Risk factors for death and survival in paraneoplastic pemphigus associated with hematologic malignancies in adults

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Background: Paraneoplastic pemphigus (PNP) occurs more often in patients with hematologic malignancies (HMs) than in patients with solid cancer. Lung bronchiolitis obliterans (BO) is a severe complication of PNP.

Objective: To determine the precise clinical and biologic features of HM-associated PNP and identify factors associated with mortality and survival.

Methods: Systematic review of previously described cases of PNP associated with HMs.

Results: A total of 144 patients were included. The HMs were non-Hodgkin lymphoma (52.78%), chronic lymphocytic leukemia (22.92%), Castleman disease (18.60%), and other underlying hematologic malignancy (5.70%). The mortality rate was 57%, and most deaths occurred within the first year after the diagnosis of PNP. Multivariate analysis showed that (1) the presence of antienvoplakin antibodies and BO were significantly associated with death, and (2) a toxic epidermal necrolysis–like clinical pattern, bullous pemphigoid–like clinical pattern, and BO were significantly associated with decreased survival.

Limitation: Only case reports with sufficient mortality data were included.

Conclusion: PNP associated with HM has a high mortality rate. The toxic epidermal necrolysis–like and BO-associated forms are independent survival factors in PNP associated with HMs. (J Am Acad Dermatol 2019;80:1544-9.)

Key words: bullous pemphigoid; Castleman disease; lymphoma; pemphigus.

Paraneoplastic pemphigus (PNP) is an autoimmune blistering skin disease associated with cancer that has various clinical presentations: lichen planus–like, pemphigus vulgaris–like, bullous pemphigoid (BP)-like, erythema multiforme–like, toxic epidermal necrolysis (TEN)-like, and chronic graft-versus-host disease–like.[1] Skin or mucosal biopsy samples of PNP usually show a lichenoid pattern and/or patterns seen in autoimmune blistering skin diseases such as acantholysis, vacuolar degeneration of basal cells, keratinocyte necrosis, and subepidermal and/or epidermal cleft.[2] The mechanism of PNP involves humoral and cellular autoimmunity,[3] including an "epitope spreading" phenomenon with multiple antigen targets in the epidermis and the basal layer that is

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associated with various clinical presentations.[4] After its first description in 1990 by Anhalt et al, diagnostic criteria to assess PNP were defined.[2] They include the presence of a painful, progressive stomatitis and a polymorphous cutaneous eruption; histologic features of acantholysis or lichenoid or interface dermatitis; direct immunofluorescence—demonstrated deposition of IgG and complement in the epidermal intercellular spaces; serum autoantibodies that bind the cell surface of skin and mucosae in a pattern typical for pemphigus; and serum autoantibodies against desmogleins 1 and 3, as well as against members of the plakin family of epithelial proteins. PNP occurs more often in patients with hematologic malignancies (HMs), especially B-cell lymphoproliferative disorders, than in patients with solid cancer.[1,5] Lung bronchiolitis obliterans (BO) is a usual complication of PNP, and it can be lethal. PNP has a high mortality rate.[6,7] We aimed to accurately define PNP associated with HMs and identify possible clinical and biologic factors associated with mortality through a systematic review of previously described cases.

CAPSULE SUMMARY

- Paraneoplastic pemphigus (PNP) may be associated with hematologic malignancies (HMs).
- HMs associated with PNP are mostly non-Hodgkin lymphoma, chronic lymphocytic leukemia, and Castleman disease.
- The survival rate of PNP associated with HMs is low. Toxic epidermal necrolysis–like PNP and PNP associated with bronchiolitis obliterans have an especially poor prognosis.

MATERIAL AND METHODS

We used the key word *paraneoplastic pemphigus* to search the National Library of Medicine's MEDLINE database (Bethesda, MD) for relevant case reports in the English and French literature that were published from 1990 to 2016. The following criteria were used to select the cases: PNP meeting the Anhalt criteria[2]; HMs associated with PNP; adult patients; biopsy-proven HMs; clinical, histologic and immunologic characterization of the PNP; and available data on mortality and cause of mortality. Data were presented as medians (interquartile ranges) or numbers (percentages). Mortality rates were analyzed first by using logistic regression models. In patients with available follow-up or survival times, Kaplan-Meier estimates of survival from diagnosis of PNP were plotted and then compared across baseline groups by using the log-rank test. Multivariable logistic or Cox proportional hazards regression models that included covariates with *P* values less than .05 from univariable analyses were used to summarize prognostic information on

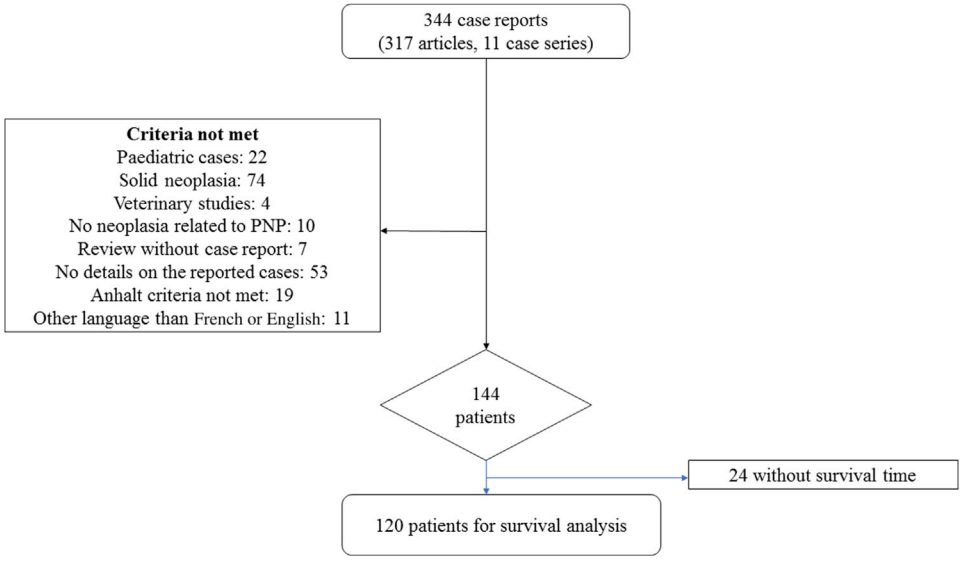

Fig 1. Flowchart of patient selection. *PNP*, Paraneoplastic pemphigus.

Abbreviations used:

BO: bronchiolitis obliterans
BP: bullous pemphigoid
CI: confidence interval
HM: hematologic malignancy
HR: hazard ratio
OR: odds ratio
PNP: paraneoplastic pemphigus
TEN: toxic epidermal necrolysis

mortality or survival, respectively—both with model selection based on a backward stepwise selection procedure. The strength of association between covariates and the outcome were measured by odds ratios (ORs) or hazard ratio (HRs) with 95% confidence intervals (CIs).

Significance was defined by 2-sided *P* values less than .05. All statistical analyses were performed with SAS software (SAS Institute Inc, Cary, NC), R software (https://www.R-project.org/), and GraphPad Prism software (version 5.0, GraphPad Software, La Jolla, CA).

RESULTS

Patient selection and general characteristics

A total of 144 patients were included for the mortality rates; they included 120 patients for whom survival data could be analyzed (see the flowchart in Fig 1). Patient characteristics are summarized in Tables I-VII. The mean patient age was 58 years (48-68), with 44.4% of patients being female. Clinical patterns were available for 76 patients (Table II), accurate histologic parameters were available for 137 patients (Table III), direct immunofluorescence data for 129 patients (Table IV), indirect immunofluorescence data for 112 patients (Table V), antigen targets (enzyme-linked immunosorbent assay or immunoblotting) for 112 patients (Table VI), and disease evolution criteria for 144 patients (Table VII). The HMs were non-Hodgkin lymphoma (n = 76 [52.8%]); chronic lymphocytic leukemia (n = 33 [22.9%]); Castleman disease (n = 26 [18.1%], including 24 unicentric and 2 multicentric cases); mastocytosis (n = 1 [0.7%]); Hodgkin lymphoma (n = 1 [0.7%]); and monoclonal gammopathy of undetermined significance, multiple myeloma, or Waldenström gammopathy (n = 7 [4.9%]). Oral involvement was present in the majority of patients (n = 133 [92.4%]). Acantholysis was the most frequent histologic pattern described (n = 86 [62.7%]), and subepidermal blister was less frequent (n = 13 [9.5%]). Envoplakin, periplakin, and desmoplakin were the most frequent antibody-targeted antigens (n = 81 [72.3%], n = 76 [67.9%], and n = 49 [43.7%], respectively). BO was present in 37 patients (25.7%). Relapse of HM was reported for 29 patients (20.1%) and relapse of PNP was reported for 30 patients (20.8%).

Table I. General characteristics of the 144 patients

Characteristic	No. or mean	% or IQR
Age	58	48-68
Sex		
F	64	44.4%
M	80	55.6%
Hematologic malignancies		
CLL	33	22.9%
NHL	76	52.8%
HL	1	0.7%
CD	26	18.1%
Mastocytosis	1	0.7%
Monoclonal gammopathy	7	4.9%

CD, Castleman disease; *CLL*, chronic lymphocytic leukemia; *F*, female; *HL*, Hodgkin lymphoma; *IQR*, interquartile range; *M*, male; *NHL*, non-Hodgkin lymphoma.

Table II. Clinical characteristics of the 144 patients

Settings	n (%)
Skin involvement	128 (88.9%)
Lichen planus–like	37 (25.7%)
GVHD-like	4 (2.8%)
BP-like	3 (2.1%)
VP-like	15 (10.4%)
Erythema multiforme–like	17 (11.8%)
TEN-like	17 (11.8%)
No pattern described	68 (47.2%)
Oral involvement	133 (92.4%)
Genital involvement	47 (32.6%)
Anal involvement	12 (8.3%)
Eye involvement	72 (50%)
ENT involvement*	28 (19.4%)
Extremities	71 (49.3%)
Blisters	91 (63.6%)

Two or sometimes 3 clinical patterns could be described for 1 patient.
BP, Bullous pemphigoid; *ENT*, ear, nose, and throat (involvement of the pharynges or epiglottis); *GVHD*, graft-versus-host disease; *TEN*, toxic epidermal necrolysis; *VP*, vulgaris pemphigus.
*ENT involvement indicates involvement of the pharynges or epiglottis.

Factors associated with mortality and survival time

A total of 82 patients (57%) died. The main cause of death was "general" for 37 patients (sepsis and alteration of general condition), BO for 28 patients, PNP without BO (extended skin or mucosal involvement) for 16 patients, and HM for 11 patients. Factors associated with increased mortality in univariate

Table III. Histologic characteristics of the 137 patients with available data

Characteristic	n (%)
Intraepidermal blister	59 (43.1%)
Subepidermal blister	13 (9.5%)
Acantholysis	86 (62.7%)
Keratinocyte necrosis	69 (50.4%)
Basal cell degeneration	45 (32.8%)
Lichenoid infiltrate	74 (54.0%)

Multiple histologic patterns are often seen in 1 patient, which is common in paraneoplastic pemphigus.

Table IV. Results of DIF of skin biopsy samples from the 129 patients with available data

Indicator	n (%)
IgG	108 (83.7%)
C3	92 (71.3%)
C1q	5 (3.8%)
IgM	11 (8.5%)
IgA	9 (7.0%)
Intercellular only*	41 (31.8%)
Linear only*	6 (4.6%)
Linear and intercellular*	71 (55.0%)
Negative DIF	11 (8.5%)

C1q, Component q of fraction 1 of the complement deposits; *C3*, fraction 3 of the complement deposits; *DIF*, direct immunofluorescence analysis.
*Intercellular indicates deposits that are localized between keratinocyte in the epidermis following desmosome formation, and linear indicates deposits that are localized along the basal membrane following hemidesmosome, lamina densa, or lamina lucida.

Table V. Results of IIF of samples from the 112 patients with available data

Settings	n (%)
Rat bladder	94 (83.9%)
ICS only	66 (58.9%)
BMZ only	4 (3.6%)
ICS and BMZ	12 (10.7%)
IIF negative	8 (7.1%)

Depending on the case reported, the substrates for IIF were mostly monkey esophagus, monkey bladder, rat bladder, and sometimes a combination thereof.
BMZ, Basal membrane zone antibody; *ICS*, intercellular substance antibody; *IIF*, indirect immunofluorescence.

analysis were absence of intraepidermal blister, presence of antienvoplakin antibodies, presence of antiperiplakin antibodies, and presence of BO. The following criteria remained significantly associated with death in the multivariate logistic model: presence of antienvoplakin antibodies (OR, 5.6; 95% CI, 1.2-25.8; $P = .027$) and BO (OR, 5.4; 95% CI, 1.7-16.9; $P = .0034$).

Table VI. ELISA and immunoblot results for the 112 patients with data available

Settings	n (%)
BP 180 (180 kD)	8 (7.1%)
BP 230 (230 kD)	38 (33.9%)
Dsg1 (160 kD)	21 (18.7%)
Dsg3 (130 kD)	45 (40.2%)
Alpha-2-macroglobulin like 1 (170 kD)	22 (19.6%)
Periplakin (190 kD)	76 (67.9%)
Laminin 3-3-2	2 (1.8%)
Collagen VII α chain (290 kD)	2 (1.8%)
Desmocollin	5 (4.4%)
Envoplakin (210 kD)	81 (72.3%)
Desmoplakin (250 kD)	49 (43.7%)

BP, Bullous pemphigoid; *Dsg*, desmoglein; *ELISA*, enzyme-linked immunosorbent assay.

Table VII. Evolution and outcome of the 144 patients

Outcome	n (%)
BO	37 (25.7%)
Relapse PNP	30 (20.8%)
Relapse HM	29 (20.1%)
Death	82 (56.9%)
Death subsequent to BO	28/82 (34.1%)
Death subsequent to PNP	16/82 (19.5%)
Death subsequent to HM	11/82 (13.4%)
Death subsequent to other causes	37/82 (45.1%)

Relapse PNP is defined as relapse of paraneoplastic pemphigus during patient follow-up; relapse HM is defined as relapse of HM during patient follow-up; and other causes include causes other than bronchiolitis obliterans, hematologic malignancy, and paraneoplastic pemphigus.
BO, Bronchiolitis obliterans; *HM*, hematologic malignancy; *PNP*, paraneoplastic pemphigus.

The 1-year survival rate was 62.4% (95% CI, 53.8-72.4). Survival outcome is depicted in Fig 2, *A*. The factors associated with decreased survival in univariate analysis were BP-like pattern (Fig 2, *B*), TEN-like pattern (Fig 2, *C*), BO (Fig 2, *D*), and antienvoplakin (Fig 2, *E*). The following criteria remained significantly associated with survival in a multivariate Cox model: TEN-like pattern (HR, 5.31; 95% CI, 2.6-10.8; $P < .001$), BP-like pattern (HR, 6.1; 95% CI, 1.30-28.6; $P = .022$), and presence of BO (HR, 2.12; 95% CI, 1.14 to 3.93; $P = .018$).

DISCUSSION

Our study is, to our knowledge, the first review from 1990 (the first description of PNP) to 2016

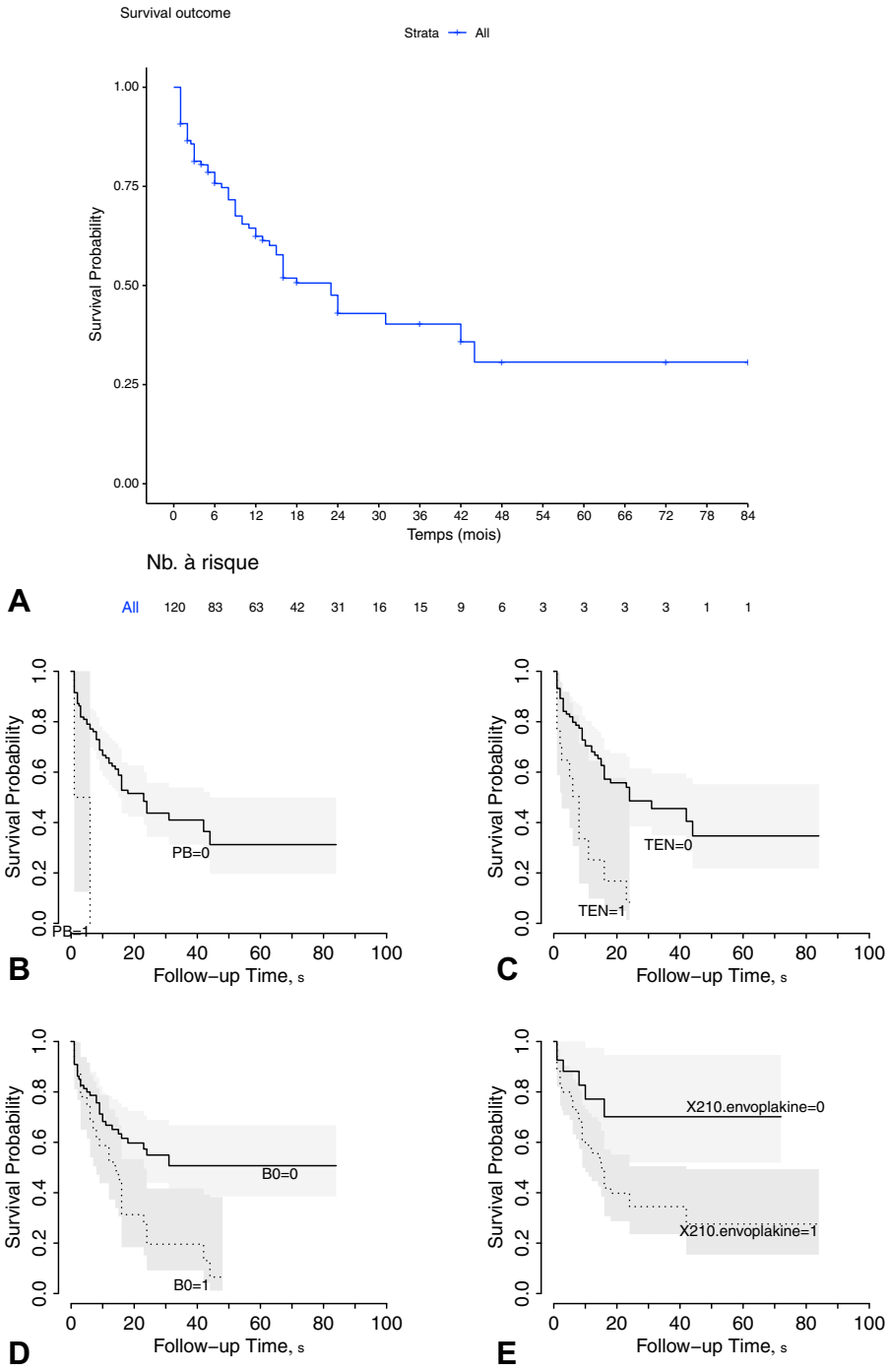

Fig 2. A, Kaplan-Meier probabilities of overall survival in 120 patients with paraneoplastic pemphigus. **B**, Probabilities of overall survival in patients with paraneoplastic pemphigus according to the presence or absence of a bullous pemphogoid (BP)-like pattern. **C**, Probabilities of overall survival in patients with paraneoplastic pemphigus according to the presence or absence of a toxic epidermal necrosis (TEN)-like pattern. **D**, Probabilities of overall survival in patients with paraneoplastic pemphigus according to the presence or absence of bronchiolitis obliterans (BO). **E**, Probabilities of overall survival in patients with paraneoplastic pemphigus, according to the presence or absence of antienvoplakin antibodies. *P* values have been estimated by using the log-rank test.

concerning PNP associated with HMs that analyzed prognostic factors by using either prevalence of death or survival time as the end point. A French retrospective study of 50 patients analyzed HMs and solid neoplasms (carcinoma and sarcoma) and defined an erythema multiforme–like clinical pattern and skin necrosis in histologic samples (possibly seen in TEN-like PNP) as possible poor prognostic factors.[6] The following 4 factors were independently associated with mortality and/or decreased survival in our study: presence of anti-envoplakin antibodies, BO, TEN-like clinical pattern, and BP-like clinical pattern. In mouse studies, envoplakin appeared to be a crucial protein for skin integrity and survival.[8] BO has already been described as a poor prognostic factor in PNP.[9,10] Cases of TEN-like PNP are often severe,[11] but a TEN-like clinical pattern has not yet been studied as an independent survival factor. A BP-like clinical pattern was associated with death in our study. However, only 3 patients had BP-like PNP (the 3 of them died rapidly), making it difficult to draw firm conclusions. To summarize, the rate of survival of PNP associated with HM is low. TEN-like PNP and PNP associated with BO are particularly severe.

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