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Diagnostic patterns and delays in autoimmune blistering diseases of the mouth; a cross-sectional study

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Abstract

Objectives: To describe the natural history and factors influencing diagnostic delays among patients with autoimmune blistering diseases of the mouth.

Materials and methods: In this cross-sectional study, 27 newly diagnosed patients were interviewed, and professional and patient delays were calculated. Disease extent and severity scores were determined using Saraswat scoring system.

Results: Twenty-seven patients were interviewed and examined. Patient delay was significantly longer in patients who had desquamative gingivitis as initial presentation, in those who tried to use home remedies and over the counter medications, and in patients with less severe disease. Most patients (n= 21 [77.7%]) made more than one consultation, and the mean time needed to reach a definitive diagnosis (*i.e. professional delay*) was 83.2 ± 21.4 days (range from 21 to 130 days). Professional delay was significantly correlated with the number of previous consultations (r=0.78), and was significantly longer in patients who had desquamative gingivitis as initial presentation.

Conclusion: Diagnosis of oral blistering diseases is often delayed. Diagnostic delay is more common in patients presenting with desquamative gingivitis and those with less severe disease. Improving patients and health care professionals' awareness about oral blistering diseases might help reduce diagnostic delay.

Introduction

Autoimmune blistering diseases (AIBDs) are a heterogeneous group of relatively uncommon disorders that affect skin and mucosae. These diseases are associated with autoantibodies that target distinct components of either the basement membrane zone (*i.e*. sub-epidermal blistering diseases) or the inter-cellular adhesion apparatus (*i.e.* intra-epidermal blistering diseases) causing blisters, ulcers, and erosions (Celentano and Cirillo, 2017; Cirillo, Cozzani, Carrozzo, & Grando 2012). AIBDs typically run a chronic course leading to pain, discomfort, dysfunction, and impaired quality of life.

The oral mucosa is frequently affected in AIBDs, particularly in pemphigus vulgaris (PV) and mucous membrane pemphigoid (MMP) (Mahajan, Sharma, Sharma, & Garg, 2005). The mouth is a frequent site for initial presentation, and occasionally the exclusive site of involvement. Ishii et al., 2008, for example, reported an initial oral involvement in 75% of patients with PV (Ishii et al., 2008), and Sirois et al., 2000 reported that the mouth was the only site of involvement in 24% of patients with PV (Sirois, Fatahzadeh , Roth, & Ettlin, 2005). Compared with skin, clinical manifestations of AIBD affecting the mouth are less characteristic, typically occurring as multiple painful erosions and superficial ulceration; intact vesicles or bullae are rarely seen because of the trauma-intense environment of the mouth (Sultan, Villa, Saavedra, Treister, & Woo, 2017; Casiglia, Woo, & Ahmed, 2001; Scully, Paes De Almeida, Porter, & Gilkes, 1999; Sciubba, 2011; Sirois et al., 2000).

The diagnosis of AIBD affecting the mouth is often delayed because of the uncommon nature of these diseases, the nonspecific clinical presentations, and the unfamiliarity of health care providers with oral mucosal diseases (Sirois et al., 2000; Scully et al., 1999; Sarumathi, Saravanakumar, Datta, & Nagarathnam, 2013). Importantly, delays in diagnosis and management of AIBD can adversely affect disease progression, treatment response and prognosis resulting in patient suffering, increased treatment duration and cost, and reduced productivity and quality of life (Heelan, Mahar, Walsh, & Shear, 2015; Penha, Farat, Miot, & Barraviera, 2015; Sirois et al., 2000; Fitzpatrick and newcomer, 1980).

The scientific literature offers only limited data on diagnostic pattern and factors influencing delays in the diagnosis of AIBDs of the mouth. Previous studies on this topic have not described the influence of various factors, including disease sub type, clinical presentation, and disease severity and distribution, on diagnostic delay. The aim of the present study, therefore, is to explore the natural history and factors influencing diagnostic delays among patients with AIBDs of the mouth.

Materials and Methods

Study design and setting: This cross-sectional study was conducted in the Oral Medicine unit at University of Jordan. The protocol was reviewed and approved by the School of Dentistry Research Committee. The study was conducted in full accordance with the World Medical Declaration of Helsinki, and conformed to the STROBE statement for observational studies.

Inclusion criteria: Only patients who were newly diagnosed with an immune mediated oral blistering disease during the study period were eligible to participate. Cases were included only when the clinical diagnosis was confirmed and subtype determined by histopathology and immunological findings defined by international consensus statements (Hertl et al, 2015; Murrell et al, 2015; Murrell et al, 2012; Murrell et al, 2008; Chan et al, 2002). Patients who had a previous diagnosis of an immune mediated oral blistering disease, or who were previously diagnosed with a cutaneous blistering disease were excluded (**Table 1**).

Patient interview and data collection: Patients who met the inclusion criteria and granted their consent were interviewed by one of the authors (Y.H). Patients were interviewed at their first appointment in the Oral Medicine clinic. The interview involved explaining the nature of the study and asking the participants specific questions about the onset of oral symptoms, presence and onset of cutaneous, genital, or ocular symptoms, date of first medical consultation, number of previous medical consultations, types of specialties consulted, and previous therapeutic attempts including prescribed drugs, over the counter medications, and home remedies. Data was collected using a specially designed data collection sheet. The duration between the onset of symptoms and the first medical consultation was considered as a patient delay, while the duration between the first medical consultation and the definitive diagnosis was considered as a professional delay. The total diagnostic delay was considered as the whole duration between the onset of symptoms and definitive diagnosis. In an attempt to control for the potential bias resulting from patients being unable to recall dates of previous appointments, specialties consulted, and medications prescribed, patient's medical records were consulted, and when there was inconsistency, healthcare professionals previously consulted by the patient were called by phone to provide any missing information on consultation dates and medications prescribed (if any).

Patient examination and severity scoring: All participants were examined by a single Oral Medicine specialist (Y.H) according to the method proposed by the World Health Organization, and the severity of presentation was determined using Saraswat scoring system (Kramer, Pindborg, Bezroukov & Infirri, 1980; Saraswat, Bhushan, &India, 2003). This scoring system incorporates both objective and subjective

parameters. According to this system, disease extent score is determined objectively by evaluation of 11 anatomical sites in the oral cavity and oropharynx. The presence or absence of lesions at these sites is scored as 1 or 0 respectively, and the total score (range from 0-11) is calculated by adding all site scores. The severity of symptoms is scored based on patient's reported pain and/or bleeding during eating or drinking of nine types of solid and liquid foods, and ranges from 0 (no symptoms) to 45 (most severe symptoms). We also devised a list of mediterranean food equivalents for some categories to make the score more applicable to our patients.

Although there are several scoring systems for AIBDs, no consensus exists on the most useful or recommended scoring systems. We choose to use the Saraswat scoring system because it is easily performed and eliminates subjective evaluation of extent or severity by the examiner. In addition, symptom score does not require any individual assessment of severity by the patient, relying only on the presence and frequency of symptoms on eating and drinking common foods. Although this scoring system was originally devised for oral pemphigus, it can also be used for other erosive/ ulcerative oral conditions (Saraswat et al, 2003).

Statistical analysis: Statistical analysis was performed using SPSS for Windows release 16.0 (SPSS Inc., Chicago, IL, USA). Descriptive statistics were generated, and Chi-square test, Pearson correlation test, and Student's t-test were used to examine differences between groups. The significance level was stated as $P < 0.05$.

Results

Patient demographics

A total of 31 patients were diagnosed with an immune mediated oral blistering disease during the study period, but 4 patients were excluded: three because they had a previous diagnosis of cutaneous AIBDs and 1 because the mouth was not the initial site of presentation. The final sample therefore was composed of 27 patients (4 males and 23 females). The mean age at presentation was 52.6 years (range from 13 to 79 years).

In all cases, the clinical diagnosis was confirmed by oral mucosal biopsies examined by histopathology and direct immunoflurescence. All biopsies were performed on the first Oral Medicine visit. The final diagnosis was PV in 21 patients (77.8%), MMP in 4 patients (14.8%), Linear IgA disease in 1 patient (3.7%), and paraneoplastic autoimmune multiorgan syndrome (PAMS) in 1 patient (3.7%). The medical histories of the 27 patients included, diabetes mellitus (4 patients), essential hypertension (2 patients), and Hodgkin lymphoma (1 patient). None of the patients had other autoimmune disorders.

Clinical presentation and scoring

Of the 27 patients included, 10 (37%) presented initially with desquamative gingivitis (gingival erythema, erosion, desquamation or ulceration), while the rest (*n*= 17 [63%]) presented initially with oral mucosal erosions and ulcers. Buccal mucosae were the most commonly affected sites (*n*=17 [62.9%]), followed by soft palate/oropharynx (*n*=14 [51.9%]), gingivae (*n*= 12 [44.4%]), tongue/floor of the mouth (*n*=9 [33.3%]), lips (*n*=7 [25.9%]), and hard palate (*n*=2 [7.4%]) (**Table 2**).

The disease was confined to the oral cavity in 16 patients (59.3%); while in the rest (*n*=11[40.7%]), an additional involvement of skin, genitalia, or eyes was identified after the appearance of oral lesions (**Table 2**).

All patients complained of oral pain, and more than half (51.9%) complained of difficulty in eating. Symptoms severity scores ranged from 4 to 40.5 (mean= 21.3 ± 13.7), and disease extent scores ranged from 1 to 11(mean= 5.8 ± 3.6). A positive correlation was identified between disease extent score and symptoms severity score (*r*=0.89). Symptoms severity scores and disease extent scores were not significantly associated with patients' age or gender ($p>0.05$). However, the mean symptoms severity score was significantly lower in patients who presented with desquamative gingivitis (8.3 ± 5.7) compared with those who presented with mucosal ulcers and erosions (31.7 ± 7.8) ($p<0.05$).

Diagnostic pattern and delay

The mean time to seek medical opinion after the onset of symptoms (*i.e. patient delay*) was 92.6± 22.7 days (range from 7 to 320 days). Patient delay in seeking medical help was not significantly associated with age, gender, the presence of extra-oral involvement or disease subtype, but was significantly longer in patients who had desquamative gingivitis as initial presentation (105.4±14.2 days) compared with those who presented with ulcers and erosions (79.8±19.3 days) ($P<0.01$) (**Table 3**). Most patients (66.7%, *n*=18) tried home remedies and over the counter medications including mouth washes, antibiotics, and analgesics before consulting a health care professional. Home remedies reported by patients included olive oil, sesame oil, honey dressing, water and salt mouth wash, chamomile, and sage. Importantly, patient delay was significantly longer in patients who tried home remedies and over the counter medications (113.8 ±23.4 days) compared with the rest of patients (71.4±28.9 days) ($p<0.01$). A statistically significant negative correlation was observed between patient delay and symptoms severity scores (*r*= -0.71) (**Table 3**).

Most patients (*n*=21 [77.7%]) made more than one consultation prior to definitive diagnosis. The average number of medical and dental specialties that were consulted before reaching a definitive diagnosis was

3.1(range from 1 to 6). General medical practitioners and general dental practitioners were the first health care professionals to be consulted by 25.9% and 22.2% of patients respectively (**Figure 1**). The most commonly consulted specialties prior to diagnosis were dermatology (48.1%, *n*=13), maxillofacial surgery (44.4%, *n*=12), periodontics (44.4%, *n*=12), ENT (25.9%, *n*=7), and internal medicine (18.5%, *n=5*) (**Figure 1**). The mean time needed to reach a definitive diagnosis and start treatment (*i.e. professional delay*) was 83.2 ± 21.4 days (range from 21 to 130 days). Noteworthy, the mean time needed for the patient to get an appointment at the Oral Medicine was 3.4 days (range from 1 to 5 days), and the mean time needed to have a histological/immunological confirmation of the diagnosis was 5.8 days (range from 4 to 8 days), contributing only to a small portion of professional delay. Professional delay was significantly correlated with the number of previous consultations (r=0.78), and was significantly longer in patients who had desquamative gingivitis as initial presentation (94.2 ± 17.2 days) compared with those who presented with ulcers and erosions (72.4 ± 11 days) ($p<0.05$). Professional delay was not significantly associated with patient age, gender, presence of extra-oral involvement, disease subtype or symptoms severity score (**Table 3**).

Discussion

There have been surprisingly few studies describing the natural history and diagnostic patterns of AIBDs affecting the mouth, perhaps reflecting the low frequency of presentation. Our study examined the pattern of diagnosis and diagnostic delays among a cohort of 27 patients with oral AIBDs. Findings of our study demonstrated that the diagnosis of AIBDs of the mouth is often delayed with a mean total diagnostic delay of 5.9 months. Similar to our findings, Scully et al., 1999 and Sirois et al., 2000 reported that oral pemphigus vulgaris was less commonly recognized than cutaneous pemphigus vulgaris, and diagnostic delays of more than 6 months were common in oral pemphigus.

There are two phases in diagnostic delay: patient delay from the first discovery of a symptom to consultation with a doctor, and professional delay from the first consultation with a doctor to definitive diagnosis (Coates, 1999). Our study demonstrated that patient delay (mean=92 days) and professional delay (mean=83 days) contributed almost equally to the total diagnostic delay.

In our cohort, patient delay was not significantly influenced by age or gender; although a previous study reported that the diagnosis of oral pemphigus tends to be delayed in male patients (Scully et al., 1999). Self medication of oral diseases is a common practice in some communities and cultures (Sawair, 2010; Scully, Gorsky, & Lozada-Nur, 2003). Most patients in our study tried home remedies and over the counter medications including mouth washes, antibiotics, analgesics, and herbal medicines before consulting a health care professional; a factor that can contribute to diagnosis delay.

The clinical presentation of AIBDs affecting the mouth is nonspecific and characteristic features, such as intact bullae/vesicles and Nikolsky sign, are often absent (Scully et al., 1999; Sirois et al., 2000; Sultan et al., 2017; Sciubba, 2011). In fact, most patients in our study presented with non-specific oral ulcers and erosions, and almost one third presented primarily with gingival involvement in the form of desquamative gingivitis (gingival erythema, desquamation, erosion or ulceration). Findings of our study showed that both patient delay and professional delay were significantly longer in patients presenting primarily with desquamative gingivitis compared to patients presenting with oral ulcers and erosions. The reason for this difference is not known, but it could be attributed to the less severe nature and to the more chronic course of AIBDs presenting primarily as desquamative gingivitis. In fact, symptoms severity scores were significantly lower in patients who presented with desquamative gingivitis (8.3 ± 5.7) compared with those who presented with mucosal ulcers and erosions (31.7 ± 7.8). Furthermore, the diagnosis of desquamative gingivitis is often challenging because of the non-specific features and the large number of conditions that present as gingival inflammation, the most common being plaque-related gingivitis and oral lichen planus (Lo Russo et al., 2009; Al-Abeedi, Aldahish, Almotawa, Kujan, 2015; Arduino et al., 2017).

A large number of local and systemic conditions might cause oral mucosal ulceration and erosion (Compilato et al., 2009), and patients with oral ulcers might present to various medical and dental specialties (Gill and Scully, 2007), probably reflecting the diverse etiology and the nonspecific presentation of oral ulcers. Most patients (77.7%) in our study made more than one consultation prior to definitive diagnosis; Dermatology, Maxillofacial Surgery, and Periodontics were the most commonly consulted specialties. Multiple consultations have been shown to be associated with delayed diagnosis and a negative patient experience in several disease conditions including various types of cancer (Lyratzopoulos, Wardle, &Rubin, 2014). Sirois et al., (2000) reported that an average patient with oral pemphigus would need to make 4 consultations prior to definitive diagnosis compared to only two consultations for a patient with cutaneous pemphigus. Similar to these findings, the average number of consultations made by our patients prior to definitive diagnosis was 3.1 consultations. Importantly, multiple consultations were associated with longer diagnostic delay. The cause for multiple consultations prior to the diagnosis of AIBDs is not known, but could be attributed to the uncommon nature of these diseases, the non-specific clinical features, and the unfamiliarity of health care providers with oral mucosal diseases. This is not surprising given that the vast majority of general practitioners experience difficulties in the diagnosis of oral mucosal lesions (Ergun et al., 2009).

The findings of the present study are limited by the relatively small sample size which probably reflects the rarity of these diseases. A large female preponderance in our patient population was also seen.

Although this might be just a reflection of the tendency of autoimmune diseases to affect women more than men, male to female ratio (1:5.75) in our cohort was unexpectedly high. In addition, the present study did not examine the extent of treatment delay or the influence of delayed diagnosis on treatment response, disease activity and outcome. Studies however are currently in progress to examine the relation between the time to diagnosis and treatment response and the occurrence of relapse among patients with oral pemphigus vulgaris. Finally, the present study is vulnerable to recall bias. In an attempt to control for the potential bias resulting from patients being unable to recall dates of previous appointments, specialties consulted, and medications prescribed, patient's medical records were consulted, and when there was inconsistency, healthcare professionals previously consulted by the patient were called by phone to provide any missing information on consultation dates and medications prescribed.

Conclusion

Diagnosis of AIBDs affecting the mouth is often delayed. Diagnostic delay is more common in patients presenting with desquamative gingivitis and those with less severe disease. Possible causes include the nonspecific clinical presentation and the tendency of patients to use home remedies and over the counter medications before seeking help from health care professionals. Multiple consultations are common among patients with oral AIBDs, and might lead to diagnostic delay. Improving patients and health care professionals' awareness and knowledge about AIBDs affecting the mouth might help reduce diagnostic delay.

Author contribution:

Y.Hassona: designed study, collected data, and wrote the manuscript

F.Sawair: contributed to manuscript writing, data analysis, study design

D.Taimeh: collected data and contributed to manuscript writing

H.Al-Khawaldeh: collected data and contributed to manuscript writing

N.Cirillo: contributed to literature review and manuscript writing

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Legends to figures:

Figure 1: Type, frequency, and order of medical and dental consultations performed by patient prior to diagnosis at Oral Medicine

Table 1: inclusion and exclusion criteria

Inclusion criteria
Mouth is the initial site of involvement
Clinical diagnosis is confirmed by oral mucosal biopsy examined by histopathology and direct immunoflurescence *
Patient consented
Exclusion criteria
Case is previously diagnosed with a cutaneous or oral AIBDs
Clinical diagnosis is not confirmed by an oral mucosal biopsy examined by histopathology and immunoflurescence *
Mouth is not affected
Mouth is not the initial site of involvement

*: According to international consensus statements (Hertl et al, 2015; Murrell et al, 2015; Murrell et al, 2012; Murrell et al, 2008; Chan et al, 2002).

Table 2: Summary of affected sites among study population

Oral	**% (*n*)**	**Extra oral**	**% (*n*)**
Buccal	62.9 (17)	Eyes	22.2 (6)
Soft palate/oropharynx	51.9 (14)	Skin	14.8 (4)
Gingivae	44.1 (12)	Genitalia	11.1 (3)
Tongue/floor of mouth	33.3 (9)		
Lips	25.9 (7)		
Hard palate	7.4 (2)		

Table 3: Factors associated with diagnostic delay in AIBDs of the mouth

	Patient delay (days ± SD)	*P* value	Professional delay (days ± SD)	*P* value	Total delay (days ± SD)	*P* value
Clinical presentation						
Desquamative gingivitis	105.4 ± 24.1	<0.01	94.2 ± 17.2	<0.05	199.6 ±18.2	<0.05
Ulcers/erosions	79.8 ± 19.3		72.4 ± 11		152.2 ± 13.9	
Disease subtype						
Intra-epithelial blistering (PV & PNP)**	98.7± 12.1	>0.05	87.5± 27.1	>0.05	186.2± 19.6	>0.05
Sub-epithelial blistering (MMP & linear IGA)**	86.5± 16.8		79.1± 19.3		165.6± 23.9	
Extraoral involvement						
Yes	93.4 ± 13.6	>0.05	76.3 ± 21.9	>0.05	169.7± 18.9	>0.05
No	91.6 ± 18.7		90.1 ± 27.7		181.7± 17.3	
Gender						
Male	96.9 ± 14.2	>0.05	81.2 ± 15.7	>0.05	178.1 ± 18.3	>0.05
Female	88.3 ± 11.3		85.3 ± 17.9		173.6 ± 16.3	
Age*	*r*= 0.23	>0.05	*r*= 0.31	>0.05	*r*= 0.27	>0.05
Use of home remedies/OTC						
Yes	113.8 ± 23.4	<0.01	86.3 ± 20.4	>0.05	200.1 ± 21.2	<0.05
No	71.4 ± 28.9		80.1 ± 17.5		151.5 ± 29.7	
Number of consultations*	-----	----	*r*= 0.78	<0.05	----	----
Symptoms severity score*	*r*= - 0.71	<0.05	*r*= 0.42	>0.05	*r*= 0.127	>0.05

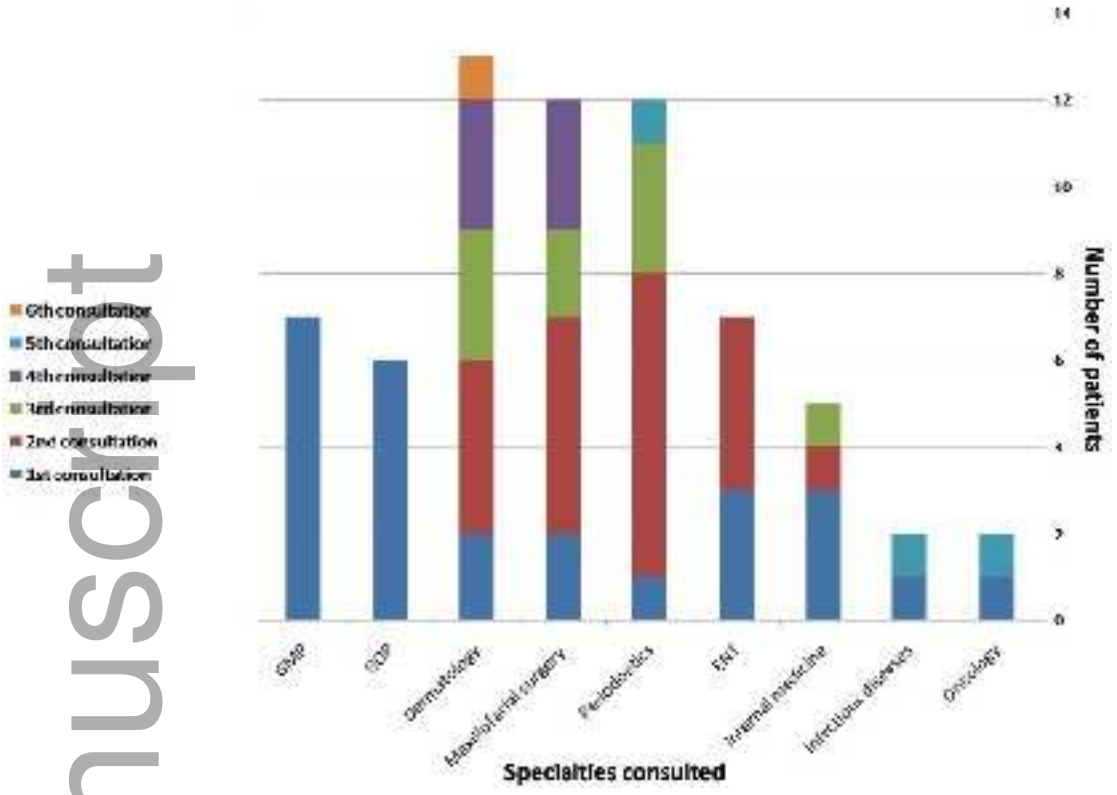
*: Pearson correlation

**: Due to the small number of cases in some subtypes, we combined intraepithelial blistering diseases (i.e. pemphigus vulgaris and paraneoplastic pemphigus) in one group and sub-epithelial blistering diseases (i.e. linear IgA disease and mucous membrane pemphigoid) in another group. In addition, there

was no statistically significant difference in diagnostic delay between pemphigus vulgaris and mucus membrane pemphigoid patients.

----: Not applicable

OTC: over the counter medications



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