Calcium-sensing receptor expression in insulin-negative, intrapancreatic insulinoma

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Dear Editor

Pancreatic neuroendocrine tumours (p-NETs) are a group of tumours with neuroendocrine differentiation[1].

A 66-year-old man who had experienced paroxysmal unconsciousness after fatigue or hunger, accompanied by eye gaze and stiff limbs, for 6 months was referred to the hospital. He first went to the department of neurology; doctors found no abnormalities on cranial imaging, but a 4-cm space-occupying mass in the pancreatic head which was accompanied by obvious dilatation of the pancreatic duct. Enhanced CT showed an non-homogeneous enhancement mass in the head of pancreas (*Fig. 1a*, red arrow) with two intrapancreatic duct masses on the arterial phase of abdominal enhanced CT (yellow and blue arrows). Levels of carbohydrate antigen (CA)19-9, CA125, and neurone-specific enolase were within the normal range, but the immune-reactive insulin (IRI)/blood glucose ratio was up to 1.24. A typical Whipple's triad was detected at 6:00 hours on the second morning in hospital. The patient declared no previous disease history or long-term medication history.

A diagnosis of insulinoma was suspected and a standard pancreatoduodenectomy was performed. Interestingly, two polypoid bulges were observed in the pancreatic duct besides the pancreatic main mass, but the duct was not invaded by tumour; the tumour was simply growing along the lumen (*Fig. 1b*). Histopathological examination of these masses revealed a uniform solid, trabecular, and nest structure accompanied by hypervascularity and without nesidioblastosis in adjacent normal pancreas (*Fig. 1c*). Immunostaining was positive for chromogranin A and synaptophysin, but, strangely, negative for insulin (less than 1 per cent focal insulin-positive tumour cells) (*Fig. 1d*). Hence, the pathological diagnosis was G2 (5 per cent Ki-67-positive, mitosis 2 per 2 mm^2) p-NET.

After resection, the paroxysmal hypoglycaemia did not recur. In contrast, transient postoperative rebound hyperglycaemia was observed. Postoperative PET–CT showed no retained mass in the pancreas. The follow-up data revealed that the patient's IRI and C-peptide levels exhibited a stable trend after undergoing a significant decline. Hence, the suggested diagnosis was insulin staining-negative (type IV non-granular), intrapancreatic ductal insulinoma. Indeed, to recognize this unusual p-NET, screening was undertaken for a possible molecular marker named calcium-sensing receptor (CaSR) according to the GSE73338[2] (*Fig. 1e*), and strong expression was found, even in insulin-negative insulinoma (*Fig. 1f*).

Another case of insulin-negative insulinoma has been reported[3]. It may not be accurate to diagnose p-NET solely by staining for hormone indicators because abnormal storage and rhythmic release of insulin are pathophysiological mechanisms of insulinoma[4]. However, staining for CaSR, a critical molecule in the cellular calcium pathway (core signalling of islet cells on releasing insulin), maybe a useful marker for distinguishing pathological subgroups of p-NET, and even for recognizing insulin-negative insulinoma. Doctors should first exclude the diagnosis of non-functional p-NET combined with nesidioblastosis or microinsulinoma and other p-NET-related special syndromes[5].

Disclosure

The authors declare no conflict of interest.

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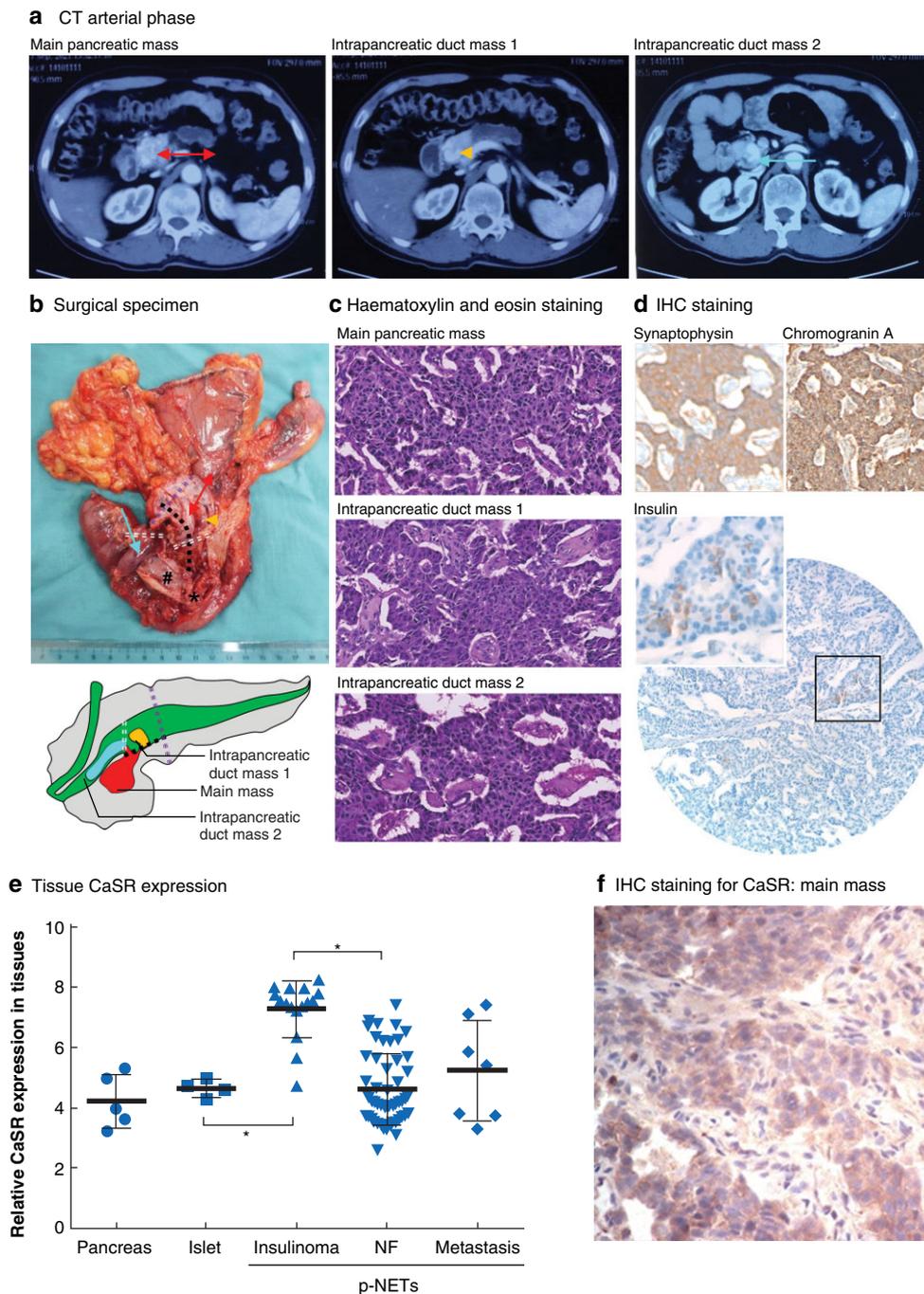
Fig. 1 Evaluation of patient with insulin-negative, intrapancreatic insulinoma

a Three-phase enhanced CT images of patient before hospital admission, showing main pancreatic mass in unciform process (double-head arrow), intrapancreatic duct mass 1 (arrow head), and intrapancreatic duct mass 2 (single-head arrow). **b** Anatomical location in surgical specimen showing main pancreatic mass in unciform process (double-head arrow), intrapancreatic duct mass 1 (arrow head), intrapancreatic duct mass 2 (single-head arrow), dilated pancreatic duct (symbol #), duodenal papilla (symbol *), surgical margin of pancreatic duct (treble-row dotted line), dissection margin for separating intrapancreatic duct mass (double-row dotted line), and dissection margin for exposing main pancreatic mass in unciform process (single-row dotted line); diagram of pancreas is shown below. **c** Microscopic view of haematoxylin and eosin-stained sections of the three masses (original magnification × 200). **d** Immunohistochemical (IHC) staining for chromogranin A (CgA), synaptophysin (Syn), and insulin in main pancreatic mass in unciform process (original magnification of CgA, Syn and Insulin × 200 and interested magnification of Insulin × 400, hematoxylin counterstain). **e** Relative calcium-sensing receptor (CaSR) expression in normal pancreas, normal islets, insulinoma, non-functional (NF) pancreatic neuroendocrine tumours (p-NETs), and metastatic p-NETs according to GSE73338 data sets. Bold line and error bars represent mean value and standard deviation. *$P \leq 0.050$ (Limma-trend test which based on empirical Bayes prior trend embedded in limma package of R software). **f** IHC staining for CaSR in insulin-negative insulinoma tissue (main pancreatic mass in uncinate process) (original magnification × 400, hematoxylin counterstain).

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