Case report

A pregnant woman with hypereosinophilia and a neuroendocrine tumor

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Abstract:

Eosinophilia is a common problem in general practice, and the most common cause is reactive condition. Paraneoplastic eosinophilia is a rare clinical manifestation in neuroendocrine tumors and may be associated with advanced-stage disease. We highlight the case of a pregnant woman presenting progressive dyspnea and hepatosplenomegaly. Liver and bone marrow biopsy revealed a metastatic neuroendocrine tumor. Genetic mutation tests for clonal myeloid diseases were negative. The patient did not respond to steroid or cytoreductive drugs. Tissue biopsy is needed to confirm the diagnosis.

Keywords : ● *Hypereosinophilia* ● *Paraneoplastic eosinophilia* ● *Hypereosinophilic syndrome* ● *Neuroendocrine tumor*

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รายงานผู้ป่วย

ผู้ป่วยตั้งครรภ์ที่มีภาวะเม็ดเลือดขาวชนิดอีโอซิโนฟิลสูงร่วมกับมะเร็งนิวโรเอ็นโดรไครน์

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บทคัดย่อ

ภาวะเม็ดเลือดขาวชนิดอีโอซิโนฟิลสูง พบได้บ่อยในเวชปฏิบัติ และสาเหตุที่พบได้บ่อยที่สุดคือภาวะการถูกกระตุ้นจากโรคอื่นๆ ภาวะเม็ดเลือดขาวชนิดอีโอซิโนฟิลสูงที่มีสาเหตุจากมะเร็งชนิดนิวโรเอ็นโดรไครน์ นั้นเจอได้ไม่บ่อยนักและน่าจะเกี่ยวข้องกับระยะลุกลามของโรค รายงานฉบับนี้บรรยายถึงผู้ป่วยตั้งครรภ์ มาด้วยอาการหอบเหนื่อยและตรวจร่างกายพบตับม้ามโต ผลตรวจชิ้นเนื้อในตับและไขกระดูก พบว่าเป็นมะเร็งนิวโรเอ็นโดรไครน์ระยะลุกลาม ไม่พบการกลายพันธุ์ของยีนจากภาวะมะเร็งเม็ดเลือดขาวกลุ่มมัยอีลอยด์ ปริมาณของเม็ดเลือดขาวชนิดอีโอซิโนฟิลไม่ตอบสนองต่อการรักษาด้วยการให้ยา สเตียรอยด์และ Cytoreductive drug การตรวจชิ้นเนื้อจึงเป็นสิ่งที่จำเป็น เพื่อได้ประโยชน์ในแง่ของการยืนยันการวินิจฉัย

คำสำคัญ : ● *ภาวะเม็ดเลือดขาวชนิดอีโอซิโนฟิลสูง* ● *ภาวะเม็ดเลือดขาวชนิดอีโอซิโนฟิลสูงทีเกิดจากโรคมะเร็ง* ● *มะเร็งนิวโรเอ็นโดรไครน์*

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Introduction

Eosinophilia is a common problem in general practice.[1] Mild eosinophilia, defined as an absolute eosinophil count between 0.5-1.0 x10^9/L, is more common than hypereosinophilia, defined as absolute eosinophil count greater than 1.5 x10^9/L[2]. Reactive eosinophilia, such as that caused by parasitic infection, allergy or autoimmune disease,[2] is the most common. Investigating the causes of and complications associated with eosinophilia is important. Hypereosinophilic syndrome is a term for persistent eosinophilia with organ involvement by eosinophilic infiltration and is diagnosed using tissue pathology.

Paraneoplastic syndrome is rare in solid tumors and may be associated with advanced stage, especially in adenocarcinoma[3]. We present the case of a pregnant woman presenting hepatosplenomegaly. The final diagnosis was neuroendocrine tumor with paraneoplastic eosinophilia.

Case presentation and clinical course

A 38-year-old previously healthy woman at 23 weeks of pregnancy presented with progressive dyspnea and abdominal discomfort for 4 weeks. She denied any symptoms of fever or significant weight loss. Physical examination revealed moderate jaundice and marked hepatosplenomegaly without lymphadenopathy. No jugular venous engorgement or peripheral edema was found.

A complete blood count revealed hemoglobin, 10.2 g/dL, white blood cells, 19.09 x10^9/L (neutrophil 69%, lymphocyte 3%, monocyte 1%, eosinophil 19%), and platelet 300 x10^9/L. A peripheral blood smear revealed left-shifted myeloid cells and abnormal eosinophils. Nucleated red cells were found, and no significant increase in tear drop cells was found (Figure 1). A liver function test revealed cholestatic hepatitis.

Whole abdomen ultrasonography using doppler sonography showed hepatosplenomegaly with parenchymatous disease of the liver with no definite focal mass lesion. Hepatic vessels were patent. An echocardiogram revealed no evidence of infiltrative disease. Fetal ultrasonography revealed an estimated fetal weight of 782 g without gross anomaly. Fetal weight was appropriate for gestational age.

Differential diagnosis of hypereosionphilia for this patient is shown in Table 1. Specific investigations

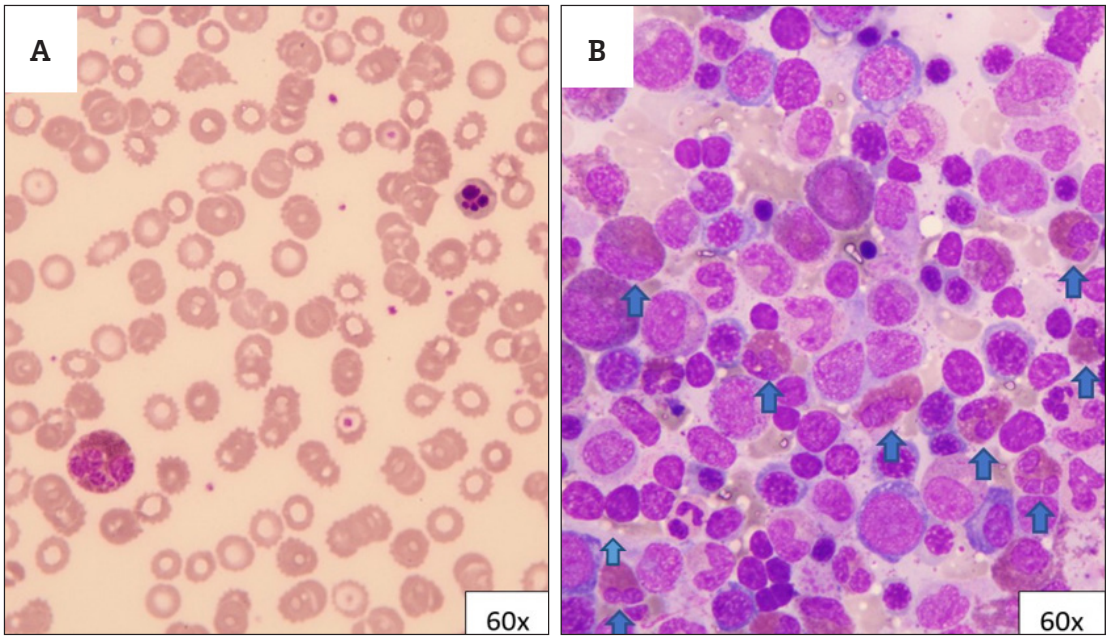

Figure 1 A peripheral blood smear revealed a multilobulated eosinophil and dispersed nucleus of a nucleated red blood cell, suggesting dysplastic features (**A**). Bone marrow aspiration showed normocellularity and an increased number of eosinophils, some of which were multilobulated (**B**).

Table 1 Differential diagnosis of hypereosionphilia

Parasitic infection
● Strongyloidiasis
● Angiostrongyliasis
● Gnathostomiasis
Autoimmune disease
● Systemic lupus erythematosus
● ANCA associated vasculitis
● IgG4-related disease
Clonal myeloid disease
● Myeloid/lymphoid neoplasms with eosinophilia and abnormalities of FIP1L1-PDGFRA
● Chronic eosinophilic leukemia
● Myeloproliferative neoplasm
Paraneoplastic eosinophilia
Idiopathic hypereosinophilic syndrome

Table 2 Specific investigations for the causes of eosinophilia

Special investigation for parasitic infections	**Special investigation for autoimmune diseases**
Stool concentration for parasite: negative	ANA: negative
Stool cultivation for Strongyloides stercoralis: negative	Anti DsDNA: negative
Strongyloidiasis antibody: negative	ANCA: negative
Angiostrongyliasis antibody: negative	Ig G4 level: 0.147 g/L (0.0032-0.864 g/L)
Gnathostomiasis antibody: negative	
Special investigation for clonal myeloid diseases	**Other investigations**
Chromosome: 46, XX [25]	Serum tryptase < 1 ng /mL
PCR for FIP1L1-PDGFRA fusion gene: negative	B 12 level: 601 pg/mL
RT-PCR for BCR/ABL gene: negative	Immunoglobulin E level: < 30 IU /mL
PCR for JAK2V617F mutation: negative	
PCR for MPL mutation: negative	
PCR for CALR mutation: negative	

to identify causes of eosinophilia, including parasitic infections, autoimmune diseases and clonal myeloid diseases, were all negative (Table 2).

The patient was initially treated with high dose corticosteroids, but the eosinophilia did not improve. Hydroxyurea was administered after steroid treatment failed, but the response remained minimal.

After hydroxyurea failure, the pregnancy terminated at a gestational age of 24 weeks. The infant was safely delivered. Bone marrow and liver biopsy were performed after terminating pregnancy. Interferon-alpha was administered by injection, but the response was limited (Figure 2).

Bone marrow biopsy revealed normocellular marrow with progressive maturation of multilineage hematopoiesis, increases in megakaryocytes and eosinophils. No excess blasts were found. Clusters of atypical epithelioid cells were occasionally seen (Figure 3). Immunohistochemical studies were positive for AE1/AE3 and CK7 and negative for CK20, CD61, CD68 and S100. Metastatic carcinoma was diagnosed.

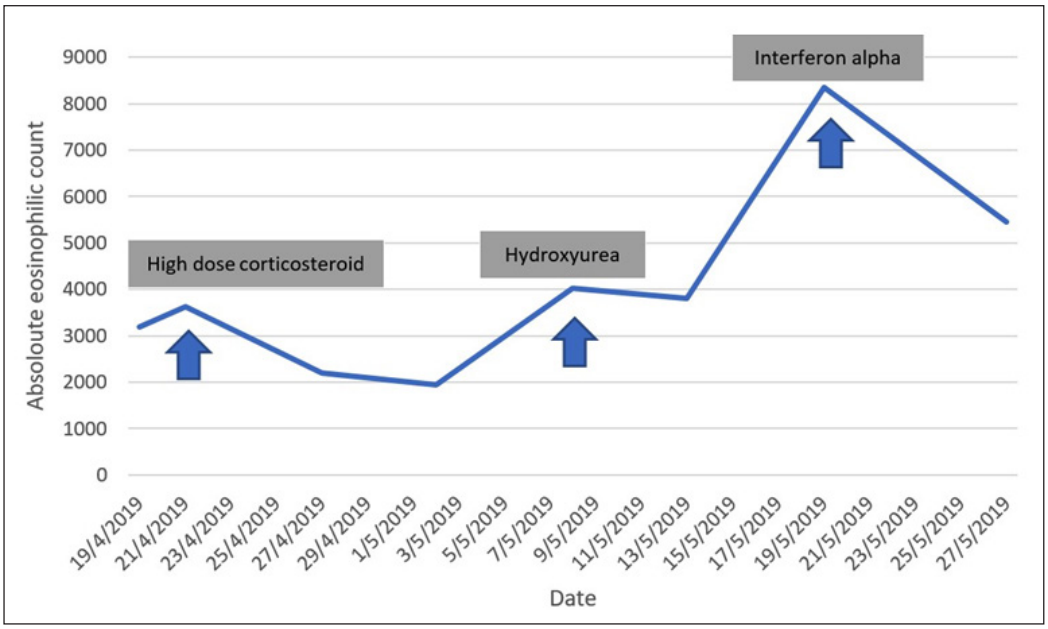

Figure 2 Absolute eosinophilic count during treatment

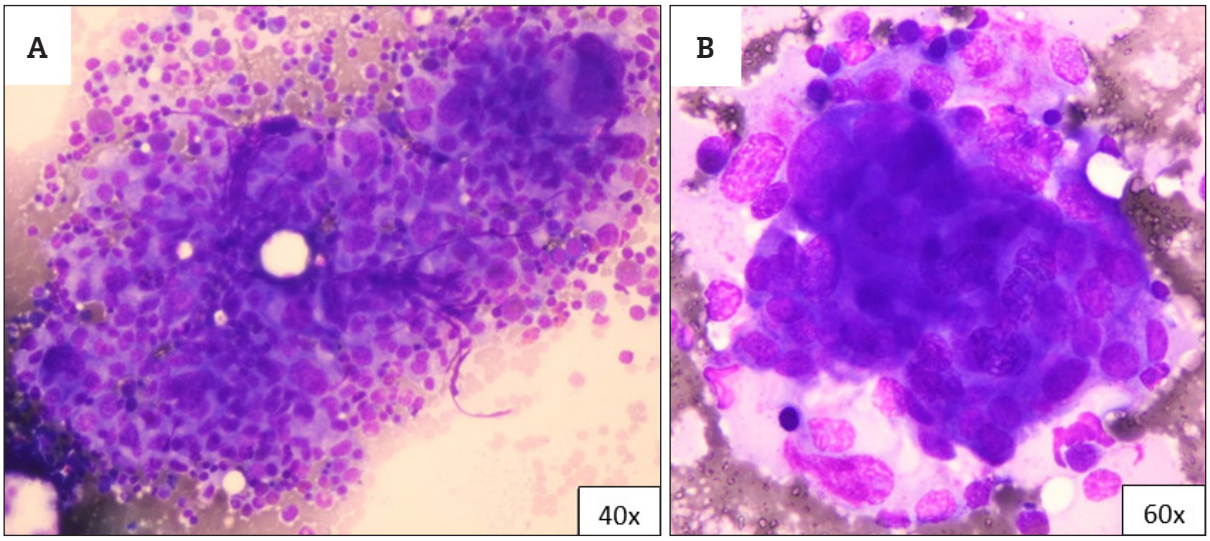

Figure 3 Large cohesive cells in bone marrow aspiration, suggesting bone marrow metastasis by sheets of nonhematologic tumor.

Liver biopsy showed scattering intrasinusoidal aggregation of the atypical lobules containing monotonous round cells with a focal spindle appearance. Also, lobulitis was found with scattered lymphocytes and eosinophils with focal necrotic cells. Immunohistochemical studies were positive for AE1/AE3, CK7 and synaptophysin and negative for S100, Herpar-1, Glutamine synthetase, and CD68. Immunohistochemical evidence suggested a metastatic epithelial tumor with neuroendocrine differentiation, indicating neuroendocrine tumor. The final diagnosis was metastatic neuroendocrine tumor with paraneoplastic eosinophilia.

After bone marrow and liver biopsy revealed a metastatic neuroendocrine tumor, the patient and relatives discussed the results with the oncologist and choose to undergo palliative treatment. The infant experienced intraventricular hemorrhage and necrotizing enterocolitis and passed away after a few weeks.

Discussion

Eosinophils are involved in various immune system process es, especially innate immunity[3]. Due to its involvement in the immune system, eosinophilia is associated with several cancers, the most common of which

is hematologic malignancy. Some reports have found paraneoplastic eosinophilia in solid tumors, especially in adenocarcinoma.[3]

The prognosis of paraneoplastic eosinophilia in solid cancers is still controversial. Some studies have suggested better prognoses in prostate or colon cancers[3] due to activation of the immune system, but poor prognosis in lung cancer.[4] Some case reports of nonsmall cell lung carcinoma[5-6] have revealed that eosinophilic levels decrease with tumor reduction (after either surgery or chemotherapy) and rise again in cases of disease relapse or progression, suggesting a direct correlation between the presence of the tumor and elevated peripheral eosinophilic count.

Verstraeten et al.[6] reported a case similar to ours. Their patient presented unexplained hypereosinophilia with nonproductive cough. Tissue biopsy revealed advanced stage nonsmall cell lung carcinoma with bone marrow metastasis. High dose corticosteroids and cytoreductive drugs were administrated but eosinophilic count increased and clinical symptoms did not improve. The patient's family was informed that no curative measures were possible and palliative treatment was initiated. The patient died due to severe hypoxemia.

One report described tissue eosinophilia in a neuroendocrine tumor,[7] but none with paraneoplastic eosinophilia. Immune activation, tumor necrosis and bone marrow metastasis have been proposed as mechanisms for paraneoplastic eosinophilia in solid cancers.[3] In our case, a complete blood count revealed left-shifted myeloid cells and nucleated red blood cells, which may have indicated bone marrow metastasis.

Elevated serum immunoglobulin E levels are common in reactive conditions but rare in clonal myeloid disease.[8] In this case, serum immunoglobulin E levels were quite low, so we assumed that direct metastasis in the bone marrow may have alternate regulation of myeloid proliferation.

Wang et al.[9] found that most patients with chronic eosinophilic leukemia and about 20% of those with the idiopathic hypereosinophilic syndrome have abnormal bone marrow morphology. In this patient, we found dysplastic features of eosinophils and erythroid cells, which may be clinical clues for malignant eosinophilia rather than reactive eosinophilia.

The liver biopsy revealed metastatic neuroendocrine with occasional eosinophilic infiltration. Tissue diagnosis should be performed in patients who present eosinophilia, especially in those patients not responding to corticosteroids or cytoreductive drugs.

Conclusion

Paraneoplastic eosinophilia is a rare manifestation in solid tumors and may be associated with advanced stage. The prognosis of paraneoplastic eosinophilia in solid cancers is still inconclusive. Appropriate investigation, including tissue biopsy, is needed to confirm a diagnosis. Corticosteroids and cytoreductive drugs are inadequate to control eosinophilic count in paraneoplastic eosinophilia.

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