A case of parathyroid carcinoma discovered at post-mortem

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Abstract

We present a post-mortem (PM) case of a patient who died from complications of a previously undiagnosed parathyroid carcinoma (PC). The typical clinical signs and symptoms are highlighted. The histology of PC is reviewed, and we discuss the key genetic alterations, and hereditary conditions, in which it is typically seen. Trainees should be aware of the findings of PC that may be encountered at PM, as well as the implications of PC for surviving first degree family members.

Keywords Acute pancreatitis; hypercalcaemia; parathyroid carcinoma

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Case report

A male patient in his mid-40s was taken to the emergency department for symptoms of hypotension and severe dehydration. His condition deteriorated, he had a cardiac arrest with unsuccessful attempts at CPR, and died. His adjusted calcium levels were significantly elevated prior to this acute event. One month leading up to his death, the patient complained of unintentional weight loss and progressive dysphagia, managing only thickened fluids in his final days. He smoked 20 cigarettes a day and was otherwise fit and well. His next of kin reported a family history of 'throat' cancer. A post-mortem, at the request of the coroner, was undertaken to ascertain the cause of death.

The body was that of a male with a BMI of 28. The external examination was otherwise unremarkable.

Post-mortem computerised tomography (PM CT) scan was performed. It showed patchy consolidation throughout both lung lobes that was discordant with the findings of a normal chest X-ray taken on the day of death. There were no other significant findings and so a full invasive post-mortem was conducted. Internal examination revealed a 6 cm mass in the neck soft tissues, located just to the right of the trachea. The pancreas showed extensive surrounding fat necrosis. The lungs showed mild pulmonary oedema only. A 1 cm nodule was also noted in the apex of the right lung. The remaining internal examination of the cardiovascular system, central nervous system, gastrointestinal system, genitourinary system, endocrine system and musculoskeletal system was unremarkable. Histology of the neck mass revealed the unexpected diagnosis of a parathyroid carcinoma (Figure 1). Sections of the pancreas showed acute inflammation and extensive fat necrosis, representing acute pancreatitis (Figure 2). Numerous metastatic calcifications were seen in the kidney, spleen, liver, heart and pancreas (Figure 3). The apical right lung nodule was revealed to be an incidental benign pulmonary hamartoma.

The cause of death was given as 1(a) acute pancreatitis, caused by hypercalcemia due to excessive parathyroid hormone secretion from a 1(b) parathyroid carcinoma.

All other findings were deemed to be incidental, and did not contribute to death in this case. The patient's progressive dysphagia was attributed to compression of the oesophagus by the expanding tumour. Given the patient's young age and a family history of "throat cancer" it was recommended that family members approach their GP for consideration of genetic testing.

Discussion

Parathyroid carcinoma (PC) is a rare malignancy which can cause markedly elevated serum calcium levels, via autonomous secretion of parathyroid hormone (PTH). Patients typically present with manifestations or complications of hypercalcaemia, colloquially summarised to include: stones (renal stones), bones (fractures) and psychiatric moans (confusion, neurocognitive dysfunction).

The majority of cases of PC are sporadic. However, cases have been reported in the setting of multiple endocrine neoplasia type 1 and hyperparathyroidism-jaw tumour syndrome (HPT-JT).[1] Over two thirds of cases of PC carry a somatic mutation in the tumour suppressor gene CDC73.[1] Germline mutations of CDC73 are seen in one third of patients with PC, and is also responsible for HPT-JT; an autosomal dominant disorder characterised by the development of parathyroid tumours, ossifying fibromas and renal and uterine pathologies.[1,2]

Macroscopically, PCs are typically larger than parathyroid adenomas (PA) with a firm, lobulated appearance.[3]

As seen in other endocrine neoplasms, it can be difficult to distinguish PC from PAs on histological examination, as both show polygonal cells arranged in solid sheets or trabeculae. Features which favour PC are: thick fibrous bands separating the sheets of cells, (atypical) mitotic activity, coagulative necrosis and vascular and/or capsular invasion.[1,3] Macronuclei in many of the tumour cells can be a helpful clue.[1] Nuclear pleomorphism itself is not a diagnostic feature of malignancy.[3]

The gold standard treatment is the *en bloc* resection of the parathyroid tumour with removal of adjacent involved structures.[1,3] After surgery, local recurrence or metastasis is

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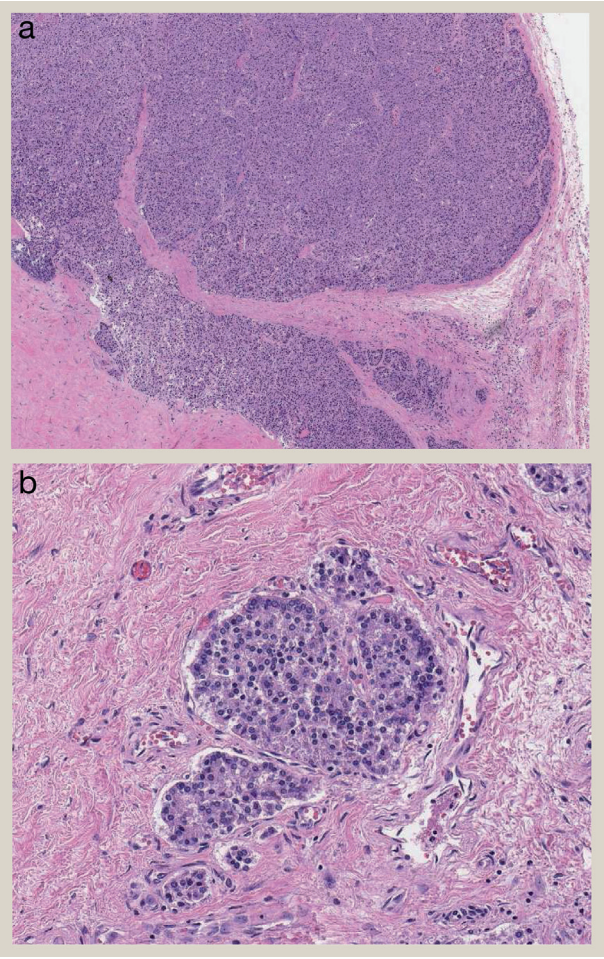

Figure 1 Haematoxylin and eosin (H&E) stained slides of the neck mass showing (**a**) low power view of sheets of polygonal cells separated by thick fibrous bands and (**b**) vascular invasion.

uncommon, and the disease-free interval can be up to 20 years.[1] Disease progression is often identified because of the return of the clinical manifestations of hypercalcaemia.

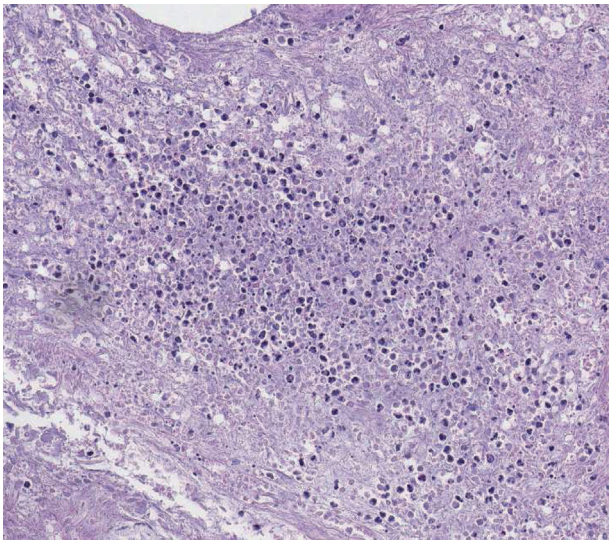

Figure 2 H&E stained slide of pancreas showing necrosis with scattered neutrophils.

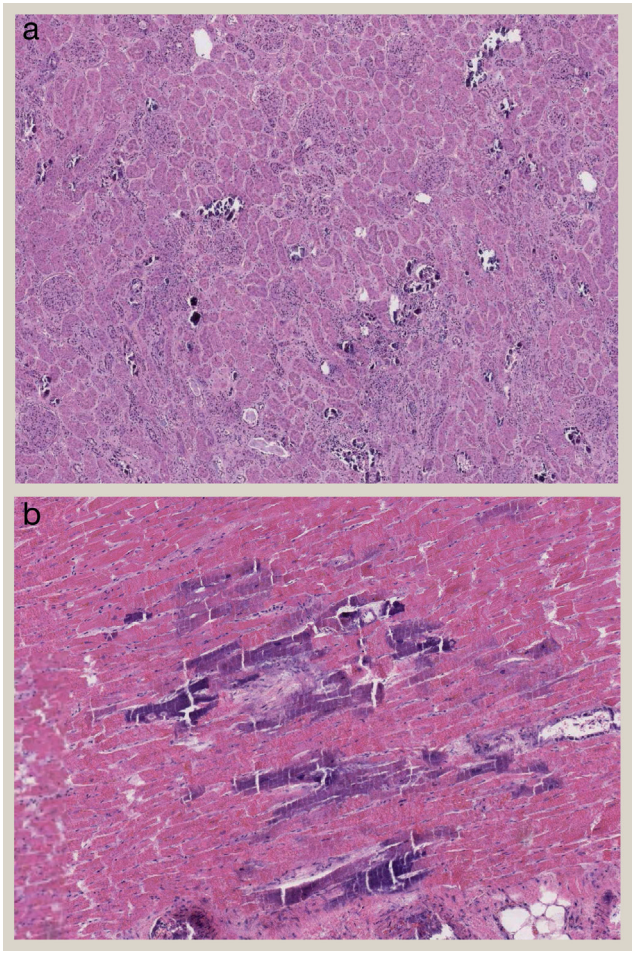

Figure 3 H&E stained slides showing metastatic calcification in (**a**) section from kidney and (**b**) section from heart.

Currently, it is recommended that CDC73 genetic testing should be offered to first-degree relatives of patients who develop PC.[1] It is known that CDC73 mutation carries a worse survival rate.[1]

Conclusion

Parathyroid carcinoma is a rare malignancy which can present as symptoms and/or complications of hypercalcaemia. We have presented a case of a male patient in his mid-40s who was first diagnosed with PC at post-mortem. Histology confirmed acute pancreatitis and widespread metastatic calcifications. Genetic testing is currently in progress to determine if the patient harbours a germline mutation in the CDC73 gene. ◆

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Practice points

- Parathyroid carcinoma is a rare malignancy which may first present with hypercalcaemia, the clinical symptoms of which are colloquially summarised as "stones, bones and psychiatric moans"
- Other than alcohol and gall stones, there are other rarer causes of pancreatitis that need to be considered when it is seen at PM, as in this case
- Somatic and (less frequently) germline mutations in the CDC73 gene have been reported in parathyroid carcinomas
- Parathyroid carcinoma can occur in patients with hyperparathyroidism-jaw tumour syndrome; an autosomal dominant disorder caused by a mutation in the CDC73 gene
- A constellation of histological features need to be considered to distinguish parathyroid carcinoma from a parathyroid adenoma

Self-assessment questions

1. Which are the following clinical symptoms are not commonly seen in patients with hypercalcaemia?

A. Pancreatitis
B. Confusion
C. Resting tremor
D. Renal stones
E. Bone fractures

Answer: C

2. On histology, parathyroid carcinoma can be difficult to distinguish from a parathyroid adenoma. Which feature would favour a parathyroid carcinoma?

A. Infrequent typical mitotic figures
B. Capsular invasion
C. Sheets of monotonous cells
D. Nuclear pleomorphism
E. Abundant lymphoplasmocytic infiltrate

Answer: B

3. Other than hyperparathyroidism-jaw tumour syndrome, which other hereditary condition is associated with the development of parathyroid carcinoma?

A. Multiple endocrine neoplasia type 1
B. Familial medullary thyroid cancer
C. Multiple endocrine neoplasia type 2A
D. Multiple endocrine neoplasia type 2B
E. Wiskott-Aldrich syndrome

Answer: A