Renal Replacement Therapy

CASE REPORT

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Salazosulfapyridine-induced agranulocytosis in a patient on chronic hemodialysis with seronegative spondyloarthropathy: a case report

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Abstract

Background: Salazosulfapyridine is a generally safe drug often used to treat rheumatoid arthritis and ulcerative colitis. However, agranulocytosis is a rare but serious adverse effect of this drug. To date, there have been no reports describing the clinical course of salazosulfapyridine-induced agranulocytosis in a chronic hemodialysis patient.

Case presentation: The patient was a 64-year-old man with IgA nephropathy who had been on chronic hemodialysis for about 3 years. For 1 month, he had general fatigue, mild fever, and pain in multiple joints of the upper extremities. He was hospitalized and underwent detailed examinations in our department. Laboratory investigations revealed an erythrocyte sedimentation rate of 67 mm/h and a C-reactive protein level of 7.73 mg/dL. Rheumatoid factor and anti-cyclic citrullinated peptide antibody were negative. Musculoskeletal ultrasonography showed inflammation of the tendon sheath in both wrists and the right shoulder joint. Computed tomography scans revealed osteosclerosis and narrowing of the sacroiliac joint. The diagnosis was seronegative spondyloarthropathy. He was started on salazosulfapyridine. Four weeks later, he had a high fever and low granulocyte count. Treatment with granulocyte colony-stimulating factor was started. The agranulocytosis could not be ascribed to any other cause and was considered an adverse effect of salazosulfapyridine, which was then stopped. Nine days later, the granulocyte count had recovered and the fever had resolved.

Conclusions: Currently, there are no guidelines on the use of salazosulfapyridine in chronic hemodialysis patients. The starting dosage should be smaller for these patients than for patients without renal impairment. Also, the laboratory monitoring interval for complete blood count should be shorter than usual.

Keywords: Salazosulfapyridine, Agranulocytosis, Hemodialysis, Seronegative spondyloarthropathy

Background

Salazosulfapyridine (SASP) is a generally safe drug that is often used to treat rheumatoid arthritis and ulcerative colitis. However, agranulocytosis is a rare but serious adverse effect of this drug. Case reports describing the course of SASP-induced agranulocytosis are not uncommon but no case has been reported in patients on chronic hemodialysis and no guidelines have been established for the use of SASP in such patients. Here we describe a case of SASP-induced agranulocytosis in a patient on chronic hemodialysis with seronegative spondyloarthropathy.

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Case presentation

The patient was a 64-year-old man with IgA nephropathy who had been on chronic hemodialysis for about 3 years. His medical history included diabetes mellitus and hip fracture. His condition had been stable since the introduction of hemodialysis. Although laboratory investigations revealed mild inflammation, he remained asymptomatic and detailed examination did not reveal the cause. For 1 month before presentation in our department, he had general fatigue, mild fever, and pain in multiple joints of the upper extremities. He was hospitalized and underwent detailed examinations in our department. Physical findings included swelling and tenderness in both wrists, several distal interphalangeal joints, and the right shoulder joint. Laboratory investigations revealed an erythrocyte sedimentation rate of 67 mm/h and a C-reactive protein (CRP) level of 7.73 mg/dL. Rheumatoid factor and anti-cyclic citrullinated peptide antibody were negative (Table 1). Musculoskeletal ultrasonography showed inflammation of the tendon sheath in both wrists and the right shoulder joint. Computed tomography scans revealed osteosclerosis and narrowing of the sacroiliac joint. The diagnosis was seronegative spondyloarthropathy.

SASP was started at a dosage of 500 mg/day (day 1). No side effects were noted after 8 days of treatment, so the dosage was increased to 1000 mg/day (day 9). The patient developed high fever on day 26. Although no focus was evident, bacterial infection could not be excluded. Therefore, antibacterial therapy was started. However, the fever did not resolve and the white blood cell (WBC) count decreased. On day 31, WBC and granulocyte counts were 1100/μL and 349/μL, respectively. Filgrastim (granulocyte-colony stimulating factor; G-CSF) 75 μg was started for agranulocytosis. After ruling out other differential diagnoses, the agranulocytosis was considered an adverse effect of SASP, which was stopped on day 33. G-CSF and broad-spectrum antibacterial therapy were continued. By day 42, the WBC and granulocyte counts had recovered to 5600/μL and 1725/μL, respectively, and the fever had resolved. Therefore, the G-CSF and antimicrobial agents were stopped (Fig. 1). Although a drug-induced lymphocyte stimulation test was negative, we diagnosed SASP-induced agranulocytosis based on the clinical course. After resolution of the agranulocytosis, the CRP level decreased to around 1 mg/dL and the joint symptoms disappeared.

Table 1 Laboratory test results

Complete blood counts	
White blood cell	5000/μL
Granulocytes	78.8%
Lymphocytes	11.3%
Monocytes	9.9%
Red blood cells	466×10^4/μL
Hemoglobin	12.0 g/dL
Hematocrit	38.5%
Platelets	20.8×10^4 /μL
Electrolytes	
Na	133 mEq/L
K	3.8 mEq/L
Cl	98 mEq/L
Ca	7.3 mg/dL
Inorganic phosphorus	5.2 mg/dL
Chemistry	
Total protein	6.5 g/dL
Albumin	2.4 g/dL
Total bilirubin	0.4 mg/dL
Aspartate aminotransferase	22 U/L
Alanine aminotransferase	11 U/L
Lactate dehydrogenase	236 U/L
Alkaline phosphatase	316 U/L
γ-glutamyl transpeptidase	9 U/L
Amylase	68 U/L
Creatine phosphokinase	52 U/L
Blood urea nitrogen	35.6 mg/dL
Creatinine	4.34 mg/dL
C-reactive protein	7.73 mg/dL
Procalcitonin	0.5–2.0 ng/mL
Serology	
Rheumatoid factor	13 U/mL
Anti-cyclic citrullinated peptide antibody	1.0 U/mL
Antinuclear antibodies	1:40
Erythrocyte sedimentation rate	67 mm/h
Matrix metalloproteinase 3	1109.7 ng/mL
IgG	1981 mg/dL
IgA	691 mg/dL
IgM	67 mg/dL

Discussion and conclusions

SASP is often used to treat rheumatoid arthritis and ulcerative colitis and has a good safety profile. Agranulocytosis is a rare but serious adverse effect of this drug. In previous reports on the adverse effects of SASP, the incidence of blood disorders was 0.26% (27/10,332) [1], with neutrophil counts of < 800/μL in 1% of cases (3/300) [2] and agranulocytosis in 0.08% (3/3586) [3]. The pathogenesis of SASP-induced agranulocytosis is not completely understood but is thought to be mediated by immune hypersensitivity or direct damage to myeloid precursors [1, 4, 5]. The onset of this side effect is usually within 2 months of starting the drug [6, 7]. Treatment consists

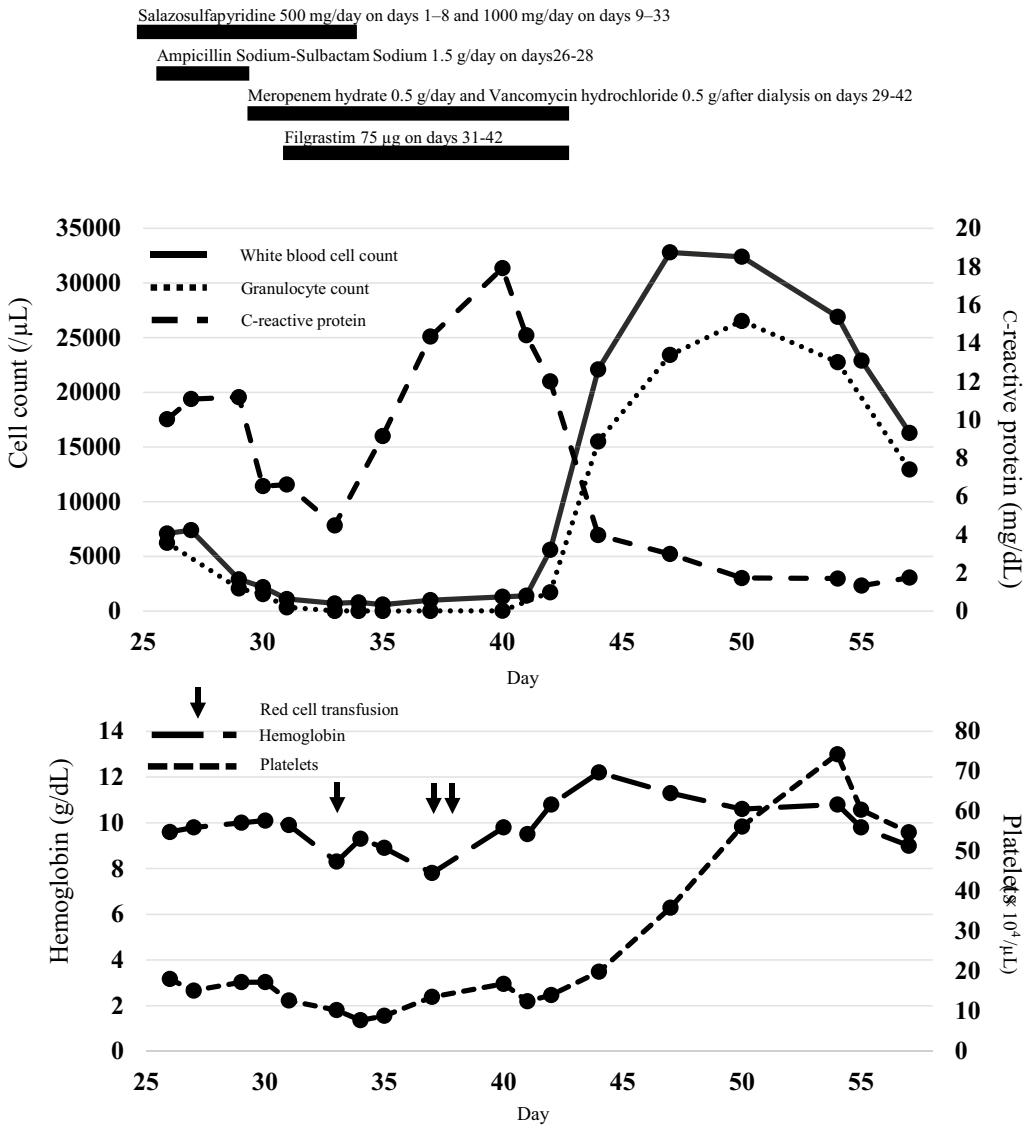

Fig. 1 Clinical course

of stopping SASP and starting G-CSF. WBC and granulocyte counts are reported to recover after about 10 days [7]. In our case, the onset of agranulocytosis was at around 1 month after starting the drug, and WBC and granulocyte counts recovered 9 days after stopping SASP. Thus, this clinical course of SASP-induced agranulocytosis in our chronic hemodialysis patient did not differ substantially from that in patients without end-stage renal failure described in previous reports.

Approximately 10% of orally administered SASP is absorbed unchanged in the small intestine. The remainder is metabolized to sulfapyridine (SP) and 5-aminosalicylic acid (5-ASA) in the large intestine. Most of the SP is absorbed in the large intestine and undergoes N-acetylation in the liver, whereas acetylsulfapyridine (Ac-SP) is excreted in the urine [8–10]. The pharmacological activity of SASP is attributed mainly to the parent drug, but its adverse reactions are associated with SP [8, 11]. The pharmacokinetics of SASP and its metabolites in our patient may have differed from those in the general population because of end-stage renal failure. There are no guidelines for the use of SASP in patients on hemodialysis. Moreover, there have been only three reports on the pharmacokinetics of SASP in such patients [8, 12, 13], both of which mention that SASP, which binds to human serum albumin above 99% [14], was not dialyzable but SP

and Ac-SP were dialyzable. Akiyama et al. reported accumulation of SASP, SP, and Ac-SP with continuous administration at 500 mg/day for 5 days but remained within the safe range [12, 13]. Inami et al. reported accumulation of SASP and SP when a dose of 250 mg was administered followed by a dose of 500 mg after an interval of some days [8]. Given that there have been few relevant case reports, we cannot reach a conclusion as to whether accumulation of SASP, SP, and Ac-SP is a problem in patients on dialysis. However, adverse effects of SASP have been reported to be significantly more likely in patients with renal impairment than in those with normal kidney function (34.5% [41/119] vs 20.9% [589/2813], $P<0.001$) [3]. Therefore, renal impairment might lead to accumulation of SP and an increased likelihood of adverse effects. Furthermore, in our case, end-stage renal disease might have contributed to the agranulocytosis.

All other drugs (roxadustat, olmesartan medoxomil, amlodipine besilate, carvedilol, febuxostat, limaprost alfadex, tramadol hydrochloride/acetaminophen, famotidine, nalfurafine hydrochloride, folic acid, and clostridium butyricum) were started some time before hospitalization. None of these medications is suspected to induce agranulocytosis on its own. In terms of drug–drug interactions with SASP, folic acid was reported to have reduced absorption when co-administered with SASP [15]. Roxadustat was reported to be a substrate of breast cancer resistance protein (BCRP) and have an inhibitory effect against it in vitro [16]. In addition, BCRP gene polymorphism affects the pharmacokinetic of SASP [17]. Olmesartan medoxomil was also reported to be a substrate of BCRP [18]. Therefore, the pharmacokinetics of SASP might have been affected by the concomitant use of roxadustat and olmesartan medoxomil, but as far as we know, there are no clinical reports to suggest drug–drug interactions between SASP and these two drugs. Adverse effects of SASP were also reported to be associated with genetic variations in N-acetyltransferase 2 gene [19, 20]. However, this gene was not examined in our patients. Such variations might have affected the agranulocytosis in this case.

After successful treatment of the agranulocytosis, the joint swelling and tenderness resolved and the CRP level decreased from 5–7 mg/dL on admission to around 1 mg/dL. This phenomenon is interesting, particularly given that there has been a similar report of remission of ulcerative colitis in a patient who developed SASP-induced agranulocytosis [21]. However, its etiology was not entirely clear.

There have been no reports describing the clinical course of SASP-induced agranulocytosis in patients on chronic hemodialysis and no guidelines have been established for the use of SASP in these patients. The starting dosage of SASP should be smaller for patients on chronic hemodialysis than for patients without renal impairment. Given that WBC and granulocyte counts rapidly decreased within 1 week in our patient, the laboratory monitoring interval for complete blood count should be shorter than the 2–4 weeks recommended by the American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis (22).

Abbreviations

Ac-SP: Acetylsulfapyridine; 5-ASA: 5-Aminosalicylic acid; BCRP: Breast cancer resistance protein; CRP: C-reactive protein; G-CSF: Granulocyte-colony stimulating factor; SASP: Salazosulfapyridine; SP: Sulfapyridine; WBC: White blood cell.

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Authors' contributions

All authors contributed to this case report. Conception and design, analysis and interpretation of data: TI, KN, and MU. Drafting and revising the manuscript: TI. Providing intellectual content of critical importance to the work described: KN, MF and MU. Collection of data: TI. Final approval of the version to be published: KN, MF and MU. All authors read and approved the final manuscript.

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Availability of data and materials

All data in this case are available from corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Informed consent for publication was obtained from the patient in this report.

Competing interests

The authors declare that they have no competing interests.

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