

Hodgkin's Lymphoma as a Rare Cause of Vanishing Bile Duct Syndrome: A Case Report

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ABSTRACT

Vanishing bile duct syndrome (VBDS) is a disorder presented with jaundice and prolonged cholestasis due to intrahepatic cholestasis with the paucity of interlobular bile ducts. Liver involvement of Hodgkin's lymphoma (HL) is well-known however VBDS is an extremely rare presentation of HL. Lack of well-established pathogenetic mechanism and rarity of disorder may cause diagnostic confusion. We reported a VBDS case related to Hodgkin's lymphoma, presented with generalized jaundice.

Keywords: Cholestasis, Hodgkin's lymphoma, vanishing bile duct syndrome

ÖZ

Kaybolan safra kanalı sendromunun nadir bir nedeni olarak Hodgkin Lenfoma: Olgu sunumu

Kaybolan safra kanalı sendromu (VBDS), interlobüler safra kanallarının yetersizliği ile birlikte intrahepatik kolestaza bağlı sarılık ve uzamış kolestaz ile ortaya çıkan bir hastalıktır. Hodgkin lenfomanın (HL) karaciğer tutulumu iyi bilinir, ancak VBDS, HL'nin oldukça nadir görülen bir bulgusudur. Patolojik mekanizmanın tam açıklanmamış olmaması ve bozukluğun nadir olması tanısız karışıklığa neden olabilir. Yaygın sarılık ile başvuran Hodgkin lenfoma ile ilişkili bir VBDS olgusunu sunuyoruz.

Anahtar kelimeler: Hodgkin lenfoma, kolestaz, kaybolan safra kanalı sendromu

Introduction

Vanishing bile duct syndrome (VBDS) defines different pathological conditions that occur with infection, ischemia, drug side effects, autoimmune diseases, allograft rejection and malignancy related humoral factors (1). Due to intrahepatic bile duct injury and ductopenia, various clinical tables such as cholestasis, biliary cirrhosis or liver failure can occur. Although the incidence of VBDS associated with Hodgkin's lymphoma (HL) is not high, the paraneoplastic effect of malignancy mediated cytokines is highly responsible

for its mechanism. In this article, a VBDS case with HL diagnosis is presented.

Case Presentation

A 19 year old male admitted to our hospital with generalized jaundice and no other remarkable findings on physical examination. He had a history of claritromycine use for upper airway infection. On laboratory examination, liver function tests and cholestasis parameters were severely elevated: ALT: 51 U/L, AST: 49 U/L, ALP: 395 U/L, GGT: 45 U/L, total

bilirubin: 39 mg/dl, direct bilirubin: 30 mg/dl, prothrombin time: 17.7 seconds, INR: 1.36 IU. Other laboratory parameters including whole blood count, viral hepatitis markers, ferritin, transferrin, ceruloplasmin, serum copper level, 24-hour urine copper level and autoimmune panel including ANA, anti-dsDNA, ASMA, AMA, LKMA, p-anca and c-anca were in normal range. Ophthalmologic examination failed to indicate Kayser-fleischer ring. Written informed consent was obtained from the patient.

No evident dilatation in intrahepatic or extrahepatic bile ducts was observed on ultrasonographic and magnetic resonance imaging. He underwent to liver biopsy that showed intracanalicular cholestasis, minimal lymphocytic infiltration, ductopenia and mild portal fibrosis suggesting VBDS (Figure 1). Due to failure of medical therapy including methylprednisolon and ursodeoxcholic acid (UDCA), the patient referred to a university hospital and at there steroid therapy was ceased and tacrolimus was initiated.

After 6 month follow-up, patient admitted to our hospital with fever exceeding 39° C, abdominal pain and fatigue lasting for few days. Laboratory analysis revealed out leukocytosis (WBC:15000 mm³), CRP: 126 mg/L, AST: 43 U/L, ALT: 37 U/L, ALP: 553 U/L, GGT: 71 U/L, total bilirubin: 17.7 mg/dl, direct bilirubin: 15.8 mg/dl. Empiric ampicillin-sulbactam therapy was initiated to the patient that was considered as fever of unknown origin and no specific organism was isolated on blood, urine and sputum cultures. Tomographic examination of thorax and abdomen showed hepatomegaly (22 cm), splenomegaly (17 cm) and multiple lymphadenomegaly on right axillary region. Histopathologic examination of axillary lymphadenomegaly revealed out nodular sclerosing type HL (Figure 2).

Discussion

VBDS is characterized by a group of diseases that result in the disappearance of bile ducts with progressive damage resulting in cholestasis (2). There are several factors may be responsible

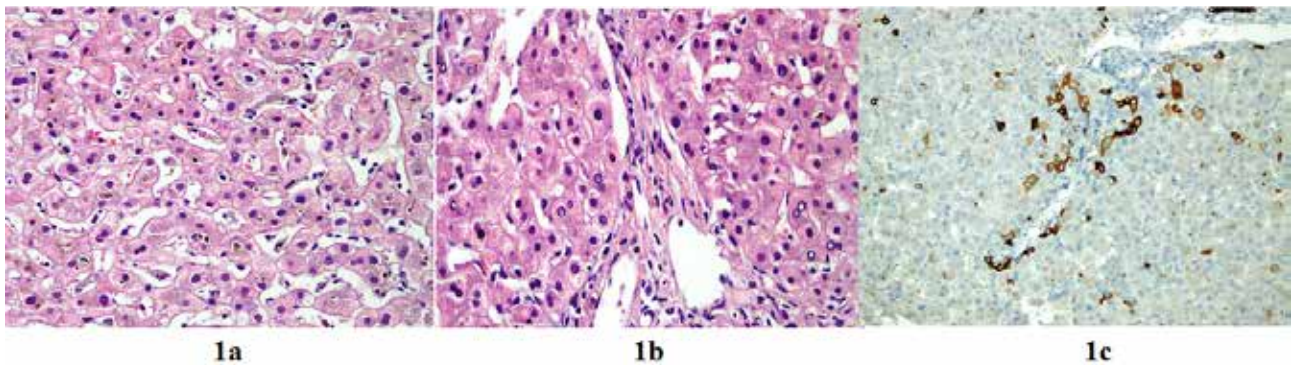


Figure 1: 1a-intracanalicular bile duct plug (Hematoxyline eosine-200X), 1b-portal area with paucity of intralobular bile ductus (Hematoxyline eosine-400X), 1c-ductular reaction in periportal hepatocytes (keratin immune stain -20X).

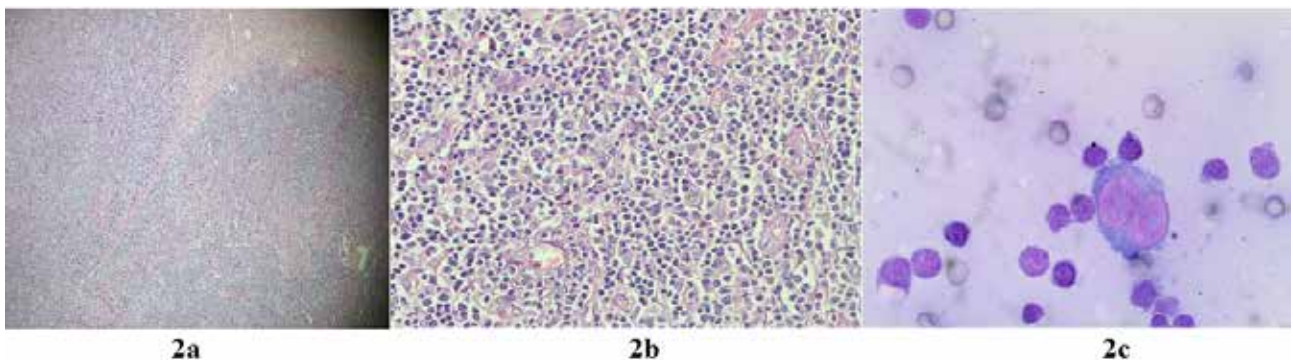


Figure 2: 2a-Nodular sclerosing HL: Nodular pattern separated by fibrous band, 2b-Background appearance consisting mixed cell, 2c-Reed Stenberg (RS) cells typically to HL.

in the etiology of this syndrome, that described by Ludwig et al. in 1988 first time (3). These factors may include genetic disorders, infections, neoplastic and autoimmune diseases, toxins and drugs, and ischemic processes.

Ductopenia is a pathological term to define loss of at least 50% of interlobular bile ducts in the portal region which is essential for diagnosis (4). Staining the biopsy specimen with cytokeratin 7 and 19 which is sensitive to bile duct epithelium may increase the chance of accurate diagnosis (5).

Drug related cholestasis is a common form of drug toxicity which is seen in 2-5% of hyperbilirubinemia in hospitalized patients and 20% of hyperbilirubinemia in elderly population (6,7). Presenting symptom is usually acute cholestasis due to bile duct injury however prolonged cholestasis may be seen in small percentage of these patients regardless of cessation of testing toxic drug suggesting the presence of VBDS. A number of drugs have been accused of causing to VBDS secondary to cholestasis including allopurinol, amoxicillin-clavulanic acid, ampicillin, erythromycin, ibuprofen, and meropenem. Our case had a history of clarithromycin use for upper airway infection before the onset of jaundice.

Currently, there is no diagnostic method to distinguish lymphoma related VBDS from drug related VBDS however recovery is usually achieved by cessation of toxic agent while patients with malignancy require anti-cancer therapy for improvement of VBDS. Similarly, we failed to achieve remission of VBDS by discontinuation of clarithromycin suggesting the role of HL on the development of VBDS.

The association of HL and VBDS was first described by Hubscher et al in 1993 (8). Although pathogenetic mechanism of HL related bile duct injury is not exactly understood, direct infiltration of bile duct with lymphoma cells or paraneoplastic cytokine secretion of lymphoid cells are two common theses. Other causes of jaundice in patients with HL are extrahepatic obstruction of bile duct by lymphadenomegaly, hemolysis and bile obstruction due to viral infections including acute CMV infection. A report of 36 HL related VBDS cases, in 2017 showed that those patients are commonly presented with jaundice, pruritis and weight loss similar to our case (9).

Because the HL related VBDS mechanism cannot be clearly defined, the treatment is complex and controversial. Depending on the underlying etiology, assessment of risk of drug use is among the options for UDCA, immunosuppressive agents, and



Figure 3: Icterus of the patients at admission.

chemoradiotherapy. It has been shown that treatment with an anion modulating apheresis may be effective in resistant cases (10). Liver transplantation may be necessary in cases involving severe complications of liver decompensation (11).

Prognosis of VBDS depends on etiology as well as the severity of the damage. Malignancy-associated VBDS has a poor prognosis compared to other causes, but the VBDS that occurred as a result of medical treatment of HL is usually reversible. In a statistical analysis of the reported cases in the literature, 30% of patients receiving standard therapy for HL have been shown to have positive results on lymphoma progression and liver function (12). Therefore, HL therapy appears to be the most important factor in increasing survival. Early aggressive treatment, which is started by determining the

relationship between the results of appropriate laboratory and radiological examinations, is crucial for achieving a successful outcome by regenerating the bile duct epithelium.

Bilirubin levels can be used as a more reliable laboratory marker in the evaluation of response to treatment, when compared to ALP (13). In conclusion, the differential diagnosis of lymphoma and other malignancies must be done in VBDS patients who are thought to be unrelated to clinical and laboratory parameters.

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