Original Article

Endoscopic and clinicopathological characteristics of gastrointestinal adult T-cell leukemia/lymphoma

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Background: Adult T-cell leukemia/lymphoma (ATLL) frequently involves the gastrointestinal (GI) tract, and patients mainly show an aggressive clinical course despite of intensive cytotoxic treatments. We investigated the characteristic clinicopathological and endoscopic features of GI ATLL.

Methods: This was a retrospective analysis of 61 GI tract lesions in 54 ATLL patients.

Results: Thirty-six (67%) patients were classified as having lymphoma-type ATLL and 18 (33%) patients were classified as having acute-type with leukemic changes. Examined ATLL lesions in the stomach and intestine (small intestine and colorectum) were 40 (66%) and 21 (34%), respectively. Gastric ATLL lesions were frequently found in the lymphoma-type (29/38; 76%) compared with the acute-type lesions (11/23; 48%; P=0.023). Intestinal ATLL lesions were frequent in the acute-type (12/23; 52%) compared with the lymphoma-type lesions (9/38; 24%; P=0.023). Endoscopically, tumor-forming type lesions were significantly more frequent in lymphoma-type ATLL lesions (29/38 lesions; 76%) compared with acute-type lesions (10/23; 44%; P=0.0096). The superficial spreading-type was significantly more frequent in acute-type lesions (12/23 lesions; 52%) compared with lymphoma-type lesions (3/38; 8%; P=0.0003). Additionally, gastropathy-, enteropathy-, or proctocolitis-like lesions were distinct features, mainly in the acute type (9/23 lesions; 39%). Twenty three of 39 tumor-forming-type lesions (59%) were significantly composed of pleomorphic or anaplastic large cell lymphoma, and 13 of 15 superficial spreading-type lesions (87%) were significantly composed of pleomorphic medium-sized cells (P=0.007, in each). Six patients (11%) who were estimated as having primary GI ATLL based on restricted clinical stages, showed a significantly better overall survival (OS) compared with the 48 advanced-stage patients (P=0.017). Twenty patients with solitary tumor-forming-type lesions showed a significantly better OS than 17 patients with the multiple tumor-forming-type (P=0.015) and five with the mucosal-thickening-type lesions (P=0.04). Twenty-six patients with pleomorphic or anaplastic large cell ATLL showed a significantly better prognosis compared with 28 patients with pleomorphic medium-sized ATLL (P=0.034).

Conclusions: ATLL predominantly involves the stomach. Leukemic behavior of ATLL had a large influence on the tumor location and endoscopic features of GI tract lesions. Gastropathy-, enteropathy-, and proctocolitis-like lesions showed additional distinct characteristics. Primary GI ATLL in the early clinical stages, solitary tumor-forming-type lesions and large tumor cells showed better prognostic factors than other factors, respectively.

Keywords: Adult T-cell leukemia/lymphoma (ATLL); gastrointestinal tract; endoscopy; gastroenteropathy

Submitted Jan 24, 2019. Accepted for publication Feb 26, 2019.
doi: 10.21037/jgo.2019.03.03
View this article at: http://dx.doi.org/10.21037/jgo.2019.03.03

Introduction

The gastrointestinal (GI) tract is the most common extranodal site that is involved in non-Hodgkin's lymphomas (1,2). Primary GI lymphomas are mainly composed of B-cells, and T/natural killer (NK)-cell neoplasia occurs rarely. In primary GI T-cell lymphomas, enteropathy-associated T-cell lymphoma (EATL) is considered to be a neoplasia of the T-intraepithelial lymphocytes (T-IELs), and it is divided into two groups based on the recent World Health Organization (WHO) classification (3,4). In Northern Europe and America, about 80% of patients had type I EATL, which is closely associated with celiac disease (5). Type II EATL, which is now called monomorphic epitheliotropic intestinal T-cell lymphoma (MEITL), is more prevalent in East Asia and has no correlation with celiac disease (6). Additionally, primary GI T/NK-cell lymphomas are reported to be mainly located in the small intestine and colon (7).

Adult T-cell leukemia/lymphoma (ATLL) mainly consists of $CD4^+$ T-cell neoplasms that are associated with long-standing human T-lymphotropic virus-1 (HTLV-1) infection (8). HTLV-1 is transmitted from mothers to infants through breastmilk (8,9). ATLL is characterized by a high tendency for leukemic changes and involves various organs, including the GI tract, liver, spleen, and skin (10). In a previous study, GI ATLL showed three typical endoscopic features: solitary or multiple tumor-forming-type lesions, superficial spreading-type lesions, and mucosal thickening-type lesions (11-13). We have previously demonstrated that GI ATLL as well as MEITL show high CD103 (αEβ7 integrin) homing receptor expression in T-IELs (31/56 patients, 55%) and ATLL had some characteristics that are similar to the histopathological features of MEITL (14). The current study reports differences in the clinical and endoscopic features of 61 GI tract lesions from 36 lymphoma- and 18 acute-type ATLL patients. Among these patients, we endoscopically demonstrated that gastropathy-, enteropathy-, and proctocolitis-like ATLL lesions were occasionally encountered characteristic features. Additionally, early clinical stages of Lugano's classification, solitary tumor-forming lesions, and pleomorphic large tumor cells were better prognostic factors in GI ATLL patients. We discussed differences in endoscopic and clinicopathological findings among patients with GI ATLL and other types of primary GI lymphoma.

Methods

Patient selection and clinical findings

This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the institutional review board at our hospital (Institutional review board approval number: 14-8-08). We retrospectively reviewed medical records and analyzed samples from ATLL patients at the Department of Pathology, Fukuoka University from 1990 to 2018. This study focused on 54 Japanese patients from whom 61 GI ATLL lesions were examined. We classified ATLL patients into clinical subgroups based on the Japanese Lymphoma Study Group classification (15). The clinical stage was classified based on the Lugano-modified Ann Arbor staging system (16). Histological classification was performed in accordance with the WHO classification that was proposed in 2017 (8).

Endoscopic examination

All 54 patients underwent endoscopic examination of the upper and/or lower GI tract. A video endoscope (Olympus Medical System, Tokyo, Japan) was used for all endoscopic examinations. The endoscopic images or records were reviewed retrospectively by two experienced endoscopists (H.I. and Y.K.). Biopsy specimens for histologic examination were taken from the stomach and/or small intestine and/or colon using standard biopsy forceps. Endoscopic findings for GI ATLL were classified into five types, based on a previous classification (13,14) with modifications, as follows: (I) solitary tumor-forming-type lesion (including solitary ulcerated and/or elevated tumor (*Figure 1A,B*), and submucosal tumor-like lesion); (II) multiple tumor-forming-type lesion (including multiple ulcerated and/or elevated tumors (*Figure 1C*) or multiple lymphomatous polypoid lesions); (III) superficial spreading-type lesion [including early gastric cancer-like lesion (*Figure 1D*)]; (IV) gastropathy-like (gastritis-like) lesion

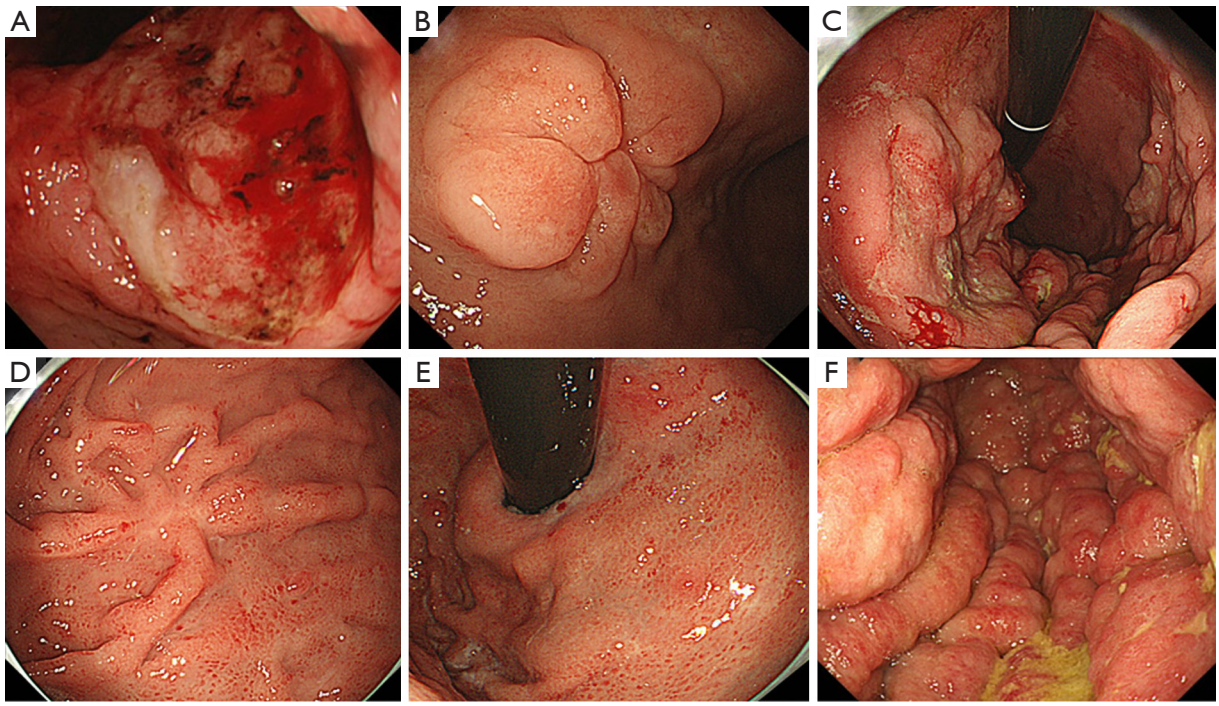

Figure 1 Endoscopic features of patients with GI ATLL. Upper GI endoscopic views of the stomach show a single ulcerated tumor (A), single elevated tumor (B), multiple ulcerated tumors (C), early gastric cancer-like lesion (D), gastritis-like lesion (E), and giant thickening folds (F). GI, gastrointestinal; ATLL, adult T-cell leukemia/lymphoma.

(*Figure 1E*) and enteropathy-like lesions (enteritis-like or proctocolitis-like lesions); and (V) mucosal thickening-type lesions (large thickening of folds; *Figure 1F*).

Histology and immunohistochemistry

We performed a histologic examination of biopsy specimens from 43 ATLL patients, surgical specimens from ten patients with GI tract involvement, and endoscopic mucosal resection (EMR) from one patient. We examined three main histologic findings because ATLL has similar features as EATL (14). In non-neoplastic mucosal layers, >30 small IELs per 100 epithelial cells was considered to be a significant increase. Scattered small IELs without irregular nuclei were considered to be reactive, and medium-sized or large atypical lymphocytes with irregular swollen nuclei were defined as neoplastic IELs. For immunohistology, monoclonal and polyclonal antibodies were applied to formalin-fixed tumor samples using a Leica BondMax automated stainer (Leica Biosystems, Buffalo Grove, IL, USA). Immunostaining of CD3 (PS1; Leica Biosystems, Newcastle, UK), CD4 (4B12, Leica Biosystems), CD8 (C81/44B, Leica Biosystems), CD25 (4C9; Leica Biosystems), CD30 (BerH2, DakoCytomation, Glostrup, Denmark), CD103 (EPR4166^{2}, Abcam, Cambridge, MA, USA), and CD194 [chemokine receptor (CCR) 4, 1G1, BD Bioscience, San Jose, CA, USA] was performed after antigen retrieval. Samples in which more than 30% of the tumor cells were labeled with a particular antibody marker were classified as positive. Histological findings were reviewed by two pathologists (M.T. and S.N.).

Statistical analysis

Clinicopathological data were analyzed using the Chi-square test and Fisher's exact test. A value of $P<0.05$ was considered significant. Overall survival (OS) curves for all patients were generated using the Kaplan–Meier method and analyzed using the log-rank test.

Results

Patient characteristics

The clinical features of 54 ATLL patients with GI tract

Table 1 Clinical findings of two types of 54 ATLL patients with GI tract invasion

Clinical subtype	Lymphoma type	Acute type	Total	P value
No. of cases [%]	36 [67]	18 [33]	54	
Median age [range] in years	61 [49–89]	63 [47–83]	62 [47–89]	
Male:female	17:19	10:8	7:27	NS
Clinical stage, n [%]				
I	2 [6]	0 [0]	2 [4]	NS
II (II1, II2, IIE)	13 [36]	0 [0]	13 [24]	0.0096
II1	4 [11]	0	4 [7]	NS
II2	2 [6]	0	2 [4]	NS
IIE	7 [19]	0	7 [13]	NS
IV	21 [58]	18 [100]	39 [72]	0.0001
Histological types, n [%]				
Pleomorphic medium-sized	15 [42]	13 [72]	28 [52]	0.034
Pleomorphic large cell	13 [36]	2 [11]	15 [28]	0.034
Anaplastic large cell	8 [22]	3 [17]	11 [20]	
Treatments, n [%]				
Surgery	5 [14]	0 [0]	5/53 [9]	NS
Chemotherapy	20 [56]	11/17 [65]	31/53 [58]	NS
Radiation	1 [3]	0 [0]	1/53 [2]	NS
Surgery and chemotherapy	5 [14]	2/17 [12]	7/53 [13]	NS
Radiation and chemotherapy	1 [3]	0 [0]	1/53 [2]	NS
Chemotherapy and BMT	2 [6]	2/17 [12]	4/53 [8]	NS
Surgery, chemotherapy, radiation and BMT	1 [3]	0 [0]	1/53 [2]	NS
No treatment	1 [3]	2/17 [12]	3/53 [6]	NS
Prognosis: 50% survival (months)	11	10	10.5	NS

*, comparison of sum of two large cell types. stage I, tumor confined to GI tract; II1, local nodal involvement; II2, distant nodal involvement; IIE, penetration through serosa to involve adjacent organs; IV, disseminated extranodal involvement or a GI tract lesion with supradiaphragmatic nodal involvement. ATLL, adult T-cell leukemia/lymphoma; GI, gastrointestinal; NS, not significant; BMT, bone marrow transplantation.

invasion are summarized in *Table 1*. Thirty-six patients (67%) were classified as having lymphoma-type and 18 patients (33%) were classified as having acute-type lesions. The median patient age at diagnosis was 62 years (range, 47–89 years), and 2 patients (4%) were stage I, 13 (24%) were stage II, and 39 (72%) were stage IV. The 15 patients (28%) at stage I or II all had lymphoma-type lesions. Among them, 6 patients (11%) at stages I and II1 showed primary GI ATLL (stomach, 4; small intestine, 2). Twenty-one patients with lymphoma-type lesions (58%) and 18 patients with acute-type lesions (100%) were classified as stage IV, which was significantly different between the two groups (P=0.0001). Gastrectomy, jejunectomy, and ileotomy were performed to remove the main tumor in 5 patients (9%), while 31 patients (57%) received chemotherapy and 5 (10%) underwent bone marrow transplantation (BMT) after surgery and chemotherapy. Cyclophosphamide, doxorubicin, vincristine, and prednisolone (CHOP) therapy was administered to 25 patients, and mogamulizumab therapy was administered to three patients. All six primary GI ATLL patients were treated

Table 2 Involved sites and endoscopic features of 61 GI tract lesions in ATLL patients

Variables	Lymphoma type (n=38)	Acute type (n=23)	Total (n=61)	P value
Site of examined lesions, n [%]				
Stomach	29 [76]	11 [48]	40 [66]	0.023
Intestine (small intestine and colon)	9 [24]	12 [52]	21 [34]	0.023
Small intestine	6 [16]	5 [22]	11 [18]	NS
Colorectum	3 [8]	7 [30]	10 [16]	NS
Endoscopic features n [%]				
Tumor forming type	29 [76]	10 [44]	39 [64]	0.0096
Solitary tumor forming type	17 [45]	4 [18]	21 [34]	NS
Multiple tumor forming type	12 [31]	6 [26]	18 [30]	NS
Superficial spreading type	3 [8]	12 [52]	15 [25]	0.0003
Early gastric cancer-like	2 [5]	3 [13]	6 [10]	NS
Gastropathy- or enteropathy- or proctocolitis-like	1 [3]	9 [39]	9 [15]	0.0007
Mucosal thickening type	6 [16]	1 [4]	7 [11]	NS

In 2 lymphoma type patients, one has solitary tumor lesions in small intestine and colon, and another has mucosal thickening lesions in stomach and colon. In 4 acute type patients, one has mucosal thickening lesion in ileum and multiple tumors in colon, one has superficial spreading lesions in stomach, small intestine and colon, and two have superficial spreading lesions in small intestine and colon. GI, gastrointestinal; ATLL, adult T-cell leukemia/lymphoma; NS, not significant.

by gastrectomy or jejunectomy with subsequent combination chemotherapy or BMT.

Histological and immunohistochemical findings

For tumor cell features, 28 patients (52%) had pleomorphic medium-sized lymphoma, 15 patients (28%) had pleomorphic large cell lymphoma, and 11 patients (20%) had CD30-positive anaplastic large cell lymphoma. Three (two in lymphoma-type and one in acute type) of the examined 22 ATLL patients (14%) showed an increase in reactive IELs in the overlying epithelium and epithelial glands outside the tumors. Nineteen (12 in lymphoma-type and 7 in acute type) of the examined 46 patients (41%) showed small nests of tumorous IELs in the epithelial glands and covering the superficial epithelium. Lymphoma cells in all 54 patients (100%) were $CD3^+$, 40 (74%) were $CD4^+$, and nine (17%) were $CD8^+$; 44 patients (100%) were $CD25^+$, 13 of 41 patients (32%) were $CD30^+$, and 24 of 31 patients (77%) were CD194 ($CCR4^+$). Among the 54 ATLL patients with GI tract involvement, 26 (48%) were $CD103^+$. Seventeen of 36 lymphoma-type patients (47%) and nine of 18 acute-type patients (50%) were $CD103^+$.

Lesions and endoscopic features

The sites involved and endoscopic features of 61 GI ATLL lesions in acute and lymphoma-type ATLL patients are summarized in *Table 2*. Gastric ATLL lesions were present in 40 lesions (66%) and intestinal lesions were present in 21 lesions (34%). Among these, small intestinal ATLL lesions were present in 11 lesions (18%) and colorectal lesions were present in 10 lesions (16%). Significantly more gastric ATLL lesions were found in 29 of 38 lymphoma-type lesions (76%) compared with 11 of 23 acute-type lesions (48%; P=0.023). Small intestinal and colorectal ATLL lesions were significantly more frequent in 12 of 23 acute-type lesions (52%) compared with 9 of 38 lymphoma-type lesions (24%; P=0.023). The tumor-forming type (solitary and multiple tumor-forming types) was significantly more frequent in 29 of 38 lymphoma-type ATLL lesions (76%) compared with ten of 23 acute-type lesions (44%; P=0.0096). The superficial spreading type was significantly more frequent in 12 of 23 acute-type ATLL lesions (52%) compared with three of 38 lymphoma-type lesions (8%; P=0.0003). In the superficial spreading type, gastropathy-, enteropathy-, or proctocolitis-like lesions showing reddish and mildly edematous mucosa were significantly more

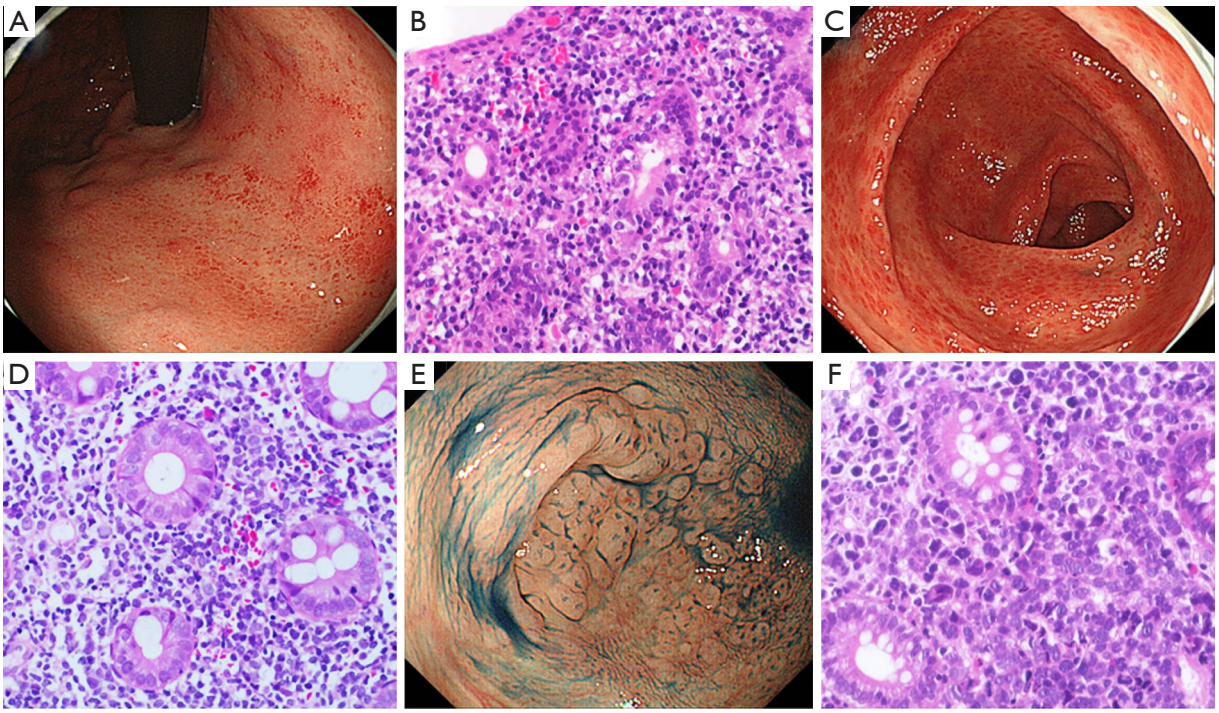

Figure 2 Superficial spreading-type lesions in acute-type adult T-cell leukemia/lymphoma (ATLL) patients. (A) Upper GI endoscopic view of the gastric body shows reddish, mildly edematous mucosa; (B) histological analysis of (A) shows scattered small intraepithelial lymphocytes (IELs), several large atypical IELs, preserved glands, and diffuse invasion by pleomorphic medium-sized atypical lymphocytes (hematoxylin and eosin stain); (C) lower gastrointestinal (GI) endoscopic view of the ascending colon shows reddish, mildly edematous mucosa similar to fish scales; (D) histological image of (C) shows diffuse invasion by pleomorphic medium-sized lymphocytes; (E) lower GI endoscopic view of the cecum shows many aphthoid colitis-like lesions; (F) histological analysis of (E) shows diffuse invasion by pleomorphic large atypical lymphocytes with irregular nuclei. Hematoxylin eosin stain, (B), (D), (F): ×400.

frequent in acute-type lesions (9 of 23, 39%) compared with lymphoma-type lesions (1 of 38, 3%; P=0.0007). The endoscopic and pathological features of gastropathy- and proctocolitis-like lesions in acute-type ATLL are shown in *Figure 2*.

The endoscopic features of 40 gastric lesions are summarized in *Table 3*. The tumor-forming type was found in 23 of 29 lymphoma-type ATLL lesions (79%) and 6 of 11 acute-type lesions (55%). Even in gastric lesions, the superficial spreading-type ATLL was significantly more frequent in 5 of 11 acute-type ATLL lesions (45%) compared with 2 of 29 lymphoma-type lesions (7%; P=0.016). Gastropathy, including gastritis- and gastric erosion-like lesions, were present in 2 of 11 lesions (18%) in gastric acute-type ATLL. The endoscopic features of 21 intestinal lesions are summarized in *Table 4*. The tumor-forming type was present in 6 of 9 lymphoma-type ATLL lesions (67%) and in 4 of 12 acute-type lesions (33%). The superficial spreading-type lesion was present in 7 of 12 acute-type lesions (58%) and in 1 of 9 lymphoma-type lesions (11%). All three enteropathy-like lesions were present in the superficial spreading-type of acute-type ATLL. Proctocolitis-like lesions were present in four superficial spreading lesions of the acute-type and one of the lymphoma-type lesions.

Relationship between endoscopic features and tumor cell size

Tumor-forming-type tumors were composed of predominantly pleomorphic or anaplastic large cell lymphoma in 23 of 39 lesions (59%), which was significantly more frequent compared with that of the superficial spreading-type lesions (2 of 15, 13%; P=0.007). The superficial spreading-type tumors were mainly composed of pleomorphic medium-sized cell lymphoma in 13 of 15 lesions (87%), which was significantly more frequent

Table 3 Endoscopic features of 40 gastric adult T-cell leukemia/lymphoma (ATLL) lesions

Endoscopic features	Lymphoma type (n=29)	Acute type (n=11)	Total (n=40)	P value
Tumor forming type, n [%]	23 [79]	6 [55]	29 [73]	NS
Solitary tumor forming type	12 [41]	2 [18]	14 [35]	NS
Multiple tumor forming type	11 [38]	4 [36]	15 [38]	NS
Superficial spreading type, n [%]	2 [7]	5 [45]	7 [18]	0.016
Early gastric cancer-like	2 [7]	3 [27]	6 [15]	NS
Gastropathy-like	0 [0]	2 [18]	1 [3]	NS
Mucosal thickening type, n [%]	4 [14]	0 [0]	4 [10]	NS

NS, not significant.

Table 4 Endoscopic features of 21 intestinal adult T-cell leukemia/lymphoma (ATLL) lesions

Endoscopic features	Lymphoma type (n=9)	Acute type (n=12)	Total (n=21)	P value
Tumor forming type, n [%]	6 [67]	4 [33]	10 [48]	NS
Solitary tumor forming type	5 [56]	2 [17]	7 [33]	NS
Multiple tumor forming type	1 [11]	2 [17]	3 [14]	NS
Superficial spreading type, n [%]	1 [11]	7 [58]	8 [38]	NS
Enteropathy-like	0	3 [25]	3 [14]	NS
Proctocolitis-like	1 [11]	4 [33]	5 [24]	NS
Mucosal thickening type, n [%]	2 [22]	1 [8]	3 [14]	NS

NS, not significant.

compared with 16 of 39 tumor-forming-type tumors (41%; P=0.007). Mucosal thickening-type tumors were mainly composed of pleomorphic medium-sized cell lymphoma in six of seven lesions (86%).

Analysis of patient prognosis

Lymphoma and acute-type ATLL patients showed a progressive clinical course, and 50% OS was observed at 11 and 10 months, respectively. The 50% OS of six patients with primary GI ATLL in the early stages (I and II1) was over 110 months, and these patients showed a significantly better prognosis than that of 48 advanced patients at other stages (P=0.017; *Figure 3A*). Twenty patients having solitary tumor-forming-type ATLL lesions showed significantly better OS compared with 17 multiple tumor-forming-type (P=0.015) and five mucosal-thickening-type lesions (P=0.04), but not 11 superficial spreading-type lesions (P=0.38; *Figure 3B*). Sites involved in the GI tract showed no prognostic factors in any of the ATLL patients. Histologically, 26 patients with pleomorphic or anaplastic large cell ATLL showed a significantly better prognosis compared with 28 patients with pleomorphic medium-sized ATLL (P=0.034).

Discussion

The incidence of ATLL invasion in the stomach and intestine was 29% and 25%, respectively, in an autopsy study (17). In the current study, ATLL invasion of the stomach, small intestine, and colon was found in 66%, 18%, and 16% of patients, respectively. Gastric invasion by ATLL was significantly higher than those of other types of primary GI T-cell lymphoma and $CD56^+$ and EBV^+ NK/T-cell lymphoma, which mainly involved the small intestine and colon (7,18). Additionally, gastric ATLL lesions were significantly more frequent in lymphoma-type lesions (29 of 38 lesions, 76%) compared with acute-type lesions (11 of 23, 48%; P=0.023). Small intestinal and colonic ATLL

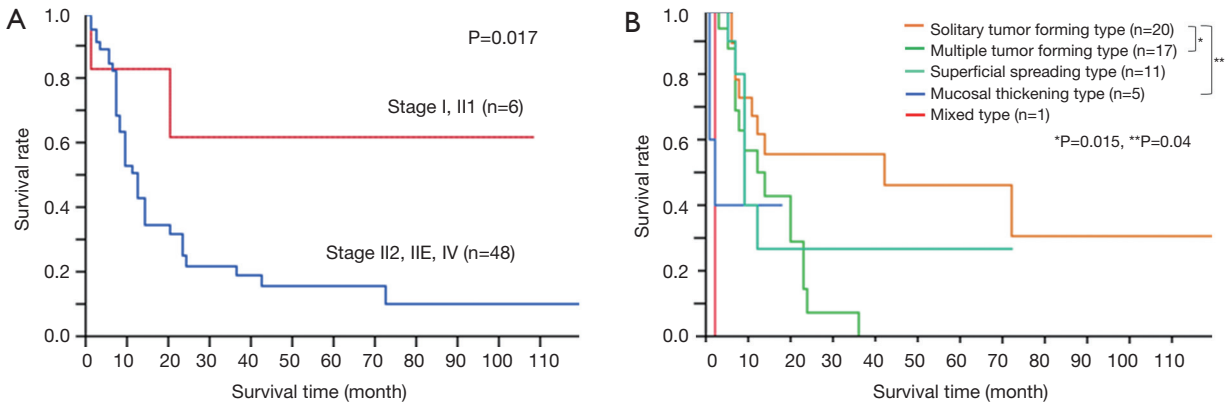

Figure 3 Survival curves for 54 patients with primary gastrointestinal adult T-cell leukemia/lymphoma (ATLL), which are stratified based on early and advanced clinical stages and five endoscopic features. (A) Six ATLL patients at stage I and II1 show significantly better OS compared with the 48 patients at stages II2, IIE, and IV (P=0.017); (B) 20 ATLL patients with solitary tumor-forming-type lesions had significantly better OS compared with 17 patients with multiple tumor-forming-type (P=0.015) and 5 patients mucosal thickening-type lesions (P=0.04), but not compared with 11 patients with superficial spreading-type lesions (P=0.38).

lesions were significantly greater in acute-type lesions (12 of 23 lesions, 52%) compared with lymphoma-type lesions (9 of 38, 24%; P=0.023). We demonstrated that ATLL significantly involved the stomach and leukemic behavior had a large influence on the GI sites that were involved.

Iwashita *et al.* reported 40 GI tract lesions from 27 ATLL patients, which were endoscopically classified into the solitary tumor-forming type (2 lesions, 5%), multiple elevated type (15, 37.5%), superficial spreading type (9, 22.5%), mucosal thickening type (4, 10%), and mixed type (10, 25%) (13). Among these, multiple elevated-type lesions were mostly seen in lymphoma-type patients (9 of 19 lesions, 47%). Additionally, superficial spreading-type lesions were frequently found in acute-type ATLL patients (7 of 21 lesions, 33%). Utsunomiya *et al.* also reported an endoscopic study of five acute-type ATLL patients showing diffusely spreading gastric and colonic mucosal lesions with erosion, multiple small nodules, and mucosal thickening (11). In the current study, the tumor-forming type was mainly present in lymphoma-type ATLL lesions (29 of 38 lesions, 76%) and the superficial spreading type was mainly found in acute-type lesions (12 of 23, 52%), both of which were statistically significant (P=0.0096, P=0.0003). Additionally, 23 of 39 tumor-forming type-lesions (59%) were composed of pleomorphic or anaplastic large cell lymphoma, and 13 of 15 superficial spreading-type lesions (87%) were composed of pleomorphic medium-sized cells (P=0.007). In 20 patients with HTLV-1 negative primary gastric T-cell lymphoma, Kamamoto *et al.* demonstrated that 13 large cell lymphoma patients (65%) mainly showed tumor formation by lymphoma cells with frequent CD30 expression, and two of the remaining seven medium-sized lymphomas showed a superficial spreading tumor with enteropathy-like features (19). This suggested that endoscopic types of the GI ATLL were largely influenced by leukemic behavior and the ATLL tumor cell size.

Over 80% of MEITL patients showed the intramucosal spreading of lymphoma cells with preserved glands and neoplastic $CD103^+$ and $CD8^+$ IELs in and beside the main tumors (20). CD103 is also expressed on subsets of $CD4^+$ regulatory T-cells in the peripheral blood and dendritic cells of the GI tract (21). The frequent expression of CD103 and histological features of GI ATLL suggested that ATLL had the characteristics of T-IELs or mucosal T-cells or their neoplasias (14). The endoscopic features of MEITL were reported as edematous mucosa with mosaic and diffuse thickening patterns and shallow ulceration as well as ulcerative tumors in the small intestine (22). Additionally, EATL also shows mucosal flattening, thickening, and ulcerating lesions as well as multiple tumor formations (23). In the current study, superficial spreading lesions were significantly more frequent in 12 of 23 acute-type ATLL lesions (52%) compared with three of 38 lymphoma-type lesions (8%; P=0.0003). We found distinct features of gastropathy-like lesions in two of 11 gastric acute-type ATLL (18%) and enteropathy-like lesions in three of 12 intestinal acute-type lesions (25%), which had similar endoscopic and histological features as those of MEITL and

EATL; these are rarely reported in ATLL (24). Additionally, we identified features of proctocolitis-like lesions in four of 12 intestinal acute-type ATLL lesions (33%), which were rarely seen even in MEITL patients (25). Endoscopically, it is necessary to recognize gastropathy-, enteropathy-, and proctocolitis-like lesions in GI ATLL.

The current study reported six lymphoma-type patients (11%) who were thought to have primary GI ATLL. Tanaka *et al.* summarized 15 previously reported patients with primary gastric ATLL in clinical stages I and II1 (26). Among these patients, eight showed an aggressive clinical course and three showed long-term remission from 50 to 132 months. In the current study, six patients with primary GI ATLL showed a significantly better prognosis compared with those of 48 patients in more advanced stages of the disease (P=0.017). Further study is necessary to clarify the clinicopathological findings and appropriate treatments for patients with primary GI ATLL.

Endoscopically, ATLL patients with solitary tumor-forming-type lesions showed a significantly better OS compared with those with multiple tumor-forming- and mucosal thickening-types (P=0.015, P=0.04). Sakata *et al.* only demonstrated that five acute-type ATLL patients with gastric lesions had a significantly worse prognosis compared with 15 acute-type ATLL patients without gastric involvement (P<0.05) (12). In 73 primary gastric DLBCL patients, lesions that were more than 30 mm in diameter and more than 11 mm deep, as assessed endoscopically, were significantly worse prognostic factors (P=0.01 and 0.039, respectively), as were patients diagnosed at clinical stages greater than IIE and those with multiple gastric lesions (P<0.01 and 0.034, respectively) (27). Endoscopic tumor growth patterns indicated no prognostic factors even in patients with primary GI T/NK-cell lymphoma and DLBCL (7,18,27). We demonstrated that solitary tumor-forming-type lesions were mainly found in lymphoma-type ATLL patients and patients with this type of lesion had a better prognosis compared with the other endoscopic lesion types.

Self-limited and indolent T/NK-cell lymphoproliferative disorders (LPDs) of the GI tract are rarely reported. Matnani *et al.* summarized that indolent CD4-positive, CD8-positive and both negative T-cell LPDs of the GI tract showed various endoscopic features including nodules, polypoid lesions, fissures, superficial ulcers, erosions, and normal mucosa (28). Superficial spreading-type lesions including gastroenteropathy-like lesions often found in the indolent T/NK-cell LPDs patients were also characteristic in GI ATLL. We found increased reactive T-IELs in three of 22 non-neoplastic ATLL lesions (14%), which are frequently found in celiac disease and non-neoplastic mucosa of EATL (3). To detect the prodromal and early ATLL lesions, it is necessary to examine how persistent HTLV-1 infection influences T-IELs and mucosal lymphocytes in the GI tract.

Conclusions

GI T/NK-cell lymphoma frequently involves the small intestine and colon. ATLL predominantly involves the stomach. Leukemic behavior of ATLL had a large influence on tumor location and endoscopic features of GI tract lesions. Gastroenteropathy- and proctocolitis-like lesions were additional characteristic features of the GI ATLL lesions. Patients with primary GI ATLL in the early clinical stages were occasionally found and showed a rather prolonged clinical course. Additionally, solitary tumor-forming-type lesions and large tumor cells were better prognostic factors. It is important to recognize the patient's clinical stage and endoscopic features of GI ATLL.

Acknowledgments

We are grateful to Tomoko Fukushige and Tomomi Okabe for their excellent technical assistance. We thank Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Funding: Supported in part by a Grant-in-Aid for Scientific Research © (No.17K08732) from the Ministry of Education, Science and Culture of Japan.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by institutional review board of Fukuoka University Hospital (No. 14-8-08) and all consent requirement was met based on the institutional policy for retrospective study.

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Cite this article as: Ishibashi H, Nimura S, Kayashima Y, Takamatsu Y, Iwasaki H, Harada N, Momosaki S, Takedatsu H, Sakisaka S, Takeshita M. Endoscopic and clinicopathological characteristics of gastrointestinal adult T-cell leukemia/lymphoma. J Gastrointest Oncol 2019;10(4):723-733. doi: 10.21037/jgo.2019.03.03

