



Multiple cavities with halo sign in a case of invasive pulmonary aspergillosis during therapy for drug-induced hypersensitivity syndrome



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ABSTRACT

A 67-year-old female with rheumatoid arthritis and asthma-chronic obstructive pulmonary disease overlap syndrome was admitted for drug-induced hypersensitivity syndrome (DIHS) caused by salazosulfapyridine. Human herpes virus 6 (HHV-6) variant B was strongly positive on peripheral blood. Multiple cavities with ground glass opacities rapidly emerged predominantly in the upper and middle lobes. She was diagnosed with invasive pulmonary aspergillosis (IPA), and was treated successfully with antifungal agents. Therapeutic systemic corticosteroids, emphysematous change in the lungs, and the worsening of the patient's general condition due to DIHS were considered major contributing factor leading to IPA. HHV-6 reactivation could have an effect on clinical course of IPA. Cavities with halo sign would provide an early clue to IPA in non-neutropenic and immunosuppressive patients.

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1. Introduction

Invasive pulmonary aspergillosis (IPA) predominantly affects severely immunocompromised patients, particularly those with prolonged neutropenia or organ transplantation [1]. IPA is increasingly being recognized as an emerging disease in non-neutropenic patients such as COPD, connective tissue diseases requiring corticosteroid therapy [2].

Drug-induced hypersensitivity syndrome (DIHS) or drug reaction with eosinophilia and systemic syndrome (DRESS) presents clinically as an extensive mucocutaneous rash, accompanied by fever, lymphadenopathy, hepatitis, hematologic abnormalities with eosinophilia and atypical lymphocytes, and may involve other

organs with resultant damage in several systems [3]. An immune response against the drug with secondary viral reactivation related to a cytokine storm, and early viral reactivation responsible for most of the manifestations of DIHS [4]. It has a relapsing-remitting course despite withdrawal of causative drugs. Herpes viruses such as HHV-6/HHV-7, Epstein-Barr virus and cytomegalovirus can be reactivated during the course of DRESS/DIHS [3]. The treatment of DIHS was based on systemic glucocorticoids.

This patient has a lot of risk factors in non-neutropenic IPA including asthma-chronic obstructive pulmonary disease overlap syndrome, systemic corticosteroids use, and duration of antibiotic treatment longer than 10 days. In addition to these factors, HHV-6 reactivation may have some effect on the clinical course of IPA. This case showed unique imaging findings on computed tomography (CT) scan at the early phase of IPA.

2. Case report

A 67-year-old woman admitted for a febrile skin rash that progressed erythroderma for a week. One month earlier, she had diagnosed with rheumatoid arthritis and received anti-rheumatic drugs for prednisolone:PSL 5 mg/day, salazosulfapyridine:SASP 0.5 g/day. She is well controlled asthmatic patient with inhaled

Abbreviation: BAL, bronchoalveolar lavage; BG, 1,3-β-glucan; CMV, cytomegalovirus; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DIHS, drug-induced hypersensitivity syndrome; DRESS, drug reaction with eosinophilia and systemic syndrome; GGO, ground glass opacity; GM, galactomannan antigenemia; HHV-6, Human herpes virus 6; IPA, invasive pulmonary aspergillosis; LAA, low attenuation area; MCFG, micafungin; VRCZ, voriconazole.

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fluticasone furoate 200 µg/vilanterol 25 µg. Her past medical history included chronic obstructive pulmonary disease (COPD). She was an ex-smoker (40 pack years of smoking).

The physical findings on admission consisted of erythroderma, erosion of the lips, persistent high fever, superficial lymphadenopathy at neck, purpura over the extremities, and hypovolemic shock. Laboratory tests showed neutrophilic leukocytosis with mild eosinophilia (WBC: 13130/µl, neu: 75%, and eos: 13%), (AST: 16 IU/L, ALT: 20 IU/L, LDH 359 IU/L, total bilirubin:0.4 mg/dL, C-reactive protein 10.7 mg/dL, BUN 41.6 mg/dl and serum creatinine 1.29 mg/dl, RA 17 U/ml, anti-SS-A/Ro Ab 46.2 U/ml). Blood cultures resulted normal. The *aspergillus* galactomannan antigenemia (GM) and anti-*Aspergillus* IgG antibodies were negative, but *Aspergillus* precipitating antibody was positive on admission. The level of 1,3-β-glucan (BG) was within normal limits as 5.0 pg/ml. A chest X-ray showed infiltration in middle lesions of both lungs (Fig. 1a). A chest CT scan showed low attenuation area (LAA) throughout in upper lobe and small thin-walled cavities surrounded by GGO (Fig. 1b). Pulmonary function test performed on day 47 showed an obstructive pattern with no reversibility: FEV₁/FVC 63.8%, pre bronchodilator FEV₁ 1.55L (89.1%), post bronchodilator FEV₁ 1.58L (+1.9%).

The course of treatment was shown in Fig. 2. SASP was discontinued on admission, an antibiotic treatment and an increase in corticosteroid dose by 5 mg–25 mg/day showed a small effect on erythroderma and erosion of the lips. The temperature has gone down to normal. Skin biopsy revealed that the superficial infiltration of inflammatory cells at junction of the epidermis and dermis, perivascular inflammation. Nine days after admission, her clinical condition (erythroderma, erosion of the lips, and high fever) exacerbated again. The IgG titer against human herpes-6 (HHV-6) increased from × 80 to × 160. The PCR test for HHV-6 variant B was strongly positive on peripheral blood (8000 copies/ml). DIHS was diagnosed based on the presence of a skin rash developing more than 3 weeks after SASP initiation, clinical symptoms persisting more than 2 weeks after stopping SASP, fever >38 °C, leukocytosis, kidney dysfunction, lymphadenopathy, HHV-6 reactivation [4]. High dose methylprednisolone (500 mg/day) was administered on day 11–13. However, multiple cavities rapidly emerged predominantly in the upper and middle lobes on day 12

(Fig. 3a and b), when positive conversion of GM test was identified. Because she refused to undergo bronchoscopic examination at first, micafungin (MCFG) 150 mg/day was administered for clinically diagnosed invasive pulmonary aspergillosis. PCR tests were positive for cytomegalovirus (CMV) and negative for the Epstein-Barr virus on day 21, however they were both negative on admission. Treatment of Ganciclovir 500 mg/day was started on day 26 for two weeks. Multiple cavities persisted despite antifungal treatment, she decided to have bronchoscopic examination on 26 days after admission. The culture of bronchoalveolar lavage (BAL) fluid performed at left B³ was positive for *Aspergillus fumigatus*. The total cell count in BAL fluids was significantly increased (78 × 10⁴/ml) and the inflammatory cell profile showed the increased percentage of neutrophils (macrophages 31%, neutrophils 65%, lymphocytes 4%, eosinophils 0%). Transbronchial lung biopsy specimen obtained from left B³ showed inflammatory cell infiltration, necrotic tissue destruction and bleeding, but acid fast bacilli and fungus were undetected. A dose of 200 mg voriconazole (VRCZ) (400 mg for starting dose) was concurrently administered on day 29. Severe cough disappeared and cavity walls became thinner afterward. She left the hospital on day 52. Multiple cavities disappeared on CT scan one year after discharge from the hospital (Fig. 4).

3. Discussion

It has been reported that IPA may be identified by chest CT at an early stage of disease.

The lesion of CT images as having a 'halo sign' (i.e., GGO surrounding a nodule or mass), 'hypodense sign' (i.e., hypodensity or low attenuation within the mass or nodule), or cavitation were commonly observed in IPA [5]. The halo sign has been pathophysiologically characterized as a discrete nodule of angioinvasive aspergillosis with infarction and coagulative necrosis surrounded by alveolar hemorrhage. This sign is seen only in the first 10 days of angioinvasion [6]. Typical chest CT scan findings include multiple nodules and the halo sign is seen in neutropenic patients with IPA early in the course of infection. Halo sign can be also seen in Bronchiolitis Obliterans with Organizing Pneumonia, granulomatosis with polyangiitis, metastatic angiosarcoma and focal lung injury. In this case, pathological findings consistent with the

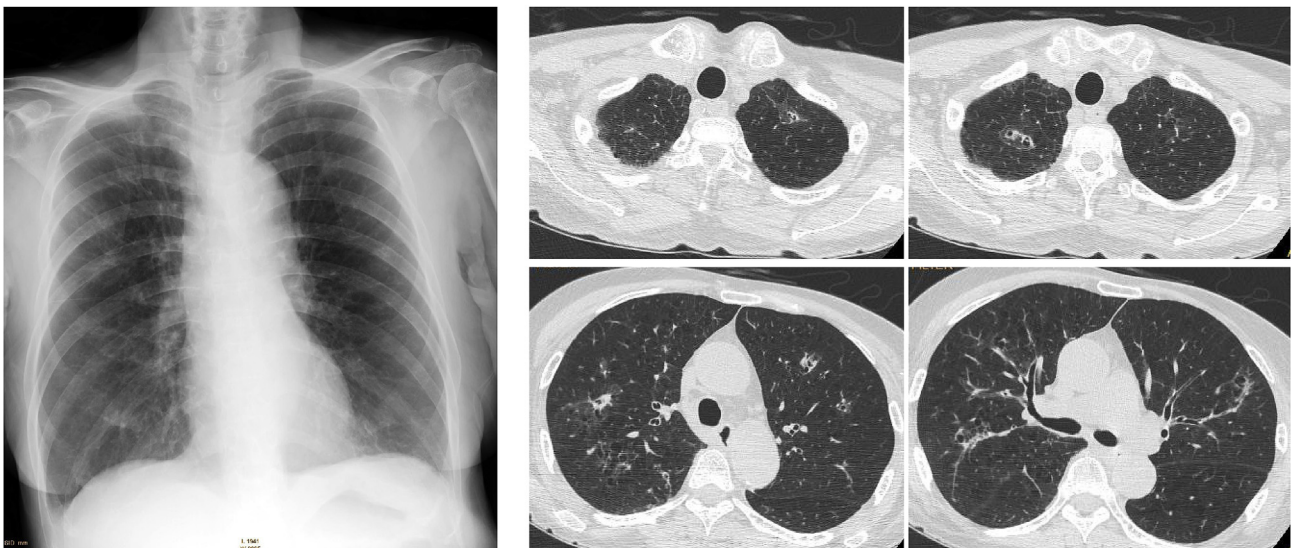


Fig. 1. a: A chest X-ray showed infiltration in middle and lower lesions of both lungs on admission. b: Chest CT images showed low attenuation area (LAA) throughout in upper lobe and small thin-walled cavities surrounded by GGO on admission.

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