Gastrointestinal Neuroendocrine Tumors in Two Children

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Background: Enterochromaffin-like cell hyperplasia and neuroendocrine tumors are relatively rare in childhood. Case characteristics: A 15-year-old girl who presented with epigastric pain and a 6-year-old boy who was admitted with hematochezia. Endoscopy revealed nodules in the stomach in Case 1, and polyploid lesion in the rectum in Case 2. Outcome: Enterochromaffin-like cell hyperplasia in Case 1 and neuroendocrine tumor in Case 2. Message: A low index of suspicion for neuroendocrine tumors in children can result in delay in the detection of these rare but potentially malignant diseases.

Key words: Abdominal pain, H. pylori, Hematochezia.

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Neuroendocrine tumors (NETs) – slow-growing tumors that arise from cells within the neuroendocrine system — are rarely seen in childhood [1,2]. The incidence in children and adolescents is low at 2.8 per million population under the age of 30 years. Despite their low incidence, NETs represent the most frequent tumor of the gastrointestinal tract in children [3].

Enterochromaffin-like (ECL) cell hyperplasia constitutes the substrate for the development of gastric NETs type 1, which represents the most common (65–75%) type of gastric NETs. There is increasing diagnosis of NETs of the colon and rectum [4]. We present two cases of NETs and ECL cell hyperplasia.

CASE REPORTS

Case 1: A 15-year-old girl presented with a 3-month history of epigastric pain which was unresponsive to a 2-month course of proton pump inhibitor (PPI). Physical examination was unremarkable. Complete blood count, metabolic panel, lipase, C-reactive protein, erythrocyte sedimentation rate, and celiac serology were normal. Esophagogastroduodenoscopy revealed numerous 2 to 4 mm nodules in the body of the stomach and in the transitional and pyloric region. The histopathological investigation demonstrated focal intestinal metaplasia and ECL cell hyperplasia in the stomach. Synaptophysin staining highlighted an increase in ECL cells within the glands (linear hyperplasia) and florets of ECL cells in the lamina propria (nodular hyperplasia) (Fig. 1). Helicobacter pylori staining was positive. Further laboratory evaluation revealed serum gastrin: 293.6 pmol/L (Normal 6.2-54.8), anti thyroglobulin: 322.7 IU/mL (Normal 0-115), and anti-Jo-1 positive. Serum vitamin B₁₂, calcium, parathormone, adrenocorticotropic hormone, free serum T₃, and free serum T₄ levels were normal. The PPI treatment was stopped after the result of the serum gastrin level was available. An abdominal computed tomography scan was normal. The secretin stimulation test was negative. Endoscopic and pathological investigations were repeated one year after diagnosis. H. pylori staining was negative and the histopathological findings were similar to those seen on the earlier biopsies. In the second year of follow-up, she had no significant abdominal pain. Third esophagogastroduodenoscopy revealed multifocal atrophic gastritis and focal intestinal metaplasia. ECL cell hyperplasia was identified in the cardia, corpus and antrum-corpus junction. Additional laboratory reports included anti-parietal cell antibodies positive and chromogranin A elevated at 298.5 ng/mL (Normal 0-100). Serum gastrin level was high (376 pmol/L) despite no use of PPI after the diagnosis. Given her negative evaluation for H. pylori, positive anti-parietal cell antibodies and gastric pathology, the patient was diagnosed with autoimmune metaplastic atrophic gastritis (AMAG) with associated ECL cell hyperplasia.

Case 2: A 6-year-old boy was admitted with abdominal pain for two weeks and hematochezia for 2 days. The physical examination, upper gastrointestinal system endoscopy, routine laboratory findings and Meckel scintigraphy were unremarkable. Colonoscopy revealed polyploid architecture (0.6 cm in diameter) located in the rectum and 5 cm from the anal verge (Fig.
Endoscopic resection was performed and the histopathological examination was consistent with a NET (Fig. 2b and 2c). Hematochazia was not observed during the hospitalization period. Due to the low risk of metastatic spread, and as the tumors were small (<1 cm, without muscularis invasion), we planned to perform endoscopic investigation every year.

**DISCUSSION**

There are three situations in which clinicians suspect ECL-cell hyperplasia. The simplest is when a nodule or polyp is identified by the endoscopist. The second situation involves the evaluation of gastric atrophy, and finally in PPI use as a result of iatrogenic hypergastrinemia [5]. Initially, atrophic gastritis was not determined in case 1, although she had nodules in the stomach with history of PPI use.

Neuroendocrine nests are seen on the hematoxylin and eosin-stained sections; there is no need to perform special staining. ECL cells, typically found in the gastric corpus, are rare or absent in other compartments of the stomach [5]. ECL cells were identified in the cardia, corpus and antrum-corpus junction in Case 1. Long-standing hypergastrinemia and, acid suppression exerts a proliferative pressure on ECL cells, especially in the presence of *H. pylori* infection [6]. The time of ECL hyperplasia regression after *H. pylori* eradication is not known. In Case 1, there was PPI use together with *H. pylori* infection. At follow-up, 1 year after diagnosis, *H. pylori* was negative in the endoscopy examination but ECL had not regressed. Surveillance endoscopic biopsy revealed *H. pylori*–negative atrophic gastritis.

To date, there have been few published information regarding ECL cell hyperplasia in children [7]. ECL
hyperplasia together with autoimmune thyroid disease and autoimmune gastritis has been previously reported [8]. Anti-thyroglobulin antibody was positive in case 1. Colonic and rectal NETs are also very rare in children [9]. Due to the low risk of metastatic spread, tumors that are small and confined to the mucosa or submucosa can be managed with endoscopic resection. Hindgut NETs have a substantial risk of relapse after resection and need to be followed up for at least 7 years [4]. In case 2, a small rectal tumor (<1 cm, without muscularis invasion) was excised, and it was planned to perform endoscopic investigation every year.

Chromogranin A levels correlate positively with ECL cell mass in patients with AMAG [10]. Only a small fraction of hindgut NETs produce and secrete serotonin or other bioactive hormones [3].

In conclusion, gastric NETs are usually solitary and large and have frequently metastasized by the time of presentation. Pediatric gastroenterologists and pathologists must be aware that NETs can begin at a young age, and their immediate precursors such as ECL cell hyperplasia develop in the pediatric age group.

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