Aplastic anemia presenting as hemophagocytic lymphohistiocytosis

Hemofagositik lenfohistositoz olarak başlayan aplastik anemi

Tiraje Celkan
Department of Pediatric Hematology-Oncology, İstanbul University, Cerrahpaşa Faculty of Medicine, İstanbul, Turkey

Abstract

Two unusual cases of hemophagocytic lymphohistiocytosis (HLH) complicating aplastic anemia (AA) are described. Each patient had a history of preexisting acute hepatitis of unknown cause at the time of HLH diagnosis and infection-associated secondary HLH. They developed high fever and pancytopenia. Hemophagocytes were seen in the bone marrow. With steroid (in combination with etoposide and CyA in 1 patient), high fever disappeared and the patients' liver function gradually recovered. As severe pancytopenia persisted, bone marrow became acellular and AA was diagnosed. Since HLH is known to be able to cause an aplastic bone marrow if untreated for a prolonged time, it is therefore in line that hepatitis-associated AA may also be associated with HLH.

Aplastic anemia-associated HLH has been reported rarely, and problems in the diagnostic procedure are discussed.
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Key words: Hemophagocytosis, aplastic anemia, hepatitis

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Özet

Bu makalede hemofagositik sendrom (HLH) tanısı alıp daha sonra aplastik anemi (AA) gelişen 2 hasta sunulmuştur. Her 2 hastada da HLH tanısından önce etyolojisi net olarak konulmamış akut hepatit öyküsü vardı ve bu enfeksiyon nedeni ile HLH'leri enfeksiyon ilişkili HLH olarak değerlendirilmişti. İki olguda da ateş ve pansitopeni vardı. Hemofagositoz iki olguda da kemik iliği aspirasyon materyalinde gösterilmişti. Bir olguda steroid diğerinde steroide ek olarak etoposid ve siklosporin (CyA) ile yüksek ateş ve karaciğer fonksiyonlarında düzelme saptanmaya başlanmıştı. Tedaviye rağmen ağır sitopeninin devam etmesi üzerine kemik iliğinin tekrar değerlendirilmesi sonucunda hastalara aplastik anemi tanısı konuldu. Hemofagositik sendrom uzun süreli tedavi edilmediğinde kemik iliğinde aplaziye neden olabilir, bu nedenle hepatite bağlı gelişen aplastik anemilerin gelişim sürecinde HLH' da olabilir. *(Turk J Hematol 2010; 27: 38-42)*

Anahtar kelimeler: Hemofagositoz, aplastik anemi, hepatit

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Address for Correspondence: Assoc. Prof. Tiraje Celkan, Konaklar mah. Şebboy sok. Armakent sitesi B2/8 4. Levent / 80620 İstanbul, Türkiye
Phone: +90 212 283 69 22 Office: +90 212 414 30 00 / 21956 E-mail: tirajecelkan@yahoo.com

Introduction

Differential diagnosis of hemophagocytic lymphohistiocytosis (HLH) and aplastic anemia (AA) is very confusing for a clinician who must initiate life-saving therapy with immunosuppressive/immunomodulatory agents in time [1-3]. Brown et al. [4] reported that post-hepatitis AA typically occurs in young, previously healthy males with self-limited but severe liver inflammation with very high serum aminotransferase and bilirubin levels; profound pancytopenia follows several weeks later.

We present herein our experience with two adolescent boys ages 11 and 12 years who both presented with hyperbilirubinemia and secondary HLH resulting in AA. Both diseases may have some similar immune-mediated conditions involving the activation of T lymphocytes. Moreover, immunosuppressive therapy with antithymocyte globulin (ATG) and cyclosporine (CyA) is very effective for AA, while intensive immunosuppressive therapy with ATG and CyA might be a useful strategy for steroid-resistant HLH [5].

Aplastic anemia is an immune-mediated disease that is associated with increased apoptosis of bone marrow stem cells. The increase in apoptosis is due to various cytokines that inhibit hematopoiesis, produced by activated T-cells. As is well known, HLH is characterized by a systemic activation of macrophages/histiocytes, which are induced to undergo phagocytosis of hematopoietic elements. This hyperinflammatory condition is associated with genetic inheritance, infection, malignancy, and immune deficiencies. The cardinal symptoms are prolonged fever, cytopenias, hepatosplenomegaly, and hemophagocytosis by activated, morphologically benign macrophages. Biochemical markers include elevated ferritin and triglycerides and low fibrinogen. Impaired function of natural killer (NK) and cytotoxic T-cells is characteristic. Two forms of HLH, primary (genetic) and secondary (acquired), have been reported. Secondary HLH has been reported in association with a variety of conditions [6]. Children with HLH have a higher probability of malignancy, suggesting a possible predisposing role. However, there are only rare reports of an association between AA and HLH.

Generally, the diagnosis of HLH is difficult unless there is suspicion. HLH initially may masquerade as a normal infection since all symptoms may be common.

Case Reports

Written informed consent was obtained from all patients.

Case 1: A 12-year-old boy was followed with hepatitis in a local health center for 40 days. Serologic tests for Epstein-Barr virus (EBV), cytomegalovirus (CMV), herpes simplex virus (HSV)-I, HSV-II, hepatitis B virus (HBV), hepatitis C virus (HCV), hepatitis A virus (HAV), and parvovirus B-19 were either negative or consistent with prior exposure. As liver enzymes remained elevated (AST 1975 U/L, ALT 2950 U/L) and total bilirubin increased to 4.73 mg/dl, with international normalized ratio (INR) of 4.67, he was referred to our hospital. Persistent pancytopenia was noticed, and he was consulted to the hematology ward after 25 days. The patient met the diagnostic criteria of HLH described by the Histiocyte Society [2]. Bone marrow aspiration was performed and showed an increased number of histiocytes with hemophagocytosis. As he was suspected to have infection-associated secondary HLH, steroid therapy was started (dexamethasone 10 mg/m^2 in the beginning and tapered after 2 weeks, planned for a total period of 8 weeks). After steroid, the long-lasting fever disappeared in 2 days and there was an unexpected rapid resolution of hepatosplenomegaly (each 2 cm below the costal margin). Although the clinical manifestations, which were attributed to hypercytokinemia, were controlled with steroid, the pancytopenia persisted even after etoposide was added to the HLH regimen after a 4-week period. Bone marrow biopsy performed after 6 weeks of HLH treatment due to no response of cytopenia revealed AA. He was lost 25 days after ATG treatment due to aspergillus in the lung and pseudomonas bacteremia.

Case 2: An 11-year-old boy was followed with persistent hepatitis in a local health center for 2 months until gastrointestinal bleeding was detected. Viral documentation was normal. Liver enzymes remained elevated (AST 2930 U/L, ALT 3460 U/L), INR increased to 6.3, and he was referred to our hospital. Pancytopenia and fever were noticed and he was consulted to the hematology ward after 15 days. The liver biopsy performed before hematology consultation revealed infection. The patient was diagnosed as secondary HLH after an increased number of histiocytes with hemophagocytosis were noticed in the bone marrow aspiration, supported by decreased fibrinogen and increased ferritin, which until the HLH diagnosis were thought to be due to numerous transfusions. He was given dexamethasone at a dose of 10 mg/m^2. Fever and splenomegaly disappeared in the first week, but pancytopenia resulting in near-fatal infection persisted. Granulocyte colony-stimulating factor (G-CSF) was added to steroid treatment due to no hematological relief, and bone marrow biopsy was done. His parents refused any treatment for AA and the patient died due to uncontrolled bleeding and sepsis.

Discussion

Both of the presented patients had no family history suggestive of familial HLH. The patients died before any mutational analysis or NK cell function studies could be performed. The diagnosis of secondary HLH, therefore, is based on fulfillment of a minimum of five clinical criteria [6]. Gupta et al. [7] mentioned in their commentary that despite the availability of genetic and immunological tests in the diagnosis of HLH, there is a lack of a confirmatory diagnostic test for acute situations. There are also no clear-cut definitions for HLH bone marrow infiltration. Three smears with at least 2 histiocytes demonstrating hemophagocytosis on each are suggested for HLH diagnosis, which were detected in both of our patients [7]. No fatty infiltration was detected during HLH diagnosis. Bone marrow examination showed normal maturation of the three series

Table 1. Findings of patients (ND: not done)

	Case 1	Case 2
Clinical findings		
Fever	+	+
Hepatomegaly	2 cm	1.5 cm
Splenomegaly	2 cm	2 cm
Infection	+	+
Jaundice	+	+
Bleeding	-	+
Laboratory findings		
Hemoglobin gr/dl		
At the beginning of complainment	9.6	10.8
At the admission our hospital	5.6	6.8
At the diagnosis of HLH	3.6	8.7(With transfusions)
At the diagnosis of AA	3.7	7.5
WBC mm^3		
At the beginning of complainment	12.600	17.000
At the admission our hospital	5400	6700
At the diagnosis of HLH	3000	1400
At the diagnosis of AA	2200	1100
Platelet mm^3		
At the beginning of complainment	178.000	186.000
At the admission our hospital	98.000	79.000
At the diagnosis of HLH	6000	8000
At the diagnosis of AA	9000	4000
Reticulocyte	<0.1	0
AST ıu/L		
At the beginning of complainment	1108	2089
At the admission our hospital	1975	1790
At the diagnosis of HLH	46	47
At the diagnosis of AA	44	39
ALT ıu/L		
At the beginning of complainment	1963	2298
At the admission our hospital	2950	1810
At the diagnosis of HLH	27	45
At the diagnosis of AA	660	43
bilirubin		
At the beginning of complainment	4.8	Not known
At the admission our hospital	1.35	1.77
Triglyceride mg/dL		
At the diagnosis of HLH	456	780
At the diagnosis of AA	115	ND
Fibrinogen g/dL		
At the admission our hospital	ND	180
At the diagnosis of HLH	80	56
At the diagnosis of AA	170	ND
Bone marrow aspiration		
At the diagnosis of HLH	hemophagocytic features	hemophagocytic features
At the diagnosis of AA	Bone marrow failure, hypoplasia	Hypoplasia
Bone marow biopsy		
At the diagnosis of AA	devoid of hematopoietic elements, fat and reticulum cells	Diminished hematopoietic elements, increased showing largely fatty tissue and reticulum cells

without dysplastic features or any blast. The most prominent feature was an increase in hemophagocytosing histiocytes. Based on these findings, the patients were diagnosed as HLH and not AA. Then, after 15-21 days of HLH treatment, the bone marrow became severely hypoplastic. However, the hemophagocytic features that were apparent before the HLH regimen had disappeared in both patients.

Both patients were diagnosed as having severe bone marrow failure after HLH that was similar to severe AA. Severe pancytopenia with fatty infiltration of the bone marrow is characteristic of AA, but high fever or liver dysfunction is not common if there is no coexisting infection.

Hemophagocytic lymphohistiocytosis and AA represent distinct disease entities, but they have some pathologically similar aspects with activation of T lymphocytes. As mentioned in the literature, HLH can be diagnosed before or after AA [8-10]. In our patients, post-hepatitis AA, or HLH associated with an undiagnosed viral infection in a patient with AA, or a coexistence of HLH and AA could be considered in the differential diagnosis. However, no fatty change of the marrow was found in the beginning, and its cellularity was not severely depressed at the time of admission, while hemophagocytic histiocytes were prominent.

These findings were characteristic of HLH rather than AA. The diagnosis of AA is often difficult because of the presence of local hemapoietically active spots that can lead to an erroneous assessment before fatty bone marrow. Thus, marrow examinations need to be repeated if pancytopenia persists. The histiocyte count is sometimes increased in AA just like plasma cells, but this is a relative increase and is not associated with hemophagocytosis. Ost et al. [11] reported that the cellularity of the marrow was decreased in some patients and this tissue was severely hypoplastic, even in some children who had not been treated with cytostatic drugs. They also reported that the histological pattern in HLH resembles that of chronic persistent hepatitis. In other words, there is a potential link between AA, HLH and hepatitis-associated AA [11].

Hyperbilirubinemia usually coexists with pancytopenia in HLH, while bone marrow failure secondary to acute hepatitis generally occurs after the hepatitis has resolved if the diagnosis is AA. Immunosuppressive therapy with ATG and CyA, which is a common treatment strategy for severe AA, is sometimes used successfully for HLH, especially for steroid-refractory HLH [5,12].

Impaired function of NK cells and cytotoxic T-cells is characteristic for both genetic and acquired forms of HLH. Frequent triggers are infectious agents, mostly viruses of the herpes group [13,14]. HLH has been identified to be related with genes encoding perforin (PRF1/FHL2), Munc 13-4 (UNC13D/FHL3), and syntaxin-11 (STX11/FHL4). In order to show the relation of AA and HLH, Solomou et al. [15] studied perforin levels in patients with AA. They found that in AA disease with hematopoietic stem cells, which were destructed by activated T-cells and Th1 cytokines, perforin protein levels were very low or absent, and perforin granules were completely diminished [15]. NK cells are the predominant perforin-containing cell type. As a result, NK cell cytotoxicity in these patients was significantly decreased [13]. In one of the HLH subgroups with normal perforin levels, syntaxin-deficient patients, it was shown very recently that their NK cells failed to degranulate when they encountered susceptible target cells [16,17].

Patients with HLH, however, cannot control the hyperinflammatory response which, if untreated, is fatal. Awareness of the clinical symptoms and of the diagnostic criteria of HLH is important to start life-saving therapy with immunosuppressive/immunomodulatory agents in time. Therefore, we suggest that patients with hepatitis who develop pancytopenia and high liver enzymes that remain elevated for longer than expected should be examined with bone marrow aspiration and biopsy for demonstration of hemophagocytosis or for bone marrow failure resulting in AA.

Conflict of interest

No author of this paper has a conflict of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included in this manuscript.

References

1. Kumakura S, Ishikura H, Kobayashi S. Hemophagocytic syndrome, a possible association with aplastic anemia? Intern Med 2003;42:1262-4.
2. Matsunawa M, Kawakami K, Hisatake J, Suzuki J, Nakamaki T, Hino K, Tomoyasu S. Hepatitis-associated aplastic anemia preceded by a hemophagocytic syndrome-like state. Rinsho Ketsueki 2003;44:1010-4.
3. Omagari K, Ashida R, Oh-I H, Minamino Y, Sasaki O, Ozono Y. Successful treatment with cyclosporine in a case of hemophagocytic syndrome manifesting as severe liver dysfunction. Am J Med Sci 1997;314:403-7.
4. Brown KE, Tisdale J, Barrett AJ, Dunbar CE, Young NS. Hepatitis-associated aplastic anemia. N Engl J Med 1997;336:1059-64.
5. Kaito K, Otsubo H, Takei Y, Usui N, Kobayashi M. Immunosuppressive therapy with antithymocyte globulin and cyclosporine for prolonged marrow failure after hemophagocytic syndrome. Ann Hematol 2003;82:699-701.
6. Henter JI, Horne A, Aricó M, Egeler RM, Filipovich AH, Imashuku S, Ladisch S, McClain K, Webb D, Winiarski J, Janka G. HLH-2004: diagnostic and therapeutic guidelines for hemophagocytic lymphohistiocytosis. Pediatr Blood Cancer 2007;48:124-31.
7. Gupta A, Weitzman S, Abdelhaleem M. Commentary: the role of hemophagocytosis in bone marrow aspirates in the diagnosis of HLH. Pediatr Blood Cancer 2008;50:192-4.
8. de la Serna FJ, Lopez JI, Garcia-Marcilla A, Ortiz-Conde MC, Mestre MT. Hemophagocytic syndrome causing complete bone marrow failure. Report of an extreme case of a reactive histiocytic disorder. Acta Haematol 1989;82:197-200.
9. Stephan JL, Galambrun C, Pozzetto B, Grattard F, Bordigoni P. Aplastic anemia after Mycoplasma pneumoniae infection: a report of two cases. J Pediatr Hematol Oncol 1999;21:299-302.

10. Yashima A, Narigasawa Y, Ishida Y, Uchiyama T, Oyake T, Enomoto S, Kaneko J, Ono Y, Sugawara T, Numaoka H, Shimosegawa K, Murai K, Itoh S, Ito T, Kuriya S. Hemophagocytic syndrome due to miliary tuberculosis in the course of aplastic anemia. Rinsho Ketsueki 1998;39:392-7.
11. Ost A, Nilsson-Ardnor S, Henter JI. Autopsy findings in 27 children with haemophagocytic lymphohistiocytosis. Histopathology 1998;32:310-6.
12. Erduran E, Gedik Y, Sen Y, Yildiran A. Successful treatment of reactive hemophagocytic syndrome with cyclosporin A and intravenous immunoglobulin. Turk J Pediatr 2000;42:168-70.
13. Janka GE. Hemophagocytic syndromes. Blood Rev 2007; 21:245-53.
14. Gurgey A, Secmeer G, Tavil B, Ceyhan M, Kuskonmaz B, Cengiz B, Ozen H, Kara A, Cetin M, Gumruk F. Secondary hemophagocytic lymphohistiocytosis in Turkish children. Pediatr Infect Dis J 2005;24:1116-7.
15. Solomou EE, Gibellini F, Stewart B, Malide D, Berg M, Visconte V, Green S, Childs R, Chanock SJ, Young NS. Perforin gene mutations in patients with acquired aplastic anemia. Blood 2007;109:5234-7.
16. Bryceson YT, Rudd E, Zheng C, Edner J, Ma D, Wood SM, Bechensteen AG, Boelens JJ, Celkan T, Farah RA, Hultenby K, Winiarski J, Roche PA, Nordenskjöld M, Henter JI, Long EO, Ljunggren HG. Defective cytotoxic lymphocyte degranulation in syntaxin-11 deficient familial hemophagocytic lymphohistiocytosis 4 (FHL4) patients. Blood 2007;110:1906-15.
17. Horne A, Ramme KG, Rudd E, Zheng C, Wali Y, al-Lamki Z, Gürgey A, Yalman N, Nordenskjöld M, Henter JI. Characterization of PRF1, STX11 and UNC13D genotype-phenotype correlations in familial hemophagocytic lymphohistiocytosis. Br J Haematol 2008;143:75-83.