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Case Report

Eosinophilia complicated with cerebral infarction: a case report and literature review

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Abstract: Eosinophilia refers to the absolute value of eosinophils in the peripheral blood > 0.5 × 10^9/L. The disease usually involves multiple organ systems, such as the skin, lungs, heart, spleen and nervous system. Neurological involvement can be manifested as peripheral neuropathy, thromboembolism, dementia, epilepsy, eosinophilic meningitis, etc. In this paper, a case of watershed eosinophilia complicated with multiple cerebral infarctions was reviewed, combined with laboratory examination, imaging examination and therapeutic effect. At the same time, combined with relevant literature, the clinical manifestations, laboratory examination and imaging features, diagnosis and treatment of eosinophilia and cerebral infarction were reviewed.

Keywords: Eosinophilia, cerebral infarction, thromboembolism

Introduction

Eosinophilia refers to the absolute value of eosinophils in peripheral blood > 0.5 × 10^9/L [1]. The disease usually involves multiple organ systems, such as the skin, lung, heart, spleen and nervous system [2]. Nervous system involvement can be manifested as peripheral neuropathy, thromboembolism, dementia, epilepsy, eosinophilic meningitis and so on [3, 4]. Recently, a case of eosinophilia with multiple cerebral infarctions in watershed distribution was treated in our hospital.

Case profile

A 66-year-old female patient was admitted to the Department of Neurology, Baotou Central Hospital, Inner Mongolia on April 6, 2020, due to "numbness and weakness of the left limb for 16 hours". Sixteen hours before admission, the patient presented left limb numbness and weakness without obvious inducement, manifesting as the left upper limb which could be lifted, while the left lower limb was inflexible and she could walk, but the left lower limb was mopping when walking. There was no risk factor of cerebrovascular disease such as hypertension, diabetes, coronary heart disease, hyperlipidemia or smoking.

Physical examination: BP 157/85 mmHg, the patient was awake and was able to respond to simple questions, but her articulation was slightly slurred. Her Glasgow Coma Scale was E4V4M6. Her muscle power was graded as one and four (MRC grade) for the left upper and lower limbs. Babinski signs were present on the left side.

Laboratory test results were as follows: Routine blood work: WBC 24.21 × 10^9/L, RBC 4.84 × 10^9/L, Hb 145.00 g/L, PLT 210.00 × 10^9/L, the absolute value of eosinophils was 10.84 × 10^9/L and eosinophil ratio was 44.80%. ESR 38.00 mm/h, C-reactive protein 156.00 mg/L, procalcitonin 0.159 ng/ml. Antinuclear antibody: titer 1:100 was strongly positive +++, titer 1:320 was positive +. IgG 19.70 g/L was slightly higher, Ig A and IgM were normal. The anti-mitochondrial M2 subtype antibody was weakly positive, and the antinuclear antibody

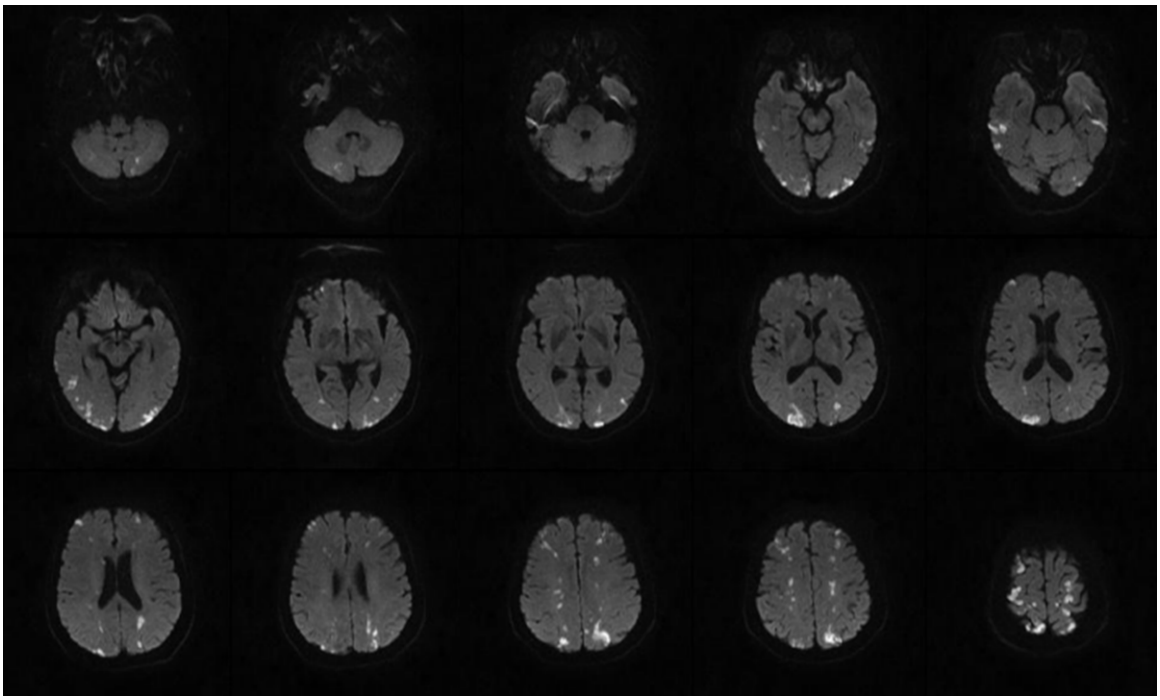

Figure 1. Diffusion weighted images revealed multiple high signal intensity lesions in the right basal ganglia region, bilateral frontal parietal occipital lobe and bilateral cerebellar hemisphere.

spectrum was negative. The results of rheumatoid test, complement, ANCN, tumor markers and coagulation function were not abnormal. Brain CT showed ischemic changes. Cranial MRI (**Figure 1**) showed multiple acute infarcts in the right basal ganglia, bilateral frontoparietal occipital lobe and bilateral cerebellar hemisphere, multiple lacunar cerebral infarction in the bilateral frontoparietal lobes, and no obvious abnormality in cranial MRA. Cervical ultrasonography showed uneven intimal thickening of bilateral carotid arteries with plaques (multiple). TCD showed unsatisfactory detection bilaterally in the temporal window, changes of blood flow spectrum of high resistance arteriosclerosis and stenosis of left vertebral artery. The NCV of the extremities was damaged in the right median nerve (wrist), but the rest was normal. There was no obvious abnormality in H reflex of both lower limbs and EMG in muscles of extremities. Bilateral lung CT (**Figure 2**) revealed interstitial changes in both lungs with exudation, multiple pulmonary vesicles in the right lung and multiple mediastinal lymph nodes. Cardiac Holter showed sinus tachycardia, the fastest 125 beats/min, multiple ventricular extrasystole, some showed duplex rhythm, some had two ventricular extrasystole, myocardial blood supply was insufficient, and cardiac color ultrasound showed decreased left ventricular diastolic function. Double lower limb arteriovenous ultrasonography: the arterial intima of both lower extremities thickened unevenly with plaques (single), and there was no obvious abnormality in both lower extremity venous ultrasonography.

The patient's condition worsened on the second day after admission, with weakness of the right limb and difficulty in lifting of the right upper limb. Physical examination: BP 140/90 mmHg, clear mind, slow reaction, poor computational ability, poor memory, simple questions could be answered, answered to the point, dysarthria, slow speaking, equal size of both pupisl, 2.5 mm in diameter, light reflex, normal eye movement, no nystagmus, no obvious central facial and lingual paralysis, and acupuncture was in confusion. The acupuncturing sensation decreased in face, neck and T4. The muscle strength of the right upper limb was grade 3 and that of left upper limb was grade 2, the right hand was flexion, the left hand could grasp, the lower limb muscle strength was 4+ grade. The masonic movement did not cooperate, the knee tendon reflex of the right lower

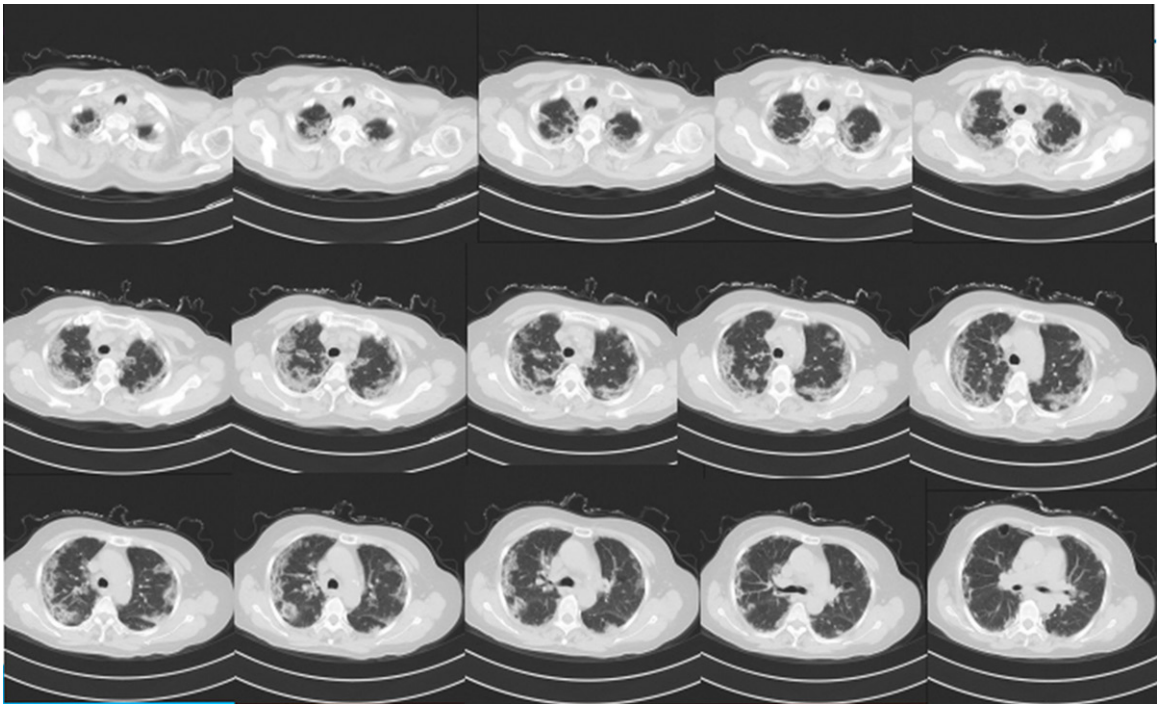

Figure 2. Bilateral lung CT: revealed interstitial changes in both lungs with exudation, multiple pulmonary vesicles in the right lung and multiple mediastinal lymph nodes.

limb was weakened, and the Babinski signs were positive on both sides. Analysis of the disease; the patient's cerebral infarction occurred across multiple vascular dominated areas, but the examination did not trace the embolism from the heart or lower limbs.

Combined with the consultation opinion of the Hematology Department, the patient was diagnosed with eosinophilia, multiple cerebral infarction (bilateral cerebral hemisphere, cerebellum), the nature of bilateral lung lesions undetermined, highly suspected eosinophilic pneumonia. Multiple cerebral infarctions and pulmonary lesions are associated with eosinophilia. We suggest that the patient do bone marrow puncture, but the patient and her family did not agree. The patient was given methylprednisolone 60 mg intravenously once a day. One day later, routine blood examination showed that WBC were 9.73×10^9/L and eosinophil absolute value was 0.68×10^9/L, which all returned to normal. At the same time, symptomatic treatments such as antiplatelet aggregation, improvement of circulation and nutrition of nerves were given. On April 29, the 12th day of hormone therapy, the patient agreed to do bone marrow puncture. The results of bone marrow examination were as follows: bone marrow smear showed that bone marrow hyperplasia was obviously active, the proportion of granulocyte increased, the proportion and morphology of cells in each stage were not significantly abnormal, the proportion of erythroid was decreased, and the megakaryocyte line was basically normal. Bone marrow immunophenotype showed that the proportion of each line was normal (eosinophil group was 0.41%), and no abnormal immunophenotype was found; FISH detections of PDGFRA, PDGFRb, FGFR1 genes showed no abnormality; TEL/PDGFRA fusion gene was negative. Combined with immune related examinations, considering eosinophilia, not excluding connective tissue disease secondary. We suggested that the patient should further improve the immune related examinations, but the patient and her family refused. The patient's condition gradually improved, her spirit was improved, her speech was more fluent, the body was more powerful, and the neck muscle strength was stronger. Physical examination: clear mind, slow speaking and answering questions to the point. The muscle strength of the right upper limb was grade 3, the distal limb was grade 4+, the left upper limb was grade 3, both the lower limbs

was grade 4+, the knee tendon reflex of the right lower limb was weakened, and the Babinski sign was positive on both sides. On the 28th day of hospitalization, the patient was discharged from the hospital. After discharge, the patient was instructed to continue oral hormone and regularly review the blood routine. Up to now, the patient has no recurrence and new symptoms, and the absolute value of eosinophil is normal.

Discussion

The patient was admitted to the Department of Neurology due to "numbness and weakness of the left limb for 16 hours". Based on the patient's clinical manifestations and various examination indexes after admission, the diagnosis of eosinophilia, multiple cerebral infarction (bilateral cerebral hemispheres, cerebellum), and the uncertain nature of bilateral pulmonary lesions were considered, and eosinophilic pneumonia was highly suspected.

The main causes of acute cerebral infarction are arteriosclerosis, cardiogenic embolism and small artery occlusion. The pathogenesis of arteriosclerotic cerebral infarction is closely related to abnormal lipid metabolism, endothelial cell damage, hypertension, hemorheology and hemodynamic changes. Specifically, it can be divided into distal vascular embolization cerebral infarction, transient cerebral insufficiency and boundary (watershed) cerebral infarction. According to the infarct area it can be divided into large cerebral infarction, and lacunar cerebral infarction. Hemorrhagic cerebral infarction with bleeding. Cerebral embolism, also known as embolic cerebral infarction, can be divided into cardiogenic, non-cardiogenic, iatrogenic and unidentified emboli according to different emboli sources. Cardiogenic embolus is the most common clinical embolus. The onset of the disease is acute, patients can appear with a brief disturbance of consciousness, often with multiple or large area cerebral infarction. Laboratory examination of peripheral blood infection is usually leukocytosis, bacterial neutrophils, or parasitic, mainly eosinophil.

The patient had no history of parasitic infection, no history of rheumatic immune disease, no history of asthma, and no family history of hypereosinophilia. Bone marrow examination found no evidence of eosinophil cloning. After excluding reactive eosinophilia, such as worms, drugs and paraneoplasm, patients admitted to hospital should be screened for FIP1L1-PDGFRα, TCR/IgH/IgK rearrangement, chromosome karyotype, PDGFRα, PDGFRβ and FGFR1 fusion genes. Except for primary eosinophilia. It is usually accompanied by abnormal karyotype 4q12, 5q31-33 or 8p11-12 translocation, and FISH detection is recommended for confirmation. PDGFRB or FGFR1 rearrangement is free of eosinophilia and can be detected by RT-PCR or RNA sequencing if necessary. The patient's antinuclear antibody was positive, and the antimitochondrial M2 subtype antibody was weakly positive, but ANCA and antinuclear antibody profiles were negative. We recommend that patients re-examine immunopositive indicators to further improve immune-related tests to exclude secondary eosinophilia caused by connective tissue disease. If connective tissue disease is excluded, idiopathic hypereosinophilia should be considered.

Idiopathic hypereosinophilia is a heterogeneous disease with unknown causes that exclude the three types of HE. IHE is called idiopathic hypereosinophilia syndrome (IHES) if it is accompanied by eosinophil related organ damage. The diagnostic criteria of IHES are 1. A peripheral blood eosinophil count of > 1.5×10^9/L was met with eosinophilia at least twice. Duration ≥ 6 months. 2. Evidence of eosinophile-mediated damage to the target organ. 3. Other causes of eosinophilia are removed. There is still no recognized therapeutic standard for this disease.

Regarding the treatment of hypereosinophilia, the aim of treatment is to reduce eosinophile count and eosinophile mediated organ dysfunction. According to relevant guidelines, the treatment of several subtypes of hypereosinophilia varies as follows. The primary and idiopathic hypereosinophilia are treated with organ involvement and dysfunction. Secondary hypereosinophilia is mainly targeted at the primary disease. HES treatment options are as follows. For patients with an eosinophil count > 100×10^9/L, leukocytosis may be considered. The patients with positive FIP1L1-PDGFRα and PDGFRβ rearrangement preferred Gleevec therapy, until clinical, hematological, molecular biological remission, maintenance therapy; Glucocorticoid therapy was preferred for FGFr1-

negative patients with FIP1L1-PDGFRα and PDGFRβ; When glucocorticoids cannot be controlled or the required dose is too large, hydroxyurea can be added for treatment, and vincristine, CTX, etc., can be used for eosinophil count > 100 × 10^9/L. IFNα-2b could be used in patients with poor response to glucocorticoid and hydroxy-urea. HSCT may be considered in patients younger than 50 years of age whose disease progression cannot be controlled by drugs.

The patient had multiple cerebral infarctions caused by eosinophilia. After hormone therapy, the eosinophilia returned to normal in absolute value and the symptoms improved significantly, including her spirit was improved, her speech was more fluent, her body was stronger, and her neck muscle strength was stronger. The mechanism of cerebral infarction caused by eosinophilia may be: (1) The damage of endocardium causes mural thrombosis, and the thrombus falls off and the embolism concentrates in the watershed area to cause infarction. Cardiac damage caused by eosinophilia is usually divided into three stages [5]. Eosinophil infiltration of endocardium and myocardium, myocardial necrosis and mural thrombosis, myocardial fibrosis. The transthoracic and transesophageal echocardiography were mostly negative. (2) Hypercoagulable state of blood, *in situ* thrombosis or micro embolus formation leads to cerebral infarction. Eosinophils mainly release basic proteins, eosinophil neurotoxin, eosinophil cationic protein and eosinophil peroxidase, which can be used as platelet agonists and increase vascular permeability, stimulate the activation of factor XII and reduce the anticoagulant effect of heparin to facilitate thrombosis [6]. In addition, eosinophils can also induce endothelial cells to secrete tissue factor [7], thus promoting thrombosis. (3) Insufficient perfusion [8]. The direct toxic effect of eosinophils results in increased vascular permeability, microcirculation disturbance and insufficient oxygen supply, while a variety of pro-inflammatory mediators released by eosinophils cause vascular endothelial injury, vasoconstriction and even spasm, further aggravating microcirculation ischemia and hypoxia. The above three mechanisms do not exist alone but interact and co-exist. No thrombus or structural abnormality was found in this patient after two cardiac color Doppler ultrasound examinations. Therefore, the possibility of apoplexy caused by the heart is very low. We believe that the small bilateral infarction of the anterior and posterior circulation in this patient is caused by a variety of cerebral vascular injuries. The reason is that the toxic effect of eosinophils on cerebral arteries causes vascular intimal injury, leading to thrombosis, and then leads to extensive cerebral infarction.

In summary, timely diagnosis and early intervention of hypereosinophilia are directly related to the prognosis of patients. Moreover, the absolute value of peripheral blood eosinophilia is not necessarily proportional to terminal organ damage. Therefore, in the absence of definite organ involvement and dysfunction, in order to avoid irreversible organ damage, it is very important to diagnose and treat patients with hypereosinophilia complicated with cerebral infarction early.

Disclosure of conflict of interest

None.

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