Secondary Sclerosing Cholangitis and Hodgkin's Lymphoma

Seyed Hassan Abedi, Maryam Ghassami, Mahsa Molaei, Zhaleh Mohsenifar and Amir Houshang Mohammad Alizadeh

Gastroenterology and Liver Diseases Research Center, Research Institute for Gastroenterology and Liver Diseases, Shahid Beheshti University of Medical Sciences, Tehran, Iran.

ABSTRACT

CONTEXT: Liver damage is relatively common in patients affected by HL, but paraneoplastic cholestasis is an uncommon presenting symptom in HL.

CASE REPORT: We report the case of a 38-year-old man who came to our hospital with jaundice, pruritis, nausea, vomiting, weight loss, and recurrent episodes of fever without any hepatosplenomegaly or lymphadenopathy. Laboratory findings showed abnormal liver functioning with mixed hepatocellular and cholestatic patterns. Sonographic evaluation of the biliary tract was normal. We ruled out viral infections, autoimmune process, and hemochromatosis. The patient was put on ursobile and NAC (*N*-acetyl-systeine) and prednisolone treatment. In magnetic resonance cholangiopancreatography examination, there were multiple strictures in the intrahepatic and extrahepatic bile ducts with mild dilatation. Histologic finding of liver biopsy was compatible with sclerosing cholangitis or drug-induced cholestasis. General condition and laboratory examination results of the patient became better, but we found lymphadenopathy on monthly follow-up examination. Histological finding of the lymph node was compatible with HL.

CONCLUSION: This report emphasizes that HL can be presented with different paraneoplastic symptoms and that one of them is secondary sclerosing cholangitis. It has better prognosis than vanishing bile duct syndrome, and perhaps steroid treatment can be suggested.

KEYWORDS: sclerosing cholangitis, Hodgkin's lymphoma, paraneoplastic symptoms

CITATION: Abedi et al. Secondary Sclerosing Cholangitis and Hodgkin's Lymphoma. *Clinical Medicine Insights: Case Reports* 2015:8 83–87 doi: 10.4137/CCRep.S23665.

RECEIVED: January 20, 2015. **RESUBMITTED:** March 09, 2015. **ACCEPTED FOR PUBLICATION:** March 16, 2015.

ACADEMIC EDITOR: Athavale Nandkishor, Associate Editor

TYPE: Case Report

FUNDING: Authors disclose no funding sources.

COMPETING INTERESTS: Authors disclose no potential conflicts of interest.

CORRESPONDENCE: ahmaliver@yahoo.com

Paper subject to independent expert blind peer review by minimum of two reviewers. All editorial decisions made by independent academic editor. Upon submission manuscript was subject to anti-plagiarism scanning. Prior to publication all authors have given signed confirmation of agreement to article publication and compliance with all applicable ethical and legal requirements, including the accuracy of author and contributor information, disclosure of competing interests and funding sources, compliance with ethical requirements relating to human and animal study participants, and compliance with any copyright requirements of third parties. This journal is a member of the Committee on Publication Ethics (COPE).

Published by Libertas Academica. Learn more about this journal.

Introduction

Liver damage is relatively common in patients affected by Hodgkin's lymphoma (HL). Nonspecific inflammation in portal areas is seen in approximately 50% of liver biopsies, but Reed–Sternberg cells can be observed in about 5% of them.[1] However, a smaller proportion of cases develop jaundice.[2] Other causes of cholestasis in HL include biliary obstruction (by lymph node enlargement), hemolysis, viral hepatitis, and drug toxicity. In the past, many cases that presented no detectable cause of jaundice were called "idiopathic jaundice". Recently, the vanishing bile duct syndrome (VBDS) was described in HL, and it is a rare and severe cause of intrahepatic cholestasis in HL.[1,3] VBDS could be an uncommon paraneoplastic manifestation of HL.[4–6]

Patients with liver disease as the initial manifestation of HL have a poor prognosis. In particular, VBDS is a progressive and always a fatal complication in this setting, although some reversible cases have been described in association with other liver transplantations.[7] Primary sclerosing cholangitis (PSC) is a chronic cholestatic liver disease of unknown etiology, and to date, no specific treatment has been identified that alters its natural course.[8] Secondary sclerosing cholangitis (SSC) has also been reported in association with various conditions, including intraductal stone disease, surgical or blunt abdominal trauma, intra-arterial chemotherapy, recuand autoimmune pancreatitis, portal biliopathy, eosinophilic and/or mast cell cholangitis, hepatic inflammatory pseudotumor, recurrent pyogenic cholangitis, primary immune deficiency, and AIDS-related cholangiopathy.[9]

Case presentation. A 38-year-old man came to our hospital with jaundice, pruritis, nausea, vomiting, weight loss, and recurrent episodes of fever. These symptoms had been present for 1 month. He did not have any lymphadenopathy or splenomegaly initially nor did he have any history of previous jaundice, alcohol abuse, or blood transfusion.

Laboratory tests revealed the following abnormalities: AST (aspartate aminotrasferse) = 194 IU/L (reference range = 6–40 IU/L), ALT (alanine aminotransferase) = 385 IU/L (reference range = 6–40 IU/L), ALK-ph = 1070 IU/L (reference range = 30–120 IU/L), Alb = 4.7 g/dL, total protein = 6.5 g/dL, INR = 1, total bilirubin = 11.7 mg/dL (reference range = 0.1–1 mg/dL), direct bilirubin = 4.6 mg/dL (reference range = 0.1–0.4 mg/dL), WBC (white blood cell count) = 19,600 10^3/μL,

Hb = 12 g/dL, MCV (mean corpuscular volume) = 85 fL, and PLT (platelet count) = 351,000 × 10^3/μL.

An abdominal ultrasonography was performed to evaluate the biliary tract, which was found to be normal. A thoraco–abdomino–pelvic CT scan with oral and i.v. contrast was done, which did not show any hepatosplenomegaly or lymphadenopathy. The patient was referred for MRCP (magnetic resonance cholangiopancreatography), and it showed multiple strictures in the intra- and extrahepatic bile ducts with mild dilatation, which was compatible with PSC with acute cholangitis process (Fig. 1). Colonoscopy findings and biopsy of the colon were normal.

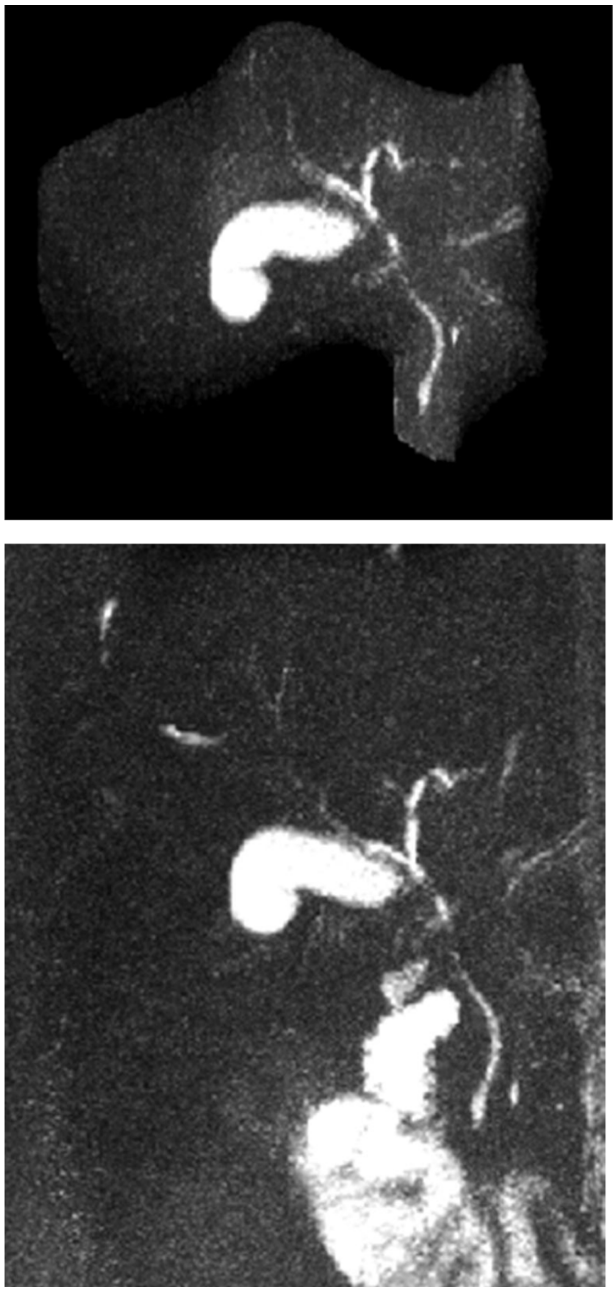

Figure 1. Intrahepatic ducts are prominent and appear dilated with irregular border and q few focal strictures. CBD is less prominent and measure up to 4 mm in diameter. No stone or mass lesion is seen in the biliary tree (multiplanar MRCP with a 1.5-T Acheiva 16 channel scanner without contrast).

Some additional laboratory examinations had been done for the patient, but these revealed negative serologic tests for hepatitis A, B, and C and HIV, negative AMA titer, and normal iron study. Laboratory tests for autoimmune hepatitis including ANA, ASMA, anti-LKM1, serum protein electrophoresis, and serum IgG_4 were done, but all of them were negative. P-ANCA and C-ANCA were negative.

He was on ceftriaxon, azithromycin, celecoxib, and some herbal medicines whose names he did not know.

During these evaluations, the patient became ill and his general condition worsened gradually. The liver function was decreasing and the bilirubin level was rising (total bilirubin = 26.1 mg/dL, direct bilirubin = 15.6 mg/dL, INR = 1.4.

We recommended the patient for liver transplantation, and his name was put on the liver transplantation waiting list.

Because of worsening laboratory findings and considering his history of some herbal medicine use, the probability of drug-induced hepatitis could not be ruled out. The patient became ill gradually, and so we started treatment with the tablet ursobile 1200 mg/day and ampoule NAC 20-hour i.v. protocol. We administered an initial loading dose of 150 mg/kg i.v. over 60 minutes, next four-hour infusions at 12.5 mg/kg/h i.v., and, finally, 16-hour infusion at 6.25 mg/kg/h.

Liver biopsy had been done, and before preparation of the report, we started prednisolone trial (50 mg/day) with the concept of drug-induced cholestasis.

Liver biopsy revealed ballooning degeneration and severe intracellular and intracanalicullar cholestasis, especially in pericentral areas. Portal tract showed mild infiltration of lymphocytes and bile duct loss, and Masson trichrome showed fibrous expansion of portal spaces. Iron was negative. These changes in liver biopsy were compatible with PSC or SSC or drug-induced cholestasis. (Fig. 2)

We followed up the patient every month, and about 3 months after starting prednisolone, the general condition and laboratory examination results of the patient became substantially better (total bilirubin = 1.3 mg/dL, direct bilirubin = 0.4 mg/dL, and an improvement in liver function test), but on physical examination, we found lymph nodes on the left axillary and cervical regions. These lymph nodes were fixed and firm with sharp borders and without any tenderness. After we ruled out Epstein–Barr virus (EBV) and toxoplasmosis infection, we referred him for surgery for excisional lymph node biopsy. Histologic evaluation of the axillary lymph node biopsy demonstrated HL with mixed cellularity. Bone marrow biopsy revealed no invasion (Fig. 3).

Thereafter, we tapered glucocorticoid administration and referred the patient to an oncologist, and he was put on chemotherapy with ABVD protocol for treatment of HL: adriamycin 25 mg/m^2, bleomycin 10 IU/m^2, vinblastine 6 mg/m^2, and dacarbazine 375 mg/m^2. He received six cycles of ABVD chemotherapy over 4 weeks, with two doses in each cycle (on days 1 and 15). All four chemotherapy drugs were

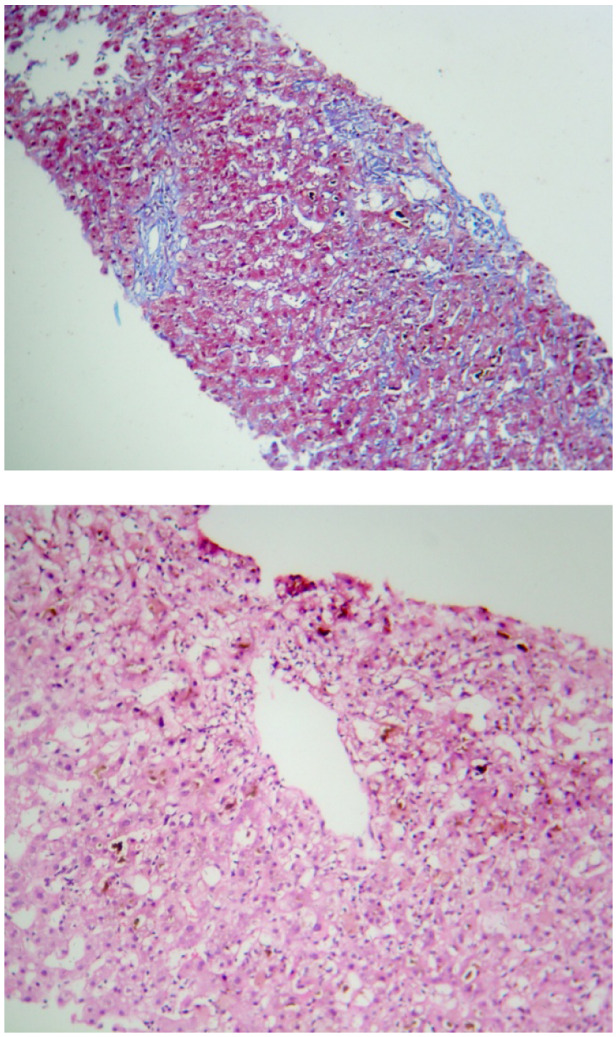

Figure 2. Liver biopsy with Masson's trichrome stain revealing ductopenia.

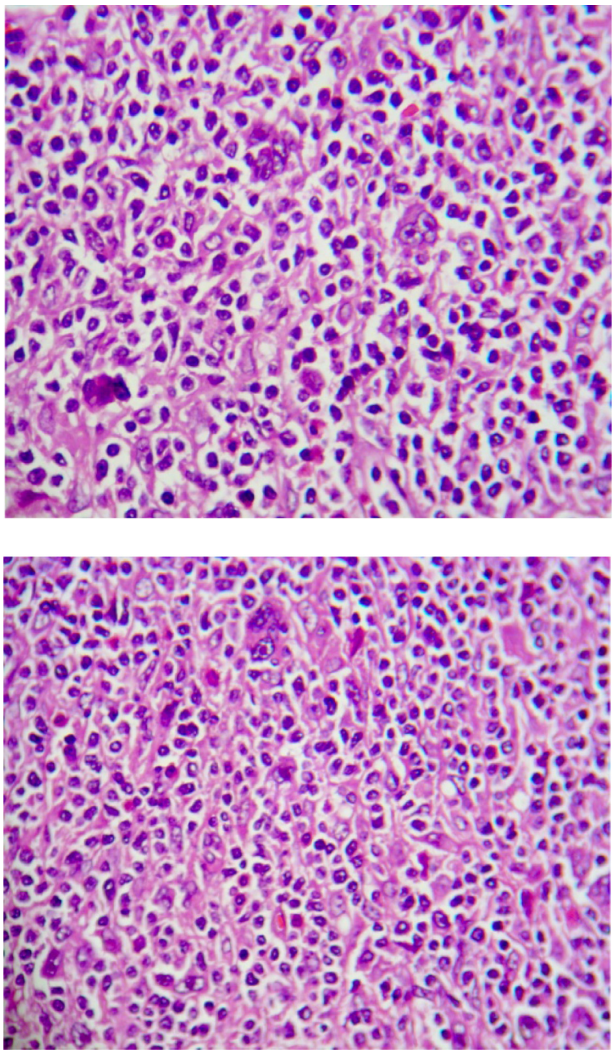

Figure 3. Axillary lymph node biopsy with Reed–Sternberg cells.

given intravenously. After that, he received 15 sessions of radiotherapy. Fortunately, he had very few side effects. He was sick for ~2–3 days after each session of chemotherapy.

After 18 months of follow-up, laboratory examinations revealed AST = 28 U/L, ALT = 41 U/L, ALK-ph = 268 U/L, total bilirubin = 0.6 mg/dL, direct bilirubin = 0.1 mg/dL, and INR = 1.

MRCP after treatment showed alteration of subtle segmental dilation, and strictures with mural irregularity at intrahepatic, main hepatic, common hepatic, and common bile duct were seen (beading and mural irregularity pattern). Bile duct findings were compatible with PSC (Fig. 4).

Discussion

Cholestasis is an uncommon presentation in HL.[10] The possible mechanisms causing cholestasis include direct intrahepatic involvement of lymphoma, extrahepatic obstruction secondary to lymphadenopathy, or causes unrelated to lymphoma such as viral hepatitis, autoimmune disorder, drug toxicities, or metabolic diseases. In a small proportion of patients, intrahepatic cholestasis results from paraneoplastic syndrome of HL. They can further be divided into two distinct groups by liver biopsy: VBDS and idiopathic cholestasis (IC).[11]

VBDS secondary to HL is a rare cause of intrahepatic cholestasis. Intrahepatic cholestasis was most marked in acinar zone 3 and presented with a "pure" form without any evidence of accompanying hepatitis.

Loss of small bile ducts was the other main histologic finding. They demonstrated that 80%–94% of small portal tracts lacked interlobular bile ducts in the liver biopsy. The mechanism of VBDS is poorly understood. Various theories have been proposed to explain VBDS in HL, such as a paraneoplastic hormone-mediated effect and release of toxic cytokines from lymphoma cells.[4]

Hubscher et al.[2] suggested that toxic cytokines are released from lymphoma cells in HL. The destruction of bile ducts in primary biliary cirrhosis, PSC, and liver allograft rejection seem to be related to cell-mediated immunologic attack by

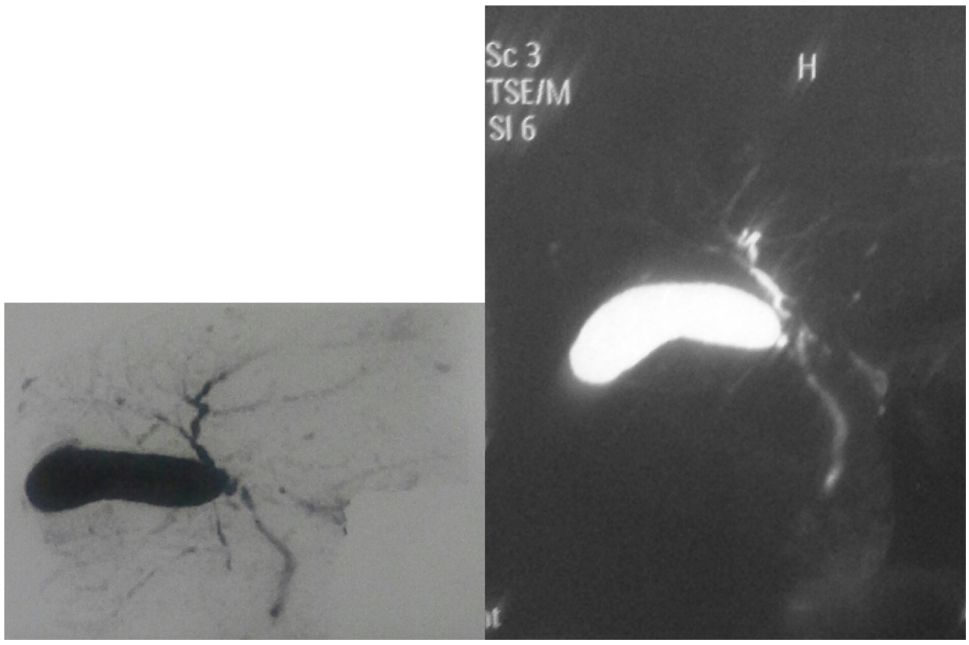

Figure 4. MRCP after treatment: bile duct findings are compatible with PSC.

cytotoxic T lymphocytes of either CD4 or CD8 phenotype. Other investigations have indicated the presence of immunoglobulins in interlobular bile ducts, suggesting the involvement of humoral immune reactions. HL may be associated with autoimmune manifestations, but even with complete remission of HL after chemotherapy, VBDS is irreversible, probably due to the fact that the affected bile ducts have a low regeneration capacity.[12]

In our patient, MRCP findings and liver biopsy were compatible with sclerosing cholangitis. Because there were no causes except HL and good response to steroid therapy in this case, sclerosing cholangitis associated to HL was thought to be secondary to an immunologic disturbance or autoimmune mechanism. However, it was unclear.

In our patient, sclerosing cholangitis presented 3 months before HL, and at the time of diagnosis of sclerosing cholangitis did not have any findings according to HL. Because of these, perhaps the progression of sclerosing cholangitis and HL are independent of each other.

IC is a diagnosis of exclusion. When cholestasis is the presenting picture of a patient with HL, other causes of jaundice must be eliminated before making this diagnosis.[5] Liver biopsy usually reveals intrahepatic cholestasis and an intact bile duct.[13] Most studies suggest that IC is a paraneoplastic phenomenon of HL.[2,14,15]

The association of cholestatic jaundice and ductopenia in HL is a severe complication with a high rate of death in a neoplastic disease, which is otherwise curable in more than 80% of patients.[16] In the Scalabrini et al case report comparing different methods of treatment in 36 patients with HL and ductopenia, 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 lymphoma and HL.

There have been some published reports regarding the development of lymphoma following long-term treatment of sclerosing cholangitis.[17]

These findings confirm our suggestion, but steroid therapy does not affect lymphoma, and many experts do not agree with steroid therapy.

Steroid therapy is not typically recommended for treatment of sclerosing cholangitis despite the possible autoimmune mechanism, as it may not alter the course of the disease.[1,2] Currently, there are only a limited number of reports of positive response to steroid therapy.[18]

There were a few reports on SSC in the background of HL. But it was very rare condition for SSC to be the presenting symptom of HL. SSC has better prognosis.

Conclusion

This report emphasizes that HL can be presented with different paraneoplastic symptoms, and one of them is SSC. It has better prognosis than VBDS, and perhaps, we could suggest steroid therapy for its treatment. We need more case studies for better judgment.

Author Contributions

Conceived and designed the experiments: SHA. Analyzed the data: MG. Wrote the first draft of the manuscript: SHA. Contributed to the writing of the manuscript: MM, ZM. Agree with manuscript results and conclusions: AHMA. Developed the structure and arguments for the paper: SHA. Made critical revisions and approved final version: AHMA. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Jaffe ES. Malignant lymphoma: pathology of hepatic involvement. *Semin Liver Dis*. 1987;7:257–68.
2. Hubscher SG, Lumley AL, Elias E. Vanishing bile duct syndrome: a possible mechanism for intrahepatic cholestasis in Hodgkin's lymphoma. *Hepatology*. 1993;17(1):70–7.
3. Gottrand F, Cullu F, Mazingue F, Nelken B, Lecomte-Houcke M, Farriaux JP. Intrahepatic cholestasis related to vanishing bile duct syndrome in Hodgkin's disease. *J Pediatr Gastroenterol Nutr*. 1997;24:430–3.
4. Guliter S, Erdem O, Isik M, Yamac K, Uluoglu O. Cholestatic liver disease with ductopenia (vanishing bile duct syndrome) in Hodgkin's disease: report of a case. *Tumori*. 2004;90:517–20.
5. Barta SK, Yahalom J, Shia J, Hamlin PA. Idiopathic cholestasis as a paraneoplastic phenomenon in Hodgkin's lymphoma. *Clin Lymphoma Myeloma*. 2006;7(1):77–82.
6. Joseph M, Connors MD. Clinical manifestations and natural history of Hodgkin's lymphoma. *Cancer J*. 2009;15(2):124–8.
7. Hubscher SG, Buckels JA, Elias E, McMaster P, Neuberger JM. Reversible vanishing bile duct syndrome after liver transplantation: report of 6 cases. *Transplant Proc*. 1991;23(1):1415–6.
8. LaRusso NF, Shneider BL, Black D, et al. Primary sclerosing cholangitis: summary of a workshop. *Hepatology*. 2006;44:746–64.
9. Abdalian R, Heathcote EJ. Sclerosing cholangitis: a focus on secondary causes. *Hepatology*. 2006;44(1063):1074.
10. Levitan R, Diamond HD, Carver LF. Jaundice in Hodgkin's disease. *Am J Med*. 1961;30:99–111.
11. Hong CL, Tsai JH, Wang VY, et al. Hodgkin's lymphoma presenting as idiopathic cholestatic jaundice, Division of Hematology and Oncology, Department of Internal Medicine, National Cheng Kung University, Tainan. *J Med*. 1961;30:99–111.
12. Rossini MS, Lorand-Metze I, Borba Oliveira G, De Souza CA. Vanishing bile duct syndrome in Hodgkin's disease: case report. *Sao Paulo Med J*. 2000;118(5):154–7.
13. David A. Intrahepatic cholestasis due to Hodgkin's disease. *J Clin Gastroenterol*. 1986;8(3):304–7.
14. Bournocle BA, Old JW, Vazques AG. Pathogenesis of jaundice in Hodgkin's disease. *Arch Intern Med*. 1962;110:872–83.
15. Seymour JF, Talpaz M, Hagemeister FB, Cabanillas F, Kurzrock R. Clinical correlates of elevated serum levels of interleukin- 6 in patients with untreated Hodgkin's disease. *Am J Med*. 1997;102:21–8.
16. Scalabrini DR, Caravelli D, Carnevale Schianca F, et al. Complete remission of paraneoplastic vanishing bile duct syndrome after the successful treatment of Hodgkin's lymphoma: a case report and review of the literature. *BMC Res Notes*. 2014;7:529.
17. Tae HJ, Lee HL, KimJ O, Joo YW, Choi HS. Sclerosing cholangitis and non-Hodgkin's lymphoma. *Korean J Pancreas and Biliary Tract*. 2013;18(1):20–2.
18. Sekhon JS, Chung RT, Epstein M, Kaplan MM. Steroid-responsive (autoimmune?) sclerosing cholangitis. *Dig Dis Sci*. 2005;50:1839–43.