

CLINICAL STUDY

Pemphigus vulgaris: a 11-year review

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Abstract: *Background:* Pemphigus vulgaris (PV) is a rare, chronic life-threatening autoimmune blistering disease of the skin and mucous membranes.

Methods: A retrospective analysis of 31 patients with the diagnosis of pemphigus vulgaris, admitted for hospitalization from January 1996 to December 2006. Descriptive statistics has been used for data evaluation.

Results: The average age at onset was 49.0±16.2 years, with female to male ratio 1.4/1. Diagnosis was confirmed histologically and by a direct immunofluorescence. Mucocutaneous form of PV was observed in 25 patients (80.7 %), mucous form in 3 patients (9.7 %), cutaneous form in 3 patients (9.7 %). Factors preceding the onset of PV were most often viral (38.7 %) and bacterial (35.5 %) infections, dental focuses (25.8 %), stress (16.1 %), and contact with chemical substances (16.1 %). 6 patients (19.4 %) did not indicate any triggering factor. Corticosteroids alone were given to 18 patients, combined with azathioprin or cyclosporin to 13 patients, and 1 patient was treated with intravenous immunoglobulin. Adverse events were mostly osteopenia/osteoporosis (41.9 %), hyperlipoproteinemia (41.9 %), cataract (32.3 %) and Cushing's syndrome (32.3 %). Cutaneous and mucous infections were most often caused by *Staphylococcus aureus* and *Candida albicans*, respectively. 3 patients died (9.7 %), and in 3 patients (9.7 %) in a long term remission, the immunosuppressive treatment was discontinued.

Conclusion: Pemphigus vulgaris is still a life-threatening disease. Although corticosteroids dramatically improved the mortality, and are still considered the first-choice therapy, significant morbidity of the disease and the corticosteroid treatment still exists. The combination of corticosteroids with corticosteroid-sparing agents delays the onset of adverse events (Fig. 2, Ref. 33). Full Text (Free PDF) www.bmj.sk.

Key words: pemphigus vulgaris, triggering factors, therapy, corticosteroids, side-effects.

Pemphigus vulgaris (PV) is a rare, chronic life-threatening autoimmune blistering disease of the skin and mucous membranes. It is caused by autoantibodies directed against the epidermal keratinocyte desmosomal cadherins Dsg3 or Dsg3/Dsg1, resulting in loss of adhesion between the keratinocytes and blister formation (1). It is the commonest type of pemphigus which accounts for approximately 70 % of pemphigus cases (2). PV particularly affects women more than men (3), although some data show an equal prevalence in both sexes (2). The average age at the onset is between the fourth and sixth decades, but can also arise in children and older people (4). According to various authors, the onset and course of PV could be the result of an interaction between the host's genetic factors and environmental triggering factors such as drugs, diet, UV, viruses and other (5, 6, 7).

The treatment consists of systemic corticosteroids (CS) and corticosteroid-sparing agents. Before the administration of corticosteroid therapy, PV was lethal in more than 90 % of cases, with mortality 75 % in the first year of the disease onset (8). In present, mortality is 5–10 %, although it is primarily caused by

the adverse drug reactions (9). The aim of our study was to compile a review from the medical files of 31 PV patients admitted to our department from 1996 to 2006.

Methods

A retrospective analysis of the medical files of 31 patients with the diagnosis of pemphigus vulgaris, admitted to the Department of Dermatovenereology, Faculty of Medicine, Comenius University, Bratislava between January 1996 and December 2006. Some of the patients were hospitalized several times. The diagnosis of PV was confirmed clinically, histologically and using a direct immunofluorescence. We observed the age, sex, history of PV in family, the first onset of the disease, clinical picture, diagnostic methods, triggering or aggravating factors, course of the disease, treatment and its adverse reactions, accompanying skin infections, laboratory values of blood count and biochemical parameters. Descriptive statistics has been used for data evaluation.

Results

A total of 31 patients, including 18 women (58.1 %) and 13 men (41.9 %) with female to male ratio 1.4:1, were studied. The average age at the disease onset was 49.0±16.2 years (50.6±15.9 for males, 47.2±17.0 for females) with the range from 17 to 78 years (Fig. 1).

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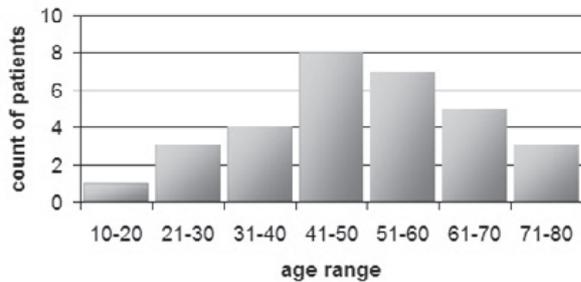


Fig. 1. The age range of 31 patients at the first onset of PV.

Histological examination was performed in all patients, direct immunofluorescence in 14 patients and blister smear cytology in 18 patients (Tzank test). For the histological examination, one biopsy specimen of bullous lesion was taken from each patient. A suprabasal acantholytic blister formation was present in all of them, which was confirmative for the PV diagnosis. For a direct immunofluorescence, perilesional biopsy was done. 14 patients showed an intercellular deposition of IgG and 5 of them also C3 in epidermis, the findings typical for PV. In 14 out of 18 patients, Tzank smear test was positive and acantolytic (Tzank) cells were found.

None of the patients had a family history of PV, one patient had a sister with psoriasis vulgaris. From associated diseases, rheumatoid arthritis was detected in one patient. In 16 patients (51.6 %), initial lesions were observed in the oral cavity, in 2 of them (6.5 %) at the same time lesions appeared on the back and in 1 patient (3.2 %) on the scalp. In the rest of the patients, first lesions appeared on the back, scalp, abdomen, arms, neck or thorax. From 13 patients (41.9 %), in which initial lesions appeared in the oral cavity, skin involvement was observed, on average, after 5 months (range from 2 weeks to 18 months). The average period (median) from the onset of the disease to first hospitalization was 159 days. Mucocutaneous form of PV was observed in 25 patients (80.7 %; 15 women, 10 men), mucous form in 3

patients (9.7 %; 2 women, 1 man), and cutaneous form in 3 patients (9.7 %; 1 woman, 2 men). Localization of lesions in patients varied during the course of the disease. During hospitalizations, the majority of lesions was observed on thorax (79.4 %), back (64.1 %) and in oral cavity (63.0 %) (Fig. 2). Pain (68.3 %), burning (30.7 %) and itching (30.6 %) of the lesions were recorded in some patients. Due to subjective difficulties and extend of oral lesions, administration of liquid/mushy food was necessary in some cases (28 %). Factors preceding the onset of PV were most often viral (38.7 %) and bacterial infections (35.5 %), dental focuses (25.8 %) and stress (16.1 %). Also, the contact with chemical substances (16.1 %) (glues, colorants, varnishes, artificial colorants), mechanical irritation (6.5 %), pregnancy (3.2 %), and sun exposure (3.2 %) were recorded as triggering or aggravating factors. 4 patients (12.9 %) were taking diclofenac, ACE inhibitors, acetylsalicylic acid, propionic acid derivatives, levodopa or isoniazid at the time of the onset/aggravation of PV. In some patients, several possible aggravating factors were observed. 6 patients (19.4 %) did not indicate any triggering factor.

During a 11-year period, systemic CS (methylprednisolon, prednison) were administered to all 31 hospitalized patients, either alone (18 patients, 58.1 %) or in combination with azatioprin (13 patients, 41.9 %), cyclosporin (3 patients, 9.7 %) or intravenous immunoglobulin (1 patient, 3.2 %). The average daily doses of prednison and methylprednisolon used in the controlling phase of the therapy were 50.9 mg (0.5–1.5 mg/kg/day) and 43.6 mg (0.5–1.5 mg/kg/day), respectively. The average dose of azatioprin and cyclosporin were 127.8 mg (1–3 mg/kg/day) and cyclosporin 245 mg (3–4 mg/kg/day) per day, respectively. After the controlling and consolidation phase of the therapy, the maintenance phase was initiated and doses were reduced. The doses of intravenous immunoglobulin in 5 days together were 150 g (2 g/kg; 30 g daily). Adverse events occurred in 100% of patients taking CS. The most frequent adverse reactions of CS were osteopenia/osteoporosis (13 patients, 41.9 %), hyperlipoproteinemia (13 patients, 41.9 %), cataract (10 patients, 32.3 %) Cushing's syndrome (10 patients, 32.3 %), and iatrogenic depression/anxiety

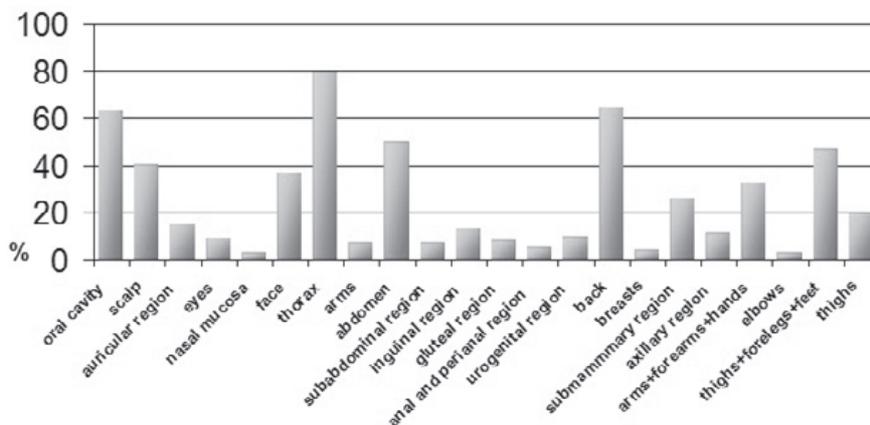


Fig. 2. Localisation of PV lesions in 31 patients hospitalised in 1996–2006.

(9 patients, 29.0 %). Also, abnormal liver function tests (7 patients, 22.6 %), weight gain (7 patients, 22.6 %), iatrogenic diabetes mellitus (5 patients, 16.1 %) and high blood pressure (4 patients, 12.9 %) were recorded. The adverse reactions in 13 patients (41.9 %) taking azatioprin were abnormal liver function tests (4 patients), myopathy (2 patients), arthralgia (2 patients), nausea (2 patients), acute bone marrow suppression (1 patient) and alteration of renal functions (1 patient). The adverse reactions in 3 patients (9.7 %) taking cyclosporin were gingivitis hypertrophica, and severe hepatotoxic effects, leading to discontinuation in all of them. As a result of the immunosuppression, secondary infections developed in hospitalized patients. Mucous infections were most often caused by *Candida albicans* (14 patients, 45.2 %) and cutaneous infections by *Staphylococcus aureus* (13 patients, 41.9 %). In 1 patient, dermatophytic infection by *Trichophyton rubrum* spread from the infected toenails, causing tinea corporis (3.2 %). In 1 patient, herpes zoster infection and recurrent herpetic keratitis developed (3.2 %). Some patients had a severe course of the disease, with repeated admissions to hospital. A graver course of PV was observed in female patients. From the 25 patients (80.6 %) with mucocutaneous form of PV, 9 were female patients (29.0 %), and 3 male patients (9.7 %) hospitalized repeatedly. In each of the 2 groups of patients with mucous or cutaneous form of PV, 1 male patient was hospitalized repeatedly. All of the 5 most often hospitalized patients were women with the mucocutaneous form of PV. The average hospitalization duration at our department was 24.7 ± 16.5 days (males 19.7 ± 9.5 days, females 22.1 ± 11.5 days). The shortest hospitalization was 2 days and the longest 83 days. In this 11-year period, 3 patients died, 2 due to pneumonia, and 1 due to complications of the ischemic heart failure. In 3 patients (9.7 %) in a long term remission, the immunosuppressive treatment was discontinued after a negative direct immunofluorescent examination.

Discussion

Female to male ratio in our study was 1.4:1. Similar findings were recorded also by other authors (10, 11). Some data point out that PV incidence is the same in both sexes (1, 12) or that PV appears more often in males (13, 14). In our study, PV onset was most often between the 41–50 years of age. The youngest patient was 17 and oldest 78 years old when first diagnosed with PV. In other studies, patients were also between 40–60-years old at the PV onset, but it PV noted also in children and older people until 89 years (4, 7, 8, 11, 15). In more than half of the patients in our study (51.6 %) first lesions appeared in oral cavity. Also other authors observed the formation of first lesions in oral mucosa in approximately 50 % of patients (16, 17). Mucocutaneous form of PV was observed in 25 patients (80.7 %), mucous form in 3 patients (9.7 %), and cutaneous form in 3 patients (9.7 %). The majority of lesions were observed on thorax (79.4 %), back (64.1 %) and in oral cavity (63.0 %). A similar incidence of oral mucosa lesions was observed in Bulgarian patients (66 %), compared to higher number in patients from Israel (92 %) and Italy (83 %) (18). Some patients had a severe course of the disease, with re-

peated admissions to the hospital. A graver course of PV was observed in female patients. From the 25 patients with the mucocutaneous form of PV, 9 were females (29.0 %), and 3 male patients (9.7 %) hospitalized repeatedly. All of the 5 most often hospitalized patients were women with the mucocutaneous form of PV.

Factors preceding the onset of PV were most often viral (38.7 %) and bacterial infections (35.5 %). Other authors also consider infection as a possible triggering factor for PV onset (19, 20, 21, 22). Factors such as stress, chemical substances, mechanical irritation, pregnancy, and sun exposure recorded in our study, have been detected in several studies as triggering or aggravating factors of PV onset (2, 7, 8, 18, 23, 24, 25, 26, 27). Some authors listed drugs such as diclofenac, ACE inhibitors, acetylsalicylic acid, propionic acid derivatives, levodopa and isoniazid as possible triggering factors of PV in predisposed individuals (18, 28). 4 of our patients (12.9 %) also used these drugs, they suffered from concomitant illnesses and this medications could not be discontinued. We cannot therefore exclude that administration of above mentioned drugs could hinder remission.

During hospitalizations of our patients, the daily average initial dose of prednisone and methylprednisone was 50.9 mg (0.5–1.5 mg/kg/day) and 43.6 mg (0.5–1.5 mg/kg/day), respectively. In our study, administration of corticosteroid-sparing agents (azatioprin, cyclosporin, i. v. immunoglobulin) proved to be beneficial and high doses of corticosteroids were not necessary in most cases. Doses of prednisolon 40–80mg daily in patients with mild PV and of 80–120 mg/day in moderate and severe PV, in combination with azatioprin (2–3 mg/kg/day) were the mainstay of treatment in 123 PV patients in Turkey (11). In 159 PV patients in Croatia, authors observed good therapeutic effect with the average initial dose of prednisone 150 mg daily, in 81 % of the patients in combination with adjuvant therapy such as azatioprin, intramuscular gold, or plasmaferesis (8).

PV is a serious illness that is potentially lethal. Before administration of systemic CS, mortality of PV was more than 90% (8). Nowadays, mortality is 5–10 %, mostly due to adverse drug reactions. Adverse events occurred in all 31 patients in our study taking CS, mostly osteoporosis, hyperlipoproteinemia, cataract, Cushing's syndrome and iatrogenic depression/anxiety. Adverse reactions of CS, azatioprin, and cyclosporin therapy observed in our patients were also recorded in patients from Turkey (11), United States (29), Croatia (8), Mali (14), Malaysia (30).

Due to a prolonged administration of systemic CS and immunosuppressives, secondary bacterial and mycotic infections developed in hospitalized patients. Other authors also claim that one of the most frequent complications of the immunosuppressive therapy is the occurrence of bacterial, mycotic, viral and parasitic infections (31, 32). Generalization of *Trichophyton rubrum* infection observed in 1 of our patients (33) was recorded also in other pemphigus patients (32).

Conclusion

Pemphigus vulgaris is still a life-threatening disease. Although corticosteroids dramatically improved the mortality and

are considered the first-choice therapy, there exists a significant morbidity of the disease and the corticosteroid treatment. The combination of corticosteroid treatment with corticosteroid-sparing agents enables a delay of adverse events. Early diagnosis as well as appropriate initial and maintenance therapeutic doses allow better prognosis with lower mortality rates. A regular follow-up, decrease of adverse events, proper modification of treatment and elimination of triggering factors are inevitable for the long-term remission.

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