Prognostic Factors of Paraneoplastic Pemphigus

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Objective: To identify the prognostic factors of overall survival in a series of patients with paraneoplastic pemphigus (PNP).

Design: Multicenter retrospective cohort study.

Setting: Twenty-seven dermatology departments in France.

Patients: A total of 53 patients (31 men and 22 women; median age, 59 years; age range, 30-88 years) were diagnosed as having PNP between 1992 and 2010.

Main Outcome Measures: Overall Kaplan-Meier survival rates were estimated, and features associated with survival were assessed using univariate (log-rank test) and multivariate (Cox regression) analyses.

Results: The study included 53 patients with PNP. Thirty-six patients (68%) died during the study. The 1-, 3-, and 5-year overall survival rates were 49%, 41%, and 38%, respectively. The main causes of death were infections (n=21) and evolution of neoplasia (n=6). In univariate analysis, the main detrimental prognostic factors identified were erythema multiforme–like skin lesions (P=.05) and histologic keratinocyte necrosis (P=.03). None of the 5 patients with Castleman disease died during the study. After adjustment for age and sex in multivariate analysis, erythema multiforme–like skin lesions remained predictive of fatal outcome, with a 2-fold increase in death rate (hazard ratio [HR], 2.3; 95% CI, 1.05-5.03; P=.04). The prognosis of patients with PNP was even poorer when erythema multiforme–like skin lesions were associated with severe skin or mucosal involvement at presentation (HR of death, 3.0; 95% CI, 1.01-8.92; P=.049).

Conclusion: Patients with PNP with erythema multiforme–like skin lesions and histologic keratinocyte necrosis, especially when associated with extensive lesions at presentation, are likely to have a more severe and rapid fatal outcome and should be managed very carefully.


PARANEOPLASTIC PEMPHIGUS (PNP) is a rare type of pemphigus that is characterized by the production of autoantibodies directed against a complex of desmosomal proteins, including desmoplakin I and II; bullous pemphigoid (BP) antigen 1 (BPAG1); envoplakin; and perilakin, a recently identified 170-kDa antigen, as well as desmoglein (Dsg)-1 and Dsg-3. It is mainly associated with lymphoproliferative disorders such as non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and Castleman disease. Nonlymphoid malignant neoplasms are more rarely associated. The prognosis of PNP is severe, with a mortality rate ranging from 75% to 90% and a mean survival of less than 1 year. However, patients with PNP and a long-term survival have also been described. Moreover, the course of PNP does not necessarily parallel the evolution of the associated neoplasm. Because of a widely variable course and the absence of prognostic factors identified to date, the treatment of PNP remains controversial. Many treatments have been proposed, including oral corticosteroids, cyclosporine, azathioprine, cyclophosphamide, mycophenolate mofetil, and rituximab.
ELISA tests were used to detect antienvoplakin antibodies: care & Biological Laboratories) with 1:100 diluted serum. Two available Dsg-1 and Dsg-3 ELISA tests (MESACUP Dsg; Medi-
DEJ staining were observed in 20 cases (50%) and 1 case, respectively. A positive IIF staining result on rat bladder was observed in 37 of 46 cases (80%). The results of immunoblot analyses of patients’ serum samples on human epidermal extracts are shown below.

<table>
<thead>
<tr>
<th>Antigen (kDa)</th>
<th>No. (%)</th>
</tr>
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<tbody>
<tr>
<td>Periplakin (190)</td>
<td>35 (66)</td>
</tr>
<tr>
<td>Envolplakin/desmoplakin (210)</td>
<td>34 (64)</td>
</tr>
<tr>
<td>DSG-3 (130)</td>
<td>12 (23)</td>
</tr>
<tr>
<td>BPAG1 (230)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>Desmoplakin I (250)</td>
<td>7 (13)</td>
</tr>
<tr>
<td>DSG-1 (160)</td>
<td>7 (13)</td>
</tr>
</tbody>
</table>

Forty-two of 53 serum samples (79%) recognized at least 1 of the following 190-, 210-, 230-, or 250-kDa bands of periplakin, envolplakin, BPAG1, and desmoplakin I. Thirty-nine serum samples (74%) recognized the 190- and/or 210-kDa bands of periplakin and envolplakin, including 30 serum samples that recognized the 190-kDa/210-kDa doublet and 9 serum samples that recognized only 1 of these 2 bands. Also, 3 serum samples recognized the 250-kDa (n = 2) and/or 230-kDa bands exclusively. Thirty-one serum samples were available for retesting both by immunoblotting and by the commercially available antienvoplakin ELISA and our bead-based antienvoplakin assay. Of the 31 serum samples, 15 (48%) and 22 (71%) recognized envolplakin with the commercially available ELISA and our bead-based assay, respectively, and 24 (77%) recognized the 190- and/or 210-kDa bands of envolplakin and/or periplakin (including 20 serum samples [65%] that recognized the 190-kDa/210-kDa doublet). Also, 2 of the 31 serum samples recognized the 250-kDa band of desmoplakin alone. The last 5 serum samples (16%) did not react with any band of the PNP complex by immunoblotting. Interestingly, 2 of these 5 immunoblotting-negative serum samples were strongly positive (ELISA values, 5.65 and 3.26), and 3 serum samples had weak ELISA reactivity (ELISA values, 1.58, 1.32, and 1.16). Desmoglein-ELISA tests were performed in 42 patients. Anti–Dsg-1 and -3 antibodies were detected in 17 (40%) and 30 (71%) cases, respectively.

Overall, 2 patients with NHL whose serum sample was no longer available to be retested by ELISA had only 4 of the 7 diagnostic criteria (these 2 patients did not have circulating antibodies by IIF and immunoblotting and therefore lacked the 3 PNP diagnostic criteria based on serum analysis), 16 patients had 5 criteria, 20 had 6 criteria, and 15 had all 7 criteria. The PNP diagnostic criteria of subgroups of patients depending on the associated neoplasm are shown in Table 1.

We carefully examined the PNP diagnostic criteria in the 3 patients with exclusive skin involvement. The associated neoplasms were 1 CLL, 1 NHL, and 1 cutaneous CD30+ T-cell lymphoma. The 190- and 210-kDa bands of periplakin and envolplakin were recognized in 3 of 3 cases, and an IIF labeling of rat bladder was observed in 2 of the 3 serum samples. Two and 1 of these 3 patients had 5 and 6 PNP diagnostic criteria, respectively. We then examined the PNP diagnostic criteria in the 11 patients whose serum samples did not recognize the PNP complex by immunoblotting. Five of these 11 immunoblotting-negative serum samples were available for retesting by ELISA and had positive envolplakin ELISA values. The associated neoplasms were 5 NHL, 4 CLL, and 2 carcinomas (serum samples from the 2 latter patients showed a weak labeling on rat bladder by IIF). Two patients with NHL and no circulating antiepidermal antibodies had 4 of the 7 PNP diagnostic criteria (lacking the 3 criteria based on serum analysis), and 7 and 2 patients had 5 and 6 PNP diagnostic criteria, respectively. Finally, we examined the PNP diagnostic criteria in the 10 patients with an associated carcinoma. All 10 patients had mucosal lesions suggestive of PNP. Eight of the 10 serum samples (80%) recognized the 190- and/or 210-kDa bands of periplakin and envolplakin. Four patients had 5 PNP diagnostic criteria, and 5 and 1 had 6 and 7 diagnostic criteria, respectively.

### TREATMENT AND OUTCOME

High doses of oral corticosteroids, eg, prednisone, 1 to 1.5 mg/kg/d, were used as the first line of treatment in...
40 of the 53 patients (75%). Corticosteroids were used alone in 37 cases (70%). Four patients (8%) were treated with an immunosuppressant as first-line treatment, including 3 cases treated with corticosteroids and immunosuppressants (azathioprine, cyclosporine, mycophenolate mofetil, methotrexate); CS + IS, CS combined with immunosuppressive drugs; Other, thalidomide (n = 1) or rituximab alone (n = 1) or no treatment (n = 2); CS + IVIG, corticosteroids combined with intravenous immunoglobulins; CS + Ritux, corticosteroids combined with rituximab.

In univariate analysis, the main deleterious prognostic factors, which were associated with a shorter overall survival, were the presence of erythema multiforme–like skin lesions (P = .05) and keratinocyte necrosis in skin biopsy specimens (P = .03) (Table 4). When the whole population of patients was considered, the type of associated neoplasm was not associated with overall survival (Figure). However, the patients with NHL had a significantly shorter survival when compared with patients with other types of neoplasia, excluding CLL and carcinoma (P = .03). Indeed, all 5 patients with Castleman disease were alive at the end of the study. There was no association between sex or age and patients’ prognosis whether age was coded as a continuous variable or dichotomized (≤59 years, >59 years). No particular PNP antigen patterns recognized by patients’ serum samples were found to be associated with prognosis on immunoblot analysis. Interestingly, the initial extent of skin and/or mucosal lesions at baseline was not associated with patients’ prognosis, although there was a nonsignificant trend for patients with initial lesions classified as severe to have shorter survival than patients with moderate lesions (P = .11).

In age- and sex-adjusted multivariate analysis, only the presence of erythema multiforme–like skin lesions (HR, 2.3; 95% CI, 1.05-5.03; P = .05) and keratinocyte necrosis (HR, 2.5; 95% CI, 1.00-8.92; P = .049) were found to be associated with shorter survival. The overall survival of patients with PNP was even shorter when erythema multiforme–like skin lesions were associated with severe skin and/or mucosal involvement at presentation (HR, 3.0; 95% CI, 1.01-8.92; P = .049). The presence of histologic keratinocyte necrosis was no longer found to be associated with overall survival in multivariate analysis (HR, 1.8; 95% CI, 0.91-3.60; P = .09). However, the presence of histologic keratinocyte necrosis when associated with severe disease at presentation (HR, 2.5; 95% CI, 1.00-6.22; P = .05) or the presence of erythema multiforme–like skin lesions (HR, 2.7; 95% CI, 1.18-6.05; P = .02) was found to be associated with a fatal outcome.

The main findings of this study are (1) the demonstration that PNP has a highly variable course in both se-

### Table 2. Main Treatments Used (First and Second Line) and Their Results, Depending on Paraneoplastic Pemphigus Severity

<table>
<thead>
<tr>
<th>Disease Severity</th>
<th>Disease Severity</th>
<th>First-Line Treatment</th>
<th>Second-Line Treatment</th>
<th>Patients Alive at the End of the Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>CS</td>
<td>CS+IVIG</td>
<td>CS+CS+Ritux</td>
</tr>
<tr>
<td>Moderate (n = 41)</td>
<td></td>
<td>28 (76)</td>
<td>3 (100)</td>
<td>0</td>
</tr>
<tr>
<td>Severe (n = 12)</td>
<td></td>
<td>9 (75)</td>
<td>0</td>
<td>1 (8)</td>
</tr>
</tbody>
</table>

#### PROGNOSTIC FACTORS

The main deleterious prognostic factors, which were associated with a shorter overall survival, were the presence of erythema multiforme–like skin lesions (P = .05) and keratinocyte necrosis in skin biopsy specimens (P = .03) (Table 4). When the whole population of patients was considered, the type of associated neoplasm was not associated with overall survival (Figure). However, the patients with NHL had a significantly shorter survival when compared with patients with other types of neoplasia, excluding CLL and carcinoma (P = .03). Indeed, all 5 patients with Castleman disease were alive at the end of the study. There was no association between sex or age and patients’ prognosis whether age was coded as a continuous variable or dichotomized (≤59 years, >59 years). No particular PNP antigen patterns recognized by patients’ serum samples were found to be associated with prognosis on immunoblot analysis. Interestingly, the initial extent of skin and/or mucosal lesions at baseline was not associated with patients’ prognosis, although there was a nonsignificant trend for patients with initial lesions classified as severe to have shorter survival than patients with moderate lesions (P = .11). In age- and sex-adjusted multivariate analysis, only the presence of erythema multiforme–like skin lesions (HR, 2.3; 95% CI, 1.05-5.03; P = .05) remained associated with shorter survival. The overall survival of patients with PNP was even shorter when erythema multiforme–like skin lesions were associated with severe skin and/or mucosal involvement at presentation (HR, 3.0; 95% CI, 1.01-8.92; P = .049). The presence of histologic keratinocyte necrosis was no longer found to be associated with overall survival in multivariate analysis (HR, 1.8; 95% CI, 0.91-3.60; P = .09). However, the presence of histologic keratinocyte necrosis when associated with severe disease at presentation (HR, 2.5; 95% CI, 1.00-6.22; P = .05) or the presence of erythema multiforme–like skin lesions (HR, 2.7; 95% CI, 1.18-6.05; P = .02) was found to be associated with a fatal outcome.
vere and indolent cases, and (2) the main deleterious prognostic factors are the presence of erythema multiforme-like skin lesions and the presence of keratinocyte necrosis on histologic examination, especially when the latter is associated with the presence of extensive skin and/or mucosal lesions at presentation. The main clinical, histologic, and immunologic features of the 53 patients included in the present study were similar to those previously reported in different series of patients with PNP: (1) frequent association with lymphoproliferative disorders (75%), eg, NHL and CLL; (2) high frequency of erosive mucosal lesions; (3) polymorphism of skin lesions; (4) histologic features associated with keratinocyte necrosis, acantholysis, and a lichen planus–

![Table 3. Main Causes of Death According to Disease Severity and Associated Neoplasia](image)

**Table 3. Main Causes of Death According to Disease Severity and Associated Neoplasia**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death, No. (%)</th>
<th>Infections</th>
<th>Evolution of Neoplasia</th>
<th>Respiratory Failure</th>
<th>Other or Undetermined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease severity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate (n = 41)</td>
<td>25 (61)</td>
<td>15</td>
<td>3</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>Severe (n = 12)</td>
<td>11 (92)</td>
<td>6</td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Associated neoplasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHL (n = 14)</td>
<td>12 (86)</td>
<td>7</td>
<td>1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>CLL (n = 16)</td>
<td>11 (69)</td>
<td>8</td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Carcinoma (n = 10)</td>
<td>6 (60)</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other (n = 13)</td>
<td>7 (54)</td>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: CLL, chronic lymphocytic leukemia; NHL, non-Hodgkin lymphoma.
series of patients with PNP. In fact, the frequency of episodes, which is associated with a high death rate in some series died of respiratory failure due to bronchiolitis obliterans over an 18-year period. Also, only a few patients in this Study Group on Autoimmune Bullous Skin Disease during this period were referred to the 27 dermatology departments of the French network. Mortality rates previously reported in patients with PNP were estimated from small series or even case studies, including 15 children and adolescents who all had Castleman disease, to 18% and 17% in 2 series that included 10% and 6% of patients with Castleman disease, and 9% of patients with Castleman disease. Remarkably, the 9% rate of Castleman disease in the present study was very close to the 10% and 6% rates found in the 2 adult series of patients with PNP described by Anhalt and Maldonado et al. Although it has been suggested that bronchiolitis obliterans in patients with Castleman disease might reflect a more severe type of PNP, none of the 5 patients with Castleman disease in the present series died during the study. However, it should be emphasized that in all series of the literature, including the present one, the diagnosis of bronchiolitis obliterans is more frequently suspected than histologically proved. We observed a wide spectrum in the severity of skin and mucosal lesions in our series, as 41 (77%) and 12 (23%) patients had the moderate or severe type of PNP, respectively. Accordingly, the treatment regimens used were highly variable, from topical corticosteroids to high doses of oral corticosteroids combined with immunosuppressants. Although, to our knowledge, no direct comparison of the combination of immunosuppressants and corticosteroids vs corticosteroids alone has been published in the literature to date, immunosuppressive drugs are the most often recommended treatment of PNP. Only 4 patients in our study received an immunosuppressive drug as the first line of treatment. In view of the rather low mortality rate in this series compared with others in the literature, our findings suggest that treatment of PNP should preferentially be adapted to disease severity to limit severe adverse effects, such as infections, in these immunocompromised patients and not to favor the evolution of the associated neoplasia. Interestingly, 4 of 9 cases of PNP treated with topical corticosteroids alone could even be adequately controlled without systemic treatment.

The prognostic factors identified in this study were in accordance with the main causes of death of patients in this series. Indeed, patients with Castleman disease or thymoma had a favorable prognosis compared with patients with other types of malignant neoplasms, particularly NHL, possibly because they were not treated with chemotherapy, which highly increased the risk of severe infections and death in patients with PNP who were concomitantly treated with high doses of corticosteroids. Moreover, Castleman disease occurred in younger patients (mean age, 44 years) compared with patients with NHL (mean age, 59 years), CLL (mean age, 65 years), or carcinoma (mean age, 63 years), which might also explain the better prognosis of these patients, although age was not associated with prognosis in univariate analysis. The presence of erythema multiforme–like lesions and keratinocyte necrosis in association with extensive skin involvement was reminiscent of toxic epidermal necrolysis and might reflect a more severe type of PNP. Patients with erythema multiforme–like lesions were more likely to die because of a higher risk of severe infections, especially patients who did not achieve disease control after initial treatment and had an increase in their immunosuppressive treatment. The poor prognosis of toxic epidermal necrolysis–like forms of PNP has previously been reported in some cases. It is possible that patients with PNP and erythema multiforme–like lesions and keratinocyte necrosis might have high serum levels like inflammatory infiltrate; and (3) frequent recognition of envoplakin and periplakin by immunoblot analysis of patients’ serum samples.

The prognosis of patients with PNP is usually considered poor, with a mortality rate ranging from 75% to 90%. The 49%, 41%, and 38% 1-, 2- and 5-year overall survival rates based on the present study confirmed the severe prognosis of PNP, although this prognosis was rather better than previously reported. Most deaths were observed during the first year after diagnosis, whereas survival curves only slightly decreased in patients who were still alive 1 year after the diagnosis of PNP. Interestingly, the survival of patients in the present series was longer than previously reported in the literature. This discrepancy is likely attributable to the fact that the high mortality rates previously reported in patients with PNP were estimated from small series or even case studies, which probably reported the most severe cases, whereas the present study included all consecutive cases of PNP referred to the 27 dermatology departments of the French Study Group on Autoimmune Bullous Skin Disease during an 18-year period. Also, only a few patients in this series died of respiratory failure due to bronchiolitis obliterans, which is associated with a high death rate in some series of patients with PNP. In fact, the frequency of bronchiolitis obliterans is highly variable in the literature, from 93% in a series of 28 patients with PNP, including 15 children and adolescents who all had Castleman disease, to 18% and 17% in 2 series that included 10% and 6% of patients with Castleman disease and 8% in the present series, which included 9% of patients with Castleman disease.
of tumor necrosis factor and Fas ligand, as previously reported in toxic epidermal necrolysis.30,41

As in all retrospective studies, various biases are possible in this study. To avoid selection bias of cases, we aimed at exhaustively recruiting all consecutive cases of PNP from the 27 dermatology departments of the French Study Group on Autoimmune Bullous Diseases, which allowed us to include not only the most severe forms of PNP but also a significant proportion of patients with moderate disease, who have more rarely been described in the literature. The centers belonging to our group, although not standardized, were quite precise. Moreover, the dead or alive status of patients at the time of the study was systematically verified from their birthplace city hall death register. Finally, despite the limited sample size of this study, which is attributable to the fact that PNP is an extremely rare disorder, we performed an age- and sex-adjusted multivariate analysis, which confirmed the association between the presence of erythema multiforme-like skin lesions and fatal outcome, especially in association with severe involvement of skin and mucosal lesions or with keratinocyte necrosis, suggesting that combinations of some markers of disease severity could define subgroups of patients with severe prognosis.

In conclusion, this study showed that the prognosis of PNP is heterogeneous and rather better than previously reported. Treatment regimens should be adapted to disease severity, from “mild” treatments in patients with limited disease and in the most immunocompromised patients to “aggressive” regimens in patients with the most severe disease. The prognostic factors identified in the present study could be a useful tool for optimal treatment of patients with PNP.

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Author Contributions: Drs Leger, Picard, and Joly had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Leger, D’Incan, and Joly. Acquisition of data: Leger, Ingen-Housz-Oro, Arnault, Aubin, Carsuzza, Chaumentin, Chevrent-Breton, Chosidow, Crickx, D’Incan, Dandurand, Debarbieux, Delaporte, Dereure, Doutré, Guillet, Jullien, Kupfer, Lacour, Leonard, Lok, Machet, Martin, Paul, Pignon, Robert, Thomas, Weilier, Ferranti, Gilbert, Courville, and Joly. Analysis and interpretation of data: Leger, Picard, Lok, Houivet, Benichou, and Joly. Drafting of the manuscript: Leger, Picard, Dandurand, Kupfer, Ferranti, and Joly. Critical revision of the manuscript for important intellectual content: Ingen-Housz-Oro, Arnault, Aubin, Carsuzza, Chaumentin, Chevrent-Breton, Chosidow, Crickx, D’Incan, Debarbieux, Delaporte, Dereure, Doutré, Guillet, Jullien, Lacour, Leonard, Lok, Machet, Martin, Paul, Pignon, Robert, Thomas, Weilier, Ferranti, Gilbert, Courville, and Joly. Statistical analysis: Leger, Houivet, Benichou, and Joly. Obtained funding: Courville and Joly. Administrative, technical, and material support: Aubin, Dereure, Jullien, Paul, Robert, Thomas, Ferranti, and Joly. Study supervision: Leger, Picard, Crickx, Lacour, Lok, and Joly.

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