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Hypoglycemia in a Patient With a Polyhormonal Pancreatic Neuroendocrine Tumor With Evidence of Endocrine Progenitors

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A 55-year-old woman with a large polyhormonal neuroendocrine tumor with unusual pathology is described. The patient presented with intermittent neuroglycopenic symptoms between more protracted asymptomatic periods occurring over the preceding 4 years. During a diagnostic 72-hour inpatient fast, she exhibited hypoglycemia at 70 hours after initiation. On computed tomography scan, a 6-cm mass was identified at the pancreatic head. The patient underwent a pylorus-preserving pancreaticoduodenectomy, and pathology was positive for cells staining for pancreatic polypeptide, insulin, and occasional double hormone (insulin plus pancreatic polypeptide)–positive cells. In addition, the tumor exhibited broad staining for ALDH1A3, a new marker of endocrine progenitors. This case serves to highlight the clinical and pathologic variability of insulin-producing tumors and raises the potential for cells in these tumors to exhibit hormone interconversion and progenitor-like states.

Freeform/Key Words: hypoglycemia, insulin, pancreatic polypeptide, neuroendocrine tumor

Insulinoma is the most common tumor type that leads to recurrent fasting hypoglycemia. Most insulinomas have an average size of 1.5 cm, fewer than 5% are >3 cm at the time of diagnosis, and there appears to be no correlation between the size of an insulinoma and its malignant potential [1]. Moreover, a recent retrospective case study suggested that neither insulinoma tumor size nor a patient's anthropometric features correlated with time to hypoglycemia during a diagnostic 72-hour fast [2]. By contrast, tumor size directly correlates more closely with histopathologic characteristics, including Ki-67 index and tumor grade [3]. Whereas these observations may hold true for pure insulinomas, correlations of these types have not been assessed in general for polyhormonal pancreatic neuroendocrine tumors (PNETs), which represent a broader category in which insulinomas are a subset. We present a case of a patient presenting with late-onset hypoglycemia during a 72-hour fast and a large PNET containing cells with single and double positivity for insulin and pancreatic polypeptide (PP), with evidence of endocrine cell progenitors.

1. Case Report

A. Clinical Presentation

A 55-year-old woman with a medical history of Hashimoto thyroiditis, depression, and obstructive sleep apnea presented to her primary care physician with recurrent episodes of syncope.

Abbreviations: PNET, pancreatic neuroendocrine tumor; PP, pancreatic polypeptide.

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She reported four episodes of losing consciousness over the previous 4 years, and each episode occurred 1 to 2 hours postprandially. Dizziness, diaphoresis, blurry vision, and headaches preceded the syncope, and she described mild confusion upon awakening. Notably, she had a ~20-pound weight gain over this time period. She had no previous surgeries, including bariatric surgery, or history of seizures. She worked as a pediatric nurse and denied alcohol, tobacco, and illicit drug use. Home medications included citalopram, levothyroxine, and vitamin D3.

Self-monitoring of blood glucose levels revealed values between 40 and 60 mg/dL (2.2 to 3.3 mmol/L) 1 to 2 hours postprandially; blood glucose values at other times, including periods of fasting, were between 60 and 110 mg/dL (3.3 to 6.1 mmol/L). She attempted to follow a low glycemic index diet, but she did not report any substantial improvement. Prompted by another episode of syncope, she presented to the emergency department at a community hospital. Based on her reported neuroglycopenic symptoms and concerns regarding a possible insulinoma, the patient underwent a computed tomography scan of her abdomen, which revealed a 6-cm mass at the head of the pancreas (Fig. 1A). She was then transferred to our institution for further evaluation. Physical examination was pertinent for a body mass index of 26.7 kg/m^2, normal vital signs, no thyromegaly, a regular heart rate and rhythm without murmur, a soft abdomen without a palpable mass, and no rashes.

B. Results of the 72-Hour Fasting Protocol

Upon arrival at our institution, the patient underwent a diagnostic 72-hour fasting protocol to assess for a possible insulinoma. At 70 hours into the fasting protocol, she experienced neuroglycopenic symptoms, and plasma glucose was 35 mg/dL (1.9 mmol/L). At the time of hypoglycemia, proinsulin was 90 pmol/L (reference range, 3 to 20 pmol/L), C-peptide was 1.03 nmol/L (reference range, 0.36 to 1.46 nmol/L), and insulin was 70 pmol/L (reference range, 28 to 208 pmol/L). Per protocol, she was administered 1 mg glucagon intravenously, and plasma glucose rose to 65 mg/dL (3.6 mmol/L) 30 minutes later, just exceeding the accepted increase of 25 mg/dL (1.4 mmol/L) that would be consistent with insulin-mediated hypoglycemia [4]. Sulfonylurea and meglitinide screens were negative. Because the aforementioned laboratory studies were consistent with inappropriate endogenous insulin secretion for the degree of hypoglycemia, she subsequently underwent a pylorus-preserving pancreaticoduodenectomy for removal of the pancreatic tumor on suspicion of insulinoma. Her postoperative course was uncomplicated. Six months postoperatively, she reported no further symptoms of hypoglycemia, and ambulatory monitoring demonstrated euglycemia.

C. Tumor Histopathology

Gross examination of the tumor revealed an encapsulated tumor measuring 5.3 × 4.7 × 4.3 cm. Histopathology demonstrated a well-differentiated tumor with adjacent normal pancreatic tissue (Fig. 1B), with cells in the tumor staining positive for the neuroendocrine markers chromogranin A (Fig. 1C) and synaptophysin (not shown). Patchy positivity for insulin immunostaining was noted (Fig. 1D), and the tumor exhibited a Ki-67 proliferative index of <1% (Fig. 1E). Based on these immunostaining characteristics, the tumor was classified as a low-grade PNET. Lymph node metastasis was not identified.

Because a significant fraction of tumor cells did not immunostain for insulin, we next performed immunofluorescence staining of the tumor for other islet hormones, as shown in Fig. 2. Whereas islets in the normal pancreatic tissue exhibited immunofluorescence for glucagon, somatostatin, and ghrelin, tumor tissue did not show presence of these cells (note: the red fluorescence seen in tumor sections is attributable to spectral bleed-through by red blood cells) (Fig. 2). By contrast, tumor tissue contained cells that immunostained for PP, with occasional cells double-staining for both insulin and PP (arrows in Fig. 3). Because recent studies suggest that PP cells might represent de-differentiated or transdifferentiated β cells in some cases [5–7], we next performed immunofluorescence staining of the tumor tissue for ALDH1A3, a recently identified marker of endocrine progenitors [8]. As shown in Fig. 3, cells in the tumor showed broad positivity for ALDH1A3, suggesting that the tumor exhibits features of endocrine progenitor–like cells.

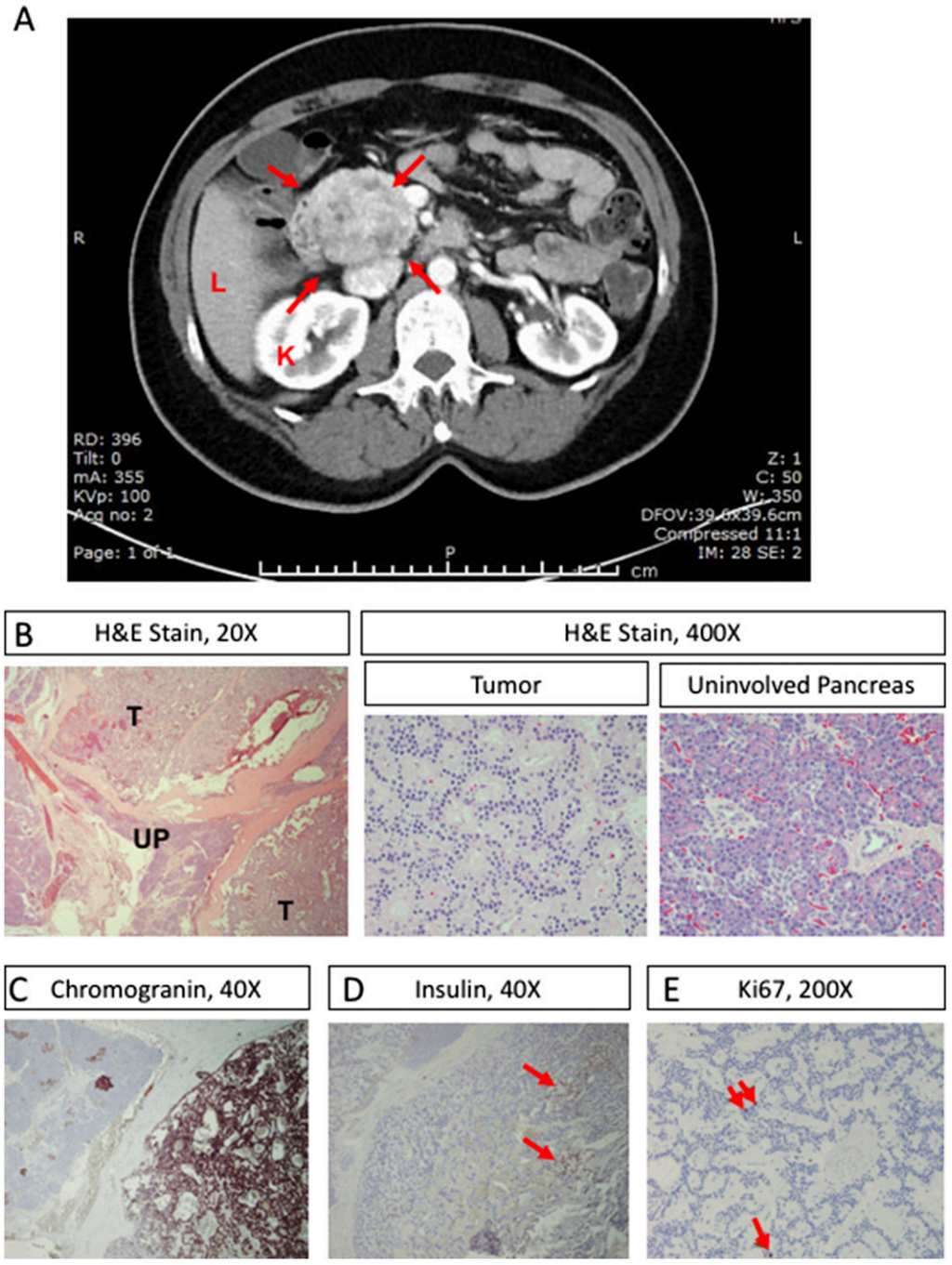

Figure 1. Gross and microscopic features of the pancreatic neuroendocrine tumor. (A) Computed tomography scan of the abdomen highlighting the location of the tumor (red arrows) relative to the liver (L) and right kidney (K). (B) Hematoxylin and eosin (H&E) staining of the tumor (T) and uninvolved pancreas (UP) upon removal. (C) Chromogranin A immunostaining of the tumor (T) and portion of the uninvolved pancreas (UP). (D) Insulin immunostaining of the tumor (arrows indicate regions of positive immunostaining). (E) Ki-67 immunostaining of the tumor (arrows indicate nuclei with positive immunostaining).

2. Discussion

The case presented here serves to highlight several clinical and pathologic features that are distinct from pure insulinomas and are more consistent with a mixed hormonal PNET. The average age of presentation of insulinoma is in the fifth decade of life. Over 90% of these

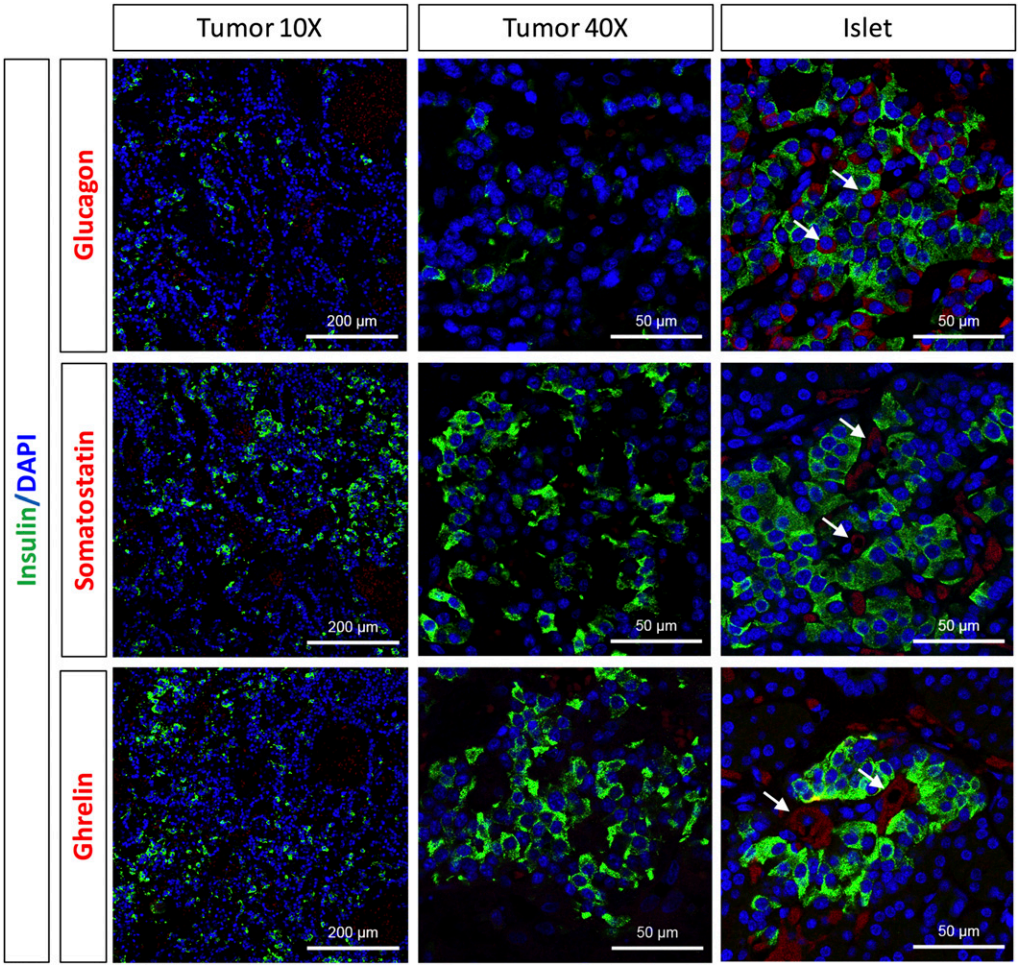

Figure 2. Immunofluorescence staining for islet hormones. Shown are representative sections of the tumor at ×10 and ×40 magnification and of normal islets from the uninvolved pancreas immunostained for islet hormones insulin (in green) and glucagon, somatostatin, and ghrelin (all in red), as well as 4′,6-diamidino-2-phenylindole (DAPI) counterstain (in blue) for nuclei. Arrows indicate examples of hormone-positive cells.

tumors are benign, and only 5% of these patients have multiple endocrine neoplasia type 1 (MEN1) syndrome [9]. Symptomatic hypoglycemia is classically most prominent with fasting. However, variable presentations have been described. Our patient had four episodes of syncope over a 4-year period, all of which happened shortly after eating. Self-monitoring of blood glucose was suggestive of postprandial hypoglycemia, whereas fasting blood sugars were in the normal range. Postprandial hypoglycemia has been observed in cases following postbariatric surgery and has been attributed variably to dumping syndrome and nesidioblastosis-like pathologies [10]. The patient described in this report did not have a history of bariatric surgery, and therefore her presentation stands in contrast to a more typical presentation of fasting hypoglycemia, as seen with classic insulinomas. A Mayo Clinic study reviewed 237 patients presenting over a 20-year period with insulinomas and found that 73% of patients had hypoglycemia in the fasting state, 21% of patients presented with hypoglycemia in the fasting and postprandial states, and only 6% of patients presented with hypoglycemia in only the postprandial state [11].

During the 72-hour fasting protocol, our patient did not exhibit symptoms or laboratory evidence of hypoglycemia until very late (70 hours) into the fast. Previous studies have shown that most patients with insulinomas developed hypoglycemia well before 72 hours. A retrospective examination of data from 119 patients with insulinomas who completed a 72-hour

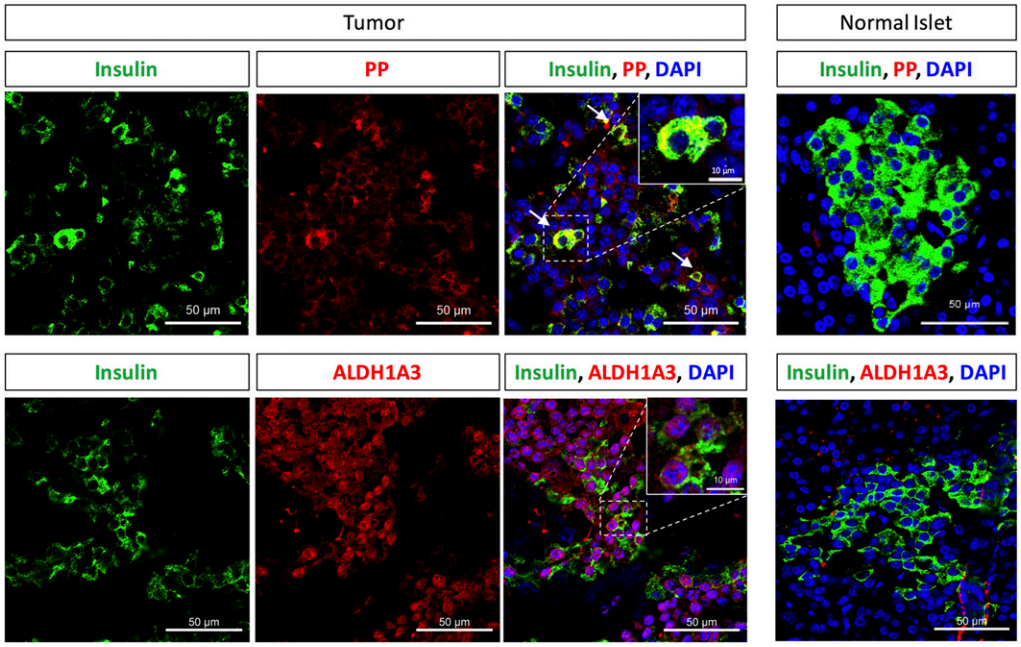

Figure 3. Immunofluorescence staining for pancreatic polypeptide and ALDH1A3. Shown are representative sections of the tumor and normal islets immunostained for insulin (in green) and PP and ALDH1A3 (both in red), as well as 4′,6-diamidino-2-phenylindole (DAPI) counterstain (in blue) for nuclei. Arrows identify cells showing immunofluorescence staining for both insulin and PP (brighter, yellowish color), and insets show magnified regions indicated.

fast at the National Institutes of Health found that 42.5% of patients developed hypoglycemia by 12 hours, 66.9% by 24 hours, and 94.5% by 48 hours [12]. The authors of that study concluded that the remaining patients actually had glucose and insulin levels consistent with the diagnosis of insulinoma by 48 hours but missed the neuroglycopenic symptoms. Another study from the Cleveland Clinic showed that of 49 patients who underwent a 72-hour fast, 48 developed hypoglycemia by 48 hours [13].

Our patient presented with a large tumor that, if it were a classic insulinoma, would have been associated with a higher Ki-67 index and more severe grading on histopathology [3]. The finding that the tumor had polyhormone positivity and was uniformly positive for neuroendocrine markers (chromogranin A and synaptophysin) is consistent with a PNET rather than a classic insulinoma. A notable finding in our case was that the two major hormones present in this tumor were insulin and PP. PP is a hormone secreted from cells in the uncinate lobe and head of the pancreas that is associated with decreased gastric emptying and increased satiety [14, 15]. A previous report described cases of PNETs with increased PP levels associated with diabetes, where the diabetes resolved or improved following resection of the tumor [16]. It is possible that the secretion of PP by the tumor may have mitigated the frequency and severity of hypoglycemia that may have been expected from the excess insulin production.

Finally, a relevant finding in our patient's tumor was the occurrence of insulin/PP double-positive cells. To our knowledge, such double positivity has not been previously reported and suggests that interconversion between cell types may be occurring during the evolution of the tumor. The possibility that insulin-producing β cells can transdifferentiate or de-differentiate into PP cells has been suggested in cases of human diabetes [6] and in rodents where smad signaling pathways promote islet cell replication [5]. Consistent with this possibility, we found that the PNET described here shows broad immunostaining for a marker of endocrine progenitor cells, ALDH1A3, whereas normal islets do not. This finding suggests that the tumor contains cells that are phenotypically distinct and progenitor-like compared with cells of a normal islet.

In conclusion, we present a case of a large PNET with insulin- and PP-positive cells in a 55-year-old woman. Her presentation was notable for its insidious nature and histopathologic features. It is postulated that the unusual hormonal milieu of the PNET may have served to counteract the more frequent fasting hypoglycemia that is typically seen with insulin-hypersecreting tumors.

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