

they have low specificity and with no history of prior reaction usually reflects asymptomatic sensitization, as they did initially in our patients. In studies of certain high-risk pediatric populations (atopic dermatitis, anaphylaxis), 95% PPV cutoff values exist for predicting allergic reactions to milk, egg white, and peanut. Wheat and soy have performed less reliably, with 50% and 75% PPV, respectively.¹⁰ In an adult study, wheat-specific IgE PPV was 57%. Thus, performance characteristics may not be applicable between different populations (age, food, type of food allergy).

The previously reported milk reactions initially lacked IgE to milk, and post-reaction had milk IgE associated with high milk PPV in a different patient population; in contrast, our patients had evidence of wheat or soy IgE both initially and after their reaction, albeit levels associated with lower PPVs. Whether previously reported food-specific IgE/PST PPVs are applicable to children and adults with EoE reintroducing previously IgE tolerated foods remains to be seen.

Third, should all patients on a restricted diet for EoE be (re-) evaluated for specific IgE before reintroducing a food, or is this a phenomenon of just more “highly” allergenic foods? Fourth, who should be reexposed via in-office graded oral food challenge? Time, cost, and inconvenience become additional considerations. Finally, what is the mechanism by which, during food restriction, the immune response changes from non-IgE TH2 response to include an IgE response?

In discussing EDs and topical corticosteroids with patients and their families, the risks and benefits should be thoroughly detailed so that an informed decision can be made. A small, but real, risk of a more serious IgE-type food reaction developing in EoE patients after a period of restriction is apparent. Means to identify those at risk is needed and will help direct which patients should have in-office, physician-supervised, graded food challenges, continued restriction, or at-home food reintroduction. Further epidemiologic and immunologic studies are needed to gain insight into this increasingly recognized phenomenon.

A peripheral cause of asthma

Peripheral T-cell lymphoma

Peripheral T-cell lymphoma, not otherwise specified (PTCL, NOS) is an aggressive subtype of T-cell non-Hodgkin's lymphoma. Despite the poor prognosis associated with PTCL, NOS, prompt diagnosis and treatment are critical to prevent further morbidity and mortality.¹ We report a case of new-onset asthma with peripheral eosinophilia, subsequently diagnosed with PTCL, highlighting the need to consider a broad differential in the setting of uncontrolled atypical respiratory symptoms.

A 49-year-old woman without significant medical history or known atopy was transferred from an outside hospital for new-onset asthma, peripheral eosinophilia, diffuse rash, recently diagnosed thymoma, and respiratory distress. Eight months before presentation, the patient developed a pruritic papulonodular rash to her upper chest and proximal upper extremities, which improved with steroid treatment. Two months later, the patient noted a new nonproductive cough and dyspnea after the completion of a marathon. She presented to an outside physician and received treatment for pneumonia, with improvement in symptoms. Four months later, her respiratory

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symptoms recurred, and the patient was referred to a pulmonologist, who performed pulmonary function testing notable for a forced expiratory volume in 1 second (FEV₁)/forced vital capacity ratio of 0.62, FEV₁ 36% of predicted, and a 24% improvement in FEV₁ after the administration of a bronchodilator. A methacholine challenge was also performed and was reportedly positive. She was diagnosed with new adult-onset asthma and treated with a short course of oral corticosteroids and eventually continued on inhaled corticosteroids with little improvement. A computed tomography (CT) scan of her chest demonstrated an anterior mediastinal mass that was consistent with a thymoma, and a complete blood count revealed peripheral eosinophilia. Given this constellation of symptoms, the patient underwent a bone marrow biopsy, which was negative for malignancy but did demonstrate 10% eosinophils. Before her thymoma could be evaluated further, the patient's respiratory symptoms worsened over the course of a month, and she was admitted to an outside hospital for worsening dyspnea, a cough productive of thick, string-like sputum (Fig 1A), new nasal congestion with a sensation of fullness in her nose, and progressive rash involving all 4 extremities.

On presentation to our hospital, her white blood cell count was 14,500 cells/ μ L, with a peak absolute eosinophil count of 1,312 cells/ μ L.

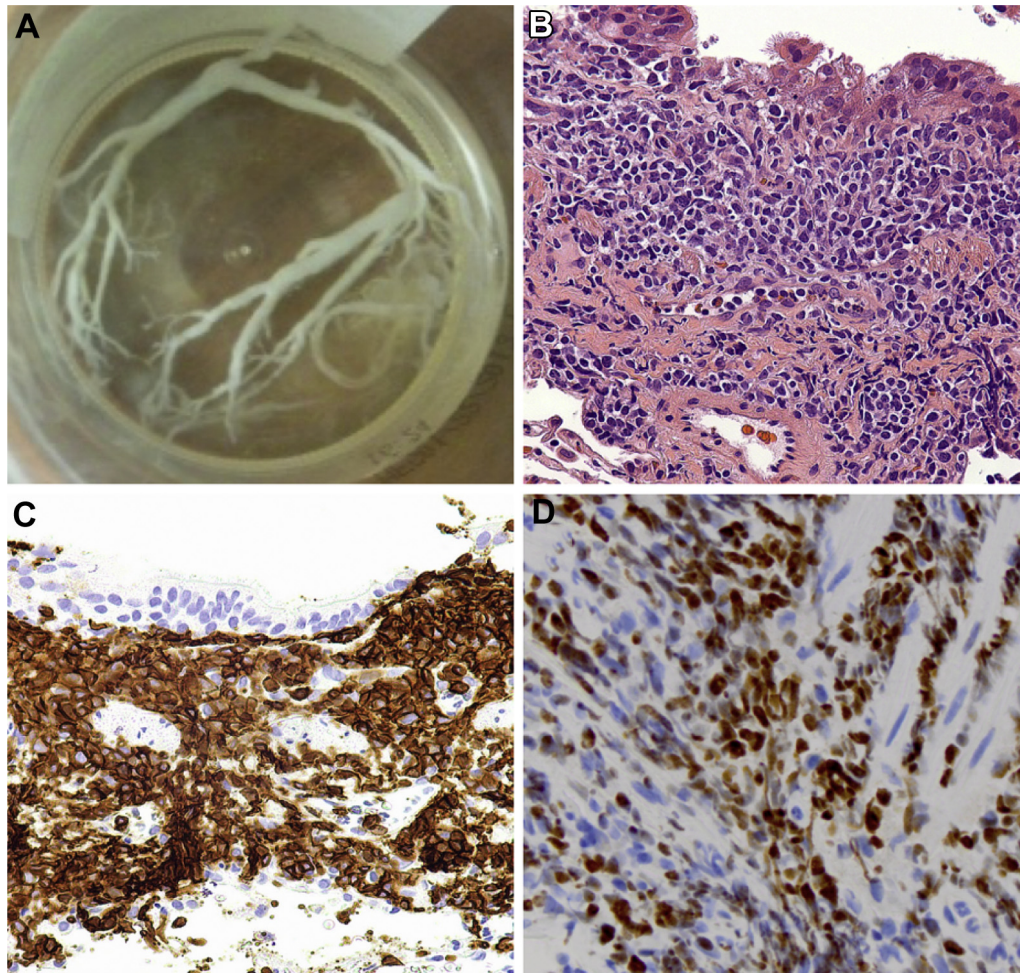


Figure 1. Bronchial cast (A). Transbronchial lung biopsy showing atypical lymphocytic infiltration (B, hematoxylin and eosin staining, 40× magnification), with dense infiltration of CD4+ lymphocytes by immunohistochemistry (C), and with positive GATA-3 staining of lymphocytes (D).

Pathologic examination of the sputum showed aggregates of eosinophils and admixed atypical lymphocytes. The patient had wheezing on examination, and a CT of the chest without contrast showed an anterior mediastinal mass, bilateral lower lobe tree-in-bud opacities, bronchial wall thickening with mucous plugging, and mosaic attenuation. A CT of the paranasal sinuses showed a 3.7 cm mass-like soft tissue density obscuring the anterior nasal cavity, which was inseparable from the nasal septum.

She underwent a biopsy of her nasal septum, which showed a mixed inflammatory cell infiltrate but was negative for malignancy. However, flow cytometric immunophenotyping of the nasal septal mass biopsy suggested a clonal population of T-cells, concerning for a T-cell lymphoproliferative disorder. Bronchoscopy with bronchoalveolar lavage and transbronchial lung biopsy was then performed, which demonstrated dense bronchocentric atypical lymphocytic infiltrate positive for CD3 and CD4 consistent with PTCL, NOS (Fig 1B, 1C). GATA-3 staining of the transbronchial lung biopsy specimen was diffusely positive (Fig 1D).

A skin biopsy of the extremities confirmed the diagnosis, and a lumbar puncture identified malignant cells in the cerebrospinal fluid. The patient was diagnosed with stage IV PTCL, NOS, and systemic and intrathecal chemotherapy was initiated. Quite rapidly, she was found to be treatment-refractory and developed acute hypoxemic respiratory failure requiring intubation. After a family discussion, she was transferred to an inpatient hospice unit and passed away within 1 month of presentation.

Peripheral T-cell lymphomas represent approximately 12% of all non-Hodgkin's lymphomas and arise from T-cells and natural killer (NK) cells in organs other than the thymus.² The incidence of PTCL is less than 1 per 100,000 people in the United States, and it is associated with a very poor prognosis. Although rare, infection with human T-cell leukemia-lymphoma virus-1 and Epstein-Barr virus have been implicated in PTCL development.^{3,4} Both reactive peripheral eosinophilia and tissue infiltration with eosinophils can occur in PTCL, NOS. Overall, PTCL portends a poor prognosis, but patients with PTCL, NOS with severe disease have only an 11% 5-year overall survival.¹

This case highlights the importance of considering a broad differential when evaluating newly diagnosed asthma patients who present with uncontrolled symptoms and peripheral eosinophilia refractory to the administration of oral corticosteroids. Eosinophilia can be a misleading clue and can delay an accurate PTCL diagnosis, whereas other entities such as eosinophilic granulomatosis with polyangiitis and hypereosinophilic syndrome are considered. Making the diagnosis of PTCL is further complicated by the rich inflammatory tissue infiltrate and the relative paucity of malignant cells. Definitive diagnosis in small biopsy specimens can therefore be difficult, as exemplified in this case. The degree of initial eosinophilia significantly increases the odds ratio of subsequent diagnosis with a hematologic malignancy, highlighting the importance of comprehensive evaluation of unexplained severe eosinophilia.⁵

T-cell lymphomas such as PTCL can cause eosinophilia through cytokine production by clonal T-cell subsets. Transcription factors such as GATA-3 distinguish CD4 T-cell subsets from other T-cell phenotypes, promote secretion of Th2 inflammatory cytokines including interleukin (IL)-4, IL-5, and IL-13, and epigenetically regulate the IL-10 locus.^{6,7} Interleukin-5 is a known eosinophilic survival factor and is often associated with eosinophil production and survival.⁶ In this patient's transbronchial lung biopsy, up-regulation of GATA-3 expression was a prominent feature (Fig 1D), which suggested both the presence and ongoing proliferation of Th2 inflammatory cells. These cells, in turn, produce cytokines, which cause uncontrolled eosinophil proliferation and tissue infiltration. GATA-3 expression in a cohort of 66 patients with PTCL, NOS was associated with decreased progression-free and overall survival when compared with patients with GATA-3–negative PTCL, NOS.⁶

In summary, a broad approach should be taken in the appraisal of new-onset asthma and peripheral eosinophilia with an unusual constellation of symptoms. In this case, the presence of diffuse rash, new-onset sinusitis, bronchial casts, lack of steroid responsiveness, and thymic enlargement should raise concerns to consider alternative diagnoses such as PTCL.

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Oral challenge outcomes in children with adverse aminopenicillin reactivity



Aminopenicillins, including ampicillin, amoxicillin, and amoxicillin-clavulanate, commonly cause dermatologic symptoms in children, who become diagnosed as being penicillin allergic. Without further investigation, children are prevented from receiving penicillin antibiotics when indicated as first-line therapy.^{1,2} There is a need to confirm or negate this diagnosis during childhood, but referral for penicillin testing is frequently deferred. Pediatricians and parents may not be aware of the clinical efficacy of penicillin testing, the effect of this misdiagnosis on future need, and, in young children, concern for the intrusiveness and pain of skin test procedure. We asked whether children with aminopenicillin reactivity could safely be tested with oral challenge alone. Our study investigates the prevalence of positive skin test results in children negatively reacting to aminopenicillins and the association between clinical history to skin test and oral challenge outcomes.

We enrolled patients younger than 18 years who were referred to the St. Louis Children's Hospital Allergy Clinic for elective penicillin skin testing from 2011 to 2017. No patients were excluded, but none had history of anaphylaxis. Patient data were collected from parents and referring physicians before the visit using detailed questionnaires (eAppendix 1) developed for this study. Two allergists (A.G.E. and G.R.B.) reviewed the questionnaires to determine whether the reported reaction was consistent with antibiotic

allergy. Written informed consent was obtained from parents before testing.

Skin testing used benzylpenicilloyl polylysine (PRE-PEN; ALK-Abello Inc, Copenhagen, Denmark), benzylpenicillin (penicillin G), and ampicillin as test reagents. Patients were instructed to discontinue use of antihistamines for 1 week and antibiotics for 8 weeks before testing. Histamine (6 mg/mL) was used as a positive control and saline as a negative control to validate testing. Skin prick tests (SPTs) to the above reagents were performed. A wheal that measured 3 mm or greater was considered a positive SPT result. If the SPT result was negative, intradermal testing followed, using a volume of 0.02 mL to make a 3-mm initial bleb in duplicate. After 15 minutes, an increase of at least 2 mm from the initial 3-mm bleb was considered a positive intradermal test result. Patients with negative skin test results were given an oral challenge of amoxicillin or amoxicillin-clavulanate (pending history) and observed for 2 hours in the office (dose of 45 mg/kg of amoxicillin). Families were instructed to call the allergist if any symptoms occurred after discharge.

Age at both time of initial reaction and time of testing, the antibiotic that caused the initial reaction (including route of administration), and underlying illness were recorded. Symptoms of reported antibiotic reaction, whether the patient was examined, whether the patient had concurrent fever, and reaction treatment and duration were recorded. This study was approved by the Washington University School of Medicine Institutional Review Board.

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