

Review

Paraneoplastic Intrahepatic Cholestasis in Supradiaphragmatic Classical Hodgkin Lymphoma Successfully Treated With Brentuximab Vedotin: A Case Report and Review of the Literature

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Abstract. *Background:* Hepatic dysfunction in patients with classical Hodgkin lymphoma (cHL) is of multifactorial aetiology. Prompt evaluation with laboratory tests and imaging methods is sufficient for diagnosis in most cases. Intrahepatic cholestasis and vanishing bile duct syndrome (VBDS) may complicate cHL as rare paraneoplastic phenomena. Liver biopsy provides crucial evidence of cholestasis, and ductopenia, if present, confirms the diagnosis of VBDS. *Case Report:* We report on a cHL patient that presented with jaundice and bulky mediastinal disease and unfold the therapeutic dilemmas we confronted. Marked hyperbilirubinemia was successfully reversed with brentuximab vedotin (BV) at a dose of 1.2 mg/kg and the patient was subsequently treated with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) at full doses, achieving complete metabolic response. A literature review of intrahepatic

cholestasis in cHL is also presented based on currently available data with focus on treatment options and clinicopathologic associations. *Conclusion:* VBDS and intrahepatic cholestasis are rare and potentially fatal complications of cHL. Their prompt recognition and appropriate treatment can dramatically affect cHL patients' outcome. BV, used at a reduced dose as a bridging therapy, should be considered as a high-priority treatment plan in these challenging cases.

Classical Hodgkin lymphoma (cHL) is a lymphoid neoplasm characterized by malignant Hodgkin/Reed-Sternberg cells mixed with a heterogeneous population of non-neoplastic inflammatory microenvironment. Most patients with cHL present with asymptomatic cervical lymphadenopathy or a mediastinal mass evident on chest radiograph either asymptomatic or with B-symptoms. Hepatic dysfunction in patients with cHL is uncommon and of multifactorial aetiology (1, 2). In extremely rare cases, intrahepatic cholestasis and vanishing bile duct syndrome (VBDS) have been reported in newly diagnosed patients with cHL as a paraneoplastic syndrome (3). Liver biopsy is necessary for definitive diagnosis of both entities, with ductopenia being characteristic of the latter.

The prognosis of cHL with cholestasis is dismal, with a significant risk of progression to liver failure and death (4). Most of the chemotherapy protocols used in newly diagnosed cHL, include drugs metabolized in the liver that may not

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Key Words: Hodgkin Lymphoma, intrahepatic cholestasis, vanishing bile duct syndrome, ductopenia, ABVD, Brentuximab Vedotin.

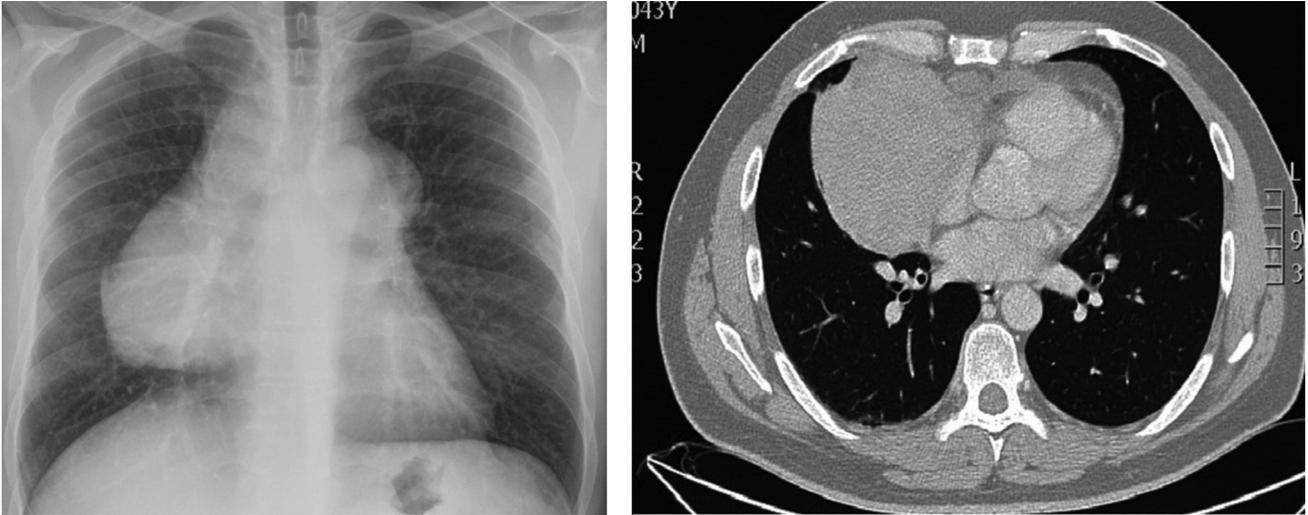


Figure 1. Chest X-ray (left) revealed a mediastinal mass, while a chest computed tomography (CT) revealed a soft tissue mass (13×9.2×5.0 cm) in the right hemithorax, that was causing pressure on the right lung (right).

ameliorate and even worsen cholestasis. Therefore, the diagnostic and therapeutic approach of these patients is challenging, and alternative, liver-friendly treatment strategies should be sought. Timely treatment is of paramount importance for the survival of this small, yet intriguing population of HL patients.

We present a case of HL with marked hyperbilirubinemia and mediastinal bulky disease at diagnosis successfully reversed with brentuximab vedotin (BV) and subsequently treated with doxorubicin, bleomycin, vinblastine and dacarbazine (ABVD) at full doses. A literature review of intrahepatic cholestasis in cHL is also presented based on currently available data with focus on treatment options and clinicopathologic associations.

Case Report

A 44-year-old man was admitted to the hospital with jaundice, pruritus and night sweats. He had an unremarkable past medical history; he was a heavy smoker and denied receiving any medication. On physical examination, he was afebrile, slightly tachycardic, but jaundiced, though without ascites or other signs of hepatic failure. A right supraclavicular lymph node was palpable.

His full blood count was normal (hemoglobin 13.4 g/dl, white blood cell count $9.18 \times 10^9/l$, neutrophils $6.86 \times 10^9/l$, lymphocytes $1.08 \times 10^9/l$, monocytes $1.1 \times 10^9/l$, platelets $339 \times 10^9/l$) and erythrocyte sedimentation rate (ESR) highly elevated at 120 mm/h. Biochemistry tests revealed a highly increased total bilirubin of 18.9 mg/dl, predominantly direct (11.8 mg/dl), a mild increase in aminotransferases (AST 52 IU/l, ALT 56 IU/l) and a threefold increase in γ GT (135 IU/l,

upper limit of normal 52 IU/l) and alkaline phosphatase (348 IU/l, ULN 125 IU/l). His Child-Pugh score was B. An elevated IgE (4600 U/ml) was present, not monoclonal, without a concurrent IgG, IgM or IgA alteration, while serologic tests for autoimmune diseases, Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus, and hepatitis viruses were all negative.

Chest X-ray (Figure 1, left) revealed a bulky mediastinal mass, while a chest computed tomography (CT) revealed a soft tissue mass (13×9.2×5.0 cm) in the right hemithorax, that was causing pressure on the right lung (Figure 1, right) and enlarged mediastinal lymph nodes (5.6×5.0 cm). The CT of the abdomen and pelvis revealed only a contracted gallbladder and diverticulitis of the colon. Upper abdominal MRI had no additional abnormal findings. Interestingly no liver pathology was demonstrable by this thorough conventional staging.

Following a right supraclavicular lymph node biopsy and while awaiting the diagnosis, the patient was started on ursodeoxycholic acid (UDCA) and high-dose dexamethasone (40 mg/day). Intravenous fluids and allopurinol were given to avoid tumor lysis syndrome. A liver biopsy was requested, but was postponed, since it was considered by the gastroenterologists as a high-risk procedure at that time point.

A slow decrease in total and direct bilirubin was noted during the following week. The lymph node biopsy was consistent with nodular sclerosing cHL, EBV negative, since EBV was not detected in neoplastic cells by EBER *in situ* hybridization. Positron emission tomography (PET)/CT showed hypermetabolic right supraclavicular (SUVmax 4.1), mediastinal (SUVmax 7.4) and paratracheal lymphadenopathy and a normal liver uptake pattern. A bone marrow biopsy of

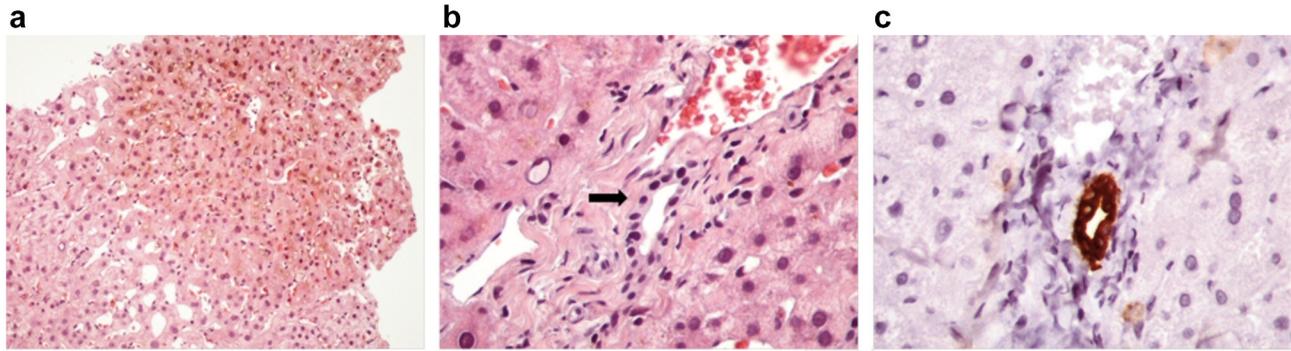


Figure 2. Liver biopsy showed cholestasis and sinusoidal dilatation (a: hematoxylin-eosin staining, magnification $\times 200$). The biliary ducts were present (black arrow, b: hematoxylin-eosin staining, magnification $\times 600$) as demonstrated by immunostaining of cytokeratin 7 (c: DAB, magnification $\times 600$).

the posterior iliac crest was negative for cHL infiltration and there were no signs of hemophagocytosis.

Staging according to the Ann Arbor system with the Cotswolds modification was IIBX. Prognostic classification according to the European Organization for the Research and Treatment of Cancer (EORTC) was early unfavorable.

Based on an extensive workup, there were no signs of liver infiltration, no obstruction due to lymph nodes proximal to the liver hilum, no hemolysis, no viral infections, serologic screening for autoimmune disorders was negative, there was neither hepatic peliosis nor hemophagocytic lymphohistiocytosis. There was no record of any drugs or substances that could induce hepatotoxicity. While awaiting a liver biopsy, the possibility of a paraneoplastic intrahepatic cholestasis or VBDS was the most likely diagnosis at that point.

Despite severe hepatic dysfunction, the presence of bulky disease was urging for initiation of treatment. In the absence of marked hyperbilirubinemia, ABVD would be the regimen of choice. However, doxorubicin and vinblastine cannot be administered in patients with highly elevated bilirubin levels and the same is applicable for BEACOPP (bleomycin, etoposide, adriamycin, cyclophosphamide, vincristine, procarbazine, and prednisone). Monotherapy with mechlorethamine could be given, but the drug is not readily available, while cis-platinum monotherapy is not an established first-line option for cHL. Patients with markedly elevated bilirubin constitute a small proportion of cHL patients, therefore no relevant therapeutic guidelines exist.

Taking into consideration the contraindication of prescribing the most used regimens due to their hepatic metabolism, we decided to treat the patient with BV on an urgent basis at a reduced adjusted dose of 1.2 mg/kg, as a bridging therapy for ameliorating the hepatic dysfunction.

There was a rapid decrease of bilirubin levels and four days after the first dose of BV, a liver biopsy was performed. The

pathology report confirmed the presence of intrahepatic cholestasis and hepatic sinusoidal dilatation, however criteria for VBDS in the submitted biopsy were not met since the percentage of bile ducts was 90% as defined by the number of portal tracts with ducts and dividing this by the total number of portal tracts present according to Hubscher *et al.* (3). The bile ducts were present in nine out of ten included portal spaces with no evidence of ductopenia or bile duct injury (Figure 2). No lymphomatous liver infiltration was noted.

Two weeks later, with a total bilirubin of 1.7 mg/dl (Figure 3), the patient safely received ABVD, with all drugs at full doses. Aminotransferases, γ GT and alkaline phosphatase returned to normal values by the end of the first cycle of ABVD, while his total bilirubin remained below 1 mg/dL throughout treatment. Interim PET-CT scan following ABVD cycle 2 was negative with a Deauville Score (DS) of 3. He received a total of four ABVD cycles and two AVD cycles. End of treatment PET/CT was consistent with complete metabolic response (DS 2).

Discussion

Hyperbilirubinemia is described in 3-13% of patients during the course of cHL. The main causes of jaundice are lymphomatous liver infiltration, biliary obstruction in the presence of porta hepatitis lymphadenopathy, haemolysis, viral infections, such as hepatitis and CMV, hemophagocytic lymphohistiocytosis or cytokine-driven alkaline phosphatase and γ -glutamyl-transferase (γ GT) elevations due to the action of M-CSF (1, 2). In rare cases, intrahepatic cholestasis or VBDS are the underlying cause of hepatic dysfunction as paraneoplastic syndromes.

Intrahepatic or functional cholestasis can be the consequence of parenchymal liver (intrahepatic) or intrahepatic bile duct (extrahepatic) disease. VBDS is characterized by intrahepatic cholestasis and ductopenia.

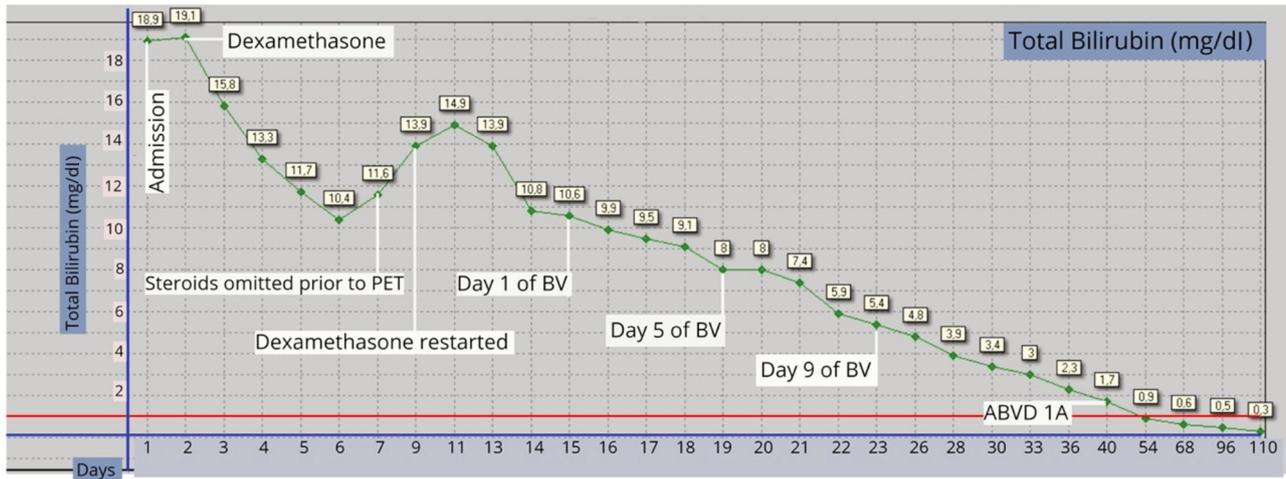


Figure 3. The chart depicts the total bilirubin values at diagnosis and during treatment with steroids, BV and ABVD. BV: Brentuximab vedotin; ABVD: adriamycin, bleomycin, vinblastine, dacarbazine.

Intrahepatic cholestasis and VBDS are two distinct entities, however intrahepatic cholestasis might represent an earlier stage, that may progress to VBDS or not (4). Ductopenia is diagnosed pathologically, as a reduction in the number of intrahepatic bile ducts. The small size of the affected ductules, less than 15 μm, highlights the diagnostic insufficiency of imaging methods and the necessity of a liver biopsy (5).

The diagnosis of both intrahepatic cholestasis and VBDS require the exclusion of other disorders that could lead to liver failure and liver biopsy. Intrahepatic cholestasis combines canalicular stasis with inflammation. Ductopenia, the hallmark of VBDS, is defined as the loss of interlobular bile ducts in more than 50% of portal tracts, in a specimen that contains at least ten portal tracts. Portal inflammation, fibrosis or atypical proliferation of the ducts may also be present. Serial liver biopsies might be needed to demonstrate ductopenia, as it is a dynamic process (6). Immunostaining for cytokeratins 7 and 19 (7) is useful in the diagnosis of ductopenia.

VBDS as a possible mechanism for intrahepatic cholestasis in cHL was first described in 1993 (3), based on review of the findings in liver biopsies of three patients, who were initially registered as cases with intrahepatic cholestasis. VBDS might precede the diagnosis of cHL by even several months (8). Ductopenia can be reversible with regeneration of bile ducts or it can progress to biliary cirrhosis and liver failure. Multiple conditions (9-11) apart from lymphomas have been associated with VBDS, including drugs, autoimmune diseases, infections and neoplasms (Table I).

Intrahepatic cholestasis was initially recorded in two cHL patients in 1961. The mechanism of cholestasis in these cases was probably immune-mediated (3, 6, 12). There is evidence of cytokine involvement, either by causing direct toxicity to

Table I. Causes of vanishing bile duct syndrome.

Drugs	Amoxicillin/clavulanic acid, carbamazepine, clindamycin, co-trimoxazole, ibuprofen, tetracyclines, valproic acid, temozolomide, azithromycin, etc.
Food supplements	Non FDA/EMA approved
Congenital diseases	Congenital hepatic fibrosis, Caroli disease, Bile duct atresia
Graft <i>versus</i> host disease	In chronic GVHD
Infections	Escherichia Coli, CMV, HBV, HCV, Reovirus type 3
Autoimmune disorders	Sarcoidosis, primary sclerosing cholangitis
Neoplastic disorders	Solid tumours, lymphomas, histiocytosis X
Idiopathic adulthood ductopenia	Includes rare atypical disorders

CMV: Cytomegalovirus; EMA: European medicinal agency; FDA: food and drug administration; GVHD: graft *versus* host disease; HBV: hepatitis B virus; HCV: hepatitis C virus.

the epithelial cells or by leading to adhesion and cytotoxicity *via* T-lymphocytes. In this second scenario, biliary epithelial cells express major histocompatibility complex antigens (both classes I and II) or adhesion molecules like ICAM-1, as a response to lymphoma-related cytokines, thus increasing susceptibility to cytotoxicity (13). Single-nucleotide polymorphisms in ABCB11 and ATP8B1 (14) are usually associated with benign recurrent intrahepatic cholestasis (BRIC). Common single-nucleotide polymorphisms in the macrophage stimulating 1 (*MST1*) gene (15), similar to the ones in primary sclerosing cholangitis, have been implicated in the pathogenesis of intrahepatic cholestasis.

In an analysis of 37 cHL patients (4) (nineteen with VBDS, sixteen with intrahepatic cholestasis, one with portal inflammation, and one with cholestatic hepatitis), the median age at diagnosis was 36.5 years, 65% were male and the histologic subtype was nodular sclerosis in the majority of cases. In a review of 23 patients with cHL and VBDS (16), the mean age at presentation was 28 years, males predominated, all patients had jaundice and pruritus, while B-symptoms were nearly always present. The mean total bilirubin levels were 17.8 mg/dl, and the increase of alkaline phosphatase was more profound than that of aminotransferases.

Treating cHL patients with severe cholestasis is a challenging task. Some of the standard chemotherapy regimens have potential hepatotoxicity and, in the lack of formal guidelines, some experts recommend using these protocols with dose modifications, whereas others recommend using drug combinations with minimal hepatic metabolism, such as mechlorethamine or cis-platinum.

cHL is quite radiosensitive and upfront radiation (4, 17) therapy, initially mantle field radiation followed by a boost at possible important sites, may be helpful especially in early stages (18). Ballonoff *et al.* mentioned better liver failure-free survival when radiation therapy was administered (4).

However, most cHL patients with cholestasis described in the literature received chemotherapy in combination with corticosteroids (11, 15) and some authors added UDCA (13, 19). In high doses, UDCA increases the expression of transporter proteins in the canalicular membrane and has antiapoptotic properties. Rifampicin, antihistamines, and cholestyramine have been used to ameliorate pruritus that usually accompanies jaundice (20).

ABVD, the most used regimen in upfront treatment of cHL, has limitations in severe hyperbilirubinemia. Vinca alkaloids and anthracyclines are considered as possibly hepatotoxic drug classes (13, 16, 21) and their use has not been extensively studied in cases with markedly elevated bilirubin levels. However, there are reports of patients (10) that received full or modified doses of doxorubicin and vinblastine despite cholestasis. BEACOPP regimen also contains an anthracycline and a vinca alkaloid, resulting in the same limitations (20). In other cases, nitrogen mustards (9, 15, 22), mainly mechlorethamine, have been used in jaundiced cHL patients. ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin) in modified drug doses has also been administered in a case report (23), leading to only a mild decrease of total bilirubin. Rituximab (8, 20) has been combined with BEACOPP-14 (20) and gemcitabine/cisplatin (8) leading to bilirubin normalization after several months. In another case with relapsed/refractory cHL and cholestasis, cyclophosphamide and methylprednisolone were used as bridging therapy to nivolumab with excellent outcome (24).

The use of the CD30-directed antibody-drug conjugate BV has changed the therapeutic approach for many patients with

relapsed cHL (25, 26). BV has been used at the reduced dose of 1.2 mg/kg in three cases with relapsed/refractory cHL and jaundice, with improvement in bilirubin levels (27, 28). BV in combination with sequential procarbazine, cyclophosphamide and prednisolone was also administered in another case with cHL-related VBDS with good results (29).

Intrahepatic cholestasis and VBDS in patients with lymphoma result in a high mortality rate and prompt referral for liver transplantation should be considered in selected cases that do not respond to cHL-directed therapy. There are reports of cHL patients that were evaluated in transplant centres, but further data are scarce (30).

The prognosis of intrahepatic cholestasis and VBDS in patients with cHL depends on the rates of biliary epithelium apoptosis and regeneration (16). Factors that influence outcome are the severity of hyperbilirubinemia, stage of the lymphoma, performance status, comorbidities and previous liver diseases (9). Cholestasis may be reversible in around one-third of patients and achieving complete response to the treatment of lymphoma is the key for improvement of liver dysfunction.

Liver biopsy in our case was performed after the use of dexamethasone and BV. The diagnostic criteria of VBDS were not met, but the possibility that VBDS was present on admission and that treatment halted apoptosis and led to regeneration of the biliary epithelium – although highly unlikely- cannot be excluded.

More than one third of cHL cases with intrahepatic cholestasis or VBDS achieved one year liver failure free survival (4). Our patient shared some common characteristics with this favourable subset of cases. The most encouraging fact was his response to chemotherapy that was confirmed by the Interim PET/CT scan. Stage II disease (4), Performance Status 0, absence of previous liver diseases or other comorbidities and the presence of biliary regeneration in the biopsy specimen, were favourable prognostic factors based on the literature review (9).

Regarding the initially high IgE, a gradual decrease to a value of 226 U/ml (ULN: 165 U/ml) was noticed at the end of the fifth cycle of ABVD. Markedly elevated IgE as a presenting feature of cHL is rare (31). When no indications of allergy or parasitic infections exist, broadening the differential diagnosis is necessary, with sporadic cases of IgE elevation at diagnosis of lymphoproliferative disorders being of special interest (31).

Conclusion

VBDS and intrahepatic cholestasis are rare and potentially fatal complications of cHL. Most of the drugs used in newly diagnosed cHL treatment protocols are metabolized in the liver and may be associated with extensive toxicity and/or worsen cholestasis. Mediastinal bulky disease and intrahepatic cholestasis in this case report urged the need for

an effective treatment plan. BV, used at a reduced dose as a bridging therapy, paved the way for safe administration of ABVD with resolution of hyperbilirubinemia and lymphadenopathy and should be considered as a high-priority treatment plan in these challenging cases. Medical imaging methods combined with liver biopsy procedures and reports of cases like ours can expand the knowledge of liver dysfunction in cHL and aid in the diagnosis of these rare entities. Their prompt recognition and appropriate treatment can dramatically affect cHL patients' outcome.

Conflicts of Interest

The Authors have no relevant conflicts of interest to declare regarding this study.

Authors' Contributions

I.P. and E.H. were involved in patient care, conceived the current study and wrote the manuscript; M.K., K.P., El.K, and H.M. were involved in patient care and made comments to the final version of the manuscript; Ep.K. performed literature search and contributed to the writing of the manuscript; T.P.V. interpreted the data and revised critically the manuscript; A.P-B performed the immuno-histochemical staining and examination of the liver biopsy and provided expert opinion. All Authors read and approved the final version of the manuscript.

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