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Letter to the editor

Ibrutinib-associated oral ulcers

Background

Bruton tyrosine kinase (BTK) is a critical downstream mediator of B-cell antigen receptor (BCR) signaling pathway, commonly involved in the pathogenesis of hematological malignancies, in particular chronic lymphocytic leukemia (CLL) and mantle cell lymphoma (MCL) [1]. BTK inhibition by the monoclonal antibody ibrutinib has been shown to be effective in clinical trials, with acceptable tolerability, as monotherapy in naïve and refractory/relapsed CLL and other hematological malignancies [2].

Oral adverse effects are not reported in ibrutinib treatment safety studies [3]. However, an efficacy clinical trial reported non-specific "stomatitis" in 11% of patients [4], and recently Vigarios et al. [5] documented grade ≥3 oral toxicity in three CLL patients as "dose-limiting stomatitis associated with ibrutinib therapy".

We report an additional case consistent with ibrutinib-associated oral ulcers in a CLL patient and contemplate on the management and pathogenesis of this adverse effect.

Case report

A 72-year old male presented in July 2019 with a chief complaint of painful lip lesions of 10 days duration, causing dysphagia. He had used several over-the-counter topical healing creams to no avail. The patient was diagnosed with CLL five years before presentation and was initially put in active surveillance. On January 2018 he developed CLL-associated autoimmune hemolytic anemia and was treated with four courses of rituximab and cyclophosphamide with favorable response. On March 2019, due to worsening of CLL, he started oral ibrutinib (420 mg/day) as monotherapy, with concomitant use of prophylactic antibiotic (cotrimoxazole), antifungal (fluconazole) and antiviral (valacyclovir) drugs. His medical history was, also, remarkable for hypertension treated with perindopril arginine, nebivolol and manidipine dihydrochloride; diabetes mellitus under metformin; hypothyroidism under levothyroxine; osteoporosis managed with alendronate; and elevated uric acid treated with allopurinol. No history of previous recurrent oral ulcerations was provided.

His most recent complete blood count revealed anemia [RBC = 3.93 M/μL (4.5–6.3 M/μL) and HGB = 12.7 g/dl (14–16.5 g/dl)], thrombopenia [PLT = 83 K/Ml (140–440 K/Ml)], lymphocytosis [LYM = 4.85 × 10^3/μL (1.5–3 × 10^3/μL)] and neutropenia [1.03 × 10^3/μL (1.5–8 × 10^3/μL)].

Clinical examination revealed three large, ovoid ulcers surrounded by erythematous halo and covered by thick, green-shaded pseudomembranes on the lower labial mucosa (Fig. 1); two smaller ulcers were present on the dorsal surface of the tongue and the upper lip. There was also, intense halitosis, although his dental and periodontal condition was satisfactory. The overall presentation of the ulcers was consistent with stomatitis associated with ibrutinib [6], grade 3, and no further laboratory testing was performed.

After consulting his hematologist, ibrutinib treatment was not modified, and the patient was medicated daily with 0.5 mg/Kg prednisolone (total 40 mg) and metronidazole 1.5 gr, as well as an oxygenating mouthwash. Significant improvement was noted two weeks later and full healing in 3 weeks (Fig. 2), prednisolone was tapered and metronidazole use was terminated; the application of a topical corticosteroid cream was advised. The initial lesions resolved completely, but smaller ulcers continued to develop on the lips during the two month follow-up period, successfully medicated with topical applications of triamcinolone in orabase. The patient was, also, advised to maintain good oral care and avoid hard or irritating foods.

Discussion

In the case presented herein, large, necrotic ulcers surrounded by erythematous halo developed on the lips and dorsal tongue in a CLL patient medicated for approximately five months with ibrutinib. Their late occurrence and clinical presentation are consistent with the stomatitis associated with ibrutinib monotherapy reported by Vigarios et al. [5] that appeared 4 weeks to 16 months after ibrutinib initiation and presented on both keratinized (dorsal tongue) and non-keratinized (ventral tongue and lips) oral mucosa. These features are in contrast to oral mucositis from other targeted therapies and immune checkpoint inhibitors, such as mammalian target of rapamycin (mTOR) inhibitors-induced aphthous stomatitis (mIAS), that appear soon after mTOR inhibitor introduction and are limited to the non-keratinized mucosa [7,8].

In the cases of Vigarios et al. [5], temporal treatment interruption and dose reduction, complemented with basic oral care, systemic and topical corticosteroids and/or photomodulation, lead to healing of the lesions in one week. In our case, the ulcers significantly improved in two weeks following systemic medication with corticosteroids and antibiotics, without necessitating treatment interruption or dose reduction.

As continuation of the treatment with 420 mg ibrutinib may lead to the rapid reappearance of the lesions, a lower dose (280 mg) was prescribed in all previous cases [5]. In our case, the education of the patient in early recognition and medication of new lesions with a topical corticosteroid, along with good oral care maintenance and diet modification, prevented the reappearance of ulcers of the same severity as the initial ones during the two-month follow-up period while continuing treatment with the same dose (420 mg). This scheme has been proven successful in the prevention of oral complications in cancer-targeted therapies, most notably mIAS [9].

The pathogenesis of oral ulceration associated with ibrutinib is not elucidated and can been attributed to its many off-target effects that may cause autoimmune-like inflammatory responses [10] or inhibit other kinase pathways [11,12], resulting in deregulations associated

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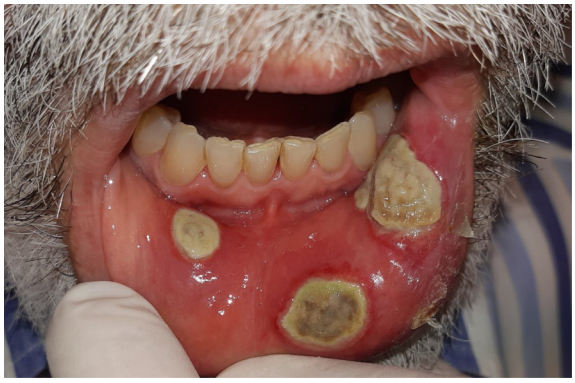

Fig. 1. Initial examination. Three large, ovoid, necrotic ulcers on the lower labial mucosa.

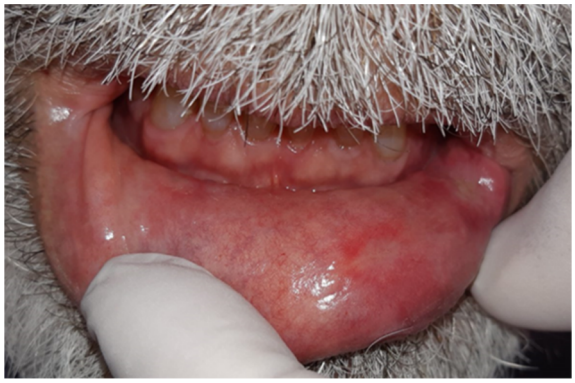

Fig. 2. Two-week follow up. Significant clinical improvement.

with oral aphthous-like ulcerations [13]. Although a common side effect of ibrutinib is neutropenia and neutropenic patients are prone to the development of necrotic oral aphthous-like ulcers [14], the patients of Vigarios et al. [5] were not neutropenic and had negative bacterial or viral swabs; neutropenia in our patient was less severe than in previous blood counts when the ulcers appeared and an erythematous halo, a lacking feature in most neutropenic ulcers [14], was seen in all cases. We did not perform microbial swabs on our patient, but the appearance of the ulcers, the presence of halitosis and the more favorable response to metronidazole compared to cotrimoxazol, suggest the presence of anaerobic bacteria in the ulcers.

Finally, the exclusive appearance of lesions on mobile oral mucosa indicates involvement of trauma in its pathogenesis. It is noticed that up-regulation of the Bone Marrow tyrosine kinase gene in chromosome X (BMX), a kinase that may be inhibited by ibrutinib, accelerates the wound healing process of the skin [11].

In conclusion, oral adverse events of ibrutinib may cause treatment delays or interruptions, or dose reductions. To avoid this, patients' education and oncologists' information for the prevention and early recognition of oral adverse effects of ibrutinib, as applied in mIAS [9], may be helpful. Finally, we suggest that the descriptive term "ibrutinib-associated oral ulcers" is more appropriate to "stomatitis" that may encompass any form of inflammation of the oral mucosa.

Declaration of Competing Interest

None declared.

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References

[1] Advani RH, Buggy JJ, Sharman JP, Smith SM, Boyd TE, Grant B, et al. Bruton tyrosine kinase inhibitor ibrutinib (PCI-32765) has significant activity in patients with relapsed/refractory B-cell malignancies. J Clin Oncol 2013;31:88–94.
[2] Byrd JC, Furman RR, Coutre SE, Flinn IW, Burger JA, Blum KA, et al. Targeting BTK with ibrutinib in relapsed chronic lymphocytic leukemia. N Engl J Med 2013;369:32–42.
[3] Tran PN, O'Brien S. The safety of Bruton's tyrosine kinase inhibitors for the treatment of chronic lymphocytic leukemia. Expert Opin Drug Saf 2017;16:1079–88.
[4] Byrd JC, Brown JR, O'Brien S, Barrientos JC, Kay NE, Reddy NM, et al. Ibrutinib versus ofatumumab in previously treated chronic lymphoid leukemia. N Engl J Med 2014;371:213–23.
[5] Vigarios E, Beylot-Barry MH, Jegou LO, Ysebaert L, Sibaud V. Dose-limiting stomatitis associated with ibrutinib therapy: a case series. Br J Haematol 2019;185(4):784–8.
[6] https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_8. 5x11. pdf. Last accessed on 21/9/2019.
[7] Carrozzo M, Grau-Eriksen J, Bensadoun RJ, Boers-Doets CB, Lalla RV, Peterson DE. Oral mucosal injury caused by targeted cancer therapies. J Natl Cancer Inst Monogr 2019;53:30–44.
[8] Vigarios E, Epstein JB, Sibaud V. Oral mucosal changes induced by anticancer targeted therapies and immune checkpoint inhibitors. Support Care Cancer 2017;25(5):1713–39.
[9] Boers-Doets CB, Raber-Durlacher JE, Treister NS, Epstein JB, Arends ABP, Wiersma DR, et al. Mammalian target of rapamycin inhibitor-associated stomatitis. Future Oncol 2013;9:1883–92.
[10] Fabbro SK, Smith SM, Dubovsky JA, Gru AA, Jones JA. Panniculitis in patients undergoing treatment with the bruton tyrosine kinase inhibitor ibrutinib for lymphoid leukemias. JAMA Oncol 2015;1:684–6.
[11] Berglof A, Hamasy A, Meinke S, Palma M, Krstic A, Mansson R, et al. Targets for ibrutinib beyond B cell malignancies. Scand J Immunol 2015;82:208–17.
[12] Dubovsky JA, Beckwith KA, Natarajan G, Woyach JA, Jaglowski S, Zhong Y, et al. Ibrutinib is an irreversible molecular inhibitor of ITK driving a Th1-selective pressure in T lymphocytes. Blood 2013;122:2539–49.
[13] Dalghous AM, Freysdottir J, Fortune F. Expression of cytokines, chemokines, and

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chemokine receptors in oral ulcers of patients with Behcet's disease (BD) and recurrent aphthous stomatitis is Th1-associated, although Th2-association is also observed in patients with BD. Scand J Rheumatol 2006;35:472–5.

[14] Hematologic disorders. In: Neville B, Damm DD, Allen C, Chi A. Oral and maxillofacial pathology 4th Ed. Saunders/Elsevier; 2016. p. 542–3.

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