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The utility of bronchoalveolar lavage findings in the diagnosis of eosinophilic esophagitis in children

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ABSTRACT

Introduction: Bronchoalveolar lavage (BAL)-nucleated cell counts and the lipid-laden alveolar macrophage index (LLMI) have been investigated in predicting chronic aspiration as well as reflux esophagitis with variable results. To date, BAL neutrophil percentages and the LLMI have not been described in patients with eosinophilic esophagitis (EoE).
Objectives: To evaluate BAL neutrophil percentages and LLMI levels in patients with EoE and compare these levels in patients with aerodigestive concerns without biopsy-proven EoE.
Methods: Retrospective review of patients referred to an aerodigestive evaluation team for overlapping aerodigestive complaints (dysphagia, stridor, subglottic stenosis, feeding intolerance, and chronic aspiration). Patients underwent microlaryngoscopy, esophagogastroduodenoscopy with biopsy, and bronchoscopy and BAL were indicated by symptoms. BAL neutrophil percentages, LLMI levels, esophageal biopsy results, and esophageal dual-probe pH/impedance were recorded and compared.
Results: Fifty-one patients were included in the study that underwent comprehensive workup for aerodigestive complaints. Patients were subdivided into two groups: (1) negative esophageal biopsy (for EoE) and (2) positive esophageal biopsy. There were no significant differences between the groups in percentage neutrophils ($p = 0.55$, unpaired t-test) or LLMI levels ($p = 0.14$, unpaired t-test).
Discussion: BAL neutrophil percentages and the LLMI are unreliable in identifying patients with silent aspiration and gastroesophageal reflux. To date, there is no report of the utility of BAL neutrophil percentages and the LLMI in diagnosing patients with EoE. Our series indicates no correlation in neutrophil percentages or LLMI in patients with EoE versus patients without EoE that are referred to tertiary centers with aerodigestive concerns.
Conclusion: BAL neutrophil percentages and LLMI levels are not a reliable predictor of eosinophilic esophagitis in children with complex aerodigestive concerns. Esophageal biopsy remains the gold standard for diagnosis of EoE and the challenge remains to find other markers that raise suspicion for EoE for the non-gastroenterologist or that stage the extent of disease beyond the esophagus.

1. Introduction

In its introduction, the lipid-laden alveolar macrophage index (LLMI) showed promise in identifying chronic aspiration in patients with parenchymal lung disease. Early reports suggested a high level of sensitivity in detecting chronic aspiration, and subsequent quantitative studies appeared to have adequate sensitivity when compared to radiographic evaluation of aspiration [1–3]. Complicating the issue, later studies in children have demonstrated that the index is elevated in children with pulmonary disease without clinical or radiographic evidence of aspiration, indicating a lack of specificity for silent aspiration [4]. Regarding gastroesophageal reflux disease (GERD), a small series has suggested that the LLMI does have a correlation with duration of reflux symptoms, but there is not a difference between LLMI levels in reflux patients and healthy controls [5]. Further studies have also shown in a series of 50 children that underwent simultaneous impedance testing for GERD and bronchoscopy that there was no correlation between LLMI values and acid or non-acid reflux events [6].

While there are questions regarding the utility of LLMI in aerodigestive disease as a whole, there is some utility in the

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evaluation of children with laryngeal cleft. Children with more severe laryngeal clefting were shown to have significantly higher LLMI levels [7]. A large series correlated various diagnoses (cystic fibrosis, asthma, and immunosuppression) and LLMI levels and showed significant variability between and within groups [8]. While LLMI levels have been investigated in multiple aerodigestive complaints, to date no studies exist evaluating lipid-laden alveolar macrophage index levels or Bronchoalveolar lavage (BAL) neutrophil percentages in children with biopsy-proven eosinophilic esophagitis (EoE).

Bronchoalveolar lavage findings have also been investigated in a variety of pulmonary processes including chronic wheezing/cough, bacterial bronchitis, and cystic fibrosis [9–11]. Because of the high level of variability in sample technique in performing BAL, total cell counts are often unreliable in the workup and should be interpreted with caution [12]. As an alternative, percentages of cell types are often used as markers, and the cutoff of greater than 10% neutrophils has been shown to be associated with inflammation or infection [9,10,12]. As is the case with the LLMI, no study has evaluated the proportions of inflammatory nucleated cells recovered through BAL in patients with eosinophilic esophagitis.

Eosinophilic esophagitis (EoE) is a clinico-pathologic entity whose manifestations may include feeding difficulties, food impaction, dysphagia, and chest pain. Likely due to increasing disease awareness, the annual incidence of eosinophilic esophagitis rose from 1 in 10,000 in the year 2000 to 4.3 cases per 10,000 in 2003 [13]. The diagnostic criteria are both clinical and pathologic, combining upper aerodigestive symptoms with >15 intraepithelial eosinophils/high power field in one or more esophageal mucosal biopsy specimens [14]. Because eosinophils may be increased in the esophagus in the setting of GERD, the diagnosis of EoE is aided by the exclusion of GERD (although the diseases may coexist) [15]. Outside of the esophagus, several small series indicate that chronic rhinosinusitis, asthma, atopy, Eustachian tube dysfunction, sleep disordered breathing, dysphagia, and airway stenosis are present in an elevated rate in patients with EoE, possibly suggesting a systemic inflammatory disorder [16–21]. Our hypothesis was that EoE facilitates laryngeal inflammation, dysphagia, and aspiration with lower airway soilage that would manifest itself as an elevated LLMI or altered inflammatory cell count. The following study was designed to evaluate LLMI and BAL cell counts in patients with clinical symptoms of aerodigestive dysfunction (cough, chronic aspiration, dysphagia, and recurrent aspiration pneumonia) and histopathologic confirmation of eosinophilic esophagitis and compare these with similar patients that have normal esophageal biopsy.

2. Methods

After Vanderbilt University Medical Center institutional review board approval was obtained, a retrospective chart review was conducted at a single tertiary children's hospital, and children who were evaluated in the complex aerodigestive tract evaluation team (CADET) clinic and otolaryngology clinic were identified consecutively. Patients underwent direct laryngoscopy with biopsy, esophagogastroduodenoscopy (EGD) with esophageal biopsy, and flexible bronchoscopy with bronchoalveolar lavage as indicated for a variety of upper aerodigestive complaints (dysphagia, recurrent aspiration pneumonia, recurrent croup, and asthma). Patients also underwent impedance probe testing as indicated and had videofluoroscopic swallow studies to evaluate for aspiration. Bronchoalveolar lavage samples were taken at time of bronchoscopy and cell counts, neutrophil percentages, and lipid-laden macrophage index levels were obtained and quantified. Patients were subdivided into two groups: (1) negative esophageal biopsy (for EoE) with or without impedance testing consistent with reflux and (2) positive esophageal biopsy for EoE.

Features were summarized with means and ranges. Two statistical analyses were performed to evaluate neutrophil percentage counts and LLMI levels. Chi-square and Fisher's exact tests were used to compare EoE and non-EoE patients based on positive LLMI (5 or greater) versus negative LLMI (4 or less), and positive neutrophil percentage greater or less than 10%. Unpaired t tests were employed to evaluate differences in LLMI levels and BAL neutrophil percentages between groups as continuous variables. *P*-values of less than 0.05 were considered statistically significant.

3. Results

3.1. Demographic data

Fifty-one consecutive patients were included that underwent multi-disciplinary workup for aerodigestive complaints between 2009 and 2015. Symptoms necessitating referral to our tertiary center included cough, asthma, airway stenosis, dyspnea, dysphagia, dysphonia, and aspiration pneumonia (Table 1). Patients were subdivided into two groups based on the results of esophageal biopsy taken during EGD. Patients with EoE were significantly more likely to be male gender ($p = 0.047$). The average age of patients with normal esophageal biopsy was 3.9 years (range 0.6–15 years), and the average age of patients with biopsy-proven EoE was 5.9 years (range 1.6–16.3 years) ($p = 0.09$).

3.2. Lipid-laden alveolar macrophage indices and BAL neutrophil percentages

The average LLMI in patients with eosinophilic esophagitis was 3.4 (range 1–6) versus 4.4 (range 1–9) in patients without eosinophilic esophagitis ($p = 0.14$, unpaired *t*-test) (Fig. 1). The average BAL neutrophil percentage in patients with eosinophilic esophagitis was 40% versus 34% in patients without eosinophilic esophagitis ($p = 0.55$, unpaired *t*-test) (Fig. 2). Patients within each group were also subdivided according to a LLMI level 4 or less (not indicative of aspiration) versus 5 or greater (indicative of aspiration) and neutrophil percentages above or below 10 percent, which are used as cutoffs for normal and abnormal values at our institution. There was no difference in the incidence of low LLMI (<4) versus high (>5) in patients with EoE and normal biopsy ($p = 0.35$ Fisher's exact test). Additionally, there was no difference in BAL neutrophil percentages above versus below 10% in patients with EoE versus those without ($p = 0.63$, Chi-square test)

Table 1
Patient overview.

	Normal esophageal biopsy	Eosinophilic esophagitis
Number of patients	32	19
Males (%)	18 (56)	15 (79)
Age, years	3.9 y (0.6–15)	5.9 y (1.6–16.3)
Cough (%)	13 (41)	7 (37)
Asthma (%)	7 (22)	3 (16)
Airway stenosis (%)	7 (22)	4 (21)
Dyspnea (%)	8 (25)	7 (37)
Dysphagia (%)	18 (56)	14 (74)
Dysphonia (%)	11 (34)	3 (16)
Aspiration pneumonia (%)	12 (38)	8 (42)
BAL% neutrophil, mean (range)	34 (1–97)	40 (0–95)
LLMI, mean (range)	4.4 (1–9)	3.4 (1–6)