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Original Article

Incidence of upper digestive tract inflammation in children with acute lymphoblastic leukemia at diagnosis

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Abstract: Inflammatory lesions in upper digestive tract are common adversary events in children with acute lymphoblastic leukemia (ALL). However, when these lesions initiate is still not clear. In this study, we retrospectively analyzed the endoscopic detection results of 129 children who suffered from ALL at diagnosis. 107 (82%) patients were found with gastrointestinal inflammation, of which 101 patients had lesions in the stomach, 11 had lesions in the esophagus and 51 had lesions in the duodenal bulb. Only 2 patients were found with helicobacter pylori infection, and 1 patient was found with a mycotic infection in the esophagus. We demonstrate that most patients with ALL have gastrointestinal inflammation at the diagnosis of the basic disease, and in contrast to adult patients in China, these inflammatory lesions were mostly not caused by HP infection.

Keywords: Acute lymphoblastic leukemia, gastrointestinal inflammation, endoscope, histochemical staining, helicobacter pylori

Introduction

Acute lymphoblastic leukemia (ALL), which accounts for more than 80% of acute leukemia cases in children and young adolescents [1], is the most common malignancy that occurs in these age groups [2]. Since the development of chemotherapy for pediatric ALL over the decades, over 80% of children who suffer from ALL can now be cured with multidrug chemotherapeutic regimens [1]. In contrast to this dramatic progress in efficacy, the toxicity of the chemo drugs causes various adverse events which contribute to the most common reasons for treatment interruption or discontinuation [3-5] and thus lead to a poor prognosis of leukemic children [6]. Moreover, evidence suggests that the toxicity induced by the chemo agents could negatively influence the quality of life and the long term survival of the children who suffered from ALL [7, 8].

Gastrointestinal lesions were common in patients suffering from leukemia. Previous studies [9] had elucidated that adverse gastrointestinal events could be induced during chemotherapy. During the induction of therapy for children with ALL, the application of glucocorticoid (GC) [10] and daunorubicin (DNR) [11] could induce adverse gastrointestinal events. Another cause of gastrointestinal lesions reported in patients with leukemia was the infiltration of leukemic cells, cases that have been reported in patients with adult T-cell lymphoblastic leukemia (ATL) [12] and acute myeloid leukemia (AML) [13] and late relapse ALL [14], but there are few studies about the initiation of these lesions.

To evaluate the incidence of upper gastrointestinal tract lesions in children suffering from ALL at diagnosis, we retrospectively analyzed endoscopic detections in the upper digestive tract from the esophagus to the duodenum bulb, and the staining of biopsy tissues results of 129 patients who suffered from ALL, and statistically analyzed the initiation ratio of upper digestive tract lesions that occurred at diagnosis.

Table 1. Characteristics and clinical manifestations of recruited ALL patients

Characteristics	Cases	Percentage (%)
Gender	129	
Male	84	65
Female	45	35
Age (years)	129	
<10	107	83
≥10	22	17
Type of ALL	129	
B-ALL	116	90
T-ALL	13	10
Morphology of ALL	129	
L1	47	36
L2	75	58
L3	7	6
Immuno-phenotype of B-ALL	116	
Pro-B	2	2
C-B	81	70
Pre-B	33	28
Risk stratification	129	
Standard risk	64	50
Intermediate risk	33	26
High risk	32	24

Table 2. The sites of lesions in upper digestive tract

Position	Cases	Percentage (%)
Overall positions	129	
Normal	22	18
With lesions	107	82
Esophagus	129	
Normal	118	91
With lesions	11	9
Stomach	129	
Normal	28	22
With lesions	101	78
Duodenal bulb	129	
Normal	78	60
With lesions	51	40

Patients and methods

Patients

A total of 129 patients under the age of 18 with newly diagnosed ALL who were hospitalized in the Children's Hospital of Chongqing Medical University (CHCMU) from may, 2013 to november, 2014 were recruited for this study. Patients were excluded if they had gastric or duodenal ulceration, had prior gastric surgery, or had taken a proton pump inhibitor or antibiotics within the previous month. This study was approved by the research ethics commission of CHCMU, and informed consents were obtained from all patients or their guardians, in accordance with the declaration of Helsinki. The diagnosis of ALL was performed using a standard French-American-British (FAB) morphological analysis [15], and the morphology-immunology-cytogenetics-molecular biology (MICM) criteria from the who classification of tumors of hematopoietic and lymphoid tissues in 2008 [16], and the immunological phenotype was determined for each patient.

Detection and evaluation of digestive tract lesions

Endoscopy detection was carried out for each patient in this study after the diagnosis of leukemia and before the glucocorticoid was applied. Endoscopy detections were carried out by the clinicians from the Gastroenterology Division of Children's Hospital of Chongqing Medical University (CHCMU), applying olympus CV240 video endoscopy (olympus Inc., Shinjuku-ku, Tokyo, Japan), and the images were obtained from the esophagus, stomach and duodenum when lesions on the mucosa were observed. The detection and diagnosis of lesions in upper digestive tract were determined by experienced doctors from the gastroenterology division through the careful examination of the endoscopic images.

The severity of inflammation in the stomach and duodenum were determined by histochemical staining with hematoxylin and eosin in the tissue obtained through biopsy. Biopsies were taken using 2.2 mm Radial Jaw® biopsy forceps. Biopsy tissues of patients with the endoscopic appearance of duodenitis or gastritis were taken from visually abnormal mucosa. The tissues were fixed in 4% buffered formalin and processed for paraffin embedment. Sections were routinely stained with hematoxylin-eosin (H&E) using the standard protocol, and the stain pictures were observed and photographed using a Leica® DM1000 microsystems microscope (Leica Inc., Wetzlar, Germany).

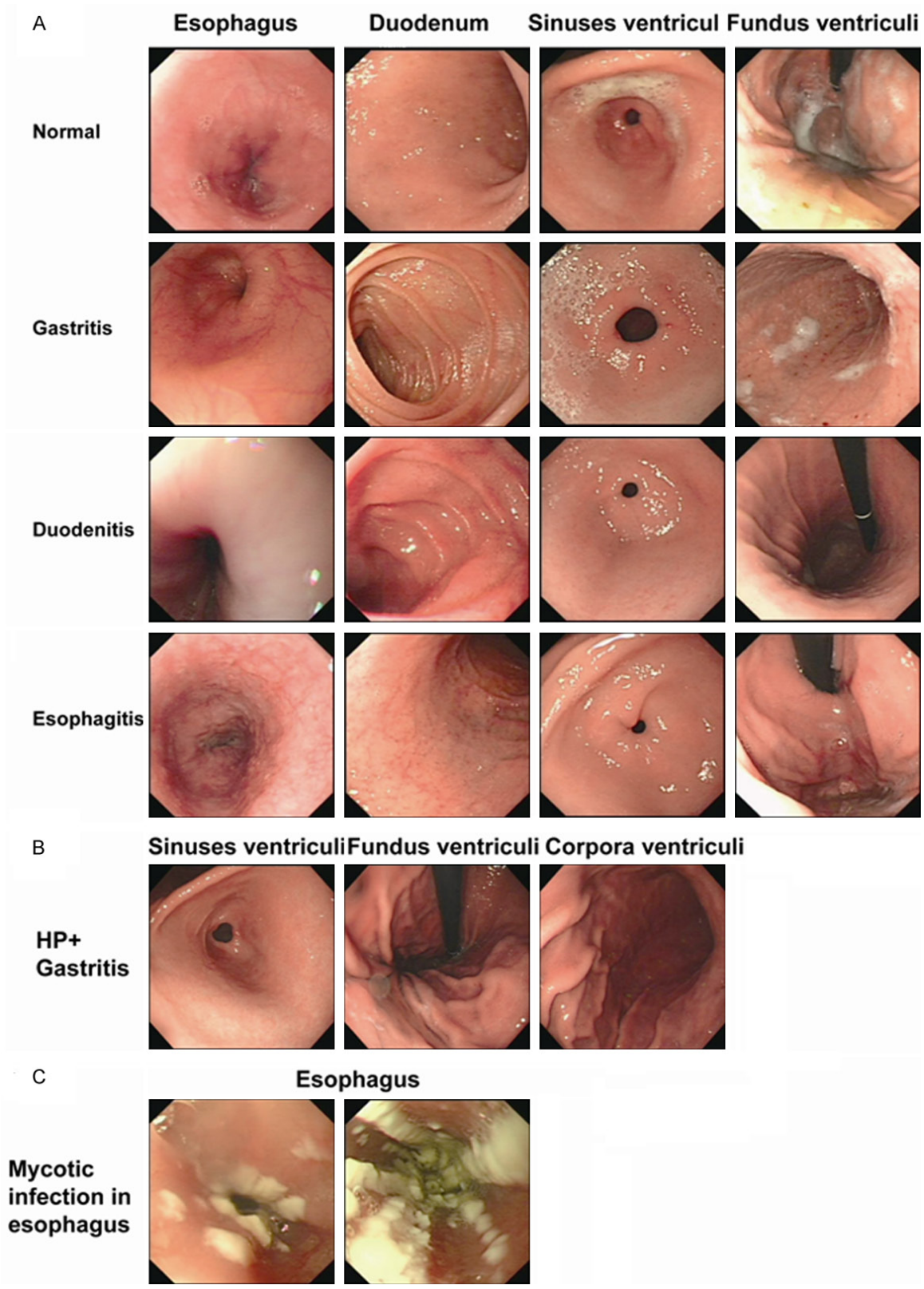

Figure 1. Endoscopic graphs of the esophagus, stomach and duodenum bulb of children with ALL. A. The endoscopic graphs of children with ALL at diagnosis. Four patients respectively with typical normal (Row 1), gastritis (Row 2), duodenitis (Row 3) and esophagitis (Row 4) in the upper digestive tract mucosa were shown. Four graphs obtained from esophagus (panel 1 "Esophagus"), duodenal bulb (panel 2 "Duodenum"), antrum (panel 3 "Sinuses ventriculi") and fundus (panel 4 "Fundus ventriculi") were shown for each patient. Hyperemia and edema of the mu-

cosa and a fresh bleeding point could be seen in the mucosa of the inflammation sites. B. The endoscopic graphs of a patient with gastritis caused by HP infection. The endoscopic graphs obtained from antrum (panel 1 "Sinuses ventriculi"), fundus (panel 2 "Fundus ventriculi") and corpora ventriculi (panel 3 "Corpora ventriculi") of a child with HP infection related gastritis are shown. Roughness, hyperemia and edema of gastric mucosa can be seen in the mucosa of the stomachs; the coarse-grained protrusion could be seen in antrum; and the HP infection was determined by ^{14}Carbon-urea breath test. C. The endoscopic graphs of the patient with mycotic infection esophagitis are shown. The graphs were obtained from middle (left panel) and inferior (right panel) segments of the esophagus. Longitudinally moss-like covers could be seen in the graphs of the esophagus.

^{14}Carbon-urea breath tests were used to diagnosis Helicobacter pylori (HP) infection. Tissue cultures were done to determine the bacteria and fungi which were infected in the lesions. All these experimental examinations were carried out by the Clinical Laboratory Department of CHCMU, and the results were analyzed by experienced pathologists.

Statistics

Statistical analyses were performed using the IBM SPSS statistics software version 19.0 (IBM Corporation, Armonk, NY, USA). The data from patients were presented as medians (range).

Results

Patients characteristics

All 129 patients in this study were diagnosed with acute lymphoblastic leukemia according to WHO MICM criteria. Data from all patients at diagnosis is shown in **Table 1**. The median age of patients was 64 months, with a range from 18 months to 193 months. Among all the patients, there were 45 female and 84 male patients, 116 patients suffered from B-ALL and the others suffered from T-ALL, depending on the immunological features. According to the morphological detection evidence, the all cases were divided into three groups: 47 cases (36%) with L1-ALL, 75 cases (58%) with L2-ALL and 7 cases (6%) with L3-ALL. Immuno-phenotypic detection suggests that among all the 116 patients who suffered from B-ALL, most had the common-B ALL (81/116), less common was pre-B ALL (33/116), and only 2 cases were diagnosed as pro-B type.

Followed the risk stratification criteria of the CCLG-2008ALL protocol, all the patients enrolled in this study were divided into three risk groups at diagnosis (**Table 1**): standard risk (64/129, 50%), intermediate risk (33/129, 26%) and high risk (32/129, 24%).

Upper digestive tract lesions were found in most patients suffered from ALL at diagnosis

Endoscopic detection for the lesions in the esophagus, stomach and duodenal bulb was carried out for each patient after the diagnosis of leukemia, and the occurrence and sites of inflammatory lesions were also recorded, and all these data are shown in table II. Among all the 129 patients, 107 patients (82%) were found to have inflammatory lesions in the upper digestive tract. Esophagitis was found in 11 patients (9%), gastritis was found in 101 patients (78%), and the duodenitis was found in 51 patients (40%). Only 22 patients were found with no lesions in the upper digestive tract at diagnosis.

The stomach alone (56 cases) and the stomach combined with the duodenal bulb (35 cases) were the more common lesion sites of lesions in ALL children at diagnosis. The duodenal bulb alone (5 cases), and the duodenal bulb combined with the esophagus (1 case), and the stomach, esophagus and duodenal bulb together (10 cases) were less common lesion sites (**Table 2**).

All patients were given a ^{14}Carbon-urea breath test to detect the infection of Helicobacter pylori (HP), but only 2 patients were found positive in these tests. One patient was found with a fungal infection from the tissue culture of the lesion site.

Inflammatory lesions in children with ALL at diagnosis

The graphs of mucosa lesions detected by the gastric endoscope (**Figure 1A**) showed the typical manifestations of esophagitis, gastritis, and duodenitis in the children who suffered from all at diagnosis. Graphs were obtained from the inferior segment of the esophagus, duodenum bulb, gastric antrum (sinuses ventriculi) and stomach fundus (fundus ventriculi); the graphs obtained from patients with a normal appear-

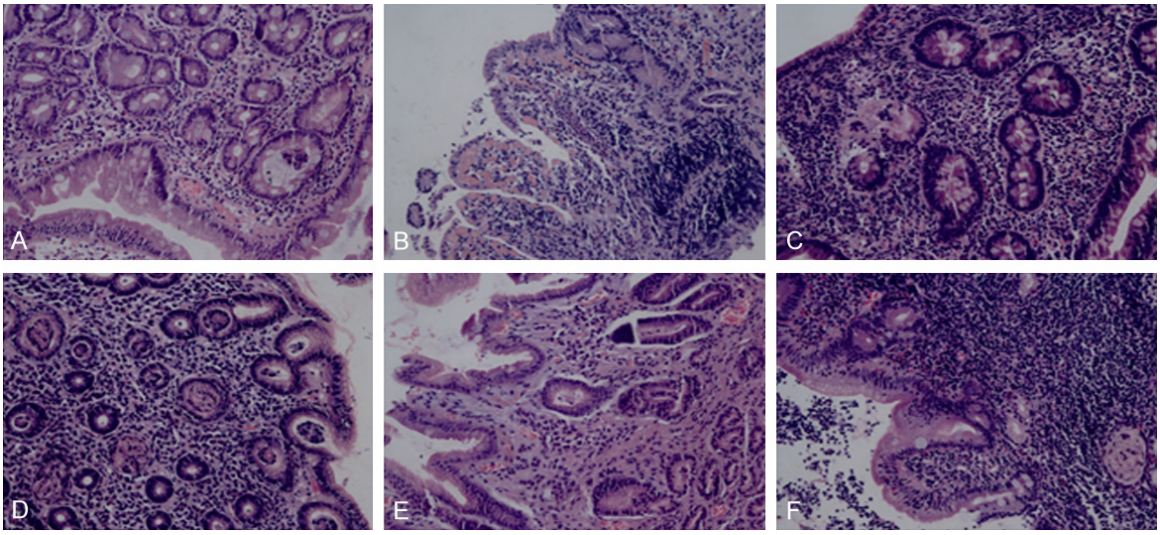

Figure 2. Histochemical staining of the gastritis and duodenitis biopsy tissue. A-C. The graphs of hematoxylin-eosin staining of the gastritis biopsy tissue are shown. The graphs were obtained from three patients with gastritis. The infiltration of a large number of immune cells can be seen in the graphs. D-F. The graphs of hematoxylin-eosin staining of duodenitis biopsy tissue are shown. The graphs were obtained from three patients with duodenitis. The infiltration of a large number of immune cells can be seen in the graphs.

ing digestive tract were used as controls (Normal). Endoscopic graphs obtained from sinuses ventriculi, fundus ventriculi and corpora ventriculi of patient with HP positive gastritis were shown in **Figure 1B**, asperous gastric mucosa, hyperemia and edema at the antrum of stomach. The graphs obtained from the esophagus of the patient with the fungus infection are shown in **Figure 1C**, with a moss-like, white covering seen covering the hyperemia esophagus mucosa. The biopsy of these coverings suggests a possibility of aspergillus infection in the esophagus.

The histochemical staining of the gastric and duodenal tissue from the patients with inflammations is shown in **Figure 2**, where the infiltration of the inflammatory cells is seen in the mucosa of the stomach (A, B, C) and the duodenum (D, E, F).

Discussion

During the last decades, it has been reported that anti-cancer chemotherapy [9-11, 17] and leukemic cell infiltration [12-14, 18, 19] were the main causes of adverse events in the gastrointestinal tract and further caused the interruption of chemotherapy [20]. In our study, we intended to investigate the initiation of inflammatory lesions in the upper digestive tract, and the results of endoscopic detections carried out before chemotherapy suggest that most (82%) of the patients who suffered from all had gastrointestinal inflammations that initiated in this stage, which implied the possibility that most of the adverse events in the upper digestive tract occurred during chemotherapy might not be induced only by chemo agents, but also could be a primary disease of gastrointestinal infection or secondary disease induced by the leukemic cells. Although only two HP infection cases and one aspergillus infection case were found in the present study, we cannot simply exclude the infection factors from most of the patients with upper digestive tract inflammation since the leukemic cells could impair the immunity of patients.

We note the epidemiological conclusion that HP was one of the main causes of gastrointestinal ulceration or gastritis in Chinese adults [21], but in our study, only 2/129 (1.8%) patients suffered from HP infection, which suggests a difference between the children and adult patients.

In summary, the present study has identified that most upper digestive tract lesions occurring in children with all was initiated before chemotherapy and implies that a prophylaxis treatment might be needed for these lesions when the patients undergo chemotherapy, which harms to the gastrointestinal mucosa.

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Disclosure of conflict of interest

None.

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