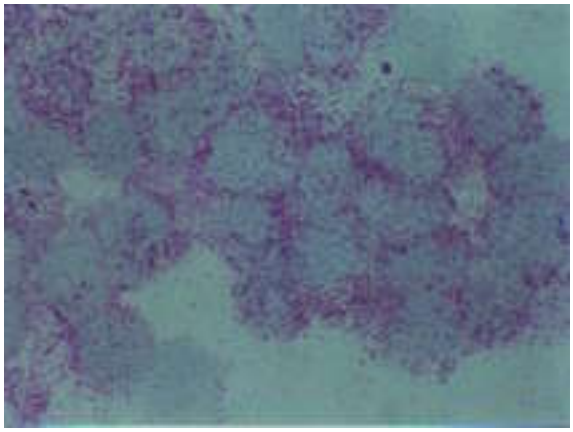

Figure 1. High expression of cytoplasmic wild-type p53 in megaloblastic marrow at diagnosis (APAAP, x1,000).

damage caused by uracil misincorporation into DNA, in agreement with a report that high levels of wt-p53 are associated with an increased rate of apoptosis in late-stage erythroblasts in folate deficiency states.[5] We suggest, therefore, that p53 is one of the main mediators which induces apoptosis in MA and helps to maintain genetic stability in this disease. On the other hand, the overexpression of $p21^{ras}$ may reflect the activation of this signal transducer in part by elevated levels of erythropoietin determined by the anemia or other hematopoietic growth factors known to stimulate this signaling pathway.

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Acute monocytic leukemia in the adult presenting with associated extramedullary gastric infiltration and ascites

Involvement of the stomach in acute myelogenous leukemia has been rarely described. We report a case of an adult patient with acute monocytic leukemia who presented with an abdominal mass and ascites due to massive intramural involvement. Leukemic gastric infiltration in the adult leading to a tumoral presentation and melena has, to our knowledge, not been previously reported.

Sir,

Acute monocytic leukemia (AMoL), referred to as M5 in the FAB classification, is the morphologic subtype of acute myelogenous leukemia (AML) that most frequently presents with extramedullary involvement, including liver, spleen, lymph nodes, gingiva, skin, eyes, larynx, lung, bladder, meninges and the central nervous system. Involvement of the gastrointestinal tract is rare, the mouth, rectum and anal canal being the most affected sites.[1] By contrast, leukemic infiltration of the stomach has been rarely described, and when it has, mainly in children.[2,3] We report a case of an adult patient with AMoL who presented with an abdominal mass, ascites and melena due to massive intramural gastric infiltration.

A 32-year old woman was referred to our department with a 1-month history of constitutional symptoms, abdominal pain and melena, with a normal blood smear. There was no relevant past medical history. Examination upon admission revealed pallor, ascites and an epigastric mass, without palpable lymphadenopathy, hepatomegaly or splenomegaly. Examination of ascitic fluid revealed an exudate containing abundant monocytic blasts. Laboratory tests showed a hemoglobin of 99 g/L, MCV 88 fL, WBC 15.7×10^9/L (1% eosinophils, 28% neutrophils, 35% lymphocytes, 13% monocytes, 23% blast cells) and a platelet count of 84×10^9/L. Prothrombin and partial thromboplastin times were normal. Biochemistry data were unremarkable except for LDH 16 mkat/L (normal 3.9-6.7), albumin 36 g/L (normal 39-50), total proteins 59 g/L (normal 64-80) and β_2-microglobulin 3.7 mg/L (normal 0.8-2.4).

Bone marrow examination revealed a blast population making up more than 50% of the cellular marrow components. The blast cells had an immature monocytic appearance and a diagnosis of acute monocytic leukemia (FAB M5a) was made. Blast cells were positive for non-specific esterase and negative for peroxi-

dase; immunophenotyping showed markers of myeloid/monocyte lineage (CD33, HLA-DR,CD13, CD14, CD11b). A 46,XX,9q-, inv(16) (p13q22) karyotype was found. Examination of the cerebrospinal fluid and chest radiograph were normal.

Gastrointestinal barium study and a CT scan of the abdomen showed diffuse thickening of the gastric wall, with multiple small mesenteric and retroperitoneal enlarged lymph nodes (diameter less than 1cm) and ascites (Figure 1).

Esophagogastroduodenoscopy showed diffuse thickening of the gastric wall with prominent hemorrhagic mucosal folds. Gastric biopsies showed chronic inflammation with focal areas of necrosis infiltrated by a monocytic blast population. *Helicobacter pylori* investigation was negative.

The patient was treated with chemotherapy, including idarubicin, cytarabine and etoposide. During the aplastic period, the patient suffered an acute gastric hemorrhage that was controlled with blood and platelet support. After the first course, the abovementioned CT findings were no longer detectable. Subsequent esophagogastroduodenoscopy demonstrated normal appearance of the gastric mucosa, and further gastric biopsies were negative. Therapy led to a marked reduction of the blast cells in the bone marrow aspirate (6%), but complete remission was never achieved and the patient died on day +17 of the second chemotherapy course due to sepsis.

In recent years, leukemia-related gastrointestinal complications are becoming more common and should no longer be considered unusual. About 10 per cent of leukemia patients suffer from significant gastrointestinal complications,[4] although this percentage increases to almost half of the patients in autopsy series.[5] Involvement of the gastrointestinal tract in acute leukemias may result from leukemic infiltration, chemotherapy and opportunistic infections.

The gastrointestinal tract in AML may be infiltrated at any site, but functional disturbances are unusual.[4,6,7] The mouth, colon and anal canal are the sites of involvement that most commonly lead to symptoms. Gingivitis is a consequence of leukemic invasion of the gums resulting in hypertrophy and inflammation causing oral pain and bleeding. Infiltration of the bowel may produce polypoid masses, plaque-like thickenings, ulcers, and diffuse masses that may cause obstruction, hemorrhage, or intussusception.[8] Proctitis is especially common in the monocytic variant of AML and can be a presenting sign.[6]

In spite of the high frequency of gastric involvement in the lymphoproliferative disorders, myelogenous leukemic infiltration of the stomach has been only rarely reported. Interestingly, symptomatic involvement of the stomach has been only described in children with a few published cases in the English literature.[2] By contrast, leukemic gastric infiltration in the adult leading to a tumoral presentation and melena has, to our knowledge, not been previously described, although Kasantikul *et al.* reported an isolated case of subacute combined degeneration of the spinal cord secondary to impairment in vitamin B_{12} absorption, due to gastric infiltration in an adult with acute monoblastic leukemia.[3]

In summary, our case shows that AML can present with symptomatic gastric involvement in the adult. This possibility should be considered in the evaluation of patients with AML and abdominal pain or bleeding, severe gastric hemorrhage being a possible event requiring more intensive platelet support. Moreover, although rare, we point out that AML should be included in the differential diagnosis of patients presenting with a gastric mass in addition to adenocarcinoma and lymphoma.

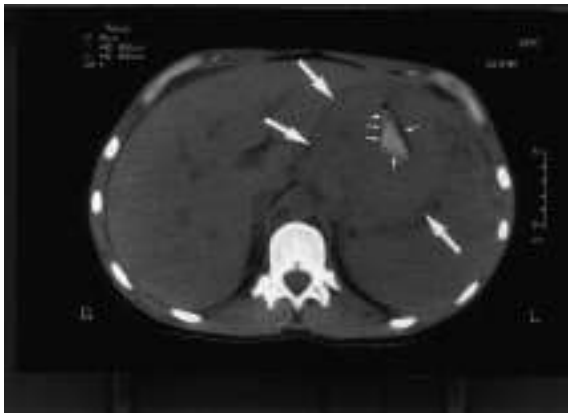

Figure 1. CT scan shows marked circumferential thickening of the gastric walls (large arrows), causing narrowing of the contrast-filled lumen (small arrows). Note normal size of the spleen.

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Key words

Acute monocytic leukemia, acute myelogenous leukemia, gastric infiltration, adults.

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Molecular and clinical prognostic factors in BFM-treated childhood acute lymphoblastic leukemia patients: a single institution series

We analyzed the impact on outcome of minimal residual disease (MRD) and clinical factors in 97 children with acute lymphoblastic leukemia. Unfavorable factors were early-B and -T immunophenotype, hyperleukocytosis, non-response to steroids, detection of MRD at the end of induction therapy. A level of MRD ≥ 1/10³ leads to a lower probability of disease-free survival.

Sir,

Ninety-seven children with acute lymphoblastic leukemia (ALL) were treated in our institution according to the ALL-BFM protocol[1] from November 1986 to December 1997. The polymerase chain reaction (PCR) protocol used for detection of IgH and TCRδ gene rearrangements in diagnostic bone marrow and follow-up samples was similar to those previously published.[2-4] In diagnostic samples specific bands from PCR reactions were separated and recovered from a 2% low melting temperature agarose gel. A PCR second round was carried out to generate the probe using the ELJH/Bam 5'TGAGGAGACGGTGACCAGGATCCCTTGGCCCCAG3' and FRA/Pst 5'ACACCTGCAGTGTATTACTGT3'primers.[3]

Following restriction digestion with Bam HI and Pst1, the amplified fragment was labeled using the random primer method with dig-11-dUTP digoxigenin. Following hybridization, filters were washed under astringent conditions, detected by chemoluminescence and visualized using X-rays. Sensitivity of IgH and TCRδ probes ranged from 1/500 to 1/10,000, and from 1/500 to 1/1,000 respectively.

The patients' characteristics are shown in Table 1. With a median follow-up of 6 years (range 1-135 months) the probability of disease-free survival (DFS) was 0.75 (0.04 SD). There were 20 relapses, 15 in the bone marrow, 3 combined, and 2 extramedullary. DFS probability was negatively affected by the following factors: complete response (CR) not achieved by day +33 ($p< 0.0001$), early-B and T immunophenotype ($p< 0.01$), leukocytes ≥100x10⁹/L ($p= 0.02$), no response to steroids ($p= 0.0002$), and presence of minimal residual disease (MRD) at the end of induction ($p = 0.0009$). Patients included in the MRD study (n=36) were in CR but in 14 cases MRD was detected. A threshold value of 1:10³ was used to separate patients who were MRD negative (<1:10³) or MRD positive (≥1:10³). With a median follow-up of 50 months (range 22-81) DFS probability for these patients was 0.80 (0.07 SD). Six patients relapsed between 21 and 50 months after diagnosis, all of them in the MRD positive group. DFS probability was 1.0 in the MRD negative group whereas in the MRD positive group it was 0.52 (0.14 SD) (log-rank test; $p< 0.0009$; 95% CI 0.01-0.3). There was no correlation between level of MRD and clinical data (Table 2). Reports on MRD in childhood B-precursor ALL have suggested that PCR positivity and MRD level at the end of the induction predict clinical outcome.[3,5,6] However, in other studies prolonged persistence of MRD correlates with outcome better than a single PCR positive/negative determination at a given time.[7,8] Our data suggest that patients with MRD ≥ 1/10³ at the end of induction

Table 1. Patients' characteristics (n=97).

Variable	*Number of patients (%)*
Sex	
Male	58 (59.8)
Female	39 (40.2)
Age (years)	
<1	0 (0)
1-9	83 (85.6)
>10	14 (14.4)
White blood cell count (x10⁹/L)	
<10	45 (46.4)
10-<50	30 (30.8)
50-<100	13 (13.4)
>100	9 (8.2)
Hemoglobin (g/100 mL)	
<10	74 (76.2)
>10	23 (23.8)
Central nervous system involvement	1 (1)
Mediastinal involvement	12 (12.3)
Immunophenotype	
early-B ALL	15 (15.5)
c-ALL	63 (64.9)
pre B ALL	1 (1)
T-ALL	16 (16.5)
null ALL	2 (2.1)
Prednisone response (peripheral blood blasts, day 8)	
<1x10⁹/L	89 (91.8)
>1x10⁹/L	8 (8.2)
Chromosome study (n=25)	
Hyperdiploid	14 (56)
Diploid	8 (32)
Pseudodiploid	2 (8)
Hypodiploid	1 (1)

Table 2. Patients' characteristics with regard to MRD positivity.

Variable	*MRD negative n=22*	*MRD positive n=14*	*p value*
Age (years), median (range)	4 (1-12)	5 (2-12)	n.s.
Gender			
Male	14	5	n.s.
Female	8	9	
WBC count (x10⁹/L), median (range)	11.5 (1.3-85)	5 (2-132)	n.s
Estimated disease-free survival	100%	52%	0.0009