



Immune-mediated Skin Disorders and their Oral Manifestations in the Omani Population: A Hospital-based Study

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ARTICLE INFO

Article history:

Received: 31 January 2019

Accepted: 25 March 2019

Online:

DOI 10.5001/omj.2020.02

Keywords:

Dermatology; Dental Clinics;
Comorbidity; Oman.

ABSTRACT

Objectives: We sought to determine the prevalence of immune-mediated skin disorders (IMDs), their oral manifestations, and the related comorbidity among Omani patients with IMDs attending the outpatient Department of Dermatology and Dental Clinic at Al Nahdha Hospital, Muscat. **Methods:** We conducted a retrospective study of 236 newly-diagnosed patients with IMDs who attended the outpatient clinic between September 2014 and September 2017. Data, such as age, sex, investigations, diagnosis, comorbidity, and associated oral manifestations of the affected individuals, were collected from the hospital health information system. **Results:** Of the 236 diagnosed cases of IMD, lichen planus substantially comprised over half of the total cases (59.7%). This was followed by relatively fewer cases of discoid lupus erythematosus (11.0%), systemic lupus erythematosus (10.2%), and erythema multiforme (8.1%). Pemphigus vulgaris and bullous pemphigus comprised only 3.0% and 4.2% of the total studied cases, respectively. The other less common disorders found in our study were toxic epidermal necrolysis (1.7%), pemphigus foliaceus (1.3%), and gestational pemphigoid (0.8%). Oral mucosal involvement was seen more commonly with lichen planus (78.7%), pemphigus vulgaris (71.4%), and erythema multiforme (75.0%), while systemic lupus erythematosus and discoid lupus erythematosus were shown to appear with more comorbidities compared to the other skin disorders studied. **Conclusions:** Several IMDs have considerable oral involvement. These oral manifestations of the diseases may be overlooked by other specialists leading to a delay in the diagnosis and its management. In order to circumvent this delay, the analysis and evaluation of a disease need to be done by a team comprising of a dental surgeon, dermatologist, and an oral medicine specialist.

Dermatological disorders may not be localized to the cutis. In addition, they can be detected in the contiguous oral mucosa because both the oral mucosa and cutis are considered one organ.^{1,2} Oral manifestations of disorders of the cutis or skin can occur simultaneously with skin lesions or precede these skin manifestations, or they can be the only sign of skin disorders.^{1,3} Among the various disorders affecting the skin and mucosa (mucocutaneous disorders), various diseases are autoimmune or immune-mediated in nature and have variable clinical manifestations.⁴ Autoimmune disorders occur more frequently in cases with pre-existing autoimmune disorders.⁵

Some of these disorders are labelled autoimmune bullous disorders (ABDs) and are classified into

two groups: intraepidermal or subepidermal, the distinction of which is based on the level of blister formation.⁶ Oral blisters and ulcerations are the common manifestations of autoimmune disorders and manifest moderate to severe pain that impairs the patient's quality of life.⁴ The early recognition and accurate diagnosis of these blisters have become mandatory for early management because this eventually may help in reducing the further spread of the disease.⁷ Also, it is equally important to study the epidemiological profile of a disease to evaluate its burden on the health system and facilitate appropriate health care planning.⁸

Numerous epidemiological surveys have been conducted, and they either have described a single ABD or group of immune-mediated disorders.⁶ These are the studies that have reported a spectrum

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of immune-mediated diseases for example, from Tunisia,⁶ Iran,^{9,10} and Greece.¹¹ However, until now, there have been no epidemiological surveys conducted in Oman on the spectrum of the immune-mediated skin disorders (IMDs) that have associated oral manifestations. Therefore, a retrospective study was conducted to study the prevalence of IMDs, their oral manifestations, and their related comorbidities.

METHODS

This retrospective study is based on a review of 236 diagnosed cases of IMDs. The study was given ethical approval by the Medical Research Committee at Al Nahdha Hospital, Oman. We used archived case files of patients who attended the outpatient department (OPD) of Dermatology and Dental Clinic at Al Nahdha Hospital between September 2014 and September 2017. Only the case records of the patients diagnosed with IMDs during this three-year period were included. The criteria for the diagnosis of an IMD were based on clinical features, biopsy, immunohistochemical investigations, and blood investigations for the presence of circulating autoantibodies or antigens. Complete information about the age, sex, investigations, diagnosis, and comorbidity were noted for the affected individuals. The data of individuals with autoimmune skin diseases were checked and cross-verified by two researchers. The presence of any oral manifestations associated with these diseases, if any, were also recorded. Exclusion criteria were the removal of old cases of IMD diagnosed before 2014 and those

patients who attended the OPD for a follow-up during the study period. Case records with an incomplete medical history, missing information, or with a questionable diagnosis were excluded. Other developmental, neoplastic and inflammatory skin disorders not associated with autoimmunity were excluded as well. The admitted cases of IMDs during these three years were also excluded.

RESULTS

The spectrum of patients with diagnosed cases of IMDs who attended the OPD during the study period is shown in Table 1. Affected and diagnosed individuals with IMDs totaled 236 cases. Lichen planus (LP) was the most common disease, comprising 141 (59.7%) cases. Out of the total 141 cases of LP, 111 (78.7%) cases significantly showed oral mucosal involvement and had oral lichen planus lesions (OLP). Four (3.6%) cases of OLP came back positive for the hepatitis C virus (HCV) antibody.

Discoid lupus erythematosus (DLE) was the second in our case series, comprising 26 (11.0%) cases. This was followed by cases of systemic lupus erythematosus (SLE) ($n = 24$, 10.2%).

There were 19 (8.1%) cases of erythema multiforme (EM) and four (1.7%) related yet insignificant cases of toxic epidermal necrolysis (TEN). The most common ABDs, namely pemphigus vulgaris (PV), appeared less prevalently with seven (3.0%) cases, while there were only 10 (4.2%) cases of bullous pemphigoid (BP) and three (1.3%) cases of pemphigus foliaceus (PF). The other fewer cases of IMDs, such as gestational pemphigoid

Table 1: Number and percentage of immune-mediated skin disorders, the female (F)-to-male (M) ratio, and the mean of the age of occurrence along with the mean age.

Immune-mediated skin disorders	Number of cases	Percentage	F:M ratio	Mean age, years	Age range (min-max)
Lichen planus	141	59.7	1:0.41	48.0	6-81
Discoid lupus erythematosus	26	11.0	1:0.37	33.0	5-70
Systemic lupus erythematosus	24	10.2	1:0.33	36.0	14-60
Erythema multiforme	19	8.1	1:0.73	39.0	6-83
Bullous pemphigoid	10	4.2	2:1	55.0	22-77
Pemphigus vulgaris	7	3.0	1:0.75	53.0	28-69
Toxic epidermal necrolysis [Lyell]	4	1.7	1:1	34.0	18-52
Pemphigus foliaceus	3	1.3	1:2	45.0	23-67
Gestational pemphigoid	2	0.8	All females	34.0	33-36
Total	236		1:0.50	46.2	0-83

Table 2: Number and percentage of cases of immune-mediated skin disorders with oral manifestations.

Immune-mediated skin disorders	Number of cases with oral involvement	Percentage
Lichen planus	111	78.7
Toxic epidermal necrolysis [Lyell]	3	75.0
Pemphigus vulgaris	5	71.4
Erythema multiforme	9	47.4
Discoid lupus erythematosus	5	19.2
Systemic lupus erythematosus	3	12.5
Bullous pemphigoid	1	10.0
Gestational pemphigoid	0	0.0
Pemphigus foliaceus	0	0.0
Total	137	58.0

(GP), which is generally a rare disorder, accounted for two (0.8%) cases.

LP, DLE, and EM appeared in a very wide age range, from 6–81 years, 5–70 years, and 6–83 years, respectively. The other skin disorders, such as SLE and TEN, had a smaller age range (14–60 years and 18–52 years, respectively). The mean age of the occurrence of the diseases showing a wide age range were 48.0 (LP), 33.0 (DLE), and 39.0 (EM) years, while SLE and TEN showed a mean age of 36.0 and 34.0 years, respectively. The supraepithelial ABDs, namely PV and PF, affected the 28–69 years and 23–67 years age group, respectively, with mean ages of 53.0 and 45.0 years, respectively. On the other hand, the subepidermal disease BP was the only one to show an increased age range from 22–77 years with a mean age of 55.0 years. For GP, the least frequent case had an age range of 33–36 years and a mean of 34.0 years. All IMDs showed a slight female preponderance, except for PF, which had a female-to-male ratio of 1:2.

As expected, we saw frequent oral involvement in LP (78.7%) and PV (71.4%) cases [Table 2].

However, the second most common disease with frequent oral lesions was TEN (75.0%). EM had nine (47.4%) cases of oral involvement. Other diseases such as DLE, SLE, and BP showed relatively less oral involvement. PF and GP showed no oral manifestations.

Tables 3 and 4 show the comorbidity and details of the associated diseases. The most common comorbidity was SLE (33.3%), followed by DLE (30.8%), EM (26.3%), and LP (12.1%). However, the other diseases did not show any other associated disorders. The patients with SLE and DLE had associated rheumatoid arthritis and alopecia areata. Both LP and EM were associated with thyroid and hematological disorders, while a few LP cases were also reported as coming with psoriasis and alopecia areata. Of all the autoimmune disorders, the diagnostic blood investigations revealed about 13 cases of SLE and two cases of DLE that were positive for antinuclear antigen, while four cases of OLP showed the presence of HCV-RNA. The other autoimmune skin disorders did not show any diagnostic serological features.

Table 3: Number and percentage of cases of immune-mediated skin disorders (IMDs) with comorbidities.

Autoimmune bullous disorders and other IMDs	Number of cases with comorbidities	Percentage
Lichen planus	17	12.1
Discoid lupus erythematosus	8	30.8
Systemic lupus erythematosus	8	33.3
Erythema multiforme	5	26.3
Bullous pemphigoid	1	10.0
Pemphigus vulgaris	0	0.0
Toxic epidermal necrolysis	0	0.0
Gestational pemphigoid	0	0.0
Total	39	16.5

Table 4: Associated disorders with autoimmune bullous disorders and immune-mediated skin disorders .

Disorders	Psoriasis	Alopecia areata	Thyroid diseases	Hematological diseases	Rheumatological diseases	Others	Total
Bullous pemphigoid	0	0	0	1	0	0	1
Discoid lupus erythematosus	0	6	0	0	2	0	8
Erythema multiforme	0	0	3	2	0	0	5
Lichen planus	2	2	6	4	2	1	17
Systemic lupus erythematosus	0	3	0	0	5	0	8
Total	2	11	9	7	9	1	39

DISCUSSION

Numerous studies have described clinical and epidemiological evaluations of single IMDs. Studies have shown that pemphigus is the most common blistering autoimmune disease, with an estimated prevalence of 24.8 per 100 000 individuals;⁴ studies from Tunisia⁶ and Iran^{9,10} support this.

Our retrospective study showed LP as being a common disease, affecting about 141 (59.7%) cases. Out of these, a significant number (78.7%) were found affecting the oral cavity. The reason for these increased cases of OLP may be because of referrals given by the dermatology department. Otherwise, in a different meta-analysis, the reported prevalence of OLP is variable, ranging from 1.27–67%.⁴ The preponderance of OLP cases (59.7%) we recorded is almost in agreement with other studies,^{4,12} which holds true as well for a study from Brazil that showed 76.56% of the cases had OLP.¹³

The mean age of LP in the current study was 48.0 years, and the disease was found to be more prevalent in females, with a female-to-male ratio of 1:0.41. This is consistent with studies from Italy¹⁴ and Turkey.¹⁵ Our study showed that a total of 12.1% of the LP cases had various associated conditions, with the most common being hypothyroidism. Less frequently associated conditions were psoriasis, alopecia areata, hematological disorders, and rheumatological disorders. However, the relationship between LP and thyroid disease is questionable, despite some reports linking the two conditions, as in a recent meta-analysis that revealed a statistically significant correlation between LP and thyroid disease.¹⁶

We found four (3.6%) cases of OLP that were positive for the HCV antibody, which is in agreement with a study showing the prevalence of the HCV antibody in LP ranging from 3.8–65%.¹⁷

DLE was the second most common disorder (11.0%) in our study, followed by SLE, which comprised 10.2% of the total cases. Between 1970–2000, the prevalence of SLE is reported between 5.8–130 per 100 000 cases.^{18,19}

Epidemiological studies of CLE (of which DLE is a subtype according to the Gilliam classification) are rare.²⁰ A recent systematic review of epidemiological studies of SLE showed that its peak incidence ranges from 30–70 years old, with it generally being found in females at a 2:1 (F:M) to 15:1 (F:M) ratio.²¹ Studies related to DLE also have reported the mean age of occurrence to be about 36 years (range = 8–69 years). The disease is also more common in females with a 5:1 female-to-male ratio.²² Our study also showed that both SLE and DLE occur in middle-aged individuals (mean age of 36.0 years and 33.0 years, respectively), but only a slight female predilection was seen (1:0.33 and 1:0.37, respectively). Another study reported that oral mucosal involvement ranges from 9–54% in SLE to 3–20% in CLE.²³ Our study also showed the oral involvement of SLE (12.5%) and DLE (19.2%) which conforms with other studies. The lupus cases showed associated alopecia areata, which is in agreement with a study from Taiwan.^{24,25}

The epidemiological data regarding EM is scarce. However, reports based on hospital admissions for this disease have shown the prevalence to be as low as 4.2 per million patients per annum, while in Western Australia, the incidence of its related disease, TEN, has been reported to be as low as 0.4 cases per million.^{26,27} There were only a few cases of EM and TEN in this study because these cases only included patients who attended the OPD and therefore, did not include hospital admissions for EM and TEN. EM occurs in young adults and

more often in females.²⁶ This is in accordance with the current study, which showed a mean age of 39.0 years. However, there was no significant female predominance. A study from Brazil reported the predominant age of occurrence of TEN as between 30 and 40 years old based on hospital admissions, and there were more affected female patients.²⁸ There were only a few cases of TEN reported in our study with an equal male-to-female predilection (1:1) and a mean age of 34.0 years. More studies should be done by incorporating admitted hospital cases of EM and TEN. About 47.4% of the total cases of EM and 75.0% of the total cases of TEN showed oral involvement.

The annual incidence report of PV ranges between 0.76 per million and 16.1 per million, while BP has incidence rates ranging between 2.4–21.7 new cases per million.^{29,30} The observed prevalence of BP and PV in our study was very low. The reason for the low prevalence of BP has been discussed by authors from Singapore (as cited in a study from Tunisia),⁶ who explained that the referral of BP cases to tertiary departments may be underestimated in some countries. Moreover, BP and PV respond readily to corticosteroids, which eventually lowers their adverse events. Thus, the lower number of cases in our study might have occurred as a result of the treatment of the disease at the primary level, hence not requiring a follow-up. A study of a larger sample size encompassing more hospital OPDs needs to be done in the future to study the prevalence of ABDs

BP is a disease that comes with old age (range = 66–83 years), and it is seen mostly in females.²⁹ In accordance with a study from Tunisia,⁶ we observed BP in a younger age range (22–77 years) with a mean age of 55.0 years. On the other hand, the mean age reported for PV has been reported at 50 years,⁶ 43 years,⁹ and 43.3 years.¹⁰ The study conducted in Northwest Romania that reported a mean age of 53 years in PV is consistent with the results of our study.³¹ The number of female patients was greater than males at a ratio of 2:1, which aligns with data from an Iranian study.¹⁰

PV was the third most frequently found IMD that involved the oral mucosa, occurring in about 71.4% of cases. Oral mucosal involvement of PV ranges from 50%–70% as reported in a study from Brazil,¹ and this conforms with our study. BP generally shows oral involvement in the range of

10–30%,⁷ and our study showed that the number of oral lesions fell within this range (10.0%). There was, however, no comorbidities associated with PV and BP.

The prevalence of PF and GP was the lowest in our retrospective analysis. PF is generally found less frequently when compared with PV, except in countries such as Brazil, Tunisia, and some parts of Latin America.⁹ Concerning age, PF occurrence has a mean age of 44.8 years in females and 63 years in males.⁶ We reported individuals suffering from PF with a mean age of 45.0 years, which is similar to previous reports. In another study, PF was observed two times more often in females,⁶ while another study reported PF as occurring more frequently in males.¹¹ This is in line with our study, which showed a female-to-male ratio of 1:2. There are rare manifestations of oral mucosa in PF,⁴ and our analysis of the cases also showed no oral involvement.

The incidence of GP is seen in one out of 60 000 pregnancies.³² We found GP had the least prevalence of all the studied dermatological disorders. Indeed, in Tunisia, GP has been reported as occurring more frequently in 19–40 year olds, with a mean age of 31.7 years.⁶ Our study sample showed the age range for female individuals with GP as 33–36 years with a mean of 34.0 years. There was no oral involvement and no comorbidities.

CONCLUSION

Some IMDs primarily manifest with symptomatic or asymptomatic oral mucosal involvement. In particular, asymptomatic disorders may be the markers of coexisting or underlying disease. These asymptomatic disorders may also be underestimated or overlooked by dental clinicians. Also, oral mucosal lesions may be seldom examined in dermatological clinics. This means that these underestimated disorders generally do not represent the correct overall prevalence of the disease. Furthermore, the neglect and delay in the identification and diagnosis of these diseases give a chance for the disease to disseminate and become chronic and recurring, affecting the patient's quality of life. Early oral detection of the disease and regular oral examinations in dermatological clinics can pre-emptively curb the disease and circumvent any possible complications. Further studies need to be done with a larger sample size to identify the statistical correlation

between skin diseases and their oral manifestations and the related comorbidity. Future prospective studies also need to be carried out to evaluate and correlate these clinical oral manifestations with clinical manifestations of IMDs. This will help in the identification and diagnosis of lesions by dental practitioners and dermatologists, eventually strengthening the multidisciplinary diagnostic approach towards a disease.

Disclosure

The authors declared no conflicts of interest. No funding was received for this study.

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