Drug-induced hypersensitivity syndrome with rapid hematopoietic reconstitution during treatment for acute myeloid leukemia

Drug-induced hypersensitivity syndrome (DIHS) is a rare but severe life-threatening, drug-induced, systemic hypersensitivity reaction. We report two patients who developed DIHS during treatment for acute myeloid leukemia. Awareness of DIHS is necessary when systemic eruptions and high fever occur in leukemic patients, especially with rapid hematopoietic recovery after chemotherapies.

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Leukemic patients show various cutaneous manifestations such as leukemia cutis, septic eruptions, viral exanthemas, fungal eruptions, and drug eruptions. DIHS has rarely been reported among them. It generally occurs after 3-6-week exposure to a specific drug such as anticonvulsants, and is characterized by rash, fever, tender lymphadenopathy, hepatitis, and leukocytosis with eosinophilia. DIHS has some distinguishable features from other severe drug allergies such as toxic epidermal necrolysis and Stevens-Johnson syndrome. These are late onset, paradoxical deterioration, slow resolution and several flare-ups after drug withdrawal, and unexpected cross-reactivity to different drugs.[1,2] Here, we describe two cases of DIHS associated with rapid hematopoietic recovery after chemotherapy for acute myeloid leukemia.

Case #1 was a 77-year-old female with acute monocytic leukemia with leukemia cutis (Figure 1A-D), treated with induction chemotherapy consisting of cytarabine and idarubicin. Allopurinol was given for prevention of tumor lysis syndrome. Leukemia cutis resolved within one week. Neutropenic fever was managed with a combination of antibiotics and antifungal agents, as summarized in Figure 2A. After the twenty-second day, liver dysfunction gradually developed. Antibiotics and antifungal agents were therefore discontinued. On the thirty-second day, a pruritic erythematous maculopapular rash spread over her trunk and extremities with a high fever and facial edema (Figure 1E and F). Cultures and serological studies detected no bacteria or fungi. At approximately the same time, rapid bone marrow recovery was observed with remarkable leukocytosis (32,500 /mm^3) including an increment in atypical lymphocytes (26% of leukocytes, 8,450/mm^3) and eosinophils (13%, 4,225/mm^3), without any myeloid growth factors. The majority of lymphocytes were CD4$^+$ T cells. Hypogammaglobulinemia (IgG 492 mg/dL) was also observed. Skin biopsy revealed dense infiltration of CD68$^+$ histiocytes and CD4$^+$ lymphocytes with broad necrosis of keratinocytes, partial liquefaction degeneration, and perivascular lymphocytic infiltration (Figure 1G and H). Suspecting DIHS, prednisolone (0.75 mg/kg body weight (BW)/day) was administered and her skin eruption rapidly improved.

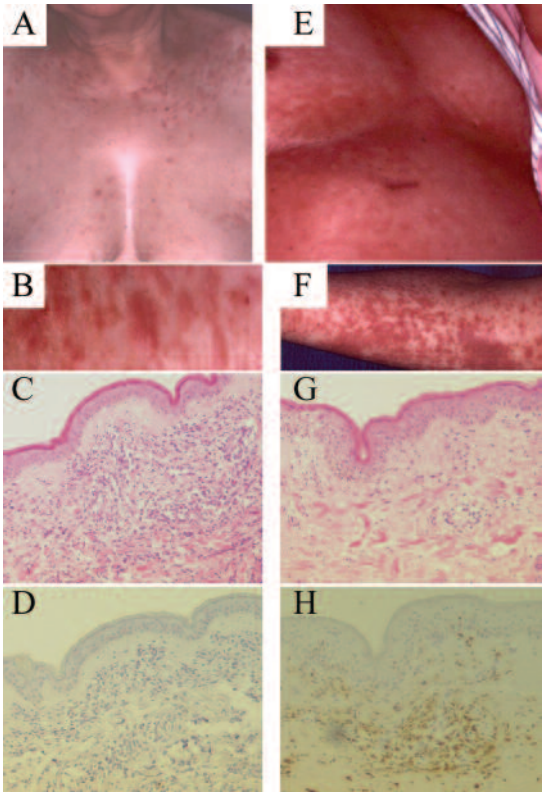

Figure 1. Leukemia cutis (A-D) and skin eruptions of DIHS (E-H) in case 1. C and G: Hematoxylin-Eosin stains, x100, D and H: immunohistochemical stains for CD68 (brown), x100. (A,B) Nonpruritic indurated nodules of leukemia cutis on the trunk. (C,D) Skin biopsy from leukemia cutis showed dense infiltration of leukemic cells. (E,F) Erythematous maculopapular rashes of DIHS on the trunk (E) and the upper extremity (F). (G,H) Biopsy of DIHS showed that leukemic cells disappeared and CD68$^+$ histiocytes infiltrated through the dermis.

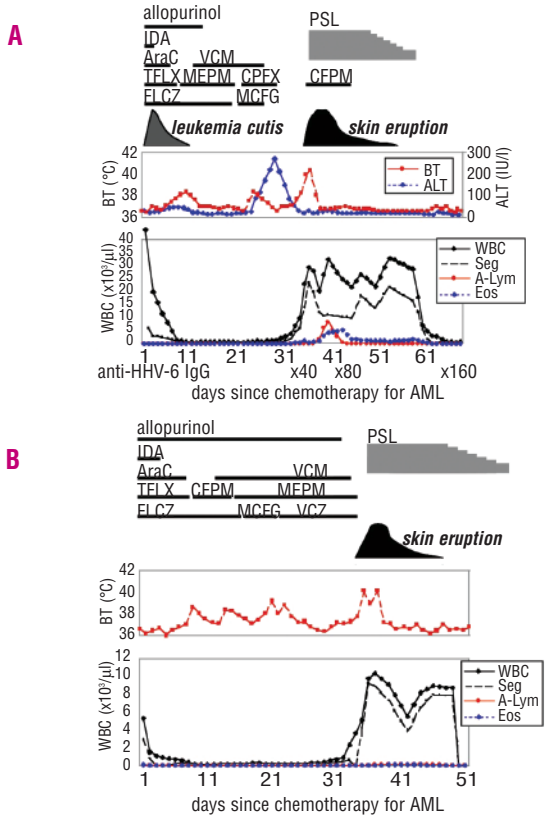

Figure 2. Clinical course of case 1 (A) and case 2 (B). Day1 indicates the first day of chemotherapy for leukemia. Abbreviations: IDA: idarubicin, AraC: cytarabine, TFLX: tosufloxacin, MEPM: meropenem, VCM: vancomycin, CPFX: ciprofloxacin, CFPM: cefepime, FLCZ: fluconazole, MCFG: micafungin, VCZ: voriconazole, PSL: prednisolone, ALT: alanine aminotransferase, BT: body temperature, WBC: white blood cells, Seg: segmented neutrophils, A-Lym: atypical lymphocytes, Eos: eosinophils.

During the salvage chemotherapy after the first relapse she showed hypersensitivity to glycopeptides and amikacin, which was confirmed by drug-induced lymphocyte stimulation tests.

Case #2 was a 53-year-old female diagnosed with acute myelomonocytic leukemia with abnormal eosinophils, inv(16)(p13q22) and add(7)(q22). At first relapse, she was treated with chemotherapy consisting of cytarabine and idarubicin. Allopurinol was given for the same reason as case #1. In the immunosuppressive period, sepsis by *Staphylococcus epidermidis* and invasive pulmonary aspergillosis were treated with a combination of antibiotics and antifungal agents (Figure 2B). After initiation of bone marrow recovery, she expressed a pruritic erythematous maculopapular rash with a high fever. Although allopurinol and antibiotics were discontinued, skin eruption progressed to severe systemic erythematous eruptions, followed by facial edema, axial lymphadenopathy and mild renal dysfunction. Laboratory tests showed leukocytosis (10,400/mm^3) without eosinophilia, and hypogammaglobulinemia. A diagnosis of DIHS was made on the basis of clinical signs and history of medications. The general condition and skin lesions improved rapidly after administration of prednisolone (1 mg/kg bw/day). Skin eruptions occurred again with administration of cefpirome and vancomycin during the consolidation therapy.

DIHS has been reported with various drugs, such as sulfasalazine, anticonvulsants, dapsone, allopurinol, and mexiletine. Our cases are thought to be caused by multiple drugs including antibiotics and antifungal agents in addition to allopurinol. Coupling of viral reactivation and drug eruption has been well documented in DIHS. In the majority of DISH cases, human herpesvirus 6 (HHV-6) reactivation, represented by an increase in HHV-6 IgG titers and HHV-6 DNA levels, usually occurs 2-3 weeks after the onset of a rash.[1,2] These phenomena are characteristic to DIHS.[3] Furthermore, recent reports have demonstrated reactivation of other herpesviruses such as cytomegalovirus (CMV), Epstein-Barr virus (EBV), HHV-7, and multiple and/or sequential reactivation of various herpesviruses.[4,5]

In case #1, an anti-HHV-6 IgG titer of 1:40 at onset of rash mildly increased to 1:160 one month later. While sequential monitoring is insufficient, the qualitative PCR analysis of the serum showed 2×10^2 copies/mL of HHV-6 DNA in case #1 one month after the onset, suggesting the occurrence of HHV-6 viremia. But an increase in anti-HHV-6 IgG titers and HHV-6 viremia was not confirmed in case #2. There were no significant changes in the levels of antibodies against CMV, EBV, herpes simplex virus or varicella zoster virus in either case. Although the clinical features of our cases fulfilled the criteria for DIHS, typical reactivation of HHV-6 was not observed in case #2. DIHS without detecting HHV-6 reactivation has been previously reported,[6] and involvement of another viral species should be considered in these cases. Because serological studies may show equivocal results in immunosuppressive settings with hematologic malignancies, a sequential and intensive survey of viral DNA should be recommended in these patients. In settings other than native immunosuppressive conditions, drug-induced transient hypogammaglobulinemia and B lymphopenia is presumed to induce viral reactivation.[7] In our cases, immunosuppression by the underlying disease and chemotherapy might have triggered viral reactivation.

Systemic administration of corticosteroids has been recommended for the treatment of DIHS. In considering its immunosuppressive effects, immune and inflammatory responses induced by viral reactivation may be responsible for the development of DIHS, rather than viral reactivation itself.[8] Clinical similarity was previously documented between DIHS and graft-versus-host disease or immunorestitution disease (IRD).[1,2,4] Classically, IRD has been known to appear along with neutrophil recovery from chemotherapies or engraftment after bone marrow transplantations.[9-11] Simultaneous appearance of rapid bone marrow recovery and DIHS in our cases suggests that clinical symptoms in DIHS are likely to be mediated by an excessive immune response against pre-existing infectious pathogens, triggered by a rapid immune recovery from chemotherapies or discontinuation of the drugs with potential immunosuppressive properties, such as those in IRD. In addition, it has been reported that an increase in white blood cells in the early phase of DIHS may correlate with the severity of systemic symptoms and the increase in anti-HHV-6 IgG titers.[6] This finding supports our view on the pathogenesis of DIHS in leukemic patients. Our cases indicate the importance of considering DIHS when systemic eruptions and a high fever occur in leukemic patients, especially with rapid hematopoietic recovery after intensive chemotherapies.

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