World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/esps/
wjge@wjgnet.com
doi:10.4253/wjge.v4.i8.376

World J Gastrointest Endosc 2012 August 16; 4(8): 376-378
ISSN 1948-5190 (online)

CASE REPORT

Drug associated vanishing bile duct syndrome combined with hemophagocytic lymphohistiocytosis

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Received: May 18, 2011 Revised: March 2, 2012
Accepted: August 8, 2012
Published online: August 16, 2012

Abstract

A 28-year-old woman with untreated autoimmune disorder, demonstrated skin rash and fever after taking Amoxicillin-clavulanate and developed progressive jaundice. A bone marrow aspiration indicated an increased number of macrophages with hemophagocytosis and liver biopsy showed pure centrilobular cholestasis with necrosis and some absence of portal bile ducts. Furthermore, a serological test for Epstein-Barr virus was positive. Under treatment by liver dialysis and administration of steroids led to rapidly defervescence and clinical improvement. However, liver enzymes were still markedly elevated with persistent anemia, even after immunosuppressive treatment. The patient is currently waiting for liver transplantation. This is the first description of vanishing bile duct syndrome combined with hemophagocytic lymphohistiocytosis, with underlying causes including infection, drug-induced factors and untreated autoimmune disorder.

Key words: Vanishing bile duct syndrome; Hemophagocytic lymphohistiocytosis; Epstein-Barr virus; Amoxicillin-clavulanate

Peer reviewers: Venerino Poletti, MD, Professor, Department of Diseases of the Thorax, Ospedale GB Morgagni, Forlì, Italy; Michael Swan, MBBS, FRACP, Department of Gastroenterology, Monash Medical Centre, Clayton Road, Clayton, 3168 Victoria, Australia; Wai-Keung Chow, Visiting Staff, Division of Gastroenterology, Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan, China

Li H, Li X, Liao XX, Zhan H, Xiong Y, Hu CL, Wei HY, Jing XL. Drug associated vanishing bile duct syndrome combined with hemophagocytic lymphohistiocytosis. *World J Gastrointest Endosc* 2012; 4(8): 376-378 Available from: URL: http://www.wjgnet.com/1948-5190/full/v4/i8/376.htm DOI: http://dx.doi.org/10.4253/wjge.v4.i8.376

INTRODUCTION

Hemophagocytic lymphohistiocytosis (HLH) is a group of disorders of the mononuclear phagocyte system that are characterized by histiocyte proliferation and hemophagocytosis, resulting in fever, hepatosplenomegaly, lymphadenopathy, pancytopenia, liver dysfunction, and coagulopathy. Vanishing bile duct syndrome (VBDS) is another severe cholestatic disease characterized by progressive loss of small intrahepatic ducts, caused by a variety of diseases and leading to chronic cholestasis, cirrhosis, and premature death from liver failure. Multiple similar etiologies of these two types of disease have been described including neoplastic, infectious, autoimmune, and medication/toxin mediated routes. However, concurrent diagnoses of HLH and VBDS have not previously been reported. Here, we describe a case of HLH combined with VBDS, with underlying causes including infection, drug-induced factor and untreated autoimmune disorder.

CASE REPORT

A 28-year-old Chinese woman was transferred to our

hospital with persistent fever and progressive jaundice. The presentations were preceded by mild upper respiratory tract infection 2 wk earlier. She took a single dose of Amoxicillin-clavulanate for the upper respiratory tract infection, after which a skin rash developed on her back, arms and thighs and jaundice appeared gradually. After admission to hospital, the patient suddenly developed high fever, marked by remittent fever up to 40.5 ℃, as well as progressive obstructive jaundice. Physical examination showed no signs of infection or hematological disease, and was only notable for hepatosplenomegaly. Laboratory studies showed normal white blood cell levels, but progressive decline of hemoglobin and platelets; elevated liver enzymes (alanine aminotransferase 408 U/L, normal 0-37 U/L; aspartate aminotransferase 608 U/L, normal 0-40 U/L); elevated bilirubin (839 μmol/L, normal 0-22.6 μmol/L); elevated ferritin level (> 40 000 μg/L, normal 16-313 ug/L); hypertriglyceridemia (4.58 mmol/L, normal 0.33-1.77 mmol/L); prolonged prothrombin time and activated partial thromboplastin time; normal complement level; ANA > 1:5120; Anti-dsDNA antibody, ENA, anti-SSA antibody, ribonuclear protein antibody and Epstein-Barr virus (EBV)-IgG were positive. Serology for human immunodeficiency virus, hepatitis A, B, and C, tubercle bacillus, and hemococcidium were negative. Computed tomography (CT) scan and magnetic resonance cholangiopancreatography of the upper abdomen revealed a normal extrahepatic biliary tree. Skin biopsies were non-specific and immunohistochemical staining was negative. Liver biopsy showed pure centrilobular cholestasis with necrosis and some absence of portal bile ducts. Repeat bone marrow aspirations revealed hemophagocytosis by macrophages, without any evidence of hematologic malignancy. Positron emission tomography-CT indicated non-cancerous proliferative. The patient had a 2-year history of ANA 1:1280, without any clinic manifestation and a history of immunodeficiency, and denied allergies to previously used medications including antibiotics.

The patient's combination of clinical features (fever, hepatosplenomegaly) and laboratory evaluation (cytopenia in peripheral blood, hypertriglyceridemia, elevated ferritin, and hemophagocytosis in bone marrow without any obvious evidence of malignancy) fulfilled the diagnosis criteria for HLH. A diagnosis of VBDS, combined with drug-associated HLH was made. She was treated with pulsed methylprednisolone (1000 mg/d for 3 d), intravenous immunoglobulins (0.4 g/kg per day for 3 d), ursodeoxycholic acid and immediate blood transfusion. In addition, although methylprednisolone was followed by oral prednisolone 50 mg/d, the fever and symptoms still persisted. Considering the patient's desire for fertility, further immunosuppressive treatment was not administered immediately. Later, the patient was put on the artificial liver support system treatment and given 3 rounds of immunoadsorption therapy, after which she rapidly defervesced and improved clinically. However, bilirubin levels were elevated soon after liver dialysis and the patient therefore agreed to immunosuppressive therapy. In addition to methylprednisolone, the combination therapy of cyclophosphamide (400 mg once weekly) and mycophenolate mofetil (1.5 g/d) were continued for approximately 6 wk, with the addition of closporine A. This was eventually suspended because of repeated gastrointestinal bleeding. Thereafter, 6 mo after presentation, liver enzymes were still markedly elevated with persistent anemia. The patient is currently waiting for liver transplantation.

DISCUSSION

HLH is a life threatening clinic and pathologic disorder, in which impaired or ineffective T cells and natural killer lymphocyte cells are activated. This results in hypercytokinemia leading to uncontrolled activation of benign scavenger macrophages and development of hemophagocytosis in the reticuloendothelial system[1]. In most cases, HLH is not a single disease but is frequently associated with infections, malignancies or rheumatological disorders[2]. HLH has been associated with various infections, of which EBV appears to be the most commonly associated triggering infection[3-5]. Associated rheumatic disorders have included rheumatoid arthritis, systemic lupus erythematosus, Sjogren syndrome, mixed connective tissue disease[4-6]. Drug induced hypersensitivity reaction may include hemophagocytic syndromes, with or without reactivation of EBV[7-9]. Regardless of the etiology, the cardinal clinical signs are prolonged fever, which is unresponsive to antibiotics, and hepatosplenomegaly. A third of the patients' neurological signs, such as irritability, altered consciousness, seizures, and signs of increased intracranial pressure, can be present[10,11]. On histological examination, erythrophagocytosis in HLH is commonly present in lymphoid tissues (liver, spleen, and bone marrow), but rarely evident in skin biopsy specimens. However, phagocytic activity in liver, spleen and marrow biopsy specimens is not universally present. Only one third of initial bone marrow biopsy specimens demonstrate hemophagocytosis[12].

In 1991, the International Histiocyte Society established diagnostic guidelines in an effort to facilitate early diagnosis and management[13]. According to the updated guideline, the diagnosis of HLH is definitive[14,15]. On the other hand, in contrast to the complex origins of HLH, drug-induced cholestasis has its definite inducing agent. Cholestasis can occur with nearly all classes of drugs although antibiotics seem to be responsible more often than other groups. The most often reported culprits are erythromycin and amoxycillin-clavulanate[16]. The most severe form of cholestatic injury is VBDS. This condition is characterized by progressive ductopenia with portal tract fibrosis that leads to secondary liver cirrhosis with a complete absence of small bile ducts. Drug induced ductopenia has been described to continue long after the offending drug is withdrawn[17]. The syndrome is extremely rare, representing 0.5% of small bile duct disease[18].

Results of the international consensus protocol sponsored by the Histiocyte Society for treatment of patients newly diagnosed with HLH (HLH-94) were published in 2005. The goals of the trial were to achieve clinical remission of the life-threatening inflammation and to provide potentially curative therapy through allogenic hematopoe-

itic cell transplantation. HLH can be rapidly fatal in the absence of specific intervention bleeding; infection and progressive cerebral damage are the usual causes of death. Therefore, it is recommended that treatment should be started when there is a high degree of clinical suspicion, even when results of diagnostic studies are still pending[19]. Today, effective initial therapy of HLH consists of combinations of proapoptotic chemotherapy and immunosuppressive drugs targeting the hyperactivated T cells and histiocytes[20]. The recommended treatment consists of a combination of etoposide and dexamethasone (for central nervous system penetration), with or without intrathecal methotrexate, followed by maintenance therapy with the addition of closporine A. Projected survival rates, 5 years from diagnosis, range from 50% to 70%[21].

By comparison, therapy of toxin or drug-induced bile duct injury has remained largely ineffective and is mainly limited to the treatment of symptoms and the consequences of prolonged cholestasis. Corticosteroids have been invariably ineffective. The role of ursodeoxycholic acid remains controversial[22]. Although ursodeoxycholic acid has also been shown to be effective in other cases of VBDS related to drugs, it remains ineffective in cases of bile duct damage related to amoxicillin-clavulanate, as in the current case[23,24]. Liver transplantation is obviously the only alternative in patients who develop secondary biliary cirrhosis and liver failure.

In conclusion, immune-mediated destruction triggered by drugs is the underlying mechanism common to both HLH and VBDS, and antibiotics have been linked to both of these conditions. The initial episode seems to be the result of a direct hypersensitivity disorder. This is the first description of a diagnosis of VBDS combined with HLH. This case illustrates the importance of considering all possible underlying causes in a patient, including an infectious etiology, a drug-induced factor and an underlying immunologically mediated reaction. The co-existence of VBDS and HLH suggests that common pathogenic mechanisms are involved, with excessive activation of T lymphocytes or cytokine storm[24,25].

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