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Spatial Distribution of Pemphigus Occurrence over Five Decades in Southeastern Brazil

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Abstract. Well-defined locations of pemphigus cases support the hypothesis of environmental factors' involvement in its etiopathogenesis; however, these foci have never been described using specialized geographical tools. This is the first report to geo-reference pemphigus cases in a high-prevalence Brazilian region using geographic information systems. We aimed to report the spatio-temporal behavior of pemphigus foliaceus (PF) and vulgaris (PV) in southeastern Brazil, over the last five decades to describe geographical clusters, as well as to characterize the land use in the city with the highest number of cases. Patients were identified from 1965 to 2014. Maps were developed using ArcGIS software and organized into decades from 1965 to 2014. Ribeirão Preto was identified as the city with the greatest number of cases. Land use was analyzed within a 2 km-buffer surrounding the residence of each patient. A total of 426 cases of pemphigus were identified. PF was the predominant form (285 cases); notwithstanding, the number of new cases of PV rose, overtaking the number of new cases of PF in the last decade studied. Agricultural area (42%) and exposed soil (33.2%) are the most predominant land uses in Ribeirão Preto surrounding patients' residences. This study shows high-confidence geographical foci of PF and PV, as well as provides evidence of an increase of both clinical forms over the last five decades. All cases of PV and PF are in proximity to rivers and agricultural areas which reinforce the hypothesis that environmental factors play a role in pemphigus etiopathogenesis.

INTRODUCTION

Challenges in environmental epidemiology require new tools and innovative techniques for the management and analysis of spatial and temporal data. In environmental health, geographic information systems (GIS) provide maps with a symbolic representation of the role of environmental variables in determining health status, elucidating the spatial relationships among relevant biophysical measurements, environmental exposure, and chronic diseases.[1,2] This study is the first to geo-reference endemic pemphigus cases in Brazil using GIS.

Pemphigus encompasses a group of autoimmune bullous diseases characterized by the production of IgG autoantibodies against desmosomal proteins, mainly desmogleins (Dsg). Pemphigus is divided into two main forms: pemphigus vulgaris (PV) and pemphigus foliaceus (PF).[3] Clinically, PV is characterized by flaccid blisters or lesions histologically caused by suprabasal acantholysis, which could involve mucous membranes and/or the skin. PV patients with mucocutaneous lesions have autoantibodies against Dsg1 and Dsg3, and PV patients with mucosal lesions present antibodies against Dsg3. PF patients display superficial blisters on the skin with histological subcorneal acantholysis, without mucosal involvement.[3] PF is subdivided into classical PF (also called *Cazenave*'s pemphigus) and endemic PF (known in Brazil as *Fogo selvagem*). Both PF forms share the same immunopathogenesis characterized by the presence of anti-Dsg1 autoantibodies, but differ in their epidemiological and distribution patterns.[3,4]

PV is the most common form of pemphigus worldwide. According to geographic region, PV incidence varies between 0.5 and 16.1 cases per million.[5] PV incidence is higher in Jewish populations, in particular those of Ashkenazi origin, where its incidence can reach 32 cases per million.[5] To our knowledge, there are no studies reporting PV incidence and/or prevalence in Latin-America. While classical PF is seen around the world sporadically, without evidence of geographical clustering, its endemic form has been described mainly in Latin-America,[6,7] with well-defined geographical foci in Brazil,[8] Colombia,[9] Peru,[10] Paraguay,[11] and Venezuela[12]; it is also found in some countries of Northern Africa,[13] with clearly identified clusters in Tunisia.[14] In some endemic regions of Amerindians, in Mato Grosso do Sul State, Brazil, PF prevalence varies between 1.3% and 3%.[15,16] Thus, Brazil presents the highest incidence of PF worldwide (25–35 cases/million/year)[8,17] followed by Tunisia (6.7 cases/million/year).[14]

Although pemphigus pathogenesis remains unclear, a combination of genetic and environmental factors has been indicated in relation to individual susceptibility to this disease.[4,18] *HLA* class II alleles are associated with PV and PF pathogenesis in several populations.[19–21] Recently, we reported differential *HLA* class I/II groups/alleles related to susceptibility/resistance to PF and PV in patients from southeastern Brazil. *HLA-A**11 and *33, *-B**14; *-DRB1**01:01 and *01:02; *-DQA1**01:02; and *-DQB1**05:01 were associated with susceptibility to PF. *HLA-A*26, -B**38, *-C**12; *-DRB1**04:02, *08:04, *14:01, and *14:04; *-DQA1**03:01; and *-DQB1**03:02 and *05:03 alleles were related to susceptibility to PV.[22] Several environmental factors have been related to PV, including drugs (mainly Thiol and Phenol drugs), viral infection (mainly the herpes virus), physical agents (e.g., UV radiation), diet, and smoking; however, its etiopathogenesis is still unclear.[4] In the same way, PF has also been linked to various external factors, such as viral infection, contaminated soil and/or water, agricultural additives, and insect bites.[4,18,23]

PF was first described in São Paulo (SP) state, southeastern Brazil, in the beginning of the last century.[24] In the 1940s, Vieira described the epidemiology of PF in SP state, showing

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several well-defined foci, especially near rivers and mainly in northeastern portion of the state.[8,24] Further reports described a peak incidence of PF in SP state during the 1930s and 1940s, followed by a remarkable decline from the 1960s to the 1980s.[6,25,26] Despite the well-established endemicity of PF, recent reports have also demonstrated "endemic" behavior for PV in Brasília, Federal District, Brazil.[27] In fact, a 21-year series in northeastern SP state showed that PV incidence passed PF incidence in 1998.[28]

This study reports the spatial distribution and temporal behavior of PV and PF in the northeastern SP state over the last five decades to describe geographical clusters, as well as to characterize land use in the city with the highest number of cases to identify possible environmental factors that might influence the development of pemphigus.

METHODS

Study population. Patients were identified at University Hospital, Ribeirão Preto Medical School, University of São Paulo, Brazil, which is the main reference institution for the diagnosis and treatment of pemphigus in northeastern São Paulo state (hereafter referred to as NSPS). Four hundred and twenty-six cases of pemphigus were analyzed based on the medical records existing from 1965 to 2014. Pemphigus diagnosis was confirmed by skin or mucosa biopsy, demonstrating intraepidermal acantholysis between 1965 and 1991. Beginning in 1992, serum samples from pemphigus patients were collected and stocked at the Laboratory of Dermatology, University Hospital. Then, pemphigus diagnosis was confirmed by skin or mucosa biopsy demonstrating intraepidermal acantholysis and by direct and indirect immunofluorescence. Allocation into PV or PF groups was defined by suprabasilar or subcorneal acantholysis, respectively, found in histopathology and/or by commercial ELISA Dsg1&3 (MBL®, Nagoya, Japan).

Geographical area. The study area was located in NSPS—southeastern Brazil—between the coordinates 19°52′ and 22°51′ south-latitude, and 46°16′ and 49°20′ longitude-west. The region is composed of 125 cities, covering an area of 51,725 km^2, which represents around 21% of the total area of SP state.[29]

Mapping. Thematic maps were developed using the ArcGIS 10.2 software (ArcGIS, V. 10.2, Environmental Systems Research Institute [ESRI]). Map data were based on two main points of each patient: 1) address at the onset of pemphigus, where geo-reference data are described and 2) year of pemphigus onset, where new cases and cumulative new cases are presented per decade. Maps were organized into decades from 1965 to 2014, in five periods as follows: 1965 to 1974, 1965 to 1984, 1965 to 1994, 1965 to 2004, and 1965 to 2014. Color range was used to differentiate PV and PF cases and to visualize temporal evolution.

Characterization of Ribeirão Preto cases and land cover analysis. Ribeirão Preto was identified as the city with the greatest number of PF and PV cases (17%). Ribeirão Preto is located at 47°48′24″W and 21°10′42″S.[30] Land use regarding dams, native vegetation, agriculture, exposed soil, urban area, and hydrography was analyzed for Ribeirão Preto. First, the geographical locations were obtained from *Google Earth* (Google©) using the home addresses at which the initial symptoms and signs of pemphigus occurred. Later, spatial distribution of pemphigus cases across the city were related to the use and land coverage for the year 2010, based on *GeoEye* image scanning dated February 23, 2010 (available in ArcGIS). The spatial distribution of cases was restricted to the period 2006–2014, according to the land coverage analysis, presuming no critical changes during this ±4-year periods. To prepare the map's layers, the following sources were used: satellite images LandSat 2, sensor MSS from August 17, 1975 and LandSat 8, and sensor OLI220/75 from July 1, 2015.

Environmental analyses in Ribeirão Preto. *Settings.* A radius of 2 km was set surrounding the residence of each patient, based on the Bilthoven Division of the World Health Organization report, which deals with risk assessment methods for health conditions derived from exposure to hazardous substances in degraded areas.[31] This radius set was also supported by the fly-range of fly and mosquito species present in NSPS, which can fly an average of 2 km looking for blood-feeding. The classification of uses was performed according to the standards established by the Brazilian Institute of Geography and Statistics (IBGE) (exposed soil, urban infrastructure, native vegetation, and agricultural activity), the third level, contained in the manual technical land use.[32]

Hydrography mapping. The elements of hydrography were extracted from the topographic maps of the IBGE at a 1:50,000 scale, from which rivers, streams, and dams have been scanned. These letters were registered in terms of projection latitude/longitude and horizontal datum SIRGAS 2000.

Statistical analysis. Data were summarized using frequency tables, summary statistics, and P values. Between groups, categorical variables were contrasted using Chi-square (χ^2) test, and continuous variables using the Mann-Whitney U test and Spearman correlation rank test. Significance was set at $\propto = 5\%$, using two-tails comparison. The statistical analysis was performed using SPSS 22.0 (IBM©, North Castle, NY).

Ethics. The study complies with the 1975 Declaration of Helsinki, as revised in 2013 (Declaration of Helsinki World Medical Association, 2014), and was approved by the committee for ethics in Research of Clinics Hospital, Ribeirão Preto Medical School, University of São Paulo, under number 12248/2010.

RESULTS

Spatial and spatial-temporal behavior of PV and PF in the northeastern SP state over the last five decades. A total of 426 cases of pemphigus were identified after review of medical charts. Between 1965 and 2014, PF was the predominant form of pemphigus, totaling 285 cases (67%), while PV was diagnosed in 141 patients (33%).

Figure 1 shows the spatial and temporal evolution of PV and PF in the NSPS between 1965 and 2014. PV was not reported during the period 1965 to 1974 (Figure 1A); notwithstanding that, the number of new cases of PV rose in the next four decades ($r = 0.969$, $P = 0.006$). Furthermore, new cases of PV overtook the number of new cases of PF in the last decade studied. Regarding cumulative new cases, both, PV and PF have shown an increase through time in NSPS ($r = 0.942$, $P = 0.017$, and $r = 0.996$, $P < 0.001$, respectively).

Spatially, the 16 PF cases diagnosed in 1965–1974 period were distributed in 13 cities (Figure 1F). After the next decade (1975–1984), 9 PV cases emerged in the region distributed in eight cities (Figure 1B). In the same period, 65 new cases of PF were recorded in 19 new cities, totaling 81 cases of PF in 32 cities (Figure 1G).

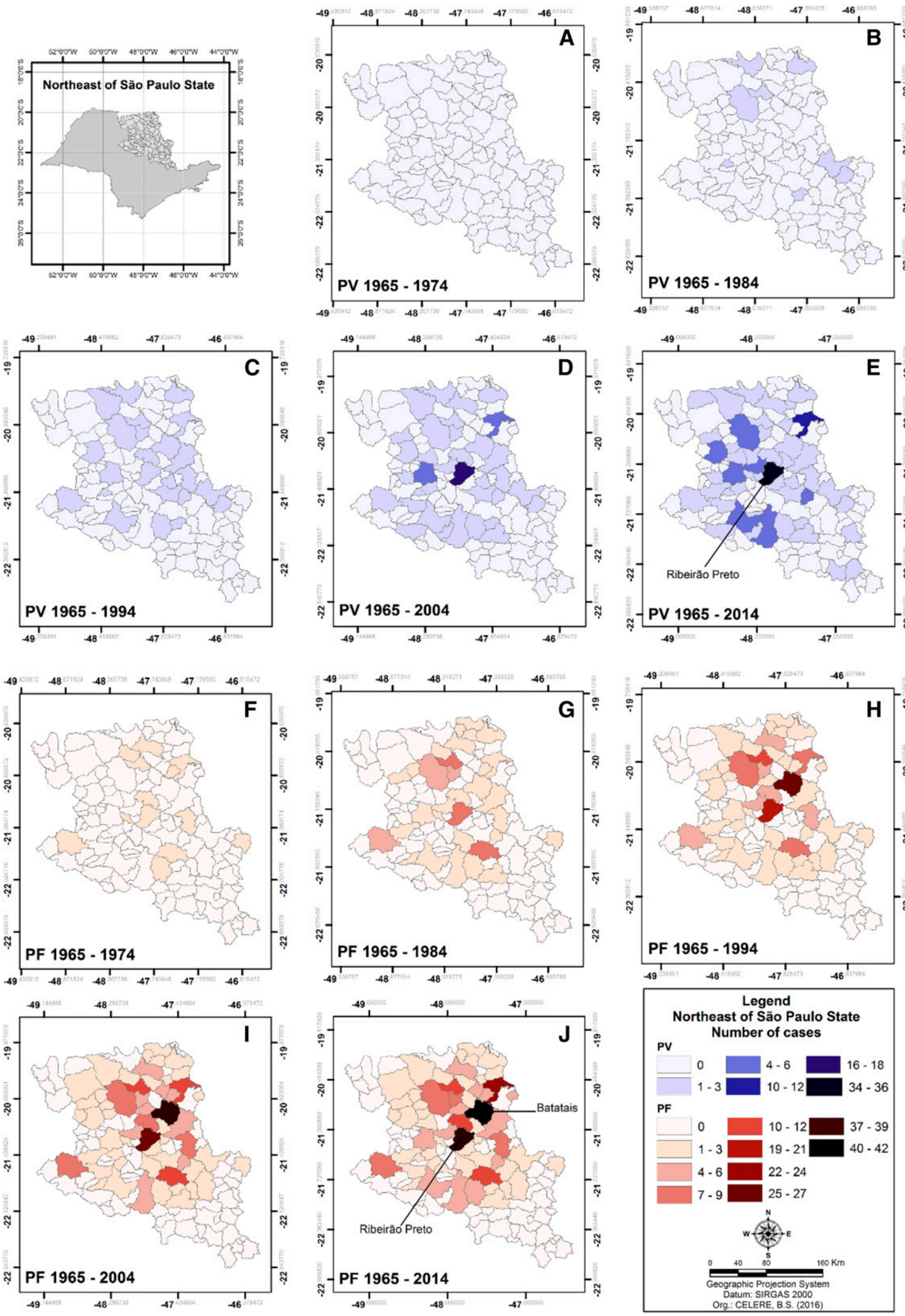

FIGURE 1. Temporal and spatial vulgaris (PV) and pemphigus foliaceus (PF) case evolution in the northeastern part of the state of São Paulo over five decades. (**A**) Distribution of PV cases from 1965 to 1974. (**B**) Distribution of PV cases from 1965 to 1984. (**C**) Distribution of PV cases from 1965 to 1994. (**D**) Distribution of PV cases from 1965 to 2004. (**E**) Distribution of PV cases from 1965 to 2014. (**F**) Distribution of PF cases from 1965 to 1974. (**G**) Distribution of PF cases from 1965 to 1984. (**H**) Distribution of PF cases from 1965 to 1994. (**I**) Distribution of PF cases from 1965 to 2004. (**J**) Distribution of PF cases from 1965 to 2014. This figure appears in color at www.ajtmh.org.

The growth of new cases and territorial expansion was also detected in the period of 1985–1994, with 21 new cases of PV review (Figure 1C) and 89 PF cases (Figure 1H). From 1995 to 2004, over 40 cases of PV and 63 cases of PF were recorded, affecting 35 and 56 cities, respectively (Figure 1D and I). In the last decade analyzed (2005–2014), 71 new PV cases and 52 new PF cases were reported. Interestingly, this decade was the first to report more cases of PV than PF. The total increase involved 141 PV cases distributed in 49 cities (Figure 1E) and 285 PF cases in 60 cities (Figure 1J). The city with the highest number of PV cases until 2014 was in Ribeirão Preto (25%), and for PF cases the city was Batatais (14%). Overall, Ribeirão Preto presented the highest combined number of PV and PF until 2014.

Ribeirão Preto environmental analyses. Ribeirão Preto showed the highest number of pemphigus cases recorded, totaling 72 occurrences over the five decades studied (35 PV cases and 37 PF cases).

Figure 2 illustrates Ribeirão Preto land use in 2010, considering the pemphigus cases between 2006 and 2014, and shows the distribution of PV cases (points 1 to 18) (Figure 2A) and PF cases (points 19 to 27) (Figure 2B) surrounded by a 2-km buffer. It is possible to identify the urban area (surface with anthropogenic changes from buildings and paved areas), native vegetation (riparian, shrub formation, and forest fragments), agricultural region (agricultural territory with cultivation), dams, exposed soil (areas where the vegetation was removed for grazing or harvesting and/or soil preparation for planting), and hydrography (rivers and streams). According to the total characterization of Ribeirão Preto (611 km^2), the following areas were obtained: agricultural area 257 km^2 (42%), urban area 132 km^2 (21.6%), exposed soil 203 km^2 (33.2%), native vegetation 18 km^2 (3%), hydrography (length) 487 km, and dams 1 km^2 (0.2%). All PF cases are located within urban areas (100%). On the other hand, 16 PV cases are located in urban areas, and another two are located in exposed soil land and an agricultural region (PV cases, numbers two and four, respectively) (Table 1).

Table 1 represented the minimum distance between the residences of PV and PF cases, respectively, and the land use based on the categories found in Ribeirão Preto. Table 2 compares the demographic data of pemphigus cases in Ribeirão Preto, as well the different characteristics of the environmental factor studies between PV and PF cases.

DISCUSSION

Spatial distribution and epidemiological data of pemphigus in northeastern São Paulo state over a 50-year period. Most of the PV epidemiological data come from European and

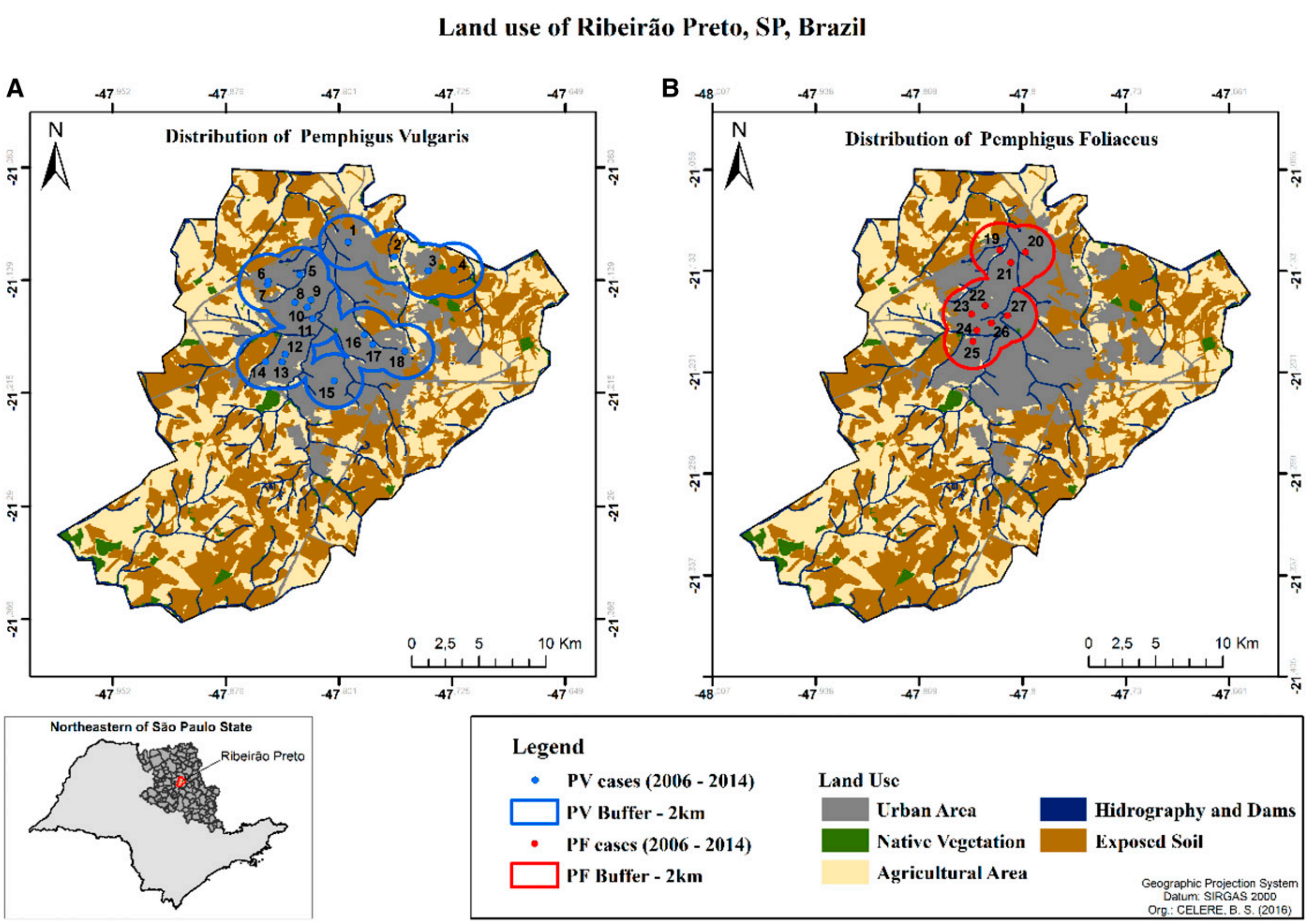

FIGURE 2. (**A**) Description of the land use of Ribeirão Preto within a 2-km buffer of the PV cases residence at the onset of clinical manifestation. (**B**) Description of the land use of Ribeirão Preto within a 2-km buffer of the pemphigus foliaceus cases residence at the onset of clinical manifestation. This figure appears in color at www.ajtmh.org.

TABLE 1
Minimum distance between residences of PV and pemphigus foliaceus cases to native vegetation agricultural areas, hydrography, dams, and exposed soil in Ribeirão Preto, SP, Brazil

			Proximity with (in meters):				
Type of pemphigus	Point/Case	Type of area	Native vegetation	Agricultural area	Hydrography (rivers and streams)	Dam	Exposed soil
Pemphigus vulgaris	1	Urban	–	970	1,007	–	695
	2	Rural	640	70	367	–	258
	3	Urban	744	444	1,483	–	202
	4	Rural	580	500	983	–	5
	5	Urban	755	163	310	1,229	1,586
	6	Urban	1,653	479	646	–	432
	7	Urban	1,745	423	662	–	215
	8	Urban	853	928	1,076	–	1,353
	9	Urban	1,268	125	1,043	–	–
	10	Urban	1,517	580	762	–	–
	11	Urban	1,643	1,373	88	–	–
	12	Urban	801	944	841	–	973
	13	Urban	850	872	955	–	1,034
	14	Urban	167	311	134	1,900	209
	15	Urban	–	1,908	1,025	–	–
	16	Urban	1,271	185	242	–	335
	17	Urban	–	129	217	–	598
	18	Urban	–	328	563	682	411
Pemphigus foliaceus	19	Urban	1,240	170	280	859	852
	20	Urban	–	1,339	207	–	1,513
	21	Urban	–	803	509	1,912	–
	22	Urban	1,249	670	927	–	1,896
	23	Urban	1,541	1,273	789	–	918
	24	Urban	827	261	341	–	1,522
	25	Urban	631	321	504	–	1,147
	26	Urban	1,762	1,159	421	–	–
	27	Urban	1,073	1,553	253	–	–

Asian studies. European studies describe an incidence range of PV between 0.5 and 16.1/million[5]; however, this range can vary according to the region and population studied. To our knowledge, there is no expressive number of reports concerning PV epidemiology in Brazil. Only one study in NSPS reported an increase in PV cases during a 21-year period,[28] and a small-series of 20 cases (10 PV cases) in Pará state[33] compared its behavior with PF in the same region. Gonçalves et al.[28] demonstrated that new cases of PF were decreasing, being overtaken since 1998 by new cases of PV. Our results confirm these facts, with 71 new PV cases as opposed to 52 new PF cases in the last decade, proving a change in the epidemiological behavior of pemphigus in NSPS, where PV arises as the predominant form in a region that has historically been dominated by PF.[8,24,25] In spite of the proposed term "*endemic PV*" by Rocha-Alvarez et al.[27] there is not enough data to support this concept. Environmental factors related to landscape modifications through the years, including transformation from rural to urban regions in NSPS, may explain the epidemiological transition, rather than there being a similar triggering factor for PV and PF; furthermore, differences in genetic background—*HLA* class I and II—have been reported in NSPS for PV and PF,[22] making it improbable that there is a common environmental trigger factor for both diseases.

Despite the reduction of PF cases in NSPS, especially during the seventies and eighties,[26] PF maintains a positive curve of new cases over the decades ($r = 0.996$, $P < 0.001$), still exhibiting frequent occurrences in the last 10 years in some cities and still showing well-defined geographical foci (Figure 1). Our data updated the geographical findings by Diaz et al.[8] in which NSPS mapping showed clustering of PF cases especially near rivers and streams. Furthermore, our results evidenced a current increase in PF cases after a decline in the seventies.[26] Most Brazilian PF data came from studies of the

TABLE 2
Surrounding environmental data for pemphigus cases in Ribeirão Preto, SP, Brazil, between 2006 and 2014

	Pemphigus vulgaris		Pemphigus foliaceus		
	N	%	*N*	%	*P* value α = 5%
Type of area					0.538
Urban	16	88.9	9	100	
Rural	2	11.1	0	0	
Land use	Median	Min/Max	Median	Min/Max	*P* value
Native vegetation surrounding area (m)	852	167/1,745	1,240	631/1,762	0.551
Farming surrounding area (m)	462	70/1,908	803	170/1,553	0.237
Dam surrounding area (m)	1,229	682/1,900	1,386	859/1,912	0.564
Hydrography (rivers and streams) surrounding area (m)	712	88/1,483	412	207/927	0.165
Exposed soil surrounding area (m)	422	5/1,586	1,330	852/1,896	**0.013**

Bold value represents a significant *P* value.

Amerindian population, which are very homogenous and isolated samples, where PF prevalence varies between 1% and 3%.[15,16] Here, we displayed new features regarding PF epidemiological data in Brazil, using a mixed population sample in Southeastern Brazil.

Incidence rates were also calculated per 100,000 inhabitants by city according to population in each time period for PF and PV. After incidence calculation, Ribeirão Preto still prevails as the main focus for PF and PV. However, in this study, we presented prevalence rates and cumulative prevalence to better map interpretation and environmental factors analysis.

Ribeirão Preto land conditions and the highest number of pemphigus cases. Over the past 50 years, Ribeirão Preto has experienced important changes in landscape, such as sugarcane expansion and urbanization. Figure 3 shows two satellite images (LandSat 2, sensor MSS from August 17, 1975 and LandSat 8, sensor OLI220/75 from July 1, 2015) with the growth of the urban area of the city over 40 years: 1975–2015 (before 1975, we did not find satellite images or aerial photographs with enough quality to distinguish the Ribeirão Preto urban area). The urban area increased approximately from 24 km^2 from 1975 to 174 km^2 in 2015, with expansion that has become notorious to areas previously occupied by native vegetation.[30]

The expansion of urban boundaries is also accompanied by the appearance of numerous diseases, previously restricted to rural activities (e.g., leishmaniasis).[34] The urban invasion of forest regions presents a new stage of cohabitation with local fauna previously confined outside the cities, especially related to greater exposure to fly bites.[34] The epidemiological relationship between *Simulium nigrimanum* (Macquart, 1838) and PF, described over 70 years ago in the city of Franca, NSPS,[24] has always been the focus of discussions on the relationship between Simuliidae (Diptera: Simuliidae) and endemic PF in Brazil. Another group of insects studied in PF pathogenesis are the Phlebotomies (Diptera: Psychodidae), specifically the sandfly *Lutzomyia longipalpis* (Lutz and Neiva, 1912) related to PF in an Amerindian Brazilian reserve[35] and the sandfly *Phlebotomus papatasi* (Scopoli, 1786) related to endemic PF in Tunisia.[36] Studies of the distribution of Simuliidae and Phlebotomies species in the NSPS are desirable to corroborate the epidemiological link between bites from black flies and/or sandflies and PF, especially due to the historical data and presence of a well-defined focus in our region, which maximized the hypothesis of environmental factors playing a role in PF' etiopathogenesis.

In addition to the urban expansion in Ribeirão Preto, there was also an increased agricultural perimeter area (42%) and exposed soil (33.2%) (Figure 2). Even when most pemphigus patients are located in urban areas at the start of clinical disease, it is presumed that agricultural fields exert influence on urban environmental conditions because they are very close. Sugar cane culture is predominant and shows low coverage of native vegetation, which is essential for soil conservation and high erosion due to nonrotation of crops. This means that there is a loss of soil nutrients. The consequences of these factors are the carrying of large amounts of organic soil matter and agricultural inputs into the system of watercourses, mainly in the rainy season, causing deterioration of or change in water quality.[37] According to Merten and Minella,[38] the contamination of the water resources of a river basin is caused by different sources, such as agricultural runoff, resulting in pollutants such as sediment, nutrients, pesticides, and animal waste.

Soil sealing and increased runoff also occur in urban areas. Soil sealing in urban environments caused by asphalt surfaces results in less water infiltration into the soil and increased runoff into rivers. Thus, any residual body that is in the water runoff pathway can be taken to the rivers, and depending on their physical characteristics, can be transported to places far from their place of origin, polluting the areas through which they pass and changing the chemical and biological physical characteristics of the water.[39,40] Depending on the rivers' courses, these pollutants can reach the city center where citizens use rivers and lakes as water resources and/ or for recreation activities and fishing, which are common in

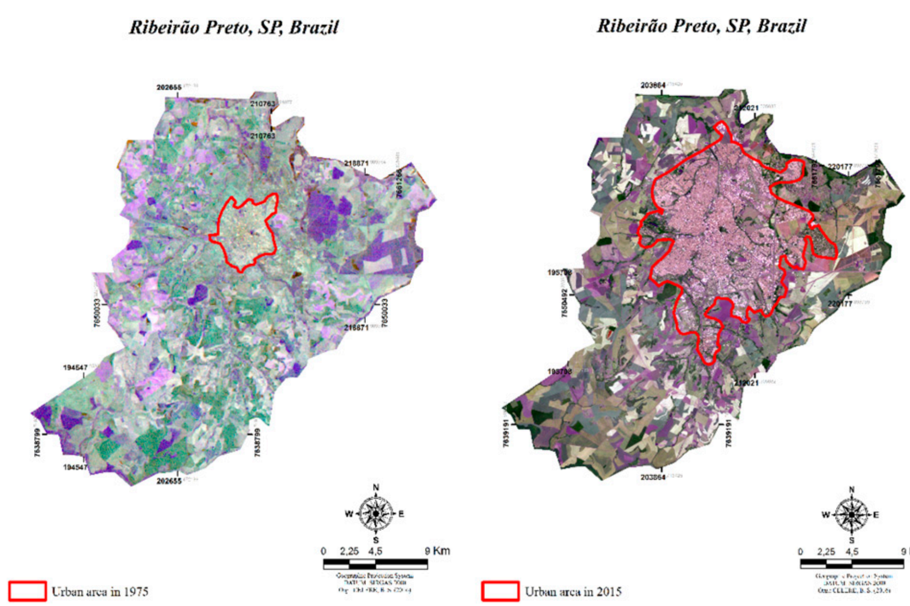

FIGURE 3. Expansion of the urban area of Ribeirão Preto from 1975 to 2015. This figure appears in color at www.ajtmh.org.

Ribeirão Preto streams.[41] Interestingly, as we mentioned before, PF has historically been reported in regions near rivers. In this study, we introduced the importance of agricultural inputs in Brazilian pemphigus epidemiology. Therefore, more specific studies related to agricultural environment and water sources in endemic pemphigus areas are desirable to define a relationship with pemphigus etiopathogenesis. Furthermore, even when PF have been of the clinical form related to rural areas in Brazil, our analysis demonstrated the same influence of environmental factors in PV cases, especially in terms of contact with exposed soil ($P = 0.013$), which may play a role in its etiopathogenesis (Table 2).

Despite PF and PV patients living in NSPS, wherein pemphigus clinical manifestations began, and that the patients have not moved out from the region in a short time period (confirmed by questionnaire—data not shown), the autoimmune nature of pemphigus and a possible long-term subclinical evolution of the disease before clinical onset, it is very difficult to assess previous migration and/or contact with other environmental risk factors outside of NSPS. In the same way, it is not possible to standardize recreational and leisure activities (e.g., fishing) where risk factor as fly bites or exposure to contaminants may have occurred.

Agricultural additives, such as fertilizers, pesticides,[42–44] metals, including zinc (Zn), copper (Cu),[45,46] mercury (Hg),[47,48] and lead (Pb)[49–51] are considered sources of exogenous agents that may affect the immune system, the onset of pemphigus, and the environment. Studies have shown that PV patients had three-times greater exposure to pesticides than healthy subjects, and the exposure to metals[52] and pesticide vapors may also be associated with worsening of PV.[43,53,54] A study by Alves et al.[55] found high Zn values and significant differences between the waters analyzed in the Pardo River (in Ribeirão Preto upstream and downstream), indicating that the use of fertilizers and other agricultural practices (e.g., burning of sugar cane) exert a significant influence on water quality in this city. It is possible that the populations of other cities of NSPS are subjected to the same environmental conditions as Ribeirão Preto because the region was urbanized[56] and developed, surrounded by agricultural areas.[57]

According to the Report of the Meeting of Division of Bilthoven World Health Organization,[31] most studies use from 1–2 kilometers as an area of possible impact and contamination by hazardous substances. However, it is important to be aware that some means may provide a route of indirect exposure of human populations located at greater distances. According to the report, the contaminants that generate concern regarding human and environmental health are metals and pesticides. These substances are defined as priority pollutants based on their toxicity, environmental persistence and mobility. In the case of pemphigus patients, this exposure may be by epidermal contact, direct contact with contaminated soil, and/or contact with contaminated water.[31]

The use of space as an analytical category for understanding the occurrence and distribution of diseases predates the emergence of epidemiology as a scientific discipline. It is an old perception that certain diseases occurred preferentially in this or that place.[58] Pemphigus is a disease still less known to many people and researchers who are seeking answers about the factors that drive the onset of the disease. Land use maps with geo-referencing of PV and PF cases represent tools to introduce possible hypotheses for researchers seeking to understand the possible environmental causes related to pemphigus.

The use of GIS in the public and environmental health field is becoming a powerful tool that helps researchers to understand the occurrence and trends of some events, leading to improved interventional strategies and disease control. This study is the first to geo-reference pemphigus cases in Brazil using GIS, showing high-confidence geographical clustering for both PF and PV, as well as providing evidence of an increase of both clinical forms over the last five decades. All cases of PV and PF are in proximity to rivers and agricultural areas within 2-km buffer, which reinforce the hypothesis that environmental factors play a role in pemphigus etiopathogenesis.

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