ADVANCES IN UPPER GI DISORDERS

Current Developments in the Management of Upper GI Disorders

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Does Eosinophilic Esophagitis Predispose to Achalasia?

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G&H Currently, how is achalasia defined and viewed in relation to eosinophilic esophagitis?

SS Traditionally, we have thought of eosinophilic esophagitis (EoE) primarily as a disease that involves the mucosa of the esophagus, whereas achalasia is viewed as a motility disorder involving esophageal muscle. Achalasia is characterized by 2 major manometric features. One major defect is that swallowing does not induce peristalsis. The other is that swallowing does not relax the lower esophageal sphincter (LES), the muscle at the end of the esophagus that acts as a one-way valve that must relax to let food pass into the stomach. In fact, achalasia is derived from a Greek word that means failure to relax. Failure of the LES to relax prevents swallowed food from passing into the stomach, and this causes the symptoms of dysphagia, regurgitation of material trapped in the esophagus, and chest pain, probably when the esophagus spasms or stretches because of the obstruction.

The symptoms of EoE typically are dysphagia, heartburn, and chest pain, which can be similar to the symptoms of achalasia, but both have very different disease processes. EoE results from type 2 (allergic) inflammation triggered by food and other allergens. With achalasia, nobody really knows how it develops. For many years now, achalasia has been assumed to be an autoimmune disease targeted at nerves in the wall of the esophagus—the nerves needed to orchestrate peristalsis and to relax the LES.

G&H What novel pathologic aspects and clinical manifestations of EoE might cause achalasia and perhaps a variety of other motility disorders?

SS My colleagues at Baylor University Medical Center and I became interested in these 2 diseases as being potentially related about 8 years ago, when we saw a patient who had both EoE and achalasia. At the time, we thought it was unusual for a patient to have these two relatively uncommon diseases simultaneously. As we looked into the reason why these diseases might occur together, we found that there is actually a long history of eosinophils associated with achalasia. In achalasia patients, the eosinophils that would be occasionally found in biopsies of their esophageal mucosa were often attributed, with no proof, to stasis (ie, food stuck in the esophagus resulting in inflammation and for whatever reason causing eosinophils to accumulate in the esophagus). We also considered that EoE is thought of as a mucosal disease because the mucosa is the only part of the esophagus that can be examined and biopsied easily during endoscopy. There is no easy way to biopsy esophageal muscle other than with an invasive procedure. In the rare instances when pathologists have been given a whole specimen of the esophagus from a patient with EoE and examined the whole, full-thickness organ, they found eosinophils infiltrating all layers, including the muscle layers of the esophagus. Conversely, there are older studies that looked at esophagectomy specimens from patients with achalasia, and some of those also described heavy infiltrations of eosinophils throughout the esophagus. This information that eosinophils could infiltrate all layers of the EoE and achalasia esophagus led us to think that maybe the diseases presenting together was not just a chance association.

In 2018, we proposed a hypothesis that a form of EoE might affect the muscle of the esophagus and cause achalasia, and it could be doing it through a few different mechanisms. First, although we use the term *eosinophilic*

esophagitis, mast cells are just as heavily infiltrated as eosinophils in EoE, and the eosinophils and mast cells that infiltrate the esophagus are little toxin factories. They make all kinds of bad products, many of which could affect the muscle either directly or indirectly by activating the neurons that control the muscle. Maybe those eosinophil and mast cell products might actually be causing the motility abnormalities that we attribute to the loss of neurons in achalasia.

G&H What is the role of mast cells in allergic disorders, such as EoE, and how might mast cell activation predispose to an allergy-induced type of achalasia?

SS Eosinophils and mast cells probably evolved primarily as a means to kill parasites because they make a lot of toxic products that were pretty good at killing certain parasites. One of the toxic products that the eosinophil makes is eosinophil-derived neurotoxin, which is so named because it can kill neurons. Consequently, activated eosinophils in esophageal muscle may be destroying the nerves, and so the loss of esophageal nerves may not be the primary process in achalasia, but rather collateral damage resulting from the allergic disorder that brought eosinophils and mast cells into the muscle in the first place. That was the hypothesis that we proposed back in 2018, that a form of EoE that involves esophageal muscle predominantly might cause the disturbances of achalasia. One basis for this hypothesis is that there was another eosinophilic gastrointestinal disease (EGID), one that we had known about for much longer than EoE, called eosinophilic gastroenteritis that could present in 3 histologic forms. Patients with the mucosal form of eosinophilic gastroenteritis may have symptoms such as pain, bloating, and diarrhea. The muscular form of eosinophilic gastroenteritis causes obstructions in the gastrointestinal tract. There is also a serosal form that involves the outermost layer of the intestine and causes ascites with eosinophils. As EoE is also an EGID, could it have 3 histologic forms as well?

We have conducted studies in our laboratory in an effort to obtain support for this hypothesis. One of the studies involved having our surgeons remove a piece of LES muscle during Heller myotomy used to treat patients with achalasia. Since the surgeons were cutting the muscle for treatment, we thought why not get a piece of it, so we can take a look at it under the microscope, and that is what we did. It turned out that patients with achalasia had profound degranulation of mast cells in that muscle. Allergy is a major etiology for mast cell degranulation, and this finding would support the idea that these toxic cell products released during type 2 inflammation were causing a problem, either directly affecting the muscle or killing the nerves that control those muscles, thus causing the achalasia-like motility disturbance.

G&H Could you describe the recent study findings supporting the association between achalasia and EoE?

SS We conducted one study with our colleagues at the University of Utah who have a huge population database that is a wonderful epidemiologic resource. Our objective was to seek support for our hypothesis that allergy can underlie achalasia. We used the International Classification of Diseases (ICD), Ninth Revision and Tenth Revision codes to identify patients who were diagnosed with achalasia in the Utah population from 1995 to 2021. ICD codes also were used to identify allergic disorders, including EoE, in the achalasia patients, and we determined the relative risk of having these allergic disorders in the achalasia patients. The results were striking in that the relative risk for having EoE was about 33-fold increased in all the achalasia patients compared with the control population. In a subgroup analysis of achalasia patients aged 40 years or younger, the age group typically affected by EoE, the relative risk for EoE was about 70-fold increased. As far as other allergic disorders, we found significantly increased incidence of asthma, allergic rhinitis, hives, and anaphylaxis more than 3-fold above the control population.

Clearly, achalasia is strongly associated with EoE and other allergic disorders. At the moment, our hypothesis is that some forms of achalasia can be caused by a T helper 2 type inflammatory response in the esophagus, one that causes activated eosinophils or mast cells to accumulate in that muscle of the esophagus and then release products that alter muscle function and damage neurons.

G&H Is your current hypothesis that achalasia may be caused by a mucosal-predominant or muscle-predominant form of EoE?

SS Basically, we are saying the same thing. EoE is a type 2 inflammatory disorder that involves the esophagus, and so a muscle-predominant form of EoE might cause achalasia. One reason why we have altered the hypothesis to type 2 inflammation rather than just EoE is because we do not always find eosinophils in the muscle wall of achalasia patients, even though they can exhibit profound degranulation of mast cells in that muscle. It is possible that the mast cells are doing more of the damage than the eosinophils. Mast cells are often not seen in a biopsy specimen because special stains are required to identify them, but the mast cells are very dramatically increased in the esophagus of patients with EoE. If those special stains

had been used in early studies of the condition, then EoE might have been called mast cell esophagitis because mast cell infiltration is at least as prominent as eosinophil infiltration in EoE. Anytime a disorder is named by the inflammatory response it evokes, it likely means no one knows what is going on. EoE is really an allergic disorder, but the most dramatic histologic evidence has been the presence of eosinophils. I have absolutely no doubt that there is a form of achalasia caused by EoE involving the muscle. What is not known is whether that is unusual or whether that is the typical reason why someone develops achalasia. For at least some cases of achalasia, there is strong evidence to suggest that it is caused by this muscle-predominant form of EoE.

G&H Should treatment of EoE or achalasia change based on this association?

SS Recognizing that there is at least a possibility that EoE might be what is causing achalasia changes the management in that it should encourage clinicians to look very carefully for EoE in achalasia patients. Muscle-predominant EoE does not mean muscle-exclusive EoE, so there could be mucosal involvement for patients with the muscle-predominant form. We generally recommend that the gastroenterologist obtain a number of biopsies of the esophagus in patients with achalasia before embarking on an invasive treatment. Current treatments of achalasia are palliative and designed primarily to destroy the LES muscle, which removes the obstruction and helps with swallowing. However, these are irreversible, muscle-destructive treatments that do make patients feel better but do not cure the disease and have their own set of complications. If there is a chance that achalasia might be caused by a medically treatable, reversible condition like EoE, I think that ought to be vigorously pursued.

We are not recommending that gastroenterologists perform muscle biopsies routinely, but they should at least biopsy the esophagus extensively endoscopically and make sure there is no mucosal evidence of EoE in their achalasia patients. If EoE is found, I would recommend treating the EoE for 2 to 3 months. There have been case reports that suggest by treating the underlying EoE, the motility disturbance can resolve. The downside of this is the delay of treatment for 2 or 3 months. However, generally, patients with achalasia have had symptoms for years before presenting. Delaying treatment for another couple of months generally does not make much difference in the long term and may well be worth it if the disease is cured without having to resort to a muscle destructive procedure.

G&H What further research is needed?

SS What we need to know is how often a muscle-predominant form of EoE is the cause of achalasia. As I mentioned, there are case reports showing that after treatment of EoE, patients with achalasia get better, but more studies confirming that are needed. Again, it makes sense to look for the treatable disease rather than resorting to an irreversible muscle destructive therapy. For patients with a muscle-predominant form of achalasia, dupilumab (Dupixent, Sanofi and Regeneron) is probably the treatment of choice. However, without proof that the patient has EoE, it is probably difficult to get dupilumab. Insurance companies will pay for dupilumab for EoE but probably not for achalasia, although they may pay for it for the patient who has both EoE and achalasia.

The effect of eosinophils and mast cells on esophageal muscle also is an understudied area simply because it is difficult to obtain esophageal muscle to study. We recently obtained permission from the Southwest Transplant Alliance to harvest esophagi from organ donors. One of the members of our Center for Esophageal Diseases is a thoracic surgeon whose team routinely harvests heart and lungs from organ donors for heart and lung transplants. Once the heart and lungs are removed, the esophagus is right there. Being able to harvest that esophagus has enabled us to establish muscle cell lines and obtain other information that has greatly helped our studies on this condition.

Disclosures

Dr Spechler has served as a consultant for Phathom Pharmaceuticals and Takeda Pharmaceuticals.

Suggested Reading

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