CASE REPORT

Ménétrier's Disease Secondary to Cytomegalovirus Infection

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Abstract

Compared to nephrotic syndrome, gastrointestinal protein loss (exudative enteropathy) is rare in healthy children. Of these, hypertrophic gastroenteropathy is the most common entity, and cytomegalovirus is the most frequent causative agent. Coinfection with *Streptococcus pneumoniae* is even rarer. We report on a case of a previously healthy 16-month-old girl that was admitted with fever, diarrhea, abdominal distension, and generalized edema. Severe hypoalbuminemia was present, without proteinuria, with a C-reactive protein of 4.1 mg/dL. Upper gastrointestinal endoscopy revealed hypertrophy of gastric folds and histological cytomegalic inclusions, confirming the diagnosis of Ménétrier's disease secondary to cytomegalovirus infection. She was started on intravenous ganciclovir (21 days), human albumin infusion, bowel rest (19 days), and parenteral nutrition (22 days). Blood cultures were positive for *Streptococcus pneumoniae* and, consequently, she was treated with ceftriaxone (10 days). She experienced slow but progressive clinical improvement, with full recovery.
This case report serves to revisit this nosological entity, with the particularity of coinfection by cytomegalovirus and *Streptococcus pneumoniae*.

Keywords: Coinfection; Cytomegalovirus Infections; Gastritis, Hypertrophic/diagnosis; Gastritis, Hypertrophic/therapy; Infant; Pneumococcal Infections

Introduction

The Ménétrier's disease is a type of hypertrophic gastroenteropathy and an uncommon cause of hypoalbuminemia in adults and children.[1,2] Described by Ménétrier in 1888, it is characterized by the hypertrophy of gastric folds associated with secondary protein loss.[1]
The Ménétrier's disease in children occurs more frequently before the age of 5 years and is usually benign and self-limiting,[1] occurring spontaneous resolution in four to six weeks, with no sequelae.[3,4] It is often associated with infection by cytomegalovirus (CMV),[1] but can also be provoked by other infections (Epstein-Barr virus, herpes simplex virus type 1, *Helicobacter pylori*, or *Mycoplasma pneumoniae*), or by allergic pathology (eosinophilic enteropathy) or autoimmune reactions.[3,4]
The clinical presentation is characterized by the appearance of edema, ascites, or pleural effusion and by non-specific symptoms, such as vomiting, abdominal pain, and food refusal.[3] The diagnosis is confirmed by upper digestive endoscopy and histology.[1]
The infection by CMV is frequent (infection rate of 50%-80% in childhood), which is mostly asymptomatic. Pneumonia, hepatitis, and protein-losing enteropathy stand out as clinical manifestations. The laboratory diagnosis is made by serological tests, culture tests, or by molecular diagnostic techniques, namely the polymerase chain reaction.[2]
Concomitant infection by *Streptococcus pneumoniae* is rarely described in cases of Ménétrier's disease.[5]

Case Report

We report on a case of a previously healthy female child aged 16 months with a sudden onset of edema in the eyelids and limbs, abdominal distension, watery diarrhea, and fever. On examination, she was in good general condition and hemodynamically stable. She presented bilateral eyelid and lower limb edema, abdominal distention, and mild ascites. She showed no hepatomegaly, signs of portal hypertension, or of congestive heart failure.
In laboratory tests, severe hypoalbuminemia (17 g/L), without proteinuria, stood out. C-reactive protein was 4.1 mg/dL and renal function, hepatic function, and diuresis were normal. Abdominal ultrasound revealed mild ascites and thickening of the gastric wall. Serological tests for cytomegalovirus (CMV), Epstein-Barr virus (EBV), and *Mycoplasma pneumonia* were negative. Two blood cultures isolated *Streptococcus pneumoniae* and

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she was treated with intravenous ceftriaxone 50 mg/kg/day qd for 10 days. After 24 hours of antibiotic therapy she was apyretic.

She was maintained on complete bowel rest and was started on parenteral nutrition which was maintained for 22 days. In day two, the intestinal transit normalized. She underwent an upper gastrointestinal endoscopy which revealed a marked thickening of the folds in the gastric fundus and body, generalized erythema, and luminal mucous exudates. These findings were compatible with Ménétrier's disease. Biopsies were performed histology and immunohistochemistry for CMV, EBV, and herpes simplex virus 1 (HSV1) by polymerase chain reaction. Cytomegalovirus was detected (HSV1 and EBV were not detected) and histological analysis revealed cytomegalic inclusions confirmed with class-specific antibody, with marked regenerative foveolar hyperplasia, confirming the CMV gastritis diagnosis. Intravenous ganciclovir (10 mg/kg/day bid) was started at this time, while maintaining ceftriaxone.

The patient maintained severe hypoalbuminemia with a minimum value of 11.1 g/L and daily need for the infusion of human albumin until day five. Immunoglobulin assay revealed values below the normal range: immunoglobulin (Ig) A 0.16 g/L (0.22-1.78 g/L), IgM 0.33 g/L (0.35-2.0 g/L), and IgG 1.57 g/L (4.0-12.5 g/L).

Meanwhile, there was a progressive improvement of general condition, edema, and hypoalbuminemia. Restored oral feeding in day 19.

In day 28 of hospitalization, after 21 days of intravenous ganciclovir, the patient had a stable body weight, no edema, and laboratory testing showed no alterations, therefore the patient was discharged. She was reassessed in the pediatric gastroenterology clinic one month later, remaining clinically and analytically well, with the last albuminemia of 38.1 g/L.

Discussion

In the literature, a CMV-associated protein-losing enteropathy presentation is described as a form of benign hypertrophic gastropathy of childhood (Ménétrier's disease).

Ménétrier's disease is an uncommon entity in pediatrics, with the number of pediatric cases described to date of about 68.[4,6]

The analysis of the symptoms of these cases shows the presence of hypoproteinemic edema (88%) in its most severe state with anasarca, vomiting (78%), abdominal pain (45%), anorexia (40%), upper digestive hemorrhage (12%) as well as ascites.[1,7]

At the base of the pathophysiology of edema there is an inflammatory process that triggers abundant protein loss conditioned by hypertrophy of the gastric mucosa, increased mucus secretion, and gastric epithelial cell tight junction disruption, causing hypoalbuminemia.[2,4]

Besides albumin, there is also gamma globulin loss, translated by hypogammaglobulinemia, as seen in our case, with an increased risk of superinfection.[5,8]

In children, it is associated to CMV infection in about 30% of cases. It manifests itself in the first years of life and is more frequent in males.[2]

The association with *Streptococcus pneumoniae* infection is described in the literature but it is rare.[5] If there is ascites, spontaneous bacterial peritonitis is possible, but this situation is more frequent in chronic ascites in cirrhotic patients. In the present case, no paracentesis or culture of the ascitic fluid were made, which could have clarified the hypothesis.

For the differential diagnosis, all causes of pediatric digestive and extra-digestive protein loss should be considered, such as nephrotic syndrome, inflammatory bowel disease or exudative enteropathy, malformations of the intestinal lymphatic system, and other diseases including eosinophilic gastritis, allergic gastritis, Zollinger-Ellison syndrome, gastric lymphoma, and infiltrative carcinoma (these latter are very rare).[6]

Fecal alpha-1-antitrypsin, a protein resistant to degradation by digestive enzymes, can be used as an endogenous marker of protein loss through the digestive tract. Elevated levels are found in protein-losing enteropathies, having a role in determining the source of this loss.[9] However, no alpha-1-antitrypsin assay was performed in the patient, since upper digestive endoscopic was performed early.

In adults, partial or complete resection of the stomach is sometimes required as a form of treatment, but in children it is usually benign and self-limiting.[7] The evolution with spontaneous remission may explain the fact that it is rarely diagnosed in this age group.[2] Thus, the treatment is essentially supportive, relieving symptoms, providing comfort and treating intercurrences (namely infectious ones) in order to promote a faster recovery. When there is etiopathogenic agent isolation, this treatment is then directed to the possible cause, as in the case of CMV infection, with the recommended therapy being intravenous ganciclovir 10 mg/kg/day bid for a minimum of 14 to 21 days.[10] Due to the *Streptococcus pneumoniae* bacteremia there was also a need for antibiotic therapy with intravenous ceftriaxone 50 mg/kg/day qd for 10 days.

In the present clinical case, regardless of CMV serological testing being negative, the presence of cytomegalic inclusions, the detection of the virus by polymerase chain reaction in a biopsy fragment, and the presence of gastric hypertrophy upper gastrointestinal endoscopy, characteristic of hypertrophic gastropathy was important for the diagnosis.[2,3] Thus, the presence of the virus in the gastric and duodenal mucosa allows us to conclude that it is an enteropathy caused by CMV.[1-4]

The absence of positive serological testing may be related to the hypogammaglobulinemia, which occurs in approximately 40% of the cases, reinforcing the need for the multiple and complete evaluation of the presence of CMV.[11] Thus, the diagnosis should be made through serological and cultural examinations, molecular diagnostic techniques, such as upper digestive endoscopic, immunohistochemistry, and histology, each of which is of particular importance and complementarity.

With this case report, the authors would like to draw attention to the less frequent clinical manifestations of infection by CMV and to the importance of molecular diagnostic techniques, namely upper gastrointestinal endoscopy, which allow for a more accurate diagnosis.[7]

In fragile patients with hypogammaglobulinemia,[8] the risk of bacterial superinfection exists, and physicians should be alert to its presence,[5] as proven in this patient by the isolation of *Streptococcus pneumoniae* in blood culture.

It is estimated that the CMV-associated protein-losing hypertrophic gastropathy is an underdiagnosed entity.[12] Only children who present evident clinical deterioration, conditioned by excessive protein loss, as in the case reported, are subject to etiological study.[2,12]

This case is yet another report of the Ménétrier's disease in the pediatric age, which should be part of the diagnostic hypotheses for generalized edema and hypoproteinemic ascites due to loss through the digestive system (protein-losing enteropathy).

WHAT THIS CASE REPORT ADDS

- The cause of generalized edema of the pediatric age is not always renal, so protein-losing enteropathy shall be considered as a differential diagnosis.
- Ménétrier's disease shall be suspected before cases of gastrointestinal symptoms and hypoalbuminemia due to non-renal or hepatic causes.
- Gastrointestinal endoscopy and histological and molecular biology techniques are essential for the etiological diagnosis and establishment of a directed medical therapy, when possible.
- There is a relation of this nosological entity with cytomegalovirus infection.
- One must be aware of the risk of bacterial superinfection in these patients, which is aggravated by the immunoglobulin loss.
- In the pediatric age, although there is a possibility of complications secondary to protein loss and gastrointestinal manifestations, it is a disease with a benign course and most often with spontaneous remission.

Conflicts of Interest

The authors declare that there were no conflicts of interest in conducting this work.

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Doença de Ménétrier secundaria a infeção por CMV

Resumo:
Comparativamente ao síndrome nefrótico, a perda gastrointestinal de proteínas (enteropatia exsudativa) é rara na criança saudável. Destas, a gastropatia hipertrófica é a mais comum e o citomegalovírus o agente mais frequente. A co-infecção por *Streptococcus pneumoniae* é ainda mais rara.
Caso: menina de 16 meses, saudável, que iniciou febre, diarreia, distensão abdominal e edema generalizado. Constatada hipoalbuminémia grave, sem proteinúria, proteína C reativa de 4,1 mg/dL. A endoscopia digestiva alta revelou hipertrofia das pregas gástricas e a anatomia patológica inclusões citomegálicas, confirmando o diagnóstico de Doença de Ménétrier secundária a infeção por citomegalovírus. Iniciou ganciclovir ev (21 dias), perfusão de albumina humana, pausa alimentar (19 dias) e alimentação parentérica (22 dias). As hemoculturas foram positivas para *Streptococcus pneumoniae*, associando-se ceftriaxone (10 dias). Houve melhoria clínica progressiva, mas lenta, com recuperação total.
Serve este caso para revisitar esta entidade nosológica, com a particularidade de haver co-infeção por citomegalovírus e *Streptococcus pneumoniae*.

Palavras-Chave: Coinfeção; Gastrite Hipertrófica/diagnóstico; Gastrite Hipertrófica/tratamento; Infeções por Citomegalovirus; Infeções Pneumocócicas; Lactente