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Clinical Pearl

A patient with idiopathic angioedema presenting with superior vena cava syndrome and lymphedema

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A 40-year-old woman with a history of 2 episodes of corticosteroid-responsive angioedema without urticaria presented to the allergy clinic for evaluation of recurrent angioedema after a third episode. Her medical history was significant for papillary thyroid carcinoma that required anterior neck dissection and radiation as well as epithelioid hemangioendothelioma of the right internal jugular vein that required resection and graft placement. Her first episode of laryngeal edema occurred while she was completing radiation treatment 10 months earlier and was accompanied by 1 day of shortness of breath and stridor that required admission to the intensive care unit. Direct laryngoscopy and computed tomography revealed supraglottic swelling and diffuse edema, respectively, confirming the diagnosis of angioedema. She had no history of allergy, and the episode was attributed to the toxic effects of radiotherapy. She responded to intravenous dexamethasone.

Two months later, she had a second, less severe episode of laryngeal angioedema, which was complicated by dysphagia and the sensation of throat fullness. The episode was also treated successfully with systemic corticosteroids but was not associated with radiotherapy administration. Because no trigger was identified, she was diagnosed with idiopathic angioedema. Of note, neither corticosteroid-responsive episode involved skin changes or rashes. Ten days before allergy evaluation, she visited her primary care physician with a 1-day history of neck edema without lip or facial swelling. She noted mild laryngeal fullness and dizziness but no dysphagia or tightness as experienced during the prior episodes. She was again prescribed systemic corticosteroids, but symptoms did not improve. After 12 days of edema, she was referred to the

allergist for evaluation of possible recurrent or refractory angioedema.

Supporting Data

Laboratory testing revealed normal serum tryptase (3.9 $\mu\text{g/L}$), C4 (42 mg/dL), C1 esterase inhibitor (32 mg/dL) levels and function (116%). On physical examination, she had symmetric edema of the submandibular area without facial involvement and diffuse erythema of the neck and face. The symptom duration, incomplete corticosteroid response, and negative in vitro test results indicated that bradykinin- or histamine-mediated angioedema was unlikely. On review of her records, she was prescribed warfarin after the vascular graft, and her international normalized ratio of 1.7 was subtherapeutic the previous month. Given concern for superior vena cava (SVC) syndrome, she was sent to the emergency department for evaluation. Computed tomography angiography revealed an occlusive clot in the left brachiocephalic vein and right atrial graft.

Clinical Outcome

After confirmation of the presence of thrombosis, the patient underwent thrombolysis, and most of the edema, erythema, and dizziness improved. Follow-up computed tomography 1 month later did not reveal any evidence of recurrent malignant tumors, but she continued to have the sensation of laryngeal fullness. Additional laryngoscopy revealed minimal edema of the bilateral vocal cords. She was also diagnosed with lymphedema of the head and neck as a consequence of her previous surgery and radiation therapy. She improved with physiotherapy.

Neck swelling has a broad differential diagnosis, including angioedema, SVC syndrome, hypothyroidism, lymphedema, and others (Table 1).¹ The characteristics, duration, and response to therapy vary widely. Proper diagnosis can be complicated when multiple processes are involved or have been previously causal, as in this patient.

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Table 1
Causes of Neck and Face Swelling

Permanent	Transient
Superior vena cava syndrome	Angioedema: histamine or bradykinin mediated
Hypothyroidism	Infection
Dermatomyositis	Acute contact dermatitis
Granulomatosis	Drug rash with eosinophilia and systemic symptoms

The patient had a history of angioedema, as confirmed by direct laryngoscopy and computed tomography. Angioedema manifests as episodic and asymmetric nondependent swelling that involves subcutaneous or submucosal surfaces mediated by histamine or bradykinin. Recurrent histaminergic angioedema may be caused by exogenous triggers or may be idiopathic. Idiopathic angioedema is typically associated with urticaria, but up to 10% of patients have recurrent swelling only.² Histaminergic angioedema is responsive to corticosteroids, antihistamines, and epinephrine, and a response helps differentiate it from bradykinin-mediated angioedema. Her previous response to corticosteroids indicated that her second angioedema episode was likely histamine mediated. The exact cause of the first episode of angioedema is less clear. Radiotherapy can cause acute local tissue swelling because of direct cell toxicity that is responsive to corticosteroids.³ The timing and corticosteroid responsiveness of her first episode were consistent with toxic effects of radiotherapy. However, because she presented 2 months later with idiopathic angioedema, it is possible that the first episode also was idiopathic and the timing was coincidental.

When she had a third episode not responsive to corticosteroids, it was reasonable to evaluate for bradykinin-mediated angioedema. Because of her history of malignant tumors, this patient would have been at risk for acquired C1 inhibitor deficiency (ACID), although this is typically associated with B-cell malignant tumors.⁴ ACID is attributable to depletion of or autoantibodies against C1 inhibitor. Both acquired and hereditary angioedema are bradykinin mediated, are unresponsive to corticosteroids, typically involve the face or lips, and last 2 to 5 days.^{5,6} Patients will generally have a low C4 level. This patient had a normal C4 level, no facial involvement, and a 2-week duration of swelling, which made bradykinin-mediated angioedema (hereditary angioedema or ACID) unlikely.

SVC syndrome is caused by compression or rarely thrombosis of the SVC, causing impairment of blood flow back to the heart.⁷ It is

manifested by dyspnea, facial or upper extremity swelling, plethora, dysphagia, hoarseness, and dizziness. In severe cases, it can lead to laryngeal or cerebral edema, which is a medical emergency. This patient had appropriate risk factors for SVC thrombosis, including vascular graft placement and subtherapeutic international normalized ratio. In addition, her facial plethora, dizziness, limited neck edema, and symptom duration were consistent with SVC syndrome. Treatment depends on the underlying cause and may include a combination of thrombolytics or stenting.

The last complication of this case was neck lymphedema after papillary thyroid cancer treatment. It is estimated that up to 50% of patients with head and neck cancer after treatment will develop neck lymphedema.⁸ Edema of the neck and submental region are common, and up to one-third will experience difficulty swallowing or breathing.⁹ Poor venous flow and damage from the SVC syndrome further predisposed this patient to this problem. In summary, the long duration, lack of steroid response, swelling location, and history of vascular graft led to the right diagnosis in this patient. This case highlights the importance of reevaluating the diagnosis when characteristics and therapeutic response are inconsistent and recognizing that not all swelling is secondary to angioedema.

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