Case Report

Ethambutol-induced Bullous Skin Lesions in *Mycobacterium kansasii* Lung Infection

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Abstract

Mycobacterium kansasii is the second most common cause of nontuberculous mycobacterial (NTM) lung disease after *Mycobacterium avium* complex infection in the United States.[1] The first-line therapy for *M. kansasii* is a three-drug regimen including rifampin, isoniazid, and ethambutol. We present a case of a patient with pulmonary *M. kansasii* who developed bullous skin lesions while receiving this regimen and again after rechallenge with ethambutol. In patients with intolerance to one of the first-line antibiotics, a multidisciplinary team approach to starting second-line agents is needed. Ethambutol should be included in the differential diagnosis of drug-induced bullous skin lesions in treated patients with NTM, who develop new onset rash with blisters or ulceration.

Keywords: Direct immunofluorescent, drug-induced skin reactions, ethambutol, *Mycobacterium kansasii,* pemphigus vulgaris, suprabasilar bullous skin lesion

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Introduction

M. kansasii is an insidious acid-fast bacillus which has a similar presentation to *Mycobacterium tuberculosis.* Local water supplies are the major reservoir for the transmission in immunocompromised patients.[1] For susceptible isolates, a rifampin based 3-drug regimen including ethambutol and either isoniazid (INH) or macrolide is the cornerstone therapy.[1] A second-line regimen should be considered based on response, resistance patterns, and side effect profile of first-line medications through a multidisciplinary team approach.[2] Determining which agent is the inciting drug in the context of an adverse reaction during the treatment for mycobacterial disease is often difficult because of the multidrug regimens utilized, but discontinuation of therapy and reintroducing agents stepwise may help identify the causative agent. The development of blistering lesions may be life-threatening and mandate discontinuation of the offending drug. We present a case of ethambutol-induced bullous skin lesions in a patient with *M. kansasii* lung infection.

Case Report

A 56-year-old HIV-negative male with a medical history of severe chronic obstructive pulmonary disease (COPD), pulmonary sarcoidosis, bronchiectasis, past tobacco use, and coronary artery disease presented with worsening dyspnea, fever, and fatigue. He was maintained on as needed low dose prednisone. Physical examination findings included tachypnea and diffuse expiratory wheeze. Chest computed tomography scan revealed right middle lobe infiltrate with interlobular thickening and pulmonary nodules. Sputum demonstrated 3+ acid-fast bacilli that were speciated as *M. kansasii*. INH, rifampin, and ethambutol were initiated, and then rifampin was switched to clarithromycin to avoid a potential drug interaction

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with ranolazine. Respiratory symptoms improved, and he was discharged in the stable condition.

The patient presented 6 weeks later with oral and truncal blisters, which started in the right upper buccal mucosa [Figure 1] and easily ruptured. Antimicrobials were held, and a punch biopsy of a truncal skin ulcer was obtained. Pathology revealed suprabasilar bulla with acantholysis (loss of intercellular cohesion between keratinocytes), and separation of epidermis from dermis, consistent with pemphigus [Figure 2]. Specimens sent for direct immunofluorescence (DIF) lacked epidermis to allow confirmation of pemphigus. HSV and VZV immunostains were negative. INH and ethambutol were considered the most likely inciting antimycobacterial agents by the dermatology consultant and were discontinued. He was started on prednisone 60 mg daily for 2 weeks with the resolution of dermal lesions. His antimycobacterial regimen was changed to rifampin, clarithromycin, and inhaled amikacin.

He was readmitted 5 weeks later with worsening dyspnea, attributed to amikacin-induced bronchospasm, which was discontinued. He was rechallenged with ethambutol, as his previous drug reaction was considered relatively more likely due to INH. He again developed bullous skin rash of his oral cavity and trunk. Ethambutol was discontinued, and treatment adjusted to rifampin, azithromycin, and intravenous amikacin for 2 months. He was then continued on rifampin, azithromycin, and linezolid for 16 months, with negative serial sputum AFB cultures. There was no recurrence of mycobacterial infection or skin lesions off therapy for 18 months.

Discussion

M. kansasii is typically susceptible to anti-tuberculous agents, with rifampin the cornerstone of therapy. In patients with rifampin-susceptible *M. kansasii* pulmonary disease, a regimen of rifampin, ethambutol, and either INH or macrolide is recommended for a duration of at least 12 months.[1] Adverse reactions, including drug-induced blistering, may interfere with treatment.

Pemphigus is a group of life-threatening blistering disorders characterized by acantholysis that results in the formation of intraepithelial blisters in the mucous membranes and skin. Acantholysis is induced by the binding of circulating autoantibodies to intercellular adhesion molecules. The differential for suprabasilar bullous lesions includes pemphigus vulgaris (PV), bullous pemphigoid, Pemphigus vegetans, Hailey Hailey, Grover's disease, and Darier's disease were unlikely clinically.

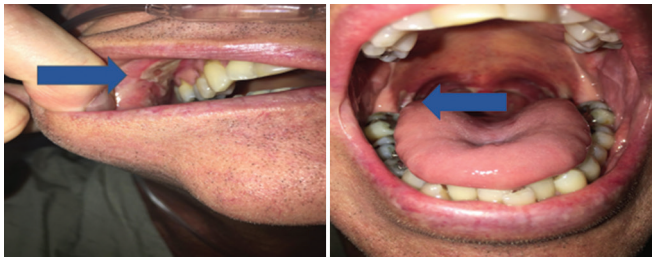

Figure 1: Right upper buccal mucosa lesion

Drug-induced bullous pemphigoid has been reported with INH, rifampin, loop diuretics, spironolactone, angiotensin-converting enzyme inhibitors, penicillins, beta blockers, and antiepileptics,[3,4] etanercept, and sulfasalazine.

Drug-induced biochemical and/or immunological reactions may contribute to the development of acantholysis in drug-induced pemphigus (DIP). These medications can be classified based on their chemical structure, as thiol drugs, phenol drugs, and nonthiol/phenol drugs. Most of the DIP is associated with thiol compounds in the drug, but many nonthiol drugs contain sulfur in their molecules. Such drugs have been termed "masked thiols," as the sulfur may undergo change to active thiol groups.[5] Potential mechanisms for DIP include effects on enzymes that mediate keratinocyte aggregation, production of IgG autoantibody against desmoglein 1 and 3, and stimulation of neoantigen formation.

The types of pemphigus are distinguished by clinical features, associated autoantigens, and laboratory findings: IgG autoantibodies against desmoglein 3 are the characteristic of mucosal PV; autoantibodies against desmoglein 1 have been linked to pemphigus foliaceus; and autoantibodies to desmoglein 1 and desmoglein 3 have been linked to mucocutaneous PV.[6] The amino-terminal portions of desmogleins are epitopes for pathogenicity as evidenced by studies that demonstrate IgG directed against an amino-terminal recombinant fraction of desmoglein 3.[6] Skin biopsy in PV demonstrates suprabasilar bulla with acantholysis and separation of epidermis from dermis, and DIF shows intercellular deposits of IgG and C3 deposits. DIF and in direct immunofluorescence (DIF) studies aid in the diagnosis but can be negative in DIP. In a case series of 93 patients with pemphigus, the normal pattern on DIF was seen in 70% of DIP compared to 16% in idiopathic pemphigus.[7]

The development of blistering skin lesions in our patient treated for *M. kansasii* with a regimen including ethambutol, with recurrence following ethambutol rechallenge, strongly implicates

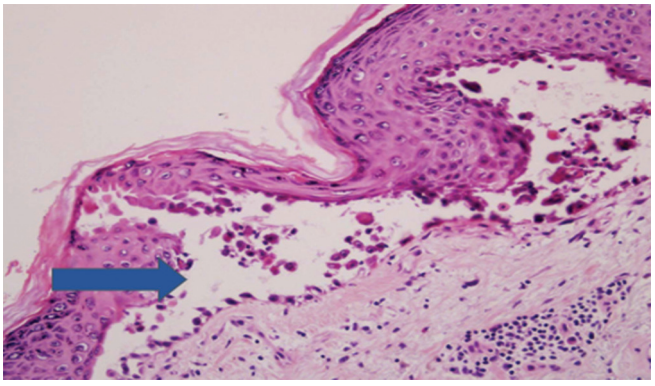

Figure 2: H and E stain (×10) of punch of the skin showed suprabasilar bulla with acantholysis and separation of the epidermis from dermis consistent with pemphigus

ethambutol as the etiology. He responded to prednisone and discontinuation of ethambutol. In addition to bullous skin lesions,[8] additional skin reactions noted with ethambutol include lichenoid eruptions,[8] toxic epidermal necrolysis,[9] and hypersensitivity reactions[10] and ashy dermatosis-like pigmentation.[11] In patients treated with ethambutol, a new bullous skin eruption should raise concern for pemphigus or other serious adverse drug reaction, which mandates discontinuation, and if necessary, vigilant stepwise reintroduction of potentially responsible medications, as guided by a multidisciplinary team.

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Conflicts of interest

There are no conflicts of interest.

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