Abstract

Background Pemphigus vulgaris (PV) is a rare autoimmune blistering disease of the skin and mucous membranes. It varies in its clinical profile and epidemiologic characteristics in different parts of the world.

Objective To determine the clinical features of PV in Iran in a prospective manner.

Methods The study included 140 patients with newly registered PV attending our dermatology clinic between January 2003 and June 2004.

Results The mean age at the onset of the disease was 41.5 ± 15.7 years, with a female to male ratio of 1.59:1. At presentation to our clinic, both skin and mucosal involvement was observed in 95 patients (67.9%). Cutaneous lesions without the involvement of the mucous membranes were seen in nine patients (6.4%), and exclusive mucosal involvement was present in 36 patients (25.7%). The most common initial localization of the disease was the oral cavity, which was involved in 93 patients (77.5%). The most frequent cutaneous and mucosal sites involved were the thorax and oral cavity, respectively.

Conclusion Although minor differences were noted, the results of this study are in relatively good agreement with the literature with regard to the age, gender, and initial presentation of PV in Iran. Some skin sites, such as the scalp, thorax, and axilla, may be more commonly affected in men. Patients with initial mucosal lesions were significantly younger than those with initial cutaneous involvement. Mucosal lesions other than the oral mucosa may be more common than previously thought.

Introduction

Pemphigus vulgaris (PV) is a rare autoimmune blistering disease of the skin and mucous membranes characterized by the presence of autoantibodies targeting desmoglein 3, a surface antigen of keratinocytes, engaged in the maintenance of cell–cell junctions. The incidence of the disease varies in the range 0.07–3.2 cases per 100,000 population per year depending on the geographic location, and is about 1 per 100,000 population in Iran. PV typically runs a chronic course, with blisters, painful erosions, and ulcers on the mucosa and skin. It is a worldwide disease and varies in its presentation, severity, clinical profile, and epidemiologic characteristics in different areas. The purpose of this study was to determine the demography and clinical features of PV in Iran in a prospective manner. The characteristics of PV in 140 newly diagnosed patients during an 18-month period are described.

Patients and methods

The study included 140 patients with newly registered PV attending the dermatology clinic during the period January 2003 to June 2004 (18 months). The study was carried out at the Pemphigus Research Unit, Razi Hospital, Tehran University of Medical Sciences, Tehran, Iran. In all patients enrolled, the diagnosis of PV was based on the typical clinical features of the disease, confirmed by histopathologic and direct immunofluorescence (DIF) findings based on revised diagnostic criteria. Indirect immunofluorescence (IIF), using a substrate of monkey esophagus, was performed in a number of patients. In patients with mucosal lesions only, a biopsy was obtained from intraoral lesions and DIF was performed on perilesional normal mucosa. Only newly diagnosed patients who had not received any immunosuppressive therapy were enrolled in the study. Each patient was subjected to a detailed review of clinical history, similar disease in other family members, drug intake, and a complete physical examination. Various clinical parameters were studied, including age, sex, duration of the disease, anatomic sites affected at the onset of disease and subsequently, number of skin lesions, and size of the largest skin lesion.

Statistical analysis was performed using the chi-squared test for differences in proportion and the Mann–Whitney U-test for differences in means. Fisher’s exact test was used when necessary.
Results

Demographic features
The patients included 54 men (38.6%) and 86 women (61.4%), with a female to male ratio of 1.59 : 1. The age of the patients at the onset of the disease ranged from 13 to 82 years (mean, 41.5 ± 15.7 years). The majority of patients (36, 25.7%) were in the fifth decade, whereas 16 cases (11.4%) occurred in individuals older than 60 years. Eight (5.7%) patients were less than 18 years of age. The mean age at the onset of the disease was 42.7 ± 14.3 years (range, 15–76 years) for women and 39.7 ± 17.7 years (range, 13–82 years) for men. Although women were approximately 3 years older, the difference was not statistically significant. Figure 1 shows the distribution of patients according to age and sex. None of the patients had taken any drugs in the weeks preceding the onset of PV.

Disease profile
At presentation to our clinic, both skin and mucosal involvement was observed in 93 patients (67.9%). Cutaneous lesions without the involvement of the mucous membranes were seen in nine patients (6.4%), and exclusive mucosal involvement was present in 36 patients (25.7%). All 36 patients with mucosal lesions only were followed up for at least 6 months, and none developed cutaneous lesions similar to PV. Two patients (1.4%) had family members with confirmed PV. The diagnosis for all 140 patients was confirmed by histologic examination, which showed suprabasal acantholysis. DIF test was performed in all 140 patients, and proved positive for intercellular immunoglobulin G (IgG) and IgM deposits. IIF was performed in 59 patients; 19 patients (32.2%) had negative results. Of those with positive results, 17 patients (74%) had titers of less than 1/40 and six patients (24%) had titers of between 1/40 and 1/160. Of the 36 patients with mucosal lesions only, IIF test was performed in six, all showing positive results.

The duration of the disease before diagnosis was less than 3 months in 40 patients (28.6%), 3–6 months in 37 patients (26.4%), 6–12 months in 37 patients (26.4%), and more than 12 months in 25 patients (17.9%). The duration of disease was not significantly different between male and female patients (P = 0.72).

In patients with cutaneous lesions, the diameter of the largest lesion was less than 1 cm in 46 patients (46.5%), 1–5 cm in 49 patients (49.5%), and greater than 5 cm in four patients (4%). The number of skin lesions was limited to less than 20 in 35 patients (35.4%), 20–49 in 22 patients (22.2%), 50–100 in 34 patients (34.3%), and more than 100 in eight patients (8.1%).

Initial lesions
Of the 120 patients whose initial disease localization was reliably known, the most common location was the oral cavity, which was involved in 93 patients (77.5%). No other mucosal site was involved as the initial presentation of the disease. The scalp and face were involved as initial disease localization in 18 patients (15%), and were the most frequent cutaneous regions involved initially. The disease presented initially in other parts of the body (trunk and limbs) in nine patients (7.5%). The mean ages of the patients with initial mucosal and cutaneous lesions were 39.8 ± 15.6 and 47.2 ± 16.5 years, respectively. Patients with initial mucosal lesions were significantly younger than those with initial cutaneous lesions (P < 0.05). None of the patients presented initially with generalized disease.

Clinical manifestations
The most frequent cutaneous and mucosal sites involved were the thorax and oral cavity, respectively. Table 1 shows the sites of involvement in the patients. The disease was generalized.

Table 1 Anatomic sites of involvement in 140 patients with pemphigus vulgaris

<table>
<thead>
<tr>
<th>Site of involvement</th>
<th>Number of patients (%)</th>
</tr>
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<tbody>
<tr>
<td>Oropharynx</td>
<td>128 (91.4)</td>
</tr>
<tr>
<td>Larynx</td>
<td>65 (46.4)</td>
</tr>
<tr>
<td>Genitalia</td>
<td>35 (25)</td>
</tr>
<tr>
<td>Conjunctiva</td>
<td>37 (26.4)</td>
</tr>
<tr>
<td>Nasal mucosa</td>
<td>65 (46.4)</td>
</tr>
<tr>
<td>Urethra</td>
<td>15 (10.7)</td>
</tr>
<tr>
<td>Acute paronychia</td>
<td>19 (13.6)</td>
</tr>
<tr>
<td>Nail dystrophy</td>
<td>10 (7.1)</td>
</tr>
<tr>
<td>Nail hematoma</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Scalp</td>
<td>68 (48.6)</td>
</tr>
<tr>
<td>Face</td>
<td>51 (36.4)</td>
</tr>
<tr>
<td>Breast</td>
<td>27 (19.3)</td>
</tr>
<tr>
<td>Thorax</td>
<td>86 (61.4)</td>
</tr>
<tr>
<td>Back</td>
<td>68 (48.6)</td>
</tr>
<tr>
<td>Abdomen</td>
<td>65 (46.4)</td>
</tr>
<tr>
<td>Groin</td>
<td>35 (25)</td>
</tr>
<tr>
<td>Axilla</td>
<td>48 (34.3)</td>
</tr>
<tr>
<td>Limbs</td>
<td>53 (37.9)</td>
</tr>
</tbody>
</table>
over the skin in 33 patients (23.6%). Acute paronychia was the most frequent nail change due to PV. The site of involvement was not significantly associated with the age of the patients. Scalp lesions were observed in 40.7% of females and 61.1% of males. This difference was statistically significant (P < 0.05). Similarly, the thorax and axilla were also more commonly involved in men than in women (P < 0.05).

Discussion

In a previous study, we analyzed the different clinical forms of pemphigus in 1209 patients from 1984 to 2003. In this study, we present data on patients visiting the Pemphigus Research Unit from 2003 to 2004. We only included patients with PV.

PV is the major clinical form of pemphigus in many countries. It is particularly common in Jews and in individuals of Mediterranean descent. According to a previous study, PV accounts for 91.9% of all cases of pemphigus. The female to male ratio of 1.49 : 1 in our patients is similar to the ratio of 1.5 : 1 reported previously from Iran. A female preponderance has been observed in many studies, with female to male ratios of 1.2 : 1 in Italy (Sicily), 1.1 : 1 in Sofia, 1.16 : 1 in India, 1.2 : 1 in France, 2 : 1 in Kuwait, 1.5 : 1 in Korea, 4 : 1 in Mali, and 4.1 : 1 in Tunisia. An equal sex predisposition has been reported in patients from the south-eastern USA. A male preponderance of 2.2 : 1 has been reported from Saudi Arabia. Our mean age of onset of pemphigus was 41.5 years, which is comparable with that (42 years) given in a previous report from Iran, but lower than that in Africa (48 years), Italy (54 years), Finland (57 years), Saudi Arabia (43.1 years), Croatia (53 years), Italy (Sicily) (56 years), and Mali (52 years). A recent report from southern Iran showed an even lower mean age of onset of 38 years. Considering these data, the age of onset of PV in Iran is lower than that in most reports from other countries. Even lower mean ages of onset of the disease have been reported from Kuwait (35.8 years) and Tunisia (36.7 years).

Juvenile cases were relatively common in our series, comprising 5.7% of patients (female to male ratio, 1). In a previous report from Iran, this figure was 2.1% with a female to male ratio of 2.25 : 1. Only one in 222 patients reported from Tunisia and none of 203 patients reported from Croatia had the juvenile form of the disease. In a study from India, 12.9% of patients were less than 18 years of age, with a male to female ratio of 2.5 : 1.7 Because of the small number of juvenile cases, it is not possible to draw conclusions on the differences between genders in this form of PV.

Although the mean age of onset of PV was higher in men than in women in our study, and in other series, only one report from Tunisia showed a statistically significant difference, with men being nearly 20 years older than women. We observed only two cases of familial PV (1.4%), similar to the other report from Iran. From a search of the literature, we found only a few case reports of familial PV.

In our study, involvement of both the skin and mucosa was observed in 67.9% of patients. This is comparable with a previous report from Iran (70%), and other reports from Sofia (64.8%) and India (63.3%), but lower than a report from Kuwait (79%). PV with exclusive mucosal involvement was observed in 25.7% of patients. This is higher than the previous report from our center (18%), as well as reports from Sofia (10.8%), Kuwait (13%), India (6.81%), and Saudi Arabia (5.3%). Exclusive skin involvement was observed in 6.4% of patients. This is lower than the other report from our center (12%), as well as the reports from Sofia (24.3%), Kuwait (8%), India (47.7%), Saudi Arabia (15.8%), Finland (22%), and Korea (15.6%). With regard to these data, our cases showed more exclusive mucosal involvement, rather than being limited to the skin. In a multicentric multinational study, exclusive skin involvement was observed in 50% of patients, mucous membrane alone in 23% of patients, and both skin and mucous membrane involvement in 27% of patients. The results obtained from this report are not in accordance with our findings or with those of many other studies, as exclusive skin involvement was extraordinarily frequent in this report.

Classically, it has been presumed that PV commonly presents with oral lesions that may precede cutaneous lesions by months, but most patients eventually develop cutaneous lesions. Our cases showed a higher frequency of initial mucosal involvement (77.5%) compared with the reported average figure of 50–70%. In Croatia, only 31% of patients showed pemphigus initially localized to the oral mucosa. In 61.2% of our patients whose initial site of involvement was the oral mucosa, the skin was affected later. In 66.7% of patients with initial cutaneous disease, the condition progressed to show additional mucosal lesions. Although conjunctival, laryngeal, esophageal, and genitourinary mucosa are known to be affected in pemphigus, the presentation of the disease as involvement of the mucosa other than the oropharynx is rare, and none of these areas was involved initially in our patients.

Similar to the previous series reported from our center, the scalp and face were the most common cutaneous sites of initial localization of the disease (15%), being twice as common as other skin sites (7.5%). Desmoglein 3 is expressed more strongly in the buccal mucosa and scalp skin than in the skin of the trunk. This may explain the more common initial localization of the disease to these sites. None of our patients showed generalized skin involvement of the disease at presentation, but 3% of patients in a previous report showed generalized involvement from the beginning.

Circulating pemphigus autoantibodies are detected by IIF in over 80% of patients. In this study, IIF testing was performed in 59 patients, and 40 (67.8%) showed positive results.
Our previous report showed 81.1% positivity for the IIF test. This difference in IIF results, despite the use of the same substrate, is not clear, but may depend on the technician’s experience and equipment used.

In 17.9% of patients, the onset of disease was approximately 1 year before a correct diagnosis was made; 41.9% of patients with initial mucosal lesions and 65% of patients with initial cutaneous lesions had a disease onset at least 6 months before presentation to our clinic. Although cutaneous lesions seem to be diagnosed later, the difference is not statistically significant (P > 0.05). Jubojevic et al. reported four patients who had oral lesions for more than 5 years before the correct diagnosis was established. They believe that oral PV is often misdiagnosed by family physicians or dentists. In Iran, oral manifestation is the major presentation of PV, and general practitioners or dentists are familiar with this form of the disease; however, a large proportion of patients presenting with cutaneous disease may escape diagnosis for prolonged periods. Another reason for the earlier referral of patients with oral involvement may be the severely painful character of oral erosions, making patients seek medical attention. In this series, patients with initial PV presentation in the mucosa were about 7 years younger than those with initial cutaneous lesions. This observation needs to be confirmed by further studies with larger series.

Acute paronychia was observed in 13.6% of patients. This is higher than that observed in previous reports from Iran (6%) and Africa (4%). Similar to the other report from our center, the thorax was the most common cutaneous site of involvement, and generalized disease was seen in nearly 20% of patients. Our patients showed a higher frequency of conjunctival involvement (26.5%) than patients in previous reports from Iran (16%) and Africa (2.6%). In our patients, mucous membranes other than the oral cavity were involved more frequently in comparison with other reports. Our patients showed a higher frequency of nasal and laryngeal involvement (both 46.5%) compared with a previous report from Iran (nasal involvement, 11%; laryngeal involvement, 6%). This difference may be partly a result of a more precise examination of patients, which was performed by at least two academic dermatologists in our research unit. Consultation with an otolaryngologist, performed in all cases suspected of having laryngeal or nasal involvement, may have contributed to the high detection rate in these cases.

The finding that the thorax, scalp, and axilla were more commonly affected in men than in women has not been reported previously. If this observation is supported by other larger series, its physiopathologic background will need to be elucidated.

Conclusion

Although minor differences were noted, the results of this study are in relatively good agreement with the literature with regard to the age, gender, and initial presentation of PV in Iran. Some skin sites, such as the scalp, thorax, and axilla, may be more commonly affected in men than in women. Patients with initial mucosal lesions were significantly younger than those with initial cutaneous involvement. Mucosal lesions other than the oral mucosa may be more common than previously thought.

Acknowledgments

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References