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Indolent NK cell proliferative lesion mimicking NK/T cell lymphoma in the gallbladder

Su Hyun Hwang [a], Joon Seong Park [a], Seong Hyun Jeong [a], Hyunee Yim [b], Jae Ho Han [b,*]

[a] Department of Hematology-Oncology, Ajou University School of Medicine, Suwon, Korea
[b] Department of Pathology, Ajou University School of Medicine, Suwon, Korea

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ABSTRACT

Natural killer (NK) cell-associated lymphoproliferative disorder includes NK/T cell lymphoma, nasal type and aggressive NK cell leukemia which exhibit poor outcomes. However, benign NK cell proliferative lesion has been recognized in the gastrointestinal tract under the name of NK-cell enteropathy or lymphomatoid gastropathy. We report a case of a similar CD56-positive NK-cell proliferative disorder involving the gallbladder and gastrointestinal tract in a 33-year-old woman who presented with chronic cholecystitis and underwent cholecystectomy. The gallbladder showed a few scattered polyps which were infiltrated by medium-sized atypical lymphoid cells with eosinophilic cytoplasmic granules. On immunohistochemistry, the lymphoid cells were positive for CD2, CD56, T-cell-restricted intracellular antigen-1, and granzyme B, but negative for CD3, CD4, CD5, CD8, CD20, CD30, CD34, CD68 and myeloperoxidase. In situ hybridization for Epstein–Barr virus-encoded RNA was negative and T-cell receptor gene rearrangement was polyclonal. The patient is under close observation for 36 months without any evidence of lymphoma.

1. Introduction

Natural killer (NK) cells are an element of innate immunity and are distributed in lymphoid tissue, spleen, and extranodal sites. NK cells also influence adaptive immune responses. In event of acute inflammation, localization of NK cells at various anatomic sites, including gastrointestinal (GI) mucosa and skin, has been described [1].

Neoplastic proliferations of CD56-positive NK cells are predominantly seen at extranodal sites, and these include NK/T cell lymphoma, aggressive NK cell leukemia and type II enteropathy-associated T-cell lymphoma (EATL) which commonly have shown extremely poor clinical outcomes even with anti-cancer chemotherapy [2,3].

A benign or indolent NK cell proliferative lesion involving the GI tract has been described [4–9]. It was diagnosed as NK/T cell lymphoma, nasal type because of similar histopathologic findings, and was treated with chemotherapy. However, these patients do not require aggressive chemotherapy and have a good prognosis. It is important to recognize a unique clinicopathologic entity in order to prevent unnecessary treatment and harmful consequences in the patient.

Here, we report a unique case of benign NK-cell proliferation in the gallbladder and GI tract in a patient presenting with cholecystitis. To the best of our knowledge, this is the first report in the literature.

2. Clinical history

A 33-year-old Korean woman presented with right upper quadrant pain and indigestion. She had no other symptoms than fever, febrile sensation, and myalgia. On physical examination, specific abnormalities were not found. The peripheral blood smear examination showed a white blood cell count of $11.1 \times 10^3/\mu l$ (range, 4–$10.5 \times 10^3/\mu l$), neutrophils 74.2% (range, 33.0–74.0%), lymphocytes 17.3% (range, 19.0–49.0%), hemoglobin 8.8 g/dL (range, 10.7–14.6 g/dL) and platelets $258 \times 10^3/\mu l$ (range, 143–$376 \times 10^3/\mu l$). Lactate dehydrogenase level was 144 U/L (range, 100–200 U/L). All other laboratory findings were within normal limits. The abdominal computed tomography scan showed distension and diffuse wall thickening of the gallbladder. Under the clinical impression of chronic cholecystitis, cholecystectomy was performed.

One month later, esophagogastroduodenoscopy was performed and it revealed atrophic mucosal change with whitish nodularity (Fig. 1A, B). Multiple flat erosions with blood clots were noted in the body and fundus of the stomach. A few erosions with blood clots were also noted on the duodenal bulb. *Campylobacter*-like organism test documented *Helicobacter pylori* infection. Colonoscopy was also performed for change in bowel habits. A few polyps and erosions were noted in the sigmoid colon and hyperemic mucosa with oozing of blood documented (Fig. 1C, D).

Positron emission tomography scan showed no evidence of abnormal uptake to suggest malignancy, mass, or lymphadenopathy. This patient was treated with conservative therapy only and the patient is still

* Corresponding author at: Department of Pathology, Ajou University School of Medicine, 164 Worldcup-ro, Yeongtong-gu, Suwon-si, Gyeonggi-do, Republic of Korea, 443–380. Tel.: +82 31 219 5932; fax: +82 31 219 5934.
E-mail address: hanpathol@naver.com (J.H. Han).

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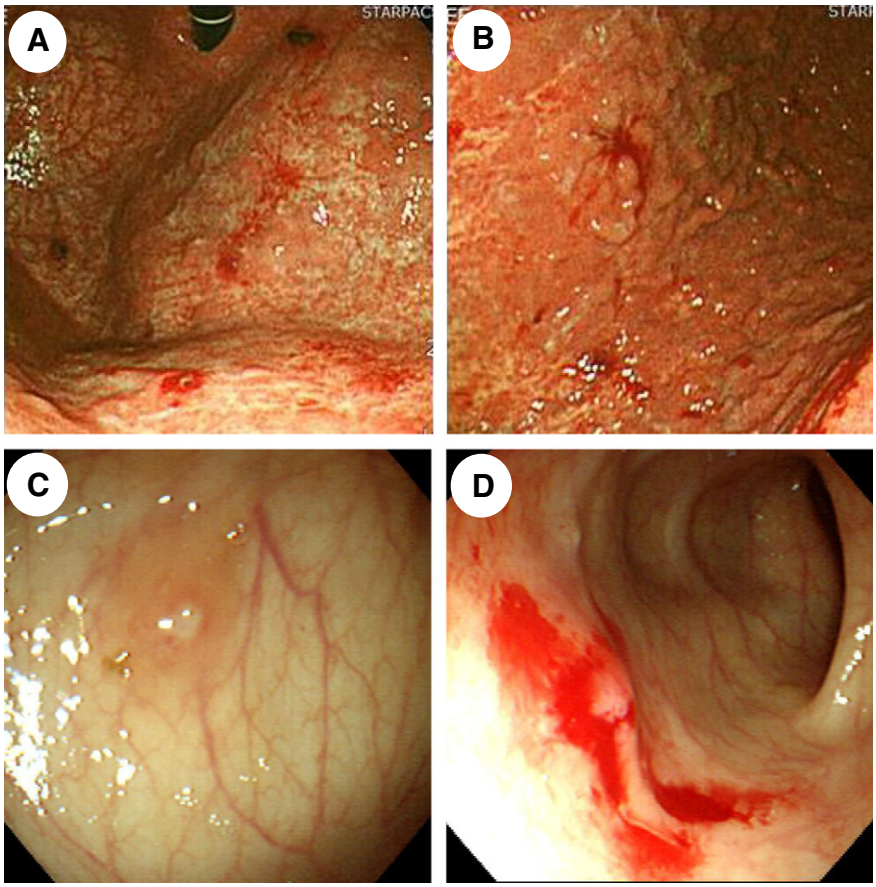

Fig. 1. Esophagogastroduodenoscopy shows atrophic and whitish nodular gastric mucosa (A). Multiple flat erosions with blood clots are noted in the fundus. A shallow ulcer is noted in the mid body (B). The sigmoid colon shows a sessile polyp and surrounding mucosa is slightly hyperemic (C). A small polyp combined with mucosal erythema and erosions with oozing are detected (D).

under close observation for 36 months without any evidence of malignancy.

3. Pathologic features and immunohistochemical findings

Grossly, the gallbladder showed a few polyps, measuring up to 0.5 × 0.4 cm. Histologically, the medium-sized atypical lymphoid cells diffusely infiltrated the lamina propria (Fig. 2A). The infiltrates were associated with surface erosion and focal necrosis, and were limited to the mucosa. Apart from areas of erosion, necrosis was absent. The mucosal glands were displaced and there was an absence of epitheliotropism in glandular epithelium. The lymphoid cells showed slightly irregular nuclear contour, inconspicuous nucleoli, and moderate amount of clear to eosinophilic cytoplasm (Fig. 2B). Mitotic figures were found occasionally and a few apoptotic bodies were present. On immunohistochemistry, the lymphoid cells were positive for CD2, CD56, T-cell-restricted intracellular antigen-1 (TIA-1) and granzyme B, and negative for CD3, CD4, CD5, CD8, CD20,CD30, CD34, CD68 and myeloperoxidase (Fig. 2C and D). The Epstein–Barr virus (EBV) was not detected by EBV-encoded RNA (EBER) in situ hybridization. T cell receptor (TCR) β and γ gene arrangement study using BIOMED-2 polymerase chain reaction (InVivo-Scribe Technologies, San Diego, CA, USA) failed to demonstrate monoclonality.

The biopsied gastric and colonic mucosa showed relatively intact architecture with focal patchy infiltration of lymphoid cells in the lamina propria (Fig. 3). Erosion and *Helicobacter pylori* were seen on the surface of gastric mucosa. The cellular morphology was similar to that of the gallbladder. On immunohistochemistry, these cells in the gastric and colonic mucosa were positive for CD3, CD4, CD8, CD56, TIA-1, and granzyme B, but lymphoid cells in the colonic mucosa were weakly positive for CD56. The bone marrow aspirate and biopsy showed 50% cellularity without any evidence of lymphoproliferative disorder.

4. Discussion

In this case report, we described a case of benign NK cell proliferative lesion mimicking NK/T cell lymphoma in the gallbladder and EATL in the GI tract. Although a benign NK cell proliferative lesion has been reported in the GI tract, this case is unique since in this case NK cells accumulated in the gallbladder presenting as several polyps.

The lymphoid cells infiltrating into the gallbladder were positive for CD2 and CD56 and negative for CD3, CD4, and CD8. NK cells constitutively express CD56, and the T cell associated antigens CD2. They also express some subunits of the CD3 complex and variably express CD8 [10]. In contrast, cytotoxic T cells express a fully assembled TCR-CD3 complex. However, they variably express NK cell-associated antigens, including CD56 and CD57. NK cells and cytotoxic T cells are closely related in their ontogeny and function. These similarities can make it difficult to distinguish these cell types. In addition, NK-like T cells represent a minor subset of T cells that share cell surface proteins with conventional T cells and NK cells and these subsets can be CD4 or CD8 positive. However, 1–2% of NK-like T cells are negative for both CD4 and CD8 [5]. Expression of CD56 is unique to NK cells and has not been reported for NK-like T cells [11]. These above findings suggest that proliferating cells in our patient are purely NK cells. The distribution of NK cells is not static because these bone marrow-derived cells can migrate through the blood to the spleen, liver, lung, and many other organs [12]. The NK cell proliferation in the gallbladder has not been described in the literature. However, it can be found in the gallbladder considering that NK