High Risk of Death in Elderly Patients With Extensive Bullous Pemphigoid

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Objective: To evaluate survival and factors predicting death in bullous pemphigoid.

Design: Retrospective analysis of cohort.

Setting: Three referral centers (university hospitals).

Patients: Among 237 patients recruited between January 1, 1985, and December 31, 1992, 20 were excluded because of doubtful diagnosis. The 217 remaining patients were 79±11 years old (mean±SD); 120 were women and 97 were men; and 79% had been treated with oral corticosteroids, 40 to 90 mg/d.

Interventions: Missing information on follow-up was minimized by letters and/or telephone calls to patients, families, nursing homes, and physicians.

Main Outcome Measures: Actuarial survival curve, compared with the expected curve as derived from census data, and evaluation of prognostic factors by comparing initial characteristics between patients alive at 6 months and those who died before that point.

Results: Survival curve demonstrated an early increased mortality: 17% at 3 months and 31% at 6 months, mainly from sepsis and cardiovascular diseases. Of the factors related to bullous pemphigoid activity (duration; pruritus; and number and extent of blisters, eosinophilia, and serum antibodies) only generalized pemphigoid was predictive of death in comparison with localized forms. In multivariate analysis, age of 86 years or more (relative risk, 7.1; 95% confidence interval [CI], 2.0-25.4; \( P = .01 \)), poor general condition (relative risk, 8.2; 95% CI, 3.0-22.4; \( P = .001 \)), female sex (relative risk, 2.4; 95% CI, 1.1-5.4; \( P = .05 \)), and generalized disease (relative risk, 4.4; 95% CI, 1.4-13.7; \( P = .01 \)) were associated with increased risks of death at 6 months.

Conclusion: In this series, generalized bullous pemphigoid had a poor prognosis especially in older patients and those in poor general condition.

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Bullous pemphigoid (BP) is an acquired autoimmune blistering disorder that occurs mostly in people older than 65 years. This disease is not rare in the elderly. Its incidence has been estimated in France as 7 new cases per million person-years in adults, ie, an age-adjusted incidence greater than 50 cases per million person-years for people older than 65 years. Bullous pemphigoid is usually considered a benign and easily manageable disease with a “low mortality rate” and a prognosis “significantly better than that of pemphigus.” These opinions, however, were not based on comparative data. In 2 classic articles, Savin studied the risk factors among patients who died of pemphigus or BP, as reported in death certificates. In these studies, most causes of death appeared to be related to corticosteroid therapy, but no data on death rates were provided. In published series, death rates varied from 6% at 2 years to 40% at 1 year. Such variations demonstrate that death rates in patients with BP have been poorly quantified but may be higher than expected in the elderly. The aim of our study was to estimate the death rate and to look for risk factors for death in patients with BP, taking advantage of homogeneous data collection on autoimmune blistering diseases in several centers in France.

RESULTS

The 217 patients included in the study were 120 women and 97 men. Their mean (±SD) age was 79±11 years (median, 80 years). Women were slightly older than men (80±10 years and 78±12 years, respectively; \( P = .11 \)). Mean and median follow-up were 27 and 18 months, respec-
PATIENTS AND METHODS

PATIENTS

A retrospective multicenter study was conducted in 3 departments of dermatology in France (Amiens, Créteil, and Limoëges).

All 237 cases registered as BP between 1985 and 1992 in these centers (University of Amiens, January 1, 1985, to December 31, 1991, n = 53; University Paris XII, Créteil, January 1, 1986, to December 31, 1991, n = 106; University of Limoëges, January 1, 1987, to December 31, 1992, n = 78) were included. The study of patients from Limoëges has been previously reported. Inclusion criteria were a diagnosis of BP based on clinical characteristics and confirmed by at least a typical histological pattern and linear deposits of IgG and/or C3 along the basement membrane zone on direct immunofluorescence testing. In 20 of the 237 potential cases, the diagnosis of BP was insufficiently documented and/or another diagnosis was finally established. Of the 217 remaining patients, 96 (44%) had at least 1 of the following laboratory investigations: indirect immunofluorescence on salt-split skin (n = 20), direct immunoelectron microscopy (n = 34), and/or detection of serum antibodies by Western immunoblotting on proteins extracted from normal epidermis (n = 62). One or more of these examinations confirmed the diagnosis of BP in 89 of 96 patients. In 7 patients, an immunoblot was negative. For the 217 patients included in the study, follow-up information was obtained up to December 31, 1994. Information on the status of patients who became unavailable for follow-up by the hospital department between the diagnosis and December 1994 was obtained by letters and telephone calls to patients, family members, general practitioners, or nursing homes.

DATA COLLECTION

Factors of potential prognosis value were extracted from the patients' medical charts filled at the time of initial diagnosis of BP, ie, independently from information on follow-up. A similar chart had been used for all patients with autoimmune blistering disorders in the 3 participating centers, allowing for a homogeneous evaluation of patient data at the time of initial hospitalization. Recorded information included the date of onset of pruritus and skin lesions, severity of pruritus (measured on an arbitrary scale in which 0 indicates none; 1, mild; 2, moderate; and 3, severe), daily number of new blisters as the mean of counts observed on the 2 days preceding initiation of therapy, nature of immune deposits on the basement membrane zone detected by direct immunofluorescence, titer of blood antibodies as determined by dilutions on indirect immunofluorescence, count of blood eosinophils, associated diseases, general condition (overall determination by the treating dermatologist on an arbitrary scale mainly based on autonomy of patients, in which 1 indicates normal or slightly impaired; 2, mild or moderate impairment; and 3, severe impairment).

ANALYSIS

Survival curves were calculated by the actuarial method. Expected survival and expected causes of death for persons of the same age and sex were derived from French census data.

Prognosis factors were first evaluated in univariate analysis by comparing the initial findings between patients who died within 6 months and those who were still alive at 6 months. Qualitative data were compared by χ² test and quantitative data by Student t test.

To take in account simultaneously all potential prognosis factors, multivariate analyses were performed by means of logistic regression (BMDP programs, BMDP Statistical Software Inc, Los Angeles, Calif). For these analyses, all factors that emerged from univariate analyses with P < .20 were considered. Relative risks were estimated with their 95% confidence intervals (CIs).
Table 1. Characteristics of Bullous Pemphigoid at Diagnosis Among Patients Who Died Within 6 Months and Patients Who Survived

<table>
<thead>
<tr>
<th></th>
<th>Dead Patients (n = 66)</th>
<th>Survivors (n = 149)*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of disease, mo‡</td>
<td>2.4 ± 2.5</td>
<td>2.9 ± 3.9</td>
<td>.30</td>
</tr>
<tr>
<td>Daily No. of new blisters§</td>
<td>56 ± 87</td>
<td>51 ± 105</td>
<td>.60</td>
</tr>
<tr>
<td>Generalized/localized pemphigoid, No.</td>
<td>47/7</td>
<td>102/30</td>
<td>.08</td>
</tr>
<tr>
<td>Pruritus, No. none/mild/severe</td>
<td>3/38/23</td>
<td>8/76/60</td>
<td>.60</td>
</tr>
<tr>
<td>Blood eosinophils, ×10^9/L</td>
<td>1.30 ± 1.72</td>
<td>1.41 ± 1.79</td>
<td>.70</td>
</tr>
<tr>
<td>Serum antibody titer‡</td>
<td>547 ± 1045</td>
<td>519 ± 959</td>
<td>.80</td>
</tr>
<tr>
<td>Treatment with oral glucocorticoids, No. (%)</td>
<td>57 (86)</td>
<td>114 (77)</td>
<td>.12</td>
</tr>
<tr>
<td>Initial dose, mg/d ‡</td>
<td>58.6 ± 31.4</td>
<td>51.4 ± 37</td>
<td>.17</td>
</tr>
<tr>
<td>Treatment with cytotoxic drugs, No. (%)</td>
<td>9 (14)</td>
<td>17 (11)</td>
<td>.58</td>
</tr>
</tbody>
</table>

* Two patients were unavailable for follow-up before 6 months.
† P values for univariate analyses.
‡ Mean ± SD.

Table 2. Characteristics at Initial Diagnosis of Patients Who Died Within 6 Months and Patients Who Survived

<table>
<thead>
<tr>
<th></th>
<th>Dead Patients (n = 66)</th>
<th>Survivors (n = 149)*</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y‡</td>
<td>83 ± 8</td>
<td>77 ± 11</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Sex, No. F/M</td>
<td>41/25</td>
<td>77/72</td>
<td>.15</td>
</tr>
<tr>
<td>General condition, No.</td>
<td>16/19/27</td>
<td>66/39/27</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>No. normal/moderately altered/poor</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High blood pressure, No. (%)</td>
<td>23 (35)</td>
<td>60 (40)</td>
<td>.54</td>
</tr>
<tr>
<td>Ischemic heart disease, No. (%)</td>
<td>6 (9)</td>
<td>15 (10)</td>
<td>1.0</td>
</tr>
<tr>
<td>Stroke, No. (%)</td>
<td>7 (11)</td>
<td>16 (11)</td>
<td>1.0</td>
</tr>
<tr>
<td>Dementia, No. (%)</td>
<td>13 (20)</td>
<td>14 (9)</td>
<td>.05</td>
</tr>
<tr>
<td>Diabetes mellitus No. (%)</td>
<td>5 (7.6)</td>
<td>15 (10)</td>
<td>.80</td>
</tr>
<tr>
<td>Cancer, No. (%)</td>
<td>8 (12)</td>
<td>11 (7)</td>
<td>.30</td>
</tr>
<tr>
<td>Chronic lung condition, No. (%)</td>
<td>11 (17)</td>
<td>18 (12)</td>
<td>.40</td>
</tr>
</tbody>
</table>

* Two patients were unavailable for follow-up before 6 months.
† P values for univariate analyses.
‡ Mean ± SD.

years, and 62% at 5 years. The survival curve of patients with BP strikingly differed from the expected curve in the first months, but not after 1 year (Figure). There was a slight non–statistically significant difference in the death rates observed in the 3 participating centers (25%, 29%, and 35% at 6 months in Amiens, Limoges, and Créteil, respectively; P=.36).

For the 66 patients who died in the first 6 months after diagnosis (mean±SD , 2.7±1.6 months), the cause of death was known in 46. The main causes of death were sepsis in 23 patients (including 11 patients with pneumonitis) and cardiovascular diseases in 11. Cancer was the cause of death for 3 patients. According to mortality data in the elderly French population, the expected numbers of deaths from sepsis, cardiovascular diseases, and cancer in a 6-month period were 0, 3, and 2, respectively. Observed figures were higher than expected ones for sepsis and cardiovascular diseases (P<.001 and P=.06, respectively). Most patients who died within 6 months (57/66 [86%]) were receiving oral corticosteroids, often in high dosage (mean daily dose, 42 mg; range, 10-120 mg).

Among the factors often considered to characterize the severity of BP at initiation of therapy (severity of pruritus, and number of daily blisters, blood eosinophilia, and level of serum antibodies) or that could be related to clinical variants (involvement of mucous membranes), none appeared predictive of death in the first 6 months (Table 1). The death rate at 6 months was higher in generalized than in localized forms of BP (47/149 [32%] and 13/37 [19%], respectively; P=.08).

Three factors appeared significantly linked to an increased mortality in univariate analysis: older age, poor general condition, and dementia (Table 2). Female sex and treatment with oral corticosteroids were associated with an increased risk of borderline statistical significance.

Apart from dementia, none of the most frequent comorbid conditions was associated with an increased mortality.

From multivariate analysis, older age, poor general condition, female sex, and generalized forms of disease appeared independently predictive of early death (Table 3). Dementia disappeared in multivariate analysis because it was associated with both an older age (83.8±10.0 years) and a poorer general condition. Treatment with oral corticosteroids disappeared as an independent risk factor because of its strong association with the generalized forms of BP.

Patients older than 75 years had a 6-fold increase in the risk of dying within 6 months when compared with younger patients (RR, 5.8; 95% CI, 1.7-20.0). For those older than 86 years, the RR was 7.1 (95% CI, 2.0-25.0). When compared with those in good condition, patients
with marked alterations in their general status were at increased risk of death (RR, 8.2; 95% CI, 3.0-22.0). When compared with localized forms, generalized BP was associated with a 4-fold increase in the risk of death (RR, 4.4; 95% CI, 1.4-13.7). Women had a higher mortality rate at 6 months (RR, 2.4; 95% CI, 1.1-5.4).

**Table 4. Death at 6 Months in Patients Treated With Immunosuppressive Drugs**

<table>
<thead>
<tr>
<th>No. Treated</th>
<th>Death at 6 mo. No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azathioprine alone</td>
<td>3 1 (33)</td>
</tr>
<tr>
<td>Azathioprine + oral corticosteroids</td>
<td>22 8 (36)</td>
</tr>
<tr>
<td>Cyclophosphamide + oral corticosteroids</td>
<td>1 0 (0)</td>
</tr>
</tbody>
</table>

**COMMENT**

In this follow-up study of 217 patients with BP, we observed a high mortality rate. Increased mortality occurred mostly during the first 6 months after the diagnosis and treatment of the disease. The mortality rates were 31% after 6 months and 41% after 1 year. Later on, the survival curve was a little different from that expected in the French elderly population.

There are few data in the literature on the prognosis of BP. In previous studies, death rates were usually lower than in the present one: 6% at 2 years, 19% at 1 year, 28% at 3 years, 30% at 3 years, and 40% at 1 year. All previous studies were on smaller numbers of patients and some may have included selected patients. However, the older age of our patients was the most probable explanation for the observed differences. The mean (±SD) age of patients included in the present study was 79±11 years in comparison with 70 years, 74 years, and 75 years, and 79 years in previous series.

Our patients had been referred to university hospitals. Even though not all were treated as inpatients, there may have been some bias toward the selection of more severe cases in older patients with more comorbid conditions and a poorer prognosis. That might be true for 1 center ( Créteil) located in a large urban area where direct and indirect fluorescence tests are easily available in many medical wards. The other 2 centers are the only dermatology wards with all facilities in their regions, where it is generally agreed by all dermatologists that patients with blistering diseases should be referred to the hospital to establish the diagnosis. On the basis of this hypothesis, these 2 centers (Amiens and Limoges) participated in a study of the incidence of BP that provided estimates similar to those observed in Germany. We, therefore, believe that there was no important selection bias in these 2 regions. Because death rates differed little among the 3 centers, we estimate that selection bias could contribute only marginally to the high mortality observed in our cohort.

Strikingly, we found that with the exception of generalized vs localized forms of BP, none of the clinical markers of progression or severity of BP was predictive of an early death. This is concordant with the previous findings of Venning and Wojnarowska. Other factors that appeared significantly associated with a poorer prognosis were older age, poor general condition, and female sex.

The poor survival of older patients has been previously seen in BP. Such a deleterious effect of age has been well documented in many serious conditions. The mean age of the patients in our cohort (79 years) is higher than in most series, including previous French studies. We believe that this older age did not result from a referral bias in the present cohort but rather from exclusion of the sicker (and older) patients from previous randomized therapeutic studies and from specific demographic characteristics of the French population. As the result of a sharply decreased birth rate during World War I (1914-1918), the age distribution of the elderly population in France in 1990 was characterized by an important deficit of persons aged 72 to 76 years. For example, in that year in France, there were 240,000 persons aged 75 years and 325,000 aged 80 years. This demographic pattern probably contributed to raising the mean age of French patients with BP, as observed in another recent study, where it was 82 years.

The increased risk of death of patients in poor general condition is not surprising. Unfortunately, our questionnaire used only the dermatologist’s global assessment of the general status of the patient. We did not use a standardized score and, therefore, we were not able to analyze more specific criteria related to the “general condition.”Because the assessment was mainly based on the autonomy of patients, we assume that our global assessment was probably a reflexion of the Karnofsky Scale. None of the many comorbid conditions that were recorded in the charts appeared to contribute to an early death.

We were concerned by the potential effects of therapy on mortality. The main cause of death in our patients was sepsis, an otherwise uncommon cause of death in the general elderly population. Sepsis is reported as the cause of death in only 1.5% of death certificates for persons older than 80 years in France. In our series, one half of early deaths had been attributed to sepsis. This observation is concordant with previous findings by Savin. In our series as well as in Savin’s study, most patients were receiving oral corticosteroids when they died. Cardiovascular disorders, the second cause of death in our series, might also have been aggravated by systemic corticosteroids. We, therefore, strongly suspected that oral corticosteroid therapy could be a factor in mortality in our patients. This was not confirmed by the multivariate analysis of potential risk factors, where the risk of death did not appear increased in patients treated with oral corticosteroids. The borderline risk observed in univariate analysis disappeared because oral corticosteroids had been more often used in generalized forms that emerged as significantly related to death. Because treatment modalities had not been controlled in this series, and because 80% of patients received oral corticosteroids, we were not in an optimal situation to study the effect of treatment modalities on the prognosis.

In the present series, immunosuppressive drugs, mainly azathioprine, did not appear to change the prognosis (Table 4), although too few patients received im-
munosuppressive drugs to allow a real evaluation. When associated with corticosteroids, immunosuppressive drugs have been previously suspected to increase the early mortality in BP.10,13

Topical high-potency corticosteroids have been shown to be effective in the control of BP.16,17 Because topical corticosteroids are expected to result in fewer systemic adverse effects than oral corticosteroids,17 a therapeutic study comparing the effectiveness and side effects of topical vs oral corticosteroid therapy would be important for the future treatment of patients with BP. Until the results of such a study are available, we suggest the use of topical corticosteroids in the management of BP in older patients and in those in poor general condition who are at high risk of early death, especially from infection.

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REFERENCES