

Case report

Cytomegalovirus infection in a child with menetrier's disease: a case report

Eleni Volonaki¹, F. Haliotis¹, Catherine van Vliet-Constantinidou², S. Avlonitis¹, Eleftheria Roma³

SUMMARY

Pediatric Menetrier's disease, a rare hypertrophic gastropathy, has been associated with several infectious agents, the etiologic relevance of which remains to be elucidated. Clinical findings include vomiting, diarrhea, abdominal pain and anorexia, as well as peripheral edema in most cases. Pediatric Menetrier's disease is a transient condition usually resolving clinically within a few weeks, although endoscopic and radiologic resolution may take longer. We present a case of a two and a half year-old girl with Menetrier's disease who was admitted with vomiting and generalized edema secondary to hypoalbuminemia. An upper-gastrointestinal endoscopic examination was performed, which revealed severe Menetrier's gastritis, whereas cytomegalovirus was detected at biopsy specimens. Serology indicated acute cytomegalovirus infection. Patient received substitution therapy with plasma and human albumin, and was fed with MCT formula. She was discharged after two weeks. At follow-up, hypoalbuminemia was restored and patient remained asymptomatic.

Key-words: Menetrier's disease, hypertrophic gastropathy, Cytomegalovirus

INTRODUCTION

Menetrier's disease (MD) is a rare hypertrophic gastropathy which has been described in adults, as well as in the pediatric population. A small number of cases have been reported in neonates.^{1,2} In contrast with adult patients, where the course of the disease is more chronic and gas-

trectomy may be required in order to relieve symptoms, MD in childhood is considered a transient condition, usually resolving within five months.³ MD has been attributed to several infectious agents, although any etiologic association remains unclear.⁴

We present a two and a half-year old girl with MD associated with acute cytomegalovirus (CMV) infection, who was admitted to the hospital due to vomiting and periorbital edema. Diagnosis and management is described and the causative role of CMV in MD is discussed.

CASE REPORT

A previously well two and a half-year old girl presented with a four-day history of vomiting and swollen eyes. She was afebrile, her stool habits were normal and she had not received any medication.

On examination, she had mild periorbital edema and distended abdomen, without tenderness. Her weight was 12kg and blood pressure 107/50 mmHg. Soon after admission her clinical status deteriorated, as oliguria and marked peripheral edema were added.

Initial blood tests revealed anemia with profound iron deficiency (Hb 8 g/dl, Ht 32,7 %, MCV 50 fl, MCH 12,3 pg), white blood cell count 15.970/mm³ (41% neutrophils, 44% lymphocytes, 7% monocytes, 1% eosinophils, 7% atypical lymphocytes and 2% enucleated red blood cells), platelets 475.000/mm³, reticulocytes 2,3%, positive direct Coombs, while indirect Coombs was negative, ESR 10 mm/h and CRP 2,32 mg/l). The patient had hyponatremia (125 mmol/l), hypocalcemia (7,3 mmol/l) and severe hypoproteinemia with hypoalbuminemia (3,1 and 1,8 g/dl respectively). Urinary protein loss was excluded and her liver synthetic function was normal. Chest x-ray showed no pleural effusion, while cardiac ultrasonography revealed only a limited amount of pericardial fluid. Stool cultures,

¹Pediatrics, ²Pathology and ³Pediatric Gastroenterology, Athens University, «Aghia Sophia» Children's Hospital

Author for correspondence:

Eleni Volonaki, Thivon & Levadias Str., «Aghia Sophia» Children's Hospital, 11527 Goudi, Athens, e-mail: e.volonaki@yahoo.gr, Phone/ Fax: 0030-210-7467420

microscopic and parasitology, as well as anti gliadin, antiendomysial and anti-tissue transglutaminase antibodies were negative. Antibodies to common food allergens were not detected, and stool trypsin and sweat chloride levels were within normal limits. Abdominal ultrasonography and computed tomography showed spleen size at upper normal limits, enlarged kidneys (maximum 7.87 cm) with increased echogenicity of parenchyma, multiple enlarged mesenteric lymph nodes and a moderate amount of ascitic fluid.

An upper-intestinal endoscopy revealed scant nodules surrounded by normal mucosa at the lower third of the oesophagus, as well as marked multinodular duodenitis. The gastric body presented with marked edema, erythema, friability and enlarged rugal folds with patchy whitish exudates, namely marked Menetrier gastritis. Urease test was negative. Histologic examination confirmed a profound chronic active hypertrophic gastritis. Special stains and tissue culture for *Helicobacter pylori* were negative. Although Giemsa, Dako and Novocarska stains revealed no intranuclear CMV inclusion bodies and immunostaining with monoclonal antibody against CMV early antigen was negative, polymerase chain reaction (PCR) for CMV on gastric biopsy specimens was positive.

Serology for viruses, bacteria and parasites revealed positive serum IgM and IgG antibodies against CMV, as well as positive IgG antibodies against EBV, Coxsackie, Echo, Toxoplasma and *Helicobacter pylori*. CMV DNA was detected in blood and in bone marrow aspirate.

During her stay in the hospital, she received substitution therapy with packed red blood cells, plasma and human albumin, and she was put on MCT Peptide 1+. The patient was discharged in good clinical condition two weeks after her admission. At regular follow-ups over a three-month period, her hemoglobin, serum electrolytes and serum protein levels were normal and she was free of symptoms with satisfactory weight gain.

DISCUSSION

Hypertrophic gastropathy occurs at a mean age of 5 years in children, ranging from 2 days to 17 years of age. The most common clinical features are vomiting, diarrhea, abdominal pain, anorexia and peripheral edema, while ascites and pleural effusions may also be present. Hematemesis or melena due to gastric rugae ulceration occur rarely. Clinical recovery is common within 4 to 6 weeks, although radiologic and endoscopic resolution may take longer.^{3,4}

Hypoalbuminemia is a constant finding in pediatric Menetrier's disease. Enlarged edematous rugal folds is

the site of protein loss, which is thought to be secondary to inflammatory disruption of sulphated of vascular and connective tissue glycosaminoglycans, as observed in inflammatory bowel disease.⁵ As opposed to intestinal protein loss, stool α_1 -antitrypsin is less useful for documenting gastric protein loss, since it is degraded at $\text{pH} < 3$.⁶ Other diagnostic methods that have been used to demonstrate gastric protein loss are measurement of protein content in the gastric juice and $^{99\text{m}}\text{Tc}$ -labeled human serum albumin abdominal scintigraphy.⁷

Abdominal ultrasound showing thickened mucosal folds in gastric fundus and corpus may suffice to establish diagnosis of Menetrier's disease in uncomplicated cases. Barium study of the upper gastrointestinal tract will confirm gastric mucosal hypertrophy sparing pylorus, as well as normal small bowel appearance. Nevertheless, definite diagnosis is set with endoscopy and histologic examination, which enables the search of pathogens and the exclusion of serious medical conditions, especially in patients with atypical clinical features or symptoms that persist beyond two weeks.

Differential diagnosis of Menetrier's disease in childhood includes many other diseases. Eosinophilic gastroenteritis may also involve gastric antrum and small intestine and there is often a family history of allergic disorders. Primary gastric lymphoma presents with abdominal pain, weight loss and chronic clinical course. Gastric lymphoma and carcinoma are exceedingly rare in children and not related with edema or hypoproteinemia. On the contrary, gastric inflammatory pseudotumor, also rare in childhood, may appear as a gastric mass with hypoalbuminemia and diagnosis requires histologic examination. Other conditions associated with hypertrophic gastric folds, such as Crohn's disease and Peutz-Jeghers syndrome, have different signs and symptoms. Very rare diseases which have similar radiologic appearance with Menetrier's disease include Zollinger-Ellison syndrome, hypertrophic hypersecretory gastritis, gastric varices and lymphangiectasis. Endoscopy with histologic examination should be performed in all suspected cases.

Hypertrophic gastropathy has been associated with several infectious agents, such as CMV, adenovirus, enterovirus, *Helicobacter pylori* (HP), mycoplasma, herpes virus and *Giardia lamblia*.^{3,8} The etiologic relation among these agents and Menetrier's disease remains to be elucidated. In this case-report, CMV infection was shown not only serologically, but also with CMV DNA detection with polymerase chain reaction in blood, bone marrow aspirate and gastric biopsy specimen.

In many cases, association of Menetrier's disease with

CMV is established by urine culture or serology, which cannot discriminate primary infection from reactivation of a latent infection or reinfection with a different antigenic strain. Furthermore, CMV is persistently excreted for months to years after primary infection. The above raise the need for more specific diagnostic tests that provide direct evidence of gastric infection.

The identification of inclusion bodies in gastric biopsy specimen is not a safe diagnostic method, since their number during an acute infection can be relatively small. Immunohistochemical detection of the CMV early nuclear antigen is also used. In a study on pediatric Menetrier's disease, no CMV early nuclear antigen was detected in control patients (children with normal gastric mucosa, gastritis due to HP, non-specific gastritis or PGE1-induced hyperplasia). This fact indicates that CMV is neither an incidental organism under hyperplastic conditions nor a commensal organism superinfecting inflamed gastric mucosa.⁹ Direct evidence of gastric CMV infection can also be obtained by either gastric culture or detection of CMV nucleic acids by in situ hybridization and PCR.^{10,11} It seems that use of several approaches is needed to establish diagnosis of CMV infection in suspected Menetrier's disease, since no single diagnostic test has been shown to detect gastric CMV in all cases associated with the disease.

In our patient, negative urease test, Giemsa stains and tissue culture for HP excluded a possible association of the disease with the above microorganisms, which is common in children. Since HP is a treatable pathogen, eradication therapy has been suggested in HP-associated protein-losing hypertrophic gastropathy.¹² Simultaneous presence of gastric HP and CMV has been described in pediatric Menetrier's disease.¹³ Nevertheless, Oderda et al report failed to establish a causal relationship with HP, as HP infection was still present after resolution of the disease, while CMV in the urine had cleared.

Menetrier's disease of childhood is usually a benign and self-limiting condition. Albumin infusions is not a standard therapeutic procedure, as supportive therapy alone may lead to clinical resolution. In certain cases, though, total parenteral nutrition was required.³ Our patient was also treated with MCT Peptide 1+, a special formula containing medium chain triglycerides. MCTs enter blood circulation directly and do not aggravate co-existing lymphangiectasia, since they are not absorbed by lymphatics.

Conclusively, our report further supports a causal relationship between CMV infection and pediatric Menetrier's disease. Although several pathophysiologic mechanisms are implicated in the disease, CMV infection should always be considered in cases of abrupt onset and marked gastrointestinal protein loss. In accordance with existing bibliographic data, describing Menetrier's disease in children as a transient and self-limiting condition, our patient had a quick and full recovery.

REFERENCES

1. Knight JA, Matlak ME, Condon VR. Menetrier's disease in children: report of a case and review of the pediatric literature. *Pediatr Pathol* 1983; 1:179-186.
2. Konstantinidou AE, Morphopoulos G, Korkolopoulou P, et al. Menetrier disease of early infancy: a separate entity? *J Pediatr Gastroenterol Nutr* 2004; 39:177-182.
3. Fenoglio-Preiser CM, Noffsinger AE, Stemmermann GN, et al. Hypertrophic hyperplastic gastropathies. In: *Gastrointestinal Pathology. An Atlas and Text*. 2nd ed. Philadelphia: Lippincott Raven; 1999:209-213.
4. Jacobe S, Lam A, Elliott. Transient hypertrophic gastropathy [Case Report]. *J Pediatr Gastroenterol Nutr* 1998; 26:211-215.
5. Murch SH, MacDonald TT, Walker-Smith JA, et al. Disruption of sulphated glycosaminoglycans in intestinal inflammation. *Lancet* 1993; 341:711-714.
6. Gleason WA Jr. Protein-losing enteropathy. In: Wylie R, Hyams JS, eds. *Pediatric Gastrointestinal disease: Pathology, diagnosis and management*. 1993:536-543.
7. Lan JA, Chevru LR, Marans Z, et al. Protein-losing enteropathy detected by ^{99m}Tc-labeled serum albumin abdominal scintigraphy. *J Pediatr Gastroenterol Nutr* 1988; 7:872-876.
8. Eisenstat DDR, Griffiths AM, Cutz E, et al. Acute cytomegalovirus infection in a child with Menetrier's disease [Case Report]. *Gastroenterology* 1995; 109:592-595.
9. Sferra TJ, Pawel BR, Qualman SJ, et al. Menetrier disease of childhood: role of cytomegalovirus and transforming growth factor alpha. *J Pediatr* 1996; 128:213-219.
10. Hochman JA, Witte DP, Cohen MB. Diagnosis of cytomegalovirus infection in pediatric Menetrier's disease by in situ hybridization. *J Clin Microbiol* 1996; 34:2588-2589.
11. Pass FR. Cytomegalovirus infection. *Pediatrics in Review* 2002; 23:163-170.
12. Yamada M, Sumazaki R, Adachi H, et al. Resolution of protein-losing enteropathy by eradication of *Helicobacter pylori*. *Eur J Pediatr* 1997; 156:182-185.
13. Oderda G, Cinti S, Cangiotti AM, et al. Increased tight junction width in two children with Menetrier's disease. *J Pediatr Gastroenterol Nutr* 1990; 11:123-127.