The past, the present and the promising: a report of a rare case of parathyroid carcinoma

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Abstract

Parathyroid carcinoma (PTC) is an uncommon endocrine neoplasm. There are well-established criteria for its diagnosis, but diligent practical application of these criteria can be challenging for even the most discerning pathologist. We report a case of PTC demonstrating classical lymphovascular invasion, and review how pathologists can confidently and effectively diagnose PTC utilising the correct morphological histopathological features, supported by a panel of immunohistochemical stains and ancillary molecular testing.

Keywords Atypical parathyroid tumour; CDC73; lymphovascular invasion; parafibromin; parathyroid carcinoma

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Case report

A 27 year old male underwent surgery for primary hyperparathyroidism. He had a known past medical history of hyperparathyroid jaw tumour syndrome (see discussion) with heterozygous partial gene deletion of Cell Division Cycle 73 (CDC73). The resected surgical excision specimen was referred to our institution for expert opinion.

Macroscopically the piece of tan, haemorrhagic and nodular tissue weighed 5.9 g and measured 25 × 20 × 17 mm. The surface appeared smooth and congested. Serial slicing revealed a partly nodular, partly cystic cut surface with haemorrhagic contents measuring up to 10 mm in maximum dimension.

Microscopically *s*ections demonstrated an encapsulated parathyroid neoplasm (Figure 1) composed of sheets of tumour cells with oncocytic-type cytoplasm and round to ovoid nuclei with coarse chromatin and inconspicuous nucleoli (Figures 2 and 3). Focally there was perinuclear clearing and scattered endocrine-type atypia (nuclear atypia occasionally seen in normal endocrine organs). Mitotic figures were infrequent and necrosis was absent.

Sheets of tumour were intersected by an arborising network of thin walled, hyalinised blood vessels and occasional broad fibrous bands. Peripherally the lesion was well circumscribed with no capsular invasion or infiltrative growth. Two foci of unequivocal lymphovascular invasion were present with associated fibrin thrombus (Figures 4 and 5). A small quantity of residual normal parathyroid gland was also included at the periphery of the lesion. The Ki67 proliferation index was <1%.

We made a diagnosis of parathyroid carcinoma (PTC) that was clear of margins.

Discussion

PTC is a rare and challenging entity for both clinicians and pathologists alike. The reported incidence is between 0.5 and 1% of all cases of primary hyperparathyroidism.[1–3] Most cases that occur are sporadic, however there are well known associations with multiple endocrine neoplasia (I and IIA), familial isolated hyperparathyroidism (FITP) and hyperparathyroidism jaw-tumour syndrome.[1,4] Hyperparathyroidism jaw-tumour syndrome, as noted in our patient, is known to have a lifelong risk of PTC of approximately 15%.[1]

Patients can present with symptoms of hyperparathyroidism, including tiredness, bone pain and cognitive dysfunction.[2,5] However, a minority can present with late-stage compressive symptoms from an enlarging neck mass with completely normal parathyroid hormone (PTH) levels.[1,5]

Imaging is helpful in determining the location of lesions[5] but is neither sensitive nor specific for malignancy. However, the presence of lymphadenopathy, alongside the radiological features of large size, cystic change and internal calcifications,[2,5] increases the likelihood of carcinoma.[5]

Fine needle aspiration is not recommended due to capsular disruption of the lesion, causing potential seeding and consequent spread of carcinoma. However, it also is frequently non-diagnostic, and not useful as a means of differentiating PTC from atypical parathyroid tumour (APT) or adenoma.[2,5]

The mainstay of treatment for PTC is surgical excision, with negative resection margins essential for curative intent.[5] There is a limited role for adjuvant chemotherapy and radiation therapy, with a lack of large-scale data to support any significant benefit with regards to disease free survival and local recurrence.[5]

Schantz and Castleman[6] first described the salient histopathological features for PTC, suggesting a diagnosis of PTC could be made if fibrous trabeculae, mitotic figures, capsular invasion or blood vessel invasion were identified. Further refinements by the WHO in 2017 and 2022 gave histopathologists five well-defined histopathological features[1] required for diagnosis of PTC (Table 1).

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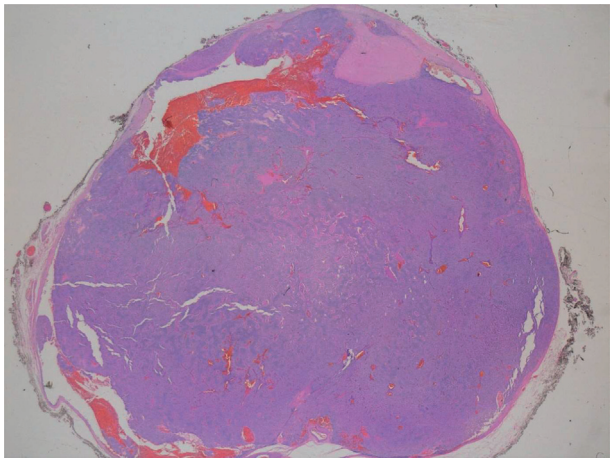

Figure 1 Parathyroid tumour, H&E ×1. Showing a well circumscribed, but partly haemorrhagic parathyroid lesion.

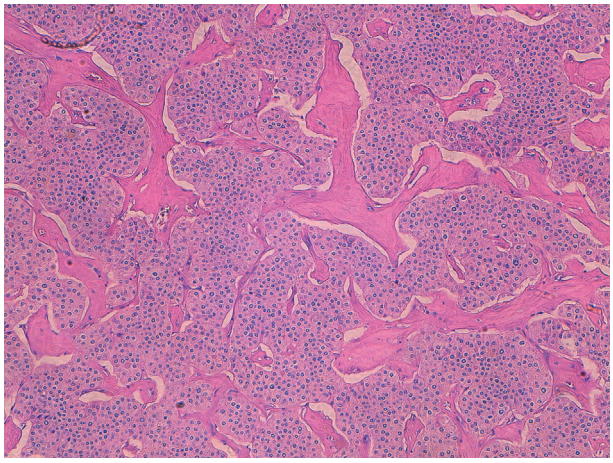

Figure 2 Parathyroid tumour, H&E ×100. Trabeculated nature of the parathyroid lesion.

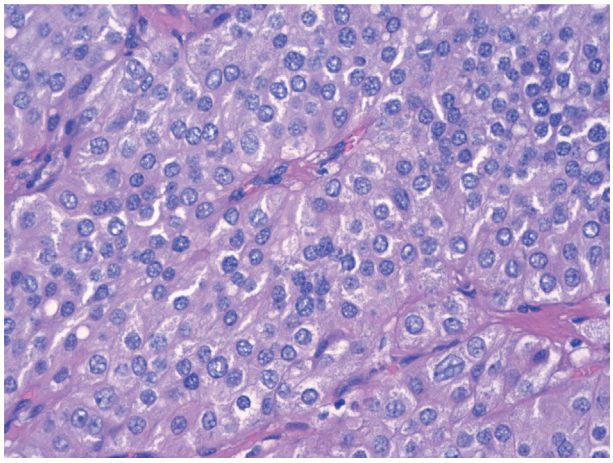

Figure 3 Parathyroid tumour, H&E ×400. Tumour cells showing rounded nuclei with coarse chromatin.

From January 2024, the International Collaboration on Cancer Reporting (ICCR) and RCPath recommended further sub-dividing PTC into in to low or high histological tumour grade.[1] However, this core data item is yet to be incorporated into the WHO Classification of PTC.).

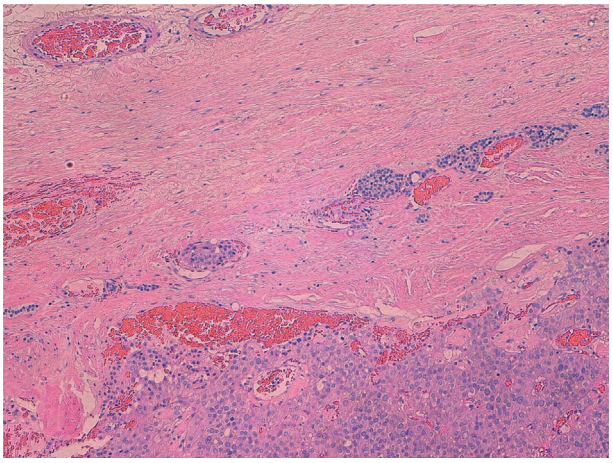

Figure 4 Parathyroid tumour, H&E ×100. Two foci of angioinvasion, with tumour cells and associated fibrin within an overt blood vessel.

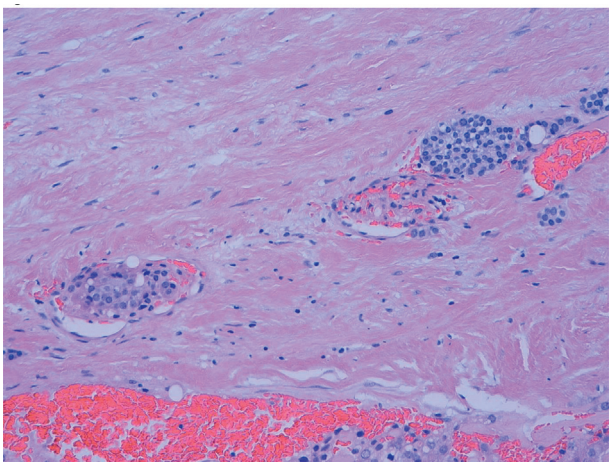

Figure 5 Parathyroid tumour H&E ×200. Two foci of angioinvasion.

An important differential diagnosis of parathyroid carcinoma is atypical parathyroid tumour (APT). APT is a challenging diagnosis, and used to reflect a parathyroid neoplasm of uncertain malignant potential (UMP).[4] It is often utilised in specimens that show cytopathological features suggestive of PTC, but do not wholly fulfil the WHO criteria for it.[1,4] Macroscopically specimens are commonly smaller in dimension, weight and volume and lack coagulative tumour necrosis.[1] Microscopically, cases are devoid of invasion, with 2 or more features of; fibrous bands, mitotic figures, necrosis and trabecular growth.[1,4] If these microscopic features are found they are graded as 'Tis', reflecting their UMP.

Ancillary studies, such as immunohistochemistry (IHC) and molecular analysis are an area of expanding interest in helping to distinguish between APT and PTC.[3] Mutation within the tumour suppressor gene, CDC73, which encodes the protein Parafibromin, is implicated in both germline and somatic PTC.[3,5] This is the gene implicated in hyperparathyroidism jaw-tumour syndrome. Loss of nuclear staining within PTC cells for Parafibromin is considered an abnormal finding, that warrants further referral for germline molecular testing.[1,4] Parafibromin and retinoblastoma (RB1) deficiency alongside the positivity of other surrogate IHC markers such as PGP9.5, and galectin3[1,4] and

Histopathological features required for diagnosis of PTC

WHO 2022 criterion	Histopathological definition	IHC
Angio-invasion	Presence of fibrin associated with tumour cells within an endothelial lined space. Tumour should invade through a vessel wall and have associated thrombus, or intravascular tumour cells admixed with thrombus.	GATA3 or PTH compared with CD61 or Martius-Scarlet blue can be helpful in assessing the tumour/non tumour interface
Lymphatic invasion	Presence of tumour cells within in a lymphatic space.	D2-40 can be helpful in distinguishing lymphatic spaces
Perineural invasion	Extension into the epineurium, either in small nerves, or the recurrent laryngeal nerve which lies close to the parathyroid glands.	S100
Local malignant invasion	Invasion into adjacent structures, including soft tissue, muscle or organs.	
Regional or distant metastasis	Histologically confirmed metastatic spread.	

Adapted from the RCPath Standards and datasets for reporting cancer: Dataset for the histopathological reporting of carcinomas of the parathyroid[1]

Table 1

overexpression of WT1 and p53 have been suggested as a PTC IHC panel.[1,5] However, the poor availability, interpretative difficulties, and variable expression of these IHC stains mean their role in PTC diagnosis is still supportive and not yet definitive. ◆

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Practice points

- On macroscopic examination, the presence of coagulative of necrosis should be documented
- Angio-invasion is important to correctly identify, as PTCs with true vessel invasion are associated with a worse prognosis and indicate a high risk of recurrence
- If the diagnostic criteria of PTC cannot be fulfilled, but worrisome cytopathological features are seen, a diagnosis of ATP should be considered
- Immunohistochemical testing is of some supportive value, but the primary modality of PTC diagnosis is still on the morphological features exhibited. Morphology is still king!

Self-assessment questions

1. Which of the following symptoms is not in keeping with a suspected diagnosis of parathyroid carcinoma?

a) Tiredness
b) Increased appetite
c) Bone pain
d) Cognitive dysfunction

Answer: b

2. In an atypical parathyroid tumour, which histopathological parameter would necessitate an upgrade to a diagnosis of parathyroid carcinoma?

a) Fibrous bands
b) Mitotic figures
c) Necrosis
d) Peri-neural invasion

Answer: d

3. Which of the following investigations is most commonly diagnostic of parathyroid carcinoma?

a) CT scan
b) Histopathology
c) PET scan
d) MRI scan

Answer: b