Complete remission of paraneoplastic vanishing bile duct syndrome after the successful treatment of Hodgkin’s lymphoma: a case report and review of the literature

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Abstract

Background: Vanishing bile duct syndrome has been associated with different pathologic conditions (adverse drug reactions, autoimmune diseases, graft versus host disease, and cancer). Though its causes are unknown, an immune-related pathogenesis is the most likely one. Vanishing bile duct syndrome can evolve to hepatic failure and, eventually, to death. The treatment is uncertain, but it needs the resolution of the underlying pathologic condition.

Case presentation: We describe the association of Hodgkin’s lymphoma with a syndrome characterized by cholestasis, aminotransferase elevation and an histological picture of bile duct loss. All other causes of hepatic function impairment were excluded (in particular, drugs, viral and autoimmune related diseases) eventually leading to the diagnosis of vanishing bile duct syndrome. Despite the fact that the dysfunction is not caused by hepatic Hodgkin’s lymphoma involvement, liver impairment can limit the optimal therapy of Hodgkin’s lymphoma. A treatment consisting of ursodeoxycholic acid, prednisone, and full dose chemotherapy restored hepatic function and achieved complete and long-lasting remission of Hodgkin’s lymphoma.

Conclusion: We reviewed all case reports showing that vanishing bile duct syndrome is a dismal paraneoplastic syndrome being fatal in a high proportion of patients if not adequately treated. Indeed, this syndrome requires both an early recognition and an appropriate aggressive treatment consisting of full dose upfront chemotherapy which is the only way to achieve a resolution of the vanishing bile duct syndrome. Delayed or reduced intensity treatments unfavorably correlate with survival.

Keywords: Vanishing bile duct syndrome, Ductopenia, Hodgkin’s lymphoma, Ursodeoxycholic acid, Paraneoplastic syndrome

Background

Vanishing bile duct syndrome (VBDS) is defined as an intrahepatic cholestasis with paucity of interlobular bile ducts [1]. The cause is unknown and it has been associated with different pathologic conditions: adverse drug reactions, autoimmune diseases, graft versus host disease, and cancer. These associations make the immune-mediated pathogenesis the most likely one. Histology is characterized by marked cholestasis without evidences of an accompanying hepatitis, but with a characteristic loss of bile ducts in the portal tracts. Clinical outcome is hepatic failure unless the underlying disease can be appropriately cured. We present a case of a VBDS that heralded the successive diagnosis of Hodgkin’s lymphoma (HL).

Case presentation

A 42-year-old Caucasian woman was admitted to an infectious disease unit because of jaundice and fever. Her
medical past history was unremarkable except for a mild allergy to cat hair. On admission her abnormal chemical tests were: total and direct bilirubin of 18.3 milligrams/deciliter (mg/dL) and 15.3 mg/dL, respectively (normal value up to 1.3 and 0.4 mg/dL, respectively); aspartate (AST) and alanine aminotransferase (ALT), 151 and 322, respectively (normal value up to 35 units/liter (U/L) and 40 U/L, respectively); alkaline phosphatase (ALP) 322 U/L (normal value up to 240 U/L); gamma-glutamyl transpeptidase (GGT) 482 U/L (normal value up to 35 U/L). Blood counts were normal except for leukocytosis (15170/μL).

The patient was not taking any drug, and an extensive infectious disease work-up was negative. Particularly, hepatotropic viruses such as hepatitis A virus (HAV), hepatitis B virus (HBV) and hepatitis C virus (HCV) were excluded as well as Epstein-Barr virus (EBV) and cytomegalovirus (CMV). A computed tomography (CT) scan showed enlarged mediastinal lymph nodes without any abdominal pathological feature, and no sign of biliary tract dilatation. At that time, the patient was referred to our center, and a mediastinal biopsy was performed showing a picture of classic HL of nodular sclerosis histotype. Furthermore, the most common antibodies responsible for autoimmune hepatitis (ANA - antinuclear antibodies, ASMA – anti-smooth-muscle antibodies, anti-LKM1 – anti-liver-kidney microsomal type 1, anti-SLA - antibodies against soluble liver antigen, AMA - antimitochondrial antibody, antiphospholipid antibodies) were evaluated without any pathological findings. Since biochemical cholestasis had worsened (total bilirubin 33.8 mg/dL), a hepatic biopsy was performed showing marked cellular and canalicular perivenous cholestasis. Remarkably, bile ducts were absent (Figure 1) in all seven portal tracts examined and no sign of HL could be detected in a picture consistent with a VBDS [1]. Bone marrow trephine was negative. We also carried out a positron emission tomography (PET) scan that showed increased 18 F-fluoro-deoxy-glucose (18 F-FDG) uptake in multiple mediastinal lymph nodes defining a stage IIB HL. She was started on ursodeoxycholic acid (UDCA) (1350 mg daily) and prednisone (50 mg daily). A dramatic improvement of her clinical and biochemical conditions occurred with a decreased total bilirubin to 10 mg/dL. At this point, doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) chemotherapy was delivered and, after 4 cycles, we performed interim restaging with the PET scan showing a complete response. Therefore, she subsequently received two additional cycles of ABVD with a complete response confirmed after six cycles. Despite the fact that total bilirubin was increased at the time of the first cycle, we delivered a full dose of doxorubicin and vinblastine. At completion, prednisone was tapered and UDCA interrupted. The patient declined to receive a hepatic biopsy at the end of chemotherapy. Six years later, she is still in complete remission with a thoroughly normal hepatic function.

Conclusion
Several conditions may cause jaundice in HL. Biliary obstruction secondary to lymph nodes enlargement, hemolysis, hepatotropic and other viruses (e.g. CMV) are among the most common causes. Hepatic direct involvement by HL is a relatively rare, but well known complication [2]. The association of cholestatic jaundice and hepatic bile duct loss (a picture called “ductopenia”) in HL has been described in other 39 other cases in the literature (Table 1). This is a
| Author             | Number of patients | Hodgkin lymphoma treatment* | Dosage | Ursodeoxycholic acid | Outcome            |
|--------------------|--------------------|-----------------------------|--------|---------------------|--------------------|
| Bouroncle B. [9]   | 2                  | Yes                         | Full   | Unknown             | Hepatic failure    |
| Groth C. [11]      | 1                  | Yes                         | Full   | Unknown             | Hepatic failure    |
| Perera D.R. [12]   | 3                  | Yes                         | Full   | Unknown             | Hepatic failure    |
| Juniper K. [10]    | 1                  | Yes                         | Reduced| Unknown             | Hepatic failure    |
| Groth C. [11]      | 1                  | Yes                         | Full   | Unknown             | Hepatic failure    |
| Perera D.R. [12]   | 3                  | Yes                         | Full   | Unknown             | Hepatic failure    |
| Piken E.P. [13]    | 1                  | Yes                         | Full   | Unknown             | Unknown            |
| Trewby P.N. [14]   | 4                  | Yes                         | Full   | Unknown             | Cure               |
| Lieberman D.A. [15]| 1                  | No                          | No     | No                  | Respiratory arrest |
| Birrer M.J. [16]   | 1                  | Yes                         | Full   | Unknown             | Sepsis             |
| Hubser U.SG. [1]   | 3                  | Yes                         | Reduced| No                  | Hepatic failure    |
| Jansen P.L.M. [17] | 1                  | Yes                         | Full   | Late                | Hepatic failure    |
| Warner A.S. [18]   | 1                  | Yes                         | Full   | No                  | Cure               |
| Gottrand F. [19]   | 1                  | No                          | No     | No                  | Hepatic failure    |
| De Medeiros B.C. [21]| 2               | Yes                         | Full   | No                  | Hepatic failure    |
| Yalcin S. [22]     | 2                  | No                          | No     | No                  | Hepatic failure    |
| Dourakis S.P. [23] | 1                  | Yes                         | Reduced| No                  | Hepatic failure    |
| Yusuf M.A. [24]    | 1                  | No                          | No     | Late                | Hepatic failure    |
| Rossini M.S. [25]  | 1                  | Yes                         | Full   | No                  | Hepatic failure    |
| Allory Y. [3]      | 1                  | Yes                         | Full   | Yes                 | Cure               |
| Ozkan A. [26]      | 1                  | No                          | No     | Late                | Hepatic failure    |
| Ripoll C. [27]     | 2                  | Yes                         | Full   | No                  | Hepatic failure    |
| Komurcu S. [28]    | 1                  | Yes                         | Full   | No                  | Hepatic failure    |
| Liangpunsakul S. [29]| 1                | Yes                         | Full   | No                  | Cure               |
| Gulütl S. [30]     | 1                  | Yes                         | Full   | Late                | Hepatic failure    |
| Córdoba Iturriagagoitia A. [31]| 1          | Yes                         | Full   | No                  | Cure               |
| Han W.S. [32]      | 1                  | No                          | No     | No                  | Recurrent Hodgkin's Lymphoma |
| Schmitt A. [33]    | 1                  | No                          | No     | No                  | Hepatic failure    |
| Barta S.K. [34]    | 1                  | Yes                         | Full   | No                  | Cure               |
| DeBenedet A.T. [35]| 1                  | Yes                         | Reduced| No                  | Hepatic failure    |
| Leeuwenburgh I. [36]| 1                  | Yes                         | Reduced| No                  | Cure               |
| Pass A.K. [37]     | 2                  | Yes                         | Reduced| Yes                 | Cure               |
| Ballonoff A. [38]  | 1                  | Yes                         | Full   | No                  | Cure               |
| Umit H. [39]       | 1                  | Unknown                     | Unknown| Unknown             | Unknown            |
Table 1 Summary of all cases reported in the literature regarding vanishing bile duct syndrome in lymphomas
(Continued)

| Author(s) | Number | Treatment | Response | Outcome |
|-----------|--------|-----------|----------|---------|
| Gill R.M. [40] | 1 | Yes | Reduced | No | Hepatic failure |
| Foramiti S. [41] | 1 | Yes | Full | Yes | Hepatic failure |
| Gagnon MF [42] | 1 | Yes | Full | No | Cure |
| Wong KM [43] | 1 | Yes | Full | No | Cure |
| Aleem A1 [44] | 1 | Yes | Full | No | Hepatic failure |
| Nader K [45] | 1 | Yes | Full | No | Hepatic failure |
| Our patient | 1 | Yes | Full | Yes | Cure |

*either chemotherapy or radiotherapy.

severe complication with a high rate of death in a neoplastic disease otherwise curable in more than 80% of patients. In 18 HL patients steroid plus lymphoma treatment (both chemotherapy and radiotherapy) was described to improve hepatic function and eventually led to complete remission of both hepatic and Hodgkin's diseases. All other cases died because of hepatic failure. A clear pathogenetic relationship between HL and VBDS cannot be identified. Nevertheless, the concomitance of the two diseases and the case reported by Allory [3] makes the hypothesis of VBDS likely to be a paraneoplastic manifestation of HL. Furthermore, Bruguera [4] has shown hepatic sinusoidal dilatation (a feature of VBDS) in 90% of patients presenting systemic symptoms (so called B symptoms) without any evidence of direct liver involvement by the lymphoma. This datum suggests the role of HL as the trigger event of cytokine-mediated hepatic damage [5]. There is evidence that biliary epithelial cells [6] express major histocompatibility complex (MHC) antigens (both class I and II) as well as adhesion molecules like intercellular adhesion molecule 1 (ICAM-1) in response to cytokines produced by HL. In this context, both types of molecules may contribute to adhesion and cytotoxicity due to T lymphocytes. As of today, there is no recognized treatment for VBDS. We, as well as other authors, used UDCA because of its demonstrated activity in primary biliary cirrhosis. Indeed, beneficial effects of treatment with UDCA have been reported in other immune-mediated disease involving the biliary tree as primary sclerosing cholangitis [7] or hepatic involvement by graft versus host disease [8]. UDCA acts at three levels: increasing the expression of transporter proteins into the canalicular membrane, inhibiting apoptosis induced by toxic bile acids, and altering the composition of the micelles of bile acids [7].

In the present report we stress two aspects. First, the therapeutic choice to use high-dose of UDCA [46] and prednisone which rapidly determined an improvement of our patients. Secondly, although still icteric, we delivered a full dose chemotherapy achieving a sustained complete remission that, in a paraneoplastic disease, is the most important result. An appropriate aggressive treatment (either chemotherapy or radiotherapy) was reported in all patients who were, in the end, cured (Table 1). Notwithstanding, several good reasons stand for a dose reduction in both doxorubicin and vinblastine in a jaundiced patient, we emphasize the “full dose” chemotherapy choice. ABVD chemotherapy is conceived as a 2-weekly treatment and, therefore, 25 mg/m² doxorubicin was felt appropriate regardless of jaundice. Indeed, it is half the dose used in other combinations (e.g. CHOP regimen - Cyclophosphamide, Doxorubicin, Vincristine, Prednisone or CODOX-M/IVAC – Cyclophosphamide, Vincristine, Doxorubicin, Methotrexate, Ifosfamide, Etoposide, Cytarabine [47,48]). Moreover, it is well known that the ABVD dose intensity affects the HL outcome [49,50]. Lastly, only 1 out of 8 (12%) patients receiving an upfront reduced chemotherapy overcame the vanishing bile duct, compared to 51% (17/33) of patients treated with upfront full dose chemotherapy (see Table 1). In these patients the efficacious treatment of the lymphoma preceded the hepatic improvement and, ultimately, the cure.

This case report demonstrates that in the presence of a histological diagnosis of HL associated with signs of cholestasis and liver function impairment without gross liver involvement or biliary tract dilatation, the prompt treatment of the underlying disease in association with high doses of UDCA is crucial. Indeed, data available in the literature strengthen the theory that the therapy able to restore liver function is full dose chemotherapy only. In this setting, waiting for the histological confirmation of VBDS may be harmful because a delayed start might be detrimental to patient outcome. Indeed, liver impairment could evolve to liver insufficiency and eventually to death as is clearly outlined in Table 1.

In conclusion, VBDS must be considered a rare but possible complication of HL. Its prompt recognition and appropriate treatment can dramatically affect patients’ outcome.

Consent
Written informed consent was obtained from the patient for publication of this Case Report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.
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