A Rare Complication of a Common Drug- Bullous Pemphigoid Due to Isoniazid- Case Report

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Abstract
Bullous pemphigoid is anautoimmune blistering disease with the unknown aetiology in the majority. However, certain drugs have been recognized to precipitate bullous eruption resembling pemphigoid. Though cutaneous drug reactions are commonly reported in association with first line anti tuberculous medications, bullous pemphigoid is encountered exceedingly rarely. We report a case of bullous pemphigoid secondary to isoniazid therapy.

A 55 year old female presented with cough, fever and constitutional symptoms for 2 months duration and diagnosed with bacteriologically confirmed pulmonary tuberculosis. She was treated with antituberculous therapy comprising of isoniazid, rifampicin, ethambutol and pyrazinamide with standard doses. Eleven days later she presented with generalized erythematosus skin rash followed by blistering and diagnosed as drug induced bullous pemphigoid according to clinical, histopathological and immunological evidence. The anti-tuberculous drug was withheld and re-challenged gradually while bullous eruptions were controlled with oral prednisolone, topical steroids and dapsone therapy. Recurrence of blisters was noted while the introduction of isoniazid, hence diagnosis of isoniazid induced bullous pemphigoid was made.

In conclusion, the first line of antituberculous drugs induced bullous pemphigoid is rare. But, early recognition is vital to prevent the deleterious outcome. Serious cutaneous reactions due to anti-tuberculous medications evoke an especial situation, where careful re-challenge is required to delineate the exact culprit drug.

Key words: *Antituberculous medications, isoniazid, adverse drug reactions, bullous pemphegoid*

Introduction

Bullous pemphigoid (BP) is considered as the commonest autoimmune blistering disease, which usually occurs in the elderly population without gender predilection. The incidence of BP is increased over the past decades due to the aging population, increased risk of exposure to potential triggering medications and improvement in clinical and laboratory diagnostics (1).

Presentation of BP could be either acute or subacute onset of characteristic large tense subepidermal blisters which arise on erythematosus or normal appearing skin. Typically, lesions are distributed over the lower abdomen, inner or anterior thighs and flexor forearms, though they may occur anywhere. However, mucous membrane involvement is rare (2).

The pathogenesis of BP is characterized by tissue-bound and circulating IgG autoantibodies against two components of the hemidesmosome of stratified epithelia, BP 230 kD and BP 180 kD (2). Diagnosis relies on the demonstration of the histopathological evidence of eosinophilicspongiosis orsubepidermal detachment with eosinophils; the detection of IgG and/or C3 deposition at the basement membrane zone; and quantification of circulating autoantibodies against BP180 and/or BP230 (1).

Most cases of BP are idiopathic. However, epidemiological studies demonstrate an association with chronic neurological diseases, other autoimmune diseases and malignancies (1, 2). Several drugs are reported to trigger BP like skin eruptions (1, 2). However, anti-tuberculous medications precipitating BP have been reported extremely rarely.

Case presentation

A 55year old Sri Lankan female presented to our unit with a chronic productive cough, evening fever with night sweats, loss of appetite and loss of weight for 2months duration. Her past medical history only revealed satisfactorily controlled diabetes mellitus for 6 months and hypothyroidism for 3 years. There was no history of any significant skin rashes. Drug history noted regular intake of metformin, gliclazide and thyroxin for control of co-morbidities. However, she denied ingestion of any other medication including over the counter drugs and medications related to traditional or alternative medicine. There was no past experience of drug or food allergy.

Her chest radiograph demonstrated right upper zone consolidation and pleural thickening with fibrosis and cavity formation. Further investigations with sputum smear revealed tuberculosis bacilli and diagnosed as bacteriologically confirmed pulmonary tuberculosis. Anti-tuberculous therapy was commenced with a world health organization (WHO) defined standard category 1 treatment comprising Isoniazid, Rifampicin, Pyrazinamide, and Ethambutol with Pyridoxine according to body weight.

Eleven days later she developed a generalized erythematosus rash involving palms, soles, upper limbs, neck and trunk symmetrically. Two days later, multiple non-painful blisters appeared over the erythematosus areas except palms and soles. The rash and blisters developed gradually over the last 3 days; however generalized pruritus was noted during the preceding 5 days. There was no deterioration of pre-existing respiratory symptoms. Examination revealed tense blisters ranging from 0.5 -2 Cm in size containing serous colour fluid symmetrically distributed over upper limbs, neck and trunk symmetrically(Figure 01 and 02). Additionally, there were multiple erythematic patches resembling target lesions (Figure 03). Rubbing with fingers over the normal-appearing skin near the bullous lesions failed to separate epidermis from deeper layers; i.e. - Nikolsky's sign was negative. The face, eyes and oro-genital regions were spared.

Investigations revealed total white count of 13000/mm3 with 70% of neutrophils, C- reactive protein 34 mg/dl (normal <10) and sedimentation rate 16mm/hr. Renal and liver function tests were within the normal range.

The dermatological opinion was obtained and differential diagnosis of erythema multiforme and drug induced bullous pemphigoid were considered. All anti-tuberculous medications were withheld immediately and treatment commenced with local applications of clobetasol (a steroid) and cetirizine (second generation antihistamine). Since the blisters were not adequately resolved after two weeks of omission of culprit drugs, further investigations with skin biopsy were carried out and oral prednisolone 20 mg daily and dapsone 50 mg daily were commenced. Meanwhile, bridging therapy for pulmonary tuberculosis was initiated with streptomycin, ofloxacin and ethambutol. Histopathology of skin biopsy demonstrated sub-epidermal edema with infiltration of eosinophils and lymphocytes with early separation of epidermis form the dermis suggestive of bullous pemphigoid. Direct immunofluorescence staining recognized deposition of IgG at the basement membrane which was consistent with bullous pemphigoid. Since bullous pemphigoid was rarely reported in association with first line anti-tuberculous medications, she was re-commenced on isoniazid, rifampicin, ethambutol and pyrazinamide once the blisters were resolved. Oral prednisolone and dapsone were continued further.

After 8 days, the patient presented again with newly developing blisters involving the forearms. Therefore all anti-tuberculous drugs were omitted. Once all the eruptions were healed, drug desensitization was attempted; starting with Isoniazid gradually and she developed similar eruptions in the forearms two days later. Therefore isoniazid was omitted and rifampicin and pyrazinamide were successfully introduced to the regimen slowly without recurrence of the eruptions. The oral steroid was continued for about 1 month and slowly tailed off. She has continued the total duration of anti-tuberculous therapy without further recurrence.

Discussion

Tuberculosis poses a serious threat to public health throughout the world, placing it among the top ten causes of death globally and is considered as the leading cause of mortality due to a single infectious agent. It is estimated that one quarter of the global population is infected with tuberculous bacteria (3). Effective treatment of tuberculosis requires a combination of multiple antituberculous medications given for several months for complete eradication. Antituberculous medications are classified into 5 groups according to WHO, in which group 1 is considered as the first line medications which include isoniazid, rifampicin, ethambutol and pyrazinamide(4). These first line medications are highly effective in treating WHO defined

new and re-treatment cases of tuberculosis in the absence of drug resistance, thereby forming the core of tuberculosis management.

Adverse drug reactions (ADR) to first line antituberculous medications are considered common. The prevalence of ADR varies widely from 8- 85% according to studies conducted globally (5). Though the majority of first line antituberculous medication associated ADR are mild; serious hepatic, cutaneous, renal, rheumatological and neuropsychaitric manifestations may develop leading to significant morbidity and potential mortality unless recognized earlier(5). Development of ADR depends on several determinants like dose, age, nutritional status, alcoholism and pre-existing co-morbidities like HIV co- infection, renal and liver dysfunctions (6).

Cutaneous adverse drug reaction associated with antituberculous medications are diverse; ranging from mild to moderate reactions like pruritus, morbilliform eruptions, lichenoid eruptions, fixed-drug eruptions, cutaneous vasculitis and urticaria to severe and even life-threatening conditions, such as drug hypersensitivity syndrome (DHS), acute generalized exanthematouspustulosis, Stevens-Johnson syndrome (SJS) and Toxic epidermal necrolysis (TEN) (7). It is recognized that an individual antituberculous drug can induce multiple patterns of cutaneous reactions, while a specific reaction can occur due to several drugs (7).

Bullous eruptions as a cutaneous adverse reaction of first-line antituberculous medications have been reported exceedingly rarely. Two cases of rifampicin induced bullous pemphigoid have been reported by Garrido-Colmenero et al. and SA Ibn et al. earlier (8, 9). Akrout reported a rare case of ethambutol induced bullous and lichenoid skin eruption in an elderly woman (10). However, our patient developed a reaction of bullous pemphigoid due to isoniazid. K Vinitha et al. reported a case of bullous eruption due to isoniazid similar to our case before (11).

The establishment of a causal relationship between the adverse reaction and the pharmacological agent by objective assessment using probability scales is desirable. The causality assessment system proposed by the World Health Organization Collaborating Centre for International Drug Monitoring, the Uppsala Monitoring Centre (WHO–UMC), and Naranjo Probability Scale is the generally accepted and most widely used methods for causality assessment in clinical practice (12, 13). Our case was classified as a probable case of ADR according to both Naranjo and WHO-UMC assessment systems.

So far, more than 50 drugs have been recognized to be associated with bullous pemphigoid and the number is expected to rise as the emergence of new drugs (14). Furosemide, thiazide, non-steroidal anti-inflammatory drugs, captopril, phenacetin, penicillamine, etarnacept, and systemic antibiotics are well recognized as triggers according to the literature (2). Genetic predisposition is suspected of operating in the development of drug induced bullous pemphigoid, though no specific genetic mutation is identified yet (1). Diverse clinical forms with varying severity of bullous pemphigoid have been described in association with drugs. However, clinical presentations and immunopathological findings of drug induced bullous pemphigoid may be indistinguishable from classic form (1). Further, no specific biomarker for drug induced bullous pemphigoid has been recognized up to date (1). However, the onset of disease at a younger age and within three months of the introduction of a new drug, and rapid clinical response to the withdrawal of offending drugs with little or no recurrence following drug withdrawal suggest the possibility of drug induced disease (1).

Drug induced bullous pemphigoid should be distinguished from other bullous eruptions secondary to medications such as pemphigus, linear IgA disease, erythema multiforme major, SJSand TEN. Drug induced pemphigus characteristically causes flaccid blisters accompanied by Nikolsky's sign and frequent mucosal involvement as opposed to pemphigoid (15).Erythema multiforme major is characterized by target lesions with or without blistering (16). Key clinical features of SJS/TEN include a triad of mucous membrane erosions, target lesions, and epidermal necrosis with detachment. Blisters can occur in patients with SJS/TEN and are typically flaccid (16). Though erythema multiforme was a differential diagnosis in our patient due to the presence of target lesions, histopathological and immunological findings were more in favour of bullous pemphigoid.

Histopathological and immunological investigations aid confirmation of the diagnosis of bullous pemphigoid. Histologically, mixed inflammatory cell infiltration with eosinophilic predominance with spongiosis and subepidermal blistering can be recognized (2). Deposits of IgG antibodies and C3 can be demonstrated on normal appearing perilesional skin within 2 cm of a lesion by direct immunofluorescence studies in 90-95% and in 100% of cases respectively (2). Indirect immunofluorescence (IIF) studies document IgG circulating autoantibodies in the patient's serum that target the skin basement membrane in 60-80% cases (2). Serum anti-BP180 and anti-BP230 autoantibodies may also be quantified using ELISA, immunoprecipitation and immunobloting techniques (1).

The occurrence of severe cutaneous reaction for combine antituberculous therapy poses a management challenge for the treating physicians. It is generally recommended to avoid any medication that induced a serious cutaneous adverse reaction from future therapy. But, antituberculous medications are usually given as combination formulations, and therefore, it is practically unfeasible to recognize the culprit medication at first instance. Since first line medications are highly effective in tuberculosis management in a susceptible drug infection, complete replacement with second line agents may not provide optimal resolution of the disease. Moreover, second line medications are associated with more serious adverse effect profile. Therefore, in clinical practice, gradual re-challenge with careful monitoring for the recurrence of cutaneous reaction is an accepted protocol for precise identification of the culprit drug.

Conclusion

First line antituberculous medications including isoniazid are commonly utilized in clinical practice and mild cutaneous adverse reactions are frequently encountered. Serious cutaneous reactions are rare, however can lead to significant morbidity and potential mortality. Drug induced bullous pemphigoid is a rare form of serious drug eruption reported in association with isoniazid. Early recognition and termination of therapy followed by gradual re-introduction is the key to the precise identification of offender medication.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal

Competing interest

The authors declare that they have no competing interests.

Authors' contribution

DM made the clinical diagnosis and supervised the manuscript drafting. AB, SAL and NR drafted the first manuscript, reviewed the literature and involved in direct management of the patient. All authors read and approved the final manuscript.

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Bullous pemphigoid figures

Figure 01- A large tense blister

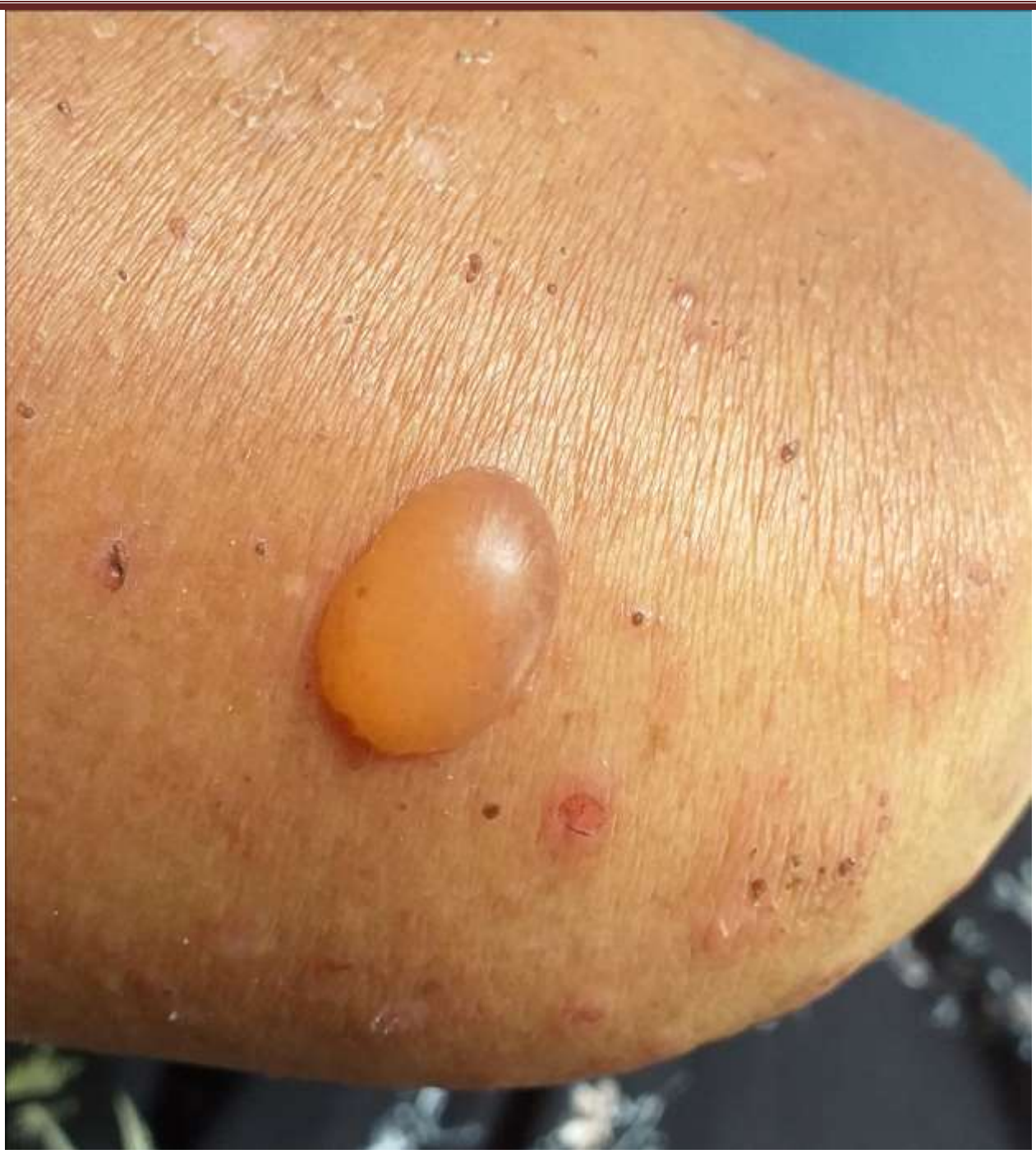

Figure 02- Multiple small blisters on erythematosus background

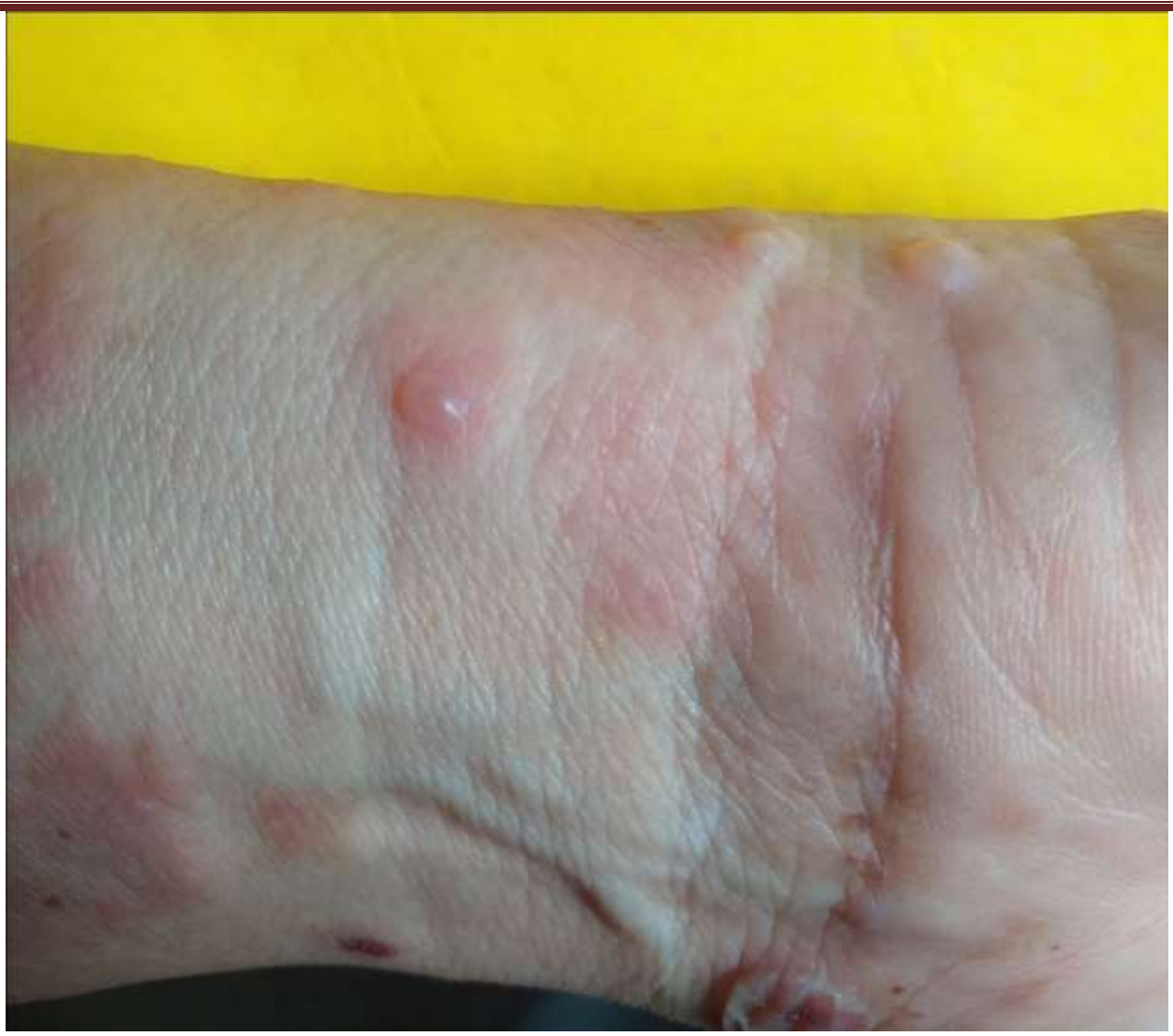

Figure 03- Target lesions