CLINICAL VIGNETTE

A Tale of Eosinophilia: ABPA or Chronic *Strongyloides* Infection?

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Case Presentation

A 90-year-old man with long-standing moderate-to-severe persistent asthma, allergic rhinitis, benign prostatic hypertrophy, and type 2 diabetes presented to primary care clinic for an evaluation of asthma. He reported daily shortness of breath and intermittent nighttime awakenings, which required albuterol inhaler use approximately twice per day. He also had a chronic cough with intermittent yellowish sputum production. He had been hospitalized multiple times for asthma exacerbations with the last hospitalization occurring one year prior, which necessitated a one-week hospitalization with BiPAP support despite steroids and oxygen. He is followed by an allergist for 15 years with monthly allergy shots. He reports a 20 lb. weight loss over the last 6 months, attributed to an intermittently reduced appetite. He denied fevers, chills, night sweats, abdominal pain, nausea, vomiting, diarrhea, dysphagia, itching, or rashes. He had no travel outside of California in the last 5 years and was taking no new medications. He was a lifelong non-smoker, but had significant secondhand smoke exposure from his mother for the first 18 years of his life. He was originally from Puerto Rico, joined the US military at age 18, and served in Korea and Japan over 70 years ago. He denied other international travel. Current medications included an albuterol inhaler, budesonide/formoterol inhaler, montelukast, metformin, glipizide, pioglitazone, alogliptin, and alfuzosin. He was a rare social drinker and denied recreational substance use. On examination, he was breathing comfortably on room air and all vitals were normal. Cardiopulmonary exam revealed a regular cardiac rate and rhythm without overt murmurs and lungs were clear bilaterally without wheezing. There was no clubbing or cyanosis in the extremities.

Routine labs revealed an elevated absolute eosinophil count which ranged from 1780 to 3310 over the last five years (normal <500). Eosinophil percentage was 26% (normal 1-6%). Review of remote labs included a CBC from 13 years prior that also showed an elevated eosinophil percentage of 19.7%. Other than the elevated eosinophil count, the remainder of the CBC was normal at this visit. His white blood cell count in prior years occasionally rose to 12-14 with an eosinophil predominance. A vitamin B12 level was normal at 499 pg/mL. Other normal labs included tryptase level of 6.2, HIV, ANCA, myeloperoxidase, ANA, and hsCRP were negative. ESR was appropriate for age at 23. Total serum IgE levels were >3000, prompting CT scan of the lungs and a fungal serology panel, including *Aspergillus* IgG, *Schistosoma* IgG, *Strongyloides* IgG, *Coccidiomycosis* panel, aeroallergen panel, AFB + sputum mycology, bacterial respiratory cultures, and stool studies.

The CT scan showed mild patchy ground-glass opacities and a suggestion of tree-in-bud nodularity in the right upper lobe compatible with an infectious bronchiolitis. There was also diffuse bronchial wall thickening and multiple nonspecific pulmonary micronodules. The patient was referred for consultation with Allergy and Pulmonary specialists.

At the time of the Pulmonary evaluation, the serum aeroallergen panel showed very high levels of sensitivity to most trees, pollens, dust mites, as well as a moderate level of sensitivity to *Aspergillus fumigatus* based on the level of IgE antibodies. However, the *Aspergillus* IgG antibody was negative. Sputum mycology culture grew *Aspergillus fumigatus*. All other cultures and stool studies were negative. In conjunction with the CT scan findings, the Pulmonary team determined that the patient met criteria for allergic bronchopulmonary aspergillosis (ABPA). Concurrently, the *Strongyloides* IgG came back strongly positive. The treatment team decided to defer treatment until the *Strongyloides* was addressed.

He saw the Infectious Disease consultants treated him with ivermectin 12mg PO daily for 2 days followed by repeat course two weeks later. After treatment, his eosinophilia completely resolved although his IgE level remained high at >3000. Respiratory symptoms remained stable.

Discussion

Given the patient's long-standing history of poorly controlled asthma, the pretest possibility of having ABPA was high. However, after treatment for *Strongyloides*, the diagnosis for ABPA was no longer clear given the resolution of eosinophilia. The diagnostic criteria for ABPA are imprecise as the American College of Chest Physicians does not have well established criteria. The most commonly used criteria are disseminated by a working group of the International Society for Human and Animal Mycology (ISHAM). At a minimum, their criteria require a diagnosis of asthma or cystic fibrosis since ABPA is otherwise uncommonly seen in other populations. This includes rare occurrences in populations with other chronic respiratory

conditions such as COPD. Our patient clearly meets this first criterion. The second obligatory criterion for ABPA is having both positive serology for *Aspergillus* IgE and a total IgE level >1000. This patient had positive serology and an IgE level >3000, which easily satisfies this criterion. The final diagnostic measure requires 2 out of the 3 following features: a serum precipitin/*Aspergillus* IgG level that is positive (our patient was negative), a peripheral eosinophil count >500 (his was over 1700), and a high-resolution CT scan consistent with ABPA.[1] For this particular patient, he did not have classic bronchiectasis on imaging, but there is an array of radiographic findings that are consistent with ABPA including tree-in-bud opacities with an upper lobe predominance, mucus plugging, or ground-glass opacities.

Additionally, this patient had a sputum culture growing *Aspergillus*, but this is not part of the diagnostic criteria at this time. However, a positive culture is supportive since the mechanism by which *Aspergillus* causes symptoms is through chronic colonization of an impaired respiratory tree with no direct invasion. The bronchial wall inflammation and mucus plugging only occurs in individuals with underlying hypersensitivity.

In this case, treatment with ivermectin for *Strongyloides* caused the patient's peripheral eosinophil count to plummet to normal levels, so he no longer meets criteria for ABPA. *Strongyloides* is considered to be a forgotten tropical disease even though the prevalence rate in tropical and subtropical countries has been estimated to be between 10-40%, with Brazil and Thailand being particular hot spots.[2] The disease is caused by a nematode that usually lives in the soil and enters the human body through uncovered skin of the feet. Wearing shoes is a maneuver to reduce transmission. Once the nematode migrates through the skin and lymphatics (the former causing itching, urticaria, or other rashes), it migrates to the respiratory tree, ascends to the upper airway, and is eventually swallowed into the GI track where it lives chronically. Auto-inoculation through this mechanism only tends to occur in individuals who are immunocompromised. It is common to have infection for decades and remain asymptomatic. Only about 50% of infected people complain of at least one symptom and 70% have peripheral eosinophilia. Symptoms include respiratory complaints, itching, skin rash or urticaria, nausea/vomiting, abdominal pain, abdominal distension, and diarrhea. Symptoms consistently improve after successful treatment, although itching is the least likely to fully abate.[3]

There is no gold standard test for *Strongyloides* but serology is generally favored in the United States with a sensitivity rate of 70-95%.[4] Fecal examination is generally low yield since larvae are not consistently produced in the stools. One study reported increased fecal sensitivity when 4-7 separately collected specimens were tested.[5]

Since treatment is straightforward – and well tolerated, some propose screening high-risk populations. One case series of strongyloidiasis in migrants, found seroprevalence of 12.2%. Migrants from East Asia and the Pacific had the highest rate of seroprevalence at 17.3%.[6] The other high-risk group is military staff returning from deployment to high- risk areas overseas. A study of veterans who were World War II prisoners-of-war in Burma and Thailand found a high prevalence of infection 40 years after their tour.[7]

For this veteran, it is possible that he became infected with *Strongyloides* as a child in Puerto Rico or during his military service in Korea. With more time, his IgE level might decline from the successful *Strongyloides* treatment unless the main driver for its elevation is ABPA.

REFERENCES

1. **Agarwal R, Sehgal IS, Dhooria S, Aggarwal AN**. Developments in the diagnosis and treatment of allergic bronchopulmonary aspergillosis. *Expert Rev Respir Med*. 2016 Dec;10(12):1317-1334. doi: 10.1080/17476348.2016.1249853. Epub 2016 Nov 7. PMID: 27744712.
2. **Schär F, Trostdorf U, Giardina F, Khieu V, Muth S, Marti H, Vounatsou P, Odermatt P**. Strongyloides stercoralis: Global Distribution and Risk Factors. *PLoS Negl Trop Dis*. 2013 Jul 11;7(7):e2288. doi: 10.1371/journal.pntd.0002288. PMID: 23875033; PMCID: PMC3708837.
3. **Buonfrate D, Fittipaldo A, Vlieghe E, Bottieau E**. Clinical and laboratory features of Strongyloides stercoralis infection at diagnosis and after treatment: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2021 Nov;27(11):1621-1628. doi: 10.1016/j.cmi.2021.07.016. Epub 2021 Jul 26. PMID: 34325063.
4. **Buonfrate D, Requena-Mendez A, Angheben A, Cinquini M, Cruciani M, Fittipaldo A, Giorli G, Gobbi F, Piubelli C, Bisoffi Z**. Accuracy of molecular biology techniques for the diagnosis of Strongyloides stercoralis infection-A systematic review and meta-analysis. *PLoS Negl Trop Dis.* 2018 Feb 9;12(2):e0006229. doi: 10.1371/journal.pntd.0006229. PMID: 29425193; PMCID: PMC5823464.
5. **Dreyer G, Fernandes-Silva E, Alves S, Rocha A, Albuquerque R, Addiss D**. Patterns of detection of Strongyloides stercoralis in stool specimens: implications for diagnosis and clinical trials. *J Clin Microbiol*. 1996 Oct;34(10):2569-71. doi: 10.1128/jcm.34.10.2569-2571.1996. PMID: 8880521; PMCID: PMC229319.
6. **Asundi A, Beliavsky A, Liu XJ, Akaberi A, Schwarzer G, Bisoffi Z, Requena-Méndez A, Shrier I, Greenaway C**. Prevalence of strongyloidiasis and schistosomiasis among migrants: a systematic review and meta-analysis. *Lancet Glob Health*. 2019 Feb;7(2):e236-e248. doi: 10.1016/S2214-109X(18)30490-X. Erratum in: *Lancet Glob Health*. 2019 Apr;7(4):e419. PMID: 30683241.
7. **Pelletier LL Jr, Baker CB, Gam AA, Nutman TB, Neva FA**. Diagnosis and evaluation of treatment of chronic strongyloidiasis in ex-prisoners of war. *J Infect Dis*. 1988 Mar;157(3):573-6. doi: 10.1093/infdis/157.3.573. PMID: 3343527.