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A 78-year-old woman with bilateral tongue necrosis

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A 78-year-old woman presented to the emergency department complaining of a sore tongue. Her medical history included essential hypertension managed with atenolol, 100 mg/d, and enalapril, 5 mg/d, osteoporosis managed with calcium and vitamin D (with no past bisphosphonate treatment), and gastroesophageal reflux disease managed with omeprazole, 20 mg/d. Seventeen years before admission, she had suffered from ovarian carcinoma that was treated by chemotherapy and oophorectomy without therapeutic irradiation. She had no known hypersensitivities or drug allergies. The patient reported pain of the right head, neck, face, and shoulder (ranked 8 on a 0 to 10 visual analog scale, with "10" the most painful), especially while eating. She also reported fatigue, and visual blurring that had developed 2 months before, weight loss over the preceding 8 weeks (from 67 to 60 kg; a 10.4% reduction), and tongue pain of 4-weeks' duration, which she rated as 10 on a 10-point scale. Ten days before presentation at the emergency room, she had undergone a complete blood count (CBC) and computed tomography (CT) of the head to rule out any underlying systemic conditions and space-occupying lesions. CBC and CT results at that time were normal, except for a mild anemia (hemoglobin, 10.7 g/dL; normal = 12-16 g/dL for women). Her platelet count was normal (397×10^9/L, normal = $140–400 \times 10^9$/L).

On clinical examination, the anterior third of the tongue was enlarged bilaterally and painful to palpation. The tissue was necrotic, without bleeding. An ulcerated fissure was noted at its proximal border. The dorsal surface of the tongue was yellowish-gray with elongated papillae that could not be wiped off (Fig. 1).

DIFFERENTIAL DIAGNOSIS

Considering the clinical presentation of bilateral tongue necrosis, we considered several broad categories in our differential diagnosis: trauma, infectious diseases, neoplasms and vascular compromise related to vasculitic disorders, cardiovascular and cerebrovascular disease, and other systemic conditions.

Electrical, thermal, and chemical injury are potential causes of tongue necrosis[1]; however, the patient denied any relevant history. Such extensive necrosis secondary to biting is rare in adults. In addition, this was considered unlikely because the patient had no oral parafunctional habits and was edentulous.

Necrosis of the tongue may develop because of deep fungal (e.g., histoplasmosis, blastomycosis), bacterial (e.g., tertiary syphilis), or viral infection (e.g., members of the human *Herpes viridea*). The tongue is reported as being the intraoral site preferentially affected by Epstein Barr virus– and cytomegalovirus (CMV)-associated necrosis in patients with Human Immunodeficiency Virus (HIV) infection. CMV has been isolated from tongue lesions in patients suffering from graft-versus-host disease following allogeneic hematopoietic stem cell transplantation.

The tongue is a common site of involvement by both primary and metastatic tumors. Squamous cell carci-

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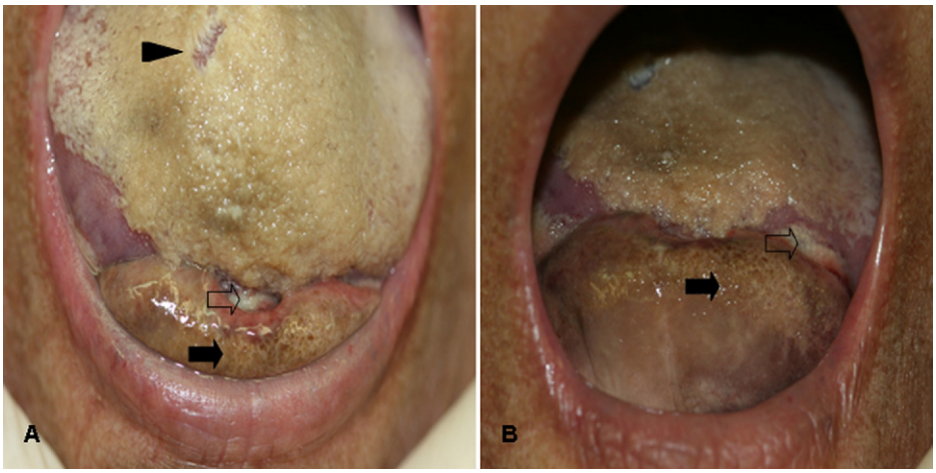

Fig. 1. The patient's tongue at admission: **A,** dorsal and **B,** ventral views. Black arrows indicate necrotic tissue. Open arrows indicate area of ulceration. Black arrowhead points to elongated papillae.

noma is the most common primary malignant neoplasm developing at this site. Although metastasis is not common in the oral cavity, accounting for approximately 1% of oral malignancies, a quarter of the metastases in the oral cavity occur in the tongue, which appears to be a particularly common site in edentulous patients.[2]

Giant cell arteritis (GCA), also known as temporal arteritis and cranial arteritis, is a chronic vasculitis of large and medium-sized arteries, with both localized and systemic inflammatory features. This condition affects 10 to 70 per 100,000 individuals annually. Disease onset occurs exclusively in those older than 50 years (average, 70 years), with women affected 1.4 to 3.0 times more commonly than men. Failure to treat this condition may lead to serious ischemic complications, such as visual disturbances and sudden blindness owing to ischemic optic neuropathy, stroke, aneurysm of the aorta, infarction of the intestine, renal insufficiency, and myocardial infarction.[3] Clinical features of GCA include a gradual worsening of diffuse unilateral headaches and scalp tenderness, facial pain or sore throat without headache, temporal artery abnormalities (e.g., tenderness, nonpalpable pulse), chest pain, fever, anorexia, weight loss, and scalp necrosis. Jaw and tongue claudication upon chewing or talking is relatively common; however, tongue infarction is rare.[4] Anemia and elevated platelet count are often noted.

Oral involvement is noted in 6% to 50% of patients with antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (Wegener's granulomatosis [WG]), but only rarely do the presenting features include ulceration, strawberry gingivitis, salivary gland enlargement, palate osteonecrosis, and oro-antral communication. Other orofacial manifestations of WG include facial paralysis, labial mucosal nodules, dental pain caused by sinusitis, jaw claudication, and pain. Carter and Brizman[5] reported a 56-year-old woman with WG who developed necrosis of the tongue mucosa 3 weeks after initial presentation.

Ergotamine, an alkaloid ergot commonly used for migraine relief that may cause peripheral vasoconstriction, vascular stasis, and thrombosis, has been associated with tongue necrosis.[6] Similarly, vasopressin therapy for control of acute bleeding has been reported as a possible cause of tongue necrosis, especially in the presence of underlying atherosclerotic disease.[7] Review of our patient's medical history effectively ruled out these possibilities.

Radical neck dissection with ligation of the external carotid artery in patients with subsequent radiotherapy to the neck has been reported as a cause of unilateral tongue necrosis.[8] Other causes of tongue necrosis include complications from arterial embolization and anticancer chemotherapy or radiotherapy.[1] Our patient had no history of neck dissection, radiation therapy, or arterial embolization.

Tongue necrosis can result from ischemia related to hematologic conditions, such as essential thrombocytosis[9] or disseminated intravascular coagulation (DIC),[10] and to cardiovascular disease, such as myocardial infarction. However, no other manifestations of thrombocytosis were observed, and the patient's platelet levels were reportedly normal 10 days before initial presentation. The patient's history and clinical manifestations ruled out DIC and myocardial infarction.

Orita et al.[11] described a case of tongue necrosis following transient ischemic attack (TIA) that was accompanied by occlusion of the external carotid

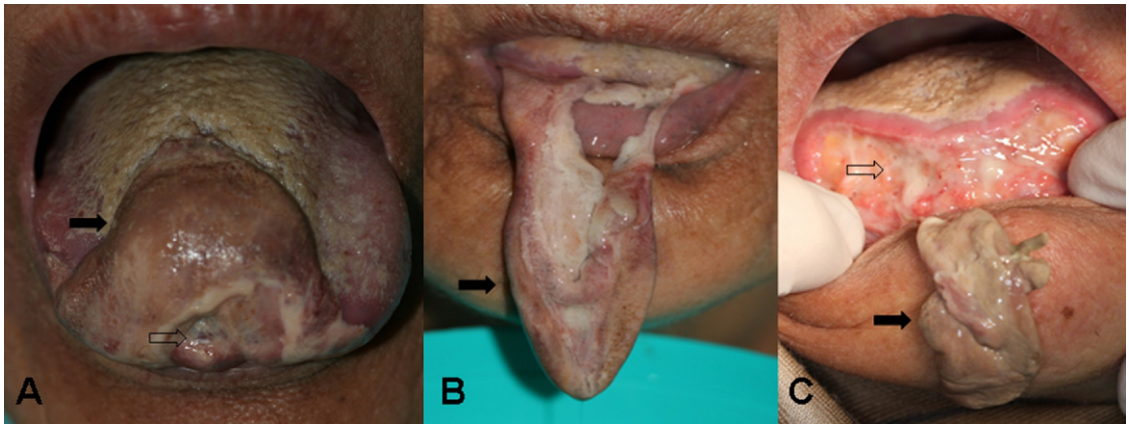

Fig. 2. The patient's tongue at **A,** third, **B,** fifth, and **C,** sixth day of hospitalization demonstrating auto-amputation of the necrotic tissue and exposure of underlying ulcerated tissue.

artery in a 67-year-old man. However, bilateral tongue necrosis is not compatible with a unilateral presentation of TIA.

Tongue necrosis has also been reported in patients with other systemic conditions associated with vascular involvement, such as systemic lupus erythematosus, Raynaud's phenomenon, and anti-phospholipid syndrome.[12]

Renal insufficiency–related calciphylaxis has also been reported as a cause of tongue necrosis.[13]

DIAGNOSIS AND MANAGEMENT

The patient was admitted to the hospital. Follow-up blood tests demonstrated an elevated erythrocyte sedimentation rate (ESR; 69 mm/h, normal = 1-20 mm/h), elevated C-reactive protein (6.1 mg/L, normal = 0-1 mg/L), mild normocytic anemia with hemoglobin level of 10.2 g/dL, and mean corpuscular volume of 86.1 μm^3 (normal = 77-91 μm^3); and elevated leukocyte (15.6 $\times$ 10^9/L, normal = 4-10 $\times$ 10^9/L) and platelet levels (572 $\times$ 10^9/L). Creatinine was within the normal range (0.63 mg/dL, normal = 0.60–1.06 mg/dL). Cytoplasmic and perinuclear ANCA were negative. A microbial culture from the tongue revealed normal oral flora. Polymerase chain reaction was negative for herpes simplex virus-1, herpes virus-2, and CMV infection. CMV antibodies were not detected in the serum. Plain occlusal mandibular and chest radiographs were without any pathologic findings. Color-coded duplex sonography of the temporal arteries revealed occlusion of the left artery and normal flow of the right artery.

Although the patient had an elevated ESR level and reported weight loss, fatigue, malaise, and jaw claudica-

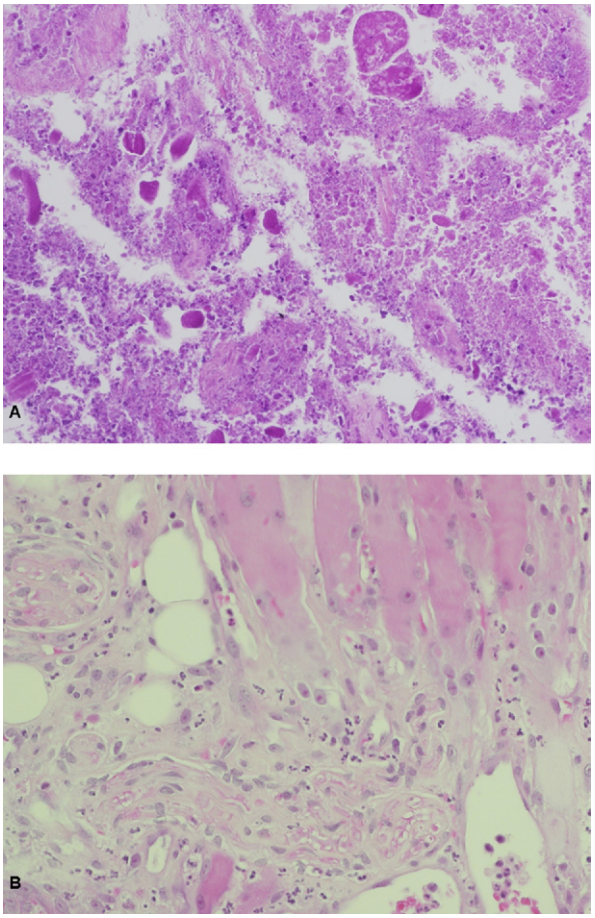

Fig. 3. Photomicrographs of tongue tissue: **A,** self-amputated necrotic material with acute inflammation and bacterial colonization (hematoxylin and eosin stain $\times$200). **B,** Viable tissue with acute inflammation within biopsied tongue tissue proximal to necrosis (hematoxylin and eosin stain $\times$200).

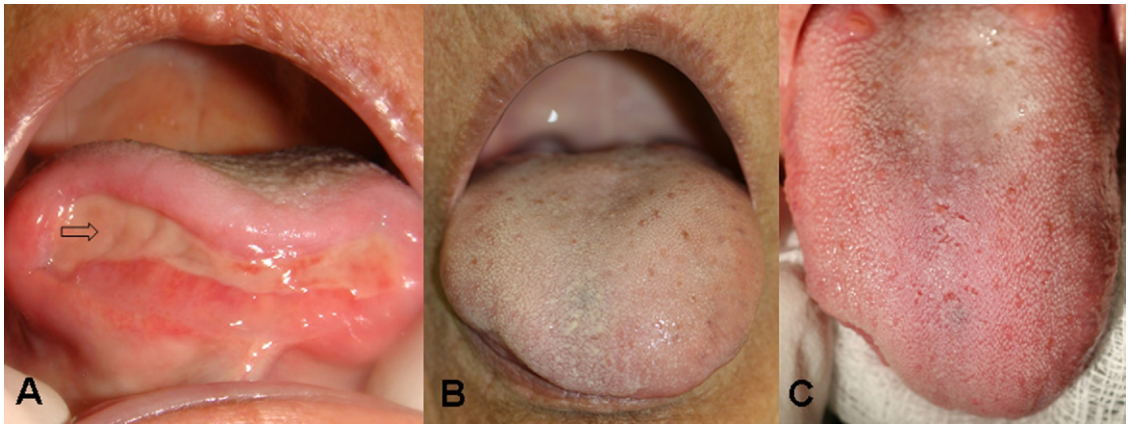

Fig. 4. The patient's tongue at **A,** 14th day of hospitalization; **B,** 1 month after discharge; and **C,** 12-month follow-up demonstrating full epithelization. Open arrow indicates ulceration.

tion and pain, WG was ruled out based on the normal ANCA serum test, normal creatinine levels, and the absence of pulmonary findings on plain chest radiographs.

According to American College of Rheumatology (ACR) criteria, at least 3 of the following 5 criteria are needed for a diagnosis of GCA: (1) age older than 50 years at disease onset, (2) new onset of localized headache, (3) temporal artery tenderness or a decreased temporal artery pulse, (4) ESR higher than 50 mm/h, and (5) a biopsy sample, including artery, showing necrotizing arteritis, characterized by a predominance of mononuclear cell infiltrates or a granulomatous process with multinucleated giant cells.[14] The presence of 3 or more of ACR's 5 criteria is associated with a sensitivity of 93.5% and a specificity of 91.2%.[14]

Our patient fulfilled 4 of the 5 GCA diagnostic criteria: age at onset, new headache, a nonpalpable temporal artery pulse, and elevated ESR. In addition, the occlusion of the left temporal artery demonstrated by sonography was compatible with GCA.[15]

Our final diagnosis was GCA.

Upon diagnosis, prompt therapy, even before confirmation by a temporal biopsy, was necessary to avoid serious complications, especially irreversible eye damage.[3] Treatment with prednisone, 60 mg/d was initiated. Topical nystatin and chlorhexidine, as well as enteric opioid analgesics were also administrated.

On the sixth day of hospitalization, the necrotic tissue underwent self-amputation (Fig. 2, *A–C*). Histopathological examination of the amputated tissue (Fig. 3, *A*) and an incisional biopsy of the proximal intact tongue tissue (Fig. 3, *B*) revealed necrosis and acute inflammation with no evidence of fungal organisms.

The planned biopsy of the temporal artery was ultimately not performed because of the inability to clinically palpate the artery and the gradual improvement seen following the initiation of steroid therapy.

With progressive healing of the tongue after autoamputation (Fig. 4, *A*) and with diminishing pain in the head, face, and neck, the patient was discharged after 2 weeks of hospitalization, with the restoration of painless eating. The patient was continued on 60 mg of prednisone per day. Full epithelization was evident a month later (Fig. 4, *B*). A tapering of the steroid therapy was instituted with continuation of topical antifungal therapy. After 12 months, the patient was in good health and showed a gain in weight (70 kg). Her tongue morphology was normal with minimal limitations during function (Fig. 4, *C*).

DISCUSSION

Orofacial manifestations of GCA include temporal pain, jaw claudication and pain, and diplopia. Dental pain, dysphagia, chin hypoesthesia, macroglossia, glossitis, necrosis of lip or tongue, and facial swelling have been also reported. Temporal pain may vary in character from throbbing, burning, boring, to lancinating, and can vary from mild to severe in intensity and may present as allodynia (pain upon touch). Jaw claudication, which affects up to 65% of the patients, is attributable to involvement of the maxillary artery and the resulting masticatory muscle ischemia and pain. Pain of the temporalis and masseter muscles on chewing is virtually pathognomonic of GCA. To avoid misdiagnosis,[16] the health care provider has to be familiar with these orofacial manifestations because they may be the presenting symptoms.

In our patient, despite the absence of a temporal artery biopsy, a diagnosis of GCA was rendered with confidence based the presence of 4 of 5 ACR GCA diagnostic criteria. Although the temporal artery biopsy

is still considered the gold standard for the diagnosis of GCA by some clinicians, it is well accepted that its diagnostic role is partial or confirmatory,[14] as inflammation is not seen in all temporal artery biopsies. Because of the sporadic localization of the vasculitis lesions along the vessel, several biopsies or a biopsy of 2 to 3 cm in length and examination of serial sections of the specimen may be required to identify the characteristic histopathologic features. Considering that even bilateral temporal artery biopsy is not highly sensitive, patients who satisfy the other ACR criteria but demonstrate negative unilateral or even bilateral temporal artery biopsy should be treated as if there is a very high probability of GCA.[3]

Our diagnosis was reinforced by subsequent course of her condition and response to therapy, using the additional criteria described by Breuer et al.[17]: improvement of symptoms within 3 days of corticosteroid therapy, and no other condition relevant to the patient's symptoms diagnosed during a follow-up of 6 months.

The further course of GCA can be predicted according to the initial systemic inflammatory response of the patient, which is determined by the following 5 parameters: sedimentation rate greater than 100 mm/h, thrombocytosis $> 400 \times 10^9$/L, hemoglobin below 11 g/dL, leukocytosis greater than 11×10^9/L, and fever higher than 37.5°C. Patients with a strong response (at least 4 positive parameters) may have a prolonged disease course with more flare-ups, and require higher steroid doses than moderate and weakly responding patients.[18] Our patient showed 3 positive inflammatory response parameters (thrombocytosis, anemia, and leukocytosis), and was therefore classified as a moderate inflammatory response with a favorable predicted course (that is, a good chance for steroid therapy not being required 3 years after diagnosis). Tapering of the steroid dose was instituted in the sixth week of therapy.

Because of the rich blood supply from the lingual, facial, pharyngeal, and palatine arteries, as well as collateral circulation, ischemia (infarction) and necrosis of the tongue is generally rare, which is most often unilateral.[19] GCA is by far the most common cause of unilateral or bilateral tongue necrosis[19] and should serve as the starting point for investigation of tongue necrosis. In fact, in the absence of a history of physical or chemical trauma or head and neck irradiation therapy, bilateral necrosis of the tongue should be regarded as pathognomonic of GCA. Rapid diagnosis of GCA is essential to prevent development of further serious ocular or cardiovascular complications.

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