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Case Report

Helicobacter pylori: A key player in pathogenesis of Gastric Non-Hodgkin's Lymphoma: A case report

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Abstract

Background: Primary gastric lymphoma is one of the less common gastric malignancies as compared to adenocarcinoma. Numerous bacterial and viral infections are linked to their etiology. One of the most frequent associations is with *Helicobacter pylori* infection that predisposes to the development of gastric lymphoma.

Case Presentation: Here we present a case of 48 years old Female with complains of nausea, vomiting, weight loss and epigastric pain since 2 months. Upper Gastrointestinal endoscopy showed ulcerative lesion involving pre pyloric region and lesser curvature. Patients have undergone surgery, and we received distal gastrectomy specimen in histopathology. The representative sections were given and stained with hematoxylin and eosin stain. Microscopy showed stomach walls infiltrated by small to medium sized atypical cells. Immunohistochemistry was positive for CD -45 and CD - 20 and negative for Synaptophysin and CK -7. The final diagnosis of Non – Hodgkin's Lymphoma – diffuse large B cell type was given. The patient was managed by multidisciplinary approach including partial gastrectomy, *Helicobacter pylori* eradication therapy and chemotherapy regimen including cyclophosphamide, adriamycin, vincristine, prednisolone and rituximab. The patient was followed up for six months and has no relapse or any other symptoms related to lymphoma. Regular follow up was advised for next 5 years.

Conclusion: *Helicobacter pylori* infection usually remains as an asymptomatic carrier state. This case is worth reporting as only in rare instances, it results in severe outcomes like lymphoma. It highlights the association of *Helicobacter pylori* with primary gastric lymphoma and helps in understanding the pathogenesis of the disease.

Keywords: Stomach, *Helicobacter pylori*, Lymphoma, Non – Hodgkin's lymphoma, Immunohistochemistry.

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1. Introduction

About 5% of primary gastric malignancies are primary gastric lymphomas (PGLs). Non-Hodgkin's type lymphoma (NHL) accounts for almost 95% of stomach lymphomas.[1]

Helicobacter pylori (H. Pylori) is a rare pathogenic bacterium that colonizes the stomachs of approximately 4-4.5 billion people globally due to its capacity to withstand extreme circumstances of the stomach.[2]

In most infected individuals, *Helicobacter pylori* cause chronic active gastritis, with 10%-20% progressing to peptic ulcer disease, stomach adenocarcinoma, and/or lymphoma.

Helicobacter pylori is known for its genetic variation across clinical isolates. *Helicobacter pylori* isolate have a varied genome that changes often due to substitutions, point mutations, deletions and insertions.[3]

Helicobacter pylori genetic content varies by strain, making it crucial to assess the impact of strain-specific

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virulence factors. The cytotoxin-associated gene A (*CagA*) is a key virulence factor in these bacteria. It is expressed via the *Cag* pathogenicity islands (PAIs) and is categorized into four classes based on the nucleotide sequence of EPIYA motifs. The *CagA* pattern in East Asian populations is often ABD, but strains with ABC, ABCC, and ABCCC patterns have been found in Western countries. Previous research indicates a high prevalence of *CagA*-positive strains among individuals with stomach ulcers and precancerous lesions.[2]

Helicobacter pylori antigens trigger tumor-infiltrating T lymphocytes that enhance B lymphoma cell proliferation and differentiation via CD40-mediated signaling and *Th2*-type cytokines (*IL-4, IL-5, and IL-10*).[4]

PGLs are a diverse category of stomach-originating lymphoproliferative diseases that include a wide range of histological subtypes, either the histology of mucosa-associated lymphoma tissue (MALT) or the diffuse large B-cell lymphoma (DLBCL) subtype.

The occurrence of *Helicobacter pylori*–associated lymphoma, particularly gastric MALT lymphoma, differs worldwide, tending to be more frequent in areas with high *Helicobacter pylori* infection rates like certain developing areas and among older individuals. Still, it remains uncommon, with reported incidence in Europe estimated at roughly 0.3 to 0.8 cases per 100,000 people.

The infection with *Helicobacter pylori* has been proven to increase the risk of gastric NHL as per the evidence from previous research. *Helicobacter pylori* have been implicated as a causative organism for chronic gastritis and approximately sixty percent of the gastric NHL evolves from preexisting chronic gastritis.[5]

PGL is the second most common gastric cancer worldwide, after stomach adenocarcinoma. The latter is the fifth most frequent cancer worldwide and the most prevalent type of stomach cancer.[6,7]

Helicobacter pylori infection usually remains as an asymptomatic carrier state. Only in rare instances, it results in severe outcomes like lymphoma.[2] This case highlights the association of *Helicobacter pylori* with primary gastric lymphoma and helps in understanding the pathogenesis of the disease.

2. Case Report

2.1. Ethics statement

Appropriate informed consent from patient and Institutional ethical committee approval (SVIEC/ON/MEDI/RP/JUNE/25/69) taken.

2.2. Clinical presentation

In this study we present a rare case report of 48 years old female patient with complaints of nausea, vomiting, weight loss and epigastric pain for 2 months.

2.3. Investigations

Patient had history of *Helicobacter pylori* infection and tested positive for rapid urease test. Upper Gastrointestinal endoscopy showed ulcerative lesion involving pre pyloric region and lesser curvature, which was further confirmed by contrast enhanced computed tomography of abdomen. The patient underwent surgery, and we received a specimen of partial distal gastrectomy in our histopathology department.

2.4. Gross findings

The specimen comprising of distal part of stomach along with attached omentum measuring 21.5 ×14.5 ×2 cm. Stomach measures 14 ×6.8 ×1.2 cm. Outer surface was smooth and glistening. No perforation was seen. On cut section, a raw ulcerative area was seen near the distal end measuring 2.5× 1.4× 0.6cm. (**Figure 1**) The rest of the inner surface appeared normal. Representative sections were given from lesion, margins and lymphnodes. The sections were stained with hematoxylin and eosin (H & E) stain.

2.5. Microscopy

On microscopic examination, the section studied showed distal stomach wall infiltrated by small to medium sized atypical cells with vesicular chromatin, small visible nucleoli and mild irregular nuclear membrane. The atypical cells infiltrating lamina propria and submucosa were seen. (**Figure 2a-b**). There was no neuro – endocrine cell hyperplasia. Rest of the stomach mucosa, all margins and lymphnodes were free from tumor.

2.6. Immunohistochemistry

Immunohistochemistry (IHC) panel was kept using CD -45, CD – 20, CK – 7 and synaptophysin. (**Figure 3a-d**). The internal and external controls were found to be satisfactory. The small round atypical cells stained positive for CD -45 and CD – 20 and they did not stain by synaptophysin and CK -7.

2.7. Final diagnosis

Based on the above findings, neuroendocrine tumors and carcinoma were ruled out. So, the final diagnosis was given as Non – Hodgkin's Lymphoma of B cell lineage – diffuse large B – cell lymphoma.

2.8. Management and outcome

The patient was managed by multidisciplinary approach including partial gastrectomy, post - surgical *Helicobacter pylori* eradication therapy and chemotherapy. The *Helicobacter pylori* eradication therapy was given with 20mg Omeprazole and 500mg Clarithromycin along with 1000mg of Amoxicillin 12 hourly for 10 days. Chemotherapy regimen

included cyclophosphamide, adriamycin, vincristine, prednisolone and rituximab. The patient was followed up for six months and showed no signs of recurrence or any other symptoms related to lymphoma. Regular follow-up was advised for next 5 years.

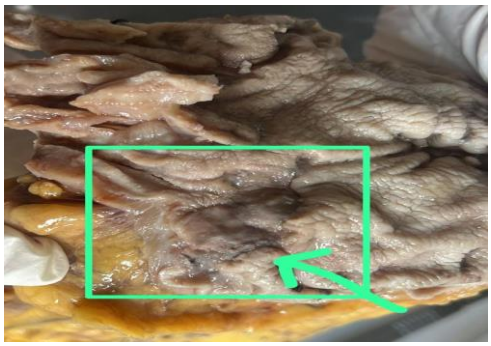

Figure 1: Gross picture showing ulcerated lesion with surrounding normal mucosa

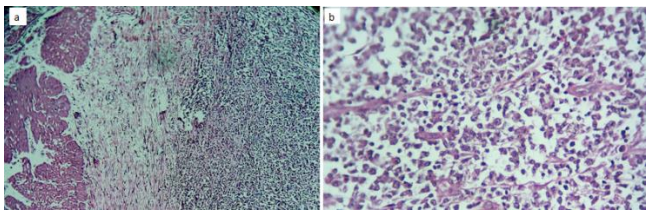

Figure 2: a: Diffuse infiltrate of atypical cells in mucosa and lamina propria (Low power, H & E); **b:** Atypical cells showing vesicular chromatin and at places prominent nucleoli (High Power, H & E)

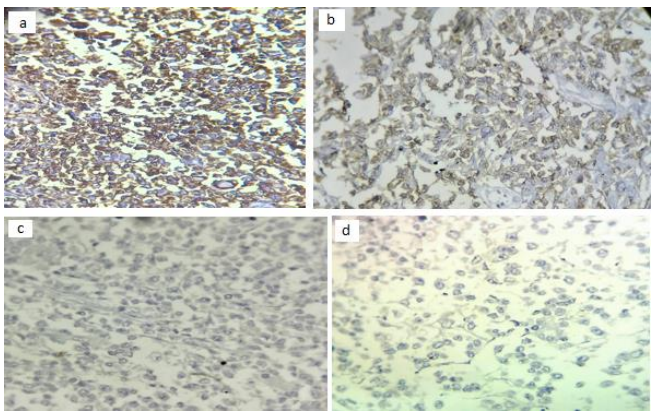

Figure 3: a: Immuno positivity for CD – 45; **b:** Immuno positivity for CD – 20; **c:** Immunonegativity for Synaptophysin; **d:** Immunonegativity for CK – 7

3. Discussion

A wide spectrum of lymphoproliferative malignancies is referred to as non-Hodgkin lymphoma (NHL).[8] The majority of extra nodal NHLs occur in the gastrointestinal (GI) tract. Around 80 to 90 percent of NHLs are B cell derived.[9]

The spectrum of PGL can range from marginal zone B-cell lymphoma to diffuse large B-cell lymphoma as per the recent World Health Organization (WHO) classification.[2]

Abdominal distension, fullness or pain, nausea, vomiting, anorexia, indigestion, dyspepsia, and weight loss are the primary symptoms. Weakness, fever, jaundice, hematemesis, night sweats, or melena are the less frequent symptoms. A good endoscopic evaluation using tissue samples of a adequate size can accurately diagnose primary gastric lymphomas. *Helicobacter pylori* infection, HIV, Epstein-Barr virus, Hepatitis B virus, and human T cell lymphotropic virus are among the possible risk factors linked to the pathophysiology of primary gastric lymphoma. Tumor features, host-related variables, histological subtypes, patient age, and performance status all affect the overall prognosis of primary gastric lymphoma.[7]

A study done by Zayati M et al linked the *Helicobacter pylori* infection to the development of the gastric lymphomas.[10] This finding was in accordance with our findings.

Helicobacter pylori infection can be traced in around 35% of patients with diffuse large B cell lymphoma. There were still higher percentage of patients having *Helicobacter pylori* infection who were diagnosed as diffuse large B cell lymphoma with low-grade MALT lymphoma components. This supports the fact that low-grade MALT lymphoma may predispose to or transform into diffuse large B cell lymphoma.

Several steps are involved in evolution of lymphoma that is induced by *helicobacter pylori*. Some of the examples are factors related to host and environment. The most important virulence factors of the *Helicobacter pylori* are *CagA* and *VacA*. *Cag A* gene related with cytotoxins is the most researched *Helicobacter pylori* virulence factor. It is a protein found on the surface of *Helicobacter pylori* cells. By interacting with phosphatidylserine, it can directly cross the host membrane and disrupt cell signalling, which may result in oncogenesis. *Helicobacter pylori* infections are linked to less aggressive types of DLBCL with overall favourable prognosis. One potential reason for the significant impact of *Helicobacter pylori* infection on the prognosis of gastric DLBCL is antigenic mimicry between *Helicobacter pylori* and gastric mucosal tissues. This mimicry may trigger immune cross-reactions that target tumour cells and inhibit their progression. These immune responses, involving malignant cells that display mimicry are associated with better survival rates in patients with *Helicobacter pylori*-positive gastric lymphoma.[11]

The study done by Rodriguez LV et al established the etiopathological association between gastric lymphoma and chronic *Helicobacter pylori* infection.[12]

According to laboratory tests, the total blood count is typically within normal limits at the onset of the illness or in its localized manifestations. Hemoglobin levels can occasionally drop if there is associated bleeding, most often from stomach issues.[13] Gastric lymphomas should be

differentiated from the advanced gastric cancers, adenocarcinomas or neuroendocrine tumors. Upper GI endoscopy findings, histopathological examination and immunohistochemical studies help in this differentiation.[14]

The prognosis can be significantly affected by the grade and histological subtype of the lymphoma. Low grade illness has a five-year survival rate of 80–90%, while high grade lymphomas have a five-year survival rate of 39–74%. A dismal prognosis is also indicated by the progression of the disease up to the gastric serosal layer and intra-abdominal lymph nodes.[15]

Helicobacter pylori-associated low-grade gastric lymphoproliferative disease is amenable to cure by *Helicobacter pylori* eradication therapy in children as per the conclusion derived from the study by Blecker U et al. This approach should be considered before attempting aggressive surgical management and chemotherapy.[16]

Surgical excision is considered as the major treatment strategy. For the treatment of high-grade NHLs, multimodality therapy involving *Helicobacter pylori* eradication therapy along with neoadjuvant chemotherapy regimens are suggested.[12,17]

The limitation of our study was that it being a single case report with relatively shorter follow up duration, the findings cannot be generalized to the larger population.

4. Conclusion

Although primary gastric non-Hodgkin's lymphomas are not common, they are not uncommon either. Because of the vague symptoms, the diagnosis of stomach lymphoma may not be made for years. The prognosis and treatment of the patient are greatly impacted by prompt identification and histopathological subtyping. This case report assists in understanding the pathogenesis of *Helicobacter pylori* associated gastric lymphoma in depth to the medical professionals and contributes to the betterment of society by early diagnosis and treatment.

5. Source of Funding

None.

6. Conflict of Interest

None.

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