Enteric NK/T Cell Lymphoma-induced Recurrent Perforation in the Intestine: A Case Report

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AIM: To report a rare case of recurrent intestinal perforation caused by primary intestinal extranodal NK/T-cell lymphoma (ENKTL), analyze the diagnostic challenges of this rare and aggressive malignancy, and raise clinical awareness for its early identification and optimal management in patients with unexplained gastrointestinal perforation.

CASE PRESENTATION: A 31-year-old female presented with 3 days of persistent hypogastric abdominal pain and a 1-day history of high fever up to 39 ℃. She had undergone emergency surgery for jejunal perforation 20 months prior, with a postoperative pathological diagnosis of Epstein-Barr virus (EBV)-associated T- and NK-cell lymphoproliferative disorders. Multiple follow-up colonoscopies and bone marrow aspiration examinations failed to confirm the diagnosis of ENKTL, due to negative immunohistochemical staining of cluster of differentiation (CD)56 and EBV-encoded small RNA (EBER) in biopsy specimens. Abdominal contrast-enhanced computed tomography on this admission confirmed intestinal perforation, and emergency partial ileectomy was performed. Histopathological examination of the resected specimen showed diffuse full-thickness intestinal infiltration of atypical lymphoid cells, with positive immunohistochemical staining for CD2, CD3, CD56, T-cell intracellular antigen-1 (TIA-1) and EBER, and a Ki-67 proliferation index of approximately 70%. The final diagnosis of ENKTL (Ann Arbor stage IVA) was confirmed, and the patient received systemic chemotherapy with a regimen of methotrexate, etoposide, dexamethasone and pegaspargase after surgery.

RESULTS: The patient's general condition improved significantly after combined surgical intervention and systemic chemotherapy. During the 26-month continuous follow-up, the patient remained in good general condition, with no recurrence of abdominal pain, intestinal perforation, disease progression, or severe treatment-related adverse events.

CONCLUSIONS: Primary intestinal ENKTL is a rare and highly aggressive subtype of non-Hodgkin lymphoma, whose non-specific clinical and imaging manifestations pose major challenges for early diagnosis, which may lead to delayed treatment and unfavorable prognosis. This disease should be included in the core differential diagnosis for young patients, especially Asian populations, presenting with unexplained gastrointestinal perforation. Repeated deep tissue biopsy, EBER detection combined with comprehensive imaging evaluation are essential for early definitive diagnosis, and timely surgical intervention combined with standardized systemic chemotherapy can effectively improve the clinical outcomes of affected patients.

Keywords: NK/T cell lymphoma; perforation; intestine; CD56; EBER

Introduction

Extranodal NK/T-cell lymphoma (ENKTL), a subtype of non-Hodgkin lymphoma (NHL), originates from either cytotoxic T cells or natural killer cells. ENKTL consists of nasal and non-nasal types [1]. Although the underlying etiology remains elusive, immunohistochemistry and cytogenetic analyses suggest the involvement of Epstein-Barr virus (EBV) infection. ENKTL demonstrates a higher prevalence in Asia, Central and South America, and occurs predominantly in young and middle-aged males with a median age of 50 years [2,3]. Moreover, ENKTL typically manifests in the nasopharyngeal area, with approximately 10–20% of cases involving the intestinal tract [4]. Notably, the primary intestinal ENKTL is accompanied by a spectrum of symptoms such as abdominal pain, diarrhea, fever, intestinal bleeding and perforation [5,6].

A variety of proliferative diseases in the digestive tract, including tumors, tuberculosis, inflammatory bowel dis-

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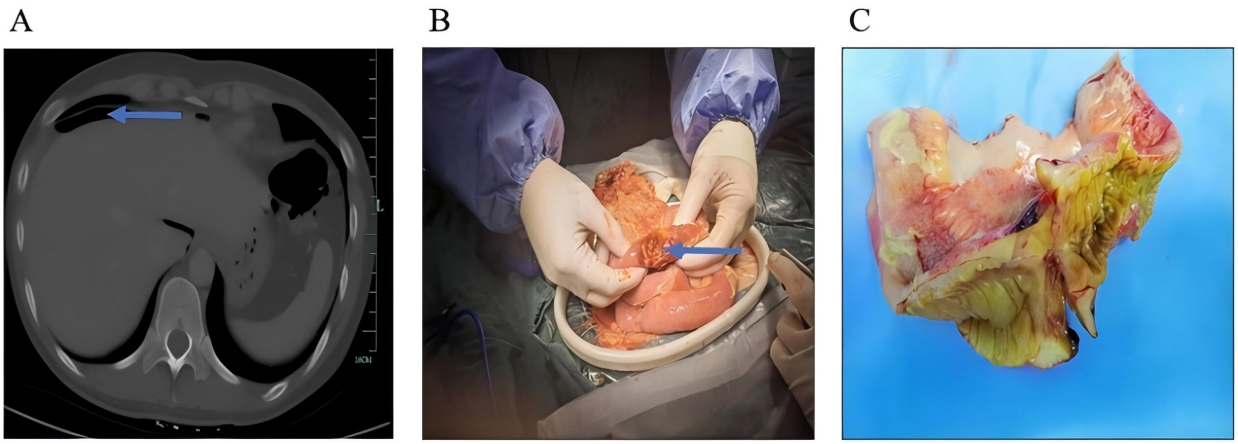

Fig. 1. Computed tomography (CT) scan and the intraoperative perforation. (A) CT scan showing free gas in the abdominal cavity, indicated by the arrow; (B) Perforation in the ileum found during surgery, indicated by the arrow; (C) Markedly thickened intestinal wall and mesentery in the vicinity of the perforation.

ease and typhoid fever, may contribute to the development of gastrointestinal perforation. Among these disorders, lymphoma, which consists of diverse subtypes including the primary intestinal NK/T-cell lymphoma (PINKTL), accounts for 7% of all NK/T cell lymphomas [7]. The early diagnosis of PINKTL is considered to be challenging, primarily due to the non-specific nature of the clinical symptoms and imaging findings. Herein, we present a case of ENKTL resulting in multiple intestinal perforations in a patient.

Case Presentation

A 31-year-old female presented with persistent abdominal pain in the hypogastrium for 3 days and was admitted to our hospital. Simultaneously, she developed a fever up to 39 ℃ one day ago without abdominal distention, nausea or vomiting. Physical examination revealed rebound tenderness in the hypogastrium. With regard to the patient's medical history, the patient underwent partial jejunectomy and enterorrhaphy at a local hospital for gastrointestinal perforation 20 months previously. During the surgical procedure, a perforation measuring 0.2 cm in diameter was found in the jejunum, located 100 cm from the ligament of Treitz. The pathological diagnosis was EBV-associated T- and NK-cell lymphoproliferative disorders. Multiple colonoscopies and bone marrow aspiration examinations were subsequently conducted; however, the diagnosis of ENKTL was not confirmed due to negative immunohistochemical staining of CD56 and EBV-encoded small RNA (EBER). Besides, the patient claimed to have no other previous or familial history of malignant tumors.

After admission, laboratory examinations revealed an increase in leukocytes (20.57×10^9/L) and elevated C-reactive protein (55.87 mg/L) and procalcitonin (2.94 ng/mL) in the blood. A Contrast-enhanced computed tomography (CT) scan of the entire abdomen revealed the presence of intestinal perforation in the pelvic cavity (Fig. 1A). Thus, an emergency surgery was performed. During the surgery, a perforation measuring 2 cm in diameter was found located in the distal ileum at a distance of 15 cm from the ileocecal junction (Fig. 1B). The patient underwent partial ileectomy and enterorrhaphy. The resected intestinal segment in the vicinity of the perforation exhibited a markedly thickened intestinal wall and mesentery (Fig. 1C).

Histological examination of the surgical specimen demonstrated scattered atypical lymphoid cells infiltrated the entire intestinal wall and large necrotic areas were observed (Fig. 2A). The tumor cells were mainly characterized by small to medium-sized, irregular nuclei, condensed chromatin and visible nuclear fragmentation (Fig. 2B). A mixed inflammatory response, mainly comprising neutrophils and lymphocytes, was observed throughout all layers of the ileum. Immunohistochemical staining demonstrated that markers of CD2, CD3, CD4, CD7, CD8, CD20, CD56 and TIA-1 were all positive (Fig. 2C–J), whereas CD5, CD10 and anaplastic lymphoma kinase (ALK) were negative (data not shown). Additionally, EBER analysis revealed a positive result (Fig. 2K). The Ki-67 labeling index was approximately 70% (Fig. 2L). Thus, the diagnosis of ENKTL was finally confirmed by pathology.

During the patient's surgical recovery, an F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) scan was performed to screen for potential lesions. The results revealed increased FDG uptake in multiple regions, including the bilateral carotid sheaths, left clavicular region, mesentery, retroperitoneum, bilateral iliac vessels, bilateral pelvic walls and left inguinal region (Fig. 3A–C). Then, the patient was finally diagnosed with ENKTL stage IVA according to the Ann Arbor system [5,8], and received systemic chemotherapy consisting of methotrexate, etoposide, dexamethasone and pegaspargase. To date of this report, the patient has completed 26 months of continuous follow-up after treatment, during which her general condi-

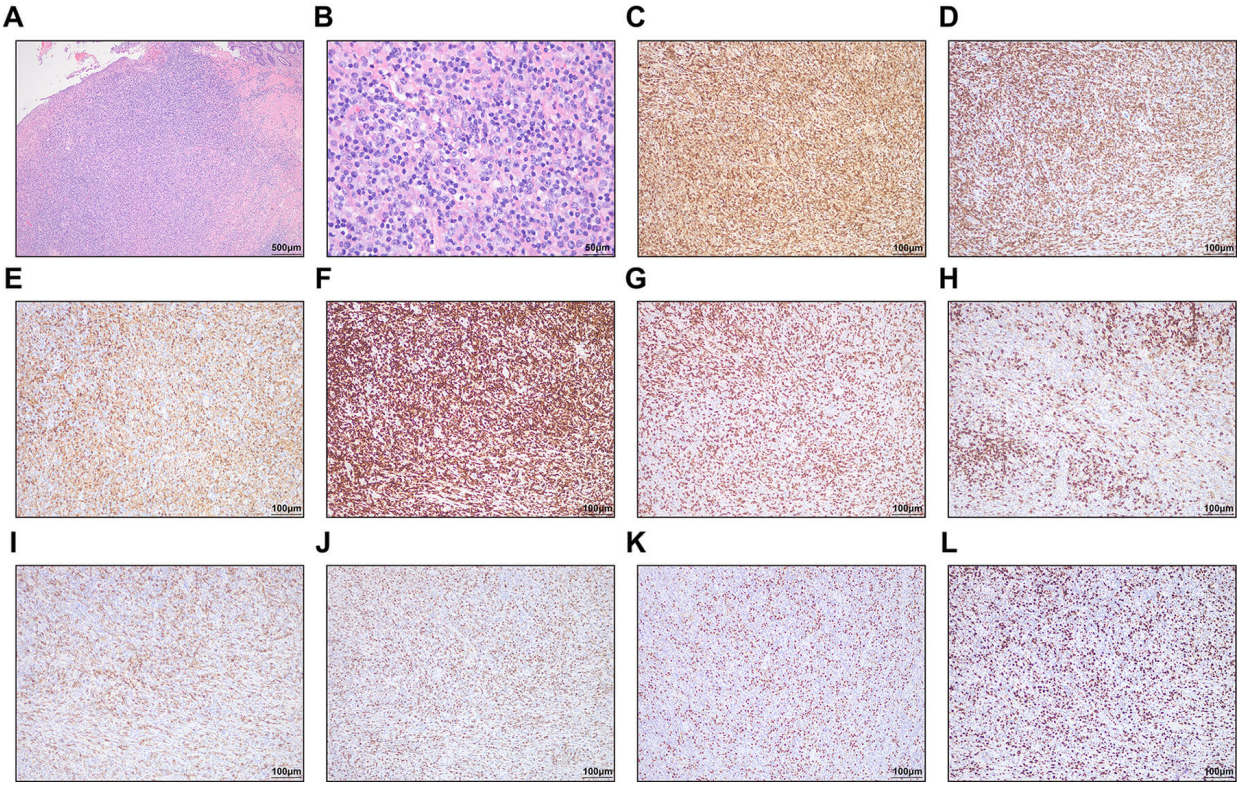

Fig. 2. Histological and immunohistochemical sections of the lymphoma. (A) The tumor cells infiltrated the entire intestinal wall (Hematoxylin and eosin (HE) staining, 50× magnification). (B) Diffuse infiltration of small to medium-sized tumor cells with irregular nuclei (HE staining, 400 × magnification). (C–L) Immunohistochemical staining of CD2, CD3, CD4, CD7, CD8, CD20, CD56, TIA-1, EBER and Ki-67 (100× magnification). CD, cluster of differentiation; TIA-1, T-cell intracellular antigen-1; EBER, EBV-encoded small RNA.

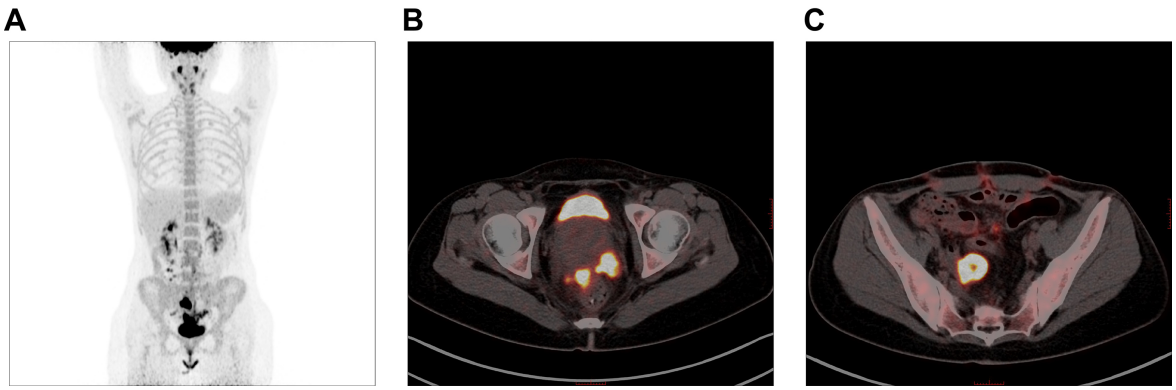

Fig. 3. F-18 fluorodeoxyglucose (FDG) positron emission tomography/computed tomography showing increased FDG uptake in the mesentery, retroperitoneum and bilateral pelvic walls. (A) The whole abdomen image. (B,C) Images of the hypogastrium at two axial sections.

tion remained consistently favorable, with no recurrence of abdominal pain, intestinal perforation, disease progression, or severe treatment-related adverse events.

This case has been reported in line with the case report guidelines: Case Report (CARE) Guidelines to ensure the accuracy and completeness of the report (**Supplementary Material**).

Discussion

ENKTL is a rare subtype of NHL, accounting for 2% to 10% of cases [9], and is more likely to affect middle-aged individuals, with only a few cases reported in children and adolescents [10,11,12]. The majority of diseased regions are the nasopharyngeal area (approximately 80%–90%), and rare cases are found in the gastrointestinal tract, lung, skin, testis and muscles. PINKTL is highly invasive and correlated with a poor prognosis, with an average survival

time of 3–9 months [13]. The most common clinical manifestations of PINKTL include abdominal pain, vomiting, diarrhea, irregular fever, gastrointestinal hemorrhage and gastrointestinal perforation [5]. The infiltration of proliferating tumor cells and mesenteric vascular involvement were contributing risk factors to the development of perforation.

A retrospective study showed that patients with ENKTL who underwent combined surgery and chemotherapy treatments exhibited a better prognosis compared to those who received either surgical or chemotherapy treatment alone [5]. Similarly, a study in China revealed that surgery before perforation is extremely important that affected prognosis and that combination therapy is necessary [14]. Based on these, we suggest that early diagnosis and prompt treatment are crucial for improving prognosis, while emergent surgical intervention is the palliative option when gastrointestinal perforation occurs.

Histologically, the tumor cells of ENKTL are mainly composed of small to medium-sized cells that are distinguished by the presence of basophilic granules. Coagulative necrosis, ulceration, granulation, angiocentricity, and anginodestruction are commonly observed, which are always serosal but rarely mucosal infiltration, making biopsy-based diagnosis difficult [15]. Pathologically, in most cases, the tumor cells originate from NK cells, with typically positive markers such as CD2, CD56, cytoplasmic CD3ε, granzyme B, TIA-1 and perforin. CD56, a marker of NK cells, has a positive rate of 84–89.1% in PINKTL [16,17]. Tumor cells derived from T-cells are less common and typically positive for CD3 and negative for CD56, which can be identified through TCR gene rearrangement. Almost all cases of PINKTL are associated with EBV infection, which can be confirmed through *in situ* hybridization (ISH) for EBER or elevated plasma EBV DNA levels [18]. In our case, histopathological examination of the surgical specimen revealed positive staining for CD2, CD3, CD56, TIA-1 and EBER, which met the diagnosis of PINKTL. However, CD20 positivity is infrequent, which is commonly accompanied by a distinctly aggressive clinical course and unfavorable prognoses [19,20].

The diagnosis of PINKTL can be challenging due to its atypical clinical manifestations and endoscopic features, particularly in the early stages. In most cases, diagnosis is only confirmed through pathological findings of surgical specimens. PINKTL may often be wrongly identified as tuberculosis or inflammatory bowel disease, such as Crohn's disease and ulcerative colitis. When patients with early PINKTL present with abdominal pain and/or intestinal bleeding, colonoscopy merely finds irregular ulcers, and histological examination reveals chronic inflammation and proliferation of lymphocytes, which may potentially lead to a misdiagnosis of Crohn's disease [21,22]. Obtaining a histological diagnosis by light, small biopsy may prove difficult, as atypical lymphoid cells are located in the submucosa or may have broken through the serous membrane [16]. In such cases, repeated and deeper tissue biopsies are highly recommended, and additional PET-CT scanning or even exploratory laparotomy is potentially necessary [9]. Presently, histological examination and immunohistochemistry remain the only standard diagnostic methods for PINKTL, and previous studies showed the strong association between almost all ENKTL cases and EBV infection, which confirmed the important ISH value for EBER [2,23]. In this case, the patient underwent multiple endoscopies and bone marrow examinations after her initial intestinal perforation. However, the histological examination of biopsy specimens revealed CD56 and EBER staining all negative, which ultimately led to a failure of precise diagnosis.

In summary, the diagnosis of PINKTL at an early stage proves to be challenging due to the presence of nonspecific clinical features and image findings. In cases where there exists suspicion of intestinal malignant lymphoma without definitive diagnosis, exploratory laparotomy may be finally necessary. In clinical practice, when young Asians present with unexplained bowel perforation, PINKTL should be considered as a potential diagnosis.

Conclusions

This report presents a case of recurrent intestinal perforation caused by primary intestinal extranodal NK/T-cell lymphoma in a 31-year-old Asian female. Despite an initial nondiagnostic work-up, the final diagnosis was established through deep surgical tissue sampling, which revealed characteristic immunohistochemical positivity for CD2, CD3, CD56, TIA-1, and EBER, with a high Ki-67 index. Ann Arbor stage IVA was confirmed by PET/CT, and the patient responded well to combined surgical intervention and systemic chemotherapy with no disease progression at 26-month follow-up. This case highlights the diagnostic challenges of primary intestinal ENKTL, particularly in its early stages, and underscores the importance of including this entity in the differential diagnosis of young Asian patients presenting with unexplained gastrointestinal perforation. Repeated deep biopsy, EBER testing, and timely integrated therapy are essential for improving outcomes.

Availability of Data and Materials

All data and materials generated or analyzed during this study are included in this manuscript.

Author Contributions

JSS and LW designed the case report and analyzed the patient data. JSS drafted the manuscript. JSS and XYH contributed to the collection of samples and patient photos. YXY and LW contributed to the analysis and interpretation of imaging examinations. All authors contributed to the critical revision of the manuscript for important intellectual content. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of The First Affiliated Hospital, Zhejiang University School of Medicine ([2026B] IIT Ethics Approval No. 0658). Written informed consent was obtained from the patient to approve the publication of any potentially identifying images and clinical information. The study conformed to the provisions of the Declaration of Helsinki.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.62713/aic.4662.

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