Pancreatic neuroendocrine tumor in a child of 3.5 years old

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Case report

Background: **Pancreatic neuroendocrine tumor is rarely seen, particularly in children. One of the symptoms of this tumor is jaundice that may be misdiagnosed as the sign of hepatitis A, especially in countries with a high prevalence of this infectious disease.**

Methods: **We present a 3.5-year-old girl with four weeks of icterus, who was misdiagnosed with hepatitis A.**

Results: **The patient was finally diagnosed as having a low grade pancreatic neuroendocrine carcinoma.**

Conclusion: **Pediatricians should be aware of or consider a tumor in differential diagnosis of jaundice, especially prolonged one in children.**

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Key words: **hepatitis A;**
icterus;
neuroendocrine tumor;
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Introduction

Neuroendocrine tumors are referred to a heterogeneous group of neoplasms, which arise from neuroendocrine cells.[1] Pancreatic neuroendocrine tumors (PNETs) are relatively rare and represent 1%-2% of all pancreatic tumors.[1,2] The purpose of this article is to report a case of PNETs misdiagnosed with hepatitis A.

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Case report

A 3.5-year-old girl with jaundice for 4 weeks, who had a positive total anti hepatitis A virus (anti-HAV) antibody test and a primary diagnosis of hepatitis A, was referred to Ali Asghar Children's Hospital.

She had no fever, abdominal pain, or nausea before and after appearance of jaundice, but 2 kg of weight loss, dark urine, and clay-colored stool were observed during this period. She had no medical history of jaundice.

Physical examination showed icterus and hepatomegaly (liver span: 10 cm) but splenomegaly. No tenderness or palpable mass was shown by abdominal examination. The primary laboratory data are shown in the Table. IgM anti-HAV, HBs Ag, and hepatitis C virus antibody (HCV Ab) tests were negative except IgG anti-HAV. The girl was diagnosed with a choledochal cyst by ultrasound examination, but abdominal CT scan with oral and intravenous (IV) contrast revealed an enhanced intermediate mass in the head of the pancreas, suggesting a hypervascular pancreatic lesion.

Magnetic resonance cholangiopancreatography (MRCP) confirmed the dilation of the intra- and extra-hepatic biliary ducts and the common bile duct,

Table. Initial blood test values (bold values are out of range)

Tests	Patient value	Normal value
SGOT (IU/L)	321	5-40
SGPT (IU/L)	249	5-40
Total bilirubin (mg/dL)	18.6	0.2-1.2
Direct bilirubin (mg/dL)	8.1	0.0-0.4
PT (s)	17.1	12-14
PTT (s)	37	28-34
INR	1.9	0.9-1.0
Alpha-feto protein (ng/mL)	1.3	Up to 10
Anti-LKM (titer)	1.1	Negative: <20
Amylase (IU/L)	65	<100
Lipase (IU/L)	146	Up to 190
Ceruloplasmin (g/L)	0.45	0.2-0.4
LDH (IU/L)	899	Up to 480

SGOT: serum glutamic oxaloacetic transaminase; SGPT: serum glutamic pyruvic transaminase; PT: prothrombin time; PTT: partial thromboplastin time; LDH: lactate dehydrogenase; INR: international normalized ratio; Anti-LKM: anti-liver kidney microsomal antibodies.

Fig. 1. Magnetic resonance cholangiopancreatography cholangiogram reveals distended gall bladder and dilated common bile duct with distal tapering which is indicative of obstruction by pancreatic head mass.

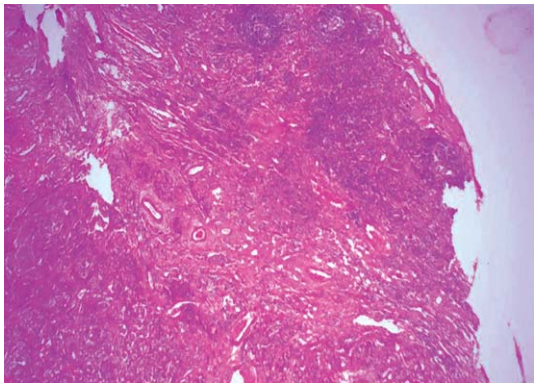

Fig. 2. Metastastatic involvement of a lymph node by the tumor. The remnant of lymph node is seen in right upper corner (H&E staining, original magnification × 400)

which resulted to an ampullary mass (Fig. 1). The patient underwent a laparatomy and a firm mass was found at the head of the pancreas. Frozen section revealed a neuroendocrine tumor with lymph node metastasis that led to a Whipple operation (Fig. 2). Post-operative examination revealed a relatively well-circumscribed mass with a diameter of 4 cm, extending to the duodenal wall without vascular and perineural invasion, mitosis or necrosis. Immunohistochemical staining of the tumor was positive for epithelial (cytokeratin, EMA) and endocrine (Synaptophysin and Chromogeranin) markers. Ki-67 was positive in 2% of the tumor cells and CD99 and leucocyte common antigen were negative.

Because of histological pattern of the tumor, low Ki-67 labeling index, and metastatic involvement of regional lymph nodes, the patient was finally diagnosed with well-differentiated neuroendocrine carcinoma. Post-operative follow-up for two years showed no significant complication.

Discussion

PNETs have an incidence of 1-5 per million and are extremely rare in the pediatric population.[3,4] Most of PNETs are functional and may secrete some hormones such as insulin, glucagon and gastrin.[1] Non-functional PNETs account for 15%-30%.[1] The clinical manifestations of PNETs are dependent on types of the tumor (benign or malignant and functional or non-functional).[1] Symptoms of the functional tumors depend on the type of secreted hormones, which may cause diarrhea, weight loss, weight gain, skin rash, flushing, and dizziness.[1]

The non-functional PNETs are silent clinically until the appearance of symptoms secondary to pressure effect or metastasis.[1] The distinctive phenotypic profile of classic neuroendocrine tumors can be demonstrated by a variety of specific techniques. Histochemical analysis of the tumor shows argentaffin cells. Ultra-structurally, numerous dense-core secretory granules could be detected,[5] and immunohistochemical analyses could show an epithelial and neuroendocrine differentiation.

Epithelial differentiation is caused by cytokeratin and epithelial membrane antigen. The neuroendocrine properties are shown by a series of panendocrine markers, such as neuron-specific enolase, chromogranin and synaptophysin.[5] In this case, tumor cells were positive for both of these immunohistochemical markers.

According to the World Health Organization classification, local invasion to duodenal wall and lymph node metastasis led us to make a well-differentiated endocrine carcinoma diagnosis in the present case despite a low proliferative index (Ki-67=2%).[6] There are some non-specific serologic tumor markers for PNETs.[1] The most common tumor marker for patients with non-functional tumors of the mid gut and pancreas is chromogranin A.[7] Chromogranin A is particularly useful in postoperative follow-up of patients with PNETs.[1] We did not check neuroendocrine markers in serum and tissue since our patient had no signs or symptoms of PNET and she was not initially diagnosed with a neuroendocrine tumor. Patients who are members of multiple endocrine neoplasia type 1 (MEN-1) or Von Hippel Lindau family or have these syndromes should undergo gene mutational analysis.[7] Our patient did not fulfill the criteria of above-mentioned diagnoses. In addition, no family history of cancer/tumor and consanguinity in her close relatives was reported so mutational analysis was not performed for this patient.

Currently, surgery is the treatment of choice for resectable PNETs.[8] The extension of surgery depends on the size, location and type of the tumor.[8] Tumors larger than 3 cm or malignant ones usually need

aggressive treatments such as Whipple procedure or distal pancreatectomy depending on the location of the tumor.[8] In this case, the patient had a Whipple procedure due to tumor size and lymph node, and duodenal wall metastasis. It is recommended that ultrasound examination, CT or MRI (depending on the availability and experience) be carried out every 3 months and if negative, taken every 3 months indefinitely.[7] This patient was misdiagnosed with hepatitis A due to jaundice, positive total anti-HAV Ab test and high prevalence of this infectious disease in Iran.

It seems that total anti-HAV Ab may not be a proper indicator for detecting hepatitis A, and serologic evaluation with HAV IgM and IgG is needed for an accurate diagnosis. In conclusion, despite the very low incidence of PENTs, pediatricians should be aware of tumors in differential diagnosis of jaundice especially prolonged one.

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