

Appendix S1

MATERIALS AND METHODS

Study population

This was a retrospective, database study of the records of all cases of BP diagnosed at the Department of Dermatology, Oulu University Hospital, Finland, between 1985 and 2012. The patients were identified based on the International Classification of Diseases (ICD) (coded as 694 in ICD 8, 694.5 and 694.6 in ICD 9, and L12 in ICD 10) from the hospital database and the patient records were checked. Patients admitted to the hospital, together with those treated in the outpatient clinic, were included. The patients diagnosed with BP between 1985 and 2009 ($n = 159$) were the same as those included in our previous study (2). The present study had an extended study period that included the years 2010–2012 and included an additional 39 patients with BP.

Patients were not contacted; therefore an ethics committee statement was not required. Permission to use patient records was obtained from the Medical Director of Oulu University Hospital.

Diagnostic criteria

The inclusion criteria were the same as in our previous study (2): clinical features appropriate for BP and positive direct or indirect immunofluorescence microscopy (IF). Patients with only clinical features typical of BP were excluded, as were patients with only positive histology and/or BP180 enzyme linked immunosorbent assay (ELISA). The diagnostic criteria were regarded as positive if the following features (applied according to the BAD's guidelines for the management of BP (27)) were fulfilled. Clinical features of BP were: non-scarring blisters and/or erosions of the skin with or without lesions of the mucous membranes. Clinical features in cases of atypical BP were: eczematous and itchy lesions of the skin without blistering, seen by a dermatologist. Histopathological examination included: subepidermal blistering (Department of Pathology, Oulu University Hospital). Direct IF features were: linear deposits of immunoglobulin G (IgG) and/or complement C3 along the basement membrane zone (BMZ) (Department of Pathology, Oulu University Hospital). Indirect IF features were: circulating autoantibodies in the serum against the BMZ detected by indirect IF performed on frozen sections of monkey or rabbit oesophagus (HUSLAB, Helsinki, Finland). ELISA: circulating autoantibodies against recombinant human BP180 protein's NC16A domain (HUSLAB, the manufacturer of the BP180 ELISA kit: Mbl, Medical & Biological Laboratories Co., Ltd, Japan). ELISA assays have been taken in the Oulu University Hospital since 2002 and analysed in HUSLAB according to the manufacturer's instructions. The BP180 ELISA kit has remained the same over the entire study period. Oulu University Hospital is the only department of pathology that performs IF in The Northern Ostrobothnia Hospital District. Thus, all suspected cases of BP are referred to Oulu University Hospital.

Variables

All of the treatments used for BP were registered from patient records. Also, the highest dose of prednisolone used, usually at the outset of treatment, was recorded, but the cumulative

prednisolone dose was not available. To examine the possible association between medications used to treat BP and mortality, 3 groups were formed according to expected different prognoses. Group 1 comprised those patients treated solely with oral prednisolone together with topical corticosteroids, group 2 comprised those patients treated with topical corticosteroids with or without oral tetracycline, and group 3 comprised those patients who had both oral prednisolone and adjuvant immunosuppressant (azathioprine and/or methotrexate, not used simultaneously). Patients in group 3 may have also used topical corticosteroids and/or tetracycline and/or dapson, usually for a short time without adequate response, before prednisolone was started.

In addition, certain comorbidities were recorded: autoimmune diseases, malignancies, diabetes type 2, cardiovascular diseases, neurodegenerative diseases, as well as other skin conditions occurring prior to the diagnosis of BP. Autoimmune diseases were defined according to a study conducted in Denmark (29), except for autoimmune skin diseases, which were recorded as other skin conditions, and multiple sclerosis, which was registered as a neurodegenerative disease. Cardiovascular diseases included all forms of cardiac and blood vessel diseases. Neurodegenerative diseases included, for instance, strokes, dementias, Parkinson's disease and multiple sclerosis, whereas epilepsy and congenital conditions were excluded. The total number of medications documented in the patient records at the time of diagnosis was registered, as was the date of death. In cases of missing information concerning the date of death in patient records, this was obtained from the Local Register Office of Northern Finland or from Statistics Finland.

Outcomes

The primary outcome in this study was the SMR of patients with BP. The secondary outcomes were medications and comorbidities and their possible predictive effect on mortality.

Statistical analysis

Statistical analyses were performed using STATA (Data Analysis and Statistical Software, MP 11.2, StataCorp LP, College Station, TX 77845, USA) and PASW (Predictive Analytics Software, Versions 18 and 20, Chicago, IL, USA). Characteristics of the study population were presented as proportions, means (with standard deviation (SD)) and medians, when appropriate. All rates and ratios were reported with 95% confidence interval (95% CI). Kaplan–Meier survival analyses were used to estimate the mortality for patients with BP for different subgroups of medication. Hazard ratios (HR) were computed by Cox regression analysis and adjusted for age at the time of diagnosis as well as for sex. Differences in dose of prednisolone, mean age, and number of concomitant medications between the 3 subgroups of BP medication were tested by Kruskal–Wallis test. The negative binomial model was applied to determine the risk ratio of the increased number of concomitant medications, and statistical significance was tested using the log-rank test for equality of survival functions. SMRs were calculated using indirect methods comparing the mortality rates among persons with BP with the rates in the general population; the mortality data on the general Finnish population between 1985 and 2012 for different age groups were provided by Statistics Finland (<http://www.tilastokeskus.fi>).