Extranodal T- NK-cell lymphoma, nasal type masquerading as ileal inflammatory bowel disease

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ABSTRACT

Introduction: ENKL (Extranodal Natural killer/T cell lymphoma) of the gastrointestinal tract can be indistinguishable from Inflammatory bowel disease or from an infectious etiology affecting the terminal ileum.

Case Report: We report a case of a 36-year-old Mexican male who presented with severe non-specific lower abdominal pain, fever and laboratory data suggestive of a systemic disease. The initial differential diagnosis was inflammatory bowel disease because of the non-specific finding of terminal ileum thickening seen on a computed tomography scan. As occurs in most patients with ENKL, the patient died rapidly in the setting of an aggressive lymphoma and the complication of intestinal perforation.

Conclusion: The differential diagnosis of localized inflammation of the distal ileum most commonly is seen in Crohn’s disease but the differential diagnosis is very broad and includes aggressive lymphomas such as ENKL. This diagnosis should be considered in a clinical setting of a patient from Asia or Latin America with the appearance of unexplained small bowel localized inflammatory disease. Early recognition and treatment can be life-saving.
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Keywords: Abdominal pain, Gastrointestinal lymphoma, Ileitis, Inflammatory bowel disease

INtrODUctION

ENKL (Extranodal natural killer/T cell lymphoma) of the gastrointestinal tract can be indistinguishable from Inflammatory Bowel disease or from any infectious or systemic etiology affecting the terminal ileum. This disease is a non-Hodgkin's lymphoma that is rare in Western Countries but endemic to East Asia and parts of Central and South America [1]. Most patients (80-90%) present with localized nasal and para-nasal disease with symptoms of nasal obstruction and epistaxis due to a destructive mass involving midline facial tissues. Extra-nasal sites include the skin, lung and gastrointestinal tract [2–4]. In general, gastric lymphomas account for only 2% of gastrointestinal malignant neoplasms and diagnosis is usually made late in the clinical course because of
their non-specific and localizing symptoms [5, 6]. Extra-
nasal ENKL which can involve the gastrointestinal tract 
occur in the small intestine with bleeding, intestinal 
obstruction and perforation. Such patients undergo 
emergency primary surgical resection and often die 
within 12 months.

CASE REPORT

A 36-year-old immigrant from Mexico presented to 
our hospital with a two-month history of intermittent 
non-bloody diarrhea, abdominal pain, occasional 
fever and sweats. Before he presented to us, he was 
hospitalized at another institution where he told that 
he had a colonoscopy for similar symptoms which was 
reported to be normal. His main complaint on admission 
to our hospital was persistent severe right lower quadrant 
pain refractory to opiates. He denied exposures to 
tuberculosis and his chest X-ray on admission had 
been unremarkable. Laboratory examinations showed 
a microcytic anemia with a hemoglobin of 8.9 g/dL, an 
initial white blood cell count (WBC) of 5.2x10^3/uL falling 
to 3.8x10^3/uL one day after admission and platelet count 
of 120x10^3/uL, total bilirubin concentration of 2.7 mg/
dl, serum albumin of 2.3 g/dL, aspartate transaminase 
AST) of 456, alanine aminotransferase (ALT) of 349 
U/L and alkaline phosphatase of 766 U/L. He had 
initial intermittent fevers 101.5°F. A contrast computed 
tomography (CT) was performed (Figure 1) showing 
extensive thickening of the wall of the terminal ileum 
with stranding of the mesentery which the primary team 
felt might be secondary to inflammatory bowel disease.

Our gastrointestinal consultation suggested that 
despite the CT findings, the presentation, history and 
elevated liver enzymes did not support a diagnosis of 
inflammatory bowel disease. An abdominal X-ray was 
performed and showed free peritoneal air because of 
an increasingly rigid abdomen suggesting a perforated 
viscus. He was taken immediately to the operating 
room. Extensive inflammation of the terminal ileum 
with a perforation was found, he underwent ileocolonic 
resection and anastomosis. Shortly after surgery his WBC 
count fell to 2.3x10^3/uL.

Pathologic findings

Microscopic examination revealed ulcerated and 
perforated bowel segment with transmural involvement 
by diffuse population of cytologically atypical medium 
to large lymphoid cells. The photomicrograph (Figure 
2) shows diffuse infiltration of bowel wall by lymphoid 
cells with superficial ulceration. Inset shows medium to 
large atypical lymphoid cells. Mesenteric lymph nodes 
also showed involvement. Immunohistochemistry 
revealed reactivity of the neoplastic cells for CD2, CD3, 
CD56, Epstein–Barr virus-encoded small RNAs (EBER) 
and were negative for CD20, CD5, CD4, CD8, CD15, 
TIA (cytotoxic granule-associated protein expressed in

natural killer (NK) cells and cytotoxic T lymphocytes), 
Activin receptor-like kinase-1 (ALK-1), CD23, and CD21. 
Polymerase Chain Reaction (PCR) for T cell receptor 
gene rearrangement was negative. These morphological 
and immunohistochemical features were classical of 
extranodal T/NK cell lymphoma, nasal type. A bone 
marrow biopsy showed involvement by T/NK cell 
lymphoma, along with florid hemophagocytic syndrome. 
Figure 3 shows neoplastic cells showing immunoreactivity 
for CD3; inset shows CD 56 positive neoplastic cells.

DISCUSSION

Extranodal natural killer (NK)/T cell lymphoma, nasal 
type (ENKL) is a predominantly extra-nodal lymphoma
mainly occurring in the nasal/para-nasal area, skin/soft tissue, or gastrointestinal tract. It is a non-Hodgkin’s lymphoma (NHL) that is rare in Western Countries but common in East Asia and Latin America. While lymphoma genesis specific for NK/T cell lymphoma is largely unknown, the Epstein–Barr virus (EBV) has been detected in almost all ENKLs [7]. EBV has a transforming activity on lymphocytes and may play an important role in lymphoma genesis. Histological specimens of ENKL have been shown to have diffuse proliferation of lymphoma cells with an angiocentric or angiodestructive growth pattern. The lymphoma cell express NK cell markers including CD2, cytoplasmic CD3, CD7 and CD56 [7, 8].

While the nose and para-nasal areas are most commonly affected sites for ENKL, the disease entity can affect skin and the gastrointestinal tract [7]. Nasal ENKL frequently presents as a localized disease and extra-nasal ENKL is usually detected at an advanced stage.

When extra-nasal ENKL does involve the gastrointestinal tract it is exceptionally rare and usually follows an aggressive clinical course with a poor survival outcome. Gastrointestinal involvement is primarily localized to the small and large intestine. Stomach involvement is rare. The small intestine has been shown to be the most commonly involved site [9]. Symptoms are broad and include abdominal pain, gastrointestinal bleeding and perforation, which most often times is misdiagnosed as inflammatory bowel disease or appendicitis [4]. Nongastrointestinal manifestations of ENKL include nasal obstruction of systemic symptoms such as fever and night sweats.

Localized inflammation of the distal ileum most commonly is seen in Crohn’s disease but the differential diagnosis is broad and includes lymphomas, endometriosis, vasculitides, systemic disorders such as amyloidosis and sarcoidosis as well as infectious etiologies [10]. *Mycobacterium tuberculosis*, *Yersinia enterocolitica*, *Salmonella*. *Clostridium difficile* causing typhlitis is some of the common infectious causes of terminal ileitis [10].

In one case review of ENKL cases involving the small intestine 10 out of 17 patients underwent primary surgical resections as emergency treatments due to intestinal obstruction or perforation. A correct diagnosis of lymphoma was established after surgery. For the surgical patients all died within 12 months [11].

In general diagnosis of primary gastric lymphomas can be very difficult and the clinician’s index of suspicion should be very high to allow for extensive investigation. CT scans of the abdomen and pelvis can detect multiple large tumors with visualization of bowel segments with lumen that is narrowed, enlarged or both. Bowel wall segments with homogenous thickening > 2 cm with a normal or enlarged lumen should necessitate further evaluation and biopsy as should mesenteric nodal masses [5, 6]. PET (Positron emission tomography) scan findings vary depending and there is very little data with regard to its usefulness in the detection of gastrointestinal lymphomas and FDG activity may also related to inflammatory conditions and infections[12].

Colonoscopy with TI intubation of the terminal ileum can be revealing as well as push enteroscopy for the detection of proximal small bowel lesions, with biopsy of lesions which can be diagnostic. In one case study patients diagnosed by endoscopy were alive for more than 14 months with diagnosis by DBE (double balloon enteroscopy) followed by DBE during chemotherapy [11]. Multiple endoscopies may be necessary before the diagnosis is reached but the index of suspicion must be high enough.

While there is a role for surgery in management of localized intestinal B cell lymphomas, the role of surgery in gastrointestinal tract ENKTL is undefined [9, 11]. Most patients have undergone resection of their primary mass lesion in early staged lesions for complications such as bleeding or perforation. After surgery patients usually undergo systemic chemotherapy if they have localized disease and have a good performance status. Some of these patients have gone on the stem cell transplantation and radiation. In general, overall survival has been shown to be significantly better for patients treated with combined radiation and chemotherapy rather than radiation therapy alone. The five-year overall survival in localized ENKL has been reported to be about 39–46% and patients with extra-nasal disease have been shown to have significantly shorter five year overall survival [4]. Our patient died abruptly before chemotherapy could be initiated.

**CONCLUSION**

We present a case of ENKL (Extranodal Natural Killer/T cell lymphoma) of the gastrointestinal tract...
involving primarily the small intestine which was indistinguishable from Inflammatory Bowel disease or from an infectious etiology affecting the terminal ileum. Our patient presented with severe non-specific lower abdominal pain, fever and laboratory data suggestive of a systemic disease. The initial leading diagnosis was inflammatory bowel disease because of the non-specific finding of terminal ileum thickening seen on a CT scan. As occurs in most patients with ENKL, the patient died rapidly in the setting of an aggressive lymphoma and the complication of intestinal perforation. This diagnosis should be considered in a clinical setting of a patient from Asia or Latin America with the appearance of unexplained small bowel localized inflammatory disease. Early recognition and treatment can be life-saving.

Author Contributions
Olanma Y. Okoji – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published
Abul Ala Syed Rifat Mannan – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Peter R. Holt – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published
Donald P. Kotler – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

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The corresponding author is the guarantor of submission.

Conflict of Interest
The authors whose names are listed certify that they have NO affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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