Synchronous Nesidioblastosis, Endocrine Microadenoma, and Intraductal Papillary Mucinous Neoplasia in a Man Presenting With Hyperinsulinemic Hypoglycemia

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Abstract: Herein, we report the first case of concomitant nesidioblastosis, pancreatic neuroendocrine tumor, and intraductal papillary mucinous neoplasia. The combination is significant as each of these pathological entities is independently very rare. The patient was a 33-year-old man who presented with symptomatic hyperinsulinemic hypoglycemia and no risk factors for pancreatic disease. Abdominal imaging showed an isolated 12 mm pancreatic lesion, whilst selective arterial calcium stimulation testing demonstrated multiple territories of insulin excess. He proceeded to subtotal pancreatectomy. Histopathology revealed an endocrine microadenoma, α and β cell nesidioblastosis, and multifocal intraductal papillary mucinous neoplasia. The endocrine microadenoma and nesidioblastosis stained for insulin, suggesting both likely contributed to hypoglycemia. Glucagon immunohistochemistry was also positive, though there were no clinical features of glucagon excess. Hypoglycemia resolved postoperatively. This case and other evidence from the literature suggest that hyperplasia and neoplasia may occur sequentially in the pancreas, and that endocrine and exocrine tumorigenesis may be linked in some individuals. Further study is required to identify a unifying mechanism, and to elucidate potential ramifications in the management of patients with pancreatic neoplasms.

Key Words: nesidioblastosis, pancreatic neuroendocrine tumor, intraductal papillary mucinous neoplasia, hyperinsulinemic hypoglycemia, insulinoma

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Nesidioblastosis, pancreatic neuroendocrine tumor (NET) and intraductal papillary mucinous neoplasia (IPMN) are all independently rare and their combination has not been reported to date. Herein, we report the first case of synchronous nesidioblastosis, pancreatic NET and IPMN. This occurred in the context of hyperinsulinemic hypoglycemia, a clinical syndrome most commonly due to insulinoma which has a reported incidence of 4 per 1 million person-years.[1] Adult-onset nesidioblastosis may also cause hyperinsulinemic hypoglycemia, though it is very uncommon outside the setting of postbariatric surgery, accounting for only 0.5% to 7% of the cases.[2] Intraductal papillary mucinous neoplasia is a slowly progressive exocrine tumor,[3] with a frequency of 1 per 100,000.[4] This case highlights the emerging relationships between endocrine hyperplasia, endocrine neoplasia, and exocrine neoplasia seen in various settings including familial cancer syndromes, postbariatric surgery, with the use of incretin mimetics and, now, in the absence of such risk factors.

CASE REPORT

A 33-year-old man presented with a generalized tonic-clonic seizure and a concurrent blood glucose level (BGL) of 1.9 mmol/L a few hours after breakfast. He regained consciousness despite remaining hypoglycemic and felt no better after intravenous dextrose. He had been diagnosed with epilepsy 3 years before, after exclusion of hypoglycemia. The patient had mild intellectual impairment since childhood. His parents had noticed recent development of clouded thinking, increased hunger, and fatigue. Medications included levetiracetam and clonazepam. There was no personal or family history of endocrine neoplasia. The patient had a body mass index of 28.7 kg/m^2 but denied recent weight gain. Examination was otherwise unremarkable.

Fasting BGL was 3.0 mmol/L, with an insulin level at the upper limit of normal at 20 mU/L (0–20) and an inappropriately normal C-peptide level of 1270 pmol/L (400–1500). A 72-hour supervised fast induced symptomatic hypoglycemia at 42 hours, with a BGL of 1.8 mmol/L, C-peptide of 1632 pmol/L (200–1200), insulin of 31.4 mU/L (2–15), proinsulin of 71.1 pmol/L (0–13.3), and suppressed β-hydroxybutyrate at 0.1 mmol/L, all consistent with hyperinsulinemic hypoglycemia. Symptoms resolved with intravenous dextrose and eating, thereby fulfilling Whipple triad of hypoglycemia. Sulphonylurea drug screen and insulin autoantibodies were negative. Morning cortisol, thyroid-stimulating hormone, growth hormone, and insulin-like growth factor 1 were normal.

Computed tomography (CT) abdomen revealed a 12-mm nodule arising from the posterior pancreatic body (Fig. 1). Endoscopic ultrasound (EUS) demonstrated a 13-mm isoechoic solid vascular lesion at the same site. However, there was no increased uptake on 68Ga-DOTATATE PET/CT. Selective arterial calcium stimulation testing (SACST) showed multiple regions of excess insulin production (Fig. 2).

Pending surgical review, the patient was advised to consume small, frequent carbohydrate-containing meals yielding mild improvements in fatigue and cognition. Fasting BGL remained around 3 to 4 mmol/L. He declined diazoxide.

At laparotomy, surgical palpation and intraoperative ultrasound were unremarkable. The lesion seen on CT and EUS corresponded with a normal fold of pancreas. The patient underwent subtotal pancreatectomy from the right of the portal and superior mesenteric veins, with preservation of the spleen and a ring of pancreatic head in proximity to the duodenum. Histopathology revealed a 2-mm endocrine microadenoma, background islet hyperplasia with α and β cell ductuloinsular complexes consistent with nesidioblastosis and multifocal IPMN (Fig. 3). The endocrine microadenoma and nesidioblastosis stained for insulin, suggesting both likely

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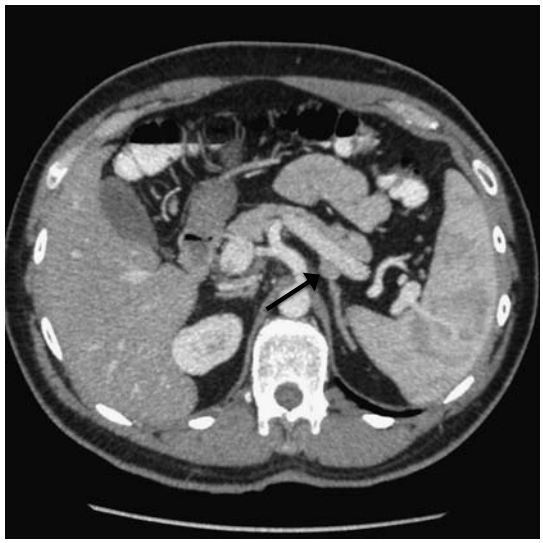

FIGURE 1. The CT abdomen revealed a 12-mm hypointense exophytic nodule arising from the posterior pancreatic body (arrow). No other parenchymal lesions were visualized.

contributed to hyperinsulinemic hypoglycemia. The endocrine lesions additionally stained for glucagon, although there were no clinical features of the glucagonoma syndrome.

Two months after surgery, the patient had an glycohemoglobin of 5.6% and fasting BGL of 5.8 mmol/L with an insulin of 15 mU/L (0–20). Hunger had resolved, and his neurocognitive state had improved. Postoperative glucagon, vasoactive intestinal peptide, gastrin, parathyroid hormone, and pituitary profile were normal.

DISCUSSION

Our patient presented with hypoglycemia requiring extensive evaluation. Diagnosis of endogenous hyperinsulinism requires demonstration of symptomatic hypoglycemia with elevated insulin and C-peptide levels, either captured spontaneously or during a 72-hour fast or mixed meal test.[5,6] Precisely localizing insulin-producing tumors and distinguishing them from nesidioblastosis is integral in planning the extent of pancreatic resection.[7] Clinically, insulinoma typically causes fasting hypoglycemia, reflecting the autonomous nature of insulin secretion by neoplastic tissue,[5] whereas nesidioblastosis usually manifests as postprandial hypoglycemia due to the retained physiological response to meals.[2]

Computed tomography, magnetic resonance imaging, somatostatin receptor scintigraphy, and EUS facilitate tumor localization and can document metastatic disease, with malignant disease observed in 6% to 8% of insulinomas.[1,7] Endoscopic ultrasound alone successfully locates a tumor in 92%, and this success rate rises to 96% when combined with CT and magnetic resonance imaging.[7] As highlighted by our case, functional localization via SACST is

Insulin concentration (mU/L) Fasting insulin reference interval: 2.0 - 15.0 mU/L

Site of stimulation	Time after injection (seconds)				
	0	30	60	90	150
Superior mesenteric artery	118	1842	1454	802	383
Distal splenic artery	220	181	380	1339	500
Proximal splenic artery	262	1806	2853	1940	978
Gastroduodenal artery	435	349	924	742	442
Hepatic artery	298	262	988	753	383

Insulin ratio (concentration compared to baseline sample)

Site of stimulation	Time after injection (seconds)				
	0	30	60	90	150
Superior mesenteric artery	1	15.6	12.3	6.8	3.2
Distal splenic artery	1	0.8	1.7	6.1	2.3
Proximal splenic artery	1	6.9	10.9	7.4	3.7
Gastroduodenal artery	1	0.8	2.1	1.7	1.0
Hepatic artery	1	0.9	3.3	2.5	1.3

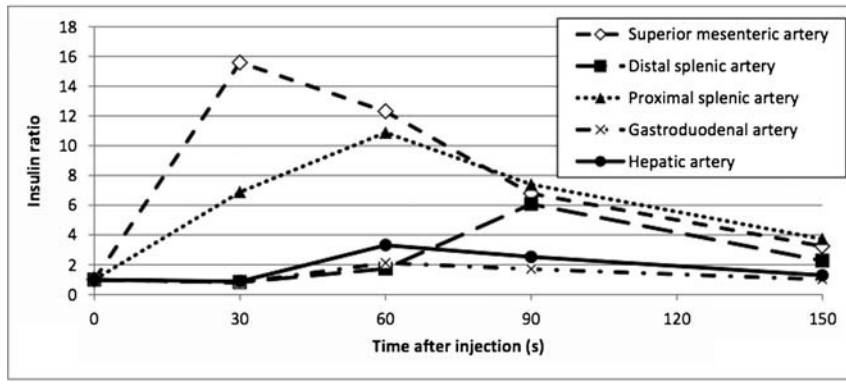

FIGURE 2. Selective arterial calcium stimulation test revealed multiple arterial segments with insulin baseline-to-stimulation ratios greater than 2 consistent with a diffuse etiology of hyperinsulinism. The greatest area of insulin production was the superior mesenteric artery which typically corresponds to the uncinate process. The splenic artery territories which usually correspond with the pancreatic body, and where a lesion was visualized in this patient on CT and EUS, demonstrated an intermediate degree of insulin production.

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critical when imaging fails to identify a tumor or where results are discrepant. In insulinoma, the rise in venous insulin should be at least 2-fold when calcium is delivered to the arterial distribution containing the tumor, whereas nesidioblastosis typically demonstrates a gradient of insulin excess.[8]

Surgical palpation and intraoperative ultrasound identifies a tumor in 92% of insulinomas.[7] If preoperative and intraoperative localization techniques fail, blind distal pancreatectomy has been traditionally performed.[5] However, occult insulinomas are frequently located in the pancreatic head and may thus be left in situ with such an approach.[7]

Pancreatic NETs

In accordance with the World Health Organization tumor classification system,[9] the pancreatic NET found in our patient is classified as an endocrine microadenoma as it is less than 5 mm. We believe it may have been functional, given the positive immunohistochemistry and the presence of fasting hypoglycemia,

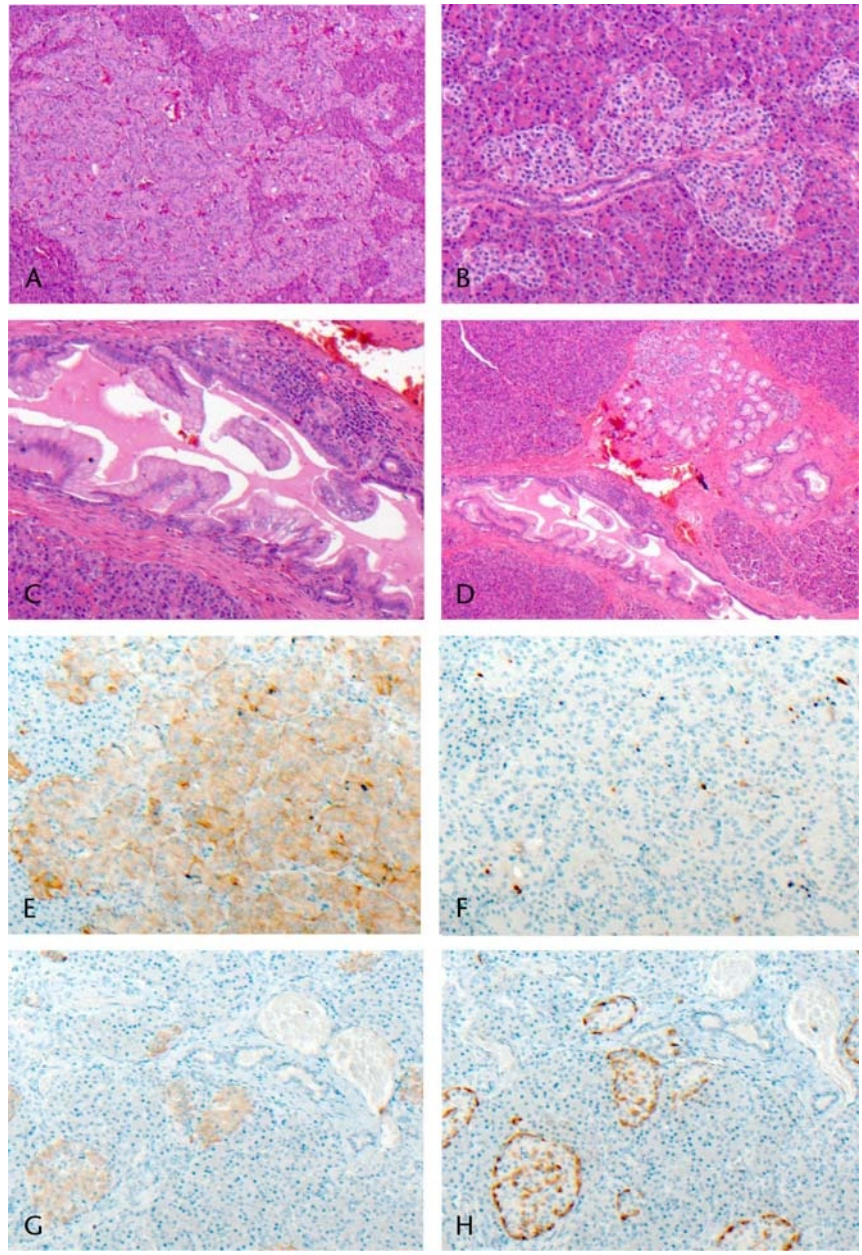

FIGURE 3. Hematoxylin-eosin staining revealed a well-circumscribed unencapsulated 2 mm × 2 mm endocrine microadenoma (A, 4× magnification), prominent background islet hyperplasia with frequent ductuloinsular complexes (B, 10× magnification), and multifocal intraductal papillary mucinous neoplasms of low-grade dysplasia (C, 10× magnification), some of which were in close proximity to ductuloinsular complexes (D, 4× magnification). The microadenoma contained predominantly insulin-positive cells (E, 10× magnification) and occasional glucagon-positive cells (F, 10× magnification), with a Ki67 proliferation index of 1% (not shown). The ductuloinsular complexes demonstrated mixed positivity for insulin (G, 10× magnification) and glucagon (H, 10× magnification), consistent with β and α cell nesidioblastosis, respectively. The hyperplastic islets contained many somatostatin-positive cells (not shown); however, microadenoma was not included in the somatostatin receptor–stained section. **Editor's note:** A color image accompanies the online version of this article.

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though most pancreatic microadenomas do not produce syndromes of hormone excess.[10] Pancreatic NETs are usually sporadic, occurring as part of multiple endocrine neoplasia type 1 (MEN1) in only 8% to 11% of patients.[1,7] The MEN1-associated insulinomas demonstrate an earlier onset of the disease with a median age at diagnosis of 28 years versus 53 years when sporadic.[7] The young age of our patient, as well as the plurihormonal profile of the endocrine microadenoma, was suggestive of MEN1.[10] However, there was no personal or family history of MEN1-related tumors, and phenotypic screening for other endocrine neoplasms was negative. The MEN1-associated insulinomas are also more likely to be multifocal, malignant, and recurrent.[1,7] Familial NETs may rarely occur in the setting of von Hippel-Lindau disease and the newly labeled condition, MEN4, due to *CDKN1B* mutations.[11] The preferred treatment of pancreatic NETs is tumor enucleation.[7]

Nesidioblastosis

The term nesidioblastosis is generally used to denote β cell proliferation. The α cell nesidioblastosis has been more recently described, and both α and β cell nesidioblastosis was uniquely demonstrated in our case. It is a pathological diagnosis defined by budding of endocrine cells from pancreatic ductules and proliferation of pancreatic islet cells.[12] Histopathological features include hyperplastic islets with hypertrophic endocrine cells, demonstrating prominent pleomorphic nuclei and abundant clear cytoplasm, and ductuloinsular complexes with islet neoformation.[2,6]

The β cell nesidioblastosis manifests clinically as a persistent neonatal hyperinsulinemic hypoglycemia when it occurs in infancy, and as noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) when it arises in adulthood.[2] Neonatal-onset is much more common and often attributable to mutations in the genes encoding sulphonylurea receptor (*SUR1*), inwardly rectifying potassium channel (*KIR6.2*), glucokinase, and glutamade dehydrogenase.[2] Genetic sequencing in adults with sporadic β cell nesidioblastosis has failed to implicate the *SUR1*, *KIR6.2*, and *MEN1* genes.[13,14] However, a kindred with adult-onset familial hyperinsulinism was recently found to have an activating mutation in the glucokinase gene,[15] illustrating that genetic factors should be considered in adults with familial nesidioblastosis.

The NIPHS more frequently occurs as an acquired condition after bariatric surgery, where patients present with "late dumping" syndrome consisting of hypoglycemic symptoms 1 to 3 hours after meals.[6,8] This may be due to incretin upregulation with increased GLP1 levels demonstrated in patients with NIPHS after bariatric surgery compared to euglycemic subjects postbariatric surgery.[6] There is usually no convincing evidence of insulinoma on imaging in this population.[8] In our case, the patient had a pancreatic mass on CT. However, the multiple suspicious territories on SACST and negative somatostatin receptor scintigraphy raised the possibility of NIPHS preoperatively.

Hyperplasia-Adenoma Sequence

The settings of familial endocrine cancer and bariatric surgery, though not present in our case, provide insights into a possible hyperplasia-adenoma sequence and suggest that concomitant findings in patients such as ours may not be purely incidental. Pancreatic specimens from patients with MEN1 and von Hippel-Lindau demonstrate endocrine hyperplasia, dysplasia, and neoplasia, which are thought to occur in this respective sequence. Maintenance of *MEN1* heterozygosity in hyperplastic endocrine tissue and loss in endocrine adenomas supports this hypothesis.[16] Insulinoma has also been described after bariatric surgery where patients with hypoglycemia are typically thought to have pure nesidioblastosis.[17] In 1 patient, after gastric bypass surgery, distal pancreatectomy revealed multifocal insulinoma and islet hypertrophy, suggesting that adenoma formation may have followed.[8]

Coexistence of pancreatic NETs and nesidioblastosis has rarely been described in the sporadic setting. In 1 such case report, the patient had fasting hyperinsulinemic hypoglycemia and a focal increase in insulin concentration on transhepatic portal venous sampling suggestive of insulinoma.[18] Imaging was unrevealing, illustrating that discordant clinical features may indicate concomitant diagnoses similar to our case. The specific combination of sporadic nesidioblastosis and endocrine microadenoma has previously been described where the patient had postprandial hypoglycemia and insulin staining of the microadenoma was negative, suggesting that nesidioblastosis alone was responsible for the clinical features.[19] It is unclear if background nesidioblastosis in the absence of familial cancer syndromes increases recurrence. However, caution is suggested by a case report of a man with hyperinsulinemic hypoglycemia where the initial pathological diagnosis on enucleation was insulinoma, followed 6 years later by symptomatic nesidioblastosis requiring distal pancreatectomy, and another 5 years later by metastatic insulinoma.[20]

Although α cell nesidioblastosis is extremely rare, the hyperplasia-adenoma sequence has been better observed in reference to the α cell with several cases reported of concomitant α cell nesidioblastosis and glucagonoma.[11,12] Some of these patients have been found to harbor glucagon receptor mutations.[21] Furthermore, α-cell hyperplasia, dysplasia, and neoplasia occur sequentially in glucagon receptor-knockout mice,[22] suggesting that loss of negative feedback promotes endocrine tumorigenesis.

Endocrine-Exocrine Neoplasia

Coexistence of pancreatic NET and IPMN is increasingly recognized with rates of 1.3% to 4.6% and frequent topographic intimacy of the tumors in surgical series.[4] Theoretical explanations include transdifferentiation between exocrine and endocrine neoplastic cells, and concomitant endocrine and exocrine neoplasia arising from a common progenitor. Support for cellular plasticity is derived from histological studies showing endocrine markers in exocrine neoplasms and vice versa,[23,24] and ductuloinsular complexes representing islet neogenesis from ductal exocrine tissue.[2] Animal models illustrate the notion of facultative stem cells whereby differentiated cell lines, particularly ductal cells, and less so acinar and islet cells, have the capacity to dedifferentiate to a stem cell role and redifferentiate along alternative cell lines.[25]

It is possible that a trophic factor or genetic mutation stimulates proliferation of both endocrine and exocrine tissue, though a unifying genetic basis has not yet been identified. Moriyoshi et al[26] reported a patient with MEN1 where pancreaticoduodenectomy revealed endocrine and exocrine neoplasms; however, loss of heterozygosity in the *MEN1* gene was demonstrated only in the former, suggesting additional factors contributed to exocrine tumorigenesis. Endocrine-exocrine relationships were also observed in a small post-mortem study[27] where subjects on incretin mimetics had increased endocrine and exocrine pancreatic mass, as well as pancreatic intraepithelial neoplasia, compared to diabetic subjects on other treatments and nondiabetic controls. The authors hypothesized that this may have been mediated by glucagon downregulation in response to increased GLP1. This emerging association is particularly concerning in light of the purported increased rate of pancreatic carcinoma in some, but not all, postmarketing data of incretin mimetics.[28]

Endocrine Hyperplasia, Endocrine Neoplasia, and Exocrine Neoplasia

The first report of nesidioblastosis, endocrine adenoma, and intraductal papillary mucinous changes in the setting of hypoglycemia

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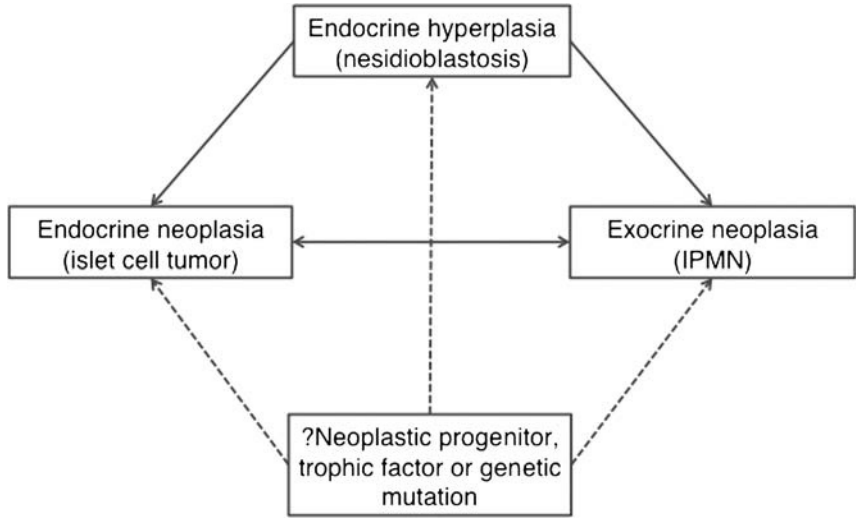

FIGURE 4. Hypotheses explaining the coexistence of nesidiblastosis, endocrine microadenoma, and IPMN seen in our case. The neoplastic progenitor may be facultative stem cells within the pancreas, whereas potential trophic factors include downstream signals in the incretin pathway and genetic factors include MEN1 mutations. None of these explanations have yet been definitively proven to account for human cases of such concomitant disease.

was published in 2001 by Zhao et al.[3] However, in this case, the islet cell tumor appeared to be nonfunctioning, and the intraductal mucinous changes were deemed to represent hyperplasia rather than neoplasia. Moriyoshi et al[26] recently reported the aforementioned patient with MEN1 where pancreaticoduodenectomy revealed multiple neuroendocrine neoplasms, endocrine microadenoma, islet hyperplasia, IPMN, and ductal adenocarcinoma. In contrast to our case, there were no ductuloinsular complexes to suggest nesidioblastosis, and the patient had no evidence of hormone hypersection. Al-Sarireh et al[29] published a related case of concurrent α cell hyperplasia, dysplasia, and microadenoma together with IPMN. However, there was again no evidence of hormone excess. No similar cases have since been documented until now. It is possible that the surgical preference for endocrine tumor enucleation[7] and frequent primary medical therapy for nesidioblastosis[2] prevents identification of the other pathologies where they exist.

Our case together with those reported by Zhao et al,[3] Moriyoshi et al,[26] and Al-Sarireh et al[29] suggest that endocrine hyperplasia, endocrine neoplasia, and exocrine neoplasia represent different components of a pathological spectrum. Animal and in vitro studies are required to examine the hypothetical sequences (Fig. 4). More clinical data are needed to determine if the coexistence of these conditions bears impact on the natural history of pancreatic disease and, therefore, whether they necessitate more extensive pancreatic resection and more intensive follow-up.

In summary, the presented case demonstrates that nesidioblastosis is a key differential in adults with hyperinsulinemic hypoglycemia, even if symptoms occur only on fasting and that discrepant results on investigation may indicate concomitant diagnoses. The exceptional finding of concurrent endocrine hyperplasia, endocrine neoplasia, and exocrine neoplasia may reflect a true pathogenic relationship. How endocrine and exocrine neoplasms might affect proliferation of the other is unclear and requires further study.

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