International Journal of Paediatric Dentistry 2005; **15:** 287–293

Oral pemphigus vulgaris in children and adolescents: a review of the literature and a case report

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Summary. This paper describes a case of oral pemphigus vulgaris (PV) in a child that was diagnosed in its early stages and managed successfully. The authors also report a literature review. Although oral PV in children and adolescents is extremely rare, it should be included in the differential diagnosis of oral ulcerative disease. It is of utmost importance to diagnose PV in children and adolescents in its initial stages in order to prevent the serious morbidity that may result from the disease, and to institute phamacotherapeutic measures so that they have the greatest effect. Furthermore, it is essential for dentists to be aware of the existence of PV in child and adolescent patients so that they may refer such cases for specialist management without undue delay.

Introduction

Pemphigus vulgaris (PV) is a rare mucocutaneous vesiculobullous disease [1,2]. The disease is characterized by suprabasal acantholysis, which leads to the formation of blisters which readily rupture, leaving erosions and ulcers of the skin or the mucosa [2]. Pemphigus vulgaris is the commonest variety of pemphigus, accounting for over 80% [3]. It is an autoimmune disease caused by IgG antibodies directed against desmoglian 3, a desmosomal transmembrane glycoprotein that belongs to the cadherin family of cell-to-cell adhesion molecules [3–6].

Oral lesions are the first sign of the disease in approximately 60% of patients, and such lesions may be followed by skin involvement over varying periods of time [5]. Of those who have skin lesions, 80–90% develop oral lesions at some time during the course of the disease [1,3]. Pemphigus vulgaris is regarded as a disease of middle-aged adults, with a peak incidence between the fifth and sixth decades of life. There appears to be no significant gender difference [1].

Oral PV during childhood and adolescents is extremely rare, and less than 50 cases have been reported in the world literature. The intention of this paper is to discuss the oral involvement of PV in children and adolescents, and the importance of early intervention. The authors present a review of case reports of the disease involving the oral mucosa in children and adolescents, and other relevant literature available in the English language, and a case of PV affecting a 14-year-old Sri Lankan girl.

Case report

A 14-year-old girl was referred to the Department of Oral Medicine and Periodontology, Faculty of Dental Sciences, University of Peradeniya, Peradeniya, Sri Lanka, with oral mucosal ulcers of 10 days duration and bleeding gingiva. During this period, she had experienced fever and difficulty in swallowing.

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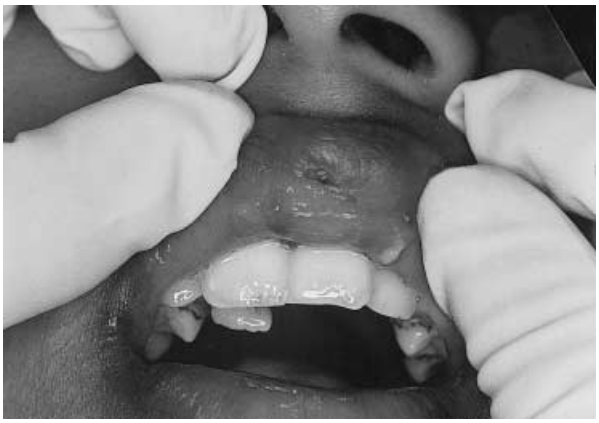

Fig. 1. Multiple erosive areas and ulcers with slough involving the upper lip.

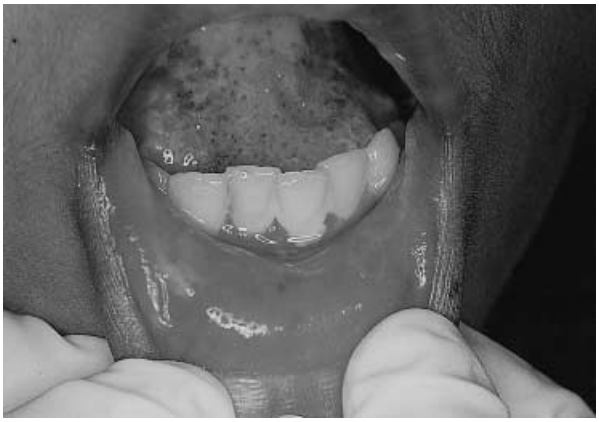

Fig. 2. Multiple erosive areas and ulcers with slough involving the lower lip.

Her past medical history was unremarkable, and there was no family history of oral ulcers of a similar nature or any autoimmune diseases. The girl denied recent use of any drugs or other chemicals which could have lead to such a complaint. She had not experienced anorexia, fatigue, shortness of breath or recent weight loss. She also had no history of erosions or ulcers on the skin or other mucosal surfaces. Physical examination revealed that she was febrile. The submandibular lymph nodes on both sides were palpable and tender. There was no hepatosplenomegaly. On examination of the mouth, there were multiple erosive areas and ulcers with slough involving the lips, buccal mucosae, lateral borders of the tongue, soft palate and gingivae (Figs 1 and 2).

Full blood counts (FBCs) revealed reduced mean corpuscular volume (MCV = 72 fl) and mean corpuscular haemoglobin (MCH = 25 pg). However, other parameters were within normal limits. The subject's blood picture was normochromic and normocytic. Taking the overall results of the FBCs and blood picture into account, low values of MCV and MCH were considered to be insignificant. A tentative differential diagnosis of herpetic gingivostomatitis, erythema multiforme and vesiculobullous disease with a possible secondary infection of the ulcers was made. It was decided to initiate symptomatic treatment in order to control possible superficial mucosal infection, to improve oral hygiene and control pyrexia. A course of antibiotics (amoxycillin 250 mg three times a day for 5 days) and antiseptic mouthwash (0·2% chlorhexidine) were prescribed along with paracetamol 1 g every 6 hours to control the fever. The subject was advised to drink plenty of fluids. She was reviewed one week later when improvement of oral hygiene and normal body temperature were noted. However, the mucosal ulcers remained unchanged. In addition, during the intervening period, the patient had noticed the appearance of blisters which readily ruptured leaving ulceration. On this second visit, an oral mucosal biopsy was taken for routine histopathology and direct immunofluorescence. Microscopic features of intraepithelial blister formation (suprabasal), together with acantholytic cells were observed in the Haemotoxylin and Eosin sections (Fig. 3). Direct immunofluorescence showed intercellular positivity for IgG and C3 (Fig. 4). A definitive diagnosis of PV was made from these histological and clinical features.

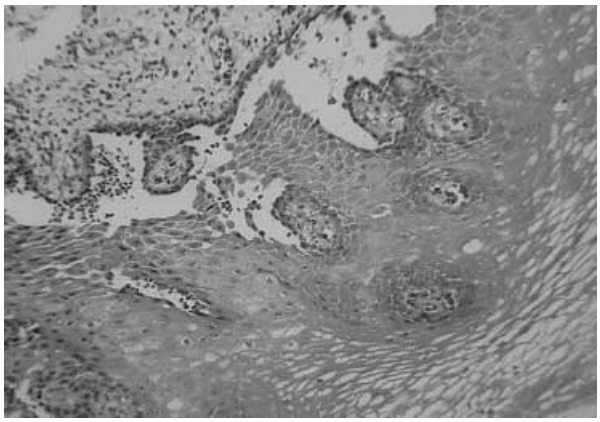

Fig. 3. Photomicrograph showing intraepithelial blister formation (suprabasal) and acantholytic cells (H&E, × 100).

The patient was managed jointly by the oral medicine staff at the Peradeniya dental hospital and

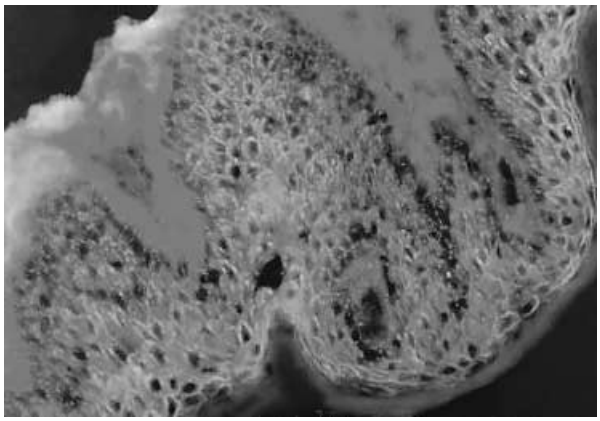

Fig. 4. Direct immunofluorescence photomicrograph showing intercellular positivity for IgG and C3 (× 100).

a consultant dermatologist. A drug regime was prescribed comprising systemic prednisolone 10 mg twice a day, tailing off to 5 mg a day over a one-month period, together with dapsone 100 mg a day. A significant improvement of the condition was seen within one month of starting treatment, and therefore, systemic treatment was terminated. Residual lesions on both the right and left buccal mucosae were treated using the topical application of 0·1% triamcinolone acetonide in orabase twice a day for a period of 3 months, during which complete remission was achieved. Following treatment, the patient was reviewed once a month for 12 months. The condition remained under good control without relapse during this period.

Discussion

Pemphigus vulgaris affecting individuals below 20 years of age has been described using various terms such as 'juvenile PV' [7–10], 'adolescent PV' [11–13], 'childhood PV' [14–18] and 'paediatric PV' [19]. Since such terminology causes confusion, as Gorsky *et al.* suggested, the authors used the terms 'childhood PV' to describe the condition in individuals under 12 years of age and 'adolescent PV' in those aged between 12 and 18 [11].

Pemphigus vulgaris is a relatively rare disease that characteristically affects middle-aged individuals, with an increased incidence among Ashkenazy Jews [1,5]. It is extremely rare in children. Table 1 summarizes the age and sex distribution of the cases reported in the literature since 1969 in which the oral cavity is involved. Only 35 cases (including the present one) of childhood and adolescent PV affecting the oral cavity have been reported in the world literature since 1969. Including the present case, the mean age of these 35 cases was 13.2 years (range = 3·5–18 years). There was a slight female predilection (male to female ratio = 1:1·4). Although there were no significant gender differences amongst cases listed in Table 1, some studies have found a female preponderance among adult patients [20,21].

Pemphigus vulgaris is rare in children, and hence, it was not suspected at the time of the initial presentation. The clinical course of oral mucosal pemphigus in children and adolescents starts with vesicles which rupture easily, resulting in erosions and ulcers which are painful and bleed readily. The differential diagnosis of PV in children and adolescents includes erythema multiforme, acute herpetic gingivostomatitis, bullous impetigo, linear IgA disease, epidermolysis bullosa, cicatrical pemphigoid, bullous pemphigoid of childhood and paraneoplastic pemphigus [8,13,22,23]. In the present case, primary herpetic gingivostomatitis was suspected in the first instance, based on the clinical evidence. Supportive measures were taken accordingly. However, since the lesions persisted for one week after the first visit to the hospital, the authors considered the possibility of a autoimmune vesiculobullous disease, especially PV. Diagnosis of PV may be confirmed by histological and direct immunofluorescence studies. The detection of characteristic antiepidermal antibodies by indirect immunofluorescence further supports the diagnosis. However, in the present case, the authors were unfortunately not able to carry out indirect immunofluorescence because of the lack of the necessary facilities in their hospital.

Erythema multiforme, one of the important differential diagnoses, is a chronic inflammatory mucocutaneous disease that may occur at any age in both sexes. Although the exact aetiology remains obscure, a wide range of antigenic factors, including drugs, herpes virus and bacterial infections, and malignancy, have been suggested as triggering factors [24].

Paraneoplastic pemphigus (PNP) is one of the very important differential diagnoses which should be taken into consideration [23]. It is an autoimmune syndrome that was first described in 1990 by Anhalt *et al.* [25]. This is associated with B-cell lymphoproliferative neoplasms: non-Hodgkin lymphoma, chronic lymphocytic leukaemia, Castleman disease, and less commonly, thymoma and sarcoma [26]. Although, adult patients are commonly affected,

Table 1. Age and sex distribution of cases of pemphigus vulgaris reported in the literature since 1969 in which the oral cavity was involved.

Number	Year	Author	Age (years)	Male	Female	Oral lesions alone	Oral and skin lesions
1	1969	Jordon *et al*. [14]	13	+			+
2	1972	Murphy and Harrell [30]	9		+	+	
3	1972	Elias *et al*. [15]	13		+	+	
4	1973	Berger *et al*. [31]	3·5	+		+	
5	1978	Harrington *et al*. [32]	15		+		+
6	1980	Bennett *et al*. [33]	8	+			+
7	1981	Laskaris *et al*. [8]	15		+	+	
8	1981	Laskaris *et al*. [8]	18		+	+	
9	1983	Ahmed *et al*. [34]	16		+		
10	1983	Ahmed *et al*. [34]	5	+			+
11	1983	Ahmed *et al*. [34]	17		+		+
12	1983	Ahmed *et al*. [34]	17	+			+
13	1983	Ahmed *et al*. [34]	12	+			+
14	1983	Ahmed *et al*. [34]	18	+			+
15	1983	Ahmed *et al*. [34]	18	+			+
16	1984	Lynde *et al*. [35]	15	+			+
17	1984	Hempstead and Marks [36]	13		+	+	
18	1987	Jacyk and Dyer [37]	13	+			+
19	1988	David *et al*. [38]	11	+			+
20	1988	David *et al*. [38]	17		+		+
21	1988	David *et al*. [38]	13		+		+
22	1988	David *et al*. [38]	16	+			+
23	1990	Laskaris *et al*. [19]	6		+		+
24	1991	Graff-Lonnevig and Kaaman [39]	13		+		+
25	1994	Gorsky *et al*. [11]	15		+		+
26	1998	Bjarnason *et al*. [17]	5	+			+
27	1999	Navarro *et al*. [40]	18		+		+
28	1999	Wananukul and Pongprasit [18]	12		+		+
29	1999	Wananukul and Pongprasit [18]	13		+		+
30	1999	Wananukul and Pongprasit [18]	11		+		+
31	1999	Ogata *et al*. [12]	15		+		+
32	2000	Pires *et al*. [13]	16		+		+
33	2001	Harangi *et al*. [9]	10	+			+
34	2002	Jun and Antaya [29]	18		+		+
35	2003	Present case	14		+	+	
Total [*n* (%)]				14 (40%)	21 (60%)	7 (20%)	28 (80%)

there have been few reports of the condition affecting children and adolescents. Mimouni *et al*. [23] compiled 14 cases of PNP affecting children and adolescents. A constant clinical finding in these patients was oral mucosal involvement with painful mucositis. Eight out of 14 patients had lichenoid lesions of the skin and oral mucosa, while 12 out of 14 were diagnosed with Castleman disease [23]. In the present case, there were no clinical features suggestive of underlying malignancy. Furthermore, the condition also responded well to a relatively low dose of systemic prednisolone and dapsone. This also helped to exclude the possibility of PNP in the present case.

Pemphigus vulgaris was considered potentially lethal before the advent of effective immunosuppressive therapies [19,20,27]. Immunosuppression is the basis of therapy for PV and typically involves the administration of corticosteroids. The drug of choice for PV is prednisolone, with the dosage adjusted according to the clinical response. An initial dose of 100–150 mg prednisolone alone or with azathioprine (100–150 mg) and a maintenance prednisolone dose of 5–20 mg daily for varying periods of time has been recommended for adult patients by Ljubojevic *et al*. [27]. Robinson *et al*. [20] suggested 60–80 mg prednisolone as a single morning dose alone, or in combination with azathioprine 100–150 mg per day as an adjunct. In treating child patients, the dose should be adjusted according to age, body weight, the severity of the condition and the side-effects of the drug. Bjarnason *et al*. have suggested a dose

of 2–3 mg kg^{-1} day^{-1}, with a slow tapering to 0·5–0·8 mg kg^{-1} day^{-1}, for a period of approximately 2 weeks [28]. Once the disease begins to go into remission, the dose can be gradually reduced, and when the lesions disappear, the drug can be completely withdrawn [1]. However, for certain patients, a maintenance dose of 5–20 mg day^{-1} may be required on a long-term basis.

Immunomodulating drugs can also be used concomitantly as steroid sparing agents and to enhance the therapeutic response of steroids [14]. Such adjuvant drugs include azathioprine, cyclophosphamide, cyclosporin, methotrexate, dapsone and gold [9,17,20,21,27]. Bjarnason *et al*. have also summarized the use of adjuvant therapy in child patients [28]. Other procedures, such as plasmapheresis and immunoadsorption, have also been found to be effective in severe cases [12,27].

Jun and Antaya recently reported a case of PV in an adolescent involving the oral mucosa in the initial manifestation [29]. However, a biopsy was not carried out until 4 months after the initial visit, which led to a delay in diagnosis. Having confirmed the diagnosis with direct immunofluorescence, the patient was then treated with 60 mg of prednisolone, which was tailed off over a 3-month period, and intravenous immunoglobulin therapy involving 100 mg dapsone per day.

Harangi and colleagues reported a case who recovered completely after 4 years of therapy with no relapse for another 4 years [9]. This patient was treated with 2 mg kg^{-1} day^{-1} of prednisolone, which was tailed off to 1·5 mg kg^{-1} day^{-1} over 4 weeks. At the end of 4 weeks, they added 2 mg kg^{-1} day^{-1} of azathioprine, which resulted in a symptom-free condition without relapse. Thereafter, the patient received a dose of 4 mg methyl prednisolone and 50 mg azathiprine per day for 4 years.

In a further report, Pires *et al*. presented a case whose the initial lesions appeared in the oral mucosa [13]. There was a 5-month delay before the diagnosis of juvenile PV was made, and by that time, skin lesions had appeared. However, the above authors were able to manage the patient and bring about a favourable outcome using 45 mg day^{-1} of systemic prednisolone.

In this case, the authors were able to establish the diagnosis of PV at a very early stage (within 2 weeks of the initial visit to the hospital) and initiate treatment. This may have prevented a more extensive progression of the disease. The lesions were not widespread, and consideration of the side-effects of systemic corticosteroids in a growing child led to the decision to manage the subject with a relatively low dose of prednisolone together with steroid-sparing dapsone. With additional meticulous oral care measures, the patient responded well to the prescribed drug regimen. However, mild isolated lesions still needed topical steroid application. The authors did not continue with a maintenance dose so as to prevent the long-term side-effects of systemic steroids. Topical corticosteroids may be used for mild cases of PV and the systemic dosage may be lowered when these are combined with a topical steroid [3]. The agent used, 0·1% triamcinolone acetonide in orabase, is a popular topical steroid available for application in the oral mucosa. Furthermore, more potent fluorinated corticosteroids such as fluocinonide, clobetasol and halobetasol are available in the form of 0·05% ointment or gel. In this case, the authors used a local application of triamcinolone to control the residual lesions. There appear to have been no studies available evaluating the use of topical steroids in the management of PV in children and adolescents, and therefore, it is difficult to assess the value of the method more generally.

Because there are no studies which have used large series of patients with long-term follow-up in the literature, only case reports, it is not possible to comment on the long-term prognosis of childhood and adolescent PV at present.

However, it is of utmost importance to diagnose PV in children and adolescents in its initial stages in order to prevent the serious morbidity that may result from the disease and to institute phamacotherapeutic measures to greatest effect. Cases such as this one show that PV should be included in the differential diagnosis of oral ulcerative disease in children and adolescents. It is essential for dentists to be aware of the existence of PV in child and adolescent patients so that they may refer such cases for specialist management without undue delay.

What this paper adds

• This paper describes the case of a 14-year-old girl diagnosed with oral pemphigus vulgaris, a condition much more often seen in older people.

Why this paper is relevant to paediatric dentists

• Oral ulceration in children may arise from a variety of causes. This case illustrates that, although rare, pemphigus vulgaris may need to be included in differential diagnosis.

Résumé. Nous rapportons dans cet article un cas de pemphigus vulgaire buccal chez un enfant, diagnostiqué très tôt et pris en charge avec succès, de même qu'une revue de la littérature. Bien que le pemphigus vulgaire soit extrêmement rare chez l'enfant et l'adolescent, il devrait être inclus dans le diagnostic différentiel lors de maladie buccale ulcérative. Il est de la plus haute importance de diagnostiquer PV aux stades initiaux chez l'enfant et l'adolescent afin de prévenir la sérieuse morbidité en résultant et de mettre en place les mesures pharmacothérapeutiques les plus efficaces. De plus, il est essentiel pour les dentistes d'être au courant de son existence chez les enfants et adolescents afin d'adresser de tels cas chez des spécialistes permettant une prise en charge sans délai.

Zusammenfassung. In dieser Veröffentlichung berichten wir über einen Fall von oralem Pemphigus vulgaris (PV) bei einem Kind, welcher erfolgreich behandelt werden konnte; eine Übersicht über die Literatur wird gegeben. Auch wenn Pemphigus vulgaris bei Kindern und Jugendlichen extrem selten ist, sollte er bei der Differentialdiagnose von oralen Ulzerationen einbezogen werden. Gerade die frühzeitige Diagnose im Kindes-/Jugendalter ist besonders wichtig, um schwerwiegende Krankheitsfolgen zu verhindern und dazu eine wirksame Pharmakotherapie einzuleiten. Es ist erforderlich, sich als Zahnarzt der Möglichkeit von PV auch bei Kindern und Jugendlichen bewusst zu sein, um eine Überweisung solcher Fälle zur fachärztlichen Behandlung ohne unnötige Verzögerung zu veranlassen.

Resumen. En este artículo informamos de un caso de pénfigo vulgar en un niño que se diagnosticó en su estadío temprano y se trató exitosamente, junto con una revisión de la literatura. Aunque el pénfigo vulgar oral en niños y adolescentes es extremadamente raro debería incluirse en el diagnóstico diferencial de la enfermedad ulcerosa oral. Es de la máxima importancia diagnosticar PV en niños/adolescentes en sus estadíos iniciales para prevenir la seria morbilidad que puede resultar de la enfermedad e instituir medidas fármaco-terapéuticas con el mayor efecto. Además, es esencial para los dentistas estar atentos de la existencia de PV en pacientes niños/adolescentes para que puedan referir tales casos para el tratamiento del especialista sin producirse ningún retraso.

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