Gastric Adenocarcinoma With Signet Ring Cell: A Case Report of a 10-year-old Girl.

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Research Article

Keywords: Gastric Adenocarcinoma, signet-ring cell carcinoma, gastric carcinoma, gastric cancer, stomach neoplasms, children

Posted Date: August 3rd, 2021

DOI: https://doi.org/10.21203/rs.3.rs-738601/v1

Abstract

Background

Gastric cancer is an extremely rare diagnosis in children and adolescents. Representing 5% of neoplasia's in childhood. Gastric adenocarcinoma has a prevalence of below 0.05% of all childhood cancers. The objective of this clinical case report is to describe the clinical presentation of this rare cancer in children, including it as a differential diagnosis, and to look for genetic causes in order to perform genetic counseling.

Case presentation

A 10 year old girl, experience epigastric pain, vomit and weight loss in 2 months period. Previously treated with proton pump inhibitors (PPIs), however without improvement of symptoms. Physical exam revealed a slim appearance, and a firm, painful, palpable mass in the upper abdomen. Esophagogastroduodenoscopy revealed a mass with neoplastic appearance. Biopsy report described a poorly differentiated, diffuse pattern of signet ring cells, with positive immunohistochemical studies for the expression of MLH1, MSH6; PMS2. *H. pylori* was negative. Because this cancer presented during childhood, CDH1 gene was analyzed, however no findings of pathologic variants, point mutations, or duplications or deletions were found. The patient underwent hospice care and died 7 months after the initial diagnosis.

Discussion/Conclusion

The majority of gastric tumors during childhood are benign. Gastric adenocarcinoma is a rare diagnosis in pediatric patients. Currently, there are few reports of children with this cancer. The rarity of gastric adenocarcinoma with signet ring cells in pediatric patients makes early diagnosis difficult to make with treatment options limited to the pediatric population due to rarity, and worse prognosis. Knowledge of this disease in children could help physicians to identify atypical clinical manifestations and warning signs in order to have this as a differential diagnosis. Currently, genetic studies are essential to guide the treatment plan and to make genetic counseling to the patient and family members.

1. Introduction

Gastric cancer is an extremely rare diagnosis in children and adolescents. Representing 5% of neoplasia's in childhood, lymphomas and sarcomas being the most frequent. Gastric adenocarcinoma has a prevalence of below 0.05% of all childhood cancers (1, 2). Gastric adenocarcinoma with signet ring cells specifically does not have a precise reported incidence in children (3, 4).

Development of gastric adenocarcinoma in children are theorized by three main ways: de novo, secondary to a polyposis syndrome, or secondary to gastric lymphoma treatment (4, 5). In adult patients, the main risk factors are clearly described, such as diet, tobacco, and *Helicobacter pylori (H. pylori)*

infection. However, in children these risk factors are still unknown and studies that correlate the possible etiology and other risk factors are lacking (6, 7). Recently, *H. pylori* infection in children has been reported to be associated with cancer due to an ongoing chronic inflammation in the gastric mucosa that eventually generates gastric atrophy, especially at the gastric antrum (2, 8). The strongest associations for the development of gastric cancer in children are gene mutations that have been reported. There are variants described in genes such as CDH1, KRAS, TP53, APC, MLH1, and ERBB2 (9).

To our knowledge, there are relatively few pediatric cases of gastric adenocarcinoma with signet ring cells reported. This case report aims to describe the clinical presentation of this rare cancer in children, including it as a differential diagnosis, and to look for genetic causes in order to perform genetic counseling.

2. Case Report

A 10 year old female patient, who presented to the emergency department with 2 months of epigastric pain, vomit with undigested food, and 11 kg weight loss. Previously treated with proton pump inhibitors (PPIs), however without improvement of symptoms. Physical exam revealed a slim appearance, and a firm, painful, palpable mass in the upper abdomen. Cardiopulmonary system and extremities were normal without neurological deficits. Initial laboratory tests showed anemia, and normal hepatic and renal studies.

Thoracic and abdominal CT scan reported concentric wall thickening of the body and gastric antrum, with adjacent enlarged lymph nodes. Esophagogastroduodenoscopy revealed a mass with neoplastic appearance, pyloric antrum with subepithelial infiltrative phenomenon, and critical stenosis of the pylorus. Biopsy report described a poorly differentiated, diffuse pattern of signet ring cells, with positive immunohistochemical studies for the expression of MLH1, MSH6; PMS2 (Fig. 1). *H. pylori* was negative. These results confirmed the diagnosis of gastric adenocarcinoma with signet ring cells.

The patient underwent a staging laparoscopy with evidence of neoplastic seeding in the peritoneum, peritoneal fluid, and left diaphragm. Peritoneal immunohistochemical studies were positive for cytokeratin that indicated metastatic involvement. Because this cancer presented during childhood, CDH1 gene was analyzed, however no findings of pathologic variants, point mutations, or duplications or deletions were found.

In a joint decision, Pediatrics, adult oncology, pediatric surgery, and palliative care decided that the patient would receive treatment with cisplatin and 5-fluororacil with palliative intention, additionally parenteral nutrition support. By the end of the third cycle of chemotherapy, the mass reduced in size with improvement of symptoms and better food tolerance. Before the fifth cycle, control CT showed a new concentric thickening of the gastric wall associated with peritoneal carcinomatosis, ascites, collapse of small bowel loops and partial distention of the colon. Despite progression of the disease, the patient continued on chemotherapy because of the improvement in symptoms and quality of life. The patient underwent hospice care and died 7 months after the initial diagnosis.

3. Discussion

The majority of gastric tumors during childhood are benign. Gastric adenocarcinoma is a rare diagnosis in pediatric patients. Currently, there are few reports of children with this cancer. In 1999, *Sasaki H et al*. reported a case of an 11 year old female patient with gastric adenocarcinoma located at the gastric esophagus junction and referenced 21 other cases with similar histopathology, all were children between 11–19 years (10). *Subbiah V et al.* collected 4.204 patients with diagnosis of gastric cancer between 1990 and 2008, just 5 of those patients were under 18 years of age, which represent just 0.11% in almost an18 year period (2).

Lu J et al. reported the case of a 12 year old female patient with gastric adenocarcinoma with signet ring cells, who presented with similar clinical manifestation as our patient, unfortunately with a late diagnosis (11). Zheng Na et al. Collected 15 patients between 1993–2014 with a diagnosis of a space-occupying gastric injury, in ages 8 months and 13 years. Those patients had similar clinical presentation to the patient of this report such as fever, upper abdominal pain, and blood in stool, but just 1 patient had a diagnosis of gastric adenocarcinoma, 60% of the remaining patients had benign lesions (12).

Bonilla-Lanza et al. Reported a case of a 17 year old patient with gastric adenocarcinoma with signet ring cells, who initially presented with epigastric tenderness, vomit and weight loss and later development of ascites and peritoneal carcinomatosis. Undergoing palliative treatment (13). In all previously reported cases, upper abdominal pain was the leading symptom at initial presentation. Peritoneal carcinomatosis was a late clinical presentation, common in all the cases mentioned. The age range for initial symptoms was between 8 and 20 years. The majority of the biopsy reports described gastric adenocarcinoma.

The genetic causes of gastric cancer have been studied in the last decades. CDH1 gene, which codifies for E-cadherin, a transmembrane glycoprotein that is related to cellular adhesion has been previously related with diffuse gastric cancer with signet ring cells (14, 15). CDH1 loss of function mutations generate an increase in cellular proliferation rate and are related with gastric cancer but with breast, colorectal, thyroid, and ovarian cancer as well (16). Huntsman Et al. studied CDH1 gene mutations in two families that had the index case below 25 years of age with gastric cancer. They reported some family members who were pathologic mutation carriers, 5 of them underwent total gastrectomy with biopsy result of signet ring cells malignant cells (17).

The majority of cancer that develops is associated with a pathology variant in CDH1 gene which has an early onset in patients below 40 years, 30 to 50% of those cases are point mutations, and 5% are deletions or duplications (18). Other studies have reported an association with MAP3K6 and CTNNA1 genes and germinal mutations, but currently there is not a solid correlation as to CHD1 gene, which makes these genes poorly used in clinical practice.

In regard to the patient in our case, there was no family or personal history as a risk factor and because of the early onset of symptoms, de novo disease was suspected, and genetic studies were performed. CDH1 sequencing was performed without any pathologic variants reported. Gene sequencing for APC,

KRAS, TP53, MLH1, and ERBB1 were not performed because it would not change the course of action and genetic counseling (8, 19, 20).

In a Colombian population study, APC, KRAS, TP53 were analyzed by gene sequencing in 59 patients between 12 and 94 years of age with gastric and colon cancer, they reported that APC gene (15.3%) was the most common affected gene, followed by KRAS (10.1%) and TP53 (5.1%). They did not include CDH1 gene. Which increased the importance to developing studies that included CDH1 and with focus on the pediatric population.

4. Conclusion

The rarity of gastric adenocarcinoma with signet ring cells in pediatric patients makes early diagnosis difficult to make with treatment options limited to the pediatric population due to rarity, and worse prognosis. Knowledge of this disease in children could help physicians to identify atypical clinical manifestations and warning signs in order to have this as a differential diagnosis. Currently, genetic studies are essential to guide the treatment plan and to make genetic counseling to the patient and family members.

Declarations

Acknowledgements: The authors would like to thank Pathology Department of Universidad de Antioquia in Medellin, Colombia.

Funding: No funding was received.

Conflict of interest: The authors have no conflict of interest to disclose.

Ethics approval: All procedures followed have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Case report was approved by the Hospital Universitario San Vicente de Paul Ethic Board Committee. No. 25-2019.

Consent to participate and for publication: Informed consent was obtained from the patient mother for this case report.

Availability of data and material: Not applicable.

Code availability: Not applicable.

Author Contributions: All authors collected the data (clinical history and test), Jose Tascon Arcila, Lizeth Marin Gomez, and Luisa Parras Rodas prepared the manuscript and contributed equally to the article.

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Figures

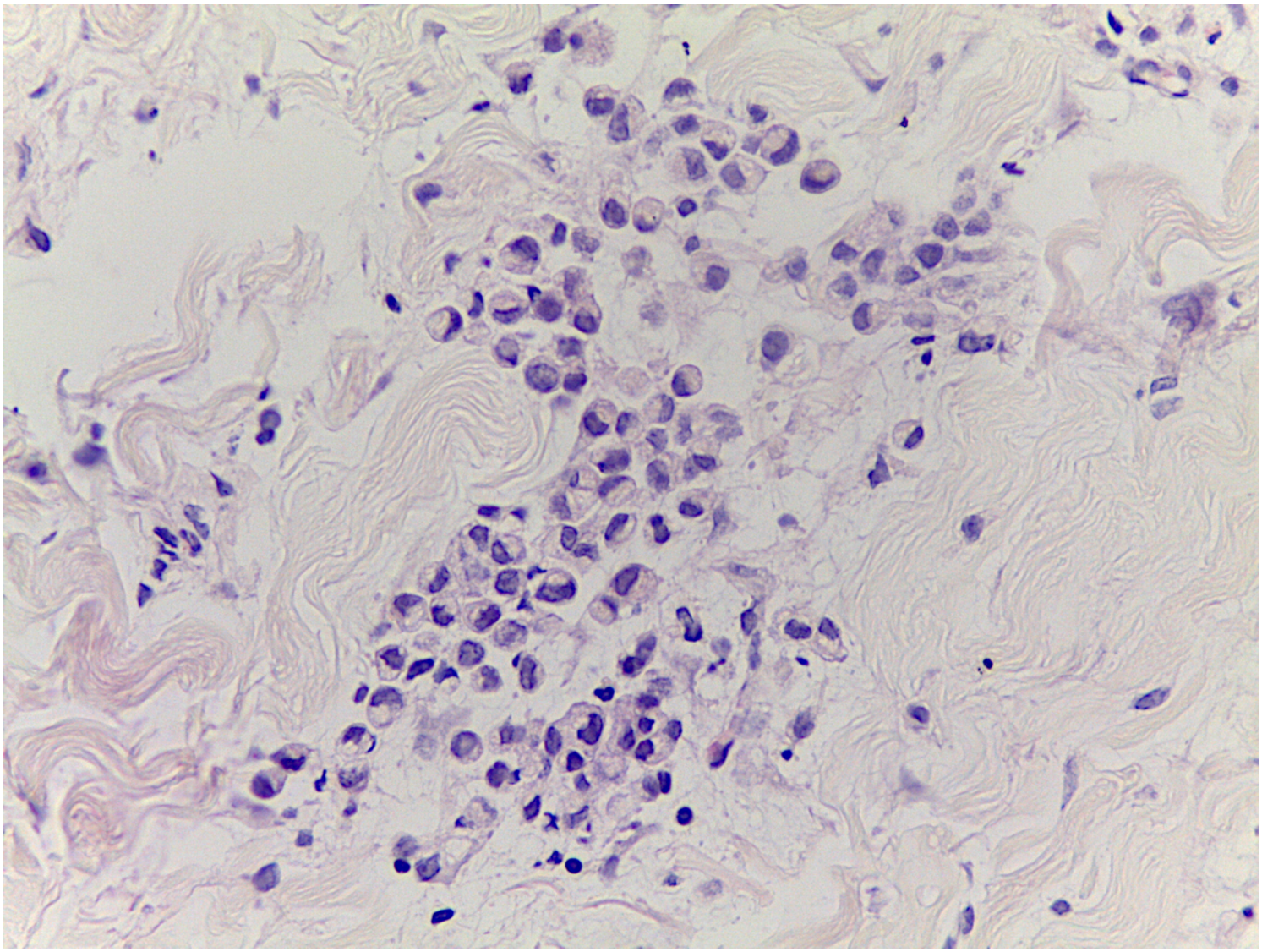

Figure 1

Fibrous stroma and diffuse infiltrate due to signet ring cell malignant epithelial neoplasia. (40X). Source: Pathology Department, School of Medicine, Universidad de Antioquia. Medellin, Colombia.