BULLOUS PEMPHIGOID ASSOCIATED WITH CARCINOMA OF THE RECTUM

Dr. Sai-Siong Wong,† MB Ch(Wales) MRCP(UK)
Senior Medical Officer
Dr. S Rajakulendran*, MB BS(Cey) FRCPA
Senior Medical Officer
Dr. E Chow, MBBS(HK) FRACP
Consultant Physician
Department of Medicine, Our Lady of Maryknoll Hospital,
Shatin Pass Road, Wong Tai Sin, Kowloon, Hong Kong
* Department of Pathology, Kwong Wah Hospital, Waterloo Road, Kowloon.

Summary

Bullous pemphigoid (BP) is an auto-immune blistering skin disorder of elderly people. We report a case of an 83-year-old male patient who developed bullous pemphigoid, eight months after he has had a curative resection for carcinoma of the rectum. There is debate regarding the association of malignant disease with bullous pemphigoid. We review the literature on the advances made in the pathogenesis and the treatment of bullous pemphigoid, and its relationship with malignancy.

Case Report

A 83-year-old man presented with a history of rapidly spreading blisters in the trunk and limbs. The blisters were preceded by a non-specific pruritic and urticarial rash for one week. There was no drug history of any relevance. Eight months prior to presentation, he underwent an uneventful abdominal-perineal resection for Duke’s B carcinoma of the rectum. There was no other relevant past medical history. He lives with his children and is physically active and independent. He managed the colostomy well with no complications. Two days prior to admission to hospital, the blisters erupted rapidly, spreading to the limbs and the colostomy site. He was subsequently admitted to the hospital for further management.

On admission to hospital, he was afebrile and had no systemic upsets. There were large, tense blisters scattered in the upper and lower limbs (Figure 1). The hands and feet were swollen with blisters (Figure 2). Large ruptured blisters were found in the abdomen surrounding the colostomy, leaving behind denuded patches of skin (Figure 3). The other area of the skin in the abdomen was free of any blisters. Nikolsky’s sign was negative. There were no oral or mucous membrane involvement. Physical examination of the other organ systems was otherwise unremarkable. There was no clinical evidence of infection or malignancy. A clinical diagnosis of bullous pemphigoid was made.

A skin biopsy of a blister in the upper arm revealed a portion of skin with subepidermal bulla formation (Figure 4). The bulla contained moderate amount of eosinophils. There was no acantholytic cells. The upper dermis showed...
Fig. 3  Ruptured bullae with denuded patches of skin around the colostomy.

Fig. 4  Lower power photomicrograph of the skin biopsy showing the subepidermal split.

Fig. 5  Immunofluorescence study of the perilesional skin biopsy showing linear deposit of C3 along the basement membrane zone.

Discussion

Bullous pemphigoid (BP) is an acquired, autoimmune blistering disease of elderly people, characterised by large tense, subepidermal bullae that are often found on the flexural areas of the limbs and on the central abdomen.1 The blisters are often preceded by non-specific urticarial and pruritic lesions. The possibility of pemphigoid should always be considered in the elderly patient with fixed erythematous lesions. Lever 2 first described BP in 1953 and Jordan et al 3 demonstrated circulating and tissue-bound autoantibodies directed against antigens of the basement membrane zone in 1967. The binding of BP autoantibodies to the cutaneous basement membrane zone was shown by the detection of C3 complement by direct immunofluorescence in 1973.4 However, recent rapid advances in molecular biology and cutaneous immunology have greatly enhanced our understanding of this bullous disorder. Two autoantigens, designated BP 180 and BP 230, which are 180 and 230 kilodalton proteins recognized by autoantibodies from patients suffering from BP, were found to be specifically localised to the epidermal hemidesmosome in 1990,5 nearly 40 years after Lever first described the skin disorder. Epidermal hemidesmosomes are attachment complexes at the basal keratinocyte-lamina lucida interface within the dermal-epidermal basement membrane zone which function to maintain basement membrane cohesion. These two autoantigens were subsequently cloned and mapped to human...
chromosomes 10 and 6 respectively in 1991. However, previous attempts to demonstrate the pathogenicity of patients autoantibodies have been unsuccessful until in 1993 when Liu et al demonstrated subepidermal blistering that resembled the human disease in an animal model, by the passive transfer of rabbit anti-BP 180 antibodies into neonatal mice. Two years later, they also demonstrated that anti-BP180 antibodies triggered subepidermal blistering in their animal model via complement activation. These findings provided more support for BP for being a disease triggered by the binding of anti-BP 180 antibodies to their target site in the hemidesmosome, resulting in local antibody-mediated activation of the complement system and the induction of a secondary inflammatory injury to the cutaneous basal membrane zone which leads to the loss of structural integrity of the skin and subsequent subepidermal vesiculation.

BP often runs a chronic, self-limiting course over months or years and is rarely fatal in elderly people. The mainstay of therapy is systemic corticosteroid, often in combination with other immunosuppressive agents such as azathioprine, gold, dapsone, cyclophosphamide in patients who cannot tolerate the side effects of systemic steroids or whose condition cannot be controlled on high dose corticosteroids. Systemic steroids with or without adjuvant therapy has considerable potential toxicity and morbidity especially in elderly patients with pre-existing medical problems. However, recent uncontrolled studies have indicated that alternative treatment like tetracyclines with nicotinamide was safe and effective in clearing the skin lesions of BP. Our patient responded and tolerated well to systemic steroids without the need of adjuvant therapy.

Our patient developed BP eight months after the rectal tumour was resected. Apart from blisters affecting the limbs, our patient also had blisters surrounding the colostomy site, with sparing of the skin on the rest of the abdomen. The peristomal blisters could have arisen as a result of tumour antigenic stimulation although there was no direct evidence of metastasis from the skin biopsies taken around the colostomy. Trauma inducing Koebner phenomenon is not likely as the phenomenon is not a feature of BP. The association between the autoimmune disease of BP and malignancy has been a subject of debate and controversy. Despite the many published case reports describing the association, a definite association was not found in some of the earlier controlled studies. However, such studies involved small number of patients and therefore lacked statistical power to detect an actual association between BP and malignancy. Of the more recent controlled study that involved large number of patients, the British case-control study involving 84 patients with BP reported a higher rate of malignant disease of 17.9% in BP patients, compared to 5.3% in the controls. A Swedish study involving 497 cases with anti-basement membrane antibodies, however, concluded that pemphigoid is not statistically associated with malignancy and that the association was based on age only. Evidence supporting the association between BP and malignancy came from the largest and the latest study from Japan which involved 1113 BP patients from 393 hospitals. The authors reported a significant increase in malignancy compared to the general population. The study showed that the association ratio of malignancy in BP (5.8%) was statistically and significantly higher than that of the controls aged over 70 years (0.61%). 50% of all these tumours involved the gastrointestinal tract. In this study, it was also found that the majority of BP (75.6%) occurred after malignancy in the BP patients associated with malignancy. The Swedish study also reported 59% of patients with BP associated malignancy developed the skin disease after malignancy (Table 1). It could be seen from these two studies that the majority (between two-thirds to three-quarters) of patients developed malignancy before the onset of BP and between one-third to a-quarter of patients developed malignancy in parallel with or after the development of BP. Of the patients (26.2%) who developed malignancy after the onset of BP in the Swedish study, the mean lag time to uncovering the malignancy was 2 years and 8 months (range 12 months-8 years). However, for patients where malignancy was already diagnosed before the BP, no information was available on tumour relapse or metastasis in these associated cases in both the Swedish and Japanese. From these data available, detailed clinical examinations and relevant investigations for malignancy for pa-

Table 1. Temporal correlation of BP and malignancy- comparison of two studies.

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<th>Swedish study13</th>
<th>Japanese Study14</th>
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<tr>
<td>BP preceded malignancy</td>
<td>16 (26.2%)</td>
<td>7 (15.6%)</td>
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<td>BP in parallel with malignancy</td>
<td>9 (14.8%)</td>
<td>4 (8.8%)</td>
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<tr>
<td>BP followed malignancy</td>
<td>36 (59%)</td>
<td>34 (75.6%)</td>
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<tr>
<td>Total number of cases</td>
<td>61 (100%)</td>
<td>45 (100%)</td>
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tients in whom BP developed before malignancy, at presentation and during subsequent follow-up for up to 3 years, will lead to the detection of tumours, some of which may be potentially treatable.

References

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“The ward was full, so I put him in my room as he was moribund and screaming and I did not want to wake the ward. I examined him. He had obvious gross bilateral crepitations and a severe pleural rub. I thought the latter was the cause of the pain and screaming. I had no morphia, just aspirin, which had no effect. I felt desperate. I knew very little Russian then and there was no one in the ward who did.”

“I finally instinctively sat down on the bed and took him in my arms, and the screaming stopped almost at once. He died peacefully in my arms a few hours later. It was not the pleurisy that caused the screaming, but loneliness. It was a wonderful education about the care of the dying. I was ashamed of my misdiagnosis and kept the story a secret.”

Quoted from the last page of Cochrane Collaboration on evidence-based medicine

Tak-Kwan Kong
Department of Geriatrics
Princess Margaret Hospital, Hong Kong