Pyostomatitis vegetans: A review of the literature

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Abstract
Pyostomatitis vegetans (PV) is a rare condition characterized by pustules that affect the oral mucosa. It is a highly specific marker for inflammatory bowel disease and its correct recognition may lead to the diagnosis of ulcerative colitis or Crohn’s disease. Thus, a presumptive diagnosis of PV should suggest a complete gastrointestinal investigation.

PV pathogenesis is as yet unknown, although immunological and microbial factors have been suggested as possible aetiological factors.

Pyostomatitis vegetans is characterized by erythematous, thickened oral mucosa with multiple pustules and superficial erosions. A peripheral eosinophilia has been observed in most cases reported.

Histology shows epithelial acanthosis and superficial ulceration with intraepithelial and/or subepithelial abscesses containing large numbers of eosinophils. The underlying connective tissue exhibits neutrophil and eosinophil infiltration, with miliary abscesses in some cases. Treatment of PV focuses on control of the underlying disease.

Key words: Pyostomatitis vegetans, neutrophilic dermatoses, ulcerative colitis.

Introduction
Oral ulcers and erosions can be the final manifestation, often clinically undistinguishable, of a wide spectrum of conditions, including gastrointestinal diseases (1). Indeed, patients with signs or symptoms of oral ulcers are frequently referred to gastroenterology clinics, although the ulcers does not necessarily reflect gastrointestinal disease (2,3).

For instance, recurrent aphthous stomatitis (RAS) may be the common manifestation of a broad group of disorders of different etiology, rather than a single entity, and the nature, site, duration and frequency of oral ulcers can be determined by the underlying systemic condition.

In addition to recurrent oral ulcerations, patients affected by Crohn’s disease and ulcerative colitis may present a number of concomitant conditions affecting the oral mucosa, including pyostomatitis vegetans (PV) (4). The aim for this work was to deal with PV in order to provide guides for correct diagnosis.

PV is an uncommon benign chronic mucocutaneous disease of unknown etiology characterized by miliary pustules that affect mucosal membranes (oral, vaginal, nasal and rarely periocular membranes). These pustules develop across the mucosa and their rupture lead to widespread ulceration (5).

Most investigators today believe that PV is an unusual...
Pyostomatitis vegetans is considered the oral equivalent of pyoderma vegetans on cutis and is, always, occurs in association with an inflammatory bowel disease (IBD) (6). PV, together with aphthous stomatitis, pyoderma gangrenosum, necrotizing vasculitis, erythema nodosum/panniculitis, epidermolysis bullosa acquisita, represents an IBD-associated disease. Of all these conditions, PV represents a specific marker of ulcerative colitis even if the nature of this association is not clear (6,9).

The appearance and distribution of lesions vary from patient to patient and may change as the disease progresses (12).

The literature largely substantiates the observation that bowel disease invariably can precede oral involvement of several years (13).

Although IBD may precede the onset of oral or cutaneous lesions by months or years, sometimes the symptoms may be minimal and not sufficient to make an early diagnosis. In these cases the identification of PV could represent a reason to encourage diagnostic investigations intended to reveal subclinical intestinal diseases (11).

Oral lesions are distinct and appear as multiple white or yellow friable pustules, with an erythematous and thickened mucosa that often ruptures, resulting in ulceration and erosions. The oral mucosa may have a granular morphology but vegetating pustules undergo degeneration, ulceration and suppuration, leading to a folded, fissured “snail track” appearance (9).

Oral lesions may affect all areas of oral mucosa, although the most commonly affected sites are the labial attached gingiva, soft and hard palate, buccal and labial mucosa, vestibule and tonsillar regions. The floor of the mouth and tongue are usually spared; the filiform and fungiform lingual papillae may be atrophic. Vegetations in areas of erythema can be seen especially on the gingiva and palate (6,14).

The buccal mucosa may have a granular appearance and become thickened, erythematous and may exhibit vegetations or cobblestoning while the gingival and alveolar mucosa often exhibit tiny nodular growths. There may be inflammation and ulceration of the epiglottis and larynx (10).

Oral pain or discomfort is variable and is not related to clinical phenomenology as it may not be prominent even when there is extensive oral involvement.

Patients may occasionally be febrile and manifest enlarged, tender submandibular lymph nodes (6).

Peripheral eosinophilia has been reported in 90% of the cases. Thornhill et al suggested that eosinophilia may be a feature of the condition and therefore a valuable aid to diagnosis (15).

McCarthy has suggested the oral lesions to be the counterpart of pyoderma vegetans (PD) (8).

Skin lesions of PD can appear shortly after or prior to the occurrence of oral PV lesions. Cutaneous lesions are asymmetrical, crusted, erythematous papulopustules that extend peripherally and coalesce to form large vegetating plaques. These lesions commonly manifest in the axillary folds, groin and scalp areas, and to a lesser extent involve the face, trunk and distal extremities. Liver dysfunction has been reported to be associated with PV (sclerosing cholangitis, chronic hepatitis, and pericholangitis) (16).

Pathogenesis

The pathogenesis of PV is poorly understood. As the disorder is included among the chronic pyoderma (skin infections caused by external pyogenic agents), its etiology would be expected to be of infection (microbial) origin. However, all searches have persistently yielded negative results for pathogenic bacteria, viruses, and fungi. Cultures have consistently shown normal oral flora (12).

Several authors hypothesized that PV results from an aberrant immune response to yet unidentified factors. Depositions of proteins in skin vessels in PG lesions have suggested an Arthus-like reaction (17,18).

Given that inflammatory bowel disease is the most common underlying disorder, other authors suppose the cross-reacting antigens in the bowel and skin to be responsible for secondary mucosal-cutaneous manifestation (16,19).
Histological Features
Microscopic examination reveals a intraepithelial and/or subepithelial microabscesses comprised of eosinophils and neutrophils. Pseudoepitheliomatous hyperplasia with intraepithelial clefting, acanthosis, hyperkeratosis, and areas of intraepithelial dissociation evocative for acanthisis can be highlighted. This may be the result of the accumulation of numerous eosinophils within the spinous layer and responsible of forming intraepithelial abscess (11,20). Direct immunofluorescence in PV is usually negative for deposits of IgA, IgG, and C3, and this helps to distinguish it from pemphigus vulgaris. Atypical immunofluorescence may be seen at the basement membrane in some cases, but may represent a secondary response to epithelial damage while not being responsible of lesions (21,22).

The papillary lamina propria displays an acute and chronic inflammatory cell infiltrate with containing eosinophils, neutrophils, lymphocytes, and plasma cells which aggregate to form small abscesses leading to necrosis and ulceration. With time, the older lesions show less eosinophilia, and the pustules evolve into hyperplastic tissue with an increase in lymphocytes and plasma cells. Perivascularg inflammation may also be present (14,23).

Diagnosis
The diagnosis of PV is founded on clinical features, association with inflammatory bowel disease, peripheral eosinophilia, negative culture of pus from lesions and histological features (5).

The differential diagnosis of PV includes blistering dermatoses that affect both the skin and the oral cavity, such as pemphigus vulgaris, bullous pemphigoid, acquired epidermolysis bullosa, bullous drug eruption, herpetic infections, erythema multiforme, Behçet’s disease, and Sweet’s syndrome. The presence of skin and oral pustules, the typical histology and negative immunofluorescence, the peripheral eosinophilia, and the association with IBD narrow the differential diagnosis to PV (24,25).

A differential diagnosis should be established with Neumann and Hallopeau types of pemphigus vegetans, since both variants of pemphigus vulgaris manifest in over 50% of cases in the oral cavity with the lesions clinically similar to pyostomaticis vegetans.

In the Neumann type, there are intraepidermal vesicles with suprabasilar acantholysis. No eosinophilic microabscesses are present. In the Hallopeau type, eosinophilic spongiosis and microabscesses are present. In the later vegetative plaques, there is prominent epidermal hyperplasia with hyperkeratosis, papillomatosis, and occasional acantholysis.

The main difference is that pyostomatitis vegetans presents no blisters whereas highlights characteristic pustular lesions, and is most often associated to chronic intestinal inflammatory disease (26,27).

Therapy and Management
Management of PV is often based on treating the underlying gastrointestinal disease. Surgical treatment in severe cases IBD involves total colectomy and has resulted in permanent remission of symptoms (1). The oral lesions can be managed with local therapies utilizing antiseptic mouthwashes such as chlorhexidine, and topical corticosteroids such as triamcinolone acetonide paste or betamethasone mouthwash. However, topical steroid therapy has limited success. Strategic treatment initially consists of systemic steroid therapy aimed at resolving and controlling the lesions (27,28). This therapy can be associated with azathioprine and sulfamethoxypyridazine that can be used for their steroid sparing effect. Dapsone has been effectively employed as a second line agent to control a relapse when steroid therapy has been halted or tapered down. Unfortunately, dapsone’s utility is limited by its side effects, which include hemolytic anemia, hepatitis, agranulocytosis, and the possibility of a drug mediated allergic reaction (29). A recent study declare that three injections of infliximab and successive maintenance therapy with methotrexate can cause a rapid and complete regression of both the pyostomatitis vegetans and the Crohn’s disease (30).

Discussion
Pyostomatitis vegetans has long been a matter of great confusion. Several authors considered this disease as a mucosal variant of pyodermitis vegetans and therefore both diseases would represent a single identity. This claim is corroborated by the finding of identical histological features and association with IBD for both conditions (27) Other authors identify the pyodermitis vegetans as a variant of pemphigus vulgaris: pemphigus vegetans of Hallopeau. In support of this thesis there is the finding of clear suprabasal acantholysis, positivity both of direct immunofluorescence that reveals deposits of IgG and C3 in the intercellular spaces of the epidermis and of indirect immunofluorescence that reveals circulating antiepithelial IgG antibodies (26,27). Thus, pyostomatitis and pyodermitis would be distinct conditions. We prefer to distinguish between two different entities with identical clinical manifestations but with different pathogenesis: pyodermitis vegetans as cutaneous variant of pyostomatitis vegetans and pyodermitis vegetans or pemphigus vegetans of Hallopeau (25).

Consistently today’s the literature is inclined to believe that pyodermitis-pyostomatitis vegetans is an identical entity belonging to the spectrum of chronic pustular dermatoses and that it must be differentiated from pemphigus vegetans of Hallopeau (first described as “pyodermit vegetans”) even if the cutaneous lesions
of both disease do not show significant clinical differences (11,30).

In fact, the association of pyodermitis vegetans and ulcerative colitis has rarely been reported in literature, (27,31) unlike pyodermitis-pyostomatitidis vegetans, which is strongly associated with inflammatory bowel diseases (32).

Oral lesions of PV can be seen without skin lesions but it is rare for them to be present in the absence of gastrointestinal disturbances (33).

The pathologist must distinguish lesions of pemphigus vegetans both Neumann and Hallopeau types from those of pyodermitis-pyostomatitidis vegetans. In presence of the diagnosis of pyostomatitidis vegetans, patients must be programmed for a follow up with a complete gastrointestinal workup. Indeed, gastrointestinal disorders sometimes present with very subtle symptoms and may remain undetected unless a thorough gastrointestinal examination is performed (33,34).

Although IBD may precede the onset of oral or cutaneous lesions by months or years, the symptoms may be minimal and difficult to diagnose. Hence, it is important to establish the correct diagnosis of PV and refer all patients to a bowel investigation.

References