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Marked Deposition of Eosinophil-Derived Neurotoxin in Adult Patients With Eosinophilic Esophagitis

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Summary

A study about eosinophil-derived neurotoxin (EDN) as a biomarker for eosinophilic esophagitis (EoE) has been reported in the February issue of Am J Gastroenterology 2010.[1] A diagnostic hallmark of EoE is the number of eosinophils infiltrated in the esophageal epithelium, but there seems to be no universal agreement on either the number or the location of eosinophils required to diagnose EoE. Although the role of eosinophils in the pathophysiology of EoE is not fully understood, eosinophils have a key role in eosinophil related gastrointestinal disease. Therefore eosinophil granule protein and EDN released by eosinophils, and eotaxin-3 have been studied as other possible biomarkers of EoE. Blood, urine or tissue levels of eosinophil granule proteins and EDN are elevated in eosinophilic associated diseases.[2-6] However, information regarding localization of EDN in the diseased tissues has not been available.

The authors investigated tissue specimens from 10 adult EoE patients and 8 histologically normal controls. Using a polyclonal rabbit antibody to EDN, sections from mid-esophageal biopsy specimens were stained for EDN by immunofluorescence. Cellular staining (infiltration of intact eosinophils) and extracellular staining (deposition of released EDN) were scored in a blinded manner on an established 7-point scale.

In the results, esophageal biopsy specimens from normal controls showed no or few intact eosinophils and extracellular EDN depositions. In contrast, EDN staining was clearly observed in specimens from all EoE patients. In some EoE patients, marked extracellular EDN deposition was observed despite a relatively small numbers of intact eosinophils. And there was no correlation between the eosinophil infiltration and the extracellular EDN staining scores.

They concluded that tissue eosinophil counts might underestimate how extensively eosinophils are involved, particularly in individuals with marked eosinophil degranulation. Evaluation of EDN in esophageal biopsy specimens was suggested as an useful mean to diagnose and manage patients with EoE.

Comment

EoE is a clinicopathologic disease characterized by an intense

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eosinophilic infiltration in the esophageal epithelium, upper gastrointestinal symptoms (dysphagia, food impaction and heartburn etc) and lack of responsiveness to treatment with proton pump inhibitors.[7] There are some limitations in histologic diagnosis of EoE. Occasionally EoE is diagnosed as a patchy disease with variations in both numbers of eosinophils and histological findings. Because of the invasiveness and cost of endoscopy with insufficient tissue specimens to find eosinophils, and repeated procedures, we need noninvasive biomarkers of EoE which correlate with presence and severity of disease, and response to therapy.

The complex pathophysiology of EoE provides several candidate biomarkers, for examples, eotaxin, chemokine receptor-3, IL-5, mast cell and eosinophil products.[8] Eosinophils contain cytoplasmic granules which is composed of major basic protein (MBP), eosinophil cationic protein, eosinophil peroxidase and EDN. High levels of such eosinophil granular proteins have been reported in serum and urine of patients with asthma, EoE or eosinophilic gastroenteritis.[2-6] In the recent EoE study, plasma EDN levels correlated with esophageal eosinophilic density and plasma EDN levels have been proposed as a noninvasive biomarker for diagnosing and monitoring EoE.[3] EDN levels in blood and stool significantly decreased at week 4 compared to baseline, after 4 weeks of corticosteroid therapy in a longitudinal study of children with EoE.[9]

The authors had interests in the correlation of presence or distribution of EDN in esophageal tissues from EoE. They examined the distribution or location of EDN or MBP in the esophageal epithelial tissues by immunofluorescence. They found that 3 different patterns of EDN staining were observed in EoE patients: (1) primarily cell-associated, (2) a combination of cell associated and extracellular EDN deposition and (3) primarily extracellular EDN deposition. In addition, consistent with the patchy nature of EoE histology, heterogeneous EDN staining was seen not only in different biopsies taken from the same site, but also within the same biopsy specimen.

Besides the several limitations explained by the authors, I think that applying EDN immunofluorescence may not be a practical diagnostic method before confirming EoE, since we usually use the fresh tissues for the immunofluorescence method. Easier technique to stain EDN or MBP is expected to be developed in the future. Another potential biomarker of EoE is eotaxin-3. Eotaxin mRNA is expressed constitutively in various parts of the gastrointestinal tract, and eotaxins may be involved in the selective regulation of eosinophil homing into the gastrointestinal tract. Eotaxin-3 gene, mRNA and protein were up-regulated in esophageal biopsies of children with EoE compared with normal controls.[4,10] Moreover, by means of correlation of biomarker levels with mean esophageal eosinophilic density, blood eosinophils, EDN and eotaxin-3 are potential biomarkers of EoE.[3]

In conclusion, we can learn 2 facts newly from this article: localization of EDN in esophageal tissue with EoE, reevaluation of extracellular EDN deposition in some EoE biopsies that contained few eosinophils, and noninvasive biomarkers of EoE that correlate with disease presence, severity and response to therapy.

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