Reminder of important clinical lesson

Pemphigus vulgaris – a report of three cases

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Pemphigus vulgaris (PV) is a potentially life-threatening illness that manifests in the mouth and on skin. In a majority of patients it affects the oral mucosa and is sometimes difficult to diagnose when only mucosal involvement is present. In an attempt to highlight the proper treatment plan of this potentially fatal disorder, the authors document a report of three cases. These patients were prescribed conventional steroids which brought about partial relief but early recurrence with discontinuation of the drug. Subsequent management of these patients with azathioprine along with corticosteroids improved the outcome of the disease with longer remission periods. In this case series, the steroid sparing effect of azathioprine was achieved successfully and hence needs to be considered as a primary drug in management of PV.

BACKGROUND

Pemphigus is a chronic autoimmune mucocutaneous disease, with blister formation. The annual incidence of pemphigus reported is 1 to 5 per million populations per year.¹ The Indian literature on pemphigus has history of over five decades and shows that pemphigus is common in Indians and pemphigus vulgaris (PV) is the commonest type encountered. However, there is no systematic study on its incidence and prevalence.^{2,3} The reported incidence and prevalence of pemphigus in the Indian subcontinent varies from author to author. Wohl and Brenner⁴ reported

a high incidence of pemphigus foliaceus in India while Kanwar *et al*² documented that PV was the commonest variant in Indians. He also stated that a significant number of patients of Indian origin belonged to younger age group (<40 years) as compared with the other parts of the world (40–60 years).² High incidence of pemphigus has been recorded in lower socioeconomic strata of north Indian population whereas a study in Thrissur district of Kerala, India, suggests a prevalence of 4.4 cases per million.³

CASE PRESENTATION

Case 1-A 51-year-old lady reported with the chief complaint of ulcerations in the mouth and over the body since last 1 month. History revealed that she was suffering from this problem since 2 years and was on corticosteroids that provided temporary relief. There was a relapse of short duration and once medication was stopped there was recurrence. She experienced burning in the mouth, which was continuous and aggravated on eating. She presented with eruptions on the skin (neck, back, shoulder

Figure 1 Ulcers on neck. **Figure 2** Ulcerations on back.

and chest) (figures 1 and 2) and oral cavity which later burst, leaving raw areas. Intraoral examination showed ulcerations on buccal mucosae, lower lip and ventral surface of tongue. There was diffuse white coating on dorsal surface of tongue (figure 3). An intact bulla was present on dorsal surface of right leg (figure 4). Bilateral submandibular lymph nodes were enlarged, soft, mobile and tender.

Case 2-A 48-year-old man reported with ulcers in mouth and throat since 4 months. These oral ulcers were preceded by blister formation. Intraoral examination showed diffuse

Figure 3 Ulcers on lip mucosa.

Figure 4 An intact bulla on dorsal surface of right leg.

ulcerations on labial mucosa with surrounding erythematous area. Lip, palate, buccal mucosa and tongue showed erosions with pseudomembrane formation (figures 5–8). Bilateral submandibular lymph nodes were palpable, mobile and non-tender.

Case 3-A 23-year-old boy reported with difficulty in eating and opening the mouth due to multiple painful ulcers. He first noticed blisters on the lower lip which later burst to form erosions (figure 9). He presented with erosions on body (figure 10) and multiple ulcers on palate and buccal mucosa with erythematous area (figure 11).

The clinical presentation and positive Nikolsky's sign in all cases led to a provisional diagnosis of PV.

INVESTIGATIONS

Oesophageal ulcerations were ruled out by endoscopy. Dual-emission x-ray absorptiometry (DEXA) scan, in the female patient who was on long-term corticosteroids, revealed osteopenia. Light microscopic examination showed spongiotic epithelium with acantholysis of the spinous cell layer resulting in intraepithelial split containing few rounded 'Tzanck cells' characterised by loss of intercellular bridges. Connective tissue showed moderate chronic inflammatory cell infiltrate along with blood vessels and extravasated red blood cells (figure 12). Direct immunofluorescence showed intercellular deposits of IgG and C3 confirming a diagnosis of PV (figure 13).

Figure 5 Ulcers on lower lip mucosa.

Figure 6 Erosions of the palate.

DIFFERENTIAL DIAGNOSIS

Case 1-benign mucous membrane pemphigoid, paraneoplastic pemphigus.

Case 2-erythema multiforme, benign mucous membrane pemphigoid.

Case 3-erythema multiforme, benign mucous membrane pemphigoid, bullous lichen planus.

TREATMENT

Treatment plan for all three patients comprised of prednisolone (80 mg) and azathioprine (50 mg twice a day).

In case 1, prednisolone was tapered to 60 mg after 2 weeks and eventually stopped after 6 weeks while azathioprine was continued for another 2 weeks.

Figure 7 Extensive erosions of buccal mucosa.

Figure 8 Collapsed bullae with ulcers on ventrum of the tongue.

Figure 9 Erosions of lip.

In case 2 and 3, prednisolone was administered for 3 weeks after which it was tapered. Azathioprine was continued in them for another 2 weeks. Oral ulcerations were treated symptomatically with topical benzocaine and chlorhexidine ointment.

OUTCOME AND FOLLOW-UP

Follow-up showed marked healing of skin lesions after 20 days in case 2 and 3 (figure 14) while case 1 showed signs of healing after 4 weeks. After 6 weeks skin lesions had regressed, although oral lesions regressed slowly. Reduction in the oral ulcerations and complete healing of skin lesions was observed at the end of 2 months and the patients continued to be under regular follow-up.

All the patients underwent oral prophylaxis and periodontal therapy after the regression of the oral lesions.

DISCUSSION

PV is a mucocutaneous autoimmune bullous disease. There are several types of pemphigus such as vulgaris, foliaceus, vegetans and paraneoplastic, 80 per cent of all patients with pemphigus have vulgaris type. It affects both sexes equally and is more common among Ashkenazie Jews and persons of Mediterranean origin, than among members of any other racial or ethnic group.¹⁻⁵ PV most commonly develops during the fifth to seventh decades of life even though rare pediatric cases have been reported. Before systemic steroids were available, the disease often was fatal. Although it accounts for only 2 per cent of intraoral ulcerative lesions, the serious nature of the disease validates

Figure 10 Flaccid bullae and ulcers on the shin.

Figure 11 Erosions of the palate.

its consideration in conditions with multiple chronic oral ulcerations or desquamative gingivitis.⁵

PV has got two phenotypes: one mucosal dominant and the other mucocutaneous dominant, with possible shifting of one form to other over time.¹ The oral mucosa is the first site of involvement in the majority of cases of PV and may remain confined to the mucosal surfaces or extend to involve the skin with an average lag period of 4 months. A minority of cases will present with cutaneous erosions but oral erosions occur in almost all cases.⁶

The aetiology of PV is unknown, although the disease has attracted considerable interest. The pemphigus group of disease is characterised by the production of autoantibodies against intercellular substances and is thus classified as autoimmune disease.⁷ The major PV autoantigen is desmoglein 3 (Dsg3), a desmosomal cadherin. Anti-Dsg3 autoantibodies bind to the extracellular domain of the NH2 region of Dsg3, which is proposed to have a direct effect on the adhesive function of Dsg3.⁸

The diagnosis of PV should include a skin or mucosal biopsy for histology and direct immunofluorescence. Suprabasal acantholysis and blister formation is highly suggestive of PV but the diagnosis should be confirmed by the characteristic deposition of IgG and often C3 antibodies that bind to the cell surfaces of perilesional skin or mucosa.^{2 6} Indirect immunofluorescence is less sensitive than direct immunofluorescence but may be helpful if a biopsy is difficult. ELISA are now available for direct measurement of Dsg1 and Dsg3 antibodies in serum.⁶ In

Figure 12 Photomicrograph of pemphigus vulgaris.

Figure 13 Direct immunofluorescence slide deposition of immunoreactions.

Figure 14 Regressing lesions on palate.

the present cases, histopathological examination along with direct immunofluorescence was done for diagnosis. They revealed suprabasilar split and deposit of IgG and C3 respectively, suggestive of PV.

The investigations like full blood and differential counts, urea and electrolytes, liver function tests, glucose, antinuclear antibody (differential of pemphigus erythematosus), thiopurine methyltransferase levels, chest x-ray, urinalysis and blood pressure are suggested before commencing the treatment. A bone density scan early in the course of treatment may be recommended to find osteoporosis.⁶ In our cases, complete haemogram, liver function tests and blood glucose were within normal limits. DEXA scan in the female patient revealed osteopenia as she was on long-term steroid therapy.

The predominant therapy for pemphigus continues to be corticosteroids. Before the development of corticosteroid therapy in the 1950s, the death rate for patients with pemphigus was greater than 90%.⁹ Ever since, the high mortality has reduced to less than 10%. Even today the corticosteroids remain the mainstay treatment of pemphigus. However, the relatively high doses and long duration of treatment lead to a variety of adverse effects. Today, corticosteroids are usually given in combination with adjuvant immunosuppressant therapy to reduce the cumulative corticosteroid dose and adverse effects. Among the different immunosuppressants, azathioprine and cyclophosphamide have been widely used to control pemphigus.⁸ Pemphigus has also been successfully treated with a combination therapy using mycophenolate mofetil.^{10–11} Our patients were treated with azathioprine and regularly followed up to 1 year without a report of any new lesions.

Robinson *et al* emphasised the value of early diagnosis and early treatment on prognosis and the course of PV.¹² Dental professionals must be sufficiently familiar with the clinical manifestations of PV to ensure early diagnosis and treatment, since this in turn determines the prognosis and course of the disease.¹³ PV is generally managed with topical, oral and intralesional corticosteroids. The current therapeutic regimen of PV is largely based on systemic immunosuppressants such as systemic corticosteroids along with other adjuvants like azathioprine, cyclophosphamide, mycophenolate mofetil and intravenous immunoglobulins.¹⁴ Maintaining or improving the oral hygiene and minimising irritation to the lesions are an integral part of supportive management of chronic autoimmune disorders.¹

Learning points

- ▶ The oral physician may be the first to encounter this disease, hence early detection and treatment can aid in better prognosis.
- ▶ Early introduction of steroid sparing agents like azathioprine can ensure longer remission periods and reduce steroid related complications.
- ▶ Incidence and prevalence of this disease in Indian subcontinent needs to be evaluated in the context of its varied picture from other parts of the world.
- ▶ Dermatologist's opinion should be sought in case of dermal lesions as mucocutaneous lesions can be managed as a team.

Competing interests None.

Patient consent Obtained.

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