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*Case Study*

# Primary Gastric T-cell Lymphoma Associated with Human T-cell Leukemia Virus Type I shows 'Lymphoepithelial Lesions' : Case report

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We describe an unusual case of adult T-cell leukemia/lymphoma (ATL) appearing in a 44-year-old female without leukemic change and systemic lymphadenopathy, which originated from the gastric wall and partially involved the paragastric lymph nodes. No other intraabdominal or intrathoracic organs, such as the liver, spleen, kidneys, adrenals, lungs, or bone marrow, were involved at the time of surgery. The clinical stage of this case was evaluated as IIE according to the Ann Arbor classification. Lymphoma cells were CD3+, CD4+, CD8−, and CD79a−. Southern blot analysis revealed monoclonal integration of proviral DNA from human T-cell leukemia virus type I. Interestingly, the lymphoma cells formed 'lymphoepithelial lesions' which are usually observed in gastric mucosa-associated lymphoid tissue (MALT) B-cell lymphomas. A rare pattern involving ATL cells and the presence of lymphoepithelial lesions in this case indicated a diagnostic pitfall of gastric MALT lymphoma.
**Key words** stomach, HTLV-I, ATL, lymphoepithelial lesion

## INTRODUCTION

Adult T-cell leukemia/lymphoma (ATL) is associated with human T-cell leukemia virus type I (HTLV-I). Most Japanese patients come from the southwestern region. ATL cells originate from the CD4+ subset of peripheral T cells. ATL shows diverse clinical features but can be divided into four subtypes : acute, chronic, smoldering (prodromal), and lymphoma[1]. The vast majority of patients in the acute leukemia phase are resistant to chemotherapies and die of the disease within a short period[1]. In these patients, ATL cells usually involve the generalized lymph nodes and frequently the cutaneous regions, but rarely involve the gastrointestinal tract. [2]This is also the case in patients in the chronic phase and prodromal phases.

Non-Hodgkin's lymphomas occur almost equally in nodal and extranodal organs. Of all extranodal sites, the stomach is most frequently affected by diffuse large B-cell lymphoma and mucosa-associated lymphoid tissue (MALT) lymphoma. The latter is associated with *Helicobacter* (H.) *pylori* -related chronic inflammation. T-cell lymphomas are rarely found in the stomach. In the present paper, we report an unusual case of primary gastric T-cell lymphoma (PGTCL) that was associated with HTLV-I infection.

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## *CASE REPORT and PATHOLOGICAL FINDINGS*

A 44-year-old female, who lived outside the

ATL-endemic, southwestern, area of Japan, consulted her physician about abdominal discomfort and was hospitalized for chronic cholecystolithiasis. During her hospitalization, a gastric ulcer was detected. An endoscopic examination revealed an irregular-shaped ulcer at the posterior wall of the upper portion of the corpus. Histology of biopsy specimens taken from this lesion disclosed medium-sized lymphoid cells infiltrating and destroying glands. In some areas, lymphoid cells infiltrated into glands, and epithelial elements with intermingled lymphoid cells looked very similar to the lymphoepithelial lesions (LEL) of gastric MALT lymphoma (Fig. 1). The destroyed gastric glands were easily detected by immunostaining for keratin. A tentative diagnosis of MALT lymphoma was returned to the clinician, and *H. pylori* was eradicated. *H. pylori* disappeared within a short period without improving the ulcer.

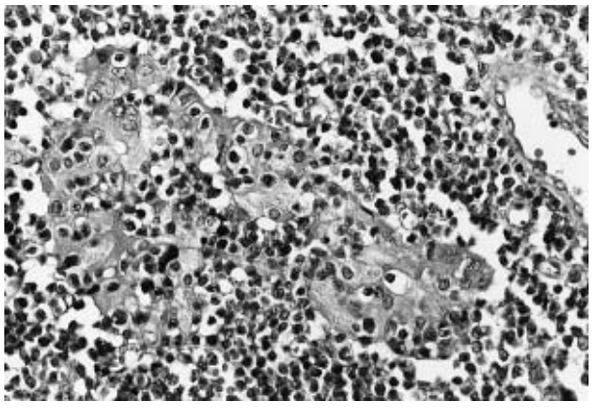

Fig. 1. Histology of the first biopsied specimen. Lymphoma cells involving gastric glands show a structure similar to lymphoepithelial lesions in mucosa-associated lymphoid tissue lymphoma.

Fig. 2. Resected gastric tissue. An irregular-shaped ulcer (arrowhead), approximately 3 cm in diameter, is found at the posterior wall of the gastric corpus.

The second endoscopic examination, performed three months later, revealed that her gastric lesion had worsened. The biopsied specimens at this time showed no LEL, and immunohistological examination indicated that the infiltrating lymphoid cells were $CD3^+$, $CD4^+$, $CD79a^-$, and $CD8^-$. This finding strongly indicated that the patient had T-cell lymphoma. She was hospitalized again, and a scanning CT examination detected mild swelling of the paragastric lymph nodes, but there were no hepatosplenic or other abdominal organ abnormalities. Her heart and lungs showed no particular findings. The results of laboratory examination were as follows: RBC, $482 \times 10^4/\mu l$; WBC, $7600/\mu l$; platelets, $30.1 \times 10^4/\mu l$; GOT, 16 IU/l; GPT, 16 IU/l; LDH, 155 IU/l (normal 230–490 IU/l); $\gamma$GTP, 14 IU/l; total bilirubin, 0.39 mg/dl; BUN, 10.7 mg/dl; creatinine, 0.64 mg/dl; CPK, 40 IU/l; amylase, 210 IU/l; total protein, 6.0 g/dl; albumin, 3.6 g/dl; Na, 140.6 mEq/l; K, 4.0 mEq/l; Cl, 106 mEq/l; Ca, 8.3 mg/dl; total cholesterol, 82 mg/dl. Abnormal lymphocytes were not evident. The titer of antibodies against HTLV-I was 20 x. The clinical stage of the patient was estimated at IIE, and her entire stomach was surgically resected.

The resected gastric specimen showed moderate thickening of the wall with an ulcer 3 cm in diameter at the corpus (Fig. 2). The lymphoma cells had a medium-sized nucleus and infiltrated from the mucosal to the subserosal layer. They involved 4 of 15 resected neighboring lymph nodes. Scattered mitotic figures were, and LEL were found in a part of the mucosal layer. The lymphoma cells in and out of the glands were immunohistologically positive for CD3 (Fig. 3a) and CD4, and negative for CD8, CD79a (Fig. 3b), and CD56. Southern blot analysis of the unfixed material revealed monoclonal integration of HTLV-I proviral DNA (Fig. 4). The patient has been free from disease for 6 months since her gastrectomy.

## DISCUSSION

We report a rare case of adult T-cell lymphoma that originated from the stomach

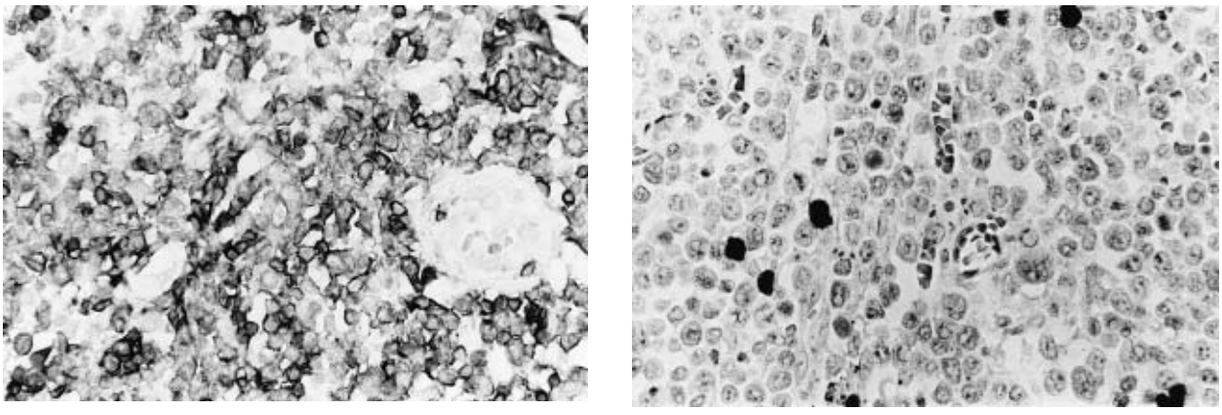

Fig. 3. Immunohistology of the lymphoma cells. (a) CD3, (b) CD79a.

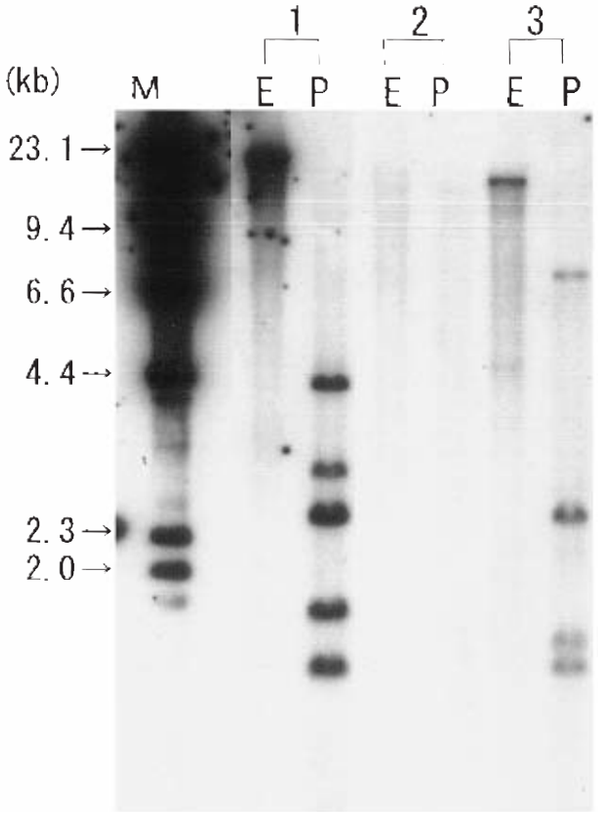


Fig. 4. Southern blot analysis of the resected gastric tissue for HTLV-I proviral DNA. M, size marker ; lane 1, positive control for HTLV-1 proviral DNA monoclonal integration ; lane 2, negative control ; lane 3, present case. E : Eco RI digestion. P : Pst I digestion.

without leukemic change or generalized lymphadenopathy. To our best knowledge, only thirteen such cases have been reported in the English literature with detailed clinicopathological findings[3−10]. According to the literature, about two-thirds of PGTCL cases were associated with HTLV-I[11].

The clinical features of HTLV-I-associated PGTCL are quite different from those not associated with HTLV-I[6]. HTLV-I-associated patients showed leukemic manifestations and tumor involvement of the skin at a later stage of the disease, and had a poorer prognosis than those without association to HTLV-I[11]. According to these findings, the present case should probably be treated intensively though apparent remission was achieved by surgical resection. A patient with ATL localized in the right tibial bone without leukemic change was reported who achieved complete remission after amputation of the right lower leg and two courses of chemotherapy[12].

The reason this patient's disease was restricted to her stomach remains unclear. To date, at least three organ-specific homing systems have been determined : peripheral node, mucosal and cutaneous[13]. In each system, the specific homing receptor and its ligand, vascular addressin, have been reported. Mucosal homing is regulated through $\alpha 4\ \beta 7$integrin and its ligand, MAdCAM-1. The $\alpha 4\ \beta 7$integrin is detected on MALT, mantle cells and precursor B-cell lymphomas, which involve the mucosal region[14,15]. Moreover, it has been reported that PGTCL expressing CD103 are thought to originate from intraepithelial T lymphocytes[10,16]. The lymphoma cells in our case may have had such

mucosal homing receptors; however, immunohistology of these antigens could not be performed since we lacked frozen materials.

It is quite interesting that LEL were found in the biopsied and surgically resected materials. The lymphoma cells not only infiltrated the gastric glands, but transformed the normal structure. These findings usually strongly suggest MALT lymphoma. No such cases of PGTCL have been reported. We did not find any LEL in the second biopsied specimen after the eradication of *H. pylori*. In the resected gastric material, LEL were located in some areas but were not found in other areas. This irregular distribution may explain the transient presence of LEL. Though the meaning of LEL presence in gastric ATL was not determined by this single case, we should recognize that LEL can exist in gastric non-MALT lymphomas.

In conclusion, the present case was a rare example of HTLV-I-associated PGTCL. According to previous reports, the patient should be carefully monitored to detect further involvement and appropriately treated to prevent recurrence. It is quite important for pathologists to understand that LEL can be found even in T-cell lymphomas.

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