Massive Macroglossia Secondary to Angioedema: A Review and Presentation of a Case

Todd A. Kovach, DDS, MD,* David R. Kang, DDS, MD,† and R. Gilbert Triplett, DDS, PhD‡

Macroglossia is a rare condition, but can severely affect the oral and maxillofacial region. Angioedema is a condition resulting from multiple mechanisms, all of which can result in macroglossia. This report describes an unusual case of acquired macroglossia in an adult resulting from chronic edema secondary to angioedema in the setting of stroke. The patient had a morbidly enlarged tongue and presented with clinical signs and symptoms consistent with massive macroglossia. She required surgical intervention for acute management of her symptoms and definitive treatment of her macroglossia. © 2015 American Association of Oral and Maxillofacial Surgeons


Macroglossia is considered rare,4 and its sequelae are most often described in children. Such cases are usually in the form of lymphovascular anomalies, relative macroglossia in children with Down syndrome, or muscular hypertrophy in association with Beckwith-Wiedemann syndrome.3

This report describes an unusual case of acquired macroglossia in an adult. The patient had a morbidly enlarged tongue and presented with clinical signs and symptoms consistent with massive macroglossia. She had dyspnea, dysphagia, and dysphonia requiring tracheostomy and gastrostomy tube for nutrition.

Report of Case

A 57-year-old woman was found on the ground by her family and taken to the emergency department. In the emergency department, the patient presented with malignant hypertension (250 and 150 mmHg) and computed tomography of the head depicted a large right-sided hemorrhagic stroke. The hemorrhage was approximately 2.8 cm in the distribution of the right middle cerebral artery affecting the right thalamus and basal ganglia and the internal capsule and insula, resulting in a 4-mm midline shift to the left (Fig 1). She was admitted to the intensive care unit and started on a nicardipine drip and amlodipine.

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FIGURE 1. Computed tomogram without contrast, axial view, showing hemorrhagic stroke involving the distribution of the right middle cerebral artery measuring approximately 2.8 cm with a 4-mm midline shift to the left.

The patient began to develop lip and tongue swelling within the first few days of admission, resulting in the need for a tracheostomy and a percutaneous endoscopic gastrostomy tube on hospital day 10. She had little to no response to steroids or histamine blockers, and C1-inhibitor levels were within normal limits.

Three weeks 3 days after admission, a surgical service was consulted; however, no intervention was undertaken because the macroglossia was expected to resolve over time. Even with physical and mental improvements after her stroke, her macroglossia showed no improvement. Nearly 6 months after the initial event, the patient was transferred to the inpatient rehabilitation hospital at the authors’ institution, and the authors were consulted by the physical medicine and rehabilitation service.

On examination, the patient exhibited a large tongue protruding well beyond the teeth and alveolus (Fig 2A, B). She had copious drooling, and her tongue was mildly tender to touch. No vascular bruits or thrills were noted. She had movement of all her anterior teeth, including her mandibular incisors, being shifted perpendicular to the alveolar bone.

FIGURE 2. Massive macroglossia on initial presentation. A, Frontal and B, profile views.


FIGURE 3. A, Computed tomogram, sagittal view, showing macroglossia, no suspicion of neoplasm, and relatively uninvolved base of the tongue. (Fig 3 continued on next page.)

Computed tomography and magnetic resonance imaging did not show any underlying neoplastic process and the base of the tongue appeared minimally affected (Fig 3A, B). Multiple punch biopsy examinations were completed and histologic examination showed fibrosis with areas of mucositis (Fig 4A, B).

The patient was taken to the operating room and the anterior portion of the tongue was resected. Lingual arteries were easily identified and controlled during dissection. With the central, anterior, and peripheral resections, the tongue was sutured in the midline in a sagittal direction and along the peripheral margin (Fig 5A, B). The anterior mandibular teeth were extracted because they were hopelessly malpositioned, but the maxillary teeth were left undisturbed in their current position with the expectation that they would improve with the return of normal physiologic forces (Fig 6A-D).

The patient recovered well after tongue surgery, and her tracheostomy was decannulated on postoperative day 13. The patient’s speech improved and she tolerated a full puree diet at 1 month. At 2 months, her

FIGURE 3 (cont’d). B, Panoramic radiograph showing orthodontic movement.


FIGURE 4. A, Multiple punch biopsy examinations were performed to rule out intrinsic pathology as a cause of macroglossia. B, Histology showing fibrosis and skeletal muscle without abnormal pathology.

FIGURE 5. Resected tongue. A, Ventral and B, lateral surfaces.


speech was considerably improved, and 100% of her diet could be taken orally. Her maxillary teeth returned to a stable position (Fig 7A, B).

**Classification of Macroglossia**

In addition to clinical descriptors used to define macroglossia, a typical patient with macroglossia can present with a myriad of signs and symptoms ranging from mild to life threatening. Commonly, patients will present with some form of dyspnea or obstructive breathing pattern and with difficulty chewing or speaking. Additional dental and anatomic anomalies can include dental spacing, open bite, or scalloping of anterior and lateral borders of the tongue (Table 1).

Furthermore, macroglossia can be described by assigning certain classifications. Myer et al. classified macroglossia as a localized versus a generalized condition. Localized conditions, such as a lingual lymphatic malformation, affects a portion of the tongue and generalized

<table>
<thead>
<tr>
<th>True macroglossia</th>
<th>Relative macroglossia</th>
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<tbody>
<tr>
<td>Congenital</td>
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</tr>
<tr>
<td>Vascular malformation (lymphangioma)</td>
<td>Systemic disorder (Down syndrome, cretinism)</td>
</tr>
<tr>
<td>Muscular enlargement (Beckwith-Wiedemann syndrome)</td>
<td>Acquired</td>
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<td>Functional (postoperative maladaptation)</td>
</tr>
<tr>
<td>Relative macroglossia</td>
<td>Elevation (Ludwig angina, edentulism)</td>
</tr>
<tr>
<td>Acquired</td>
<td>Systemic disorder (myxedema)</td>
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**Table 1. SEQUELAE OF MACROGLOSSIA**

<table>
<thead>
<tr>
<th>Dyspnea</th>
<th>Airway obstruction</th>
<th>Noisy breathing</th>
<th>Dysphagia</th>
<th>Difficulty chewing, eating</th>
<th>Dysphonia</th>
<th>Sialorrhea or drooling</th>
<th>Slurred speech</th>
<th>Perception of mental retardation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Orthodontic anomalies</td>
<td>Widened interdental spaces</td>
<td>Open bite deformity</td>
<td>Mandibular prognathism</td>
<td>Anatomical anomalies</td>
<td>Scalloping or crenulations</td>
<td>Dry, cracked surface</td>
<td>Ulceration</td>
<td>Secondary infection, hemorrhage</td>
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**Table 2. CLASSIFICATION OF MACROGLOSSIA**

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conditions affect the entire tongue. The classification of Vogel et al describes the condition in terms of true versus relative macroglossia. A true macroglossia has an identifiable intrinsic pathology and therefore the physical findings are substantiated by demonstrable histologic abnormalities. Relative macroglossia shows increased size and clinical malfunction, but a normal histologic architecture. In addition, Vogel et al classified true and relative macroglossia into congenital and acquired causes (Table 2).

Review of Angioedema

Angioedema is a known cause of an enlarged tongue; it has been described as nonpitting edema of the dermis and subcutaneous layers. Most commonly, it presents as swelling of the tongue, lips, face, and throat but also can present in the extremities, genitalia, and viscera.

Angioedema can be categorized as allergic and nonallergic. Allergic angioedema might be associated with hives because it is mediated by immunoglobulin E (IgE) with resultant mast cell degranulation. IgE-mediated angioedema would include allergic reactions to penicillins and cephalosporins. Other medications can cause angioedema, but usually not because of an allergic-type reaction (Table 3). Nonallergic angioedema includes the subdivisions of hereditary angioedema, angiotensin-converting enzyme (ACE) inhibitor-induced angioedema, pseudoallergic angioedema, and hereditary angioedema.

Pseudoallergic angioedema typically resembles an allergic reaction, but it is caused by a particular drug’s underlying effect as opposed to being mediated by IgE. Nonsteroidal anti-inflammatory drugs (NSAIDs), opiates, and intravenous contrast agents are the most common culprits. These can cause an angioedema reaction by direct activity on mast cells in the case of opiates and contrast, and by increasing cysteinyl leukotrienes associated with arachidonic acid metabolism in the case of NSAIDs, including aspirin.

Bradykinin is the main mediator in nonallergic angioedema. Bradykinin is an active peptide released in tissues and plasma when kallikreins act on precursor

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<th>Medication</th>
<th>Type of Reaction</th>
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<tr>
<td>ACE inhibitors</td>
<td>RAAS-blocker induced</td>
</tr>
<tr>
<td>Bupropion</td>
<td>Pseudoallergic</td>
</tr>
<tr>
<td>Penicillins, cephalosporins</td>
<td>Allergic, IgE mediated</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitors</td>
<td>Pseudoallergic</td>
</tr>
<tr>
<td>COX-2 inhibitors</td>
<td>Pseudoallergic</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>Pseudoallergic</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Pseudoallergic</td>
</tr>
<tr>
<td>Angiotensin II receptor antagonists</td>
<td>RAAS-blocker induced</td>
</tr>
<tr>
<td>Statins</td>
<td>Pseudoallergic</td>
</tr>
</tbody>
</table>

Abbreviations: ACE, angiotensin-converting enzyme; COX-2, cyclooxygenase-2; IgE, immunoglobulin E; NSAIDs, nonsteroidal anti-inflammatory drugs; RAAS, renin-angiotensin-aldosterone system.


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**FIGURE 8.** Diagram depicting bradykinin’s role in the development of angioedema. Inhibition of kininase II by an ACE inhibitor (red X) results in increased levels of bradykinin and subsequent effects at the 2 bradykinin receptors. ACE, angiotensin-converting enzyme.

kininogens. As a result, all kinins, including bradykinin, are enzymatically cleaved from the precursor kininogens. Then, bradykinin binds B₂ receptors, causing vasodilation and increasing vascular permeability, resulting in rapid swelling of the face and lips. In the normal state, kininases I and II break down bradykinin into active and inactive metabolites, respectively. Active metabolites (Lys-Des-Arg-BK) also contribute to vasodilation by binding B₁ receptors.⁸

Increased levels of bradykinin are present when angioedema results secondary to ACE inhibitors. In addition to converting angiotensin I to angiotensin II in the renin-angiotensin-aldosterone system, ACE is known as kininase II, which typically degrades bradykinin into inactive metabolites. When ACE is inhibited, bradykinin and its active metabolites are present in greater concentration, thus predisposing to mucosal edema (Fig 8).

Hereditary angioedema is a condition resulting from continuous activation of the complement system and related cascades. In the physiologic state, C₁-inhibitor is present in sufficient quantities to prevent unregulated activation of multiple pathways, including the kinin-kallikrein system and the complement system. Individuals with hereditary angioedema have low levels or decreased function of C₁-inhibitor, resulting in continuous activation of kallikreins and resultant overproduction of bradykinin. The additional continuous activation of the complement system results in mast cell degranulation and histamine release, causing further vasodilation.

**Angioedema in the Setting of Stroke**

Angioedema has been reported in patients hospitalized for stroke. Typically this occurs after administration of alteplase, a recombinant tissue plasminogen activator (tPA). This was first documented in 1997¹⁰ and multiple times thereafter, with an incidence up to 5%.¹¹-¹⁴ tPA is a protease that breaks down plasminogen to plasmin through a hydrolysis reaction. Similar to kallikrein, the activated plasmin

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**FIGURE 9.** A, Incision technique described by Dingman and Grabb²⁸ in 1951 to reduce overall dimensions of the tongue. B, An anterior wedge resection, which has a great historical presence in the literature, was first described by Harris³⁸ in 1837 but it also has been credited to Blair¹⁵ (1912) and Hendrick⁴⁰ (1956). (Fig 9 continued on next page.)

cleaves kininogens to form bradykinin. Thus, the higher levels of bradykinin predispose to an angioedema reaction. In addition, patients taking ACE inhibitors are associated with increased incidence and severity of angioedema when it occurs after tPA administration. Concomitant β-blocker use also has been implicated.

Angioedema in the setting of stroke also has been reported in patients who did not receive tPA. The location of brain infarcts can cause central dysfunction of the autonomic nervous system, which enhances the susceptibility to angioedema. Acute lesions in the distribution of the middle cerebral artery resulting in injury to the insular cortex have had the greatest association with the development of angioedema. In addition, lesions involving the postcentral cortex, basal ganglia, and internal capsule have been associated with autonomic imbalance.

### Traumatic and Obstructive Phenomena

Macroglossia also can occur due to trauma resulting in hematoma or edematous swelling. Tracheostomy has been required for patients with self-induced bite trauma during seizures. Continued biting causes venous and lymphatic obstruction, leading to further tongue swelling. A bite block and muscle relaxants have been used in the critical care setting to treat this condition in the acute phase.

### Treatment

Airway management is the most important acute intervention in a patient with angioedema and macroglossia. Angioedema is still typically treated medically with empiric use of antihistamines (H1 and H2 blockers), corticosteroids, and in some cases epinephrine. However, despite common use, these drugs have not been shown to be efficacious unless the angioedema is due to a true allergy. Most cases of angioedema related to ACE inhibitors or stroke are minor and spontaneously resolve in 24 to 48 hours.

Bradykinin blockers and C1-inhibitor replacement are newer therapies approved for hereditary...
angioedema, but also show great promise in the treatment of ACE inhibitor-induced angioedema.\textsuperscript{7,24}

Reduction glossectomy is typically performed in children with congenital conditions, but could be necessary in acquired conditions when symptoms become major. There is no consensus on a particular design for glossal reduction, and no one design is suitable for all patients.\textsuperscript{25} This is illustrated by the multitude of different techniques that have been described (Fig 9).\textsuperscript{26-40}

Resections of peripheral margins described by Dingman and Grabb\textsuperscript{28} allow reduction of overall size. Central portions of the tongue have been resected to better preserve speech, sensation, and taste.\textsuperscript{29,30,41} Pichler and Trauner\textsuperscript{31} combined central resections with an anterior wedge to allow better reduction in length and width, and Köle\textsuperscript{32} and Egyedi and Obwegeser\textsuperscript{33} joined the central and anterior components in a contiguous resection. With further modification, Morgan et al\textsuperscript{34} were the first to describe the keyhole-type resection, which has become quite popular.\textsuperscript{34,35,42} Kruchinsky\textsuperscript{36,37} described an asymmetric reduction method to decrease length and width while maintaining the native tip.

**Postoperative Management of Glossectomy**

The mainstay of rehabilitation of patients after undergoing a glossectomy procedure involves speech therapy and focuses on addressing and repairing the newly acquired deficits. Although more common in patients with cancer requiring glossectomy for wide excision of a lesion, the same principles might be applicable for patients requiring a very large reduction glossectomy. The resultant deficits most notably relate to speech and deglutition.

Speech intelligibility is markedly decreased in patients after glossectomy,\textsuperscript{13} and speech therapy is a
A valuable tool for improvement. A speech pathologist can help improve a patient’s condition by activating articulatory adaptation, compensations, and maximizing remaining structures. Although patients with larger surgical resections (ie, total glossectomy) prove to have greater deficits in the immediate postoperative period, these patients also show the greatest improvement in speech intelligibility after working with a speech therapist.

In addition to speech therapy, maxillofacial prostodontists can fabricate and fit palatal augmentation prostheses. Many types of oral prostheses have been used, but a palatal augmentation prosthesis functionally decreases the volume of the oral cavity by creating a lower palatal vault that can make contact with the residual tongue and allow for better production of speech. This type of prosthesis has been shown to help improve speech and deglutition. Reconstruction with vascularized tissue also can help replace a large defect and allow better linguopalatal contact when speaking.

Angioedema is a well-known cause of macroglossia, and this report has described a unique case of macroglossia in an adult. This patient’s angioedema developed into a chronic state with fibrosis resulting in dyspnea and dysphagia requiring surgical intervention. The patient had a large hemorrhagic stroke of the right hemisphere affecting the thalamus and basal ganglia in addition to the insular cortex and internal capsule. Most strokes are ischemic in nature, and to the authors’ knowledge, this patient is the only reported case of a hemorrhagic stroke leading to angioedema requiring surgical intervention. By combining techniques previously described for other etiologies of macroglossia, the authors were able to return proper form, function, and cosmesis to this patient.

**FIGURE 9 (cont’d).** G, Egyedi and Obwegeser developed their own design, which combined the central component with the anterior wedge. H, Morgan et al described the “keyhole”-type resection, as did Kacker et al; this type of design has become quite popular. (Fig 9 continued on next page.)

References


FIGURE 9 (cont’d). I, The method of Kruchinsky36,37 is intended to decrease the length and width while maintaining the native tip.