

Clinical characteristics of adult T-cell leukemia/lymphoma infiltration in the gastrointestinal tract

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Abstract

Background: Adult T-cell leukemia/lymphoma (ATLL) is a peripheral T-cell malignancy caused by human T-cell lymphotropic virus type 1 (HTLV-1). The clinical course of ATLL is very heterogeneous, and many organs, including the gastrointestinal (GI) tract, can be involved. However, there are few detailed reports on ATLL infiltration in the GI tract. We investigated the clinical characteristics of ATLL infiltration in the GI tract.

Methods: This retrospective observational single center study included 40 consecutive ATLL patients who underwent GI endoscopy. The patients' demographic and clinical characteristics and endoscopic findings were analyzed retrospectively. Patients with ATLL who were diagnosed via histological examination, were divided into two groups based on GI tract infiltration.

Results: Multivariate analysis revealed that the absence of skin lesions was significantly associated with GI infiltration ($P < 0.05$). Furthermore, the infiltration group tended to have similar macroscopic lesions in the upper and lower GI tracts.

Conclusions: The absence of skin lesions and characteristic endoscopic findings may aid in detecting ATLL infiltration in the GI tract.

Background

Adult T-cell leukemia/lymphoma (ATLL) is a peripheral T-cell malignancy caused by human T-cell lymphotropic virus type 1 (HTLV-1) [1–3]. HTLV-1 infection is usually transmitted vertically, and ATLL develops over the course of several years. The clinical course of ATLL is very heterogeneous, and many organs, including the gastrointestinal (GI) tract, can be involved. However, there are few detailed reports on ATLL infiltration into the GI tract. This study investigates the characteristics of ATLL infiltration in the GI tract. The current retrospective study was conducted to evaluate whether ATLL infiltration in the GI tract had related to the skin lesion.

Methods

Patients and study design

In this retrospective observational study, the demographic and clinical data of 40 consecutive ATLL patients who underwent GI endoscopy between April 1, 2009 and December 31, 2015 at the University of Miyazaki Hospital were analyzed. ATLL was diagnosed according to the Japan Clinical Oncology Group-Lymphoma Study Group criteria (Shinoyama criteria) [4] and classified as four clinical subtypes: acute, lymphoma, chronic, and smoldering. ATLL diagnoses were made based on anti-HTLV-1 positivity in sera and the presence of malignant mature T-cells.

The study included patients who performed upper GI endoscopy for ATLL. Exclusion criteria included age less than 20 years, a performance status value greater than 4, mental disability, contrast medium allergy, severe heart disease (New York Heart Association class III or IV heart failure), severe pulmonary disease (peripheral oxygen saturation < 90%), actual or possible pregnancy, women wishing to become pregnant, nursing mothers, and refusal to provide informed consent.

All 40 patients who provided consent in this study underwent upper GI endoscopy, while 29 patients underwent lower GI endoscopy. Macroscopic GI findings were classified as follows: diffuse type, tumor-forming type, and giant-fold type, as previously described [5]. Endoscopic examinations were performed using GI endoscopes that emitted white light. However, five patients had stable disease activity. If ATLL infiltrated their GI tracts, magnifying endoscopes (GIF-Q240Z, H260Z, PCF-Q260AZI, CF-H260AZI, Olympus, Tokyo, Japan) were used instead. IEE findings were assessed by one specialist (TM).

This study was approved by the Research Ethics Committee of the Faculty of Medicine, University of Miyazaki (IRB approval number: O-0003) and performed in accordance with the provisions of the Declaration of Helsinki (as revised in Fortaleza, Brazil, October 2013).

Statistical analysis

Patients were divided into the infiltration and non-infiltration groups based on whether ATLL infiltrated the GI tract. Descriptive statistics such as mean, odds ratios (OR) and 95% confidence intervals (CI) were calculated. Inferential statistical methods such as Chi-squared test and multivariate logistic regression were also applied to assess potential associations between infiltration and non-infiltration, respectively. A P-value below 0.05 was considered as the statistical significance level through bivariate analysis and $P < 0.1$ for selecting the variables to introduce into the multivariate regression model. All analyses were performed using STATA/SE 14.2 (Stata Corp., College Station, TX, USA).

Results

Patients' clinical characteristics are summarized in Table 1. Positive findings, such as diffuse type, tumor-forming type, and giant-fold type [5] were observed in 21 of the 40 patients who underwent upper GI endoscopy and 6 of the 29 of the 40 total patients who underwent lower GI endoscopy (Table 2). Of these 6 patients of the 29 patients, 4 had both gastric and colonic lesions and 2 only had colonic lesions (Table 3). Upper and lower GI endoscopic findings included duplicative cases. Twenty-two patients of the 40 total patients revealed some kind of endoscopic findings. We observed candida esophagitis in 5 patients, diffuse gastric ulcers in 11 patients, gastric tumor-forming lesions in 3 patients, diffuse gastric fold lesions in 3 patients, diffuse duodenal ulcers in 1 patient, diffuse colonic ulcers in 2 patients, colonic tumor-forming lesions in 2 patients, and diffuse colonic fold lesions in 2 patients. Biopsy examinations were subsequently performed for histological diagnosis. Of the 22 patients of the 40 total patients who had upper/lower GI tract endoscopic findings, 12 were diagnosed with ATLL infiltration in the GI tract via histological examination (Table 3). Upper GI endoscopy showed findings such as scattered reddish protruding lesions, diffuse ulcerative lesions, and localized/diffuse areas of coarse mucosal granularity

(Fig. 1,2,3). Image-enhanced endoscopy (IEE) showed cases of obscure glandular structures and irregular bifurcated meandering blood vessels (Fig. 4). Lower GI endoscopy showed similar colonic findings to IEE.

Table 1
Characteristics of 40 patients with adult T-cell leukemia/lymphoma

Age, median (range) (years)	67.5 (40–84)
Gender, n/n (male/female)	23/17
Digestive symptoms, n/n (+/-) [†]	11/29
Clinical subtypes of ATLL, n/n/n/n (acute/lymphoma/chronic/smoldering)	23/6/5/6
Superficial lymphadenopathy, n/n (+/-)	26/14
Hepatosplenomegaly, n/n (+/-)	17/23
Skin lesions, n/n (+/-)	26/14
Opportunistic infections, n/n (+/-) [‡]	15/25
[†] Digestive symptoms include nausea, diarrhea, epigastralgia, anorexia, and tarry and bloody stools.	
[‡] Opportunistic infections include herpes zoster, cytomegalovirus infection, pneumonia (mycotic, mycobacterial, pneumocystis), candida esophagitis, and enteritis.	
ATLL, Adult T-cell leukemia/lymphoma; +, positive; -, negative	

Table 2
Proportion of patients with positive findings and adult T-cell leukemia/lymphoma infiltration in the gastrointestinal tract[†]

Examination	Number	Positive findings, % (n/n) [‡]	ATLL infiltration, % (n/n)
Upper GI endoscopy	n = 40	52.5% (21/40)	52.4% (11/21)
Lower GI endoscopy	n = 29	20.7% (6/29)	100% (6/6)
[†] Characteristics of upper and lower GI endoscopic findings include duplicative cases.			
[‡] Positive findings include some kind of endoscopic findings.			
GI, Gastrointestinal; ATLL, Adult T-cell leukemia/lymphoma			

Table 3

Macroscopic findings of 12 patients with adult T-cell leukemia/lymphoma infiltration in the gastrointestinal tract

Case number	Age [†] (years)	Gender	Clinical subtype of ATLL	Macroscopic findings [‡]	
				Stomach	Colon
1	70 s	F	Lymphoma	Diffuse	-
2	60 s	F	Lymphoma	Tumor-forming	Tumor-forming
3	60 s	M	Acute	Tumor-forming	-
4	60 s	M	Acute	Diffuse	Diffuse
5	70 s	M	Acute	Diffuse	Diffuse
6	60 s	M	Acute	Tumor-forming	No findings
7	60 s	F	Acute	Diffuse	-
8	70 s	F	Acute	Giant-fold	Giant-fold
9	70 s	M	Acute	No findings	Giant-fold
10	70 s	F	Acute	Giant-fold	No findings
11	80 s	F	Lymphoma	Diffuse	-
12	60 s	F	Acute	No findings	Tumor-forming
† For the purpose of protecting personal information, we did not specifically state patients' age.					
‡ Macroscopic GI findings were classified as follows: diffuse type, tumor-forming type, and giant-fold type, as previously described [5].					
ATLL, Adult T-cell leukemia/lymphoma; M, Male; F, Female; -, Not performed					

Univariate analysis showed no significant difference between the infiltration and non-infiltration groups in terms of clinical features (Table 4). However, digestive symptoms ($P = 0.045$) and acute-type and lymphoma-type ATLL ($P = 0.053$) were more prevalent in the infiltration group, and skin lesions were significantly more prevalent in the non-infiltration group ($P = 0.009$). Multivariate analysis revealed that ATLL infiltration in the GI tract was significantly associated with the absence of skin lesions ($P = 0.041$) (Table 5).

Table 4

Comparison of patients with and without adult T-cell leukemia/lymphoma infiltration in the gastrointestinal tract

Characteristics	Infiltration group [†]	Non-infiltration group [‡]
	n = 12	n = 28
Age, median (range) (years)	69 (61–82)	66.5 (40–84)
Gender, n/n (male/female)	5/7	18/10
Digestive symptoms, n/n (+/-)	6/6	5/23
Clinical subtypes of ATLL, n/n/n/n (acute/lymphoma/chronic/smoldering)	9/3/0/0	14/3/5/6
Superficial lymphadenopathy, n/n (+/-)	7/5	19/9
Hepatosplenomegaly, n/n (+/-)	6/6	11/17
Skin lesions, n/n (+/-)	4/8	22/6
Opportunistic infections, n/n (+/-)	4/8	11/17
[†] Group of ATLL patients with infiltration in the gastrointestinal tract		
[‡] Group of ATLL patients without infiltration in the gastrointestinal tract		
ATLL, Adult T-cell leukemia/lymphoma		

Table 5

Statistical analysis of patients with and without adult T-cell leukemia/lymphoma infiltration in the gastrointestinal tract

	Univariate analysis			Multivariate analysis		
	Odds ratio	95% CI	P-value	Odds ratio	95% CI	P-value
Age	0.397	0.099–1.583	0.190	-		
Gender	1.026	0.962–1.095	0.436	-		
Digestive symptoms	4.600	1.038–20.381	0.045	2.443	0.423–14.106	0.318
Clinical subtypes of ATLL	0.375	0.139–1.014	0.053	0.468	0.165–1.329	0.154
Superficial lymphadenopathy	0.663	0.164–2.676	0.564	-		
Hepatosplenomegaly	1.545	0.396–6.035	0.531	-		
Skin lesions	0.136	0.030-0.6035	0.009	0.184	0.036–0.934	0.041
Opportunistic infections	0.773	0.187–3.196	0.722	-		
ATLL, Adult T-cell leukemia/lymphoma; CI, Confidence interval						

Discussion

ATLL is a systemic disease with an unfavorable prognosis, and any organ can be impaired by ATLL cell infiltration. We observed endoscopic characteristic findings of ATLL infiltration in the GI tract in 12 patients (30%). Previous studies have also reported a prevalence of about 30% [5, 6]. Moreover, in our study, IEE showed that ATLL infiltration in the GI tract is characterized by obscure glandular structures and irregular bifurcated meandering blood vessels.

Our study presents several novel findings. Firstly, we observed a correlation between gastric and colonic lesions. Nakamura et al. previously proposed that, in GI infiltration, the stomach and intestine would present different ATLL lesion types [7]. However, our study shows similar macroscopic findings in the stomach and colon, even though it is generally accepted that the macroscopic forms of ATLL vary throughout the GI tract. Therefore, endoscopy is necessary for both regions to closely evaluate GI tract infiltration. Secondly, we observed obscure glandular structures and irregular bifurcated meandering blood vessels on the magnified endoscopic images of five ATLL patients with GI tract infiltration. These findings seem characteristic of lymphoproliferative diseases. Nonaka et al. [8] found that magnified endoscopic images from the narrow-band imaging of gastric mucosa-associated lymphoid tissue

lymphoma present obscure glandular structures and irregular blood vessels with minimal changes in size and caliber, despite lymphoma cell infiltration. These common features between B cell lymphoma and ATLL may be caused by lymphoma cell infiltration in stromal tissue, the concomitant destruction of glandular structures, and neoplastic growth. The displacement of superficial vessels caused by proliferating lymphoid tissue may have resulted in the minimal size and caliber changes and meandering observed. Moreover, the destruction of glandular structures may be caused by the initial diffuse permeation of ATLL cells around the muscularis mucosa, followed by the aforementioned changes in blood and lymphatic vessels.

Furthermore, we found that patients with digestive symptoms, and no skin lesions may have a high risk of GI tract infiltration. Our multivariate analysis showed that the absence of skin lesions significantly correlated with ATLL infiltration in the GI tract. Skin lesions have been observed in about half of all ATLL patients [4] and are more prevalent in patients with chronic-type or smoldering-type ATLL than in those with acute-type or lymphoma-type ATLL. Additionally, aggressive ATLL may be more likely to infiltrate the GI tract [9–13]. We recommended physicians be more attentive to the lack of skin lesions in ATLL patients.

Although this study provides useful data regarding ATLL infiltration in the GI tract, it has several limitations related to its observational, non-randomized, single center, and retrospective design. Firstly, selection bias for both groups could not be avoided because there were no assessments of real-time diagnosis performance. Secondly, because ATLL has an unfavorable prognosis, it was difficult to perform GI endoscopy multiple times when investigating GI tract infiltration. Thirdly, IEE findings were assessed by one specialist at a single institution. Fourthly, the number of cases was limited. Fifthly, All ATLL patients did not undergo colonoscopy. More cases are needed to clarify the usefulness of IEE in diagnosing ATLL infiltration in the GI tract.

Conclusions

Physicians should perform GI endoscopy to actively investigate ATLL infiltration in the GI tract and evaluate the endoscopic findings characteristic of lymphoproliferative disease. The absence of skin lesions and the presence of characteristic endoscopic findings may be helpful in detecting ATLL infiltration in the GI tract.

Abbreviations

ATLL, Adult T-cell leukemia/lymphoma; GI, Gastrointestinal; HTLV-1, Human T-cell lymphotropic virus type 1; IEE, Image-enhanced endoscopy; NBI, Narrow band imaging; N.S., Not significant; OR, Odds ratio; CI, Confidence interval

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the Declaration of Helsinki, and the study protocol was reviewed and approved by the Ethics Committees of the Research Ethics Committee of the Faculty of Medicine, University of Miyazaki (Approval number: O-0003). Informed consent was omitted and information of this study was disclosed in the form of opt-out on our hospital website. Information regarding the conduct of the research including the objectives was disclosed and the research subjects were provided an opportunity to refuse inclusion in the research.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author (TM) on reasonable request.

Competing interests

The authors declare no conflicts of interest for this article.

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Authors' contributions

YK1 corresponding to Yoko Kubuki. YK2 corresponding to Yoshimasa Kubota. YA1 corresponding to Yutaka Akiyama. YA2 corresponding to Yasuji Arimura. HK1 corresponding to Hiroshi Kawakami. HK2 corresponding to Hiroaki Kataoka.

TM, HK1 and TK contributed equally to this work.

TM, HK1, TK, SY, YT, TH, YK1, KY, YA1, YK2, HK2, and KS conducted the study. TM and YS performed endoscopy. TM, TK, TH and YK1 collected the data. TM assessed image enhanced endoscopic findings. TM, HK1, and YA2 interpreted the data. TM, HK1, and YA2 analyzed the data. KY, YA1, and HK2 performed the histological examination. TM, HK1, and KS drafted the manuscript. All authors read and approved the final draft.

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Figures



Figure 1

Macroscopic gastrointestinal findings (1a) A 60s woman underwent endoscopy for screening purposes. Her upper gastrointestinal (GI) endoscopy shows scattered reddish mucosal protrusions on the greater curvature of the gastric body. (1b) Colonoscopy image shows sporadic protrusions.



Figure 2

Macroscopic gastrointestinal findings (2a) A 70s man underwent endoscopy due to a tarry stool. His upper GI endoscopy shows diffusely ulcerative mucosa on the anterior wall of the gastric body. (2b) Colonoscopy image shows sporadic ulceration.



Figure 3

Macroscopic gastrointestinal findings (3a) A 70s woman underwent endoscopy due to diarrhea. Her esophagogastroduodenoscopy shows diffuse areas of coarse mucosal granularity on the greater curvature of the gastric body. (3b) Colonoscopy image shows sporadic diffuse granularity.



Figure 4

Magnified endoscopic images on Image-enhanced endoscopy. (4a) A 70s man underwent endoscopy due to epigastralgia and diarrhea. His colonoscopy shows diffuse areas of coarse mucosal granularity. (4b) Chromoendoscopy with indigo carmine clearly shows coarse mucosal granularity. (4c) Magnified endoscopic examination with narrow-band imaging (NBI) reveals obscure glandular structures. (4d) Magnified endoscopic examination with NBI reveals irregular bifurcated meandering blood vessels.