International Journal of Dermatology

Reminiscence

Historical notes on endemic pemphigus in South America

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Introduction

Pemphigus is an autoimmune blistering disease that involves the skin and mucous membranes. Its two types, pemphigus foliaceus (PF) and pemphigus vulgaris (PV), are rare and occur sporadically throughout the world, with the exception of some areas in South America. Pemphigus foliaceus is endemic in Brazil, Colombia, and Peru, and has been described in other South American countries. This paper presents an historical review of pemphigus and summarizes work on the disease in South America.

Until the development of immunofluorescent techniques during the 1960s, diagnosis was based on clinical and histologic findings. Immunofluorescent techniques demonstrated autoantibodies in the sera of pemphigus patients that bound to an intercellular substance present in the skin and mucosa.[1] During the next few decades, such techniques were refined and used to identify the antigens associated with specific varieties of pemphigus.[2,3] Desmoglein 1 (Dsg1) was thus linked to PF and to endemic PF (EPF),[4,5] and desmoglein 3 (Dsg3) was linked to PV.[6]

Endemic PF in South America

Endemic PF and non-endemic PF are clinically, histologically, and immunologically similar. Both are characterized by the presence of small, flaccid bullae that evolve into scaly and crusted lesions, sometimes with pustules, mainly in seborrheic areas of the skin.[7,8] However, the epidemiology of endemic forms varies from country to country.[9–13]

The first reference to pemphigus in South America is attributed to Boissier de Sauvages, who used the term "pemphigus brasiliensis" to describe a bullous disease observed in 1719 by Bougeant, a French missionary in Brazil. The eruption occurred following contact with the skin of a venomous snake and lasted for three months, which makes it unlikely to have been EPF.[14]

In Brazil, EPF is usually called *fogo selvagem* (which means *uncontrolled* or *wild fire* in Portuguese), whereas in Colombia it is often referred to as *El Bagre* (after the region in which it is most prevalent). Although the term *fogo selvagem* was long used by people from endemic areas to describe the burning sensation caused by the skin disease, its use in dermatology is attributed to Paes-Leme (1903).[15] Ulisses Paranhos (1939) offered a more fantastic explanation based on popular mythology: *fogo* was a terrible curse inflicted on populations by the gods, who blew the evil through a magic horn.[16]

The earliest convincing accounts of *fogo selvagem* date from the late 1800s, when Professor Alexandre Cerqueira described characteristic cases of the disease at his dermatology clinic at the Bahia Faculty of Medicine in 1891.[17] The patients were natives of Bahia, where cocoa and coffee plantations were replacing the native vegetation of the region.[18] In 1903, Paes-Leme described an epidemic of a blistering disease in isolated regions of the state of São

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Paulo.[15] At the time, he thought this to be a variant of tinea corporis (tinea imbricata or "Tokelau") because of the scaly and circinate characteristics of the lesions.[15] Soon afterwards, Candido Teixeira suggested that the familiar Brazilian skin disease called *fogo selvagem* was a form of PF.[19]

In 1937, Vieira[20] established the salient clinical and histologic features of this endemic form of PF and noted that the Paes-Leme cases exhibited the clinical features of PF reported by Cazenave[21] in Paris in 1844.

Over the next few decades, it became apparent that PF was endemic in many parts of Brazil and that prevalences were greater in river valleys. Such was the number of cases in the state of São Paulo during the 1930s that the government built a hospital for these patients. By 1946, hundreds of cases had been treated at Pemphigus Hospital, where a mortality rate of 40.7% was recorded.[22]

In 1940, Vieira described the epidemiology of EPF in the state of São Paulo, emphasizing its contagiousness and the symptoms of frequent fever, chills, cutaneous pain, and alopecia.[23] Vieira reported the disease as most common in people aged <30 years and showed a correlation between geographic prevalence and the natural habitat of the *Simulium* fly (black fly, "borrachudo" in Portuguese), hinting at a possible infectious etiology.[23] Later writers would describe a peak incidence of EPF in the state of São Paulo during the 1930s and 1940s, followed by a remarkable decline from the 1960s to 1980s.[22–24] This raised as yet unanswered questions about the etiology of the disease.[18]

Mario Fonzari, a therapeutic researcher, pioneered the use of cortisone and thereby revolutionized the treatment of EPF.[25] The use of systemic corticosteroid treatment represented a milestone in reducing the mortality of patients with EPF.

The Fogo Selvagem Research Group, created in the 1980s by Diaz *et al.*, has made numerous and ongoing contributions to the investigation of endemic pemphigus in Brazil. In 1989, Diaz *et al.* summarized the clinical, epidemiologic, and immunopathologic features of EPF,[18,26] confirming earlier reports that it is commonly found in rural areas and disappears following urbanization.[18,22]

During the 1990s, immunoglobulin G4 (IgG4) was shown to be the main autoantibody in the pathogenesis of EPF; almost all EPF patients have circulating IgG autoantibodies directed against stratified epithelial desmosomes. Endemic PF was also related to specific human leukocyte antigen (HLA) types.[7,8,27,28]

In 2000, Warren *et al.* identified Dsg1 antibodies in 98% of Brazilian patients with *fogo selvagem*.[29] The incidence of anti-Dsg1 antibodies in unaffected Brazilians from areas endemic for *fogo selvagem* ranged from 19 to 55% but was only 2% in healthy American and Japanese individuals. This supported the notion that both environmental triggers and genetic factors play a role in the development of EPF.[29]

In 2003, Li *et al.* suggested that anti-Dsg1 autoantibodies in EPF are initially raised against the EC5 domain of Dsg1 in individuals without the skin disease; in genetically predisposed subjects, the autoimmune response may then spread toward epitopes on the EC1 and EC2 domains of Dsg1, leading to disease onset.[30]

Recent research efforts have been directed toward identifying the preclinical stage of EPF, of which IgM anti-Dsg1, IgE and non-IgG4 autoantibodies against Dsg1 are known to represent serologic markers. The rise of pathogenic IgG4 anti-Dsg1 autoantibodies characterizes the disease stage. The transition of the autoimmune response from the preclinical stage to disease state may have an incubation time of several years. The pathogenic IgG4 response in *fogo selvagem* may be triggered by hematophagous insect bites or unknown environmental factors.[31,32] It has also been demonstrated that selection for mutant anti-Dsg1 B cells begins before the onset of disease.[33] Anti-Dsg1 response in EPF patients may be initiated by sensitization to an environmental allergen(s).[34]

Family cases are frequent, but not everyone living in an endemic region develops EPF, which suggests that host factors play a role in determining whether an exposed individual will be affected. Endemic PF affects people of many races and ethnic backgrounds.[35]

In Colombia, EPF was first observed in 1970 by a dermatologist who was looking for leprosy patients in the rural mining municipality of El Bagre; he related these cases to Abréu-Vélez *et al.* in a personal interview.[36] In 1983, a dermatologist in Medellin reported patients with EPF in the gold-mining areas of El Bagre and Nechi.[37] An EPF outbreak between 1982 and 1986 was also reported by Robledo *et al.*[38] During 1981–1991, Rodriguez observed many cases among the natives of the Colombian Amazon and Orinoquia river basins.[39] Abréu-Vélez *et al.* later labeled El Bagre as a focus of EPF in northern Colombia.[12] The El Bagre EPF cases shared features with Senear–Usher syndrome (pemphigus and lupus); however, the major antigen in both Colombian and Brazilian EPF is Dsg1.[6,40] The recent discovery of immunoglobulin and complement autoreactivity in peripheral nerves in EPF patients may explain the burning sensations typically experienced.[41]

In Peru, pemphigus was recognized in pre-Columbian times; representations of the disease can be found in Incan ceramic figures (*huacos*) of the Moche and Chimu cultures.[41] During a medical geography trip in 1925, Weiss Harvey observed cases of EPF in the village of Pucallpa on the banks of the Ucayali river.[42] In 1949, at the Santa Rosa Military Hospital in Iquitos, Loreto, Muñoz

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Table 1 Approximate dates of first references to or reports on endemic pemphigus foliaceus in some countries of South America

Historical data	Brazil	Colombia	Peru	Paraguay	Venezuela
First references	Mid-1800s	1976	1925	1950	1952
First scientific report	1903	1983	1976	1996	2001
Clinical and epidemiologic characterization	1939–1952	1988	1993–2005	1996	2001
Immunopathologic characterization	1989–2007	2003	2005–2009	1995–1999	2006
Immunogenetic characterization	1991	No data found	Not done	Not done	2006
Entomologic studies	1998	No data found	Not done	1998	No data found

These data refer to all reports in journals and theses available on the Internet and elsewhere. Older reports may also exist.

observed the disease in soldiers whose headquarters were close to two endemic foci in that area. Aranha-Campos later documented more EPF cases in Iquitos.[43]

While working in Puerto Inca, near the Pachitea River in the Amazon rainforest, Heimgartner and Heimgartner observed EPF in children, adolescents and adults aged 20–30 years.[44] During the late 1980s, many severely ill patients from Pucallpa were transferred to Lima, the capital of Peru, for treatment (A. Ortega-Loayza; personal communication 2010). More EPF cases from the provinces of Requena and Ucayali were described by Castillo *et al.* in 1993.[45] Since 2000, various authors have reported EPF in numerous Peruvian regions (in the departments of Ucayali, Loreto, Huanuco, Amazonas, Junin, and San Martin). The majority of these areas are in the Amazon rainforest, but some lie in the Andes mountains.[10,46–48]

Aldama *et al.* reported the clinical manifestations and epidemiology of 71 cases of EPF in the central zone of the eastern region of Paraguay between 1990 and 1995; all were similar to Brazilian pemphigus.[49] Between 1990 and 1999, Aldama *et al.* saw an additional 70 cases of pemphigus at the National Hospital of Paraguay, of which 86% were EPF and 14% were PV.[50,51]

In Venezuela in 1950, patients with PF were hospitalized at the clinic of Professor Vegas in Caracas.[43] In 2006, Gonzalez *et al.* reported EPF in native Yanomami children from an area called Boca Mavaca, in the Venezuelan Amazon rainforest. A study of these children showed that HLA class II exhibited DRB1*04 subtype *0411. However, this shares a common epitope with all the HLA DRB1 alleles that have been involved in this disease in Brazilian populations.[52]

In Argentina, there have been sporadic reports of non-endemic pemphigus from 1889 until the present.[53–56] A non-endemic form of PF has also been reported sporadically in Bolivia.[57].

Table 1 shows the approximate dates of first references to or reports on EPF in those countries in South America for which we were able to find historical information.

Endemic PV in South America

In 2006, investigators from Brazil and the USA described a new endemic variant of PV, represented by a mucocutaneous disease that resembles PV clinically and histologically but has the epidemiologic features of *fogo selvagem*.[58,59] Similar observations were reported in Peru.[60] It is possible that this disease phenotype was overlooked because of its rare occurrence.

Over the centuries, the use of the term "pemphigus" has evolved from that of a descriptor for all types of bullous eruption to use as a term to designate a few well-defined clinical entities. It is the only endemic autoimmune disease in the world, and we are only now beginning to understand its complexity. Studies are underway to clarify the relationships among genetic and environmental factors. The possible existence of an infectious trigger conveyed by hematophagous insects remains an intriguing focus of research in South America and offers hope for future prevention and therapy.

Acknowledgment

We thank Dr. Arnaldo Aldama, Professor of Dermatology, Dermatology Department of the National Hospital, College of Medicine at the National University of Asunciœn, Asuncion, Paraguay, for information on endemic pemphigus in Paraguay.

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