Primary Lymph Node Gastrinoma: A Rare Cause of Abdominal Pain in Childhood

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Summary: Gastrinoma is a hormone-secreting tumor associated with the Zollinger-Ellison syndrome. It is quite rare among children. The discovery of gastrinomas in unusual locations such as lymph nodes, bones, ovaries, and the liver poses a diagnostic dilemma as to whether the tumor is primary or metastatic. Here, we present a case of a primary gastrinoma within a lymph node.

Key Words: gastrinoma, lymph node, children

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Gastrinomas in childhood are rare, accounting for < 5% of all gastrinomas. The first description of signs and symptoms related to this tumor was reported by Zollinger and Ellison in 1955.[1] The Zollinger-Ellison syndrome (ZES) is characterized by gastric hypersecretion, recurrent and atypical peptic ulceration, and a gastrin-producing pancreatic islet cell tumor.[2] It accounts for 0.1% to 1% of peptic ulcer disease in adults.[2] Since its first description, < 60 cases have been reported in children.[3–7]

During childhood, gastrinomas are hardly ever diagnosed due to difficulties related to their clinical and radiologic characterization. Diagnosing gastrinoma in an unusual location such as a lymph node poses a dilemma as to whether the tumor is primary or metastatic. To our knowledge, only a few adult cases and 1 child case of primary lymph node gastrinoma with no identifiable tumor in the duodenum and pancreas have been reported in the literature.[3,8–13]

In this manuscript, we present the case of an 11-year-old boy, who complained of recurrent upper abdominal pain and was diagnosed with a gastrinoma in the lymph node.

CASE REPORT

An 11-year-old boy with frequent relapses of abdominal pain has been studied at the Pediatry Clinic of Mersin University Medical School for a 6-month period. The pain was localized in the periumblical region was intermittent and cramping and aggravated with food intake. During the entire hospitalization period, he denied having fever, chills, joint pain, and skin rash. There was no family history of gastrointestinal disorders. During the course of the disease, the frequency and severity of the paroxysmal abdominal pain increased gradually accompanied with nonbilious vomiting. The patient was consequently referred to the Mersin University Medical School. Upon admission to the Medical School, the initial physical signs were stable. Blood count, serum electrolytes, liver function tests, amylase, lipase, and the coagulation profile were normal. Abdominal ultrasonography revealed a solid hypoechoic nodular lesion of 28×18 mm, which was located posterior to the left hepatic lobe. The stomach was distended with fluid despite 12 hours of fasting. Dynamic multislice computed tomography (CT) examination (Toshiba-Aquillon, 64 detector system) of pancreas was performed with intravenous contrast and peroral water. Water was used for optimal visualization of the gastric and duodenal wall. An ovoid nodular lesion with well-defined margins was detected between the pancreas and the left lobe of the liver on the CT examination (Fig. 1). The lesion was 3×2 cm in size, was slightly indenting the pancreatic parenchyma, and had a similar density to the pancreas on both non–contrast-enhanced and contrast-enhanced series. No lesion was seen in the pancreas. Endoscopy was conducted due to the radiologic findings. Upper gastrointestinal endoscopy revealed multiple linear ulcers at the distal 1/3 of the esophagus, prominent gastric folds and generalized nodularity of the gastric mucosa, and ulcers at the duodenum bulb without evidence of *Helicobacter pylori* infection. The histopathologic examination of pathology of the esophagus, the stomach, and duodenum revealed only mild chronic inflammation. ZES was suspected and confirmed by high fasting serum gastrin levels (ie, 550 and 968 pg/mL on 2 different occasions). Gastrin levels were measured at 15-day intervals. Parathyroid hormone and calcium levels were normal. Magnetic resonance imaging of hypophysis was normal. Somatostatin receptor imaging (In-111 Octreoscan) was performed with a dual-head gamma camera equipped with a medium-energy collimator. Whole-body and 256-matrix static images were taken 24 hours after intravenous injection of 5 mCi Indium-111-pentetreotide. After single-photon emission computed tomography (SPECT), study of the abdomen was also performed. Scintigraphic evaluation revealed intensive radiopharmaceutical uptake in the upper abdominal region located above the left kidney posterior to the left liver lobe. Another pathologic uptake was also observed on the right side of the abdomen at the level of right kidney (Fig. 2). In explorative laparotomy, a 4×3 cm regular, bilobular solid mass was found. The solid mass was protruding from the minor omentum located next to the minor curvature of the stomach. After the mobilization of the duodenum and the pancreas, a second mass of 0.8×0.5 cm was found around the head and neck regions of the pancreas and was resected. Other lympadenopathy or metastatic focus were not determined. The histologic examination of the larger mass showed a tumor confined to the lymph node, which still showed a small rim of lymphatic tissue at the margin (Fig. 3A). Histologic examination of the smaller mass showed similar morphology. The tumor consisted of medium-sized tumor cells with uniform oval-round orthochromatic nucleus and narrow cytoplasm, which formed trabculae and organoid pattern in a collagen rich stroma (Fig. 3B).

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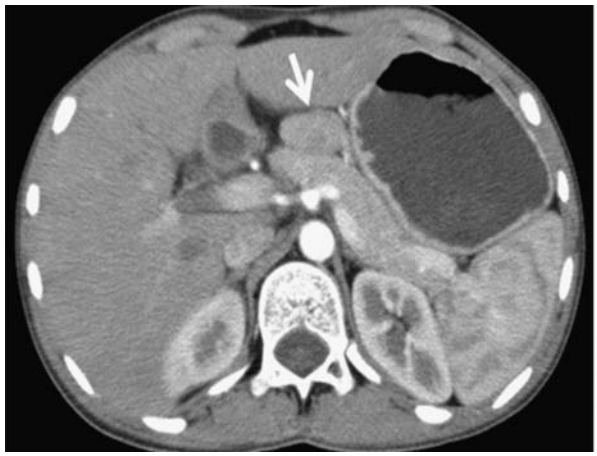

FIGURE 1. On computed tomography, a solid mass was seen between pancreas and left lobe of liver (white arrow).

With these findings, neuroendocrine differentiation of the tumor was considered in the differential diagnosis. To verify this differentiation gastrin, chromogranin A, synaptophysin, and neuron-specific enolase (NSE) were performed immunohistologically.

The tumor cells showed strong reaction to gastrin antibody (Fig. 4A). The staining intensity was less for chromogranin A, synaptophysin, and NSE (Figs. 4B-D) than gastrin in both masses that showed similar immunohistochemical staining.

The postoperative period was uneventful, and the patient has been free of symptoms, ever since. The patient was clinically followed-up with through ultrasound, scintigraphy, and gastrin level examinations at 3-month intervals (a duration of 6 mo), and then through ultrasound only at 3-month intervals (for an additional 2 y). No further suspicious mass was detected and the gastrin levels normal throughout the follow-up period. In addition, annual In-111octreotide scintigraphy was also performed, with no anomaly detected. The patient has been disease-free for 2.5 years after the initial diagnosis.

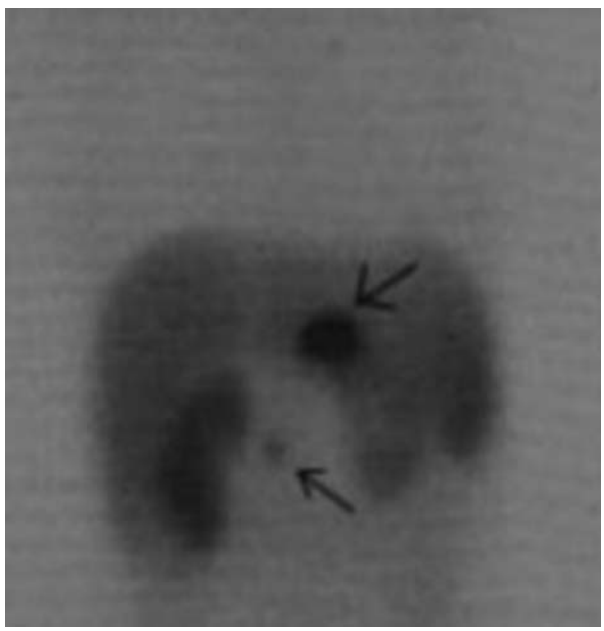

FIGURE 2. Octreoscan has revealed 2 focuses of radiopharmaceutical uptake in the upper abdomen (arrows).

MATERIALS AND METHODS

Histologically, 5-μm-thick sections of the lymph node samples were obtained from 10% formaldehyde paraffin-embedded tissues. Hematoxylin-eosin staining was performed to all samples. The deparaffinized sections were pretreated with citrate buffer, pH: 6 and incubated with hydrogen peroxidase for 10 minutes before primary antibody incubation. Immunohistochemical staining was performed similarly for gastrin (Lab Vision; RB-1459-R7, 1/100 dilution), chromogranin A (Neomarkers; 91125903A, 1/100 dilution), synaptophysin (Neomarkers; 901A, 1/100 dilution), and NSE (Neomarkers; AP-9003, 1/1600 dilution) using standard streptavidin-biotin immunoperoxidase method. Positive and negative controls were included in the staining procedure for each antibody. The staining pattern was evaluated under the light microscope using Olympus BX50.

DISCUSSION

Gastrinoma is a rare (0.5 to 1.5 new cases per million population per year) pancreatic endocrine tumor in children.[10] Gastric acid hypersecretion, peptic ulceration, and even diarrhea are symptoms of the gastrinoma.[14] The most common symptoms of gastrinomas are abdominal pain and diarrhea found in 75% and 73% of patients, respectively.[15] Clinical conditions including prolonged course of peptic ulcer despite treatment and peptic ulcer with diarrhea should alert the clinician for an underlying ZES. Prominent gastric folds and unusual locations of ulcers are also important signs. The mean age of the onset of ZES is approximately 41 years. Only 3% of the patients have a disease onset under the age of 20. As ZES may present many vague and common gastrointestinal symptoms, the correct diagnosis is often delayed by 4 to 6 years. The duration of the symptoms in the case presented in this manuscript was 2 years.

When ZES is suspected, elevated fasting gastrin levels >5- to 10-fold of normal range (normal limit <125 pg/mL in fasting children) and/or positive secretin test with increased gastric level after secretin administration confirms the diagnosis. Further radiologic survey is necessary to locate the tumor.[16]

The common location is the gastrinoma triangle, which lies between the pancreas, duodenum, and the junction of the cystic duct and the common bile duct. Pancreas and duodenum are the most common sites of primary tumors. Tumors may even coexist at both locations (1.9% to 10%). Other sites include lymph nodes, liver, heart, bile ducts, and ovaries.[3,7–10,14] The lesion in our patient was in the gastrinoma triangle similar to other reported cases.[14] The pathologic examination of the surgical specimen showed gastrinoma only in the lymph node, and hence was diagnosed as primary lymph node gastrinoma.

Most gastrinomas arise in the pancreas. The existence of primary lymph node gastrinomas, however, has been controversial. It is debatable whether these gastrinomas arise primarily in the lymph node or represent metastasis from a primary tumor located in the duodenum or the pancreas. Possible explanations include spontaneous regression of the primary tumor (eg, similar to lateral aberrant thyroid and melanoma), a missed microscopic

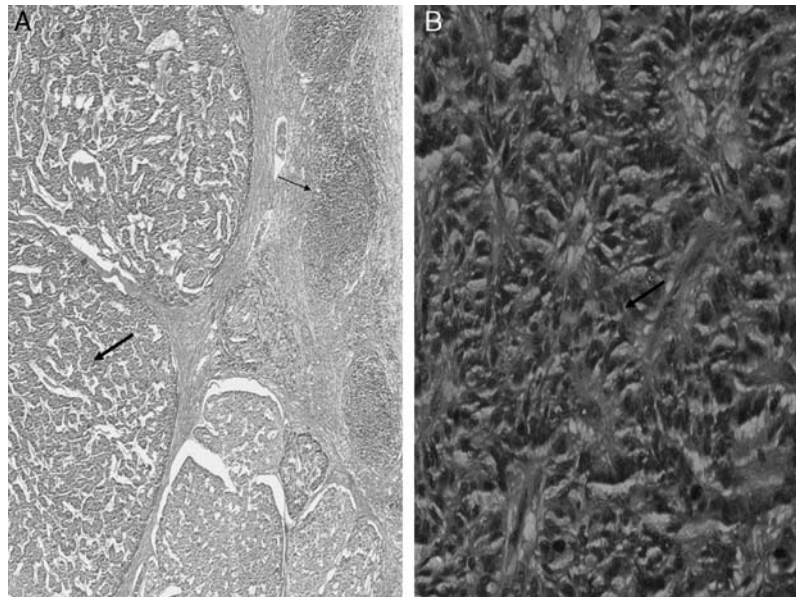

FIGURE 3. Histologic features of the tumor. A, The tumor cells which were seen at the big mass were localized within a lymph node, which still showed a small rim of lymphatic tissue at the margins (H-E, ×40). (Thick arrow shows tumor cells, thin arrow shows lymphoid tissue). B, Medium-sized tumor cells have uniform oval-round orthochromatic nucleus and narrow cytoplasm-formed trabeculae and organoid fashion that were embedded in a collagen-rich stroma (H-E, ×400) (Thick arrows show tumor cell). H-E indicates hematoxylin-eosin.

focus of the primary tumor at the duodenal wall, and gastrinomas that arise from aberrantly migrated G cells of the fetal pancreas.[3,8,9] Passaro et al[17] hypothesized that the precursor cells of gastrinoma originating from the ventral pancreatic bud are dispersed during dorsal rotation in the embryonic period and get incorporated into the developing lymphatic tissue in the vicinity of the pancreas.

In large series of neuroendocrine tumors, the overall scan detection rate of somatostatin receptor imaging (octreoscan) was reported as 88%. With endocrine pancreatic tumors, the sensitivity of octreoscan has been reported as high as 95% to 100% for gastrinomas.[18,19] In the detection of metastatic gastrinomas, octreoscan is established as being more sensitive than the conventional imaging modalities such as ultrasound, CT, magnetic resonance imaging, and angiography. Although sensitivity for small lesions (< 1 cm) is limited, performing SPECT increases detectability.[18,19] The lesions of our patient were detectable both on the planar images and the SPECT examination.

Between 20% and 50% of gastrinoma cases have multiple endocrine neoplasia syndrome (ie, the MEN-1 syndrome), which is associated with tumors of the parathyroid, pancreatic islets, and pituitary gland.[14,20] Our patient had no family history of cancer. It has been suggested that other endocrine glands such as the adrenal, parathyroid, thyroid, and pituitary glands should also be evaluated. The radiologic and ultrasonographic evaluation of the endocrine glands of our patient did not reveal any other sign of endocrine disorder. According to these findings, MEN-1 was ruled out and the patient was diagnosed with sporadic gastrinoma.

Previous studies have reported that most of the patients with gastrinoma treated with surgery will have recurrent or persistent disease in the long-term follow-up.[21,22] Maire et al[23] showed the recurrence occurred within 2 years after surgery in more than half of the patients in their study. Liver and lymph nodes are the most frequent sites of relapse and all patients could receive a second treatment (surgery, chemotherapy, or hepatic intra-arterial chemotherapy, alone or in combination). Prognostic factors associated with disease free survival are the size and the pancreatic location of the primary tumor. Nishio et al[24] reported a recurrence of gastrinoma 19 years after primary resection. Because of the recurrence risk, our patient was followed-up ultrasound, scintigraphy, and gastrin level measurements. There was no evidence of metastasis or recurrent disease in the follow-up.

The main criteria for the diagnosis of possible primary lymph node gastrinoma are: (a) rapid normalization of the serum gastrin level after extirpation of the lymph node tumor; (b) continuous normalization of the serum gastrin level without clinical symptoms during a long postoperative period; (c) absence of another primary with a pathologic examination of the surgical specimen; (d) absence of tumor relapse verified by all imaging techniques, including somatostatin receptor scintigraphy and repeated endoscopy.[21] The diagnosis of a gastrinoma also requires the presence of a neuroendocrine tumor immunohistochemically expressing gastrin and associated with ZES. Gastrinomas do not show any histologic features that distinguish them from other neuroendocrine tumors. Histologic examination on hematoxylin-eosin–stained sections must be accompanied by immunostaining for chromogranin A, synaptophysin, and gastrin.[25] The present case fulfilled all the criteria mentioned above. Gastrin levels dropped immediately after surgery, there was no elevation of gastrin levels in the follow-up, and no other lesion was found in laparotomy. Two additional ocreotid scintigraphies and abdominal CT showed normal findings in the follow-up and repeated endoscopies after the surgery were normal in our patient. These findings further support the primary lymph node gastrinoma diagnosis in our patient.

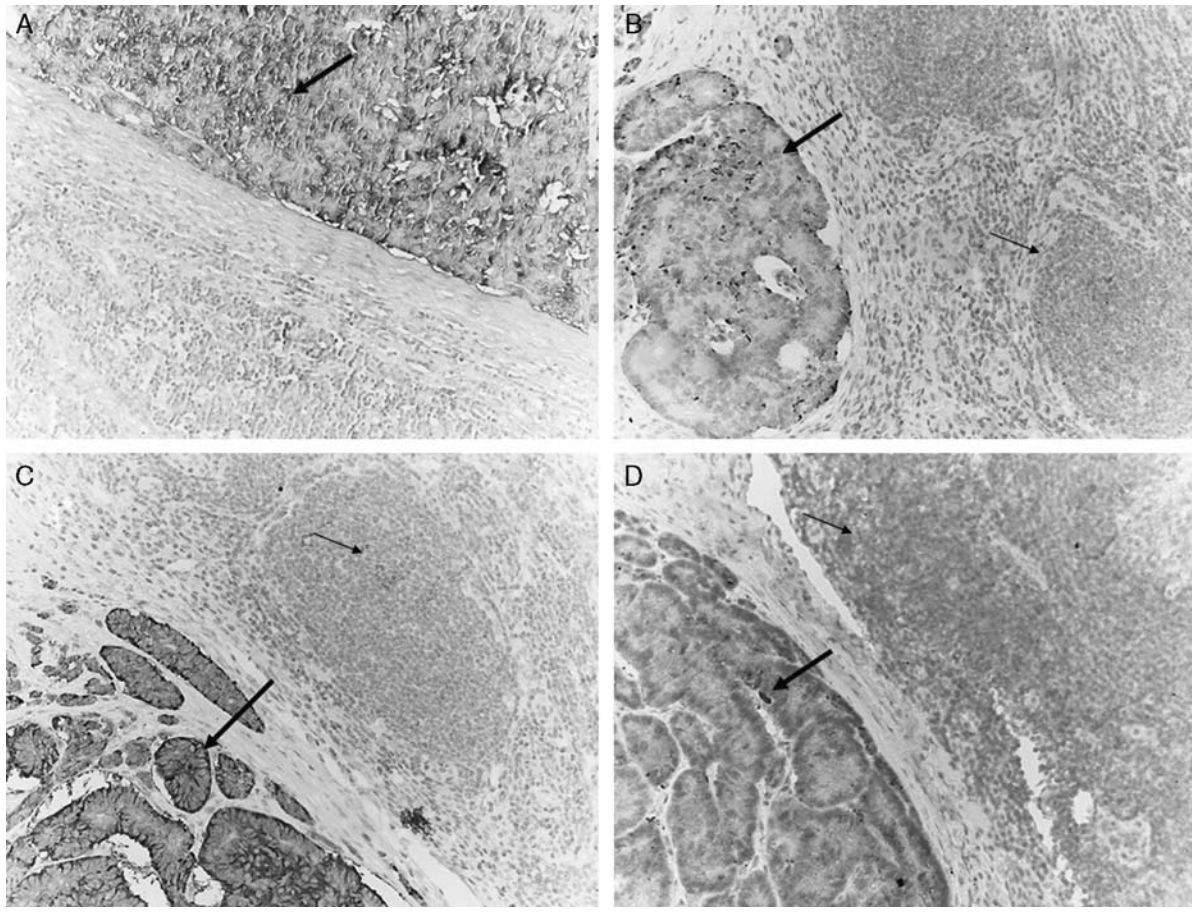

FIGURE 4. Immunohistochemical features of the tumor. A, The strong gastrin positivity is seen at tumor cells (arrow) (gastrin, ×200). B, Chromogranin staining of the tumor cells at the big mass (chromogranin, ×200) (Thick arrow shows chromogranin staining of the tumor cells, thin arrow shows lymphoid tissue). C, Synaptophysin staining of the tumor cells at the big mass (synaptophysin, ×200) (Thick arrow shows synaptophysin staining of the tumor cells, thin arrow shows lymphoid tissue). D, Neuron-specific enolase (NSE) staining of the tumor cells at the big mass (NSE, ×200) (Thick arrow shows NSE staining of the tumor cells, thin arrow shows lymphoid tissue).

In conclusion, the occurrence of primary lymph node gastrinomas, though rare, seems to be valid. We have presented a case of a primary lymph node gastrinoma in a peripancreatic node. The fact that no other lesion was identified preoperatively and intraoperatively and rapidly declining gastrin levels after excision of the tumor confirm the fact that the tumor was confined to the lymph node. Hence, primary lymph node gastrinomas are not entirely nonexistent, but seem to be rare.

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