

CASE REPORT

Paraneoplastic Bullous Pemphigoid Masquerading as Hand-foot Syndrome: A Case Report of Rare Entity

Subhatharshni Mohan¹, Nazatul Shima Abdul Rahim¹, Amizatul Aini Salleh², Hasni Mahayidin³, Ikmal Hisyam Bakrin³

¹ Dermatology Unit, Department of Medicine, Hospital Putrajaya, 62250 Putrajaya, Wilayah Persekutuan Putrajaya, Malaysia

² Department of Pathology, Hospital Serdang, Jalan Puchong, 43000 Kajang, Selangor, Malaysia

³ Department of Pathology, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, 43400 UPM Serdang, Selangor, Malaysia

ABSTRACT

Bullous pemphigoid (BP) is a chronic and the most frequent immune-mediated subepidermal blistering disorder which mainly affects elderly individuals. The autoantibodies produced following T-cell dysregulation are directed against BP180 (BPAg2) and BP230 (BPAg1), hemidesmosomal proteins located in the basement membrane zone (BMZ) of the epidermis. BP may present with polymorphic dermatological features including non-bullous manifestations and blisters. Therefore, a wide range of differential diagnoses such as eczema, urticaria, pemphigus and the differentials for subepidermal blister with eosinophils such as epidermolysis bullosa acquisita (EBA) and bullous drug eruptions should be considered in such cases. The associations of solid organ internal malignancies and BP are quite rare and vary between studies. Here, we present a case of paraneoplastic bullous pemphigoid (PNBP) in a patient with underlying renal cell carcinoma who was initially diagnosed with worsening hand-foot syndrome (HFS) which has led to withdrawal of his oral chemotherapy treatment.

Keywords: Bullous pemphigoid, Paraneoplastic, Hand-foot syndrome

Corresponding Author:

Ikmal Hisyam Bakrin, MPath

Email: ikmalhisyam@upm.edu.my

Tel: +603-89472671

INTRODUCTION

Bullous pemphigoid (BP) is the commonest type of autoimmune bullous skin disease predominantly seen in the elderly. It is characterised by the presence of circulating and tissue-bound autoantibodies specific for two hemidesmosome components, which are transmembrane BP180 protein and intracellular BP230 protein. Most of BP cases are idiopathic in origin. The lesions are described as large, tense blisters with round or oval in shape which may be preceded by a localised or generalised eczematous or urticarial eruptions (1). In contrast to the pemphigus disorders, mucosal involvement is uncommonly encountered and only seen in 30% of cases. BP may be associated with other conditions such as other dermatologic disorders, neurologic disorders, certain medications and rarely malignancies, particularly haematological

malignancies (1). A large German study has shown that haematological malignancies, particularly B-cell lymphoma, mature T/NK-cell lymphoma and leukaemia were present in about 7% of BP patients. In half of them, the haematological malignancy preceded the BP diagnosis. However in that study, no association between BP with solid organ malignancies was found (2). Paraneoplastic syndrome is a term describing a group of conditions affecting any organ or system that occurs secondary to an underlying malignancy. The association of paraneoplastic bullous pemphigoid (PNBP) with renal cell carcinoma is exceptionally rare. To date, there were only six cases of PNBP in association with renal cell carcinoma which had been reported (3). Clinically, PNBP may mimic non-bullous manifestations at the early stage of the disease and blistering manifestations which include drug eruptions especially in patients taking medications for other pre-existing conditions.

CASE REPORT

A 62-year-old gentleman who came for follow-up at the oncology clinic in January 2020 presented with

multiple tense painful bullae over his hands and feet for the past one month. The skin lesion was associated with erythema and swelling of his feet which developed one week prior to his presentation. He denied of having fever or chills. The patient has underlying type II diabetes mellitus, hypertension, dyslipidaemia and renal cell carcinoma which was diagnosed in October 2014. He underwent a nephron-sparing wedge resection in the same month. In December 2016, he was diagnosed with lung and brain metastases and was started on oral Sunitinib shortly after. At the time of presentation, he was on 50mg Sunitinib once daily (3 weeks on, 1 week off). He had at first noticed a pruritic, eczematous rash over his palms and soles of his feet 3 months prior to the current presentation, which was treated as HFS grade I. Diagnosis of adverse cutaneous drug reaction (ACDR) of HFS with a possibility of drug-induced bullous pemphigoid was made. Sunitinib was withheld by the oncology team and referral to dermatologist was made.

Dermatological examination was notable for multiple well-defined tense bullae over the dorsum of his hands (Fig. 1). These bullae were mainly filled with clear fluid; however, some were haemorrhagic. Nikolsky's sign was negative. The mucous membranes were unremarkable. There were also crusted erosions over the dorsum of his hands, forearms, elbows, feet, shins and inguinal region (Fig. 2). At this point, the clinical diagnosis was revised to PNPB. Two punch biopsies were performed; one was of the vesicles for haematoxylin and eosin (H&E) staining and the other was of the perilesional skin for direct immunofluorescence (DIF) study.



Fig. 1 : Multiple well-defined tense bullae over the dorsum of hands with several containing haemorrhagic fluid.



Fig.2 : Crusted erosions over the dorsum of forearm, elbow and hand.

On histopathological examination, the epidermis showed presence of subepidermal blisters with predominant eosinophilic cell infiltrates (Fig. 3a). The epidermis also showed mild to moderate spongiosis accompanied by eosinophils exocytosis (Fig. 3b). No dyskeratotic cells or vacuolar degeneration of the basal layer was seen (Fig. 3b). The upper dermis showed moderate mixed inflammatory cells infiltrate mainly of eosinophils and neutrophils mixed with lymphocytes and occasional plasma cells. Moderate perivascular and peri-adnexae of similar inflammatory cells infiltrate were also observed. The deeper dermis and subcutaneous tissue/region appear unremarkable.

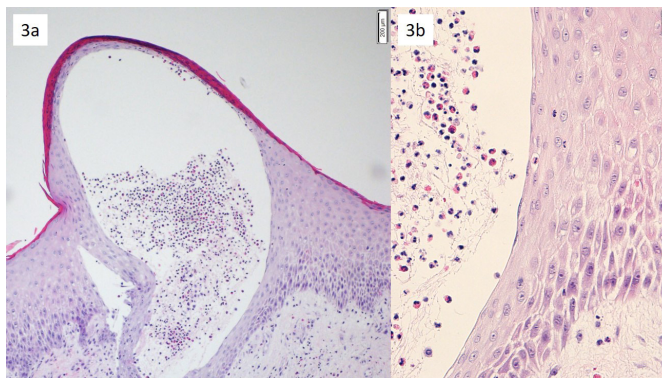


Fig. 3 : Subepidermal blister with predominant eosinophilic cell infiltrates (Haematoxylin and eosin stain, original magnification x 100) (Fig. 3a). The epidermis also showed mild to moderate spongiosis accompanied by eosinophils exocytosis. There were no dyskeratotic cells or vacuolar degeneration of the basal layer seen (Haematoxylin and eosin stain, original magnification x 200) (Fig. 3b).

DIF study of the perilesional skin showed C3 (2+) deposition along the dermo-epidermal junction (Fig. 4a). Apart from IgG (3+) deposition along the dermo-epidermal junction, intraepidermal IgG (1+) net-like deposition, particularly within the lower half of the epidermis was also seen (Fig. 4b). Serum sample was sent for indirect immunofluorescence analysis of the four skin-specific autoantibodies which were anti-BP180, anti-BP230, anti-desmoglein 1 and anti-desmoglein 3 antibodies. This patient was found to be positive for anti BP-230.

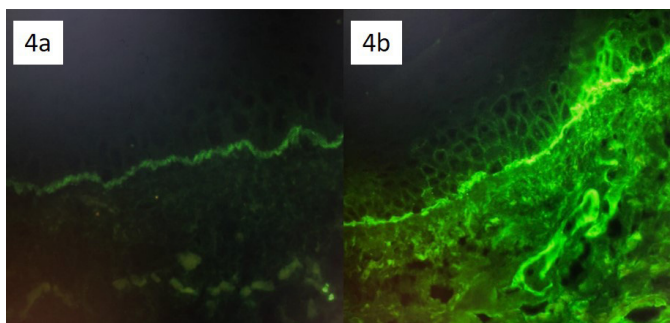


Fig.4: DIF study of a perilesional skin showed C3 (2+) deposition along the dermo-epidermal junction (Direct immunofluorescence stain, original magnification x 100) (Fig. 4a). DIF study of a perilesional skin showed IgG (3+) deposition along the dermo-epidermal junction as well as intraepidermal (1+) net-like deposition at the lower half of the epidermis (Direct immunofluorescence stain, original magnification x 100) (Fig. 4b).

The histological features together with the positive pattern of DIF study, particularly the combination of dermo-epidermal junction as well as intraepidermal immune deposit of IgG were in favour of PNBP. Furthermore, there was no interface dermatitis observed to support the possibility of bullous drug eruption. The patient was started on oral prednisolone 20mg once daily. Betamethasone 0.1% was also prescribed for topical application. The oral Sunitinib treatment was restarted. Patient had noticed a significant improvement of his skin lesions, and the rash as well as the blisters have not recurred since then.

DISCUSSION

Hand-foot syndrome (HFS) which is also known by a few other names such as palmo-plantar erythrodysesthesia, toxic erythema of the palms and soles and Burgdorf's reaction was first described in 1974 (4). It is a clinical manifestation of dermal toxicity which is associated with many oncologic or chemotherapy drugs. Clinical manifestations of this syndrome include skin reddening, blisters and hyperkeratotic changes which associated with pain, paraesthesia and dysaesthesia (4). Due to his known diagnosis of renal cell carcinoma on Sunitinib treatment, the diagnosis of HFS was initially made.

Bullous pemphigoid (BP) is the commonest presentation of autoimmune bullous skin disease. It is frequently seen in the elderly with average disease onset at 65 years old (1). Most BP cases are idiopathic without identified underlying cause. The 1-year mortality rate among these patients was reported to be between 19-38% (1). BP that were associated with internal solid malignancies were rarely reported and they were most likely to be part of the complex manifestation of paraneoplastic syndrome.

BP180 and BP230 hemidesmosomal proteins are identified as the target antigens in BP. Anti-BP180 antibodies are more commonly detected in BP patients. They are found early in the disease process and correlates well with the disease activity. Anti-BP230 antibodies on the other hand, are found in a smaller proportion of BP patients either with or without the presence of anti-BP180 antibodies. Although the exact pathogenic role of anti-BP230 autoantibodies is still unclear, it is reported that patients with BP230-type BP tends to have milder clinical presentations than BP180-type BP.

Paraneoplastic syndrome refers to non-metastatic metabolic or neuromuscular manifestations of certain malignancies and are not attributable to direct tumour invasion or compression, as well as distant spread of tumour cells (5). It can affect endocrine, neurologic, dermatologic, rheumatologic and haematologic systems. PNBP is associated more with the non-solid organ cancers than solid cancers such as breast, lung and squamous

cell carcinomas. However, PNBP in association with renal cell carcinoma is exceptionally rare with only a few cases being published (3). Management of PNBP consists of cancer-directed therapy plus standard treatment of its non-paraneoplastic counterpart.

In this patient, the diagnosis of PNBP was initially missed, and his oral chemotherapy agent was unnecessarily withheld despite the absence of a temporal association between the introduction of the chemotherapy agent and the onset of the lesions. This was because the clinical presentation mimicked the findings commonly found in HFS. Furthermore, emerging data has shown that Sunitinib, an oral multitargeted tyrosine kinase inhibitor is an important cause of HFS with rate of 10–28% (4). The onset of HFS in patients on Sunitinib however, typically occurs after 1-3 months of therapy commencement (4).

This patient had experienced pruritic and eczematous rash over his palms and feet for 3 months prior to the development of bullae, which was initially attributed to HFS. Although the classic presentation of BP is a widespread pruritic bullous eruption, a localised or generalised eczematous or urticarial eruption may precede formation of bullae by weeks to months (1). The patient had also been on Sunitinib for nearly 3 years prior to the rash onset, further making the diagnosis of HFS unlikely.

Fortunately, the timely skin biopsies, DIF and autoantibodies studies which are crucial in establishing the diagnosis were carried out. A correct diagnosis is important for initiating prompt management for this patient. In addition, the oral chemotherapy agent was restarted without a prolonged break.

CONCLUSION

This case highlights the need for clinicians to have a higher suspicion and utilise a broader approach in cases involving cancer patients on chemotherapy to reach a correct diagnosis. It is to ensure that patients receive the best care and proper treatment options available.

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