Eosinophilic esophagitis (EoE) is an inflammatory disease characterized by eosinophil infiltration into the esophageal mucosa with a peak count of ≥15 eosinophils per high-powered field (eos/hpf) following endoscopic biopsy. However, the range of esophageal eosinophilia can vary markedly from patient to patient. A key question in the field is to understand the relationship of eosinophil levels with disease features, especially since eosinophil-targeted therapies are now available. Patients with extremely high levels of esophageal eosinophilia have not previously been studied. It is unknown whether these patients exhibit different characteristics compared to EoE patients that have esophageal eosinophilia that is not in the threshold of disease diagnosis. Given this, we aimed to establish whether any significant clinical, endoscopic, histologic, or transcriptomic features differ between patients with extremely high levels of esophageal eosinophilia and those with levels near the threshold of disease diagnosis.

Methods

Subject selection
Amongst a registry of patients with EoE, we identified a group of patients with the highest recorded levels of esophageal eosinophilia (eos/hpf >350), referred to as EoE-Hi. We subsequently identified a second group that had relatively low levels of esophageal eosinophilia (15-24 eos/hpf), referred to as EoE-Low. There were 74 patients in the registry with the EoE group of 16-24 eos/hpf on a distal esophageal biopsy. A random number generator was used to select the 14 patients that comprised the EoE-Low group.

Analysis
Phenotypic and clinical characteristics were gathered on the basis of electronic medical records and detailed questionnaires as part of a research registry. Endoscopic characteristics were assessed on the basis of findings from EGD operative reports. Histologic characteristics were classified on the basis of the histologic scoring system. Molecular analysis was performed using the 96-gene EoE Diagnostic Panel (EDP).

Trends for More Severe Symptoms in EoE-Hi Group

Table: Patients in the EoE-Hi Group Have a Greater Incidence of Furrows, Exudates and Thickening on Endoscopy

<table>
<thead>
<tr>
<th>Symptom</th>
<th>EoE-Hi (n=14)</th>
<th>EoE-Low (n=14)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furrows</td>
<td>13 (92.8)</td>
<td>7 (50)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Exudates</td>
<td>13 (92.8)</td>
<td>7 (50)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thickening</td>
<td>10 (71.4)</td>
<td>5 (35.7)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

When individual expression of the EoE Diagnostic Panel genes was compared between the 2 groups, there were 43 genes with significantly different expression (p < 0.05, fold change >2.0). This graph displays gene expression by category and negative log_{10} p-value.

Transcriptomic Analysis Revealed 30 Upregulated and 13 Downregulated Genes When Comparing EoE-Hi vs EoE-Low

IL-13 Related Pathways Associate with Eosinophilic Esophagitis Levels

Summary

- Compared with patients with EoE with relatively low esophageal eosinophilia, patients with extremely high levels of esophageal eosinophilia present with:
  - (1) increased incidence of atopic co-morbidities (specifically atopic rhinitis upon subcategorization)
  - (2) older age at the time of esophageal biopsy
  - (3) longer disease duration
  - (4) more severe endoscopic effects
  - (5) more severe histologic disease
  - (6) a distinct molecular signature, otherwise enriched for IL-13-regulated genes.

- These patients may represent a unique endotype
- Patients with extremely high levels of esophageal eosinophilia may require more aggressive therapeutic intervention, including anti-IL-13-based agents.

References and Acknowledgements

5. Motley A, Rothenberg ME. Intratracheal IL-13 induces eosinophilic esophagitis by IL-4, IL-5.
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