

## CLINICAL REPORT

# Pyodermatitis–Pyostomatitis Vegetans: A Clinical Course of Two Decades with Response to Cyclosporine and Low-dose Prednisolone

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**Pyodermatitis–pyostomatitis vegetans is a rare, polymorphous inflammatory disorder of the skin and oral mucosa first described by Hallopeau in 1898. On the skin papules, pustules and reddish brown annular vegetating plaques develop, most frequently in the intertriginous areas. In the mouth, yellowish flat ulcerations arise, typically in the shape of “snail tracks”. The association with inflammatory bowel disease is very common. An unusual case with a chronic relapsing course of 2 decades is presented. Gastrointestinal inflammation was absent. Prednisolone in high and medium doses suppressed most lesions. Various attempts with other drugs (dapsone, isotretinoin, azathioprine) to reduce the corticosteroid dose failed. This is the first report of the successful treatment of pyodermatitis–pyostomatitis vegetans with cyclosporin A, which proved to be highly effective in this regard. The unknown aetiopathology of pyodermatitis–pyostomatitis vegetans is discussed. Key words: Hallopeau; pathogenesis; inflammatory bowel disease.**

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After a century of scientific dispute, at present pyodermatitis–pyostomatitis vegetans (PPV) is generally considered to be a distinct clinical entity in the spectrum of chronic pustular dermatoses. It is an uncommon inflammatory disease of the skin and/or mucosal membranes with characteristic vegetating lesions. The infiltrate is polymorphic and eosinophils are often present. However, diagnosis is largely based on exclusion criteria. The aetiology and pathogenesis of PPV are unknown. An association of PPV with inflammatory bowel disease is well established.

## CASE REPORT

In October 1979, a 32-year-old Caucasian clerk was referred to our department with a 1-week history of pustular orogenital lesions (Fig. 1) and a papulopustular skin eruption affecting his back, intertriginous areas, feet and heels. Systemic therapy with corticosteroids, antibiotics and immunoglobulins caused remarkable relief. One year later, in September 1980, the patient was admitted again presenting with rapidly progressive, erythematous, sharply demarcated, discoid to annular, pustule-fringed plaques, located predominantly on his extremities, axillae and groins (Fig. 2). Antecedent drug intake was denied, and no other trigger factor was detectable. The patient was otherwise healthy, afebrile and on no medications. His family history was non-contributory. Treatment was similar to that on the previous stay. After 4 weeks the patient was discharged with a grossly healed integument. Since 1991 mild exacerbations with hyperkeratotic plaques



Fig. 1. Confluent pustules on the palate (early stage).



Fig. 2. Late-stage vegetating annular lesions on the legs.

occurred on the inguinal skin and could be controlled by local application of triamcinolone ointment.

In April 1998 the patient developed a generalized recurrence of erythematous papulopustules involving the scalp, inguinal areas, perianal region and elbows. The enanthema was characterized by friable tiny yellow pustules affecting chiefly the buccal and labial mucosa, soft and hard palate, as well as the tip of the tongue. The patient was hospitalized with the working diagnosis of PPV. Systemic administration of corticosteroids, starting with 80 mg methylprednisolone per day and slowly titrated to a maintenance dosage of 8 mg, once more succeeded in complete remission. The patient was discharged in May 1998. After an acute re-exacerbation in the groins in August 1998 a trial with dapsone (100 mg/day) was undertaken but failed because of a new bout in October 1998. In the groins and axillae large indurated plaques were present with draining sinuses. There were no oral lesions on this occasion. The patient was readmitted and dapsone was discontinued. In addition to oral prednisolone (20 mg/day) the patient received antibiotic infusions with ceftriaxone and ampicillin/sulbactam

because of bacterially colonized skin lesions. A treatment with isotretinoin 50 mg/day was started while prednisolone was tapered off. After 3 weeks the draining plaques in the intertriginous areas dried up. The patient was discharged in November 1998 with marked regression of his skin lesions.

Five months later isotretinoin was discontinued because of a remarkable elevation in the liver enzymes. Within the next month the predilection sites at his groins and buttocks displayed new painful lesions. Oral prednisolone (20–30 mg/day) was required again. In September 1999 a new combination therapy with azathioprine (50–100 mg/day) was initiated to lower the corticosteroid maintenance dose. Within 7 weeks of drug intake the vegetations had not improved considerably. The patient had to stop taking azathioprine because of transient diarrhoea. He continued on a monovalent medication of 20–30 mg prednisolone on alternate days. Several attempts to taper the dose below 20 mg/day led to relapse. In December 1999 the patient agreed to a combination with cyclosporin A (4.5 mg/kg per day) in an oral formulation. All skin lesions healed within 3 months. The dose of oral prednisolone was lowered to 7.5 mg/day and cyclosporin A was reduced to 2.5 mg/kg per day. He continues to receive these doses.

### Investigations

Haematological investigations revealed leukocytosis (median white blood cell count  $13 \times 10^9$  cells/l) and a differential count with lymphopenia (20%). Further routine biochemical investigations (haematology, serum chemistry) were normal on several occasions. A urinalysis failed to indicate increased excretion of halogens. The three main classes of immunoglobulins (IgG, IgM, IgA) were slightly raised. Auto-antibodies, antinuclear antibodies and antineutrophil cytoplasmic antibodies were within normal limits. Infection markers [TPHA, Tine test, hepatitis screen, anti-herpes simplex virus (HSV)-1/2, anti-human immunodeficiency virus (HIV)-1/2, anti-cytomegalovirus (CMV)] were negative. The relative distribution of all lymphocyte subpopulations revealed no evident aberrations. Human leukocyte antigen (HLA)-B27 and -B5 were negative.

Various lesional skin swabs for microbiology produced bacterial growth for *Staphylococcus aureus*, *Klebsiella*, *Bacteroides coli*,  $\alpha$ -haemolytic *Streptococci* and *Enterococcus* species. Controls were negative after treatment.

X-ray photographs of the chest, paranasal sinus and teeth were always within normal limits. Screening for gastrointestinal involvement was negative using abdominal ultrasonography and laboratory (faecal occult blood tests, stool cultures), endoscopic (colonoscopy) or radiological (Sellink) techniques as well as magnetic resonance imaging scans.

The main histopathological findings of repeated skin biopsies comprised a hyperparakeratotic and acanthotic epidermis with intraepidermal abscess formation. A dense perivascular cell infiltrate was composed of histiocytes, a few plasma cells and eosinophils. Stains for bacteria and fungi were negative. Repeated direct and indirect immunofluorescence studies were consistently negative for intercellular or basement membrane zone staining. In addition, immunoblotting did not show any characteristic bands.

### DISCUSSION

The diagnosis of a chronic vegetating pustular dermatosis must be considered as a general term which needs further differentiation. Hallopeau (1) was the first to enlarge the old terminology, coining the term "pyodermite vegetante". PPV may occur in any age group and shows a gender predilection for males. The oral cavity is not always affected in this disease, although it can be the sole manifestation (2). Pyostomatitis may precede, coincide with or follow pyodermatitis. The skin lesions in PPV, seen in approximately 40 patients to date, have repeatedly been reviewed, preferentially in tabular form (3–9). The typical manifestation sites in PPV are the oral mucosa and the intertriginous areas of the skin. As in the present case, PPV may exhibit extremely variable clinical manifestations within the same patient. Skin lesions characteristically start as

erythematous papulopustules and extend to annular vegetating plaques. The typical "snail track" appearance of oral lesions refers to eroded lesions that coalesce. The histological features are summarized in Table I. The association with inflammatory bowel disease (IBD) occurs in about 70% of cases (10). A link between PPV and liver dysfunction or primary sclerosing cholangitis has also been supposed (4, 11). Immunofluorescent investigations are obligatory to differentiate PPV from pemphigus vegetans (12, 13). In the present case neither immunofluorescent investigations nor immunoblotting (14) were positive, which separates it clearly from the bullous autoimmune diseases. Important differential diagnoses were carefully excluded (Table II).

The aetiopathogenesis of PPV is unknown. The observation that lesions tend to develop in the intertriginous areas where moisture and friction promote microbial growth suggests an idiosyncratic reaction to microbial agents. Potentially toxin-producing bacteria were cultured from the vegetating lesions in this patient. It seems incongruous, however, that bacterial and fungal cultures can be negative (5, 10). Consequently, the idea of non-causative infections superimposed on the underlying disease has been favoured (15). Nevertheless, it is possible that microbes are relevant to disease progression in patients with PPV. Hidden immune dysfunction might play a synergistic role (16). Infectious agents and immunological mechanisms have also been discussed as putative causes of IBD (17). PPV serves the function as a marker for associated IBD since the gastrointestinal disease can be asymptomatic for a certain period (5, 9). Pathogenetically, there are still knowledge gaps related to how exactly components of the immune system regulate functions of spatially separated tissues (18). Some authors envisage a model in which reactive cutaneous lesions in patients with IBD may be immunologically mediated via cross-antigenicity between the skin and the gut (19) or via epitope spreading (20). It is noteworthy that few patients with pyostomatitis vegetans and ulcerative colitis showed complete remission of the oral lesions immediately after a total colec-

Table I. *Histological features of pyodermatitis-pyostomatitis lesions*

Microabscesses with neutrophils and eosinophils within the epidermis and dermal papillae/upper dermis
Suprabasilar clefts with no or little cell dissociation/acantholysis
Acanthosis/epidermal hyperplasia
Focal ulceration
Papillomatosis
Perivascular and diffuse inflammation with lymphocytes, neutrophils and eosinophils
No bullae, vasculitis or granulomas

Table II. *Differential diagnoses of pyodermatitis-pyostomatitis vegetans*

Pemphigus vegetans
Acne conglobata
Atypical pustular granulomatous drug reaction
Behcet's disease
Syphilis (late stages)
Tuberculosis cutis verrucosa
Deep fungal infections (e.g. blastomycosis)
Bromoderma/iododerma

tomy (9, 21). The question arises as to whether in patients without IBD, including the present case, enteric bacteria and/or hidden abnormalities in the immunologically competent colonic mucosa could have functioned as a triggering factor for subsequent inflammatory reactions (or reactivation of memory cells) in the skin or oral mucosa.

PPV is often treated with an empirical multimodal regimen. Topical and systemic therapy with corticosteroids is the approach of choice (5, 6, 9, 10). Dapsone and azathioprine are considered as second-line agents (10). In this patient systemic corticosteroids were repeatedly used to gain control of the condition. Dapsone could not prevent new outbreaks. Under oral isotretinoin healing of the verrucous plaques was accelerated. Isotretinoin has been used for the first time in PPV but may be critical in patients with IBD because of its mucocutaneous toxicity. A good response of PPV to systemic corticosteroids has been confirmed in the present case. However, comedication with cyclosporine was needed to remain below the Cushing threshold. There are no previously reported cases of PPV treated with cyclosporine. Joint application with low-dose oral corticosteroids could be of value in recalcitrant cases.

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