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Blood hyperreosinophilia: A diagnostic challenge

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ABSTRACT

Blood hyperreosinophilia: A diagnostic challenge

A very detailed differential diagnosis is necessary to investigate the causes of blood hypereosinophilia. In the differential diagnosis of hypereosinophilia with pulmonary involvement, primary and secondary eosinophilic lung diseases should be kept in mind, and more specific diagnoses should be considered in those with a history of nasal polyposis and asthma. Here, it was aimed to present a case of organ-limited hypereosinophilia with asthma and nasal polyposis.

Key words: Hypereosinophilia; chronic eosinophilic pneumonia; eosinophilic asthma; chronic rhinosinusitis; nasal polyposis

ÖZ

Hipereozinofili: Tanısal zorluklar

Hipereozinofilinin nedenlerini araştırmak için çok detaylı bir ayırıcı tanı gereklidir. Pulmoner tutulumlu hipereozinofili ayırıcı tanısında primer ve sekonder eozinofilik akciğer hastalıkları akılda tutulmalı, nazal polipozis ve astım öyküsü olanlarda daha spesifik tanıları düşünülmelidir. Bu olguda astımlı ve nazal polipozisli organ sınırlı bir hipereozinofili olgusunu sunmak istedik.

Anahtar kelimeler: Hipereozinofili; kronik eozinofilik pnömoni; eozinofilik astım; kronik rinosinüzit; nazal polip

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INTRODUCTION

Eosinophilic asthma is increasingly recognized as one of the most severe and difficult-to-treat asthma phenotype (1-3). Eosinophilic asthma with chronic rhinosinusitis and/or nasal polyposis (EA-CRS/NP) is a subphenotype of eosinophilic asthma and is more common in the adulthood (4,5). Blood eosinophil levels are shown to be highly elevated in patients with EA-CRS/NP and have the potential for tissue infiltration. More than 1500 cells/ μ l is accepted as eosinophilia with the potential for tissue infiltration and hypereosinophilia (6). We noticed that in some patients with EA-CRS/NP, this potential pulmonary tissue infiltration could be demonstrated by radiological imaging. We defined this group as "Eosinophilic Asthma with chronic Rhinosinusitis and/or nasal polyposis with Radiological findings related to blood eosinophilia (EARR)" (7). Eosinophilic lung disease comprises a rare group of heterogeneous diffuse parenchymal lung diseases characterized by marked accumulations of infiltrating eosinophils in the alveolar space and the interstitium (8). Chronic eosinophilic pneumonia (CEP) is a rare disorder among diffuse parenchymal lung diseases and may be accompanied by nasal polyps (9). In this study, it was aimed to report an adolescent patient of EARR + CEP overlap, making the differential diagnosis, eosinophilic lung diseases, a diverse group of pulmonary disorders associated with peripheral and tissue eosinophilia.

CASE PRESENTATION

A 15-year-old male patient, who had been healthy until the age of 12, had a cough and shortness of breath three years before, and pneumonia was detected on his admission. The patient with a prolonged cough after pneumonia was diagnosed with asthma due to his history and positive reversibility and obstructive pattern in respiratory function tests. There was a frequent need for oral corticosteroid (OCS) use due to uncontrolled asthma in the last three years. While skin prick test was negative, an increase in eosinophilia was detected in the exacerbation periods of asthma. Clinical improvement and decrease in eosinophilia were found after systemic steroids (40 mg methylprednisolone for a short time for five days) (Table 1). In the last three years, some of the asthma exacerbations had been diagnosed as pneumonia and treated with antibiotic treatments and with systemic steroids (methylprednisolone 40 mg 5 days) except one (Table 1). The tests performed

Table 1. Thorax CT and laboratory data during pneumonia and asthma exacerbation

		WBC ($\times 10^9$ /L)	Eosinophil levels ($\times 10^9$ /L)	Eosinophil levels (%)	CRP (mg/dl)	PCT (ng/ml)	Thorax CT	CS
September 2017 (asthma exacerbation)	Pre-treatment	10.9	3.16	28.9	<0.02			Yes
	Post-treatment	4.5	0.01	0.2	2.62			Yes
March 2018 (asthma exacerbation and pneumonia)	Pre-treatment	8.5	1.81	31.2	1.58		Common mild tubular bronchiectasis, bronchial wall thickening	Yes
	Post-treatment	7.8	0	0	<0.02			No
January 2020 (pneumonia)	Pre-treatment	17.4	5.45	31.2	19	0.04		Yes
	Post-treatment	12.4	2.52	20.9	4.95	0.03		Yes
April 2020 (asthma exacerbation and pneumonia)	Pre-treatment	14.9	7.9	59.3	125	0.04	Consolidated areas with diffuse peripheral prominent patchy ground glass density, bronchial dilatation and consolidations in peribronchial areas, subpleural nodules	Yes
	Post-treatment	8.38	0.52	6.2	4.65	0.04		Yes
August 2020 (pneumonia)	Pre-treatment	18.8	9.92	67.1	104	0.1	Patchy consolidated lung areas with ground glass density in the anterior of the upper lobe of the right and left lung	Yes
	Post-treatment	17.5	0.02	0.1	10.3	0.1		Yes

WBC: White blood cell, CRP: C-reactive protein, PCT: Procalcitonin, CT: Computed tomography, CS: Corticosteroid.

for immunodeficiency and hypereosinophilia during the illness period about 30 months due to his frequent pneumonia history and thorax CT findings are shown in Table 2. The August 2020 Thorax CT image is shown in Figure 1A.

Nasal steroid + antihistaminic and low-dose systemic steroid (5 mg prednisolone for three months) were started due to the detection of nasal polyposis in Paranasal Sinus Computed Tomography (PNSCT) (Figure 1B) but withdrawn due to frequent rhinosinusitis symptoms, and the inability to smell and nasal congestion affecting the quality of life. Nasal polypectomy was performed in 2019 because nasal polyp symptoms did not regress in the patient whose asthma was under control with low dose OCS in addition to the high dose inhaled corticosteroid (ICS) +

long-acting β 2-agonist (LABA) + leukotriene receptor antagonist (LTRA) treatment he received for his asthma. He was most recently hospitalized in August 2020 due to the etiology of pneumonia and eosinophilia. Since an immunosuppressive state could not be ruled out due to fever (38.6°C), and because of high C-reactive protein (CRP), eosinophilia and total IgE elevation were attributed to an immunosuppressive state, and meropenem and fluconazole were initiated. The patient, whose cough, shortness of breath, and wheezing continued under this treatment, was referred to our clinic because he had a high fever (38.2°C) and eosinophils did not decrease. The results of the tests performed for the etiology of hypereosinophilia in August 2020 are summarized in Table 3. In the microscopic examination of the BAL sample, 79% of eosinophils were found (Figure 2).

Table 2. Detailed examination results after frequent pneumonia

	March 2018	August 2020
Alpha-1 antitrypsin	223 mg/dl (90-200)	
CD45	99%	100%
CD3	67%	58%
Lymphocyte subgroups		
CD4	37.5%	29%
CD8	23%	20.6%
CD19	23.2%	24.6%
IgA	166 mg/dl (85-220)	237 mg/dl (85-220)
IgM	137 mg/dl (75-197)	129 mg/dl (75-197)
IgG	1000 mg/dl (800-1900)	1242 mg/dl (800-1900)
IgE	1010 IU/ml (0-200)	3229 IU/ml (0-200)
BAL cytology		%79 eosinophil
BAL culture		Normal flora elements
Sputum culture		Normal flora elements
ANCA		Negative
Aspergillus specific IgE		Negative
Skin prick test		Negative
Vitamin B12		276
Uric acid		4.1
ECHO		Negative
Troponin		0.001
Stool test for parasite (3 times)	Negative	Negative
Hepatosplenomegaly		Negative
PGDFR α		Negative
JAK2		Negative

Ig: Immunoglobulin, BAL: Bronchoalveolar lavage, ANCA: Anti-neutrophil cytoplasmic antibody, ECHO: Echocardiography, PGDFR α : Platelet-derived growth factor receptor alpha, JAK2: Janus kinase 2.

Figure 1. A. Thorax CT (August 2020) and **B.** Paranasal Sinus CT (September 2019).

Table 3. The properties of CEP and EARR

	EARR	CEP
Age, years	35-55	30-50
Female gender	Dominant	Dominant
Asthma	Yes	About half
Asthma severity	Severe	Moderate
Atopy	Low	High
Nasal polyp	Yes	Rare
Smoking	Low	Low
Fever, weight loss	None	Usually
ESR	Usually normal	Usually high
CRP	Usually normal	Usually high
ANCA	Negative	Negative
High blood eosinophil level	Yes	Yes
High total IgE level	Yes	Yes
Thorax CT	Ground-glass opacities, Centrilobular nodules	Airspace consolidation, ground glass attenuations
Response to systemic steroid	Very good	Very good
Conversion to systemic disease	Rare (EARR plus= idiopathic HES phenotype)	Rare (EGPA or idiopathic HES)

ESR: Erythrocyte sedimentation rate, EARR: Eosinophilic asthma with chronic rhinosinusitis and/or nasal polyposis with radiological findings related to blood eosinophilia, CEP: Chronic eosinophilic pneumonia, EGPA: Eosinophilic granulomatosis with polyangiitis, CRP: C-reactive protein, HES: Hypereosinophilic syndrome.

The results of immunophenotyping by flow cytometric examination made from peripheral blood are shown in Figure 3.

Primary and secondary immunodeficiencies and secondary and other primary causes of eosinophilic lung

diseases were ruled out. The patient was diagnosed with the eosinophilic asthma phenotype, called EARR in the literature, and CEP overlap, a disease with organ-limited hypereosinophilia localized in the respiratory tract. Forty-eight mg methylprednisolone

Figure 2. BAL microscopic examination, eosinophil 79%.

was started. On the second day of treatment, EOS decreased to 0.1% - $0.02 \times 10^9/L$. His symptoms disappeared completely; there was no need for nasal oxygen (O_2 saturation > 95). The antibiotic and antifungal treatment was discontinued when the patient was afebrile for 48 hours. The patient, with significant improvement on lung X-ray, was discharged with the recommendation of decreasing doses of steroids.

DISCUSSION

In this case, we presented a patient with organ-limited hypereosinophilia, characterized by respiratory tract involvement, which we define as EARR + CEP overlap. Besides, the primary and secondary causes of hypereosinophilia should be investigated, especially if there is a history of nasal polyposis and chronic eosinophilic pneumonia, and if there is organ damage or dysfunction after primary immunodeficiency causes are excluded. We wanted to emphasize the importance of bearing EARR in mind. We think that this case report is vital in terms of showing EARR and CEP cases, which may rarely be seen in childhood.

More than 1500 cells/ μl is accepted as eosinophilia with the potential for tissue infiltration and hypereosinophilia (6). We noticed that in some patients with EA-CRS/NP, this potential pulmonary tissue infiltration could be demonstrated by radiological imaging. We defined this group as EARR (7). EARR is the most

severe clinical form of adult-onset eosinophilic asthma and is mainly seen in aspirin exacerbated respiratory disease (AERD) and EA-CRS/NP patients. These patients had the most severe form because they had very high eosinophil levels and radiological infiltrations associated with eosinophilia. They were all dependent on systemic corticosteroids, and only a small percentage were able to discontinue corticosteroids (7).

One of the hallmarks of chronic rhinosinusitis with nasal polyps (CRS/NP) is enhanced tissue eosinophilia compared to healthy sinonasal tissue (10). The unified airway hypothesis also suggests that disease in the upper and lower airways is related. Patients with CRS/NP and asthma have significantly more severe radiological evidence of sinonasal inflammation (11). This is supported by a previous study in which CRS patients with asthma had more severe sinonasal inflammation and were more likely to have nasal polyps than CRS patients without asthma (12). Also, another study found a significant positive association between the asthma severity and both the degree of sinonasal inflammation and the likelihood of having nasal polyps (13). Thus, these observations led to the hypothesis that eosinophils are more highly activated in the new phenotype than CRS/NP. We could see the infiltration radiologically on thorax CT if the degree of sinonasal inflammation could be reflected in the radiological appearance (PNSCT) or even lead to nasal polyps by releasing their granule contents, and the increased eosinophils could lead to eosinophilic infiltration. In our case, there were abnormal radiological findings together with nasal polyposis and severe hypereosinophilic asthma. It was revealed that these abnormal findings were secondary to eosinophilic infiltration by bronchoalveolar lavage (BAL) examination. This result was confirmed with complete radiological recovery with systemic steroids.

In differential diagnosis, eosinophilic lung diseases which are a diverse group of pulmonary disorders associated with peripheral or tissue eosinophilia (drug-induced eosinophilic pneumonia, Löffler's syndrome, hypereosinophilic syndrome (HES) (primer, seconder, and idiopathic), lymphocytic HES (also called subgroup of secondary HES), allergic bronchopulmonary aspergillosis, microscopic polyangiitis, granulomatosis with polyangiitis (Wegener's), eosinophilic granulomatosis with polyangiitis (EGPA),

Hücre Dağılımı	Tüm Hücre Kapısı	Lenfosit Kapısı	T Hücre Kapısı
Blast (CD45.....)	-	-	
Diğer (CD45 negatif)	-	-	
Nötrofil	%89		
Monosit	%3		
Eozinofil	-		
Lenfosit	%8	%100	
NK (CD56)	%1	%12	
B (CD19)	%4	%50	
T (CD3)	%3	%38	%100
TCR ab			%80
TCR gd			%20

Referans Aralığı (%) (Erişkin)	
Lenfosit %100	
T (Lenfosit)	56-82
B (Lenfosit)	7.7-22
NK (Lenfosit)	6-33

Figure 3. Peripheral blood immunophenotyping (CD4/CD8 ratio was 58/39 in TCRAB + T cells).

malignancies (lymphoproliferative, myeloproliferative, and solid organ), and collagen vascular diseases (14-16) have been excluded in the case with clinical and laboratory results in the case (Table 2). Coincidental bacterial or viral pneumonia may occur in patients with asthma and eosinophilia. In our patient, pneumonia had been ruled out using the patients' clinical and laboratory findings (BAL cul-

ture, sputum culture), and corticosteroid response without antibiotics. The patient was accepted as EARR + CEP overlap after making all these differential diagnoses. We, therefore, believe that this specific group (EARR) can be considered as a phenotype of severe eosinophilic asthma and an organ restricted hypereosinophilic condition like CEP. CEP was diagnosed based upon the combination of greater than

two weeks of respiratory symptoms, BAL and/or blood eosinophilia (usually with BAL cell count differential >40% or serum eosinophils >1.000/mm³), pulmonary infiltrates with a peripheral predominance and exclusion of other known causes of eosinophilic lung diseases (9). This patient also met the diagnostic criteria for CEP.

The other primary and secondary causes of hypereosinophilia were ruled out in this case. We think that this case is CEP, a disease accompanied by organ-restricted hypereosinophilia, and EARR overlap. The case is accompanied by fever and high CRP, which are seen in typical CEP cases but are not usually seen in EARR. Nasal polyposis and severe asthma, seen in EARR but not detected very much in CEP, accompanied. CEP and EARR properties are shown in Table 3. CEP seems to be more dominant in this overlap diagnosis because fever is accompanied in the case, CRP and sedimentation are high, and responses to systemic steroids are very good in EARR, but recovery is not expected as fast as in this case. The other point is that similar to atopic dermatitis, atopic rhinitis, and atopic asthma, there is also an allergic march among this group of patients as CRS nasal polyps, asthma, AERD; however, it does not always have a particular order and may have variations (11). Our study showed that the end stage of this eosinophilic march consists of eosinophilic pulmonary infiltrates, depending on the severity of eosinophilic inflammation (7). However, in the literature, patients with EARR and extrapulmonary involvement have been very rarely identified (17). Although speculative, it suggests that this group can be called EARR and meets the diagnostic criteria for idiopathic HES, which may affect the organ functions because of peripheral hypereosinophils by going to tissues through extrapulmonary eosinophilic chemoattractants.

In conclusion, here we presented a case of EARR + CEP overlap, accompanied by organ-limited hypereosinophilia, with detailed differential diagnosis. It should be kept in mind that EARR/CEP overlap might have the potential to become systemic due to possible eosinophil chemoattractants in other organs and that it may turn into idiopathic HES or EGPA.

CONFLICT of INTEREST

The authors reported no conflict of interest related to this article.

AUTHORSHIP CONTRIBUTIONS

Concept/Design: All of authors

Analysis/Interpretation: İY, GPÇ, BA

Data Acquisition: All of authors

Writing: İY, GPÇ, BA

Critical Revision: İY, MK, GPÇ

Final Approval: İY

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