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REVIEW ARTICLE

A Systematic Review of Proinsulin-Secreting Pancreatic Neuroendocrine Tumors

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Abstract

Background Pancreatic neuroendocrine tumors (PNETs) are a heterogeneous group of islet cell-derived neoplasms with a propensity toward hormone production. Among PNETs, proinsulin-secreting tumors (proinsulinomas) are exceedingly rare. The objective of this study is to collect and summarize the existing literature to provide a comprehensive evaluation of this uncommon disease.

Methods A systematic review was performed to characterize the clinicopathologic features of proinsulinoma. Using the electronic biomedical databases PubMed, Ovid Medline, and Embase, 316 publications were screened for relevance of which 14 were selected. We also present two patients with proinsulinoma treated at Yale New Haven Hospital.

Results Of the 16 patients included in the study, the mean age was 56.8 and there was a 2:1 female predominance. The majority of patients presented with symptomatic hypoglycemia with normal or low insulin levels. Median tumor diameter was 1.2 cm and 80% were located in the body and tail of the pancreas. Following resection, most patients had normalization of hormonal levels without recurrence (75%; 12/16).

Conclusion Proinsulinomas are rare pancreatic neuroendocrine tumors that have the potential to cause hypoglycemia. While insulinomas and proinsulin-secreting tumors have many physiologic parallels, these cases illustrate several key distinctions in their diagnosis and management.

Keywords Proinsulin · Pancreas · Neuroendocrine tumor

Introduction

Functional pancreatic neuroendocrine tumors (PNETs) comprise a wide range of well-differentiated neoplasms characterized by their profile of hormone synthesis. Among them, proinsulin-secreting tumors (proinsulinomas) are exceedingly rare with the majority of available literature confined to case reports. Proinsulin, the biosynthetic precursor to insulin, is first produced by pancreatic beta cells and is then converted into equimolar amounts of C-peptide and insulin via enzymatic cleavage. While the biologic activity of proinsulin is 10% that of insulin, the hormones share similar physiologic functions.[1] Thus, proinsulin-secreting tumors typically present with symptomatic hypoglycemia accompanied by normal or low insulin levels.[2, 3]

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Materials and Methods

Literature Review

A systematic review of the literature was performed using the electronic biomedical databases Ovid Medline, Embase, and PubMed. Cases of proinsulin-secreting PNETs were based on

the clinical presentation, laboratory values, immunohistochemistry, and other available biochemical data. Using the search terms "proinsulinoma," "proinsulin + pancreas," "proinsulin + neuroendocrine," and "proinsulin-secreting," 316 articles were identified and their abstracts were screened for relevance. Forty articles were selected for full-text screening of which 14 were included in the final review (Tables 1 and 2). Selected publications were cross-referenced for additional reports of proinsulinoma.

Results

Including the two cases presented below, a review of the published accounts of proinsulinomas revealed a 2:1 female predominance (female, n = 11; male, n = 5) and a mean age of 56.8 years (Table 1). The observed gender disparity is similar, but slightly more pronounced, than that of insulinoma where 59% of the patients are female.[4] Tumors were most often found in the body and tail of the pancreas (80%; 12/15) and had a median diameter of 1.2 cm with a range from 0.8–13 cm. Following surgery, 75% of patients (n = 12/16) had normalization of hormonal levels without signs of recurrence (Table 2). One patient had persistent disease; however, the tumor was not resected during his distal pancreatectomy.[5]

Table 1 A summary of 16 cases of predominantly proinsulin-secreting pancreatic neuroendocrine tumors

Variable	Number (%)
Total	16 (100)
Age, mean, ±SD	56.8 ± 14.6
Female	11 (68.8)
Male	5 (31.3)
Primary pancreatic tumor location	
Head	3 (18.8)
Body	3 (18.8)
Body/tail	6 (37.5)
Tail	3 (18.8)
Unknown	1 (6.3)
Metastatic	1 (6.3)
Tumor diameter, cm, median, ± SD	1.2 ± 3.1
Range, cm	0.8–13
Operation	
Distal pancreatectomy	5 (31.3)
Distal pancreatectomy and splenectomy	4 (25)
Enucleation	3 (18.8)
Pancreaticoduodenectomy	1 (6.3)
Other[a]	1 (6.3)
Unknown	2 (12.5)

SD standard deviation

[a] Distal pancreatectomy, total gastrectomy, transverse colectomy, and left nephrectomy

In regard to complications, one patient developed diabetes mellitus 4 months after the procedure, another succumbed to postoperative necrotizing pancreatitis, and the third expired due to complications associated with a metastatic proinsulinoma (Table 2). The individual with metastatic disease is unique in that the patient initially presented with an aggressive, nonfunctional PNET that directly invaded the transverse colon, stomach, and left ureter. The patient then developed hepatic and pulmonary metastases, the latter of which was associated with increased proinsulin secretion.[6] The incidence of metastatic disease in this cohort was 6.3% (n = 1/16) which is similar to the rate in patients with insulinomas (5–15%).[7] To our knowledge, no cases of nonmetastatic, extrapancreatic proinsulinoma have been described.

Patient A

A 64-year-old female presented to her primary care physician with new onset palpitations. Her past medical history was significant for sarcoidosis, nephrolithiasis, hypertension, and cataracts. During her cardiac workup, routine laboratory testing revealed a serum glucose concentration of 62 mg/dL (3.44 mmol/L). The patient was referred to an endocrinologist, where inquiry into her symptoms revealed only a recent 5-lb weight gain. She denied excessive hunger, anxiety, confusion, or other constitutional symptoms typically associated with hypoglycemia. The patient's physical exam and vital signs were unremarkable and her body mass index (BMI) was 24.2 kg/m^2.

After the patient's initial visit, the index of suspicion for a true hypoglycemic disorder was low due to the absence of the typical symptom profile and failure to fulfill Whipple's triad, defined as follows:

1. Symptoms consistent with hypoglycemia
2. Low plasma glucose measured at the time of symptoms
3. Resolution of symptoms when plasma glucose level returns to normal

To rule out excess insulin production, laboratory values were drawn following a 14-h fast. They demonstrated only hypoglycemia (53 mg/dL; 2.94 mmol/L), with normal insulin (2.3 μIU/mL), C-peptide (1.52 ng/mL), ACTH (21 pg/mL), and sulfonylurea levels. Due to her unexplained and reproducible hypoglycemia, a 72-h inpatient fast was performed. The test was terminated prematurely at 26 h when the patient developed bradycardia and subjective fevers. Plasma glucose at that time was 46 mg/dL (2.55 mmol/L). Labs acquired at 22 h demonstrated an elevated proinsulin level of 66.2 pmol/L (reference range = ≤18.8 pmol/L) with depressed insulin and

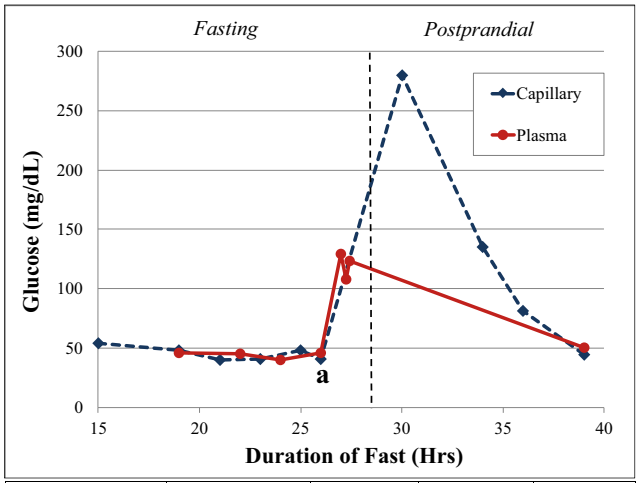
Table 2 Clinicopathologic characteristics of proinsulinomas

Author, year of publication	Age (years)	Gender	Glucose (mg/dL)	Insulin (MIU/mL)	C-Peptide (ng/mL)	Proinsulin (pmol/L)	Location of pancreatic mass	Tumor diameter (cm)	Complication
Reference range			70–100 mg/dL	2.0–19.6 μIU/mL	0.9–7.1 ng/mL	≤18.8 pmol/L			
[23]	78	F	24	<5	N/A	PLC = 66.5% (RR = 5–22%)	N/A	N/A	
[18]	62	F	48.6	70.1	5.3	368	Body	1.0	Fatal necrotizing pancreatitis after resection
[15]	70	F	46	3	N/A	150	Body/tail	1.0	
[5]	47	M	39.6–81.1	21.7	6.6	61.8	Head	1.5	Persistent proinsulinoma after distal pancreatectomy and splenectomy without tumor resection
[16]	37	M	23	3.8	1.2	604	Body	1.5	
[3]	74	M	40–50	4.4–6.0	2.9–3.1	110–143	Body	1.0	
[19]	51	F	46	3	0.9	19.8 (RR = <8.8)	Tail	1.2	
[20]	49	F	53	<2	0.7	29.2	Body/tail (multifocal)	3.5	
Gómez-Pérez et al. 2010	46	F	20	0.7	2.1	>200	Head	2.5	Diabetes mellitus (type II) 4 months after resection
[21]	33	F	38	5.3	1.7	37.9	Tail	0.9	
[2]	69	F	34	9	0.8	7.2 (RR = < 1.1)	Body/tail	1.0	
[22]	49	M	52	64	0.6	IHC positive	Body/tail	0.8	
[6]	69	F	24	15.7	2.3	IHC positive	Body/tail (metastatic)	13	Deceased from metastatic disease
[12]	38	M	55	<2	1.4	57.4	Head	1.0	
Current Report: Patient A	64	F	46	1.1	0.7	67	Body/tail	1.5	
Current Report: Patient B	72	F	22	8.4	3	64.8	Tail	3.4	

Fourteen published reports of proinsulinomas and the two current cases were evaluated. Laboratory values were obtained at the conclusion of the longest fast available

The reference range presented may differ based on the institution in which it was measured) ([2]; [3]; [5]; [6]; [12]; [15]; [16]; [18]; [19]; [20]; [21]; [22]; [23]; [24])

PLC proinsulin-like components, *RR* reference range, *IHC* immunohistochemistry, *N/A* not available



	Reference Range	20 hours	22 hours	27 hours
Glucose	70–100 mg/dL	48	45	129
Proinsulin	≤ 18.8 pmol/L	-	66.2	67
Insulin	2.0–19.6 μIU/mL	1.1	1.1	1.8
C-peptide	0.9–7.1 ng/mL	0.77	0.74	0.89
β-hydroxybutyrate	< 0.28 mmol/L	-	0.85	1.0
IGF-1	41–279 ng/mL	54.3	192	188

Fig. 1 Plasma glucose concentration during prolonged fast. Patient A demonstrated fasting hypoglycemia with an enhanced response to glucagon after 26 h of fasting. The attached *table* demonstrates the laboratory values obtained during fast. (*a* glucagon administered. *N/A* not available)

C-peptide levels of 1.1 μIU/mL and 0.74 ng/mL, respectively (Fig. 1). After the administration of glucagon, her symptoms abated and plasma glucose concentration increased from 46 to 129 mg/dL (Δ83 mg/dL; Fig. 1). A subsequent oral glucose tolerance test confirmed that the proinsulin level was inappropriately elevated (Table 3).

The discovery of proinsulin elevation increased the suspicion for a functional PNET. Computed tomography (CT) imaging with pancreatic protocol contrast enhancement demonstrated a 1.7 × 1.5 × 1.4 cm solid enhancing mass at the junction of the body and tail of the pancreas (Fig. 2a). Careful review of a prior CT scan from 7 years earlier revealed a faint mass in the same location measuring 1.2 × 1.2 × 1.2 cm. An endoscopic ultrasound (EUS) was then performed with fine-needle aspiration biopsy. Pathology revealed a PNET.

The patient was brought to the operating room for a laparoscopic distal pancreatectomy. Intraoperative pancreatic ultrasound was used to clarify the location of the mass. After mobilizing the body of the pancreas away from the splenic vasculature, the pancreas was transected and the procedure was completed without complications. The patient did well postoperatively and was discharged home on hospital day 3. Proinsulin concentration immediately following surgery decreased to 23.0 pmol/L and remained below the upper limit of normal in all subsequent measurements (Fig. 3).

The resected specimen was a 1.5 × 1.2 × 0.8 cm well-circumscribed, soft, tan mass (Fig. 2b). Histology was consistent with a well-differentiated PNET (Fig. 2c). The cells were arranged in trabeculae and small nests with moderate amounts of granular eosinophilic cytoplasm and round nuclei. The mitotic count was low (<2/10 high-power field), as was the Ki-67 index (<2%). Lymph node sampling was negative for metastasis. Immunostaining was strongly and diffusely positive for chromogranin, insulin, and proinsulin (Fig. 2d; Abcam [Mouse monoclonal C-PEP-01], 1:1000). The tumor was determined to be stage IA (pT1N0) per the seventh edition of the American Joint Committee on Cancer guidelines.

Patient B

A 72-year-old female with a history of paroxysmal atrial fibrillation, hypertension, and asthma presented to the emergency department after a syncopal episode with associated diaphoresis and bilateral lower extremity fasciculations. Capillary blood glucose level at that time was 22 mg/dL (1.22 mmol/L). She was treated with intravenous dextrose and her plasma glucose level increased to 200 mg/dL (11.10 mmol/L). Endocrinology evaluation revealed a 14-year history of monthly 5–10-min episodes of flushing, palpitations, dizziness, and diaphoresis. She did not experience these symptoms during menopause. She also reported steady weight gain over the past several years. The patient's physical exam was notable only for obesity (BMI 31.4 kg/m^2).

Additional diagnostic testing demonstrated normal levels of C-peptide (3.0 ng/mL), insulin (8.4 μIU/mL), and insulin autoantibodies, but revealed an elevated proinsulin concentration (64.8 pmol/L). Abdominal magnetic resonance imaging (MRI) identified a 3.7 × 3.6 × 3.1 cm hemorrhagic cystic lesion in the pancreatic tail, consistent with a PNET. The diagnosis was confirmed via EUS-guided biopsy.

The patient was taken to the operating room where a laparoscopic distal pancreatectomy and splenectomy were

Table 3 Serial laboratory values of Patient A obtained during glucose tolerance test

Time (h) Reference range	Glucose (mg/dL) 70–100 mg/dL	Insulin (μIU/mL) 2.0–19.6 μIU/mL	C-peptide (ng/mL) 0.9–7.1 ng/mL	Proinsulin (pmol/L) ≤18.8 pmol/L
0	–	3.6	1.92	98.2
1	188	17.1	7.51	160.7
2	93	4.3	4.54	170.1

Serum glucose, insulin, C-peptide, and proinsulin levels were collected following the oral administration of 75 g of glucose

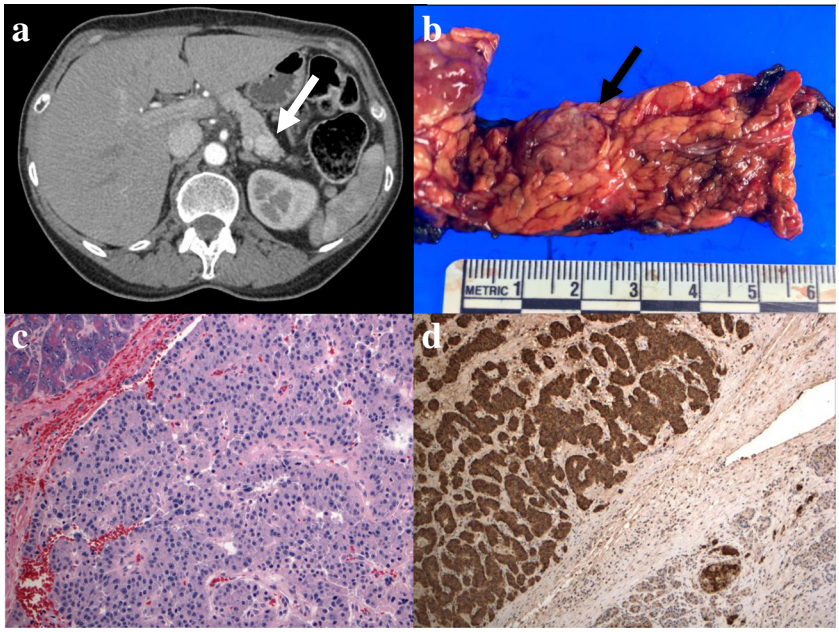


Fig. 2 Imaging and pathological analysis of proinsulin-secreting neuroendocrine tumor in patient A. **a** Axial computed tomography with pancreatic protocol contrast enhancement demonstrates a hyperenhancing mass at the junction of the body and tail of the pancreas. (*White arrow* indicates tumor.) **b** Gross photograph showing a well-circumscribed unencapsulated tumor in the distal pancreas. (*Black arrow* indicates tumor.) **c** Low-power view with hematoxylin and eosin staining showing the pseudocapsule separating the tumor from the adjacent pancreas. The tumor cells are arranged in thick trabeculae or small nests. **d** Immunostaining for proinsulin with strong cytoplasmic positivity. Note that normal islets in the adjacent pancreas are also positive

performed. By postoperative day 2, proinsulin levels normalized and remained within the reference range in all successive measurements (Fig. 3). The patient's hospital course was complicated only by a transient oxygen requirement and she was discharged home on postoperative day 3.

The specimen was a 3.4 × 3.0 × 2.1 cm well-differentiated endocrine tumor. Nuclear chromatin was finely stippled and rare nucleoli were observed. There was evidence of central hemorrhage in the tumor, likely related to fine needle aspiration. As with patient A, immunostaining of the tumor was strongly and diffusely positive for chromogranin, proinsulin, and insulin. All other tumor characteristics, including stage, histology, and lymph node status, were identical to those described for patient A.

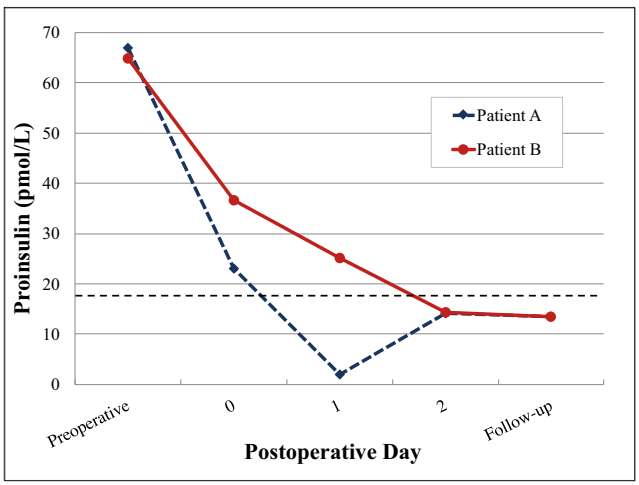


Fig. 3 Proinsulin level in relation to operation. Proinsulin levels in patients A and B decreased following surgery, normalized by postoperative day 2, and remained below the upper limit of normal on subsequent measurements. (*dashed line* upper limit of normal of proinsulin concentration [≤18.8 pmol/L])

Discussion

PNETs are composed of a group of islet cell-derived masses that account for less than 3% of all pancreatic neoplasms.[8] Mean age at diagnosis is 56.7 years and there is an equal gender distribution.[9] One third to one half of PNETs secrete hormones such as insulin, gastrin, glucagon, and vasoactive intestinal peptide (VIP) that can cause an array of paraneoplastic symptoms.[10, 11] Of these subtypes, proinsulin-producing PNETs are exceedingly rare, with only a small number of cases reported in the literature.

Presentation

Adult-onset hypoglycemia in non-diabetic patients is most commonly caused by exogenous or endogenous insulin excess. Exogenous insulin intake may be accidental, surreptitious, or malicious, while endogenous causes of hypoglycemia include critical illness, alcohol use, cortisol excess, or a hormone-secreting tumor. Weight gain, as demonstrated in

both patients A and B, is a common precursor to the diagnosis of an insulin or proinsulin-producing neoplasm as the typical neuroglycopenic symptoms encountered during a hypoglycemic episode may be alleviated with oral intake.[3]

Patient A did not exhibit any sympathoadrenal or neuroglycopenic symptoms typically observed with insulin-secreting tumors. This state of hypoglycemia unawareness may be explained by the indolent nature of the tumor which allowed a progressive physiologic acclimation to the altered biochemical milieu without typical constitutional symptoms. Imaging in patient A demonstrated that the mass was likely present for at least 7 years prior to her diagnosis, during which it enlarged only 0.5 cm. Further, patient B reported more than a decade of episodic diaphoresis and flushing that may have been caused by undetected hypoglycemia. The symptoms associated with proinsulinomas do not appear to be as severe as in the majority of insulinomas; thus, these tumors may go undetected for a prolonged interval. The low Ki-67 indices (<2%) seen in our patients and others further supports the argument that proinsulinomas are indolent tumors.[6, 12]

Laboratory Testing

Recommended biochemical testing for occult hypoglycemia includes plasma glucose, insulin, C-peptide, β-hydroxybutyrate, and screening for oral hypoglycemic agents.[13] If preliminary testing is nondiagnostic, insulin autoantibodies and a fasting proinsulin level should be measured. The original insulin assay was nonspecific, so insulin, proinsulin, and insulin-like molecules were detected together. However, with the recent advent of new, highly specific monoclonal insulin antibodies, proinsulin may be missed. This technological shift may increase the importance of proinsulin testing as the true incidence of proinsulin-producing tumors may have been historically underestimated.

The 72-h fast followed by intravenous injection of glucagon is another useful aid in uncovering metabolic dysregulation. Normally, fasting results in the release of nearly all available hepatic glucose. Excess insulin or proinsulin secretion preserves, glucose stores due to insulin's antiglycogenolytic effect. An increase in glucose of >25 mg/dL (1.39 mmol/L) in response to a glucagon challenge is suggestive of inappropriate glycogen storage.[14] In a similar fashion, glucagon administration in patient A increased plasma glucose by 83 mg/dL (4.61 mmol/L) despite sustained glucose levels below 50 mg/dL (2.77 mmol/L).

Localization

While both patients had clearly identifiable pancreatic masses on imaging, localization can present a challenge. Noninvasive modalities including abdominal ultrasound, CT, and MRI can allow visualization of the majority of PNETs; however, reports from Hiura, Chia, and Piovesan describe proinsulinomas undetectable by MRI or CT that were only found on laparotomy or EUS.[3, 15, 16] In occult PNETs, EUS is a valuable diagnostic tool as it allows for additional anatomical definition and often provides a histopathological diagnosis preoperatively. While selective angiography with venous sampling can aid in localizing insulinomas after calcium infusion, proinsulinomas have not been shown to have a similar secretory response to intravenous calcium gluconate.[2, 17]

Treatment

Much of the clinical management of proinsulinomas has been extrapolated from the existing insulinoma literature. Treatment with diazoxide and octreotide can improve symptoms in insulinomas, but their efficacy in proinsulinomas appears mixed. Gama and Arioglu describe improvement in symptoms with diazoxide, but the agent was ineffective when used by Piovesan and Yoshioka.[3, 5, 6, 18] While the sample size is limited, octreotide does not appear to improve symptoms, and in certain cases, may worsen hypoglycemia.[3, 18]

Surgical resection is the mainstay of treatment and offers the best probability of complete symptom resolution. Enucleation avoids the complications of resection; however, distal pancreatectomy may be preferred when the lesion is located in the distal portion of the gland or is in close proximity to the pancreatic duct. As demonstrated in this and other studies, laparoscopic resection is both a safe and effective treatment option for endocrine tumors of the pancreas.[19–22] Advances in intraoperative ultrasonography have improved the localization of PNETs and decreased the amount of healthy tissue that must be sacrificed to ensure complete tumor resection.

Conclusion

Proinsulinomas are predominantly benign neuroendocrine tumors that have the potential to cause symptomatic or asymptomatic hypoglycemia. These cases illustrate that the diagnosis of organic hypoglycemia can be challenging, but favors a methodical approach and may be improved with the inclusion of proinsulin levels. While CT or MRI will identify the majority of PNETs, EUS and intraoperative ultrasound are valuable adjuncts. Although symptom control with diazoxide is possible in select patients, surgical resection provides a safe and effective path to a durable cure and can often be performed laparoscopically.

Author's Contribution All persons listed as authors have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing, and

revision of the manuscript. Furthermore, each author has approved the final version of the work to be published and agrees to be accountable in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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