

Pulmonary Tuberculosis with Fixed Drug Eruption to All First-Line Anti-Tuberculosis Drugs

Tüm İlk Seçenek Antitüberküloz İlaçlarına Karşı Fiks İlaç Döküntüsü Gelişen Akciğer Tüberkülozu

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Abstract

Tuberculosis (TB) is still one of the leading causes of mortality worldwide. Treatment with anti-TB drugs sometimes results in side effects for patients, including drug reactions, both allergic and non-allergic. Cutaneous adverse drug reaction is the most common side effect of anti-TB drugs, but severe reaction is rare. Here, we report rare case of a 34-year-old male who presented with pulmonary TB and fixed drug eruption to all first-line anti-TB therapies. After ingesting anti-TB regimen, multiple skin erosions and blisters occurred. Skin biopsy was performed and result was epidermis with subepidermal bullous. The patient's condition deteriorated, he developed severe hypoxemia, and unfortunately, he died during fixed drug eruption treatment.

Key words: Adverse drug reaction, anti-tuberculosis drugs, drug eruption, tuberculosis.

Özet

Tüberküloz tüm Dünya'da önemli bir mortalite nedeni olmaya devam etmektedir. Antitüberküloz tedavi sırasında kullanılan ilaçlarla, allerjik veya non-allerjik reaksiyonlar şeklinde yan etkiler ortaya çıkmaktadır. Ciddi reaksiyonlar nadir görülmekle beraber, ilaca bağlı cilt reaksiyonları antitüberküloz ilaçların en sık görülen yan etkileridir. Burada, ilk seçenek antitüberküloz ilaçların tümüne karşı fiks ilaç döküntüsü olan akciğer tüberkülozlu 34 yaşındaki erkek olguyu sunuyoruz. Antitüberküloz ilaçların alımından sonra hastanın tüm vücudunda çok sayıda erozyon ve kabarcıklar oluştu. Cilt biyopsisi yapıldı ve sonucu epidermal ve sub-epidermal büller olarak tanımlandı. Hastanın durumu ağır hiposemi nedeniyle kötüleşmeye başladı. Ne yazık ki, fiks ilaç döküntüsü tedavisi sırasında hasta vefat etti.

Anahtar Sözcükler: İlaç yan etki, antitüberküloz ilaç, ilaç döküntüsü, tüberküloz.

Tuberculosis (TB) is still a health problem in the world, and one of the leading causes of morbidity and mortality, particularly in developing countries in Asia and Africa. First-line anti-TB therapy with rifampin, isoniazid, pyrazinamide, ethambutol, and streptomycin is still very effective for pulmonary TB. However, adverse drug reaction (ADR) may

complicate anti-TB treatment. Fixed drug eruption (FDE) is part of cutaneous ADR (CADR), which may be related to anti-TB drugs (1). FDE has been reported with rifampin, isoniazid, and ethambutol singly in some case reports (2-4). Presently described is rare case of pulmonary TB with FDE to all first-line anti-TB therapy.

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CASE

A 34-year-old male patient was admitted to our hospital with chief complain of shortness of breath and productive cough. He had been diagnosed as pulmonary tuberculosis at a private clinic 1 year before admission. Oral first-line anti-TB drugs (combination of rifampin, isoniazid, pyrazinamide, and ethambutol) had been administered, but blisters appeared all over his body 4 days after consuming the drugs. Three months later, challenge test with rifampin and isoniazid was performed in district hospital, and blisters arose on the skin. Challenge test was discontinued until skin lesions healed. Following month, challenge test with pyrazinamide alone was initiated. Once again, similar skin lesions appeared and test was halted. Challenge test performed a month later with ethambutol also resulted in appearance of blisters. He was then referred to our hospital. Challenge test was re-initiated in outpatient clinic with rifampin and then with streptomycin injection, but blisters still appeared after each drug was administered singly. Desensitization test was planned, but the patient was lost to follow up after about 2 months.

On physical examination, the patient was in moderately good general condition, respiratory rate was 32 breaths per minute, and oxygen saturation was 96% with oxygen flow of 3 liters per minute via nasal canula. Widespread erosion, crust, and hyperpigmentation were observed on the skin. Pulmonary auscultation revealed reduction of breath sounds in the left upper lung field and bronchovesicular sound with crackles in bilateral lung field.

Chest X-ray revealed bullae in the left upper lung field with diffuse infiltrates (Figure 1). Acid-fast bacilli of sputum were positive and Xpert MTB/RIF test (Cepheid, Inc., Sunnyvale, CA, USA) of sputum result was *Mycobacterium tuberculosis* sensitive with rifampin. Antinuclear antibody test and rheumatoid factor were also checked to eliminate possibility of autoimmune etiology and results were negative. HIV antibody test was also negative. Skin biopsy performed at outpatient clinic revealed epidermis with subepidermal bullae containing eosinophil, fibrotic dermis, and chronic inflammatory cells (Figure 2). Conclusion was bullous drug eruption and was managed with oral steroid and topical cream. Anti-TB drug desensitization was planned for after skin lesions healed, but the patient's condition deteriorated. He died as result of severe hypoxemia.

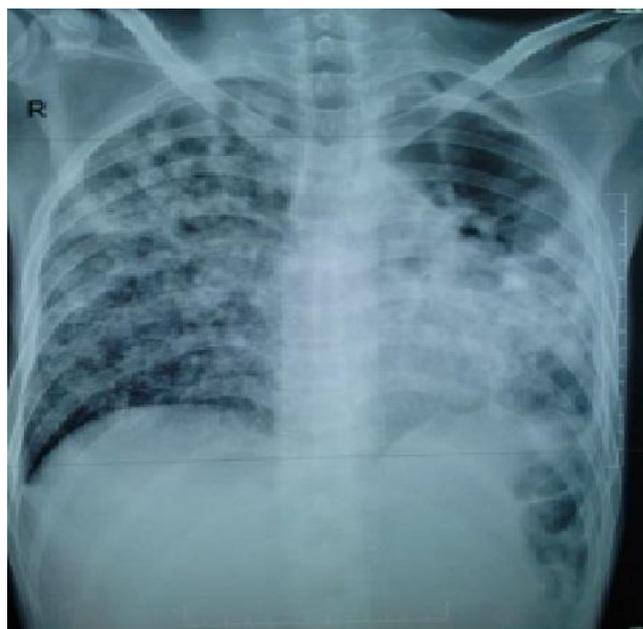


Figure 1: Chest X-ray revealed diffuse infiltrates with bullae in the upper left lung field

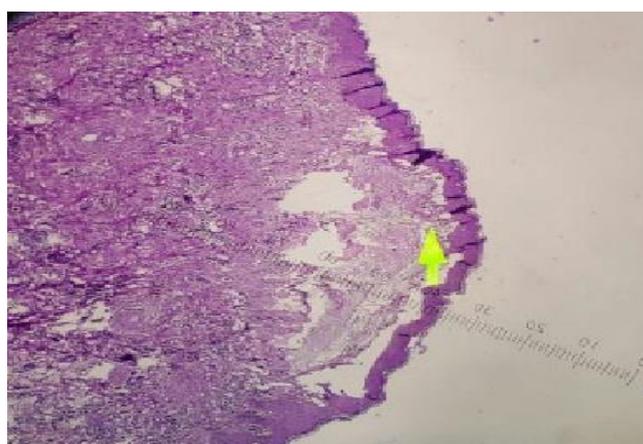


Figure 2: Histopathology examination of skin biopsy revealed subepidermal bullous (arrow) (H&E x100)

DISCUSSION

The Anti-TB drugs used for pulmonary TB treatment are associated with ADR. ADR may include immunologically-mediated drug hypersensitivity (drug allergy) or non-immune mediated/idiosyncratic reactions. Mechanism of drug allergy may be immunoglobulin E (Ig-E) or non-Ig-E mediated (5,6). Anti-TB drugs contain low molecular compounds that may induce allergic reaction through antigen presenting cell (APC)-hapten binding. Hapten is a low molecular substance that binds to carrier, such as protein, before APC presentation. According to classification of Coombs and Gell, allergic reaction is divided into 4 types, and most reactions to low-molecular-weight drugs are type I and type IV (7). CADR is part of ADR and one of the most commonly observed side effects of anti-TB drugs. There are several types of CADR, such as mor-

biliform and maculopapular drug eruption, exfoliative dermatitis, lichenoid drug eruption, cutaneous vasculitis, FDE, Steven Johnson Syndrome, and toxic epidermal necrolysis (5). FDE has many variant forms of lesion, including solitary or small number of erythematous macules and widespread lesion with blisters. Lesion can appear on any part of the skin or mucous membranes within a day to a few weeks after administering the causative drug. It resolves with residual hyperpigmentation (8,9). Generalized bullous drug eruption is severe form of FDE with mortality rate of 22% (10). In our patient, blisters appeared after administration of combination of anti-TB drugs and after challenge test with all anti-TB drugs. Diagnosis of FDE was confirmed by histopathology examination.

There are limited available data about incidence of anti-TB drug related CADR. Severe CADR may result in discontinuation of anti-TB drug use and thereby increase morbidity and even mortality (1). Nahid et al. (11) found that HIV status, positive result of sputum smear at baseline, and drug interruption during intensive phase was associated with high mortality rate in TB patient. Severe FDE in our patient interrupted pulmonary TB treatment and time was required for healing of skin lesions before re-starting anti-TB drug administration. Poor outcome in this patient was related not only to severe FDE, but also to patient declining to continue therapy.

Reintroducing anti-TB treatment following TB-associated CADR is important to diminish mortality rate. There are 2 methods to this process: challenge and desensitization. Challenge test aims to identify the offending drug and eliminate it from the regimen of therapy, whereas desensitization seeks to relieve immune response to causal drug by prolonged or repeated stimulus. Neither is recommended for drugs that have been associated with severe allergic reaction. However, exclusion from challenge test can lead to high risk of death, so risk-benefit ratio should be considered before performing these tests on patient with severe allergic reaction (5).

Challenge test protocol may begin with isoniazid 50 mg on day 1. If there is no allergic reaction, the dose may be increased to 300 mg on day 2. This dose should continue for 4 days if allergic reaction does not occur. Drugs are then added in order and dose specified in Table 1. Dose of each drug is increased until recommended dose is achieved and is then continued for 4 days. If allergic reaction occurs during challenge test, desensitization test may be performed for the causative drug. General protocol for desensitization test may be initiated with 1/10 of

the day 1 dose. Each dose is doubled and administered twice daily until recommended daily dose has been achieved and it is continued for 3 days before it may be replaced by once daily dosing. If allergic reaction occurs during desensitization process, dose is decreased to the highest dose that did not cause any allergic reaction and increased in smaller increments (12).

Table 1: The Challenge Test Protocol

Drug	Challenge Doses	
	Day 1	Day 2
Isoniazid	50 mg	300 mg
Rifampicin	75 mg	300 mg
Pyrazinamide	250 mg	1000 mg
Ethambutol	100 mg	500 mg
Streptomycin	125 mg	500 mg

In conclusion, CADR is one of possible side effects of anti-TB drugs. Severe reaction will interrupt pulmonary TB treatment for long period of time and will likely increase either complication of underlying disease or mortality risk. Re-introducing anti-TB drugs is required for patients with CADR before they continue anti-TB treatment. Although severe reaction in CADR is rare, it may be fatal. Close monitoring and proper management are needed for patient with this case.

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CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - G.A., F.N., F.I.; Planning and Design - G.A., F.N., F.I.; Supervision - G.A., F.N., F.I.; Funding - G.A., F.N.; Materials - G.A.; Data Collection and/or Processing - G.A.; Analysis and/or Interpretation - G.A., F.I.;

Literature Review - G.A.; Writing - G.A.; Critical Review - G.A., F.N.

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