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Extranasal T/NK-Cell Lymphoma Presenting as Intestinal Diverticulum

A case of intestinal angiocentric T/NK-cell lymphoma in a 58-year-old man is reported. The patient presented initially with panperitonitis because of perforation of sigmoid colon diverticulum. He underwent segmentectomy of involved bowel. Histologically, the intestinal wall showed diffuse infiltration of medium or large size lymphoma cells with angiocentric growth and necrosis. The lymphoma cells were CD56+, CD45RO+, CD3+, CD4-, CD8-, CD20-, and CD30- in paraffin sections with germline configuration of TCR-γ gene, consistent with T/NK-cell lymphoma. Further staging revealed splenomegaly. Intestinal angiocentric T/NK cell lymphoma represents a distinct etiology of diverticulum with perforation.

Key Words: *Lymphoma, T/NK-Cell; Neoplasms, Sigmoid; Gastrointestinal Neoplasms; Diverticulum*

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INTRODUCTION

CD56 antibody, a natural killer (NK) cell marker, recognize the neuronal cell adhesion molecule (N-CAM) (1). Its expression is a rare phenomenon in malignant lymphoma, and is mostly limited to those of T-cell phenotype (2). CD56+ lymphomas is a distinctive clinicopathologic entity, currently referred to angiocentric lymphoma in the REAL classification or nasal T/NK cell lymphoma in the WHO classificaton (1998) because of uncertainties regarding its true lineage (3-6). CD56 expression in lymphoma is thought to play a role in their localization and behavior (7). This lymphoma produces usually ulcerative, destructive lesion in the nasal/nasopharyngeal region and displays the histologic feature of angiocentric and angiodestructive growth pattern. T/NK-cell lymphoma rarely occurs outside the nasal or nasopharyngeal region. Non-nasal T/NK-cell lymphoma exhibits predilection for the skin, testis, gastrointestinal tract, and soft tissue. Also, interesting is that these are the same sites where both the nasal and non-nasal CD56+ lymphomas tend to disseminate to (8). Superficial lymphadenopathy and leukemic manifestation are relatively rare. These tumors show a highly aggressive clinical course. The immunophenotypic profile is highly characteristic; CD2+, surface CD3-, cytoplasmic CD3ε+, CD56+, and frequently negative for other T lineage markers. Most studies have failed to show rearrangements of the T-cell receptor genes; thus, this does not appear to be a usual T-cell lymphoma. Features favoring an NK cell lineage are the lack of surface CD3 expression, lack of expression of T-cell antigen receptor, and lack of T-cell receptor gene rearrangements (2). Because of the paucity of information on T/NK-cell lymphoma of the gastrointestinal tract, this study aims to characterize the clinicopathologic features of the present case which presented initially with intestinal diverticulum and no previous history or pathologic evidence of celiac disease.

CASE REPORT

A 58-year-old man presented with a two month history of left neck mass. During follow up for further evaluation, the patient developed multiple pulmonary masses in the bilateral lower lobes, up to 2.0×3.0 cm, on the chest plain film and computerized tomography. Physical examination showed a solitary mass, about 1.0×1.0 cm, in the left submandibular area. It was movable and tender. Weight loss was 6-7 kg during 2 years. He had a past history of sialolithiasis in the left submandibular gland 20 years ago and chronic gastritis in February 1997. On the physical examination, there were no

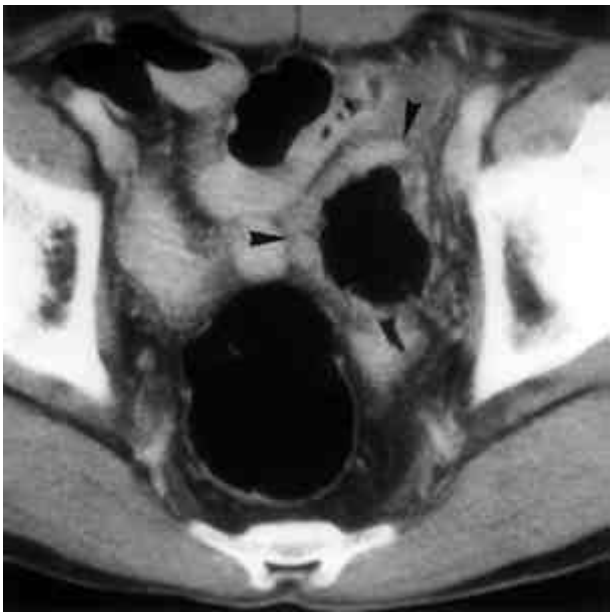

Fig. 1. Abdominal computerized tomography shows a diverticulated lesion with irregularly thickened wall (arrow heads), 3.0 cm at its greatest diameter, in the sigmoid colon.

other sites of disease. Nasal or nasopharyngeal regions were unremarkable. On hospital day 7, he underwent biopsy of the left submandibular gland. The biopsy revealed marked chronic inflammatory cell infiltration and fibrosis in the parenchyme, atrophy of parenchymal cells and proliferation of excretory ductules, consistent with chronic sialadenitis. On hospital day 10, the patient abruptly developed acute abdominal pain and rebound tenderness. Free air was noted on the plain abdomen film. Abdominal computerized tomographic examination showed a diverticulated lesion, 3.0 cm in the greatest diameter, with irregularly thickened intestinal wall in the sigmoid colon (Fig. 1). Clinical diagnosis was acute panperitonitis due to perforation of intestinal diverticulum. He underwent segmentectomy for sigmoid colon. On the operative field, purulent fluid was noted in the splenic fossa, left paracolic gutter and pelvic cavity. Mesenteric and superficial lymphadenopathy were not found. The submitted specimen comprised a 6 cm length of sigmoid colon which contained a diverticulated lesion, 3.0×2.5 cm, on the antemesenteric border, accompanied by perforation, 0.3×0.3 cm, with surrounding edematous change and mucosal ulceration. The intestinal wall diffusely thickened up to 1.5 cm in thickness. The adjacent mucosa was macroscopically unremarkable. Histologically, the tumor showed a diffuse transmural infiltrate of atypical medium to large sized lymphocytes (Fig. 2). Nuclei were round or irregularly indented, with variably clumped chromatin and one to three small nucleoli (Fig. 3). The lymphoma cells were concentrated around and within vessel with infiltration and destruction of the wall (Fig. 4). There were multifocal necrotic areas. Reactive small lymphoid infiltrates, admixed with plasma cells and eosinophils, were noted at the tumor margin and adjacent mucosa. No evidence of villous atrophy was detected in the tumor or in non tumor areas. Immunogenetic analysis revealed that the genes for γ chain of the TCR, and Ig heavy chain were in germline configuration. DNA analysis was performed by polymerase chain reaction

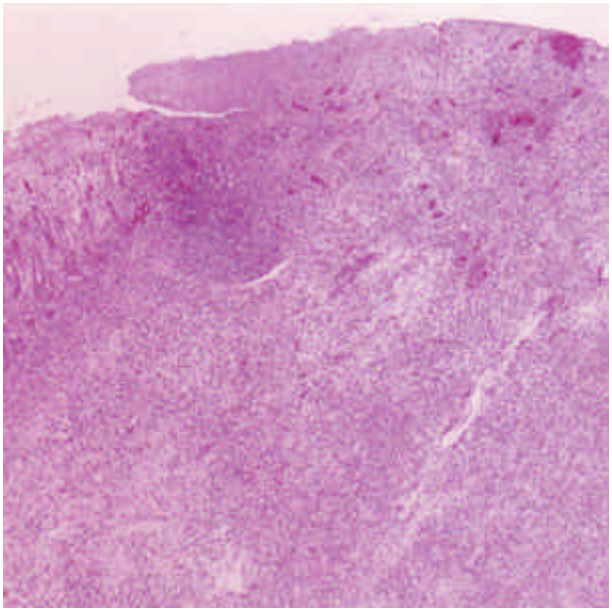

Fig. 2. Diffuse transmural infiltration of atypical lymphocytes and mucosal ulceration (H&E, ×40).

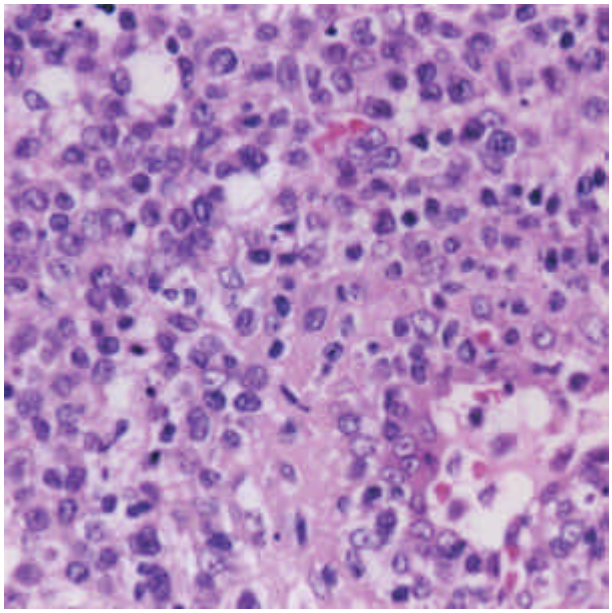

Fig. 3. Round or irregularly indented nuclei with variably clumped chromatin and one to three small nucleoli (H&E, ×400).

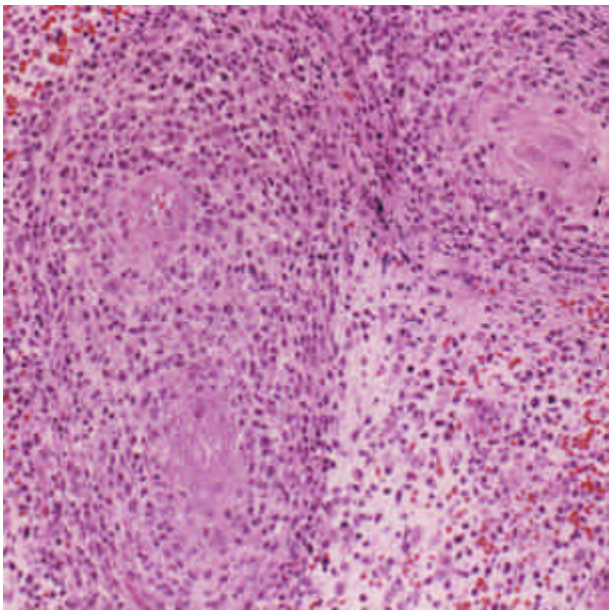

Fig. 4. Angiocentric feature of lymphoma cells (H&E, ×100).

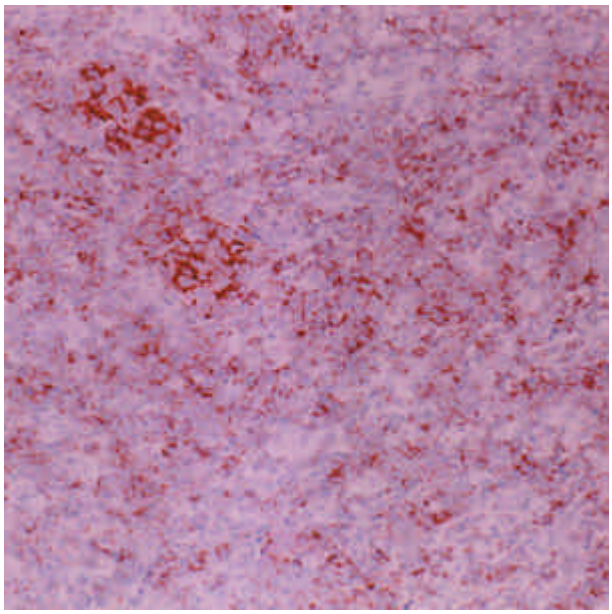

Fig. 5. Immunohistochemical staining for CD56 shows diffuse positive reaction (×100).

using consensus primer for immunoglobulin heavy chain gene CDR III portion (FRIII; 5'-CTGTCGACACCGCC-GTGTATTACTG-3' and VLJH; 5'-AACTGCAGAGG-AGACGGTGAC-3') and T-cell receptor (TCR) gamma chain gene (Jg; 5'-GAAGCTTCTAGCTTTCCTGTCTC-3' and 5'-CGTCGACAACAAGTGTTGTTCCAC-3', Vg; 5'-CTCGAGTGCOCTGCCTACAGAGAGG-3' and 5'-GGATCCACTGCCAAAGAGTTTCTT-3'). We applied known B- & T- cell lymphoma for a positive control and saline for negative control. Immunoperoxidase staining of paraffin sections confirmed that infiltrating cells strongly expressed CD3, CD45RO and CD56 antigen, and did not express CD4, CD8, CD20 and CD30 antigen (Fig. 5). EBV was not demonstrated using in situ hybridization for EBV-encoded small RNAs (EBERs). Further staging revealed splenomegaly. Lung wedge resection for evaluation of pulmonary nodules revealed localized organizing pneumonia. Two cycle combination chemotherapy of cyclophosphamide, doxorubicin, vincristine and prednisolone was repeated. The patient was free of disease in four months.

DISCUSSION

Primary gastrointestinal lymphomas are almost of B-cell lineage, with a few cases of T-cell lymphoma (9). In East Asia, T-cell lymphoma have been reported in the stomach, colon and rectum (10). In the West, T-cell lymphoma of the gastrointestinal tract are generally uncommon (11). T-cell lymphoma of the intestine have been described by Chott et al. (12) as separable into three histologic categories; a) enteropathy-associated T-cell lymphoma (EATCL) b) EATCL-like lymphoma without enteropathy, and c) T-cell lymphoma without feature of EATCL. In most cases, primary gastrointestinal T-cell lymphoma is a form of EATCL, associated with long-stand celiac sprue or related malabsoption syndrome. This lymphoma show prominent intramucosal lymphoma spread and uninvolved mucosa often shows changes typical of celiac disease; villous atrophy, crypt hyperplasia, plasmacytosis of the lamina propria and an increase in intraepithelial lymphocytes. Most lesions arise in the jejunum and cause multiple ulcers, strictures or tumor nodules. EATCL-like lymphoma without enteropathy shows that villous atrophy is only involved in the tumor margin and intraepithelial lymphocytes were less conspicuous the further away from the tumors. T-cell lymphoma without any histologic features of EATCL have sharply demarcated lesions from normal-appearing adjacent mucosa as in our case. Of the T-cell lymphoma unassociated with enteropathy, CD56+ T/NK-cell lymphomas rarely have been reported in the gastrointestinal tract. The commonest immunophenotype is CD2+, surface CD3−, cytoplasmic CD3+, CD56+. TCR and Ig genes are usually germline. But other specific intestinal T-cell lymphoma with CD56 expression often express surface CD3 and show rearrangement of the T-cell receptor genes. The histologic features of these lymphomas are variable, corresponing to the specific lymphoma types. T/NK cell lymphoma arising outside the nasal region, or known as non-nasal T/NK cell lymphoma, is a form of

extranodal lymphoma with a predilection for skin, testis, gastrointestinal tract, soft tissue and spleen. In the series of Chan et al. (13), 4 of 49 patients with non-nasal T/NK cell lymphoma showed gastrointestinal involvement without history of enteropathy. The median age at diagnosis is 50 years (21 to 76 years). Males are affected slightly more often than females (25 men and 9 women). A high mortality rate (82.8%) and very short median survival are observed. In most series, T/NK-cell lymphoma has been associated with high stage disease and a highly aggressive course. This would be probably the most aggressive lymphoma type. A correlation between the clinical course and the number of large cells has been reported, but other studies have not confirmed.

Hsiao et al. (14) reported seven unusual cases of T/NK cell lymphoma of the intestine presenting with bowel ischemia or perforation. Edema, congestion, and plaque-like ulceration indicative of ischemic change of the mucosa and intestinal wall were seen in all seven patients. Five patients had intestinal perforation. The intestinal lesions were ulcerated and transmurally necrotic or gangrenous. These lesions were small satellite lesions without a bulky mass, in contrast to that seen in B-cell lymphoma. Our case presented an unusual manifestation of T/NK-cell lymphoma with divertilculum-like protruded mass associated with perforation. The angiodestruction of the tumor cells may be responsible for the presenting bowel ischemia. The tumor cell exhibit a broad range of cytologic appearances (small cells, medium-sized cells, large cell, or mixture). The lymphoma lesions contain a mixture of normal-appearing small lymphocytes, plasma cells and, less often, eosinophils and histiocytes (2). A characteristic feature is invasion of vascular walls by atypical lymphoid cell usually with thrombosis and occlusion of lumina. Vascular occlusion is usually associated with a variable degree of coagulative necrosis in the involved tissues. This lymphoma type is associated with an increased risk of developing hemophagocytic syndrome (13); the systemic histiocytic activation presumably results from cytokines or other products released by the lymphoma cells. Hemophagocytic syndromes are responsible for some of the fatalities. Even patients receiving third generation combination chemotherapy have an unfavorable outcome.

In summary, we report an unusual case of T/NK-cell lymphoma of probably NK-lineage arising primarily from the sigmoid colon. T/NK-cell lymphoma may occur initially presenting with perforation of intestinal diverticulum as in our patient. This unique type of lymphoma should be considered in diverticular perforation. Recognition of this disease entity is important because of the aggressive nature and poor prognosis.

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