

Pemphigus Vulgaris: Case Reports of Patients Managed by a Multidisciplinary Team

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Abstract

Pemphigus vulgaris is an autoimmune, vesiculobullous condition affecting the skin, mucous membranes, eyes and genitalia. It is caused by damage to desmosomes by desmogleins and cadherins with immunoglobulin deposits; this leads to intercellular damage and acantholysis which causes bullae or vesicle formation. Diagnosis of pemphigus vulgaris involves direct and indirect immunofluorescence which are able to detect serum immunoglobulins and immunoglobulin deposits in the epithelium. Management of pemphigus vulgaris can be complex and can include use of corticosteroids and steroid sparing agents such as azathioprine, mycophenolate mofetil and dapsone.

The aim of this case report is to discuss two cases of pemphigus vulgaris which were managed at Northwick Park Hospital, London with a Multidisciplinary approach including the Department of Oral and Maxillofacial and also Dermatology. The first patient was a 34 year old female who presented with oral, scalp and facial lesions. She was managed together with the dermatologists with various topical and systemic agents. The second patient was a 36 year old male who presented with oral and genital lesions. He was similarly managed with numerous topical and systemic medications. Both patients experienced an improvement in their symptoms and are still under regular review by both specialities.

Keywords: *Pemphigus Vulgaris; Vesiculobullosus; Oral Medicine; Oral Pathology; Blistering; Dermatology; Mucosal Disease*

Introduction

Pemphigus vulgaris is an autoimmune, vesiculobullous condition which causes bullae and vesicles on the skin, mucous membranes and can also affect the eyes. It predominantly affects females aged 40 - 60 with lesions appearing in the mouth and then spreading on the skin. These lesions are not often seen intact intra-orally as the bullae burst, leaving erosions which are very painful [1,2]. The condition can be potentially life-threatening if left untreated due to dehydration or secondary systemic infection [3].

Pemphigus is caused by damage to desmosomes by desmogleins and cadherins, with intraepithelial immunoglobulin deposits and acantholysis which leads to formation of bullae. There is also a strong genetic predisposition to developing pemphigus vulgaris in certain ethnic groups [2,3]. Most cases are idiopathic but diet and drugs have been known to be a trigger in some cases [2,3].

Examination

Lesions can vary from a few millimetres to a centimetre in diameter. They are fluid filled and can contain pus or blood due to secondary infection [1]. Intra-oral lesions can be seen in the buccal mucosa, palate, ventral tongue and lips with desquamative gingivitis [2]. Gently running a finger over the mucosa may cause a bulla to appear; this is known as Nikolsky's sign [1].

Investigations

A perilesional biopsy is essential for the diagnosis of pemphigus vulgaris [3]. Direct immunofluorescence of the biopsy samples will detect antibody deposits of IgG and C3 [2,4,5]. The samples required for direct immunofluorescence must be stored in Michel's transport medium Serum antibodies may also be investigated by indirect immunofluorescence [3].

Pathogenesis

Epithelial cells lose their attachments, becoming rounded with the cytoplasm contracting around the cell nucleus [1]. Pemphigus antibodies (IgG) react with the epithelial cell surface antigen desmoglein 3, a type of cell adhesion molecule. Therefore, this leads to intercellular damage, acantholysis (separation of keratinocytes) and bulla formation [2,3]. The observation of Nikolsky's sign is caused by separation of the epithelium but is not a sensitive or specific test [5]. 50% of patients with pemphigus vulgaris also have autoantibodies to desmoglein 1; the proportions of desmoglein 1 and 3 may have an impact on clinical severity as desmoglein 1 is responsible for skin integrity [3].

Management

Lesions may be managed by topical, intralesional and systemic methods as well as good oral hygiene. Systemic treatment is usually required and includes corticosteroids with steroid sparing agents. These include azathioprine, dapsone, methotrexate, cyclophosphamide, gold, cyclosporin and more recently mycophenolate mofetil [3,4]. Adverse effects are common with these medications, however, mycophenolate mofetil has the least nephrotoxicity and hepatotoxicity. Regular clinical review and serum antibodies may be useful in determining the degree of immunosuppression required [3].

Aim

The aim of this case report is to discuss two cases of pemphigus vulgaris which presented at Northwick Park Hospital, and their complex management by a Multidisciplinary Team.

Case Report

Case Report 1: Patient AC

Patient AC was a 34 year old female, referred urgently by her General Practitioner (GP) with a history of 'ulcers on-and-off' for the past six months. The patient complained of intense pain, recurrent tonsillitis and had 5 - 6 courses of antibiotics over the past year.

Her medical history included obesity, hypothyroidism and type 2 diabetes mellitus. She was taking levothyroxine, metformin and the oral contraceptive pill. Since developing the 'ulcers' she quit smoking, however, previously smoked 3 - 5 cigarettes a day.

On examination, she had multiple soft palate and lip vesicles, pus exudate from her tonsils and multiple cutaneous scalp and facial lesions. Her main concerns were her face and scalp being painful and scarred. After the first appointment, blood tests were requested including a full blood count, B12, ferritin and folate to exclude any conditions which may be caused by haematinic deficiencies. She was also referred to Ear, Nose and Throat for her tonsillar symptoms. At this stage she was prescribed chlorhexidine, benzydamine hydrochloride (Difflam) and hydrocortisone 2.5 mg muco-adhesive buccal pellets (Corlan pellets) for symptomatic relief. Difflam is a locally actin non-steroidal anti-inflammatory mouthwash with analgesic properties and Corlan pellets contain hydrocortisone which helps to reduce pain and inflammation. The patient returned 3 weeks later with a complete resolution of symptoms.

However, the patient returned 5 months later with a recurrence of her symptoms. She complained of further lesions on her labial mucosa, palate, forehead and scalp (Figures 1 and 2). Subsequent examination confirmed these new lesions. Therefore, a biopsy was arranged for histology and direct immunofluorescence, and also tests for serum antibodies by indirect immunofluorescence. At this stage she was also referred to Dermatology.



Figure 1



Figure 2

The perilesional biopsy revealed ulcerated squamous mucosa with acantholysis and chronic inflammatory cell infiltrate. Direct immunofluorescence detected intercellular deposition of IgG in the epidermis, confirming a diagnosis of pemphigus vulgaris.

The patient had a Multidisciplinary Team approach to her management including Oral and Maxillofacial Surgery and Dermatology. She was initially prescribed 40mg of prednisolone to be taken daily for 2 weeks which is a steroid medication useful for treating inflammatory conditions and autoimmune disorders. She was also prescribed betamethasone, difflam and clobetasol (Dermovate) and Cetraben ointments for the skin lesions. Betamethasone is another steroid medication but in this case was used topically as a mouthwash. Clobetasol is also a topical steroid and cetraben is an emollient cream.

After 2 weeks, the patient was reviewed and the dose of prednisolone was reduced to 35 mg daily (with planned fortnightly 5 mg reductions) as Dermatology had commenced 200 mg of azathioprine which is an immunosuppressive drug. Prior to commencing azathioprine, her thiopurine methyltransferase (TPMT) levels were checked; a TPMT deficiency can make patients unable to metabolise azathioprine leading to bone marrow toxicity. The betamethasone mouthwashes were also stopped. She had also been prescribed 120 mg fexofenadine (an antihistamine to reduce urticaria) and 15 mg lansoprazole (a drug to inhibit gastric acid production due to the side

effects of prednisolone). Unfortunately, she was still developing new lesions despite the addition of azathioprine. It was therefore decided to commence 2g of mycophenolate mofetil daily, another type of immunosuppressant. This was then increased to 2.5 mg daily as new lesions were still developing.

Three months later, patient AC was still developing new lesions despite taking 20 mg prednisolone and 2.5g mycophenolate mofetil. Therefore, a course of 50 mg of dapsone, an antibiotic, was commenced and the patient was referred to the Complex Dermatology Clinic. Before commencing dapsone, her glucose-6-phosphate dehydrogenase (G6PD) levels were checked as taking dapsone with a G6PD deficiency can cause a haemolytic anaemia.

The outcome of the Complex Dermatology Clinic was to increase the dose of prednisolone from 20mg to 70mg due to the severity of her lesions. It was also advised that 100 mg azathioprine be recommenced with a slow weaning regime for the prednisolone. She was also prescribed betamethasone valerate 0.1% (Fucibet) ointment, another topical steroid, for her skin lesions.

Six months after her initial diagnosis and after trialling various medications, her pemphigus vulgaris lesions eventually began to subside. There were no new lesions and her forehead and scalp lesions were healing. At the time of this appointment she was taking 300 mg azathioprine daily and was on 45 mg prednisolone which was still being weaned down. Her blood test revealed high levels of aspartate aminotransferase (AST) due to the effects of azathioprine on the liver; therefore, her dose was reduced to 100mg daily and the prednisolone increased to 50 mg with a weaning regime.

The patient is still under regular review by Dermatology and Oral and Maxillofacial Surgery. It is important that her systemic therapy remains at the lowest dose possible that will control her disease and that she has regular blood tests to monitor her liver function, renal function and TPMT levels. She will also require regular blood pressure and blood glucose checks by her GP due to the effects of the corticosteroids.

Case Report 2: Patient MS

Patient MS was a 36 year old male, referred urgently by his General Practitioner (GP) with white patches in his mouth for two months. The GP had already tried anti-fungal and steroid therapy which were of no benefit to the patient. Patient MS was concerned about pain on eating and drinking, and had already been to the Genitourinary Medicine (GUM) Clinic due to genital lesions. He was otherwise medically fit and well, a non-smoker and drank approximately one bottle of whisky a week.

On examination, the patient had multiple vesiculobullous lesions on his buccal mucosa, ventral tongue, lips and oropharynx (Figures 3 and 4). He also had multiple lesions on his glans penis. A biopsy was arranged for histology and direct immunofluorescence, benzydamine hydrochloride (Difflam) prescribed and the patient was also referred to Dermatology with a planned Multidisciplinary Team approach.



Figure 3



Figure 4

Two biopsies were taken from the tongue and buccal mucosa and found suprabasal acantholysis and chronic inflammatory infiltrate. The direct immunofluorescence also confirmed a diagnosis of pemphigus vulgaris.

Two weeks later, the patient was reviewed together by Oral and Maxillofacial Surgery and Dermatology and informed of his diagnosis. He was prescribed Difflam and betamethasone mouthwashes, clobetasol (Dermovate) ointment for his genital lesions, and 70 mg of prednisolone daily.

After three weeks, the patient was reviewed by Oral and Maxillofacial Surgery with input from Dermatology. The patient's symptoms had improved and it was decided to reduce the dose of prednisolone to 65 mg with review appointments arranged with both specialties.

Two weeks later, the patient was completely asymptomatic with healing vesicles on his lower lip and ventral tongue. However, he was experiencing some side-effects from the high dose corticosteroid treatment including weight gain and acne spreading across his back, chest and face. It was then decided to reduce the prednisolone dose gradually to 40 mg. Thiopurine methyltransferase (TPMT) and liver function blood tests were performed in order to commence use of azathioprine as a steroid sparing agent.

At this patient's review appointment after two months, he was still on a reducing dose of prednisolone. He had some new oral lesions and also developed a lesion on his right nose for which he was prescribed Dermovate.

This patient is still under review by both specialties with ongoing symptoms. Similar to the first case, it is important that this patient's systemic therapy is kept to the lowest dose that will help to control his symptoms.

Discussion

These cases have demonstrated the need for management and input from both Oral and Maxillofacial Surgery and Dermatology. Both cases initially presented to Oral and Maxillofacial Surgery where they were diagnosed by performing biopsies for investigation by direct immunofluorescence. Their oral disease was managed by Oral and Maxillofacial Surgery via topical treatments, however, further input was required from dermatology for their cutaneous and genital lesions and for a joint approach to their systemic treatment. The management of the female patient was particularly complex as several adjustments had to be made to the doses of corticosteroid and other systemic agents in order to control her lesions. She also had to be closely monitored due to her liver function, diabetes and hypertension. The male patient also experienced side effects from the corticosteroids but responded well to azathioprine. They are both still on systemic therapy and may still require further adjustment to their medications.

Conclusion

Both of these patient cases of pemphigus vulgaris benefitted from a multidisciplinary team approach with Oral and Maxillofacial Surgery and Dermatology. They were both treated with topical treatments, oral corticosteroids and later steroid sparing agents. It has been important to keep their systemic therapy at as low a dose as possible to control their vesiculobullous disease and to monitor their health due to side effects of their treatment. Both patients' conditions are improving but are still under regular review by both specialties.

List of Drugs

Benzydamine hydrochloride (Difflam)

Meda Pharmaceuticals

Sky Way House, Parsonage Road, Takeley, Bishop's Stortford, CM22 6PU

Levothyroxine

Custom Pharmaceuticals Ltd

Tecore House, Conway Street, Hove, East Sussex, BN3 3LW

Metformin

Teva UK Ltd

Ridings Point, Whistler Drive, Castleford, WF10 5HX

Hydrocortisone (corlan) pellets

Auden Mckenzie (Pharma Division) Ltd

Whiddon Valley, Barnstaple, North Devon, EX32 8NS

Clobetasol (dermovate)

Glaxo Smith Kline

Stockley Park West, Uxbridge, Middlesex UB11 1BT

Cetraben

Genus Pharmaceuticals

Linthwaite, Huddersfield, West Yorkshire, HD7 5QH

Azathioprine

Sandoz Ltd

200 Frimley Business Park, Frimley, Camberley, Surrey, GU16 7SR

Fexofenadine

Dr. Reddy's Laboratories (UK) Ltd

6 Riverview Road, Beverley, Hull, HU17 0LD

Lansoprazole

Generics UK T/A Mylan

Building 4, Trident Place, Mosquito Way, Hatfield, Hertfordshire, AL10 9UL

Mycophenolate mofetil

Roche Products Ltd

Hexagon Place, 6 Falcon Way, Shire Park, Welwyn Garden City, Hertfordshire, AL7 1TW

Dapsone

Accord-UK Ltd

Whiddon Valley, Barnstaple, Devon, EX32 8NS

Fucibet

Leo Laboratories Ltd

Horizon, Honey Lane, Hurley, Berkshire, SL6 6RJ

Prednisolone

Accord-UK Ltd

Whiddon Valley, Barnstaple, Devon, EX32 8NS

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