Dapsone Hypersensitivity Syndrome-related Lung Injury without Eosinophilia in the Bronchoalveolar Lavage Fluid

Yuhei Kinehara 1, Takashi Kijima 1, Koji Inoue 1, Haruhiko Hirata 1, Yoshiko Takeuchi 1, Kiyoharu Fukushima 1, Yoshitomo Hayama 1, Masayoshi Higashiguchi 1, Osamu Morimura 1, Kotaro Miyake 1, Toshiyuki Minami 1, Izumi Nagatomo 1, Yoshito Takeda 1, Hiroshi Kida 1 and Atsushi Kumanogoh 1,2

Abstract

A 73-year-old man was admitted in respiratory failure that had subacutely progressed after five weeks of dapsone treatment for a skin rash. He also presented with fever, systemic erythroderma and liver dysfunction. Chest computed tomography showed diffuse reticular shadows with ground-glass opacity and bilateral mediastinal lymphadenopathy. Lymphocytes, but not eosinophils, were increased in the bronchoalveolar lavage fluid. Moreover, reactivation of human herpes virus-6 was confirmed on a paired serum test. Finally, we diagnosed the patient with dapsone hypersensitivity syndrome (DHS), a rare adverse event of this drug. Lung injury unaccompanied by eosinophilia in the bronchoalveolar lavage fluid is even more rare as a DHS-related lung manifestation.

Key words: dapsone hypersensitivity syndrome, human herpes virus-6, drug-induced hypersensitivity syndrome, bronchoalveolar lavage fluid


Introduction

Dapsone, 4,4’-diaminodiphenylsulphone, has the dual functions of both an antimicrobial/antiprotozoal and anti-inflammatory activity and is widely used for the treatment of bacterial and fungal infections and non-infectious skin diseases (1). The anti-inflammatory effects of this drug are expected to be efficacious for treating chronic inflammatory disorders. Dapsone hypersensitivity syndrome (DHS) was first described in the 1930’s as involving several types of adverse reactions caused by the drug, including skin rashes, fever and eosinophilia (2). DHS occurs in 0.5% to 3% of dapsone-treated patients, with the time of onset from several weeks up to six months after starting therapy (1, 3-5). DHS is characterized by a hypersensitivity response to dapsone and presents with clinical manifestations, such as fever and skin eruptions. However, the disorder sometimes affects internal organs, including the lungs, thyroid, liver, kidneys and brain, and may become life-threatening if left untreated (6). The lung is one organ involved in DHS. However, the frequency of lung involvement is unknown and only 11 cases have been previously reported in the literature (7-14). Eosinophilic pneumonia is the typical and well-known manifestation observed in cases of lung involvement.

Case Report

A 73-year-old man was diagnosed with a pruritic rash in March 2008. He had a past medical history of gastric cancer in the early stage, although he had not experienced any lung or skin diseases until that time. The rash had spread on the trunk and was diagnosed as above after a skin biopsy showed lymphocytic infiltration to the top layer of the dermis. Although the patient had been treated with anti-allergic drugs and steroid ointment for approximately five years, the
Figure 1. The patient demonstrated diffuse maculopapular eruptions and erythema on the trunk and extremities.

Figure 2. CT images obtained on admission showed the presence of bilateral infiltrate in addition to bilateral pleural effusion and mediastinal lymphadenopathy.

rash had worsened. Therefore, dapsone treatment was initiated at a daily dose of 25 mg as anti-inflammatory therapy in July 2013, until which time there had been no history of allergic reactions, such as atopic dermatitis, allergic rhinitis and asthma, or drug-induced rashes or pneumonia. After five weeks of therapy, in addition to worsening of the preexisting nodular prurigo, he presented with a fever, dyspnea, nonerousive edema of the lip and face and erythema on the trunk and extremities (Fig. 1) and was admitted to our hospital due to respiratory failure. On admission, he exhibited tachypnea, with a respiratory rate of 20 breaths per minute, and tachycardia, with a heart rate of 109 beats per minute. His blood pressure was 96/56 mmHg and his body temperature was 38.4°C. The oxygen saturation was 84% on room air, and the oral mucosa was normal. Lung auscultation revealed bilateral diffuse coarse crackles and an audible abnormal cardiac murmur; diffuse maculopapular eruption and erythema had spread over the trunk and extremities. An arterial blood gas analysis showed the following findings: pH = 7.458, PaO₂ =54.3 mmHg, PaCO₂ =38.2 mmHg and bicarbonate =24.8 mmol/L under conditions of 4 L/min oxygen inhalation. Both liver enzymes and C-reactive protein were increased, whereas globulin was decreased, in the serum, and a peripheral smear review disclosed normocytic anemia without hemolytic findings in addition to neutrophilia and the emergence of atypical lymphocytes, but not eosinophilia. A urine sample test was positive for protein. The antinuclear antibody titer was ×40; however, specific autoantibodies were negative. The serum Krebs von den Lungen-6 (KL-6) level was 167 U/mL, which was within the normal range. Chest CT images showed diffuse reticular shadows associated with ground-glass opacity and areas of consolidation in the lungs, with the existence of bilateral pleural effusion and mediastinal lymphadenopathy (Fig. 2). A cardiac mechanical assessment using ultrasound excluded the existence of congestive heart failure.

A bronchoscopic examination was performed on admission day 2, and bronchoalveolar lavage (BAL) of the right B₃ bronchus was conducted using 150 mL of normal saline; the BAL fluid (BALF) recovery rate was 52% (78/150 mL). The total cell number was 3.2×10⁴/mL, and the number of lymphocytes was increased (26%), with a predominance of CD8-positive lymphocytes (CD4/8 =0.26); however, no eosinophilia (4%) was observed. The smear and culture of the BALF was negative for any infectious pathogens. Shortly after the examination, the patient’s respiratory fail-
The patient’s symptoms became prominent only five weeks after the initiation of dapsone treatment, despite the use of other drugs for a long period. Therefore, we highly suspected this case to be DHS with lung involvement, although there was no eosinophil infiltration. Immediately after withdrawing the dose of dapsone, high-dose methylprednisolone was administered for three days, followed by prednisolone maintenance. A dramatic improvement was subsequently achieved in both the symptoms and clinical data. However, it took longer than two weeks for the serum alanine aminotransferase level to return to the normal range. Meanwhile, the chest images improved remarkably (Fig. 3, 4), as did the nodular prurigo, and the patient’s demand for oxygen decreased over time (Fig. 4). Moreover, the IgG titer against human herpes virus-6 (HHV-6) significantly increased from ×40 to ×1,260 on a paired serum test. A drug lymphocyte stimulation test (DLST) for dapsone was also positive, and the patient was found to possess HLA-B*13:01, which has recently been reported to be a genotype susceptible to DHS (15). Finally, we diagnosed this case as DHS, a form of drug-induced hypersensitivity syndrome (DIHS), with lung involvement. The steroid medication was subsequently withdrawn after gradual tapering, and the patient is now free of medication without signs of relapse.
Discussion

DIHS may be caused by a variety of medications, including anticonvulsants, sulfonamides, allopurinol, calcium channel blockers, non-steroidal anti-inflammatory drugs and dapsone (16). The diagnostic criteria for DIHS are as follows: (1) a late-onset maculopapular rash that develops more than three weeks after starting the drug, (2) prolonged clinical symptoms, as described below, that do not disappear more than two weeks after discontinuing the causative drug, (3) fever (>38°C), (4) liver dysfunction (serum alanine aminotransferase >100 U/L), (5) at least one peripheral blood cell abnormality, including leukocytosis (>1.1×10^9/L), atypical lymphocytosis (>5%) or eosinophilia (>1.5×10^9/L), (6) lymphadenopathy and (7) HHV-6 reactivation. Typical DIHS is diagnosed when all seven criteria are met, and atypical DIHS is diagnosed in cases meeting the first five of the seven criteria (17, 18). Finally, we diagnosed this case as typical DIHS with lung involvement after differentiating the patient’s condition from infection and congestive heart failure based on the results of the BALF culture and cardiac ultrasonography.

Furthermore, DLST for dapsone was positive in this patient, who had been on the same medications for five years except for dapsone. Therefore, we diagnosed him with DHS, a variant of DIHS, and considered the lung manifestations to be DHS-related lung injury rather than another type of drug-induced pneumonia. Recently, the presence of the HLA-B*13:01 genotype has been identified to correlate with susceptibility to DHS, with a sensitivity of 85.5% and specificity of 85.7% (15). The current patient also possessed the HLA-B*13:01 genotype, which strongly supports our diagnosis.

The pathogenesis of DHS is unclear, and several mechanisms may be implicated. One proposed mechanism involves the formation of hapten from metabolites of dapsone, which subsequently produce anti-dapsone antibodies, thereby inducing adverse allergic reactions (19). Another proposed mechanism is the presence of differences in dapsone metabolism participating in the production and detoxification of the reactive metabolites of this drug, which may be responsible for the differences in susceptibility of affected patients to adverse effects (20). These toxic metabolites are produced as a result of oxidative metabolism by cytochrome P450, myeloperoxidases and thyroid peroxidases and are usually further biotransformed and detoxified by epoxide hydroxylase. Patients who lack this enzyme or have dysfunctioning mutations in its gene are reported to develop DHS (2). Oxidative metabolites may also cause the release of cytokines that warn the immune system of cellular stress and damage (2).

The following mechanisms involved in HHV reactivation and the development of DIHS-related autoimmune disease have been proposed. First, DIHS begins as an allergic immune reaction to causative drugs followed by the stimulation of T cells (21, 22). Second, the viral genome of HHV, such as Epstein-Barr virus, and cytomegalovirus is reactivated in the stimulated T cells (23-25), which induces specific cellular and humoral immune responses to HHV (26). Third, the release of cryptic self-antigens during the antiviral immune response primes auto-reactive T cells that originally evolved to manage viruses. In this stage, the auto-reactive T cells are primed, although they do not cause overt autoimmune disease. Following the resolution of this antiviral immune response, however, the primed auto-reactive T cells are chronically activated by nonspecific stimuli. Therefore, autoimmune diseases may arise despite the complete recovery from DIHS following the elimination of the triggering HHV event (27). DIHS-related autoimmune diseases include type 1 diabetes, myocardiitis/myositis, pericarditis, interstitial nephritis, necrotizing granulomatous vasculitis, encephalitis, meningitis, colitis and thyroiditis (6, 28, 29). Collectively, DIHS has several unique features that cannot be explained by only the drug etiology, delayed onset, paradoxical worsening of clinical symptoms after discontinuation of the causative drug and step-wise development of organ system failure long after clinical resolution (30).

The lungs is one of the most common organs involved in DIHS, and drug-induced lung injury may cause interstitial lung damage, alveolar injury and vasculitis (7). Eleven cases of DHS with lung injury have been previously reported; all but one of which involved eosinophilic pneumonia (7-14). Only one case of hypersensitivity pneumonitis has been reported based on evidence of the lack of peripheral eosinophilia, without a BAL examination or lung biopsy (6). To our knowledge, our case involves the first presentation of rare non-eosinophilic lung injury with lymphocyte infiltration with proof of BALF findings.

The primary treatment for DHS/DIHS is the immediate discontinuation of the offending drug with the administration of systemic glucocorticoids (9, 30). It has been reported in several cases that DHS/DIHS may relapse with the onset of other autoimmune diseases, even after the withdrawal of the causative drugs. Although the dose of glucocorticoids is currently being tapered and gradually withdrawn in our patient, we should continue to carefully monitor his condition for at least several months for the potential development of autoimmune diseases.

We herein experienced a case of DHS with rare lung involvement with dapsone-induced lung injury without eosinophilia in the BALF. Patients treated with dapsone for various indications should be carefully observed for the development of DHS. Eosinophilic pneumonia is the most common manifestation of lung involvement, although lung injury without eosinophilia in the BALF may occur, as noted in our case, despite the rarity of the condition and the lack of clarification of the precise mechanisms. Therefore, clinicians should consider the possibility of DHS in cases of non-eosinophilic pneumonia and subsequently taper off the dose of glucocorticoids deliberately, as DHS/DIHS may relapse and other autoimmune diseases may occur despite withdrawing the causative drugs.
The authors state that they have no Conflict of Interest (COI).

References


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