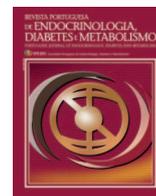




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Caso Clínico

Hipercalcitoninemia e Insulinoma: Uma Rara Associação



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R E S U M O

A calcitonina é um marcador bioquímico crucial utilizado na monitorização de pacientes com diagnóstico de carcinoma medular da tiroide. Contudo, níveis aumentados de calcitonina podem também ocorrer noutras condições clínicas, nomeadamente em tumores neuroendócrinos pancreáticos. A incidência da secreção de calcitonina por estes tumores é desconhecida. Apresentamos o caso de um homem de 72 anos com um quadro caracterizado por episódios de lipotímias, parestesias das mãos e boca, associados a hipoglicémias graves pré-prandiais. A marcha diagnóstica revelou um insulinoma com imunomarcagem para a calcitonina. É de salientar que uma hipercalcitoninemia subjacente foi detetada. Adicionalmente, fizemos uma revisão dos casos semelhantes, reportados na literatura. O presente caso destaca uma causa rara de hipercalcitoninemia e a necessidade de compreender melhor as implicações da secreção de calcitonina pelos tumores neuroendócrinos pancreáticos.

Hypercalcitoninemia and Insulinoma: A Rare Association

A B S T R A C T

Calcitonin is a crucial biochemical marker used in the monitoring of patients with medullary thyroid carcinoma. However increased levels of circulating calcitonin may also be associated with other clinical conditions, namely pancreatic neuroendocrine tumours (PanNETs). The incidence of calcitonin secretion by these tumours is unknown. We describe a case of a 72-year-old man who presented with lipothymia and paraesthesias of the mouth and hands associated with severe pre-prandial hypoglycaemia. Diagnostic work-up revealed an insulinoma with immunostaining for calcitonin. It is worth to mention that a subjacent hypercalcitoninemia was found. Additionally, we perform a review of the related literature. Our case highlights a very rare cause of hypercalcitoninemia and the need for a better understanding on the implications of calcitonin secretion by PanNETs.

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Introduction

Pancreatic neuroendocrine tumours (PanNET) include a rare group of neoplasms that arise from multipotent neuroendocrine cells with the ability to synthesize, store and secrete specific peptide hormones. These tumours can be classified as functioning (FPanNET), based on the presence of distinct clinical syndromes inherent to the secretion of biologically active substances that can be detected in serum. Some of these molecules can be detected by immunohistochemistry. The metabolic products can be inactive or produced at low levels with no obvious symptoms attributed to peptide hormone hypersecretion. If the tumour is not functional (clinically) one can forgo the immunostains for functional tumours. In this case, these tumours are classified as non-functioning (NFpanNET).^{1,2} PanNET account for 1%-2% of pancreatic neoplasms, of which 50% are functional (FPanNET).^{2,3} Insulinomas are the most common type of FPanNET, corresponding to 17% of cases, with an annual incidence of 4 per 1 million person-years. Insulinomas produce insulin and usually have an indolent course, presenting with signs and symptoms of hypoglycaemia.^{3,4} PanNETs may have multi-hormonal immunoreactivity/secretion. Besides eutopic hormonal secretion (insulin, glucagon, pancreatic polypeptide), PanNET may rarely produce non-pancreatic hormones ectopically (ACTH, GHRH, PTHrP, neurotensin, calcitonin, ghrelin, etc.).^{5,6} There are few reports in the literature of functioning calcitonin-secreting PNETs, and only 5 case reports of calcitonin secreting insulinomas.⁷⁻¹¹ We describe a case of a 72-year old man with an insulinoma secreting calcitonin, and perform a review of the related literature.

Case Report

A 72-year-old caucasian man, without remarkable past medical and family history was referred to our endocrinology clinic for evaluation of hypoglycaemias. He had history of intermittent episodes of lipothymia and paraesthesias of the hands and mouth in the previous 8 months that improved with food ingestion. The patient performed self-monitoring of blood glucose which revealed severe hypoglycaemias before meals, mainly in the fasting state (Table 1). There was no use of any medications. The laboratory findings during a spontaneous episode of hypoglycaemia revealed a glycaemia of 42 mg/dL, an inappropriately high level of plasma insulin of 30.6 mU/L [reference range (RR) 2-25] and of C-peptide of 4.04 ng/mL [RR 0.8-3.5], a high pro-insulin value of 65.6 pmol/L [RR <5.1] and a normal β -hydroxybutyrate level. An increase in plasma glucose after administration of 1 mg of intravenous glucagon was observed (10' 78 mg/dL, 20' 118 mg/dL and 30' 110 mg/dL). Hyperinsulinaemic hypoglycemia was thus confirmed. Glycated haemoglobin was 5.1%. An increased of basal calcitonin level of 149 pg/mL [RR <3] and neuron specific enolase (NSE) 20.8 μ g/L [RR < 16] was observed. Anti-insulin and anti-

insulin receptor antibodies were negative. Serum calcium, parathormone and 25-hydroxyvitamin D levels were normal. As also other hormonal studies including thyroid function, adrenocorticotrophic hormone (ACTH), serum cortisol level, IGF1, prolactin were normal. Other hormonal studies including thyroid function, adrenocorticotrophic hormone (ACTH), serum cortisol level, IGF1, prolactin were normal. A thyroid ultrasound revealed a microcyst in the right thyroid lobe. Magnetic resonance imaging (MRI) of the abdomen revealed a nodular image with 17 mm, characterized by discrete arterial enhancement, diffusion restriction, hyperintense signal on T2-weighted image and low signal intensity in T1-weighted image, suggestive of an insulinoma (Fig. 1). No

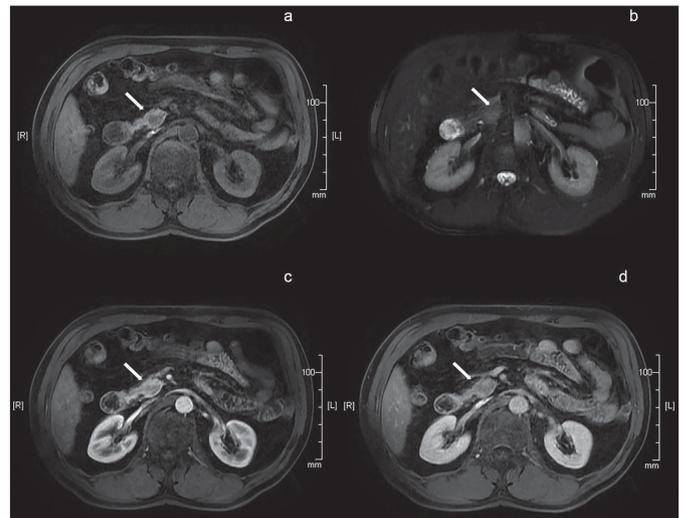


Figure 1. Magnetic resonance imaging of the abdomen. Nodular image of 17 mm in the uncinus process of the pancreas suggestive of insulinoma (arrows), demonstrating a low signal intensity on T1-weighted images (a), high signal intensity on T2-weighted images (b), hypervascularity on arterial phase (c) images and washout on delayed images (d).

evidence of lymph nodes or distant metastasis were detected. An endoscopic ultrasonography guided fine-needle-aspiration biopsy of the 20.3 mm lesion showed a neuroendocrine tumour. While on surgery waiting list, the patient was advised to do frequent meals; diazoxide treatment was started (100 mg three times daily, increasing up to 150 mg three times daily). However the patient developed fluid retention mainly in the lower limbs, which led to the discontinuation of the drug. He underwent laparotomy, the tumour was localized by palpation in combination with intraoperative ultrasonography. A pancreaticoduodenectomy/partial pancreatectomy (Fig. 2), with appendectomy and cholecystectomy were performed. In the gross section of pancreatic head, we identified an intraglandular solid tumour, measuring 22x20x18 mm,

Table 1. Daily blood glucose (mg/dL) recording of the patient.

Breakfast		Lunch		Afternoon snack		Dinner		At bedtime
Before	After	Before	After	Before	After	Before	After	Before
46	62	38	100	60	162	68	120	72
40	91	37	98	56	160	72	140	76
42	90	33	96	42	142	71	142	71
30	102	36	102	46	154	80	160	78
36	94	34	89	37	136	74	168	70

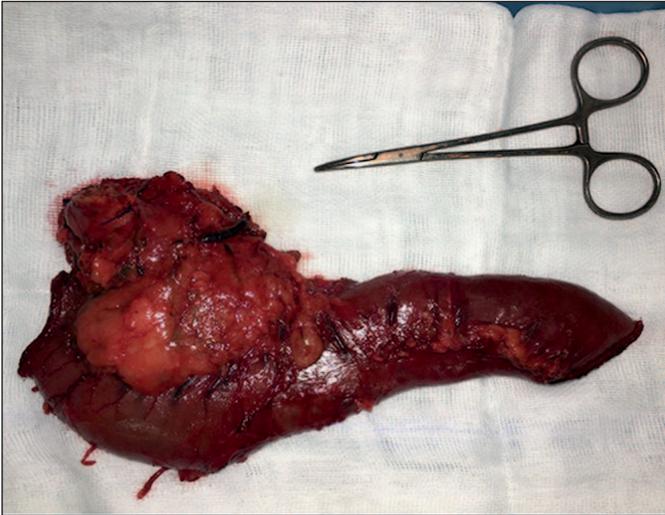


Figure 2. Surgical specimen from pancreaticoduodenectomy/partial pancreatectomy of insulinoma in the uncinate process of the pancreas.

with an expansive growth axis. Microscopically the tumour had a solid/ nested histomorphology. Phenotypically the cells were monomorphic, with moderate quantity of cytoplasm, round nucleus with stippled chromatin. There were some hyaline globules. This description is consistent with well differentiated neuroendocrine tumour. No vascular, perineural invasion or necrosis were identified. The tumour extension was limited to the pancreas, and the surgical margins were uninvolved by the tumour. The immunohistochemistry analysis (Fig. 3), unveiled a positive staining for chromogranin A, synaptophysin, NSE, calcitonin and focally for insulin. The Ki-67 immunorexpression was <3%. Therefore, the diagnosis of a well differentiated low-grade (G1) insulinoma of the pancreas [T2N0M0] was established. No episodes of hypoglycaemia were documented after surgery. The patient developed gastric stasis twelve days after the surgical procedure, with a gastro-pancreatic perianastomotic collection documented by abdominal CT scan. He received a 7-day course of intravenous empiric therapy with piperacillin/tazobactam with subsequent resolution and no need for surgical intervention. One month after surgery the patient was diagnosed with diabetes (values of fasting blood glucose of 153 mg/dL and 140 mg/dL; glycated haemoglobin of 6.3%). He was treated with metformin. Calcitonin levels dropped within undetectable values (<2 pg/mL) thereafter. The patient remains asymptomatic, without any hypoglycemic symptoms with-

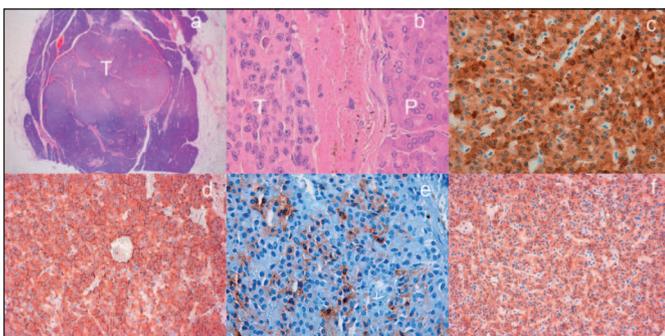


Figure 3. Immunohistochemistry analysis hematoxylin-eosin staining [(a) magnifying glass section of intra-pancreatic extension of the tumour (T); (b) tumour interface (T) at left side and normal pancreas at right side (P)]; immunohistochemistry: synaptophysin, (c); cromogranin A and NSE (d); insulin (focally positive, arrows) (e) and calcitonin (f).

in 28 months follow-up. Regarding diabetes, a worsening of the glyemic control was observed (glycated haemoglobin of 10.3 %) in the last 6 months. Insulin glargine was added to metformin (8 units before breakfast and 8 units before dinner), with improvement of glyemic control.

Discussion

Calcitonin is mainly expressed by parafollicular cells or C cells of the thyroid. The role of calcitonin is not fully understood. This hormone seems to contribute to calcium homeostasis. It lowers serum calcium by inhibiting osteoclast activity, playing a minor role in the regulation of bone turnover.¹² Moreover calcitonin decrease tubular reabsorption of calcium, promoting renal excretion.¹³ In clinical practice it represents a sensitive marker for pre-operative diagnosis and post-surgical follow-up of medullary thyroid carcinoma (MTC), however elevated levels of this hormone are not pathognomonic of MTC.¹⁵⁻¹⁷ Ectopic calcitonin secretion may occur in certain benign clinical conditions such as chronic renal disease, sepsis, autoimmune thyroiditis, mastocytosis, hypercalcemia, hypergastrinemia and may be rarely secreted ectopically by extra thyroidal tumours - NETs (pheochromocytomas, paragangliomas, larynx, lung and gastrointestinal NETs), adrenal carcinomas, lung, breast, prostate, and colorectal carcinomas.¹⁶ In the present case we evaluated calcitonin levels once we suspected of a FpanNET. There are some reports in the literature of both operational and non- functioning calcitonin-secreting PanNETs.^{7-11,17-26} The exact incidence of calcitonin expression in these tumours is unknown. Uccella S *et al*²⁶ performed a review of the literature and found a predominance of calcitonin-immunoreactive VIPomas among FpanNETs, contrary to what the authors found in their own study, in which insulinomas predominated. In the English and French literature we found 5 cases of calcitonin-secreting insulinomas.⁷⁻¹¹ In one case of a sporadic insulinoma, an abnormal karyotype was found involving chromosome 1p13 region (locus of N-Ras and Krev-1, a proto-oncogene and tumour suppressor genes respectively). Nevertheless, common chromosomal abnormalities have not been identified.⁷ Among PanNET with isolated secretion of calcitonin, none were associated with a specific syndrome. In some of the reported cases of functioning and non-functioning calcitonin-secreting PanNET, calcitonin was requested in the context of nodular thyroid disease.^{7,21-25} In others no thyroid disease was identified, leading to unnecessary total thyroidectomies due to the suspicion of a small MTC. In some case reports, calcitonin-secreting PanNET were diagnosed due to systemic or gastrointestinal symptoms (diarrhoea, abdominal pain, etc.) and the presence of a suspected image on CT scan or abdominal ultrasound.^{11,22-24,28} It appears that serum values of unstimulated calcitonin greater than 100 pg/mL are more suggestive of a MTC.^{16,27} However, some case reports calcitonin-secreting insulinomas had serum calcitonin levels above 100 pg/mL. Moreover Schneider *et al*²⁴ found that PanNETs induced an average in serum calcitonin increase of 89.2 times the upper limit of normal. An increase in the serum value of calcitonin five to ten times after the pentagastrin stimulation test is very suggestive of MTC.²⁷ We did not perform stimulation with pentagastrin test for MTC exclusion, however the possibility of a MTC was less probably, since no thyroid nodules were identified on ultrasound. It is noteworthy that in the pentagastrin test, the response may be lower or even absent in the presence of ectopic secretion compared to MTC.^{14,27} Some of the calcitonin - secreting PanNETs reported presented with hepatic metastasis. Schneider *et al* reported metastasis (mostly hepatic) in 59.7% of calcitonin - se-

Table 2. Clinicopathological features of isolated case reports of calcitonin-secreting insulinomas.

Case report	Age	Sex	Clinical presentation	Serum Insulin levels	Serum Peptide -C levels	Serum Calcitonin levels	Type of Surgery	Site	Size (mm)	Ki67	Im. St. (Calcitonin/Insulin)	Im. St. (other hormones)	Metastasis	Serum calcitonin/Follow-up
Ooi <i>et al</i> (1986)	67	M	Hypoglycaemia	Un	Un	Un	Un	Uncus	15	Un	Calcitonin/Insulin	Un	Un	Un
Price <i>et al</i> (1992)	42	F	MEN1	18.6 mU/L (<16)	1.04 nmol/l (0.2-0.63)	0.34 µg/l (<0.08)	Laparotomy	Un	Un	Un	Calcitonin/Insulin	Glucagon	No	0.14 µg/l (<0.08) Dead after surgery
Gaulier <i>et al</i> (1993)	58	F	Hypoglycaemia	Un	Un	Un	Un	Un	Un	Un	Calcitonin/Insulin	Gastrin	Un	Free of disease
Bugalho <i>et al</i> (1994)	71	F	Fasting hypoglycaemia Diarrhoea Dyspepsia	653 pmol/l (35-145)	0.96 nmol/l (0.17-0.66)	14.4 pmol/l (<2.9)	DP	B/T	12	Un	Calcitonin/Insulin	Synaptophysin NSE C peptide Proinsulin	No	0.3 pmol/l (<2.9) Un
Pusztai <i>et al</i> (2006) -C	54	F	Fasting hypoglycaemia	88.08 µU/mL (5-35)	6.1 ng/mL (1.37-3.51)	481 pg/mL (<9.9)	Pancreatic head resection	H	25	10%	Calcitonin/Insulin	Chr A Synaptophysin	No	2.89 pg/ml (<9.9) Free of disease
Dias <i>et al</i> (2018)	72	M	Pre-prandial hypoglycaemia	30.6 mU/L (2-25)	4.04 ng/mL (0.8-3.5)	149 pg/mL (<3)	Duodenopancreatectomy	Uncus	22	<3%	Calcitonin/Insulin	Chr A NSE Synaptophysin	No	Free of disease

Chr A, chromogranine A; B/T, body and tail; DP, distal pancreatectomy; F, female; H, head; HE, histopathological examination; Im.St., immunohistochemical staining; M, male; NSE, neuron-specific enolase; Sr serum; T, thyroidectomy; Un, unknown;

creting PanNETs.²⁴ A series of 6 cases revealed that these tumours were often malignant.⁵ Nozières *et al*,²⁹ found that 21/176 patients (12%) of calcitonin – secreting PanNETs, had recurrence of the disease after surgery and needed combined adjuvant therapy. This raises the question whether the secretion of calcitonin by these tumours is associated with a worse prognosis. A systematic analysis of 229 PanNET, identified 25 cases with calcitonin-immunoreactivity (10.9%) and concluded that there were no differences in prognosis regarding CT *versus* non-secreting tumours. In addition, in this study, it was found that calcitonin secreting insulinomas had an equal prognosis to those non-secreting calcitonin, which is in accordance with the present case.²⁶ In Table 2 we identified and reviewed the calcitonin-secreting insulinomas individual case reports that we found in the literature.

Although very low, benign insulinomas are not devoid of recurrence. We consider the patient should be periodically evaluated for symptoms of hypoglycaemia and calcitonin may play a role as biochemical marker.

It is worth to mention that we did not perform genetic screening for multiple endocrine neoplasia in this patient given the patient's age, the absence of family history for MEN syndrome and the clinical presentation with isolated insulinoma. The genetic screening for MEN1 is well established: it is recommended in the presence of family background of MEN1 or if there are grounds for suspecting of MEN1 diagnosis (e.g., multiple parathyroid tumours, gastrinoma, or multiple pancreatic neuroendocrine tumours). Regarding RET germline mutations, testing is recommended in cases of a personal history of medullary thyroid carcinoma, primary C-cell hyperplasia or pheochromocytoma.³⁰⁻³²

In conclusion, probably the secretion of calcitonin by func-

tioning and non-functioning PanNETs is more frequent than is thought. The calcitonin measurement in this patient was performed in the context of a suspected neuroendocrine tumour namely an insulinoma. The role of this secretion in PanNETs remains unknown. However the clinician must always keep in mind, in the presence of a high serum level of calcitonin, a possible MTC should always be excluded. Although if this diagnosis is left out, a PanNET should be evoked. The clinical importance of calcitonin secretion by these tumours remains unknown and should be addressed in future studies.

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References / Referências

- Kaltsas GA1, Besser GM, Grossman AB. The diagnosis and medical management of advanced neuroendocrine tumors. *Endocr Rev.* 2004; 25: 458-511.
- Kim JY, Hong SM. Recent updates on neuroendocrine tumors from the gastrointestinal and pancreatobiliary tracts. *Arch Pathol Lab Med.* 2016; 140:437-48. doi: 10.5858/arpa.2015-0314-RA.
- Dixon E, Pasiaka JL. Functioning and non-functioning neuroendocrine tumors of the pancreas. *Curr Opin Oncol.* 2007; 19:30-35.
- Service FJ, McMahon MM, O'Brien PC, Ballard DJ. Functioning insulinoma—incidence, recurrence, and long-term survival of patients: a 60-year study. *Mayo Clin Proc.* 1991; 66: 711-9.
- Fleury A Fléjou JF, Sauvanet A, Molas G, Vissuzaine C, Hammel P, et al. Calcitonin-secreting tumors of the pancreas: about six cases. *Pancreas.* 1998; 16: 545-50.
- Kaltsas G, Dimitriadis GK, Androulakis I, Grossman A. Paraneoplastic Syndromes related to Neuroendocrine Tumours. [Updated 2017 Feb 16]. In: Feingold KR, Anawalt B, Boyce A, et al, editors. *Endotext* [Internet]. South Dartmouth: MDText.com, Inc.; 2000-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK279135/>
- Bugalho MJ, Roque L, Sobrinho LG, Hoog A, Nunes JF, Almeida JM, et al. Calcitonin-producing insulinoma: clinical, immunocytochemical and cytogenetical study. *Clin Endocrinol.* 1994;41:257-60.
- Gaulier A, Cahen J, Buisson JL, Périé G, Vacher G, Poulet B. Pancreatic insulinoma, adenomatosis of the Wirsung's duct and chronic pancreatitis. Apropos of a case. *Arch Anat Cytol Pathol.* 1993;41:245-50.
- Ooi A, Nakanishi I, Kameya T, Funaki Y, Kobayashi K. Calcitonin-producing insulinomas. An immunohistochemical and electron microscopic study. *Acta Pathol Jpn.* 1986; 36:1897-1903.
- Price DE, Absalom SR, Davidson K, Bolia A, Bell PR, Howlett TA. A case of multiple endocrine neoplasia: hyperparathyroidism, insulinomas, GRF-oma, hypercalcitoninaemia and intractable peptic ulceration. *Clin Endocrinol.* 1992; 37: 187-188.
- Pusztai P, Sárman B, Illyés G, Székely E, Péter I, Boer K, et al. Hypercalcitoninemia in a patient with a recurrent goitre and insulinoma: a case report. *Exp Clin Endocrinol Diabetes.* 2006;114:217-221.
- Chambers TJ, McSheehy PM, Thomson BM, Fuller K. The effect of calcium-regulating hormones and prostaglandins on bone resorption by osteoclasts disaggregated from neonatal rabbit bones. *Endocrinology.* 1985;116:234-9.
- Friedman PA, Gesek FA. Cellular calcium transport in renal epithelia: measurement, mechanisms and regulation. *Physiol Rev.* 1995; 75: 429-471.
- Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised American Thyroid Association Guidelines for the Management of Medullary Thyroid Carcinoma. *Thyroid.* 2015; 25: 567-610.
- Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S, et al. Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. *J Clin Endocrinol Metab.* 2007;92:450-5.
- Toledo SP, Lourenço DM Jr, Santos MA, Tavares MR, Toledo RA, Correia-Deur JE, et al. 2009. Hypercalcitoninemia is not pathognomonic of medullary thyroid carcinoma. *Clinics.* 64:699-706.
- Manche A, Wood SM, Adrian TE, Welbourn RB, Bloom SR. Pancreatic polypeptide and calcitonin secretion from a pancreatic tumour-clinical improvement after hepatic artery embolization. *Postgrad Med J.* 1983; 59:313-4.
- Alumets J, Sundler F, Falkmer S, Ljungberg O, Håkanson R, Mårtensson H, et al. Neurohormonal peptides in endocrine tumors of the pancreas, stomach, and upper small intestine: I. An immunohistochemical study of 27 cases. *Ultrastruct Pathol.* 1983;5:55-72.
- Machens A, Haedecke J, Hinze R, Thomusch O, Schneyer U, Dralle H. Hypercalcitoninemia in a sporadic asymptomatic neuroendocrine tumor of the pancreatic tail. *Dig Surg.* 2000; 17: 522-4.
- Mullerpatan PM, Joshi SR, Shah RC, Tampi CS, Doctor VM, Jagannath P, et al. Calcitonin-secreting tumor of the pancreas. *Dig Surg.* 2004; 21:321-4.
- Delis S Bakoyiannis A, Giannakou N, Tsigka A, Avgerinos C, Dervenis C. Asymptomatic calcitonin-secreting tumor of the pancreas. A case report. *JOP.* 2006; 7:70-3.
- Schneider R., Heverhagen AE, Moll R, Bartsch DK, Schlosser K. Differentiation between thyroidal and ectopic calcitonin secretion in patients with coincidental thyroid nodules and pancreatic tumors - a report of two cases. *Exp Clin Endocrinol Diabetes.* 2010; 118: 520-3.
- Chrisoulidou A, Kaltsas G, Mandanas S, Chatzellis E, Boutzios G, Pazaitou-Panayiotou K. Pancreatic neuroendocrine tumors presenting with hypercalcitonemia. *AACE Clin Case Rep.* 2015; 1: 269-72.
- Schneider R, Waldmann J, Swaid Z, Ramaswamy A, Fendrich V, Bartsch DK, et al. Calcitonin-secreting pancreatic endocrine tumors: systematic analysis of a rare tumor entity. *Pancreas.* 2011; 40:213-21. doi: 10.1097/MPA.0b013e3182015f5d.
- Gianetta E, Gianfrilli D, Pozza C, Lauretta R, Graziadio C, Sbardella E, et al. Extrathyroidal calcitonin secreting tumors: pancreatic neuroendocrine tumors in patients with multinodular goiter: two case reports. *Medicine.* 2016; 95:e2419. doi: 10.1097/MD.0000000000002419.
- Uccella S, Blank A, Maragliano R, Sessa F, Perren A, La Rosa S. Calcitonin producing neuroendocrine neoplasms of the pancreas: clinicopathological study of 25 cases and review of the literature. *Endocr Pathol.* 2017; 28:351-61. doi: 10.1007/s12022-017-9505-4.
- Costante G, Durante C, Francis Z, Schlumberger M, Filetti S. Determination of calcitonin levels in C-cell disease: clinical interest and potential pitfalls. *Nat Clin Pract Endocrinol Metab.* 2009;5: 35-44. doi: 10.1038/ncpendmet1023.
- Eskens FA, Roelofs EJ, Hermus AR, Verhagen CA. Pancreatic islet cell tumor producing vasoactive intestinal polypeptide and calcitonin. *Anticancer Res.* 1997; 17:4667-70.
- Nozières C, Chardon L, Goichot B, Borson-Chazot F, Hervieu V, Chikh K, et al. Neuroendocrine tumors producing calcitonin: characteristics, prognosis and potential interest of calcitonin monitoring during follow-up. *Eur J Endocrinol.* 2016; 174:335-41. doi: 10.1530/EJE-15-0917.
- Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, et al. Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *J Clin Endocrinol Metab.* 2012; 97:2990-3011. doi: 10.1210/jc.2012-1230.
- Wells SA Jr, Asa SL, Dralle H, Elisei R, Evans DB, Gagel RF, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. *Thyroid.* 2015; 25:567-610. doi: 10.1089/thy.2014.0335.
- National Comprehensive Cancer Network. NCCN Guidelines: Neuroendocrine and Adrenal Tumors. Version 2.2108. Plymouth Meeting: NCCN; 2018.