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V S Nadhamuni and others | MEN1, GHRH and gigantism

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GHRH secretion from a pancreatic neuroendocrine tumor causing gigantism in a patient with MEN1

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Summary

A male patient with a germline mutation in MEN1 presented at the age of 18 with classical features of gigantism. Previously, he had undergone resection of an insulin-secreting pancreatic neuroendocrine tumour (pNET) at the age of 10 years and had subtotal parathyroidectomy due to primary hyperparathyroidism at the age of 15 years. He was found to have significantly elevated serum IGF-1, GH, GHRH and calcitonin levels. Pituitary MRI showed an overall bulky gland with a 3 mm hypoechoic area. Abdominal MRI showed a 27 mm mass in the head of the pancreas and a 6 mm lesion in the tail. Lanreotide-Autogel 120 mg/month reduced GHRH by 45% and IGF-1 by 20%. Following pancreaticoduodenectomy, four NETs were identified with positive GHRH and calcitonin staining and Ki-67 index of 2% in the largest lesion. The pancreas tail lesion was not removed. Post-operatively, GHRH and calcitonin levels were undetectable, IGF-1 levels normalised and GH suppressed normally on glucose challenge. Post-operative fasting glucose and HbA1c levels have remained normal at the last check-up. While adolescent-onset cases of GHRH-secreting pNETs have been described, to the best of our knowledge, this is the first reported case of ectopic GHRH in a paediatric setting leading to gigantism in a patient with MEN1. Our case highlights the importance of distinguishing between pituitary and ectopic causes of gigantism, especially in the setting of MEN1, where paediatric somatotroph adenomas causing gigantism are extremely rare.

Learning points

- It is important to diagnose gigantism and its underlying cause (pituitary vs ectopic) early in order to prevent further growth and avoid unnecessary pituitary surgery. The most common primary tumour sites in ectopic acromegaly include the lung (53%) and the pancreas (34%) (1): 76% of patients with a pNET secreting GHRH showed a *MEN1* mutation (1).
- Plasma GHRH testing is readily available in international laboratories and can be a useful diagnostic tool in distinguishing between pituitary acromegaly mediated by GH and ectopic acromegaly mediated by GHRH. Positive GHRH immunostaining in the NET tissue confirms the diagnosis.
- Distinguishing between pituitary (somatotroph) hyperplasia secondary to ectopic GHRH and pituitary adenoma is difficult and requires specialist neuroradiology input and consideration, especially in the MEN1 setting. It is important to note that the vast majority of GHRH-secreting tumours (lung, pancreas, phaeochromocytoma) are expected to be visible on cross-sectional imaging (median diameter 55 mm) (1). Therefore, we suggest that a chest X-ray and an abdominal ultrasound checking the adrenal glands and the pancreas should be included in the routine work-up of newly diagnosed acromegaly patients.

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Introduction

Gigantism is a rare condition which is due, in most cases, to excess growth hormone (GH) in childhood leading to accelerated growth and increased height (as the epiphyseal plates are not fused). Pituitary gigantism and acromegaly are on a continuum with most patients with gigantism also showing acromegalic features such as coarse facial features or pronounced growth of hands and feet.

The majority of cases of gigantism/acromegaly are secondary to GH-secreting pituitary adenomas, which may be syndromic or non-syndromic. Syndromic causes include Carney complex, multiple endocrine neoplasia types 1 and 4, and the paraganglioma, phaeochromocytoma and pituitary adenoma association (3PAs). Non-syndromic causes include familial isolated pituitary adenoma secondary to germline *AIP* mutations or duplication of *GPR101*, causing X-linked acrogigantism (2, 3). However, gigantism can be a sign of other conditions as well (4, 5, 6).

GH excess due to a growth hormone-releasing hormone (GHRH)-secreting tumour accounts for less than 1% of cases of acromegaly (1, 7). We describe here a rare case of gigantism due to childhood-onset GH excess secondary to GHRH secreted by a pancreatic neuroendocrine tumour (pNET) in a patient with MEN1. This is the first case of paediatric-onset gigantism from ectopic GHRH in a MEN1 setting to be reported in the literature, to the best of our knowledge.

Case presentation

An 18-year-old Caucasian male was referred for evaluation of accelerated growth velocity (Fig. 1).

His medical history started at the age of 7 years, when he experienced increasingly frequent and recurrent tonic–clonic seizures. These were found to be related to hyperinsulinaemic hypoglycaemia (lowest glucose level: 1.5 mmol/L). MRI revealed a 1cm lesion in the pancreatic neck. At the age of 10, the patient underwent enucleation of the tumour. Histopathology revealed a well-differentiated NET strongly positive for proinsulin and insulin with a few scattered cells positive for glucagon, somatostatin and calcitonin. He developed multiple post-operative complications including abdominal haemorrhage, pancreatitis, septic shock, renal failure and encephalopathy, but he completely recovered.

At the age of 11, genetic testing revealed a heterozygous germline mutation in the *MEN1* gene (c.249_252delGTCT, p.I85Sfs). His father carries the same mutation and has hyperparathyroidism as the only clinical manifestation. Several family members on his father's side are under endocrine care for MEN1 syndrome.

At the age of 14 years, he was diagnosed with primary hyperparathyroidism secondary to parathyroid hyperplasia. He underwent a subtotal parathyroidectomy (three of four glands removed, right upper parathyroid left in place) and transcervical thymectomy.

At first evaluation at the adult endocrine clinic at the age 18, he was noted to be 193.5 cm tall (>97th percentile, mid-parental height 175 cm). He was noted to have long and thin hands, UK shoe size 12 (increased by 2 sizes in the 2 years prior to evaluation), dorsal kyphosis and hyperhidrosis. He did not complain of headaches, visual problems or sleeping problems, and went through puberty normally. His skin was normal. His face did not show prominence of eyebrows and chin or enlargement of tongue. Stretch marks on both shoulders and horizontally on the back were noted, possibly secondary to accelerated growth.

Investigations

At the age of 18, IGF-1 was 2xULN (970 µg/L, normal range 247–481, Fig. 2). Random morning GH levels were elevated at 39 µg/L with GH nadir during the oral glucose tolerance test (OGTT) 1.7 µg/L (<1). He had normal serum prolactin (213 mU/L, 0–324), TSH (1.12 mU/L, 0.3–4) and FT4 levels (15.7 pmol/L, 10.5–24.5). Fasting plasma GHRH was significantly elevated at 327 ng/L (<60, Biomnis, Lyon, France). Chromogranin A and gut peptide levels were normal (gastrin 5 pmol/L (<50), glucagon 13 pmol/L (<50), VIP 4 pmol/L (<30), pancreatic polypeptide 43 pmol/L (<300), chromogranin A 44 pmol/L (<60) and somatostatin 54 pmol/L (<150). Calcitonin levels were noted to be elevated at presentation at 82 ng/L (<0.8–4). No thyroid parenchymal lesions were noted on ultrasound imaging. His corrected calcium was normal at 2.55 mmol/L (2.2–2.6) with normal phosphate 1.19 mmol/L (0.8–1.5) but slightly elevated PTH of 8.4 pmol/l (1.6–6.7) and decreased 25-OH vitamin D levels of 8 nmol/L (>50). His urinary 24-h calcium was increased at 13 mmol/L(2.5–7.5). Bone age of 19 years was noted on hand X-ray (within 2 S.D. from chronological age).

Abdominal MRI revealed two lesions in the pancreatic head and tail, measuring 27 mm (Fig. 3) and 6 mm, respectively (Table 1), in keeping with NETs. A pituitary MRI showed a diffusely enlarged gland and raised the possibility of a 3 mm microadenoma showing slightly reduced enhancement in the right inferolateral aspect of the anterior pituitary (Figs 4A and 5B).

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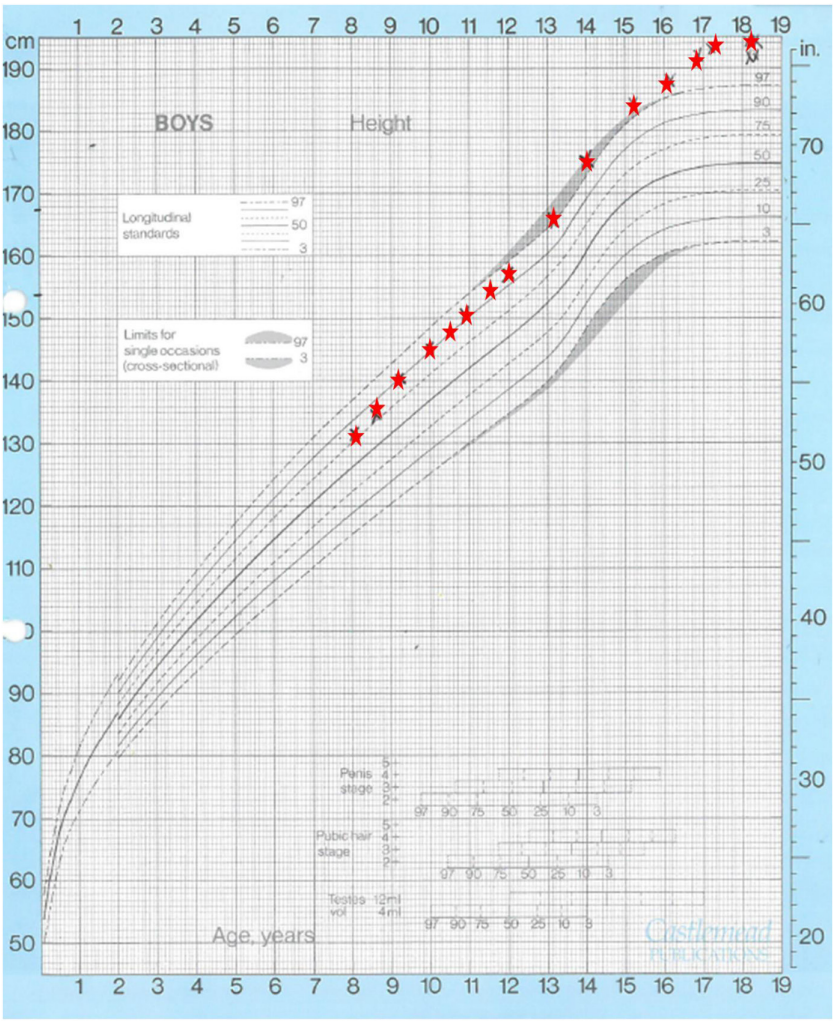

Figure 1
Patient's growth chart up to the age of 18 showing accelerated growth velocity. His final height, 193.5 cm, is corresponding to height standard deviation scores: UK Tanner Whitehouse for chronological age (18 years) +2.83, adjusted for parental height +2.87 and UK Cole: for chronological age (18 years) +2.34, adjusted for parental height +2.38.

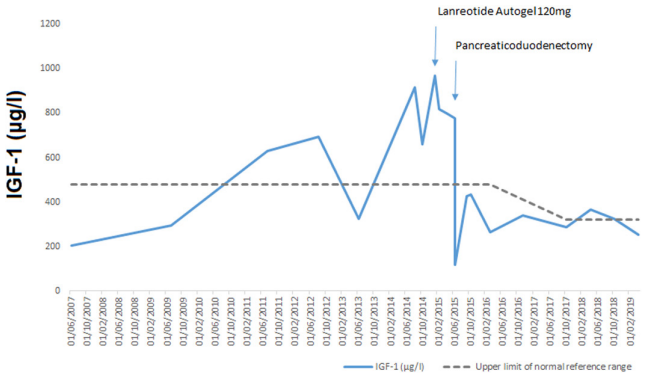

Figure 2
IGF-1 levels of the patient during the clinical course.

Treatment

He was initially started on treatment with 120 mg Lanreotide-Autogel monthly (every 28 days) for 6 months with partial biochemical response of a random serum GH 2.21 µg/L, IGF-1 778 µg/L (1.6× ULN) and a 50% drop in GHRH to 180 ng/L (<60). He received vitamin D replacement. Following careful discussion of the various therapeutic options with the multi-disciplinary team and the patient and his family, he underwent a pylorus-sparing pancreatoduodenectomy and cholecystectomy with the removal of the head and neck of the pancreas, including the largest tumour leaving the pancreatic tail (including the 6mm lesion) intact. The operation and the post-operative period was without complications.

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Histological examination identified four grade 1 and 2 NETs in the pancreas, positive for synaptophysin and chromogranin (Table 1). There was no lymph node invasion. The largest tumour was a well-differentiated NET positive for GHRH, SSTR2 and calcitonin on immunohistochemistry with a Ki-67 index of 2% (Table 1, Fig. 6). The GHRH and SSTR2 expression were strong but focal, with large negative areas and small areas with 50–100% of positive cells. The immunohistological detection of somatostatin, insulin and GH was negative in the four tumours (Table 1).

Post-operatively, GHRH and calcitonin were undetectable with IGF-1 returning into the normal range (264 µg/L) and a nadir GH of 0.5 µg/L on the OGTT. Post-operatively, mild left-sided intrahepatic duct dilatation was noted, which was secondary to a likely benign stricture at the entero-biliary anastomosis. Pituitary MRI showed a reduction in the height of the pituitary gland (Fig. 4C and D).

Outcome and follow-up

Following surgery, over the last 5 years the patient has remained largely asymptomatic. His main problems during follow-up had been related to recurrent kidney stones and he underwent successful extracorporeal shock wave lithotripsy to a right lower pole renal calculus. He was started on cinacalcet 30 mg, which was increased to 30 mg twice a day, and vitamin D3 10 000 units weekly were continued. The most recent corrected calcium is 2.24 mmol/L (2.2–2.6), phosphate 1.08 mmol/L (0.8–1.5), PTH 10.4 pmol/L (1.6–6.9) and 25-OH vitamin D3 73 nmol/L. Urinary 24 h calcium output is 11.8 mmol/day (2.5–7.5).

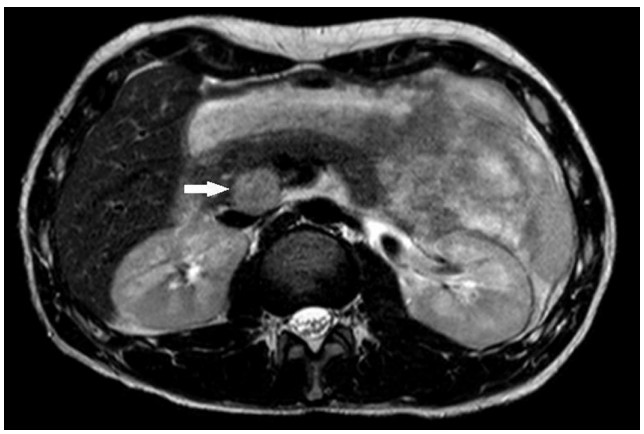

Figure 3
MRI abdomen at presentation with an arrow indicating the larger (27 mm) lesion in the head of the pancreas in keeping with a NET.

Table 1 Histological characteristics of four pancreatic NETs.

Lesion number	Maximum diameter	Grade (WHO 2010)	UICC TNM 7TH edition	Synaptophysin	Chromogranin A	Calcitonin	GH	GHRH	Somatostatin	SSTR2	SSTR5	S100	Insulin	Glucagon	Ki67 (%)
1	27	2	pT2pN0	+	Focal	Focal	–	Focal	–	Focal	–	–	–	–	2
2	8	2	pT1pN0	+	+	–	–	–	–	–	–	+	–	+	6
3	4	1	pT1pN0	+	+	–	–	–	–	+	–	+	–	–	<1
4	3	1	pT1pN0	+	+	–	–	–	–	+	–	+	–	–	<1

WHO, World Health Organisation; UICC TNM, Union for International Cancer Control tumour (T), node (N), and metastase (M) classification; GHRH, growth hormone-releasing hormone; SSTR2/5, somatostatin receptor subtype 2/5.

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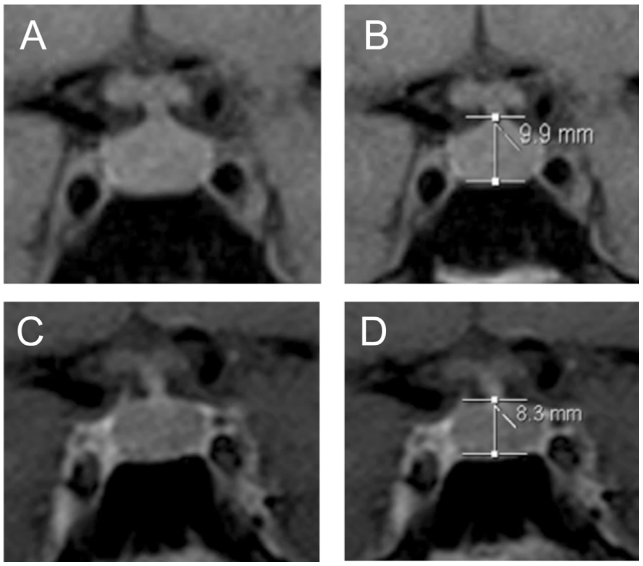

Figure 4
Coronal MRI pre- (A,B) and post-pancreatic (C,D) surgery showing shrinkage of the pituitary gland following surgery.

Post-operative fasting glucose levels 5.3 mmol/L (4–5.4) and HbA1c (27 mmol/L) (20–41) have remained normal at the last check-up. The lesions in the tail of his pancreas, pituitary as well as a hyperplastic right lower parathyroid gland are stable in size over the last 5 years. A full summary of his latest follow-up and surveillance regimen with comparison to present clinical guidelines (8) is provided in Table 2.

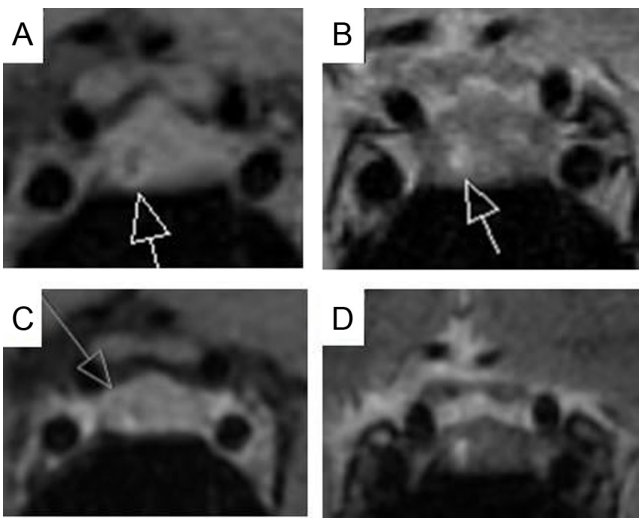

Figure 5
MRI with pituitary microadenoma (arrow), (A–B) before pancreas surgery (A: T1-weighted image, B: T2-weighted image) and (C–D) 4 years after pancreas surgery (C: post-gadolinium T1, D: T2).

Discussion

We report the case of a now 24-year-old gentleman with gigantism, multiple pNETs, a possible pituitary microadenoma and parathyroid tumour and hyperplasia due to a germline mutation in *MEN1*. He had developed gigantism due to excess of GH and IGF-1 during childhood secondary to the secretion of GHRH by a pNET. Although this is the first reported case of gigantism in a paediatric setting due to ectopic GHRH in a patient with MEN1 syndrome, ectopic GHRH secretion in an adolescent patient with MEN1 was included in a previous case series (9) and personal communication with Francoise Borson-Chazot, France who confirmed gigantism in that case).

Early detection of growth hormone excess is important as many of the effects of growth hormone cannot be reversed with treatment which aims to limit any further consequences (i.e. prevent further growth in the case of gigantism).

Ectopic secretion of GHRH is a rare cause of GH excess, accounting for less than 1% of all cases of acromegaly (1, 7). Ectopic sources mainly include NETs, usually of pancreatic (34%) or bronchial origin (53%) (1, 9). Ectopic GHRH secretion by phaeochromocytomas has also been reported (4%) (1, 10, 11, 12). However, while ectopic acromegaly is an uncommon entity, its diagnosis is important for two main reasons: (i) avoidance of unnecessary pituitary surgery (13) and institution of appropriate management of the non-pituitary NET and (ii) screening for associated syndromes such as MEN1.

GHRH-secreting pNETs in the setting of MEN1 are well described (9, 14, 15, 16, 17), with one series showing 76% of patients with a pNET secreting GHRH having *MEN1* mutations (1). Determining whether acromegaly is of pituitary or non-pituitary origin can be difficult but is of paramount importance, as unnecessary pituitary surgery and consequent potential hypopituitarism should be avoided in patients with ectopic acromegaly. It is important to note that the vast majority of GHRH-secreting tumours (lung, pancreas, phaeoechromocytoma) are expected to be visible on cross-sectional imaging (median diameter 55 mm) (1). Therefore, we suggest that a chest X-ray and an abdominal ultrasound checking the adrenal glands and the pancreas should be included in the routine work-up of newly diagnosed acromegaly patients. It is worth remembering that an elevated fasting plasma GHRH is specific for ectopic GHRH release (1, 13) and highly useful in this diagnostic setting and several assays are now available. Monitoring GHRH following treatment can help identify the persistence or recurrence of disease

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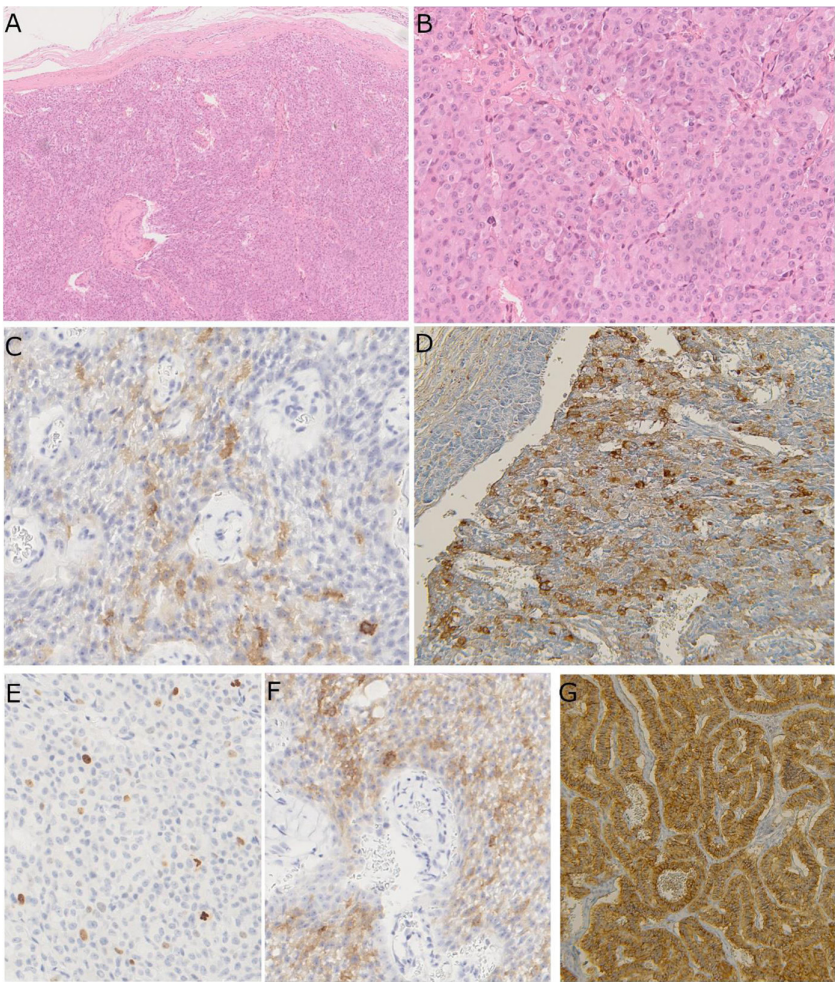

Figure 6
Representative images of the histopathology of the largest pNET. H&E, 4× (A) and 20× (B) power and immunohistochemistry for calcitonin (C), GHRH (D), Ki-67 (E), chromogranin A (F) and SSTR2 (G) (20×).

(1). In our patient's case, GHRH was undetectable after a large pancreatic resection and the removal of a pNET secreting GHRH. GHRH positive cells can be scattered or located in sheets, especially in well-differentiated cells; therefore, a systematic GHRH immunostaining is needed in all tumour fragments to prove the pancreatic origin of the GHRH ectopic secretion.

With respect to imaging, pituitary (somatotroph) hyperplasia has been observed secondary to ectopic GHRH release (1, 7, 13, 18), which could be misinterpreted as a pituitary macroadenoma (1). Indeed, in many instances from the literature, an ectopic source for acromegaly was considered only after unnecessary pituitary surgery due to misinterpretation of pituitary hyperplasia as adenoma in the context of clinical and acromegaly and elevated GH and IGF-1 levels (7, 9, 13). Interpretation of pituitary imaging by an experienced neuro-radiologist may help avoid this situation. In our patient's case, while the pituitary gland was clearly bulky (Figs 4 and 5), a possible pituitary microadenoma was also described. Due to the large lesion in the head of the pancreas and the elevated GHRH, we opted for pancreatic surgery initially, but could not be sure at the time if acromegaly would fully resolve after surgery. The pituitary lesion has remained stable, and might well represent a small non-functioning microadenoma, similarly to those observed in a surveillance study of MEN1 patients (19).

We found significantly elevated calcitonin levels in this patient. Calcitonin expression on immunohistochemistry was found in 11% of cases in a large study screening 229 pNETs (20). It is unclear how often calcitonin-secreting pNETs occur in the setting of MEN1, although previous cases have been reported (21, 22, 23, 24), including a case with both GHRH and calcitonin secretion, similar to our case.

Table 2 Summary of clinical practice recommendations for surveillance for MEN1 patients with results of investigations for our patient from last outpatient review. Adapted from Thakker *et al.* (2012) (8).

Organ system	Recommendation from Thakker *et al.* (2012) (8)	Findings from the investigation at last outpatient review
Parathyroid	*Biochemical*: Annual assessment of plasma calcium and PTH concentrations	PTH elevated at 10.4 pmol/L (reference range: 1.6–6.9) with normal corrected calcium levels
	Imaging: Not suggested	Ultrasound: residual hyperplastic right upper parathyroid gland with a stable enlargement (maximum diameter of 14 mm)
Pancreatic NET	*Biochemical*: Annual plasma evaluation of fasting GIT hormone profile including gastrin, glucagon, VIP, pancreatic polypeptide, chromogranin A, insulin and fasting glucose recommended	All normal, insulin was not tested
	Imaging: Annual pancreatic and duodenal visualisation with MRI/CT/endoscopic ultrasound	Lesion in the tail of the pancreas remained stable (measuring 6 mm)
Pituitary	*Biochemical*: Annual assessment of plasma prolactin and IGF-1	IGF-1, GH serum, FSH, LH, serum oestradiol and prolactin levels normal
	Imaging: MRI every 3–5 years	3 mm focal lesion in the right dorsal aspect of pituitary tissue (microadenoma)
Thymic, bronchopulmonary and gastric NET	*Imaging*: CT/ MRI of the chest every 1–2 yearsrecommended for thymic and bronchopulmonary carcinoid tumours.Gastroscopy with biopsy every 3 years in patients with hypergastrinaemia	Normal residual thymic tissue and no focal lung lesion. Gastroscopy not performed as patient has no symptoms, normal gastrin levels and had removal of the duodenum
Adrenal tumours	*Biochemical*: Evaluation restricted to those with clinical features or tumours more than 1cm in size	Not applicable as no relevant clinical features or focal lesions in the adrenal glands
	Imaging: CT/ MRI of the abdomen every 3 years	No focal lesions in the adrenal gland

To date, our patient has developed multiple NETs in the pancreas, six in total, with the removal of five through two surgical procedures. The possibility of total pancreatectomy was discussed with the patient as an option for managing the existing lesions as well as prophylaxis against any future lesions, but with the inevitable consequence of insulin-dependent diabetes. The patient decided against this option, given the need for life-long insulin treatment post-operatively. We continue to monitor the NET in the tail of the pancreas through biochemical assessment and surveillance imaging.

Timely diagnosis of MEN1 is important to improve disease outcomes and survival in patients as well as affected family members (25). A recent cohort study of Dutch MEN1 patients investigating the lag time between diagnosis of MEN1 in index patients and their family members (non-index patients) found that 10 patients (4% of non-index cases) died because of a MEN1-related cause that developed during or before the lag time (pre-diagnosis) (26). Patients should be managed by a multi-disciplinary team of relevant specialists experienced in the diagnosis and treatment of patients with endocrine tumours (8) in order to facilitate appropriate genetic screening of family members as well as ensure appropriate surveillance protocols are carried out in affected patients.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Patient consent
Written informed consent for publication of the clinical details and images was obtained from the patient.

Author contribution statement
VSN reviewed the case and drafted the manuscript. The other authors cared for the patient. All authors reviewed and edited the manuscript.

References

1 Borson-Chazot F, Garby L, Raverot G, Claustrat F, Raverot V, Sassolas G. Acromegaly induced by ectopic secretion of GHRH: a review 30 years after GHRH discovery. *Annales d'Endocrinologie* 2012 **73** 497–502. (https://doi.org/10.1016/j.ando.2012.09.004)

2 Vierimaa O, Georgitsi M, Lehtonen R, Vahteristo P, Kokko A, Raitila A, Tuppurainen K, Ebeling TM, Salmela PI, Paschke R, *et al.* Pituitary adenoma predisposition caused by germline mutations in the AIP gene. *Science* 2006 **312** 1228–1230. (https://doi.org/10.1126/science.1126100)
3 Trivellin G, Daly AF, Faucz FR, Yuan B, Rostomyan L, Larco DO, Schernthaner-Reiter MH, Szarek E, Leal LF, Caberg JH, *et al.* Gigantism and acromegaly due to Xq26 microduplications and GPR101 mutation. *New England Journal of Medicine* 2014 **371** 2363–2374. (https://doi.org/10.1056/NEJMoa1408028)
4 Hannah-Shmouni F, Trivellin G & Stratakis CA . Genetics of gigantism and acromegaly. *Growth Hormone and IGF Research* 2016 **30** 37–41. (https://doi.org/10.1016/j.ghir.2016.08.002)
5 Marques P & Korbonits M. Pseudoacromegaly. *Frontiers in Neuroendocrinology* 2019 **52** 113–143. (https://doi.org/10.1016/j.yfrne.2018.11.001)
6 Marques P, Collier D, Barkan A & Korbonits M . Coexisting pituitary and non-pituitary gigantism in the same family. *Clinical Endocrinology* 2018 **89** 887–888. (https://doi.org/10.1111/cen.13852)
7 Ghazi AA, Amirbaigloo A, Dezfooli AA, Saadat N, Ghazi S, Pourafkari M, Tirgari F, Dhall D, Bannykh S, Melmed S, *et al.* Ectopic acromegaly due to growth hormone releasing hormone. *Endocrine* 2013 **43** 293–302. (https://doi.org/10.1007/s12020-012-9790-0)
8 Thakker RV, Newey PJ, Walls GV, Bilezikian J, Dralle H, Ebeling PR, Melmed S, Sakurai A, Tonelli F, Brandi ML, *et al.* Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1). *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 2990–3011. (https://doi.org/10.1210/jc.2012-1230)
9 Garby L, Caron P, Claustrat F, Chanson P, Tabarin A, Rohmer V, Arnault G, Bonnet F, Chabre O, Christin-Maitre S, *et al.* Clinical characteristics and outcome of acromegaly induced by ectopic secretion of growth hormone-releasing hormone (GHRH): a French nationwide series of 21 cases. *Journal of Clinical Endocrinology and Metabolism* 2012 **97** 2093–2104. (https://doi.org/10.1210/jc.2011-2930)
10 Mumby C, Davis JR, Trouillas J & Higham CE. Phaeochromocytoma and Acromegaly: a unifying diagnosis. *Endocrinology, Diabetes and Metabolism Case Reports* 2014 **2014** 140036. (https://doi.org/10.1530/EDM-14-0036)
11 Roth KA, Wilson DM, Eberwine J, Dorin RI, Kovacs K, Bensch KG & Hoffman AR . Acromegaly and pheochromocytoma: a multiple endocrine syndrome caused by a plurihormonal adrenal medullary tumor. *Journal of Clinical Endocrinology and Metabolism* 1986 **63** 1421–1426. (https://doi.org/10.1210/jcem-63-6-1421)
12 Vieira Neto L, Taboada GF, Correa LL, Polo J, Nascimento AF, Chimelli L, Rumilla K & Gadelha MR. Acromegaly secondary to growth hormone-releasing hormone secreted by an incidentally discovered pheochromocytoma. *Endocrine Pathology* 2007 **18** 46–52. (https://doi.org/10.1007/s12022-007-0006-8)
13 Kyriakakis N, Trouillas J, Dang MN, Lynch J, Belchetz P, Korbonits M & Murray RD. Diagnostic challenges and management of a patient with acromegaly due to ectopic growth hormone-releasing hormone secretion from a bronchial carcinoid tumour. *Endocrinology, Diabetes and Metabolism Case Reports* 2017 **2017** 16–0104. (https://doi.org/10.1530/EDM-16-0104).
14 Sala E, Ferrante E, Verrua E, Malchiodi E, Mantovani G, Filopanti M, Ferrero S, Pietrabissa A, Vanoli A, La Rosa S, *et al.* Growth hormone-releasing hormone-producing pancreatic neuroendocrine tumor in a multiple endocrine neoplasia type 1 family with an uncommon phenotype. *European Journal of Gastroenterology and Hepatology* 2013 **25** 858–862. (https://doi.org/10.1097/MEG.0b013e32835f433f)
15 Weiss DE, Vogel H, Lopes MB, Chang SD & Katznelson L . Ectopic acromegaly due to a pancreatic neuroendocrine tumor producing growth hormone-releasing hormone. *Endocrine Practice* 2011 **17** 79–84(https://doi.org/10.4158/EP10165.CR)
16 Sugihara H, Shibasaki T, Tatsuguchi A, Okajima F, Wakita S, Nakajima Y, Tanimura K, Tamura H, Ishii S, Kamegai J, *et al.* A non-acromegalic case of multiple endocrine neoplasia type 1 accompanied by a growth hormone-releasing hormone-producing pancreatic tumor. *Journal of Endocrinological Investigation* 2007 **30** 421–427. (https://doi.org/10.1007/BF03346321)
17 Saleem TF, Santhanam P, Hamoudeh E, Hassan T & Faiz S. Acromegaly caused by growth hormone releasing hormone (GHRH) secreting tumor in multiple endocrine neoplasia (MEN-1). *West Virginia Medical Journal* 2012 **108** 26–30.
18 Trouillas J, Labat-Moleur F, Sturm N, Kujas M, Heymann MF, Figarella-Branger D, Patey M, Mazucca M, Decullier E, Vergès B, *et al.* Pituitary tumors and hyperplasia in multiple endocrine neoplasia type 1 syndrome (MEN1): a case-control study in a series of 77 patients versus 2509 non-MEN1 patients. *American Journal of Surgical Pathology* 2008 **32** 534–543. (https://doi.org/10.1097/PAS.0b013e31815ade45)
19 de Laat JM, Dekkers OM, Pieterman CR, Kluijfhout WP, Hermus AR, Pereira AM, van der Horst-Schrivers AN, Drent ML, Bisschop PH, Havekes B, *et al.* Long-term natural course of pituitary tumors in patients with MEN1: results from the DutchMEN1 study group (DMSG). *Journal of Clinical Endocrinology and Metabolism* 2015 **100** 3288–3296. (https://doi.org/10.1210/JC.2015-2015)
20 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. *Endocrine Pathology* 2017 **28** 351–361. (https://doi.org/10.1007/s12022-017-9505-4)
21 Jeong YJ, Oh HK & Bong JG. Multiple endocrine neoplasia type 1 associated with breast cancer: a case report and review of the literature. *Oncology Letters* 2014 **8** 230–234. (https://doi.org/10.3892/ol.2014.2144)
22 Price DE, Absalom SR, Davidson K, Bolia A, Bell PR & Howlett TA. A case of multiple endocrine neoplasia: hyperparathyroidism, insulinoma, GRF-oma, hypercalcitoninaemia and intractable peptic ulceration. *Clinical Endocrinology* 1992 **37** 187–188. (https://doi.org/10.1111/j.1365-2265.1992.tb02305.x)
23 Rigabert J & De Clermont H. Diagnostic procedures and more particularly, place of scintigraphy in neuroendocrine tumors, example of vipoma in MEN 1. *Annales d'endocrinologie* 2007 **68** 199–203. (https://doi.org/10.1016/j.ando.2006.11.006)
24 Yamaguchi K, Abe K, Adachi I, Tanaka M, Ueda M, Oka Y, Miyakawa S, Kameya T & Yanaihara N. Clinical and hormonal aspects of the watery diarrhea-hypokalemia-achlorhydria (WDHA) syndrome due to vasoactive intestinal polypeptide (VIP)-producing tumor *Endocrinologia Japonica* 1980 **27** 79–86. (https://doi.org/10.1507/endocrj1954.27.supplement_79)
25 de Laat JM, van Leeuwaarde RS & Valk GD. The importance of an early and accurate MEN1 diagnosis. *Frontiers in Endocrinology* 2018 **9** 533. (https://doi.org/10.3389/fendo.2018.00533)
26 van Leeuwaarde RS, van Nesselrooij BP, Hermus AR, Dekkers OM, de Herder WW, van der Horst-Schrivers AN, Drent ML, Bisschop PH, Havekes B, Vriens MR, *et al.* Impact of delay in diagnosis in outcomes in MEN1: results From the Dutch MEN1 study group. *Journal of Clinical Endocrinology and Metabolism* 2016 **101** 1159–1165. (https://doi.org/10.1210/jc.2015-3766)

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