

SHORT COMMUNICATION

Severe Agranulocytosis in Two Patients with Drug-induced Hypersensitivity Syndrome/Drug Reaction with Eosinophilia and Systemic Symptoms

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Drug-induced hypersensitivity syndrome/drug reaction with eosinophilia and systemic symptoms (DIHS/DRESS) is a life-threatening adverse reaction characterized by skin rashes, fever, leukocytosis with eosinophilia and/or atypical lymphocytosis, lymph node enlargement, and liver and/or renal dysfunctions (1, 2). A wide variety of other involvements have also been reported, including limbic encephalitis, myocarditis, and gastrointestinal disease, developing during the course of the disease (3–5). It has been demonstrated that human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV) and cytomegalovirus (CMV) reactivate during the course of the disease and some organ involvements are associated with these herpesvirus reactivations (6, 7). Although haematological abnormalities, such as leukocytosis, eosinophilia, and atypical lymphocytosis, are characteristic symptoms of DIHS/DRESS, little attention has been paid to other haematological abnormalities, such as neutropaenia, agranulocytosis, and leukemoid reaction, detected in the course of the disease, even though these abnormalities could induce life-threatening events (8–12). We report here 2 patients who developed agranulocytosis in the course of DIHS/DRESS.

CASE REPORTS

Patient 1. A 68-year-old man was started on allopurinol at 200 mg/day for hyperuricaemia in addition to pre-existing therapy with cardiovascular drugs for more than 6 years. On day 30 of treatment, he noted erythematous rashes on his thighs. However, intake of allopurinol was continued. The eruption spread over the trunk, and high-grade fever appeared. He visited our hospital on suspicion of drug eruptions on day 18 after onset. On examination, axillary temperature was 40°C. Erythematous eruptions on the trunk and extremities and facial oedema were apparent (Fig. S1A¹). Cervical lymphadenopathy was present. No mucosal lesions were observed. He was promptly admitted to the emergency department. Laboratory testing on admission revealed: leucocytes $0.3 \times 10^9/l$ (normal $3.5\text{--}9.0 \times 10^9/l$); neutrophils $0.03 \times 10^9/l$; no eosinophils; lymphocytes $0.02 \times 10^9/l$; platelets $271 \times 10^9/l$; haemoglobin 11.1 g/dl; and C-reactive protein (CRP) 6.7 mg/dl (normal < 0.3 mg/dl). Liver dysfunction was undetected on admission and renal function was slightly affected by hyperuricaemia (blood urea nitrogen (BUN) 27.4 mg/dl; creatinine (Cr) 1.2 mg/dl (normal 0.4–1.1 mg/dl)). Allopurinol was withdrawn immediately. Testing of bone marrow aspirate revealed myeloid aplasia with mild increases in atypical lymphocytes and macrophages.

No evidence was seen of lymphoma or other haematological malignancies. Granulocyte-colony stimulating factor (G-CSF) and intravenous immunoglobulin at 5 g/day were administered for 5 days. As high-grade fever continued, antibiotics were started. During the appearance of agranulocytosis, atypical lymphocytosis (2–11%) was detected. On day 24 after onset, leucocyte count was normalized, but liver dysfunction appeared (aspartate aminotransferase (AST) 276 IU/l (normal < 33 IU/l); alanine aminotransferase (ALT) 159 IU/l (normal < 30 IU/l)). Renal function was also exacerbated (BUN 86.6 mg/dl; Cr 2.8 mg/dl). Seven days later, leucocytes overshot to $21.3 \times 10^9/l$ (neutrophil 81.0%; eosinophil 0.5%; monocyte 8%; lymphocyte 10%; atypical lymphocyte 0.5%). Liver and renal functions showed further deterioration (ALT 303 IU/l; BUN 76.0 mg/dl; creatinine 4.9 mg/dl), and the deterioration of renal function required haemodialysis (Fig. S2A¹). HHV-6 DNAs (2.5×10 copies/ 10^9 leucocytes) in peripheral blood and anti-HHV-6 IgG antibody titre measured using the fluorescent antibody method (640-fold) were determined 20 days after the detection of agranulocytosis. These clinical and laboratory findings satisfied the criteria for DIHS and the DRESS score was 7 (13, 14). Despite administration of various antibiotics, sepsis caused by catheter infection developed, and the patient died suddenly of septic shock.

Patient 2. An 82-year-old woman with rheumatoid arthritis had been treated with oral prednisolone (PSL) at 5 mg/day for more than 10 years. Because of the deterioration of arthralgia, sulfasalazine 3,000 mg/day was added to PSL. Laboratory testing before starting sulfasalazine revealed: leucocytes $9.8 \times 10^9/l$; neutrophils $5.7 \times 10^9/l$; lymphocytes $3.3 \times 10^9/l$; platelets $233 \times 10^9/l$; and haemoglobin 10.1 g/dl. After 35 days of sulfasalazine administration, the patient noticed erythematous rashes on the upper extremities, then low-grade fever appeared. She therefore decided to discontinue taking these drugs on day 2 after onset, on suspicion of drug-induced symptoms. Nevertheless, erythematous rashes extended to the trunk and high-grade fever developed. On presentation, 3 days after withdrawal of the drugs, erythematous eruptions were observed all over the patient's body and her temperature was 39.1°C (Fig. S1B¹). No facial oedema, mucosal involvements, or lymphadenopathy were found. She was immediately admitted to hospital. Laboratory studies on admission revealed: leucocytes $0.9 \times 10^9/l$; neutrophils $0.02 \times 10^9/l$; no eosinophils; lymphocytes $0.49 \times 10^9/l$; atypical lymphocytes $0.03 \times 10^9/l$; monocytes $0.34 \times 10^9/l$; platelets $208 \times 10^9/l$; and haemoglobin 9.7 g/dl. Other biochemical examinations on admission revealed: AST 159 IU/l; ALT 220 IU/l; lactate dehydrogenase 296 IU/l; BUN 48.4 mg/dl; and creatinine 1.8 mg/dl. Treatment with G-CSF and PSL at 60 mg/day was started. G-CSF was withdrawn 5 days later and PSL was tapered steadily (Fig. S2B¹). HHV-6 DNAs (9.5×10 copies/ 10^6 leucocytes) in peripheral leucocytes and a significant increase in the anti-HHV-6 IgG antibody titre were found 16 days after the detection of agranulocytosis. Based on the clinical and laboratory findings, atypical DIHS was diagnosed and the DRESS score was 5. Cardiac failure, probably due to myocarditis, was observed 10 days after onset.

¹<http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-2420>

DISCUSSION

Agranulocytosis is a severe form of neutropaenia, representing a decline in neutrophils to under $0.5 \times 10^9/l$. Many kinds of drugs can induce agranulocytosis, including anti-thyroid drugs, anti-platelet agents, anti-epileptic agents, and anti-inflammatory agents. Various viral infections, such as influenza virus and herpesviruses, can also result in severe neutropaenia (15).

In patients 1 and 2, agranulocytosis was detected 48 and 40 days after initiation of allopurinol and sulfasalazine administration, respectively. Both have been reported to cause agranulocytosis. However, generalized erythematous rashes and high-grade fever manifested prior to the detection of agranulocytosis, and liver and renal dysfunction developed just after or concurrently with agranulocytosis and atypical lymphocytes in these patients. Other characteristics, such as a long period of drug intake, and detection of HHV-6 reactivation, were also consistent with typical DIHS and definite DRESS in patient 1. In patient 2, the swelling of lymph nodes was unclear and most likely due to a long-term administration of prednisolone for rheumatoid arthritis; she was diagnosed as having atypical DIHS and probable DRESS. Based on these findings, the appearance of agranulocytosis was obviously not simply attributable to the pharmacological actions of allopurinol or sulfasalazine, but most likely a symptom of DIHS/DRESS.

Little information is available regarding the appearance of agranulocytosis in the setting of DIHS/DRESS. Based on previously reported cases (8–11) and the 2 cases described here, no particular trend in underlying diseases or causative drugs was evident; the interval between onset of DIHS/DRESS and detection of agranulocytosis was 2–18 days (Table S1¹), and the interval between drug withdrawal and detection of agranulocytosis was 0–9 days. Considering the frequency at which agranulocytosis was detected in patients with DIHS/DRESS at our institution (2 of 45 patients), agranulocytosis in the course of this disease seems likely to have often been overlooked.

The pathomechanisms underlying agranulocytosis in the course of DIHS/DRESS remain unclear. DIHS/DRESS is generally considered a drug-induced disease, primarily mediated by an expansion of drug-specific T cells (16), and recent evidence has shown that organ failure may be associated with viral infections (6) and EBV reactivation has been demonstrated in the early phase of DRESS (7). Other herpesviruses, such as HHV-6 and EBV are also causative agents for agranulocytosis. Herpesvirus reactivations in the setting of DIHS/DRESS may thus be involved in the appearance of agranulocytosis, but the involvement of herpesviruses in the appearance of agranulocytosis could not be clarified in the present cases.

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REFERENCES

- Descamps V, Bouscarat F, Laglenne S, Aslangul E, Veber B, Descamps D, et al. Human herpesvirus 6 infection associated with anticonvulsant hypersensitivity syndrome and reactive haemophagocytic syndrome. *Br J Dermatol* 1997; 137: 605–608.
- Suzuki Y, Inagi R, Aono T, Yamanishi K, Shiohara T. Human herpesvirus 6 infection as a risk factor of the development of severe drug-induced hypersensitivity. *Arch Dermatol* 1998; 134: 1108–1112.
- Sakuma K, Kano Y, Fukuhara M, Shiohara T. Syndrome of inappropriate secretion of antidiuretic hormone associated with limbic encephalitis in a patient with drug-induced hypersensitivity syndrome. *Clin Exp Dermatol* 2008; 33: 287–390.
- Teo RY, Tay YK, Tan CH, Ng V, Oh DC. Presumed dapsone-induced drug hypersensitivity syndrome causing reversible hypersensitivity myocarditis and thyrotoxicosis. *Ann Acad Med Singapore* 2006; 35: 833–836.
- Asano Y, Kagawa H, Kano Y, Shiohara T. Cytomegalovirus disease during severe drug eruptions: report of 2 cases and retrospective study of 18 patients with drug-induced hypersensitivity syndrome. *Arch Dermatol* 2009; 145: 1030–1036.
- Kano Y, Hirahara K, Sakuma K, Shiohara T. Several herpesviruses can reactivate in a severe drug-induced multiorgan reaction in the same sequential order as in graft-versus-host disease. *Br J Dermatol* 2006; 155: 301–306.
- Picard D, Janela B, Descamps V, D’Incan M, Courville P, Jacquot S, et al. Drug reaction with eosinophilia and systemic symptoms (DRESS): a multiorgan antiviral T cell response. *Sci Transl Med* 2010; 25: 46ra62.
- Kaufmann D, Pichler W, Beer JH. Severe episode of high fever with rash, lymphadenopathy, neutropenia, and eosinophilia after minocycline therapy for acne. *Arch Intern Med* 1994; 154: 1983–1984.
- Ito S, Shioda M, Sasaki K, Imai K, Oguni H, Osawa M. Agranulocytosis following phenytoin-induced hypersensitivity syndrome. *Brain Dev* 2009; 31: 449–451.
- Fathallah N, Slim R, Rached S, Hachfi W, Letaief A, Salem CB. Sulfasalazine-induced DRESS and severe agranulocytosis successfully treated by granulocyte colony-stimulating factor. *Int J Clin Pharm* 2015; 37: 563–565.
- Funck-Brentano E, Duong TA, Bouvresse S, Bagot M, Wolkenstein P, Roujeau JC, et al. Therapeutic management of DRESS: a retrospective study of 38 cases. *J Am Acad Dermatol* 2015; 72: 246–252.
- Zeng Q, Wu Y, Zhan Y, Tang L, Zhou Y, Yin J, et al. Leukemoid reaction secondary to hypersensitivity syndrome to phenobarbital: a case report. *Int J Clin Exp Pathol* 2013; 6: 100–104.
- Shiohara T, Iijima M, Ikezawa Z, Hashimoto K. The diagnosis of a DRESS syndrome has been sufficiently established on the basis of typical clinical features and viral reactivations. *Br J Dermatol* 2007; 156: 1083–1084.
- Kardraun SH, Sidoroff A, Valeyrie-Allanore L, Halevy S, Davidovici BB, Mockenhaupt M, et al. Variability in the clinical pattern of cutaneous side-effects of drugs with systemic symptoms: does a DRESS syndrome really exist? *Br J Dermatol* 2007; 156: 609–611.
- Sheen J-M, Kuo H-RC, Yu H-R, Huang E-Y, Wu C-C, Yang KD. Prolonged acquired neutropenia in children. *Pediatr Blood Cancer* 2009; 53: 1284–1288.
- Shiohara T, Kano Y. A complex interaction between drug allergy and viral infection. *Clin Rev Allergy Immunol* 2007; 33: 124–133.