

A Rare Case of Minocycline-induced DIHS/DRESS with Predominant Pulmonary Involvement

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Drug-induced hypersensitivity syndrome (DIHS), also known as drug reaction with eosinophilia and systemic symptoms (DRESS), is a severe reaction that typically develops several weeks after drug exposure and is characterized by fever, widespread rashes, haematologic abnormalities and organ dysfunction (1). Although the liver is the most commonly affected organ, pulmonary involvement may also occur and can be clinically significant, presenting with diverse manifestations, such as interstitial pneumonia, eosinophilic pneumonia and acute respiratory distress syndrome (2). When pulmonary involvement predominates in the absence of liver dysfunction, DIHS/DRESS may be difficult to distinguish from infectious pneumonia or other lung diseases, delaying diagnosis. Here, we report a case of minocycline-induced DIHS/DRESS with predominant pulmonary involvement, highlighting the need to consider DIHS/DRESS even in the absence of liver dysfunction.

CASE REPORT

A 77-year-old Japanese woman with scrub typhus received minocycline for 10 days, after which her symptoms resolved. Thirteen days after completing medication, she presented to our department with fever and a generalized rash, mainly on the trunk (Day 1) (**Fig. 1a**). A skin biopsy specimen from the erythematous lesion of the abdomen showed lymphocytic infiltration of the epidermis with subtle

individual keratinocyte necrosis and perivascular infiltration of lymphocytes and eosinophils in the superficial dermis (**Fig. 1b**). On Day 2, the patient's condition deteriorated, and she developed respiratory failure. Laboratory tests revealed leukocytosis (19,290/ μ L), eosinophilia (1,582/ μ L), elevated C-reactive protein (CRP) level (23.5 mg/dL) and markedly elevated thymus and activation-regulated chemokine (TARC) level (28,628 pg/mL). Atypical lymphocytes were detected, accounting for 9.5% of leukocytes. No liver or kidney dysfunction was observed. Human herpesvirus 6 DNA and cytomegalovirus (CMV) pp65 antigen were not detected; Epstein-Barr virus serology was consistent with prior infection. Chest computed tomography showed extensive ground-glass opacities, infiltrates and interlobular septal thickening, mainly in the bilateral upper lobes (**Fig. 2a**). Cervical, mediastinal and hilar lymphadenopathy was also observed.

The patient was diagnosed with minocycline-induced DIHS/DRESS based on the Japanese diagnostic criteria (3) and the RegiSCAR scoring system (4). Prednisolone at 1 mg/kg/day was started on Day 2 because of severe pulmonary involvement with respiratory failure. Ampicillin/sulbactam was administered temporarily in the setting of marked inflammation and respiratory failure because infectious pneumonia could not be excluded. The rash, respiratory status and chest opacities gradually improved (**Fig. 2b**), accompanied by decreases in the leukocyte count, eosinophil count and levels of CRP and TARC. Multiple

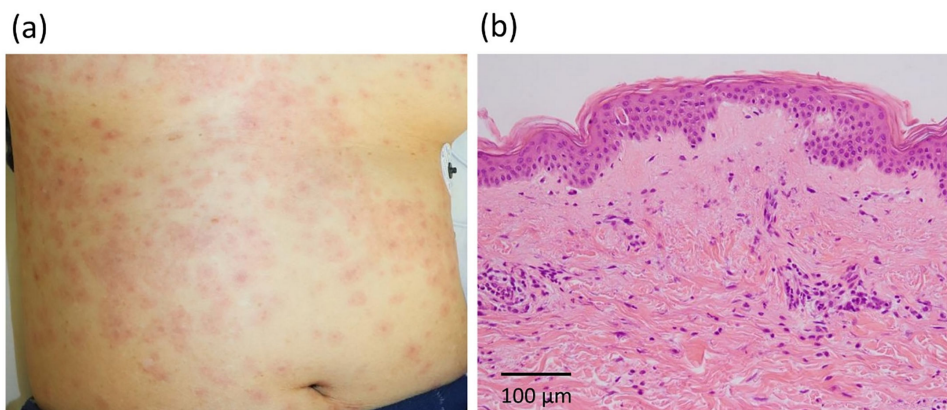


Fig. 1. (a) Clinical presentation showing edematous erythema scattered on the trunk. (b) Histopathological findings of the erythematous lesion of the abdomen (hematoxylin and eosin staining). Lymphocytes infiltrate in the epidermis, along with subtle individual keratinocyte necrosis. Perivascular infiltration of lymphocytes and eosinophils is observed in the superficial dermis.

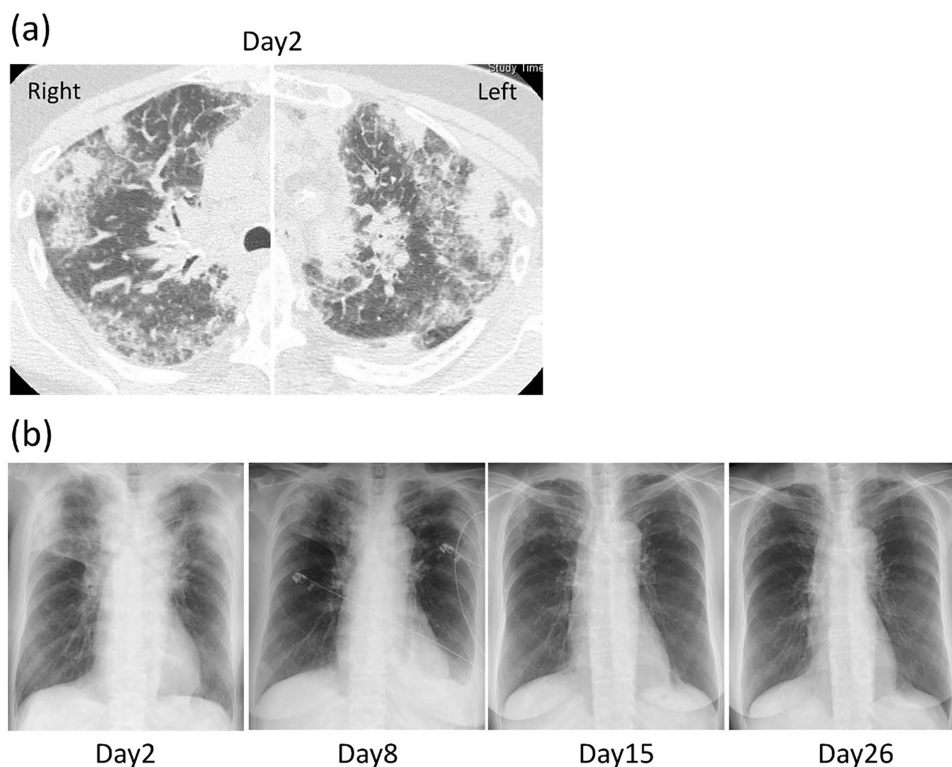


Fig. 2. (a) Chest computed tomography findings on Day 2. Extensive ground-glass opacities, infiltrates and interlobular septal thickening are observed mainly in the bilateral upper lobes. (b) Changes in chest radiographic findings during the clinical course.

episodes of thrombocytopenia and positive CMV antigenemia occurred during steroid tapering; therefore, prednisolone was tapered with caution. Prednisolone was discontinued 7 months after treatment initiation, with no recurrence. The results of a drug-induced lymphocyte stimulation test for minocycline were negative.

DISCUSSION

The present case was diagnosed as atypical DIHS according to the Japanese criteria and definite DRESS according to a RegiSCAR score of 6 (3, 4). The diagnosis was supported by a delayed onset after minocycline exposure, fever, a generalized rash, leukocytosis, eosinophilia, atypical lymphocytosis, lymphadenopathy and markedly elevated TARC level (3, 5). Notably, no liver or kidney dysfunction was observed, and the pulmonary lesions were the only evidence of visceral organ involvement. Episodes of thrombocytopenia and positive CMV antigenemia during steroid tapering may suggest immunological abnormalities associated with DIHS/DRESS (3).

Pulmonary involvement in DIHS/DRESS is relatively uncommon compared with liver or kidney involvement (2). In a systematic review, 21 of 22 cases of DRESS with pulmonary involvement showed additional extrapulmonary organ involvement, indicating that isolated pulmonary involvement is rare (2). A case

of DIHS previously reported by Naniwa et al. showed predominant pulmonary involvement in the absence of other organ dysfunction and was related to an increase in anti-paramyxovirus antibody titres (6). Pulmonary lesions associated with DIHS/DRESS may mimic other pulmonary disorders, especially infectious pneumonia, as DIHS/DRESS can present with fever, elevated inflammatory markers and ground-glass opacities or infiltrates. Indeed, 45% of DRESS cases with pulmonary involvement were initially misdiagnosed as bacterial pneumonia and treated with empirical antibiotics (2). In the present case in the absence of extrapulmonary organ involvement, although infection could not be completely excluded at disease onset, the clinical course, eosinophilia, appearance of atypical lymphocytes, lymphadenopathy and marked TARC elevation (3, 5) supported pulmonary involvement as a manifestation of DIHS/DRESS. The prompt improvement after corticosteroid therapy also supported this interpretation. Recognition of DIHS/DRESS presenting with predominant pulmonary lesions in the absence of liver dysfunction is important because delayed diagnosis may delay corticosteroid therapy and lead to unnecessary antibiotic use.

In summary, rare cases of DIHS/DRESS may present with isolated or predominant pulmonary lesions, which can be difficult to distinguish from other pulmonary disorders, leading to delayed diagnosis. When delayed-onset fever, generalized rashes, eosinophilia, atypical

lymphocytosis and pulmonary lesions occur after drug exposure, DIHS/DRESS should be included in the differential diagnosis, even in the absence of liver dysfunction.

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The patient gave consent for her photographs and medical information to be published in print and online and with the understanding that this information may be publicly available.

Data availability statement: The data that support the findings of this study are available on request from the corresponding author.

The authors have no conflicts of interest to declare.

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