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CASE REPORT

Primary non-Hodgkin's lymphoma of the common bile duct: A case report and literature review

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Summary Hepatobiliary involvement by malignant lymphoma is usually a secondary manifestation of systemic disease, whereas primary non-Hodgkin's lymphoma of the extrahepatic biliary ducts is an extremely rare entity. We describe the case of a 57-year-old man who presented with an acute onset of obstructive jaundice and severe itching. Abdominal ultrasonography and computed tomography revealed intrahepatic and common hepatic ducts dilatation. Magnetic resonance cholangiopancreatography and endoscopic retrograde cholangiopancreatography showed a mid-common bile duct stricture. The patient was presumed to have cholangiocarcinoma of the common bile duct, and an *en bloc* resection of the tumor with Roux-en-Y hepaticojejunostomy and porta-hepatis lymph nodes dissection was performed. Histopathology and immunohistochemistry revealed a large B cell non-Hodgkin's lymphoma. The patient received six cycles of combination chemotherapy using cyclophosphamide, vincristine, prednisone, and rituximab (CVP-R) protocol, and after a 5-year follow-up he is still in complete remission. We also reviewed the cases published from 1982 to 2012, highlighting the challenges in reaching a correct preoperative diagnosis and the treatment modalities used in each case.

1. Introduction

Non-Hodgkin's lymphoma (NHL) accounts for 1–2% of all cases of malignant biliary obstruction.[1] To our knowledge and after reviewing the literature since the first case was published by Nguyen[2] in 1982, only 28 cases have been reported. Herein we present another case of primary NHL of

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the common bile duct. A literature review was conducted of the challenges in arriving at the diagnosis preoperatively and the debate around the optimal treatment modalities.

2. Case report

A 57-year-old man with no previous chronic medical illnesses presented with a 2-week history of severe itching all over his body, associated with general fatigue, malaise, and nausea, without vomiting or anorexia. He also reported having a yellowish discoloration of sclera, dark (tea color) urine, and a bulky foul-smelling stool. However, he denied any history of fever or chills, abdominal pain, previous episodes of similar symptoms, recent travels, or contact with sick people. He is not on any regular medications, and he denied recent ingestion of any drug. His surgical history and family history showed no significant finding. Moreover, he has a 40 pack-year smoking history but no history of alcohol consumption or illicit drug use.

On presentation his vital signs were within normal limits. The physical examination revealed deep scleral and skin jaundice with itching marks on his skin. There was no cervical lymphadenopathy and no stigmata of chronic liver disease. An abdominal examination revealed a soft and lax abdomen with mild tenderness over the epigastric and right upper quadrant areas, and active bowel sounds but no masses or hepatosplenomegaly.

His laboratory results showed hemoglobin, white cell count, and platelets of 15 g/dL, 7 $\times$ 10^3/mm^3, and 162 $\times$ 10^3, respectively. His serum total bilirubin, direct bilirubin, alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma glutamyl transpeptidase, lactate dehydrogenase, and amylase results were 18.3 mg/dL 16.1 mg/dL, 116 U/L, 66 U/L, 161 U/L, 658 U/L, 898 U/L, and 58 U/L, respectively. His blood carbohydrate antigen 19-9 level rose to more than 1200 U/mL, and carcinoembryonic antigen was within normal levels at 0.88 ng/mL. Hepatitis A, B, and C serology was negative.

Abdominal ultrasonography revealed dilated common hepatic and intrahepatic ducts. An endoscopic retrograde cholangiopancreatography (ERCP) was subsequently performed and showed a 3-cm mid-common bile duct stricture with significantly dilated intrahepatic and common hepatic biliary ducts. The rushing cytology of the common bile duct was suspicious for malignancy. A 9-cm, 10 F stent was inserted across this for drainage (Fig. 1A).

The abdominal computed tomography (CT) scan revealed a mild intrahepatic biliary tree dilatation but was otherwise unremarkable (Fig. 1B).

Magnetic resonance cholangiopancreatography showed a marked tapered stricture at the distal common bile duct with mild to moderate dilatation of biliary tree proximally, and a normal pancreatic duct (Fig. 1C).

Based on the above presentation and investigations, a presumptive diagnosis of cholangiocarcinoma was made, and extrahepatic biliary tract excision, a Roux-en-Y hepaticojejunostomy, and porta-hepatis lymph nodes excision were performed.

A histopathologic examination of the common bile duct revealed a large B cell-type NHL with tumor-free surgical resection margins (Fig. 2), and the porta-hepatis lymph nodes showed a reactive nonspecific hyperplasia. Immunohistochemical staining was positive for CD3, CD5, CD20, CD45, BCL2, and Ki67, and negative for CD15 and CD30 (Fig. 3).

The patient was referred to the oncology clinic, where a positron emission tomography showed no evidence of malignant lesions. He received six cycles of chemotherapy using the CVP-R (cyclophosphamide, vincristine, prednisone, and rituximab) protocol. One-year follow-up chest, abdomen, and pelvis CT and whole-body positron emission tomography scans revealed no evidence of malignancy. He received six maintenance courses of rituximab (anti-CD20) and remains in complete remission 5 years from the time of diagnosis with a normal whole-body CT scan.

3. Discussion

Diffuse large B cell lymphoma (DLBCL) is the most common lymphoid neoplasm and the most common histologic subtype of NHL, accounting for approximately 25% of all cases.[3] It has an overall incidence rate of 3—7 cases per 100,000 persons per year. The incidence also increases with age (median age 64 years), and the disease appears to be

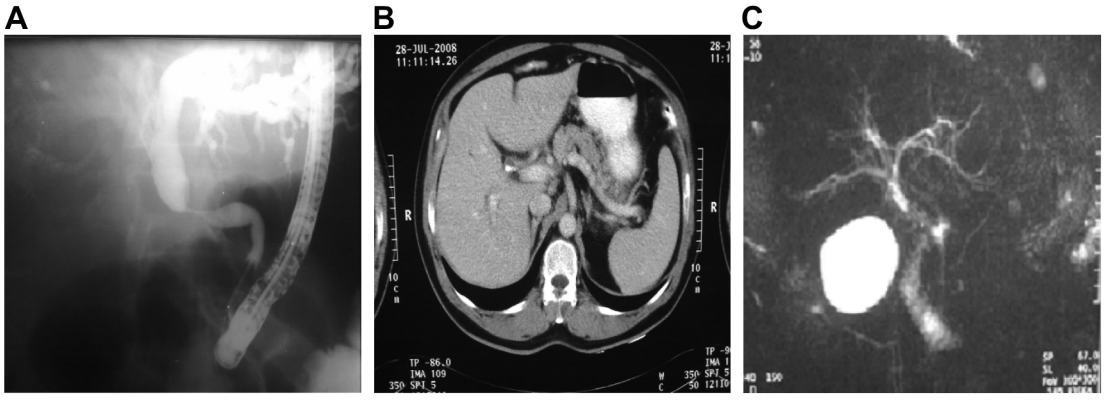

Figure 1 Imaging studies. (A) Endoscopic retrograde cholangiopancreatography showing the mid common bile duct stricture. (B) Computed tomography scan of the abdomen showing intrahepatic bile tract dilatation. (C) Magnetic resonance cholangiopancreatography showing the tapered stricture of the distal common bile duct.

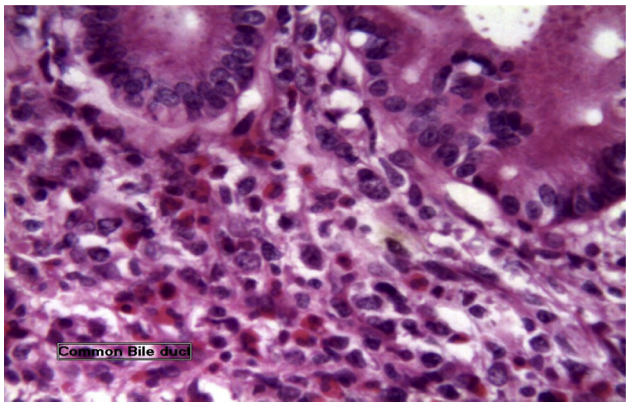

Figure 2 Histopathology of the common bile duct showing proliferating lymphocytes of medium to large size, in a background of eosinophils, neutrophils, and reactive T cell lymphocytes. Many mitotic figures and apoptotic bodies are seen.

slightly more predominant in men (55% of cases) and Caucasian Americans.[4] DLBCL typically presents with rapid nodal enlargement in the neck or abdomen, and systemic "B" symptoms are observed in 30% of patients.[5] The extranodal extramedullary disease occurs in up to 40% of the cases, and the gastrointestinal tract is the most common site of involvement. In such cases, the presenting symptoms are abdominal pain, loss of appetite, weight loss, vomiting, and night sweats.[6]

Among all patients with malignant biliary obstruction, NHL accounts for 1—2% of all cases. Their presentation with obstructive jaundice is mostly secondary to compression of the extrahepatic bile ducts by periportal, perihepatic, or peripancreatic lymphadenopathy, associated tumor lysis, or direct hepatic involvement.[1]

It is extremely rare for NHL to arise primarily from the extrahepatic bile ducts. As shown below in (Table 1),[2,7,9—34] a literature review of the period between 1982 and 2012 revealed only 28 cases, with an acute onset of obstructive jaundice being the presenting symptom in most. Of note is that only one case presented with a picture of acute pancreatitis.

In all cases reviewed, including the one reported above, the clinical presentation, the laboratory investigations, and the results of CT and cholangiography were more consistent with sclerosing cholangitis, Klatskin tumor (cholangiocarcinoma at the hepatic duct bifurcation), or pancreatic carcinoma.

It is very difficult to diagnose primary lymphoma of the extrahepatic bile ducts on the basis of CT scan, magnetic resonance imaging, and cholangiography results. However, Yoon et al[7] suggested that despite the paucity of published

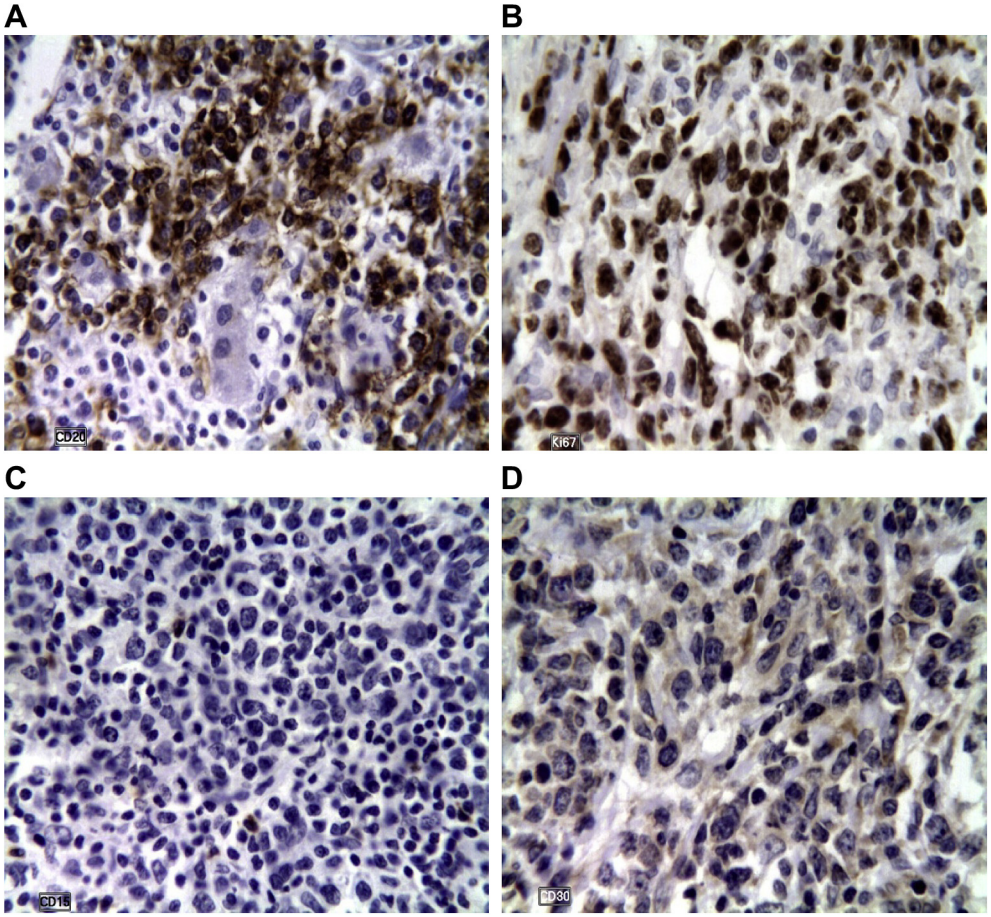

Figure 3 Immunohistochemistry showing (A) positive CD20, a marker of B cell lymphoma; (B) positive Ki67 in 80% of the slide reflecting a high grade; (C) negative CD15, a marker of Hodgkin's lymphoma; (D) negative CD30, a marker of Hodgkin's lymphoma.

Table 1 Literature review of primary NHL of the biliary ducts between 1982 and 2012.[2,7,9–34]

Case	Author	Age (y)/ sex	Preliminary diagnosis	Histopathologic diagnosis	Treatment modality	Outcome
1	Nguyen[2]	59/male	Sclerosing cholangitis	Lymphohistiocytic lymphoma, diffuse type	Surgery Chemotherapy	Died after 8 mo
2	Takehara et al[11]	60/male		Non-Hodgkin's lymphoma of the extrahepatic duct	Surgery Chemotherapy	Unknown
3	Kaplan et al[12]	42/male	Cholangitis	High-grade non-Hodgkin's lymphoma	Surgery: Cholecystectomy, segmental resection of the CBD, and hepaticoduodenostomy Chemotherapy using cyclophosphamide, vincristine, etoposide, methotrexate, and cytosine arabinoside	Died after 10 mo
4	Tartar and Balfe[13]	48/male		Bile duct wall lymphoma	Surgery Chemotherapy	Alive after 14 mo
5	Tzanakakis et al[14]	70/male		Mixed small and large cell non-Hodgkin's lymphoma	Surgery Chemotherapy	Died after 4 mo
6	Kosuge et al[15]	68/female		B cell lymphoma of the CBD	Surgery Chemotherapy Radiotherapy	Died after 16 mo
7	Brouland et al[16]	34/female	GB carcinoma vs. sclerosing cholangitis	T cell-rich B cell lymphoma (centroblastic type) of the CBD	Surgery Chemotherapy using MACOP-B	Alive after 48 mo
8	Machado et al[17]	43/female		Bile duct lymphoma	Surgery Radiotherapy	Alive after 6 mo
9	Chiu et al[18]	25/female		Malignant lymphoma of the bile duct	Surgery	Died after 12 mo
10	Andre et al[19]	44/female	Klatskin tumor	Non-Hodgkin's lymphoma of the extrahepatic duct	Surgery Chemotherapy	Alive after 48 mo
11	Maymind et al[20]	39/female		Diffuse large B cell lymphoma of the CBD	Surgery Chemotherapy using six courses of CHOP protocol Radiotherapy	Alive after 13 mo
12	Podbielski et al[21]	66/male	Klatskin tumor vs. sclerosing cholangitis	Large B cell non-Hodgkin's lymphoma	Surgery: *En bloc* resection of the tumor	Unknown
13	Oda et al[22]	58/male		Non-Hodgkin's lymphoma of the extrahepatic duct	Surgery	Died after 32 d
14	Corbinais et al[23]	29/male		High-grade T cell non-Hodgkin's lymphoma of the CBD	Chemotherapy using COP plus CHOP protocol	Alive after 12 mo
15	Eliason and Grosso[24]	41/male	Klatskin tumor	Diffuse large B cell lymphoma of the extrahepatic ducts	Surgery: CBD excision, Roux-en-Y hepaticojejunostomy, and cholecystectomy	Unknown

16	Gravel et al[25]	4/male	Sclerosing cholangitis, histiocytosis X or lymphoma	Lymphoblastic lymphoma of the pre-B type of the biliary ducts	Surgery: Exploratory laparotomy, incisional biopsy of the GB, and then cholecystectomy Chemotherapy using methotrexate, vincristine, doxorubicin, and prednisone	Alive after 18 mo
17	Kang et al[26]	73/female	Pancreatic vs. cholangiocarcinoma	Low-grade B cell lymphoma of MALT type	Surgery: Whipple's operation	Alive after 23 mo
18	Ferluga et al[27]	3/female	Klatskin tumor	Grade II follicular lymphoma of the GB, cystic duct and CBD	Surgery: Resection of GB and CBD followed by hepaticojejunostomy	Alive after 36 mo
19	Suzuki et al[28]	71/female	Bile duct carcinoma	MALT lymphoma of the CBD	Surgery: Pylorus-preserving pancreaticoduodenectomy	Unknown
20	Joo et al[9]	21/female	Bile duct cholangiocarcinoma	Diffuse large B cell malignant non-Hodgkin's lymphoma	Surgery Chemotherapy using CHOP protocol Radiotherapy using 3060 cGy external irradiation	Alive after 17 mo
21	Sugawara et al[29]	33/male	Hepatic hilar cholangiocarcinoma	Follicular lymphoma of the extrahepatic duct	Surgery: Extrahepatic duct resection with right and left hepaticojejunostomy	Alive after 12 mo
22	Shito et al[30]	71/male	Klatskin tumor	MALT lymphoma of the main hepatic duct junction	Surgery: Left hepatic and caudate lobectomy, bile duct resection and LN dissection Chemotherapy using three courses of CHOP protocol	Alive after 45 mo
23	Dote et al[10]	63/male	Pancreatic head carcinoma or cholangiocarcinoma of the CBD	Diffuse large B cell non-Hodgkin's lymphoma of the CBD	Surgery: Subtotal stomach-preserving pancreaticoduodenectomy Chemotherapy using three courses of R-CHOP protocol	Alive after 8 mo
24	Christophides et al[31]	53/female	Infiltrative cholangiocarcinoma vs. hepatocellular carcinoma	High-grade follicular lymphoma (grade 3A) of the extrahepatic ducts	Surgery: Extended right hepatectomy and Roux-en-Y hepaticojejunostomy Chemotherapy using CHOP-R protocol	Alive after 48 mo
25	Kang et al[32]	60/male	Klatskin tumor	Diffuse large B cell non-Hodgkin's lymphoma of the CHD	Surgery: CHD excision, Roux-en-Y hepaticojejunostomy and LN dissection Chemotherapy: Adjuvant chemotherapy was scheduled	Unknown
26	Yoon et al[7]	62/male	Cholangiocarcinoma of the bile duct	Marginal zone B cell lymphoma of the MALT type	Surgery: Right hemihepatectomy, bile duct resection and LN resection	Unknown

(*continued on next page*)

Table 1 (*continued*)

Case	Author	Age (y)/ sex	Preliminary diagnosis	Histopathologic diagnosis	Treatment modality	Outcome
27	Luigiano et al[33]	30/male	Acute pancreatitis	Malignant large B cell-type lymphoma of the CBD	Surgery: Resection of the CBD Chemotherapy using CHOP-R protocol	Alive after 6 mo
28	Khozeimeh et al[34]	32/male	Klatskin tumor	Follicular lymphoma of the bile duct	Surgery: *En bloc* resection of the bile duct and GB and Roux-en-Y hepaticojejunostomy Chemotherapy using four courses of rituximab (anti-CD20) and galiximab (anti-CD80)	Alive after 72 mo
29	This study	57/male	Cholangiocarcinoma of the CBD	High-grade large B cell non-Hodgkin's lymphoma of the CBD	Surgery: CBD resection, Roux-en-Y hepaticojejunostomy and LN dissection Chemotherapy using six courses of CVP-R protocol	Alive after 41 mo

CBD = common bile duct; CHD = common hepatic duct; CHOP = cyclophosphamide, hydroxydaunorubicin, oncovin and prednisone; COP = cyclophosphamide, oncovin and prednisone; CVP-R = cyclophosphamide, vincristine, prednisone, and rituximab; GB = gallbladder; LN = lymph node; MACOP-B = methotrexate, adriamycin, cyclophosphamide, oncovin, prednisone, and bleomycin.

cases, radiologists should raise the possibility of primary biliary tree lymphoma when cholangiography shows smooth, mild luminal narrowing of the extrahepatic ducts without mucosal irregularities, in spite of the diffuse thickening of the ductal wall on CT/magnetic resonance images.

It is crucial to differentiate primary NHL of the bile ducts from other causes of obstructive jaundice, as the treatment approach and prognosis are fundamentally different. There have been recent reports of success with endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNAB) in reaching a definitive tissue diagnosis, thus avoiding the surgical interventions that were performed in almost all of the reported cases for lymphomas mistakenly thought to be chemotherapy- or radiotherapy-resistant malignancies.[8]

In our case, the patient's clinical presentation, high level of carbohydrate antigen 19-9, a mid-common bile duct stricture on ERCP, brush cytology suspicious for malignant cells, and a dilated common bile duct on CT scan were consistent with cholangiocarcinoma of the bile duct. It was only upon surgical resection of the tumor and histopathologic as well as immunohistochemical examination of the specimens that a definitive diagnosis of high-grade B cell-type NHL of the common bile duct was made.

DLBCL is an aggressive form of lymphoma, and its primary extranodal involvement of the common bile duct is an extremely rare disease. There is therefore unfortunately no consensus on the best treatment modality to be used. Joo et al[9] and Dote et al[10] suggest that surgery is important for establishing the diagnosis and removing the lymphoma, and that subsequent chemotherapy and/or radiotherapy after the initial surgery might be effective.

Our case revealed that surgical resection of the tumor for definitive tissue diagnosis followed by a combination of chemotherapy using six cycles of CVP-R, maintain the patient in a complete remission for more than 5 years. However, further follow-up and more studies are required to further elucidate the most appropriate treatment modality.

In conclusion, although primary NHL of the biliary ducts is an extremely rare disease, it should be considered in the differential diagnosis of malignant obstructive jaundice. A tissue biopsy by either EUS-FNAB or surgical intervention showing a characteristic histopathologic and immunohistochemical findings is the gold standard for definitive diagnosis. The best treatment modality is still to be identified, although surgical resection of the tumor followed by chemotherapy and/or radiotherapy is considered an effective option.

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