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Original Article DERMATOLOGY

A retrospective analysis of pemphigus vulgaris patients: Demographics, diagnosis, co-morbid diseases and treatment modalities used

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ABSTRACT

OBJECTIVE: Pemphigus vulgaris is an autoimmune blistering disease affecting the mucosal surfaces as well as the skin. Twenty-eight retrospective studies about the epidemiologic data of pemphigus vulgaris patients have been performed previously in the literature.

METHODS: In this retrospective study, we evaluated 320 pemphigus vulgaris patients who applied to the bullous diseases clinic of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Dermatology, between the years 1999–2019. Epidemiologic data, diagnostic modalities, comorbidities and treatment modalities were noted.

RESULTS: The female to male ratio was 1.39. The mean age of diagnosis was 50.4±13.7 years, 50.8±12.5 years for males and 50.0±14.5 years for females. The average disease duration was 99.0±74.4 months; it was 91.6±67.2 months for males and 104.5±79.0 months for females. At the time of diagnosis, 88.7% of our patients had mucosal lesions and 68.4% of our patients had cutaneous lesions. The most common side effects were hypertension, diabetes mellitus, osteoporosis and hyperlipidemia. Adjuvant therapy was initiated 332 times. Azathioprine was used in 260 patients,Mycophenolate sodium was used in 30 patients, Mycophenolate mofetil was used in 42 patients, IVIG was used in 52 patients, Rituximab was used in 51 patients.

CONCLUSION: Pemphigus vulgaris is a disease that is more commonly seen in female patients. It has a peak incidence in the fifth decade and there is not a statistically significant difference between the age of diagnosis between the genders. It is a chronic disease with a long follow-up period; again, there no statistically significant difference between the two genders. The most commonly encountered comorbidities are hypertension, hyperlipidemia, diabetes mellitus and osteoporosis, which are due to the use of corticosteroids.

Keywords: Co-morbidity; diagnosis; epidemiology; gender; pemphigus.

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Pemphigus vulgaris is an autoimmune blistering disease that affects the skin and the mucous membranes. It has two disease sub-groups: mucosal dominant and mucocutaneous. The disease usually presents with painful erosions in the mucous membranes or easily ruptured blisters on the skin [1–4]. Previously, 28 retrospective studies regarding the epidemiology of pemphigus vulgaris were performed. In these studies, the mean age of diagnosis varied from 37 to 71 [5, 6]. All of these studies, except for two studies, both of them were performed in Saudi Arabia, showed that there was a female predominance of the disease [5–8]. Of these studies, the largest cohorts belonged to Huang et al. [9], with 853 patients and Chams-Davatchi et al. [10] with 1209 patients. These

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studies found that the age of onset of disease was 52.5 [9] and 42 [10], respectively. The female to male ratios were 1.3 [9] and 1.5 [10], respectively. The other studies had relatively smaller sample sizes compared to our study of 320 patients. The most relevant study to ours was performed by Yayli et al. [5] because it was performed in Turkey as well and it incorporated 220 patients. Yayli et al. [5] have found the age of onset as 49.5 and the female to male ratio as 1.41. Biopsy, direct and indirect immunofloresence studies and Dsg1 and Dsg3 ELISA assays are used in the diagnosis of the disease [10].

Systemic corticosteroids play a central role in the treatment of pemphigus vulgaris. In refractory patients, immunosuppressive agents, such as Azathioprine, mycophenolate mofetil, cyclophosphamide, cyclosporine, methotrexate, intravenous immunoglobulins and rituximab, can be added [1, 11–17]. According to more recent guidelines, rituximab has also become a first-line treatment for moderate to severe pemphigus vulgaris patients [18].

The use of systemic corticosteroids has its own limits due to comorbid diseases. Type 2 diabetes mellitus, hypertension, osteopenia and osteoporosis are comorbid diseases that are commonly seen in pemphigus vulgaris patients due to the concurrent use of systemic corticosteroids [19–23].

Previously, many studies were performed regarding the epidemiology, treatment and comorbid diseases of pemphigus vulgaris. However, none of these studies evaluated all of these parameters in the same patient population. With this study, we aim to assess the demographics, diagnostic modalities, comorbid diseases and treatment modalities that were preferred in the same patient population consisting of 320 cases. Furthermore, previous studies have not stratified the patient populations according to gender. In this study, we aim to find any differences in these parameters among genders if there exists any.

MATERIALS AND METHODS

The patients who applied to the bullous dermatosis outpatient clinic of Istanbul University-Cerrahpasa, Cerrahpasa Faculty of Medicine, Department of Dermatology, and who were diagnosed with and followed up as pemphigus vulgaris between 1999 and 2019 were included in this retrospective study. The positivity of either biopsy and direct immunofluorescence or indirect immunofluorescence or Dsg1 and Dsg3 ELISA assays along with clinical features were set as prerequisites for the definitive diagnosis. The sex of the patient, age of diagnosis, and average duration of the disease, cutaneous/mucosal involvement, comorbid diseases, biopsy positivity, direct immunofluorescence positivity, indirect immunofluorescence positivity and the treatment modalities used were noted.

The approval of Istanbul University Cerrahpasa, Cerrahpasa Faculty of Medicine Ethics Commitee was taken before this study was initiated (Approval date: November 15, 2019, Approval no: 39122051-604.01.01-175657).

Student t-test and Mann-U Whitney tests were used for statistical analyses.

RESULTS

In this study, 320 patients were included, of these patients, 136 were male and 184 were female. The female to male ratio was 1.39. The mean age of diagnosis was 50.4±13.7 years, 50.8±12.5 years for males and 50.0±14.5 years for females. The youngest patient was a 14 years old female; the youngest male patient was 16 years old. The oldest patient was an 87 years old female; the youngest male patient was 84 years old. The demographics of our patient group are summarized in Table 1. The ages of the patients showed a normal distribution. Thus, a student t-test was used for the statistical analysis. The p-value was calculated as 0.617, so there was no statistically significant difference between the ages of the two sexes.

The average disease duration was 99.0±74.4 months; it was 91.6±67.2 months for males and 104.5±79.0 months for females in particular. The shortest disease duration overall was one month for a male patient. The shortest disease duration for female patients was two months. The longest disease duration overall was 423 months for a female patient. The longest disease duration for male patients was 288 months. The disease durationdid not show normal distribution; the Mann-Whitney U test was used. The p-value was calculated as 0.208; thus, there was not a statistically significant difference between the disease duration of the two sexes.

As for the disease presentation, 284 patients (88.7%) presented with mucosal involvement; of these, 117 were male, and 167 were female. Thirty six of the 320 patients had no mucosal involvement, 18 women and 18 men. Two hundred nineteen patients (68.4%) had cutaneous manifestations of the disease at presentation, 98 of them were male and 121 were female. A hundred and one patients had no cutaneous involvement, 37 were male and 64 were female. The results regarding the disease presentation are summarized in Table 1.

Table 1. Patient demographics and disease presentation

	Total	Male	Female
Number of patients	320	136	184
Age at diagnosis (years)	50.4	50.8	50.07
Youngest age of diagnosis (years)	14	16	14
Oldest age of diagnosis (years)	87	84	87
Average disease duration (months)	99.0	91.6	104.4
Shortest disease duration (months)	1	1	2
Longest disease duration (months)	423	288	423
Mucosal involvement (%)	88.7	87	90
Cutaneous involvement (%)	68.4	72.6	65.4

The diagnostic modalities for pemphigus vulgaris patients are biopsy, direct and indirect immunofluorescence and desmoglein 1 and 3 levels with ELISA assay. Desmoglein levels could not be assessed in many of our patients because of financial holdbacks. At the time of the diagnosis, pemphigus vulgaris was confirmed histopathologically in 249 patients, 100 of these were male and 149 were female. The diagnosis was supported with the positivity of direct immunofluorescence in 247 patients, 107 were male and 140 were female. Indirect immunofluorescence positivity was present in 224 patients, 93 of whom were male and 131 of them were female. The diagnostic methods that were used in this study are summarized in Table 2.

Comorbid diseases were another parameter that was assessed in this study. The most common comorbidity that was observed in the pemphigus vulgaris population was hypertension: 39 patients, 16 of them were male, and 23 of them were female. The second most common comorbidity in the pemphigus vulgaris population was diabetes mellitus: 26 patients, 10 of them were male, and 16 of them were female. The third most commonly observed comorbidity was osteoporosis: 16 patients: six of them were male, and 10 of them were female. Hyperlipidemia was also a commonly observed comorbidity in pemphigus vulgaris patients: nine patients, three of them were male, and six of them were female. Apart from these commonly observed comorbid diseases, there is a wide range of diseases that coexisted in our pemphigus vulgaris population, which are summarized in Table 3.

Systemic corticosteroid therapy with gradual dose tapering is the first choice for the treatment of pemphigus vulgaris in our clinic. Adjuvant therapy is simulta-

Table 2. Diagnostic methods

	Total	Male	Female
Biopsy positivity (number of patients)	249	100	149
DIF positivity (number of patients)	247	107	140
IIF positivity (number of patients)	224	93	131

Table 3. Comorbid diseases

	Total (n)	Male (n)	Female (n)
Hypertension	39	16	23
Diabetes mellitus	26	10	16
Osteoporosis	16	6	10
Hyperlipidemia	9	3	6
Dementia	2	0	2
Hemorrhoid	2	2	0
Benign prostatic hyperplasia	4	4	0
Pulmonary tbc	1	1	0
Chorioretinitis	1	1	0
Avascular necrosis of femur	1	0	1
Cmv encephalitis	1	0	1
Coronary artery disease	4	4	0
Behçet disease	2	2	0
Sleep apnea	1	1	0
Hepatitis c	1	1	0
Hepatitis b	1	0	1
Allergy	1	1	0
Asthma	3	1	2
Schizophrenia	1	1	0
Stroke	1	1	0
Burger disease	1	1	1
Hypophysial adenoma	1	1	0
Hyperthyroidisim	6	2	4
Steroid myopathy	1	1	0
Hysterectomy	1	0	1
Rheumatoid arthritis	1	0	1
Multiple myeloma	1	0	1
Cataract	1	0	1
Pancreatitis	1	0	1
Renal insufficiency	1	0	1
Varicose veins	1	0	1
Fibromyalgia	1	0	1
Arrhythmia	2	0	1
Breast cancer	2	0	2

n: Number of patients.

Table 4. Treatment modalities used

	Total (n)	Male (n)	Female (n)
Adjuvant therapy	332	142	190
Azathioprine	260	108	152
Mycophenolate sodium	30	19	11
Mycophenolate mofetil	42	15	27
IVIG	52	20	32
Rituximab	51	16	35

n: Number of patients; IVIG: Intravenous immunonoglobulin.

neously added to systemic corticosteroids at the time of the diagnosis. The most commonly used adjuvant drugs in our clinic are Azathioprine, mycophenolate mofetil, mycophenolate sodium, intravenous immunonoglobulin (IVIG) and rituximab. Overall, adjuvant therapy was initiated 332 times, 142 times for males and 190 times for females. Azathioprine was used in 260 patients, 108 of them were males and 152 of them were females. Mycophenolate sodium was used in 30 patients, 19 male and 11 female. Mycophenolate mofetil was used in 42 patients, 15 male and 27 female. IVIG was used in 52 patients, 20 male and 32 female. Rituximab was used in 51 patients, 16 of them were male and 35 of them were female. The treatment modalities that were used are summarized in Table 4.

DISCUSSION

In this study, the female to male ratio was calculated as 1.39, which indicates a female predominance. Similar to our results, another study from Turkey conducted by Yayli et al. has also calculated the female to male ratio as 1.41 [5]. Again, similar to our results, previous studies have found a female predominance in the pemphigus vulgaris patients [6–11]. Two of the largest epidemiologic pemphigus studies were performed by Huang et al. [9], with 853 patients and Chams-Davatchi et al. [10] with 1209 patients. These studies have calculated the female to male ratios as 1.3 [9] and 1.5 [10], respectively. The ratio that was determined in our study lies between these two results. Kridin et al. [24] reviewed the previous studies about the epidemiologic data of pemphigus vulgaris patients. They also concluded that, apart from two studies that were from Arabic countries, female dominance in disease prevalence has been reported. The lowest female to male ratio was 1.1, a study from Finland, and the highest female to male ratio was 5.0, a study from the US [25]. The two studies from Arabic countries may be misleading due to under-represented status of females in these countries; female patients may have difficulties reaching healthcare. Like other autoimmune diseases, a female predominance is present for pemphigus vulgaris as well [26]. Thus, in accordance with our results, we suggest that pemphigus vulgaris is a disease that is more frequently encountered in female patients.

In this study, the mean age of diagnosis was calculated as 50.4±13.7 years; and 50.8±12.5 years for males and 50.0±14.5 years for females specifically. There is not a statistically significant difference between the mean ages at the diagnosis of the two sexes (p=0.617). Previously, Huang et al. [9] have reported the mean age at diagnosis 52.5±15.9 (for all patients). Apart from our study, Huang et al.'s study [9] was the only study to compare the difference in the mean age of diagnosis of pemphigus vulgaris between the two sexes. Huang et al. [9] have reported the mean age at diagnosis for female patients as 52.0±15.1 years and the mean age at diagnosis for male patients as 54.5±16.8 years. Although a greater difference, compared to our study, between the mean ages at the time of diagnosis for the two sexes was reported by Huang et al. [9], it was not statistically analysed; therefore, it is not known whether or not this difference is statistically significant. Chams-Davatchi et al. [10] reported the mean age at diagnosis as 42 years; however, they did not stratify the patient groups concerning gender. Yayli et al. [5] reported the mean age at diagnosis as 49.51±15.24; again, they did not stratify the patient groups concerning gender. According to Kridin et al.'s [24] review, the mean ages at diagnoses varied from 36.5, a study from Kuwait, and 71, a study from England. A study from Bulgaria conducted by Tsankov et al. [26] has reported the mean age of diagnosis as 72.4, which is the highest number that has been reported in the literature. Thus, pemphigus vulgaris, as was shown in our patient population as well, is a disease that is more commonly observed in the middle age patient group, the fifth decade in particular. However, a significant difference between the ages at the presentation of the two sexes does not exist.

The average disease duration was calculated as 99.0±74.4 months; 91.6±67.2 months for males and 104.5±79.0 months for females. There is not a statistically significant difference between the disease durations of the two sexes (p=0.208). As for the previous studies, only Huang et al. [9] have reported the disease duration.

According to Huang et al. [9], the average disease duration was 3.8±2.1 years (45.6 months) for all patients, 3.6±2.1 years (43.2 months) for males and 3.9±2.0 (46.8 months) for females. The difference was not evaluated statistically and it is not known whether or not the difference is statistically significant. Compared to our results, Huang et al.'s [9] results for the disease duration is much shorter; however, it should be kept in mind that Huang et al.'s [9] study evaluated the patients between the years 2002–2009, for seven years, on the other hand, we evaluated patients for 20 years, 1999–2019. In short, there is not a statistically significant difference concerning disease duration between the two genders.

The typical disease presentation of pemphigus vulgaris is superficial ulcers in the oral mucosa, particularly the labial and buccal mucosa [27]. However, other mucosal surfaces, although less common, may be involved. Half of the patients have cutaneous findings along with the mucosal findings: eroded or flaccid blisters on the groin, trunk, axilla, scalp and face [28]. At the time of disease presentation, 88.7% of our patients had mucosal lesions and 68.4% of our patients had cutaneous lesions. However, our data failed to show if patients had mucous membrane and cutaneous involvements simultaneously. Previously, in the literature, Chams-Davatchi et al. [10] reported that of their 1111 pemphigus vulgaris patients, 782 (70.3%) had mucous membrane and cutaneous involvements together, 200 (18%) had mucosal lesions only and 129 (11.6%) had cutaneous lesions only. Both our and Chams-Davatchi et al.'s [10] data suggest that mucosal findings are more common than the cutaneous findings at the disease presentation. Further studies could be performed to determine the gender differences between disease presentations. Our data failed to demonstrate such a difference.

A positive biopsy result is a diagnostic prerequisite for pemphigus vulgaris and preferentially, the biopsy should be taken from the oral mucosa if the disease manifests itself there. Other modalities that are commonly used are direct immunofloresence studies (DIF) and indirect immunofluorescence studies (IIF) [27]. A positive DIF result shows epithelial surface staining with IgG, showing that the disease is active and the antibodies against the desmoglein proteins are attacking the tissue [19]. Indirect immunofluorescence results reflect the circulating antibodies in the patients' sera. The antibody titers determined by the IIF assays reflect the disease severity and is used in assessing treatment response and patient follow-up for relapses [13]. Of our 320 patients, 249 (77.8%) had a positive biopsy result, 247 (77.2%) has a positive DIF result and 224 (70%) had a positive IIF result. The only retrospective epidemiological study concerning pemphigus to report diagnostic modalities was the study conducted by Chams-Davatchi et al. [10]; however, only the DIF results were reported. The authors reported that of the 1111 patients, 389 (35%) had a positive DIF result. However, DIF could only be performed on 417 patients; keeping this in mind, 93.3% of the patients showed a positive DIF result. The retrospective data concerning the diagnostic modalities are unfortunately unsatisfying due to the increased costs of these modalities.

Before the use of corticosteroids and immunosuppression, pemphigus vulgaris has been considered as a mortal disease. With the introduction of immunosuppressive agents, disease mortality has declined rapidly. The mortality rate of pemphigus vulgaris is 8.8%. The most common causes of mortality in pemphigus patients are malignancies (19.3%), infectious diseases (18.2%) and cardiovascular diseases (12.5%) [29]. However, the use of corticosteroids has its own disadvantages. The long term side effects of corticosteroids are osteoporosis, adrenal insufficiency, aseptic necrosis of femur, hypertension, hepatic and gastrointestinal side effects, cataract, hyperlipidemia, hyperglycemia, growth supression in children and congenital malformations in pregnant patients [30]. Corticosteroid therapy is considered as a cornerstone in the treatment of pemphigus vulgaris in our clinic. As a result, all of our patients receive corticosteroid therapy at the time of the diagnosis, and the dose is tapered and the corticosteroid therapy may be ceased in the follow-up. Thus, corticosteroid dependant side effects are frequently encountered in our pemphigus patient population. The most commonly observed side effects were hypertension, diabetes mellitus, osteoporosis and hyperlipidemia, all of them are due to the use of corticosteroids. According to a study performed by Hsu et al. [19], the most commonly observed co-morbidities in pemphigus vulgaris patients were type 2 diabetes mellitus, hypertension, hyperlipidemia, osteopenia and osteoporosis; which are consistent with the findings obtained in our study. Furthermore, hypertension, hyperlipidemia, osteopenia and osteoporosis were more frequently encountered in moderate to severe pemphigus patients, who received higher doses of corticosteroids, compared to mild pemphigus patients with lower doses of corticosteroid; these relationships were statistically significant with p-values less than 0.05. Thus, it can be concluded that these co- morbidities are related to the use of corticosteroids.

Conclusion

Pemphigus vulgaris is a relatively rare but chronic dermatologic condition that is frequently encountered in training hospitals like ours. We have retrospectively studied the epidemiologic data, diagnostic modalities, comorbidities and treatment modalities. Our results suggest that pemphigus vulgaris is a disease that is more commonly seen in female patients. It has a peak incidence in the fifth decade and there is no statistically significant difference between the age of diagnosis between the genders. It is a chronic disease with a long follow-up period; again, there is no statistically significant difference between the two genders. The diagnostic modalities are quite expensive, which prevents large retrospective studies concerning diagnosis. The most commonly encountered comorbidities are hypertension, hyperlipidemia, diabetes mellitus and osteoporosis, which are due to the use of corticosteroids.

Ethics Committee Approval: The approval of Istanbul University Cerrahpasa, Cerrahpasa Faculty of Medicine Ethics Commitee was taken before this study was initiated (date: November 15, 2019, number: 39122051-604.01.01-175657).

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REFERENCES

1. Bolognia J, Schaffer JV, Cerroni L. Dermatology. Philadelphia: Elsevier; 2018.
2. Kayani M, Aslam AM. Bullous pemphigoid and pemphigus vulgaris. BMJ 2017;357:j2169. [CrossRef]
3. Schmidt E, Spindler V, Eming R, Amagai M, Antonicelli F, Baines JF, et al. Meeting Report of the Pathogenesis of Pemphigus and Pemphigoid Meeting in Munich, September 2016. J Invest Dermatol 2017;137:1199–203.
4. Broussard KC, Leung TG, Moradi A, Thorne JE, Fine JD. Autoimmune bullous diseases with skin and eye involvement: Cicatricial pemphigoid, pemphigus vulgaris, and pemphigus paraneoplastica. Clin Dermatol 2016;34:205–13. [CrossRef]
5. Yayli S, Harman M, Baskan EB, Karakas AA, Genc Y, Turk BG, et al. Epidemiology of Pemphigus in Turkey: One-year Prospective Study of 220 Cases. Acta Dermatovenerol Croat 2017;25:181–8.
6. Baum S, Astman N, Berco E, Solomon M, Trau H, Barzilai A. Epidemiological data of 290 pemphigus vulgaris patients: a 29-year retrospective study. Eur J Dermatol 2016;26:382–7. [CrossRef]
7. Tallab T, Joharji H, Bahamdan K, Karkashan E, Mourad M, Ibrahim K. The incidence of pemphigus in the southern region of Saudi Arabia. Int J Dermatol 2001;40:570–2. [CrossRef]
8. Nanda A, Dvorak R, Al-Saeed K, Al-Sabah H, Alsaleh QA. Spectrum of autoimmune bullous diseases in Kuwait. Int J Dermatol 2004;43:876–81. [CrossRef]
9. Huang YH, Kuo CF, Chen YH, Yang YW. Incidence, mortality, and causes of death of patients with pemphigus in Taiwan: a nationwide population-based study. J Invest Dermatol 2012;132:92–7. [CrossRef]
10. Chams-Davatchi C, Valikhani M, Daneshpazhooh M, Esmaili N, Balighi K, Hallaji Z, et al. Pemphigus: analysis of 1209 cases. Int J Dermatol 2005;44:470–6. [CrossRef]
11. Cholera M, Chainani-Wu N. Management of Pemphigus Vulgaris. Adv Ther 2016;33:910–58. [CrossRef]
12. Sinha AA, Hoffman MB, Janicke EC. Pemphigus vulgaris: approach to treatment. Eur J Dermatol 2015;25:103–13. [CrossRef]
13. Atzmony L, Hodak E, Gdalevich M, Rosenbaum O, Mimouni D. Treatment of pemphigus vulgaris and pemphigus foliaceus: a systematic review and meta-analysis. Am J Clin Dermatol 2014;15:503–15. [CrossRef]
14. Ahmed AR, Spigelman Z, Cavacini LA, Posner MR. Treatment of pemphigus vulgaris with rituximab and intravenous immune globulin. N Engl J Med 2006;355:1772–9. [CrossRef]
15. Porro AM, Hans Filho G, Santi CG. Consensus on the treatment of autoimmune bullous dermatoses: pemphigus vulgaris and pemphigus foliaceus - Brazilian Society of Dermatology. An Bras Dermatol 2019;94:20–32. [CrossRef]
16. Doukaki S, Platamone A, Alaimo R, Bongiorno MR. Mycophenolate mofetil and enteric-coated mycophenolate sodium in the treatment of pemphigus vulgaris and pemphigus foliaceus. J Dermatolog Treat 2015;26:67–72. [CrossRef]
17. Agarwal A, Hall RP 3rd, Bañez LL, Cardones AR. Comparison of rituximab and conventional adjuvant therapy for pemphigus vulgaris: A retrospective analysis. PLoS One 2018;13:e0198074. [CrossRef]
18. Hertl M, Jedlickova H, Karpati S, Marinovic B, Uzun S, Yayli S, et al. Pemphigus. S2 Guideline for diagnosis and treatment--guided by the European Dermatology Forum (EDF) in cooperation with the European Academy of Dermatology and Venereology (EADV). J Eur Acad Dermatol Venereol 2015;29:405–14. [CrossRef]
19. Hsu DY, Brieva J, Nardone B, West D, Silverberg JI. Association of pemphigus and systemic corticosteroid use with comorbid health disorders: A case-control study. Dermatol Online J 2017;23:13030/qt1vk2m30m.
20. Heelan K, Mahar AL, Walsh S, Shear NH. Pemphigus and associated comorbidities: a cross-sectional study. Clin Exp Dermatol 2015;40:593–9.
21. Lee YB, Lee JH, Lee SY, Kim JW, Yu DS, Han KD, et al. Incidence and death rate of pemphigus vulgaris and pemphigus foliaceus in Korea: A nationwide, population-based study (2006-2015). J Dermatol 2018;45:1396–402. [CrossRef]
22. Qureshi A, Friedman A. Comorbidities in Dermatology: What's Real and What's Not. Dermatol Clin 2019;37:65–71. [CrossRef]
23. Wohl Y, Mashiah J, Kutz A, Hadj-Rabia S, Cohen AD. Pemphigus and depression comorbidity: a case control study. Eur J Dermatol 2015;25:602–5. [CrossRef]
24. Kridin K. Pemphigus group: overview, epidemiology, mortality, and comorbidities. Immunol Res 2018;66:255–70. [CrossRef]
25. Naseer SY, Gill L, Shah J, Sinha AA. Gender-based variability in disease presentation in pemphigus vulgaris. J Drugs Dermatol 2014;13:1225–30.
26. Tsankov N, Vassileva S, Kamarashev J, Kazandjieva J, Kuzeva V. Epidemiology of pemphigus in Sofia, Bulgaria. A 16-year retrospective study (1980-1995). Int J Dermatol 2000;39:104–8. [CrossRef]
27. Edgin WA, Pratt TC, Grimwood RE. Pemphigus vulgaris and paraneoplastic pemphigus. Oral Maxillofac Surg Clin North Am 2008;20:577–84. [CrossRef]
28. Santoro FA, Stoopler ET, Werth VP. Pemphigus. Dent Clin North Am 2013;57:597–610. [CrossRef]
29. Ettlin DA. Pemphigus. Dent Clin North Am 2005;49:107–25. [CrossRef]
30. Buchman AL. Side effects of corticosteroid therapy. J Clin Gastroenterol 2001;33:289–94. [CrossRef]