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CASE REPORT

Ectopic insulinomas in the pelvis secondary to rectum neuroendocrine tumour

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SUMMARY

We describe a middle-aged woman with recurrent hypoglycaemia, who confirmed with rectum G1 neuroendocrine tumour (NET) 6 years ago. Biochemical assay showed high concentration of serum insulin and C-peptide associated with hypoglycaemia. Because of recurrent hypoglycaemia in June 2015, she underwent a resection of the tail of the pancreas. However, hypoglycaemia attack happened more frequently and severely. ^{68}Ga-DOTA-NOC positron emission tomography/CT revealed five foci in the pelvis with intense uptake. Immediately after excision of the pelvic lesions, insulin and C-peptide decreased to normal levels promptly, and therefore, serum glucose increased significantly. Hypoglycaemia was disappeared, and insulin and C-peptide were normal at 2 years follow-up after surgery. Immunohistochemistry validated the primary rectum NET and pelvic tumours expressed with higher insulin, somatostatin receptor and glucagon-like peptide-1. This is the first reported ectopic pelvic insulinomas secondary to rectum NET, which may originate both from neuroendocrine cells in the rectum and pelvic tissues.

BACKGROUND

Tumour-induced hypoglycaemia (TIH) is a rare type of hypoglycaemia that usually results from insulin hypersecretion by a pancreatic islet β-cell tumour (insulinoma). However, TIH was also developed by neuroendocrine tumours (NET) mainly arising from the upper gastrointestinal tract,[1–3] which can secrete several peptide hormones. Resent retrospective study demonstrated that multiple and secondary hormone secretion occurred in a minor proportion (9.3%) of pancreas neuroendocrine tumour (pNET) and secondary hormone secretion was associated with disease progression as well as increased morbidity and mortality.[3] However, molecular basis underlying secondary hormone production and secretion in NETs was poorly understood.

Molecular imaging and positron emission tomography (PET)/CT can be used to quantitate receptor expression and characterise intratumour metabolic processes. It is well documented that ^{68}Ga-labelled somatostatin analogues (SSA) PET/CT is of great value for the diagnosis of pNETs. However, ^{68}Ga-SSA PET/CT for the localisation of insulinomas is not well described. In this rare case, the origin of the ectopic pelvis tumour detected by ^{68}Ga-DOTA-NOC PET/CT and immunohistochemistry (ICH) further validated insulinoma. The mechanism of how rectum NET transformed into ectopic insulinoma is further elucidated. To our knowledge, this is the first reported case with pelvic ectopic insulinoma secondary to rectum NET.

CASE PRESENTATION

A 53-year-old woman with recurrent attacks of hypoglycaemia came to Nanjing First Hospital (Nanjing Medical University) in June 2016. Her episodes of hypoglycaemia were characterised by dizziness, blurred vision, headache, confusion, sweating and giddiness. Also, a low serum glucose level was documented in each episode (less than 1.5 mmol/L, reference range: 4.1–6.1 mmol/L), whereas serum insulin and C-peptide increased significantly; serum insulin level was more than 50 μU/mL (reference range: 2.6–24.9 μU/mL); the curve of insulin, C-peptide and glucose changes were shown in figure 1. Preoperative serum chromogranin A (CGA) level was 2126.1 ng/mL (reference value <90.1 ng/mL). Symptoms released with the administration of glucose or dextrose. She gained about 7.5 kg within 1 year. The patient had no history of sulfonylurea drug use, medical history included a diagnosis of the rectum NET without carcinoid syndromes 5 years ago. Her primary tumour was resected, histopathology verified rectal neuroendocrine tumour (G1) and no lymphadenopathy or distant metastasis was found (figure 2). In June 2015, she was hospitalised due to recurrent hypoglycaemia (serum glucose 1.6 mmol/L); serum insulin and C-peptide levels was more. Initial diagnosis was insulinoma according to clinical symptoms and biochemical assay. However, radiographic examinations were negative. In May 2016, the tail of the pancreas lesion was resected with preservation of her spleen. Histopathology revealed a 0.2 cm (G1) neuroendocrine neoplasm. However, hypoglycaemia attacks occurred more frequently at postoperation, resulting in hospitalisation to our hospital on 9 September 2016.

INVESTIGATIONS

To address the relation between ectopic insulinoma in the pelvic floor and previously resected rectum NET and whether these tumours expressed high levels of insulin and SSTR and GLP-1. IHC was reperformed and evaluated; high expression of insulin, SSTR and GLP-1 was confirmed in

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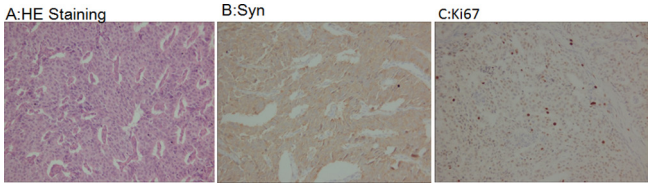

Figure 1 Postsurgical histopathology confirmed rectum neuroendocrine tumour resected in 2010. (A) H&E staining, (B) Syn(Synaptophysin), (C) Ki-67 <2%.

rectum NET (figure 3). In comparison with rectum tumour, pelvic foci showed significantly higher expression of insulin, SSTR and CGA(Chromogranin A), which indicated that pelvic ectopic insulinomas might transit from rectum NET due to disease progression; hyperinsulinaemia may develop from non-islet cell tumours.

DIFFERENTIAL DIAGNOSIS

^{68}Ga-DOTA-NOC PET/CT was undertaken to localise functional NET associated with episodes of hypoglycaemia. Five unexpected abnormal lesions were found in the pelvis, and no abnormal uptake found in the pancreas, which indicated high SSTR expression in the pelvic foci (figure 4); enhanced CT confirmed all five pelvic lesions with rapid arterial enhanced characteristics. Whether these pelvic foci were metastasis from rectum NET or ectopic insulinomas? Whether these lesions were metastatic lymph nodule? How did they achieve the capability of insulin secretion? All these questions are really clinical challenges. After multidiscipline talk, the operation was taken into account for relief of hypoglycaemia and further validating the cause of hyperinsulinaemia.

TREATMENT

Five pelvic lesions were removed completely by open operation; serum glucose level returned to a baseline level; insulin and C-peptide levels decreased to normal level rapidly; the gross observation of tumour in the operation was shown in figure 5. Histopathology and immunochemistry revealed

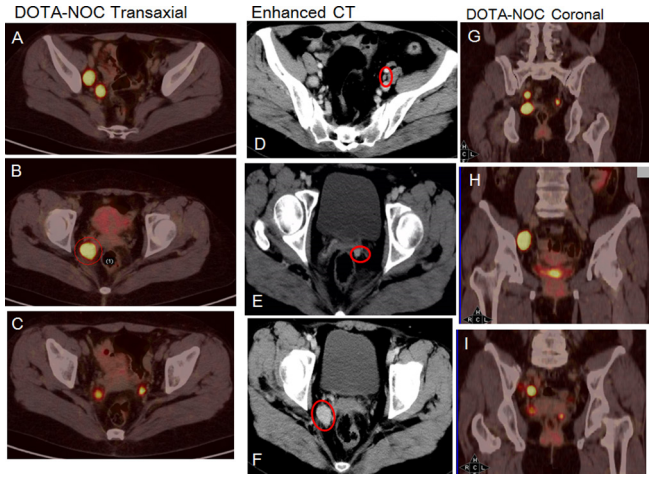

Figure 3 ^{68}Ga-DOTA-NOC positron emission tomography/CT detected unexpected five pelvic lesions with higher somatostatin receptor expression, which presented with prompt arterial enhanced character in enhanced CT. DOTA-NOC transaxial images (A–C), coronal images (G–I), transaxial enhanced CT (D–F).

well-differentiated tumours with higher SSTR, insulin and CGA expression, as was shown in figure 6.

OUTCOME AND FOLLOW-UP

She was discharged on postoperation day 10 in a stable condition and remained euglycaemic during 1.5 years of follow-up.

DISCUSSION

The persistent hypoglycaemia was due to five metastatic/ectopic non-pancreatic NETs in the pelvis. ^{68}Ga-DOTA-NOC PET/CT revealed five SSTR-positive pelvic lesions. At surgery, entire pancreas was explored and no notable mass found. With the guidance of ^{68}Ga-DOTA-NOC PET/CT and enhanced CT, all five pelvic lesions identified and removed, serum insulin level decreased significantly and blood glucose increased accordingly. ^{68}Ga-DOTA-NOC PET/CT was critical for localisation of those

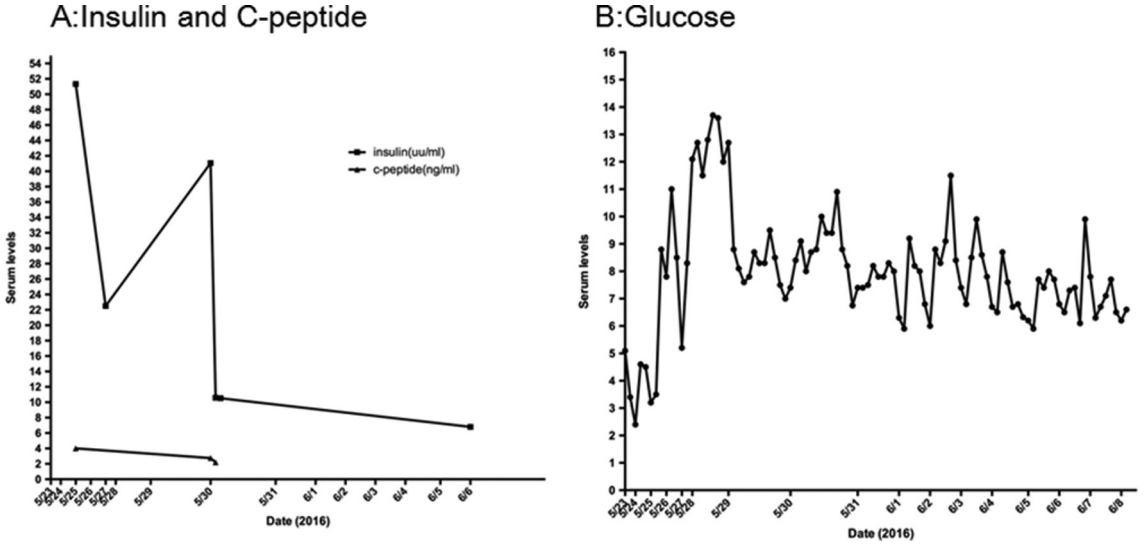

Figure 2 The curve depicting blood glucose, serum insulin and C-peptide changes before and after surgery. (A) Serum concentration of insulin and C-peptide and (B) blood glucose.

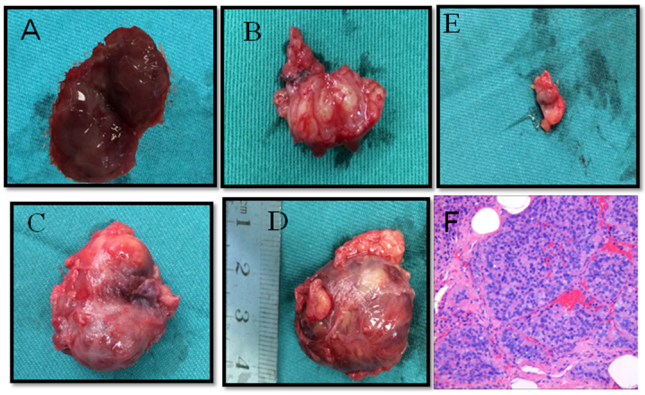

Figure 4 Gross observation on tumours during operation. (A) Tumour 1, (B) tumour 2, (C) tumour 3, (D) tumour 4, (F) tumour 5 and (G) H&E staining.

ectopic insulinomas. Histopathology and ICH confirmed all five lesions presented with NET characteristics, highly expressed insulin as well.

Ectopic insulinomas are rare and infrequently reported as bronchial carcinoid tumour, squamous-cell carcinoma of the cervix, neurofibrosarcoma, schwannoma, paragangliomas, small-cell carcinoma of the uterine cervix and gastrointestinal stromal tumour.[4–7] Although the mechanisms of ectopic insulinomas are not fully identified, non-islet cell-NET are the leading cause of ectopic insulinoma. Mid-gut NET occasionally presents with carcinoid syndromes such as flushing, generalised oedema and diarrhoea due to serotonin secretion.[8] At initial presentation, this patient had no symptoms of carcinoid syndrome, and after resection of her rectal primary NET lesion, no metastasis was found, rectum NET with G1 was confirmed. Five years later, she was readmitted because of recurrent episodes of hypoglycaemia including a persistent headache, palpitation, sweating and giddiness. Initially, we hypothesised that SSTR positive five pelvic lesions detected on PET/CT were metastatic lymph nodes. However, histopathology and ICH demonstrated that those tumours were insulin positive and with NET characteristics; insulin and SSTR were also highly expressed in the rectal NET as well, which indicated that ectopic insulinoma might be secondary to rectum NET. Furthermore, the expression of CGA, SSTR and insulin in pelvic foci was significantly higher than that of rectum tumour; this is the rational mechanism of hyperinsulinaemia-induced hypoglycaemia. Secondary insulin secretion in a minor proportion of pNET has been reported, especially in patients with metastatic disease,[9 10] but no pelvis ectopic insulinoma was reported.^{68}Ga-DOTA-NOC PET/CT might be considered as the first-line initial diagnostic imaging modality in secondary insulin secretion, which might localise the ectopic foci and guide the clinical management. These ectopic insulinomas in the pelvis secondary to rectum NET may originate from pelvic neuroendocrine cells, which was free of any functional syndrome at initiation; they tend to progress insidiously and achieve ability of hormone secretion. This rare case described whole process of ectopic insulinoma transition from non-function NET in 5 years.

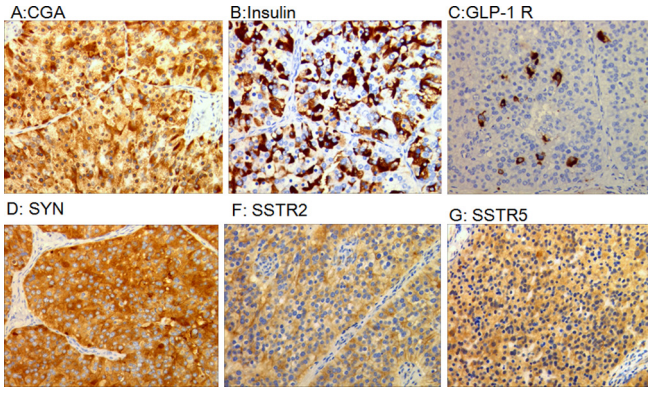

Figure 5 Immunochemistry confirmed that pelvis lesions may originated from gastro-entero-pancreatic neuroendocrine tumours, which had higher expression of somatostatin receptor (SSTR), chromogranin A (CGA), glucagon-like peptide-1 (GLP-1) and insulin in tumours. (A) CGA; (B) insulin; (C) GLP-1 R; (D) SSTR2; (E) SSTR4 and (F) SSTR5.

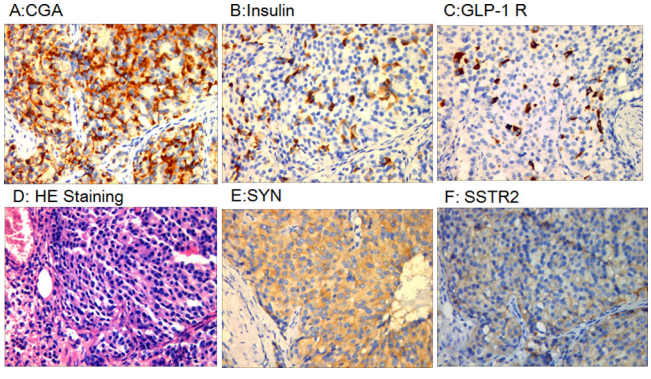

Figure 6 Immunochemistry in rectum tumour specimens verified higher expression of (A) chromogranin A (CGA), (B) insulin, (C) glucagon-like peptide-1 (GLP-1)R, (E) SYN(Synaptophysin) and (F) somatostatin receptor (SSTR)2. (D) H&E staining confirmed classical neuroendocrine tumour.

Patient's perspective

We are really grateful to Dr Wang and his team. With their effort, the culprit of hypoglycaemia was localised, I have been completely recovered, when I look back, that was really nightmare. I do hope Professor Wang continue to promote radionuclide-based precision medicine.

Learning points

- Neuroendocrine tumours (NETs) are considered to originate from multipotent cells scattered throughout the gastrointestinal system and have the ability to synthesise and secrete peptides and amines; tumour-induced hypoglycaemia can also be developed by other non-pancreatic tumours.
- Rectum NETs that were initially non-functioning may acquire the capability to secrete insulin and become functioning due to tumour progression.
- Hypoglycaemia may originate from rectum NET; ^{68}Ga-somatostatin analogue positron emission tomography/CT is recommended to be the first-line imaging for the detection of insulinoma secondary to gastro-entero-pancreatic-NET.

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Contributors T-NVL was responsible for ^{68}Ga-DOTA-NOC PET/CT and image interpretation. FW was responsible for radiolabelling and clinical management and manuscript preparation. LL was involved in the operation and tumour resection. YZ was involved in the mechanism exploration and clinical management including histopathology analysis.

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