Lymphomatoid gastropathy/NK-cell enteropathy involving the stomach and intestine

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Lymphomatoid gastropathy (LyGa)/natural killer (NK)-cell enteropathy (NKCE) is recognized as a benign NK-cell lymphoproliferative disease. Due to its histological similarity to NK/T cell lymphoma, it is easy to misdiagnose, leading to unnecessary chemotherapy and poor quality of life. This disease is typically observed in the small and large intestines in North America, whereas almost all cases in Japan occur locally in the stomach. Only 11 LyGa/NKCE cases involving both gastric and intestinal lesions have been reported, and there are few reports providing endoscopic images throughout the gastrointestinal tract. We report a case of LyGa/NKCE involving both the stomach and small and large intestines with detailed upper gastrointestinal endoscopy, colonoscopy, capsule endoscopy and pathology images. Its pathogenesis currently remains elusive, but most patients with LyGa/NKCE in Japan have Helicobacter pylori (H. pylori) infection. Our patient was also positive for H. pylori infection at disease onset, but after receiving eradication therapy, ulcerative lesions in both stomach and intestine regressed and no recurrence was observed. This case suggests a link between the pathogenesis of LyGa/NKCE and H. pylori infection.

Keywords: lymphomatoid gastropathy; NK-cell enteropathy; lymphomatoid gastropathy/NK-cell enteropathy; gastrointestinal tract; Helicobacter pylori

INTRODUCTION

Lymphomatoid gastropathy (LyGa), sometimes referred to as natural killer (NK)-cell enteropathy (NKCE), is a disease in which NK cells proliferate benignly in the gastrointestinal (GI) tract. This disease is typically observed in the small and large intestines in North America, whereas almost all cases in Japan occur locally in the stomach. Currently, LyGa and NKCE are recognized as the same entity of benign NK-cell lymphoproliferative disease and named “LyGa/NKCE” irrespective of distribution. LyGa/NKCE develops in a wide range of ages and is asymptomatic or presents with GI symptoms. Due to the histological similarity of LyGa/NKCE with NK/T cell lymphoma, it is easy to misdiagnose, leading to unnecessary chemotherapy and poor quality of life. We report a case of LyGa/NKCE involving both the stomach and small and large intestines with detailed upper GI endoscopy, colonoscopy, capsule endoscopy and pathology images. Our patient was positive for Helicobacter pylori (H. pylori) infection at disease onset, but after receiving eradication therapy, ulcerative lesions in both stomach and intestine regressed and no recurrence was observed. This case may provide insight into the pathogenesis of LyGa/NKCE in Japan.

CLINICAL SUMMARY

The patient was a 38-year-old Japanese female who presented with symptoms related to digestive and blood disorders. Upper GI endoscopy at another hospital revealed multiple erosions and atypical epithelium in the middle body of her stomach, from which gastric cancer was suspected, and she was referred to our hospital. On medical examination, her abdomen was flat and soft, intestinal peristalsis was normal and there was no hepatosplenomegaly. On upper GI endoscopy at our hospital, multiple 5-10-mm discolored depressed lesions, erosions and ulcer scars with partial mucus adhesion and easy bleeding mainly in the body of the stomach.
ach were detected without signs of epithelial tumors, necessi-
tating the differential diagnosis of submucosal tumors such as
malignant lymphoma (Fig. 1A-F). Capsule endoscopy and
colonoscopy also revealed multiple similar lesions in the
small and large intestines (Fig. 2A and B). There was no
enhancement on positron emission tomography (PET) (data
not shown). At disease onset, she was positive for H. pylori
infection. The patient underwent H. pylori eradication ther-
apy 3 months after developing the initial symptoms. Active
LyGa/NKCE lesions in the stomach and duodenum regressed
with scar formation 4 months after starting treatment. She
was followed up for five years after onset and there was no
recurrence or progression suggesting malignancy.

PATHOLOGICAL FINDINGS

In the biopsy specimens from discolored depressed
lesions or erosions in the stomach and rectum, medium-to-
large atypical cells diffusely infiltrated the lamina propria and
occasionally the glandular epithelium (Figs. 3 and 4). On
immunohistochemical examination, the atypical cells were
positive for CD3, CD56, granzyme B, cytotoxic molecule-

Fig. 1. Representative endoscopic images of the stomach. Representative endoscopic images of the greater curvature of the
lower body (A-C) and the greater curvature of the upper and middle body (D-F). These lesions were observed by white-light
imaging (A, D), indigo-carmine dye imaging (B), magnified imaging (C) and magnified narrow-band imaging (NBI) (E, F).
Note that upper gastrointestinal endoscopy in our case confirmed the presence of multiple 5-10-mm discolored depressed
lesions, erosions and ulcer scars with partial mucus adhesion and easy bleeding mainly in the body of stomach, without signs
of epithelial tumors.

Fig. 2. Representative endoscopic images of the small and large intestines. (A) Representative endoscopic images of the small intestine. Erosive lesions (an arrow)
similar to those observed in the stomach were found in the small intestine by capsule endoscopy. (B) Representative endoscopic image of the large intestine. Erosive
lesions (an arrow) similar to those observed in the stomach were found in the large intestine by colonoscopy.
associated protein of T-cell restricted intracellular antigen-1 (TIA-1) and bcl-2, and negative for CD4, CD5, CD8, CD10, CD20, CD25, CD79a, cyclin D1, pankeratin, T cell receptor (TCR)-β and TCR-δ. There was no rearrangement in TCR-γ by polymerase chain reaction analysis (data not shown). We diagnosed LyGa/NKCE considering the negative status on in situ hybridization for EBV-encoded RNA (EBER in situ), which is 90% or more positive in nasal type NK/T-cell lymphoma, pathological findings, and clinical and endoscopic observations.

DISCUSSION

In the 2017 edition of the WHO classification, there are 120 types of lymphoma and related diseases, and there are more than 10 types of diseases that frequently resolve spontaneously.4 LyGa/NKCE is also a disease in which NK cells proliferate benignly in the GI tract. LyGa/NKCE was first described as an indolent atypical NK-cell proliferation in the GI tract by Vega and colleagues in 2006.7 Since then, the clinicopathological spectrum of indolent NK-cell proliferations in the GI tract has been characterized. At present, 47 cases have been reported worldwide. Many are asymptomatic and resolve spontaneously, but some patients have lesions for years. There are no reports of metastasis or death. Females dominate in North America, but there is no sex difference in Japan. The reason for the difference in distribution of LyGa/NKCE lesions between Japan and North America remains unknown, but most LyGa/NKCE patients in Japan have H. pylori infection. Takeuchi et al. reported that 90% of LyGa/NKCE patients were positive for H. pylori infection.2 Our patient was also positive for H. pylori infection, but after receiving eradication therapy, no recurrence was observed.

Fig. 3. Representative histological images of the stomach by hematoxylin and eosin (HE) staining (A) and immunohistochemistry for CD3 (B), CD56 (C), granzyme B (D) and cytotoxic T-cell restricted intracellular antigen-1 (TIA-1) (E), and in situ hybridization for EBV-encoded RNA (EBER in situ) (F). Note that the atypical lymphocytes were positive for CD3, CD56, granzyme B and TIA-1, and negative on EBER in situ (F). Inset of the HE image: a magnified image. Scale bar, 100 μm.
The endoscopic findings of LyGa/NKCE are erythematous lesions, ulcers or erosions with slight ridges with central depression or polypoid lesions. There is no swelling of the lymph nodes or enlargement of other organs. Although our case of LyGa/NKCE involved both the stomach and intestine, the endoscopic and histological features were similar throughout the gastrointestinal tract (Figs. 3 and 4). White-light imaging, indigo-carmine dye imaging, magnified imaging and magnified narrow-band imaging on upper endoscopy demonstrated the frequent occurrence of 5-10-mm discolored depressed lesions, erosions and ulcer scars with partial mucus adhesion and easy bleeding mainly in the body of stomach, without signs of epithelial tumors. Histologically, NK/T cell lymphoma needed to be differentiated. However, the atypical lymphocytes were negative on EBER in situ and, for half a year from onset, there was no progression to suggest malignancy. These clinical, endoscopic and histological findings led us to the diagnosis of LyGa/NKCE involving both the stomach and intestine.

In the 11 cases of LyGa/NKCE involving both the stomach and intestine previously reported (Table 1), there was no exacerbation during the 2 to 10-year observation period. Although one patient was positive for H. pylori (Table 1), it is unknown whether they received H. pylori eradication therapy. As LyGa/NKCE can resolve without treatment, we cannot exclude the possibility that the lesions in our patient spontaneously disappeared irrespective of the eradication of H. pylori. However, this concept was only recognized in the last 15 years and its pathogenesis remains unknown. Recently, the JAK3 K563_C565del mutation, which was not detected in our case (data not shown), was found in 3 of 10 cases of LyGa/NKCE, suggesting that part of LyGa/NKCE is neoplastic. The clinical history in the present case also suggests a link between H. pylori infection and LyGa/NKCE, but...
further studies are needed to clarify the pathogenesis of LyGa/NKCE.

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AUTHOR CONTRIBUTIONS

MN, MS, KT and YK performed pathological examinations; TK and YI contributed essential clinical information; KT and AD performed molecular analysis; MN, MS and YI wrote the paper. All authors gave final approval for publication.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest. This case report was conducted in compliance with ethical standards set by the ethics committee of Keio University School of Medicine.

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