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CASE REPORT

Endoscopic appearance of AIDS-related gastrointestinal lymphoma with *c-MYC* rearrangements: Case report and literature review

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Abstract

Acquired immune deficiency syndrome (AIDS)-related lymphoma (ARL) remains the main cause of AIDS-related deaths in the highly active anti-retroviral therapy (HAART) era. Recently, rearrangement of *MYC* is associated with poor prognosis in patients with diffuse large B-cell lymphoma. Here, we report a rare case of gastrointestinal (GI)-ARL with *MYC* rearrangements and coinfected with Epstein-Barr virus (EBV) infection presenting with various endoscopic findings. A 38-year-old homosexual man who presented with anemia and was diagnosed with an human immunodeficiency virus infection for the first time. GI endoscopy revealed multiple dish-like lesions, ulcerations, bloody spots, nodular masses with active bleeding in the stomach, erythematous flat lesions in the duodenum, and multiple nodular masses in the colon and rectum. Magnified endoscopy with narrow band imaging showed a honeycomb-like pattern without irregular microvessels in the dish-like lesions of the stomach. Biopsy specimens from the stomach, duodenum, colon, and rectum revealed diffuse large B-cell lymphoma concomitant with EBV infection that was detected by high tissue EBV-polymerase chain reaction levels and Epstein-Barr virus small RNAs *in situ* hybridization. Fluorescence *in situ* hybridization analysis revealed a fusion between the immunoglobulin heavy chain (IgH) and *c-MYC* genes, but not between the IgH and BCL2 loci. After 1-mo of treatment with HAART and R-CHOP, endoscopic appearance improved remarkably, and the histological features of the biopsy specimens revealed no evidence of lymphoma. However, he died from multiple organ failure on the 139th day after diagnosis. The cause of his poor outcome may be related to *MYC* rearrangement. The GI tract involvement in ARL is rarely reported, and its endoscopic findings are various and may be different from those in non-AIDS GI lymphoma; thus, we also conducted a literature review of GI-ARL cases.

Key words: Acquired immune deficiency syndrome-related lymphoma; Non-Hodgkin-lymphoma; Epstein-Barr virus infection; *c-MYC* rearrangement; Endoscopic appearance

Core tip: Endoscopic findings in gastrointestinal-ac-

quired immune deficiency syndrome (GI-AIDS) related lymphoma (ARL) are miscellaneous and may be different from non-AIDS GI lymphoma. We report a rare case of GI-ARL with *MYC* rearrangements and coinfected with Epstein-Barr virus infection, and there are multiple findings involving stomach, duodenum, and colon and rectum. Magnified endoscopy with narrow band imaging showed a honeycomb-like pattern without irregular microvessels in the dish-like lesions of the stomach. Moreover we conducted literature review of GI-ARL. To our knowledge, this is the first report of GI-ARL with *MYC* arrangements and presenting an atypical endoscopic appearances.

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INTRODUCTION

Non-Hodgkin-lymphoma (NHL) occurs in 5%-10% of individuals with an human immunodeficiency virus (HIV) infection. The early diagnosis of acquired immunodeficiency syndrome (AIDS)-related lymphoma (ARL) is highly important because patients with ARL tend to exhibit an aggressive clinical course, short survival, and poor treatment response. Chromosomal translocations of 8q24, encoding the c-myc oncogene, are considered to be associated with NHL oncogenesis, and are normally seen in patients with Burkitt lymphoma[1]. Recently, *MYC* rearrangements have been seen occasionally in diffuse large B-cell lymphoma (DLBCL) and are associated with a poor prognosis[2]. Here, we report a rare case of gastrointestinal (GI)-ARL with MYC rearrangements and an Epstein-Barr virus (EBV) infection presenting with various endoscopic findings. As the endoscopic findings in ARL are variable and may be different from those of non-AIDS GI lymphoma, we conducted a literature review of GI-ARL cases.

CASE REPORT

A 38-year-old homosexual man was admitted to our hospital with shortness of breath and multiple lymphadenopathy. He was diagnosed with an HIV infection for the first time. Physical examination showed slight upper abdominal tenderness, hepatomegaly, and splenomegaly without watery or bloody stools. Blood sample tests showed a low CD4 lymphocyte count (240 cells/μL), high quantity of HIV RNA (2.9×10^7 copies/mL), anemia (hemoglobin, 93 g/L), high lactate dehydrogenase (4.882 U/L), low serum albumin (24 g/L), and high EBV-PCR levels (9.0×10^5 copies/μg DNA). The patient was *Helicobacter pylori* (*H. pylori*) negative with the titer of the *H. pylori*-antibody under 3.0 U/mL. To diagnose anemia, we performed upper and lower GI endoscopy and revealed multiple dish-like elevated lesions (Figure 1A and B), bloody spots (Figure 1C), and ulcers in the body of the stomach (Figure 1D). Magnification endoscopy with narrow band imaging (NBI) showed a honeycomb-like pattern at the edge of the elevated lesions (Figure 1E), but there was no irregular microvascular pattern in the ulcers (Figure 1F). We also found erythematous flat lesions in the duodenum (Figure 1G). Lower GI endoscopy showed multiple nodular masses in the colon and rectum (Figure 1H). Biopsy from these lesions revealed pleomorphic, atypical lymphoid cells with eosinophilic cytoplasm, marked nucleoli, and vesicular nuclei with hematoxylin and eosin staining (Figure 2). Immunohistochemistry showed positive staining for CD20, CD79a, CD38, MUM-1, BCL2, CD30, EMA, and latent membrane protein 1 and no staining for CD138, BCL6, and CD10 (Figure 2). Biopsy specimens from the upper and lower GI tract also revealed positive EBER *in situ* hybridization and high EBV-PCR levels (100000 copies/μg DNA). We also conducted a biopsy from the right inguinal lymph node. Fluorescence *in situ* hybridization analysis revealed fusion between the immunoglobulin heavy chain (IgH) and *c-MYC* genes, but not between the IgH and BCL2 loci. Computed tomography showed splenomegaly, slight hepatomegaly, and lymphadenopathy. Positron emission tomography detected radioisotope uptake within the bone marrow, lymph nodes, spleen, and gallbladder. The final diagnosis was DLBCL clinical stage 4B, according to the Ann Arbor Staging Classification for Lymphomas, and concomitant with an EBV infection. The patient was administered oral highly active anti-retroviral therapy (HAART) and R-CHOP chemotherapy. After 1 mo of treatment, the endoscopic appearance of the elevated lesions, blood spots, and ulcers had improved. The histological features of the biopsy specimens revealed no evidence of NHL. However, after 7 cycles of R-CHOP chemotherapy, blood sample tests showed high levels of lactate dehydrogenase (2568 U/L), hyperferritinemia (31810 ng/mL), and cytomegalovirus (CMV)-PCR (200 copies/μg DNA). Bone marrow aspiration revealed infiltration by activated histiocytes and hemosiderin-filled macrophages. The patient showed CMV viremia, tumor lysis syndrome, and hemophagocytic syndrome. He died of multiple organ failure on the 139th day after diagnosis.

DISCUSSION

The incidence of ARL has not decreased over time despite the widespread use of chemotherapy and the improved management of long-term HAART[3]. Furthermore, ARL remains the most frequently observed AIDS-defining event leading to death[3]. Therefore, the early diagnosis of ARL is very important. In 5%-10% of cases with DLBCL with typical morphology, a *MYC* rearrangement (MYC+) is also observed, and these cases are considered a sub-category of DLBCL[2]. The presence of

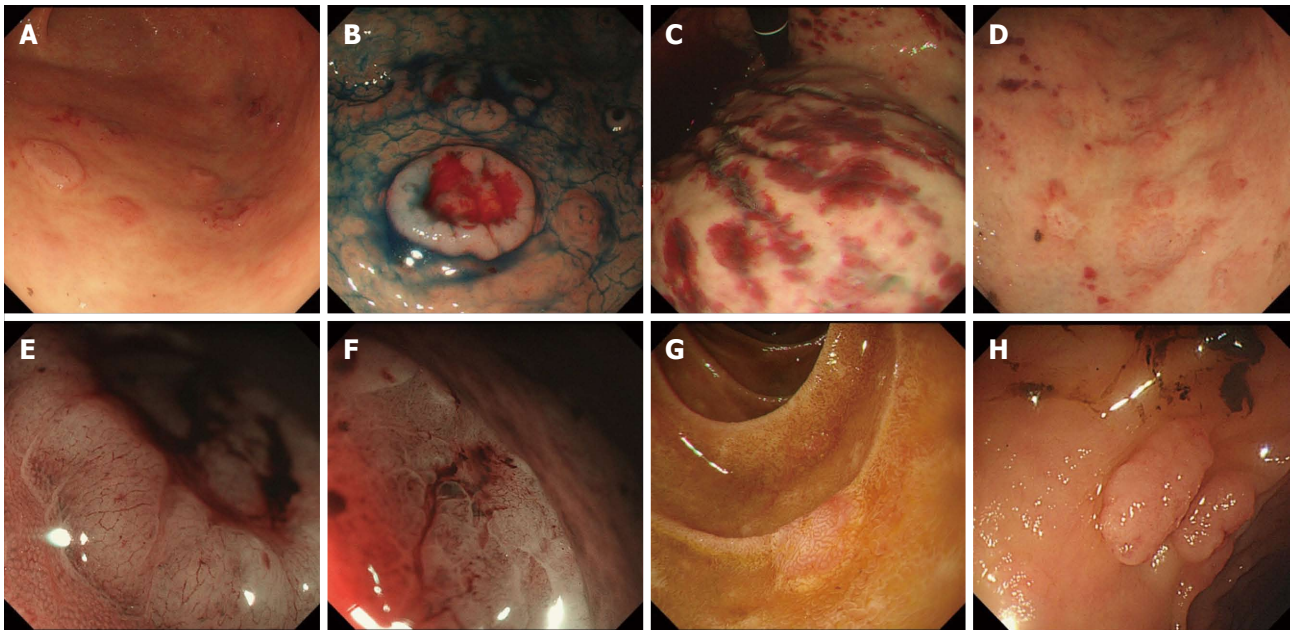

Figure 1 Upper and lower gastrointestinal endoscopic findings. A: Multiple elevated lesions in the body of the stomach; B: Multiple dish-like lesions with bleeding dyed with indigo carmine; C: Bloody spots in the body of the stomach; D: Ulceration with bleeding in the upper body of the stomach; E: Narrow band imaging (NBI) with magnification showing a honeycomb-like pattern at the edge of the elevated lesion; F: Irregular microsurface pattern in ulceration with NBI; G: Erythematous flat lesions in the duodenum; H: Multiple nodular masses in the colon and rectum.

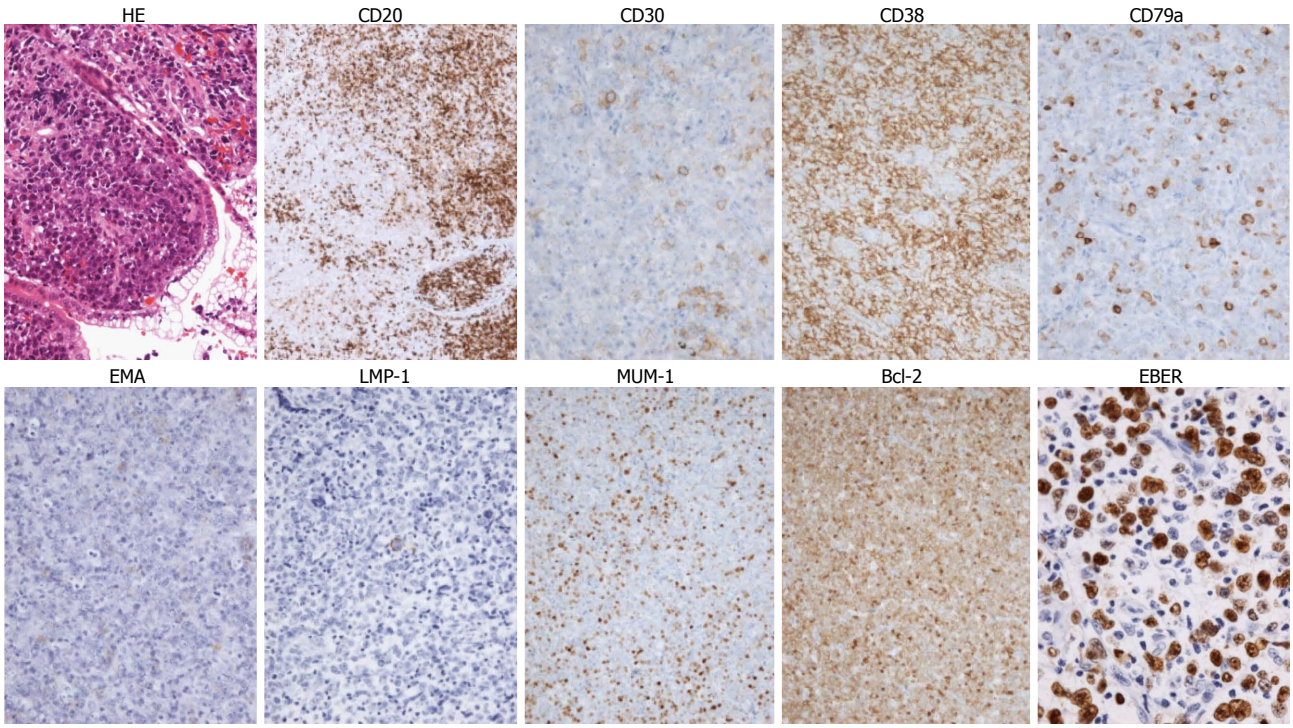

Figure 2 Histological findings and immunostaining of the biopsy specimen. Pleomorphic, atypical lymphoid cells with eosinophilic cytoplasm, marked nucleoli, and vesicular nuclei with hematoxylin and eosin staining (× 10). Immunohistochemistry shows positive staining for CD20 (× 4), CD30 (× 20), CD38 (× 10), CD79a (× 20), EMA (× 10), LMP-1 (× 10), MUM-1 (× 10), and BCL2 (× 10). Biopsy specimens revealed positive EBER-*in situ* hybridization (× 40). LMP-1: Latent membrane protein 1; MUM-1: Multiple myeloma oncogene 1; EMA: Epithelial membrane antigen.

a *MYC* rearrangement is associated with inferior overall survival and there is a trend for a reduction in event-free survival[4]. Our case had a poor prognosis in spite of their temporary clinical and endoscopic improvement after chemotherapy. We suggest that the aggressive course of his illness was related to *MYC* rearrangement.

Endoscopy with biopsy is essential to make a definite diagnosis of GI-ARL; however, it is usually indicated for patients with GI symptoms. In our case, he had only slight tenderness, but we performed endoscopy to inves-

Table 1 Literature review of the endoscopic findings in acquired immune deficiency syndrome-related lymphoma patients

Ref.	Patients	Involved GI tract	Endoscopic findings
Friedman[9]	NHL (n = 12)	Esophagus, stomach, duodenum, small bowel, colon, rectum	Multiple bulky tumor masses, small polypoid lesions
Heise *et al*[10]	NHL (n = 48)	Esophagus, stomach, duodenum, small bowel, colon, rectum	Bulky tumor mass, polypoid lesions, deep well-defined ulceration, necrotic abscesses
Corti *et al*[11]	Burkitt lymphoma (45-yr man)	Duodenum	Pseudo-polypoid masses
Andrews *et al*[12]	NHL (n = 30)	Stomach, small bowel, colon	Tumor mass, ulceration, nodular lesions
Mani *et al*[13]	Plasmablastic lymphoma (40-yr man)	Esophagus, stomach	Tumor mass, ulceration
Mahmoudi *et al*[14]	Lymphoma (38-yr woman)	Stomach	Ulceration, non-specific inflammation
Chow *et al*[15]	41-yr woman	Esophagus	A flat and solitary ulcer
Cappell *et al*[16]	GI lymphoma in AIDS patients (n = 6)	Esophagus, stomach, duodenum	Multiple volcano-like masses, ulceration, stricture with ulceration, nodular lesions, tumor mass, large sessile polypoid lesions
Yehya *et al*[17]	44-yr man	Colon	Mass with ulceration
Rezende *et al*[18]	NHL in AIDS patients (n = 6)	Stomach	Polypoid lesions, ulceration
Fujita *et al*[19]	41-yr man	Stomach	Multiple submucosal tumors with ulceration
Nakazuru *et al*[20]	68-yr man	Duodenum	Well-defined ulceration, auricle-like shaped mass with scattered tiny white spots

NHL: Non-Hodgkin-lymphoma; GI: Gastrointestinal.

tigate the cause of his anemia, which enabled us to make a diagnosis. The knowledge of the distinctive endoscopic appearance of GI-ARL also leads to an early diagnosis, but its detailed characteristics remain unknown. Therefore, we reviewed the English literature in the MEDLINE database by searching with the key words "HIV", "lymphoma", and "endoscopy" (Table 1). We identified 65 reports, but there was no description of endoscopic findings in 53; finally, we selected 12 reports.

The most frequently involved GI sites are the stomach (24%), small bowel (10%), and colon/rectum (7%). The most common site of involvement in the colon is the cecum (45%-75%), followed by the rectum[5]. However, in immunocompetent patients, GI lymphomas are found in the stomach in 50%-80% of all cases and rarely in the colon, small bowel, or perianal region[5]. There are a wide range of endoscopic findings in ARL. Findings of multiple, polypoid lesions, nodular masses, bulky tumor mass, or ulcerations are commonly found. Our search of the literature revealed no findings of multiple bloody spots with exudates or flat erythematous lesions in GI lymphoma. Previous study has shown that *H. pylori*-induced T-cell plays an important role in gastric mucosa-associated lymphoid tissue lymphoma development[6]. However, *H. pylori* was negative in this case, thus other mechanisms have been suggested. We believed that EBV activation caused by the immunosuppression in AIDS patients plays a role in the pathogenesis of the various and unique endoscopic findings, such as multiple nodular masses, bloody spots, and ulcers, because high EBV DNA blood levels are considered to be associated with the development of NHL[7].

In this case, we also perform magnified endoscopy using NBI. NBI endoscopy for diagnosing superficial gastric cancer is accurate for the diagnosis of cancer when the diagnostic triad of the disappearance of fine mucosal structures, microvascular dilation, and heterogeneity is used[8]. Our case did not satisfy this triad, suggesting that NBI endoscopy is a useful technique for the differential diagnosis of epithelial tumors and non-epithelial tumors.

Endoscopic biopsy is highly valuable to diagnose GI-ARL. We need to re-realize that GI-ARL can present with various endoscopic findings and involve the entire GI tract, which may be different from non-AIDS GI lymphoma due to differences in the immune status of patients with these conditions. NBI endoscopy may be used to differentiate GI-ARL from gastric cancer.

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