

Glucagonoma as a rare case of neuroendocrine tumor of the pancreas: a case report

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ABSTRACT

Introduction: Glucagonoma is a rare neuroendocrine tumor with characteristic features such as the presence of the glucagon-producing tumor, diabetes, and necrolytic migratory erythema.

Case presentation: the 60-year-old patient was admitted to hospital with periodic pain in the right and middle upper abdominal appearing after eating. Laboratory tests presented a high glucose level and anemia. Tumor of the body and tail of the pancreas passing the organ pouch has been found during the surgery. Diagnosis of glucagonoma was confirmed in histopathological examination in immunohistochemical stainings: a positive reaction

was observed with chromogranin, synaptophysin and CEA. The proliferative activity of Ki-67 was less than 1%. Staining for glucagon also was positive so confirmed the presence of neuroendocrine tumor - glucagonoma.

Conclusions: Glucagonoma sometimes may occur without characteristic features which may cause delayed diagnosis. Early diagnosis of glucagonoma is important because it increases the chances of successful recovery.

Keywords: Glucagonoma, pancreas, neuroendocrine tumor, diabetes

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INTRODUCTION

Glucagonoma is one of the rare pancreatic neuroendocrine tumors, accounting for only 5% of all cancers of this organ [1]. It is characterized by excessive production of glucagon by the alpha cells of the Langerhans islands and locates mainly in the pancreatic tail due to the accumulation of islands in this part of the organ. The incidence is 0.01-0.1 cases per 100 000 people per year. Glucagonoma mainly affects people 40-60 years old and occurs with similar frequency for both men and woman. The most characteristic symptom of glucagonoma is dermal necrolytic migratory erythema (NME), which is result of malnutrition and amino acid deficiency caused by increase glucagon catabolism. These lesions are present in approximately 55-90% of all patients. Other symptoms include weight loss, diabetes, glucose intolerance, inflammation of the mucous membrane (tongue, lips), venous thrombosis, diarrhea or neuropsychiatric disorders (depression, psychosis) [2]. In laboratory tests - anemia, hyperglycemia and an increase of glucagon level has been reported in most cases [3]. One of the elements of glucagonoma diagnosis is histopathological examination including immunohistochemical staining such as chromogranin or synaptophysin specific for neuroendocrine tumors. Additionally, in order to confirm diagnosis of glucagonoma, staining for glucagon should be performed. The authors describe the glucagonoma case due to the rare occurrence of this hormone-active pancreatic neuroendocrine tumor.

CASE PRESENTATION

A 60-year-old patient with a newly diagnosed diabetes was admitted to 2nd Clinical Department of General and Gastroenterological Surgery at Medical University of Bialystok for surgical treatment of a pancreatic tail tumor and cholecystolithiasis. In the previous interview, there were periodic pain in the right and middle epigastrium, occurring mainly after eating. These complaints were accompanied by significant weight loss - about 7 kg in 3 months. In a family history, a case of pancreatic cancer in a patient's brother has been reported.

High blood glucose levels (160 mg/dL) in many measurements were observed in laboratory tests, whereas normocytic, normochromic anemia (9.5 g/dL hemoglobin) was observed in the blood morphology test. The level of chromogranin A, which is a serum marker for neuroendocrine tumors, was elevated to 625.7ng/mL whereas normal range equals <94ng/mL. The serum glucagon level was 803 pg/mL (reference level 70-175 pg/mL). The Erythrocyte Sedimentation Rate (ESR) was slightly increased (31mm per hour). CEA markers (<0.50 U/ml) and CA 19-9 (2.18 U/ml) remained within the reference values.

The abdominal CT (Computed Tomography) scan showed enlargement of the pancreatic tail to 40 mm with unequal contours without focal separation except for minor calcification (Figure 1).

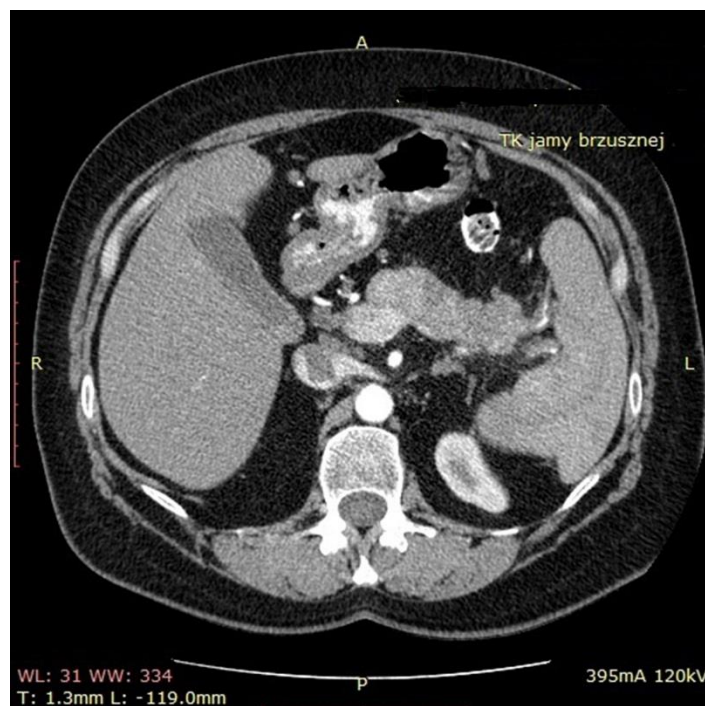


Figure 1. Contrast-enhanced computed tomography scan of the abdomen reveals a tumor mass in the body and the tail of the pancreas

In the surrounding of the pancreatic tail has been observed band-like thicknesses in the direction of the spleen, peritoneum, fundus, prerenal and adrenal fascia, segmental narrowing of the splenic artery as well as obstruction and fibrosis of the splenic vein with numerous collateral vessels. In addition, gallstones were found.

The patient was qualified for surgical treatment. During the procedure, tumor was found in the tail and body of pancreas. The tumor infiltrated peritoneum, left adrenal gland and left kidney. Peripheral pancreatectomy with splenectomy and cholecystectomy were performed. The postoperative period was without complications. Glucose

abnormalities in the patient have normalized. Diabetic counseling followed diet and glycemic control. Patient in a general good condition was discharged from hospital with a recommendation of check visit.

Histopathological examination concerned a fragment of the pancreas, cuted along a long axis. At the cross section of the tail was solid yellow tumor with poorly marked borders with small foci of bloody sputum (Figure 2 A, B). The tumor had dimensions 6.5x3x3.5cm. Pancreatic fibrosis was reported in the tumor region. Moreover in the neighborhood of the pancreas, numerous enlarged pink-gray lymph nodes were presented.

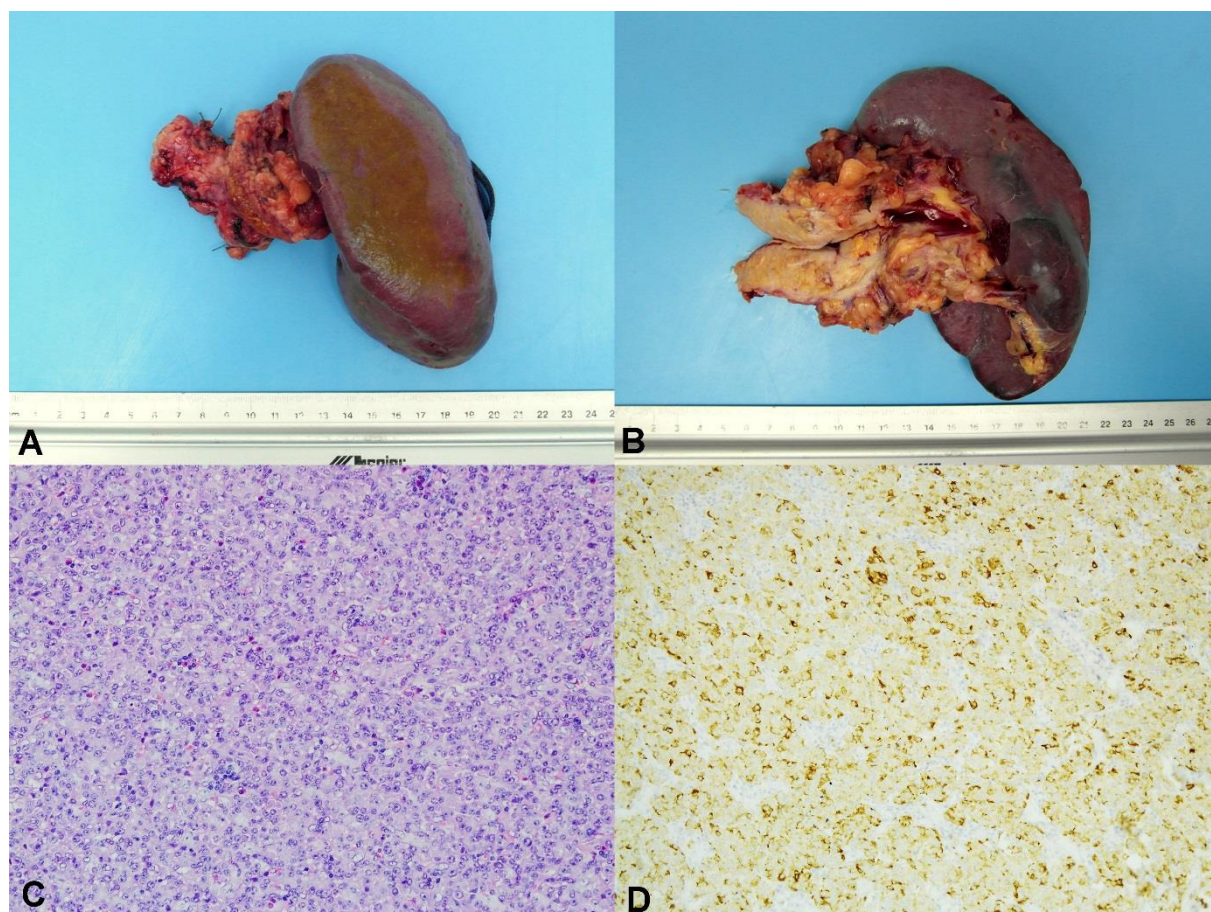


Figure 2. A, B Glucagonoma in the body and tail of the pancreas. C. Microscopic examination revealed tumor with the round cells containing fine-grained cytoplasm and the centrally located nucleus. Round or oval-shaped nuclei contained fairly uniform, scattered, fine-grained chromatine. In single cells were present small cores (H&E, original magnification $\times 40$). D. Immunohistochemical staining shows strong homogeneous positive reaction for chromogranin.

Postoperative histopathological examination confirmed that the diagnosis was a neuroendocrine tumor involving the tail of pancreas (Figure 2C). In the immunohistochemistry examination of the tumor, a strong homogeneous positive reaction with antibodies against chromogranin (Figure 2 D) and synaptophysin (Figure 3 A) was observed. In addition, staining for

carcinoembryonic antigen was made and it was positive (Figure 3 B). Ki-67 proliferation index was less than 1% (Figure 3 C). Glucagon staining was also positive (Figure 3 D). These staining confirmed the diagnosis of glucagonoma with degree of differentiation G1 and pT2 N1 M0 stage IIB. Degree of differentiation - G1 concern the tumors with low proliferation index lower or equal 2%. The degree of

pT2 indicates that the tumor is locally advanced. This criterion also includes the tumor size to 40 mm. Degree N1 attests to tumor metastases to regional lymph nodes (In the two lymph nodes that were sent

to the study were tumor metastases), while M0 indicates absence of metastases to distant organs. Stage IIB determines tumor as an average clinical stage.

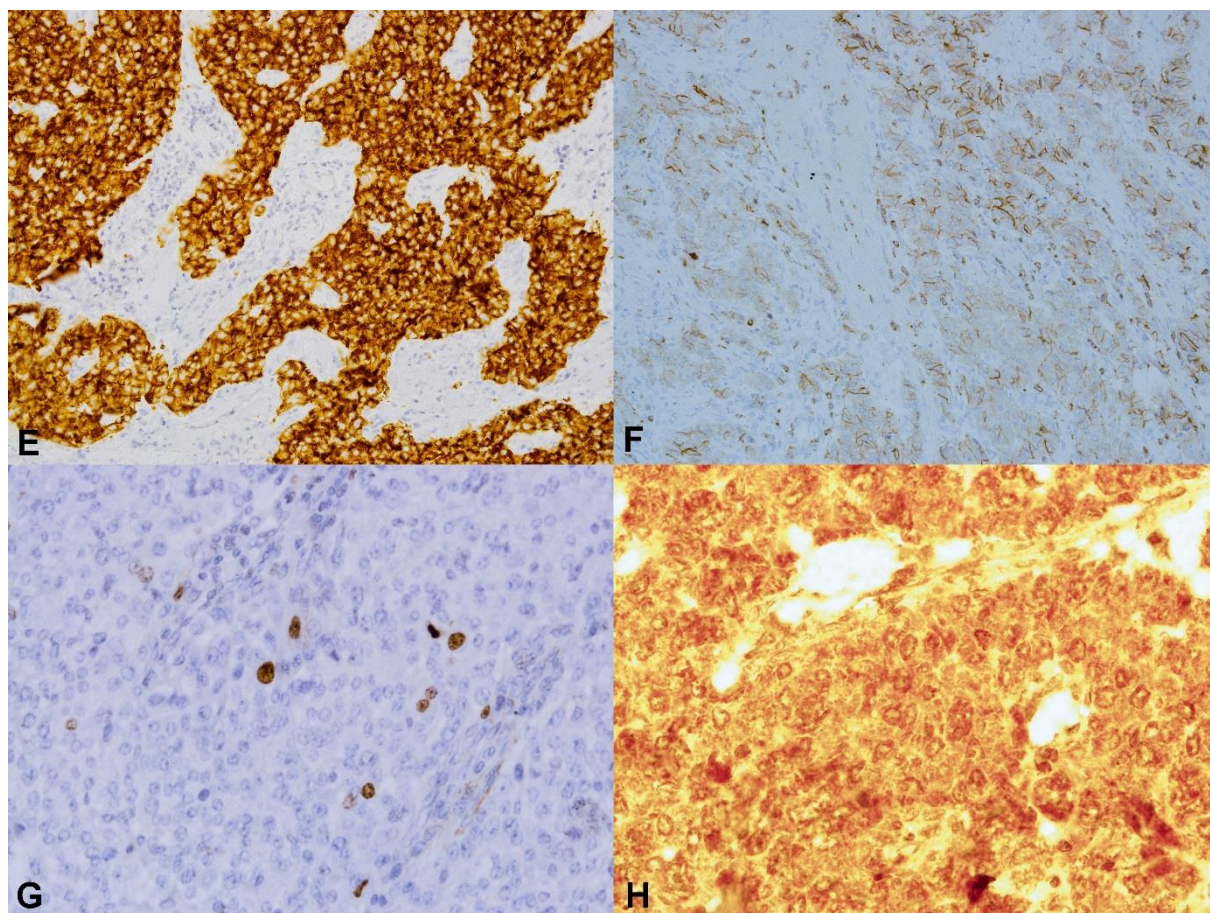


Figure 3. A. Immunohistochemical staining shows positive findings for synaptophysin. B. Immunohistochemical staining shows positive findings for CEA. C. Ki-67 proliferation index less than 1%. D. Immunohistochemical staining shows positive findings for glucagon

DISCUSSION

Glucagonoma is a rare neuroendocrine tumor with a prevalence of 1 case per 20 million people per year. The characteristic feature of glucagonoma is the presence of three symptoms typical for this disease unit. Triads of symptoms, includes the presence of glucagon-producing tumor, diabetes, and necrolytic migratory erythema [4]. This tumor was first described in 1942 by Becker [5], who was characterized it by the presence of cutaneous eczema. In 1966 McGavran et al [6] added to the symptoms hyperglucagonemia and their combination named as glucagonome syndrome (GS). The term necrolytic migratory erythema was developed in 1973 by Wilkinson [7] as a defining characteristic of skin lesions developing in the course of glucagonoma. Glucagonome syndrome is divided into three different types: glucagonoma with

accompanying necrolytic migratory erythema, glucagonoma with mild diabetes, and multi-symptom glucagonoma.

The patient which has been described in this paper had a glucagonoma syndrome with mild diabetes. The patient had a large tumor located in the tail of the pancreas with metastases to the two lymph nodes. Literature describes cases of glucagonoma with tumor localization in the head of the pancreas, but in most cases the tumor locates in the tail of this organ because of the high density of alpha islands in the region. Endocrine symptoms are more common in advanced stages of the disease and can be related to the size of the tumor. The tumor-altered organ produces large amounts of glucagon which, under physiological conditions, stimulates processes that increase blood glucose levels by demonstrating an insulin-antagonistic effect. In case of overproduction of this hormone activates additional metabolic pathways - intensification of gluconeogenesis,

glycogenolysis and lipolysis, which in consequence leads to disorders of glycemia, insulin resistance and development of diabetes.

Glucose level in our patient was 160 mg/dL, which is due to the fact that the patient developed mild diabetes mellitus. Except for diabetes, a significant weight loss was reported in the patient, as well as anemia and gall bladder stones. Weight loss, which is an inseparable part of developing glucagonoma is results of increased metabolism by the growing tumor, which in turn results in the extinction of the body. Diarrhea is often seen in patients who may further increase weight loss [7]. The patient did not have necrolytic migratory erythema - NME, which is one of the most characteristic symptoms of glucagonoma and have occurred in approximately 70% of patients with this diagnosis. In available literature has been reported only one clinical case of glucagon without skin lesions [8]. In the patient family history was diagnosed pancreatic cancer in the patient's brother. In most cases available in literature in the patient's family histories were no found any neuroendocrine tumors or other pancreatic tumors [9]. In addition, patients with suspected neuroendocrine tumors perform laboratory tests such as blood morphology, ESR or tumor diagnostic markers CA 19-9, whose elevation may indicate pancreatic cancer but its normal level does not exclude the onset of the disease.

Confirmation of neuroendocrine tumor diagnosis requires histopathological examination and immunohistochemical diagnosis based on positive staining on chromogranin or synaptophysin. Chromogranin is used to diagnose neuroendocrine tumors because it is a protein secreted by neuroendocrine cells. Synaptophysine is a protein present in all healthy and neoplastic neuroendocrine cells [10]. For the differentiation of the neuroendocrine tumor subtype, a glucagon assay was performed in our patient. Positive expression result showed that the tumor originated from pancreatic alpha cells. In addition, we were performed staining for carcinoembryonic antigen and Ki-67 protein. The Ki-67 protein is used to evaluate proliferative activity and shows of the potential for tumor malignancy [10].

CONCLUSIONS

Glucagonoma sometimes may occur without characteristic features such as necrolytic migratory erythema which may cause delayed diagnosis. The diagnosis of tumor focus on image-based diagnosis and laboratory tests, but histopathologic diagnosis is necessary to confirm the specific type of tumor. Time to diagnosis is an important prognostic factor because of its metastatic

potential to surrounding lymph nodes and the liver. Early diagnosis of the underlying symptoms of glucagonoma allows for rapid diagnosis and increases the chances of successful cure.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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