



A review of uncommon swelling provides useful reminders

Angioedema associated with insufficient activity of circulating complement component 1 (C1) inhibitor is a rare condition that can be hereditary or acquired. The clinical characteristics of this disorder are nicely reviewed by Drs. Tse and Zuraw in this issue of the *Journal* (page 303). Despite the rarity of this condition, there are good reasons to spend a few minutes with this article.

Angioedema and the urticarias differ in their clinical manifestations and diagnostic and therapeutic implications. Patients who have recurrent urticaria, no matter the severity, need not be evaluated for C1 inhibitor deficiency. Some patients who have recurrent angioedema without urticaria may respond well to antiallergic therapies (eg, antihistamines, corticosteroids), and these patients also are unlikely to have C1 inhibitor deficiency. Other patients who have intermittent localized peripheral swelling (or visceral edema manifest as abdominal pain) without urticaria may not respond, and it is in these patients that a pathophysiologic mechanism other than typical allergy should be considered.

In some patients, bradykinin-mediated angioedema is due to deficient C1 inhibitor activity, in others, to angiotensin-converting enzyme (ACE) inhibition. Although the biochemical site of action is different, both of these conditions result from an imbalance of protease activation and inhibition. If there is not enough C1 inhibition, there is too much kallikrein activity, which leads to excess proteolytic generation of the peptide bradykinin from kininogen. In contrast, ACE inhibitors occasionally cause angioedema by decreasing catabolism of bradykinin. In either case, bradykinin-mediated angioedema is generally clinically resistant to antiallergic therapy.

Thinking about these mechanisms reminds us of the complexity and overlap of many physiologic proteolytic cascades. Although C1 inhibitor is known as an inhibitor of C1 esterase and C4 levels are almost always low when C1 inhibitor activity is depressed, the angioedema in C1-inhibitor-deficiency states is more a result of decreased inhibition of enzymes in the coagulation cascade than in the complement cascade. Similarly, ACE-inhibitor-associated angioedema has little to do with the decreased generation of angiotensin that accounts for these drugs' antihypertensive effect.

Generalizing these principles should make us vigilant for unpredicted adverse reactions to other newer drugs such as protease and kinase inhibitors, which may variably affect multiple biochemical pathways.

A handwritten signature in black ink that reads "Brian Mandell". The signature is fluid and cursive, with a long horizontal stroke underneath.

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