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Pyostomatitis Vegetans in a Young Woman with Gastrointestinal Symptoms: a case report and review of literature

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Abstract

Pyodermatitis-pyostomatitis vegetans (PD-PSV) is an uncommon inflammatory mucocutaneous disease with unknown etiology. It is characterized by pustular and vegetating plaques on the skin and oral mucosa. When the oral mucosa is involved alone, it is called pyostomatitis vegetans. This disease is considered as an oral manifestation of inflammatory bowel diseases.

In the present paper, we report a case of pyostomatitis vegetans in a 23-year-old female patient with swelling of the lips and oral lesions. Our patient had simultaneously three important clinical symptoms, including the presence of intra-oral lesions, lip swelling, and gastrointestinal manifestations that may be suggestive of inflammatory bowel disease. Her oral manifestations improved with topical antifungal drug and local and systemic corticosteroids.

In addition, the results of our extensive search in reliable scientific databases including Google and PubMed for articles (case reports and literature reviews) containing the keywords: ”pyostomatitis vegetans” and "pemphigus vegetans” in recent years are presented.

Introduction

Pyodermatitis-pyostomatitis vegetans (PD-PSV) is a rare inflammatory mucocutaneous disease of unknown etiology, characterized by pustular and vegetating plaques on the skin and oral mucosa. Mucosal involvement is defined as multiple pustules and vesicles on erythematous base. PD-PSV can occur in all ages and the ratio of male to female is about 2:3 (1-3). Oral mucosal lesions involve the labial attached gingiva, as well as the labial and buccal mucosa. These lesions are distinct and appear as multiple white to yellow pustules with an erythematous base that coalesce and undergo necrosis to form a typical fissured appearance named “snail tracks” (3-5).

According to the literature, for the first time, in 1898, Hallopeau reported a few cases of unusual pustular lesions on the skin and oral mucosa, and the entity was named pyodermatitis vegetans. Mc. Carthy, in 1949, suggested the term pyostomatitis vegetants when he observed some patients with isolated oral lesions similar to those reported by Hallopeau (1, 3, 4).

PD-PSV is considered as a specific marker for inflammatory bowel diseases (IBD), especially ulcerative colitis. Pyostomatitis vegetans is associated with IBD in 75% of cases. IBD appears months or years before oral and skin manifestations in most cases; however, symptoms may not be sufficient to make a diagnosis (1-4, 6). Oral involvement is comparatively common in Crohn's disease. Pyostomatitis vegetans can be the first sign of this disease (7). Oral lesions may include numerous friable pustules with necrotic gray appearance on an erythematous base. These may affect all areas of the oral cavity, however the most commonly affected sites are the labial and buccal mucosae, hard and soft palate, gingivae, and sulci. Cobblestoning of the oral mucosa and diffuse swelling of the lips with vertical fissures are the other oral features of IBD (7-9).

The most important disease involved in the differential diagnosis of PD-PSV is pemphigus vegetans. Differentiation between them is important, even though their treatment regimen would be similar (1). Pemphigus vegetans is an uncommon variant of pemphigus vulgaris, accounting for 1–2% of all pemphigus diseases. It is thought to represent a reactive response of the skin to the autoimmune insult of pemphigus vulgaris. This type of pemphigus is characterized by cauliflower-like vegetating plaques in some areas of the skin especially flexures and commonly associated with oral involvement. Two clinical subtypes of pemphigus vegetans exist (Neumann and Hallopeau), characterized initially by bullae/erosions or pustules, respectively. Both of them develop subsequently into vegetative plaques with pustules and hypertrophic granulation tissue at the periphery (10-16).

Herein, we report a case of pyostomatitis vegetans with multiple oral mucosa involvements, without any lesion in the skin and other mucous membranes. In the presented case is a 23-year-old female patient with oral lesions, labial swelling, and some gastrointestinal symptoms. In addition, an extensive research was performed via Google and PubMed for articles (including case reports and literature reviews) containing the keywords: "pyostomatitis vegetans" and "pemphigus vegetans" in recent years.

For the presentation of this case, a written informed consent was obtained from the patient.

Case report

A 23-year-old female patient referred to the oral medicine department for the treatment of disseminated intraoral lesions. In her appearance, the lips' swelling along with scaly areas on the lips was seen (Fig. 1). The chief complaint of the patient was aesthetic problem due to the swelling of the lips and also, the presence of oral lesions since about 7 months ago. She had burning sensation in her labial mucosa and also complained of halitosis. She had previously referred to several physicians for the treatment of her oral lesions and lips' swelling. They prescribed topical and/or systemic antifungal drugs based on the diagnosis of fungal infection. During the last 2 months, the patient had been also admitted in the service of infectious diseases for 4 weeks and had received systemic antifungal drugs. According to the patient opinion, slight improvement had been achieved after antifungal therapy (this improvement can be justified by candida superimposition on most oral lesions).

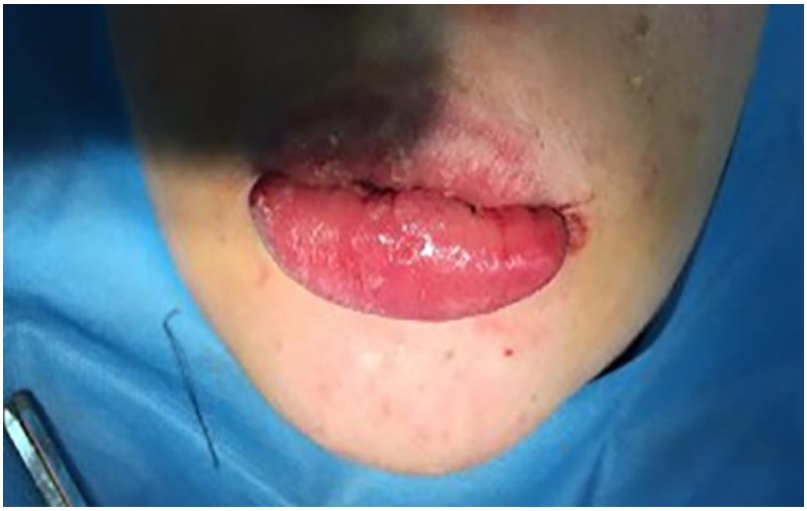

Figure 1. Lips' swelling along with scaly areas on the lips

Except some gastrointestinal symptoms such as intestinal cramps, occasionally blood in the stool, and diarrhea, there was no other problem in the patient's medical history. She was taking no medications and had no allergies to special medicine or food.

In extra oral examination, disseminated erythema along with white areas within erythema was observed in the both lips. By pulling the gauze on the lesions, white areas were removable that seemed to be tissue tags, and vermilion desquamation was also seen (Fig. 2). In the oral cavity, several regions such as labial, buccal and alveolar mucosa, and also attached gingival were involved. The lesions were present as erythematosus areas and small ulcers, and also, there were obvious folds on the labial mucosa. The upper and lower labial lesions had spread to the alveolar mucosa and attached gingiva. In addition to the labial mucosa, the buccal mucosa was also involved bilaterally and more towards the upper vestibule.

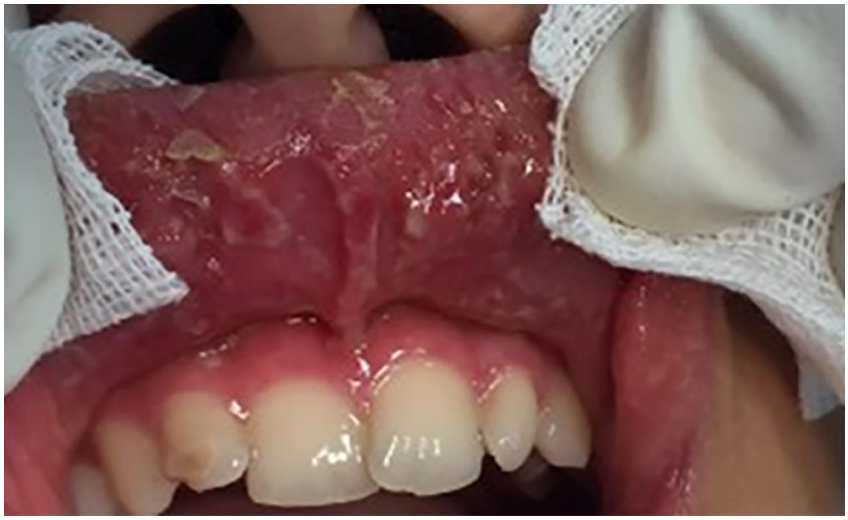

Figure 2. Labial tissue tags and vermilion desquamation

The lesions were limited to the oral cavity, and there was not any lesion on the other mucous membranes. Depending on the clinical presentation and the patient's history, differential diagnoses were included pyostomatitis vegetants, pemphigus vegetans, hereditary angioedema, and cheilitis glandularis. To confirm the diagnosis, incisional biopsy of labial mucosa was done for histopathological examination. Since the primary differential diagnosis include spyostomatitis vegetants and pemphigus vegetans, the normal buccal mucosa was also biopsied for direct immunofluorescence study (in terms of the deposition of antibodies such as IgG, IgA, and C3). Given that hereditary angioedema and cheilitis glandularis were also included in differential diagnosis due to the relatively severe lips' swelling and also because of the possible association of hereditary angioedema with inflammatory or autoimmune diseases, including inflammatory bowel disease (17), serum test for measuring C1 esterase inhibitor and histopathological examination of lower lip minor salivary gland was carried out. Based on the results of these tests, both of the diseases were ruled out.

Histopathological examination revealed subepithelial and intraepithelial vesiculobullous lesion with prominent eosinophils infiltration (Fig. 3[a,b,c]). However, direct immunofluorescence (DIF) findings were negative for all antibodies.

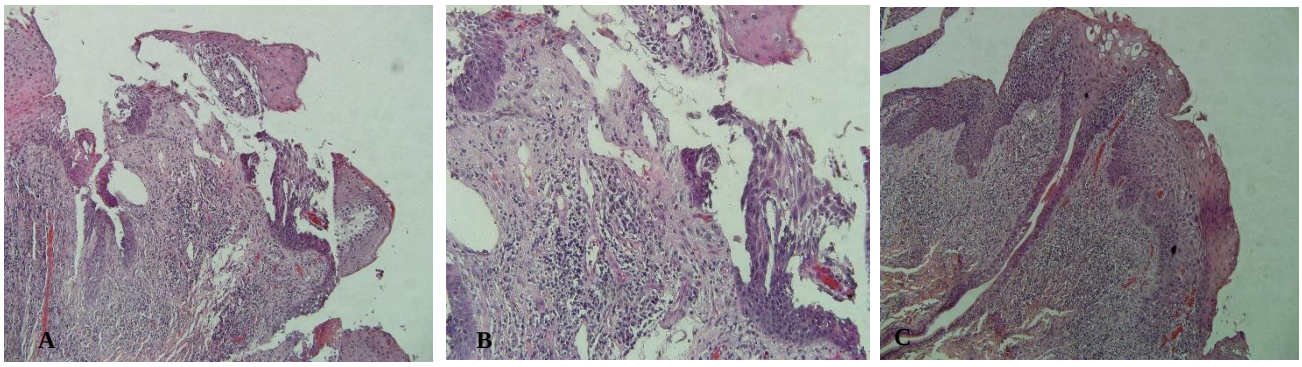

Figure 3. (a,b,c): a,b. Suprabasal acantholysis blister with acantholytic cells in superficial mucosa. Fibrosis and moderate mixed inflammatory cells infiltration in subepithelium. c. Acantholysis in superficial stratified squamous epithelium with mixed inflammatory cells infiltration and fibrosis in subepithelium

Considering the results of DIF study and also the presence of some gastrointestinal symptoms, the diagnosis of pyostomatitis was made, and the patient was advised to refer to a gastroenterologist to investigate the possible lesions of GI tract, but she refused.

First of all, topical antifungal therapy was prescribed for 2 weeks to reduce inflammation and infection. After that, we started the main treatment of oral lesions, so that intralesional injection of triamcinolone was performed segmentally and in 3 consecutive sessions at intervals of 2 weeks (in 4 areas of lesion/ each of them, 0.1-0.2 ml) and first of all, on various areas of the lips (due to the severity of lip lesions and the aesthetic problem). The treatment was associated with a significant improvement after the second session (Fig. 4). In addition, mucou-adhesive triamcinolone paste was applied 3 times a day for the attached gingiva lesions (4). Nystatin suspension 100,000 units/mL was also prescribed 3 times a day as a mouthwash for the prevention of superimposition of fungal infections.

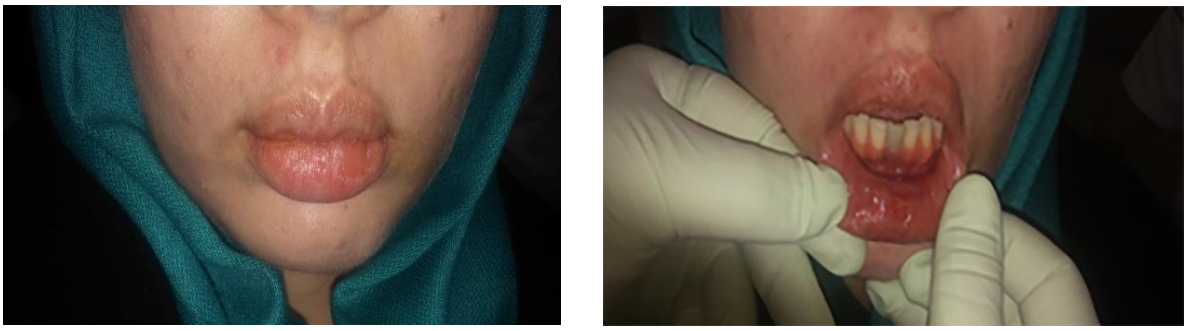

Figure 4. Significant improvement after 2 injections

In follow-up sessions, we found numerous skin acne in her face (fig. 5), so she was referred to a dermatologist. The dermatologist ordered indirect immunofluorescence (IIF) study before starting the acne treatment to complete diagnostic tests; the serum test was negative for desmoglein1 and intermediate for desmoglein3. Given that pemphigus patients whose disease remains confined to the oral mucosa, often have negative results on indirect and direct immuno-fluorescence testing (18), the diagnosis of pemphigus vegetans can be suggested for our patient with more power than before. On the other hand, Oral lesions that are associated with IBD and resemble pemphigus vegetans clinically are considered as pyostomatitis vegetans (18); therefore, due to the presence of GI symptoms in the patient and the probability of the presence of IBD, pyostomatitis vegetans is a better diagnosis for her.

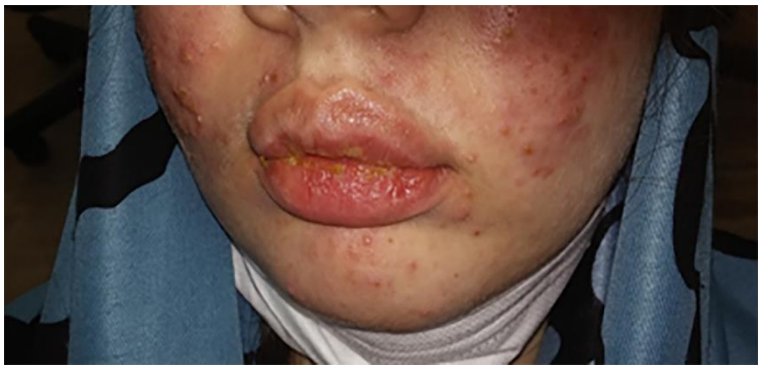

Figure 5. Numerous skin acne

Almost simultaneous with the onset of skin acne, previously improved oral lesions showed recurrence; therefore, after assessing the patient's systemic condition and the absence of contraindications for prescribing systemic corticosteroids, systemic treatment with prednisolone (50 mg per day) was started (7). Within 3 days of beginning the treatment, all oral lesions improved (Figure. 6). Thereafter, the patient no longer returned and she mentioned no oral problems in follow up$_s$ by telephone call for 3 months, and continued to refuse gastrointestinal examinations.

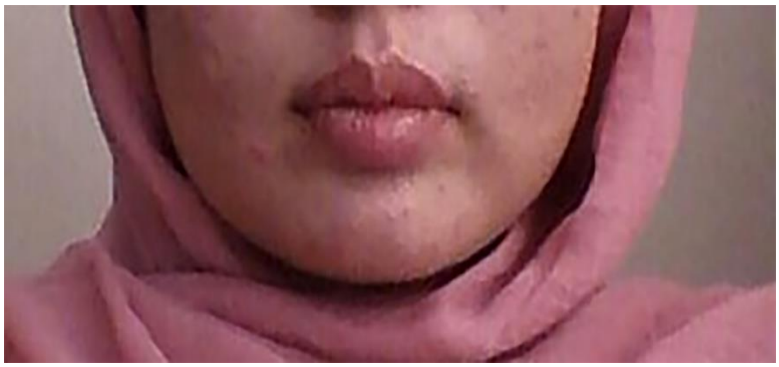

Figure 6. Oral lesions improvement after systemic corticosteroid therapy

Discussion

Pyostomatitis vegetans is an uncommen chronic inflammatory condition that is thought to be the oral mucosal counterpart of pyodermatitis vegetans, which involves the skin; the skin lesions can appear shortly after or prior to the occurrence of oral lesions. Its etiology is unknown, and pathogenesis of this disease has been poorly understood. Pyostomatitis vegetans is a highly specific marker for inflammatory bowel diseases. Gastrointestinal disturbances sometimes present with very subtle symptoms and may remain undetected unless a precise gastrointestinal examination is done. The severity of the oral lesions can reflect the activity of gastrointestinal disorders (1, 3 , 19).

One of the most important differential diagnoses of pyostomatitis vegetans is pemphigus vegetans. The clinical picture of our patient and also, the histopathological findings of the lesion were in favor of both diseases (pemphigus vegetans and pyostomatitis vegetans).The differentiation between the two diseases could be made by immunofluorescence. Direct and indirect immunofluorescence (DIF and IIF) are negative or weakly positive in pyostomatitis vegetans, whereas they are positive and show strong intercellular deposits of IgG and C3 in pemphigus vegetans (1). Considering that our patient's DIF test was negative and IIF test was negative for desmoglein 1 and intermediate for desmoglein 3, the diagnosis was more in favor of pyostomatitis vegetans (however, IIF should be checked again after 3 months for establishing the definitive diagnosis). Of course, it should be noted that pemphigus patients whose lesions remains confined to the oral cavity (like our patient), often have negative results of DIF and IIF, but on the other hand, because of the presence of GI symptoms in our patient and the possible existence of IBD, again, the diagnosis was in favor of pyostomatitis vegetans.

Corticosteroids are the suggested therapies for pyostomatitis vegetans, and cytotoxic therapies are also used as adjuncts. In cases where these lesions are a manifestation of inflammatory bowel disease, treatment of IBD may help to relieve the lesions (2, 4, 5).

To date, numerous cases have been reported regarding the clinical manifestations of pyostomatitis vegetans (Table 1).

Table 1. Reported cases with clinical manifestations of pyostomatitis vegetans

Author	Year	Sex	Age (year)	Oral manifestation	GI manifestation	Diagnosis
Ruiz-Roca	2005	F	51	exophytic lesion in vestibular zone with erythematous margins/ ulceration and pseudomembrane	+	PSV
Ruiz-Roca	2005	M	26	exophytic lesion in vestibular zone with elevated and erythematous margins/ ulceration and pseudomembrane	+	PSV
Sollecito	2006	F	9	multiple pustules in soft palate	+ (Crohn's disease)	PSV
Markiewicz	2007	M	30	swelling and thickening of buccal mucosa	+ (ulcerative colitis)	PSV
Mijandrusić-Sincić	2010	F	23	linear pustules and multiple ulceration on erythematous labial and buccal mucosa/ deep fissures on ventral side of tongue	+ (Crohn's disease)	PSV
Mijandrusić-Sincić	2010	F	32	slightly elevated pustules on erythematous soft palate mucosa and dorsal side of tongue	+ (ulcerative colitis)	PSV
Kitayama	2010	F	51	clustered pustules on gingiva	+ (ulcerative colitis)	PD-PSV
Matias	2011	F	47	early stage → absence of oral lesions/ intermittent recurrences in the form of vesicles and pustules on erythematous base	-	PD-PSV
Saghafi	2011	F	30	pustules on an erythematous base on buccal and labial mucosa, gingiva and soft palate/ ulceration and erosion	-	PSV
Mesquita	2012	M	12	coalescent ulcerations, edema, erythema and crusts on tongue, palate and lips	-	PD-PSV
Lopez-Jornet	2012	?	?	?	+	PSV
Nico	2012	M	33	multiple pustules on buccal mucosa and vestibular	+	PSV
Nico	2012	M	34	multiple pustules on gums	+ (ulcerative colitis)	PSV
Nico	2012	F	63	multiple pustules on labial mucosa, ventral tongue and palate	+ (ulcerative colitis)	PSV
Nico	2012	F	33	mucous edema and multiple pustules on labial mucosa and ventral tongue, linearly arranged	+ (ulcerative colitis)	PSV
Wu	2015	F	33	multiple curvilinear pustules on soft palate, anterior gingiva, retromolar pad and buccal mucosa	+ (ulcerative colitis)	PSV
Basirat	2016	F	30	multiple crusted ulcers and vegetation on lips with an erythematous base/ small lesions on palate, buccal and labial attached gingivae, alveolar mucosa and vestibule	+ (Crohn's disease)	PSV
Tursi	2016	F	42	coalescing pustules on gingiva	+ (ulcerative colitis)	HS & PSV

F: Female; M: Male; PSV: Pyostomatitis vegetans; PD-PSV: Pyodermatitis-pyostomatitis vegetans; HS: Hidradenitis suppurativa; ?: Unknown

Ruiz-Roca *et al.* in 2005 described two cases (a woman and a man) of pyostomatitis vegetans associated with IBD. The authors stated since in both cases, the lesions are clinically and histologically similar to Neumann type pemphigus vegetans, this disease includes in differential diagnosis. According to the authors' justifications, probably because the patients presented

no blisters and showed characteristic pustular lesions, and the lesions were also associated with chronic intestinal inflammatory disease, the diagnosis of pyostomatitis vegetans was confirmed and Neumann type pemphigus vegetans was ruled out (23). But, we believe that given the fact that Hallopeau type pemphigus vegetans is characterized by pustular lesions like pyostomatitis vegetans and additionally, patients may have accidentally at the same time both pemphigus and IBD, the reasons for rejecting pemphigus vegetans (of course, Hallopeau type) do not seem logical and immunofluorescence test can help to achieve a more accurate diagnosis.

Sollecito *et al.* in 2006 reported a girl with pyostomatitis vegetans and orofacial granulomatosis. This patient had only oral ulcers, without any lesion in other mucous membranes or skin that was similar to our patient in this respect. In the detailed GI evaluation, they found out small nodules in the terminal ileum suggestive of extensive lymphoid hyperplasia that raised the possibility of early inflammatory bowel changes (3). This suggests that the same result might have been achieved if our patient had been also evaluated for GI tract, given that our patient had gastrointestinal symptoms as well.

Mijandrusić-Sincić *et al.* in 2010 presented two young women with pyostomatitis vegetans associated with IBD-one with Crohn's disease and the other with ulcerative colitis. The diagnosis of pyostomatitis vegetans was established based on oral manifestations, histological findings, and association with IBD (5). DIF and IIF testing were not performed for this case, unlike our patient.

Kitayama *et al.* in 2010 introduced a middle-aged woman with previous history of ulcerative colitis. She had the lesions on various areas of her skin and mucous membranes (including gingiva) similar to those of pemphigus vegetans. In some recent time, GI symptoms had also recurred. Because of the clinicopathological findings resembling pemphigus vegetans, negative results of DIF and IIF and anti-desmoglein antibodies, and the presence of ulcerative colitis as an underlying disease, her mucocutaneous symptoms were diagnosed as PD-PSV (25).

Matias *et al.* in 2011 reported a case of PD-PSV that was a middle-aged woman. Their patient had multiple vesico-pustular skin and mucosal (vulvar and conjunctival regions) lesions, but she did not have any lesion in her oral mucosa at the early stage of the disease, so this patient was different from our reported case in this respect. Also, their patient had no gastrointestinal symptoms. However, direct and indirect immunofluoresecence were negative, similar to our patient (2).

Saghafi *et al.* in 2011described a case of pyostomatitis vegetans in a young woman. She presented with prominent thickening of both lips and also intraoral involvement, which these findings were very similar to our patient. In gastro-intestinal evaluation, she had no abnormalities; in addition, the authors did not report any non-oral lesions such as skin and other mucosal lesions (4).

Mesquita and Costa in 2012 described a case of pyodermatitis-pyostomatitis vegetans in a boy. He had some lesions in the oral cavity and genital area. Based on the clinical presentation and histopathological findings, the differential diagnosis included pemphigus vegetans and PD-PSV. Apparently he did not have GI symptoms. Considering that their patient's DIF test was negative similar to our patient, they made the definite diagnosis of PD-PSV (1).

Lopez-Jornet *et al.* in 2012 reported a patient with pyostomatitis vegetans. They emphasized the relationship between pyostomatitis vegetans and IBD and the importance of

the oral lesions as initial presenting signs of systemic disease or activity (6).

Nico *et al.* (2012) studied four patients (two men and two women) with IBD and oral lesions suggestive of pyostomatitis vegetans. DIF and IIF were negative in two patients, but two other patients revealed the presence of intercellular IgG and C3 on DIF; additionally, IIF revealed circulating IgG that these findings are typical for pemphigus vulgaris. The authors for various reasons including that the lesions were frankly pustular, instead of vesicular or erosive as seen in oral pemphigus vulgaris and that the oral lesions ran a parallel course with the gastrointestinal complains and were adequately controlled with the treatment of these, suggested a possible connection of the oral symptoms with course of their IBD and established the diagnosis of pyostomatitis vegetans (despite the positive results of DIF and IIF in two patients). However, based on what the authors of this article mentioned in the discussion and, also in our opinion, two latter patients according to DIF and IIF results, could have pemphigus vegetans whose oral manifestation was like those of IBD. Furthermore, these patients might have accidentally at the same time both pemphigus vegetans and IBD, so that oral involvement can be attributed to both diseases, and given that the treatment of both diseases is approximately the same (through immunosuppression), oral lesions recovered with therapeutic action for each of them (20). It should be noted that in addition to the similarity of these two diseases in terms of oral manifestations, they have similar histopathological features, so laboratory findings are needed to differentiate them (18).

Wu *et al.* in 2015 reported a young woman with multiple oral pustular lesions and a history of ulcerative colitis. In this case, in addition to clinical and histopathological findings, the presence of inflammatory bowel disease was also consistent with the diagnosis of pyostomatitis vegetans (24).These authors did not perform immunofluorescence test too.

Basirat *et al.* in 2016 presented a young pregnant woman with multiple intraoral lesions and lip involvement. The clinical presentation of the lesions was very similar to our patient. At first, the patient had no systemic signs or symptoms of IBD, but in the following sessions, cramps, abdominal pain, and diarrhea appeared and afterwards, the diagnosis of Crohn's disease and also, pyostomatitis vegetans was established by laboratory findings, histopathological examination, endoscopy, and colonoscopy. These authors also emphasized the important role of oral lesions as the first diagnostic sign of IBD (7).

Tursi in 2016 reported a case of a middle-aged female with a long history of ulcerative colitis. While underlying IBD was in clinical remission, the patient experienced occurrence of nodular and pustular lesions on the different areas of the skin and also oral cavity, that dermatological assessment posed a diagnosis of Hidradenitis suppurativa associated with pyostomatitis vegetans. Despite the absence of specific colonic symptoms, colonoscopy showed moderate ulcerative pancolitis. The authors concluded, like Markiewicz *et al.* (21), that pyostomatitis vegetans can be considered as a clinical marker of silent ulcerative colitis (22).

Some authors stated that PD-PSV is recognized as mucocutaneous lesions clinically and histologically resembling those of pemphigus vegetans, with negative or weakly positive results of immunofluorescence study and negative anti-desmoglein antibodies, associated with IBD (25, 26).

Conclusion

In the presence of pemphigus vegetans-like mucocutaneous lesions, immunofluorescence and serological studies are essential (11). If the results of these examinations suggest PD-PSV, it is important to examine the patient for the presence of IBD even in the absence of GI symptoms to confirm the presence of asymptomatic inflammatory bowel disease or an increase in the activity of IBD. Unfortunately, our patient refused to refer to the gastroenterologist and perform gastrointestinal evaluation.

The significance of the reported case is that, in comparison with many other reported cases, this case had simultaneously three important clinical symptoms, including the presence of intra-oral lesions, lip swelling, and gastrointestinal manifestations that may be suggestive of inflammatory bowel disease.

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Conflicts of Interest and Source of Funding

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