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CASE REPORT

Parathyroid carcinoma in multiple endocrine neoplasia type 1 (MEN1) syndrome: Two case reports of an unrecognised entity

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ABSTRACT. ***Context:*** **Primary hyperparathyroidism occurs in almost all patients with the syndrome of multiple endocrine neoplasia type 1 (MEN1), but the association of MEN1 with parathyroid carcinoma has only been described previously in a single patient. In this report, we describe two further cases of parathyroid carcinoma presenting in MEN1 syndrome.** ***Case reports:*** **The first patient was a 69-yr-old woman, who presented with severe primary hyperparathyroidism and tracheal compression by a large mediastinal mass, which was shown histologically to be a parathyroid carcinoma with a second similar lesion in the neck. She was treated with total parathyroidectomy followed by resection of the mediastinal mass with resolution of the hypercalemia. Remarkably, she also reported primary amenorrhea and was found to have an invasive pituitary lactotroph adenoma, which was treated with cabergoline and external beam radiotherapy. Magnetic resonance imaging (MRI) of the pancreas revealed a small lesion characteristic of an islet-cell tumor, which was clinically and biochemically non-functioning. The second patient was a 32-yr-old man who presented with symptomatic hypercalemia and markedly raised serum PTH concentration. Neck exploration revealed two parathyroid glands only. One of the parathyroid glands contained a tumor with fibrous banding, atypical mitoses, extra-capsular extension and moderate Ki 67 staining; features which are highly suggestive of carcinoma. He also had intractable dyspepsia associated with raised serum gastrin concentration. A lesion was localized to the neck of the pancreas by endocopic ultrasound, and a selective arterial calcium stimulation catheter suggested the presence of both a gastrinoma and an insulinoma, although he had no hypoglycemic symptoms. Pituitary MRI was normal. The patient's mother had primary hyperparathyroidism.** ***Conclusions:*** **This case report describes two further patients in whom parathyroid carcinomas occurred in the context of MEN1, which gives a new insight to the possible presenting phenotype of this condition. Both patients had negative genetic screening for classic MEN1 gene mutation, which may suggest that one or more novel occult mutations may be responsible for this aggressive phenotype.**
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INTRODUCTION

Multiple endocrine neoplasia type 1 (MEN1) is a syndrome that covers a combination of over 20 different endocrine and non-endocrine tumors (1). However, a practical definition of MEN1 is a case with 2 of the 3 main MEN1-related endocrine tumors, parathyroid adenomas, entero-pancreatic endocrine tumors and pituitary tumors (1). Primary hyperparathyroidism is the most frequent clinical finding in MEN1 syndrome with a prevalence reaching 100% by age 50 yr (2-6). Hyperparathyroidism is caused by multiple parathyroid adenomas, often asymmetrical in size and hence are regarded as independent clonal adenomas (1, 2). Parathyroid carcinoma is a very rare cause of hyperparathyroidism accounting for <1% of all such cases (7), but is not considered to be a feature of MEN1. To our knowledge, there has only been one previous

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publication of a patient with parathyroid carcinoma in the context of MEN1 syndrome (8). In this report, we describe two additional cases in which parathyroid carcinomas occurred in patients with otherwise typical features of MEN1.

CASE REPORTS

Patient A

This was a 65-yr-old woman who was admitted to her local hospital with severe symptomatic hypercalcemia of 3.9 mmol/l (15.6 mg/dl; normal, 2.1-2.6 mmol/l) and shortness of breath. Serum PTH concentration was markedly elevated at 37.7 pmol/l (377 ng/l; normal, 0.9-5.4 pmol/l) with raised urinary calcium excretion at 13 mmol/24 h. She responded well to treatment with iv fluids and iv pamidronate. Computer tomography (CT) of the thorax was performed because of obstructive respiratory symptoms and signs which revealed a large 4.5 cm mediastinal mass compressing the trachea (Fig. 1A). Biopsy of the mediastinal mass showed features of a neuroendocrine tumor staining positive for chromogranin A, cytokeratin and neuron-specific enolase. The differential diagnosis was between a thymic carcinoid tumor and a parathyroid carcinoma. The patient received a course of chemotherapy at her local hospital, which resulted in some shrinkage of her mediastinal tumor and significantly improved her respiratory symptoms but she remained hypercalcemic and was later transferred to our institution for further management.

A $^{99\text{-m}}$technetium-labelled methoxy-iso-butyl-isonitrile (MIBI) parathyroid scan with single proton emission CT (SPECT) scanning was performed at our hospital, which showed increased tracer uptake in the left side of the neck and also in the region of the mediastinal mass (Fig. 1B). Further localization using selective venous sampling for PTH suggested focal parathyroid gland overactivity in the left upper neck and a similarly high PTH level in the thymic mediastinal vein, indicating a possible mediastinal parathyroid lesion. MRI and CT imaging revealed a large invasive base of skull lesion (Fig. 1C), which was biopsied and the histological examination revealed an invasive pituitary adenoma that stained positively for PRL. Serum PRL was markedly elevated at 21,200 mU/l (normal, up to 400 mU/l) and remarkably, the patient reported a history of primary amenorrhea, suggesting that the lactotroph adenoma had been present since the pre-pubertal period.

The patient underwent neck exploration and three parathyroid glands were identified and removed. Two were normal parathyroid glands but the left upper parathyroid showed a 3.5 g parathyroid tumor

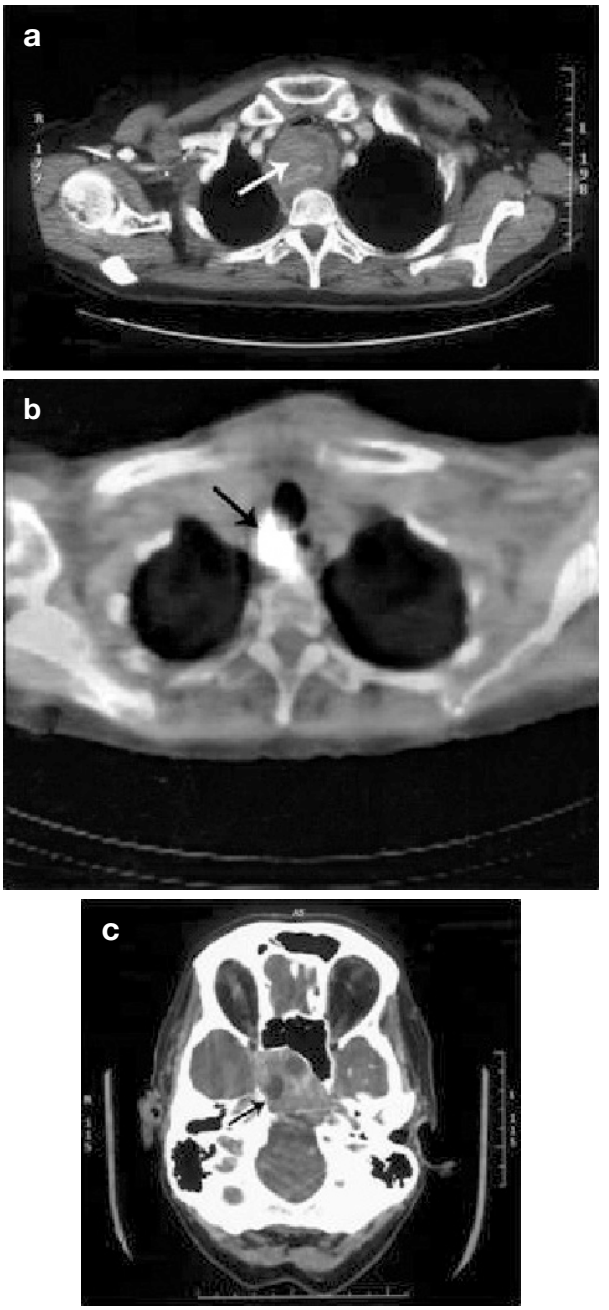

Fig. 1 - *Patient A: panel A, computer tomography (CT) scan of the chest showing a large mediastinal mass (arrow). Panel B, methoxy-iso-butyl-isonitrile (MIBI) parathyroid scan with single proton emission CT (SPECT) shows positive tracer uptake by the mediastinal lesion (arrow). Panel C: CT brain reveals a large base of skull mass (arrow) which was histologically shown to be an invasive lactotroph adenoma.*

with a dense fibrous capsule and features of infiltrative cells, mitoses, desmoplasia, fat necrosis and fibrous banding (Fig. 2A, 2B) which are all consistent

with a carcinoma (9, 10). Serum calcium and PTH concentrations remained high post-parathyroidectomy. The large mediastinal mass was subsequently excised, and post-operatively the patient developed hypoparathyroidism requiring treatment with calcium supplementations and vitamin D analogs. The histology of the resected mediastinal mass also showed similar features of a parathyroid carcinoma with invasion of adjacent bone and the tissue stained strongly positively for PTH, confirming the parathyroid origin of the lesion (Fig. 2C). The lactotroph adenoma was treated with cabergoline and conventional 3-field external beam pituitary irradiation. MRI of the pancreas showed a 2-mm lesion in the tail area, which was characteristic of an islet-cell tumor, but this was clinical and biochemically non-functioning. Genetic analysis did not demonstrate a classical germline mutation in the MEN1 gene. There was no family history of endocrine neoplasia.

Patient B

A 32-yr-old man with a long history of intractable dyspepsia was admitted to hospital complaining of severe upper abdominal pain, thirst and polyuria. He was found to be dehydrated with renal impairment and elevated serum calcium of 3.7 mmol/l with markedly raised PTH at 28 pmol/l (normal, 0.9-5.4 pmol/l). His clinical and biochemical status improved after aggressive rehydration and iv pamidronate therapy. The ^{99m}technetium-labelled MIBI parathyroid scan, neck ultrasound and parathyroid venous catheter localized a left lower parathyroid lesion.

Upper gastro-intestinal endoscopy showed severe diffuse duodenitis associated with oedema and a high

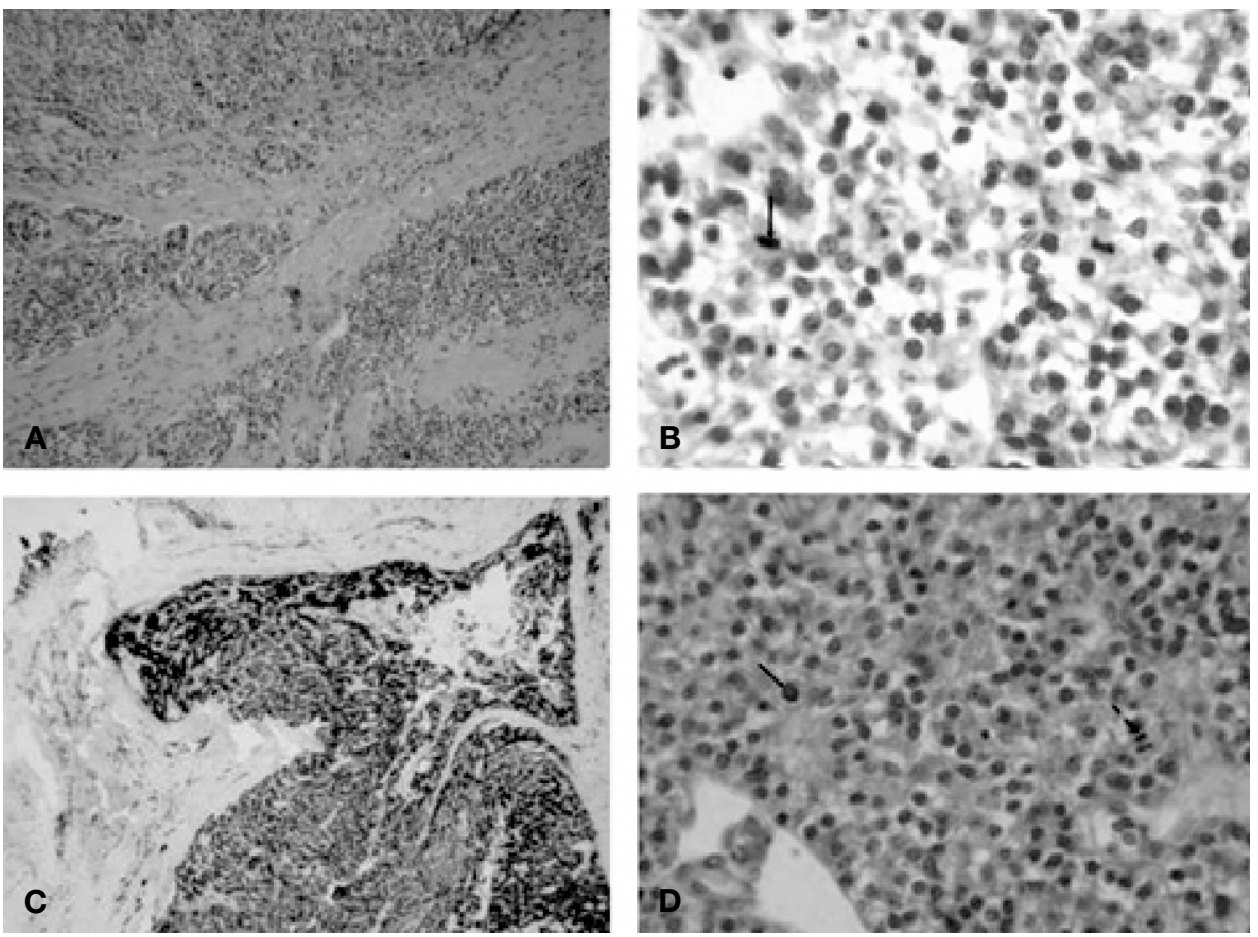

Fig. 2 - *Patient A: panel A, specimen showing a parathyroid tumor with thick fibrous bands which are extensively infiltrated with neoplastic cells. Panel B, multiple mitoses are seen (arrow). Panel C, section from the mediastinal mass showing strongly positive staining for PTH and a thick capsule. Patient B: panel D, specimen showing a parathyroid tumor with multiple mitoses (arrows). The atypical ring mitosis (solid arrow) is highly suggestive of a carcinoma.*

gastric acid output. Fasting gastrin was elevated at 82 pmol/l (normal <40 pmol/l) in the absence of proton pump inhibitor or H2-receptor antagonist treatment suggesting the probability of a gastrinoma. An endoscopic ultrasound examination showed a 1.7 cm mass in the neck of the pancreas which was confirmed by MRI scan that also showed a possible lesion in the tail. The fat-suppressed MR images were characteristic of islet cells tumors. A selective arterial calcium stimulation catheter showed a differential exuberant gastrin release after calcium injection in the gastroduodenal artery and an exuberant insulin release after calcium injection in the splenic artery, thus confirming the presence of a gastrinoma in the proximal pancreas and indicating the co-existence of an insulinoma in the distal pancreas; the patient, however, was not symptomatic of hypoglycemia and had a normal 72-h fast. The combination of both primary hyperparathyroidism and pancreatic islet cells tumors was highly suggestive of MEN1. The patient was treated with omeprazole with partial symptomatic response.

In view of the presence of MEN1, the patient was referred for total parathyroidectomy but only two parathyroid glands were successfully removed at surgery. The left lower gland weighed 5.8 g, and histological examination showed features of a parathyroid carcinoma including multiple mitoses with atypical features (Fig. 2D), fibrous banding and thick fibrous capsule infiltrated by tumor. Ten per cent of the cells stained positive for the proliferative marker Ki 67. The other parathyroid gland was normal. He had persistent postoperative hypoparathyroidism with low serum calcium and PTH concentration and remains on maintenance calcium and vitamin D analog supplementations. Subsequently, he had surgical resection of the gastrinoma but continued to have upper gastrointestinal symptoms and raised serum gastrin concentration suggesting the presence of other occult duodenal or pancreatic gastrinomas, which were not identifiable with cross-sectional imaging or endoscopy.

Pituitary MRI scan and pituitary function tests were normal. CT of the adrenal glands revealed bilateral adrenal hyperplasia. He had raised midnight sleeping serum cortisol concentration on several occasions (average, 72 nmol/l; normal <50 nmol/l) and the basal morning plasma ACTH concentration was borderline low at 12 ng/l (normal 10-65 ng//l). Serum cortisol concentration after 48-h low-dose dexamethasone suppression (0.5 mg, 6-hourly) was 57 nmol/l (normal <20 nmol/l). These results were in keeping with low grade autonomous ACTH-independent cortisol secretion, which remained unchanged after 2 yr of follow-up. The patient did not demonstrate a classical germ-line mutation in the MEN1 gene but primary hyperparathyroidism was subsequently confirmed in his mother. Interestingly, his newborn daughter initially developed transient neonatal diabetes which resolved after 8 weeks, but subsequently had recurrent attacks of spontaneous hypoglycemia with inappropriately raised insulin and C-peptide levels which responded well to diazoxide treatment.

DISCUSSION

In this report, we describe two further cases of parathyroid carcinoma presenting as part of MEN1 to add to the only case that has been hitherto described (8). Both of our patients had convincing MEN1 phenotype despite negative screening for identifiable MEN1 germline mutations. Patient A showed all three classical MEN 1 tumors and patient B showed two of the main tumors with the additional feature of bilateral adrenal hyperplasia associated with low grade cortisol secretion and a positive family history of primary hyperparathyroidism and spontaneous hypoglycemia.

Although the presence of metastases, often in lungs and bones, presents an undisputable evidence of malignancy in the case of parathyroid neoplasia, other features such as aggressive infiltration of surrounding soft tissue (case A), strap muscles and trachea, tumor thrombi in extra-capsular vessels and perineural infiltration are also accepted as evidence of malignancy (9, 10). Other criteria which were also established to diagnose a parathyroid carcinoma were: the presence of uniform sheets of cells arranged in lobular patterns and separated by dense fibrous trabeculae, mitotic figures (particularly atypical mitoses) and capsular or vascular invasion (9, 10).

The evidence for parathyroid carcinomas was strong in both patients. Patient A had a parathyroid tumor in the neck and a very large mediastinal one with histological features such as dense fibrous capsule, thick fibrous banding infiltrated by tumour cells, mitoses, desmoplasia, fat necrosis and invasion of surrounding tissues. All these features in combination are highly suggestive of carcinoma (9, 10). Although there was initial difficulty in identifying the mediastinal carcinoma as that of parathyroid origin, the findings of very positive staining for PTH and the cure of hyperparathyroidism after its removal confirmed its parathyroid origin. The mediastinal parathyroid carcinoma was a primary lesion in this localization rather than a metastatic deposit because normal parathyroid tissue could be demonstrated just outside the capsule of the neoplasm. Therefore, patient A had two parathyroid carcinomas, one in the neck and one in the mediastinum. Similar classic histological characteristics of parathyroid carcinoma, particularly multiple atypical mitoses, were seen in the

parathyroid tumor of patient B. Additional factors supporting the diagnosis of parathyroid carcinomas in both cases were: very high serum PTH concentrations, the large size of the lesions and the high Ki 67 index in the case of patient B. It is notable that the first case (patient A) presented with two aggressive MEN1 related tumors, the widely invasive lactotroph adenoma and the parathyroid carcinomas. The case was particularly unusual because the patient had primary amenorrhea, which we assume to be secondary to the lactotroph adenoma which must have been present for >50 yr. The lactotroph adenoma was locally invasive but because it invaded the base of the skull without significant suprasellar extension, the patient did not have headaches or visual disturbances and the lesion went undetected for decades. Patient B illustrates the important caveat that Zollinger-Ellison syndrome in MEN1 tends be secondary to multiple pancreatic and/or duodenal gastrinomas which explains why the patient was not cured after removal of the proximal pancreatic lesion.

The surgical removal of the parathyroid carcinomas has been successful in treating the hyperparathyroidism in both patients so far. Although no evidence of residual or metastatic disease is present after 2 yr of follow-up, parathyroid carcinomas are tenacious tumors and tend to recur even after many years of remission (7). Therefore, long-term follow-up is required in all patients. It is interesting that patient B had one parathyroid tumor only while MEN1 usually presents with multiple parathyroid gland disease. It is possible that the negative feedback of the severe hypercalcemia from the parathyroid carcinoma has suppressed the remaining parathyroid glands from becoming adenomatous or hyperplastic, but this remains speculative.

Dionisi et al. (8) have previously described a case of a 35-yr-old patient with Zollinger-Ellison syndrome and both a parathyroid adenoma and an ectopic mediastinal parathyroid carcinoma, who subsequently died from intractable hypercalcemia from parathyroid metastases. There is also a published case report of a patient with parathyroid carcinoma and multiple parathyroid adenomas who was found to have a heterozygous mutation of the MEN1 gene (11). However, in that case report, the patient did not show any evidence of other endocrine organ involvement despite extensive biochemical and radiological scrutiny. Parathyroid carcinoma has also been described in one case of MEN2A syndrome (12).

Although primary hyperparathyroidism is almost universal in MEN1 (6), only 2-4% of primary hyperparathyroidism occur as part of MEN1 (2, 13). The parathyroid tumors in MEN1 tend to be multiple with younger age of onset and tend to recur after apparent initial surgical cure (1, 2). It is unclear whether the natural history of parathyroid carcinoma in a MEN1 setting will be different to that of sporadic cases.

In conclusion, these two case reports show that parathyroid carcinoma can occur, albeit rarely, in the context of MEN1 syndrome. The negative genetic screening for classic MEN1 gene mutation in both cases may suggest that one or more novel occult mutations may be responsible for this aggressive phenotype.

REFERENCES

1. Brandi ML, Gagel RF, Angeli A, et al. Guidelines for diagnosis and therapy of MEN type 1 and type 2. J Clin Endocrinol Metab 2001, 86: 5658-71.
2. Marx SJ. Multiple endocrine neoplasia type 1. In: Scriver CR, Beaudet AL, Sly WS, Valle D eds. The metabolic and molecular bases of inherited disease. New York: McGraw-Hill. 2001, 943-66.
3. Skogseid B, Oberg K, Eriksson B, et al. Surgery for asymptomatic pancreatic lesion in multiple endocrine neoplasia type I. World J Surg 1996, 20: 872-7.
4. Brandi ML, Marx SJ, Aurbach GD, Fitzpatrick LA. Familial multiple endocrine neoplasia type 1: a new look at pathophysiology. Endocr Rev 1987, 4: 391-405.
5. Trump D, Farren B, Wooding C, et al. Clinical studies of multiple endocrine neoplasia type 1 (MENI). Q J Med 1996, 89: 653-69.
6. Skarulis MC. Clinical expressions of multiple endocrine neoplasia type 1 at the National Institutes of Health. Ann Intern Med 1998, 129: 484-94.
7. Shane E. Clinical review 122: Parathyroid carcinoma. J Clin Endocrinol Metab 2001, 86: 485-93.
8. Dionisi S, Minisola S, Pepe J, et al. Concurrent parathyroid adenomas and carcinoma in the setting of multiple endocrine neoplasia type 1: presentation as hypercalcemic crisis. Mayo Clin Proc 2002, 77: 866-9.
9. Schantz A, Castleman B. Parathyroid carcinoma: a study of 70 cases. Cancer 1973, 31: 600-5.
10. Bondeson L, Grimelius L, DeLellis RA. Parathyroid carcinoma. In DeLellis RA, Lloyd RV, Heitz PU, Eng C eds. WHO classification of tumours, pathology and genetics: tumours of the endocrine organs. Lyon: IARC Press. 2004, 124-7.
11. Sato M, Miyauchi A, Namihira H, et al. A newly recognised germline mutation of MEN1 gene identified in a patient with parathyroid adenoma and carcinoma. Endocrine 2000, 12: 223-6.
12. Jenkins PJ, Satta MA, Simmgen M, et al. Metastatic parathyroid carcinoma in the MEN2A syndrome. Clin Endocrinol (Oxf) 1997, 47: 747-51.
13. Uchino S, Noguchi S, Sato M, et al. Screening of the MEN1 gene and discovery of germ-line and somatic mutations in apparently sporadic parathyroid tumors. Cancer Res 2000, 60: 5553-7.