

Tongue Necrosis as a Manifestation of Immune Dysfunction: A Complex Case of Lupus, Histoplasmosis, and Macrophage Activation Syndrome

Madalyn Walsh¹, Alcik Feng¹, Petar Lenert², and Bharat Kumar³

¹University of Iowa Hospitals and Clinics

²University of Iowa Roy J and Lucille A Carver College of Medicine

³The University of Iowa Hospitals and Clinics

March 28, 2023

Tongue Necrosis as a Manifestation of Immune Dysfunction: A Complex Case of Lupus, Histoplasmosis, and Macrophage Activation Syndrome

Madalyn Walsh, MD¹, Alcik Feng, MD², Petar Lenart, MD PhD², Bharat Kumar, MD MME²

¹Department of Internal Medicine, University of Iowa Hospitals & Clinics

²Division of Immunology, University of Iowa Hospitals & Clinics

Abstract

Immune dysfunction can manifest in unexpected ways. We present the case of a patient with systemic lupus erythematosus (SLE) in whom the first sign of disseminated histoplasmosis and consequent macrophage activation syndrome (MAS) was tongue necrosis. In those with immune dysfunction, a high index of clinical suspicion for atypical infections is warranted.

Background

Tongue necrosis is a rare entity as the tongue is a highly vascularized structure supplied by the lingual artery, a branch of the external carotid artery. Tongue necrosis typically presents with unilateral lingual pain, swelling, discoloration and, in severe cases, necrosis. There are many underlying factors that can contribute to the development of tongue necrosis (Table 1). Giant cell arteritis (GCA), ANCA (Anti-Neutrophil Cytoplasmic Antibody)-associated vasculitis and other vasculitides have been previously described as underlying systemic causes of tongue necrosis [1-4]. Other potential causes include infection (particularly tuberculosis and syphilis), malignancy, radiation therapy, use of vasoconstricting medications and systemic hypoperfusion such as in the setting of shock [1]. This case report adds histoplasmosis to this list of differential diagnoses.

Case Report

A 65-year-old female presented with left sided tongue necrosis (Figure 1). She had a past medical history significant for SLE on mycophenolate mofetil (MMF) 1000 mg twice daily and prednisone 5 mg daily, Factor V Leiden, and atrial fibrillation. The patient initially developed pain and numbness on the left side of her tongue which worsened over the course of several weeks and prompted her to see her primary care doctor. She was started on amoxicillin-clavulanate without improvement of her symptoms. A Computed Tomography (CT) scan was performed and revealed acute inflammatory phlegmonous changes of the left tongue without any abscess or fluid collection as well as left anterior lateral facial soft tissue and left submandibular space inflammation.

Physical exam of the oral cavity revealed a left sided area of tongue necrosis that extended medially and did not cross midline (Figure 1). There was also a fissure in the mouth posteriorly as well as erythema of the lateral lower lip. No thrush was noted.

Vasculitides including GCA, polyarteritis nodosa, ANCA-associated vasculitis and cryoglobulinemic vasculitis were considered as possible etiologies. PET-CT scan was obtained and did not show any evident signs of vessel inflammation. ANCA titers and cryoglobulin levels were also within normal limits. Laboratory examination revealed a soluble interleukin 2 receptor (sIL2r) 11,141 U/mL, ferritin 42,975 ng/mL, C-Reactive Protein (CRP) 19.5 mg/dL, fibrinogen <50 mg/dL.

Infectious work up was performed with bronchoalveolar lavage (BAL) confirming disseminated histoplasmosis. Histoplasma urine and blood antigens were positive at >25.0 ng/mL (N undetectable) and >20.0 ng/mL (N undetectable) respectively. Blood cultures were obtained and revealed fungemia with speciation showing histoplasma. Tongue and lip biopsies revealed necrotic tissue with neutrophilic inflammation and fungal organisms. Bone marrow biopsy was obtained and revealed hemophagocytosis and histoplasmosis.

Malignancy was also considered given the location of necrosis as well as severe leukocytopenia and thrombocytopenia, but flow cytometry and superficial tongue biopsies did not reveal evidence of malignancy. The patient's medical history of Factor V Leiden and atrial fibrillation did raise concern for a thromboembolic event. COVID antibodies were also obtained with the spike antibody present, indicating vaccination, and the nucleocapsid antibody negative, indicating that she had not had a recent infection that could have resulted in a hypercoagulable state.

The patient was started on liposomal amphotericin for antibiotic coverage but continued to have fevers and rising levels of CRP and transaminases raising concern for cytokine storm given her underlying autoimmune disease and active systemic fungal infection. The patient was also noted to have low fibrinogen and dramatically rising ferritin in addition to her cytopenias. Serum soluble interleukin 2 receptor (sIL2r) was also markedly elevated. Flow cytometry of peripheral blood showed increased CD38++/HLA-DR/CD8+ which was highly suggestive of hemophagocytic lymphohistiocytosis (HLH). Bone marrow biopsy confirmed both hemophagocytosis and histoplasmosis. Laboratory markers and clinical picture initially did improve with the initiation of steroids, IVIG and Anakinra along with concurrent treatment of histoplasmosis. However, following stabilization for 2-3 days, she developed septic shock and passed away.

Discussion

To our knowledge, this is the first documented case in peer-reviewed literature of tongue necrosis secondary to histoplasmosis. Histoplasmosis is the most common endemic mycosis found in the United States and is the most likely fungus to cause infection resulting in hospitalization [5]. Most individuals exposed to histoplasma spores develop a subclinical infection and are asymptomatic. Those that develop acute symptoms typically present with pulmonary manifestations such as dyspnea and cough [6]. Disseminated disease may occur in patients who have a particularly high level of exposure or have immune dysfunction, such as those with autoimmune disease, those taking immune modulators, and those with inborn errors of immunity [7].

While cases of tongue necrosis have been well described in the setting of GCA, there is a paucity of literature on the occurrence of tongue necrosis as a result of fungal infection, and none published that are specifically the result of histoplasma infection [1-4]. Tongue necrosis has been seen in the setting of mucormycosis in three published cases (Table 2). These three patients had conditions that resulted in immune dysfunction, predisposing them to fungal infection [5-7]. Our patient would also be considered as having had immune dysfunction in the setting of SLE with high disease activity and long-term steroid and MMF administration.

Specifically, both SLE and the MMF used to treat SLE are associated with dysfunction in T-cell activity. Because the Th17 subset of T-cells is necessary for coordinating and regulating neutrophilic clearance of fungal infections, this is likely a root cause for this patient's susceptibility to histoplasmosis and severity of infection. The additional challenge is that T-cells play important roles in resolving inflammatory states. After all, the three previously reported cases of mucormycosis-induced tongue necrosis were associ-

ated with conditions that resulted in impaired neutrophil-mediated inflammation. In this case, we speculate that T-cell dysfunction led to a paradoxical state in which there were elements of both immune deficiency (systemic fungal infection) and hyperinflammation (HLH/MAS). This, in turn, raises a clinical dilemma in immunomodulatory treatment. We elected to administer IVIG and anakinra since they are unlikely to impair T-cell defenses, and there may be a protective element of IVIG when administering high-dose steroids to treat the cytokine storm. Nevertheless, the patient's burden of disease led to progression of sepsis to shock.

Tongue necrosis and cytokine storm (HLH/MAS) share common predisposing triggers, including infection, malignancy, and autoimmune disease. We believe histoplasmosis was the trigger for cytokine storm in our patient in the setting of T-cell dysfunction secondary to SLE and immune modulation. Laboratory findings, radiographic studies, and histopathology allowed us to exclude malignancy, thromboembolism, and vasculitis from our list of differential diagnoses for the cause of tongue necrosis. Treatment of the infection and the hyperinflammation resulted in immediate improvement but the prognosis of disseminated histoplasmosis remained poor. This case highlights the importance of maintaining a high index of clinical suspicion for fungal infection in those with immune dysfunction.

Acknowledgements

We would like to thank the patient and their family for allowing us to share her story.

Funding information

There was no funding received for this article.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Ethical approval

Ethical approval is not required by the Institutional Review Board for case report publication.

Consent

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

References

- [1] Zaragoza JR, Vernon N, Ghaffari G. Tongue necrosis as an initial manifestation of giant cell arteritis: case report and review of the literature. *Case Rep Rheumatol* 2015;2015:901795 P
- [2] Payen C, Kucharczak F, Favier V. Giant cell arteritis presenting with progressive dysphagia and tongue necrosis. *CMAJ*. 2022 Mar 21;194(11):E420. doi: 10.1503/cmaj.211483. PMID: 35314443; PMCID: PMC9053960.
- [3] Barbosa de Siqueira Sobrinho RA, Alvino de Lima KC, Carvalho Moura H, et al. Tongue necrosis secondary to giant cell arteritis: a case report and literature review. *Case Rep Med* 2017;2017:1–5.
- [4] DeBord LC, Chiu I, Liou NE. Delayed diagnosis of giant cell arteritis in the setting of isolated lingual necrosis. *Clin Med Insights Case Rep* 2019;12: 1179547619857690.
- [5] Jaclyn H. Chu, Chris Feudtner, Kateri Heydon, Thomas J. Walsh, Theoklis E. Zaoutis, Hospitalizations for Endemic Mycoses: A Population-Based National Study, *Clinical Infectious Diseases*, Volume 42, Issue 6, 15 March 2006, Pages 822–825
- [6] Wheat J. Histoplasmosis: recognition and treatment. *Clin Infect Dis*. 1994 Aug;19 Suppl 1:S19-27. doi: 10.1093/clinids/19.supplement_1.s19. PMID: 7948567.

- [7] Wheat LJ, Slama TG, Norton JA, Kohler RB, Eitzen HE, French ML, Sathapatayavongs B. Risk factors for disseminated or fatal histoplasmosis. Analysis of a large urban outbreak. *Ann Intern Med.* 1982 Feb;96(2):159-63. doi: 10.7326/0003-4819-96-2-159. PMID: 7059062.
- [8] Dua R, Poate T, Abe F, Diaz-Cano S. Lingual necrosis secondary to mucormycosis. *Br J Oral Maxillofac Surg.* 2012 Sep;50(6):e96-8. doi: 10.1016/j.bjoms.2011.11.008. Epub 2011 Dec 5. PMID: 22153179.
- [9] Pajpani M, Webb R. Lingual necrosis caused by mucormycosis in a patient with aplastic anaemia: case report. *Br J Oral Maxillofac Surg.* 2014 Dec;52(10):e144-6. doi: 10.1016/j.bjoms.2014.09.012. Epub 2014 Oct 7. PMID: 25300888.
- [10] Fattah SY, Hariri F, Ngui R, Husman SI. Tongue necrosis secondary to mucormycosis in a diabetic patient: A first case report in Malaysia. *J Mycol Med.* 2018 Sep;28(3):519-522. doi: 10.1016/j.mycmed.2018.06.004. Epub 2018 Jul 7. PMID: 30205883.

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