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

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1 Risk factors for death and survival in paraneoplastic pemphigus associated with
2 haematological malignancies in adults

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25

26 **Capsule summary**

- 27 • Paraneoplastic pemphigus (PNP) may be associated with hematological malignancies (HM).
- 28 • HM associated with PNP are mostly non-Hodgkin lymphoma, chronic lymphocytic leukemia
- 29 and Castleman disease.
- 30 • The survival rate of PNP associated with HM is low. Toxic epidermal necrolysis-like PNP
- 31 and PNP associated with bronchiolitis obliterans have an especially poor prognosis.

Abstract

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

Objective To precise clinical and biological features in HM-associated PNP and identify factors associated with mortality and survival.

Methods Systematic review of previously described cases of PNP associated with HM.

Results One hundred forty-four patients were included. HM 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%; most deaths occurred within the first year of PNP diagnosis. Multivariate analysis showed that: i/ presence of anti-envoplakin antibodies and BO were significantly associated with death; ii/ 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. TEN-like and BO-associated forms are independent survival factors in PNP associated with HM.

Introduction

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, chronic graft versus host disease-like (1). Skin or mucosal biopsies of PNP usually show a lichenoid pattern and/or patterns seen in autoimmune blistering skin diseases such as acantholysis, basal cells vacuolar degeneration, keratinocyte necrosis, sub-epidermal and/or epidermal cleft (2). PNP mechanism involves humoral and cellular autoimmunity (3) including an “epitope spreading” phenomenon with multiple antigen targets in the epidermis and the basal layer 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, lichenoid or interface dermatitis, direct immunofluorescence demonstrating 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, serum autoantibodies against desmogleins 1 and 3, as well as members of the plakin family of epithelial proteins. PNP occurs more often in patients with hematological malignancies (HM), especially B-cell lymphoproliferative disorders (LD), than in solid cancer patients (1)(5). Lung bronchiolitis obliterans (BO) is a usual complication of PNP, and can be lethal. PNP has a high mortality rate (6)(7). We aimed to accurately define PNP associated with HM and identify possible clinical and biological factors associated with mortality through a systematic review of previously described cases.

Material and Methods

We searched the National Library of Medicine's MEDLINE database (Bethesda, MD) for relevant case reports in the English and French literature using the keyword "Paraneoplastic pemphigus" (1990 to 2016). The following criteria were used to select the cases: PNP meeting the Anhalt criteria (2), HM associated with PNP, adult patients, biopsy proven HM, clinical, histological and immunological characterization of the PNP and available data on mortality and cause of mortality. Data were presented as median (interquartile range) or number (percentage). Analysis of mortality rates first used logistic regression models. In patients with available follow-up or survival times, Kaplan-Meier estimates of survival from PNP diagnosis were plotted then compared across baseline groups by the log-rank test. Multivariable logistic or Cox proportional hazards regression models including covariates with p-values < 0.05 from univariable analyses, were used to summarize prognostic information on mortality or survival, respectively, both with model selection based on a backward stepwise selection procedure. Strength of association between covariates and the outcome were measured by odds ratio (OR) or hazard ratio (HRs) with 95% confidence intervals (95%CI). Significance was defined by two-sided p-values less than 0.05. All statistical analyses were performed using SAS software (SAS Institute Inc, Cary, NC), R (<https://www.R-project.org/>), and GraphPad Prism Version 5.0 software (GraphPad Software).

Results

Patient selection and general characteristics

One hundred and forty four patients were included for mortality rates including 120 who could be analyzed for survival data (see Flow chart in **Figure 1**). Patient characteristics are summarized in **Table 1 to 7**. Mean age was 58 years (48-68) with 44.4% of female patients. Clinical patterns were available for 76 patients (**Table 2**), accurate histological parameters for 137 patients (**Table 3**), direct immunofluorescence for 129 patients (**Table 4**), indirect immunofluorescence for 112 patients (**Table 5**), antigen targets (enzyme-linked immunosorbent assay or immunoblotting) for 112 patients (**Table 6**) and disease evolution criteria for 144 patients (**Table 7**). HM were non-Hodgkin lymphoma (n=76, 52.8%), chronic lymphocytic leukemia (n=33, 22.9%), Castleman disease (n=26, 18.1%)(unicentric, n=24; multicentric, n=2), mastocytosis (n=1, 0.7%), Hodgkin Lymphoma (n=1, 0.7%) monoclonal gammopathy of undetermined significance/multiple myeloma/Waldenstrom (n=7, 4.9%). Oral involvement was present in the majority of patients (n = 133, 92.4%). Acantholysis was the most frequent histological pattern described (n=86, 62.7%), and sub epidermal blister was less frequent (n=13, 9.5%). Envoplakin (EVPL), periplakin (PPL) 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%), relapse of PNP for 30 patients (20.8%).

Factors associated with mortality and survival time

Eighty-two patients (57%) died. The main cause of death was “general” for 37 patients (sepsis, general condition alteration), 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 using univariate analysis were: absence of intra-epidermal blister, presence of anti-EVPL antibodies, presence of anti- PPL antibodies and presence of BO. The

following criteria remained significantly associated with death using multivariate logistic model: presence of anti-EVPL antibodies (OR=5.6, 95%CI: 1.2-25.8; p= 0.027) and BO (OR=5.4, 95%CI: 1.7-16.9, p=0.0034).

One-year survival was 62.4% (95%CI: 53.8-72.4). Survival outcome is depicted in **Figure 2A**. Factors associated with decreased survival in univariate analysis were: BP-like pattern (**Figure 2B**), TEN-like pattern (**Figure 2C**), BO (**Figure 2D**) and anti-EVPL (**Figure 2E**). The following criteria remained significantly associated with survival using multivariate Cox model: TEN-like pattern (HR=5.31, 95%CI: 2.6 to 10.8, p <0.001), BP-like pattern (HR=6.1, 95%CI: 1.30 to 28.6, p =0.022), and presence of BO (HR=2.12, 95%CI: 1.14 to 3.93, p = 0.018).

Discussion

Our study is the first review from 1990 (first description of PNP) to 2016 concerning PNP associated with HM that analyzed prognostic factors using either the prevalence of death or the survival time as the endpoint. A French retrospective study of 50 patients analyzed HM and solid neoplasms (carcinoma and sarcoma) and defined erythema multiform-like clinical pattern and skin necrosis on histology (possibly seen in TEN-like PNP) as possible poor prognostic factors (6). The four following factors were independently associated with mortality and/or decreased survival in our study, namely presence of anti-EVPL antibodies, BO, TEN-like clinical pattern, and BP-like clinical pattern. In mouse studies, EPVL 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). TEN-like PNP are often severe (11) but TEN-like clinical pattern has not been already studied as an independent survival factor. 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 survival rate of PNP associated with HM is low. TEN-like PNP and PNP associated with BO are particularly severe.

153 **Abbreviations**

154 PNP, paraneoplastic pemphigus; BP, bullous pemphigoid; HM, haematological malignancies;

155 TEN, toxic epidermal necrolysis; AVPL, envoplakin; PPL, periplakin

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Figure Legends

Figure 1: Flow chart of patient selection

Figure 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-pemphigoid like pattern. **C.** Probabilities of overall survival in patients with paraneoplastic pemphigus, according to the presence or absence of a toxic epidermal necrosis-like pattern. **D.** Probabilities of overall survival in patients with paraneoplastic pemphigus, according to the presence or absence of bronchiolitis obliterans. **E.** Probabilities of overall survival in patients with paraneoplastic pemphigus, according to the presence or absence of anti-envoplakine antibodies. p-values are estimated using the log-rank test

Table 1: General characteristics of the 144 patients

	Number or Mean	Percentage or interquartile
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%

*F: Female; M: Male; CLL: chronic lymphocytic leukemia; NHL: non Hodgkin lymphoma; HL: Hodgkin lymphoma
CD: Castleman's disease*

Table 2: Clinical characteristics of the 144 patients

Settings	Number (percentage for 144 patients)
Skin involvement	128 (88.9%)
Lichen planus-like	37 (25.7%)
GVH-like	4 (2.8%)
BP-like	3 (2.1%)
VP-like	15 (10.4%)
Erythema multiform 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%)

GVH: graft versus host disease BP: bullous pemphigoid; VP: vulgaris pemphigus; TEN: toxic epidermal necrolysis; ENT: ears nose throat pharynxes or epiglottis involvement
 Note: Two and sometimes three clinical patterns could be described for one patient

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220 **Table 3:** Histological characteristics (137 patients with available data)

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	Number (percentage)
Intra-epidermal blister	59 (43.1%)
Sub-epidermal blister	13 (9.5%),
Acantholysis	86 (62.7%)
Keratinocyte necrosis	69 (50.4%)
Basal cells degeneration	45 (32.8%)
Lichenoid infiltrate	74 (54.0%)

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223 *Note histological pattern are often multiple in one patient which is common in PNP*

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Table 4: Skin biopsy direct immunofluorescence (129 patients with available data)

	Number (percentage)
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%)

IgG: G-type immunoglobulin deposit; C3: Fraction number 3 of complement deposits; C1q: component q of the fraction number 1 of complement deposit; IgM: M-type immunoglobulin deposit; IgA: A-type immunoglobulin deposit; Intercellular: deposits are localized between keratinocyte in the epidermis following desmosome formation; Linear: deposits are localized along basal membrane following hemidesmosome, lamina densa or lamina lucida; DIF: direct immunofluorescence analysis

Table 5: Indirect Immunofluorescence (112 patients with available data)

Settings	Number (percentage)
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%)

IIF: indirect immunofluorescence; ICS: intercellular substance antibody; BMZ: basal membrane zone antibody. Depending on the case reported, substrates for Indirect Fluorescence were mostly monkey oesophagus, monkey bladder, rat bladder and sometimes a combination of these.

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242 **Table 6:** ELISA and Immunoblot (data available for 112 patients)

Settings	Number (percentage over 112 patients)
BP 180 (180 kD)	8 (7.1%)
BP 230 (230 kD)	38 (33.9,%)
Dsg1 (160kD)	21 (18.7%)
Dsg3 (130 kD)	45 (40.2%)
Alpha 2 macroglobulin like 1 (170kD)	22 (19.6%)
Periplakin (190 kD)	76 (67.9%)
Laminin 3-3-2	2 (1.8%)
Collagen VII alpha chain (290kD)	2 (1.8%)
Desmocollin	5 (4.4%)
Envoplakin (210 kD)	81 (72.3%)
Desmoplakin (250kD)	49 (43.7%)

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BP, Bullous Pemphigoid; Dsg, Desmoglein

Table 7: Evolution and outcome of the 144 patients

	Number (percentage)
BO	37 (25.7%)
Relapse PNP	30 (20.8%)
Relapse HM	29 (20.1%)
Deaths	82 (56.9%)
Death consecutive to BO	28/82 (34.1%)
Death consecutive to PNP	16/82 (19.5%)
Death consecutive to HM	11/82 (13.4%)
Death consecutive to other causes	37/82 (45.1%)

BO: bronchiolitis obliterans; PNP: paraneoplastic pemphigus; HM, hematologic malignancy; Relapse PNP: relapse of paraneoplastic pemphigus during patient follow up; Relapse HM: relapse of hematologic malignancy during patient follow up; Other causes: other causes than bronchiolitis obliterans s, hematological malignancy and paraneoplastic pemphigus

344 case reports
(317 articles, 11 case series)

Criteria not met

Paediatric cases: 22
Solid neoplasia: 74
Veterinary studies: 4
No neoplasia related to PNP: 10
Review without case report: 7
No details on the reported cases: 53
Anhalt criteria not met: 19
Other language than french or english: 11

144
patients

24 without survival time

120 patients for survival analysis