Sclerotherapy for atypical oral manifestation of Cowden syndrome

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Cowden syndrome is an autosomal dominant disorder characterized by hamartomas, as well as benign and malignant neoplasms that may present in organ systems throughout the body. It also poses an increased lifetime cancer risk in those with the disorder. Its clinical presentation is often variable, and diagnosis can be challenging. In the head and neck region, it can present as thyroid enlargement or mass formation, cutaneous and mucocutaneous lesions of the skin and the oral cavity. The most typical oral manifestations of Cowden syndrome are oral papillomatosis and a cobblestone appearance of the mucosa. We present a case of vascular malformation of the tongue in a patient with Cowden syndrome. This lesion was similar in appearance to a cutaneous hamartoma on the patient's upper extremity. He had received prior surgical intervention for this tongue mass, and complete resection was recommended subsequently. However, in search of a less invasive treatment to minimize impact on speech and oral function, sclerotherapy was performed, resulting in resolution of the lesion. Sclerotherapy is a well-documented treatment for head and neck vascular malformations, but it is not universally employed. In our patient with atypical oral manifestation of Cowden syndrome, bleomycin sclerotherapy was employed, resulting in resolution of the lesion, as well as preservation of speech articulation and oral function. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;130:e290–e293)

Cowden syndrome is a rare disorder characterized by hamartomas, which are focal benign neoplasms of normal tissue, native to the organ or site where they occur. These masses can develop in most organ systems throughout the body.[1] In the head and neck region, they typically appear on the skin and in the thyroid gland but can also be found in the oral mucosa.[2] Manifestation of the symptoms of this disease process is related to the location, size, and effect of the lesions on organ function. The most serious and feared consequence of Cowden syndrome is an increased risk of malignancy in any region of the body.[3]

Cowden syndrome is most commonly associated with an autosomal dominant mutation in *PTEN*, the gene coding for the phosphatase and tensin homolog (PTEN) protein; it is a tumor suppressor gene located on chromosome 10 q23, which inhibits the Akt signaling pathway. The molecular cascade is normally involved in regulating cell growth, survival, and migration.[4] However, *PTEN* mutation relieves the inhibition of various vascular growth factors, leading to unregulated angiogenesis and development of hamartomas and vascular malformations. These malformations can cause organ damage via vessel rupture and direct tissue damage or cell death.[5]

Diagnosis of Cowden syndrome is challenging because of the wide range of associated symptoms.[6] However, as a result of the mechanism noted above, hamartomatous vascular malformations are commonly reported. Although current data estimate that the prevalence of the disease is 1 in 200,000, this is likely an underestimation resulting from its variable clinical presentation.[1] Currently, treatment options for these hamartomas include surgical resection, curettage, topical agents, laser ablation, localized radiation therapy, and sclerotherapy.[7]

In this report, we discuss the case of a patient with Cowden syndrome, whose vascular malformations were treated with sclerotherapy. This treatment modality involves injecting sclerosing agents into a blood vessel, causing endothelial cell damage and exposure of subendothelial collagen. This, then, triggers the primary and secondary coagulation cascades, which cause occlusion of the feeding vessels, subsequent sclerosis and fibrosis, and degradation and reabsorption of the malformation. There is typically near-complete or complete involution of the lesion. Sclerotherapy effectively and affordably treats oral lesions while circumventing physiologic and aesthetic complications of the more invasive surgical treatments. Bleomycin is one sclerosing agent that has been proven to have a strong effect on the vascular endothelium and has, therefore, been used to treat various vascular abnormalities.[8]

CASE REPORT

A 40-year-old man with a history of Cowden syndrome presented to our oral and maxillofacial surgery service for a second opinion of a 1-cm venous malformation of the left anterior tongue (Figure 1). The patient's systemic presentation of Cowden syndrome included liver and spinal hamartomas, which were monitored with serial imaging. He had received no previous invasive intervention for these entities but had undergone thyroidectomy for Cowden syndrome–related disease. He

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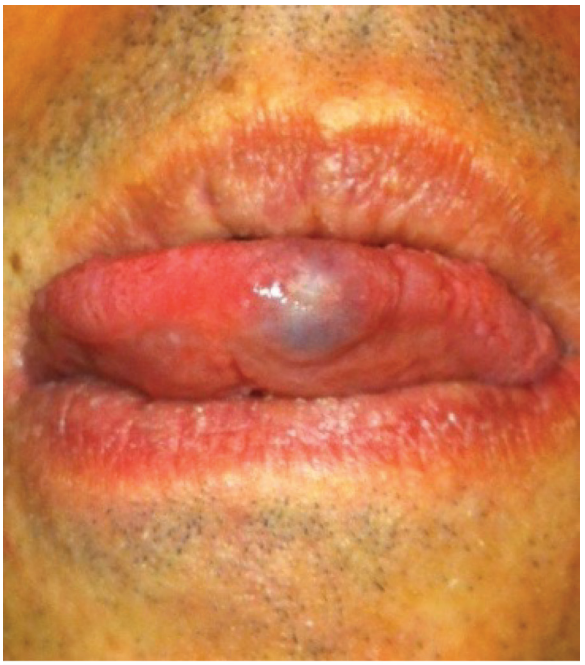

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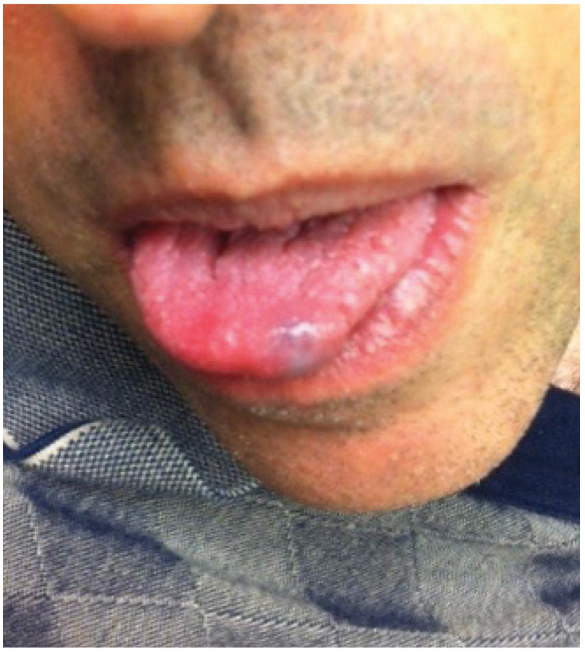

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Fig. 1. Full-thickness left anterior tongue tip vascular malformation. **A,** Anterior and ventral view. **B,** Dorsal view.

was unable to recall the exact pathologic diagnosis (inflammatory, endocrine, or neoplastic). Also, he had cutaneous manifestations, including multiple cherry angiomas on his chest and an exophytic, right upper extremity hamartoma (Figure 2).

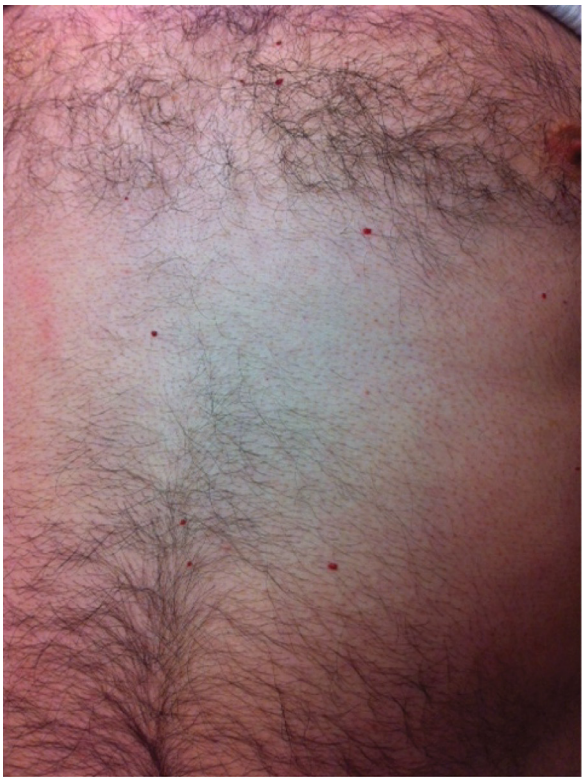
The patient's medical history also included postablative hypothyroidism, for which he was on thyroid hormone replacement via levothyroxine. His surgical history included an appendectomy as well. The patient was not taking any other medications. His social history was negative for alcohol, tobacco, or drug use, and his only allergy was to gadolinium.

Two years before his presentation, the patient had been initially treated by a dermatologist, and at that time, a punch biopsy of the lesion had been performed, and histopathologic examination yielded a diagnosis of hemangioma. The patient reported decompression of the lesion after that procedure. Approximately 1 year after the initial biopsy, the malformation returned and progressively enlarged causing difficulty in articulation of speech at times. The patient was seen by an oral surgeon, who recommended wedge excision of the lesion at the anterior tongue tip in a hospital setting. During history taking and physical examination, the patient denied having pulsatile blood flow during or immediately after the previous biopsy or at any other time and denied experiencing any change in taste or neurosensory dysfunction of the tongue. His physical examination revealed a 1-cm compressible, vascular nodule of bluish hue on the left anterior tongue tip, without palpable thrill. The lesion was documented, and the patient was scheduled for re-evaluation of the lesions in 6 weeks.

Upon return to the clinic, our patient noted no decrease in the size or symptoms of the lesion and reported occasional difficulty with speech. The patient was offered treatment options, which included surgical excision, radiotherapy, and sclerotherapy. Sclerotherapy was chosen to avoid postoperative risks associated with localized radiation therapy or surgical excision, such as fibrosis, pain, dysphagia, and further dysfunction of the tongue and speech. The patient maintained throughout the process that his primary concern was the risk of his speech being affected further by excision, and this was the most compelling reason for his choosing sclerotherapy.

TECHNIQUE

Bleomycin was obtained through the oncology pharmacy at our institution. The procedure and sclerosing agent were reviewed with the patient. The potential risks and complications, including local or systemic reaction to the agent, as well as its known potential for pulmonary fibrosis when administered systemically, were explained. The procedure began with injection of a local anesthetic with epinephrine into the tongue tip, administered near but not within the lesion to avoid distortion. Next, a 25-gauge needle was inserted into the anterior tongue lesion and 15 units of bleomycin (1.5 cc diluted to 10 units/mL) was injected into the lesion, after which the lesion was compressed with gauze and digital pressure, without complication.



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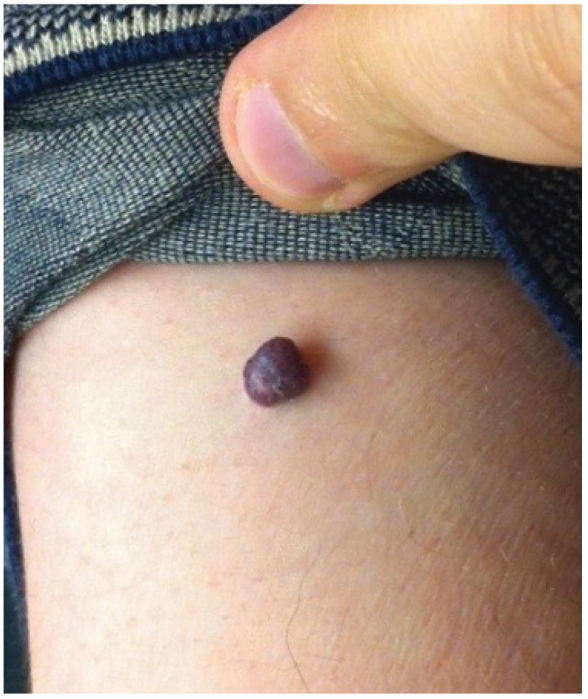

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Fig. 2. Clinical photos of cutaneous manifestations of Cowden syndrome. **A,** Multiple scattered cutaneous angiomas. **B,** Exophytic hamartoma of the right upper extremity.

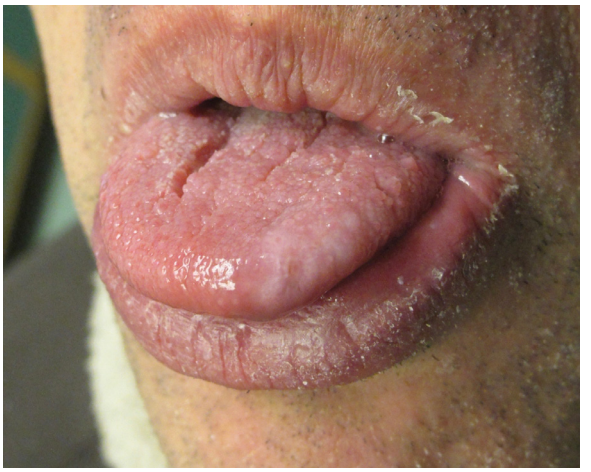

Fig. 3. Resolution of left anterior tongue vascular lesion of purplish hue, with fibrotic-appearing margins.

The patient returned at postoperative week 2, and examination showed ongoing resolution of the anterior tongue tip venous malformation. Upon return 2 weeks thereafter, the lesion was noted to have resolved—flattened , and replaced by scar tissue, as shown in Figure 3. Our patient had minimal postoperative pain or bleeding and reported his speech being maintained and improved as a result of the sclerotherapy. He continued to do well in the postinjection period without recurrence of the lesion and satisfactory speech articulation. The patient did not require further treatment.

DISCUSSION

Cowden syndrome is a disease that involves benign focal neoplastic growths that often affect the vasculature all through the body and within vital organs. The most common oral finding of Cowden syndrome, and a major diagnostic criterion, is oral papillomatosis, which often has a cobblestone appearance. This, however, was not the major clinical presentation in our patient; instead, he had a vascular hamartoma on the tongue tip and, thus, an atypical manifestation of the disease, which is known to be variable in its presentation. He did, however, have multiple cutaneous facial papules and a scrotal tongue, in addition to hamartomas in the liver and the spine.

The manifestations of Cowden syndrome may be managed by using various treatment modalities, including surgical excision, localized radiation therapy, and sclerotherapy. Although surgical excision using a wedge resection technique is commonly employed to remove these lesions, the procedure may result in various complications, including anatomic deformity or disfigurement and functional deficit. In the oral cavity, tongue dysfunction or permanent speech impediment may occur.

Localized radiation therapy may also be used to successfully treat hamartomas, but this method is associated with risks commonly perceived to outweigh acceptable risks in the treatment of a benign disease in a crucial anatomic location, such as the tongue tip. These risks include mucositis, candidosis, dysgeusia, dysphagia, soft tissue necrosis, and xerostomia, among others.[9]

Our patient expressed concerns regarding the deleterious effects associated with surgical excision and radiotherapy; therefore, he opted for sclerotherapy with bleomycin. This treatment, with an acceptable safety profile, has been shown to have a strong sclerosing effect on the vascular endothelium and has been used to successfully treat complex vascular anomalies.[10-12] Adverse effects associated with systemic administration of bleomycin include pulmonary fibrosis, anaphylaxis, hyperpigmentation, hyperkeratosis, and skin fibrosis. However, pulmonary fibrosis after intralesional injection of bleomycin has never been reported.[13] Therefore, the patient chose this treatment, given its well-known efficacy, acceptable safety profile, and reduced risk of speech impediments.

This report presents a case of atypical oral manifestation of Cowden syndrome, with recommendation for the use of bleomycin to treat such vascular malformations. In addition, it adds to and validates the well-documented efficacy of bleomycin in the treatment of vascular malformations of the head and neck, regardless of etiology. Bleomycin is an excellent choice for such cases because of the rapid and measurable clinical response, lack of systemic absorption, and limited adverse effect profile when administered locally. In addition, it offers the benefit of lower cost and less operative and hospitalization time compared with the other main treatment modalities described above. A single treatment with bleomycin (15 mL, diluted down to 10 units/mL) was sufficient for the successful treatment of Cowden syndrome in our patient. Moreover, the lesion demonstrated involution within 1 month of therapy, without any adverse effects or recurrence.

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