Pemphigus Vulgaris

Authors

David Cassar & Suzanne Cauchi
4th Year Medical Students at the Faculty of Medicine & Surgery,
University of Malta.

Reviewers

Dr. Michael Boffa
Consultant Dermatologist at Sir Paul Boffa Hospital, Malta.

Dr. Liam Mercieca
Higher Specialist Trainee in Dermatology at Sir Paul Boffa Hospital, Malta.

Mr. L.F. is a 53yr old gentleman who initially presented to his family doctor with mouth ulcers, hoarseness and odynophagia. He was given various treatments including antibiotics, anti-virals, non-steroidal anti-inflammatory drugs (NSAIDs) and oral steroids with no effect. His condition worsened and was associated with a 5kg weight loss. He subsequently developed skin blisters and erosions and was referred to the dermatology department. A clinical diagnosis of pemphigus vulgaris was made and he was started on high dose oral steroids. A skin biopsy sent for histology and immunofluorescence confirmed the diagnosis. On confirmation he was admitted for rituximab therapy and started on azathioprine.

Fact File on Pemphigus Vulgaris

Pemphigus vulgaris is a potentially life-threatening autoimmune disease with a number of clinical variants. This blistering disorder affects the mucosa and the skin. In up to 50% of cases, it initially presents with intra-oral lesions, and may remain so for about a year (Becker, et al., 2009). This emphasizes the need for dentists to be aware of this condition as it is most likely to present first in their practice. This is particularly important as early recognition results in a better prognosis (Shafer, et al., 2008).The age of presentation is often between 30-50 years, with a male predominance of 2:1. Pemphigus vulgaris is estimated to affect only 1-5 patients per million populations per year (Shamim, et al., 2008).

The aetiology of the disease is still largely unknown, however, it is characterized by the production of autoantibodies against desmosomes, particularly targeting desmoglein 3. Desmoglein 3 is predominantly expressed in the oral mucosa, hence explaining the reason why initial presentation is often with oral lesions. The loss of adhesion between these structural units gives rise to the manifestation of intraepidermal bullae (Robinson, et al., 2004).

Characteristically the oral blisters are prone to rupture, with ensuing painful erosions. There is a predilection for soft-palate, buccal mucosa and lip involvement but any site in the oral cavity can be affected (Neville, et al., 2008).

Initially pemphigus vulgaris presents with a positive Nikolsky's sign, which is a pressure-induced wrinkling of seemingly healthy skin. Clear-fluid containing bullae, occurring over both normal as well as erythematous skin, are the primary lesions. These bullae increase in size on application of pressure, with the fluid spreading to the surrounding epidermis (indirect Nikolsky's sign). Scarring is not a feature, though the healing process is slow (Pradeep, et al., 2010).

A lesional biopsy is necessary to confirm diagnosis of pemphigus vulgaris. On histology, intraepidermal clefting with acantholysis and Tzanck cells in the prickle cell layer is characteristic. Direct and indirect immunofluorescence can be used to further confirm the diagnosis of pemphigus vulgaris. On indirect immunofluorescence IgG antibodies are seen circulating in the serum whilst on direct immunofluorescence, intercellular IgG antibodies can be seen (Tamgadge, et al., 2010).

Pharmacological therapy is aimed at reducing the autoantibody production and the accompanying inflammatory response. Corticosteroids and immunosuppressants often make up the treatment regimen. Overall mortality has improved significantly with corticosteroid therapy. Despite this, steroid use is limited due to their significant side-effect profile which contributes to morbidity. Thus, steroid-sparing immunosuppressive drugs such as rituximab, are nowadays considered early on in treatment. Therapy is tailored to the patient's clinical picture, taking into consideration any other co-morbidities (Bassam, et al., 2015).

Case Report on Pemphigus Vulgaris

Presenting Complaint

The patient initially complained of discomfort whilst eating accompanied with nausea for a few weeks. He was reviewed by an E.N.T. specialist and was found to have an oedematous and erythematous uvula which resolved following a short course of prednisolone. On stopping the steroids, he developed mouth ulcers and hoarseness, resulting in odynophagia and troublesome eating. A few days later, he noted a single skin lesion in the supraclavicular region which bled after showering, however the patient

thought nothing of it. In the ensuing days, the number of mouth ulcers increased. After seeking the advice of his general practitioner, he was diagnosed with herpes zoster and started on a five-day course of acyclovir. Despite this, the mouth ulcers continued to increase in number together with the appearance of skin erosions on his chest, prompting him to attend the E.N.T. clinic. The patient was prescribed metronidazole, clarithromycin and diclofenac, however, his symptoms did not improve. He had also visited his dentist who had prescribed mouth gargles with little effect. At a subsequent dental appointment, a mucosal biopsy was taken for histology due to worsening mouth ulcers. Throughout the course of this history, he noted a five-kilogram weight loss with no associated loss of appetite. The following morning, he visited his general practitioner in view of worsening mouth ulceration and skin erosions. This prompted his general practitioner to refer him to Boffa Hospital for dermatological review and investigation.

Past Medical & Surgical History

The patient is a known case of hypothyroidism (diagnosed five years ago) and borderline hypercholesterolaemia. He wears dentures as a consequence of an extensive history of periodontal gum disease. Surgical history included two nasal polypectomies in 1991 and 2004.

Drug History & Allergies

The patient has no known drug allergies. Drug history is listed in Table 1.

Family History

The patient's father had a history of type II diabetes mellitus (TIIDM), and hypertension. He had a stroke aged 48 and died of natural causes. His mother had a history of ischaemic heart disease, heart failure, deep vein thrombosis, and died aged 81. He has five siblings. One of his brothers suffers from TIIDM and hypercholesterolaemia. His sister developed hypertension at 34 years and also suffers from hypercholesterolaemia.

Generic Drug Name	Dosage	Frequency	Formulation	Reason for Prescription
Levothyroxine	75 mcg	Once Daily	Oral Tablet	Control of hypothyroidism
Omeprazole	30mg	Once Daily	Oral Tablet	Control of dyspepsia

Table 1: Drug History.

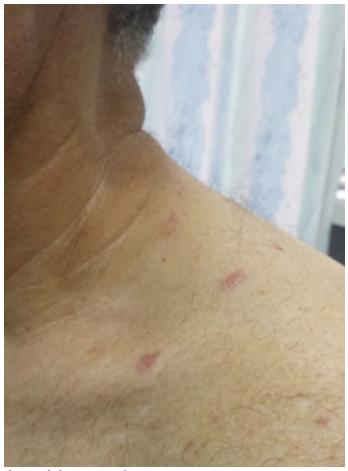

Figure 1: Mr. L.F.'s supraclavicular skin erosions.

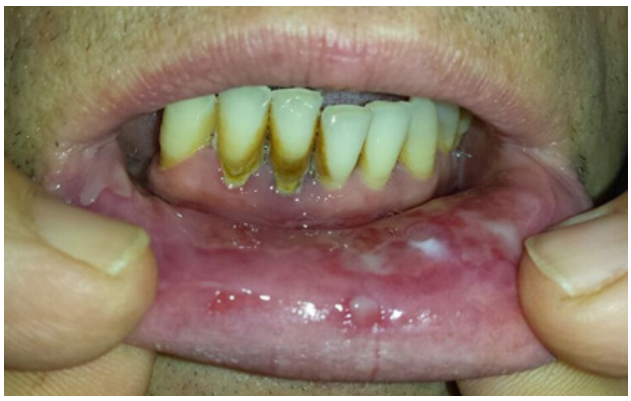

Figure 2: Mr. L.F.'s erosions on the inside of the lower lip.

Social History

The patient is married and lives at home with his wife and two healthy children. He is independent and works as an electrician in a residence for the elderly. He has no alcohol or smoking history.

Systemic Enquiry

General Health: Anxiety;
Cardiovascular System: Borderline hypercholesterolaemia;
Respiratory System: Nil to note;
Gastrointestinal Tract: Dyspepsia;
Genitourinary System: Nil to note;
Central Nervous System: Nil to note;
Musculoskeletal System: Nil to note;
Endocrine System: Hypothyroidism.

Upon dermatological consultation, the patient's lesions were examined (Figures 1 and 2).

Differential Diagnoses

1. Pemphigus vulgaris;
2. Pemphigus foliaceus;
3. IgA pemphigus;
4. Pemphigus erythematosus;
5. Bullous pemphigoid.

Diagnostic Investigations

Requested investigations: **Liver function tests & hepatitis screen**;

Justification for procedure: Possible deterioration of liver function on rituximab, and the use of rituximab in the presence of chronic viral hepatitis

may lead to worsening of pre-existing hepatitis;

Result: Normal.

Conclusion: No contraindication to rituximab therapy with respect to liver function.

Requested investigations: **Tuberculosis (TB) Quantiferon test & Chest X-Ray (CXR)**;

Justification for procedure: To investigate for latent TB as rituximab therapy needed to treat pemphigus vulgaris may reactivate latent TB;

Result: CXR and Quantiferon test both normal.

Conclusion: No evidence of previous infection with TB.

Requested investigations: **Anti-nuclear antibody (ANA), extractable nuclear antigens (ENA) antibody and immuno-globulin tests**;

Justification for procedure: Possible other associated autoimmune disorders apart from pemphigus vulgaris;

Result: Normal.

Conclusion: Other associated autoimmune disorders highly unlikely.

Requested investigations: **Skin incisional biopsy for histology and direct immunofluorescence**;

Justification for procedure: Necessary for definite diagnosis of pemphigus vulgaris

Result:

Histology: Intraepidermal clefting with acantholysis in the prickle cell layer. A sparse chronic inflammatory cell infiltrate, which includes scattered eosinophils, is present in the papillary dermis. A perivascular lymphocytic infiltrate involves the superficial plexus and vessels in the mid dermis.

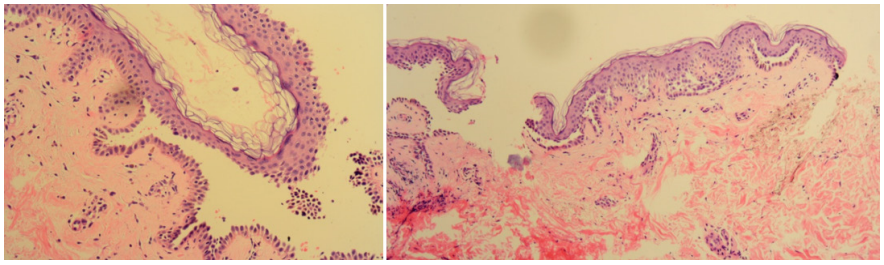

Figure 3: Mr. L.F.'s histology microscopy slides of the skin incisional biopsy.

Direct Immunofluorescence: Intercellular deposition of IgG and of C3 within the epidermis, outlining the cell membranes of keratinocytes in the prickle cell layer.

Conclusion: Diagnosis of pemphigus vulgaris confirmed.

Diagnosis

The characteristic nature of the skin lesions, coupled with the definite findings on histology and direct immunofluorescence, confirmed the diagnosis of pemphigus vulgaris. The investigations conducted revealed no contraindications to treatment with rituximab and high-dose steroids, thus, the patient was started on these two medications.

Management

Pharmacological Therapy

Following investigations, the patient was started on the following:

Follow Up

The patient received his weekly dose of intravenous (IV) rituximab for four weeks, with routine bloods and glucose monitoring. There was a partial response to treatment with some improvement but he was still getting new mouth ulcers. He will be followed up regularly at the outpatient department and will be continued on oral steroids and an increasing dose of azathioprine. Further courses of rituximab are planned in view of active disease.

Generic Drug Name	***Dosage***	***Frequency***	***Formulation***	***Reason for Prescription***
Prednisolone	*40mg*	*Once Daily*	*Oral tablet*	*To induce remission*
Rituximab	*500mg*	*Once Weekly*	*Intravenous injection*	*To induce remission*
Azathioprine	*50mg*	*Once Daily*	*Oral tablet*	*As a steroid sparing agent for maintenance.*

Table 2: Pharmacological Therapy.

References

Becker BA, Gaspari AA. Pemphigus vulgaris and vegetans. Dermatology Clin. 1993;11:429–52.

Neville D, Allen B. Dermotological Disease. 2nd ed. Saunders; 2008. Oral and Maxillofacial Pathology; pp. 664–7.

Pradeep AR, Manojkumar ST, Arjun R. Pemphigus vulgaris associated with significant periodontal findings: A case report. J Calif Dent Assoc. 2010;38:343–6.

Robinson NA, Yeo JF, Lee YS. Oral pemphigus vulgaris: A case report and review of literature.AnnAcad Med Singapore. 2004;33(4 Suppl):63–8.

Shafer, Hine, Levy. Disease of skin. 6th ed. India: Elsevier; 2009. Shafer's Textbook of Oral Pathology; pp. 816–22.

Shamim T, Varghese VI, Shameena PM. Pemphigus vulgaris in oral cavity: Clinical analysis of 71 cases. Med Oral Patol Oral Cir Bucal. 2008;13:E622–6.

Tamgadge S, Tamgadge A, Bhatt DM. Contemporary Clinical Dentistry. 2011;2(2):134-137. doi:10.4103/0976-237X.83074.