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ABSTRACT

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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

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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 occurs 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.

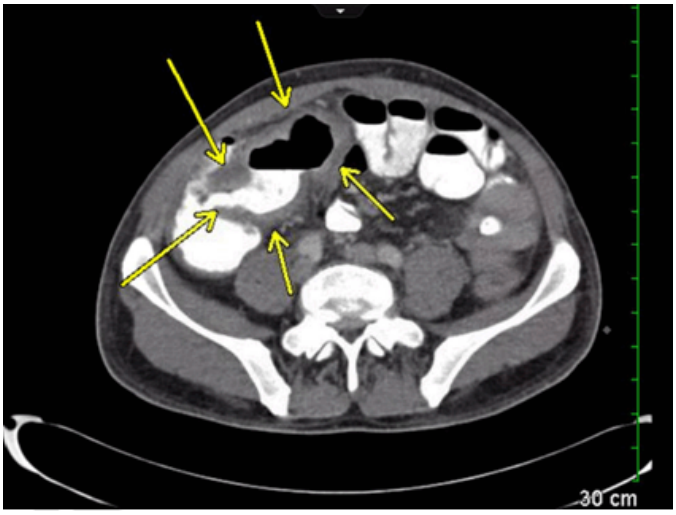

Figure 1: Cross sectional computed tomography scan of the abdomen showing from the furthest left arrow, cecum to thickening of terminal and distal ileum.

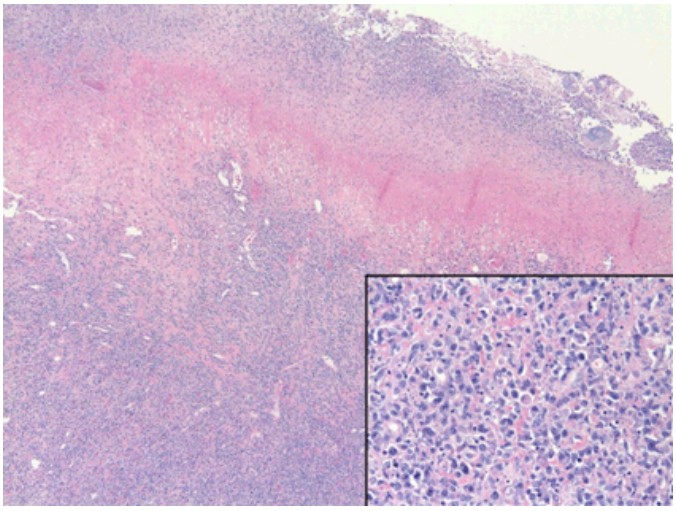

Figure 2: Photomicrograph showing diffuse infiltration of bowel wall by lymphoid cells with superficial ulceration (H&E stain, x40). Inset showing medium to large atypical lymphoid cells (H&E stain, x400).

DISCUSSION

Extranodal natural killer (NK)/T cell lymphoma, nasal type (ENKL) is a predominantly extra-nodal lymphoma

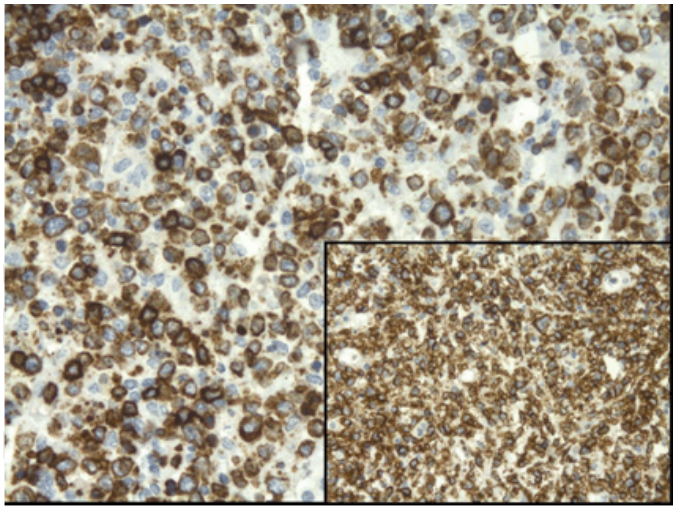

Figure 3: Neoplastic cells showing immunoreactivity for CD3 (avidin biotin peroxidase x400); inset showing CD 56 positive neoplastic cells (avidin biotin peroxidase, x400).

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.

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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

Guarantor

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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