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CASE REPORT

Lymphomatoidgastropathy mimicking extranodal NK/T cell lymphoma, nasal type: A case report

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Abstract

Extranodal natural killer (NK)/T-cell lymphoma, nasal type, exhibits aggressive tumor behavior and carries a poor prognosis. Recently, lymphomatoid gastropathy with NK/T cell infiltration into gastric mucosa has been recognized as a pseudo-malignant disease which regresses without treatment. Because the conventional immunohistochemical criteria of lymphomatoid gastropathy is similar to that of extranodal NK/T-cell lymphoma nasal type, it is difficult to distinguish between the two conditions by histopathological evaluation only. Here, we report a rare case of lymphomatoid gastropathy in a 57-year-old female. Gastroendoscopy on routine check-up revealed elevated reddish lesions < 1 cm in diameter in the gastric fornix and body. Although repeat endoscopies at 1 and 6 mo later revealed no gastric lesions at any locations without any treatments, at 12 mo later gastric lymphomatoid lesions recurred at gastric fornix and body. Histological examination of endoscopic biopsy specimens at 12 mo showed atypical NK cell infiltration with $CD3^+$, $CD4^-$, $CD5^-$, $CD7^+$, $CD8^-$, $CD20^-$, $CD30^-$, $CD56^+$, $CD79a^-$ and T-cell-restricted intracellular antigen-1^+ into gastric mucosa. After treatment for *Helicobacter pylori* (*H. pylori*) eradication, the lesions disappeared in all locations of the gastric fornix and body over the subsequent 12 mo. Here, we report a case of *H. pylori*-positive lymphomatoid gastropathy with massive NK-cell proliferation, and also review the literature concerning newly identified lymphomatoid gastropathy based on comparison of extra nodal NK/T-cell lymphoma nasal type. In any case, these lesions are evaluated with biopsy specimens, the possibility of this benign entity should be considered, and excessive treatment should be carefully avoided. Close follow-up for this case of lymphomatoid gastropathy is necessary to exclude any underlying malignancy.

Key words: Gastric lymphomatoid gastropathy; Gastric natural killer/T-cell lymphoma nasal type; *Helicobacter pylori*; Eradication

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INTRODUCTION

Extranodal natural killer (NK)/T-cell lymphoma, nasal

type, has the distinctive morphologic features of an angiocentric and angiodestructive growth pattern with frequent necrosis and apoptosis[1]. NK/T cell lymphoma frequently presents as a disease of infiltrative and ulcerative lesions around the nasal cavity, "nasal" and other midline structures, such as skin, gastrointestinal tract, salivary gland and testis, "nasal type"[2]. Characteristic immunohistochemical findings include $CD56^+$ (NK cell marker), $sCD3^-$, $cCD3^+$, and Epstein-Barr virus $(EBV)^+$ *in situ* hybridization[3]. Long-term outcomes of NK/T cell lymphoma are generally poor due to frequent systemic relapses, and only 40% of patients survive longer than 5 years[4]. Primary NK/T cell lymphoma nasal type in the stomach is rare, and the etiology, pathogenesis, and clinical characteristics are unclear[5,6].

Recently, several cases of NK-cell proliferation in gastric mucosa were reported as lymphomatoid gastropathy or NK-cell enteropathy. Newly identified lymphomatoid gastropathy has been characterized as self-limited pseudomalignant NK-cell proliferation in gastric mucosa, and to have a good prognosis irrespective of a good prognosis even when left untreated. Histological findings reveal diffuse infiltrations of medium-sized to large atypical NK/T cells in the lamina propria and glandular epithelium. The cells were $CD2^{+/-}$, $sCD3^-$, $cCD3^+$, $CD4^-$, $CD5^-$, $CD7^+$, $CD8^-$, $CD16^-$, $CD20^-$, $CD45^+$, $CD56^+$, $CD117^-$, $CD158a^-$, $CD161^-$and granzyme B^+. Previously, most cases of lymphomatoid gastropathy were expected to be diagnosed as extranodal NK/T-cell lymphoma nasal type, because of their similar histopathologic findings, and to be treated with chemotherapy, surgery or both[7,8].

Here, we report a case of *Helicobacter pylori* (*H. pylori*)-positive lymphomatoid gastropathy with massive NK-cell proliferation in the stomach, and also review the literature concerning newly identified lymphomatoid gastropathy based on comparison of extra nodal NK/T-cell lymphoma nasal type.

CASE REPORT

A 57-year-old Japanese female without symptoms such as epigastric discomfort, nausea or heart burn showed an erythematous dish-like elevated lesion less than 1 cm in diameter in the greater curvature of the lower body of the stomach and atrophic gastritis with *H. pylori* infection at check-up gastroendoscopy (Figure 1A and B). However, histological findings were no atypical lymphoid cell infiltrations or atypical glands of the gastric mucosa. Follow-up at 1 and 6 mo showed that the elevated erythematous lesion had resolved without treatment (Figure 1C and D).

Twelve months later, repeated endoscopy revealed a similar erythematous elevated lesion < 1 cm in diameter in the anterior wall of the middle body and an erythematous lesion in the fornix (Figure 1E-H). Histological examination of biopsy specimens of the two lesions showed massive atypical medium- to large-sized NK lymphocyte infiltrations with slightly irregular nuclear contours, a dispersed chromatin pattern, and clear cytoplasm (Figure 2A and B). Immunohistochemical stains of NK cells showed $CD3^+$, $CD4^-$, $CD5^-$, $CD7^+$, $CD8^-$, $CD20^-$, $CD30^-$, $CD56^+$, $CD79a^-$ (Figure 2C-I). Cytotoxic molecule-associated proteins of T-cell restricted intracellular antigen-1 (TIA-1) and granzyme B were both positive (Figure 2J and K). *In situ* hybridization for EBV-encoded RNA was negative(Figure 2L). There was no evidence of the involvement of tumor cells in peripheral blood or bone marrow, or of the involvement of small intestine, colon or other organs by computed tomography and positron emission tomography.

A diagnosis of extranodal NK/T-cell lymphoma nasal type was initially considered based on the atypical NK/T-cell infiltrations into gastric mucosa. However, owing to the negative hematological evaluation for EBV infection, including Epstein-Barr anti-viral capsid antigen immunoglobulin M (< 10 times) and anti-Epstein-Barr nuclear antigen (< 10 times), lack of any evidence of the involvement of other organs, stage IE according to the Ann Arbor classification, and lack of aggressive tumor behavior during observation period, the diagnosis was changed to lymphomatoid gastropathy. The patient was not treated with chemotherapy or gastrectomy but rather *H. pylori* eradication therapy consisting of rabeprazole 10 mg bid, clarithromycin 200 mg bid and amoxicillin 750 mg bid for 7 d. After eradication, no further manifestation of lymphomatoid gastropathy occurred endoscopically and pathologically during 12 mo of follow-up.

DISCUSSION

$CD16/CD56^+$ NK cells are a subset of lymphocytes which are associated with innate immunity and cytotoxic function against viruses and tumor cells in peripheral blood, lymphoid tissue, spleen and extranodal sites, such as gastrointestinal mucosa[9]. Nevertheless, little is known about the presence and function of these or other NK cells in gastric mucosa. Here, we reported a rare case of self-limited lymphomatoid gastropathy mimicking extranodal NK/T-cell lymphoma, nasal type, in the stomach. Microscopic observation showed sheets of large peculiar cells with indented nuclei and clear cytoplasm with eosinophilic granules. Immunohistochemical analysis of these atypical cells showed $CD3^+$, $CD4^-$, $CD5^-$, $CD7^+$, $CD8^-$, $CD20^-$, $CD30^-$, $CD56^+$, $CD79a^-$, $TIA\text{-}1^+$ and granzyme B^+. In general, although NK cells in gastric mucosa have no cytotoxic function and low levels of TIA-1 and Granzyme B[10], the relatively high TIA-1 and Granzyme B expression of gastric mucosal NK cell infiltrates in this case suggested that these cells did in fact have a cytotoxic function in this patient, most probably in responding to local inflammation or autoimmunity.

The most important differential diagnosis of lymphomatoid gastropathy is to distinguish it from extranodal NK/T cell lymphoma, nasal type, in stomach. In the present case, a diagnosis of "extranodal NK/T cell lymphoma nasal type" was suspected from the immunohistochemical finding of a strong expression of CD56

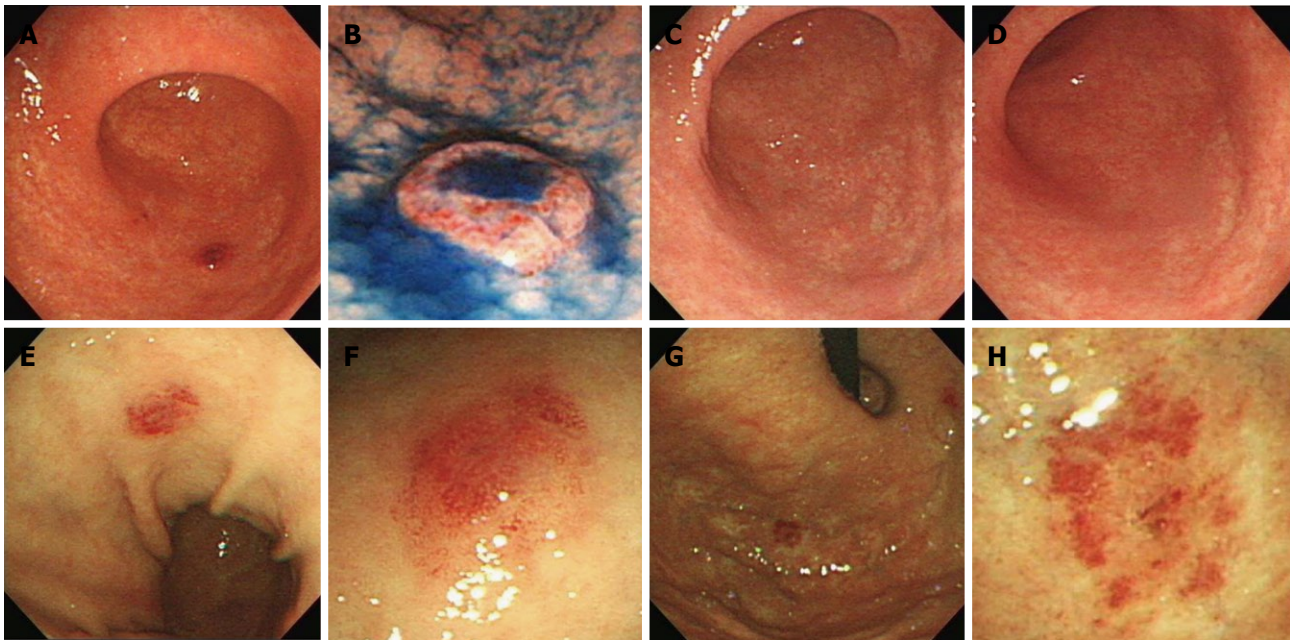

Figure 1 Gastroendoscopy revealed an erythematous dish-like elevated lesion in the greater curvature of the lower body at check-up (A and B), and at one (C) and six months later (D); Twelve months later, endoscopy revealed a similar lesion in the anterior wall of the middlebody (E and F), and an erythematous lesion in the fornix (G and H).

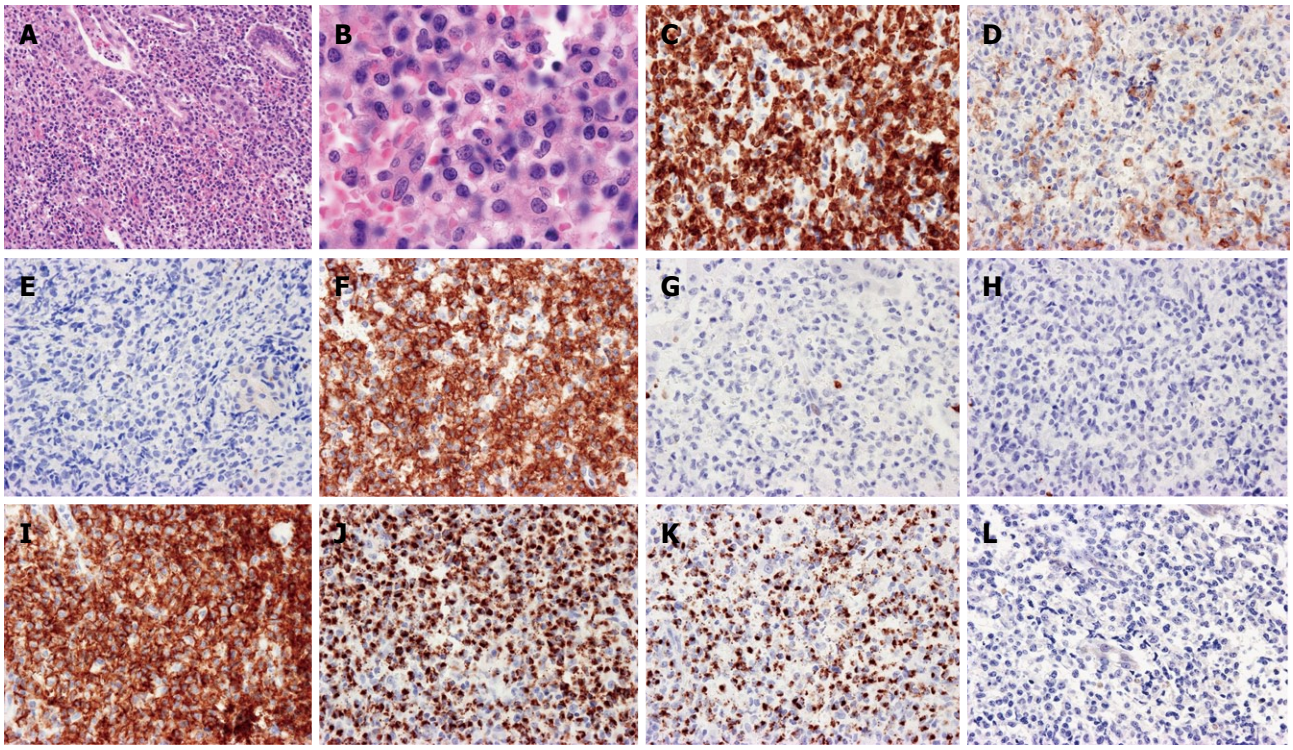

Figure 2 Histological examination showed massive atypical medium- to large-sized natural killer lymphocyte infiltrations with slightly irregular nuclear contours. A dispersed chromatin pattern and clear cytoplasm in the gastric mucosa, × 100 (A) and × 400 (B); Immunohistochemical stains showed $CD3^+$ (C), $CD4^-$ (D), $CD5^-$ (E), $CD7^+$ (F), $CD8^-$ (G), $CD20^-$ (H), $CD56^+$ (I), T-cell restricted intracellular antigen-1^+ (J), granzyme B^+ (K) and Epstein-Barr virus-encoded RNA *in-situ* hybridization (L).

and CD3. Extranodal NK/T-cell lymphoma, nasal type, is rarely seen in Western countries but is relatively common in Asia and Central-South American countries[7,11,12], where it accounts for < 2% of all newly diagnosed lymphoma in Japan, 6% in Hong Kong, 8% in Korea, and 5% in Taiwan[13-16]. Histologically, the lymphoma often shows an angiocentric and angiodestructive infiltrate of atypical lymphocytes leading to extensive necrosis. The differential diagnosis of gastrointestinal NK-cell and T-cell lymphomas includes enteropathy-associated T-cell

Table 1 Characteristics of cases of lymphomatoid gastropathy in the stomach and duodenum

Patient	Ref	Age/ sex	Symptom	*H. pylori*	Location	Endoscopic findings	Follow-up
1	[7]	52/M	UN	-	Stomach	UN	A (145)
2	[7]	58/M	UN	+	Stomach	UN	A (50)
3	[7]	51/M	UN	+	Stomach	UN	A (60)
4	[7]	50/F	UN	+	Stomach	UN	A (46)
5	[7]	55/M	UN	+	Stomach	UN	A (33)
6	[7]	46/M	UN	+	Stomach	UN	A (60)
7	[7]	65/F	UN	+	Stomach	UN	A (56)
8	[7]	56/F	UN	+	Stomach	UN	A (29)
9	[7]	59/F	UN	+	Stomach	UN	A (18)
10	[7]	75/F	UN	+	Stomach	UN	A (12)
11	[8]	31/M	NA	UN	Stomach, small intestine, colon	Superficial erythematous lesion	A/P (84)
12	[8]	27/F	Abd pain	UN	Stomach	Multiple, superficial ulcer	A/P (23)
13	[8]	53/M	NA	UN	Stomach, duodenum	Gastric lesion	A/P (30)
14	[8]	46/F	+	UN	Duodenum, colon	Superficial ulcer	A/P (36)
15	[8]	61/F	+	UN	Duodenum, colon	Multiple, ulcers	A/P (120)
This case		57/F	NA	+	Stomach	Multiple, erythematous dish-like elevated lesions	A (16)

H. pylori: *Helicobacter pylori*; M: Male; F: Female; A/P: Alive with persistent disease but without progression; A: Alive; UN: Unknown; NA: Not available.

Table 2 Immunophenotypic findings in cases of lymphomatoid gastropathy in the stomach and duodenum

Patient	Ref	cCD3	CD56	TIA/ GRZB	CD7	CD5	CD4/ CD8	CD20	EBER
1	[7]	+	+	+	+	-	NA	-	-
2	[7]	+	+	+	+	-	-	-	-
3	[7]	+	+	+	+	-	-	-	-
4	[7]	+	+	+	+	-	-	-	-
5	[7]	+	+	+	+	-	-	-	-
6	[7]	+	+	+	+	-	-	-	-
7	[7]	+	+	NA	+	-	-	-	-
8	[7]	+	+	+	+	-	-	-	-
9	[7]	+	+	+	+	-	-	-	-
10	[7]	+	+	+	+	-	-	-	-
11	[8]	+	+	+	+	-	-	-	-
12	[8]	+	+	NA	+	-	-	-	-
13	[8]	+	+	+	+	-	-	-	-
14	[8]	+	+	+	+	-	-	-	-
15	[8]	+	+	+	+	-	-	-	-
This case		+	+	+	+	-	-	-	-

cCD3: Cytoplasmic CD3; TIA: T-cell restricted intracellular antigen; GRZB: Granzyme B; EBER: Epstein-Barr virus-encoded RNA; +: Positive; -: Negative; NA: Not available.

lymphoma, T-cell lymphoma, and more rarely anaplastic large cell lymphoma[17]. Moreover, histopathological diagnosis for several reactive or borderline lesions is also required, including infectious mononucleosis, drug-induced lymphadenitis, and histiocytic/subacute necrotizing lymphadenitis; these lesions histopathologically mimic lymphoma and are occasionally misdiagnosed as malignancy.

The differentiation of extranodal NK/T-cell lymphoma nasal type and lymphomatoid gastropathy by histological findings only is difficult. The differential diagnosis of the two diseases is considered to be as follows. First, the stomach is not a common site of origin of extranodal NK/T-cell lymphoma, nasal type, and most cases of extranodal NK/T-cell lymphoma and NK-cell enteropathy in the stomach are not limited to the stomach at the time the condition is diagnosed[5,18-20]. Previous cases of lymphomatoid gastropathy in the stomach and duodenum extended further down into the gastrointestinal tract, including as far as the colon (Table 1)[5,8]. Second, although some cases of lymphomatoid gastropathy showed necrosis, none showed angiocentric or angiodestructive growth patterns, or prominent apoptotic bodies, which are common features of extranodal NK/T-cell lymphoma, nasal type[7]. Our present case also showed no angiocentric or angiodestructive growth patterns. Third, Epstein-Barr virus-encoded RNA *in situ* hybridization, which is almost always positive in NK/T-cell lymphoma, nasal type, is consistently negative in lymphomatoid gastropathy (Table 2)[3,21].

NK cells function as cytokine-producing effectors and can act as regulatory cells during inflammation and influence subsequent adaptive immune responses[22]. In acute/chronic inflammation or autoimmune reactions, localization of NK cells has been observed at variousanatomic sites, including skin and gastrointestinal tract[9]. *H. pylori* infection is characterized by marked neutrophil, lymphocyte, monocyte and plasma cell infiltration of gastric mucosa[23]. Chronic *H. pylori* gastric mucosal infection leads to chronic gastritis with severe inflammatory cell infiltration, which results in progressive gastric mucosal atrophy and intestinal metaplasia with higher potential for the development of gastric tumors[24,25]. Mucosa-associated lymphoid tissue (MALT) lymphoma (70%-80%) is well known to be caused by chronic *H. pylori* infection into gastric mucosa and after eradication therapy *H. pylori*-positive MALT lymphoma regresses. Therefore, we have lead to the hypothesis that the pathogenesis of lymphomatoid gastropathy is associated with the gastric mucosal inflammation produced by chronic *H. pylori* infection. Takeuchi *et al*[7] reported that 90% cases of lymphomatoid gastropathy were positive for *H pylori* infection and that lymphomatoid gastropathy in several patients receiving eradication therapy regressed during follow-up observation. In our case, no further manifestation of lymphomatoid gastropathy was seen for 12 mo after *H. pylori* eradication. However, other patients have also shown complete resolution without treatment for *H. pylori* eradication[7,8]. Although lymphomatoid gastropathy may be related with *H pylori* infection, a better understanding of lymphomatoid gastropathy and its relationship with *H pylori* infection awaits further study.

As shown in Table 1, endoscopic characteristics may include raised ulcers or reddish and congestive flat eleva-

tions with a shallow depression[7]. In all cases, multiple lesions of reddish flat elevations were seen. While some cases may resemble early gastric carcinoma, the endoscopic characteristics of lymphomatoid gastropathy are not clearly understood.

In conclusion, we experienced the rare case of lymphomatoid gastropathy, in which eradication treatment for *H. pylori* appeared to be effective. Differentiation of extranodal NK/T-cell lymphoma, nasal type and lymphomatoid gastropathy is difficult, and biological and endoscopic characteristics, prognosis and treatment of lymphomatoid gastropathy are unclear. Therefore, it will be better to clarify those characteristics by further case studies or basic research in feature. In any case, at the time these lesions are evaluated with biopsy specimens, the possibility of this benign entity should be closely considered, and excessive treatment should be carefully avoided. In finally, close follow-up for this case of lymphomatoid gastropathy is necessary to exclude any underlying malignancy, because nobody knows etiology of this NK-cell lymphomatoid gastropathy.

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