

Received: 15<sup>th</sup> August 2015 Accepted: 17<sup>th</sup> November 2015 Conflicts of Interest: None

Case Report

Source of Support: Nil

## Pyostomatitis Vegetans in Ulcerative Colitis; Management with Topical Tacrolimus and Systemic Azathioprine in a 10-year-old Boy (Case Report and Review of the Literature)

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### How to cite the article:

Knapp N, Albuquerque R, Khan Z, Richards A, Brown RM. Pyostomatitis vegetans in ulcerative colitis; management with topical tacrolimus and systemic azathioprine in a 10-year-old boy (case report and review of the literature). *J Int Oral Health* 2016;8(1):132-136.

### Abstract

Pyostomatitis vegetans (PV) is a rare disorder of the oral mucosa and the most common presents as multiple pustules. It is notoriously difficult to treat. It is consistently associated with inflammatory bowel disease and is consequently considered a highly specific marker. This report presents the case of a 10-year-old boy diagnosed with PV, in whom complete remission of the oral lesions was eventually achieved with topical tacrolimus.

**Key Words:** Azathioprine, pyostomatitis vegetans, tacrolimus, ulcerative colitis

### Introduction

A rare, benign, chronic inflammatory disorder of the oral soft tissues, pyostomatitis vegetans (PV) is characterized by pustular and vegetating mucocutaneous lesions, most commonly affecting the labial gingivae, buccal, and labial mucosa. The lesions consist of multiple miliary pustules on an erythematous and edematous oral mucosa.<sup>1</sup> A diagnosis of PV is considered a highly specific marker for inflammatory bowel disease (IBD), as a high incidence of IBD, most commonly ulcerative colitis,

is associated with PV.<sup>2,3</sup> The increasing number of cases being reported in the literature has helped to clarify features of the condition, but the pathogenesis of PV remains unknown, although immunological and microbial factors have been suggested as possible predisposing etiological factors.<sup>4</sup>

Management of PV has been notoriously difficult with topical steroid therapy alone having limited success.<sup>4</sup> Consequently, the first line treatment often entails administration of systemic corticosteroids to control the underlying disease.<sup>5</sup>

The use of topical tacrolimus to treat mucocutaneous conditions such as lichen planus has been widely reported. The successful use of calcineurin inhibitors in the treatment of PV has also been reported, but the literature is limited.<sup>6</sup> This report reviews the literature of therapies used in the treatment of PV and presents a case of PV in a 10-year-old child who eventually responded well after the addition of topical tacrolimus to his management.

### Case Report

A 10-year-old boy attended the emergency care department at the Birmingham Dental Hospital complaining of a 4 months history of persistent crusting of his lower lip which had not resolved with the use of antibiotics or antifungal medications. These lesions were occasionally itchy but painless. He gave no history of cutaneous, genital, or ocular lesions. At the time of presentation, the patient also reported gastrointestinal symptoms including diarrhea for several weeks, but gave no other relevant medical history and was not taking any medication. He was subsequently referred to gastroenterology and was diagnosed with ulcerative colitis.

On examination, there was no abnormality of exposed skin. He had yellow crusting and multiple fissures on the vermilion borders of the lips, predominantly the lower (Figure 1). Intraorally, multiple small papules were noted on the anterior maxillary and mandibular buccal attached gingivae (Figure 2), in addition to the left buccal mucosa. The tongue, floor of mouth and palate were completely spared.

A full blood count (FBC) revealed a mild eosinophilia of  $0.5 \times 10^9/L$  (normal range 0.04-0.4). Mean corpuscular hemoglobin was slightly low at 25.4 pg (normal range 27.0-33.0) as was the hematocrit at 0.37 L/L (normal range 0.40-0.54). All other blood test results, including FBC, U's and E's and liver function tests were normal.

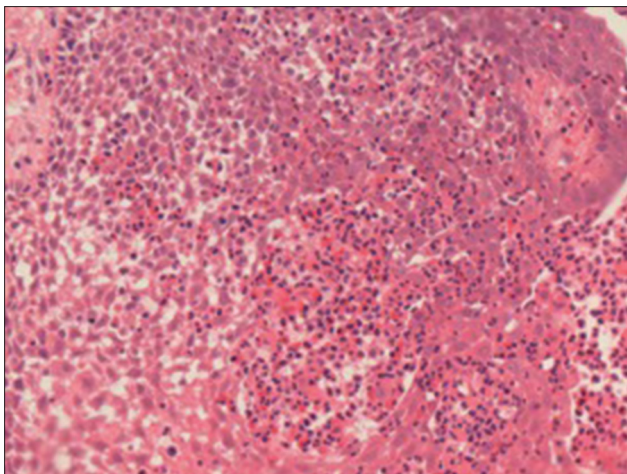
Viral and fungal cultures from swabs of the lower lip were negative but yielded a growth of *Staphylococcus aureus*. A 7 days course of flucloxacillin 200 mg, 4 times daily was subsequently prescribed.



**Figure 1:** Yellow crusting and erosions on the lower lip (pre tacrolimus and azathioprine treatment).



**Figure 2:** Multiple papules on the upper and lower gingivae (pre tacrolimus and azathioprine treatment).



**Figure 3:** Histopathology sample from biopsy on the left buccal mucosa (haematoxylin and eosin stain. Amplification  $\times 400$ ).

Histological examination of a biopsy from the left buccal mucosa showed the epithelium to be hyperplastic with elongated rete ridges extending down into the underlying stroma. There were striking intra-epithelial abscesses involving the mid and basal layers of the epithelium with neutrophil polymorphs being the predominant cell within the abscesses, but eosinophils were also present. An impression of acantholysis was noted and dissociated epithelial cells within the abscesses in addition to evidence of suprabasal clefting were also observed (Figure 3).

The patient underwent a course of intravenous steroid therapy to treat his colitis and on higher doses he noted an improvement in his oral lesions. This improvement, however, was short-lived, and his lesions subsequently returned on steroid weaning. Mild improvements were seen when the patient commenced azathioprine 150 mg once daily to control his ulcerative colitis, however after 4 months of taking this medication, his oral lesions had still not completely resolved, and he remained concerned about the appearance of his lips.

A trial of Fucidin H (fusidic acid and hydrocortisone) cream was initiated but after 2 months of treatment with no improvement, this therapy was stopped. Although his bowel disease was well-controlled on azathioprine, he still



**Figure 4:** Upper and lower lips (post treatment).



**Figure 5:** Upper and lower anterior gingivae (post treatment).



had persistent crusting of the lower lip as well as ulceration of the lower gingivae and widespread gingival inflammation. About 4 months after beginning azathioprine therapy, a trial of tacrolimus 0.1% ointment was initiated, applied once daily to the lips and oral mucosa for 6 weeks, during which the oral lesions resolved completely. The tacrolimus was then discontinued and 4 months later, the patient remained in remission (Figures 4 and 5).

### Discussion

PV is a rare inflammatory disorder consistently associated with IBD, most frequent ulcerative colitis.<sup>4</sup> It may affect any age group although it has been considered to be the most common in young and middle-aged adults.<sup>1</sup> There is a significant male predilection with a male to female ratio of 3:1.<sup>7</sup>

PV commonly presents as multiple friable pustules on an erythematous and edematous oral mucosa. These lesions eventually rupture and leave a base which erodes, coalesces, and undergoes necrosis. The pattern of widespread erosions which remains has been described as "snail track" ulcers.<sup>1</sup> The most common sites to be affected are the labial and buccal mucosa followed by the hard and soft palate, gingivae, and sulci, however, any area of the mouth can be affected. As evident in our patient, the floor of mouth and tongue are usually spared.<sup>8</sup>

Patients may also have skin lesions which can either precede or occur shortly after the appearance of oral PV lesions.<sup>4</sup> Cutaneous lesions commonly affect the axillary folds, groin and scalp areas and consist of crusted erythematous papulopustules that coalesce to form large vegetating plaques.<sup>4</sup>

Peripheral eosinophilia has been reported in 90% of cases. Thornhill *et al.*,<sup>9</sup> has suggested that eosinophilia may be a feature of the condition and, therefore, a valuable aid to diagnosis. There is also a possible link that has been identified between liver dysfunction and PV.<sup>10</sup>

The histopathological features of PV are often characteristic. Lesions generally show hyperkeratosis and acanthosis with intraepithelial and subepithelial microabscesses formed by the aggregation of eosinophils and neutrophils which exist in a dense cellular infiltrate that is present throughout the lamina propria and epithelium.<sup>11</sup> The key distinguishing factor of this disease from oral forms of pemphigus is that the immunofluorescence studies are negative.<sup>12</sup>

The pathogenesis of PV continues to be debated and is poorly understood. Cultures usually show normal oral flora and all searches for pathogenic bacteria, viruses and fungi have persistently yielded negative results.<sup>4</sup> Some theories suggest that an aberrant immune response to as yet unidentified triggers could be a cause. Others hypothesize that as IBS is the common underlying disorder, the mucosal-cutaneous

lesions manifest as a result of antigens in the bowel and skin cross-reacting.<sup>4</sup>

The following total colectomy or resolution of flare-ups of ulcerative colitis, evidence suggests that mucocutaneous lesions of PV often regress.<sup>13,14</sup> Occasionally, however, oral lesions have been known to arise concomitant or before bowel disease develops or the symptoms become apparent.<sup>15</sup> Consequently, the general consensus is that all patients presenting with PV should be tested for bowel disease as the PV appears to be a specific marker for IBD.<sup>13</sup>

Management of PV has proven to be very difficult and no single management protocol currently exists.<sup>15</sup> The mainstay of treatment is in controlling the underlying gastrointestinal disease via diet modification and the administration of systemic agents.<sup>1</sup> Total colectomy in severe cases of IBD has generally resulted in the permanent remission of symptoms of PV.<sup>14</sup> Topical agents applied intra-orally alongside the use of systemic immunosuppressant medication have been successfully used in treating PV, particularly in cases of symptomatic ulcerative colitis.<sup>4</sup> Chaudhry *et al.*,<sup>2</sup> however, reported a successful case of treating PV associated with asymptomatic ulcerative colitis with topical steroids alone,<sup>2</sup> although admittedly few authors have reported successful treatment limited to topical therapies.<sup>16</sup> High doses of systemic steroids in addition to mesalamine, mercaptopurine, azathioprine, infliximab, or adalimumab have therefore generally been considered the treatments of choice so as to control the underlying condition responsible for PV.<sup>14</sup> Based on our literature review, however, no studies have yielded solid scientific evidence of the superior efficacy of one treatment modality over the rest<sup>16</sup> and generally, lesions have been known to recur following tapering or discontinuing treatment.<sup>4,9</sup>

The patient, in this case, had been taking azathioprine for 4 months before he began a course of tacrolimus. A mild improvement was noticed in his oral symptoms prior to using tacrolimus, however, they had not completely resolved. In addition, the child had initially developed a neutropenia of  $0.8 \times 10^9$  whilst taking azathioprine, causing physicians to temporarily stop the medication before restarting it again 8 weeks later on a lower dose of 100 mg daily, which was subsequently carefully monitored via weekly blood checks for the first 2 months. It is, therefore, likely that use of topical tacrolimus contributed to a complete resolution of the lesions on his lower lip.

Limited evidence of the benefits of calcineurin inhibitors in treating PV has been documented with successful results;<sup>17</sup> however there appear to be only two reported cases in the literature of the use of topical tacrolimus<sup>18</sup> and both of these cases involved adults.

The benefits of topical Tacrolimus in treating oral vesiculo-erosive mucosal conditions that fail to respond to topical

steroid treatments have been widely documented.<sup>19-21</sup> However, the use of this medicine is not without controversy due to the small-risk of malignancy that may be attributed to its use, although the evidence is based mainly on isolated case reports.<sup>22-24</sup> There are also reports that raise concern about the development of clinically significant elevated tacrolimus serum levels.<sup>25-28</sup> However, several cohort studies have been published which appear to confirm the safety of topical Tacrolimus in managing oral mucosal diseases, such as Corrocher *et al.*,<sup>29</sup> who evaluated 11 patients who had been using tacrolimus 0.1% ointment to treat desquamative gingivitis. They demonstrated that after 4 weeks of therapy, serum levels of tacrolimus were undetectable. Thomson *et al.*,<sup>30</sup> also advocated its safety after showing that there was no evidence of systemic absorption of topical Tacrolimus following a retrospective study of patients treated with topical Tacrolimus for oral lichen planus.

### Conclusion

We present a case of the effective use of topical tacrolimus in the treatment of PV in a 10-year-old boy, where intravenous steroids and immunosuppressants (azathioprine) failed to completely relieve his oral symptoms. A 6 weeks course of topical tacrolimus appears to have contributed to the resolution of our patient's symptoms, and he has remained in remission since ceasing the treatment. No side effects from his use of Tacrolimus have been noted. Further prospective cohort studies and randomized controlled trials would be helpful to confirm the efficacy of this medication.

### Competing interests

The authors declare that there are no conflicts of interest.

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