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Epidemiology of Pemphigus in Hospital Universitario Virgen Macarena, Seville, Spain, 2005-2006

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Abstract. *Background*. Pemphigus is a serious, potentially fatal chronic autoimmune bullous disease with cutaneous and mucosal manifestations. Early diagnosis and treatment are essential.

Material and methods. We performed a retrospective cohort study that included patients diagnosed with pemphigus in the dermatology department of Hospital Universitario Virgen Macarena, Seville, Spain, in 2005 and 2006. We reviewed demographic, clinical, and therapeutic data.

Results and conclusions. Twenty-three patients, the majority women, were included in the study. Clinical onset usually occurred between 30 and 60 years of age. The most common variant was pemphigus vulgaris (79 %), and the sites most frequently affected were the oral mucosa, trunk, and scalp. Oral corticosteroids were the initial treatment of choice in all patients, and azathioprine and mycophenolate mofetil were given as adjuvant therapy. Complete remission was induced in 8.68 % of patients and partial remission in 91.32 %. The main complications were infections, osteopenia and osteoporosis, and cataracts.

Key words: pemphigus, epidemiology, treatment, complications.

EPIDEMIOLOGÍA DEL PÉNFIGO EN EL HOSPITAL UNIVERSITARIO VIRGEN MACARENA (2005-2006)

Resumen. *Introducción*. El pénfigo es una enfermedad ampollosa, autoinmune, crónica, con manifestaciones cutáneo-mucosas, grave y potencialmente mortal, que precisa un diagnóstico y tratamiento precoces.

Material y métodos. Realizamos un estudio de cohortes retrospectivo incluyendo todos los casos de pénfigo del Departamento de Dermatología del Hospital Universitario Virgen Macarena durante 2005 y 2006. Revisamos los datos demográficos, clínicos y terapéuticos.

Resultados y conclusiones. Se estudiaron 23 pacientes, con predominio del sexo femenino e inicio de la enfermedad entre la cuarta y sexta décadas de la vida. El pénfigo vulgar fue la variante más frecuente (el 79 % de los casos), la mucosa oral, el tronco y el cuero cabelludo las localizaciones predilectas; los corticoides orales, el tratamiento inicial de elección en todos los casos, y como adyuvantes utilizamos azatioprina y mofetil micofenolato. Se consiguió remisión completa en el 8,68 % de los casos y una remisión parcial en el 91,32 %. Las principales complicaciones fueron las infecciones, la osteopenia-osteoporosis y las cataratas.

Palabras clave: pénfigo, epidemiología, tratamiento, complicaciones..

Introduction

Pemphigus is a chronic autoimmune bullous disease with several variants, namely, pemphigus vulgaris, vegetans, foliaceus, erythematosus, paraneoplastic, and immunoglobulin A. Depending on the variant, the disease can present on both the skin and the mucosa. The condition is serious and potentially fatal; hence, early diagnosis and treatment are essential. The purpose of our study was to determine the demographic characteristics of pemphigus in our population and to analyze the treatments administered, as well as the clinical response and complications observed with such treatments.

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Material and Methods

We performed a retrospective cohort study that included all patients diagnosed with pemphigus who came to the

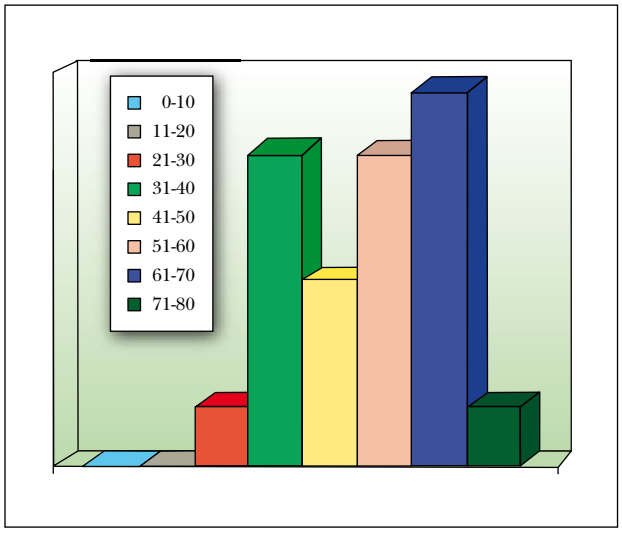

Figure. Distribution of age at onset of pemphigus lesion

outpatient clinic in the dermatology department at the Hospital Universitario Virgen Macarena, Seville, Spain, in 2005 and 2006. The variables studied were age, sex, type of pemphigus, site, treatments, and complications. Therapeutic response was assessed according to the lesions and the treatments needed to control the disease, as follows:

1. Control of the disease, considered to be when new blisters stopped forming and current blisters were resolving with treatment
2. Complete remission, with no lesions and no systemic corticosteroid or adjuvant therapy (or <5 mg/d of corticosteroids from more than 1 year)
3. Partial remission, with few new lesions (5-10) per week, and doses below 10 mg/d of systemic corticosteroids associated with adjuvant therapy[1]

Results

The mean age of the patients was 55.09 years. The age at the time of diagnosis was between 28 and 73 years, although most patients were between 40 and 60 years old (Figure). The male-to-female ratio was 1.55:1; patient follow-up ranged between 1 month and 20 years.

Pemphigus was diagnosed according to the clinical, histopathologic, and immunofluorescence characteristics. In all patients, the biopsy showed intraepidermal blisters produced by acantholysis and immunoglobin G antibodies directed against the keratinocyte surface on direct immunofluorescence. Indirect immunofluorescence performed in 47.82% of patients revealed circulating antibodies in 90% of these patients.

The most common clinical form was pemphigus vulgaris (79%), followed by pemphigus foliaceus (13%), pemphigus vegetans (4%), and pemphigus erythematosus (4%). In 45% of patients with pemphigus vulgaris, involvement was limited to the mucosa and no skin lesions were observed; the mucosal lesions were seen only in the oral mucosa, except for only 1 patient who also presented genital lesions. Thirty-three percent of the patients with pemphigus vulgaris had skin and mucosal manifestations while the remaining 22% had skin involvement only. In general, the predominant site of the skin blisters was the scalp (32%) or anterior thorax (31%). Patients with pemphigus foliaceus, vegetans, or erythematosus only presented cutaneous involvement, and the trunk was the usual site.

In all our patients, initial therapy consisted of oral (0.5-1 mg/kg/d) and topical corticosteroids. The systemic corticosteroid dose was increased by 50% if blisters continued to appear. In 91% of patients, once the disease was controlled we prescribed adjuvant therapy, consisting of the immunosuppressants azathioprine and mycophenolate mofetil. Azathioprine was prescribed at doses determined by the enzyme thiopurine methyltransferase concentration to 39% of patients and mycophenolate mofetil (1.5-2 g/d) to 9%, with good response achieved in both groups. In 43%, azathioprine was given as an initial immunosuppressant; however, the response was poor, and the drug was switched to mycophenolate mofetil, leading to progressive healing of the lesions. This drug was well tolerated in all cases, and no patients reported gastrointestinal discomfort or other adverse reactions. Treatment cycles with 2 g/kg of intravenous immunoglobulins divided into 3 days were needed by 40% of patients due to poor disease control.

On completion of the study, 91.32% of patients were still in partial remission and only 8.68% had sustained complete remission. There were no deaths during the study period.

Complications were observed in 75% of patients and were usually related to treatment. The most common were infections (70%), in particular, pneumonia, urinary tract infections, herpes, and tinea. Osteopenia and osteoporosis (43%), cataracts (22%), diabetes (17%), and skin cancer (13%) were also observed. Less common complications were fractures (8.7%), hypertension (8.7%), azathioprine-induced hepatitis (4.4%), and headaches associated with the use of intravenous immunoglobulins (4.4%).

Discussion

Pemphigus is a disease with an uneven geographic distribution. Its exact incidence is unknown, and the

Table 1. Demographic and Clinical Data of Patients with Pemphigus Reported by Spanish Series

	Hospital 12 de Octubre, 1972-2003	*Hospital Virgen Macarena, 1975-1985*	*Hospital Virgen Macarena, 2005-2006*
Number of patients	52	34	23
Male-to-female ratio	1.08:1	1.26:1	1.55:1
Mean age, y	52.44	53	55.09
Most common type of pemphigus	Pemphigus vulgaris (65%) Pemphigus foliaceus (25%) Pemphigus vulgaris (7.7%) Pemphigus herpetiformis (1.9%)	Pemphigus vulgaris (88.3%) Pemphigus foliaceus (11.7%)	Pemphigus vulgaris (79%) Pemphigus foliaceus (13%) Pemphigus vegetans (4%) Pemphigus erythematosus (4%)

published data are from specific population groups.[2,3] Although the etiology of pemphigus is unknown, the higher incidence observed in some ethnic groups (eg, Ashkenazi Jews who express certain class II human leukocyte antigen genes) suggest that genetic factors may have some influence. Environmental factors, physical agents, drugs, chemicals, food, and stress also play a role.

The onset of pemphigus usually occurs in individuals aged between 30 and 50 years; however, cases have been reported in children aged 3 years and in elderly patients aged 95 years. In most published series, the condition is more common in women, with a ratio of 2:1 or higher. In our series, we found a slight predominance of women (1.5:1); however, the sex distribution is similar in populations from North America, Finland, Malaysia, India, France, Bulgaria, and the United Kingdom. These differences could be explained by geographic or ethnic characteristics.[4] The demographic data of our series are similar to those reported in previous Spanish publications[5,6] (Table 1).

Pemphigus vulgaris is the most common clinical form in most populations (70%-90% of patients with pemphigus), followed by pemphigus foliaceus (4%-20%). Pemphigus vegetans and pemphigus erythematous are rare. However, pemphigus erythematous predominates in Finland,[7] pemphigus foliaceus in Tunisia,[8] and endemic pemphigus foliaceus or *fogo selvagem* in Brazil.[9] The clinical variants observed in our series and other Spanish studies showed a similar distribution (Table 1).

The intraepidermal blisters of pemphigus can lead to cutaneous or mucosa manifestations according to the clinical variant. In pemphigus vulgaris, mucosal lesions are extremely common, may precede the skin lesions by months or years, and occasionally impede the diagnosis if skin lesions do not appear. Oral mucosal lesions were observed in 80% of patients with pemphigus vulgaris and were accompanied by skin blisters in 45%. The most common sites were the scalp (32%) and trunk (31%).

Pemphigus is a serious illness that can cause death if not treated. No treatment consensus has been reached for pemphigus due to the lack of large studies, given that the incidence of the disease is low. The main therapeutic approach continues to be corticosteroids, which have radically changed the prognosis of the disease from the time these drugs were first discovered in the 1950s and which have lowered mortality from 90% to 30%. A large arsenal of immunosuppressants used as corticosteroid adjuvants are available and have further reduced mortality to 5% to 10% of cases.

Corticosteroids are initially used at high doses and gradually reduced until the illness is controlled at the minimal dose. The initial doses range between 100 and 200 mg/d, even though several studies show that doses above 120 mg/d do not enhance effectiveness, but do increase adverse reactions.[10,11]

Our patients were initially treated with corticosteroids. Once the lesions were controlled, we started treatment with immunosuppressants in 91% of cases. The remaining 9% were controlled with low doses of corticosteroids. Cyclophosphamide, azathioprine, mycophenolate mofetil, methotrexate, chlorambucil, and cyclosporin have been used as adjuvant immunosuppressive therapy.[12] We obtained good response with azathioprine and mycophenolate mofetil, achieving control of the lesions and a considerable decrease in the systemic corticosteroid dosage. In fact, when the study ended in December 2006, an analysis of the clinical data and doses showed that the patients had few or no lesions at doses of 5 to 10 mg prednisone every 24 to 48 hours in association with the respective immunosuppressant. We have no experience with the use of cyclophosphamide as adjuvant therapy in pemphigus, although several authors believe it offers considerable advantages in controlling the disease, fewer adverse reactions than corticosteroids in monotherapy, and shorter hospital stays.[13]

Intravenous immunoglobulins are used to treat pemphigus in patients who fail to respond to the usual

Table 2. Corticosteroid-Induced and Immunosuppressant-Induced Complications in Patients with Pemphigus

	Infections	*Hypertension*	*Diabetes*	*Cushing Syndrome*	*Psychosis*	*Cataracts*	*Aseptic Necrosis of the Hip*	*Peptic Ulcer*	*Osteoporosis*
Fernandes et al[10]	90%	17%	14%	7%	3%	3%	1.5%	1.5%	–
Ljubojevic´ et al[16]	22%	23%	14%	–	–	–	–	–	–
Manahan et al[13]			4%	1.5%	–	–	–	2%	–
Chams-Davatchi et al[2]	68%	19%	16%	–	2%	2%	2%	–	10%
Rivera et al[5]	40%	3.8%	17.3%	15.3%	5.8%	5.8%	3.8%		
Hospital Universitario Virgen Macarena, 1975-1985	44%	23%	26%	94%	11%	21%	–	11%	35%
Hospital Universitario Virgen Macarena, 2005-2006	70%	9%	17%	–	–	22%	–	–	17%

treatments or when there are contraindications for use. The mechanism of action is not well understood, but these agents appear to favor catabolism of pathogenic immunoglobulins without affecting normal immunoglobulins.[14] In our series, 40% of patients received intravenous immunoglobulins. In most patients (88%), the disease was hard to control, with poor response to azathioprine, mycophenolate mofetil, or low-dose corticosteroids. The mean number of cycles was 7.5. Clinical response was variable, and rapid control of the lesions was achieved with only a few cycles (1-4) in 50% of patients. However, the other half needed more than 10 cycles, and 1 patient required more than 20 cycles to achieve control, albeit unsustained, of his lesions.

Recently, intractable cases of pemphigus have begun to be treated with rituximab, an anti-CD20 monoclonal antibody that reduces the number of autoreactive B cells. Although the drug was rarely used in our study phase, it is now employed more often because it achieves long-lasting remissions.

Disease remission is related to the time of postdiagnosis follow-up and 25% remissions have been achieved at 2 years, 50% at 5 years, and 75% at 10 years. As commonly reported,[15] we observed that the factors that influence pemphigus remission are disease severity at the time of diagnosis and early response to treatment. By the end of the follow-up period for this series, complete remission had been achieved in 8.68% of patients and partial remission in the remainder. Ljubojević et al[16] achieved long-term remission in 12% of patients; of these, one-fourth were complete remissions and the remainder were partial remissions in which patients were disease-free with corticosteroid maintenance therapy (5-20 mg/d). Although no patients died in our study, the mortality of pemphigus is estimated at 5% and is related to the extent and severity of the disease. The actual cause of death is usually septicemia or cardiovascular problems. The study design was susceptible to bias in the assessment of remissions and mortality, due to possible losses to follow-up during the short inclusion period.

Disease complications are usually associated with immunosuppressive therapy, and the most common are infections (impetigo, septicemia, kidney infection, candidiasis, tinea, herpes simplex, herpes zoster, and molluscum), hypertension, and diabetes. Other, less common complications include osteoporosis, Cushing syndrome, cataracts, acne and steroid folliculitis, weight gain, pulmonary tuberculosis, psychosis, aseptic necrosis of the hip, and peptic ulcer.

Our data are similar to those described in previous studies, although we found a higher percentage of complications such as osteoporosis and cataracts (Table 2).

In addition, 13% of patients developed skin cancer, including 1 case of Kaposi sarcoma.[17]

Conflicts of Interest

The authors declare no conflicts of interest.

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