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*Original Article*

# Gastrointestinal manifestations of leukemia and its distinction from Crohn's disease

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**Abstract:** Aim: Leukemia can present with gastrointestinal symptoms including abdominal pain, diarrhea and anal lesions. These symptoms may lead to a misdiagnosis as Crohn's disease (CD). The aim of this study was to compare the clinical features of leukemia with those of CD. Methods: A retrospective review of 18 patients with leukemia and 54 patients with CD was carried out. Diagnosis of CD or leukemia was based on the standard criteria. Clinical, laboratory, morphological and histological features were compared between the patients with leukemia and CD. Results: Compared with CD patients, intestinal bleeding and thromboembolism were frequent in the patients with leukemia, whereas intestinal obstruction was more common in patients with CD than leukemia. As for laboratory findings, a low percentage of neutrophils and a low platelet count were more prevalent in the leukemia group than in the CD group. Prolonged prothrombin time (PT) increased in leukemia compared to CD patients. Elevated lactate dehydrogenase (LDH) was more common in leukemia than in CD. In addition, computed tomography (CT) and ultrasound examinations showed frequent ileocecal region ulceration, intestinal wall thickening, and intestinal stricture in the patients with CD than in leukemia. Among these parameters, the sensitivity of intestinal obstruction, ileocecal region ulceration and intestinal stricture was as high as 88.9% and the negative predictive value was above 90%. The specificity and accuracy of increased LDH and prolonged PT were high. Conclusion: Our results showed some unique features of leukemia patients with intestinal symptoms. These findings may provide predictive factors in distinguishing leukemia from CD.

**Keywords:** Inflammatory bowel disease, Crohn's disease, leukemia, intestinal disease, clinical research

## Introduction

Leukemia is a group of different hematopoietic forms of myeloproliferative neoplasms. Clinical presentations often include anemia, neutropenia, thrombocytopenia, variable severity of infections, and/or hemorrhagic findings. However, gastrointestinal manifestations including enterocolitis, perirectal sepsis and bleeding can become initial symptoms in some patients with leukemia. These symptoms are similar with Crohn's disease (CD) and can be misdiagnosed. In this retrospective study, we described clinical features of primary gastrointestinal manifestations of leukemia and its distinction from CD to provide a clinical basis for early diagnosis and improved prognosis.

## Materials and methods

This study was approved by the Ethics Committee of Peking Union Medical College Hospital. From June 1975 to July 2014, a total of 18 patients with leukemia admitted to the Gastroenterology Department of Peking Union Medical College Hospital for gastrointestinal manifestations for initial symptoms were enrolled in this study. Immunosuppressant or cytotoxic agent-related leukemia was not included. A computerized randomly selected 54 patients with CD were enrolled in this study. The diagnosis of CD was established according to the ECCO consensus, which included clinical features, endoscopic appearance, and radiological and histopathologic findings. Patients with a previous medication history that could have disturbed the hematologic system were excluded.

SPSS version 16.0 was used for statistical analysis. Continuous variables were tested for the normality assumption using the Kolmogorov-Smirnov test. Normally distributed variables

**Table 1.** Demographic and clinical characteristics

| Characteristics | Leukemia (n=18) | CD (n=54 ) | *P* value |
|---|---|---|---|
| Sex (male:female) ratio | 14:4 | 37:17 | 0.454 |
| Age (range), yr | 42.7±8.2 (16-76) | 37.2±13.6 (13-70) | 0.572 |
| Duration of symptoms, median (range), month | 3 (0.3-48) | 60 (0.5-240) | <0.001 |
| Appendectomy history, n (%) | 2 (11.1) | 15 (27.8) | 0.207 |
| Fever, n (%) | 13 (72.2) | 26 (48.1) | 0.076 |
| Abdominal pain, n (%) | 16 (88.9) | 51 (94.4) | 0.593 |
| Diarrhea, n (%) | 8 (44.4) | 35 (64.8) | 0.127 |
| Weight loss, n (%) | 10 (55.6) | 45 (83.3) | 0.025 |
| Intestinal obstruction, n (%) | 2 (11.1) | 30 (55.6) | 0.001 |
| Intestinal perforation, n (%) | 1 (5.6) | 15 (27.8) | 0.056 |
| Intestinal bleeding, n (%) | 13 (72.2) | 19 (35.2) | 0.006 |
| Thromboembolism, n (%) | 5 (27.8) | 2 (3.7) | 0.01 |
| Perianal lesion, n (%) | 3 (16.7) | 14 (25,9) | 0.533 |
| Arthralgia, n (%) | 2 (11.1) | 10 (18.5) | 0.718 |
| Ascites, n (%) | 2 (11.1) | 10 (18.5) | 0.718 |

**Table 2.** Laboratory findings of patients with leukemia or CD

| Laboratory findings | Leukemia (n=18) | CD (n=54 ) | *P* value |
|---|---|---|---|
| WBC (×10^9/L), median (range) | 8.89 (1.38-135.0) | 6.1 (1.61-36.09) | 0.117 |
| Neutrophils (%) median (range) | 36.05 (0.65-93.0) | 66.8 (6.20-94.1) | 0.001 |
| Hemoglobin (g/dl) (range) | 98.67±31.167 (63-172) | 105.66±29.32 (46-192) | 0.361 |
| Platelet (×10^9/L), median (range) | 111.5 (20-1264) | 310 (23-620) | 0.011 |
| Albumin less than 35 g/L, n (%) | 7 (38.8) | 30 (55.6) | 0.22 |
| ALT abnormality, n (%) | 2 (11.1) | 4 (7.4) | 0.638 |
| Elevated LDH (>250 U/L), n (%) | 6 (33.3) | 2 (3.7) | 0.002 |
| ESR median (range), mm/h | 43 (12-125) | 34 (2-115) | 0.139 |
| hsCRP, median (range), mg/dl | 141 (3-216) | 25.03 (0.24-211.04) | 0.006 |
| Prolonged PT>3 s, n (%) | 8 (44.4) | 5 (9.3) | 0.002 |
| Prolonged APTT>10 s, n (%) | 4 (22.2) | 6 (11.1) | 0.225 |

HsCRP: hypersensitive C-Reactive Protein. LDH: Lactate dehydrogenase. A *P* value of <0.05 was considered significant according to the Mann-Whitney U test. Values which showed a normal distribution were expressed as the mean ± standard deviation.

were described using means and standard deviation (SD). Qualitative parameters were analyzed using the $\chi^2$ test or Fisher's exact test. $P<0.05$ was considered statistically significant. These variables were further analyzed by multiple logistic regression (MLR) statistical analysis, and the regression equation (mathematical model) was established. Confidence intervals and odds ratios of valuable parameters were evaluated. Significant parameters were further analyzed for sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and accuracy in diagnosis of leukemia or CD.

## Results

### *Demographics, clinical characteristics and laboratory tests*

Among the 18 leukemia patients, 10 patients had acute leukemia and 8 had chronic leukemia (5 with CLL and 3 with CML). **Table 1** presents the demographic and clinical characteristics of leukemia and CD patients. No statistically significant difference was found between sex or age in either group. The duration of symptoms was significantly shorter in the leukemia group than in the CD group (median 3 months *vs.* 60 months). Gastrointestinal bleed-

**Table 3.** Radiological and morphological features of patients with leukemia and CD

| Computed tomography/ultrasound/ colonoscopy findings | Leukemia (n=18) | CD (n=54 ) | *P* value |
|---|---|---|---|
| Jejunum and ileum, n (%) | 0 | 7 (13.0) | 0.181 |
| Terminal ileum, n (%) | 3 (16.7) | 7 (13.0) | 0.703 |
| Ileocecal region, n (%) | 2 (11.1) | 37 (68.5) | <0.001 |
| Colon, n (%) | 6 (33.3) | 6 (11.1) | 0.061 |
| Intestinal wall thickening, n (%) | 7 (38.9) | 46 (85.2) | <0.001 |
| Intestinal stricture, n (%) | 2 (11.1) | 42 (77.8) | <0.001 |

**Table 4.** Colonoscopy and histopathology features of patients with leukemia and CD

| Characteristics of ulcer (colonoscopy) | Leukemia (n=9) | CD (n=54 ) | *P* value |
|---|---|---|---|
| Aphthous ulcers | 4 (44.4) | 6 (11.1) | 0.029 |
| Cobble-stone appearance, n (%) | 1 (11.1) | 6 (11.1) | 1 |
| Segmental distribution, n (%) | 2 (22.2) | 37 (68.5) | 0.021 |
| Longitudinal ulcer, n (%) | 0 | 15 (27.8) | 0.1 |
| Ulcerated mass, n (%) | 3 (33.3) | 9 (16.7) | 1 |
| Histopathology of ulcer | | | |
| Fissuring ulcers, n (%) | 0 | 12 (22.2) | 0.187 |
| Deep linear ulcers, n (%) | 1 (11.1) | 9 (16.7) | 0.434 |
| Pseudopolyp, n (%) | 1 (11.1) | 32 (59.3) | <0.001 |
| Transmural inflammation, n (%) | 0 | 29 (53.7) | 0.003 |
| Granulomatous inflammation, n (%) | 0 | 11 (20.4) | 0.339 |

**Table 5.** Multivariate logistic regression analysis of clinical and laboratory features in patients with leukemia and CD

| Variables | β | S.E. | Wald $\chi^2$ | *P* value | OR (95% CI) |
|---|---|---|---|---|---|
| Intestinal obstruction | -1.937 | 0.845 | 5.251 | 0.022 | 0.144 (0.027-0.756) |
| Neutrophils (%) | 0.063 | 0.019 | 11.484 | 0.001 | 1.066 (1.027-1.105) |
| Elevated LDH | 2.223 | 1.004 | 4.901 | 0.027 | 9.232 (1.290-66.058) |
| Prolonged PT | 1.873 | 0.778 | 5.799 | 0.016 | 6.508 (1.417-29.893) |
| Constant | -0.896 | 1.334 | .452 | 0.502 | 0.408 |

ing (72.2% *vs.* 35.2%) and thromboembolism (27.8% *vs* 3.7%) were more common in leukemia patients than in CD patients. In patients with CD, weight loss (CD: 83.3% *vs.* leukemia: 56.6%) and intestinal obstruction (11.1% *vs.* 55.6%) were more frequent than in those with leukemia. The presence of intestinal perforation was common among patients with CD (27.8% *vs.* 5.6%), but there was no statistically significant difference between the two groups. There were no significant differences in fever, abdominal pain, diarrhea or perianal lesions (**Table 1**).

In laboratory tests, platelet count and the percentage of neutrophils was significantly lower in patients with leukemia (**Table 2**). In total, 33.3% of leukemia patients (n=6) had increased level of lactate dehydrogenase (LDH). Among two CD patients (3.7%) with elevated LDH, one had concomitant IgA nephropathy and the other had drug-related hepatitis. After the patient's liver function improved, LDH levels returned to normal. This result suggests a relative specificity of LDH for use in the diagnosis of leukemia. Elevated hypersensitive C-reactive protein (hsCRP) and prolonged prothrombin time (PT) were more frequently observed in leukemia patients than in CD patients (**Table 2**).

*Radiological, endoscopic and histopathological features*

The involvement of ileocecal region lesions was less frequent in patients with leukemia compared to patients with CD (**Table 3**. 11.1% *vs* 68.5%). Intestinal wall thickening and intestinal stricture were common in the CD group. There was no significant difference in small intestine lesions between leukemia and CD (**Table 3**. 0 *vs* 13%, *P*=0.181). Colonoscopy and histopathology tests were carried out in 9 (50%) leukemia patients and in all CD patients. Aphtha ulcers were more frequent in leukemia than in CD (44.4% *vs* 11.1%, *P*=0.029). Segmental distribution, pseudopolyps and transmural inflammation were mostly found in the CD group (**Table 4**).

*Multivariate analysis to differentiate leukemia from CD*

Multivariate binary logistic regression analysis showed that intestinal obstruction, reduced neutrophil percentage, elevated LDH and prolonged PT were valuable for differentiating leu-

**Table 6.** Multivariate logistic regression analysis of radiological features in patients with leukemia and CD

| Variables | β | S.E | Wald $\chi^2$ | *P* value | OR (95% CI) |
|---|---|---|---|---|---|
| Ileocecal region | -3.660 | 1.051 | 12.131 | <0.001 | 0.026 (0.003-0.202) |
| Intestinal stricture | -4.063 | 1.038 | 15.319 | <0.001 | 0.017 (0.002-0.132) |
| Constant | 5.726 | 1.249 | 21.028 | <0.001 | 306.646 |

**Table 7.** Clinical and radiological models of leukemia and Crohn's disease

| Variables | Sensitivity | Specificity | Accuracy | PPV | NPV |
|---|---|---|---|---|---|
| Intestinal obstruction | 0.889 | 0.556 | 0.639 | 0.4 | 0.938 |
| Elevated LDH (>250 U/L) | 0.333 | 0.963 | 0.806 | 0.75 | 0.813 |
| Prolonged PT | 0.444 | 0.907 | 0.792 | 0.615 | 0.831 |
| Ileocecal region | 0.889 | 0.685 | 0.736 | 0.485 | 0.949 |
| Intestinal stricture | 0.889 | 0.778 | 0.806 | 0.571 | 0.955 |

kemia intestinal lesions and CD. A reduced neutrophil percentage (*P*=0.001, OR=1.066, 95% CI=1.027-1.105), elevated LDH (*P*=0.027, OR=9.232, 95% CI=1.290-66.058) and prolonged PT (*P*=0.016, OR=6.508, 95% CI=1.417-29.893) were indicative of a leukemia diagnosis, whereas intestinal obstruction (*P*=0.022, OR=0.144, 95% CI=0.027-0.756) was indicative of a CD diagnosis (**Table 5**). In addition, ileocecal region lesions (*P*<0.001, OR=0.026, 95% CI=0.003-0.202) and intestinal stricture (*P*<0.001, OR=0.017, 95% CI=0.002-0.132) were valuable for defining the diagnosis for CD (**Table 6**).

*Diagnostic models to differentiate leukemia from CD*

The sensitivity, specificity, PPV, NPV and accuracy were tabulated for various parameters that were significant on multivariable binary logistic regression analysis. Elevated LDH and intestinal stricture had an accuracy of 80.6% for predicting leukemia and CD, respectively. Clinical features such as elevated LDH and prolonged PT had high specificity (>90%) but low sensitivity. Intestinal obstruction, ileocecal region lesions and intestinal stricture had high sensitivity and NPV for CD (**Table 7**).

## Discussion

Gastrointestinal manifestations often appear as initial symptoms in leukemia and overlap with CD. The reported incidence of leukemic gastrointestinal manifestations varied significantly. An autopsy study showed 13% of leukemia patients with gastrointestinal involvement [1]. Other reports stated the rate may vary from 23% to 63% in all types of leukemia [2]. These symptoms are important contributory causes of death in a substantial proportion of cases. Some cases have reported an "unusual" initial presentation of the gastrointestinal tract in leukemia. Recognition of clinical features of leukemia and early diagnosis is important for improving prognosis.

The etiology of most leukemic gastrointestinal complications can be classified into the following three groups: Primary invasion by leukemic cells, altered immune state with profound neutropenia from the leukemia itself and from antileukemic drugs, and the direct and indirect gastrointestinal toxic effects of chemotherapy [3]. Leukemia of the bowels may be plaque-like, aphtha or polypoid masses, which may become quite large and ulcerated, leading to intussusception and perforation. Some cases have reported the "unusual" presentation of gastrointestinal granulocytic sarcoma (GS) before the onset of leukemia. A CT scan of the abdomen and pelvis may reveal a marked thickening of the bowel. Colonoscopy may reveal numerous aphthae [4]. As a result, a misdiagnosis is frequently made. Previously, Caspi [5] reviewed articles comparing the association between IBD and leukemia, but their emphasis is on the development of leukemia after inflammatory bowel disease. To our knowledge, our report is the first study to investigate the clinical distinction between leukemic intestinal lesions and CD.

In this report, fever, abdominal pain and diarrhea can present in both diseases. The significance of weight loss in CD patients may be due to the longer duration of CD. Intestinal bleeding and thromboembolism were more frequent in leukemia, perhaps due to qualitative platelet defects, the presence of a fibrinolytic system and hypofibrinogenemia [6]. An increased platelet count [7] and elevated hsCRP are usually used to evaluate disease activity of CD. Our

data also showed that the median platelet count was higher in CD, but the significant fluctuation in leukemia diminished its value for differential diagnosis. Increased LDH may tend to the diagnosis of leukemia, which is in accordance with previous studies [8]. LDH is an acknowledged prognostic element in leukemia [9]. In our study, elevated LDH provided an 80.6% accuracy and 96.3% specificity in predicting leukemia. However, some complications such as liver and kidney diseases in CD may also result in an elevated LDH, which interferes with the sensitivity of LDH. In addition, as is shown in our data, prolonged PT could be an accurate and specific indicator for leukemia (accuracy of 79.2% and specificity of 90.7%).

In our study, small intestine and colon lesions were often observed in leukemia, whereas ileocecal region lesions were frequently observed in CD. The sensitivity, accuracy and NPV of ileocecal lesions to classify the two diseases were 88.9%, 73.6% and 94.9%, respectively. In addition, intestinal stricture appeared more valuable in differentiating CD and leukemia with a sensitivity of 88.9% and an accuracy of 80.6%. Transmural inflammation is frequent in CD patients in our study. Taken together, gastrointestinal manifestations are less common, but they may be the initial presentation in leukemia. In this case, it is difficult to make a distinction between leukemia and CD. Patients with GI symptoms accompanying a low percentage of neutrophils, elevated LDH and prolonged PT should arouse the suspicion of leukemia. Although there are some limitations in this study, including a single center retrospective study and small size sample, our results may provide a platform to expand predictive factors to distinguish leukemia from CD in the future.

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## Disclosure of conflict of interest

None.

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