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CASE REPORT | STOMACH

A Rare Case of Gastric Extranodal NK/T-Cell Lymphoma With Orbital Involvement

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ABSTRACT

Gastric extranodal NK/T-cell lymphoma (ENKTL) is a rare presentation of a rare disease. We report a 33-year-old woman presenting with epigastric pain, nausea, and vomiting. Endoscopic examination revealed gastric and duodenal ulceration. Biopsy of the ulcers revealed ENKTL. The patient began treatment, but developed hemorrhagic shock from her ulcers and died. Gastric ENKTL is a rare disease that presents with gastric ulceration. It has a high rate of mortality, and treatment is challenging because of its aggressive nature and lack of high-quality data to guide therapy.

KEYWORDS: lymphoma; ulcer; GI bleed; cancer

INTRODUCTION

Extranodal NK/T-cell lymphoma (ENKTL) is a rare and aggressive form of non-Hodgkin lymphoma that is rarely seen in Western centers.[1] Most cases are reported from Asia and South America.[2] ENKTL accounts for 5%–18% of all cases of non-Hodgkin lymphoma and is categorized as nasal or extranasal.[3] The nasal type accounts for 80% of all ENKTLs and involves the upper aerodigestive tract including the nasal cavity. Extranasal ENKTL accounts for the remaining 20% of ENKTL cases and can involve the gastrointestinal tract, skin, or genitalia.[3] Orbit involvement is exceedingly rare, with only a few reported cases.[3] Gastrointestinal tract involvement has been reported in approximately 6% of ENKTLs, and most cases involve the small and large intestines, with stomach involvement accounting for less than 5% of all gastrointestinal ENKTLs.[4] We present a case of a 33-year-old woman with fatal gastrointestinal bleeding from gastric ENKTL with concomitant orbital involvement.

CASE REPORT

A 33-year-old Indigenous woman was admitted to a tertiary hospital with a 3-week history of intermittent epigastric pain, nausea and vomiting, and painful swelling in her left eye. She endorsed 10 kg weight loss over the past year but denied other constitutional symptoms.

Relevant medical history includes multiple presentations of abdominal pain with nausea and vomiting in the past 3 years. She underwent an esophagogastroduodenoscopy for a similar presentation 5 years ago. There was no ulceration, mass, or any abnormalities, but gastric biopsy was positive for *Helicobacter pylori*. Eradication status is not known because treatment adherence was not clear.

She denied any family history of malignancies. Physical examination revealed no abnormalities apart from epigastric tenderness and left orbital swelling with decreased adduction, abduction, supraduction, and infraduction of her left eye.

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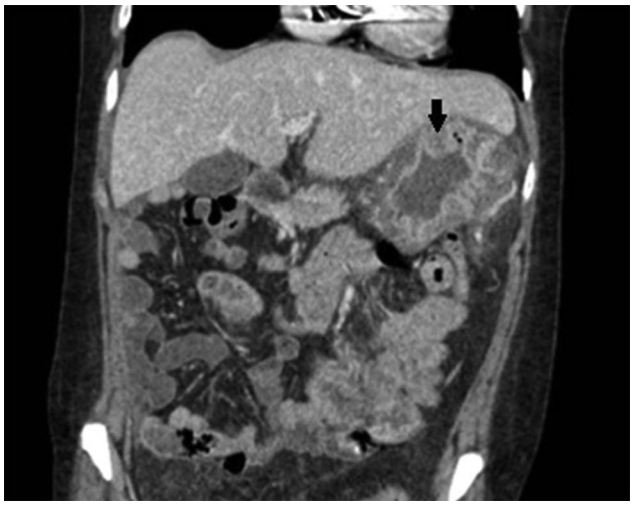

Figure 1. Contrast-enhanced CT shows edema and thickening of gastric folds (arrow). CT, computed tomography.

Initial investigations revealed a decreased lymphocyte count of 0.7×10^9/L (1.2–3.5). The rest of the complete cell count with differential and peripheral blood smear revealed no abnormalities. Basic metabolic panel and liver panel were unremarkable. Her lactate dehydrogenase level was elevated at 1,563 U/L (115–230).

An abdominal and pelvic computed tomography scan demonstrated gastric wall edema with mucosal hyperenhancement and perigastric fat stranding with 2 reactive lymph nodes (Figure 1). A head computed tomography scan demonstrated grossly enlarged left lateral rectus muscle and periorbital soft-tissue swelling suggestive of left orbital pseudotumor (Figure 2).

Esophagogastroduodenoscopy demonstrated multifocal Forrest classification II-C ulcerations throughout her stomach with diffuse erythema and edema (Figure 3). Biopsies of the ulcers showed extensive infiltration by atypical lymphoid cells (Figure 4). Immunohistochemistry demonstrated abnormal lymphoid cells with uniform expression of CD2, CD3, CD30, CD56, TIA1, perforin, and granzyme B (selective immunostains in Figure 5). EBV-encoded small RNA in situ hybridization was positive in all atypical cells. The proliferation rate was high (KI67 index >95%). Immunohistochemistry was negative for CD1a, CD4, CD5, CD10, CD20, TDT, ALK1, and cytokeratin (selective immunostains in Figure 5). These findings were consistent with gastric ENKTL. Biopsies of the left orbital fat and conjunctiva revealed similar histological findings consistent with concurrent ENKTL involvement of the orbit.

She started an intravenous corticosteroid (1 mg/kg/d) as bridging therapy to chemotherapy. Intravenous pantoprazole infusion was also initiated because of ongoing GI bleeding. After a few days, she had frank blood per rectum and hematemesis with hemodynamic instability consistent with hemorrhagic shock most likely secondary to her malignant ulceration. Based on the diffuse nature of the ulcerations, endoscopic therapy was believed to be futile. Despite resuscitative measures in the intensive care unit, she deteriorated hemodynamically and was deemed unsuitable for chemotherapy. After discussion with her family, she was transitioned to comfort care and subsequently died of multiorgan failure from worsening shock.

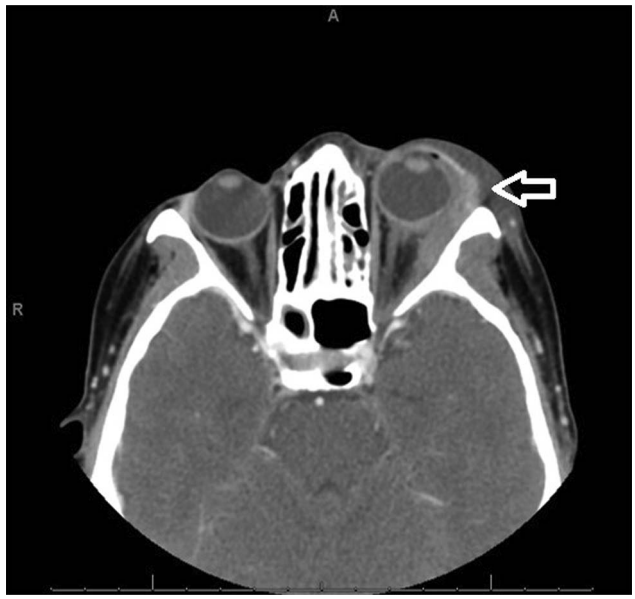

Figure 2. Contrast-enhanced CT shows enlargement of the left lateral rectus muscle with left periorbital soft-tissue swelling (arrow). CT, computed tomography.

DISCUSSION

Gastric ENKTL is a rare presentation of a rare disease and described only in a few case reports from Asia and Europe (Table 1). To our knowledge, this is the first report of gastric ENKTL in North America. Gastrointestinal ENKTL is often asymptomatic initially but can progress to abdominal pain, bleeding, and bowel perforation.[14] Based on our literature

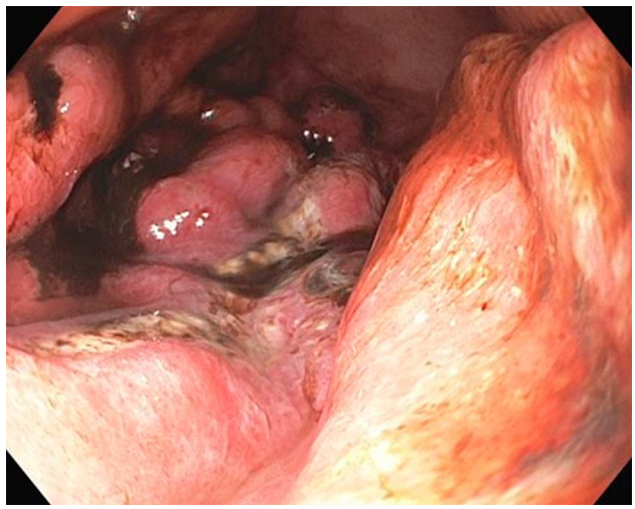

Figure 3. Endoscopic visualization of edematous gastric folds and Forrest II-c ulcerations.

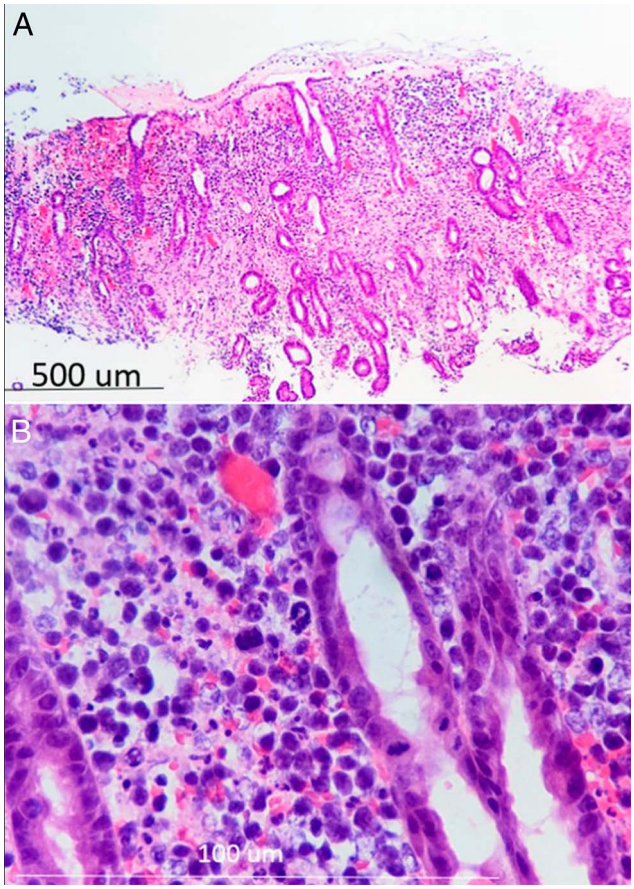

Figure 4. (A) Gastric mucosa biopsy showing ulcers and hemorrhage. There is dense cellular infiltrate in the laminar propria (H&E 40×). (B) The dense infiltrate is composed of high-grade lymphoid cells with intermediate-sized nuclei, frequent mitotic figures, and necrosis (H&E 200×). H&E, hematoxylin and eosin.

review, all published cases of gastric ENKTL had endoscopic findings of gastric ulcerations to varying degrees (Table 1).[2] However, this finding is nonspecific, and endoscopic findings can resemble inflammatory bowel disease or lymphomatoid gastropathy.[15,16]

Owing to its nonspecific clinical features and rarity, diagnosis can be difficult and requires sufficient tissue sampling with review by pathologists experienced in lymphomas. This disease presents in the deeper mucosa early on, and thus, if initial biopsy is nonspecific, full-thickness biopsy may be required.[17] This aggressive lymphoma is characterized by positive CD3, CD30, CD56, TIA, granzyme B, perforin on immunohistochemistry, and EBV-encoded small RNA in situ hybridization.[18]

The prognosis of ENTKL is poor. While localized ENTKL can be treated with radiotherapy alone with an estimated 5-year survival of 70%, prognosis for advanced ENKTL has a 5-year survival of around 40% and median overall survival of 7–8 months.[4] Advanced ENKTL is typically treated with a combination of radiation and multidrug chemotherapy regimens. SMILE (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) is the most studied chemotherapy regimen, and it has been shown to have a 5-year overall survival rate of 47%.[19] Data on SMILE and other regimens are retrospective, and there is a lack of long-term prospective clinical trials, making treatment decisions difficult.

Hematopoietic cell autotransplantation is another treatment option. The largest study from Western centers reported a 2-year progression-free survival of 33% (confidence interval 13–84%) and 40% survival (confidence interval 19%–86%).[20] However, the data are from uncontrolled clinical trials, and autotransplantation is not recommended currently.[19]

In conclusion, gastric ENTKL is a rare and aggressive disease. Advanced ENTKL is often treated with a combination of radiation and chemotherapy regimens, but the prognosis is poor, with 5-year survival being less than 40%. Advanced stage at the time of presentation, rarity of disease, and lack of standard therapy all contribute to the poor prognosis. More recognition of this disease entity and higher quality treatment data with long-term prospective trials are needed to improve the survival of patients with ENKTL.

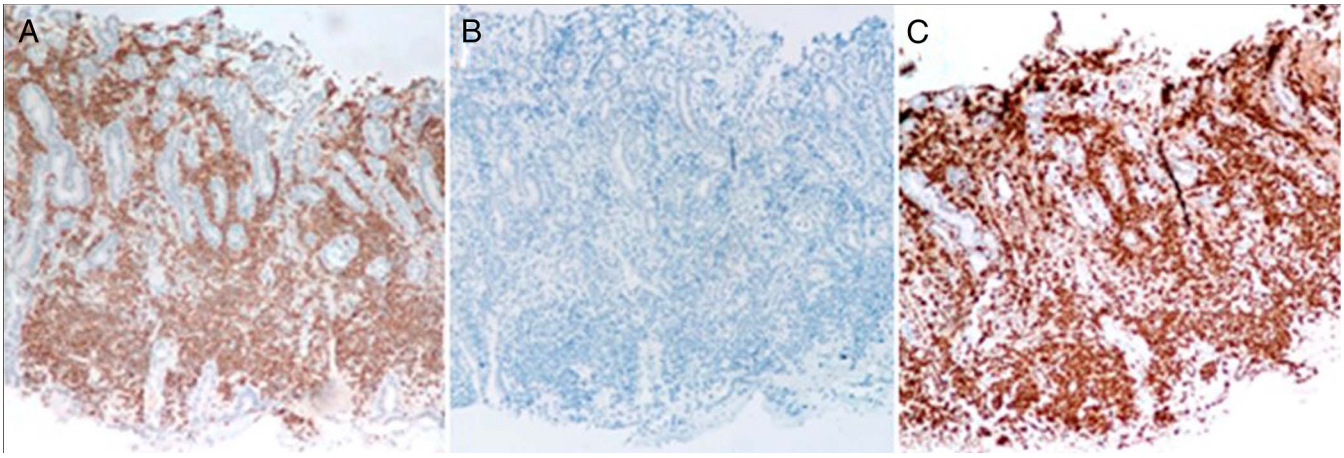

Figure 5. Immunohistochemistry studies show diffuse CD3 positivity in the lymphoid cells (A) without CD20 expression (B). The ki67 proliferation index is high.

Table 1. Country, presenting symptoms, and endoscopic findings of previously reported cases of gastric extranodal NK/T-cell lymphoma

Author	Country	Number of cases	Presentation	Endoscopic findings	Treatment	Outcome
Zhang et al[5]	China	1	Breast mass	Stomach ulcer	Modified SMILE	Refused further treatment and follow-up
Chung et al[6]	Korea	1	GI bleeding + abdominal pain	Gastric fundus ulcer, 3 × 3 cm	Modified VIDL with autologous peripheral blood-hematopoietic stem cell transplantation	Clinical remission
Zhang et al[7]	China	1	Abdominal pain	Cardia ulcer, 4 × 3.5 cm	Nonspecified chemotherapy regimen	Alive 14 mo after treatment
Kim et al[8]	Korea	2	Not reported	Not reported	Not reported	Not reported
Kim et al[2]	Korea	3	GI bleeding: 2 Abdominal pain: 1	Gastric ulcer: 2 Superficial erosion: 1	Patient 1: DICE Patient 2: DICE Patient 3: supportive	Patient 1: alive 6 mo after treatment Patient 2: died after 12 mo Patient 3: died
Kobold et al[9]	Germany	1	GI bleeding	Antral ulcer	CHOP	Died of sepsis
Ko et al[10]	Korea	2	Not reported	Not reported	Not reported	Not reported
Kim et al[4]	Korea	7	Not reported	Not reported	Not reported	Not reported
Manley et al[11]	UK	1	Abdominal pain	Multiple gastric ulcers	CHOP	Died
Zhang et al[12]	China	3	GI bleeding: 1 Abdominal pain: 2	Gastric ulcer: 3	Patient 1: CHOP + surgery Patient 2: unclear Patient 3: unspecified chemotherapy regimen	Patient 1: died after 2 yr Patient 2: died after 3 yr Patient 3: died after 2 mo
Huang et al[13]	Taiwan	1	Abdominal pain, weight loss, fever	Greater curvature ulcer	VIP + SMILE	Died after 2 mo

CHOP, cyclophosphamide, doxorubicin, vincristine, prednisone; DICE, dexamethasone, ifosfamide, cisplatin, and etoposide; GI, gastrointestinal; modified SMILE, methotrexate, dexamethasone, ifosfamide, etoposide, and pegaspargase; modified VIDL, etoposide, ifosfamide, dexamethasone, and L-asparaginase; SMILE, L-asparaginase, methotrexate, ifosfamide, etoposide, and dexamethasone; VIP, etoposide, ifosfamide, and cisplatin.

DISCLOSURES

Author contributions: B. Zhao drafted the manuscript. B. Zhao and HJ Kim collected and analyzed data from the literature. B. Zhao, HJ Kim, L. Tam, and G. Rosenfeld conceptualized and designed this study. W. Xiong and G. Rosenfeld provided images and interpretation of their respective images. HJ Kim, L. Tam, W. Xiong, and G. Rosenfeld provided critical revision of the article and provided final approval. G. Rosenfeld is the article guarantor.

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