

CASE REPORT

Zollinger-Ellison syndrome: an unusual case of chronic diarrhoea in a child

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Abstract

Most cases of Zollinger-Ellison syndrome (ZES) are described in adults. It is a rare disorder in childhood. Most cases present with abdominal pain due to peptic ulceration and chronic diarrhoea not responding to general measures. The symptom complex is initially confused with other more common diseases, which lead to a delay in diagnosis. We present a rare case of a 12-year boy who initially presented with abdominal pain, diarrhoea, vomiting and progressive weight loss for over a two-year period before he was finally diagnosed as a case of ZES with the primary tumour in the pancreatic head and with multiple metastasis in both the liver and lymph nodes.

Keywords: Zollinger-Ellison syndrome, child, chronic diarrhoea, pain abdomen

INTRODUCTION

The Zollinger-Ellison syndrome (ZES) is characterized by gastric hypersecretion, recurrent and atypical peptic ulcerations and gastrin-producing pancreatic islet cell tumour or gastrinoma. It was first reported by Zollinger and Ellison in 1955 in 2 adult patients at Ohio, USA.¹ Although, Jackson reported the first paediatric case of ZES in 1963, it is still considered a rare disorder in childhood.² The overall incidence of gastrinoma is 0.5-3 new cases per million population per year.³ It is even more rare in the paediatric age group. A prospective case series of pancreatic tumours in the paediatric age group reported only one case of gastrinoma over a 9-year period in Italy.⁴

Common clinical features are abdominal pain, watery diarrhoea or steatorrhea, peptic symptoms and weight loss of varying degrees. Considering its rarity and the lack of experience among physicians treating this condition in paediatric patients, a high index of suspicion is required to diagnose as well as to manage these patients. We report a rare case of a 12-year-old boy who presented initially with diarrhoea, abdominal pain, vomiting and progressive weight loss over a two year duration and was subsequently

diagnosed as a case of ZES with the primary tumour in the pancreatic head and with multiple metastasis in both the liver and lymph nodes.

CASE REPORT

A 12-year-old boy presented to our centre with a two-year history of abdominal pain, diarrhoea, vomiting and weight loss. The abdominal pain was intermittent, burning in nature, located in the epigastric region, moderate to severe in intensity and temporarily decreasing in intensity with the intake of antacids. The abdominal pain was associated with multiple episodes of non-bilious, non-projectile, small volume vomiting that occurred almost daily. He passed out loose to semisolid large volume stools 4-5 times daily which intermittently contained visible oil. However, the stool was not noticed to contained blood or mucus. He sustained a weight loss of 7 kg over the last 2 years with maintenance of his appetite. Therapeutically, he received multiple courses of both antibiotics and antihelminthic drugs. In addition, he also received 6 months of anti-tuberculous therapy, and was also treated with steroids and mesalamine therapy in view of the possibility of Crohn's disease. However, none of these therapeutic interventions resulted

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FIG. 1: CECT abdomen shows an exophytic soft tissue density mass in pancreatic head region (thin arrow).

in improvement of symptoms. The family history was unremarkable. On clinical examination, he was pale and had sustained loss of subcutaneous fat. The abdominal and other systemic examinations were unremarkable.

Laboratory findings

The laboratory investigations revealed a haemoglobin value of 8 gm% with a microcytic, hypochromic picture. His stool examination, serum electrolytes, renal function tests and liver function tests were unremarkable. The coeliac and HIV serology workup were negative. Interestingly, the upper GI endoscopy displayed multiple linear ulcers both in the mid and lower parts of the oesophagus involving the gastro-oesophageal junction, along with concomitant prominent folds in the body of the stomach. In addition, the scope displayed multiple superficial

ulcers in the antrum as well as the first, second and third parts of the duodenum. At this point, possibility of Zollinger-Ellison syndrome was formed as a differential diagnosis.

Basal acid output were noted to be 14 meq/hr (normal <5 meq/hr). Fasting serum gastrin levels were significantly elevated at >8000 pg/ml (normal <125 pg/ml). Abdominal ultrasound showed a 3.3 x 2.3 cm heteroechoic lesion in the head of the pancreas along with multiple hypoechoic lesions in the liver parenchyma. Contrast enhanced CT abdomen displayed a well-defined enhancing lesion in the head of the pancreas with multiple enhancing lesions in the liver parenchyma (Fig. 1). Whole body Gallium-68 dotatate PET/CT demonstrated a dotatate uptake in the lesion present at the head of the pancreas, liver and gastrohepatic region (Fig. 2A&B). USG guided FNAC from

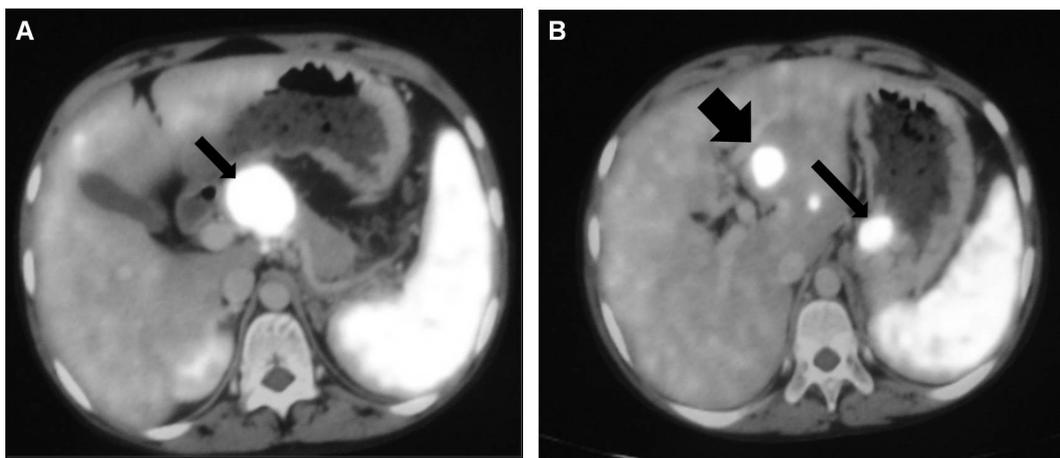


FIG. 2: Gallium-68 dotatate PET/CT show dotatate uptake by the lesion in the head of the pancreas (Thin arrow) [A], and in the liver (Thick arrow) and gastrohepatic region (Thin arrow) [B].

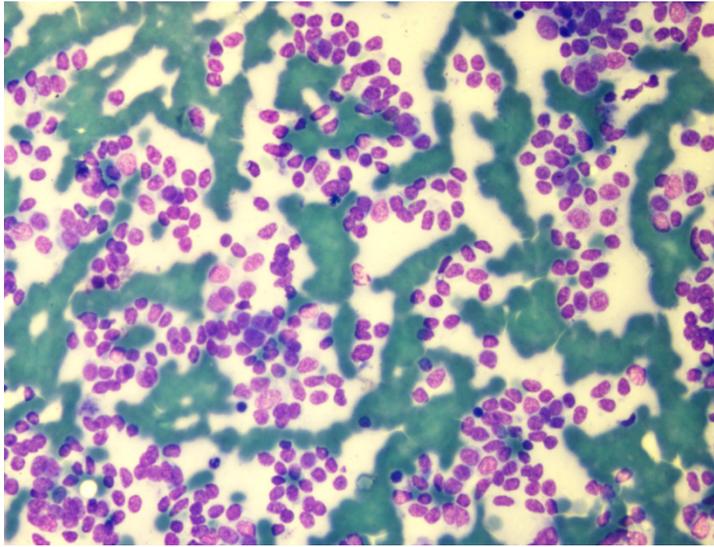


FIG. 3: Abundant discrete round monomorphic cells in the fine needle aspiration cytology smear of the pancreatic space-occupying lesion indicative of a neuroendocrine tumor. (May Grunwald Giemsa X 40)

the pancreatic as well as liver lesions confirmed the neuroendocrine nature of the tumour (Figs. 3 & 4). The immunocytochemical stain for chromogranin on FNAC smears was positive. A clinical diagnosis of ZES with primary in the pancreas and multiple liver and lymph nodal metastasis was finally concluded. Unremarkable additional supporting investigations like MRI brain, USG neck, serum calcium, phosphorous, parathyroid hormone, prolactin, insulin like growth factor-1 and thyroid function tests further ruled out the possibility of MEN syndrome.

Clinical course

The patient was commenced on high dose proton pump inhibitors (PPIs) which immediately alleviated the clinical symptoms of abdominal pain, diarrhoea and vomiting. Currently the child is under oncology follow-up and is being considered for additional chemotherapy and somatostatin analog therapy.

DISCUSSION

The Zollinger-Ellison syndrome is characterized

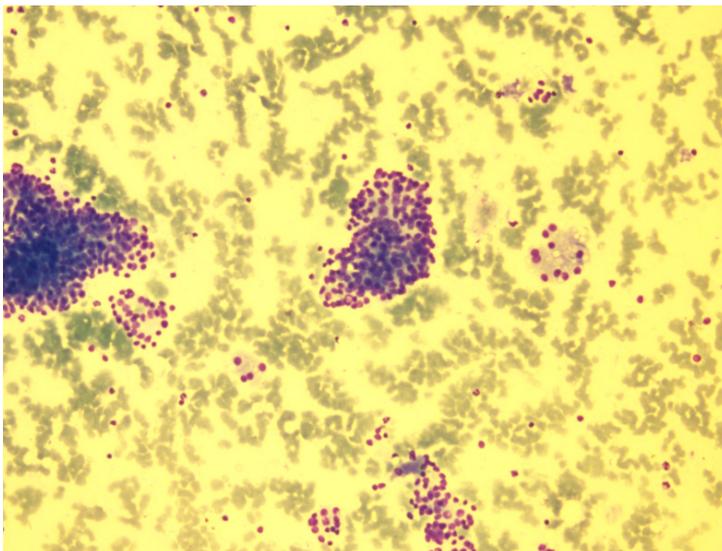


FIG. 4: Loose clusters and discrete cells occasionally arranged as rosettes in the fine needle aspiration cytology smear of liver swelling in metastatic neuroendocrine tumor of pancreas. (May Grunwald Giemsa X 20)

by hypersecretion of gastric acid and hypergastrinemia resulting in diarrhoea, peptic ulcer disease, and weight loss.⁵ It is an uncommon disease of adults, in whom it is responsible for 0.1 to 1% of total peptic ulcer disease cases.⁶ Children account for only 1% of total cases of ZES, which makes it a rare disease in the paediatric age group.⁷

More than 90% of cases are diagnosed between the ages of 20 to 60 years.⁸ The index case presented at the age of 12 years. The time gap between onset of symptoms and diagnosis was 2 years in the index case, which is much shorter than the usual reported average gap of 5 to 6 years in adults.^{8,9} This may be due to the less frequent use of strong antacids like PPIs in the index case, which usually suppress the symptoms of the disease, hence delaying the diagnosis. To prevent delay in diagnosis of ZES, any child presenting with the following should be evaluated for ZES: chronic diarrhoea, abdominal pain and weight loss, oesophageal symptoms or oesophageal stricture, recurrent or refractory ulcers or ulcers at atypical sites associated with recurrent hematemesis, gastric outlet obstruction or perforation, family history of peptic ulcer disease or endocrinopathies, prominent gastric rugal folds on endoscopy and chronic diarrhoea not responding to gluten free diet, lactose free diet or other specific treatments like anti-tuberculous treatment as well as steroids and mesalamine.^{8,9}

ZES is traditionally associated with a severe, fulminant ulcer diathesis, often present with multiple ulcers in unusual locations such as the post-bulbar region of the duodenum and proximal jejunum. Due to increasing recognition of this syndrome, as well as the availability of a radioimmunoassay for serum gastrin, most patients with neuroendocrine tumour now present with either milder forms of peptic ulcer disease, or with secretory diarrhoea.¹⁰ Endoscopy of the index case revealed multiple ulcers in the distal two-third of the oesophagus, gastro-oesophageal junction, pyloric antrum and duodenum, along with concomitant prominent folds in the body of the stomach.

The syndrome can exist in multiple forms, including benign sporadic, malignant metastatic, and as part of the MEN-I syndrome. Approximately 66% of gastrinomas are sporadic. Sporadic tumours are reported to be malignant in approximately 40-85% of cases. The duodenum has been shown to be the most common site and identified in 43-77% of patients, although they can occur in the pancreas. Duodenal wall

tumours are frequently small and multiple. Sporadic tumours occurring in the pancreas tend to be solitary as in the index case.¹¹

Abdominal pain and diarrhoea are the most common symptoms and reported in around 70%, followed by heartburn in 44%, vomiting in 25% and weight loss in 17% of patients.¹² The index case presented with abdominal pain, diarrhoea, vomiting and weight loss. Diarrhoea usually occurs due to increased acid production which causes direct damage to the small intestinal mucosa, precipitates bile acids as well as inactivates pancreatic enzymes, leading to malabsorption as well as weight loss.⁹ Increased acid production also leads to peptic symptoms like abdominal pain and vomiting. These symptoms are well controlled with high doses of strong antisecretory agents like PPIs, as in the index case.

About 60-90% cases of gastrinomas occur in gastrinoma triangle, which is formed by the junction of the cystic and common bile ducts posteriorly, junction of the pancreatic neck and body medially and junction of the second and third part of duodenum inferiorly.⁸ Other less commonly described sites for the primary tumor are lymph nodes, liver, ovary, mesentery, renal capsule, omentum, jejunum, pylorus and interventricular septum of the heart. About 60-90% of the gastrinomas are malignant with liver, lymph node and bone being the most common sites for metastases.^{8,9} In the index case, the primary was present in pancreatic head which is within the gastrinoma triangle, with multiple hepatic and lymph nodal metastases.

Over 98% of ZES cases have fasting hypergastrinemia and BAO >10 meq/hr is present in more than 94% of ZES cases.^{9,13} Both criteria were fulfilled in the index case. Furthermore, FNAC of both pancreatic lesion as well as liver metastases confirmed the neuroendocrine nature of the tumour.

Computed Tomography is the initial imaging modality of choice. But somatostatin receptor scintigraphy with an indium-111-labeled somatostatin analog (octreotide) has a higher sensitivity and specificity for detecting primary as well as metastatic disease.¹⁴ Proton pump inhibitors alone are helpful to give relief from symptoms as in the index case. Surgical management, chemotherapy, somatostatin analog therapy and various other modalities are available to treat ZES cases, based on individual cases. The Index case treated with high dose PPIs and currently he is under oncology follow-up and is

being considered for additional chemotherapy and somatostatin analog therapy. The ZES cases with primary in the pancreas, a large primary and liver metastasis have a poor prognosis.⁹ The estimated 5 year survival for metastatic disease is 35%, suggesting a poor prognosis for the index case.¹⁵

Conclusions

The Zollinger-Ellison syndrome is a rare diagnosis in childhood. It commonly manifests with abdominal, chronic diarrhoea, vomiting and weight loss. A high index of suspicion is required to make the diagnosis. It should be considered in a child with painful diarrhoea when all other common causes have been ruled out. Somatostatin receptor scintigraphy is the most important imaging modality for diagnosing gastrinomas. Proton pump inhibitors are useful in amelioration of the symptoms in most of the cases. The prognosis depends on the site and size of the primary tumour as well as on the presence of metastatic disease.

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