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Juvenile Pemphigus Vulgaris-2 Case Reports

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I. INTRODUCTION

Pemphigus is a group of chronic vesiculobullous, mucocutaneous lesions caused by the autoantibodies formed against intercellular attachments of keratinocytes leading to the loss of cell-cell epithelial adhesion, and thus mediating the process of acantholysis[3].The two major groups are Pemphigus Vulgaris and pemphigus Foliaceus. The term pemphigus was derived from a Greek word "pemphix" which means bubble or blister. The other forms are vegetans, erythematous, IgA pemphigus, and paraneoplastic pemphigus (PNP).[2]

Pemphigus vulgaris is the most common form of pemphigus, accounting for more than 80% of cases[1]. The underlying mechanism responsible for causing the intraepithelial lesion is the binding of IgG autoantibodies to DSG3[3].In most of the cases, oral mucosa is one of the first sites of attack[2]. While any area in the oral cavity can be involved, the soft palate, buccal mucosa, and lips are predominantly affected[2].However, there are 10-15% of cases that show only cutaneous manifestations[3].

Pemphigus vulgaris is an unusual disease (0.1–0.5 cases/100,000 inhabitants/yr.), with onset in the 5th or 6th decade of lifeand male-to-female ratio of 1:2[4,2].The peak incidence of pemphigus vulgaris occurs between the fourth and sixth decades of life.The PV is infrequent in children and adolescents, but some cases have been reported in children and young adults; therefore, it should be taken into account in the differential diagnosis of children and young adults

Terminology in this younger group includes childhood PV, juvenile PV, prepubertal PV, paediatric PV, and adolescent PV[4].The diagnosis depends on histopathological examination revealing intraepithelial vesicle formation, acantholysis, and the presence of Tzanck cells.

Here we report 2such cases of adolescent pemphigus vulgaris presented in young individuals.

II. CASE PRESENTATION

CASE 1

A 16-year-old male patient came to the Department of Oral Medicine and Radiology, with a chief complaint of recurrent ulcerations on his right and left inner cheek region since 7 months with burning sensation on taking hot and spicy food. The patient gave a history of vesicle formation which ruptures with watery fluids leaking out and later forming an ulcer. The patienthad consulted many dermatologists and was on topical analgesics but had no symptomatic improvement was noticed. The medical , personal and family histories were non-contributory.

On intraoral examination multiple ulcers with irregular, sloping edges surrounded by erythematous halo were seen on the attached gingiva irt 14, 15 and bilateral buccal mucosa Erosions were present on the soft palate also. On palpation, ulcers were non tender, shallow,non-indurated and Nikolsky's sign was negative.

An incisional biopsy was obtained from the site of lesion along with perilesional tissue under local anaesthesia and was sent for histopathological examination

Histopathological findings showed a keratinized stratified squamous epithelium with suprabasilar split from the underlying stroma. Certain areas of the epithelium showed acantholysis and Tzanck cells. Underlying connective tissue stroma showed diffuse dense infiltration of chronic inflammatory cells predominantly lymphocytes and plasma cells. Many vascular channels and extravasated RBCs were also noticed. The histopathological diagnosis was suggestive of pemphigus vulgaris.

The patient was put on topical application of 0.1% triamcinolone acetonide thrice daily for 7 days. The patient was reviewed after 7 days and lesions on the right and left buccal mucosa and on the soft palate showed improvement.. The doses were tapered later to twice a week for 1 week.) Oral prophylaxis was performed and the patient is kept under regular review.

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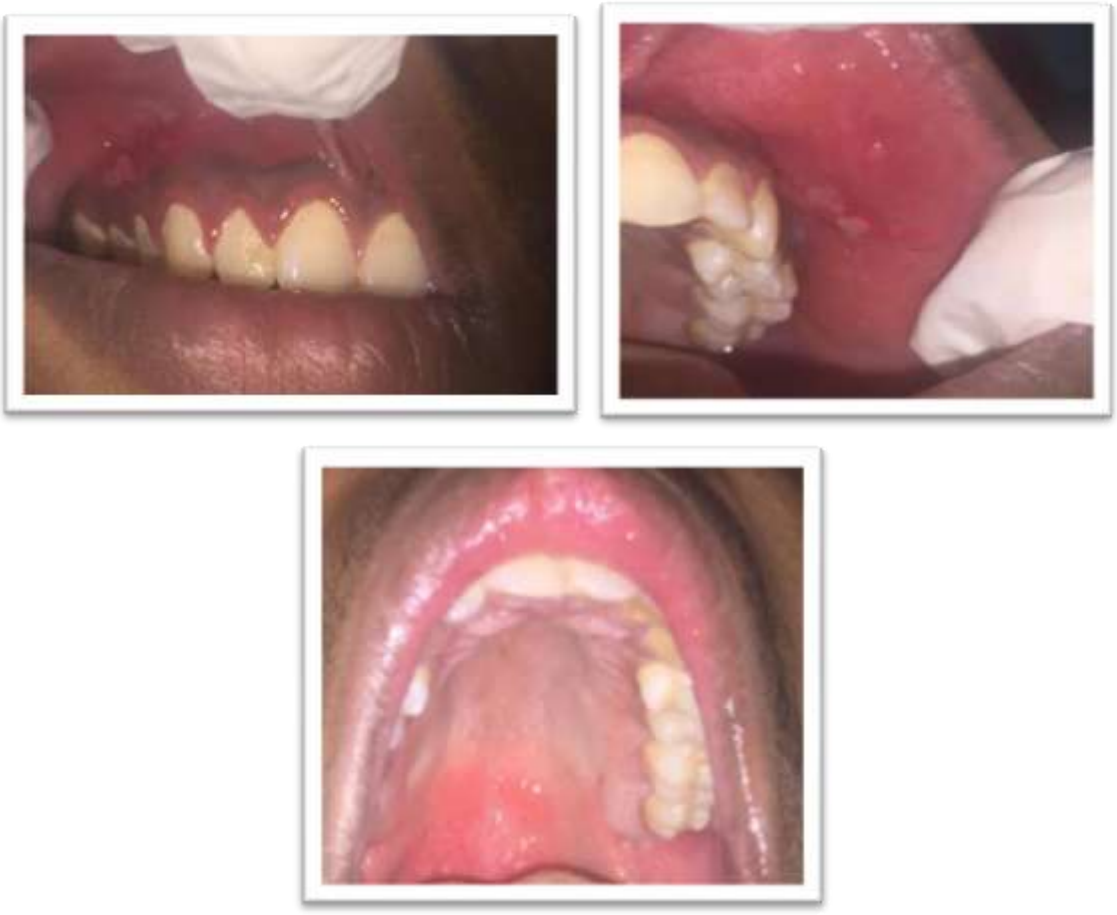
PRE-TREATMENT



POST-TREATMENT

CASE 2

An 18-year-old female patient came to the Department of Oral Medicine and Radiology, with a chief complaint of recurrent multiple ulcers in the mouth since 1 year with a history of burning sensation which aggravates on taking hot and spicy food. A history of vesicle formation which ruptures with leakage of clear fluid and turns into ulcer was elicited. Medical history revealed that she is under medication for eczema and hypothyroidism for past 10 years.

On intraoral examination,diffuse erythematous areas on the attached and marginal gingiva on the facial aspect of maxillary and mandibular teeth were seen and ulcers having irregular margins, sloping edges surrounded by erythematous halo irt attached gingiva of 24, 25, 34, 35 and 45, 46. The ulcers were shallow ulcers and wasnon tender, non-indurated was and had no tendency to bleed. Nikolsky's sign was positive.

A biopsy was obtained from the site of lesion along with perilesional tissue under local anaesthesia and was sent for routine histopathological examination

Histopathological findings showed a keratinized stratified squamous epithelium with acantholytic areas at many spots. Suprabasilar splits and Tzanck cells were presentat certain areas. Histopathological diagnosis was suggestive of pemphigus vulgaris.

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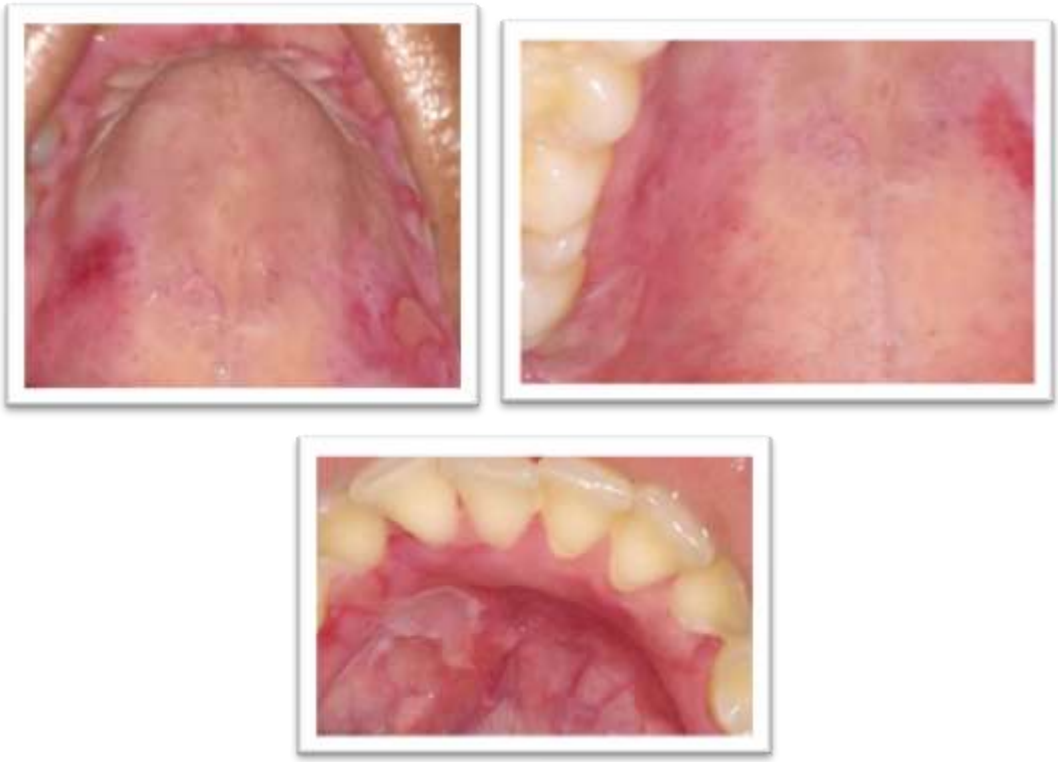
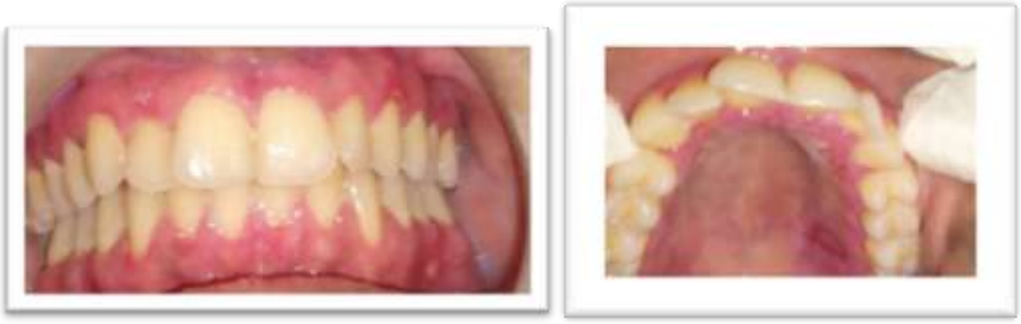
The patient was treated with topical application of steroids, 0.1% triamcinolone acetonide 3 times daily for a week, later were tapered to 2 times a week followed by once in a week for 7 days . There was reduction in the size of the lesion in the subsequent visit.Patient is kept under regular follow up.

PRE-TREATMENT



POST TREATMENT



III. DISCUSSION

The term pemphigus is derived from the Greek word "Pemphix " means "bubbles or blisters" and "vulgaris" in Latin means "common[1]. "Pemphigus is a group of chronic vesiculobullous, mucocutaneous lesions caused due to the autoantibodies formed against intercellular attachments of keratinocytes leading to the loss of cell-cell epithelial adhesion, and thus mediating the process of acantholysis[3]. The 2 major groups are pemphigus vulgaris and pemphigus foliaceus[5]. The other forms are vegetans, erythematous, IgA pemphigus and paraneoplastic pemphigus[5].

The peak incidence of pemphigus vulgaris is during the 5^{th} – 6^{th} decade of life. The PV is infrequent in children and adolescents.

Terminologies in younger age group include[6]

- Childhood pemphigus vulgaris
- Juvenile pemphigus vulgaris

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- Prepubertal pemphigus vulgaris
- Paediatric pemphigus vulgaris
- Adolescent pemphigus vulgaris

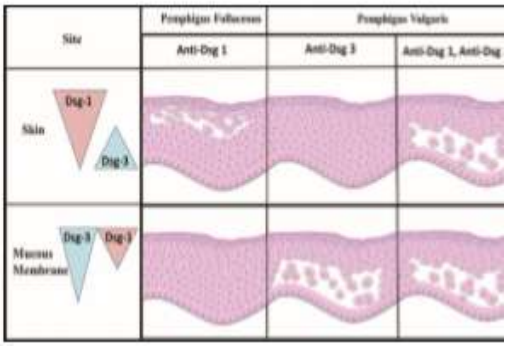
The course of the disease in this age group is similar to the course in adults, usually mild and chronic but onset of age is different[6].

The pathophysiology of Pemphigus vulgaris in juvenile patients is similar to that in adults. The mechanism is governed by the mechanism of primary acantholysiswhich, has been explained by the "Desmoglein compensation theory" and "Multiple hits hypothesis" [2].

The Desmoglein Compensation Theory was given by Mahoney M.G in the year 1999 based on the differential antigenicdistribution and generation of autoantibodies.

This theory was proposed based on two crucial experimental evidences[10]:

1. There exists a difference in the expression patterns of Desmoglein 1 and 3 in the skin and mucous membranes. Desmoglein 1 is found to be expressed in the epidermis and oral mucosa with intense expression in the sub corneal layers and weak expression in deeper layers
2. There also exists a clinical correlation of pemphigus with the anti-Desmoglein antibody profile in regard to clinical phenotypes. Patients affected by pemphigus foliaceus have only anti-Desmoglein 1 IgG in their autoantibody profile, and lesions were predominantly seen on the skin. Patients with pemphigus vulgaris have only anti-desmoglein 3 IgG in the autoantibodies profile and lesions were predominantly seen in mucosal surfaces. However, mucocutaneous variant of pemphigus vulgaris consisted of both anti-desmoglein 1 and anti-desmoglein 3-IgG autoantibodies



Multiple Hits Hypothesis[11]

- Apart from anti-Desmoglein 1 and anti-Desmoglein 3 antibodies, patients also develop antibodies against other Desmosomal proteins such as desmocollins and plakins and non-Desmosomal proteins such as cell-membrane receptors such as nicotinic acetylcholine receptor, pemphaxin, thyroperoxidase, and other annexins
- It was found by Volker et al. that desmocollin 3 is expressed in the basal, spinous, and lower granular layers of the epithelium.
- Moreover, further, blocking of its function will give rise to the developmentof intraepidermal blisters.
- Non-desmosomalautoantigens such a pemphaxin also contributed to pemphigus vulgaris.

All these data suggest that pemphigus is a complex disease which is started by at the least by three classes of autoantibodies which are directed against desmosomal, mitochondrial, and other keratinocyte autoantigens. Multiple hits hypothesis puts forward a mechanism that explains acantholysis in the disease. Acantholysis (Auspitz, 1881) means loss of coherence among epidermal cells due to the breakdown of intercellularties – chiefly made of glycoproteins desmosomes and desmocollins, in conjunction with cytoplasmic plakoglobin and plakophilin[2].

Clinical manifestations of juvenile pemphigus vulgaris are similar to those in adults.

- The classical lesions are thin-walled bullae arising on otherwise normal skin/mucosa[3].
- The bulla rapidly breaks but continues to extend peripherally eventually leaving large areas denuded of skin.
- Epithelial blistering can be seen on the cutaneous and/or mucosal surfaces including mucosa of the mouth, nose, conjunctiva, genitals, oesophagus, pharynx, and larynx[1].

The hallmark of pemphigus is positive "Nikolsky's sign" – the ability to induce peripheral extension of a blister and/or removal of epidermis as a consequence of applying tangential pressure with a finger or thumb to the affected skin, perilesional skin, or normal skin in patients affected or suspected with pemphigus.[3]

Another sign the "Asboe-Hansen sign", also known as the bulla spread sign, was originally described in 1960 as a diagnostic sign for pemphigus vulgaris[8].A positive AsboeHansen sign demonstrates the ability to enlarge a bulla in the lateral direction by applying perpendicular mechanical pressure to the roof of an intact bulla[8]. The bulla is extended to adjacent non blistered

skin[8].A positive sign demonstrates decreased adhesion between keratinocytes or between the basal epidermal cells and the dermal connective tissue[8]. In addition to pemphigus vulgaris, the Asboe-Hansen sign may be positive in TEN and Sjogren's syndrome, as well as other diseases affecting the dermoepidermal junction including pemphigus foliaceus, pemphigus vegetans, and bullous pemphigoid[8].

The skin becomes affected several weeks or months after the mucosal lesions appear, with the appearance of flaccid blisters filled with clear fluid[5]. These fragile blisters are easily broken, which leaves behind erosions surrounded by epidermal rings[6].

Oral lesions

80% to 90% of patients with PV develop oral lesions sometime during the course of the disease, and in 60% of cases, the oral lesions are the first sign[3].The oral lesions may begin as the classic bulla on a non-inflamed base; more frequently, the clinician sees shallow irregular ulcers because the bullae rapidly breaks[3].A thin layer of epithelium peels away in an irregular pattern, leaving denuded base[3] .The edges of the lesion continue to extend peripherally over a period of weeks until they involve large portions of the oral mucosa.Most commonly, the lesions start on the buccal mucosa, often in areas of trauma along the occlusal plane. The palate and gingiva are other common sites of involvement.

The incidence of juvenile pemphigus is extremely low, so the diagnosis is often delayed due to rarity of pemphigus in this age group and confusion with other entities[6]. So, a high index of suspicion is required in order to make an early diagnosis[5]. In children and adolescents, PV should be differentiated from erythema multiforme, acute herpetic gingivostomatitis, impetigo, linear IgA disease, epidermolysis bullosa, cicatricial pemphigoid, bullous pemphigus, and paraneoplastic pemphigus.

Histopathological and immunofluorescence examinations are very important in the diagnosis of pemphigus[6]. Acantholysis and intraepidermal blister formation are characteristic findings on histopathological examination[6]. Direct immunofluorescence shows the deposition of IgG around keratinocytes in a "chicken wire" or "crazy paving" pattern[6]. The detection of circulating anti-epidermal antibodies in the serum of patients with PV by indirect immunofluorescence further supports the diagnosis.

The most effective treatment is based on immune suppressors, mainly corticosteroids that suppress the pathologic immune reaction of the disease as well as the clinical manifestations of the inflammation[7]

- Since pemphigus is rare in the juvenile population, evidence-based treatment guidelines have not been reported yet[6]. Systemic corticosteroids are the treatment of choice (prednisolone 1–2 mg/kg/day) to control the disease during the acute phase[6]. In the juvenile age group, the dose should be adjusted according to age, body weight, the severity of the condition, and the side effects of the drug[6]. When the disease begins to go into remission, the dose can be tapered slowly[6]. The continuation of treatment for a long time is not preferred due to long-term side effects of systemic steroids like ulceration, hyperglycaemia, infection, cardiovascular events, adrenal suppression and fractures [6].To overcome these adverse effects , steroids sparing agents are used .The commonly used steroid sparing agents are azathioprine(1 and 3 mg/kg/d), Mycophenolate mofetil(2g/d) , Methotrexate (10–20 mg/wk.), Rituximab an anti-CD20 monoclonal antibody (1,000 mg IV every 2 weeks or 375 mg/m2 every week.) and Plasmapheresis[9].

The duration of therapies is shorter in juvenile PV patients than in adults for controlling disease[6]. The mortality rate in children (2.9%) is lesser than in adults (10–15%) due to the reduced immunosuppression[5].

IV. CONCLUSION

For accurate diagnosis of pemphigus in juvenile patients high index of suspicion is necessary because the diagnosis can be delayed due to the rarity of pemphigus among this age group. The prognosis seems to be better in juvenile patients when compared with adult's .Children and adults are given similar treatment plans but it should be taken into mind that children during periods of growth and development are extremely vulnerable to the side effects of systemic corticosteroid treatment.

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