Pyostomatitis Vegetans With Orofacial and Vulvar Granulomatosis in a Pediatric Patient

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PRACTICE **POINTS**

- Pyostomatitis vegetans (PSV) is a rare manifestation of cutaneous Crohn disease in children and can precede the onset of bowel pathology.
- Although topical and intralesional corticosteroids were beneficial in our patient, systemic corticosteroids and tumor necrosis factor α inhibitors, including infliximab and adalimumab, used to treat underlying inflammatory bowel disease appear to be the most efficacious option for treating PSV.

Pyostomatitis vegetans (PSV) is a rare disorder strongly associated with inflammatory bowel disease (IBD), most commonly ulcerative colitis, but has infrequently been found in patients with Crohn disease (CD). We present the case of a 7-year-old girl with PSV and extraintestinal findings suggestive of CD—chelitis granulomatosa, perianal and vulvar edema with biopsies revealing noncaseating granulomas, and anal skin tags—and an elevated calprotectin noted during a cutaneous flare. She did not have clinical or endoscopically identified underlying gastrointestinal involvement for 4 years after symptom onset. Given the paucity of data on managing PSV in a child without gastrointestinal findings of IBD, the literature is reviewed and treatment options discussed.

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Case Report

A 7-year-old girl who was otherwise healthy was referred by pediatric gastroenterology for evaluation of cutaneous Crohn disease (CD). The patient had a 4-year history of persistent lip swelling and a 3-year history of asymmetric erythematous labial swelling and perianal erythema with skin tags. She had been applying the calcineurin inhibitor tacrolimus ointment 0.03% 1 or 2 times daily to her lesions with minimal improvement. She did not have a medical history of recurrent or unusual infectious diseases. There was no family history of autoimmune disease.

The patient and her guardian reported intermittent perianal pain but denied constipation, diarrhea, abdominal pain, and blood in the stool. She denied throat and tongue swelling, dysphagia, dyspnea, drooling, facial paralysis, and eyelid edema. She was a well-nourished child whose height and weight percentiles tracked at 30% and 25%, respectively. Physical examination revealed confluent symmetric lip swelling with mild angular cheilitis. Multiple 1- to 2-mm white pustules with pinpoint erosions covered the upper and lower labial mucosa and extended onto the buccal mucosa (Figure 1). She had symmetric erythema and swelling of the left labia majora extending to and involving the left perianal mucosa. Three perianal erythematous skin tags and a perianal fissure were identified.

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The patient had been assessed 2 years earlier by pediatric dermatology and gastroenterology with an extensive evaluation that favored a diagnosis of cutaneous CD because the combination of orofacial granulomatosis (OFG), vulvar edema, and perianal skin tags is strongly associated.[1-3] Contact dermatitis affecting the mouth was considered; however, allergen testing did not demonstrate a trigger.

A trial of a benzoate- and cinnamon-free diet, which has been reported to improve OFG,[4] did not provide symptomatic improvement. Topical corticosteroids and tacrolimus reduced the perioral erythema, but the swelling persisted. An infectious cause was considered; however, topical mupirocin had no effect, and amoxicillin resulted in oral candidiasis.

A perianal biopsy revealed a granulomatous dermatitis. Fungal and bacterial cultures were negative. Upper and lower gastrointestinal (GI) endoscopy and a fecal calprotectin assay were not suggestive of inflammatory bowel disease (IBD). A complete blood cell count and QuantiFERON-TB Gold test measuring the immune response to tuberculosis antigens were normal. Chronic granulomatous disease, *RAG1/RAG2* deficiency, common variable immunodeficiency, and *NOD2* defects were ruled out with normal tests of dihydrorhodamine, quantitative immunoglobulins, and toll-like receptors.

Because of the discomfort associated with the patient's lesions, she was offered treatment with tumor necrosis factor α inhibitors, including infliximab and adalimumab. These agents had been offered since the onset of symptoms; however, her parents declined systemic medication unless she developed GI involvement. Instead, the tacrolimus concentration was increased to 0.1% applied to the lips, labia, and perianal area, and fluocinonide gel 0.05% applied nightly to the oral pustules was added.

Two months later the patient had notably fewer oral pustules and diminished erythema but only slightly reduced oral, vulvar, and perianal swelling. A trial of oral metronidazole, which has been reported to clear a patient with cutaneous CD,[5] was discontinued by her parents after 6 weeks because of a lack of interval improvement.

One year later, a pre-existing perianal skin tag doubled in size and became exquisitely tender. The calprotectin level—previously within reference range at less than 16 μg/g—was now elevated at 149 μg/g (reference range, 1–120 μg/g) and increased to 336 μg/g 3 weeks later. Testing for C-reactive protein, zinc, and stool occult blood; a comprehensive metabolic panel; and a complete blood cell count were unremarkable.

Repeat upper and lower GI endoscopy did not suggest CD. A biopsy using direct immunofluorescence (DIF) was obtained to evaluate for pyostomatitis vegetans (PSV) and rule out pemphigus vegetans of Hallopeau (PVH). Biopsy of a pustule was attempted but was challenging because of the patient's age and difficulty cooperating.

The captured biopsy did not demonstrate the intended pustule; instead, it included less-affected mucosa and was obtained during topical treatment when few pustules and erosions persisted. Pathologic analysis revealed noncaseating granulomas without an increase in microabscesses, neutrophils, or eosinophils (Figure 2). Direct immunofluorescence staining for IgG, IgA, and C3 and indirect immunofluorescence staining for desmoglein-1 and desmoglein-3 antibodies were negative. Although the biopsy did not capture the intended pustule, diagnosis of PV was made based on clinical features and the constellation of cutaneous findings associated with IBD.

Intralesional triamcinolone, which has been of benefit for pediatric patients with orofacial granulomatosis,[1,6,7] was instituted and normalized the vulva and perianal mucosa; however, lip swelling improved only minimally.

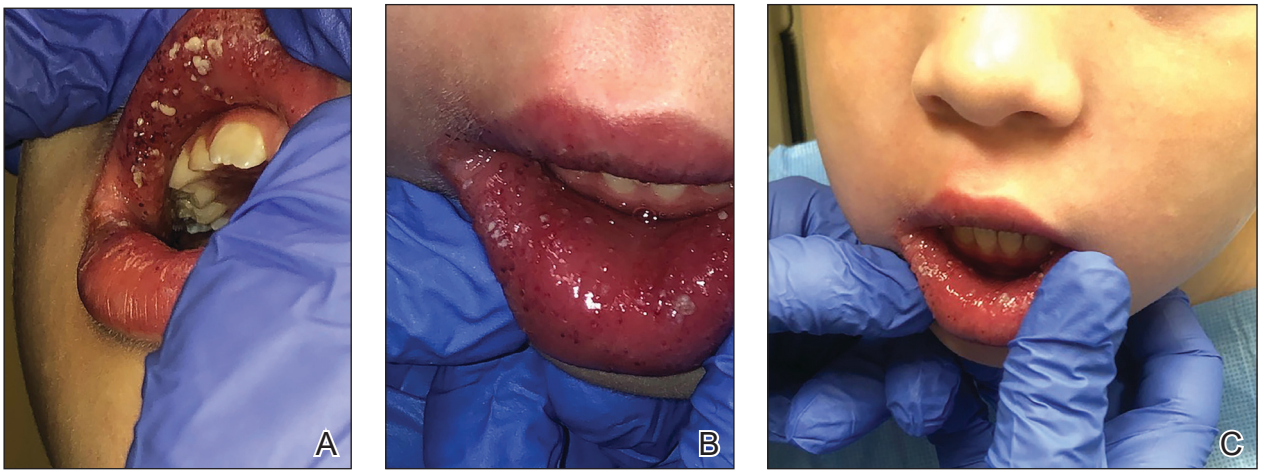

FIGURE 1. A–C, Confluent swelling of the upper and lower labial mucosa with white pustules and plaques over the upper and lower lips in a 7-year-old girl.

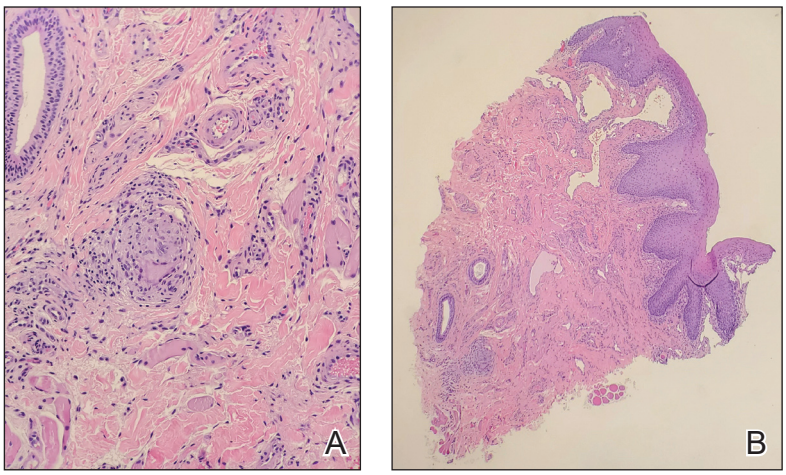

FIGURE 2. A, Histopathology revealed a well-formed deep granuloma adjacent to a blood vessel, which is characteristic of cutaneous Crohn disease (H&E, original magnification ×200). B, Mild inflammation, predominantly lymphocytic, and irregular acanthosis were noted along with the deep granuloma adjacent to a blood vessel (H&E, original magnification ×40).

Comment

Pyostomatitis vegetans is characterized by multiple white or yellow, friable, miliary pustules that rupture, leaving behind ulcerations and erosions that cause a varying degree of oral pain.[8] The disorder can involve any area of the oral mucosa—most often the labia-attached gingiva, soft and hard palates, buccal mucosa, vestibule, and tonsillar areas—but often spares the floor of the mouth and tongue.[8-11] The term *pyostomatitis vegetans* was proposed in 1949 by McCarthy[12] when he noted in a patient who presented with the characteristic appearance of the oral mucosa, though cases of vaginal, nasal, and periocular involvement have been reported.[8,13,14]

Histopathology—Pyostomatitis vegetans displays pseudoepithelial hyperplasia with acanthosis, hyperkeratosis, and intraepithelial or subepithelial microabscesses (or both) with neutrophils and eosinophils.[8,9,15] There are a few possible explanations for this patient's lack of tissue eosinophilia. It has been theorized that the presence of granulomas could mask concurrent PSV[16] or that tissue in PSV contains fewer eosinophils as the disorder progresses.[11] The oral biopsy obtained from our patient did not capture a pustule, and the condition had noticeably improved with topical tacrolimus at the time of biopsy; therefore, neither neutrophils nor eosinophils were identified. Peripheral eosinophilia, which is present in 42% to 90% of cases of PSV,[9,17] can be a diagnostic clue.[18] However, PE is associated with IBD,[24] which usually occurs with PSV, so the absence of peripheral eosinophilia in our patient may be explained by her lack of bowel disease.

Pathogenesis—The pathogenesis of PSV is unknown. A proposed etiology includes cross-reacting antigens in the bowel and skin secondary to IBD as well as an aberrant immune response to an unidentified factor.[8] Pyostomatitis vegetans is considered by many to be the mucosal variant of pyodermatitis vegetans,[9,15,19] a neutrophilic dermatosis characterized by asymmetric, crusted, erythematous papulopustules that extend peripherally and coalesce to form large vegetating plaques. These lesions commonly manifest in the axillary folds, groin, and scalp and can involve the face, trunk, and distal extremities.[9,18] Infection has been suggested as a cause of PSV, though cultures for pathogenic bacteria, viruses, and fungi consistently show only normal flora.[20] Zinc deficiency attributed to malabsorption from CD was reported in an adult with PSV.[21] The PSV resolved after 6 weeks of zinc supplementation.

Differential Diagnosis—The main entity in the clinical differential diagnosis for PSV is PVH, which is considered a variant of pemphigus vulgaris. Pemphigus vegetans of Hallopeau presents with pustules and progresses to hyperpigmented vegetative plaques with peripheral hypertrophic granulation tissue.[22] The clinical and histological presentation of PVH can be similar to PSV; in PVH, however, DIF demonstrates intercellular IgG and C3 due to circulating IgG autoantibodies specific for desmoglein 3, a cell adhesion molecule.[22-24] In PSV, DIF typically is negative for IgG, IgA, and C3.[8] Immunohistochemical

Oral Manifestations of Crohn Disease[28,29]

Angular cheilitis
Cobblestoning
Deep aphthouslike or linear ulcerations
Diffuse oral swelling
Gingival hyperplasia
Indurated fissures of the lower lip
Mucogingivitis
Mucosal tags
Orofacial granulomatosis

findings of PSV may overlap with IgA pemphigus, IgG/IgA pemphigus, and IgG pemphigus, which has sparked debate if PSV is an autoimmune blistering disorder or a secondary finding of epithelial injury.[9,18,24]

Pyostomatitis vegetans is most prevalent in patients aged 20 to 59 years[25] but can occur at any age.[8,19] Overall, extraintestinal symptoms, including mucocutaneous findings, are common in pediatric patients—in 30% to 71% of children with CD and 21% to 22% of children with ulcerative colitis[26]—and can predate onset of GI symptoms in 6% of pediatric patients.[27]

Oral disease is common in CD; manifestations are listed in the Table.[28,29] In a prospective study of 48 children with CD, 42% (20/48) had oral manifestations identified at diagnosis[28]; in a similar study of 25 children, researchers noted that 48% (12/25) had disease-specific oral lesions.[29] None of these children recognized the oral findings prior to the onset of systemic symptoms.[28] Pyostomatitis vegetans was the least common oral manifestation, reported in 1 of 73 patients in the 2 studies combined.[28,29]

Two recent articles that looked at PSV in pediatric and adolescent populations identified only 9 patients with PSV.[24,30] Only 2 patients (siblings) had documented onset of PSV before 12 years of age,[31] which suggests an underlying genetic predisposition in young children.

It has been reported that active or subclinical (ie, asymptomatic with positive endoscopic findings) IBD in adults precedes onset of PSV, which may be considered a sign of relapse.[9,30] However, PSV is incredibly rare in children and adolescents and can be an early finding of IBD in children.[16,31,32]

Our patient has not developed GI involvement since her initial presentation 5 years prior, though another pediatric patient developed symptomatic CD 9 years after onset of OFG.[5] A retrospective review of pediatric OFG without CD met criteria for CD at a median of 3.1 years (range, 0.4–6.9 years).[33] Regrettably, the early presence of PSV has been associated with future progression to CD and a complicated disease course.[12,34]

Management—Pyoderma stomatitis vegetans is treated with management of underlying IBD,[8] with scarce literature available regarding pediatric patients. Oral lesions have been treated with antiseptics and topical corticosteroids, though these have limited benefit.[8] In an adult with IBD, topical tacrolimus initially cleared PSV; however, lesions recurred until mesalamine was initiated.[35] Systemic steroids were effective in a 16-year-old patient with CD and PSV,[12] but recurrence is common after corticosteroids are stopped.[34]

Some patients benefit from steroid-sparing medications, such as dapsone, azathioprine, sulfamethoxypyridazine, methotrexate, mycophenolate mofetil, and tumor necrosis factor α inhibitors such as infliximab and adalimumab.[8,9,15,23,34,36] A 12-year-old patient with pyodermatitis–PSV without intestinal disease was treated with prednisone, dapsone, and azathioprine with improvement but not complete resolution of oral erosions after 18 weeks of treatment.[32] A 15-year-old patient with CD and pyodermatitis–PSV did not show improvement on prednisone, dapsone, and azathioprine but rapidly responded to infliximab.[23] Infliximab led to complete clearance of oral lesions in an adult with severe fistulizing CD who developed PSV.[11] However, 2 adolescent patients with CD developed PSV while on adalimumab,[6,34] though 1 did improve after increasing adalimumab from once to twice weekly.[6]

Conclusion

The case described here—PSV in a prepubertal 7-year-old with multiple cutaneous findings suggestive of CD, including OFG, perianal and vulvar edema with biopsy-proven noncaseating granulomas, anal skin tags, and an elevated calprotectin level, noted during a cutaneous flare without clinical or endoscopically identified underlying bowel involvement—is an extremely rare presentation. Literature regarding management of PSV primarily is found in the form of case reports and focuses on treating underlying IBD. In patients with intestinal disease, treatment with biologic therapy appears most effective.[6,23]

ADDENDUM

Interestingly, 3 years after the patient's original presentation to our clinic, chromosomal sequencing analysis to assess for copy number variants and whole exome gene sequencing identified a variant of unknown significance in the heat shock protein family A member 1-like gene, HSPA1L, which has an unknown mode of inheritance, but the literature suggests that both truncating and missense variants could be associated with individuals with ulcerative colitis, CD, and IBD.[37,38] Although we cannot use this information to render a molecular diagnosis, it is highly suspicious that this is the cause of her clinical findings. Additionally, the patient currently is aged 10 years with unchanged cutaneous findings and has not developed gastrointestinal findings of IBD.

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