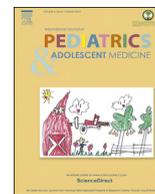


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Case report

Menetrier's disease (protein-losing gastropathy) in a child with acute lymphoblastic leukemia

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ABSTRACT

A 3-year-old boy with high-risk precursor-B ALL presented with abdominal pain, vomiting, and hypoalbuminemia just before his second scheduled course of high-dose methotrexate in interim maintenance. Examination was significant for epigastric tenderness and periorbital edema. Abdominal imaging revealed a circumferential thickening of the stomach with an increased mucosal enhancement and a mild circumferential thickening of segments of small bowel loops. Cytomegalovirus (CMV) of the patient, determined by PCR, in blood was positive with a low titer and was subsequently negative. Upper endoscopy revealed hypertrophic rugae and folds in the stomach and duodenum, and biopsy showed giant gastric folds and foveolar hyperplasia but was negative for CMV. He received supportive care and a 2-week course of ganciclovir and Cytogam with clinical improvement. We report a case of Menetrier's disease (Protein-losing gastropathy), which was diagnosed in a child with acute leukemia. Menetrier's disease should be considered in any patient with symptoms referable to the gastrointestinal tract and thickened stomach and bowel loops detected by radiologic imaging.

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1. Introduction

Menetrier's disease (protein-losing gastropathy) is a rare disease in childhood characterized predominantly by gastric fundus and body hypertrophy and by gastric mucosa protein loss, thereby resulting in hypoalbuminemia. Children usually have self-limited disease, which lasts for a few weeks and requires primarily supportive care. One of the major causes of Menetrier's disease in children is cytomegalovirus (CMV) infection [1]. The literature reported only 50–60 cases in children, and it is largely confined to case series [2,3]. We report a case of Menetrier's disease in a child on therapy for precursor B acute lymphoblastic leukemia (ALL) with an unclear association with CMV. To the best of our knowledge, this

may be the first case of Menetrier's disease (protein-losing gastropathy) to be reported in a child with ALL.

2. Case report

A 3-year-old boy received therapy for high-risk precursor B ALL. He was admitted for his second of four planned courses of high-dose methotrexate in interim maintenance. At the time of admission, his mother reported complaints of abdominal pain and vomiting for the preceding three to four days. His physical examination was significant for epigastric tenderness and the development of periorbital edema on the second day of admission.

Because of his history, chemotherapy was held and he was started on ranitidine. An abdominal ultrasound was performed and unexpectedly revealed significant anterior gastric wall thickening of up to 14 mm (normal: 1–2 mm) and fluid collections in both flanks with septae (7 × 2.5 × 3 cm and 8.6 × 2.7 × 3.3 cm). A follow-up abdominal CT scan showed significant circumferential thickening of the stomach reaching up to 13 mm in the body of stomach and associated with a significantly increased mucosal enhancement. The gastric antrum showed nonspecific mild thinning. There

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were also multiple short and long segments of small bowel loops that showed mild circumferential thickening and significantly increased enhancement (Fig. 1). The remainder of the small bowel loops was fluid distended. There were a few subcentimeter but slightly prominent lymph nodes in the root of the mesentery and a mild to moderate amount of free fluid in the abdomen and pelvis. The visualized part of the chest showed small bilateral pleural effusions. Laboratory investigations were significant for a low serum albumin at 14 g/L (32–56 g/L) with normal bilirubin, transaminase, and INR/APTT levels. Urinalysis showed no proteinuria. The child had had an episode of prolonged fever and neutropenia before the start of interim maintenance. Extended viral evaluation at that time revealed low titer CMV positivity by PCR (genomic copies 2170/ml). This had fallen to a level below the level of detection on quantitative analysis at the start of interim maintenance. CMV, determined by PCR, was tested again on this admission and was negative twice.

Upper endoscopy revealed hypertrophic rugae in the stomach and hypertrophic folds in the duodenum, which were consistent with Menetrier's disease (Fig. 2). Pathologic examination of the stomach biopsy revealed giant gastric folds and foveolar hyperplasia and glandular atrophy consistent with Menetrier's disease (Fig. 3A and B). Staining for CMV was negative. *Helicobacter pylori* infection workup was not performed. The child was managed conservatively and initially kept nothing by mouth (NPO) and started on total parenteral nutrition (TPN). He was given albumin 0.5 g/kg/dose once with furosemide and was started on therapeutic doses of ganciclovir and Cytogam. The latter therapy was discontinued after 2 weeks in the absence of evidence of active CMV infection. The child's symptoms improved remarkably, and his serum albumin level was within the normal range after 1 week. Follow-up ultrasound after 2 weeks showed that the thickening of the gastric wall improved (maximum 3.5 mm) and became less nodular with only mildly thickened small bowel loops.

With regard to chemotherapy, we did not administer high-dose methotrexate to him as per the protocol of treatment, instead we

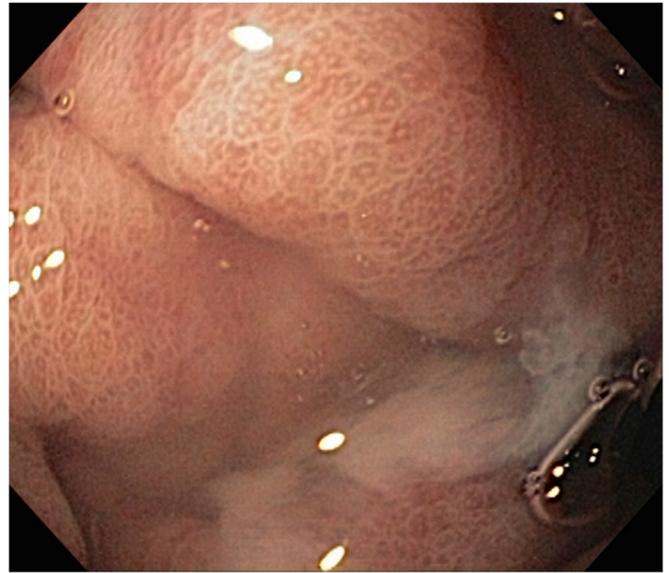


Fig. 2. Upper gastrointestinal endoscopy shows hypertrophic rugae in the stomach.

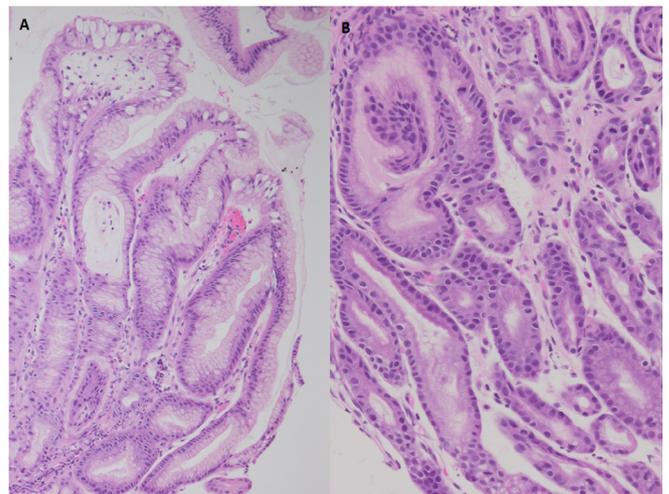


Fig. 3. Pathology of stomach biopsy H&E stain. A) Foveolar hyperplasia (magnification 10X) and B) glandular atrophy (magnification 20X).

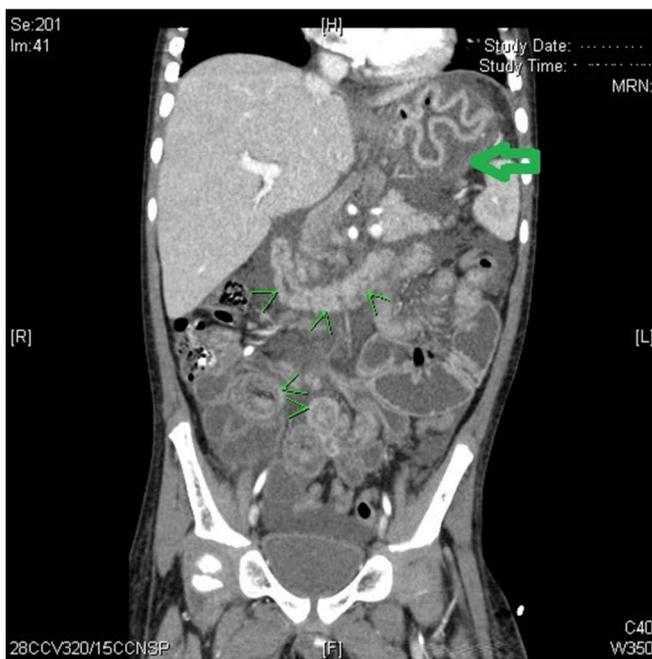


Fig. 1. CT abdomen shows significant circumferential thickening of the stomach (complete arrow) and multiple short and long segments of small bowel loops with mild circumferential thickening and significantly increased enhancement (head arrows).

administered escalating doses of methotrexate (Capizzi regimen, starting with 100 mg/m², increasing the dose by 50 mg) which was tolerated well.

3. Discussion

The etiology of Menetrier's disease in most cases is unknown. However, variants of Menetrier's disease with sudden onset and spontaneous remission have been reported to be associated with CMV in children [4–6] or *H. pylori* infection in adults [7].

Menetrier's disease associated with CMV infection is a rare entity and can cause significant morbidity in all age groups: from neonates to adults [1]. Common clinical signs of Menetrier's disease include abdominal pain, vomiting, and edema secondary to hypoalbuminemia, which result from protein leakage through the gastric mucosa. In contrast to adults, the disease in children is usually shorter, has a benign course, and resolves spontaneously within a few weeks [1]. Menetrier's disease can be diagnosed by the presence of enlarged gastric rugae and confirmed by radiology or

endoscopy and histologic documentation of the characteristic lesions [8].

The mechanism by which CMV infection affects the gastric mucosa is not fully understood. It may be due to the role of TGF- α immunoreactivity through the elevation of intracellular messengers and activation of proto-oncogenes that increase the production of TGF- α in gastric mucosal cells, which may widen tight junctions [9]. Treatment of most cases of childhood Menetrier's disease are largely supportive, as the disease is self-limited. Patients are usually treated with proton pump inhibitors, H2-receptor blockers, and anticholinergic medications. They sometimes may require symptomatic treatment for hypoalbuminemia and fluid overload, with diuretics and albumin. Ganciclovir may also be administered to CMV-positive patients who fail to resolve spontaneously within 4–6 weeks [2,10]. In addition, ganciclovir treatment should be considered for immunocompromised patients with CMV gastrointestinal infection, such as patients with HIV and bone marrow or solid organ transplantation [1]. Additionally, *H. pylori* eradication can be attempted if the organism is detected, as it has been reported that *H. pylori* eradication resulted in disease regression in adult patients with Menetrier's disease [11]. However, in most cases, an initial pathogenic agent cannot be determined. Menetrier's disease has been reported in few oncology patients who were adults. This disease presented as a paraneoplastic phenomenon as in a 59-year-old man with relapsed plasma cell leukemia [5], a 21-year-old man with T-cell large granular lymphocyte leukemia [6], and a 68-year-old man with chronic lymphocytic leukemia/small lymphocytic lymphoma [12]. It also presented in two adults who were transplanted (allogeneic bone marrow transplantation), and both were associated with CMV and both cases regressed spontaneously within 1–3 months [13,14].

Menetrier's disease has not been reported earlier in children with hematologic malignancies. It was reported only in few children with neuroblastoma. It was thought to be due to either catecholamine effects on the gut (paraneoplastic syndrome) or lymphatic obstruction resulting from mass effect [15].

Our case had a classic presentation of Menetrier's disease; however, even in his immunocompromised state, his natural history was no different from the one expected. Anti-CMV therapy was started empirically because of his recent history of F/N and low-level CMV positivity but quickly discontinued because we believe that it was not related to his recovery. We think that the recent CMV positivity may have caused the Menetrier's disease, but unlike reported cases, we were not able to document CMV in his biopsies.

In conclusion, we report a case of Menetrier's disease (protein-losing gastropathy) in a child with acute leukemia. Menetrier's

disease should be considered in any patient with symptoms referable to the gastrointestinal tract and thickened stomach and bowel loops detected by radiologic imaging.

Compliance with ethics requirements

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included.

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