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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.

32 **Abstract**

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

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

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

39 **Results** One hundred forty-four patients were included. HM were non-Hodgkin lymphoma
40 (52.78%), chronic lymphocytic leukemia (22.92%), Castleman disease (18.60%) and "other
41 underlying hematologic malignancy" (5.70%). The mortality rate was 57%; most deaths
42 occurred within the first year of PNP diagnosis. Multivariate analysis showed that: i/ presence
43 of anti-envoplakin antibodies and BO were significantly associated with death; ii/ toxic
44 epidermal necrolysis-like clinical pattern, bullous pemphigoid-like clinical pattern and BO
45 were significantly associated with decreased survival.

46 **Limitation** Only case reports with sufficient mortality data were included.

47 **Conclusion** PNP associated with HM has a high mortality rate. TEN-like and BO-associated
48 forms are independent survival factors in PNP associated with HM.

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53 **Introduction**

54 Paraneoplastic pemphigus (PNP) is an autoimmune blistering skin disease associated with
55 cancer that has various clinical presentations: lichen planus-like, pemphigus vulgaris-like,
56 bullous pemphigoid (BP)-like, erythema multiforme-like, toxic epidermal necrolysis (TEN)-
57 like, chronic graft versus host disease-like (1). Skin or mucosal biopsies of PNP usually show
58 a lichenoid pattern and/or patterns seen in autoimmune blistering skin diseases such as
59 acantholysis, basal cells vacuolar degeneration, keratinocyte necrosis, sub-epidermal and/or
60 epidermal cleft (2). PNP mechanism involves humoral and cellular autoimmunity (3)
61 including an “epitope spreading” phenomenon with multiple antigen targets in the epidermis
62 and the basal layer associated with various clinical presentations (4). After its first
63 description in 1990 by Anhalt et al, diagnostic criteria to assess PNP were defined (2). They
64 include the presence of a painful, progressive stomatitis and a polymorphous cutaneous
65 eruption, histologic features of acantholysis, lichenoid or interface dermatitis, direct
66 immunofluorescence demonstrating deposition of IgG and complement in the epidermal
67 intercellular spaces, serum autoantibodies that bind the cell surface of skin and mucosae in a
68 pattern typical for pemphigus, serum autoantibodies against desmogleins 1 and 3, as well as
69 members of the plakin family of epithelial proteins. PNP occurs more often in patients with
70 hematological malignancies (HM), especially B-cell lymphoproliferative disorders (LD), than
71 in solid cancer patients (1)(5). Lung bronchiolitis obliterans (BO) is a usual complication of
72 PNP, and can be lethal. PNP has a high mortality rate (6)(7). We aimed to accurately define
73 PNP associated with HM and identify possible clinical and biological factors associated with
74 mortality through a systematic review of previously described cases.

75 **Material and Methods**

76 We searched the National Library of Medicine's MEDLINE database (Bethesda, MD) for
77 relevant case reports in the English and French literature using the keyword "Paraneoplastic
78 pemphigus" (1990 to 2016). The following criteria were used to select the cases: PNP meeting
79 the Anhalt criteria (2), HM associated with PNP, adult patients, biopsy proven HM, clinical,
80 histological and immunological characterization of the PNP and available data on mortality
81 and cause of mortality. Data were presented as median (interquartile range) or number
82 (percentage). Analysis of mortality rates first used logistic regression models. In patients with
83 available follow-up or survival times, Kaplan-Meier estimates of survival from PNP diagnosis
84 were plotted then compared across baseline groups by the log-rank test. Multivariable logistic
85 or Cox proportional hazards regression models including covariates with p-values < 0.05 from
86 univariable analyses, were used to summarize prognostic information on mortality or survival,
87 respectively, both with model selection based on a backward stepwise selection procedure.
88 Strength of association between covariates and the outcome were measured by odds ratio
89 (OR) or hazard ratio (HRs) with 95% confidence intervals (95%CI).

90 Significance was defined by two-sided p-values less than 0.05. All statistical analyses were
91 performed using SAS software (SAS Institute Inc, Cary, NC), R (<https://www.R-project.org/>),
92 and GraphPad Prism Version 5.0 software (GraphPad Software).

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95 **Results**

96 *Patient selection and general characteristics*

97 One hundred and forty four patients were included for mortality rates including 120 who
98 could be analyzed for survival data (see Flow chart in **Figure 1**). Patient characteristics are
99 summarized in **Table 1 to 7**. Mean age was 58 years (48-68) with 44.4% of female patients.
100 Clinical patterns were available for 76 patients (**Table 2**), accurate histological parameters for
101 137 patients (**Table 3**), direct immunofluorescence for 129 patients (**Table 4**), indirect
102 immunofluorescence for 112 patients (**Table 5**), antigen targets (enzyme-linked
103 immunosorbent assay or immunoblotting) for 112 patients (**Table 6**) and disease evolution
104 criteria for 144 patients (**Table 7**). HM were non-Hodgkin lymphoma (n=76, 52.8%), chronic
105 lymphocytic leukemia (n=33, 22.9%), Castleman disease (n=26, 18.1%)(unicentric, n=24;
106 multicentric, n=2), mastocytosis (n=1, 0.7%), Hodgkin Lymphoma (n=1, 0.7%) monoclonal
107 gammopathy of undetermined significance/multiple myeloma/Waldenstrom (n=7, 4.9%).
108 Oral involvement was present in the majority of patients (n = 133, 92.4%). Acantholysis was
109 the most frequent histological pattern described (n=86, 62.7%), and sub epidermal blister was
110 less frequent (n=13, 9.5%). Envoplakin (EVPL), periplakin (PPL) and desmoplakin were the
111 most frequent antibody-targeted antigens (n=81, 72.3%, n=76, 67.9% and n = 49; 43.7%,
112 respectively). BO was present in 37 patients (25.7%). Relapse of HM was reported for 29
113 patients (20.1%), relapse of PNP for 30 patients (20.8%).

114 *Factors associated with mortality and survival time*

115 Eighty-two patients (57%) died. The main cause of death was “general” for 37 patients
116 (sepsis, general condition alteration), BO for 28 patients, PNP without BO (extended skin or
117 mucosal involvement) for 16 patients and HM for 11 patients. Factors associated with
118 increased mortality using univariate analysis were: absence of intra-epidermal blister,
119 presence of anti-EVPL antibodies, presence of anti- PPL antibodies and presence of BO. The

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

123 One-year survival was 62.4% (95%CI: 53.8-72.4). Survival outcome is depicted in
124 **Figure 2A**. Factors associated with decreased survival in univariate analysis were: BP-like
125 pattern (**Figure 2B**), TEN-like pattern (**Figure 2C**), BO (**Figure 2D**) and anti-EVPL (**Figure**
126 **2E**). The following criteria remained significantly associated with survival using multivariate
127 Cox model: TEN-like pattern (HR=5.31, 95%CI: 2.6 to 10.8, p <0.001), BP-like pattern
128 (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
129 3.93, p = 0.018).

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133 Discussion

134 Our study is the first review from 1990 (first description of PNP) to 2016 concerning PNP
135 associated with HM that analyzed prognostic factors using either the prevalence of death or
136 the survival time as the endpoint. A French retrospective study of 50 patients analyzed HM
137 and solid neoplasms (carcinoma and sarcoma) and defined erythema multiform-like clinical
138 pattern and skin necrosis on histology (possibly seen in TEN-like PNP) as possible poor
139 prognostic factors (6). The four following factors were independently associated with
140 mortality and/or decreased survival in our study, namely presence of anti-EVPL antibodies,
141 BO, TEN-like clinical pattern, and BP-like clinical pattern. In mouse studies, EPVL appeared
142 to be a crucial protein for skin integrity and survival (8). BO has already been described as a
143 poor prognostic factor in PNP (9) (10). TEN-like PNP are often severe (11) but TEN-like
144 clinical pattern has not been already studied as an independent survival factor. BP-like clinical
145 pattern was associated with death in our study. However, only 3 patients had BP-like PNP
146 (the 3 of them died rapidly) making it difficult to draw firm conclusions. To summarize, the
147 survival rate of PNP associated with HM is low. TEN-like PNP and PNP associated with BO
148 are particularly severe.

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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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193 **Figure Legends**

194 **Figure 1:** Flow chart of patient selection

195 **Figure 2:** **A.** Kaplan Meier probabilities of overall survival in 120 patients with
196 paraneoplastic pemphigus. **B.** Probabilities of overall survival in patients with paraneoplastic
197 pemphigus, according to the presence or absence of a bullous-pemphogoid like pattern. **C.**
198 Probabilities of overall survival in patients with paraneoplastic pemphigus, according to the
199 presence or absence of a toxic epidermal necrosis-like pattern. **D.** Probabilities of overall
200 survival in patients with paraneoplastic pemphigus, according to the presence or absence of
201 bronchiolitis obliterans. **E.** Probabilities of overall survival in patients with paraneoplastic
202 pemphigus, according to the presence or absence of anti-envoplakine antibodies. p-values are
203 estimated using the log-rank test

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206 **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%

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

211 **Table 2:** Clinical characteristics of the 144 patients

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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%)

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

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	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%)

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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

234 **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%)

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 236 *IIF: indirect immunofluorescence; ICS: intercellular substance antibody; BMZ: basal membrane zone antibody. Depending on the case*
 237 *reported, substrates for Indirect Fluorescence were mostly monkey oesophagus, monkey bladder, rat bladder and sometimes a combination*
 238 *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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246*BP, Bullous Pemphigoid; Dsg, Desmoglein*

247 **Table 7:** Evolution and outcome of the 144 patients

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	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%)

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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

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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

