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Case of thymic parathyroid carcinoma in a haemodialysis patient: application of tumour chemosensitivity testing

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Abstract
Parathyroid carcinoma is a rare tumour, which is often difficult to diagnose. This is especially true in patients with pre-existing tertiary hyperparathyroidism of end-stage renal disease. A case is presented of parathyroid carcinoma in a haemodialysis patient with unusual thymic involvement. After demonstrating the difficulty in pre-operative diagnosis and risk of recurrence, the importance of non-surgical treatment options is discussed and the investigation of individual tumour chemosensitivity is introduced, which is new to this type of cancer.

Key words: Thymus Gland; Hyperparathyroidism; Treatment

Introduction

Parathyroid carcinoma is a rare tumour occurring in 0.1 to five per cent of patients with primary hyperparathyroidism.[1–4] Clinical features indicating malignant parathyroid change include a palpable neck mass, recurrent laryngeal nerve palsy and severe skeletal manifestations of hypercalcaemia. Biochemical features include serum calcium, alkaline phosphatase, and parathormone levels much higher than expected for hyperparathyroidism of benign aetiology.[3] The gold standard treatment for parathyroid carcinoma is radical surgery including block dissection of the neck. Pre-operative diagnosis of parathyroid carcinoma is hence a great advantage, but it remains difficult to achieve.

We present a case of parathyroid carcinoma in a patient with end-stage renal disease (ESRD) to illustrate additional diagnostic difficulties in this patient group. As part of our discussion of non-surgical treatment options, we include the use of an experimental tumour chemosensitivity assay which may be used as a guide in the choice of chemotherapeutic agents for such rare tumours.

Case report

A 27-year-old female with ESRD secondary to reflux nephropathy presented to her nephrologist with lower back pain. Eight years prior to this she had been on immunosuppressant agents for 10 years for a renal transplant, but there was no other relevant medical history. The patient's corrected serum calcium level was 2.8 mmol/l (normal = 2.15–2.60 mmol/l), and her parathyroid hormone level was 149 pmol/l (normal = 0–4.7 pmol/l). A diagnosis of tertiary hyperparathyroidism associated with hand, pelvic and spine renal osteodystrophy was made, and an ultrasound scan of the neck demonstrated two nodules near the right lobe of her thyroid gland. A parathyroidectomy was performed and yielded four glands, which were histologically confirmed as benign hyperplastic parathyroid tissue.

The patient's hypercalcaemia resolved (serum corrected calcium 2.56 mmol/l, parathormone level 2.1 pmol/l). One year later she developed further skeletal symptoms and biochemical evidence of recurrent hyperparathyroidism (serum corrected calcium 2.96 mmol/l, parathormone 161 pmol/l). Ultrasound and sestamibi scans suggested further active parathyroid tissue near the right lower lobe of the thyroid gland. A neck exploration was performed revealing multiple nodules in the right lower thyroid lobe, right sternomastoid and around the trachea, all of which were excised and confirmed as low-grade parathyroid carcinoma.

There was no change in either serum calcium or parathormone level after this surgery and the patient remained symptomatic. In view of the histological diagnosis, radical surgery was planned. A pre-operative computerized tomography (CT) scan suggested the presence of further abnormal tissue in the right thyroid lobe extending to the supraclavicular fossa, but showed no mediastinal or chest abnormality. The patient underwent a radical neck dissection, and superior mediastinal dissection requiring a sternotomy was necessary to remove all macroscopically detectable disease. Post-operatively, the patient's calcium levels returned to normal (serum corrected calcium 2.48 mmol/l, parathormone 5.6 pmol/l). At nine-month follow up, these continued to normalize (serum corrected calcium 2.28 mmol/l, parathormone 0.8 pmol/l) and the patient remained asymptomatic. Histological analysis revealed completely excised parathyroid carcinoma in the right thyroid lobe and in the head of the thymus, with no lymph node metastasis. The histology of this tumour is illustrated in Figure 1.

Parathyroid tumour cells from our patient were subjected to an adenosine 5′-triphosphate (ATP)-based chemosensitivity assay (ATP-TCA), which has previously been successfully applied in other cancer types.[5] This is an *in vivo* assay testing tumour cell response to a variety of chemotherapeutic agents. It relies on the fact that ATP is quickly consumed by cellular enzymes after cell death. The

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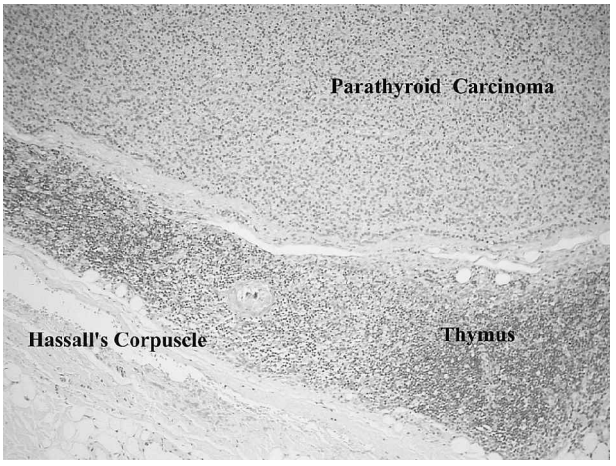
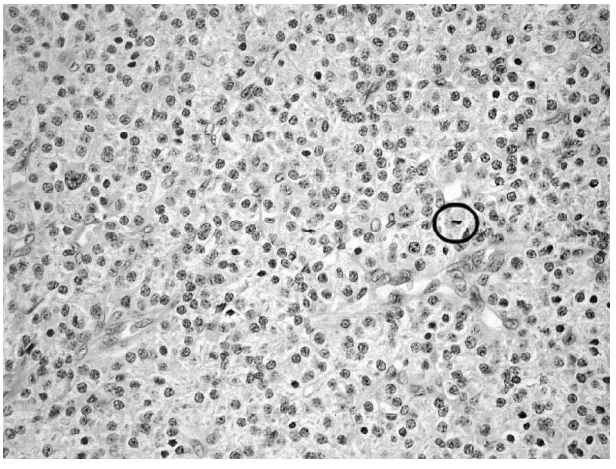


(a)



(b)

FIG. 1

(a) A lower power view of the parathyroid carcinoma forming solid sheets of cells with a fibrous capsule. This focus was situated in the thymus, which forms a layer of lymphoid cells between the carcinoma and the surrounding fatty tissue and includes a Hassall's corpuscle (H & E; ×100). (b) Higher magnification of the parathyroid carcinoma showing sheets of relatively uniform cells with clear cytoplasm forming acinar structures in places. Mitoses are present and one is marked with a circle (H & &E; ×400).

assay measures the degree of cell death following tumour culture with a variety of cytotoxic agents at different concentrations. The concentrations of ATP after culture are measured using luminescence methods, and an assessment of the degree of tumour inhibition (i.e. sensitivity to cytotoxic agent) can be drawn from the inverse relationship with ATP-induced luminescence.

The tumour cells of our patients were subjected to ATP-TCA against cisplatin, gemcitabine, doxorubicin, paclitaxel, 4-HC, as well as combinations of these drugs. The results of this assay demonstrate resistance to cisplatin and 4-HC, but good sensitivity to doxorubicin and cisplatin when combined with gemcitabine (Figure 2).

Discussion

Fewer than 20 cases of parathyroid carcinoma have been reported in patients with ESRD and approximately 700 cases in the general population,[1] making it a rare disease. Despite considerable work on the molecular mechanisms

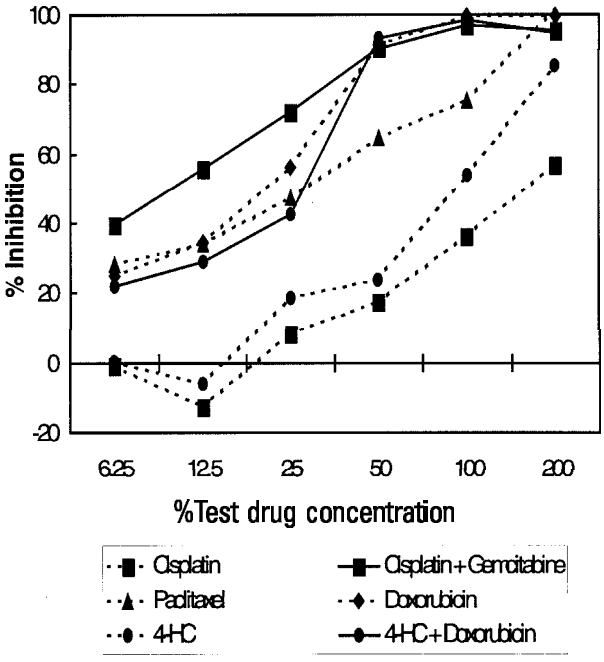


FIG. 2

ATP-based tumour chemosensitivity assay results, showing the effect of six dilutions of each drug or combination tested. The 100 per cent test drug concentration is defined according to pharmacokinetic data and is clinically achievable. There is little sensitivity to cyclophosphamide (4HC) or cisplatin, but the addition of gemcitabine augments the cisplatin activity considerably and there is evidence of some anthracycline (doxorubicin) activity.

of carcinogenesis in parathyroid carcinoma, there has been no investigation into the molecular and pathological differences between primary parathyroid malignancies in general and those occurring in patients with tertiary hyperparathyroidism of ESRD.

Many patients with ESRD develop tertiary hyperparathyroidism due to parathyroid hyperplasia, and parathyroid carcinoma in these patients is clinically less easily detected. This is because while other patients with parathyroid carcinoma often have serum calcium levels more than three times normal,[3] levels are kept lower in patients with ESRD as a result of their renal insufficiency.[2] Our patient had extremely high levels of parathyroid hormone, which should raise suspicion of malignant change. It is worth noting, however, that parathyroid hormone levels of more than twice normal are commonly seen in haemodialysis patients. This highlights the additional difficulty in pre-operative diagnosis and planning of curative radical resection in this patient group, as opposed to simple parathyroidectomy for presumed tertiary hyperparathyroidism of ESRD.

Anatomical considerations

It is noted from this case that despite resection of four histologically confirmed parathyroid glands at initial surgery, the patient still developed parathyroid carcinoma. Only one previous case of parathyroid carcinoma in the thymus has been reported.[5] The incidence of supernumerary parathyroid gland is two to six per cent,[6] but the possibility of tumour arising *de novo* in a supernumerary gland in this case is probably low due to the number of nodules formed in the thymus. It is, however, impossible to prove the origin of this tumour involvement by histological analysis.

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- **Parathyroid carcinoma is rare and is difficult to diagnose**
- **This paper presents a case, with thymic involvement, arising in a patient with end-stage renal failure and tertiary hyperparathyroidism**
- **The authors discuss non-surgical treatment options and the use of chemosensitivity – which, they speculate, may prove useful in the future in the monitoring of tumour responsiveness to chemotherapy**

This case also demonstrates the need for a high index of suspicion for malignant parathyroid change when the operative findings constitute multiple and widespread nodes of presumed benign disease. However, the role of intra-operative frozen section histology in this situation remains unknown. Furthermore, when ultrasound, sistamibi and CT scans were performed before our patient's radical surgery, none revealed evidence of the disease in the upper mediastinum, which was later histologically confirmed in the resected specimen. Radical resection of these tumours with meticulous exploration of the neck including the upper mediastinum is therefore recommended.

Non-surgical treatment and ATP chemosensitivity testing

Radical resection of these tumours gives good results. However, due to the diagnostic and anatomical difficulties described above, re-operation is not uncommon and becomes increasingly difficult. Whether disease is inoperable due to local recurrence or metastasis, treatment is still required to alleviate the symptoms of severe hypercalcaemia which may become refractory to medical therapy with bisphosphonates and other agents. This highlights the importance of non-surgical treatment modalities for parathyroid carcinoma.

Adjuvant radiotherapy may have a role in the post-operative treatment of these patients,[7] but parathyroid carcinoma is not generally considered to be radiosensitive. We believe the role of chemotherapy to be more promising, especially if used with laboratory evidence which makes it a more precise modality.

Determining the *in vitro* sensitivity and resistance of organisms to antibiotic drugs has long been practised in the management of infectious diseases. A similar application in the assessment of cancer cells would have many advantages in guiding the initiation and monitoring of treatment with chemotherapeutic agents.

Due to the rarity of parathyroid carcinoma, reports of successful treatment with specific chemotherapeutic agents have been sporadic. Chemosensitivity testing would be especially valuable if applied to these rare tumours, where information on chemotherapeutic agent choice from large clinical trials is not available.

Nine months after her radical surgery, our patient's tumour histology, as well as her clinical and biochemical markers, continued to suggest clearance of the tumour, therefore further surgery or chemotherapy were not required. However, it is important to consider that clear surgical margins of the resected nodules do not exclude the possibility of other malignant nodules outside the resected specimen, especially in such cases where malignant but slow-growing nodules are widespread and reaching the upper mediastinum. Furthermore, many of the histological features that normally guide clinicians on the need for adjuvant treatment and risk of recurrence are often difficult to determine in parathyroid carcinoma, as in the case of detecting tumour extracapsular spread. All of the above difficulties render the local recurrence and metastasis rates for each individual patient highly unpredictable, and recurrences have been reported to occur anytime up to 20 years after the initial treatment.[3] For this reason we recommend that because chemotherapy may be considered in the future, samples from the resected specimen should be sent for chemosensitivity testing. This would act as a powerful back-up strategy for the development of appropriate treatment for this rare type of cancer.[8]

References

1 Rao SR, Shaha AR, Singh B, Rinaldo A, Ferlito A. Management of cancer of the parathyroid. *Acta Otolaryngol* 2002;**122**:448–52
2 Kebebew E, Arici C, Duh QY, Clark OH. Localisation and reoperation results for persistent and recurrent parathyroid carcinoma. *Arch Surg* 2001;**136**:878–85
3 Shane E. Parathyroid carcinoma. *J Clin Endocrinol Metab* 2001;**86**:485–93
4 Castillo L, Poissonet G, Haddad A, Guevara N, Santini J, Demard F. Carcinome parathyroidien: diagnostic et traitment. *Rev Laryngol Otol Rhinol* 2000;**121**:169–73
5 Andreotti PE, Cree IA, Kurbacher CM, Hartmann DM, Linder D, Harel G, *et al*. Chemosensitivity testing of human tumours using a microplate adenosine triphosphate luminescence assay: clinical correlation for cisplatin resistance of ovarian carcinoma. *Cancer Res* 1995;**55**:5276–82
6 Kastan DJ, Kottamasu SR, Frame B, Greenwald KA. Carcinoma in a mediastinal fifth parathyroid gland. *J Am Med Assoc* 1987;**257**:1218–9
7 Chow E, Tsang RW, Brierly JD, Felice S. Parathyroid carcinoma: the Princess Margaret Hospital experience. *Int J Radiat Oncol Biol Phys* 1998;**41**:569–72
8 Cree IA. Chemosensitivity testing as an aid to anti-cancer drug and regimen development. *Rec Results Cancer Res* 2003;**161**:119–25

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