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Case Report

A case of severe hypereosinophilia in a term infant

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Abstract: Eosinophilia is common in premature infants, but severe hypereosinophilia is rare in the neonatal period, and a sustained or progressive form is particularly uncommon. We describe the clinical characteristics and course of severe hypereosinophilia in a full-term male neonate. The patient exhibited substantial abnormalities in peripheral blood leukocytes and polypnea at birth, followed by a progressive increase in peripheral blood leukocyte count and Ec ratio, reaching 32% of monocytes and an absolute value of 27.1×10^9/L. All related etiological examinations (for viral, bacterial, fungal, immunodeficiency, and immune diseases, hyper IgE syndrome, hematological malignancies, and bone marrow hyperplasia syndrome) and blood biochemistry results were normal. Biopsy revealed proliferative bone marrow with eosinophil fraction at 25%, consistent with severe hypereosinophilia. Anhelation was relieved by oxygen, atomization, and anti-infection treatments. Blood was reexamined one and three months after discharge. By three months, absolute Ec was reduced to 1.18 and absolute count to 1.02×10^9/L. At six months, Ec, motor function, and mental development were normal. Most cases of severe hypereosinophilia in neonates have unknown etiology but good prognosis. Comprehensive clinical and laboratory assessments are usually required to identify the etiology. Non-specific treatment was chosen in our case because of the unclear etiology. Serious cases necessitate blood transfusion, and all require careful monitoring of eosinophil count and organ function until at least 6 months after birth.

Keywords: Hypereosinophilia, hypereosinophilic syndrome, neonate, infant

Introduction

Hypereosinophilia (HE) is defined as an absolute value of oxyphil cells in neonatal peripheral blood > 0.5×10^9/L, but without organ injury [1]. Cases are classified as mild, moderate, or severe according to differential counting (mild, Ec differential count 0.07-0.15, absolute value $0.5\text{-}1.5\times10^9$/L; medium, 0.15-0.50, $1.5\text{-}5.0\times10^9$/L; severe, 0.50-0.90, > 5.0×10^9/L). Yen et al. [2] report mild to moderate HE in 14%-76% of preterm neonates during hospitalization. In contrast, severe HE in neonates is rare, with only one case reported in 2011 [3]. We report a case of neonatal severe HE admitted to Guangzhou Women and Children Medical Center in January, 2015, and reviewed the relevant literatures.

Case report

Clinical data and results

The case patient was male with full-term normal delivery, birth weight 3220 g, without premature rupture of fetal membranes. Amniotic fluid, umbilical cord, and placenta were normal, and 1-5-10 min Apgar scores were all 10. The mother has gestational diabetes, but no history of drugs associated with reactive HE. The patient exhibited an abnormal increase in umbilical cord blood leukocytes at birth, and an ensuing increase in peripheral blood leukocyte count and Ec ratio (**Figure 1**). Granulocyte and lymphocyte ratios were reduced, immature granulocytes and erythrocytes were non-uniform in size and large platelets were found occasionally on blood examination. The patient was given ceftriaxone sodium, imipenem, and cilastatin sodium (tienam) for anti-infection by the local hospital due to the significant abnormalities in peripheral blood leukocytes and polypnea. With oxygen uptake, atomization, and other treatments, the patient's anhelation was relieved, but routine blood test results were still abnormal, and he was admitted to our hospital 6 days after birth (January 21, 2015). Physical examination at our hospital revealed stable vital signs and age-appropriate respons-

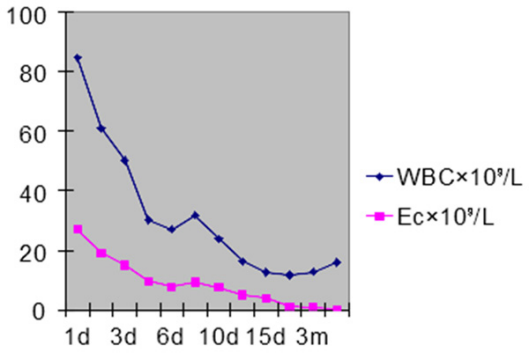

Figure 1. Changes in absolute leukocyte and eosinophil counts in a case of severe neonatal hypereosinophilia.

es, but flush complexion, loud crying, and slight xanthochromia. There were no skin rashes or swelling of superficial lymph nodes. Bregma was flat and soft, breath sounds from both lungs were clear with no rales. Heart rate was regular at 148 beats/min, and heart sounds were strong with no audible murmurs from valve areas. The abdomen was soft with slight bulging, but there was no swelling of the liver or spleen. Nervous system function was normal on physical examination. Routine blood test results were as follows: leukocytes 31.8×10^9/L, hemoglobin 120 g/L, blood platelet 356×10^9/L, Ec 29%, and Ec absolute value 9.3×10^9/L. Blood biochemistry results revealed normal liver, heart, and kidney function, and all related etiological examinations were normal (**Table 1**). The use of Tienam was continued for 7 days after admission. Lumbar puncture examination was negative, hypersensitive C-reactive protein and procalcitonin were normal, and the child exhibited no vomiting or diarrhea, anhelation, cough or wheeze, somnolence, or tic.

The patient was reexamined on the ninth day after admission (15 days after birth). Leukocyte count was reduced to 12.7×10^9/L and Ec absolute value to 4.0×10^9/L (**Table 2**). Bone marrow aspiration revealed proliferative bone marrow and a substantially elevated of eosinophil ratio of 25%, left moving nuclei with paramorphia, hemophagocytes, and signs of infection associated hemophagocytic syndrome and hypereosinophilia. Plasma amino acids analysis showed increased glutamine because of high blood ammonia, but blood amminia is normal (43.9 mmol/L). Urine GC-Ms was negative. Karyotype was normal (46 chromosomes, XY). Final diagnosis was hypereosinophilia (severe) of unknown etiology. The patient's guardians requested discharge against medical advice 13 days after admission.

Blood was reexamined at one month and three months after discharge. Absolute Ec was reduced to 1.18 and absolute value to 1.02×10^9/L. measure is normal at six months, at which time the patient's movement and mental development were also normal.

Discussion

Increased Ec in neonates may be related to anabolism, drug reaction, allergy, bronchopulmonary dysplasia (BPD), hemopoietin therapy, intravenous nutrition, or infection [4-8]. Hypereosinophilia is common in premature infants, frequently related to infection, necrotizing enterocolitis, and BPD, but etiology is also often unclear, mostly in mild and moderate cases. Severe HE in neonates is rare in clinical practice. For neonates with HE, both benign and reactive factors are considered as causes, for example allergy, infection, and drug reactions. Other diseases or syndromes associated with HE are then considered, such as hyper-IgE syndrome, Omenn syndrome, hematological malignant diseases (e.g., chronic eosinophilic leukemia), and immune diseases (e.g., systemic lupus erythematosus, vasculitis). Bone marrow aspiration, flow cytometry immunoassay of B and T cells, auto-antibody detection, and chromosome analysis should be conducted. If Ec rises repeatedly or is sustained, idiopathic/clonal hypereosinophilic syndrome(HES) should be considered.

Severe HE (HES) is a group of diseases characterized by markedly increased peripheral blood Ec and organ function impairment caused by Ec invasion. Clinical manifestations of HES vary, but mainly involve the heart, skin, lungs, and nervous system. In 1975, Chusid et al. [9] proposed diagnostic criteria as follows: Ec absolute value of peripheral blood > 1.5×10^9/L, lasting 6 months or more, with organ or tissue involvement. HE caused by other reasons are excluded. Crane et al. [10] reported that the incidence of HES is about 0.036/100 000, and is diagnosed mainly in adults 20 to 50 years old, but rarely in children. In one clinical report from Europe, the case patient was 5 months old [11], while a report from China documented

Table 1. Examination results on related causes and complications in a case of severe neonatal hypereosinophilia

Causes and complications	Items	Results
Viruses	Herpes simplex (blood, cerebrospinal fluid, CSF)	Negative
	Cytomegalovirus (CMV) (blood, CSF)	Negative
	Rubella (blood)	Negative
	MicrovirusB19 (blood)	Negative
	Coxsackie (blood)	Negative
	EB virus - four items (blood)	Negative
	Respiratory syncytial (blood)	Negative
	Influenza (blood)	Negative
	Adenovirus (blood)	Negative
Bacteria	High sensitive C-reactive protein (blood)	Normal
	Procalcitonin (blood)	Normal
	Blood culture	Negative
	Cerebrospinal fluid culture	Negative
	Throat swab culture	Negative
Fungi	Anaerobe (blood)	Negative
	Fungal dextran	Normal
	Chlamydia (blood)	Negative
	Mycoplasma (blood)	Negative
Others	Mycobacterium tuberculosis Antibodies (blood)	Negative
	Acid-fast bacilli (phlegm)	Negative
Immunodeficiency disease or immune disease	Immune items (IgA, IgG, IgM, C3, C4)	Normal
	Cellular immune function (flow cytometry)	Normal
	Auto-antibodies (8 items)	Negative
Hyper-IgE syndrome	IgE	Normal
	Fecal lactose intolerance	Negative
	Peripheral blood cell count	No abnormalities
Hematological malignancies and bone marrow hyperplasia syndrome	Bone marrow aspiration cytology	Proliferative bone marrow image
	Abdominal sonography	No swelling of liver and spleen
Bronchopulmonary dysplasia and thoracic complications	Chest radiograph	Normal
Heart complications	UCG	Normal
	ECG	Normal
Cerebral complications	Head ultrasound	Bilateral periventricular parenchyma echo enhancement, bilateral subependymal hemorrhage

HES in a 2-month-old infant [12]. If PDGFRA, PDGFRB, and FGFRI fusion genes or BCR/ABL1, or JAK2V617F+ gene mutation is detected, HES can be considered idiopathic/clonal HES.

The consensus statement on HE and related syndromes in 2012 defines HE as peripheral blood Ec > 1.5×10^9/L on two examinations separated by at least one month, with or without tectotype, which defined as: an Ec ratio of more than 20% of all karyocytes in bone marrow smear, or (and) pathology consistent with Ec infiltration of tissue, or (and) significant granin deposition of Ec (with or without tissue infiltration of Ec). HES not only meets the peripheral blood-related diagnostic criteria of HE, but in addition requires organ dysfunction caused by tectotype HE, with organ damage by other causes [13] excluded. In this current case, Ec ratio of 25% of all karyocytes in bone marrow smear, so Ec was severely increased with invasion of myeloid tissue, but without other significant organ lesions, consistent with a diagnosed of severe HE. More pathological results are required to determine whether it is tectotype or not.

HE is divided into three categories according to the Chinese classification system: reactive HE, HES, and chronic eosinophilic leukemia (CEL). HE is observed in about one third of neonates, but etiology and mechanism are generally unclear. Possible explanations include 1) reduced secretion of adrenal hormone with feedback

Table 2. Literature review

Writer	Term/ preterm	Clinical data	Ec (severe)	Ec ascending time	Ec back to nomal time	Causes	Complications	Treatment	Prognosis
Wang Y-J et al. [15]	Term	None	2/24	0-20 d	2-21 d	Infection	None	Antibotics	Normal
Rui-X et al. [16]	Term	None	6/28	0-12 d	-	Infection 1/28	None	Antibotics	Normal
						ABOhemolysis 4/28			
						HIE3/28 drug reaction 2/28			
Yen J-M et al. [2]	Preterm	None	17/142	3 w	5 w	No spefic	None	-	Normal
Shahein AR et al. [3]	Preterm	Nec	1	23 d	3 m	Unknown	None	Antibotics, exchange transfusion	Normal
Juul SE et al. [4]	-	None	50/1652-	3.3 d	-	Infection	None	Antibotics	Normal
Aguiar A et al. [17]	Preterm	Vomiting and abdominal distention	1	-	-	-	Hydrolyzed milk formula	Dietry	Normal
Krous HF et al. [18]	-	Fussy and feeding poorly	1	--	-	Unexplained	Endomyocardias	-	Dead
Manoura A et al. [19]	Both	None	-	10.2±0.8 d	-	Infection	None	Antibotics	Normal
								Immunoglobulin	

Table 3. The treatment and results of blood leukocyte and Ec ratio

Date after birth	Symptom	Treatment	WBC $\times 10^9$/L	Ec $\times 10^9$/L
1 d	Anhelation	Ceftriaxone sodium, tienam	84.7	27.10
2 d	Anhelation	Ceftriaxone sodium, tienam	60.9	19.19
3 d	Anhelation	Ceftriaxone sodium, tienam	50.2	15.06
4 d	Anhelation	Ceftriaxone sodium, tienam	30.2	9.66
6 d	Jaundice	Ceftriaxone sodium, tienam	27.1	7.80
8 d	Jaundice	Tienam	31.8	9.30
10 d	Jaundice	Tienam	24.0	7.55
12 d	Jaundice		16.4	5.05
15 d	No		12.7	4.00
1 m	No		11.7	1.18
3 m	No		12.8	1.02
6 m	No		16.0	0.15

Ec increase after birth, 2) establishment of a positiive nitrogen balance indicated by steady weight gain. 3) removal of external antigen causing an increase in Ec of the alimentary canal and respiratory tract, and 4) intake of tryptophan supplements during pregnancy [14]. Current research suggests that reactive HE is caused by Ec or precursor cell cytokine activation (IL3, IL-5, GM-CSF), resulting in Ec proliferation, while CEL/HES is primarily caused by hematopoietic disorders that induce cloning of totipotent stem cells or hemopoietic stem cells of the medullary system or lymphatic system.

Two retrospective studies have reviewed domestic cases of neonatal HE. In total, 52 cases have been reported, of which only one case was severe HE, with peak absolute Ec of 9.02×10^9/L. In this case, Ec returned to normal after 20 days, with pneumonia and IgE increase, and no abnormality was found at follow-up, consistent with reactive HE [15, 16]. Three case reports [3, 17, 18] and retrospective studies [2, 4, 19] have been published on cases outside of China. Most cases were moderate, occurring in premature infants (80.90%). Established causes included infection (39.27%), BPD (11.45%), blood transfusion (16.18%), and necrotizing enterocolitis (4.73%), but a substantial proportion were of unknown etiology (25.82%). (see **Table 2**) Clinical manifestations varied from none to rash, with one case of neonatal death due to Ec myocarditis. One case study of a premature infant with severe HE reported in 2011 absolute peak Ec of 91.48×10^9/L, but no organ damage was found and bone marrow aspiration results were normal. This case, blood exchange was implemented, and absolute peak was reduced to 47.28×10^9/L, eventually returning to normal 80 days after birth with favorable prognosis [3]. In our case polypnea and jaundice appeared in the full-term infant after birth, and antibiotics (Ceftriaxone sodium, tienam) was used during hospitalization. The absolute value of Ec reahed a peak 27.1×10^9/L and WBC reached a peak 84.7×10^9/L on the day of birth. The absolute Ec value was reduced to 5.05×10^9/L after 12 days, and slowly to normal level six month after birth. (see **Table 3**) Ec infiltration and hemophagocytes were found in bone marrow aspiration, but the patient had no three series decrease or other symptoms, and no hemophagocytic syndrome. Consistent with reactive HE, with favorable prognosis.

HE may manifest with skin lesions and neoplastic diseases. HE is associated with a variety of rashes. Organ involvement can be found as well, as evidenced by respiratory symptoms (cough, anhelation, etc), while chest radiography can show a variety of invasive changes. Possible digestive system symptoms include stomachache, diarrhea, and nausea/vomiting. Severe cases may show intestinal obstruction or hemorrhage of the digestive tract. Endoscopic biopsy is recommended to confirm invasive lesions with eosinophils. Myocardial damage, endocardial and cardiac valvular changes, severe heart failure, and arrhythmia are all possible cardiovascular outcomes, while nervous system symptoms can indicate both central and peripheral nervous system involvement. Proliferation of reticuloendothelial system (RES) cells and systemic symptoms are also observed in HE. Some child patients show fever, emaciation, weakness, and lymphadenectasis of the liver and spleen. Krous HF et al. [18]. reported one case of neonatal death due to eosinophilic myocarditis, and Xiaoran et al. [12] reported one pediatric case of HES. Although Ec ratio was only 12%, Ec absolute value was 0.9×10^9/L, and clinical manifestations included fever, rash, anemia, swollen liver and spleen, cough, rales of both lungs, and weak heart sounds. Pathology revealed bone marrow inva-

sion and myocardial involvement. Thus, in clinical practice, dynamic evaluation of organ function should be implemented even for symptomatic mild and moderate HE. The current case patient exhibited anhelation since birth, and chest radiograph showed increased lung markings. These clinical symptoms improved with the decline in Ec, and the family refused bronchoalveolar lavage to assess lung pathology. This case is not considered tectotype eosinophilia, but it is speculated that pneumonia was also present.

Clinically, the majority of neonatal HE is reactive HE, and a few cases reach the criteria of HES. If there is no clear evidence for Ec organ invasion, and there are no symptoms, intervention is not necessary. Mild to moderate HE in children requires no treatment of the primary diseases or only careful observation for changes in Ec and assessment of organs that are easily invaded. If there is evidence of eosinophil infiltration into organs or tissues, close observation is suggested, as well as chest reexamination, heart color ultrasound, and functional evaluation of other organs. Blood exchange for severe HE is also reported [18]; if Ec is greater than 5×10^9/L (or in the opinion of some $> 2\times10^9$/L), such treatments should be implemented as appropriate to protect organs from damage [20].

Disclosure of conflict of interest

None.

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