Clinical Case

Gastric Adenocarcinoma in a 13-year-old adolescent associated to *Helicobacter pylori* infection

Adenocarcinoma gástrico en un adolescente de 13 años asociado a infección por *Helicobacter pylori*

Emilia Rojas, Bach[1*], *Camilo Gómez, Bach*[1*], *Margarita Aldunate, MD*[2], *Ricardo Avila, MD*[3], *Rodrigo Contreras, MD*[3], *Mónica González, MD*[3], *Claudia Greppi, MD*[3], *Juan Ignacio Juanet, MD*[3], *Roberto Mondaca, MD*[3], *Daniel Pizarro, MD*[3], *Cristian Quezada, MD*[3], *Marianela Rojas, MD*[3], *Marcela Toledo, MD*[3], *Luis Velozo, MD*[3], *Yalda Lucero, MD-PhD*[2,4,5]

[1]School of Medicine, Faculty of Medicine, University of Chile.
[2]Department of Pediatrics and Pediatric Surgery, Faculty of Medicine, University of Chile.
[3]Hospital Roberto del Río, Santiago, Chile.
[4]Microbiology and Mycology Program, Institute of Biomedical Science, Faculty of Medicine, University of Chile.
[5]Pediatric Gastroenterology Unit, Clínica Alemana de Santiago, Facultad de Medicina, Clínica Alemana-Universidad del Desarrollo.
*These authors contributed equally.

Abstract

A 13-year-old male with neurofibromatosis type 1, a history of Burkitt's lymphoma treated at the age of 5, and chronic malnutrition presented with pyloric stenosis. Upper gastrointestinal endoscopy showed severe pyloric obstruction associated with intense nodular gastritis, confirming *Helicobacter pylori* infection. Despite *H. pylori* eradication and endoscopic balloon dilation of the pyloric area, symptoms persisted, and imaging revealed an extensive transmural infiltrative process in the antropyloric region. A benign cause was suspected, leading to a partial gastrectomy and gastrojejunal anastomosis. However, biopsies confirmed gastric adenocarcinoma (GAC) with signet ring cells. Staging studies showed metastases in lymph nodes, peritoneum, and lungs, which did not respond to chemotherapy, ultimately leading to palliative care and the patient's death. GAC is extremely rare in children, with only a few cases directly linked to *H. pylori* infection. The multifactorial etiology of GAC involves genetic predisposition, particularly relevant in pediatric cases, as well as chronic inflammation and bacterial virulence factors. Early diagnosis is challenging due to nonspecific symptoms, highlighting the need for a high index of suspicion in at-risk patients.

Key words: gastric adenocarcinoma, gastric cancer, *Helicobacter pylori.*

Resumen

Varón de 13 años con neurofibromatosis tipo 1, antecedente de linfoma de Burkitt tratado a los 5 años y desnutrición crónica, se presentó con cuadro de estenosis pilórica. La endoscopia digestiva alta mostró una obstrucción pilórica severa asociada con gastritis nodular intensa, confirmándose infección por *Helicobacter pylori*. A pesar de la erradicación del *H. pylori* y dilatación endoscópica con balón de la zona pilórica, los síntomas persistieron, y las imágenes revelaron un extenso proceso infiltrativo transmural en la región antropilórica. Se sospechó una causa benigna, por lo que se realizó una gastrectomía parcial y anastomosis gastro-yeyunal. Sin embargo, las biopsias confirmaron un adenocarcinoma gástrico (ACG) con células en anillo de sello. Los estudios de etapificación mostraron metástasis en ganglios linfáticos, peritoneo y pulmones que no respondieron a la quimioterapia, lo que condujo a cuidados paliativos y finalmente el fallecimiento del paciente. El ACG es extremadamente raro en niños, con solo unos pocos casos reportados en relación directa con la infección por *H. pylori*. La etiología multifactorial del ACG involucra predisposición genética, especialmente relevante en casos pediátricos, así como inflamación crónica y factores de virulencia bacteriana. El diagnóstico temprano es un desafío debido a los síntomas inespecíficos, lo que subraya la necesidad de mantener un alto índice de sospecha en pacientes de riesgo.

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Corresponding author:
Yalda Lucero
ylucero@uchile.cl

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Introduction

The pyloric stenosis, although not a common cause of pediatric gastroenterology consultation, is relevant due to the severity of the diagnoses that could be involved. While oncological causes are infrequent in pediatric patients, they should not be entirely disregarded if there are red-flag symptoms and a high index of suspicion.

Below, we present the case of an adolescent with pyloric stenosis in whom endoscopic biopsies did not show evidence of malignancy. Still, full-thickness samples of the antropyloric region revealed gastric adenocarcinoma with signet ring cells. This case underscores the importance of comprehensive diagnostic approaches, including imaging and full-thickness biopsies, especially when initial endoscopic biopsies are inconclusive.

Case Presentation

A 13-year-old male with a history of neurofibromatosis type 1, colon Burkitt's lymphoma treated effectively by surgery and chemotherapy consisting of methotrexate at the age of 5 years, and chronic malnutrition with short stature, was admitted to our hospital because of a 2-month history of persistent vomiting, intermittent severe upper abdominal pain, and weight loss (at least 5kg). Abdominal ultrasound was normal, and the patient was admitted for further study and management. A first upper gastrointestinal endoscopy (UGE) showed abundant food content in the stomach due to pyloric obstruction; diffuse and intense nodular gastropathy was also evidenced (Figure 1A). Rapid urease test was positive, and gastric biopsies confirmed severe gastritis with abundant *Helicobacter pylori*. First-line eradication therapy with amoxicillin 1g, clarithromycin 500mg, and omeprazole 20mg twice a day was used for two weeks according to international pediatric guidelines[1]. A second UGE was carried out one week after admission because of the persistence of vomits and poor ingestion to perform balloon pyloric dilatation and nasojejunal tube (NJ tube) placement. A follow-up UGE 3 weeks after antimicrobial treatment to verify eradication revealed persistent diffuse nodular gastropathy with positive *H. pylori* by rapid urease test and biopsies. Culture and antimicrobial susceptibility testing were not performed because they were unavailable in our center. Second-line therapy with levofloxacin, metronidazole, amoxicillin, and omeprazole for 2 weeks was administered, and eradication was successful. The patient partially improved, tolerating pureed food, allowing for removing the NJ tube, and was discharged 6 weeks after admission.

The patient relapsed with vomiting and was readmitted two weeks later due to severe dehydration and hypovolemic shock associated with acute kidney injury and severe hypokalemia. An abdominal ultrasound showed irregular thickening of the pyloric canal, and a UGE evidenced no passage of gastric content through the pylorus, with eroded and friable antral mucosa (Figure 1B). The patient underwent a Braun gastrojejunal anastomosis due to the need to allow feeding in a patient without an oncological diagnosis at that

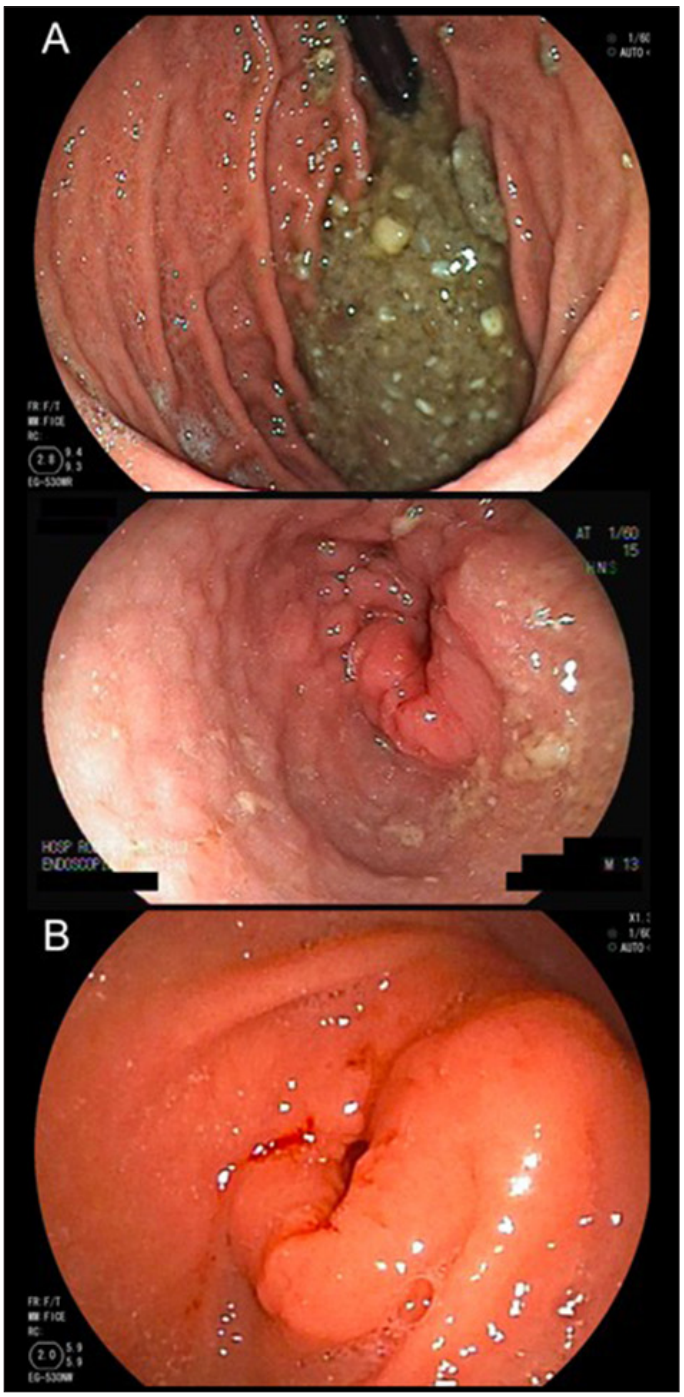

Figure 1 Endoscopic visualization of gastric mucosa at diagnosis and after readmission with pyloric stenosis. **(A)** Upper gastrointestinal endoscopy (UGE) at diagnosis showed abundant food content at fundus level associated with an obstructive pre-pyloric mass that prevents distal passage. Gastric mucosa at the fundus, body, and antrum appeared very nodular with a positive urease test. **(B)** UGE performed after readmission showed an edematous pylorus with increased folds besides an eroded and friable mucosa at the antrum.

moment, during which full-thickness pylorus and regional adenopathies were biopsied. Histopathological analysis of the gastric specimen showed infiltration of smooth muscle tissue by a combination of positive Periodic Acid-Schiff fused cells and signet ring cells, consistent with undifferentiated gastric adenocarcinoma (GAC) (Figure 2A); a similar pattern was evidenced in biopsied regional lymph nodes. Positron-emission tomography-computed tomography (PET-CT) revealed a primary antropyloric neoplasm associated with metastatic perigastric and hepatic hilum lymph nodes and small pulmonary nodules. Partial gastrectomy, extended lymphadenectomy, and Roux-en-Y gastrojejunal anastomosis were performed, and the anatomopathological analysis of these specimens (Figure 2B, 2C) revealed a poorly differentiated GAC infiltrating serosa, lesser omentum, and peripancreatic tissue, with lymph node metastasis.

The patient did not respond to chemotherapy, and a subsequent computed tomography scan revealed peritoneal carcinomatosis. Palliative care was initiated, and the patient passed away one month later.

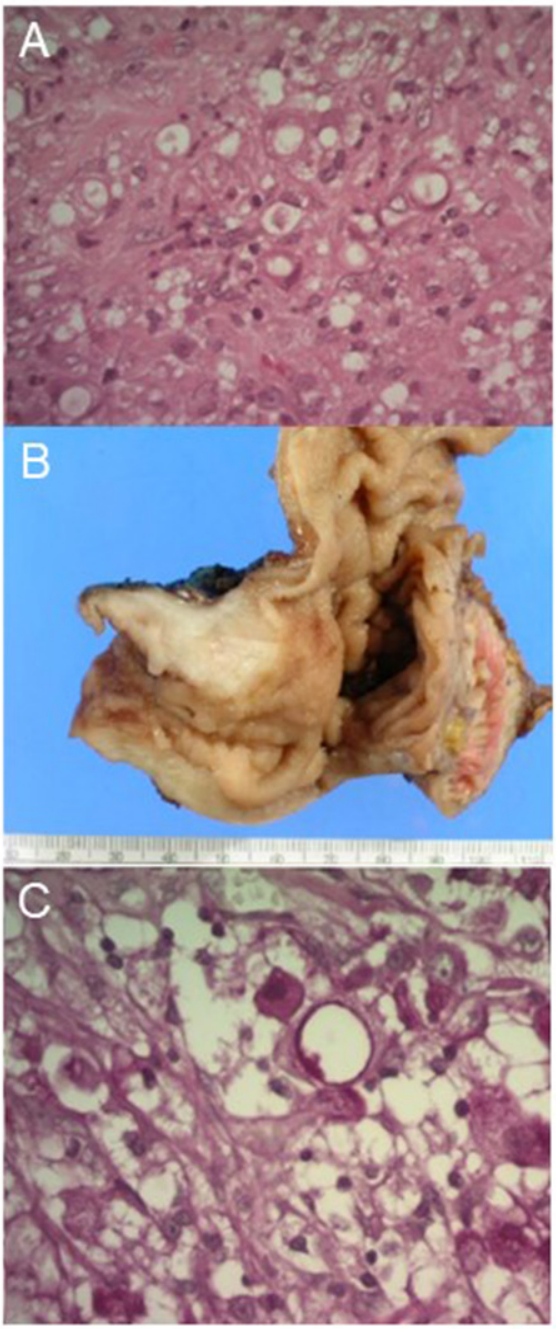

Figure 2. Anatomopathological findings of gastric specimens. **(A)** Smooth muscle layer from the first gastric specimen obtained in the Braun gastrojejunal anastomosis surgery; extensive infiltration by a mixed neoplasm of fused Periodic Acid-Schiff positive cells and signet-ring cells. 40x. **(B)** Macroscopic view of the specimen representing antrum and stenotic pyloric canal resected during the partial gastrectomy. **(C)** Microscopic aspect of the smooth muscle layer of the antropyloric region, compatible with a poorly differentiated gastric adenocarcinoma with signet-ring cells, 100x.

Discussion

The GAC is a neoplasm that affects glandular cells of the gastric mucosa. It is the fifth most common cancer in adults worldwide, with 1.1 million new cases diagnosed and 770,000 deaths in 2020[2]. On the other hand, gastric cancer is extremely rare in the pediatric population, representing only 0.05% of all cancers, with GAC an even more infrequent cause[3].

Of approximately 31 cases of GAC reported in children, only 6, including this report, have been associated consistently with *H. pylori* infection. Table 1 summarizes those patients' clinical and histological characteristics[3-7]. Okuda et al.[6] surveyed 518 Japanese Hospitals with Pediatric Services, of which 349 answered, reporting 4 cases of gastric cancer in children, of whom only 1 was tested and confirmed for *H. pylori* infection.

The etiology of GAC is multifactorial, with *H. pylori* infection being one of the main risk factors in adults. Indirect effects through triggering of unregulated gastric chronic inflammation and dysbiosis, in addition to direct damage due to its virulence factors such as cytotoxin-associated gene A (cagA) and vacuolating cytotoxin gene A (vacA), have been involved in the role of *H. pylori* in GAC pathogenesis[3,5]. These phenomena require decades to transition from chronic gastritis to atrophic gastritis, metaplasia, dysplasia, and finally, GAC. Genetic susceptibility has been suggested as a major factor in subjects developing GAC at a young age, as was likely the case with our patient[3,6]. The association between Epstein-Barr Virus (EBV) and GAC development has also been described. This is another factor to be considered in this case due to the history of Burkitt's lymphoma and its potential relation to EBV[8].

Children, especially those from developing countries, can be infected during their first years of life with *H. pylori*. Although most of them will remain asymptomatic, approximately 10% will develop symptoms during their school years

Table 1. Clinical Characteristics of Reported Pediatric Patients with *Helicobacter pylori* (+) and Gastric Adenocarcinoma

Author	Nº of patients	Onset age	History	Symptoms of first visit	egd	Imaging	Histology	HP status	Prognosis
Harting et al, 2004[7]	1	8	Maternal family history of cancer	Intermittent abdominal pain	10x5 cm gastric mass	CT scan and PET with progressive disease including metastasis	Infiltrating poorly differentiated ADC with focal signet ring cells, and active chronic gastritis	+	Alive after 15 months
Slotta et al, 2011[2]	1	15	Autosomal recessive agammaglobulinemia	Growth failure, malnutrition and megaloblastic anemia	Severe antropyloric stenosis	MRI confirmed stenosis from a semicircular intramural tumor	Invasive ulcerating moderately differentiated gastric ADC of the intestinal type, and chronic atrophic corpus gastritis type A	+	Alive after 4 months
Al-Hussaini et al, 2014[4]	1	10	None	Progressive intermittent vomiting, epigastralgia, weight loss, fatigability and bone aches	Thickened antral mucosa occluding the pylorus, and a clean base 2x1.5 cm ulcer	CT scan revealed marked thickening of antral wall and pyloric channel and densities suggestive of celiac lymphadenopathy	Active chronic gastritis grade IV, and poorly differentiated signet ring cell ADC	+	Death after a few months
Riera-Llodrá et al, 2015[8]	1	12	None	Epigastralgia associated to vomiting, diarrhea, asthenia and distended abdomen	EGD was performed for the biopsy to be carried out	CT scan revealed abundant ascites and peritoneal implants	Signet ring gastric ADC positive for e-cadherin and p53	+	Death after 2 months
Okuda et al, 2019[3]	1	12	Paternal family history of gastric cancer	Epigastralgia and tarry stool	Not described	Not described	Moderately to poorly differentiated signet ring cell ADC	+	Alive after 15 months

EGD, Esophagogastroduodenoscopy; HP status, *Helicobacter pylori* status; CT scan, Computed tomography scan; PET, Positron-emission tomography; MRI, Magnetic resonance imaging; ADC, Adenocarcinoma.

and eventually could present peptic ulcer disease and/or gastric mucosal atrophy, a known preneoplastic lesion, suggesting that the neoplastic cascade could be activated at a young age. The patient, in this case, did not have peptic ulcer disease but presented an intense and diffuse nodular gastropathy. This usually benign mucosal reaction is highly prevalent in children infected with *H. pylori*, and eradication treatment is generally not indicated, as a clear association with symptoms has not been established, and there is no evidence pointing to its role in the neoplastic pathway[9]. However, in this case, the intensity of the phenomena, with pyloric narrowing, supported eradication therapy and initially distracted from considering a neoplastic cause of the obstruction. First-line therapy failed, although antibiotics were administered using a nasojejunal tube with complete adherence and supervision. This eradication failure was probably due to antimicrobial resistance, based on the 21% of clarithromycin resistance described in Chilean children[10]. Second-line therapy was successful in our patient, but the carcinogenic process could not be reversed.

The few reported cases suggest that clinical presentation of GAC in children is usually nonspecific, with symptoms such as upper abdominal pain, persistent vomiting, and weight loss[3-7]. Upper abdominal pain is a common manifestation of functional and organic gastrointestinal pathologies, being GAC an extremely rare but relevant condition to be considered. In the presence of upper abdominal pain with red flags, UGE should be performed to visualize mucosa and

take biopsies, including the search for *H. pylori* infection in patients to whom eradication treatment could be indicated. GAC may compromise deep layers, even serosa and benign alterations in mucosa samples should not completely rule out a neoplasm. In the context of transmural compromise in imaging, full-thickness biopsies are advisable.

Although GAC is extremely infrequent in children and adolescents, patients with genetic conditions predisposing to cancer development or immunosuppression and symptoms suggestive of peptic ulcer disease, especially in countries with a high prevalence of *H. pylori* infection, should be evaluated for this infection through biopsy-based tests and consider eradication even in the absence of ulcers. A high index of suspicion for GAC is required to diagnose it at early stages and provide prompt treatment.

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