CASE REPORT

Diffuse large B-cell lymphoma as an extra-hepatic manifestation of hepatitis C and co-infection of helicobacter pylori: A case report

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Abstract

Along with infecting hepatocytes, the Hepatitis C virus (HCV) is also a lymphotropic virus. Chronic HCV infection can mutate the Bcl2, a proto-oncogene that inhibits apoptosis. This causes continuous stimulation of B lymphocytes, which results in clonal growth of these immunoglobulin-producing cells. In Western countries, there is a well-documented link between HCV and lymphoproliferative illness. HCV and Non-Hodgkin lymphoma (NHL) have been found to be significantly correlated in Europe, Japan, and the southern United States. There, however, has been no association found in central and northern Europe, the northwestern United States, and some Asian countries. A literature deficit exists in South Asia about the incidence of HCV infection in lymphoma patients. Here, the first documented instance of Diffuse Large B-cell NHL (germinal center type) is reported in a 35-year-old patient. The patient presented to the outpatient department at Ruth KM Pfau, Civil Hospital Karachi, in July of 2022, with the chief complaints of altered bowel habits due to involvement of the anorectal junction and concomitant infection by Helicobacter pylori with a prior history of HCV infection.

Keywords: Hepatitis C, Non-Hodgkin Lymphoma, Helicobacter pylori.

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Introduction

There are an estimated 58 million people living with chronic hepatitis C virus (HCV) infection worldwide, and 1.5 million new cases occur each year.[1] In terms of the prevalence of hepatitis C; Pakistan ranks second among all countries, with 4.8% of the population infected.[2] As a leading cause of chronic liver disease, HCV also increases the likelihood of developing cirrhosis and associated consequences. However, 40-74% of patients with HCV also develop extra hepatic manifestations.

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Additionally, HCV is well known for causing lymphoproliferative disease. Patients infected with this are more likely to develop bone marrow and other tissue infiltrates with monoclonal B cells, or different types of B cell non-Hodgkin's lymphoma (NHL). Among which the most common are splenic marginal zone B cell NHL, diffuse large B cell NHL and follicular lymphoma.[3,4] In the western world, lymphoproliferative disorders have already been linked to HCV, with a greater prevalence of these lymphomas in countries where HCV prevalence is high (about 10%, according to a recent systematic review).[5] However, despite the heavy burden of the disease in Pakistan, there are no reported cases of lymphoma development. Herein, the first recorded case of NHL is reported in a patient with HCV infection in the region.

Case Report

A 35-year-old married male presented to the outpatient department at Ruth KM Pfau, Civil Hospital Karachi, in July 2022, with complaints of altered bowel habits for 4 months, accompanied by weight loss. According to the patient, he began having loose faeces 4-5 times per day, 4 months ago that were watery in consistency, yellowish in colour and small in quantity without foul smell. He had a history of hepatitis C infection and was under treatment. Family medical history was irrelevant. The patient did not take any other prescriptions or ingested alcohol, herbs, or poisons. On examination, there was grade 2 clubbing, anaemia was positive, and buccal and temporal wasting was noted. His per rectal examination was insignificant. The rest of the systemic examination was unremarkable.

Laboratory findings showed low haemoglobin of 10.3 gm/dL, normal platelet level and low albumin level. Hepatic tests were also in the normal range, and Stool D/R showed 6-8 pus cells/HPF. The stool culture showed no growth. His HCV antibody test was reactive and his HCV RNA levels were 1,20,2639 IU/ml. The stool for H. Pylori antigen was positive. Laboratory blood analysis results are summarized in Table. On ultrasound, the liver, spleen and pancreas had a normal appearance with no focal liver lesion. Ascites was not visualised. Child class was A, Child-Turcotte-Pugh (CTP) score was 6 and Model for End-Stage Liver Disease and Sodium (MELD-Na) score was 11.

Treatment for H. Pylori was started with the triple regimen

Table: Laboratory characteristics throughout the hospital stay.

	Reference range	20th July	23rd July	25th July	28th July	1st August
Haemoglobin (gm/dL)	13.5-17.5	11.3	11.2	11.0	11.9	11.2
Red blood cell count (millions/µL)	4.3-5.9	3.5	3.9	4.5	3.7	3.7
Haematocrit (%)	41-53	31.4	36.7	41.5	33.4	33.5
White blood cell count (10^3/µL)	4.5-11	6.9	8.9	8.2	6.6	6.2
Neutrophils (%)	40-60	64	73	77	71	68
Lymphocytes (%)	20-40	23	15	14	20	20
Monocytes (%)	2-8	10	9	8	9	8
Eosinophils (%)	1-4	3	3	2	4	5
Basophils (%)	0.5-1	0	0	0	0	0
Platelets (10^3/µL)	150-400	325	314	313	228	249
Albumin (g/dl)	3.5-5	3	-	-	-	-
Total protein (g/dL)	6.3-7.9	6.5	-	-	-	-
International normalized ratio (INR)	0.8 to 1.1	1.03	1.08	1.07	1.19	1.08
Prothrombin time (seconds)	9.4-12.5	10.8	11.3	11.2	12.5	11.3
C-reactive protein (mg/L)	< 3	14.1	10.5	10.9	13.3	11.8
Alanine aminotransferase (U/L)	7-55	15	14	15	17	20
Alkaline phosphatase (IU/L)	40-129	72	76	80	76	71
Total bilirubin (mg/dL)	0.1-1.2	0.3	0.5	0.5	0.4	0.4

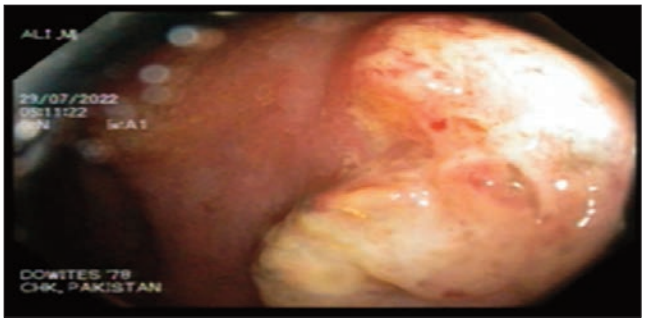

Figure: Colonoscopy findings: proctoscopy revealed a mass at the anorectal junction. Biopsy revealed it to be Diffuse Large B-cell Non-Hodgkin Lymphoma, germinal center type.

of clarithromycin, amoxicillin and proton pump inhibitor. However, diarrhoea persisted despite 4 weeks of treatment, and he was still anaemic. Hence, Oesophago-Gastro-Duodenoscopy (OGD) was performed, on which pan-gastric erythema was observed and biopsies were taken from the antrum and duodenum. Colonoscopy was also performed to rule out further causes of anaemia, where a polypoid mass at the anorectal junction was visualized and a biopsy was taken (Figure). Histopathology results from antrum biopsy revealed intact architecture, with moderate acute and chronic inflammation seen in lamina propria and crypt epithelium. Helicobacter pylori were visualized and 10% of intestinal metaplasia was seen. But there was no evidence of granuloma, dysplasia, and malignancy. Duodenal biopsy showed, intact villoglandular architecture, with only moderate acute and chronic inflammation of lamina propria. No organisms, crypt hyperplasia, granuloma or malignancy was visualized. Biopsy of the mass from the anorectal junction exhibited diffuse infiltrates of large cells with angulated nuclei and a moderate amount of cytoplasm. The following immunohistochemical stains were positive: CD20, BCL-6, CYMIC and Ki67 (70-80%). Features of the mass were those of Diffuse Large B-cell Non-Hodgkin Lymphoma (germinal center type) according to WHO Classification of Haematolymphoid Neoplasm.[6] He was started on direct antiviral agents (DAA) and referred to surgery for removal of mass. He was also asked to follow-up in Hepatitis OPD at Civil Hospital, Karachi.

Discussion

In addition to being a hepatotropic virus, the Hepatitis C virus (HCV) can also infect lymphocytes. The mechanism involves the hepatitis C virus binding via the HCV envelope E2 protein to the tetraspanin CD81 ligand; present on the surface of B lymphocytes. This interaction might trigger a mutation in Bcl2, a proto-oncogene that inhibits apoptosis, which results in continuous stimulation of B lymphocytes, thus, clonal growth of these immunoglobulin-producing cells.[7] This hypothesis proposes that persistent HCV infection, alone or in conjunction with other variables can encourage the development of B-cell NHL.

Infection with HCV is associated with different types of B-NHL. Among lymphomas detected in subtype-specific analyses; HCV prevalence was highest in marginal zone lymphomas, diffuse large B-cell lymphomas and lymphoplasmacytic lymphomas.[4] A case report also brought to light that HCV infection can co-exist with NHL, presenting as lymphoma of the liver, stomach, spleen, central nervous system, conjunctiva, nasal and even with systemic involvement.[8] HCV may have a role in the development of at least certain forms of B-cell NHL. However, this link appears to be restricted to geographic locations where the occurrence of HCV is more endemic.[4] Particular genetic and environmental factors may contribute to the development of a malignant phenotype. Evidence of substantial hepatic impairment may indicate a poorer outcome in these people.[9]

Female gender, long-lasting infection and residence in an HCV-endemic region are reported risk factors for NHL development. In patients with more than 15 years of HCV infection; NHL risk is significantly increased.As, this can be

explained by an accumulation of HCV infection risk and the long period necessary for the virus to cause lymphoid cell proliferation.[10]

An integral part of the evidence for the association between HCV and carcinogenesis is the apparent association between the achievement of a sustained virological response (SVR) and remission of B-cell NHL. The patients who achieved SVR with interferon (IFN) based therapy; early findings from a large cohort reported a decreased incidence of B-NHL. While in patients who did not reach an SVR, the risk of developing B-NHL was significantly higher in them.[11] However currently, combination therapy (IFN+Ribavirin) has been discontinued since direct antiviral agents (DAAs) have demonstrated extremely high effectiveness in obtaining SVR (range: 95%-100%) and are well-tolerated.[12] A meta-analysis of 13 studies corroborated the link between SVR and progression-free survival in B-NHL patients (OR 9.34; 95% CI 4.90-17.79; $p<0.00001$). Concluding, that DAA-based HCV eradication should be regarded as first-line treatment in HCV related NHL.[13] This is why clinicians should evaluate HCV infected patients for extrahepatic malignancies to facilitate timely diagnosis and treatment.[14]

The relationship between HCV infection and the development of lymphoproliferative illness is well-documented in Western countries. According to the meta-analysis by Gisbert et al, they aggregated data from approximately 5,500 patients and reported an HCV prevalence of 15% among B-NHL patients. This was significantly higher than the rate in the general population (1.5%).[15] Another meta-analysis, which included 8 cohort studies and 10 case-control studies; focusing diverse demographics in Western nations, revealed a relationship between HCV infection and NHL.[16] Another research including 7 member studies from the International Lymphoma Epidemiology Consortium (InterLymph) situated in Europe, North America, and Australia, discovered HCV infection in 172 NHL patients (3.60%) and 169 (2.70%) controls (odds ratio [OR], 1.78; 95% confidence interval [CI], 1.40-2.25).[4] Dal Maso et al, discovered a notable geographical heterogeneity in B-NHL prevalence. The relative risk (RR) for B-cell NHL among HCV patients in countries with high HCV prevalence (>5%) was 3.01, whereas it was 1.9 in countries with low prevalence.[17]

NHL and HCV have been found to be substantially correlated in southern and eastern Europe, Japan, and the southern United States. On the contrary, no association has been recorded in northern and central Europe, the northern United States, Canada and certain Asian nations.[8] Javier et al, reported relatively low odds ratios of NHL for HCV infection, which may be explained by significant discrepancies in the literature due to variances in research design, location, and ethnicity of study participants.[8]

Conclusion

In South Asia, there is a deficit in the literature, reporting the incidence of HCV co-existence in lymphoma patients. Considering, this is the first instance of lymphoma associated with HCV in this region. It necessitates further longitudinal, prospective studies to determine whether HCV and lymphoproliferative disease development are related in this ethnically and genetically distinct population.

Consent: Written, informed consent was taken from the patient for publishing his case report.

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Author Contribution:

NK: Conceived idea, data collection, study design, proof reading, final approval.
AA: Conceived idea, data collection, study design, final approval.
SMH, AM: Drafting, Draw table and figure, final approval.
KT: Literature review, final approval.