Leukemia Research Reports 23 (2025) 100511

Contents lists available at ScienceDirect

Leukemia Research Reports

journal homepage: www.elsevier.com/locate/lrr

A case report of vanishing bile duct syndrome and diffuse large b cell lymphoma: An uncommon association

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ARTICLE INFO

Keywords:
VBDS
DLBCL
Chemotherapy

ABSTRACT

We report a rare case of vanishing bile duct syndrome (VBDS) associated with diffuse large B cell lymphoma (DLBCL). VBDS is an uncommon ductopenic disorder associated with various underlying conditions, for which timely treatment is crucial to prevent poor outcomes. Our patient received six cycles of R-CHOP chemotherapy every 21 days with halved doxorubicin and vincristine doses, and prophylactic intrathecal chemotherapy. A complete response of DLBCL and normalization of liver parameters were achieved upon completion of treatment. We conclude that, when VBDS is diagnosed, one can consider to urgently reach lymphoma remission even balancing the dose reduction of hepatotoxic drugs.

1. Introduction

Vanishing bile duct syndrome (VBDS) is a rare, acquired ductopenic disease, histologically defined as a loss of > 50% of intrahepatic bile ducts, cholestasis and in the most serious cases death from liver failure [1]. It has been related to autoimmune diseases, drug toxicity, infections, allograft rejection and malignancy. Cell-mediated immunological reactions involving toxic cytokines released by the lymphoma or the presence of cross-reactive T cells recognizing autoantigens and inducing biliary epithelial apoptosis, have been considered as potential pathogenetic mechanisms: VBDS may become irreversible once biliary fibrosis develops [2]. In most patients, liver transplantation remains the only available treatment option, although not always feasible in the context of an oncological active disease [3]. Here, we present a rare case of VBDS associated with diffuse large B cell lymphoma (DLBCL).

2. Case report

A 33-year-old man presented to our Institution in December 2021 diagnosed with DLBCL at another Center (according to WHO 2017 classification), exhibiting a germinal-center phenotype and centroblastic cytology [Fig. 1a], based on a biopsy of a lesion infiltrating the pectineus muscle. The immunohistochemical panel showed positivity for CD20, CD10, Bcl6, MUM1, focally for c-myc (70%), while tested negative for Bcl2, CD5, CyclinD1 and CD30. FISH analysis failed due to inadequacy of the specimen.

The patient reported a one-year history of back pain and subsequent jaundice, severe itch, diarrhea with pale stools, dark colored urine and B symptoms. Personal history was negative for liver diseases or increased alcohol intake, no relevant family history was reported. At referral, clinical examination demonstrated diffuse skin and scleral icterus, one significant palpable lymphadenopathy of 3 cm in the left inguinal region, and a painful palpable center-abdominal mass. Liver biochemistry revealed cholestasis and moderate functional impairment: total and direct bilirubin levels were 27.57 mg/dl and 25.47 mg/dl, respectively, alkaline phosphatase 241 U/L, GGT 228 U/L, AST 115 U/L, ALT 320 U/L, prothrombin time 1.82, LDH 425 U/L, albumin 2.27 g/dl. Serologies for HBV, HCV, HAV, HEV, HIV, VZV, CMV, EBV, HTLV1, toxoplasmosis, syphilis and quantiferon-TBC tested negative. Autoimmune liver profile was negative. CT/PET total body scan revealed diffuse lymphoid, musculoskeletal, pancreatic, gastric and renal pathological FDG-uptake, without liver involvement or signs of biliary obstruction. Both magnetic resonance cholangiopancreatography (MRCP) and brain magnetic resonance imaging (MRI) tested negative for hepatobiliary and brain abnormalities, respectively. Bone marrow evaluation excluded lymphoma localization. Liver biopsy demonstrated preserved lobular

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https://doi.org/10.1016/j.lrr.2025.100511
Received 28 April 2024; Received in revised form 21 March 2025; Accepted 23 April 2025
Available online 24 April 2025

architecture with no evidence of lymphoma or biliary infiltration but showed a lack of bile ducts in most portal tracts [Fig. 1b-c], along with severe cholestasis, confirming the diagnosis of VBDS. Final diagnosis was DLBCL at stage IVB, with a poor risk revised International Prognostic Index (IPI), a high risk central nervous system (CNS)-IPI and associated VBDS.

After multidisciplinary discussion and taking into consideration available alternatives, the patient was treated according to R-CHOP regimen, which consists of rituximab (375 mg/m^2 on day 1), cyclophosphamide (750 mg/m^2 on day 1), doxorubicin (standard dose: 50 mg/m^2 on day 1), vincristine (standard dose: 1.4 mg/m^2, maximum dose 2 mg, on day 1), and prednisone (100 mg orally on days 1–5), administered every 21 days for six cycles. He received also prophylactic monthly triple intrathecal therapy (TIT - methotrexate 12.5 mg, cytarabine 50 mg, methylprednisolone 40 mg) for a total of four lumbar punctures. Following debulking steroid therapy, no fixed-dose regimen was introduced for VBDS treatment due to associated risk of infections. Ursodeoxycholic acid (UDCA) 6 mg/kg and cholestyramine 8 g daily were given to improve respectively intrahepatic cholestasis and pruritus.

First R-CHOP cycle was given with doxorubicin and vincristine reduced at 50% because of liver disfunction, but few days later bilirubin increased with zenith of 27 mg/dl [Fig. 2]. UDCA was increased to 15 mg/kg daily, while doxorubicin and vincristine were continued at the same dose in the subsequent cycles. Approximately eight weeks after the initiation of chemo-immunotherapy, a progressive improvement in bilirubin levels were observed, with fully normalization after the 5° R-CHOP cycle [Fig. 2]. All lumbar punctures tested negative for CNS involment of lymphoma based on cytology and flow cytometry analyses. Complete response (CR) at interim CT/PET total body scan was observed after the 4° R-CHOP cycle and at the end of treatment (EoT). The patient refused a liver biopsy at the end of treatment.

A follow-up period of 3 years and 3 months confirms persistent CR of lymphoma with fully restored hepatic function.

3. Discussion

To our knowledge, we are describing the second case of the association between VBDS and DLBCL. VBDS has been frequently associated with Hodgkin lymphoma (HL), with about 50 cases reported in literature [2], and rarely in B-cell and T-cell non-Hodgkin lymphoma (NHL), with only 6 cases described [1,4–8]. Since the most common symptoms are jaundice, pruritus, and weight loss, possible differential diagnoses of VBDS include direct lymphoma hepatic infiltration, biliary obstruction from enlarged hilar lymph nodes, hemolysis, viral illnesses, and drug induced injury. All the above have been ruled out in our patient, by imaging and liver biopsy, which was critical to reach the final diagnosis. Given the excess of mortality for liver failure in the reported cases, it's crucial to treat the underlying condition, aiming to VBDS recovery [5,6]. In our patient treatment of NHL included anthracyclines and vinca alkaloids that have liver metabolism and are relatively contraindicated in patients with severe hepatic dysfunction. According to NHS guidelines, a reduction of 50% of doxorubicin and vinca alkaloids is required for bilirubin > 20–50 micromol/L (1.17–2.92 mg/dl) and > 51 micromol/L (2.98 mg/dl), respectively [9]. An omission of doxorubicin is suggested for bilirubin > 86 micromol/L (5.03 mg/dl) [9]. Considering the known poor prognosis of this association, we opted to retain doxorubicin and vincristine, reducing their doses by 50%. Ours decision was supported by data of VBDS and HL, where only 12% of patients receiving an upfront reduced chemotherapy overcame VBDS, compared to 51% of patients treated with full dose chemotherapy [10]. Regarding CNS prophylaxis, systemic high dose MTX was excluded to restrain the hepatoxic damage. In the other VBDS-associated DLBCL case [4], vincristine was omitted, and doxorubicin was administered at a reduced dose during the two last cycles, with progressive VBDS recovery observed. Additionally, we used high dose UDCA to reduce bilirubin levels, while steroids were provided according to R-CHOP regimen only. Indeed, there is no established consensus in literature on the use of steroid for VBDS itself.

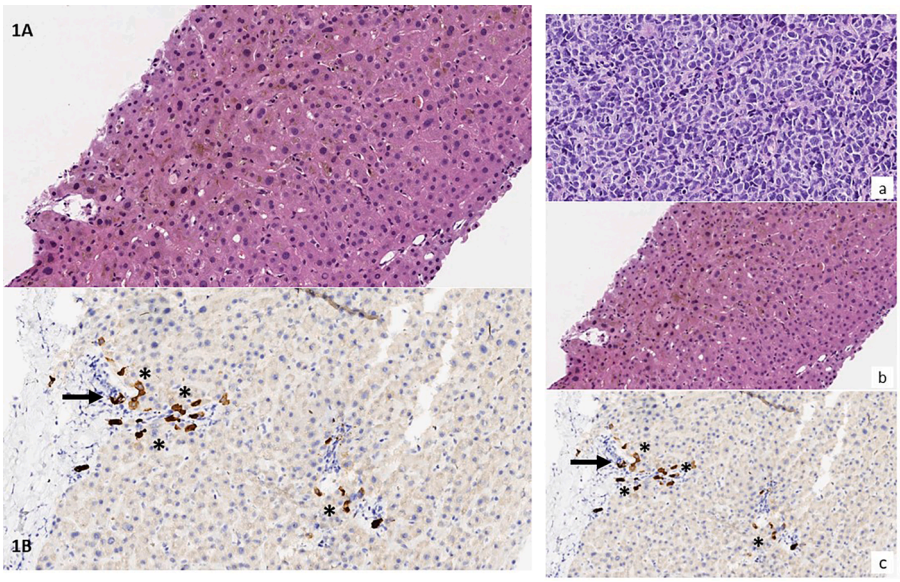

Fig. 1. Detail of the lymphomatous lesion, depicting a centroblastic morphology of proliferation, consistent with DLBCL (a; H/E, 400x). Needle biopsy of the liver (b; H/E 100x) documents a preserved lobular architecture with no lymphoma nor a remarkable inflammatory cell component, with signs of cholestasis and ductopenia, as highlighted by cytokeratin-7 staining (c; 100x), which shows only scant bile ducts in the portal spaces (arrow) and signs of reactive biliary metaplasia of the hepatocytes (asterisks). **1A**: Normal lobular architecture, paucity of inflammatory infiltrate within the portal tracts, signs of acute liver cholestasis (brown bile pigment within the hepatocytes). **1B**: Cytokeratin 7 staining confirmed the paucity of bile ducts in more than 50% of portal tracts, the positive staining was mainly observed in hepatocytes (process known as biliary metaplasia of hepatocytes, representative of reactive-regenerative changes).

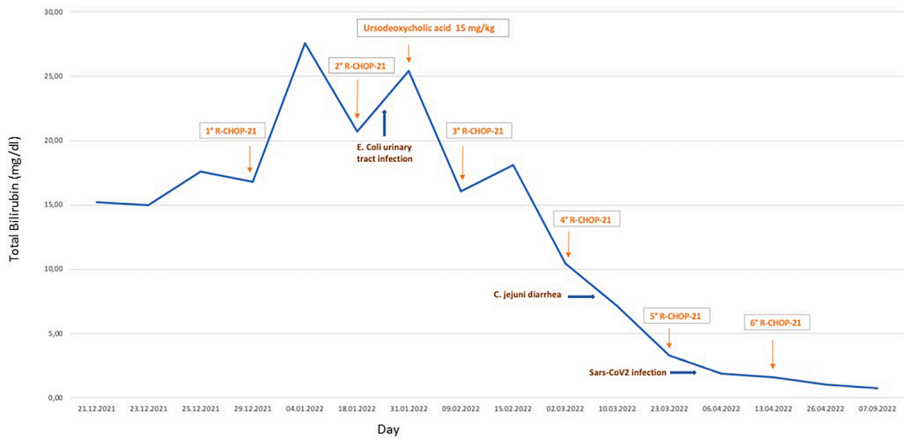

Fig. 2. Trend of bilirubin values (mg/dl) and infectious complications, during chemo-immunotherapy administration.

4. Conclusion

In conclusion, we report the first successful and reversible case of VBDS associated with DLBCL without omitting any hepatotoxic chemotherapy agents.

To the best of our knowledge, our case suggests that, in the context of a life-threatening paraneoplastic syndrome such as VBDS, one can consider to urgently reach lymphoma remission, even balancing the dose reduction of hepatotoxic drugs.

Statement of ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

Data availability statement

All data are available within the manuscript and further may be available upon reasonable request to the corresponding author.

CRediT authorship contribution statement

Cecilia Anna Fidanza: Writing – original draft, Conceptualization. **Ramona Cassin:** Writing – original draft, Conceptualization. **Francesca Cavallaro:** Writing – review & editing, Conceptualization. **Giorgio Alberto Croci:** Writing – review & editing, Resources. **Francesca Gaia Rossi Dardanoni:** Writing – review & editing. **Wilma Barcellini:** Writing – review & editing, Supervision. **Francesco Passamonti:** Writing – review & editing, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This study was funded by Italian Ministry of Health - Current research IRCCS

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