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Case report

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,[1] whereas almost all cases in Japan occur locally in the stomach.[2] Currently, LyGa and NKCE are recognized as the same entity of benign NK-cell lymphoproliferative disease and named "LyGa/NKCE" irrespective of distribution.[3] 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, and 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 stom-

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ach were detected without signs of epithelial tumors, necessitating 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 therapy 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-

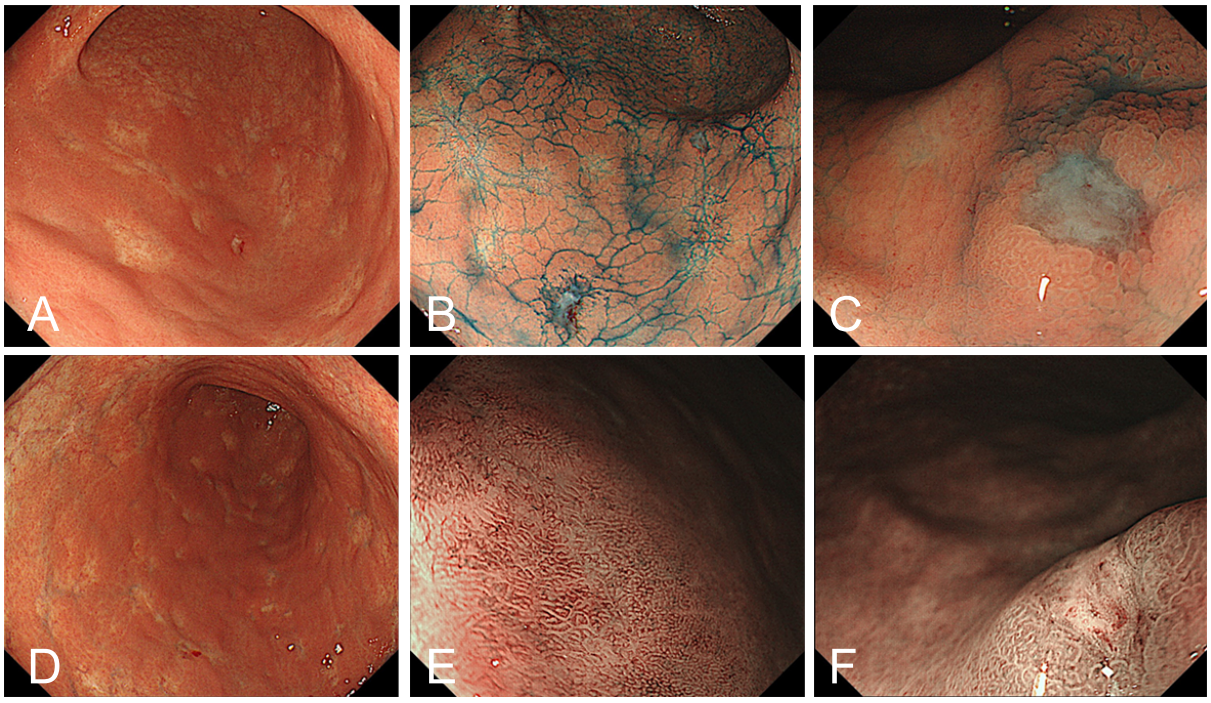

Fig. 1. Representative endoscopic images of the stomach. Representative endoscopic images of the greater curvature of the lower body (***A*-*C***) and the greater curvature of the upper and middle body (***D*-*F***). These lesions were observed by white-light imaging (***A***, ***D***), indigo-carmine 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.

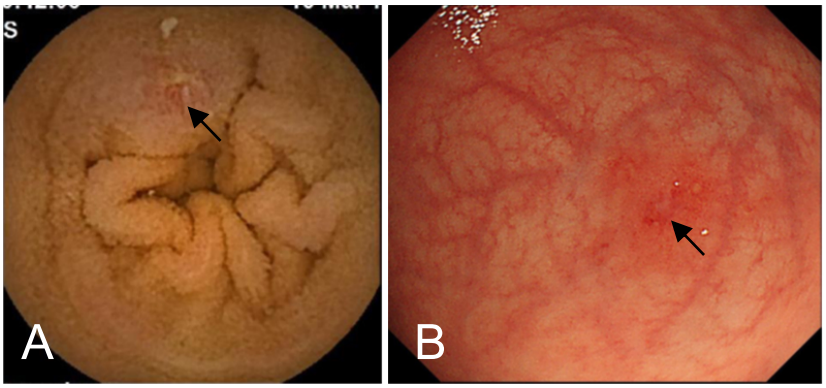

Fig. 2. Representative endoscopic images of the small and large intestines. (***A***) Representative endoscopic images of the small intestine. Erosive lesions (an arrow) similar to those observed in the stomach were found in the small intestine by capsule endoscopy. (***B***) Representative endoscopic 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.

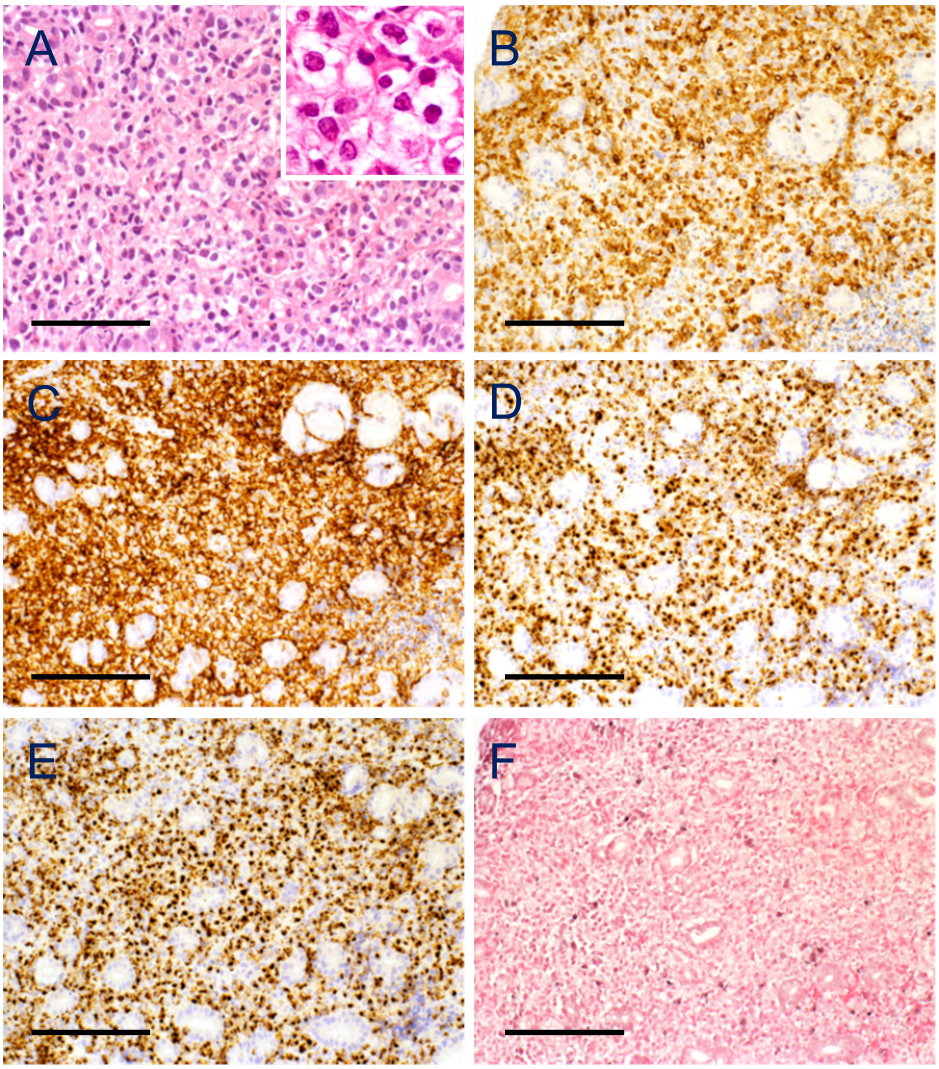

Fig. 3. Representative histological images of the stomach by hematoxylin and eosin (HE) staining (***A***) and immunohistochemistry for CD3 (***B***), CD56 (***C***), granzyme B (***D***) and cytotoxic T-cell restricted intracellular antigen-1 (TIA-1) (***E***), and *in situ* hybridization for EBV-encoded 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.

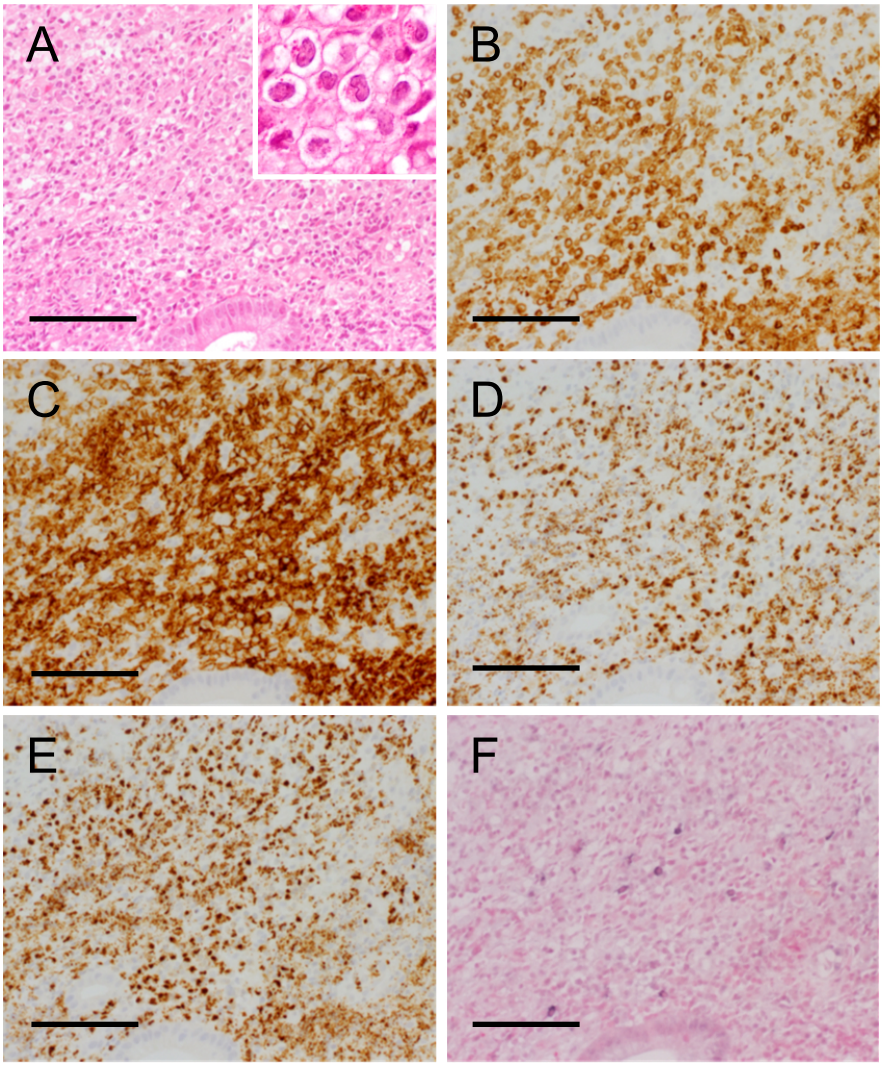

Fig. 4. Representative histological images of the large intestine by hematoxylin and eosin (HE) staining (***A***) and immunohistochemistry for CD3 (***B***), CD56 (***C***), granzyme B (***D***), cytotoxic T-cell restricted intracellular antigen-1 (TIA-1) (***E***), and *in situ* hybridization for EBV-encoded 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.[1] 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),[7-11] there was no exacerbation during the 2 to 10-year observation period.[5,6] Although one patient was positive for H. pylori (Table 1), it is unknown whether they received H. pylori eradication therapy.[10] 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.[6] The clinical history in the present case also suggests a link between H. pylori infection and LyGa/NKCE, but

Table 1. Reported cases of lymphomatoid gastropathy/NK-cell enteropathy

Race	Age/sex	Lesion	Examination	H. pylori infection	Ref. No.
Caucasian	32/M	Stomach, terminal ileum, colon	Upper GI endoscopy, colonoscopy, CT, MRI, PET, bone marrow biopsy	Unknown	7
Caucasian	31/M	Stomach, small intestine, colon	Upper GI endoscopy, colonoscopy, CT, MRI, PET	Unknown	8
Caucasian	53/M	Stomach, duodenum	Upper GI endoscopy, colonoscopy, CT, MRI, PET	Unknown	8
Caucasian	14/M	Esophagus, stomach, duodenum, small intestine, colon	Upper GI endoscopy, colonoscopy, capsule endoscopy, CT, PET	Unknown	9
Korean	33/F	Stomach, duodenum, colon, gall bladder	Upper GI endoscopy, colonoscopy, CT, PET, cholecystectomy	Positive	10
Korean	68/M	Esophagus, stomach, colon	Upper GI endoscopy, colonoscopy	Not detected	11
Korean	76/F	Stomach, duodenum	Upper GI endoscopy	Not detected	6
Korean	71/F	Stomach, colon	Upper GI endoscopy, colonoscopy	Not detected	6
Korean	48/F	Stomach, duodenum, terminal ileum	Upper GI endoscopy, colonoscopy	Not detected	6
Korean	69/F	Stomach, duodenum	Upper GI endoscopy	Not detected	6
Korean	9/F	Stomach, jejunum	Upper GI endoscopy	Not detected	6
Japanese	38/F	Stomach, duodenum, small intestine, colon	Upper GI endoscopy, colonoscopy, capsule endoscopy, PET	Positive	Our case

M, male; F, female; GI, gastrointestinal; CT, computed tomography scan; MRI, magnetic resonance imaging; PET, positron emission tomography; H. pylori, Helicobacter pylori; Ref. No., reference number

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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