



Do we need to biopsy endoscopically normal mucosa in the diagnosis of eosinophilic esophagitis?

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Eosinophilic esophagitis (EoE) is an immune-mediated chronic esophageal disease characterized by esophageal symptoms and eosinophil (eos)-rich esophagitis with at least 15 eos/high power field (hpf) (1-3). The diagnosis of EoE is a clinico-pathologic combination. The most common symptoms in infants and younger children with EoE are reflux esophagitis-like symptoms, food refusal, vomiting, abdominal pain, and failure to thrive. However, dysphagia, food impaction, and chest pain are the most common symptoms in older children and adults. Although studies have confirmed the above described clinical features of EoE, but neither of them is pathognomonic. Therefore, endoscopy with esophageal biopsy from both the distal and proximal esophagus remains the only reliable diagnostic examination for EoE. Common esophageal endoscopic abnormalities in EOE individuals include decreased vascularity, esophageal rings, white plaques/spots, longitudinal furrows, edema, stricture, narrow-caliber esophagus, mucosal fragility and even esophageal lacerations caused by routine endoscopic procedure (1,2). However, similar to clinical features, neither of the endoscopic findings is seen only for in EoE, but also be seen in other esophageal disorders, such as lymphocytic esophagitis (4). More importantly, EoE may present as normal endoscopic appearance in histologically confirmed EoE. A recent meta-analysis from 100 studies demonstrated that the endoscopic findings in EoE patients were significantly different: 44% with esophageal rings, 48% with furrows, 21% with stricture, 27% with white plaques/exudates, 9% with narrow-caliber, and 41% with decreased vascularity appearance. Of note, normal endoscopic appearance was seen in 17% (13–22%) patients who had histologic evidence

of EoE (5). Furthermore, significant inter- and intra-observer variabilities exist in describing the endoscopic findings by different endoscopists (6,7). These findings indicate that endoscopic abnormality alone cannot be used for a definitive diagnosis of EoE, esophageal biopsy in all individuals who are suspicious for EoE clinically irrespective of endoscopic findings should be performed.

EoE often cannot be diagnosed timely with a 4–11 years diagnosis delay from symptom onset (8). The persistent symptoms and inflammation in untreated EoE, a main cause due to diagnostic delay, often trigger esophageal remodeling process and finally result in a fibrostenotic phenotype with stricture formation and functional abnormalities (2). A study from 200 Swiss adult EoE individuals showed a median 6 years diagnostic delay. The diagnostic delay was associated with the presence of esophageal fibrostenotic phenotype from 46.5% (0–2 years diagnostic delay) to 87.5% (more than 20 years diagnostic delay) (9). Another study also demonstrated a 14.8 years diagnostic delay resulted in significant decrease of esophageal diameter (less than 10 mm) comparing to individuals with a diagnostic delay for 5 years (esophageal diameter of greater than 17 mm) (10). In addition, more diagnostic examinations (such as esophageal ambulatory pH or manometry tests) are prescribed on these diagnostically delayed EoE individuals. Endoscopy without biopsy in patients with normal mucosa and esophageal symptoms often leads to a diagnosis of GERD clinically, and empiric twice daily proton pump inhibitor (PPI) therapy is typically used. Although empiric PPI treatment is a reasonable approach to confirm GERD, complete response was only seen in 50% individuals in a large prospective study with an 8-week

PPI treatment. Interestingly, response to PPI treatment was not only seen in individuals with GERD endoscopic appearance or esophageal pH test abnormality, but also seen in 33% of normal esophageal pH test individuals (11). These data indicate a response to PPI treatment cannot completely differentiate EoE from GERD. Patients without response to PPI may lead to more doctor's visits, additional diagnostic examinations, and unnecessary prescriptions. Additionally, diagnostic delay of EoE may cause significant psychosocial issues such as social difficulties, anxiety, or depression, etc. Therefore, it is crucial to make a timely diagnosis with subsequent proper treatment for patients with EoE. As discussed above, endoscopy with esophageal biopsy from even normal appearing mucosa is the only reliable diagnostic test for EoE. Although biopsies of the upper GI tract (esophagus, stomach and duodenum) with normal upper endoscopies increase additional cost significantly, the yield and subsequent cost benefit improve with targeted indications that alter clinical practice, such as dysphagia for EoE, *H. pylori* for dyspepsia when serology status is unknown, or diarrhea for celiac disease (12). However, besides the cost consideration of endoscopy with or without biopsy, the treatment medication such as PPIs and/or steroids, additional diagnostic examinations such as ambulatory esophageal pH studies, esophageal manometry and/or another subsequent endoscopy with biopsy, and the patient's quality of life should be included to calculate the cost effectiveness. A cost-effectiveness model including analysis of quality of life variables, costs associated with endoscopy with or without biopsy, treatment medications with PPI (omeprazole) and steroid (fluticasone) and symptom resolution, and additional tests to determine if endoscopic biopsy is cost effective for the diagnosis of EoE in patients with refractory GERD has been established (8). The study demonstrated that endoscopy with esophageal biopsy for EoE diagnosis in refractory non-dysphagia GERD patients cost \$12,490/patient with 4.080 quality of life year (QALY) comparing to endoscopy without esophageal biopsy that cost \$12,280 with 4.076 QALY. These data indicate endoscopy with biopsy is cost effective for the diagnosis of EoE in patients with refractory GERD.

In summary, EoE shows variable endoscopic findings and none of them is pathognomonic. Significant portion of EoE patients demonstrate normal endoscopic appearance. Delayed diagnosis of EoE without proper treatment often causes persistent symptoms and inflammation leading to esophageal remodeling, and significant life quality and psychosocial problems. Endoscopic examination with

esophageal biopsy in all individuals who are suspicious for EoE clinically irrespective of endoscopic findings should be performed. The biopsy of endoscopically normal appearing esophageal mucosa is cost effective in the diagnosis of EoE.

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