Actas Dermosifiliogr. 2010;**101(6)**:524–533

ACTAS
Dermo-Sifiliográficas

Full English text available at
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ORIGINAL ARTICLE

Epidemiologic Study of 20 Cases of Pemphigus at Hospital Clínico Universitario Virgen de la Victoria de Málaga, Spain

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Manuscript received July 31, 2009; accepted for publication January 18, 2010

KEYWORDS
Pemphigus;
Blistering skin disease;
Epidemiology

Abstract
Introduction: Pemphigus comprises a group of autoimmune blistering diseases that affect the skin and mucous membranes. Its clinical and epidemiologic features vary according to geographic location and ethnic background.
Objective: An exhaustive search of the literature reveals very few reports of the epidemiology of pemphigus in our setting. Our aim, thus, was to conduct a retrospective study of the clinical and epidemiologic features of pemphigus at a secondary care hospital in Malaga, Spain.
Material and methods: We studied 20 patients diagnosed with pemphigus in our department over a period of 13 years (January 1995 to January 2008).
Results: We analyzed a large variety of clinical and epidemiologic parameters including sex; age; type of pemphigus; time since onset; associated symptoms; type, morphology, and location of lesions at the time of diagnosis; extent of skin and mucosal involvement; treatment received; treatment-related adverse effects and complications; number of hospital admissions; and patient outcome.
Conclusions: Except for minor differences, our results are in agreement with published data on pemphigus regarding sex, age, and clinical presentation. According to our results, male sex is a predictor of poor prognosis as it is associated with poorer response to treatment and a higher rate of adverse effects and hospital admission.

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PALABRAS CLAVE
Pénfigo;
Enfermedad ampollosa cutánea;
Epidemiología

Estudio epidemiológico de 20 casos de pénfigo en el Hospital Clínico Universitario Virgen de la Victoria de Malaga

Resumen

Introducción: Los pénfigos son un grupo de enfermedades ampollosas autoinmunes que afectan a la piel y a las membranas mucosas. Sus características clínicas y epidemiológicas son variables en función de factores geográficos y étnicos.
Objetivo: Si hacemos una búsqueda bibliográfica exhaustiva encontramos escasos trabajos sobre epidemiología del pénfigo en nuestro medio. El objetivo de nuestro estudio es determinar las características clínicas y epidemiológicas del pénfigo en un hospital de segundo nivel de Málaga (España), de una manera retrospectiva.
Material y métodos: El estudio incluyó 20 pacientes diagnosticados de pénfigo en nuestro Servicio en un periodo de 13 anos, comprendido entre enero de 1995 y enero de 2008.
Resultados: Se analizaron un extenso numero de parámetros clínicos y epidemiológicos, incluyendo sexo, edad, tipo de pénfigo, tiempo de evolucion de la enfermedad hasta el momento del diagnóstico, sintomatología asociada, tipo, morfología y localización de las lesiones en el momento del diagnóstico, afectación de piel y mucosas, tipo de tratamiento realizado, efectos adversos y complicaciones debidas a la terapia, número de ingresos hospitalarios y evolución final de los pacientes.
Conclusiones: Aunque con pequeñas diferencias, nuestros resultados están en buena consonancia con los ya existentes en la literatura en lo relativo al sexo, la edad y el perfil clínico de la enfermedad. Según nuestros datos ser varón es un factor de mal pronóstico, puesto que se asocia a una peor respuesta de la enfermedad al tratamiento y a mayor tasa de efectos secundarios y frecuencia de ingresos hospitalarios.

Introduction

The term *pemphigus* comes from the Greek word *pemphix*, which means blister or bubble. It describes a group of chronic autoimmune diseases of the skin characterized by the production of autoantibodies directed against the cell surface of keratinocytes, which leads to the loss of keratinocyte cell adhesion through a process called acantholysis. Clinically, the disease is characterized by the development of skin blisters and painful sores and ulcers on the mucous membranes. Pemphigus has traditionally been divided into 2 major groups: pemphigus vulgaris and pemphigus foliaceus, depending on the location of the blisters.[1-4]

Few epidemiologic data are available on pemphigus. Although it appears to be becoming more common, as reported by a recent study,[5] pemphigus is still a rare disease whose incidence, prevalence, and clinical and epidemiologic features vary according to geographic location and ethnic background.[2] Very few studies have been published on the epidemiology of pemphigus in Spain. The largest series analyzed to date consisted of 52 patients at Hospital 12 de Octubre in Madrid[6] and of 34 and 23 patients at Hospital Virgen Macarena in Seville.[7,8]

The aim of this study was to determine the clinical and demographic characteristics of pemphigus in the health care area of Hospital Universitario Virgen de la Victoria in Málaga, Spain based on a retrospective study of 20 cases of pemphigus diagnosed over 13 years. We also compared our results to those from other geographical areas based on an extensive review of the literature.

Materials and Methods

We analyzed 20 patients diagnosed with pemphigus at the Department of Dermatology, Hospital Clínico Universitario Virgen de la Victoria in Málaga, Spain between January 1995 and January 2008 (13 years). The hospital has a catchment area of 460 000 inhabitants.

All the diagnoses were initially based on the presence of typical clinical characteristics and subsequently confirmed by histopathology and direct immunofluorescence.

A wide range of clinical and epidemiologic parameters (Tables 1 and 2) were analyzed, with all data obtained retrospectively from patient records and pathology reports.

A descriptive analysis was performed of frequencies, percentages, and means, and between-group comparisons were calculated. Statistical analysis was done with the SPSS 12.0 statistical package.

Results

The prevalence of pemphigus in the study population is low, with just 20 patients with some form of pemphigus treated at the hospital between 1995 and 2008. This low prevalence is a serious limitation in terms of drawing conclusions from the results obtained.

Table 1 shows the clinical characteristics of the patients analyzed. There were 11 men (55%) and 9 women (45%) (male to female ratio of 1.22 to 1). The mean (SD) age at the time of diagnosis was 57.4 (18.8) years (range, 15-87

Table 1 Clinical Characteristics of Patients

Patient	Sex	Age, y	Time Since Onset, mo	Type of Pemphigus	Symptoms	Skin/Mucosal Lesions	Mucosal Lesions Only	Skin Lesions Only	Site of First Lesions
1	M	65	6	PF	Pain/discomfort	Skin	–	Head Chest	Head
2	M	66	2	PF	Pain/discomfort Pruritus	Skin	–	Head Chest Abdomen Lower limbs	Chest
3	F	72	18	PF	Pruritus	Skin	–	Head Chest	Head
4	M	75	1	PV	Pain/discomfort Dysphonia/dysphagia Poor general health	Skin and mucosal	Oral and genital	Chest Abdomen Upper limbs Lower limbs	Oral cavity
5	M	18	2	PV	Pain/discomfort Pruritus Poor general health	Skin and mucosal	Oral and genital	Head Chest	Oral cavity
6	F	56	12	PV	Pain/discomfort Dysphonia/dysphagia	Mucosal	Oral	–	Oral cavity
7	F	70	1	PV	Pain/discomfort Dysphonia/dysphagia Poor general health	Skin and mucosal	Oral	Head Chest Abdomen	Oral cavity
8	F	87	1	PV	Pain/discomfort Pruritus	Skin	–	Chest Abdomen	Chest
9	F	62	2	PV	Pruritus	Skin and mucosal	Genital	Chest Abdomen	Chest
10	M	49	1	PV	Pain/discomfort Dysphonia/dysphagia	Mucosal	Oral	–	Oral cavity
11	M	62	1	PV (vegetans)	Pruritus	Skin	–	Chest Abdomen	Chest
12	M	44	1	PV	Pain/discomfort Pruritus Dysphonia/dysphagia Poor general health	Skin and mucosal	Oral	Head Chest Upper limbs	Head
13	M	63	2	PV	Pain/discomfort	Skin and mucosal	Oral	Chest	Oral cavity
14	M	47	2	PV	Pain/discomfort	Skin and mucosal	Oral	Head Chest	Oral cavity
15	M	15	2	PV	Pain/discomfort Pruritus Poor general health	Skin and mucosal	Oral and genital	Head Chest Upper limbs	Oral cavity
16	M	47	2	PV	Pain/discomfort Pruritus	Skin and mucosal	Oral and genital	Chest	Oral cavity
17	F	45	3	PV	Pain/discomfort Pruritus	Skin	–	Chest	Chest

Table 1 *(continued from the previous page)*

18	F 69	1	PV	Pain/discomfort	Skin and mucosal	Oral	Head Chest Upper limbs	Oral cavity
19	F 86	4	PNP	Pain/discomfort Dysphonia/dysphagia Poor general health	Skin and mucosal	Oral and genital	Head Chest	Oral cavity
20	F 50	6	PV	Pain/discomfort Pruritus	Skin and mucosal	Oral	Head Chest	Oral cavity

Patient	Type of Lesion	No. of Lesions	Prior Treatments	Final Treatment	Treatment Complications	Remission	Hospital Admission	Death
1	Sore/crust	<10	—	Corticosteroids	Yes	Full	No	No
2	Sore/crust	>25	Corticosteroids Azathioprine	Corticosteroids + IS	Yes	Partial	Yes	Yes
3	Sore/crust	<10	—	Corticosteroids	No	Full	No	No
4	Erosion/crust Blisters/oral aphthous ulcers	>25	Corticosteroids Azathioprine	Rituximab	Yes	Full	Yes	No
5	Sore/crust Blisters/oral aphthous ulcers	>25	Corticosteroids Azathioprine Ciclosporin M. mofetil, IV Ig	Rituximab	Yes	Full	Yes	No
6	Aphthous ulcers	10-25	Corticosteroids Azathioprine	Corticosteroids + IS	Yes	Partial	No	No
7	Sore/crust Blisters/oral aphthous ulcers	10-25	Corticosteroids Azathioprine	Rituximab	Yes	Partial	Yes	No
8	Sore/crust	<10	—	Corticosteroids	Yes	Full	No	No
9	Sore/crust Blisters	10-25	—	Corticosteroids	No	Full	No	No
10	Aphthous ulcers	10-25	Corticosteroids Azathioprine	Rituximab	Yes	Partial	No	No
11	Sore/crust Blisters	10-25	—	Corticosteroids	No	Full	No	No
12	Sore/crust Blisters/oral aphthous ulcers	>25	Corticosteroids Azathioprine Ciclosporin	Corticosteroids + IS	Yes	Partial	Yes	No
13	Sore/crust Aphthous ulcers	10-25	Corticosteroids Azathioprine	Corticosteroids + IS	Yes	Full	Yes	No
14	Sore/crust Aphthous ulcers	10-25	Corticosteroids Azathioprine	Corticosteroids + IS	Yes	Partial	No	No
15	Sore/crust Blisters/oral aphthous ulcers	10-25	Corticosteroids Ciclosporin M. mofetil, IV Ig	Rituximab	Yes	Partial	Yes	No

Table 1 *(continued from the previous page)*

Patient	Type of Lesion	No. of Lesions	Prior Treatments	Final Treatment	Treatment Complications	Remission	Hospital Admission	Death
T16	Sore/crust Blisters/oral aphthous ulcers	<10	Corticosteroids Azathioprine M. mofetil	Corticosteroids + IS	Yes	Partial	Yes	No
17	Sore/crust Blisters	<10	–	Corticosteroids	No	Partial	No	No
18	Sore/crust Blisters/oral aphthous ulcers	10-25	–	Corticosteroids	No	Full	No	No
19	Sore/crust Blister/oral aphthous ulcers	>25	–	Corticosteroids	No	Partial	No	No
20	Sore/crust Blisters/oral aphthous ulcers	>25	Corticosteroids Azathioprine	Corticosteroids + IS	No	Full	No	No

Abbreviations: F, female; IS, immunosuppressants; IV Ig, intravenous immunoglobulin; M, male; M. mofetil, mycophenolate mofetil; PF, pemphigus foliaceus; PNP, paraneoplastic pemphigus; PV, pemphigus vulgaris.

years). The mean age at onset was considerably lower in men (50.1 [19.3] years; range, 15-75 years) than in women (66.3 [14.6] years; range, 45-87 years). The vast majority of patients (n=18, 90%) were older than 40 years, and just 2 patients (10%) were younger than 18 years.

The most common type of pemphigus was pemphigus vulgaris, diagnosed in 16 patients (80%), 1 of whom had the vegetans variety. There were just 3 cases of pemphigus foliaceus (15%), and 1 case of paraneoplastic pemphigus, which developed in a patient previously diagnosed with non-Hodgkin lymphoma.

In all cases, diagnosis was initially based on clinical findings and subsequently confirmed by histopathologic examination and direct immunofluorescence. This second technique revealed the presence of immunoglobulin (Ig) G deposits in the keratinocytes of all the patients in whom it was performed (n=18, 90%); it also detected IgM deposits in several cases. It was not possible to perform direct immunofluorescence for technical reasons in just 2 patients. Indirect immunofluorescence to detect circulating antibodies directed against the surface of keratinocytes is not performed at our hospital.

At the time of diagnosis, the mean time since onset was between 1 and 18 months (mean [SD], 3.48 [4.3] months). It is noteworthy that patients with mucosal lesions consulted about their condition more quickly than those with just skin lesions (2.75 [3] months vs 5.17 [6.6] months). The most common symptoms that prompted patients to seek medical attention were pain or local discomfort caused by the lesions (17 patients, 80%) and pruritus (11 patients, 55%). The general state of health of 6 patients (30%) was seriously impaired by their disease. An additional 6 patients (30%) reported odynophagia or dysphagia as a result of the mucosal lesions.

As far as clinical features are concerned, 60% of patients (n=12) had both skin and mucosal lesions, compared to 30% (n=6) who had just skin lesions and 10% (n=2) who had just mucosal lesions (Table 2). The most common mucous membrane affected was the mouth (13/14 patients, 92.8%). Eighteen patients had skin lesions. The most commonly affected skin area was the upper trunk (18 patients, 100%), followed by the face and the scalp (11 patients, 61.1%). Most of the patients (n=12, 60%) developed their first lesions in the mouth; the next most common sites were the upper trunk (5 patients, 25%), and the face and scalp (3 patients, 15%).

At the time of diagnosis, 90% of the patients (n=18) had sores (with or without crusts) and 60% (n=12) had very fragile blisters. As mentioned earlier, 13 patients (65%) had mucosal lesions in the form of sores and aphthous ulcers (Figures 1 and 2). The number of lesions at the time of consultation was 10 to 25 in 9 patients (45%), fewer than 10 in 5 patients (25%), and more than 25 in 6 patients (30%). The mean (SD) largest diameter was 1.97 (1.24) cm (range, 0.5-6 cm).

The initial treatment in all patients was topical and oral corticosteroids at a dose of 0.5 to 1 mg/kg/d. This was increased every 7 days until the disease was brought under control (ie, until no new lesions appeared). The current dose was then maintained until the majority of lesions disappeared, after which it was gradually

Table 2 Most Common Sites of Skin and Mucosal Lesions

Mucosal Lesions		Skin Lesions	
Oral mucosa only	57.1% (8)	Upper trunk	100% (18)
Genital mucosa only	7.1% (1)	Face and neck	61.1% (11)
		Abdomen	33.3% (6)
Both	35.7% (5)	Upper limbs	22% (4)
		Lower limbs	11% (2)

tapered. Of the patients studied, 40% (n=8) achieved disease control with oral corticosteroids alone, while 60% (n=12) needed adjuvant therapies at some stage. Of these, 7 patients (35%) achieved disease control with corticosteroids combined with immunosuppressants, while 5 (25%) required experimental biologic treatments. It is noteworthy that response to treatment varied with sex. Specifically, systemic corticosteroids alone resulted in disease control in 66.7% of the women (n=6) but in only 18.2% of the men (n=2).

The most common immunosuppressants used were azathioprine (11 patients, 91.7%), followed by ciclosporin (3 patients, 25%), mycophenolate mofetil (3 patients, 25%), and intravenous immunoglobulin infusion (2 patients, 16.7%). None of the patients were administered methotrexate or cyclophosphamide. Alternative drugs were prescribed for those patients in whom initial immunosuppressant treatment with azathioprine did not yield a response. Finally, it was necessary to use biologic therapy in 5 patients in whom conventional treatment did not achieve disease control. The biologic agent used was rituximab, a chimeric monoclonal anti-CD20 antibody. The results were very positive, as the disease was brought under control within a mean follow-up period of 21.6 (15.1) months (range, 6-36 months). Two of the patients are in complete remission and not currently receiving treatment and the other 3 are in partial remission and receiving low doses of corticosteroids with or without immunosuppressants (Figure 3).

Adverse effects, which were mostly treatment related, were observed in 65% of the patients (n=13). The most common effects were infections (61.5%), followed by hyperglycemia (38.5%), Cushing syndrome (38.5%), gastrointestinal disorders (30.7%), hyperlipidemia (23%), hepatotoxicity (15.4%), arterial hypertension (15.4%), cataracts (15.4%), osteoporosis (15.4%), myopathy (7.7%), and renal toxicity (7.7%). Furthermore, 3 patients required hospitalization due to treatment-related complications, including one case of nosocomial pneumonia and another of bacterial sepsis in patients receiving corticosteroids and azathioprine, respectively. The third patient, on rituximab, developed fever in association with a gram-negative bacterial infection. It is again noteworthy that a smaller proportion of men (n=10, 90.9%) than women (n=3, 33.3%) had adverse effects.

Hospitalization was required in 8 (40%) of the patients to control the disease or the treatment-related complications. The rate of hospitalization was also higher in men (7 patients, 63.7%) than women (1 patient, 11.1%).

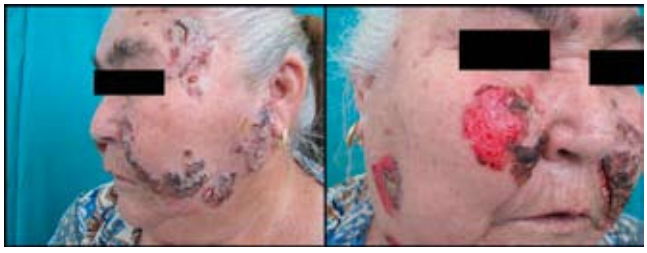

Figure 1 Typical clinical features of pemphigus vulgaris, with erythematous, crusted sores on the patient's face.

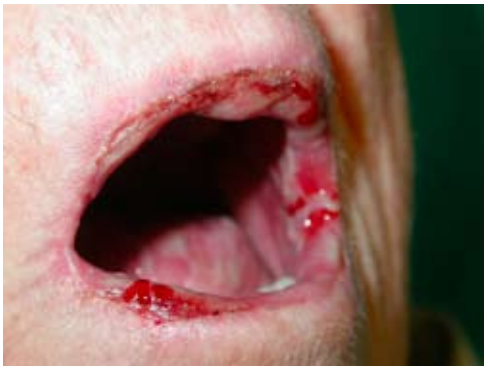

Figure 2 Severe stomatitis in a patient with paraneoplastic pemphigus.

Finally, the survival rate in our series was 95% at a mean follow-up of 6.9 (4.3) years (range, 1-13 years). The disease was controlled with treatment in all of the patients, with complete remission (no lesions and no treatment) observed in half of the patients (n=10) and partial remission (no or hardly any lesions with low-dose corticosteroids or immunosuppressants) in the other half. There was just 1 case of disease-related or treatment-related death. The patient, who was being treated with oral corticosteroids and azathioprine, died of bacterial sepsis caused by the infection of a foot ulcer, presumably favored by the immunosuppressant effect of the treatment.

Discussion

Coinciding with reports in the literature,[1-3] the most common clinical form of pemphigus in our series was pemphigus

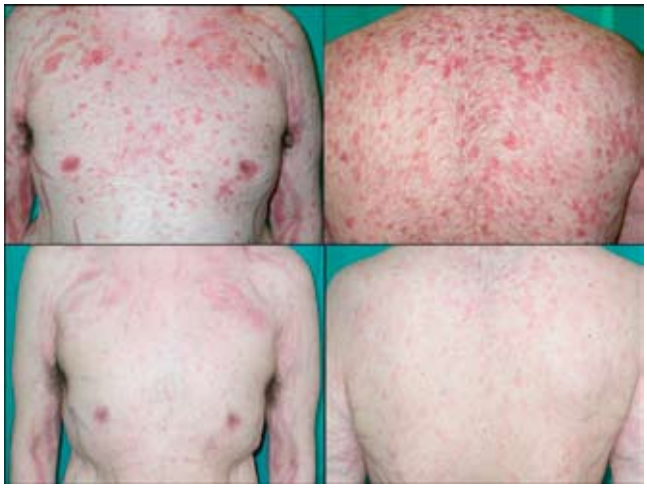

Figure 3 Patient with treatment-refractory pemphigus before (top panel) and after (bottom panel) the administration of rituximab. No lesions are observed in the bottom photographs, just residual hyperpigmentation and lines secondary to long-term corticosteroid treatment.

vulgaris (including the vegetans variety), detected in 16 patients (80%), followed by pemphigus foliaceus (3 patients, 15%). Our findings are comparable to those reported in the majority of studies, except for a Finnish study (where pemphigus erythematosus predominated),[9] and studies conducted in Tunisia,[10] Mali,[11] and South Africa[12] (pemphigus foliaceus), and Brazil[13] (fogo selvagem or endemic pemphigus foliaceus).

Traditionally, pemphigus has been considered to affect men and women equally[1-3] but in our series, the male to female ratio was 1.22 to 1 in favor of men. The majority of studies published to date, however, have reported, with varying results, that pemphigus has a predilection for women.[9-11,12,14-24] One study in the United States reported similar rates for men and women,[25] and to the best of our knowledge, the only other study apart from ours to report a higher frequency of pemphigus in men than in women (2.2:1) was conducted in Saudi Arabia.[26] On analyzing data published for other parts of Spain, we also found that pemphigus was more common in women than in men, with female to male ratios of 1.08 to 1 in Madrid,[6] and of 1.26 to 1 and 1.55 to 1 in Seville.[7,8]

Pemphigus tends to appear in the fourth to sixth decade of life.[1-3] The mean age of onset in our series was 57.4 (18.8) years, which is similar to that reported in other studies[9,11,17,18,24] and also consistent with data from other Spanish series.[6-8] Table 3 summarizes the demographic and clinical data from other national and international series.

On correlating age of onset with sex, we found that women developed pemphigus at a considerably later age than men (66.3 [14.6] years vs 50.1 [19.3] years). This difference, however, can be explained by the fact that the male group contained the youngest patients in the series (15 and 18 years) while the female group contained the oldest ones (86 and 87 years). Nonetheless, as already mentioned, no conclusions can be drawn from the difference in age of onset due to the small size of the sample. A later age of onset in women than in men has also been reported for Iran[22] and Saudi Arabia[26] but not with such a big difference. Other studies, in contrast, have reported that pemphigus appears later in men than in women.[14,18,25]

Pemphigus blisters can affect the skin, the mucous membranes, or both. In our study, 60% of the patients (n=12) had both skin and mucosal lesions, 10% (n=2) had mucosal lesions only, and 30% (6 patients) had skin lesions only. Results published elsewhere vary depending on geographic location, but, as can be seen in Figure 4, pemphigus affects both the skin and mucosa in the majority of cases. In agreement with reports from the international literature,[1-3] none of the patients with pemphigus foliaceus in our series had mucosal involvement.

In the patients with mucosal lesions (n=14, 70%), the mouth was the most commonly affected site (13/14 patients, 92.86%). Similar findings have been reported for 2 series in Iran (91.4%[21] and 81%[22]) and a series in Seville in Spain (80%).[8]

The most common site for skin lesions was the upper chest (18 patients, 100%), followed by the face and neck (11 patients, 61.1%). These results are also similar to those reported for Iran.[21,22] In Seville,[8] the chest and scalp were the most commonly affected areas (in 31% and 32% of patients, respectively), although to a lesser degree than in our series.

Pemphigus vulgaris lesions are generally reported to start in the mouth, several months before the onset of skin lesions. On questioning our patients about this, 12 of them (60%) reported that the first lesions had appeared in the mouth while 5 (25%) reported that their lesions had started on the upper trunk. These data are similar to those reported in the literature,[21-23] where 60% to 90% of patients are reported to develop their first lesions in the oral mucosa. Finally, it is noteworthy that 10 (83.33%) of the 12 patients whose lesions started in the mouth, subsequently developed skin lesions. In contrast, just 2 (25%) of the patients who developed skin lesions first (both with pemphigus vulgaris) later developed mucosal lesions.

The mean time from onset to diagnosis was 3.48 (4.3) months (range, 1-18 months). This time varies between studies as it is influenced by many factors, including the level of access to health care services and the level of awareness among doctors of the disease and its different manifestations. Indeed, many patients with pemphigus are wrongly diagnosed with gingivostomatitis. The mean time from onset to diagnosis reported in a study performed in a similar health care setting (Hospital 12 de Octubre in Madrid, Spain)[6] was higher than ours, with a mean of 8 months (range, 15 days to 36 months).

In our series, patients with mucosal lesions sought medical attention more quickly than those with just lesions affecting the skin (2.75 [3] months vs 5.17 [6.6] months). A similar finding was described by Esmaili et al[22] in Iran, where patients with skin lesions only or whose lesions had started on the skin took longer to seek medical attention than those with mucosal lesions (41.9% of patients whose lesions had first affected mucous membranes waited for at least 6 months before consulting a specialist compared to 63% of those whose lesions had first affected the skin). Thus, a possible explanation for the earlier diagnosis

Table 3 Demographic and Clinical Data From National and International Studies

	Mean Age, y	Sex, Male to Female Ratio	Clinical Variant
Malaga	57.4	1:1.22	PV
Seville (2005-2006)	55.1	1.55:1	PV
Seville (1975-1985)	53	1.26:1	PV
Madrid	52.4	1.08:1	PV
Saudi Arabia	43.1	1:2.2	PV
Brazil	—	—	PF *(Fogo selvagem)*
Bulgaria	—	1.11:1	PV
Korea	44.3	1.3:1	PV
Croatia	53	2:1	PV
USA	50	1:1	PV
Finland	57	1.1:1	PE
France	—	1.2:1	PV
Iran (Tehran)	42	1.5:1	PV
Iran (Tehran)	41.5	1.59:1	PV
Iran (south west)	38	1.33:1	PV
Italy	54	1.43:1	PV
Kuwait	36	2:1	PV
Mali	52	4.1:1	PF
Sicily	55	1.6:1	PV
South Africa	43	1.4:1	PF
Tunisia	39	4.1:1	PF
Turkey	43	1.4:1	PV

Abbreviations: PE, erythematous pemphigus; PF, pemphigus foliaceus; PV, pemphigus vulgaris.

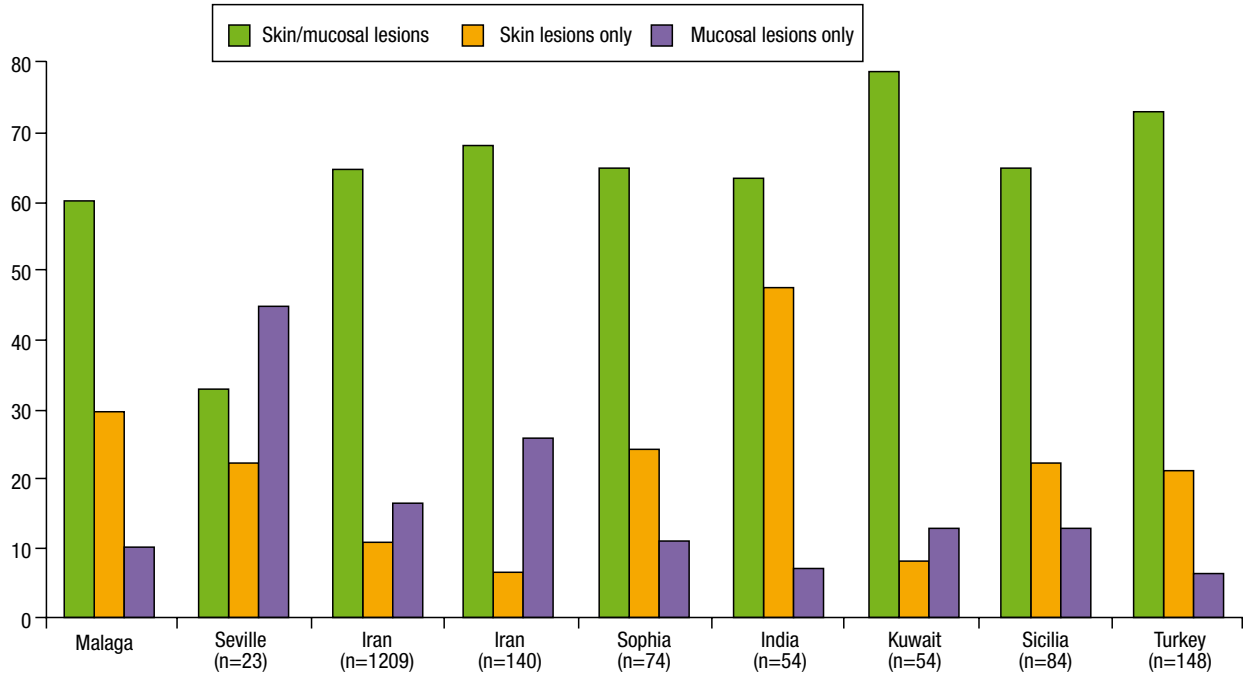

Figure 4 Frequency of skin and mucosal involvement in patients with pemphigus from national and international series.

observed in patients with mucosal lesions is that these patients would seek medical attention sooner because of the greater severity of their symptoms, with pain, local discomfort, and odynophagia.

Pemphigus vulgaris used to be fatal before the emergence of systemic corticosteroids. The mortality rate was 75% and most patients died within 5 years of disease onset. The use of systemic corticosteroids

and immunosuppressants has greatly improved prognosis, although morbidity and mortality are still considerable (<10%), with some patients dying from treatment-related complications. Although widespread consensus is lacking, systemic corticosteroids are the mainstay treatment for pemphigus, and immunosuppressants tend to be used for their corticosteroid-sparing effect (reduction in adverse effects) or when corticosteroids result in poor disease control.[1,2]

Oral and topical corticosteroids were used as initial therapy in all of the patients in our series and were effective in controlling disease in 40% of these (8 patients). The remaining patients (n=12, 60%) required adjuvant therapy at some moment during the course of treatment. There were no differences in response to treatment according to disease subtype.

In 7 patients (35%), disease control was achieved with the combined use of corticosteroids and immunosuppressants. The most common immunosuppressants were azathioprine (11 patients, 91.7%), followed by ciclosporin (3 patients, 25%), mycophenolate mofetil (3 patients, 25%), and intravenous immunoglobulin infusion (2 patients, 16.7%). We do not have experience with the use of methotrexate or cyclophosphamide in the treatment of pemphigus. Based on the results from our center, the combined use of oral corticosteroids and azathioprine is one of the safest and most effective treatments available, and in our case, it achieved disease control in 7/11 patients. The results obtained with the other immunosuppressants were not so good.

It was necessary to resort to biologic therapy with rituximab in the 5 patients (25%) whose disease was not controlled with any of the conventional treatments. The agent was administered intravenously at a dose of 375 mg/m^2 every week for 4 weeks. In our series, rituximab was a valid treatment alternative as it brought the disease under control in all of the patients treated. Excellent results have also been reported elsewehere.[27-30] Most adverse effects due to rituximab are mild, transient, and infusion related. There have, however, been reports of serious reactions, including hypotension, bronchospasm, Stevens-Johnson syndrome, serious bacterial infections, herpes zoster reactivation, viral meningoencephalitis, hepatitis B reactivation, autoimmune hemolytic anemia, liver failure, and neutropenia.[27] In our case, just 1 patient developed fever as part of a gram-negative bacterial infection successfully treated with hospitalization and the administration of intravenous antibiotics.

The rest of the complications occurred in a substantial proportion of patients (65%, 13 patients), and were mostly related to treatment. The most common complications were infections (61.5%), followed by hyperglycemia (38.5%) and Cushing syndrome (38.5%). Our data are quite similar to those reported by other authors, although with varying percentages.[6-8,15,16,21,23,24] One of our patients died of bacterial sepsis (one of the main causes of death in patients with pemphigus), probably favored by the immunosuppressive therapy.

Finally, our study revealed some interesting aspects regarding treatment-related complications. In particular, men appeared to have a worse response to treatment than did women. This would lead to a requirement for more drugs or higher doses and, in turn, to a higher rate of adverse effects and more frequent requirement for hospitalization. In our series, 81.1% of the men (9/11) and 66.7% of the women (6/9) required alternative treatments as corticosteroids were not effective in controlling their lesions; 90.9% of the men (10/11) and 33.3% of the women (3/9) had treatment-related adverse effects; 63.6% of the men (7/11) and 11.1% of the women (1/9) required hospitalization to achieve disease control or treat complications related to treatment. This is the first time that this difference in treatment response between men and women has been reported, but obviously, further studies of larger series of patients are required to confirm whether such a difference exists.

Conclusions

Except for minor differences, the demographic and epidemiologic data from our study are in agreement with those reported by studies conducted in other parts of Spain and elsewhere in the world. The only difference worth noting in our series was the greater proportion of men than women with pemphigus, as this contrasts with other reports of no differences between sexes or a greater prevalence in women.

Our results suggest, for the first time, that male sex might be an indicator of poor prognosis, as it was associated with poor response to treatment and a higher rate of adverse effects and hospitalization. Obviously, however, further studies involving much larger series of patients are required to confirm this hypothesis,

Based on our experience, rituximab appears to be a viable treatment alternative for pemphigus refractory to conventional treatment, as it is effective, well-tolerated, and has a good safety profile.

Finally, we hope that our data will help to further define the clinical and epidemiologic characteristics of pemphigus in our setting as very few publications on this aspect of the disease have been made available to date.

Conflict of interest

The authors declare that they have no conflict of interest.

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