Secondary Hemophagocytic Lymphohistiocytosis in an Adolescent Case: Is the Brucella or Coronavirus the Primary Cause?

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Abstract

Hemophagocytic lymphohistiocytosis is clinically characterized by fever, hepatosplenomegaly, pancytopenia, and coagulopathy and is histologically characterized by excessive proliferation and activation of histiocytes or macrophages. It occurs with systemic infections, immunodeficiency, and underlying malignancies. Brucellosis is one of the rare causes of hemophagocytosis. Here, we report the case of a 15-year-old male with pancytopenia due to hemophagocytosis during the course of brucellosis that responded favorably to therapy. Although rare, concomitant coronavirus infection and hemophagocytosis should be considered as a possible cause of pancytopenia in patients with brucellosis, particularly in regions where brucellosis is frequently encountered. *(J Pediatr Inf 2016; 10: 28-32)*

Keywords: Adolescent, brucellosis, coronavirus, pancytopenia, hemophagocytosis

Received: 13.03.2014

Accepted: 04.07.2014

Available Online Date: 19.06.2015

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This study was presented at the 8th Aegean Pediatrics and 4th Paediatric Nursing Congress, 10-13 Haziran 2014.

DOI:10.5152/ced.2015.1731

Introduction

Brucellosis, an endemic diseases in the countries around the Mediterranean, is the most frequent disease known to be transmitted from animals to humans. It is an infectious disease that can be transmitted by direct contact to humans from infected animals, freshly consumed milk and dairy products and/or inhalation of infected droplets (1).

Especially Brucella abortus and Brucella mellitensis-associated cases are frequently encountered in our country. In cases with brucellosis that have a wide clinical spectrum in patients, fairly non-specific hematologic abnormalities are encountered (2). During brucella infections, a decline is observed in peripheral blood elements as a result of bone marrow and spleen involvement; while mild anemia and leukopenia are among the common findings are, pancytopenia is rarely seen (3-5).

It is a clinical condition which can develop due to usually viral, bacterial and protozoal diseases is characterized by secondary hemophagocytic lymphohistiocytosis (HLH) pancytopenia. Brucella type bacteria can also lead to this picture. In this article, a case admitted with nonspecific symptoms such as a runny nose, diarrhea, vomiting and fever, and with secondary hemophagocytosis and NL63 detected in the concurrent nasal swab coronavirus is presented.

Case Report

A 15- year old male patient was admitted with the complaints of fever, diarrhea and vomiting. In patients history, it was stated that complaints of a runny nose, diarrhea, vomiting and fever started 3 weeks ago and diarrhea and vomiting continued for a week; the patient was prescribed cefdinir and paracetamol by a doctor visited during this period; as the fever continued, he was referred to our hospital. It was revealed in the background story of the patient that he was followed up with the diagnosis of subaortic

stenosis and 1st degree aortic insufficiency operated by the department of pediatric cardiology. In his family history, it was stated that during the same period, his mother had influenza and consumed cottage cheese from a dairy farm.

In his physical examination, his body weight and height were within 50-70 percentile, body temperature was 39,5°C; he had a good general appearance, and had full consciousness, an existing state of anxiety, oropharynx hyperemic, nasal serous discharge, and had 1,5 x 1 cm in diameter mobile lymphadenomegaly on the left-top the neck. The heart rate was 78/min, and there was 2/6 pansystolic murmur in the mezocardiac focus; liver was non-palpable, the spleen was 3 cm palpable; and the traube was dull.

In the laboratory tests, hemoglobin was 8,9 g/dL, MCV: 69 fL, leukocyte: 3450/mm^3 (Absolute neutrophil count: 760/mm^3), platelet: 78.000/mm^3, Sedimentation: 37 mm/hour, CRP: 46 mg/dL, AST: 122 U/L ALT: 83 U/L, LDH: 572 U/L (120-330 IU/L), Ferritin: 865 ng/ml (7-140 ng/mL), and Trigliserit: 247 mg/dL (36-138 mg/dL). In the urine test done during the febrile period, proteinuria and microscopic hematuria were present. Urea-creatinine was within normal limits. In the peripheral smear; in erythrocytes, hypochromia, anisocytosis, microcytosis and pencil cells were present. In every field, 6-7 pieces thrombosis were present. Leukocyte distribution on the other hand was as in the following; lymphocyte 66%, reactive lymphocyte 15%, monocyte 5%, PNL 12%, monocyte 5%, eosinophil 1%, stab 1%. Due to the fever level of 38.5^{0}C that lasted more than 7 days together with splenomegaly and pancytopenia in our patient, bone marrow aspiration was performed in order to exclude malignancy and illuminate the etiology. In the bone marrow examination, while atypical cells blasted in character, storage cell and no amastigote in terms of leishmania were detected, hemophagocytosis was found (Figure 1). The patient who had high fever that lasted for more than 7 days, splenomegaly, pancytopenia, triglyceride, LHD and high ferritin as well as hemophagocytosis in the bone marrow, was diagnosed with hemophagocytic lymphohistiocytosis. In the tests conducted for the etiology of HLH, it was found that Brucella agglutination was 1/640 positive; there was B.abortus grew in the bone marrow and blood cultures. The nasopharyngeal swabs polymerase chain reaction study obtained in terms of the etiology of HLH (PCR) and due to the existing viral upper respiratory tract infection symptoms in the patient, Human coronavirus NL63 (HCoV-NL63) was detected. In the bone marrow culture, due to the B.abortus growth, the patient was diagnosed with brucellosis secondary hemophagocytic lymphohistiocytosis and rifampicin and gentamycin treatment was started. Gentamycin parenteral was used for seven day and doxycycline and rifampicin were used orally for six days. In the evaluation done in the first month of the treatment, pancytopenia pictured improved thoroughly, and brucella serology receded from 1/640 to 1/40.

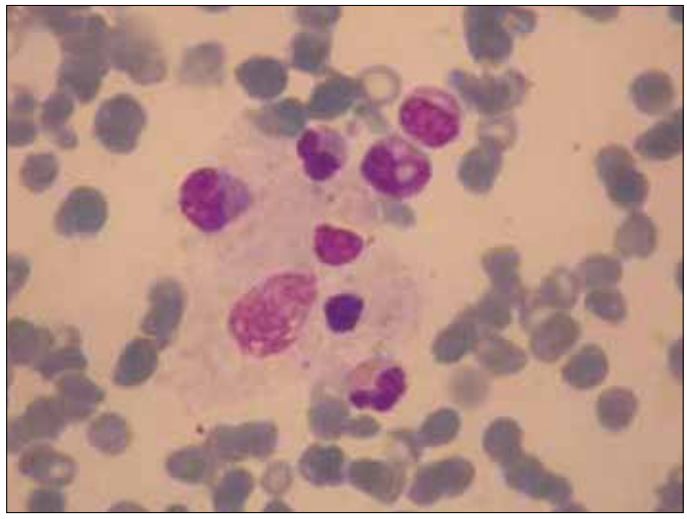

Figure 1. A bone marrow smear showing hemophagocytosis by a histiocyte (Giemsa coloration, 1000×)

Since there is no other case of the combination of brucellosis together with coronavirus in the literature, and our case admitted with the secondary and the improvement in the hemophagocytic lymphohistiocytosis, a rare clinical form of brucellosis and hemophagocytosis picture due to brucellosis treatment, this particular patient in our case has been presented.

Discussion

In brucellosis that affects all systems, the hematological changes are common. Bone marrow and spleen are often affected. While mild anemia and leukopenia can be seen frequently, pancytopenia is a rare complication of brucellosis. In different series, its frequency was reported to be in such different rates of 3-21% (6, 7). Brucella organisms are facultative intracellular pathogens and they grow within the host of phagocytic cells. In the etiopathogenesis of pancytopenia, hypersplenism disseminated intravascular coagulation, hemophagocytosis, bone marrow suppression, destructions in the blood platelets are held responsible (7).

Hemophagocytic lymphohistiocytosis (HLH) was first defined by Scott in 1939 (8). HLH cytotoxic is characterized by the clinical table of deterioration in T-lymphocytes and in the function of natural killer cells and macrophages and activation of T-lymphocytes, excessive production of pro-inflammatory cytokines and fever due to hemophagocytosis, hepatosplenomegaly, bicytopenia, hypertriglyceridaemia, hyperfibrinemia and high level of liver function tests and lactate dehydrogenase (LDH) (Table 1) (9). HLH is divided into two different groups of primary (genetic) and secondary (acquired). It can occur in all age

Table 1. Hemophagocytic Lymphohistiocytosis (HLH) diagnosis criteria (13)

1. Familial disease / known genetic defect
2. Clinic and laboratory diagnosis criteria (presence of five criteria out of eight).*
Fever (>7 days, >38.50C)
Splenomegaly
Cytopenia (at least two-cell series)
o Hemoglobin <9 g/dL (12 g/dL under 4 weeks)
o Blood platelets <100x109/L
o Neutrophils <1x109/L
Hypertriglyceridaemia and/or hypofibrinogenemia
o Fasting triglyceride >3 mmol/L
o Fibrinogen <1.5 g/L
Ferritin >500 µg/L
sCD25 >2400 U/ml
Reduction of NK cell activity or non-presence
Bone marrow, cerebrospinal fluid or hemophagocytosis in the lymph nodes
*Presence of cerebral symptoms, transaminase, findings supportive of the increase in bilirubin and lactate dehydrogenase.

groups. In addition to viral, bacterial, protozoal, fungal, and parasitic infections, malignancy, radical stress, metabolic diseases, immunodeficiency and HLH related to collagen tissue patient may develop (9).

The incidence of acquired HLH in hospitalized children in Turkey was found to be 0.052% (10). In a multicenter study in our country investigating infectious agents that cause acquired HLH, it was found that cytomegalovirus (CMV) and Epstein-barr virus (EBV) were at the top of the list (11). What caused HLH in the patient in our study who was admitted with the complaints of nonspecific symptoms such as vomiting, diarrhea and runny nose was brucellosis and it was interesting to find PCR and HCoV-NL63 on a nasal swab simultaneously. In brucellosis, gastrointestinal complaints such as nausea, vomiting, abdominal pain, diarrhea or constipation are common nearly in 70% of the cases (12). Pathological lesion together with the inflammation of the peyer's plaques is the hyperemia of the intestinal mucosa. Brucellosis-related gastrointestinal bleeding can also be seen. When there is kidney involvement, urine density may decrease. Proteinuria becomes evident; erythrocytes, leukocytes, and cylinders can be seen in the urine sediment (13). Similarly, the initial complaints in our case were vomiting and diarrhea, and in the urine examination during the febrile period, microscopic hematuria and proteinuria were detected.

In a thesis in Adana that examined 65 brucellosis cases, it was reported that the time between the onset of the complaints of the patients and when they were diagnosed with brucellosis was three and 150 days (average diagnosis time 21 days). While the most common physical examination finding in this study was hepatosplenomegaly in 20% of the patients, it was only hepatomegaly in 13% of the patients, splenomegaly in 9%, and lymphadenopathy in 12% (14).

Similarly in our case, this period was 21 days; although splenomegaly and lymphadenopathy were detected in the examination, the patient had no hepatomegaly. Similarly in the same study, transaminase value was found to be high in 37% of the cases (14). In our case, it was found that ALT and AST values were three times higher than the reference values. In the present study, although 12% pancytopenia was detected, it was reported that hemophagocytosis was seen in the bone marrow of only one patient.

In a study in Şanlıurfa where 82 brucellosis cases were investigated retrospectively, although 19,5% of the patients had anemia, 10,9% leukopenia, and 2.4% thrombocytopenia, no pancytopenia was reported (15). In a study done by Al-Essia et al. (16), they found that in only 16 of the 276 brucellosis cases had pancytopenia; hemophagocytosis was seen in the bone marrow of only one patient.

In a comprehensive series of research involving 233 cases diagnosed with brucellosis, it was found that 128 patients (55%) had anemia, 59 (26%) thrombocytopenia, and 49 (21%) leukopenia; only 18 cases (8%) was observed to develop pancytopenia (17).

In a 43-cases series done by Palanduz et al. (18), it was reported that one patient was found to have pancytopenia.

Since brucella is facultative intracellular pathogen, bone marrow cultures generate higher rate of positive results in comparison to the blood cultures. Gotuzzo et al. (19) found that 70% isolation rate in blood culture was 92% in the bone marrow culture. The isolation rate dropped in those case who had already taken antibiotics. It was found that isolations in those who had taken antibiotics was 50% in the blood culture and 90% in bone marrow culture. Furthermore, bacterial growth was quicker in the bone marrow culture in comparison to blood culture (19).

The only positive value of the wright agglutination test used in the diagnosis of brucellosis is not accepted as a diagnostic procedure in the endemic areas. However, not taking the blood cultures in every each health center and tube agglutination test producing results in a shorter period are the advantages of this test. The U.S. Centers for Disease Control and Prevention and the World Health Organization emphasize the 1:160 and above titters of the diagnostic value of this test (20, 21).

In a multicenter study conducted in our country related to the epidemiology of brucellosis, nearly 70,000 serum samples were examined and it was reported that 1.8% rate of seropositivity was found (22).

An interesting feature of this case presented is; the detection of PZR together with coronavirus NL63 (HCoV-NL63) in the nasal swab examined due to the complaint of nasal discharge while the etiology that caused the HKLH table was being investigated and being the first case in the relevant literature. Although it has created confusion in terms of the etiology of pancytopenia, together with the table of pancytopenia, the brucella that grew in the blood and bone marrow cultures enlightened the etiology. Furthermore, following the triple antimicrobial therapy given for the treatment of brucellosis, improvement in the clinic, pancytopenia and brucella agglutination tests the patient, and non-requirement of steroids and other chemotherapeutics caused us to conclude that our patient was secondary HLH. Similarly, in previous studies, it was shown that HCoV-NL63 caused not severe respiratory failure such as SARS coronavirus (SARS-CoV) which was from the same family as, and severe pancytopenia, but only mild to moderate respiratory tract infection. HCoV-NL63 was defined, for the first time in 2004, in a seven-month bronchiolitis case (23). In a subsequent study, it was found that it was effective in the 1.7-9.3% of the patients followed up due to upper and lower inspiratory track infections (24). In a study done in Korea, 64% of the HCoV-NL63-detected cases had croup and 21.4% bronchiolitis (25).

Conclusion

Brucellosis that can emerge with different clinical findings should be kept in mind especially in endemic areas. Thanks to the measures such as finding the sick animals and treating them and increasing the number of animal controls, transmission to humans should be prevented. In our country, in every patient that is taken to the health institutions with gastrointestinal symptoms such as prolonged fever, weakness, vomiting, diarrhea, constipation, and loss of appetite, the history of animal contact or the use of non-pasteurized milk and milk products should be questioned; even if there is no positive history, it is imperative that brucellosis be distinguished. In ambiguous cases with haemophagocytic lymphohistiocytosis table identified, bone marrow culture should be performed and brucellosis should come to mind. Furthermore, brucellosis may show association with the microorganisms that cause viral upper respiratory tract infection.

Informed Consent: Verbal and written informed consent was obtained from patient.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - Y.B.; Design - Y.B.; Supervision - Y.Z.A.; Collection and/or Processing - Ö.C., Y.B., F.Y.; Analysis and/or Interpretation - Y.B., Ö.C., M.A.; Literature Review - Y.B.; Writing - Y.B.; Critical Review - M.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

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