/l, albumin 3.0 g/dl. The complete blood count (CBC) showed haemoglobin 8.4 g/dl, reticulocytes 0.2%, white blood cell (WBC) count 7200/mm^3 with normal differential, and platelet count 79x10^3/mm^3. Coombs' test was negative. Plasma fibrinogen was 105 mg/dl and serum FDP was negative. SSE was discontinued and broad-spectrum antibiotics were administered during the first 14 days. Bone marrow examinations were performed on the 3rd and 24th day. The myeloid/erythroid ratio was 14:1. There was severe erythroid hypoplasia and mature normoblasts were almost absent. The megakaryocytes were increased in number. Monocytes and eosinophils were normal. The myeloid cells were hypogranular. Other tests performed to elucidate the possible aetiology of this acute hepatitis and erythroid hypoplasia were negative, which included anti-hepatitis A virus (HAV) immunoglobulin M (IgM), hepatitis B surface antigen (HBsAg), anti-hepatitis B core antigen (HBc) IgM antibody (Ab), anti-hepatitis C virus (HCV) Ab, anti-hepatitis E virus (HEV) Ab, Epstein-Barr viral capsid IgM Ab, cytomegalovirus (CMV) Ab and urine culture of CMV, antinuclear Ab (ANA), smooth muscle Ab, and anti-mitochondria Ab. Serum copper and ceruloplasmin, and 24 h urinary copper and serum α-1-antitrypsin were within normal limits.

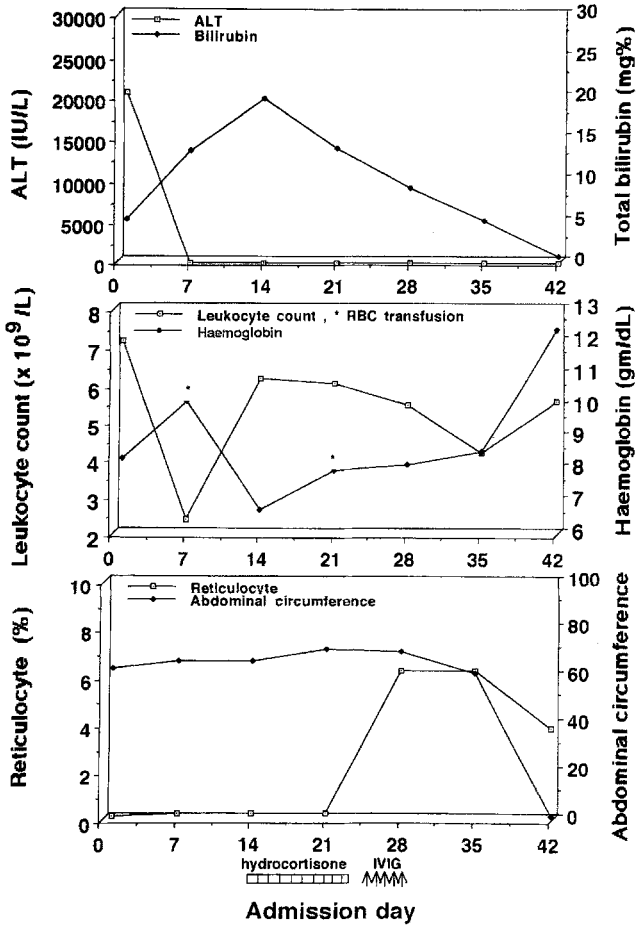

Fig. 1. Changes in laboratory data after treatment with hydrocortisone and intravenous immunoglobulin.

On the 10th admission day, the aminotransferases (ALT, AST) decreased to normal limits while cholestasis was aggravated. Serial abdominal ultrasonography only showed hepatomegaly without bile duct obstruction. Intravenous hydrocortisone was administered for 9 consecutive days (100 mg/dose every 6 h) from the 14th admission day. Anaemia, thrombocytopenia and cholestasis did not improve (Fig. 1, Table 1). Ascites progressively accumulated. Intravenous immunoglobulin (IVIg) was infused for 5 days (400 mg/kg/dose once daily) from the 24th day, because immune-complex-mediated diseases that result from SSE were suspected. Fortunately, the reticulocytes increased 8 days after first administration of IVIg and the anaemia, ascites and cholestasis gradually improved (Table 1, Fig. 1). The liver biopsy, which was not performed until the 35th admission day because of the severity of ascites and thrombocytopenia, demonstrated scattered granulomas across lobules with infiltration of lymphocytes and eosinophils. It was compatible with drug-induced

Table 1. Changes in white cell count, haemoglobin, platelet count, reticulocyte count and liver function after treatment with hydrocortisone and intravenous immunoglobulin (IVIg)

	Day 18	Day 20	Day 22	Day 24	Day 26	Day 28	Day 30	Day 32	Day 34
WBC (mm3)	11 400	6200	3500	6070	5720	5700	4500	5500	4200
Haemoglobin (g/dl)	8.9	8.6	6.8 (BT*)	8.9	6.4 (BT*)	8.8	7.4	8.6	9.2
Platelets (10^3/mm^3)	20	30	17	21	23	20	26	93	102
Reticulocytes (%)	0.1	0.1	0.1	0.2	0.1	0.2	0.2	7	4
ALT (IU/l)	10	14	15	13	15	13	190	26	58
Bilirubin (mg%) direct/ total	9.4/20	9.1/15.3	4.6/9.2	5.6/11.4	6.9/14	11/23.2	8.8/17.6	5.1/9.8	2.7/5.4

* The administration of hydrocortisone was from day 14 to day 22 (400 mg/day), and the administration of IVIg was from day 24 to day 28 (400 mg/kg/day).
BT*, packed red blood cell transfusion.

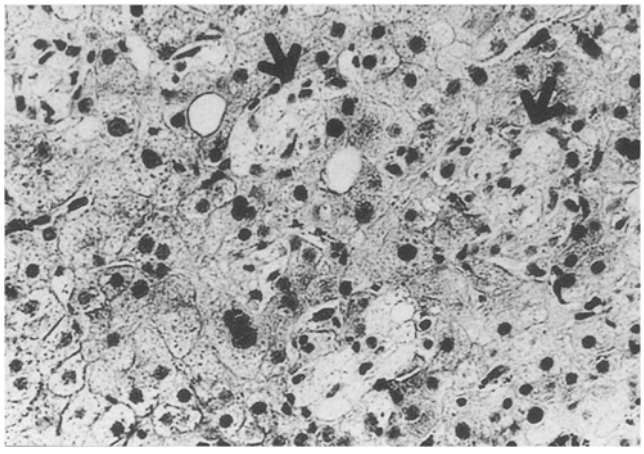

Fig. 2. The granulomas (arrows) are made up of compact aggregates of macrophages with abundant foamy cytoplasm. There is also some infiltration of lymphocytes and eosinophils. (H & E, original magnification x640.)

hepatitis (Fig. 2). The patient was discharged from hospital on no medication and has had no signs of hepatobiliary or haematological disease for 3 months; her JRA has remained in remission. The latest laboratory findings were WBC 5500/mm^3, haemoglobin 12 g/dl, platelets 213x10^3/mm^3, ALT 35 IU/l, total bilirubin 0.8 mg%, direct bilirubin 0.3 mg% and erythrocyte sedimentation rate 10mm/h.

Discussion

Sulphasalazine is now widely used as a disease-modifying agent in the treatment of children with JRA, although the mechanism of its action remains obscure. When treating children whose arthritis is not controlled with NSAIDs, SSE is usually added as a second line agent. The efficacy and safety of this drug for treating RA and JRA has been proven [3,10]. Less than 20% of children with JRA had to discontinue SSE therapy because of adverse reactions, which usually occurred within 2–3 months (range 1 day to 36 months) after starting treatment [3–6]. Skin rashes, gastrointestinal upset, leukopenia and elevation of liver enzymes were commonly encountered adverse reactions. Nearly all reactions resolved completely when the drug was discontinued.

More serious hepatotoxicity and fetal hepatic necrosis have been described, mainly in patients with inflammatory bowel disease [11,12]. Patients with systemic JRA have a much greater risk of developing adverse reactions at the start of SSE therapy, including serum sickness, thrombocytopenia and liver involvement [3,13,14]. Although concurrent hepatotoxin or antecedent liver disease may have increased the risk for hepatic adverse reaction [15], most cases are benign and reversible.

Macrophage activation syndrome (MAS), a heterogeneous disease characterised by fever, hepatic dysfunction, pancytopenia, hypofibrinogenaemia or consumptive coagulopathy [16,17], has been associated with juvenile chronic arthritis following treatment with a second-line agent such as SSE. In our study, normal plasma fibrinogen, triglycerides and the absence of reactive histiocytes in bone marrow and liver tissue had made the diagnosis of MAS unlikely.

In all the reported adult RA cases and in one JRA case associated with red cell aplasia, it was thought to be drug-induced and not related to RA. As the hepatotoxicity, thrombocytopenia and erythroid hypoplasia is probably a hypersensitivity reaction to the sulphapyridine component of the drug, corticosteroids may have been used as therapy. We, as in some reported cases [11, 18], did not find evidence that corticosteroids had altered the course of SSE hepatotoxity and red cell aplasia. In addition, the use of corticosteroids had altered neither the clinical course nor the bone marrow findings after 9-day therapy with intravenous hydrocortisone. In this case, the use of intravenous immunoglobulin seemed to improve the cholestasis, ascites, hepatomegaly and anaemia. The mechanism of development of thrombocytopenia, erythroid hypoplasia and hepatitis was not known.

Thrombocytopenia with the presence of increased megakaryocytes in the bone marrow suggests the possibilities of increased peripheral platelet destruction or ineffective thrombopoiesis. Mihas et al. [19] reported that immune complexes might play a role in mediating toxic reaction of hepatitis after SSE therapy.

In conclusion, hepatic toxicity and erythroid hypoplasia are not common but are serious adverse reactions that may be fatal. Prompt recognition of the hypersensitivity reaction associated with SSE and prompt discontinuation of the drug is of most importance as association with hepatic and bone marrow injury cannot be predicted and the injuries respond poorly to all forms of conventional treatment. In this study, there is a remarkable increase in reticulocyte count and haemoglobin and decreased serum bilirubin 8 days after the first administration of IVIg. Although the recovery of thrombopoiesis, erythropoiesis and liver function did not exclude a spontaneous recovery or a response to steroid, the administration of a high dose of IVIg may have contributed to the improvement.

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