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CASE REPORT

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Infectious mononucleosis-like syndrome induced by salazosulfapyridine in a patient with rheumatoid arthritis

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Abstract We describe a 43-year-old woman with rheumatoid arthritis (RA), who developed severe infectious mononucleosis (IM)-like syndrome during treatment with salazosulfapyridine (SASP). She presented with fever, skin rash, lymphadenopathy, and hepatosplenomegaly. Laboratory tests revealed a marked increase of atypical lymphocytes in the peripheral blood and biphasic hepatic dysfunction. IM-like syndrome can be caused by various drugs, including SASP, and the concept of drug-induced hypersensitivity syndrome has been proposed recently. IM-like syndrome due to SASP has been reported in patients taking higher dosages for the treatment of inflammatory bowel disease, but has not been reported earlier in patients with RA. The results of the drug-induced lymphocyte stimulation test tests suggested that 5-aminosalicylic acid was a possible causative metabolite. This severe type of drug-induced hypersensitivity reaction mimicking IM due to SASP should be granted wider awareness in the field of rheumatology, because the drug is widely used for the treatment of RA.

Key words Drug hypersensitivity · Infectious mononucleosis · Rheumatoid arthritis · Salazosulfapyridine

Introduction

Salazosulfapyridine (SASP) is widely used for the treatment of rheumatoid arthritis (RA) and inflammatory bowel disease (IBD).

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Recently, a drug-induced infectious mononucleosis (IM)-like syndrome that is characterized by fever, skin rash, generalized lymphadenopathy, and liver dysfunction has been reported.[1,2] This syndrome is a severe form of drug allergy, and the concept of drug-induced hypersensitivity syndrome (DIHS) has been proposed by dermatologists.[1] Certain drugs have been reported to cause DIHS, including carbamazepine, minocycline, allopurinol, and SASP.[3,4] SASP-induced IM-like syndrome has occurred earlier in patients with IBD[5–8] taking relatively high dosages of more than 2 g/day, but this syndrome has not yet been reported in patients with RA.

Here, we describe a patient with RA who developed an IM-like illness during SASP therapy. In this patient, the drug-induced lymphocyte stimulation test (DLST) test suggested that 5-aminosalicylic acid (5-ASA) was a possible causative metabolite.

Case report

A 43-year-old Japanese woman was diagnosed as having rheumatoid arthritis and drug therapy was started with SASP at a daily dosage of 1000 mg. Two weeks later, she developed a rash on her extremities and fever (38.3°C). Although SASP treatment was stopped, she developed facial edema, a generalized rash, and lymphadenopathy (including the cervical, axillary, and inguinal regions) during the next 2 weeks. Her liver was just palpable without tenderness. There were no genital lesions and the thorax showed no abnormalities.

Laboratory tests revealed a hematocrit of 40.3% and a white blood cell count of 44 400 mm^{-3}, with a differential count of 40.0% neutrophils, 2.0% eosinophils, 5.0% monocytes, and 53.0% lymphocytes (of which 32.0% were atypical). Liver function tests showed an aspartate aminotransferase (AST) of 47 U, alanine aminotransferase (ALT) of 132 U, lactic dehydrogenase of 628 U, alkaline phosphatase of 1768 U, and total bilirubin of 2.1 mg/dl. The C-reactive protein level was elevated to 4.82 mg/dl. The titers of

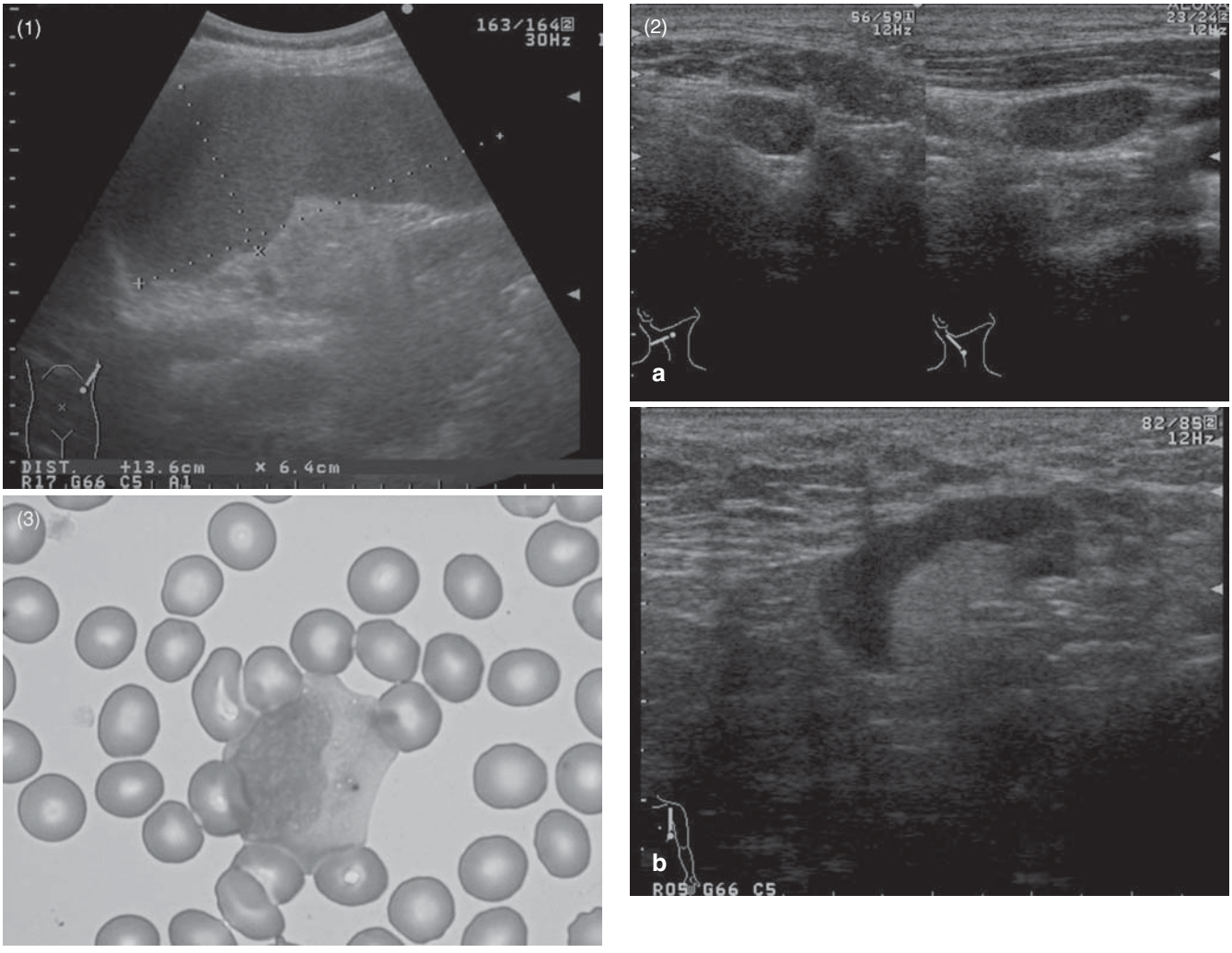

Fig. 1. (**1**) Abdominal ultrasonography shows marked splenomegaly (131.6 × 6.4 cm). (**2**) Ultrasonography shows cervical (**a**) and axillary (**b**) lymphadenopathy. (**3**) Atypical lymphocytes in a peripheral blood smear (×1000)

anti-EB-VCA IgM, EB-EA DR IgG, and EBNA antibodies were all less than 10. In addition, Epstein-Barr Virus (EBV)-DNA was not detected by polymerase chain reaction in the peripheral blood. Anti-cytomegalovirus (CMV) antibody titers were also less than 10. Thus, serology indicates no evidence of EBV or CMV infection. The chest X-ray and electrocardiogram were within normal limits. The ultrasound showed marked splenomegaly and multiple enlarged lymph nodes in the cervical, axillary, and inguinal regions (Fig. 1). After nonsteroidal anti-inflammatory drugs and antihistamines relieved her fever, rash, and lymphadenopathy, she was discharged. Three weeks later, however, laboratory tests showed the re-elevation of liver enzymes (Fig. 2). Because of her persistent skin rash, splenomegaly and liver dysfunction, oral treatment with prednisolone (10 mg/day) was commenced. Thereafter, the skin rash resolved promptly, followed by the improvement of her liver dysfunction and splenomegaly. We suspected that this illness mimicking IM was actually SASP-induced DIHS because there was no significant elevation of any viral antibodies, as well as her typical biphasic clinical course.

To clarify the causative drug metabolites, we performed a patch test and a DLST. The patch test was negative for all of SASP, 5-ASA, and sulfapyridine. In contrast, SASP and its two major metabolites significantly stimulated the patient's lymphocytes in vitro. Especially, the stimulation index for 5-ASA was extremely high (2734%), compared with those for SASP and sulfapyridine (450% and 680%, respectively). SASP is split into sulfapyridine and 5-ASA by bacterial azo reductases in the colon, with the former metabolite accounting for most of the adverse effects of this drug.[9] Analysis of the *N*-acetyltransferase 2 (NAT2) phenotype that is closely related to detoxification of sulfapyridine[10] showed that our patient was a rapid acetylator.

Discussion

Recently, IM-like syndromes induced by various drugs have been recognized as a severe form of drug hyper-

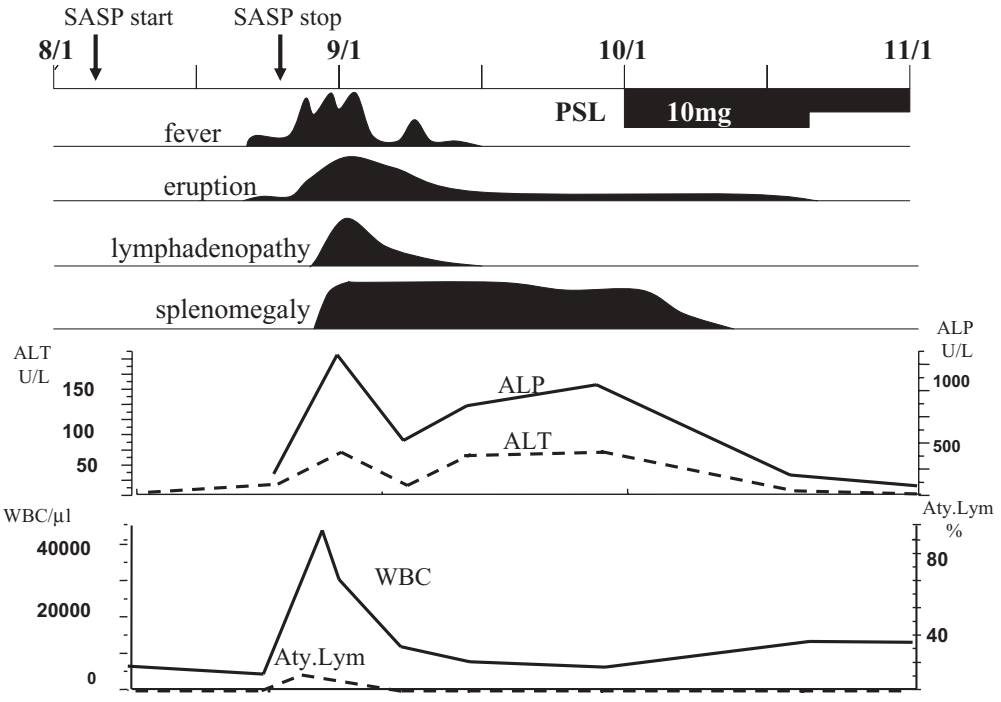

Fig. 2. Clinical course. *PSL*, prednisolone; *SASP* salazosulfapyridine, *Aty.Lym*, atypical lymphocytes

Table 1. Salazosulfapyridine-induced hypersensitivity syndrome in Japan

Age/sex	Disease	SASP dosage	Duration of treatment	WBC (Aty.Lym) μl^{-1}	DLST	Patch test	Challenge test	Steroid therapy
18/M[10]	UC	3 g	1 month	21200 (8.5%)	(–)	(+)	(+)	(–)
18/M[11]	UC	3 g	2 weeks	19300 (11%)	ND	(+)	ND	(+)
34/F[11]	UC	3 g	26 days	48400 (19%)	ND	(+)	(+)	(+)
37/M[12]	ND	ND	ND	ND (20%)	ND	ND	ND	(–)
58/M[13]	UC	ND	2 weeks	20000 (many)	ND	(–)	(+)	(+)
47/F[14]	UC	ND	2 weeks	40000 (16%)	ND	ND	(+)	60 mg
28/M[15]	CD	ND	6 weeks	ND (4%)	ND	(+)	(+)	(–)
27/W[8]	UC	1 g	2 weeks	21100 (6%)	(–)	(+)	ND	(–)
24/M[7]	UC	3 g	2 weeks	13800 (16%)	(–)	(+)	ND	Pulse × 2
52/M[9]	UC	2 g	3 weeks	ND (+)	(–)	(+)	(+)	60 mg
68/F[9]	UC	1.5 g	45 days	ND (+)	(–)	(+)	ND	30 mg
33/F[6]	UC	2 g	3 weeks	11000 (31%)	ND	ND	ND	Pulse
59/M[6]	UC	2 g	3 weeks	16000 (6%)	ND	ND	ND	Minipulse
28/M[16]	PA	2 g	32 days	26300 (20%)	(–)	ND	ND	60 mg
22/F[16]	UC	2 g	18 days	ND	ND	ND	ND	Pulse
22/F[2]	UC	3 g	2 weeks	21200 (12%)	(÷)	ND	ND	Pulse × 2
43/F	RA	1 g	2 weeks	44400 (21%)	(+)	(–)	ND	10 mg

SASP, salazosulfapyridine; WBC, white blood cell; DLST, drug-induced lymphocyte stimulation test; UC, ulcerative colitis; CD, Crohn's disease; PA, psoriatic arthritis; RA, rheumatoid arthritis; ND, not described

sensitivity reaction and the concept of DIHS has been advocated.[1–3]

Drug-induced hypersensitivity syndrome is characterized by fever, skin rash, lymphadenopathy, and an increase of circulating atypical lymphocytes; it usually occurs from 2 weeks to 5 weeks after starting the administration of the culprit drug. Reactivation of human herpes virus-6 (HHV-6) may also play an important role in the exacerbation of DIHS. The following seven diagnostic criteria for DIHS have been proposed by the Research Committee of the Japanese Ministry of Health, Labour and Welfare (http://www.dermatol.or.jp/news/news_020307.html): (1) skin rash, (2) persistence for more than 2 weeks after cessation of treatment with the culprit drug, (3) fever, (4) liver dysfunction, (5) hematological abnormalities (leukocytosis or atypical lymphocytosis or eosinophilia), (6) lymphadenopathy, and (7) reactivation of HHV-6 infection. This patient satisfied six of the criteria, but we did not have a chance to measure antibodies against HHV-6 and parvovirus B19.

Salazosulfapyridine, anticonvulsants, dapsone, allopurinol, and several other medications[3,4] have been reported to induce DIHS, and 16 patients with SASP-induced DIHS have been reported in Japan so far (Table 1); 14 of the 16 patients were taking SASP for the treatment of IBD (ulcerative colitis in 13 and Crohn's disease in 1). There have been no reports of SASP-induced DIHS in patients with rheumatoid arthritis before the present case.

Most patients who developed DIHS were taking high dosages of SASP, i.e., more than 2 g/day. Initial symptoms developed within 45 days after the start of SASP therapy. Most patients showed severe leukocytosis with an increase of atypical lymphocytes that mimicked IM. Because DIHS is a kind of allergic drug reaction, it is important to clarify the possible causative agent. We performed DLST and patch tests using SASP, 5-ASA, and sulfapyridine. According to the results of the DLST, 5-ASA was a likely candidate as the causative drug. Because sulfapyridine is responsible for most of the adverse effects of SASP, NAT2 catalytic activity is a major determinant of SASP toxicity. It has been suggested that patients who are slow acetylators have a higher risk from the adverse effects of SASP,[10,17] including DIHS, and a dose-dependent increase of adverse events has been reported. In addition, SASP-induced autoimmune abnormalities have been reported in RA patients and the majority of these patients were slow acetylator genotype.[18] Although NAT2 genotyping showed that our patient was a rapid acetylator, 5-ASA-related adverse events might also occur independently of the accetylator phenotype and at lower dosages.

For the treatment of DIHS, the efficacy of corticosteroids has been reported. In our case, low-dosage corticosteroid therapy rapidly improved the symptoms and liver dysfunction. Although a partial response might be obtained from NSAIDs and/or antihistamines, we recommend early corticosteroid therapy if DIHS is strongly suspected.

In conclusion, we presented an RA patient who developed DIHS that mimicked IM and was induced by SASP. Because SASP is one of the first-line disease-modifying anti-rheumatic drugs (DMARDs), careful follow-up later – with DIHS in mind – is necessary at the start of DMARD therapy.

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