

# Soft Tissue Sarcoma Mimicking Eosinophilic Leukemia

Naeem Latif, MD  
Robert Zaiden, MD  
Dat Pham, MD  
Fauzia Rana, MD

*Department of Medical Oncology, University of Florida  
College of Medicine, Jacksonville, Florida*

## Introduction

Blood eosinophilia is diagnosed by an absolute eosinophil count that exceeds  $0.5 \times 10^9/L$ .<sup>1</sup> Hypereosinophilia is classified as either primary, due to clonal expansion of eosinophils through acquisition of a somatic mutation (eg, *FIP1L1-PDGFR $\alpha$* ),<sup>1</sup> or secondary, as seen in response to exogenous type 2 cytokines (eg, IL-3, IL-5, and GM-CSF) secreted by various cells (eg, T-lymphocytes).<sup>2-4</sup>

Secondary eosinophilia is seen in a variety of conditions, such as parasitic infestations, drug reactions, allergic reactions, connective tissue disorders, vasculitis, endocrinopathies, and malignancy.<sup>5</sup> Rarely, secondary eosinophilia may be associated with pulmonary infections, eosinophilic gastroenteritis, and autoimmune diseases. Hypereosinophilia is present in less than 1% of patients at the time of diagnosis of malignancies such as lymphomas, leukemias, soft tissue sarcomas, lung cancer, cervical cancer, gastrointestinal cancer, renal cancer, and breast cancer. Hypereosinophilia may be a paraneoplastic manifestation of these malignancies.<sup>6</sup> Hypereosinophilic syndrome (HES) comprises a group of myeloproliferative disorders of unknown etiology that are marked by a sustained overproduction of eosinophils. HES is characterized not only by a striking and sometimes profound eosinophilia associated with the syndrome, but also by end-organ damage, most commonly involving the heart, with the development of eosinophilic endomyocardial fibrosis. The currently defined criteria for HES are: persistent eosinophilia of greater than 1,500 eosinophils/mm<sup>3</sup> for more than 6 months; exclusion of other potential etiologies for the eosinophilia, including parasitic, allergic, or other causes; and signs and symptoms of organ system dysfunction or involvement that appear to be related to the eosinophilia.<sup>7,8</sup>

### Address correspondence to:

Naeem Latif, MD, Fellow, Hematology/Oncology, University of Florida, Jacksonville, 655 West 8th Street, Pavilion 4N, Jacksonville, FL 32209; Phone: 904-244-1658; Fax: 904-244-1681; E-mail: naeem.latif@jax.ufl.edu.

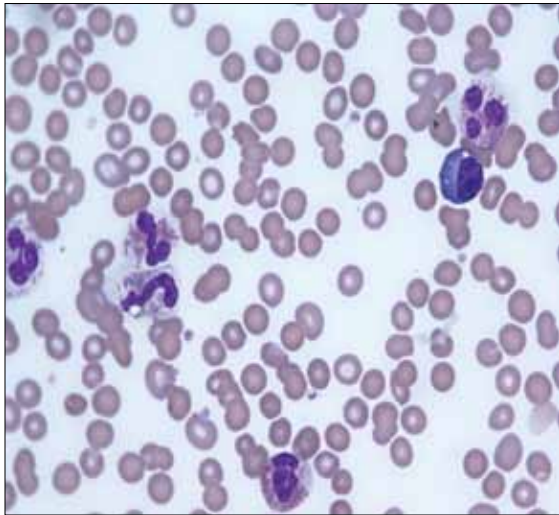
Hypereosinophilia in solid neoplasms may be reactive, whereas in myeloid leukemias, it is part of the neoplastic process.<sup>9</sup> It is sometimes difficult to differentiate reactive eosinophilia from neoplastic eosinophilia.<sup>10</sup> A bone marrow aspirate and biopsy without elevated myeloblasts and absence of clonality or *FIP1L1-PDGFR $\alpha$*  gene fusion is helpful in excluding eosinophilic leukemia.

## Case Report

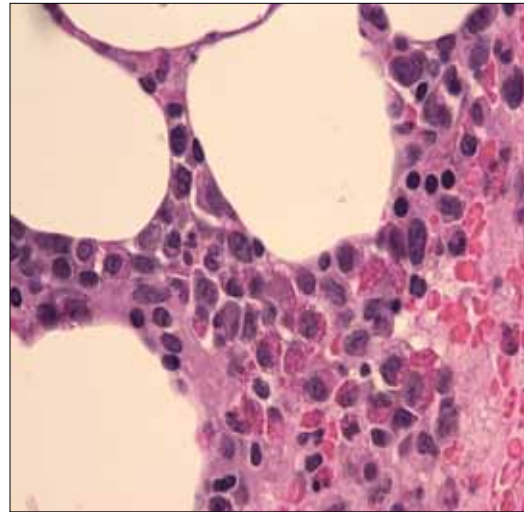
A 67-year-old African American woman presented to the emergency department reporting shortness of breath, dark stools, and generalized weakness that had persisted for 1 day. The patient had been diagnosed with high-grade pleomorphic soft tissue sarcoma of the left elbow several weeks prior and was about to start neoadjuvant radiation therapy. Her medical history was significant for coronary artery disease, congestive heart failure, and hypertension, and she had a permanent pacemaker for bradycardia. The patient had quit smoking several years before, and she was a social drinker. There was no family history of malignancy. The patient had no known drug allergies. She was currently taking carvedilol, hydrochlorothiazide, simvastatin, aspirin, folic acid, and a multivitamin.

The patient was overweight. Her physical examination revealed mild respiratory distress. Her blood pressure was 118/61 mmHg, her pulse was 101 beats per minute, and her respiration was 24 breaths per minute. She was afebrile, and her oxygen saturation was 96% on room air. There was no palpable lymphadenopathy or hepatosplenomegaly, bilateral lung crackles were auscultated, and diffuse petechial rash was seen on the lower extremities. A large, fungating mass was found around her left elbow; it was red and appeared to be infected, with serous discharge.

Previous biopsy of the elbow mass at another hospital had shown high-grade pleomorphic soft tissue sarcoma, and slide review confirmed this diagnosis at our institution. The patient was scheduled to start neoadjuvant



**Figure 1.** The peripheral blood smear showed eosinophilic leukocytosis, microcytic hypochromic anemia, and marked thrombocytopenia.



**Figure 2.** A bone marrow examination showed reactive marrow with trilineage hematopoiesis and eosinophilic hyperplasia. No tumor or granuloma were seen.

radiation therapy. Her initial blood work showed a white blood count of 83,000/mm<sup>3</sup>, hemoglobin/hematocrit of 7.8/24 gm/dL, and a low platelet count of 5,000/mm<sup>3</sup>. Her lactic acid dehydrogenase was high at 337 IU/L, with positive fibrinogen split products and D-dimers. The differential showed neutrophils at 36%, lymphocytes at 2%, bands at 10%, and eosinophils at 46%. The peripheral smear showed eosinophilic leukocytosis without any blasts or other morphologic abnormalities. Microcytic hypochromic anemia and marked thrombocytopenia were noted. Renal and liver functions were normal. The patient's bone marrow aspirate and biopsy showed reactive marrow with trilineage hematopoiesis and eosinophilic hyperplasia. No increased blasts, tumor infiltration, or granuloma were seen. Cytogenetics was normal karyotype. The flow cytometry analysis of bone marrow was negative for B-cell type lymphoproliferative and myeloproliferative disorders.

The patient was managed conservatively with steroids and platelet transfusions due to comorbid conditions. She died 1 week after presentation.

## Discussion

Hypereosinophilia of malignant diseases is rare, and the mechanism is poorly understood. It may be reactive or part of a neoplastic process, such as myeloid leukemia.<sup>9,11</sup> It has also been associated with radiation, chemotherapy, and immunotherapy (IL-2), possibly due to the release of cytokines, such as IL-6, tumor necrosis factor, and GM-CSF.<sup>12</sup>

Although hematologic malignancies—especially myeloid leukemia and lymphoma—are the main causes of hypereosinophilia, solid tumors have been reported to cause eosinophilia as well. In lung cancer, eosinophilia may be seen in 8.4% of patients<sup>13</sup>; when cancer is active, this rate may be as high as 58%.<sup>14</sup> In addition, in animal research models, transitional cell carcinoma of the urinary tract was associated with marked eosinophilia.<sup>15</sup>

This patient was evaluated for eosinophilic leukemia based on the presence of disseminated intravascular coagulation and thrombocytopenia. The bone marrow aspirate and biopsy was negative for elevated blasts, with normal flow cytometry and cytogenetics. No clearly identifiable etiology was found for hypereosinophilia. Because the patient was symptomatic with shortness of breath, we performed a computed tomography scan of the chest, which showed diffuse metastatic disease in the lungs. Steffani and associates reported a similar case of a patient with eosinophilic gastroenteritis that did not respond to steroid therapy and who had an anaplastic carcinoma of the lung that was diagnosed later.<sup>16</sup> It is conceivable that the eosinophilia may be a paraneoplastic/reactive process due to the release of cytokines (IL-6, IL-3, IL-5, and GM-CSF) from cancer cells, such as those in sarcoma,<sup>17</sup> or a distinct hematologic process. The production and survival of eosinophils are mainly regulated by IL-3, IL-5, and GM-CSF, and it has been reported that patients with ectopic production of GM-CSF by sarcoma can have refractory eosinophilia.<sup>18,19</sup> Wasserman and coworkers extracted a peptide that was preferentially chemotactic for eosinophils from a large-cell anaplastic carcinoma of the

lung.<sup>20</sup> This finding may suggest that the eosinophilia in malignancies is a paraneoplastic syndrome.

## Summary

Hyper eosinophilia may be associated with solid tumors and may be a harbinger of them. Therefore, patients with eosinophilia must be evaluated for common malignancies or recurrence of disease if they have a history of cancer.<sup>21</sup> The management approach for eosinophilia due to malignancy is to treat the underlying disease; the eosinophilia should resolve if the disease responds to treatment. Eosinophilia may not respond to usual treatment with steroids, interferon- $\alpha$  hydroxyurea, vincristine, or imatinib (Gleevec, Novartis).<sup>21</sup>

## References

1. Brigden M, Graydon C. Eosinophilia detected by automated blood cell counting in ambulatory North American outpatient: incidence and clinical significance. *Arch Pathol Lab Med.* 1997;121:963-967.
2. Hamid Q, Azzawi M, Ying S, et al. Expression of mRNA for interleukin-5 in mucosal bronchial biopsies from asthma. *J Clin Invest.* 1991;87:1541-1546.
3. Tefferi A, Patnaik MM, Pardanani A. Eosinophilia: secondary, clonal and idiopathic. *Br J Haematol.* 2006;133:468-492.
4. Strath M, Sanderson CJ. Detection of eosinophil differentiation factor and its relationship to eosinophilia in *Mesocricetus auratus* mice. *Exp Hematol.* 1986;14:16-20.
5. Yamaguchi Y, Matsui T, Kasahara T, et al. In vivo changes of hemopoietic progenitors and the expression of the interleukin 5 gene in eosinophilic mice infected with *Toxocara canis*. *Exp Hematol.* 1990;18:1152-1157.
6. Johnson BE. Paraneoplastic syndromes. In: Fauci AS, Braunwald E, Isselbacher KJ, et al, eds. *Harrison's Principles of Internal Medicine*, 14th ed. McGraw-Hill: New York, NY; 1998:622.
7. Chusid MJ, Dale DC, West BC, Wolff SM. The hyper eosinophilic syndrome: analysis of fourteen cases with review of the literature. *Medicine (Baltimore).* 1975;54:1.
8. De Vriese AS, Kips JC, Vogelaers DP, Vandewoude KH, Cuvelier CA, Colardyn FA. Pitfalls in the diagnosis of hyper eosinophilic syndrome: report of two cases. *J Intern Med.* 1997;241:165-170.
9. Bain BJ. Eosinophilic leukemias and the idiopathic hyper eosinophilic syndrome. *Br J Haematol.* 1996;95:2-9.
10. Tefferi A. Hyper eosinophilic syndrome or chronic eosinophilic leukemia? *Mayo Clin Proc.* 1999;74:742.
11. Viola MV, Chung E, Mukhopadhy MG. Eosinophilia and metastatic carcinoma. *Med Ann Dist Columbia.* 1972;41:1-3.
12. Muggia FM, Ghossein NA, Wohl H. Eosinophilia following radiation therapy. *Oncology.* 1973;27:118-127.
13. Kodama T, Takada K, Kameya T, Shimosato Y, Tsuchiya R, Okabe T. Large cell carcinoma of the lung associated with marked eosinophilia. *Cancer.* 1984;54:2313-2317.
14. Noirot C, Leynadier F, Luce F, Abuaf N, Bernard PE, Dry J. Hyper eosinophilia in cancer and cirrhosis: utility of total eosinophil count. *Semin Hop.* 1982;58:133-137.
15. Sellon RK, Rottman JB, Jordan HL, et al. Hyper eosinophilia associated with transitional cell carcinoma in a cat. *J Am Vet Med Assoc.* 1992;201:591-593.
16. Steffani GF, Addolorato G, Marsigli L, et al. Eosinophilic gastroenteritis in a patient with large cell anaplastic carcinoma: a paraneoplastic syndrome? *Ital J Gastroenterol.* 1994;26:354-356.
17. Nakanishi H, Araki N, Kudawara I, et al. Clinical implications of serum C-reactive protein levels in malignant fibrous histiocytoma. *Int J Cancer.* 2002;99:167-170.
18. Yamakawa Y, Fujimura M, Hidaka T, Yasoshima K, Saito S. Inflammatory malignant fibrous histiocytoma of the ovary producing interleukin-6: a case report. *Gynecol Oncol.* 1999;75:484-489.

19. Brito-Babapulle F. The eosinophilias, including the idiopathic hyper eosinophilic syndrome. *Br J Haematol.* 2003;121:203-223.

20. Wasserman SI, Goetzl EJ, Ellman L, Austen KF. Tumor-associated eosinophilic factor. *N Engl J Med.* 1974;290:420-424.

21. Sugimoto K. Letter to the editor. *Eur J Haematol.* 2006;78:169-170.

# Review

## Eosinophils and Eosinophilic Leukemia

Barbara J. Bain, MBBS, FRACP, FRCPath

Department of Haematology

St. Mary's Hospital, London, United Kingdom

## Introduction

Latif and colleagues present a case of a patient with hyper eosinophilia associated with metastatic soft tissue sarcoma.<sup>1</sup> It is highly likely that in this patient, the eosinophilia was reactive to the sarcoma, being mediated by cytokines. Our understanding of hyper eosinophilic syndromes has increased considerably in the last decade following the results of 2 lines of investigation. First, it is now recognized that many cases that would once have been classified as an idiopathic hyper eosinophilic syndrome in fact represent eosinophilic leukemia associated with a *FIP1L1-PDGFR* fusion gene.<sup>2</sup> Second, investigation of T-cell subsets has demonstrated that in other patients, the eosinophilia is driven by cytokines secreted by aberrant T cells, sometimes demonstrably clonal and sometimes with later evolution into an overt lymphoproliferative disorder.<sup>3</sup> This leaves the number of cases correctly classified as "idiopathic" considerably reduced and means that accounts of the idiopathic hyper eosinophilic syndrome dating from prior to this new knowledge are inaccurate because patients with eosinophilic leukemia and T-cell driven eosinophilia were inadvertently included.

## Eosinophilia and Neoplasia

Eosinophilia associated with neoplasms can be either reactive or a clonal neoplastic process. In nonhematopoietic neoplasms, the eosinophilia is reactive. In lymphoid

Address correspondence to:

Barbara J. Bain, MBBS, FRACP FRCPath, Department of Haematology, St. Mary's Hospital, Praed Street, London, United Kingdom, W2 1NY; Phone: 44 (0) 20 7886 1939; E-mail: b.bain@imperial.ac.uk.

**Table 1.** Leukemias and Myeloproliferative Neoplasms That Present as Eosinophilic Leukemia or Have an Eosinophil Component of Variable Prominence

Derived From Myeloid Stem Cells	Derived From Lymphoid-Myeloid Stem Cells
<ul style="list-style-type: none"> <li>• Acute myeloid leukemia</li> <li>• Myeloid neoplasm associated with rearrangement of <i>PDGFRB</i></li> <li>• Other chronic myeloid leukemias, including chronic myelomonocytic leukemia with eosinophilia and atypical chronic myeloid leukemia with eosinophilia</li> <li>• Systemic mastocytosis</li> </ul>	<ul style="list-style-type: none"> <li>• Lymphoid or myeloid neoplasm associated with rearrangement of <i>PDGFRA</i></li> <li>• Lymphoid or myeloid neoplasm associated with rearrangement of <i>FGFR1</i></li> <li>• <i>BCR-ABL1</i>-positive chronic myelogenous leukemia</li> </ul>

and myeloid neoplasms, it can be reactive or part of the neoplastic process.

The eosinophils can be part of a neoplastic clone in leukemia or a myeloproliferative neoplasm (MPN) that is derived either from a myeloid stem cell or from a pluripotent lymphoid-myeloid stem cell. These conditions are summarized in Table 1. Sometimes eosinophils are only a minor component at presentation, but when the leukemia or MPN enters an accelerated phase or blast transformation, they become dominant. This may be observed, for example, in *BCR-ABL1*-positive chronic myelogenous leukemia and in primary myelofibrosis. Eosinophilia at presentation is seen in chronic eosinophilic leukemia and in other chronic myeloid leukemias in which there is also involvement of granulocytic or monocytic lineages. The 2008 World Health Organization classification of tumors of hematopoietic and lymphoid tissues recognizes 3 genetic entities within this group of diseases, which are associated with rearrangement of the *PDGFRA*, *PDGFRB*, and *FGFR1* genes.<sup>4</sup> In the case of both *PDGFRA*- and *FGFR1*-related leukemias, the causative mutation has occurred in a pluripotent lymphoid/myeloid stem cell.

Eosinophilia can be a prominent feature of systemic mastocytosis. The eosinophils can be part of the neoplastic clone, but eosinophilia can also be promoted by cytokines secreted by mast cells. It is also possible for eosinophils in this condition to be clonal but to also respond to cytokines.

Acute eosinophilic leukemia is uncommon. In certain genetic subtypes of acute myeloid leukemia (AML), eosinophils are part of the leukemic clone but do not usually dominate. This is the case with AML associated with *t(8;21)(q22;q22)*, *inv(16)(p13.1q22)/t(16;16)(p13.1;q22)*, and *t(16;21)(q24;q22)*. However, occasionally there is striking peripheral blood eosinophilia, and confusion with chronic eosinophilic leukemia can then occur.<sup>5-7</sup> It is important to be alert for cases presenting as AML that actually represent transformation of an MPN associated with a *BCR-ABL1* or the *FIP1L1-PDGFRB*

fusion gene. Recognition of these patients is important because they respond to imatinib.

Reactive eosinophilia can occur in lymphoid neoplasms, including acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma,<sup>8</sup> leukemias and lymphomas of mature T and B cells and, occasionally, multiple myeloma. It can also be a prominent feature of Hodgkin lymphoma. In one rare subset of B-lineage ALL—that is associated with *t(5;14)(q31;q32)*—there is a clearly defined molecular mechanism. This translocation leads to the *IL3* gene (encoding interleukin 3) being dysregulated by proximity to the immunoglobulin heavy chain locus (*IGH*). Reactive eosinophilia in ALL can be very marked and can lead to death from eosinophil-mediated cardiac damage. It should be noted that in rare patients with lymphoid neoplasms, the eosinophils are part of the leukemic clone; this is so of cases associated with rearrangement of *FIP1L1* or *FGFR1*.

It cannot be assumed that eosinophilia associated with myeloid neoplasms always represents the presence of clonal neoplastic eosinophils. It usually does, but there have been several reports of reactive eosinophilia associated with myelodysplastic syndromes.

Reactive eosinophilia has been associated with a wide range of nonhematopoietic neoplasms, including carcinomas, sarcomas, glioma, mesothelioma, malignant melanoma, hepatoma, and metastatic pituitary tumor. Tumor-associated tissue eosinophilia may indicate a better prognosis, but blood eosinophilia does not.<sup>9</sup>

### Investigation of Hypereosinophilia

The investigation of eosinophilia should start with a clinical history (including a travel and a drug history) and physical examination. Travel, whether recent or remote, to regions with endemic schistosomiasis and strongyloidiasis is relevant. Important physical findings may include skin infiltration or a rash, hepatosplenomegaly, lymphade-

nopathy, and a soft tissue mass. A blood film is essential and will occasionally show blast cells, lymphoma cells, or filarial parasites. The cytologic features of eosinophils are not very helpful, however, because they can be abnormal in reactive as well as clonal eosinophilia.<sup>8,10</sup>

If there are no clues to the diagnosis, then an assessment of the urgency of the situation should be made. If eosinophilia is marked, and particularly if there are large numbers of degranulated eosinophils, cardiac damage may occur, and all relevant investigations should be done as soon as possible. If the situation is less clinically urgent, investigations can be targeted initially at the most likely conditions, with consideration being given to atopic disorders, drug allergy, parasitic infection, coccidioidomycosis, connective tissue disorders including Churg-Strauss syndrome, and leukemia and lymphoma. Diagnosis of parasitic infections may require serological testing (eg, for strongyloidiasis, schistosomiasis, gnathostomiasis, opisthorchiasis, trichinosis, and toxocariasis) in addition to examination of stools on 3 occasions and examination of urine if infection with *Schistosoma haematobium* is possible.<sup>11-14</sup>

If initial investigations are negative, a computed tomography scan, bone marrow aspirate, cytogenetic analysis, and trephine biopsy should be performed to investigate the possibility of leukemia, lymphoma, and systemic mastocytosis. Molecular analysis (eg, nested polymerase chain reaction and fluorescence in situ hybridization) for a *FIP1L1-PDGFR* fusion gene should be performed. Other rearrangements of *PDGFR* and also those of *PDGFRB* and *FGFR1* will be detected by cytogenetic analysis, but this fusion gene, resulting from a cryptic interstitial deletion of part of the long arm of chromosome 4 (4q12), can be detected only by molecular studies.

### Idiopathic Hypereosinophilic Syndrome

Idiopathic hypereosinophilic syndrome is a diagnosis of exclusion. It is essential that patients are investigated very thoroughly before this diagnosis is made because some of the specific known causes of eosinophilia have very effective treatments. Detection of hematologic neoplasms with rearrangement of *PDGFR* or *PDGFRB* is particularly important because they respond very well to imatinib and

other tyrosine kinase inhibitors. Delay in diagnosis may mean that serious cardiac damage will occur. Detection of connective tissue disorders and parasitic and fungal infections is likewise of considerable importance.

### Conclusion

The cause of eosinophilia is often readily apparent. However, in some patients, it is obscure, and extensive investigation is necessary in order to identify serious underlying diseases. Eosinophilia associated with lymphoid or myeloid neoplasms can be reactive or clonal. Eosinophilia associated with other neoplasms is reactive and cytokine-driven.

### References

1. Latif N, Zaiden R, Pham D, Rana F. Soft tissue sarcoma mimicking eosinophilic leukemia. *J Clin Oncol*. 2010;8:899-901.
2. Cools J, DeAngelo DJ, Gotlib J, et al. A tyrosine kinase created by fusion of the *PDGFR* and *FIP1L1* genes is a therapeutic target of imatinib in idiopathic hypereosinophilic syndrome. *N Engl J Med*. 2003;348:1201-1214.
3. Roufosse F, Cogan E, Goldman M. Lymphocytic variant hypereosinophilic syndromes. *Immunol Allergy Clin North Am*. 2007;27:389-413.
4. Bain BJ, Gilliland DG, Horny H-P, Vardiman JW. Myeloid and lymphoid neoplasms with eosinophilia and abnormalities of *PDGFR*, *PDGFRB* and *FGFR1*. In: Swerdlow SH, Campo E, Harris NL, et al, eds. *World Health Organization Classification of Tumours of Haematopoietic and Lymphoid Tissue*. 4th ed. Lyon, France: IARC Press; 2008:68-73.
5. Kaneko Y, Kimpara H, Kawai S, Fujimoto T. 8;21 chromosome translocation in eosinophilic leukemia. *Cancer Genet Cytogenet*. 1983;9:181-183.
6. Jacobsen RJ, Temple MJ, Sacher RA. Acute myeloblastic leukaemia and t(8;21) translocation. *Br J Haematol*. 1984;57:539-540.
7. Stussi G, Tichelli A, Schanz U, Goede J. Hypereosinophilia with a low blast count as the initial manifestation of acute myeloid leukaemia with *RUNX1-RUNX1T1*. *Br J Haematol*. 2009;146:346.
8. Catovsky D, Bernasconi C, Verdonck PJ, et al. The association of eosinophilia with lymphoblastic leukaemia or lymphoma: a study of seven patients. *Br J Haematol*. 1980;45:523-534.
9. Lowe D, Jorizzo J, Hutt MS. Tumour-associated eosinophilia: a review. *J Clin Pathol*. 1981;34:1343-1348.
10. Huang MS, Hasserjian RP. Case 19-2004: a 12-year-old boy with fatigue and hypereosinophilia. *N Engl J Med*. 2004;350:2604-2612.
11. Seybolt LM, Christiansen D, Barnett ED. Diagnostic evaluation of newly arrived asymptomatic refugees with eosinophilia. *Clin Infect Dis*. 2006;42:363-367.
12. Caruana SR, Kelly HA, Ngeow JY, et al. Undiagnosed and potentially lethal parasite infections among immigrants and refugees in Australia. *J Travel Med*. 2006;13:233-239.
13. Stauffer W, Walker P. Eosinophilia in refugees. *Clin Infect Dis*. 2006;42:1655-1656.
14. Nutman TB. Evaluation and differential diagnosis of marked, persistent eosinophilia. *Immunol Allergy Clin North Amer*. 2007;27:529-549.