

Title: *Ascaris lumbricoides* beyond the obstruction

Abstract

Ascaris lumbricoides infestation remains the most common cause of eosinophilia. Also, in cases of severe eosinophilia due to ~~heminth~~*helminth* infection, eosinophilic infiltration of several tissues may occur, and most likely to be clinically underestimated. If not ~~early~~ diagnosed ~~early~~, *it* can be severe and fatal. We describe the case of a 33 year-old man from Brazil, a unique case of *Ascaris* hipereosinophilia with systemic involvement including the heart, kidneys, and bone marrow, without symptoms. Transthoracic echocardiography revealed a dilated left ventricle with an endocardial thickening. Kidney biopsy revealed tubulointerstitial nephritis full of eosinophilic cells, associated with an acute and global diffuse glomerulonephritis, also infiltrated by ~~eosinophis~~*eosinophils*. Bone marrow biopsy revealed ~~eosinophilic~~*eosinophilic* infiltration without any signs of malignant disorder. The patient was successfully treated and resulted in significant organ improvement. Extensive clinical evaluation in search for alternative causes of the multiple organ involvement should be performed while institution of empiric therapy for ~~helminth~~*helminthic* infestation.

Key-words: Eosinophilia, *Ascaris*, Glomerulonephritis, Cardiomyopathies.

Introduction

Ascaris lumbricoides is a nematode parasite that infects a quarter of the world's population depending on geographic location and is a well-recognized cause of illness among persons with poor socio-economic conditions. [1]

Formatted: Font: Italic

Formatted: Font: Italic

About one third of the population in the cities of some developing countries live in slums and shantytowns where the prevalence and intensity of *A. lumbricoides* is significantly increasing due to ~~favourable~~favorable conditions of transmission.[1]

In general practice, helminth infection is the commonest identifiable cause of eosinophilia. However, there are multiple causes, both infectious and non-infectious, of a peripheral blood eosinophilia and patients may present to a range of specialities other than infectious diseases. [2, 3] In severe eosinophilia, infiltration of several tissues may occur. [3]

Eosinophilic infiltration has been associated with disorders of the lung, heart, gastrointestinal and biliary ~~tracts, biliary tract,~~ and gall-bladder.[2, 3] Although single-organ eosinophilic infiltration due to ~~heminth~~helminth infection has been reported [2, 4-6], multiple organ involvement is rare.

Herein we describe a unique case of multiple organ damage (heart, kidneys, and bone marrow) due to *Ascaris* hipereeosinophilia successfully treated and review previously reported cases in the literature.

Case Report

A 33-year-old single, black man admitted to the hospital for a multidisciplinary evaluation with a four-year history of fracture of the right tibia complicated with tibialpseudo arthrosis and cutaneous fistulae. Otherwise, he was asymptomatic and specifically denied any symptoms. He had no family history of illness. The patient was married. There was no history of alcoholism, use of recreational drugs, or smoking, although the patient admitted sexual promiscuity in the past. He kept one dog at home.

49

50 On physical examination, the patient was afebrile and appeared well. The pulse was
51 84bpm, and the blood pressure 140x80 mmHg. Punctate, erythematous, non-palpable
52 lesions were present on the pseud-arthritis area of right leg. No subcutaneous nodules
53 were discovered. The lungs and heart were normal. There was pitting (+) edema of the
54 right leg to the knee, without varicosities, palpable cords, local pain, or tenderness. No
55 edema was present in the left leg; the peripheral pulses (+) were equal bilaterally.

56

57 ~~Admission~~-Admission laboratory evaluation showed positive IgG but negative IgM
58 antibodies for both cytomegalovirus and toxoplasmosis. Serology for human
59 immunodeficiency virus 1 and 2, viral hepatitis and syphilis were negative.
60 Hemagglutination for Chagas disease was non-reactive. The hematocrit was 25,7%
61 ~~percent~~; the white-cell count was 21.100/mm³-per cubic millimeter, with 18,5%~~percent~~
62 neutrophils, 16,3%~~percent~~ lymphocytes, 3,5%~~percent~~ monocytes, and 61,3%~~percent~~
63 eosinophils. The platelet count was 321.000/ mm³-per cubic millimeter, and the total
64 eosinophil count 12.934/mm³-per cubic millimeter. A complete 3 stool samples
65 analysis revealed no abnormalities. A urinalysis showed clear, yellow urine with a
66 specific gravity of 1.005, pH 5, 1 g/~~ram-per-liter~~ of protein, 579.000 white and
67 1.189.000 red cells. The search for eosinophils cells in the urine was positive. -Chest
68 ~~*X~~-ray revealed cardiomegaly. The 12-lead electrocardiogram revealed atrial
69 enlargement. Transthoracic echocardiography revealed a dilated left ventricle (LV) with
70 an endocardial thickening in apex of LV, with diffuse hypokinesis in the both
71 ventricular walls (left ventricular ejection fraction, 47%). The ~~thicknesses-was~~thickness
72 was observed also in both the interventricular septum and posterior wall of the left
73 ventricle, indicating left ventricular hypertrophy.

74

75 At the time of presentation, the main diagnosis was reactive eosinophilia due to an
76 inflammatory reaction against the cutaneous fistulae, although other differential
77 diagnoses needed to be considered due to other organ involvement (heart and kidneys).

78

79 Despite multiple organ involvement, the patient in this case remained asymptomatic.

80 Based on the orthopaedic evaluation a surgical procedure was proposed, but the patient

81 declined. We continued the investigation of the other organ dysfunctions. A

82 pPercutaneous biopsy of the left kidney revealed tubulointerstitial nephritis full of

83 eosinophilic cells, associated with an acute and global diffuse glomerulonephritis, also

84 infiltrated by ~~eosinophilic~~eosinophils (Figure 1). Another complete 3 stool samples

85 analysis revealed no abnormalities. An ~~u~~Ultrasonographic examination of the abdomen

86 revealed no abnormalities. The IgE level was 524,8 IU/~~ml-per milliliter~~ (reference:<

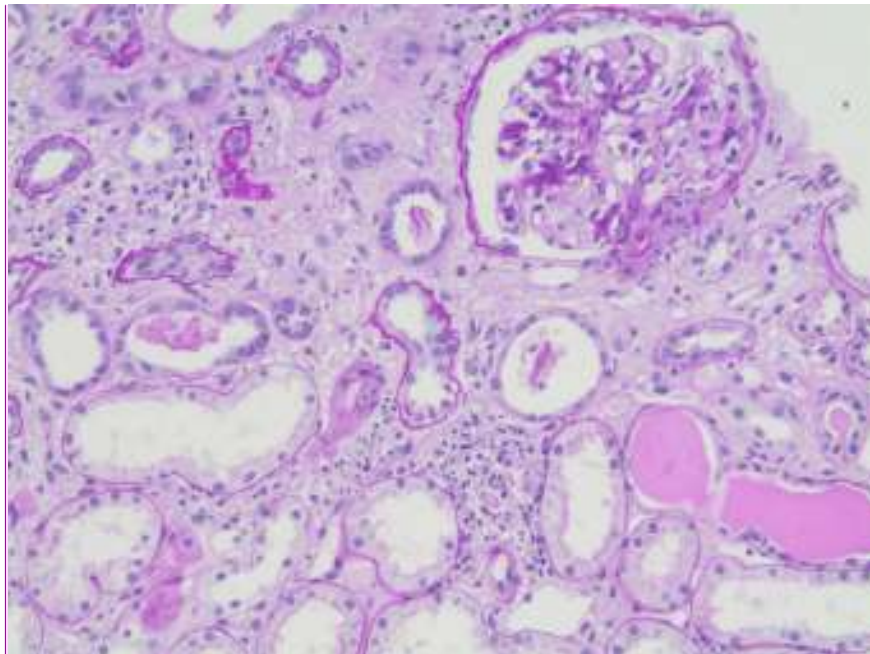
87 165,3 IU/ml). Serologic tests for *Toxocara*-specific were negative. A bone marrow

88 biopsy revealed ~~eosinophilic~~eosinophilic infiltration without any signs of malignant

89 disorder.

Comment [f1ns1]: From where? Serum?
Cavities? Aspirate?

Formatted: Font: Italic



Comment [flns2]: Please, put some arrows pointing to the eosinophils.

Figure 1. Kidney Biopsy: ~~Tubulointerstitial~~ tubulointerstitial nephritis full of eosinophilic cells, associated with global diffuse glomerulonephritis, also infiltrated by ~~eosinophis~~ eosinophils.

A new complete 3-stool samples analysis showed ~~ovae of AscarisA. lumbricoides~~ eggs, followed by another sample revealing signs of the parasite. The infestation by AscarisA. lumbricoides causing of multiple organ damage (heart, kidneys, and bone marrow) due to secondary hipereosinophilia was suspected based on clinical and laboratory correlation.

Comment [flns3]: Signs? What's signs? Sorry, but I don't understood. May you be more clear about these signs?

Twelve days after specific treatment with ivermectin (200 mcg/kg), the patient hematocrit was 26,3% ~~percent~~; the white-cell count was 14.600/~~mm³~~ ~~per cubic millimeter~~, with 51,5% ~~percent~~ neutrophils, 37,2% ~~percent~~ lymphocytes, 7,9% ~~percent~~ monocytes, and 2,7% ~~percent~~ eosinophils. The platelet count was 413.000/~~mm³~~ ~~per cubic millimeter~~, and the total eosinophil count 394/~~mm³~~ ~~per cubic millimeter~~. Several complete 3 stool samples analysis revealed no further abnormalities. Another transthoracic echocardiography revealed maintenance of left ventricular dilatation with

Comment [flns4]: Please, this sentence is confusing. May you rewrite it?

mild diffuse hypokinesis, absence of endocardial thickening, left ventricular ejection fraction, 54%). Table 1 summarizes the laboratory evolution during hospitalization.

Table 1. Evolution of laboratory test results during hospitalization.

Hematologic and blood chemical laboratory test results							
	1-year past record	Hospital admission	5-day Hospital admission	Ivermectin treatment	4-day post- treatment	8-day post- treatment	12-day post- treatment
Hematocrit (%)	32	25,7	28	24	25,4	25,4	26,3
Leukocyte (/uL)	8020	21100	23700	20800	15100	11500	14600
Eosinophils (/uL)	24	12934	15761	13728	7173	4727	394
Creatinine (mg/dL)	0,68	1,24	1,25	1,32	1	1	0,84
Urine white cells (/uL)	9000	579000	-	-	98000	41000	20000
Urine red cells (/uL)	5000	1189000	-	-	143000	45000	8000
Urine eosinophils	Negative	Positive	-	-	Positive	Negative	Negative
Stool analysis		Negative	<i>ova of AscarisA. lumbricoides</i>	<i>AscarisA. lumbricoides</i>	Negative	Negative	Negative

Discussion

This is the first report of multiple organ damage (heart, kidneys, and bone marrow) due to *AscarisA. Lumbricoides* hypereosinophilia-hypereosinophilia in an previously ~~rigid~~ healthy patient. Although single-organ eosinophilic infiltration due to ~~heminth~~ helminth infection has been reported until now, [2, 4-6], ~~until now~~ multiple organ involvement was only associated with idiopathic hypereosinophilic syndromes, and it's frequency variable from one study to another depending on the clinical subspecialty of the authors.[7, 8]

Typically, reactive eosinophilia due to an inflammatory reaction against parasitic infestation varies with the developmental stages of the parasite. In ascariasis,

eosinophilia increases in the first three weeks reaching levels of from 1,000 to 5,000 eosinophils/ μ L and then slowly decreases in subsequent weeks.[9]

In 2002, Sakakivbara *et al.* reported a case of organ eosinophilic infiltration due to heminthelminth infection. In this report, the authors describe a case of a Japanese man who had acute onset of severe cough from an unknown cause. On investigation, Chest chest CT demonstrated multiple ground glass opacities in both lungs. Bronchoalveolar lavage showed abundant eosinophils. Abdominal CT demonstrated multiple low attenuation areas in the liver. Liver biopsy with ultrasonography revealed severe eosinophil infiltrations around the portal veins. Serologically, a multi-dot enzyme linked immunosorbent assay (DOT-ELISA) and ELISA inhibition test were positive for *Ascaris suum*. The findings disappeared after 6 month of treatment with albendazolealbendazole. [5]

In 2007, Kajiet *et al.* reported the case of a 28-year-old woman complaining of acute right hypochondrial pain and dyspnea associated with systemic eruption. Several imaging modalities revealed acute cholecystitis and pericarditis with massive pericardial effusion. A marked peripheral blood eosinophilia was observed and a high titer of antibody against *AscarisA. lumbricoides*. Treatment with albendazole drastically improved all clinical manifestations along with normalization of the imaging features and eosinophilia. [2]

Also in 2007, Lau *et al.* reported the case of a 27-year-old previously diagnosed HIV/AIDS male Vietnamese with *Ascaris*-induced eosinophilic pneumonitis. He presented with shortness of breath, chest tightness and a-a pruritic rash over his body

Comment [flns5]: Sometimes you use infestation...sometimes infection. Please choose one of them.

Comment [flns6]: What's CT?

Formatted: Font: Italic

and limbs. After 3 days of hospitalization, two worms of *AscarisA. lumbricoides* were identified in his stool. [4]

More recently, Sentürket *al.* reported a case of *asearisAscaris*-induced eosinophilic myocarditis presenting with symptoms resembling acute ST elevation myocardial infarction and cardiogenic shock. A diagnosis of acute myocarditis was made by the presence of normal coronary arteries, peripheral eosinophilia and stool examination for *asearisAscaris* eggs. After corticosteroid treatment, the clinical status improved. [6]

Formatted: Font: Italic

Comment [fins7]: A.Lumbricoides?

Formatted: Font: Italic

There are no pathognomonic clinical or radiological findings for the manifestations of organ eosinophilic infiltration. As seen on previous reports, the clinical manifestations of hipereosinophilia due to *AscarisA. lumbricoides* can be variable from one patient to another, depending on target-organ involvement by eosinophils.

The organ damage and/or dysfunction are the consequences of eosinophil-release of various mediators, whose nature and functions have been enumerated in great detail by Valent et al.[7]_Although virtually any tissue or organ can be affected, major tissue targets include the skin, lungs, digestive tract, heart and nervous system.[7, 10]

Heart damage encompasses tree stages: endo/myocardial damage by mediators released from tissue-infiltrated eosinophils leading to sterile microabscesses (usually clinically silent);_soon, thrombi_develops_along these areas; most thrombi, however, become organized into fibrous tissue causing endomyocardial fibrosis. The fibrous tissue produces a restrictive cardiomyopathy and/or mitral or tricuspid valve regurgitation due to entrapment of the chordae tendineae. Similar findings could be found in our case by

transthoracic echocardiography revealing endocardial thickening and diffuse left ventricular hypertrophy.

Kidney involvement can occur due to eosinophilic infiltration of the glomerulus and tubulointerstitial space. The histological analysis of renal biopsy in our patient revealed tubulointerstitial nephritis full of eosinophilic cells, associated with an acute and global diffuse glomerulonephritis, also infiltrated by eosinophils.

An increase of eosinophilic population in bone marrow has long been described by Stransky in case of intestinal parasites, particularly hookworm. [11] So, a bone marrow examination should be performed in patients in whom a clinical suspicion of bone marrow infiltration is present. Neoplastic disorders of the bone marrow can be easily differentiated from reactive bone marrow changes. In this case, the presence of ~~anaemia~~anemia with hipereosinophilia led to a suspicion of malignancy. Bone marrow examination excluded this diagnosis.

Other causes of secondary eosinophilia are allergic conditions, such as dermatitis, rhinitis and asthma, but the values of eosinophils generally ~~don't~~do not exceed $1,500/\text{mm}^3$. There are other causes such as adrenal insufficiency, Churg-Strauss disease, atheroembolic and primary immunodeficiency syndrome, and among them hyperimmunoglobulinemia E, characterized by chronic dermatitis and recurrent infection, were not compatible with the previous history of the patient. Regarding the primary causes of eosinophilia, the myeloproliferative and myelodysplastic syndromes constitute differential diagnosis. The diagnosis of idiopathic hypereosinophilic syndrome, finally, requires the exclusion of other causes of primary and secondary

causes. The eosinophil count should be persistently greater than $1,500\text{mm}^3$ and there is evidence of target organ damage[7].

This case highlights the need for a high index of clinical suspicion among patients with poor socio-economic conditions with eosinophilia. Moreover, early institution of empiric therapy for ~~helmintic~~helminthic infestation while waiting for ~~a~~definitive ~~diagnosis~~conclusive diagnosis is advocated.

Conclusion

In summary, helminth infection is the commonest identifiable cause of ~~innocent~~ eosinophilia. In some cases, however, eosinophilic infiltration of organs can occur, and most likely to be clinically underestimated. Yet, multiple organ involvement is rare and should be considered as a diagnosis of exclusion. Extensive clinical evaluation in search for alternative causes of the multiple organ involvement should be performed while institution of empiric therapy for ~~helmintic~~helminthic infestation.

References

1. O'Lorcain, P. and C.V. Holland, *The public health importance of Ascaris lumbricoides*. Parasitology, 2000. **121 Suppl**: p. S51-71.
2. Kaji, K., et al., *Eosinophilic cholecystitis along with pericarditis caused by Ascaris lumbricoides: a case report*. World J Gastroenterol, 2007. **13**(27): p. 3760-2.
3. Akuthota, P. and P.F. Weller, *Eosinophils and disease pathogenesis*. Semin Hematol, 2012. **49**(2): p. 113-9.
4. Lau, S.K., et al., *Ascaris-induced eosinophilic pneumonitis in an HIV-infected patient*. J Clin Pathol, 2007. **60**(2): p. 202-3.

- 220 5. Sakakibara, A., et al., *Visceral larva migrans due to Ascaris suum which*
221 *presented with eosinophilic pneumonia and multiple intra-hepatic lesions with*
222 *severe eosinophil infiltration--outbreak in a Japanese area other than Kyushu.*
223 *Intern Med*, 2002. **41**(7): p. 574-9.
- 224 6. Senturk, T., et al., *Ascaris-induced eosinophilic myocarditis presenting as acute*
225 *ST elevation myocardial infarction and cardiogenic shock in a young woman.* *J*
226 *Cardiovasc Med (Hagerstown)*, 2012. **13**(3): p. 211-5.
- 227 7. Valent, P., et al., *Pathogenesis and classification of eosinophil disorders: a*
228 *review of recent developments in the field.* *Expert Rev Hematol*, 2012. **5**(2): p.
229 157-76.
- 230 8. Weller, P.F. and G.J. Bubley, *The idiopathic hypereosinophilic syndrome.*
231 *Blood*, 1994. **83**(10): p. 2759-79.
- 232 9. Ustianowski, A. and A. Zumla, *Eosinophilia in the returning traveler.* *Infect Dis*
233 *Clin North Am*, 2012. **26**(3): p. 781-9.
- 234 10. Cogan, E. and F. Roufosse, *Clinical management of the hypereosinophilic*
235 *syndromes.* *Expert Rev Hematol*, 2012. **5**(3): p. 275-90.
- 236 11. Stransky E, Quintos FN. *On hookworm anemia: aplastic anemia in hookworm*
237 *disease.* *Blood* 1947 Jan;2(1):63-71.