Pemphigus vulgaris and infections - A retrospective study

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ABSTRACT

Pemphigus Vulgaris is an autoimmune disease and is treated with immunosuppressive therapy. This reason but either the fact that the skin is not intact are predisposition factors why patients with Pemphigus vulgaris are predisposed to infections. We aimed to study the frequency of infections, categorical and numeric variables related to infection, in Pemphigus vulgaris s patients admitted to dermatology service. This retrospective study was conducted on 130 patients diagnosed with Pemphigus vulgaris and hospitalized at Dermatology Clinic during the year 2020-2022. The diagnosis of Pemphigus vulgaris was confirmed by biopsy and indirect/direct immunofluorescence findings. Data were collected through the charts in the Statistics Department, in UHC "Mother Teresa", Tirana, Albania. 130 patients (70 males, 60 females) were hospitalized in UHC " Mother Theresa) during the period 2020-20122. 48.69% of patients had infections. The occurrence of infection was significantly related to the severity of the disease, multiple admissions, and hospitalization duration. The most frequent infections encountered: are skin infections, urinary infections, pulmonary infections, and opportunistic infections (candida). The most common pathogenic germs isolated from cultures were Staphylococcus aureus and Escherichia coli. Infections are the most common complication among patients treated for Pemphigus vulgaris. Patients with longer duration disease and hospitalization have a higher probability to develop infections, mainly skin infections. Due to the limitations of a retrospective study, we recommend a prospective study.

Keywords: Pemphigus vulgaris, Infections, Staphylococcus aureus, Escherichia coli

Introduction

Pemphigus vulgaris is a pathology that affects the mucocutaneous system with the formation of intraepithelial blisters, which usually occur in the fifth or sixth decade [1-3]. There has been found a relation with the HLA Class II, implicating HLA-DR4, HLA-DRw14, and HLA-DQB. Severely studies agree that genetic predisposition is a potential factor. However, Pemphigus vulgaris is not considered a hereditary disease [2]. The physiopathology of pemphigus vulgaris is caused by an autoimmune process. The auto-antibodies IgG and C3 complement, act against the molecular adhesion of keratinocytes [1] M type [4]. The antibodies responsible for pemphigus vulgaris are normally IgG type. However, we can find even the antibodies IgA or IgM type and even the complement protein C3 [4]. There have been identified several environmental factors that trigger the disease such as medicine (thiol-containing drugs), physical and viral agents, and even diet [1, 3-6]. Usually, the diagnosis of pemphigus vulgaris is based on: clinical features, histology, and immunological tests [4, 7]. One diagnostic approach is Nikolsky sign positive. The main clinical features are painful ulcers intraoral lesions and extraoral ones. Intra-oral lesions include non-itchy erosive blisters in any part of the mucosa membrane, whereas the extra-mucosal ones include erosive blisters on the skin (face, back, or chest). They appear in normal skin. The immunological tests performed are direct immunofluorescence and indirect immunofluorescence. Direct immunofluorescence detects the intracellular deposits of IgG, IgM, IgA, and C3 protein on the epidermis and perilesional skin, it offers 100% sensitivity. Indirect immunofluorescence detects antibodies in serum. Also, the ELISA test detects and measures anti-Dsg1 and

anti-Dsg3 antibodies in serum. If there is any suspicious result, it is performed immunoprecipitation and immunoblotting techniques [1, 2, 8-10]. The main histological finding is acantholysis in the suprabasal layer. Intraepithelial vesicles, show Tzanck cells. Connective tissue stroma showed loose collagenous stroma with dense inflammatory cells. Its aggravation is mainly related to the extent of the disease, the age of the patient, the presence of comorbidities, the drug dose, and even the antibody titer [2, 8]. Currently, less than 10% did exitus, mainly to the side effects of treatment. Before the introduction of corticosteroids, the death of patients with Pemphigus vulgaris was around 75% [3, 11-13]. The treatment is based on a combination of corticosteroids and immunosuppressant therapy but is associated with many side effects.

Aim of the study

The focus of our study was to find and evaluate the correlations between the chosen variables as follows: the characteristics of patients hospitalized, complications of the disease, duration of diseases, number of admissions, hospitalization duration, development of infections and defining the trend of disease over the years.

Materials and Methods

The data were collected from the Statistics Department in the University Hospital Center "Mother Teresa". The study was performed between the years 2020-2022. A retrospective study was conducted on 130 patients diagnosed with Pemphigus vulgaris admitted to Dermatology- Venereology Department during the three years. All patients were diagnosed with Pemphigus vulgaris via biopsy and indirect/direct immunofluorescence.

There are evaluated numeric variables: duration of disease, hospitalization duration, and categorical variables: number of admissions, infections, and associated diseases. The data was processed in excel and SPSS version 20. The descriptive part is shown in tables and figures designs. The type of study is transversal.

Statistical analysis

The collected data were analyzed via statistical software Excel and SPSS.

Demographic data included age, gender, number of admissions, and pre-existing conditions such as the history of diabetes, hypertension arterial, treatment protocols, and infections identified during hospitalization.

It was used the Kendall coefficient to determine if there is a correlation between infections and:

- Duration of the disease
- Number of admissions
- Hospitalization duration

Results and Discussion

There were hospitalized 130 patients diagnosed with Pemphigus vulgaris (70 males, 60 females). during the years 2020-2022. **(Table 1)** Minimum age was 18 years and maximum age was 94 years with average age: 62.4 years $\pm$ 16,8; CI 95% (59,6-65,2) **(Figure 1)**.

The statistical analysis concluded that the ratio of females: to males is approximately 1:1.17. Hospitalization varies from 3 days standing to 67 days standing with an average of 12.27 $\pm$ 1.6; CI 95% 9.4- 13.5. 62 of 130 patients had infections with a frequency of infection of 47.6% **(Table 2, Figure 2)**. The most frequent infections encountered: are skin infections, urinary infections, pulmonary infections, and opportunistic infections (candida). The more frequent strains responsible were: Staphylococcus aureus and Escherichia coli. Comorbidity: Hypertension Arterial (HTA) outcome in 28 patients, Diabetes Mellitus (DM) in 22 patients, and 7 patients with HTA and DM. Regarding logistic regression, the significant level was $p > 0.05$. The correlation coefficient of Kendall between hospitalization duration and infection was ($r=0.75$), significant level $p < 0.05$; duration of diseases and infection was ($r=0.24$) significant level $p < 0.05$; the number of admissions and infection was ($r=0.05$) significant level $p= 0.89$. The chi-square test resulted in no significant between the number of patients with infection in treatment with corticosteroid therapy and the number of patients with infection in treatment with corticosteroid therapy and immunosuppressor preparations ($p > 0.05$). All these findings are presented with relevant tables and graphs with accompanying explanations.

	Table 1. Frequency of Pemphigus Vulgaris					
Year	Total no. of Hospitalizations	Females	Males	Total	Frequency (%)	Female/Male Ratio
2020	886	12	15	27	3.05%	1:1.25
2021	861	23	27	50	5.81%	1:1.17
2022	890	25	28	53	5.96%	1:1.12
Total	2637	60	70	130	4.93%	1:1.17

Out of the 130 PV patients, 60 (46%) were females and 70 (54%) were males. The frequency of hospitalization indicates that there is a decrease in PV cases from 5,96% in 2022 to 3,05% in 2020. Female/male ratio of 1:1.17
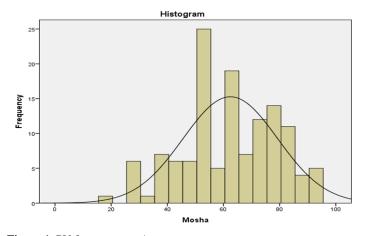
Figure 1. PV frequency on Age
Minimum age - 18 years
Maximum age - 94 years
Average age: 62.4 years $\pm$ 16,8; CI 95% (59,6-65,2)

Table 2. Hospitalization duration and Infections on hospitalization duration in years 2016-2018.

Duration of Hospitalization (Days)	Year 2020	Year 2021	Year 2022	Average	No. of patients PV	No. of patients with infections
0-10	54.7%	58.0%	53.0%	55.23%	72	22
11-20	26.0%	26.0%	35.0%	29.00%	36	21
21-30	15.6%	16.0%	4.0%	11.87%	17	14
Over 30	3.7%	0.0%	8.0%	3.90%	5	5
Total					130	62

Duration of hospitalization ranges between 3 - 67 days, with an average of 12.27 days $\pm$ 1.6;
CI 95% (9.4- 13.5). Out of 130 patients, 62 patients resulted in infections, and the frequency of infections was 47.6%.
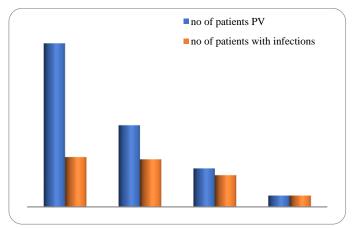

Figure 2. Correlation between infections - duration of hospitalization
Infections and duration of hospitalization
Kendall coefficient (r=0.75)
Significance $p<0.05$
As it is observed, with the increasing of days of hospitalization, the number of infections increased and when the day of hospitalization was over 30 days, all the patients had equal infections.

Table 3. Duration of diseases (PV)

Duration	No. of patients with PV	No. of patients with infections	Frequency
0-1 Year	69	34	49,28%
2-5 Years	37	18	48,65%
6-10 Years	14	6	42,86%
11-15 Years	5	2	40,00%
16-20 Years	3	0	0,00%

over 20 Years	2	2	100,00%

From **Table 3**, it is noticed that the frequency of infections depending on the duration of the disease is almost the same. The link between these two variables is poor. This is because the data is obtained only at the dermatology clinic, while patients may have been treated in regional hospitals or clinics that cover the relevant infections for which we have no data.

Table 4. Frequency of Admissions and infections regarding admission of patients

	Number of Admissions	Total (%)	Number of admissions with infections	Frequency of infection
First Admission	91	70%	38	41.76%
Multiple Admissions	39	30%	24	61.24%
Total	130	100%	62	47.69%

Study included a total of 130 patients, of which 91 (70%) were first-admission patients and 39 (30%) were multiple-admission patients. Infection and number of admissions
Kendall coefficient (r=0.05)
Significance p=0.89
Correlation is not significant. See **Table 3** , no. of admissions did not have an impact on infections.

Table 5. Frequency of all infections in PV patients and infectious agents.

Type of Infection	Number of Infections	% of Infections (% of 130 patients)	Infectious agent
Skin infections	61	46.92%	Staphylococcus aureus (9 cases confirmed with antibiogram), Bacteria gram + (1 case not specified), others diagnosed clinically
Urinary infections	7	5.38%	E. coli (2 confirmed with uroculture)
Pulmonary infections	3	2.31%	Not specified
Oral candidiasis	2	1.54%	Oral culture

Out of the 62 patients with infections, 61 presented skin infections and also several secondary infections such as urinary, pulmonary, and oral candidiasis, which have been separately listed in the table above. One of the 62 patients with infections presented only oral candidiasis and was not included under skin infections.

Infection of PV patients with associated disease as Hypertension Arterial and Diabetes Mellitus resulted as follows, with Hypertension arterial (HTA) in 15 patients with an infection in 28 patients with both diseases, with Diabetes Mellitus (DM) in 13 patients with an infection in 22 patients with both diseases, HTA and DM resulted in 4 patients with an infection on 7 patients with both diseases. The frequency of each is respectively was 53.5%, 59%, and 57%. According to the logistic regression, the link between infections and the associated diseases (HTA, DM, HTA & DM) did not result significantly (p=0.74). The existence of one or more of these associated diseases does not affect the initial infections. This is explained by the fact that the sample in the study is small, 130 patients. A regimen of therapy was another clue, we have been focused on. Our study concluded that 33 patients had infection among 79 patients treated only with corticosteroids (41.7%) and 29 patients had infection among 51 patients treated with corticosteroids and immunosuppressors (56.86%). The chi-Square test resulted in no significant p<0,05. From the statistical analysis, the link between the infection and the therapeutic regimen used is not significant.

Patients with Pemphigus vulgaris are predisposed to various infections due to the use of immunosuppressive therapy and epidermal barrier dysfunction. Referring to the literature, several similar studies have focused on infections in this group of patients [5, 6]. In our study, unlike other studies [5, 6], it was found that antibiotic therapy is initiated without the performance of the antibiogram, based on a clinical diagnosis of infection. The study found that most frequent skin infections were caused by Staphylococcus aureus and urinary infections was caused by E.

coli. Similar conclusions were also noted in other studies by Nafiseh Esmaili *et al*. [5]. Frequency of infections according to the number of admissions was not significant. Meanwhile, in the literature, there was a positive significance, almost twice of frequency of infections in multiple admissions [5]. The female-male ratio of PV disease is similar to other studies [5, 6]. No significant differences were between the genders. The age range and average age of disease: 62.4 years $\pm$ 16.8; CI 95% (59.6-65.2) resemble other studies [5, 6]. Frequency of infections in patients treated with corticosteroid therapy, there was no significant difference in the frequency of infections in patients treated with corticosteroid therapy and immunosuppressant therapy. The same conclusion also resulted in similar studies, as the retrospective study of 155 patients in Tehran by Nafiseh Esmaili *et al*. [5]. The comorbidity did not show any relation to the frequency of infections, while in the Tehran study by Nafiseh Esmaili, it was observed that in diabetic patients the frequency of infections was higher than in non-diabetic patients [5]. Our study found that, with the increase in hospitalization, the probability of the patient becoming infected increased. While the duration of the disease showed poor significance.

The retrospective nature of the study (restriction of information), the short period of study (3 years), and the small sample number (130 patients) are the major limitations of this study. The lack of cases with sepsis or the low number of deaths may be due to the short period used for the study and the small number of patients.

Conclusion

Infections are one of the most common complications in PV patients. In our study 48.69% of patients had infections. Patients with pemphigus vulgaris with longer duration disease and hospitalization, despite the treatment protocol or comorbidity, have a higher probability to develop infections, mainly skin infections. To prevent infections as potential complications in PV patients, we recommend early diagnosis and start the treatment, informed patient and family about their disease and complications, appropriate measures taken to maintain good hygiene, rational use of antibiotics with antibiogram, and use of local antiseptics.

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