

Benign Indolent CD56-Positive NK-Cell Lymphoproliferative Lesion Involving Gastrointestinal Tract in an Adolescent

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The gastrointestinal (GI) tract is the most common site of primary extranodal lymphomas. Although B-cell non-Hodgkin lymphomas account for the majority of GI lymphoma, T- or natural killer (NK)-cell lymphomas, including peripheral T-cell lymphoma, enteropathy-associated T-cell lymphoma (EATL), extranodal NK/T-cell lymphoma, and anaplastic large cell lymphoma, also involves the GI tract.^{1,2} T- or NK-cell lymphomas are an aggressive disease typically managed with systemic chemotherapy or radiotherapy; however, pathologic diagnosis of intestinal T- or NK-cell lymphoma based on a small biopsy specimen is often challenging.

Recently, a unique clinicopathologic entity involving GI tract and characterized by an atypical proliferation of NK-cells has been described under the term “NK-cell enteropathy” or “lymphomatoid gastropathy.”^{3,4} All afflicted patients were adults and had no history of celiac disease. Endoscopic findings were variable with superficial ulceration, edema, hemorrhage, and the presence of small, elevated lesions from stomach to colon. Histologically, the lamina propria of the mucosa was infiltrated by atypical NK-cells. Tests for Epstein-Barr virus (EBV) were negative, and T-cell monoclonality was not detected. Although these lesions can pathologically mimic intestinal NK- or T-cell lymphoma to the extent that some patients were diagnosed with lymphoma, all patients had a benign clinical course. Thus, early recognition of this entity could be important for

appropriate disease management. Here we report the first Korean case, as well as the first case in an adolescent, of NK-cell enteropathy.

CASE REPORT

A fourteen-year-old boy was admitted to our hospital due to chronic recurrent vomiting and abdominal discomfort, which began several months previously and intensified to occurrence of vomiting once a day. He also had intermittent diarrhea without severe abdominal pain or fever. His height and weight were both estimated to place him in the lowest 3% of the growth curve for his age. There was no remarkable family history except for hyperthyroidism in his father. Initially, under the impression of eosinophilic gastroenteritis, prednisolone therapy was administered. However after short-term improvement of symptoms, vomiting recurred. After colonoscopic biopsy, he was presumptively diagnosed with EATL. He was readmitted to our hospital for further workup and nutritional therapy. Endoscopic examinations including capsule endoscopy revealed multiple small lesions with mucosal nodularity and hyperemic change in esophagus, stomach, duodenum, small intestine, and colon with several erosions of the intestine (Fig. 1). Computed tomography scan revealed diffuse thickening of the distal esophageal wall, stomach, duodenum and small intestine, slightly enlarged mesenteric lymph nodes and borderline-sized (10 cm) splenomegaly. On positron emission tomography scan, the only notable finding was mild fluorodeoxyglucose uptake in GI tract, suggestive of physiologic change. Laboratory tests showed mild leukocytosis (white blood cell count, 12,540/ μ L) with a differential count within normal range, anemia (hemo-

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globin, 7.4 g/dL), hypoferritinemia (3.88 ng/mL), hypocalcemia (5.5 mg/dL), hypoproteinemia (total protein 3.3 g/dL), and hypoalbuminemia (1.7 g/dL). Lactate dehydrogenase (LDH) was elevated up to 372 IU/L. The presumptive diagnosis of EATL



Fig. 1. Endoscopic findings of the patient. Representative images from the stomach (A) and IC valve (B). Both lesions show mucosal nodularity or elevation with hyperemic change.

led physicians to perform serologic tests to rule out celiac disease. Anti-tissue transglutaminase antibody was negative, and the patient was positive for HLA-DQ5 and DQ6, which made the possibility of underlying celiac disease less likely. A test for food allergies was also unremarkable.

Multiple endoscopic biopsies were taken from the esophagus to the colon, which all exhibited similar histological features. The lamina propria was expanded by infiltration of atypical monomorphic lymphoid cells. The infiltrate was vaguely demarcated from the adjacent relatively unaffected mucosa in the colon. The atypical lymphoid cells were medium-sized with slightly irregular nuclei, inconspicuous nucleoli and finely clumped chromatin. They had a moderate amount of pale to eosinophilic cytoplasm (Fig. 2). Mitotic figures were occasionally observed. Necrosis, apoptosis, and angiocentricity were absent. Some scattered eosinophils were noted in the lamina pro-

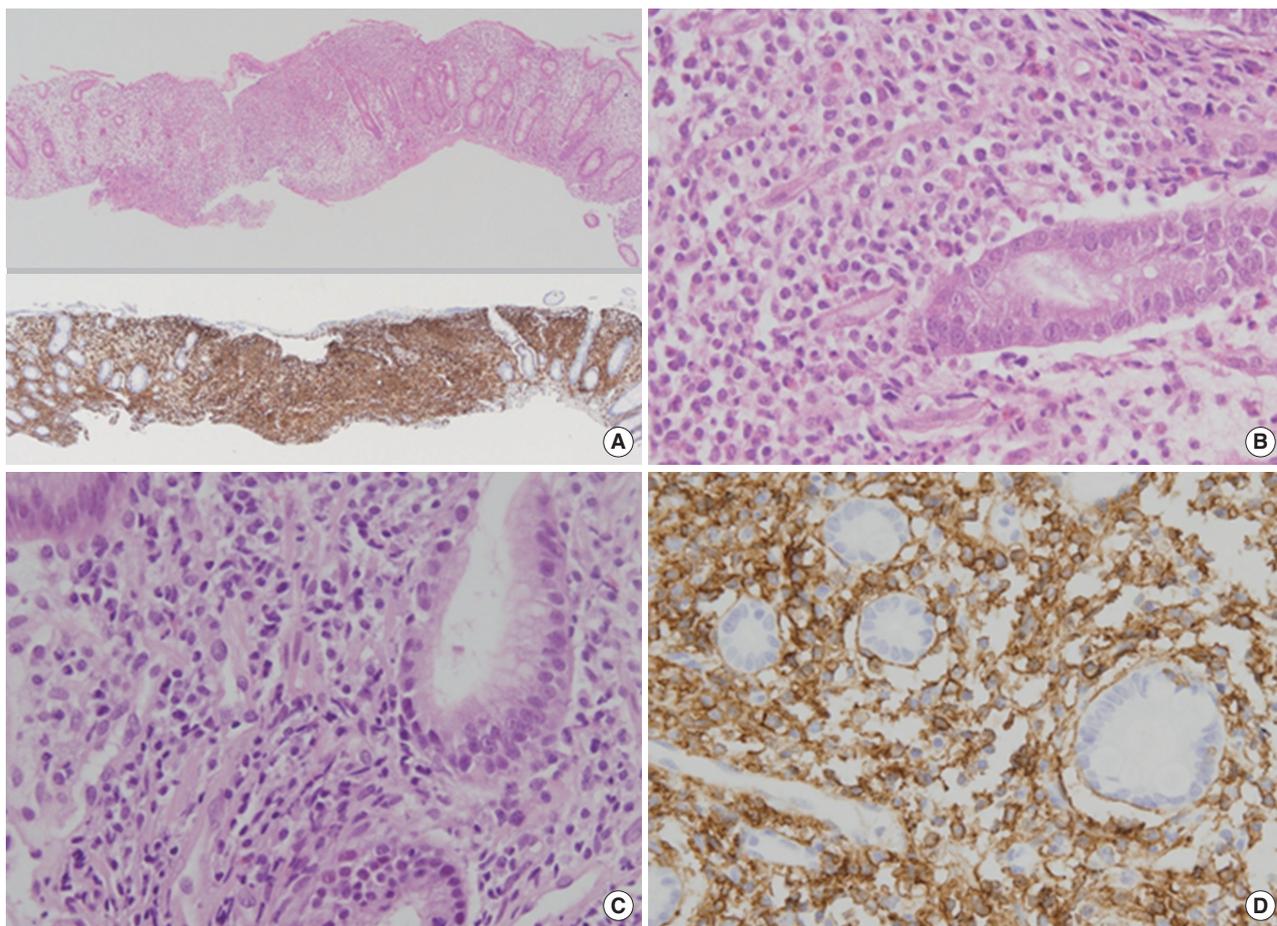


Fig. 2. Pathologic findings of colon and stomach lesions. Representative images from the colon (A, B) and stomach (C, D). (A, upper) Lamina propria of the colonic mucosa is infiltrated by atypical lymphoid cells, which resulted in separation of crypts. (A, lower) The atypical cells are diffusely positive for CD56 by immunohistochemistry. (B) The atypical lymphoid cells are monomorphic, medium to large in size, and have irregular nuclei and a moderate amount of clear to eosinophilic cytoplasm. (C) The lamina propria of the gastric mucosa is also infiltrated by atypical lymphoid cells, which are also strongly positive for CD56 (D).

pria. Enteropathy features including villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis were not observed. On immunohistochemistry, the lymphoid cells were positive for cytoplasmic CD3, CD56, CD8, and T-cell-restricted intracellular antigen-1, and negative for CD4, CD20, and TCR β 1 (clone 8A3, Thermo Scientific, Rockford, IL, USA) (Fig. 2). This immunophenotype suggested an NK-cell or $\gamma\delta$ T-cell origin. The proliferation rate as determined by Ki-67 was low, up to 19.8%. EBV was not detected by *in situ* hybridization using an EBV-encoded RNA 1/2 probe. Molecular analysis for TCR γ gene rearrangement using BIOMED-2 multiplex PCR for *TCRGA*: $V_{\gamma 1}/\gamma 10$ - J_{γ} ; *TCRGB*: $V_{\gamma 9}/\gamma 11$ - J_{γ} (InVivo-Scribe Technologies, San Diego, CA, USA) on formalin-fixed paraffin-embedded tissue showed no evidence of T-cell monoclonality. Later immunohistochemistry for TCRG (1:20, $\gamma 3.20$, Endogen, Rockford, IL, USA) was carried out, which was negative.

Despite a presumptive pathologic diagnosis of intestinal $\gamma\delta$ T-cell or NK-cell lymphoma, no chemotherapy was administered due to low clinical suspicion of malignancy and the poor nutritional status of the patient. He instead has been closely followed with regular clinical evaluation. Gastroduodenoscopy six months later demonstrated persistent mucosal nodularity in the duodenum, but biopsy revealed mild lymphoplasmal cell infiltration with only a few scattered CD3(+) cells and no CD56(+) cells. The patient's symptoms and LDH level waxed and waned, while anemia and hypoalbuminemia have been persistent. However, 40 months later, GI symptoms were aggravated and multifocal ulcerations were observed in colon and stomach. The result of endoscopic biopsy proved recurrence of disease.

DISCUSSION

In the present patient, an unusual infiltration of monomorphic cytoplasmic CD3(+), CD56(+), TCR β 1(-) cells in GI tract led us to consider extranodal NK/T-cell lymphoma or $\gamma\delta$ T-cell lymphomas. Extranodal NK/T-cell lymphoma occasionally presents with primary GI lymphoma and can have broad cytomorphic features. However, tumor cells are infected with EBV in virtually all cases, and have irregularly-folded or elongated nuclei with dark chromatin. They frequently exhibit angiocentric and angiodestructive growth patterns with necrosis and apoptosis.¹ The cytomorphology and histology of the present case and the absence of EBV varied widely from extranodal NK/T-cell lymphoma.

Current World Health Organization (WHO) classification includes two types of $\gamma\delta$ T-cell lymphoma, hepatosplenic $\gamma\delta$ T-

cell lymphoma and primary cutaneous $\gamma\delta$ T-cell lymphoma.¹ Although $\gamma\delta$ T-cells constitute only 1% to 5% of the lymphocytes in peripheral blood, they account for up to 50% of T-cells in the skin and intestine. In fact, intestinal lymphoma derived from $\gamma\delta$ T-cells has been well described in type II EATL.^{1,5-7} Type I EATL in its classical form is predominantly encountered in Western countries, and has a strong association with celiac disease and HLA-DQ2 or DQ8 expression. Usually the tumor cells are medium to large, often display a pleomorphic appearance in an inflammatory background, and typically have CD3(+), CD4(-), CD8(-), and CD56(-) immunophenotypes. On the other hand, type II EATL, or monomorphic variant EATL, is commonly found in Asian populations and has less association with celiac disease. It is characteristically composed of monomorphic small- to medium-sized cells, which frequently exhibit CD3(+), CD4(-), CD8(+), and CD56(+) phenotypes.^{1,5,7,8} Recently mounting evidences has demonstrated that type II EATL commonly expresses $\gamma\delta$ TCR, unlike type I EATL, and therefore might be a distinct form of intestinal lymphoma originating from $\gamma\delta$ T-cells.^{6,7} Nevertheless, both type I and II EATL are aggressive diseases and still share some clinicopathologic characteristics including enteropathy features such as villous atrophy, crypt hyperplasia, and intraepithelial lymphocytosis.^{1,5,8} The immunophenotype of infiltrated cells in the present patient overlaps with EATL, especially type II EATL; however, our patient had no evidence of celiac disease. Moreover, neither histological features suggestive of enteropathy nor T-cell monoclonality were observed. Most importantly, the indolent chronic clinical course of the present case was not compatible with EATL or any other type of intestinal NK- or T-cell lymphoma.

To the best of our knowledge, this case is most closely akin to a unique entity recently described as "NK-cell enteropathy" or "lymphomatoid gastropathy" by Western and Japanese researchers.^{3,4} This disorder is pathologically characterized by an infiltration of atypical cytoplasmic CD3(+), CD56(+), CD4(-), CD8(-), TCR(-), cytotoxic molecule(+) lymphoid cells into the lamina propria of the GI tract from stomach to colon. Cytomorphologically, cells were medium to large with a moderate amount of clear to eosinophilic cytoplasm. The NK-cell nature of cells was also demonstrated by flow cytometric analysis in a subset of the patients. T-cell monoclonality or typical enteropathic features have not been observed. Despite the worrisome monomorphic CD56(+) lymphoid cell infiltration mimicking intestinal NK- or T-cell lymphoma, all patients experienced a benign or indolent course without disease progression. They were alive with persistent disease or the lesions were self-

gressed with only occasional relapses.

The pathologic features of this entity are quite similar to those of our patient except for CD8 expression. Normal NK-cells show variable expression of CD8 in addition to the subunits of the CD3 complex including the ϵ and ζ chains.⁹ Considering this, the expression of CD8 seen in our patient would be plausible, and may not conflict with a diagnosis of “NK-cell enteropathy.” The possibility of a $\gamma\delta$ T-cell origin of infiltrating cells was lower considering the absence of TCRG expression by immunohistochemistry. Moreover, no instances of non-neoplastic infiltration of polyclonal $\gamma\delta$ T-cells have been reported previously.

Previous cases described as “NK-cell enteropathy” or “lymphomatoid gastropathy” occurred only in adults. The etiology and the pathogenesis of this unique lesion remain speculative. The clinical course of patients is suggestive of a non-neoplastic inflammatory process rather than a neoplastic process.^{3,4} Transient increase of circulating NK-cells has been observed in autoimmune disorders and viral infections. NK-cells are also found in the lamina propria of the intestine and involved in mucosal immunity in order to control infections or immune responses.¹⁰ The cause of abnormal NK-cell infiltration in the GI tract, if the proliferating NK-cells are monoclonal versus polyclonal, and the long-term course of patients still remain to be elucidated. Our patient is thought to be the first example of childhood or adolescent onset of this disorder, which might explain the unusual clinical manifestation, including failure to thrive. The patient’s symptoms were persistent with late recurrence, which might suggest an indolent but possibly chronic course of the disease. An otherwise unknown immunologic or inflammatory process underlying the atypical NK-cell proliferation might explain the lingering symptoms of our patient.

In summary, we reported an adolescent case of “NK-cell enteropathy” demonstrating multiple mucosal involvement of the GI tract. “NK-cell enteropathy” is regarded as a distinctive clinicopathologic entity which should be observed closely, while aggressive chemotherapy should be avoided. Because of its similarity to intestinal CD56(+) T- or NK-cell lymphoma, it is important to carefully and accurately diagnose this entity to prevent misinterpretation of the biopsy and potentially harmful consequences for the patients in clinical practice.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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