

Primary non-Hodgkin lymphoma of the extra-hepatic bile duct: A case report

NIKOLAOS PARARAS¹, PERIKLIS G. FOUKAS², ANDREAS PIKOULIS³,
GEORGE BAGIAS³, DIMITRIS PAPA-KONSTANTINOU³, VASSILIKI PAPPA⁴,
KONSTANTINOS NASTOS³ and EMMANOUIL PIKOULIS³

¹Surgical Department, Dr Sulaiman Al Habib Hospital, Riyadh 12987, Saudi Arabia; ²Second Department of Pathology;
³Third Department of Surgery, National and Kapodistrian University of Athens, Attikon University Hospital;
⁴Hematology Unit, Second Propaedeutic Department of Internal Medicine and Research Institute, School of Medicine,
National and Kapodistrian University of Athens, Attikon University Hospital, 12462 Athens, Greece

Received November 4, 2021; Accepted February 7, 2022

DOI: 10.3892/mco.2022.2548

Abstract. Lymphoma is known to be a systemic lymphoproliferative malignancy, which is divided into two subtypes: Hodgkin lymphoma and non-Hodgkin lymphoma. Non-Hodgkin lymphoma originates from nodal and extra-nodal sites. In the staging of non-Hodgkin lymphoma, the liver is implicated in 40% of cases; however, primary liver non-Hodgkin lymphoma represents <1% of all non-Hodgkin lymphoma cases. Because of its rarity, it is not usually considered in the differential diagnosis of patients that present with jaundice. Since the first case of primary non-Hodgkin lymphoma of the extra-hepatic bile ducts was presented, only 42 similar cases have been reported in the English literature. The present case report describes a rare case of non-Hodgkin lymphoma of the common hepatic duct, which presented with obstructive jaundice and represented a complex differential diagnostic issue.

Introduction

Non-Hodgkin lymphoma mimicking a Klatskin tumor is a very rare clinical entity. In the staging of non-Hodgkin lymphoma, the liver is implicated in 40% of cases; however, primary liver non-Hodgkin lymphoma represents <1% of all non-Hodgkin lymphoma cases worldwide (1). Nguyen (2) first described a case of primary non-Hodgkin lymphoma of the extra-hepatic bile duct in 1982. The clinical manifestation is very similar to

a Klatskin tumor and imaging studies cannot easily differentiate these lesions. Because of its rarity as a cause of biliary obstruction, non-Hodgkin lymphoma is rarely considered in differential diagnosis; consequently, major surgeries are undertaken in most patients with a presumptive diagnosis of cholangiocarcinoma (3,4).

Since Nguyen described the first case of primary non-Hodgkin lymphoma of the extra-hepatic bile duct, only 42 similar cases have been reported in the English literature (5). The present case report described another rare case of non-Hodgkin lymphoma of the common hepatic duct with obstructive jaundice, for which differential diagnosis was complex.

Case report

A 61-year-old woman was admitted to the Third Department of Surgery, National and Kapodistrian University of Athens, Attikon University Hospital (Athens, Greece) with a 10-day history of jaundice associated with generalized pruritus, stool discoloration and dark urine, combined with a history of nausea and vomiting. A 5 kg weight loss was reported over the previous 3 months. Her past medical history was significant only for arterial hypertension and she reported no past radiation exposure. Physical examination revealed a non-distended, non-tender, supple abdomen and the patient remained afebrile after the onset of her symptoms. Laboratory tests indicated elevated total and direct bilirubin levels of 9.95 mg/dl (normal value, <1.2 mg/dl) and 9.53 mg/dl (normal value, <0.2 mg/dl), respectively; AST of 80 U/l (normal value, <32 U/l); ALT of 81 U/l (normal value, <33 U/l); alkaline phosphatase of 298 U/l (normal values, 35-104 U/l); γ -glutamyl transferase of 232 U/l (normal values, 5-36 U/l); lactate dehydrogenase of 180 U/l (normal values, 135-225 U/l); and complete blood count within normal values. Tumor markers demonstrated a CA 19-9 of 24.9 U/ml (normal value, <27 U/ml), with normal α -fetoprotein levels of 1.6 ng/ml (normal value, <7 ng/ml) and carcinoembryonic antigen levels of 2.1 ng/ml (normal value, <3.8 ng/ml). The serology results for hepatitis B and C were

Correspondence to: Dr Nikolaos Pararas, Surgical Department, Dr Sulaiman Al Habib Hospital, Hamza Street, Al Zahra, Riyadh 12987, Saudi Arabia
E-mail: npararas@gmail.com

Key words: primary non-Hodgkin lymphoma of the extra-hepatic bile duct, obstructive jaundice, differential diagnosis, Klatskin tumor, treatment

negative. An abdominal ultrasound (US) performed before admission indicated a 9.8 mm dilatation of the intra-hepatic ducts and the common hepatic duct. Abdominal computerized tomography (CT), also performed before admission, indicated dilatation of the common hepatic duct, and of the intra- and extra-hepatic ducts, and a mass situated in the liver hilum (Figs. 1-3), as well as a 4x3 cm round mass in the left adrenal gland, with features indicative of probable adenoma.

On admission, magnetic resonance cholangiopancreatography revealed an obstructing mass measuring 3.5x3 cm in the liver hilum, probably emerging along the extra-hepatic course of the common hepatic duct, with possible extension within the gallbladder and causing dilatation of the intra-hepatic ducts through common hepatic duct compression. The peripheral part of the common hepatic duct, the pancreatic duct and the pancreas appeared to be normal. A small (11 mm) lesion in segment VII of the liver was also identified, which was considered a possible metastatic lesion. The left adrenal mass was confirmed to measure 4x3 cm and to be an adenoma.

The case was then discussed during the tumor board meeting and a biopsy from the hilar mass was requested before further treatment for extra-hepatic cholangiocarcinoma. Endoscopic US was performed to meet this goal and showed an endoluminal obstructing mass in the common hepatic duct, causing central duct dilatation and enlarged lymph nodes of the liver hilum, thus raising suspicion for lymphoproliferative disorder. Fine needle aspiration from the mass was subsequently performed, and cytological analysis revealed a high-grade lymphoproliferative disease, without evidence of adenocarcinoma cells. However, the specimen was not adequate to enable a definite diagnosis. To further identify the disease and investigate the possibility of a lymphoma mimicking a Klatskin tumor, a bone marrow biopsy was performed, which showed reactive changes from the B and T cell series with the presence of two lymphoid aggregates consisting of both small CD3⁺ T cells and CD20⁺ B cells (B=T).

Thereafter, diagnostic laparoscopy was undertaken to extract an adequate tissue sample for pathology. The mass in the liver hilum was identified during the operation, and a lymph node from the hepatoduodenal ligament was retrieved. The specimen was fixed in 10% neutral buffered formalin for 24 h at room temperature (RT), processed by routine methods and embedded in paraffin. For routine histology, sections were stained at room temperature for 30 min with hematoxylin (cat. no. CS700; Dako; Agilent Technologies, Inc.) and eosin (cat. no. CS701; Dako; Agilent Technologies, Inc.) in Dako Coverstainer (Dako; Agilent Technologies, Inc.) and studied under a light microscope (Nikon Eclipse E200; Nikon Corporation). Immunostaining was performed on 3- μ m deparaffinized sections. Primary antibodies against CD3 (rabbit polyclonal, 1:300 dilution; Zytomed Systems GmbH), CD20 (mouse monoclonal, clone L26 1:100 dilution; Dako; Agilent Technologies, Inc.), Pax-5 (mouse monoclonal, clone DAK-PAX5, ready to use; Dako; Agilent Technologies, Inc.), CD5 (rabbit monoclonal, clone SP19/4C7, 1:200 dilution; Dako; Agilent Technologies, Inc.), CD10 (mouse monoclonal, clone 56C6, ready to use; Dako; Agilent Technologies, Inc.), Bcl-6 (mouse monoclonal, clone PG-B6P, 1:20 dilution; Dako; Agilent Technologies, Inc.), Bcl-2 (mouse monoclonal, clone 124, 1:40 dilution; Dako; Agilent Technologies, Inc.), MUM-1 (mouse monoclonal, clone MUM-1P, 1:40 dilution; Dako; Agilent



Figure 1. Computed tomography scan showing the 3.5x3 cm mass in the liver hilum (arrow).



Figure 2. Computed tomography scan showing enlarged hilar lymph nodes (arrow).

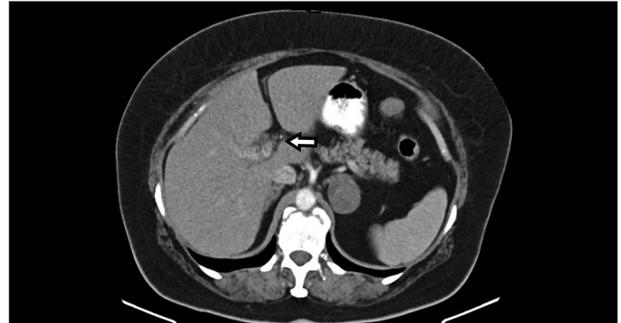


Figure 3. Computed tomography scan showing dilated intra-hepatic ducts (arrow).

Technologies, Inc.), MYC (mouse monoclonal, clone EP121, 1:50 dilution; Bio SB, Inc.), CD30 (mouse monoclonal, clone BER-H2, 1:50 dilution; Dako; Agilent Technologies, Inc.), Ki67 (mouse monoclonal, clone MIB-1, 1:200 dilution; Dako; Agilent Technologies, Inc.) were used (6). For antigen retrieval, slides were immersed in a high pH Dako EnVision Flex Target Retrieval Solution (50X, cat. no. DM828; Dako; Agilent Technologies, Inc.) at 97°C for 20 min and endogenous peroxidase activity was blocked using the Dako EnVision FLEX Peroxidase Blocking Reagent before antibody incubation (cat. no. SM801; Dako; Agilent Technologies, Inc.) (6). Immunohistochemistry was performed using the Dako Autostainer Link 48 device, with EnVision™ detection and visualization kit (cat. no. K5007) and Dako EnVision DAB + Chromogen Flex substrate buffer (dilution 1 drop/ml) for colour development (all from Dako; Agilent

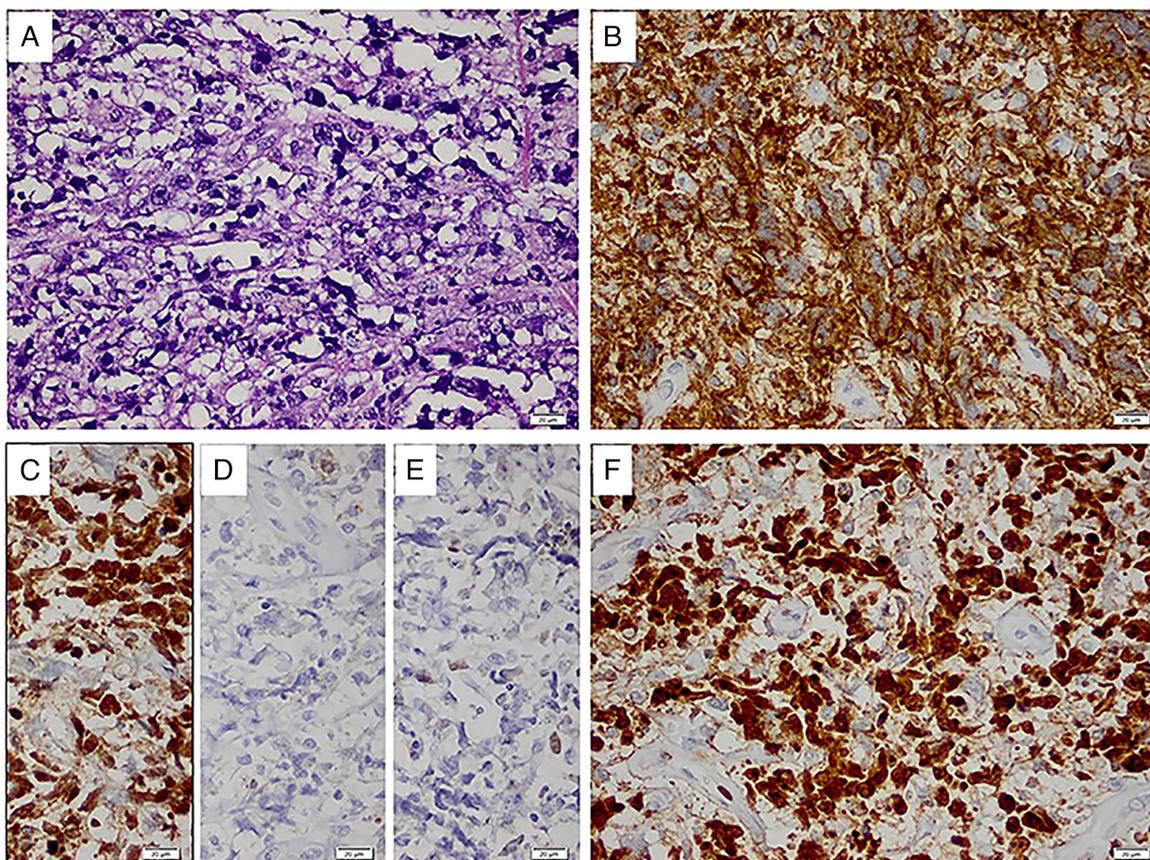


Figure 4. (A) Diffuse infiltrate comprising large lymphoid cells. (B) Neoplastic lymphoid cells expressing CD20. (C) Bcl-6 positivity in the majority of nuclei. Lack of expression of (D) CD10 and (E) MUM-1. (F) Ki67 proliferation index was high (~90%). Scale bar, 20 μ m.

Technologies, Inc.). All sections were lightly counterstained with Harris Hematoxylin (Biognost) for 45 sec at RT, prior to mounting (6).

Histology showed a diffuse infiltrate, that disrupted normal lymph node architecture, consisting of large lymphoma cells with centroblastic morphology and the following immunophenotype: CD20⁺, PAX5⁺ (data not shown), Bcl-6⁺, CD10⁻, MUM-1⁻ and CD30⁻, with a high Ki67 proliferation index (~90%) (Fig. 4). Accordingly, the neoplasm was classified as diffuse large B-cell lymphoma, not otherwise specified, germinal center B-cell-like according to Hans algorithm (7). The patient provided written informed consent for the publication of the data and accompanying images.

The revised International Prognostic Index (R-IPI) score (8) for this patient was 2, indicating a good prognosis and an estimated overall survival of 79%. Therefore, after the diagnosis of primary non-Hodgkin lymphoma of the common hepatic duct was reached, chemotherapy with cyclophosphamide, doxorubicin, vincristine and prednisolone in conjunction with the anti-CD20 monoclonal antibody rituximab (R-CHOP regimen) was scheduled. The patient was in good health 8 months after the diagnosis, without recurrence of the cholestatic phenomena.

Discussion

Non-Hodgkin lymphoma is found in only 1-2% of all malignant biliary obstruction cases in adults worldwide (9).

Because of its rarity, it is not usually considered in the differential diagnosis for patients presenting with jaundice (10). Its presentation with obstructive jaundice is mainly due to compression of the extra-hepatic ducts by periportal, perihepatic or peripancreatic lymphadenopathy (11,12). Primary non-Hodgkin lymphoma of the extra-hepatic bile duct is very rare. According to a review of the English literature, since the first case was reported by Nguyen (2) in 1982, a total of 43 total cases have been described, including the present report. In 2007, Odemiş *et al* (13) reported an incidence of primary biliary non-Hodgkin lymphoma in patients with malignant cholangiocarcinoma of 0.6%, accounting for 0.016% of all cases of non-Hodgkin lymphoma globally.

Hepatitis B virus, hepatitis C virus, HIV, Epstein Barr virus, elevated lactate hydrogenase levels or low immunity have been associated with the development of primary biliary non-Hodgkin lymphoma (1,14,15). The clinical manifestations are jaundice, fever, abdominal pain, weight loss and the presence of an abdominal mass. Diagnosing a primary lymphoma of the extra-hepatic duct is difficult through CT, MRI or magnetic resonance cholangiopancreatography because, in most cases, the associated clinical and radiological features closely resemble those of cholangiocarcinoma. Therefore, tissue biopsy is required; however, preoperative histological diagnosis remains a major challenge, particularly in lesions of the hepatic hilum.

In adults, Klatskin tumor, malignant lymph nodes (metastatic or primary) and hepatoma are the most likely causes of hilar biliary obstruction. Minimally invasive techniques for

verifying the diagnosis include US- or CT-guided biopsy of the tumor mass, and endoscopic brushing in endoscopic retrograde cholangiopancreatography, percutaneous transluminal cholangiography or cholangioscopy in patients with cholangiocarcinoma. The success rate for these techniques varies widely, from 20 to 80% (16). Success with endosonographically guided fine-needle aspiration cytology has previously been reported (16). In the present case report, attempts to perform this technique were unsuccessful, because the tissue obtained was insufficient for a diagnosis. Hence, in some cases, surgery is inevitable to obtain an adequate sample and achieve an accurate diagnosis (17,18).

Because of the rarity of primary biliary non-Hodgkin lymphoma, the treatment options are unclear. However, as soon as a diagnosis is verified, chemotherapy is considered the gold standard treatment. Immunochemotherapy with doxorubicin, rituximab plus cyclophosphamide, vincristine and prednisone (R-CHOP) is generally used (3,19). The original IPI was developed and validated before the addition of rituximab to curative anthracycline-based chemotherapy (20). Clinical trials (15-18) have confirmed that rituximab can improve the survival of patients with diffuse large B-cell lymphoma.

The R-IPI score was developed to predict the outcomes of individuals receiving rituximab with chemotherapy. The score can differentiate patients into three groups (very good, good or poor); at present, all of these groups have a survival rate of >50% (21). Although it remains unclear as to whether chemotherapy should be administered prior to biliary drainage in patients with non-Hodgkin lymphoma presenting with jaundice, chemotherapy alone usually alleviates obstructive jaundice without the need for biliary drainage (22). Dudgeon and Brower (22) described five cases of patients with non-Hodgkin lymphoma causing obstructive jaundice that were treated with combined chemotherapy without prior surgical or endoscopic biliary decompression or radiation therapy. The therapy rapidly alleviated the jaundice in all patients and had acceptable toxic side effects; notably, all five patients achieved remission (22). In some patients, radiotherapy is helpful and can also be used to treat patients with residual disease after the primary chemotherapy or to relieve pain. Nevertheless, whether radiation therapy is an essential treatment remains to be further explored, because of the scarcity of cases of the disease (10). Moreover, studies on the prognostic implications of primary biliary non-Hodgkin lymphoma are lacking.

In conclusion, the present case report described a rare case of primary non-Hodgkin lymphoma of the common hepatic duct. Although it is difficult to diagnose preoperatively, primary biliary non-Hodgkin lymphoma should be considered in the differential diagnosis for obstructive jaundice. The clinical and radiological findings resemble those of cholangiocarcinoma; therefore, preoperative diagnosis is quite challenging, owing to nonspecific clinical manifestations, laboratory profiles and imaging findings. Because misdiagnosis could lead to inappropriate treatment, tissue biopsy is mandatory. Although surgery is essential for accurate histological diagnosis and local tumor control, multidisciplinary therapy, including systemic chemotherapy, may be necessary to improve the prognosis associated with this disease.

Acknowledgements

Not applicable.

Funding

No funding was received.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

NP performed data collection, substantially contributed to the conception and the design of the study, and was a major contributor in writing the manuscript. PGF performed the pathological analysis and reviewed the paper. AP performed experiments and data collection, contributed to manuscript drafting and critically revised the intellectual content. GB performed data collection and was a major contributor in writing the manuscript. DP substantially contributed to the acquisition, analysis and interpretation of the data. VP performed the hematological analysis and reviewed the paper. KN and EP substantially contributed to the conception and the design of the study, and confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

The patient provided written informed consent for the publication of the data and accompanying images.

Competing interests

The authors declare that they have no competing interests.

References

- Emile JF, Azoulay D, Gornet JM, Lopes G, Delvart V, Samuel D, Reynès M, Bismuth H and Goldwasser F: Primary non-Hodgkin's lymphomas of the liver with nodular and diffuse infiltration patterns have different prognoses. *Ann Oncol* 12: 1005-1010, 2001.
- Nguyen GK: Primary extranodal non-Hodgkin's lymphoma of the extrahepatic bile ducts. Report of a case. *Cancer* 50: 2218-2222, 1982.
- Joo YE, Park CH, Lee WS, Kim HS, Choi SK, Cho CK, Rew JS, Kim SJ and Maetani I: Primary non-Hodgkin's lymphoma of the common bile duct presenting as obstructive jaundice. *J Gastroenterol* 39: 692-696, 2004.
- Yoon MA, Lee JM, Kim SH, Lee JY, Han JK, Choi BI, Kim SW and Jang JJ: Primary biliary lymphoma mimicking cholangiocarcinoma: A characteristic feature of discrepant CT and direct cholangiography findings. *J Korean Med Sci* 24: 956-959, 2009.
- Wu J, Zhou Y, Li Q, Zhang J and Mao Y: Primary biliary non-Hodgkin's lymphoma: A case report. *Medicine (Baltimore)* 100: e26110, 2021.
- Gallamini A and Juweid M (eds): *Lymphoma*. Exon Publications, Brisbane, AU, 2021.

7. Hans CP, Weisenburger DD, Greiner TC, Gascoyne RD, Delabie J, Ott G, Müller-Hermelink HK, Campo E, Brazier RM, Jaffe ES, *et al*: Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray. *Blood* 103: 275-282, 2004.
8. Sehn LH, Berry B, Chhanabhai M, Fitzgerald C, Gill K, Hoskins P, Klasa R, Savage KJ, Shenkier T, Sutherland J, *et al*: The revised international prognostic index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. *Blood* 109: 1857-1861, 2007.
9. Lokich JJ, Kane RA, Harrison DA and McDermott WV: Biliary tract obstruction secondary to cancer: Management guidelines and selected literature review. *J Clin Oncol* 5: 969-981, 1987.
10. Ravindra KV, Stringer MD, Prasad KR, Kinsey SE and Lodge JP: Non-Hodgkin lymphoma presenting with obstructive jaundice. *Br J Surg* 90: 845-849, 2003.
11. André SB, Farias AQ, Bittencourt PL, Guarita DR, Machado MC, Viana R and Laudanna AA: Primary extranodal non-Hodgkin lymphoma of the extrahepatic bile duct mimicking Klatskin tumor. *Rev Hosp Clin Fac Med Sao Paulo* 51: 192-194, 1996.
12. Das K, Fisher A, Wilson DJ, dela Torre AN, Seguel J and Koneru B: Primary non-Hodgkin's lymphoma of the bile ducts mimicking cholangiocarcinoma. *Surgery* 134: 496-500, 2003.
13. Odemiş B, Parlak E, Başar O, Yüksel O and Sahin B: Biliary tract obstruction secondary to malignant lymphoma: Experience at a referral center. *Dig Dis Sci* 52: 2323-2332, 2007.
14. Noronha V, Shafi NQ, Obando JA and Kummar S: Primary non-Hodgkin's lymphoma of the liver. *Crit Rev Oncol Hematol* 53: 199-207, 2005.
15. Dlouhy I, Filella X, Rovira J, Magnano L, Rivas-Delgado A, Baumann T, Martínez-Trillos A, Balagué O, Martínez A, González-Farre B, *et al*: High serum levels of soluble interleukin-2 receptor (sIL2-R), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF) are associated with adverse clinical features and predict poor outcome in diffuse large B-cell lymphoma. *Leuk Res* 59: 20-25, 2017.
16. Fritscher-Ravens A, Broering DC, Sriram PV, Topalidis T, Jaeckle S, Thonke F and Soehendra N: EUS-guided fine-needle aspiration cytodiagnosis of hilar cholangiocarcinoma: a case series. *Gastrointest Endosc* 52: 534-540, 2000.
17. Kosuge T, Makuuchi M, Ozaki H, Kinoshita T, Takenaka T and Mukai K: Primary lymphoma of the common bile duct. *Hepatogastroenterology* 38: 235-238, 1991.
18. Maymind M, Mergelas JE, Seibert DG, Hostetter RB and Chang WW: Primary non-Hodgkin's lymphoma of the common bile duct. *Am J Gastroenterol* 92: 1543-1546, 1997.
19. Luigiano C, Ferrara F, Fabbri C, Ghersi S, Bassi M, Polifemo AM, Billi P, Fornelli A, Cinquantini F and D'Imperio N: Primary lymphoma of the common bile duct presenting with acute pancreatitis and cholangitis. *Endoscopy* 42 (Suppl 2): E265-E266, 2010.
20. International Non-Hodgkin's Lymphoma Prognostic Factors Project: A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med* 329: 987-994, 1993.
21. Coiffier B, Lepage E, Briere J, Herbrecht R, Tilly H, Bouabdallah R, Morel P, Van Den Neste E, Salles G, Gaulard P, *et al*: CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med* 346: 235-242, 2002.
22. Dudgeon DJ and Brower M: Primary chemotherapy for obstructive jaundice caused by intermediate-grade non-Hodgkin lymphoma. *Cancer* 71: 2813-2816, 1993.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.