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CLINICAL VARIATIONS IN BULLOUS PEMPHIGOID WITH RESPECT TO EARLY SYMPTOMS

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Abstract. We report the clinical variations and the duration of prodromal symptoms in 20 patients with bullous pemphigoid. Nearly two-thirds of the patients had prodromal symptoms. The duration of the prodromal eruptions was up to 6 weeks if papular and/or urticarial and up to 2 years if eczematous, before the blisters appeared. Evidently longer prodromal periods were found in the present study than in earlier investigations. It is not known when in the course of the disease the direct immunofluorescence will be positive. Two of our patients were immunofluorescence-positive 1 and 2 weeks respectively before the blisters appeared. A common clinical manifestation in this study was vesicles on palms and/or soles. These eruptions, particularly as an early symptom, may cause misinterpretation in patients with bullous pemphigoid.

Key words: Bullous pemphigoid (BP); Clinical variations; Immunofluorescence (IF)

Bullous pemphigoid (BP) is a disease of the elderly which affects both sexes equally. Malignant disease has been described in association with BP (2, 10, 17) but several studies indicate that the association is probably coincidental, and only what can be expected at this age (3, 4, 8, 11, 16). BP is a chronic blistering disease that can persist for several years. The disease is characterized clinically by large tense bullae on normal or on erythematous skin; not uncommonly the erythema forms a whorled pattern. It is often forgotten that BP may start as a non-specific rash or an urticarial or eczematous eruption, which can last for a few weeks or even several months (15). Sometimes the blisters are initially localized to just one area, commonly the legs, or occur at the site of an earlier or a current skin lesion.

In addition to the clinical and histological picture, the diagnosis is usually established by using immunofluorescence (IF) techniques. Direct IF examination shows a linear deposition of IgG and/or C3, sometimes also IgA and/or IgM, along the basement membrane zone (BMZ). In 50–90% of BP patients, circulating anti-basement membrane zone antibodies can be detected.

The present investigation concerns the difficulties encountered in making an early, correct diagnosis of BP before bullae have appeared.

MATERIAL AND METHODS

During the last 3 years, 20 patients with a diagnosis of BP have been seen at the Department of Dermatology, Södersjukhuset, Stockholm. Most of the patients were hospitalized initially. The diagnosis was made on the basis of careful anamnesis, clinical examination, biopsy specimens for routine hematoxylin-eosin examination, and standard direct and indirect immunofluorescence staining procedures with commercially prepared fluorescein-conjugated antihuman IgG, IgA, IgM (Wellcome Research Laboratories, Beckenham, England) and C3 (Behringwerke AG, Marburg, W. Germany). Skin specimens were taken from affected areas of erythematous or urticarial skin and from vesicles and also from uninvolved skin.

The patients were divided into three groups according to the duration of the prodromal eruption before the true blistering eruption of BP occurred: (1) patients with prodromal symptoms of more than 3 months' duration, (2) patients with prodromal symptoms of less than 3 months' duration, and (3) patients without prodromal symptoms.

RESULTS

The results of the investigation are shown in Table I and II. Of the 20 patients, 8 were males and 12 females. Group 1 with prodromal symptoms of >3 months' duration consisted of 7 patients, group 2 with prodromal symptoms of <3 months' duration consisted of 5 patients and group 3 with no prodromal symptoms comprised 8 patients. There was a tendency to a lower mean age at which bullae occurred and the diagnosis of BP was made in group 1 (72 years) compared with group 3 (81 years). The main initial symptom of the patients in group 1 was an eczematous eruption. This eruption was localized in 2 patients, in case 3 around a colostomy

Table 1. *Summary of patient data relating to diagnosed cases of bullous pemphigoid*

	Case no.	Sex	Age when bullae occurred	Prodromal symptoms	Duration of prodromal symptoms	Vesicles on palms and/or soles
Group 1: prodromal symptoms >3 months	1	♂	63	Papular and eczematous eruption	2 (8?) years	Yes
	2	♀	73	Papular and eczematous eruption	>3 months	No
	3	♂	69	Eczematous eruption, initially localized around a colostomy	>3 months	Yes
	4	♂	69	Eczematous eruption	6 months	No
	5	♂	85	Eczematous eruption	9 months	Yes
	6	♀	68	Eczematous eruption, initially localized around a scar	4 months	Yes
	7	♀	75	Intertriginous eruption	>1 year	Yes
Group 2: prodromal symptoms <3 months	8	♀	77	Papular eruption	4 weeks	Yes
	9	♀	72	Papular, urticarial eruption	6 weeks	Yes
	10	♀	80	Papular, urticarial eruption	3 weeks	No
	11	♂	85	Papular eruption	1 month	Yes
	12	♂	74	Papular eruption	1 month	Yes
Group 3: no prodromal symptoms	13	♀	58	–	–	No
	14	♂	95	–	–	No
	15	♀	66	–	–	No
	16	♀	81	–	–	No
	17	♀	84	–	–	No
	18	♂	73	–	–	No
	19	♀	97	–	–	No
	20	♀	94	–	–	No

and in case 6 on a surgical scar. An intertriginous eruption was seen in one patient. Cases 1 and 2 presented with excoriated papules before the eczematous eruptions occurred. In contrast, in none of the patients in group 2 was BP manifested by eczematous prodromal symptoms. All patients in group 2 had instead urticarial and/or papular eruptions, which in some cases were initially misinterpreted as drug eruptions. In group 2 the prodromal urticarial and/or papular symptoms lasted from 3 to 6 weeks, whereas in group 1 the eczematous prodromal symptoms persisted from at least 3 months and up to 2 (8?) years before the bullae appeared.

On some occasion during the course of the disease 9 of the 12 patients with prodromal symptoms presented with blisters on hands and/or feet, mainly as small vesicles on the palms and soles. Two of the patients (cases 3 and 7) had this vesicular eruption on the hands and feet, before they got blisters at other sites. In these 2 patients the initial clinical picture on hands and feet was that of a vesicular eczema. None of the patients in group 3 were affected with vesicles on palms and/or soles.

All patients had a linear deposition of IgG and/or C3 along the BMZ, 3 patients (cases 2, 3 and 16) had in addition a linear deposition of IgA. In 13 of the 20 patients, anti-basement membrane zone antibodies were found in the sera.

Only one of the 20 patients (case 18) also suffered from a neoplastic disease.

CASE REPORTS

Case 1

A man, born in 1917, developed pruritic papules on legs, arms and on the trunk in 1972. The itching was intense and antihistamines and dapsone were tried, without effect. The patient gradually healed with topical steroid application and was then almost, but not totally, free of symptoms for 5 years. In 1978, he came again to a dermatological department, with severe itching and widespread papules. Histopathology was uncharacteristic. IF study was negative but was only made on uninvolved skin. The patient was hospitalized and almost healed with topical steroid treatment. A clinical diagnosis of eczema was made. Soon thereafter, the disease again became exacerbated and he suffered a generalized eruption of papules 1 cm in diameter and eczematous patches. His pruritus was intense and difficult to treat. PUVA treatment was planned, but not started, when in 1980 the patient suddenly developed blisters 0.5–2 cm in diameter on both normal and erythematous skin. The biopsy specimens from involved skin (vesicle and erythema) showed linear IgG and C3 along the BMZ, but he had a negative indirect IF test.

Table II. *Immunofluorescence data*

Case no.	Direct IF	Indirect IF
1	IgG, C3	Negative
2	IgG, IgA, C3	1/160
3	IgG, IgA, C3	1/160
4	C3	1/80
5	IgG, C3	1/40
6	IgG, C3	Negative
7	IgG, C3	Negative
8	IgG, C3	1/160
9	IgG, C3	1/40
10	IgG, C3	Negative
11	IgG, C3	1/160
12	IgG	1/160
13	C3	Negative
14	IgG	1/160
15	C3	1/40
16	IgG, IgA, C3	1/80
17	IgG, C3	Negative
18	IgG, C3	Negative
19	IgG, C3	1/40
20	IgG, C3	1/320

Case 2

A woman, born in 1907, had suffered from recurrent attacks of eczema over the last 20 years and had been hospitalized once, in 1960. In February 1980 she came to our department with a one-month history of generalized pruritus and excoriated papules, mostly on the legs. In March there was progression with a nummular eczematous eruption on the lower extremities and on the back and excoriations in the scalp. At the end of April the patient developed a few blisters 0.3–1 cm in diameter on the breasts and on the arms. The patient also had small grouped papules on the extensor aspects of the arms and on the knees. On the basis of the clinical features, dermatitis herpetiformis was suspected. A biopsy specimen showed papillary neutrophilic microabscesses. Direct IF showed a linear deposition of IgG, IgM, IgA and C3 along the BMZ in involved and perilesional skin. Circulating IgG antibodies to the BMZ were found in a titre of 1 : 160. A diagnosis of a polymorphic variant of BP was made on the basis of the clinical and immunofluorescence features. The patient was treated with dapsone and improved initially. The disease then flared up again and the patient was treated with a combined regime of dapsone and prednisone. A new biopsy specimen showed only a linear deposition of C3 and IgG but not of IgA.

Case 3

A 71-year-old man with a colostomy developed an eczematous irritation around the stoma. After 3 weeks he suffered an exacerbation with an eczematous eruption on the body. He was hospitalized and successfully treated with topical steroids. Three months later again contracted eczema around the stoma, and vesicles on the palms and soles. He had intense itching and did not heal on topical treatment. After some weeks he had an eczematous flare-up and also vesicles and bullae on the body. Direct IF showed a linear deposition of IgA, IgG and C3 and indirect IF was positive to a titre of 1 : 160.

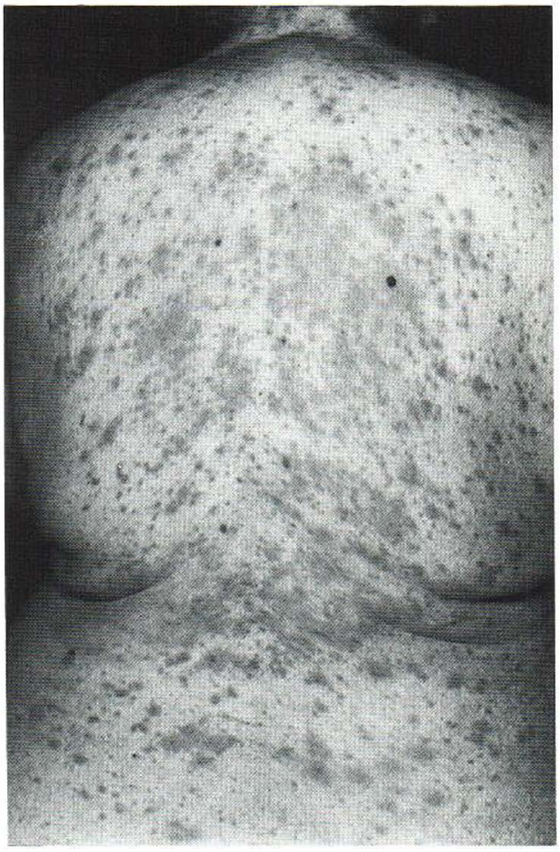

Fig. 1. Patient with a papular and urticarial prodromal eruption.

DISCUSSION

Sneddon et al. (15) have stated that BP commonly starts with a non-specific rash which may be urticarial or, occasionally, eczematous and that this rash, if urticarial, may last 1–3 weeks and if eczematous, 2–3 months before formation of bullae occurs. This is partly in accordance with the results of this study. Nearly two-thirds of the patients had prodromal symptoms, but the duration of the prodromal eruption was up to 6 weeks if papular or urticarial, and up to 2 years (or even more) if eczematous, before the true blistering eruption of

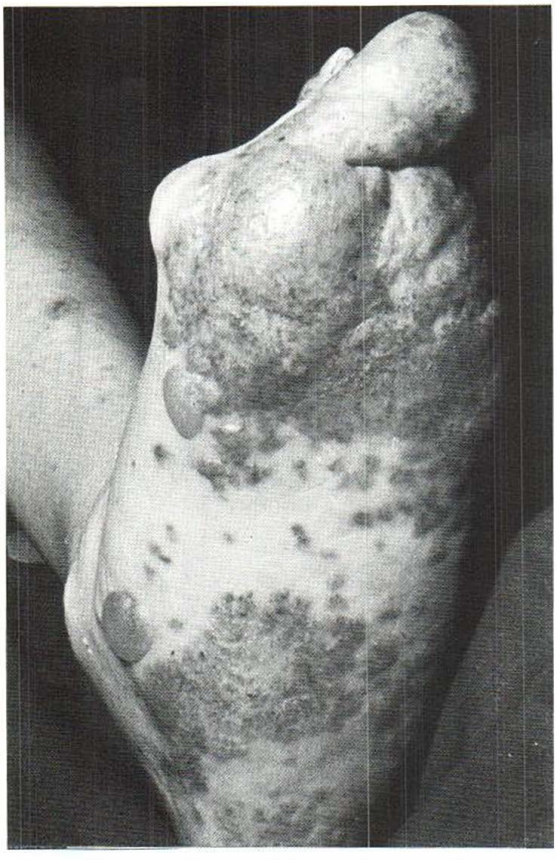

Fig. 2. Patient with an initial vesicular eruption on the soles, in which bullae also have now appeared.

BP appeared. About one-third of the patients had a prodromal duration of more than 3 months. Evidently much longer prodromal periods were found in this study in most of the patients than in earlier descriptions. To our knowledge the frequency of prodromal symptoms in BP has not been studied before. Others have described BP and eczematous skin changes (5) and BP and psoriasis or psoriasiform dermatosis (12). It seems possible that at least some of these patients could tally with our group 1 patients with eczematous prodromal symptoms.

Nearly half of the patients in the present study had vesicles on palms and/or soles, all of whom had prodromal symptoms. Accordingly among these somewhat younger patients with an eczematous or unspecific eruption initially, palmar and/or plantar vesicles were a rather common manifestation, one to which generally, perhaps, little attention is paid when multiple bullae are also present, and the diagnosis of BP clear-cut. Yet, these vesicular eruptions as an initial symptom may lead to misinterpretation or be interpreted as a second diagnosis in patients with BP. Vesicular pemphigoid has been described by Bean and co-workers (1), while other investigators (6, 7) have described patients with so-called polymorphic pemphigoid with clinical, histopathological and therapeutic features of both dermatitis herpetiformis and BP, but none of the patients they described had vesicles on hands or feet. However, in a few case reports (9, 12, 13, 14), vesicles on hands and feet are recorded.

BP should always be considered in elderly and perhaps even middle-aged patients with an uncharacteristic eczematous, papular or urticarial eruption and these patients ought to be studied with repeated immunofluorescence examinations. It is not known how long before the bullous eruption, when the patient has only an uncharacteristic dermatitis, the direct immunofluorescence findings will be positive. In the present study 2 patients with papular eruptions were IF-positive 1 and 2 weeks respectively before the blisters appeared.

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