Transformation of nonfunctioning pancreatic tumor into malignant insulinoma after 3 years: an uncommon clinical course of insulinoma

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SUMMARY

A 62-year-old man admitted to our outpatient clinic with two months of recurrent life threatening hypoglycemia episodes. He was diagnosed as malignant insulinoma with multiple metastases of liver and peripancreatic lymph nodes. Liver biopsy specimen was demonstrated grade 2 neuroendocrine tumor compatible with clinical and radiological results. He was followed under the treatment of continuous intravenous glucose infusion during the diagnostic procedures. He had a pancreatic lesion history measured 20 x 12 mm in diameter via the abdominal tomography examination approximately two years before the diagnosis. Unusual course of this case suggests the transformation of nonfunctioning pancreatic neuroendocrine tumor into functional insulin secreting tumor with metastases. The patient was found inoperable and started on chemotherapy. Arch Endocrinol Metab. 2015;59(3):270-2

INTRODUCTION

Insulinomas are the most common functioning pancreatic neuroendocrine tumors (PNETs) with a benign, solitary and small dimension characteristics (1). Malignancy criterion in insulinoma is only the presence of metastases according to the World Health Organization (2). Tumor size ≥ 2 cm, CK (cytokeratin) 19 status and tumor staging and grading (Ki 67 labelling > 2%) are reported as predictors of metastatic disease (3-5). Insulinoma diagnosed patients with distant metastases of liver, bone and lymph node have a median survival of < 2 years (6). The diagnosis of nonfunctioning PNETs are usually incidentally and recommended resection of the tumor despite conversial treatment management. In contrast to nonfunctioning PNETs, the symptoms of insulinoma are usually diagnostic however, its diagnosis is related to physician awareness and clinical presentation (7).

We present a 62-year-old man with a nonfunctional pancreatic lesion that transformed into an insulin secreting malign tumor approximately three years after the diagnosis of lesion. To the best of our knowledge, the literature includes two cases about transformation of nonfunctional PNET into functional PNET that characterized hypersecretion of insulin.

CASE REPORT

A 62-year old man was admitted from our diabetes outpatient clinic with the complain of recurrent hypoglycemic episodes. His past medical history was coronary artery disease, hypertension, atrial fibrillation, peripheral artery disease and hypothyroidism. His treatment was composed of the drugs carvedilol, enoxaparin sodium, levothyroxine and benazepril hydrochlorir. He had negative family history for pancreatic or endocrine tumors.

In 2010, he was examined in another hospital for abdominal pain. He had no symptoms of hypoglycemia at that time. A computed tomography (CT) of the abdomen was scanned and 20 x 12 mm lesion found in the conjunction of the tail and body of the pancreas. However, his abdominal pain was relieved spontaneously and he had not agreed to undergo recommended further diagnostic tests. After 24 months he had symptoms of hypoglycemia like tachycardia and diaphoresis and his fasting blood glucose was found 71 mg/dL (74 – 106 mg/dL). He was evaluated as prediabetes with oral glucose tolerance test and life style changes was recommended. After a month he was recruited to our outpatient clinic for recurrent hypoglycemia. He noted that he had a weight loss of 5 kilograms and his symptoms were becoming more frequent and severe day by day over the past two months. Also he was carried out to the emergency room with loss of consciousness two days before admission to our clinic.

On physical examination, he appeared well except the hypoglycemic period. His vital signs were within the normal range and body mass index was 25,6 kg/m^2. The blood cell count, serum liver and renal function tests and coagulation profile were within normal levels. After two hours of the meal blood glucose was measured 45 mg/dl with insulin 44,5 mU/L (3-25 mU/L, Direct Chemiluminescent Sandwich Immuno Test) and c-peptide levels of 6,3 ng/ml (0,9-7,1 ng/ml, Chemiluminescence Immunometric Test) respectively. In addition to these inappropriate insulin and c-peptide results at the time of hypoglycemia, the ratio of glucose to insulin was 1.01 compatible with insulinoma. At the time of hypoglycemia his serum cortisol and somatomedin-C level was 25,9 mcg/dl (4.30 – 22.40 µg/dL, Direct Competitive Immunochemiluminescence Test) and 110 ng/ml (94 – 252 ng /ml, Chemiluminescence Immunometric Test) respectively. He was on continuous intravenous (iv) dextrose infusion with variable doses in addition to 6 times meal during the day for preventing the life threatening hypoglycemia episodes. To localize the accurate site of abnormal insulin hypersecretion we applied radiologic non-invasive imaging procedures. Abdominal ultrasonography demonstrated multiple liver lesions and pancreatic tumor with diameter of 31 x 27 mm. An abdomen CT was scanned and showed multiple liver lesions with the largest one 13 x 11 mm and a 23 x 27 mm pancreatic lesion in diameter (Figure 1). He underwent a liver biopsy from the largest lesion and immunohistologic stains of the tumor for chromogranin A, synaptophysin, CD 56 and pan CK was positive. Ki 67 was found 10-15%. The diagnosis was grade 2 neuroendocrine tumor (Figure 2). He underwent a Ga-68 DOTANOC positron emission tomography scan that demonstrated an intense uptake in pancreas, peripancreatic lymph nodes and both of the liver lobes. His serum chromogranin A level was higher than 700 ng/mL (normal range; < 94). His serum gastrin and calcium levels were within normal ranges excluding multiple endocrine neoplasia 1 (MEN 1). Also menin gene mutation was analyzed and found negative. His treatment management was discussed with experienced surgeons and was planned to give chemotherapy. The patient was transferred to our medical oncology department and started on chemotherapy.

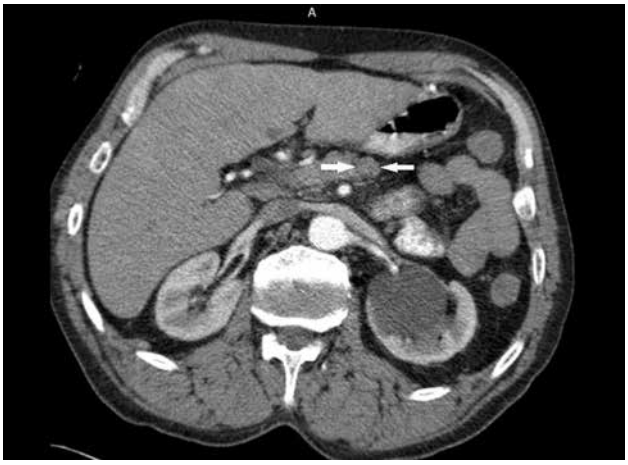

Figure 1. Smooth contoured and contrasted focal lesion located in the proximal of pancreatic corpus in an arteriel phase in contrasted computed tomography.

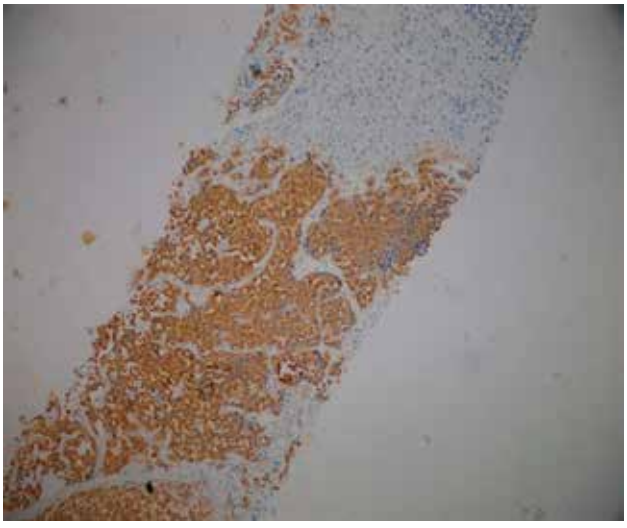

Figure 2. Synaptophysin positive stained tumoral cells with a thin chromatin structure and narrow cytoplasm forming rosette-like structures and solid groups in the liver parenchyma (Synaptophysin X 100).

DISCUSSION

We reported an insulinoma diagnosed patient presented with weight loss and life threatening recurrent hypoglycemia. He did not accept further evaluation about this lesion before. He was asymptomatic and did not attend his control visits. Also he did not take any drug or herbal medicine and have abdominal complaints during two years. We suggested that the pancreatic lesion demonstrated via the computed tomography is a nonfunctioning PNET and transformed into insulinoma by obtaining the ability of secreting insulin.

Nonfuntional PNETs constitutes about 30% percent of pancreatic endocrine tumors and majority of these have metastases at diagnosis (8). Symptoms of our patient appeared two years after the diagnosis of pancreatic lesion presented as dramatic insulin and C-peptide hypersecretion causing recurrent hypoglycemia. We suggest the hypothesis of dedifferentiation of nonfunctional tumor cells and also having slow growing insulin components (9). Secreting insulin may be provided by the way of obtaining the ability of expressing the proinsulin gene along with prohormone convertases (9). Appearing of nonhormonal components like chromogranin during fetal development in the pancreatic cells before than islet hormones support this hypothesis (10). Furthermore, the pathway of platelet-derived growth factor was shown to control age dependent beta cell proliferation in human pancreatic cells (11).

The first case about nonfunctional PNET transformation into functional PNET was reported by Vashi and cols. (12). The second case was described after 2 months therapy of Sunitinib in a patient diagnosed with nonfunctioning PNET (13). The third case was reported by Koshy AA and cols. and they also discussed the occurrence of atrial flutter after octreotide treatment (9). Our findings combined with medical history of the patient suggest that the nonfunctional PNET transformed into malignant insulinoma but we could not rule out any other temporary benign lesion at first diagnosis despite its low probability because biopsy of the pancreatic lesion was not available.

In conclusion, all cases including our case suggest that nonfunctioning PNETs has a possibility of transformation into insulin producing cells and this might lead further investigations for manipulating beta cell function.

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