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FULL PAPER

Hepatitis C infection and autoimmune hemolytic anemia in a patient with colon B-cell non-hodgkin lymphoma: a case report

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Malignant lymphoma is categorized into Hodgkin's lymphoma (HL) and non-Hodgkin's lymphoma (NHL). Lymphoma, especially NHL, can manifest outside lymph nodes, particularly in the gastrointestinal (GI) tract. Hepatitis C virus (HCV) can induce disruptions in both the liver and other organs, with NHL being the most common extrahepatic manifestation. Secondary Autoimmune Hemolytic Anemia (AIHA) can develop in patients with lymphoproliferative disorders. A 47-year-old man presented with abdominal pain, jaundice, and weight loss. His laboratory examination revealed anemia, (direct and indirect) hyperbilirubinemia, elevated levels of aspartate transaminase (AST), alanine transaminase (ALT), and lactate dehydrogenase (LDH), reactive anti-HCV, and positive HCV RNA. Biopsy results supported a diagnosis of B-cell NHL. In addition, imaging displayed multiple intra-abdominal lymphadenopathies. The patient was diagnosed with colon B-cell NHL primarily based on clinical symptoms and biopsy results. NHL in this patient could be attributed to HCV infection. Furthermore, the AIHA experienced by these patients may result from lymphoproliferative disorders, namely NHL.

KEYWORDS

NHL; hepatitis C; B-cell NHL; primary GI lymphoma; AIHA.

Introduction

Lymphomas often occur in the lymph nodes, particularly in the head and neck region. However, this disease can also manifest in extranodal sites, with non-Hodgkin's lymphoma (NHL) being the most common in the extranodal type [1-2]. Gastrointestinal lymphoma (GL) constitutes 5-10% of all NHL cases. Although gastrointestinal lymphoma is the most common extranodal NHL, primary colonic NHL itself has a very low incidence [3].

Hepatitis C virus (HCV) infection has long been known to cause disease in both intrahepatic and extrahepatic sites [4]. The NHL mechanism occurrence in patients with hepatitis C is unknown but is thought to be related to the lymphomagenesis process induced by HCV [4,5]. Autoimmune Hemolytic Anemia (AIHA) can be categorized into primary and secondary. One of the causes of secondary AIHA is lymphoproliferative diseases, such as NHL [6].

This case report will discuss a rare case of B-cell NHL in the colon, which is accompanied by the risk factor of HCV infection and the AIHA presence, possibly secondary to NHL.

Case details

A 47-year-old male patient complained of intermittent abdominal pain for the past ten months. The patient also reported watery diarrhea, without mucus or blood, for the last four months. Additional complaints included yellowish eyes, significant weight loss (18 kg in 4 months), and persistent fatigue.

The patient's medical history indicated that he had undergone colonoscopy and biopsy examinations twice, resulting in a diagnosis of NHL colon based on biopsy and CPI staining. However, at that time, he declined further treatment. Upon physical examination, the patient appeared moderately ill, with vital signs within normal limits. His body weight was 60 kg, height 178 cm, with a body mass index of 18.9 (normal). Other examinations revealed anemic conjunctiva, icteric sclera, and hepatomegaly. The laboratory tests showed hemoglobin levels of 7.5 g/dL, leukocyte count of 4,960/µL, platelet count of 322,000/µL, hematocrit of 23.2%, mean corpuscular volume of 92.8 fl, mean corpuscular hemoglobin of 30.0 pg, mean corpuscular hemoglobin concentration of 32.3 g%, red cell distribution width of 18.20%, and differential count of 2/0/0/80/15/3. The Coomb's test was 4+. In addition, AST levels were 67 mU/mL, ALT levels were 128 mU/mL, albumin was 4.51 g/dL, urea was 32.3 mg/dL, creatinine was 0.81 mg/dL, total bilirubin was 9.90 mg/dL, direct bilirubin was 1.26 mg/dL, indirect bilirubin was 8.64 mg/dL, uric acid was 5.6 mg/dL, and LDH was 593 U/L. The results of the immunoserological examination showed that HbsAg was non-reactive, anti-HCV was reactive, and HCV RNA was $1.68x10^3$ copies. The colon biopsy revealed a round cell tumor malignancy suggestive of neuroendocrine carcinoma, with a differential diagnosis of poorly differentiated adenocarcinoma or non-Hodgkin lymphoma. The immunohistochemical staining on the colon biopsy is presented in Table 1, and the abdominal CT Scan findings are summarized in Table 2.

TABLE 1 Results of immunohistochemical staining on the colon biopsy

Parameter	Result
CK	Negative in tumor cell
NSE	Positive in tumor cell cytoplasm
LCA	Negative in tumor cell
CD20	Diffuse positive and strongly positive in cytoplasm cell
CD45	Positive
CD3	Negative in tumor cell
Conclusion	**Immunophenotype is suggestive of B-cell Non-Hodgkin Lymphoma**

TABLE 2 Results of abdominal CT scan

Abdominal CT scan	Result
	• Multiple paraaortic lymphadenopathy and left paralic due to NHL, • Dilatation in the vena cava inferior, the left renal vein, and the bilateral iliac vein due to congestion, and • Spondylosis thoracolumbar.

Case analysis

A 47-year-old male patient presented with abdominal pain and diarrhea, persisting for ten months, with a previous diagnosis of colonic NHL in August 2019. Laboratory examinations revealed anemia with low erythrocyte count, elevated MCV and MCH, and a +4 Coombs test. Chemical and immunoserological examinations indicated an increase in both direct and indirect bilirubin (especially indirect), elevated AST (1.5x URL), ALT (3x URL), and LDH levels, along with a reactive anti-HCV result. HCV RNA PCR showed $1.68x10^3$ copies. The colon biopsy confirmed the presence of B-cell NHL in the colon. Based on history, physical examination, laboratory results, and radiology, it was concluded that the patient had B-cell NHL in the colon, HCV infection, and AIHA.

NHL accounts for approximately 80-90% of all lymphomas, with extranodal NHL constituting about 25% of all NHL cases. The lymphoma incidence in the colon itself is very rare [7]. Although the gastrointestinal tract is the most common site for extranodal lymphoma, primary gastrointestinal lymphoma is exceptionally rare, accounting for only about 1-4% of all gastrointestinal malignancies [7-9].

Gastrointestinal lymphoma can be categorized as primary or secondary. Primary gastrointestinal lymphoma manifests symptoms in the gastrointestinal tract before appearing in the lymph nodes. Secondary GI lymphoma refers to lymphoma originating outside the gastrointestinal tract, and then spreading to it [8, 10-11].

The patient may have primary gastrointestinal (colon) lymphoma based on the predominance of gastrointestinal symptoms rather than lymph node symptoms. The patient's histopathology results were positive for CD45, which is highly specific for NHL, CD20, a specific marker for B cells, and LCA, found in almost all NHL cases, whether T-cell or B-cell NHL [8].

The association between chronic HCV infection and B-cell NHL is supported by various epidemiological studies. A meta-analysis involving 48 studies (5,542 patients) concluded that the rate of HCV infection in B-cell NHL was 13%. Another study involving 4049 patients determined that the odds ratio (OR) for B- and T-cell NHL in hepatitis C was 5.04 and 2.51, respectively [13-16].

The precise mechanism through which chronic hepatitis C infection causes lymphoma is still unknown. However, three theories have been hypothesized: (1) Continuous stimulation of external lymphocyte receptors by viral antigens leading to their proliferation; (2) HCV replication within B cells and mediation of its oncogenic effects via intracellular HCV proteins; and (3) the ''hit and run'' theory, implying permanent damage to B cells caused by intracellular viruses (e.g., tumor suppressor gene mutations) [17-18].

The patient had a reactive anti-HCV result on the HCV RNA PCR examination, suggesting a positive result for HCV infection. However, it was not clear when the patient contracted hepatitis C. Concerning the substantial body of case reports and studies linking hepatitis C infection and NHL, it is likely that this patient has chronic hepatitis C, and the B-Cell NHL in the colon is a result of chronic HCV infection.

Secondary AIHA occurs in 50% of all AIHAs, and common comorbidities include other autoimmune diseases and lymphoproliferative disorders. B-cell NHL is the most prevalent cause of AIHA among all lymphomas. The AIHA mechanism in patients with NHL involves clonal antibodies produced by lymphoma cells that cause the destruction of the patient's erythrocytes [19].

The patient was found to be anemic with a Coombs test result of +4. Furthermore, the patient experienced hyperbilirubinemia and icteric symptoms for the last two months. Based on the available data, the patient had secondary AIHA caused by NHL.

Conclusion

The patient was diagnosed with B-cell NHL in the colon (including gastrointestinal lymphoma) based on clinical symptoms and other examinations. The suspicion of gastrointestinal lymphoma in this patient was supported by the primarily gastrointestinal symptoms and the dominant colon staining from the biopsy.

HCV infection is a risk factor for NHL. Based on the possible relationship between chronic HCV infection and NHL, it is likely that hepatitis C in this patient was chronic.

AIHA in this patient was secondary AIHA caused by a lymphoproliferative disorder, namely NHL.

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Authors' Contributions

Singgih Pudjo Wahono, M.D., Clinical Pathologist, contributed to data collection, drafted the case report, and revised the manuscript. Yessy Puspitasari, M.D., Clinical Pathologist Consultant provided expertise in gastrohepatology and contributed to the article's revision.

Conflict of Interest

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References

[1] R. Singh, S. Shaik, B. Negi, J. Rajguru, P. Patil, A. Parihar, U. Sharma, Non-Hodgkin's lymphoma: A review, *J. Fam. Med. and Prim. Care.*, **2020**, *9*, 1834. [Crossref], [Google Scholar], [Publisher]

[2] A. Bowzyk Al-Naeeb, T. Ajithkumar, S. Behan, D.J. Hodson. Non-Hodgkin lymphoma. *BMJ*, **2018**, *362*, k3204. [Crossref], [Google Scholar], [Publisher]

[3] M. Pandey, J. Swain, H.M. Iyer, M. Shukla, Primary lymphoma of the colon: Report of two cases and review of literature, *World J. Surg. Oncol*, **2019**, *17*. [Crossref], [Google Scholar], [Publisher]

[4] L. Couronné, E. Bachy, S. Roulland, B. Nadel, F. Davi, M. Armand, D. Canioni, J.M. Michot, C. Visco, L. Arcaini, C. Besson, O. Hermine, From hepatitis C virus infection to B-cell lymphoma. *Ann. Oncology.*, **2018**, *29*, 100. [Crossref], [Google Scholar], [Publisher]

[5] K. Hagymási, The Nobel Prize in Physiology or Medicine-2020., *Structural Chemistry*, **2021**, *32*, 909-913 [Crossref], [Google Scholar], [Publisher]

[6] L. Xing, M. Zhao, Y. Wang, Y. Feng, Y. Qu, N. Duan, Y. Wang, H. Wang, C. Liu, W. Qu, Y. Wu, J. Guan, G. Wang, J. Song, L. Li, X. Wang, R. Fu, Z. Shao, Characteristics of patients with autoimmune haemolytic anaemia secondary to lymphoproliferative disorder: A single-centre retrospective analysis, *Scientific Reports*, **2019**, *9*. [Crossref], [Google Scholar], [Publisher]

[7] J. Das, S. Ray, S. Sen, M. Chandy, Extranodal involvement in lymphoma-A Pictorial Essay and Retrospective Analysis of 281 PET/CT studies, *Asia Oceania J. Nuclear Medicine & Biology*, **2014**, *2*, 42-56. [Crossref], [Google Scholar], [Publisher]

[8] P. Ghimire, G.Y. Wu, L. Zhu, Primary gastrointestinal lymphoma. *World J. Gastroenterol.*, **2011**, *17*, 697–707. [Crossref], [Google Scholar], [Publisher]

[9] L.M. Juárez-Salcedo, L. Sokol, J.C. Chavez, S Dalia, Primary gastric lymphoma,

epidemiology, clinical diagnosis, and treatment. *Cancer Control*, **2018**, *25*, 1-12. [Crossref], [Google Scholar], [Publisher]

[10] M. Jiang, N.N. Bennani, A.L. Feldman, Lymphoma classification update: T-cell lymphomas, Hodgkin lymphomas, and histiocytic/dendritic cell neoplasms, *Expert Rev. Hematol.*, **2017**, *10*, 249. [Crossref], [Google Scholar], [Publisher]

[11] J. Taylor, W. Xiao, O. Abdel-Wahab, Diagnosis and classification of hematologic malignancies on the basis of genetics. *Blood*, **2017**, *130*, 410-423. [Crossref], [Google Scholar], [Publisher]

[12] B. Suresh, V. Asati, K.C. Lakshmaiah, *et al*. Primary gastrointestinal diffuse large B-cell lymphoma: A prospective study from South India. *South Asian J. Cancer*, **2019**, *8*, 57-59. [Crossref], [Google Scholar], [Publisher]

[13] A. Flores-Chávez, J.A. Carrion, X. Forns, M. Ramos-Casals, Extrahepatic manifestations associated with chronic Hepatitis C Virus infection, *Rev Esp Sanid Penit*, **2017**, *19*, 87-97. [Crossref], [Google Scholar], [Publisher]

[14] L. Kuna, J. Jakab, R. Smolic, G.Y. Wu, M. Smolic, HCV Extrahepatic Manifestations. *J Clin Transl Hepatol*., **2019**, *7*, 172-182. [Crossref], [Google Scholar], [Publisher]

[15] B. Songtanin, K. Burden, Outcome, and Comorbidities of Extrahepatic Manifestations in Hepatitis C Virus Infection. *Biology*, **2023**, *12*, 23. [Crossref], [Google Scholar], [Publisher]

[16] S. Tasleem, G.K. Sood, Hepatitis c associated b-cell non-hodgkin lymphoma: Clinical features and the role of antiviral therapy, *J. Clin. Transl.Hepatol.*, **2015**, *3*, 139. [Crossref], [Google Scholar], [Publisher]

[17] H. Khaled, F. Abu-Taleb, &, R. Haggag, Hepatitis C virus and non-Hodgkin's lymphomas: A minireview. *J. Adv. Res.*, **2017**, *8*, 131-137. [Crossref], [Google Scholar], [Publisher]

[18] J.P Oberhag, Arcaini L. Jan, M.L. Hansmann, S. Zeuzem, Hepatitis C-associated B-cell non-Hodgkin lymphomas. Epidemiology, molecular signature and clinical management, *J. Hepatol*, **2013**, *59*, 169-177. [Crossref], [Google Scholar], [Publisher]

[19] AW Hauswirth, C Skrabs, Ch Schützinger, A Gaiger, K Lechner, U Jäger. Autoimmune haemolytic anaemias (AIHA), Evans' syndromes and pure red cell aplasia (PRCA) in non-Hodgkin lymphomas. *Leuk. Lymphoma.*, **2007**, *48*, 1139-49. [Crossref], [Google Scholar], [Publisher]

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