Hypereosinophilia in a Young Woman with a History of Childhood Asthma

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Hypereosinophilia is a rare clinical entity. It is associated with a wide differential diagnosis including neoplasm, infection, and allergic etiologies. Clinicians should have a well defined approach to hypereosinophilia in order to find treatable causes. We present a case of hypereosinophilia caused by parasitic infection with Toxocara canis. We also review epidemiology, transmission, microbiology, and management of Toxocara canis.

CASE PRESENTATION

A 39-year-old woman with a past medical history of childhood asthma presented to the emergency department with complaints of five days of back and right upper quadrant pain, nausea, vomiting, and shortness of breath. She had taken over the counter acetaminophen but was on no other medications. She denied any drug use and endorsed intermittent alcohol use. She stated she grew up near a farm and was exposed to wildlife and house pets. The patient reported her mother had thyroid disease and her father had hypertension.

Upon arrival to the emergency department, her temperature was 99.7°F, respirations were 20 breaths/minute, pulse was 95 beats/minute, blood pressure was 131/71 mmHg, and oxygen saturation was 100%. On physical exam, she was in mild distress, but alert and oriented. There was no cervical or axillary lymphadenopathy. On lung exam she exhibited mild wheezes but no crackles. Her abdomen was tender to palpation in the right upper quadrant but without rebound tenderness, distension, or rigidity.

Other significant test results included 3,900/ul (0.0-700/ul), alkaline phosphatase (ALP) of 363 U/L (40-150 U/L), aspartate transaminase (AST) of 94/U/L (10-58 U/L), and an alanine transaminase (ALT) of 78/U/L (5-50 U/L). Abdominal ultrasound showed hepatic steatosis, and chest radiograph (CXR) showed small bilateral lower lobe infiltrates. Computed tomography (CT) of the abdomen revealed gastric thickening and patchy infiltrates in the lower lung lobes. She was treated with piperacillin-tazobactam and azithromycin. Over the next week, her white blood cell count (WBC) continued to rise reaching a maximum of 42,200/ul. This was accompanied by a synchronous rise in her absolute eosinophil count reaching a maximum of 34,700/ul. Her liver enzymes along with ALP remained elevated. Throughout this time, she was afebrile and mildly hypertensive. She continued to have wheezing. Follow-up studies including flow cytometry and chromosomal analyses were negative for a monoclonal process or karyotypes associated with an eosinophilic neoplasm.

She underwent esophagogastroduodenoscopy (EGD) with biopsies which demonstrated mild scattered eosinophils throughout the esophagus and an increased number of eosino-
Given her hypereosinophilia, liver abnormalities, lung imaging abnormalities, wheezing, and other possibilities reasonably excluded, the decision was made to treat the patient for visceral larva migrans due to Toxocara canis. The ophthalmology department was consulted to ensure there was no evidence of ocular larva migrans. She was started on albendazole and prednisone. Her symptoms quickly improved with a substantial drop in WBC to 14,800/ul and absolute eosinophils to 10,800/ul. She was discharged from the hospital to complete her course of therapy and received follow up in the outpatient setting.

On initial follow-up (two weeks later) her WBC had risen back to 20,200/ul and absolute eosinophils to 10,000/ul. Over the next month her WBC remained between 16,800/ul and 13,000/ul with an absolute eosinophil count approximately 9,000/ul. A decision was made to treat her again with albendazole. After the second round of therapy her symptoms improved with complete resolution of shortness of breath and abdominal pain. Her WBC and eosinophils continue to trend down.

**Epidemiology**

Toxocara canis is a parasite that causes infection when humans ingest contaminated soil or infected animal meat. Approximately 14 percent of the population in the United States is seropositive for toxocariasis, with the highest incidence in young, non-Hispanic African Americans. Other risk factors include low socio-economic status, an occupation involving soil handling, and young age. Though larvae can survive in freezing temperature, the ideal climate is between 20 and 30 degrees Celsius. The average Louisiana temperature approximates 20.83 degrees Celsius, making Louisiana a high prevalence environment for toxocara to embryonate.

The full life cycle of toxocara only occurs in dogs and cats ( definitive host). However adult worms can live in stools or tissues of multiple animals including rabbits, chicken or small rodents (paratenic host). Toxocara is passed through the stool of these animals and contaminates the soil. Ingestion of the stool in contaminated soil or the meat of a paratenic host can transmit the larvae to humans.

Toxocara larvae act the same way in humans as in other hosts. Ingestion of eggs allows embryosis to occur in the intestine which produces larvae that penetrate through the gut wall and migrate to other organs (most commonly lung and liver).

Most transmission of toxocara occurs via ingestion. There is some thought that toxocara in the coats of dogs may be able to be transmitted, though this would be very rare. Glickman was not able to show a direct link between pet ownership and seropositive humans. However, his study did show that of the 14 participants who denied past or present dog ownership, none of them were antibody positive.

**Immunology**

The first clue of a Toxocara infection other than symptoms may be marked eosinophilia. Eosinophils are tissue dwelling cells and the absolute number of eosinophils seen in the blood does not necessarily correlate to the activity within tissues. Stimulation of the marrow to produce eosinophils is triggered by three main factors: interleukin (IL) -5, IL-3, and granulocyte macrophage colony stimulating factor (GM-CSF). Of these, IL-5 is the most specific and provokes the largest response from bone marrow. IL-5 is produced by Th2 cells which are lymphocytes activated in response to helminth infections. Not only does this stimulate production of eosinophils, but it also activates already circulating eosinophils to become more cytotoxic and immuno-active.
The microbiology of eosinophils makes them uniquely equipped to fight helminth infections. First, they have a high affinity for IgA antibodies which exist near mucosal surfaces, where helminths typically enter the body. Activation of eosinophils via IgA or Th2 cell mediation stimulates production and degranulation of the marrow and existing eosinophils. Since eosinophils are not particularly effective phagocytes, unicellular protozoan infection typically cause a macrophage and neutrophil response. However, eosinophils contain specific enzymes which are cytotoxic to multicellular helminths that are too large for phagocytosis. These proteins include major basic protein (MBP), eosinophilic cationic protein, eosinophil derived neurotoxin, and eosinophil peroxidase. Degranulation of eosinophils leads to release of these proteins and a hypodense appearance of eosinophils in the periphery. The exact mechanism of these proteins is not known, but they have been shown to be toxic to parasites, certain types of cancers, and host tissues.

Once there is infestation of tissues with embryos of Toxocara there is migration of eosinophils to that tissue by the aforementioned mechanisms. The enzymes released by the now activated eosinophils are not specific to the pathogen. They also have the ability to destroy and inflame host tissues, providing the basis for tissue damage and symptoms which occur with Toxocara infection. The organism itself does not cause damage per se; rather the invoked inflammatory response can cause severe and permanent damage if left untreated.

Clinical Presentation

Toxocariasis can have several different clinical manifestations. The most common are visceral larva migrans (VLM) and less common, occurring ocular larve migrans (OLM).

The organs usually involved in visceral larva migrans are the liver and lung. This correlates with the circulation pattern of the parasite as it burrows through the intestinal wall and circulates through the hepatic and pulmonary vasculature. Though larvae often cause objective liver-associated findings, more often patients present with pulmonary complaints such as wheezing, dry cough, and dyspnea. Other patients may present with vague flu-like complaints such as fatigue, mild fevers, or joint pain.

With the increasing incidence of childhood asthma, Toxocara canis has potentially increased importance. Wheezing with an increased eosinophil count is a hallmark of childhood asthma. It has been postulated that helminth infections may be a risk factor or predisposition to future reactive airway disease and asthma. This would likely be due to the large Th2 response to the parasite, causing some cross-reactivity and stimulating the symptoms of asthma. A pediatric study in Hungary showed improvement in children with both seropositivity for ascariasis and asthma who received therapy directed at asthma and one course of anti-helminthic drugs.

Ocular larve migrans (OLM) involves the migration of the larva into the posterior portion of the eye, leading to granulomatous inflammation. An ophthalmology evaluation for ocular larva migrans is necessary if treatment is being considered. A dreaded consequence of OLM is retinal infiltration leading to dragging and eventual retinal detachment.

The most common laboratory finding associated with toxocariasis is hypereosinophilia. The degree of elevation can vary from mild to dramatically elevated, as seen in our case. Hepatic granuloma formation can present with signs of transaminitis along with elevations in ALP. Hypergammaglobulinemia may also be present in the setting of symptomatic patients, as was also seen in our patient.

Imaging is also variable with VLM. Ultrasonography, CT, and magnetic resonance imaging have been evaluated. In Lim’s review in 2008, liver imaging typically showed multiple ill-defined lesions that measured from 1-1.5 cm. It is important to note that these lesions are best seen in the venous phase of CT liver images, differentiating it from most metastatic cancers.
Pulmonary imaging is similar in that there are multifocal nodules with ill-defined margins.\textsuperscript{15}

\textbf{Diagnosis and Treatment}

Diagnosis of Toxocara infection relies heavily on the clinical scenario and epidemiology. A thorough history including childhood exposures, animal exposures, family history, and work environment should be obtained before pursuing the diagnosis. Clinical symptoms, leukocytosis, eosinophilia, and hypergammaglobulinemia should all be evaluated before further testing. In a study by Jones in 1980, certain populations can have high seropositivity, but clinical disease is uncommon.\textsuperscript{16} This supports the concept that only individuals with suspicious epidemiology or exposure history should be evaluated.

Currently there is an ELISA antibody assay available through the Centers of Disease Control (CDC). This assay detects human IgG antibodies to Toxocara, though it does have some cross-reactivity with other parasites. The sensitivity and specificity of the ELISA is 78 percent and greater than 92 percent, respectively.\textsuperscript{17} The gold standard for diagnosis is biopsy with visible larvae seen. However this procedure is rarely indicated and must be weighed in terms of risk and benefit to the patient.

As with many parasitic infections, the best approach to toxocariasis is prevention. Given its prevalence for infecting children it is important to teach proper hand washing and hygiene in high risk areas. Avoiding intake of soil and properly disposing of pet feces can also help limit exposure.

Therapy for toxocariasis is determined by symptom and disease burden. Patients with less severe disease respond well to albendazole therapy for two weeks.\textsuperscript{18} There are instances of patients with mild disease resolving without therapy which would be optimal given the price of albendazole. Severe disease should be treated with concomitant steroids in order avoid the robust inflammatory response that will likely occur as larvae die. Prednisone is also cytototoxic to eosinophils.

Definitive cure for toxocariasis is not well defined. Treatment studies for toxocara infection have used clinical resolution of symptoms to define cure.\textsuperscript{19} Symptom relief is typically accomplished before resolution of eosinophilia, which may take weeks. However, prednisone plus albendazole therapy results in a more dramatic decrease in eosinophils than therapy with albendazole alone. The eosinophil count should be rechecked after steroid therapy is completed.

Ocular larva migrans should be ruled out prior to initiation of therapy as steroid use is always recommended for treatment of this presentation.

In summary, toxocariasis is a rare clinical entity despite a high seroprevalence within our population. Susception for the disease should be increased in patients with hypereosinophilia and the appropriate epidemiologic history.

\textbf{REFERENCES:}


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