Acta Derm Venereol (Stockh) 1984; 64: 316–319

Bullous Pemphigoid and Malignancy: Relationship to Indirect Immunofluorescent Findings

PIERRE Y. VENENCIE,* ROY S. ROGERS III, and ARNOLD L. SCHROETER

Department of Dermatology, Mayo Clinic and Mayo Foundation, Rochester, Minnesota, USA

Venencie PY, Rogers RS III, Schroeter AL. Bullous pemphigoid and malignancy: Relationship to indirect immunofluorescent findings. Acta Derm Venereol (Stockh) 1984; 64: 316–319.

In a group of 93 patients with generalized bullous pemphigoid seen at the Mayo Clinic from 1970 to 1980, the frequency of concomitant malignancies did not appear to be higher than in the general population or in previously reported series from the Mayo Clinic. However, the subgroup with negative indirect immunofluorescent tests had an unexplained higher frequency of malignancy (4/28) than the subgroup with positive immunofluorescent tests (5/65). *Key words*: *Bullous pemphigoid*; *Malignancy*; *Indirect immunofluorescent test*. (Received October 5, 1983.)

R. S. Rogers III, Mayo Clinic, 200 First Street SW, Rochester, MN 55905, USA.

Bullous pemphigoid has been reported in association with malignancies of the urinary tract, lung, genitalia, breast, pancreas, gastrointestinal tract, skin, and lymphoreticular system (1). The significance of such an association is controversial. Using patients with contact dermatitis and psoriasis as control groups, Stone & Schroeter (1) did not find a higher frequency of malignancies in patients with bullous pemphigoid. Ahmed, Maize & Provost (2) also did not find an increased incidence of malignant neoplasms in their patients with bullous pemphigoid. However, Chorzelski et al. (3) found that the frequency observed in their group of patients with bullous pemphigoid was higher than that expected in the general population. In 1979, Savin (4), in reviewing the events leading to the deaths of patients with pemphigoid, did not find evidence for such an association.

Person & Rogers (5), after reviewing the patients with bullous pemphigoid seen at the Mayo Clinic from 1968 to 1975, suggested that patients with negative indirect immunofluorescent findings had a higher frequency of malignancy than those with positive findings. Recently, a similar result has been reported by Hodge et al. (6). To reevaluate this hypothesis, the records of patients with bullous pemphigoid seen at the Mayo Clinic from 1970 to 1980 were reviewed for their clinical, histologic, and immunofluorescent findings.

MATERIALS AND METHODS

A total of 93 patients with generalized bullous pemphigoid were seen at the Mayo Clinic from 1970 to 1980. The diagnosis of bullous pemphigoid was based on classic clinical and histopathologic criteria (7) in 86 cases. The other seven cases had compatible clinical findings and a positive indirect immunofluorescent test. In 61 cases, the diagnosis of bullous pemphigoid was reinforced by a positive direct immunofluorescent test of the skin.

The immunofluorescent studies were performed and interpreted according to Beutner and Nisengard (8), with a titer of 1 : 20 or greater being considered a positive indirect immunofluorescent test.

Control groups conforming to the heterogeneity of age, duration of follow-up, and geographic origin were not available for statistical comparison.

* Dr Venencie is a visiting clinician from the Clinique Dermatologique, Hôpital St. Louis, Paris, France.

RESULTS

Of the 93 patients, 46 were men, 47 were women, and 17 (18%) had oral involvement (Table I). Their ages at the onset of bullous pemphigoid varied from 21 to 89 years (mean 63.5), and the duration of follow-up varied from 1 to 15 years.

The indirect immunofluorescent test was positive in 65 cases (70%) and negative in 28 (30%). In terms of age at onset of the bullous pemphigoid, the two groups were virtually indistinguishable from each other. The frequency of oral involvement was higher in the patients with negative serologic findings (25%) than in the patients with positive serologic findings (15%), but the difference was not statistically significant. The percentage of females was higher in the patients with negative serologic findings (57%) than in the patients with positive serologic findings (46%), but this difference also was not statistically significant.

Of the 93 patients, 9 (9.7%) had histories of malignancy or malignancy developed during follow-up (Table II). Of these nine patients, five had a positive indirect immunofluorescent test and four had a negative test. The malignancy was diagnosed in five patients (cases 2, 3, 4, 5 and 6) before the development of the pemphigoid and in four patients (cases 1, 7, 8 and 9) after the development of the pemphigoid. In cases 2, 3, 4 and 6, the bullous pemphigoid began more than 5 years after a malignancy was treated surgically in cases 2, 3 and 4 and with diethylstilbestrol in case 6. In case 5, bullous pemphigoid developed 1 year after surgery for a left hypernephroma.

In case 1, an adenocarcinoma of the prostate was diagnosed 1 year after the onset of bullous pemphigoid was treated with corticosteroids and azathioprine. Surgical treatment of the adenocarcinoma was followed by resolution of the bullous pemphigoid, and the patient has been free of both tumor and skin lesions for 2 years while receiving no treatment. In case 7, a non-Hodgkin malignant lymphoma was discovered 3 years after the onset of bullous pemphigoid that had been treated with only topical corticosteroids. In case 8, an adenocarcinoma of the left breast was discovered 1 year after the onset of bullous pemphigoid that had been treated with systemic corticosteroids. No improvement of the bullous pemphigoid occurred during the 2 years after surgery. In case 9, a squamous cell carcinoma in situ of the uterine cervix was discovered 2 years after the onset of bullous pemphigoid that had been treated with systemic corticosteroids. Nine years after this discovery, the patient was still alive, the bullous pemphigoid still required control with azathioprine and systemic corticosteroids, and the tumor had not recurred after conization.

Table I. *Patients with bullous pemphigoid and malignancy and relationship to indirect immunofluorescent findings*

	No. of patients		
	Total	Seropositive	Seronegative
Indirect immunofluorescence	93 (100%)	65 (70%)	28 (30%)
Males	46	34	12
Females	47	31	16
Oral involvement	17 (18%)	10 (15%)	7 (25%)
Age			
Range	21–89 yr	21–89 yr	25–87 yr
Mean	63 yr	64 yr	62 yr
With malignancy	9 (9.7%)	5 (7.7%)	4 (14.3%)

COMMENT

The finding of positive indirect immunofluorescence in 70% of the patients is in accord with previous studies (2, 5, 6, 9).

In our series, the percentage of females was higher in the group with negative serologic findings (57%) than in the seropositive group (46%), although the difference was not statistically significant. Hodge et al. (6) reported a higher percentage of males in their seronegative group.

The higher percentage, although not statistically significant, of patients with oral involvement in the seronegative (25%) than in the seropositive (15%) group is in accord with previous studies (5, 6).

The relationship between bullous pemphigoid and malignancy is unlikely in cases 2, 3, 4, 6, 7 and 9 because the intervals between the two diseases were longer than 1 year and in case 5 because the bullous pemphigoid was noted 1 year after operation for hypernephroma, at which time there was no evidence of recurrence of the tumor.

In two patients, a relationship could not be excluded, because the prostatic adenocarcinoma in one (case 1) and the breast adenocarcinoma in the other (case 8) could have been overlooked at the onset and because the bullous pemphigoid resolved after the surgical treatment of the prostatic adenocarcinoma in case 1. In one patient described by Hodge et al. (6), the removal of a recurrent gastric carcinoma was followed by clearing of the skin lesions. However, there was no skin improvement in case 8 after the surgical treatment of the breast carcinoma. Thus, there was a suggestion of a relationship between bullous pemphigoid and malignancy in only 1 of the 93 cases in our series.

Of the patients with bullous pemphigoid and malignancy by history or follow-up, the frequency of such an association was higher in patients with negative indirect immunofluorescent findings (14.3%) than in patients with positive findings (7.7%). Because of the small numbers of these two subgroups, this difference was not statistically significant. Such results are in accord with the previous studies of Person & Rogers (5) and Hodge et al. (6). The latter authors accepted a relationship only if the bullous pemphigoid and malignancy occurred within a 6-month period. In their series, 23% of the subgroup with negative indirect immunofluorescent findings had a concurrent malignancy, compared with only 4% of their subgroup with positive findings (statistically significant difference).

Table II. *Characteristics of patients with bullous pemphigoid and malignancy*

Case	Sex	Indirect IF test[a]	Age at onset (yr)		Malignancy
			Of bullous pemphigoid	Of malignancy	
1	M	1:40	81	82	Adenocarcinoma of prostate
2	F	1:60	73	41/65	Adenocarcinoma of rectum and carcinoma of thyroid
3	M	1:640	73	66	Adenocarcinoma of rectum
4	M	1:640	64	53	Adenocarcinoma of colon
5	M	1:1280	78	77	Hypernephroma
6	M	Negative	83	78	Adenocarcinoma of prostate
7	M	Negative	77	80	Lymphoma
8	F	Negative	75	76	Adenocarcinoma of breast
9	F	Negative	42	44	Squamous cell carcinoma (in situ) of uterus

[a] IF = Immunofluorescent.

The higher frequency of malignancy in the seronegative group with bullous pemphigoid is unexplained. In our series, it does not appear to be related to previous treatment received for bullous pemphigoid or for the malignancy or to the ages of the patients. Interestingly, Hodge et al. (6) suggested that patients with malignancy and negative indirect immunofluorescent tests have a poorer prognosis than patients with malignancy and positive indirect immunofluorescent tests, a finding that we cannot confirm from review of our patients.

In our series, no clear relationship between bullous pemphigoid and malignancy was found; however, despite the small number of patients with malignancy by history, concomitantly, or by follow-up, a correlation between negative indirect immunofluorescent findings and malignancy is suggested.

REFERENCES

1. Stone SP, Schroeter AL. Bullous pemphigoid and associated malignant neoplasms. Arch Dermatol 1975; 111: 991–994.
2. Ahmed AR, Maize JC, Provost TT. Bullous pemphigoid: clinical and immunologic follow-up after successful therapy. Arch Dermatol 1977; 113: 1043–1046.
3. Chorzelski TP, Jablonska S, Maciejowska E, Beutner EH, Wronkowski L. Coexistence of malignancies with bullous pemphigoid (letter to the editor). Arch Dermatol 1978; 114: 964.
4. Savin JA. The events leading to the death of patients with pemphigus and pemphigoid. Br J Dermatol 1979; 101: 521–534.
5. Person JR, Rogers RS III. Bullous and cicatricial pemphigoid: clinical, histopathologic, and immunopathologic correlations. Mayo Clin Proc 1977; 52: 54–66.
6. Hodge L, Marsden RA, Black MM, Bhogal B, Corbett MF. Bullous pemphigoid: the frequency of mucosal involvement and concurrent malignancy related to indirect immunofluorescence findings. Br J Dermatol 1981; 105: 65–69.
7. Lever WF. Pemphigus and pemphigoid: a review of the advances made since 1964. J Am Acad Dermatol 1979; 1: 2–31.
8. Beutner EH, Nisengard RJ (eds). Defined immunofluorescence in clinical immunopathology. In: Immunopathology of the Skin: Labeled Antibody Studies (eds. E. H. Beutner, T. P. Chorzelski, S. F. Bean, R. E. Jordon), pp. 197–247. Dowden, Hutchinson & Ross, Stroudsburg, Pennsylvania, 1973.
9. Tuffanelli DL. Cutaneous immunopathology: recent observations. J Invest Dermatol 1975; 65: 143–153.