Pediatric hypereosinophilia and toxoplasma: Peregrination beyond facileness

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ABSTRACT

Evaluation of pediatric hypereosinophilia (HE) is challenging, especially in the tropical developing countries, as appropriate diagnostic facilities may be lacking, parasitic/helminthic infections are common, and existing data on the etiology of severe eosinophilia are sparse. Second, data on long-term follow-up of these children including the temporal course of eosinophilia are also scarce. Besides, questions regarding the coexistence of multiple etiologies and their association with the severity of HE are largely unexplored. These challenges and questions often lead to diagnostic and therapeutic dilemmas. We highlight these difficulties utilizing a real-life clinical description. We emphasize the need for long-term follow-up of such children as HE may be the combinatorial effect of multiple etiologies, rather than a single cause. We also describe an unusual association of severe eosinophilia in a child with toxoplasmosis that was treated successfully with 8-week combination therapy with azithromycin and cotrimoxazole (sulfadiazine and pyrimethamine were not available).

Keywords: Azithromycin, Cotrimoxazole, Hypereosinophilia, Steroid, Toxoplasma

Introduction

Hypereosinophilia (HE) in children is defined as persistent (>1 month) moderate-to-severe eosinophilia on complete blood count (CBC) or severe eosinophilic infiltration documented in tissue specimens. Although moderate eosinophilia ($>1.5 \times 10^9$ cells/L) may be a common clinical scenario in children, severe eosinophilia ($>5.0 \times 10^9$ cells/L) is rare.[1] HE in children is challenging as it is frequently underrecognized, and the exact etiology may remain an enigma despite a thorough evaluation. Intriguingly, etiological diagnosis may even change over time.[2]

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Moreover, evaluation of pediatric HE in developing countries is more problematic as appropriate diagnostic facilities are often lacking, parasitic/helminthic infections are commoner, and existing data on the etiology of HE are scarce.[3] Empirical treatment with oral albendazole/mebendazole, ivermectin, antimalarials, diethylcarbamazine (DEC), and even steroids is often employed before evaluation. Besides, questions regarding the coexistence of multiple etiologies and their association with the severity of HE are largely unexplored. Data on long-term follow-up of these children including the temporal course of eosinophilia are also scarce. These challenges and questions often lead to diagnostic and therapeutic dilemmas that result in difficulties in the appropriate care of children with HE. These problems may be further perplexing when an unusual cause of HE is found on evaluation or an unexpected course of eosinophilia is noted. Herein, we highlight these difficulties utilizing a real-life clinical description.

Case Description

A 9-year-old boy presented with intermittent low-grade fever for 8 weeks. He had a similar history 2 years back for which he was treated with DEC for 3 weeks, prednisolone for 3 months, and multiple doses of albendazole (400 mg). There was no history of recurrent or persistent infection, failure to thrive, atopic dermatitis, rhinitis, or asthma. Physical examination was noncontributory. A careful review of history and medical records revealed exposure to a pet cat over the last 4 years and severe eosinophilia (absolute eosinophil count of 8.0×10^9 cells/L) 2 years back. At the current presentation, CBC showed severe eosinophilia on multiple occasions [Figure 1]. Laboratory evaluation [Table 1] revealed positivity for anti-toxoplasma IgM. Polymerase chain reaction (PCR) from peripheral blood was positive for *Toxoplasma gondii*. Ophthalmology evaluation was normal and toxoplasma PCR in cerebrospinal fluid was negative. Bone marrow examination showed normocellular marrow with 22% eosinophils/precursors with no features suggestive of leukemia or myelodysplasia. No parasite was detected on bone marrow examination. On genetic evaluation, there were no *FIP1L1-PDGFRA* and *PDGFRB* translocations, *BCR-ABL1* fusion, or *JAK2* V617F and CALR (type 1 and 2) mutations. He was treated with oral cotrimoxazole and azithromycin for 8 weeks. Further pet contact was prevented and all possible contaminated materials at home were cleansed. At follow-up after 8 weeks of treatment with antimicrobials, repeat CBC showed resolution of eosinophilia [Figure 1]. A repeat toxoplasma PCR from peripheral blood was negative and antimicrobial therapy was stopped. However, after 6 months, he again developed asymptomatic severe eosinophilia. Toxoplasma PCR was again negative this time and he was treated with oral prednisolone at a dose of 1 mg/kg/day initially with gradual tapering over 3 months. The eosinophil count got normalized over 2 weeks. At 24-month follow-up, he is off steroids and doing well with normal eosinophil counts [Figure 2].
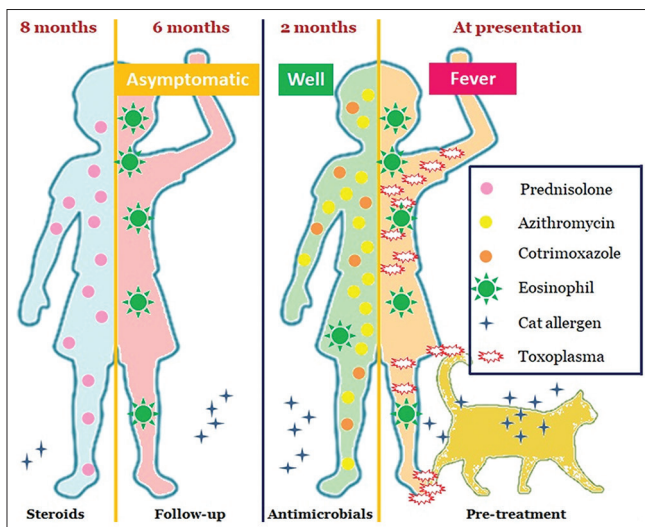
Discussion

Association of acquired toxoplasmosis with severe HE in an immunocompetent child is rare. Toxoplasmosis is not a well-recognized cause of eosinophilia in children; on the contrary, reports suggest toxoplasma infection to blunt eosinophilia owing to the strong T_H1 host immune response.[4-8] Literature suggests that associated factors, like coinfection with other parasites or drug hypersensitivity, may play a role in the development of eosinophilia with acquired toxoplasmosis.[9,10] In our case, no associated parasitic coinfection or drug allergies could be identified. Toxoplasma infection in the index patient was treated successfully with a combination of oral azithromycin and cotrimoxazole. Sulfadiazine and pyrimethamine, which are preferred agents, could not be commenced due to nonavailability. Post-treatment, eosinophil counts normalized, and repeat toxoplasma PCR was demonstrated to be negative. The asymptomatic recurrence of HE after 6 months with negative toxoplasma PCR prompted the use of oral corticosteroids. We suggest that this could be a secondary allergic response resulting from exposure to notoriously persisting cat allergens that are known to last in the environment for many months despite the physical removal of the cat.[11] The allergic trigger may have been a contributing factor at the initial presentation also, but a favorable response to antimicrobial therapy prevented the use of corticosteroids at that time. It would have been appropriate to reinvestigate the child on the recurrence of eosinophilia; however, lack of parental consent prevented further evaluation.

Our case reiterates the role of long-term follow-up in children with HE. Even if the supposed etiological diagnosis is established, more studies may be required to demonstrate causality. Long-term follow-up of the eosinophil counts (after successful treatment of cause considered) may provide vital evidence in favor of causality, even when experimental data are lacking. Besides, the severity of HE in children may be a combinatorial effect of multiple etiologies, rather than a single cause. Although toxoplasmosis may result in eosinophilia, the exact mechanisms of eosinopoiesis, despite the strong T_H1 immune response, need to be elucidated. Whether the inciting trigger can lead to an aberrant T_H2 skewing of immune response

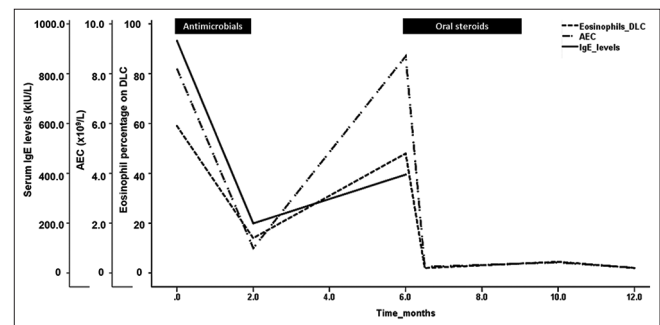**Figure 1:** A pictorial summary of follow-up details of the index child.

Figure 2: Trend of serum IgE levels, eosinophil percentage, and absolute counts in relation to drug therapy. (Abbreviations: AEC: absolute eosinophil count, DLC: differential leukocyte count)

Table 1: Laboratory investigations at presentation (in addition to those mentioned in text)

Parameter	Result (Normal value)
Total serum bilirubin	0.6 mg/dL (< 1)
Conjugated bilirubin	0.2 mg/dL
ALT	15 U/L (5-45)
AST	11 U/L (15-50)
ALP	196 U/L (145-420)
Urine examination	No red/white blood cells, no casts
Urine albumin (dipstick)	Negative
Urine protein/creatinine ratio	0.14 (< 0.2)
Gastric lavage for acid-fast bacilli	Negative on 3 occasions
Gastric lavage for mycobacterial culture	Negative
Gastric lavage for MTB complex CBNAAT	Negative
Brucella serology	Negative
Anti-HIV Antibody I/II	Negative
Stool workup (routine, parasitic, culture, AFB staining)	Unremarkable
Antibody detection (IgG) for hydatidosis (ELISA)	Negative
Antibody detection (IgG) for toxocariasis (ELISA)	Negative
Antibody detection (IgG) for filariasis (ELISA)	Negative
Antibody detection (IgG) for trichinellosis (ELISA)	Negative
Antibody detection (IgG) for cysticercosis (ELISA)	Negative
Ultrasonography of abdomen	Normal
IgG (g/L)	12.94 (5.40-16.10)
IgA (g/L)	0.78 (0.50-2.40)

ALT: alanine aminotransferase, AST: aspartate aminotransferase, ALP: alkaline phosphatase, MTB: *Mycobacterium tuberculosis*, CBNAAT: cartridge-based nucleic acid amplification test, HIV: human immunodeficiency virus

and result in persistent or recurrent HE, despite treatment of the primary cause, also needs to be determined.

Conclusions

Toxoplasmosis is among the common parasitic infections diagnosed and treated by primary care physicians. Although rare, severe eosinophilia may be noted at the presentation of acquired toxoplasmosis. A combination of azithromycin and cotrimoxazole is an effective therapy for the treatment of toxoplasmosis,[12,13] which may be used by primary care physicians for the treatment of acquired toxoplasmosis in case of nonavailability of sulfadiazine and pyrimethamine.

Key Messages/Key points

1. Toxoplasma is a rare cause of severe eosinophilia in children.
2. If sulfadiazine and pyrimethamine are unavailable, combination therapy with azithromycin and cotrimoxazole may be employed for the treatment of toxoplasmosis.
3. HE in children may be the combinatorial effect of multiple etiologies. Hence, long-term follow-up of such children is desirable.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the parents have given their consent for their child images and other clinical information to be reported in the journal. The parents understand that their child name and initials will not be published and due efforts will be made to conceal his identity, but anonymity cannot be guaranteed.

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