

Gastrointestinal manifestations as initial presentation of acute leukemias in children and adolescents

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Summary

Objective: this study aimed to determine the prevalence and characteristics of gastrointestinal manifestations on initial clinical presentation of acute leukemias (AL) in childhood. **Material and methods:** this is a retrospective and descriptive study that assessed medical records of 354 patients with AL from January 1995 to December 2004. **Results:** acute lymphoid leukemia (ALL) was diagnosed in 273 (77.1%) patients and acute non-lymphocytic leukemia (AML) in 81 (22.9%). There were 210 males (59.4%) and 144 females (40.6%). The most common presenting features were: abdominal pain (19.5% in ALL and 11.8% in AML), nausea and vomiting (14.9 in ALL and 14% in AML), abdominal distention (18.5 in ALL and 8.6% in AML; p 0.024), constipation (5% in ALL and 6.5% in AML), diarrhea (3.6% in ALL and 11.8% in AML; p 0.03%), and gastrointestinal bleeding (7.9% in ALL and 9.7% in AML). Ultrasound scanning was made in 61.1% and hepatomegaly was found on 33.6% and esplenomegaly on 28.5% of the patients with AL. Seventy-seven (21.7%) and 15 (4.2%) patients received nonsteroidal anti-inflammatory drugs and glucocorticoids before the diagnostic of AL. An association is well-defined between abdominal symptoms like nausea, vomiting and pain and use of this therapy but this association did not occurred clearly in this study. **Conclusions:** gastrointestinal symptoms

are not very well-documented as initial manifestation of leukemia in children and should be considered on the differential diagnosis of gastrointestinal symptoms of unknown etiology in children.

Key words: acute leukemias, gastrointestinal manifestations, children and adolescent, presentation.

Manifestaciones gastrointestinales como presentación de las leucemias agudas en niños y adolescentes

Resumen

Objetivo: el objetivo del estudio fue determinar la prevalencia y las características de las manifestaciones gastrointestinales en la presentación clínica inicial de las leucemias linfoides agudas (LLA) en la infancia. **Material y métodos:** se trata de un estudio descriptivo y retrospectivo que evaluó los registros médicos de 354 pacientes con LLA de enero de 1995 a diciembre de 2004. **Resultados:** la (LLA) ha sido diagnosticada en 273 (77,1%) pacientes y leucemia mieloide aguda (LMA) en 81 (22,9%). Hubo 210 niños (59,4%) y 144 niñas (40,6%). Los síntomas más comunes de presentación han sido los siguientes: dolor abdominal (19,5% en LLA y 11,8% en el LMA), náuseas y vómitos (14,9 en LLA y 14% en LMA, P 0.024), distensión abdominal (18,5 en LLA y 8,6% en LMA, p 0,024), estreñimiento (5% en LLA y 6,5% en LMA), diarrea (3,6% en LLA y 11,8% en LMA, p 0,03%) y hemorragia gastrointestinal (7,9% en LLA y 9,7% en LMA). La ecografía fue realizada en 61,1% de los pacientes encontrándose hepatomegalia en 33,6% y esple-

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nomegalia en 28,5% con LLA. Setenta y siete (21,7%) y 15 (4,2%) pacientes recibieron los fármacos antiinflamatorios no esteroideos y glucocorticoides antes del diagnóstico de LLA. Hay una asociación bien definida entre síntomas abdominales como náuseas, vómitos y dolor y el uso de esta terapia pero esta asociación no se produjo claramente en este estudio. Conclusiones: las manifestaciones gastrointestinales no están bien documentadas como manifestaciones iniciales de la leucemia en los niños y debe considerarse en el diagnóstico diferencial de los síntomas gastrointestinales de etiología desconocida en estas edades.

Palabras claves: leucemias agudas, manifestaciones gastrointestinales, en niños y adolescentes, presentación.

Gastrointestinal manifestations are extremely common in the pediatric age group and may at first represent many pathologies. Acute leukemia is the most common cancer occurring in children representing 25% of cancer diagnoses among youngsters than 15 years old and occurring at an annual rate of approximately 30 to 40 per million.¹ Acute lymphoblastic leukemia (ALL) is the most common type of leukemia occurring during childhood, representing 75% of all acute leukemia diagnoses in this specific age group. The initial clinical manifestations of acute leukemia are highly variable and non-specific. In children, acute leukemia can mimic several rheumatologic pathologies and this variable presentation creates difficulties in achieving the correct diagnosis.² Although they are rarely the first symptoms of leukemia, these gastrointestinal complaints can delay the diagnosis of leukemia when the classic features of the disease are uniformly absent.

Many authors described the gastrointestinal manifestations in patients with acute leukemia, especially in the course of disease, with symptoms and signs of acute abdominal pain and in granulocytopenic patients secondary to chemotherapy.³⁻⁵ The prevalence and characteristics of gastrointestinal manifestations on initial clinical presentation of childhood acute leukemia. Have not been reported before and the aim of the present study.

Patients, material and method

This is a retrospective, descriptive and an explora-

tory study assessing medical records of 354 children and adolescents with AL from January 1995 to December 2004, with AL previously diagnosed at ONCO - Bahia Oncology Society Ltda. Of the 354 children, eight patients with ALL were excluded from the study because there was insufficient data related to their initial presentation of disease.

The diagnosis of acute leukemia was based on morphologic findings of the bone marrow content.⁶ Complete disease remission was defined as the absence of leukemia blasts in the blood or cerebrospinal fluid and less than 5% lymphoblasts in bone marrow aspirates, evidence of regeneration of normal cells, absence of symptoms and signs of leukemia and a normal clinical performance status. An institutional Research Ethics Committee approved this study project.

Variables used in the study were: patient's age and sex, ALL, AML, gastrointestinal complaints, use of nonsteroidal antiinflammatory drugs and glucocorticoids, abnormalities in abdominal ultrasound scans and laboratory tests.

Statistical Analysis

To test for association between categorical factors statistical analysis was performed by the Fisher's exact test or the χ^2 as appropriate. The Mann-Whitney test or student's-*t* test were used to compare continuous variables. Continuous variables were described by mean and, standard deviation or median and categorical variables were described by their relative frequencies. All p values reflected two-sided tests. Statistical analyses were performed using Statistical Package for Social Sciences (SPSS, Inc, Chicago, Il) version 12.

Results

Medical records of 354 patients were systematically reviewed. Acute lymphoid leukemia (ALL) was diagnosed in 273 (77.1%) patients and acute non-lymphocytic leukemia (AML) in 81 (22.9%). Two hundred and ten patients (59.4%) were boys and 144 girls (40.6%). Age varied between 0.75 year and 15 years (average: 6.18 years). When evaluating the time between the onset of symptoms and the final diagnosis of leukemia there were no differences between ALL and AML (50.2 ± 66.7 days and 64.7 ± 85.3 days; $p=0.083$).

Table I. Gastrointestinal symptoms in the early course of the disease: children and adolescents with acute leukemia, 1995-2004.

Complaints	LLA ^a		AML ^b		PR ^c	P ^d
	n	%	n	%		
Abdominal pain	59	19.5	11	11.8	1.64	0.09
Náusea/vomiting	45	14.9	13	14.0	1.06	0.83
Abdominal distention	56	18.5	8	8.6	2.5	0.024
Flatulence	1	0.3	-	-	-	-
Constipation	15	5.0	6	6.5	0.77	0.59
Diarrhea	11	3.6	11	11.8	0.31	0.003
High gastrointestinal bleeding	11	3.6	3	3.2	1.25	1.0
Low gastrointestinal bleeding	13	4.3	6	6.5	0.66	0.40
Jaundice	3	1.0	-	-	-	-

a - ALL: Acute lymphoid leukemia

b - AML: acute non-lymphocytic leukemia

c - PR: Prevalence ratio

d - p: p values

LLA was considered for calculus of PR.

The most common complaints at the beginning of the disease were: fever (18.5%), diffuse musculoskeletal tenderness (15.0%), pallor (11.4%) and leg tenderness (5.7%). Constitutional symptoms in the early course of the disease, such as weight loss, dizziness, weakness, lethargy, paleness, anorexia and fatigue, were present and more frequent in ALL than in AML.

The most common presenting features at the beginning of the disease were: abdominal pain (19.5% in ALL and 11.8% in AML), nausea and vomiting (14.9 in ALL and 14% in AML), abdominal distention (18.5 ALL and 8.6% in AML; $p 0.024$), constipation (5% in ALL and 6.5% in AML), diarrhea (3.6% in ALL and 11.8% in AML; $p 0.03$), and gastrointestinal bleeding (7.9% in ALL and 9.7% in AML). (Table I)

Abdominal ultrasound scanning was performed in 61.1%; hepatomegaly was found in 33.6% and splenomegaly in 28.5% of the patients with AL. (Table II)

Laboratory findings show an increase in serum transaminase activities with normal liver function and without important clinical manifestations (In the present series, jaundice was not present in AML and in only three patients with ALL). (Table III)

Table II. Abnormal findings in the abdominal ultrasound scanning in the early course of the disease: children and adolescents with acute leukemia, 1995-2004.

Abnormal findings	N	%
Hepatomegaly	151	33.6%
Esplenomegaly	128	28.5%
Hepatoesplenomegaly	118	26.3%
Ascites	9	2.0%
Urinary lithiasis	2	0.4%
Lymphadenopathy	18	4.0%
Dilatation of renal parenchyma	11	2.4%
Periportal fibrosis	1	0.2%
Portal infiltration	1	0.2%
Cholelithiasis	4	0.9%
Ascaris lumbricoides	1	0.2%
Retroperitoneal hematoma	1	0.2%
Pancreatitis	1	0.2%
Cholestasis	1	0.2%

Table III. Laboratory tests in early course of the disease: children and adolescents with acute leukemia, 1995-2004.

	LLA ^a	AML ^b	P ^c
	Average ± sd ^d	Average ± sd ^d	
	Median	Median	
Alanine aminotransferase (U)	47.41 ± 49.53 31	34.19 ± 34.38 26	0.005
Aspartate aminotransferase (U)	29.55 ± 28.87 21	20.09 ± 14.56 17	0.391
Amylase (U/dl)	115.96 ± 182.49 83.5	92.25 ± 86.00 60.50	0.221
Albumina (g/dl)	3.75 ± 0.46 3.75	3.64 ± 0.91 3.82	0.920
Serum globulin (g/dl)	2.67 ± 0.78 2.6	3.07 ± 0.75 3.23	0.054
Serum protein (g/dl)	6.40 ± 0.87 6.1	6.71 ± 1.38 7.12	0.129
Bilirubin (total) (mg/dl)	0.59 ± 0.34 0.50	0.81 ± 0.59 0.55	0.583
Bilirubin (unconjugated) (mg/dl)	0.42 ± 0.55 0.29	0.47 ± 0.34 0.3	0.170
Phosphatase alkaline (U/l)	265.54 ± 245.78 273	219.28 ± 120.04 222.5	0.749
Prothrombin time (%)	94.27 ± 88.30 81	74.94 ± 22.70 76	0.281
Activated partial thromboplastin time (sec)	42.01 ± 53.06 29.65	34.42 ± 13.52 31.25	0.709

a - ALL: Acute lymphoid leukemia

b - AML: acute non-lymphocytic leukemia

c- p: p values

d- standard deviation

Discussion

Acute leukemia is the most common childhood malignancy and it can produce a host of complaints that mimic other more common pediatric diseases.⁷⁻¹⁰

The initial presentation of childhood acute leukemia consists of diverse signs and symptoms and they should be considered in the differential diagnosis of gastrointestinal symptoms of unknown etiology.

Gastrointestinal complaint is a common and challenging clinical presentation in many conditions of general pediatrics and pediatric gastroenterology. The differential diagnostic is extensive and full at-

tention is necessary to identify a child at greater risk for a specific underlying organic cause. These manifestations have been described in the course of lymphoproliferative diseases by few authors,¹¹ and requires attention from the pediatrician.

In this study, gastrointestinal manifestations were described only at the *initial clinical presentation* of acute childhood leukemia. Gastroenteritis is a major cause of diarrhea in children and most common causes are viruses, but bacterial, protozoal and helminthic gastroenteritis do occur, particularly in developing countries. Vomiting, nausea and diarrhea

are nonspecific symptoms in childhood and is important to carefully evaluate these patients to guarantee the absence of organic disease. In this study, diarrhea was present in 3.6% in ALL and 11.8% of patients with ALL and AML, respectively; p 0.03%).¹²

Constipation was present in 11.5% (5% in ALL and 6.5% in AML). In the pediatric population without AL this complaint is responsible for 3% and 25% of pediatric and gastroenterologic pediatric office visits.¹³ The most common serious causes of constipation in the newborn and infant are imperforate anus, anal stenosis, meconium plug syndrome, meconium ileus, Hirschsprung's disease, volvulus, anal fissure, infant botulism, hypocalcemia, hypercalcemia, and hypothyroidism. Constipation in the older infant or child is commonly related to changes in diet, especially from breast milk to formula or advancement to solid baby foods. Inadequate fluid intake is another common cause of constipation. The school-aged child may present with constipation caused by high carbohydrate diets and hesitance to go to the bathroom at school. A lower abdominal mass may be found by palpation, and fecal impaction may be found on rectal examination. Older children may present with abdominal pain, which may be in the right lower quadrant and mimic appendicitis.¹⁴ Abdominal pain was present in this study before the diagnosis of AL (19.5% in ALL and 11.8% in AML). Vomiting and abdominal pain are symptoms that may arise from a number of different causes.¹⁵

A substantial percentage of pediatric office visits and pediatric emergency room visits are due to abdominal pain.¹⁶ Only 5% to 10% of patients have a defined etiology. Common causes of acute abdominal pain include gastroenteritides, appendicitis, intussusception, small bowel obstruction, incarcerated hernia, cholecystitis, bowel obstruction, urinary colic, perforated peptic ulcer, pancreatitis, diverticulitis and nonspecific nonsurgical abdominal pain.¹⁷ Abdominal pain may also be a symptom of leukemia. Leukemia cells can collect in the kidneys, liver, spleen and intestines, causing enlargement of these organs. Vague abdominal pain is a common presenting symptom reported in about 19% of cases in one series and it presumably results from areas of inflammation or nodal involvement within the intestinal tract.⁵ Abdominal distention, constipation, functional abdominal pain, use of drugs and protozoal and helminthic infection are less serious causes

of abdominal symptoms¹⁸ and can be involved in the mechanism of the abdominal pain in this series (helminthic infection is a probable cause, especially when one analyzes the demographic characteristics of the patients in the present study). In a series of 117 children with acute leukemia and lymphoma, at the authors' institution, protozoal and helminthic infection tests showed positivity for 11% of patients. The most common enteroparasites were *E. nana* (n=4) and *E. coli* (n=4) followed by *E. histolytica* (n=3) and *G. Lamblia* (n=3), *A. Duodenale* (n=2) and *A. Lumbricoides* (n= 2), *S. Stercoralis* (n=1) and *T. Trichura* (n= 1). It should be pointed out that four patients had more than one parasitic infection.¹⁹ In the present study, the majority of stool samples asked for by physicians were not obtained.

The association between abdominal pain, nausea and vomiting with use of nonsteroidal antiinflammatory drugs and glucocorticoid at the time of diagnosis was studied, and no statistical association was found. Out of a total of seventy-seven patients (21.7%) that received nonsteroidal anti-inflammatory drugs, only 13% had complaints of abdominal pain (patients without drugs: 18.8%; p 0.23) and 14.3% of nausea and vomiting (patients without drugs: 15.2%; p 0.85). Fifteen (4.2%) patients received glucocorticoids, with complaints of abdominal pain in 13.3% (patients without drugs: 17.7%; p 1.0) and nausea and vomiting in no patient (patients without drugs: 15.6%, p 0.14).

Anamnesis, physical examination and especially follow-up are extremely important instruments for the management of such patients.²⁰

Acute abdominal abnormalities are referred during the treatment of leukemia, especially in adult patients with ALL.²¹⁻²⁹ Abdominal pain secondary to acute appendicitis in children with AL during induction is possible but not frequent. Similarly, typhlitis occurring during induction chemotherapy may present and is the main differential diagnosis.^{30,31} Typhlitis is a necrotizing colitis with inflammation of the cecum and often of the surrounding tissues. This life-threatening condition is seen only in the setting of neutropenia related to severe underlying disease or treatment and is traditionally associated with leukemia in the terminal stages.³²

Manglani et al. described an ileocecal intussusception that developed in a 7-month-old infant with ALL during induction therapy.³³ Didilio et al. reported a case of ALL in a child presenting with an acu-

te abdomen following surgery for choledochal cyst.³⁴

Ultrasound scanning was performed in 61.1%; hepatomegaly was found in 33.6% and splenomegaly in 28.5% of the patients with AL.

Liver involvement in ALL is frequent. Hepatomegaly occurs in approximately two thirds of the patients and often in conjunction with splenic involvement in 68% of the cases. Hepatomegaly is one of the most frequent presenting symptoms in AL as a manifestation of the spread of extramedullary leukemia and is usually asymptomatic. Laboratory findings in ALL frequently show an increase in serum transaminase activities but bilirubin, gammaglutamyl transpeptidase (GGT) and alkaline phosphatase are usually normal or only slightly elevated at the time of diagnosis, however jaundice is uncommon.³⁵ The present findings are in accordance to those described by other authors. Severe liver disease is rare, but acute hepatic failure can occur in the advanced stages and terminal phases of the disease.³⁴⁻³⁷ Liver failure as a presenting symptom in children has been described rarely in sporadic reports. Felice *et al.*, reported a 7-year old girl with acute severe hepatic failure and a diagnosis of T-cell ALL during evaluation.³⁵ Devictor *et al.* reported a 14-year-old boy with hepatic failure and an acute early pre-B ALL³⁸ and Zafrani et al also described four cases of fulminant hepatic failure due to massive infiltration of the liver by acute leukemia.³⁹ In patients with liver and spleen enlargement, malignant hematological diseases must always be in the differential diagnosis.

In conclusion, the authors consider it important to note that in a patient with gastrointestinal complaint with decrease of peripheral WBC, severe anemia and sometimes thrombocytopenia, these manifestations should alert the physician and the diagnosis of malignancy must not be excluded, especially when the clinical pattern is not characteristic of a specific gastrointestinal disease and there is no presence of other systemic manifestations. In these cases, pediatricians must be aware that AL may be considered in the differential diagnosis, which should lead to additional investigations and demands systematic follow-up of patients.

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