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Early detection by ultrasound scan of severe post-chemotherapy gut complications in patients with acute leukemia

MARCO PICARDI, CARMINE SELLERI, ANDREA CAMERA, LUCIO CATALANO, BRUNO ROTOLI
Division of Hematology, Federico II University Medical School, Naples, Italy

ABSTRACT

Background and Objective. **Acute leukemia patients may develop life-threatening gut complications after intensive chemotherapy. We evaluated the role of abdominal and pelvic ultrasound (US) examination in early detection of these complications.**

Design and Methods. **A cohort of twenty adult acute leukemia patients undergoing intensive chemotherapy for remission induction entered the study. All chemotherapy regimens included cytarabine by continuous i.v. infusion for several days.**

Results. **Three patients had severe gut complications: 2 cases of enterocolitis and 1 case of gall bladder overdistension in the absence of calculi. In all cases the abnormality was documented by US examination: US scan showed thickening of the intestinal wall (two cases), and gall bladder overdistension with biliary sludge (one case). Immediate medical care included bowel rest, a broad-spectrum antibiotic, antimycotic treatment, and granulocyte colony-stimulating factor. All patients recovered from the complication.**

Interpretation and Conclusions. **We believe that the favorable outcome obtained in our small series can be attributed to early diagnosis followed by appropriate treatment. Early recognition by US and immediate medical management can lead to complete recovery of severe intestinal complications in patients with acute leukemia undergoing intensive chemotherapy.**
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Key words: acute leukemia, intensive chemotherapy, remission induction, severe intestinal complications, ultrasound scan

The intensive chemotherapy regimens used for treating patients with acute leukemia may induce several types of gastro-intestinal damage, including necrosis of mucosal epithelial cells, bacterial invasion, infarction and occasionally perforation.[1,2] Nausea, vomiting, abdominal pain and distension, diarrhea, ileus and fever are the most frequent symptoms in these patients.[1] Unfortunately, in most cases the clinical presentation is puzzling and the correct diagnosis is not immediately suspected.

We investigated adult acute leukemia patients undergoing intensive chemotherapy, with the aim of evaluating diagnosis, clinical management and outcome of these potentially fatal complications.

Design and Methods

From September 1996 to April 1998 we studied 20 consecutive adult patients (12 males and 8 females) with acute leukemia admitted to hospital to receive intensive chemotherapy for remission induction. Their mean age was 44 years (range 25-58). Seventeen had acute myeloid leukemia and received an induction regimen according to the EORTC-GIMEMA AML 10 protocol [containing either idarubicin or mitoxantrone or daunorubicin in combination with etoposide and cytarabine (Ara-C) by continuous i.v. infusion]. Three patients had acute lymphoblastic leukemia and received the GIMEMA ALL 0394 protocol induction regimen (Ara-C by continuous i.v. infusion over 7 days, etoposide and idarubicin). At the time of chemotherapy, all patients had a central venous line inserted, all received similar bacterial and fungal prophylaxis (ciprofloxacin and fluconazole) and none received pre-emptive total parenteral nutrition (TPN). In all patients we evaluated the occurrence of severe gastro-intestinal symptoms according to WHO recommendations. Physical examination, laboratory tests, blood and stool cultures and toxin assay for *C. difficile* were performed in all patients with gastro-intestinal symptoms. An abdominal and pelvic ultrasound (US) examination, using portable equipment at the patient's bedside, was carried out by a hematologist trained in medical ultrasonography within the first 12 hours of the appearance of symptoms and on subsequent days. US was meant to monitor changes in intestinal wall thickness, formation of intraparietal microabscesses, intestinal pneumatosis and intraperitoneal effusion.

Results

Of the 20 patients studied, 3 (15%) developed severe gut complications: 2 cases of enterocolitis and 1 case of gall bladder overdistension without calculi (Table 1). Clinical manifestations were high grade fever, right abdominal pain, abdominal distension and tympany; patients #1 and #2 also had diarrhea

Correspondence: Bruno Rotoli, M.D., Divisione di Ematologia Clinica, Nuovo Policlinico, via S. Pansini 5, 80131 Naples, Italy.
Phone: international +39-081-7462068 – Fax: international +39-081-7462165.

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Table 1. Clinical characteristics and outcome of patients with severe gut complications after induction chemotherapy.

Pt.	Sex, age	Basic disease	Intestinal complication	Abdominal symptoms	US finding	Medical management	Complication outcome
1	F, 26	AML (M4)	enterocolitis	fever, right lower quadrant pain, distension, diarrhea with melena, vomiting	terminal ileal loop wall thickening (about 6 mm), ileal loop superdistension with reduction of peristaltic activity, moderate ascites	meropenem 3 g/daily, amikacin 1 g/daily, teicoplanin 200 mg/daily, amphotericin-B 50 mg/daily, metronidazole 1,5 g/daily, G-CSF 300 µg/daily, TPN, nasogastric suction	recovery
2	M, 50	AML (M3)	enterocolitis	fever, abdominal pain, distension, diarrhea with melena, vomiting	wall thickening of ileal loop (about 7 mm) and proximal colon, overdistension, reduced peristaltic activity, moderate ascites	meropenem 3 g/daily, amikacin 1 g/daily, teicoplanin 200 mg/daily, fluconazole 300 mg/daily, metronidazole 1.5 g/daily, G-CSF 300 µg/daily, TPN, nasogastric suction	recovery
3	F, 58	ALL (L2)	gall bladder overdistension without calculi	fever, abdominal pain, distension, vomiting	overdistension of gall bladder, containing biliary sludge, pericholecystic effusion, positive US Murphy's sign	ceftazidime 6 g/daily, amikacin 1 g/daily, vancomycin 2 g/daily, fluconazole 300 mg/daily, G-CSF 300 µg/daily, nasogastric suction	recovery

ALL= acute lymphoblastic leukemia, AML= acute myeloid leukemia, US= ultrasound scan, G-CSF= granulocyte colony-stimulating factor, TPN= total parenteral nutrition.

and melena. Fever and right abdominal pain appeared before the other manifestations. The symptoms started during profound neutropenia, between the twelfth and the sixteenth day after the start of chemotherapy. In all cases the diagnosis of severe gut complication was defined by US scan. The main findings were moderate wall thickening (between 5 and 7 mm) of terminal ileal loops (patients #1 and #2) (Figure 1), and a distended gall bladder containing sludge, but without wall thickening (patient #3) (Figure 2). In patient #1 computer axial tomography confirmed the US findings. Only patient #3 had a microbiologically documented infection (*Staphylococcus aureus* and *Streptococcus mitis* grown from blood culture). Stool cultures for toxin-producing *C. difficile* were negative in all patients. All patients were immediately managed with bowel rest (nasogastric suction and TPN), vigorous broad-spectrum antibiotic treatment (including specific anti-anaerobic drugs), empirical systemic antimycotic treatment and granulocyte colony-stimulating factor (G-CSF) administration. During this treatment, US follow-up documented improvement of the intestinal damage. All patients responded to medical management without requiring a surgical intervention and survived. In all patients the resolution of fever and of abdominal symptoms coincided with the resolution of neutropenia.

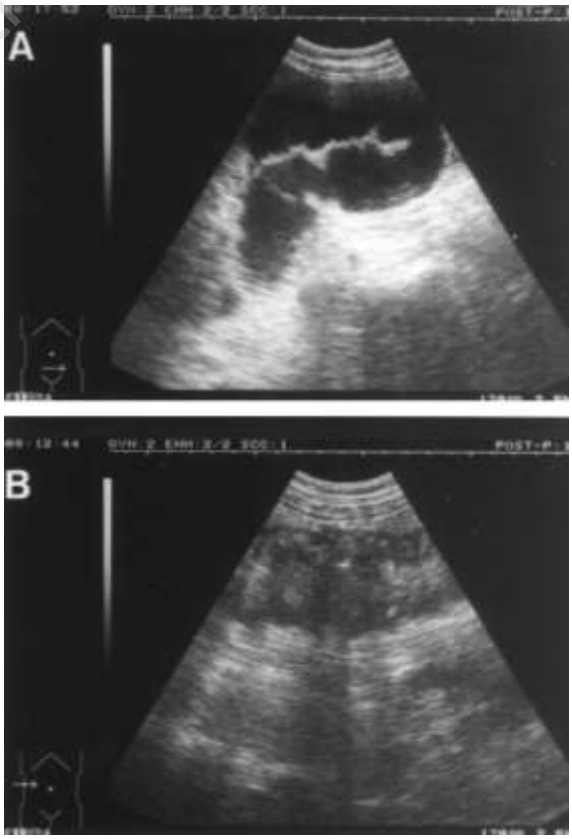

Figure 1. US scan of patient #2 showing overdistended ileum (A) and proximal colon wall thickening (B).

Discussion

While in relapsed or resistant leukemia patients the pathogenesis of gastro-intestinal complications may

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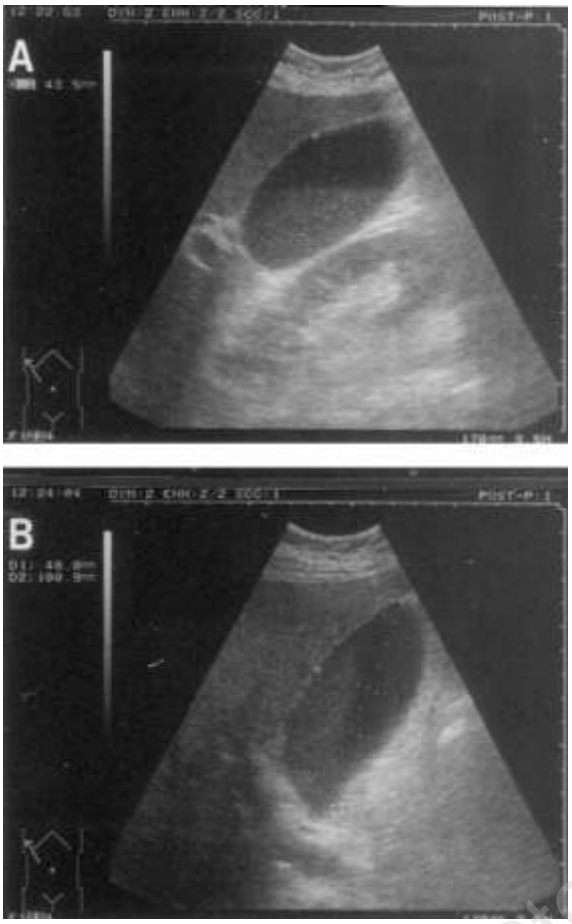

Figure 2. US scan of patient #3 showing an overdistended gall bladder containing biliary sludge.

be multifactorial (repeated chemotherapy courses, prolonged periods of profound neutropenia, broad-spectrum parenteral antibiotic treatments and intestinal leukemic infiltration),[1,2] in patients receiving a first course of chemotherapy for remission induction the main mechanism is drug-induced epithelial toxicity followed by local infection. The dosage and the modality of administration of Ara-C seem to be crucial in the development of acute gut complications.[3,4] In particular, continuous i.v. infusion of Ara-C over 7 to 10 days has become popular in the most recent regimens; thus acute gut complications are an emerging problem. Enterocolitis and acute cholecystitis in the absence of calculi are severe complications during the aplastic phase, with a reported mortality from 50% to 100%.[3,5] The management is controversial, and therapeutic approaches vary from early surgical intervention to only supportive treatment.[3,5] Rapid recognition of these complications seems to be crucial for patient survival.

Our small study shows that early use of abdominal and pelvic US may be valuable for rapid detection of severe gut complications.[6,7] Proper antibiotic and supportive treatment associated with close US follow-up[3,8,9] are effective methods for avoiding surgical intervention, which is extremely risky in aplastic patients.[9] The failure of medical management of similar cases reported by other authors[2,4] is probably related to delayed diagnosis; indeed, the reported patients had advanced intestinal damage, as demonstrated by the findings of ileal wall thickening > 9 mm, intestinal pneumatosis, perforation and peritonitis.

Since neutrophil recovery is a pivotal event for the resolution of such complications,[8] we suggest early use of G-CSF and/or of white blood cell transfusions from G-CSF-treated donors, as has been suggested for other neutropenia-related severe complications.[10-12] Proper studies should also be carried out to test whether oral glutamine supplementation is effective in preventing chemotherapy-induced gastro-intestinal damage.[13,14]

Contributions and Acknowledgments

MP designed the study and performed the ultrasound examinations. CS, AC and LC were responsible for patient care and follow-up. BR was responsible for data interpretation and writing the paper.

Disclosures

Conflict of interest: none.

Redundant publications: no substantial overlapping with previous papers.

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