Severe erosive gingivostomatitis in a patient treated by vedolizumab

L Semeria[1], A Dadban[1] MD, F Brazier[2] MD, M Fumery[2] MD PhD, JF Ikoli[3] MD, JP Arnault[1] MD, A Adas[1], M Dairi[1], C Lok[1] MD PhD, G Chaby[1] MD

Affiliations: [1]Department of Dermatology, Amiens University hospital, Amiens, France, [2]Department of Gastroenterology, Amiens University hospital, Amiens, France, [3]Department of Pathology, Amiens University hospital, Amiens, France

Corresponding Author: Lucile Semeria, Department of Dermatology, Amiens University Hospital, Victor Pauchet, 80054 Amiens Cedex 1, France, Tel: 33-616482504, Fax: 33-322455794, Email: lucile.semeria28@gmail.com

Abstract

Vedolizumab is a humanized monoclonal antibody that binds to the human α4β7 integrin and is approved for use in inflammatory bowel diseases. We describe a patient with severe, refractory erosive gingivostomatitis, which appeared a few days after the first dose of vedolizumab and resolved after discontinuation of the drug. We believe the gingivostomatitis to be a direct side effect of vedolizumab, rather than an extraintestinal manifestation of the underlying inflammatory bowel diseases. The clinicians need to be aware of this adverse event, which could be mistakenly considered as an extraintestinal manifestation of inflammatory bowel diseases.

Keywords: vedolizumab, inflammatory bowel disease, ulcerative colitis, aphthous stomatitis, gingivostomatitis.

Introduction

Vedolizumab is a humanized monoclonal antibody that binds to the human α4β7 integrin, approved for use in inflammatory bowel diseases (IBD), [1]. Our patient presented with refractory erosive gingivostomatitis, a few days after the initial dose of vedolizumab. After multiple failed treatments lesions resolved after discontinuation of the drug.

Case Synopsis

A 31-year-old man started vedolizumab for severe ulcerative colitis (UC). He was previously treated with mesalazine, systemic corticosteroids, azathioprine, 5-mercaptopurine, infliximab, adalimumab, and golimumab; each was discontinued for intolerance or loss of response. Five days after the first vedolizumab administration, oral mucosal erythema and erosions appeared. These were initially mild and treated with oral antifungal solutions. After two further injections, the patient's gastrointestinal symptoms started to improve but oral involvement worsened, with progression of severe painful oral ulcers (**Figure 1A)** that also involved gingiva and tongue. Antifungals were stopped. Bacterial and viral samples were negative. Oral erosions did not respond to oral mesalazine, topical corticosteroids, or systemic corticosteroids and worsened after the next two injections of vedolizumab.

Oral mucosal biopsies showed intense inflammatory infiltrates with polymorphonuclear neutrophils and

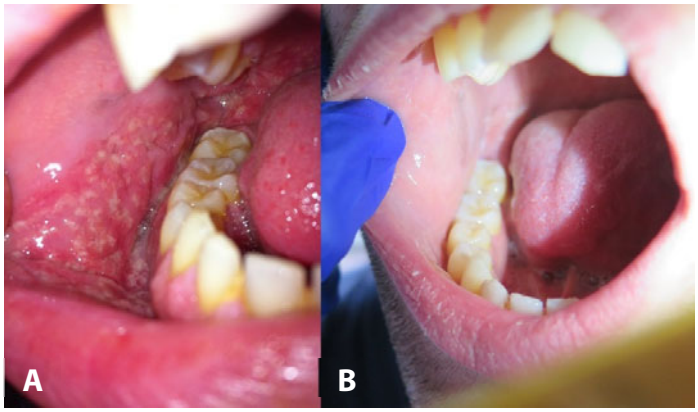

Figure 1. ***A)*** *Severe painful oral mucosal lesions started five days after the first vedolizumab injection.* ***B)*** *Oral lesions healed completely within two months after the last vedolizumab injection.*

eosinophils in the lamina propria and a few inflammatory cells in the epithelium (**Figure 2**). No granulomas were present. Direct immunofluorescence did not show immune deposits in the epithelium or on the basement membrane. Circulating anti basement membrane and anti-intercellular substance, anti-BPAG 1 and 2, anti-desmoglein 1 and 3, and anti-collagen VII antibodies were negative, ruling out autoimmune bullous diseases. Vedolizumab was discontinued. Oral lesion started to improve and had completely resolved within two months after the last vedolizumab injection (**Figure 1B)**. However, UC symptoms exacerbated and the patient was enrolled in a clinical trial evaluating the efficacy of filgotinib in UC.

Case Discussion

Involvement of oral mucosa in IBD is common. It occurs more often in Crohn disease than in UC [2]. Oral mucosal ulcers have also been described and compared in patients treated by TNF antagonists and vedolizumab [3]. The incidence of aphthous stomatitis was reported to be three times higher on vedolizumab compared to TNF antagonists [3]. In vedolizumab-treated patients, the hypothetical mechanism is that vedolizumab's gut-selective leukocyte migration inhibitor mechanism may lead to α4β7-expressing lymphocytes trafficking to other organ systems, where extraintestinal manifestations (EIMs) with a parallel course to IBD would appear. However, in this report, Dubinsky et al. [3] considered aphthous stomatitis as an EIM of IBD, similar to Sweet syndrome, erythema nodosum, or sclerosing cholangitis.

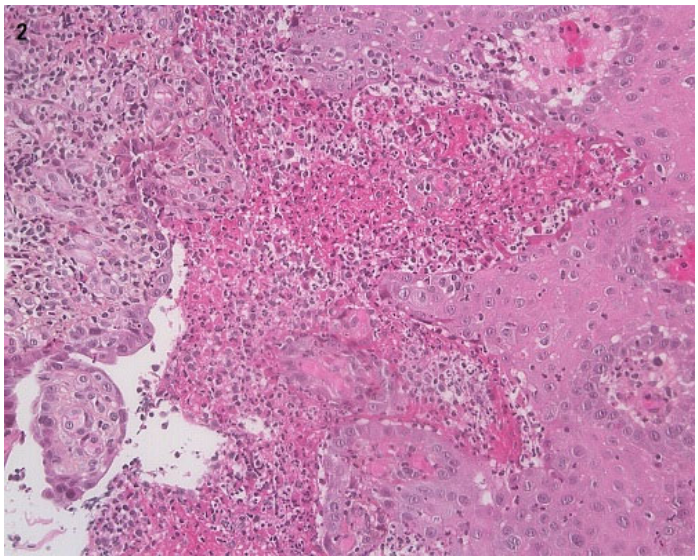

Figure 2. *Oral mucosal biopsy shows intense inflammatory infiltrates with polymorphonuclear neutrophils and eosinophils in the lamina propria and a few inflammatory cells in the epithelium. H&E, 10×.*

In our patient the stomatitis appeared a few days after the first dose and worsened in the following weeks, in spite of improving UC symptoms on vedolizumab. There was no previous history of similar oral lesions or symptoms. We ruled out infections and immunobullous diseases. Several treatments, including high-dose systemic corticosteroids, did not improve the stomatitis. Oral lesions healed completely after vedolizumab was discontinued.

We postulate that vedolizumab, through binding with α4β7 integrin expressed in T cells and plasma cells blocks infiltration of the oral mucosa by these cells. This in turn may lead to overexpression of innate immune mediators, which in our case led to neutrophilic infiltration of oral mucosa and severe stomatitis, in which pathological findings were different from UC.

Conclusion

In view of the evolution, resolution, and histology, we believe the gingivostomatitis to be a direct side effect of vedolizumab, rather than an EIM of the underlying IBD. The clinicians need to be aware of this adverse event, which could be mistakenly considered as an EIM of IBD.

Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Zhou W, Huang Y, Lai J, et al. Anti-inflammatory biologics and anti-tumoral immune therapies-associated colitis: A focused review of literature. *Gastroenterology Res*. 2018;11:174-188. [PMID: 29915627].
2. Harty S, Fleming P, Rowland M, et al. A Prospective study of the oral manifestations of Crohn's disease. *Clin Gastroenterol Hepatol.*

2005;3:886-891. [PMID: 16234026].

3. Dubinsky M, Cross R, Sandborn W, et al. Extraintestinal manifestations in vedolizumab and Anti-TNFtreated patients with inflammatory bowel disease. *Inflamm Bowel Dis*. 2018;24:1876-1882. [PMID: 29668916].