



## Diagnostic certainty and the eosinophil

This issue of the *Journal* contains an article by Dr. David A. Katzka, titled “The ‘skinny’ on eosinophilic esophagitis” (page 83). Reading it, I was struck by two messages, one clinical and one biological.

The clinical message relates to the psychology of diagnosis, or as Dr. Jerome Groopman discussed in his book *How Doctors Think*, misdiagnosis. In many patients, eosinophilic esophagitis, especially early in its course, can mimic gastroesophageal reflux disease (GERD), causing dysphagia and discomfort with eating that may be relieved at least in part with a proton pump inhibitor. When evaluating a patient who relates a history compatible with a common condition, we instinctively tend to embrace the diagnosis of that common syndrome, in this case GERD, rather than initially explore in depth the possibility of less-common mimics. Once the disease has progressed, with the patient experiencing frequent postprandial emesis or needing to dramatically limit the size of meals despite taking a full dose of a proton pump inhibitor, we will hopefully revisit and reassess our initial diagnosis, often with endoscopy and biopsy. But that may not always occur promptly, because we may have committed (per Groopman) an “anchoring error,” seizing on an initial symptom or finding, allowing it to cloud our clinical judgment, reaching “premature closure,” and not keeping our minds open to alternative diagnoses such as eosinophilic esophagitis. I wonder how many of the younger patients I have diagnosed with GERD who had histories of “food intolerances” actually had eosinophilic esophagitis.

The biological message is that the eosinophil is a fascinating and generally misunderstood cell, not just a marker and mediator of allergy. As an apparent defender against the macro-invaders—worms and other parasites—it carries an arsenal of defensive weapons. But eosinophil-dominant inflammatory reactions started by various molecular triggers and perpetuated by interleukin 5 and other promoters of eosinophil proliferation and chemotaxis have a common histopathologic footprint—fibrosis.

Long-standing significant asthma is characterized as much by airway remodeling and fibrosis as it is by bronchospasm. A myocardial hallmark of hypereosinophilic syndrome is fibrosis. Eosinophilic pneumonia can be followed by local scarring. Eosinophils have been implicated in the pathogenesis of primary biliary cirrhosis and the granulomatous cirrhosis of schistosomiasis. And as Dr. Katzka reminds us, the confluence of food hypersensitivity, gastric acid, and the products of eosinophil activation (likely including transforming growth factor beta) in the esophageal wall can result in a marked fibrotic reaction with dysmotility. It is unclear whether this is a dysregulated attempt at healing with resultant maladaptive “scar” formation, or perhaps a misdirected inflammatory response, with the goal of walling off a perceived invader (an allergen is not a worm).

There are probably many other mimic diseases that we are not recognizing often enough. And tissue eosinophils may portend detrimental fibrotic remodeling.

BRIAN F. MANDELL, MD, PhD  
Editor in Chief

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