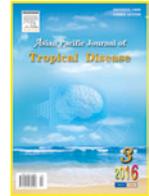




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DRESS syndrome caused by para-aminosalicylic acid: a case report and literature review

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ABSTRACT

The aim of this study was to evaluate the reaction of the use of para-aminosalicylic acid (PAS). We reported the cases of multidrug-resistant tuberculosis treated with anti-tuberculosis therapy and PAS to develop drug rash with eosinophilia and systemic symptoms (DRESS syndrome). Therefore, the findings may enable readers to be aware of the extreme possibility of severe hypersensitivity reaction from the use of PAS. This is especially relevant as an alarming increase that has been found worldwide in the incidence of multidrug-resistant tuberculosis.

1. Introduction

The incidence rate of multidrug-resistant tuberculosis (MDR-TB) is increasing. The report from the World Health Organization found that new tuberculosis cases of MDR-TB in worldwide accounted for about 5%[1]. However, in Thailand, approximately 93%–94% of the MDR-TB strains were susceptible to aminoglycosides, 85%–98% to fluoroquinolones, 78% to ethionamide, 85% to para-aminosalicylic acid (PAS) and 99% to linezolid, respectively. Therefore, the roles of second-line drugs are increasing[2].

PAS is a second-line drug in the treatment of MDR-TB in combination with the other anti-tuberculosis drugs[3]. This drug was firstly used in 1944 and was commonly used during the 1950s and 1960s[4,5]. PAS produces bacteriostatic activity for *Mycobacterium tuberculosis* (*M. tuberculosis*). However, it prevents the emergence

of isoniazid-resistant organisms. Consequently, this drug is used in reserve regimens for treating MDR-TB. PAS is contraindicated for patients with serious renal disease because it can produce acetylated forms including toxic metabolites[3]. Moreover, PAS interferes with thyroid metabolism and the uptake of vitamin B12. However, this effect may occur among patients with long-term administration. Dermatological side effects include skin rash, erythematous, maculopapular and pruritic lesions often starting on the face and neck[3,4]. Other toxicities include lymphadenopathy, jaundice, leukocytosis, conjunctivitis, headaches and joint pains.

Drug rash with eosinophilia and systemic symptoms (DRESS) is a severe allergic reaction. The common triad is characterized by fever, rash and internal organ involvement[6]. Moreover, the mortality rate is approximate 8%, especially among patients with hepatitis[6].

2. Case report

A 23-year-old female was admitted to the hospital with generalized maculopapular rash. She also had fever, oral ulcer, facial swelling and difficult breathing. Her body weight was 64 kg. She had a diagnosis of MDR-TB. The MDR-TB treatment regimen comprised 750 mg cycloserine once daily, 750 mg prothionamide

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once daily, 750 mg levofloxacin once daily, 4000 mg PAS twice daily and 1000 mg kanamycin intra-muscular once daily. Molecular test (GeneXpert) of her sputum was used to detect *M. tuberculosis* and resistant to rifampicin. Sputum cultured for *M. tuberculosis* was also positive and resistant to isoniazid, rifampicin, ethambutol and streptomycin. Chest X-ray when MDR-TB treatment started showed right upper zone patchy infiltration. Her liver function test results showed aspartate aminotransferase (AST) [449 IU/L (5–40)], alkaline aminotransferase (ALT) [388 IU/L (5–35)], alkaline phosphatase [107 IU/L (15–112)], total bilirubin (0.39) and direct bilirubin (0.23) (Figure 1). A complete blood cell count revealed the following laboratory values: white blood cell count ($19\,870/\text{mm}^3$) (21% eosinophils, 59% neutrophils, 11% lymphocytes and 6% monocytes) and platelet count ($241\,000/\text{mm}^3$).

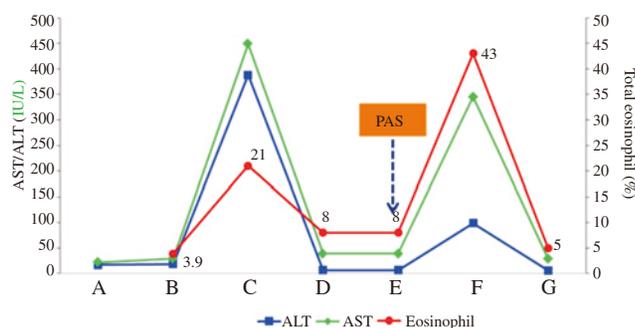


Figure 1. Clinical characteristics of the patients with DRESS syndrome, laboratory data and re-challenge with AST, ALT and PAS.

A: Day 90 before DRESS; B: Day 90 before DRESS; C: DRESS; D: Day 9 after DRESS; E: Start rechallenge PAS; F: Day 6 after rechallenge PAS; G: 1 month after stop PAS.

All anti-TB drugs were discontinued for 15 days until the patient recovered. The schedule of anti-TB drugs graded challenge id was described below.

1. Levofloxacin once daily orally: 50 mg (Day1 and Day 2), 100 mg (Day 3 and Day 4), 250 mg (Day 5), 500 mg (Day 6) and 750 mg (Day 7)also forward when no adverse reaction was observed.

2. Kanamycin once daily intramuscularly: 50 mg (Day 8), 100 mg (Day 9), 250 mg (Day 10), 500 mg (Day 11), and 750 mg (Day 12) also forward when no adverse reaction was observed.

3. Cycloserine orally: 50 mg once daily (Day 13), 100 mg once daily (Day 14), 250 mg once daily (Day 15), 250 mg twice daily (Day 16), 250 mg three times daily (Day 17) and 750 mg once daily (Day 18) also forward when no adverse reaction was observed.

Table 1

Clinical characteristics of the two patients with DRESS syndrome cause by PAS.

Authors, year	Age/sex	Diagnosis	Final regimen	Onset of reaction	Signs and symptoms	Abnormal laboratory values
Kim <i>et al.</i> , 2013	33/M	MDR-TB	KM, MFX, CS, PTH, PAS	3 weeks	High fever, tachycardia, generalized maculopapular exanthema, facial edema with desquamation and cervical lymphadenopathy	EOS = 15%, AST = 1 091 IU/L; ALT = 1 483 IU/L; ALP = 220 IU/L;
Present case	23/ F	MDR-TB	KM, LFX, CS, ETH, PAS	6 weeks	Generalized maculopapular rash, fever, oral ulcer, facial swelling and difficult to breath	EOS = 21%, AST = 449 IU/L; ALT = 388 IU/L; ALP = 107 IU/L;

F; Female; M; Male; EOS: Eosinophils; KM; Kanamycin; MFX: Moxifloxacin; CS: Cycloserine; PTH: Prothionamide; LFX; Levofloxacin; ETH; Ethionamide.

4. Ethionamide orally: 50 mg once daily (Day 18), 100 mg once daily (Day 19), 250 mg once daily (Day 20), 250 mg twice daily (Day 21), 250 mg three times daily (Day 22) and 750 mg once daily (Day 23) also forward when no adverse reaction was observed.

5. PAS orally: 50 mg once daily (Day 24), 100 mg once daily (Day 25), 250 mg once daily (Day 26), 500 mg once daily (Day 27), 1000 mg once daily (Day 28), 1000 mg twice daily (Day 29), 4000 mg twice daily (Day 30) also forward when no adverse reaction was observed.

At Day 30, the patient presented face swelling and generalized erythematous rash. Laboratory testing showed similar findings, with eosinophilia (43%) and liver function test abnormalities (345 IU/L of AST and 99 IU/L of ALT). As a result, PAS was discontinued.

The clinical characteristics for our patient are summarized in the last row of Table 1.

3. Discussion

For the review of published cases, a PubMed search was performed combining the terms (DRESS or PAS) and (PAS or drug rash with eosinophilia and systemic symptoms) and (PAS or DRESS) from January 1959 to February 2015. References were also checked for relevant articles, including review papers.

A study was considered eligible for inclusion in the systematic review when reported data on the clinical and laboratory was sufficient enough to evaluate diagnostic criteria for DRESS syndrome caused by PAS.

Diagnostic criteria for DRESS syndrome included the simultaneous presence of three conditions below[7].

- Drug-induced skin eruption
- Eosinophilia $\geq 1\,500/\text{mm}^3$ (10%) and at least one of the following systemic abnormalities:
 - Lymphadenopathy
 - Hepatitis (transaminases > 2 ULN)
 - Interstitial nephropathy
 - Interstitial lung disease
 - Myocardial involvement[8]

Our patient described here met the criteria for a diagnosis of DRESS syndrome induced by PAS.

Data regarding clinical characteristics, diagnosis, onset of reaction,

abnormal laboratory values, signs and symptoms of these patients are shown in Table 1.

A severe cutaneous adverse drug reaction of DRESS syndrome typically develops 2–8 weeks after initiation of the drug responsible for the reaction[9]. Our patient developed systemic reactions within 6 weeks and recovered about 1.5 weeks after PAS was discontinued.

However, Kim *et al.*[9] reported that the patient's clinical symptoms and laboratory abnormalities developed within 3 weeks and gradually resolved over 4 weeks[9].

The pathogenesis of DRESS is not fully understood. However, the proposed mechanism is the hapten theory and p-i concept[10]. Haptenation is initiated by a small and immunologically neutral molecule becoming antigenic when bound to a protein. Pro-hapten molecules must firstly be metabolized by detoxification enzymes to become able to bind to proteins. When haptens cannot select between individual patients, and detoxification enzymes are expressed by all drug recipients, it has been proposed that polymorphisms in the genes that encode detoxification enzymes may be responsible for the development of DRESS in some patients[10].

Moreover, the direct hepatotoxicity from this drug occurs within 2 h of dosing. Up to 10% of the drug is acetylated in the stomach to *N*-acetylated PAS, a known hepatotoxin[3]. Jeffery *et al.*[11] suggest that sensitization caused by PAS containing an aminophenol group may on occasion be caused by that group and not by the whole molecule. The reaction occurs because the skin transforms all these substances to quinone-imines and di-imines, or their derivatives[11].

Wilson *et al.*[4] reported successful oral PAS desensitization in a patient with anaphylaxis reaction. In contrast, our report showed that the patient with DRESS syndrome cannot tolerate desensitization or graded challenge[4]. Kim *et al.*[9] report that re-challenge with 3.3 g of PAS in a patient with DRESS syndrome resulted in the patient presenting the same systemic reactions within several hours after taking the drug. Thus, the authors suggest that we should not treat patient with DRESS syndrome by desensitization, graded challenge or re-challenge.

The sulphonamides and aromatic anticonvulsants such as carbamazepine, phenobarbital and phenytoin are the most common causes of DRESS syndrome (incidence ranging between 1 in 1000 and 1 in 10000 exposures)[12]. However, a few case reports exist of severe adverse reactions such as DRESS from PAS[9].

To our knowledge, this is the second case of PAS associated with DRESS syndrome. However, we should be aware of this severe hypersensitivity reaction from this substance. The increasing incidence of MDR-TB is worldwide as a result of increased use of second-line drugs such as PAS.

Conflict of interest statement

We declare that we have no conflict of interest.

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