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FEVER, PANCYTOPENIA, HEMOPHAGOCYTOSIS—CLINICAL ANALYSIS OF A CASES OF HEMATOLOGICAL SYSTEM DISEASE WITH BONE MARROW FAILURE AS THE PROMINENT MANIFESTATION

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Abstract: The object is to improve the recognition and differentiation of rare diseases of bone marrow failure. The method is to report a case with fever as the main symptom, pancytopenia, myelodysplasia and hemophagocytosis in the laboratory and to review literature. Results: The patient have had fever for more than one month, no lymphadenopathy, but with hepatosplenomegaly, myelodysplasia with hemophagocytosis, EB virus infection. The hemogram recovered after 20 days of treatment. Conclusion: Hemophagocytic syndrome, acute aplastic crisis and severe aplastic anemia, the clinical manifestations can overlap. When the diagnosis is not very clear, the treatment should be based on strong support treatment, at the same time actively look for the causes, and remove the relevant factors.
Keywords: fever; pancytopenia; hemophagocytic syndrome

INTRODUCTION

In hematological diseases, pancytopenia can be caused by many reasons. The typical causes are aplastic anemia (AA), myelodysplastic syndrome (MDS), paroxysmal nocturnal hemoglobinuria (PNH), and pancytopenia caused by some secondary factors. The identification of these diseases is very important in clinical practice, and delayed treatment may lead to delayed condition, or even death. Recently a patient is admitted and whose clinical manifestations are atypical and difficult to diagnose. The summary is as follows.

CLINICAL DATA

First hospitalization

The female patient, 24 years old, was hospitalized on July 25, 2018 due to repeated fever for more than one month. One month ago, the patient had fever after cold. The body temperature was over 38.5 ℃. The patient was relaxant, with slight pharyngeal pain. There was no shivering, coughing or backache. She was hospitalized in a county-level hospital in Zhejiang Province. And was diagnosed as "viral infection". She was given antiviral treatment. Her body temperature did not drop. She was transferred to a municipal hospital. She was diagnosed as "EB virus" infection. The relevant examination indexes were not available, and she was given "antiviral". The peak temperature slightly decreased. The patient returned to the local area 20 days ago due to the temperature rising to 40 ℃, and went to two top three hospitals one after another. She was still diagnosed with "EB virus" infection, and continued antiviral treatment. The temperature drop was not obvious, and the active tuberculosis infection was excluded. At this time, the blood routine showed that WBC was 0.64×10^9 / L, N 0.01×10^9 / L, HGB was 73g / L, PLT was 11.0×10^9 / L, and he was admitted to our hospital with "the cause of pancytopenia". Before the onset of the disease, the patient lived outside the province with her husband, and was not exposed to chemicals and radioactive substances. There was no epidemic situation in the area. Physical examination: T38 ℃, P 100 times / min, R 22 times / min, BP 105 / 61mmhg, slight paleness of skin and mucous membrane of the whole body, no swelling of superficial lymph nodes, but with bleeding spots on buccal mucosa and tongue surface, congestion of pharynx, enlargement of tonsil I degree, no tenderness of sternum, clear breath sounds of both lungs, no dry and wet rales, 100 times / min heart rate, regular rhythm, soft abdomen, no tenderness, no swelling of liver and spleen. There was no edema in the lower limbs and no abnormality in the nervous system. Initial diagnosis: 1. Cause of pancytopenia: 1) hypocellular acute myeloid leukemia? 2) Aplastic anemia? 3) Myelodysplastic syndrome? 4) Acute aplastic crisis? 2. EB virus infection; 3. Pharyngitis.

Examination and treatment process:

Blood routine test: WBC 0.38×10^9 / L, N 0×10^9 / L, HGB 67g / L, PLT 3×10^9 / L, reticulocyte 0; blood biochemistry: creatinine 142.10umol/l, LDH 10^9.4u/l, triglyceride 3.44mmol/l, albumin 26.0g/l, hypersensitive C-reactive protein 31.69mg/l; urine routine test: urinary protein (+); coagulation index

test: partial thromboplastin time 60.4 seconds, fibrinogen 6.31g/l, D-dimer 2.16 μ g / ml; Thyroid function: total T3 and free T3 slightly decreased; calcitonin zymogen 3.09ng/ml (↑), g-lipopolysaccharide 5.15pg/ml (↓), 1-3-β-d-glucan normal; serum ferritin > 1650.0ng/ml; autoantibody not detected positive results; EBV-DNA qualitative positive, quantitative < 1.00e + 03, micro virus (b19-dna) and cytomegalovirus (CMV-DNA) qualitative negative; pharyngeal test, blood and bone marrow No bacteria were detected in culture; B-ultrasonic examination: liver, spleen and celiac lymph nodes were not large; chest CT: heart and lung were normal, mediastinal lymph nodes were not swollen; myelogram (iliac bone): bone marrow hyperplasia was reduced, granulocyte red line accounted for 1%, morphology was approximately normal, lymphocyte accounted for 94%, morphology was approximately normal, abnormal lymphocytes were seen, phagocytes were significantly increased, hemophagocytosis was seen; Blood slice: the shape of nucleated red blood cells was generally normal, abnormal lymphocytes and severe thrombocytopenia could be seen. According to the condition of bone marrow, HLH was considered, and immediately treat it according to "hemophagocytic syndrome 2004 plan" [1]. The antibiotics were upgraded from "cefuroxime" to " Carbon cyanogenases (meropenem)", "ganciclovir antiviral, fluconazole antifungal, immunoglobulin, component blood transfusion, granulocyte colony stimulating factor subcutaneous injection" and other treatments. At the same time, a piece of bone marrow was sent to the third party inspection center (Jinyu). The report indicated that: the bone marrow hyperplasia was severely reduced, the proliferation of hematopoietic cells was extremely low, the percentage of lymphocytes was 93.5%, the percentage of plasma cells was 5.5%, the small particles of bone marrow were easy to see, most of them were empty reticular structure, mainly non hematopoietic cells. Etoposide was stopped and the rest of the treatment was unchanged. After one week's treatment, the patient's body temperature did not drop significantly, the patient coughed slightly, and there was no sputum. The bone marrow picture (iliac bone) was reexamined: bone marrow small particles (+ +), fat drops (+), bone marrow hyperplasia decreased, megaly hyperplasia of granular red severely decreased, non-hematopoietic cell mass was easily seen, and hemophagocytosis was easily seen. In accordance with the previous week, the above treatment should be continued. At the same time, NK cell activity, soluble interleukin-2 receptor detection and sternal bone marrow puncture should be performed. The patient refused and transferred to another third top hospital 8 days after hospitalization.

Second hospitalization (outside hospital):

The patient was hospitalized on August 3, and the treatment was continued. Laboratory examination: thyroid function: free T3 decreased, thyroid peroxidase antibody and thyroglobulin antibody increased. Endocrine Department considered that it was related to the primary disease. Blood routine examination: WBC 0.41 × 10^9 / L, Neutrophils 0.01 × 10^9 / L, RBC1.84 × 10^{12} / L, HGB 53.0g/l, reticulocytes 0.12%, PLT 10.0 × 10^9 / L; sternal bone marrow examination: small particles (+ +), oil drops (+ +), active to decreased proliferation, severe granulocytopenia reduction, a few malformed promyelocytes, rare erythroblast, roughly normal mature erythrocytes; high lymphocyte proliferation There were a few abnormal lymphocytes, a slight increase in plasma cells, a slight increase in tissue cells, a megakaryocyte in the whole film, a rare platelet, and a few giant platelets; a few small grains were in the form of network empty structure, and some small grains were full, mainly non hematopoietic cells. Serum ferritin was more than 2000.0 μ g / L. Fibrinogen 8.73g/l, calcitonin and interleukin-6 slightly increased; immune SSA antibody weak positive, Ro-52 (+ +), urine protein (+), rheumatology and Immunology Department considered the correlation with the primary disease. The DNA of EBV was qualitative positive and quantitative 1.51e + 03copies/ml. Blood biochemical examination: total bilirubin 75.2umol/l, direct bilirubin 58.1umol/l, indirect bilirubin 17.1umol/l, transaminase normal, LDH 319u / L. Treatment: continue to give "carbon cyanogenase alkene, acyclovir, component blood, cyclosporine, androgen" and other treatment, the body temperature dropped to normal after 3 days, the blood picture and biochemical indicators improved, and the blood routine was basically normal after 12 days in hospital. The patient continued to take cyclosporine and testosterone undecanoate after discharge. One month later, the patient recovered basically by telephone. The recent blood routine was WBC 8.1 × 10^9 / L, PLT 111.0 × 10^9 / L, HGB 121.0 × 10^{12} / L.

ANALYSIS

Clinical features of the case: fever, pancytopenia, myelodysplasia, hemophagocytosis, EB virus infection, and recovery within one month.

Diagnose the problem:

(1) Hemophagocytic syndrome (HLH), aplastic anemia (AA) and their relationship? The definition of HLH is a kind of excessive inflammatory response syndrome caused by primary or secondary immune abnormality. Its mechanism is a series of inflammatory reactions caused by abnormal activation, increment and secretion of a large number of inflammatory cytokines by lymphocyte, monocyte and macrophage systems. Its clinical manifestations are persistent fever, hepatosplenomegaly, pancytopenia and bone marrow, liver and spleen Hemophagocytosis was found in lymph nodes. According to the "consensus of Chinese experts on the diagnosis and treatment of hemophagocytic syndrome" [2], the diagnosis is divided into primary and secondary causes, which are caused by infection,

tumor, rheumatic immune disease, and secondary causes in adults. In the diagnostic criteria, the first molecular diagnosis is not the first choice for unconventional diagnosis due to the limitation of conditions. In the second 8 items, except NK cell activity and scd25 (soluble interleukin-2 receptor, sIL-2R) cannot be routinely detected, the other 6 items are relatively easy to obtain. The patient had the basis of virus infection. Except NK cell activity and sIL-2R were not detected, 4 of the remaining 6 were consistent with each other. It is reasonable to consider HLH, especially the reexamination of bone marrow one week later suggested that there was significant hemophagocytosis. However, there is a consensus on the diagnosis of HLH that hemophagocytosis is not necessarily HLH [3], the sensitivity and specificity of increased ferritin in the diagnosis of adults are lower than that of children [4], the decrease of blood cells in HLH should exclude the factors of decreased hematopoietic function of bone marrow, that is to say, the bone marrow of patients with aplastic anemia can have hemophagocytosis, clinical does not think that aplastic anemia combined with HLH, only accompanied by hemophagocytosis. Yin Xiaohua and others reported a case of chronic aplastic anemia with HLH 15 years ago [5]. At that time, the diagnosis system was not so perfect. With the development of medicine, the diagnosis was more rigorous.

(2) Acute severe aplastic anemia and acute hemopoietic stagnation: the former is acute severe marrow failure, clinical manifestations are extremely low whole blood cells, high mortality, and its pathogenesis is immune-mediated hematopoietic damage; the latter is also called acute aplastic crisis, which is a serious transient hemopoietic failure caused by a variety of reasons, manifested as red line or whole blood cells It can be seen in the middle and later stages. Unlike the aplastic anemia, it can recover naturally in a short period of time. Before its onset, it can have upper respiratory tract infection. The infection of parvovirus B19 and EB is closely related to it [6]. It is difficult to distinguish the two in clinical practice. The transient course of the latter may be the differentiation point. The clinical course of this case is more consistent with the acute hemopoietic stagnation. The author once diagnosed and treated a six-month pregnant female patient with pancytopenia. The bone marrow indicated hypo proliferation, absence of hematopoietic cells, relative increase of non-hematopoietic cells, small empty grains, and bad and dead change of bone marrow scaffold. The pregnancy was terminated, and male hormone was taken at the same time. The bone marrow picture was reexamined one week later. The bone marrow hyperplasia was obviously active, and the hematopoietic tissue hyperplasia was good. The blood picture was recovered after one month often; this is more in line with the process of acute aplastic crisis.

(3) Both acute aplastic crisis and HLH (or hemophagocytosis) have common pathogenic factors - EB virus infection. Antiviral treatment should be actively carried out. Because they are all critical cases in emergency, support treatment is particularly important.

Treatment decision

The treatment decision-making HLH is a high inflammatory storm, with a high mortality rate. At present, "94 scheme" or "2004 scheme" is used in the treatment. It is questionable whether etoposide should be used or reduced when myelodysplasia is low. After the clinical diagnosis of aplastic anemia in our case, etoposide was stopped immediately and cyclosporine, an immunosuppressant, was applied. The effect on bone marrow was relatively small, both sides considered. Perhaps, this patient is the acute hemopoietic function stagnation, supporting the symptomatic treatment, the key problem is how to treat hemophagocytosis in the case of myelodysplasia? The main difference between them is to choose the antithymocyte globulin for aplastic anemia or the etoposide for HLH?

DECLARATION OF CONFLICTING INTERESTS

The author(s) declared no potential conflicts of interest with respect to the research, author- ship, and/or publication of this article.

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