Research Article

Proinsulin-Secreting Neuroendocrine Tumors of the Pancreas: A Single-Centre Experience

Andrey Germanovich Kriger^a Stanislav Valer'evich Berelavichus^a
Ayrat Radikovich Kaldarov^a Vladimir Igorevich Panteleev^a
David Semjonovich Gorin^a Rimma Sangaevna Dugarova^a
Marina Yur'evna Yukina^b

^aAbdominal Surgery, Department of A.V. Vishnevsky Centre of Surgery, Moscow, Russian Federation; ^bTherapeutic Endocrinology Department, National Medical Research Centre of Endocrinology, Moscow, Russian Federation

Keywords

Proinsulinoma · Neuroendocrine tumor · Pancreas · Hyperinsulinism · Hypoglycemia

Abstract

Background: Proinsulinoma is a neuroendocrine tumor (NET) of the pancreas that produces prohormone proinsulin. These tumors are very rare. In the literature, they are most often presented in the form of case reports. **Materials and Methods:** We studied 177 patients with NET of the pancreas who underwent surgical treatment in the A.V. Vishnevsky National Medical Research Centre of Surgery from January 2007 to December 2018. **Results:** Of 81 patients with organic hyperinsulinism caused by functioning NETs of the pancreas during the study period, 3 (3.7%) had a proinsulinoma; 2 were female; and 1 was male. None of them admitted to weight gain during this period, and their BMI was normal. All patients presented with Whipple's triad during the 72-h fast. Tumor-enucleating surgery was performed: one robot assisted, two laparotomies. A normal glucose level after treatment was achieved in all cases. **Conclusion:** In cases where clinical hypoglycemia is present, but the serum insulin level is within the normal range or even decreased, proinsulinoma should be suspected. For now, surgical resection remains the only effective method of treatment. Further investigation of proinsulinomas is needed.

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Ayrat Radikovich Kaldarov
Department of A.V. Vishnevsky Centre of Surgery
27, B. Serpuhovskaja
Moscow 117997 (Russian Federation)
E-Mail kaldarov@ixv.ru, ayratikus@gmail.com

Introduction

Proinsulinoma is a neuroendocrine tumor (NET) of the pancreas that produces a prohormone precursor to insulin – proinsulin. The incidence of pancreatic NETs is 5% of all pancreatic neoplasms [1]. Of these, insulinomas constitute about 20–30% and are the most common cause of organic hyperinsulinism [2]. Proinsulinomas are exceedingly rare. In the literature, they are most often presented in the form of case reports. This article outlines our experience in the treatment of proinsulin-producing NETs at the A.V. Vishnevsky National Medical Research Centre of Surgery.

Materials and Methods

This is a retrospective analysis of 177 patients with NET of the pancreas who underwent surgical treatment in our center from January 2007 to December 2018. In total, 81 of the patients (45.7%) had organic hyperinsulinism. All these patients were diagnosed clinically (Whipple's triad). This was proven using the 72-h fasting test with analysis of plasma glucose, insulin, proinsulin, and C-peptide.

Preoperative localization of the tumor was studied using a combination of radiological methods such as contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), selective arterial calcium stimulation with hepatic venous sampling (ASVS), ultrasound (US), and endoscopic US (EUS).

The histopathological examination confirmed localization, size, margin status, lymph node metastases, and immunohistochemistry (IHC). Tumors were classified according to international TNM pathological staging recommendations for NETs.

Results

Of 81 patients with organic hyperinsulinism caused by functioning NETs of the pancreas during the study period, 3 (3.7%) had a proinsulinoma; 2 were women and 1 was a man. Their ages were 44, 57, and 61 years (mean age 54). None of the patients had associated MEN-1 syndrome.

All of the patients had clinical presentation of hypoglycemia, which was manifested in episodes of overall weakness, dizziness, disorientation, confusion, sweating, and loss of consciousness. They managed to alleviate this by simple carbohydrate intake. The durations of the symptoms were 9 months, 3 years, and 5 years. None of them admitted to weight gain during this period, and their BMI was normal.

In 1 case during the examination for NET, a tumor of the left breast was detected. In the preoperative period, a course of octreotide (100 mg 3 times a day) was performed, during which there were no episodes of hypoglycemia. In July 2015 the patient underwent a modified radical left-sided mastectomy ("Madden mastectomy"). The histology revealed an infiltrative ductal cancer, Ki67 – 10%. After surgery, the patient was treated with tamoxifen.

All patients presented with Whipple's triad (hypoglycemic symptoms in the presence of low-plasma glucose, which is relieved upon the administration of glucose) during the 72-h fast. Serum glucose, insulin, proinsulin, and C-peptide were taken during the test. The results are presented in Table 1.

Localization of the tumor was defined by various imaging modalities. All patients underwent CT. In 1 case, a visualization of a solid enhancing rounded mass at the head of the pancreas (16 × 11.8 mm) was achieved. Another patient was diagnosed with 2 rounded, solid nodules in the body of the pancreas, the larger of which was 10 mm in diameter. MRI was performed in the second case as an additional survey and revealed only one solid mass (10.1 × 9.4 mm), consistent with a NET. In the third case, MRI, which was performed in

Table 1. Comparison of insulin, C-peptide, and proinsulin levels during the fasting test

	Glucose, mmol/L	Insulin, mU/mL	C-peptide, ng/mL	Proinsulin, pmol/L
Patient A	2.5	1.9	2	14.56
Patient B	1.7	15.6	1.68	14.84
Patient C	1.6	4.1	2.56	34.5

C-peptide reference range 0.8–3.1 ng/mL; proinsulin reference range 0.7–4.3 pmol/L.

Table 2. Clinical cases of proinsulinoma of the pancreas described in the literature

No.	Study	Year	Cases, <i>n</i>
1	Alsever et al. [5]	1975	1
2	Gama et al. [6]	1995	1
3	Hiura et al. [7]	1999	1
4	Arioglu et al. [8]	2000	1
5	Chia and Saudek [9]	2003	1
6	Piovesan et al. [10]	2003	1
7	Gutelius et al. [11]	2007	1
8	Clark et al. [12]	2009	1
9	Gómez-Pérez et al. [13]	2010	1
10	Rodriguez et al. [14]	2011	1
11	Fadini et al. [15]	2011	1
12	Bertheau et al. [16]	2014	1
13	Yoshioka et al. [17]	2015	1
14	Volkova et al. [4]	2015	1
15	Perez-Pevida et al. [18]	2016	1
16	Murtha et al. [3]	2017	2
17	This article	2019	3
Total			20

the pre-hospital phase, did not show a mass suggestive of a NET. CT helped in the localization of the tumor, showing a rounded neoplasm in the tail of the pancreas (16.6 × 9.6 mm). ASVS was also performed. During stimulation, a response was found at the points of the distal splenic artery, which corresponds to the hormone-producing tumor of the pancreatic tail.

All patients underwent an enucleation for a solitary lesion of the pancreas – one robot assisted, two laparotomies. During surgery, lesions were identified based on intraoperative bimanual palpation and intraoperative US. In 1 patient, who was suspected of having 2 masses upon CT imaging, intraoperative US showed only 1 nodule in the body of the pancreas. After the removal of the tumor, the specimens were submitted for frozen section analysis to confirm the presence of NET.

All patients developed postoperative hyperglycemia, which did not require insulin administration. Two patients had complications resulting from the surgery, which were manifested in postoperative pancreatitis. One patient also had postoperative pancreatic fistula (biochemical leak). These complications were treated conservatively. All patients were discharged in a stable condition. The mean hospital stay was 10 days (range 9–12).

In all 3 cases, a histopathological examination revealed the neoplasms to be a well-differentiated NET with immunostaining strongly and moderately positive for chromogranin A and synaptophysin. Two tumors showed less than 1% of proliferation index against Ki-67 and no mitotic figures, and one had a Ki-67 index of less than 5%. Resection margins and lymph

Fig. 1. Axial CT scan, arterial phase. Proinsulinoma of the body of the pancreas (arrows): before surgery (**a**) and after tumor enucleation (**b**).

nodes were negative. The mean size was 1.1 cm (ranging from 0.9 to 1.5 cm). All tumors were classified as pT1N0M0 according to international TNM pathological staging recommendations for NETs.

Discussion

Proinsulin is a precursor of insulin, consisting of two chains in the insulin molecule (A- and B-chain) linked together by a C-peptide (C-chain), which is removed during insulin biosynthesis. Proinsulin and insulin have the same physiological effect, although the activity of the first is 10 times lower than the activity of the second [3]. Thus, proinsulinomas have a clinical picture of hypoglycemia with normal or even reduced insulin levels. In the literature, proinsulinomas are described as immensely rare, with most publications being case reports. According to Murtha's systematic review of proinsulinoma-secreting NET, 16 tumors are described (Table 2) [3]. One more case was presented in Russian by Volkova et al. [4] in 2015 (Table 2).

One clinical feature of proinsulinomas that we have noticed is the lack of weight gain due to the disease in these patients. All our patients had a BMI within the normal range. Thus, proinsulinoma should be suspected when there is clinical hypoglycemia and normal or even decreased insulin levels and the patient is not overweight.

In the 3 cases of clinical hypoglycemia proinsulin described, the serum level was elevated, while the insulin level was within the normal range (Table 1). None of the 3 patients experienced excessive hunger, nor did they suffer from obesity, which is typical for insulinoma. Symptoms of hypoglycemia are non-specific, so proinsulinoma, as well as insulinoma, can mimic several other conditions, such as seizures, psychiatric illness, and vague symptoms. Neurological symptomatology in most cases normalizes after the correction of hypoglycemia [19]. All our patients were clinically cured after surgery.

The diagnosis included non-invasive and invasive methods. In 2 cases, the tumor was visualized on CT. In 1 case, where two tumors were detected by CT, an MRI scan was performed as an additional study, which visualized one mass. Selective ASVS was performed to confirm the tumor localization. In 1 case, radiological diagnostic methods were uninformative, and only selective angiography with stimulation confirmed the presence of a tumor (Fig. 1, 2).

Fig. 2. Axial MRI scan, T2W SPAIR. Proinsulinoma of the head of the pancreas (arrow).

According to the literature, CT and MRI often allow for the visualization of pancreatic NETs. However, in some cases proinsulinomas were only found upon endoscopic US or even laparotomy [9, 10]. In a case reported by Fadini et al. [15], during selective ASVS the tumor showed no response to any calcium gluconate stimuli. In our selection, angiography was effective and helped to localize the neoplasm and confirm its hormonal activity.

The treatment of proinsulinomas, as described in the literature, is similar to that of insulinomas. Conservative therapy includes diazoxide and octreotide intake; however, the efficacy of this is questionable. Some authors report improvements in symptoms with diazoxide, while others report its ineffectiveness [10, 17]. The case described by Gama et al. [6] shows no improvement with octreotide treatment. However, one of our patients, who received octreotide as a preoperative preparation for breast tumor surgery, noted the absence of hypoglycemia symptoms during this course. A further study is needed in regard to this question.

Surgical resection remains the only effective method of treating proinsulinomas. It provides complete symptom resolution and normal glucose and hormone blood levels after surgery. Tumor enucleation should be performed whenever possible. It prevents complications from pancreas resection, such as the development of diabetes and POPF. In our case, all patients underwent tumor-enucleating surgery.

According to the literature reviews and case reports, proinsulinoma is often presented as well-differentiated NET with immunostaining positive for chromogranin A and synaptophysin. Most pancreatic NETs produce and secrete both proinsulin and insulin [20]. That was confirmed by the recent Celli et al. [1] review, which studied the expression of proinsulin by IHC in 136 pancreatic NETs. Thirty-six (26%) of them were positive for proinsulin, 89% of which also co-expressed insulin. In our case, IHC was not the main guide in the final diagnosis. The diagnosis of proinsulinoma was made according to clinical presentation and an elevated serum proinsulin level.

Cross-reactivity may occur during an IHC study of NET, so in our center we had several cases of insulinomas, IHC positive for insulin, as well as somatostatin. At the same time, there were no clinical signs of somatostatinoma and the somatostatin serum level was within the normal range. Thus, a diagnosis of hormone-producing NET (including proinsulinoma) can be made only according to a clinical presentation and elevated serum proinsulin level.

Conclusion

Proinsulinomas are extremely rare tumors, with the majority of the literature confined to case reports. In cases where clinical hypoglycemia is present, but the serum insulin level is within the normal range or even lower, proinsulinoma should be suspected. The diagnosis should include laboratory testing (plasma glucose, insulin, C-peptide, proinsulin), and non-invasive (CT, MRI) and sometimes invasive diagnostic methods, such as selective ASVS. The surgical treatment of proinsulinomas is an effective method that provides a durable cure. Further investigation of proinsulinomas is needed.

Statement of Ethics

This article does not contain any studies with human participants or animals performed by any of the authors.

Disclosure Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.G.K. and S.V.B. conceived and designed the study, performed the analysis, and wrote the paper. A.R.K. conceived and designed the study, collected the data, contributed the data, performed the analysis, and wrote the paper. V.I.P. collected the data, contributed the data, performed the analysis, and wrote the paper. D.S.G. performed the analysis and wrote the paper. R.S.D. and M.Y.Y. collected the data and performed the analysis.

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