Isoniazid-induced Drug Rash with Eosinophilia and Systemic Symptoms (DRESS) Syndrome Presenting as Acute Eosinophilic Myocarditis

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Abstract

It has been reported that hypereosinophilic syndrome may be induced by antituberculosis drugs. We herein report the case of a 43-year-old man who had been on antituberculosis drugs for two months to treat tuberculous meningitis. During therapy, he suffered from drug rash with eosinophilia and systemic symptoms (DRESS) presenting as acute eosinophilic myocarditis, as confirmed on a histopathologic examination. According to the patient’s medication history, clinical features and accessory examination findings, the eosinophilic myocarditis was thought to be possibly induced by isoniazid. Although further investigations are needed to confirm causality, isoniazid may be added to the list of drugs with the potential to cause DRESS syndrome.

Key words: hypereosinophilic syndrome, acute eosinophilic myocarditis, isoniazid

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Introduction

Drug rash with eosinophilia and systemic symptoms (DRESS), also called drug-induced hypersensitivity syndrome (DIHS), is a severe reaction usually characterized by fever, rashes and multi-organ failure, occurring one to eight weeks after drug introduction (1). Hypereosinophilic syndrome (HES), a form of DRESS, is characterized by increased eosinophils accompanied by target organ damage. Systemic organ involvement can present as hepatitis, interstitial pneumonia, interstitial nephritis and carditis (2). It has been demonstrated that the most probable related drugs are sulfonamides, non-steroidal anti-inflammatory drugs (NSAIDs), anticonvulsants and allopurinol (3). The pathophysiology of DRESS syndrome remains unclear, although defects in the detoxification of the causative drug, immunological imbalances and infection have been suggested (4). Antituberculosis drugs are considered to be one of the most efficient treatments. However, it is not uncommon to observe adverse drug reactions during therapy. For example, rifampicin has been reported to cause blood eosinophilia in the presence of other drugs, including isoniazid and streptomycin (5). In addition, it has been reported that both ethambutol and isoniazid partly cause pulmonary eosinophilia (6, 7). We herein describe the case of a patient who suffered from DRESS presenting as acute eosinophilic myocarditis closely related to the administration of antituberculosis therapy with isoniazid. To the best of our knowledge, this association has not been documented previously in the literature.

Case Report

In March 2012, a 43-year-old man presented to our unit with complaints of chest pain and tightness lasting for 10 days, with exacerbation and fever for the past three days. Two months earlier, he had been diagnosed with tuberculous meningitis on our unit and started on antituberculosis therapy with rifampicin, isoniazid, pyrazinamide and ethambutol. Unexpectedly, he presented with hepatic dysfunction during the early period of antituberculosis therapy. Consider-

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The possibility that the patient’s condition was related to the antituberculosis drugs, rifampicin was withdrawn and the other drugs were maintained. No abnormal findings were noted on routine clinical examinations, and the patient showed no evidence of skin eruptions or lymphadenopathy. Hematological examinations were notable for a platelet count of 36*10^9/L (reference range, 100*10^9/L to 300*10^9/L), an EOSR of 29.8% (upper limit of normal, 5%), creatine kinase (CK)-MB level of 44 U/L (reference range, 38 to 174 U/L) and cardiac troponin-T (cTnT) level of 11.63 ug/L (reference range, 0 to 0.15 ug/L). Computed tomography revealed pericardial effusion (Fig. 1A arrow), whereas coronary angiography showed no abnormalities. During the early period of hospitalization, hematological examinations showed a decrease in the platelet count to 34*10^9/L and an increase in the EOSR to 44.5%. With the adhibition of the cardiac drugs, the CK-MB level declined to 97 U/L, while the cTnT level returned to normal (15.37 ug/L). Unexpectedly, however, the patient experienced sudden cardiac arrest. Cardiopulmonary resuscitation (CPR), mechanical ventilation and drug therapy (noradrenaline: 1.8 mg iv-vp st; methylprednisolone: 80 mg ivgtt st) were administered immediately. An endomyocardial biopsy showed moderately heavy inflammatory cell infiltrates dominated by eosinophils admixed with lymphocytes, histiocytes and areas of fibroblast proliferation (Fig. 1B-D), fibroblast proliferation (Fig. 1D) and disarrangement of myocardial cells (Fig. 1C), which was conclusive for eosinophilic myocarditis. A case discussion was conducted, and the eosinophilic myocarditis was possibly considered to be induced by the antituberculosis drugs; therefore, the clinical medication regimen was adjusted. Ethambutol was replaced by ofloxacin and rifampicin was again applied in the antituberculosis regimen in addition to steroid therapy (prednisone: 20 mg, po, tid, 14 days) to alleviate the eosinophilia. The patient’s condition stabilized and his symptoms improved. The dose of steroids was gradually reduced over two weeks [prednisone: from 20 to 5 mg (bi-weekly), po, tid]. After hospitalization for more than one month, laboratory examinations showed an EOSR of 0.5%, with a near-normal eosinophil count (Fig. 2, line*, upper limit of normal) and normal CK-MB and cTnT levels. The patient was discharged from the hospital with a full recovery, and rifampicin, isoniazid and ofloxacin were used as antituberculosis therapy on an outpatient basis. In order to confirm the anti-inflammatory effects of treatment, short-term steroid therapy was applied (prednisone: 5 mg, po, from tid to qd gradually over 14 days). At the nine-month follow-up visit, the eosinophil count was higher than normal and clinical symptoms of myocarditis were again detected following the withdrawal of steroid therapy (Fig. 2). A short-term course of steroid therapy was therefore applied (prednisone: 5 mg, po, qd, seven days). Considering that the
Figure 2. Follow-up visit. Eosinophil count, normal reference range: 0-0.5×10⁹/L. Line* represents the upper limit of normal. Day 0 represents the day the patient was discharged from the hospital. Day <0 represents the day of hospitalization. Day >0 represents the day the patient received outpatient treatment. →a: drug withdrawal of ethambutol. b←: drug withdrawal of isoniazid. M: methylprednisolone, 80mg ivgtt, st; P1: prednisone, 20mg, po, tid, 14 days; P2: prednisone, from 20mg to 5mg (biweekly), po, tid, 14 days; P3: prednisone, 5mg, po, from tid to qd gradually over 14 days; P4: prednisone, 5mg, po, qd, seven days

eosinophilia was mostly likely induced by isoniazid, only rifampicin and ofloxacin were used in the antituberculosis therapy regimen. Significantly, the eosinophil count returned to the normal range after isoniazid was discontinued (Fig. 2, line*, upper limit of normal). In the latter period of follow-up without isoniazid therapy, there were no signs of recurrence of eosinophilia. Both rifampicin and ofloxacin were used during the later period of antituberculosis therapy. The patient remained in stable condition and successfully completed the course of antituberculosis treatment and subsequent drug withdrawal. The above signs and symptoms indicate that isoniazid was most likely the causative agent of the acute eosinophilic myocarditis.

Discussion

DRESS syndrome is a rare, but potentially life-threatening, drug-induced hypersensitivity reaction that includes rashes, hematological abnormalities, lymphadenopathy and internal organ involvement (1). HES, the pathogenesis of which remains unclear, has been reported to be involved in the onset of endocardial/cardiac diseases (8, 9). There are numerous reports that antituberculosis medications may induce eosinophilia. In particular, it has been demonstrated that ethambutol may induce the accumulation of pulmonary infiltrates with eosinophilia and skin involvement (7). However, no cases of rifampicin-related eosinophilia have been reported to date (10).

In the present case, although the patient exhibited no skin manifestations or lymphadenopathy, he was diagnosed with DRESS syndrome according to the associated medication use and clinical features, including fever, hypereosinophilic syndrome and cardiac trauma. The development of eosinophilic myocarditis in this case was possibly thought to be due to isoniazid. During treatment with rifampicin, ofloxacin and steroids, the eosinophilia was ameliorated. The exact pathological findings of eosinophilic myocarditis induced by isoniazid were ascertained, indicating that the onset of eosinophilic myocarditis was intimately related to the administration of isoniazid. During the follow-up period, rifampicin, ofloxacin and steroids were successfully reintroduced, and the patient’s condition remained stable.

Isoniazid has been administered as a first-line drug for routine therapy and chemoprophylaxis of tuberculosis since its discovery in 1952. The mechanism of action of this drug is to inhibit the mycolic acid synthesis required to maintain the integrity of the mycobacterial cell wall. Common adverse reactions of isoniazid include liver and nervous system toxicity, allergies (fever, polymorphous skin rashes), blood system effects (granulocytopenia, increased eosinophils, thrombocytopenia) and so on. Mattioni previously reported a case of recurrent pancreatitis induced by isoniazid treatment (11). In addition, eosinophilia with pleural exudative effusion induced by the administration of isoniazid has been reported (12). Isoniazid (INH) is one of over 80 medications implicated in the onset of drug-induced lupus erythematosus (DILE), a lupus-like syndrome temporally related to continuous drug exposure that resolves after the cessation of the offending pharmacologic agent (13). Although a wide range of isoniazid-induced side effects have been reported, most adverse reactions do not affect the course of treatment. However, it must be noted that rare adverse reactions have occurred in clinical application resulting in lethal damage. In the current case, the patient was close to sudden cardiac death as a result of eosinophilic myocarditis induced by treatment with antituberculosis drugs.

The pathophysiology of DRESS syndrome has not yet been clarified. Nevertheless, it has been suggested that primarily drug-specific immune reactions act as a trigger of viral activation via yet unknown mechanisms (14-16). Early recognition of adverse drug reactions and the discontinuation of possible causative agents are significant steps in regarding the progression of DRESS syndrome. There is a general consensus among experts regarding the use of systemic corticosteroids to treat DRESS syndrome with severe organ involvement, particularly in patients with renal and/or pulmonary involvement (17, 18). In the current case, early treatment with steroids significantly contributed to the patient’s recovery.

We would like to propose, subject to further experience, that isoniazid be considered a possible causative agent of eosinophilic myocarditis. This case highlights the need for awareness and monitoring for hematological eosinophilia in patients receiving antituberculosis therapy, especially those with underlying diseases.
The authors state that they have no Conflict of Interest (COI).

References


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