

Parathyroid carcinoma: clinical course, diagnosis and management

Gabriella Captur, Lissa Micallef Grimaud, Alexandra Betts,
James Degaetano, Alex Attard, Josanne Vassallo

Abstract

Parathyroid carcinoma is a rare cause of primary hyperparathyroidism often resulting in severe hypercalcaemia. It tends to follow a rather aggressive course with a high propensity for locoregional spread and distant metastasis. *En bloc* resection is the mainstay of treatment, with surgery also playing a role in the palliation of hypercalcaemia for recurrent and metastatic disease. While adjuvant chemotherapy and radiotherapy have shown disappointing outcomes, bisphosphonates and calcimimetic agents are effective in the management of recalcitrant hypercalcaemia in parathyroid carcinoma.

We report a case of parathyroid carcinoma in a lady who initially presented with a neck mass, severe hypercalcaemia, a bony swelling over the shin and elevated parathyroid hormone levels. The diagnosis was confirmed histologically following a thyroid lobectomy, isthmectomy and parathyroidectomy. In the three years which followed the patient received two courses of palliative radiotherapy, two thoracotomies for pulmonary metastatectomy, an extensive neck re-exploration and fashioning of a tracheostomy for aggressive local recurrence with invasion of the larynx.

Introduction

Parathyroid carcinoma is a rare cause of primary hyperparathyroidism often resulting in severe hypercalcaemia. We report the case of a patient whose tumour caused severe hypercalcaemia apart from following an aggressive course with multiple local recurrences and metastasis.

In one review of 4,239 patients with hyperparathyroidism, 2.1% had functioning parathyroid carcinomas.¹ A systematic review of 22,225 cases of primary hyperparathyroidism reported between 1995 and 2003 revealed that parathyroid carcinoma accounted for 0.74% of the cases.²

Parathyroid carcinoma accounts for 0.5 to 5% of cases of primary hyperparathyroidism although a relatively higher incidence has been reported in Italy and Japan.³ The average age of presentation is in the mid fifties^{4,5} but our patient presented in her early forties.

The aetiology of parathyroid carcinoma is unclear although cases have been reported to develop within, or to coexist with, a parathyroid adenoma or a hyperplastic parathyroid gland. Parathyroid carcinomas have been associated with a prior history of neck irradiation, with end stage renal disease⁶ and with familial hyperparathyroidism, particularly the autosomal dominant variant⁷.

Case report

We present the case of a 41 year old lady, with a past history of hyperprolactinaemia despite a normal looking pituitary on serial computed tomography (CT) and magnetic resonance imaging (MRI) scans.

She presented to hospital complaining of a tender lump over the left side of the neck, and another painful bony swelling over the left shin. She also reported recent dyspepsia, nausea, polyarthralgia, constipation and polyuria. On examination she appeared pale, dehydrated and was vomiting. A hard irregular left neck mass approximately 3 to 4 cm diameter was discovered in the absence of distinct palpable lymph nodes.

Urgent investigations revealed a severe hypercalcaemia and hypophosphataemia with a calcium level of 4.9mmol/l (reference range 2.15 - 2.55mmol/l) and a phosphate level of 0.77mmol/l (reference range 0.87 - 1.45mmol/l). Serum albumin was normal (47.3g/l) but parathyroid hormone (PTH) was elevated at 1831.00pg/ml (reference range 12.00 - 72.00pg/ml).

Her prior history of hyperprolactinaemia and the newly diagnosed hyperparathyroidism, raised the possibility of Multiple Endocrine Neoplasia Type I (MEN-1). The pituitary gland had however, appeared normal on serial scans. Additionally she denied

Keywords

Parathyroid gland, carcinoma, gene, parathyroid hormone, calcium

Gabriella Captur* MD, MRCP

Department of Cardiology, Mater Dei Hospital, Malta
Email: capturgaby@hotmail.co.uk

Lisa Micallef Grimaud MD, MRCP

Department of Medicine, Infectious Diseases Unit
Mater Dei Hospital, Malta

Alexandra Betts BChD, MPhil

Department of Pathology, Mater Dei Hospital, Malta

James Degaetano MD, FRCPA

Pathology Department, Mater Dei Hospital, Malta

Alex Attard Ch.M, FRCS

Department of Surgery, Mater Dei Hospital, Malta

Josanne Vassallo MD, FRCP

Department of Medicine, Division of Endocrinology,
Mater Dei Hospital, Malta

*corresponding author

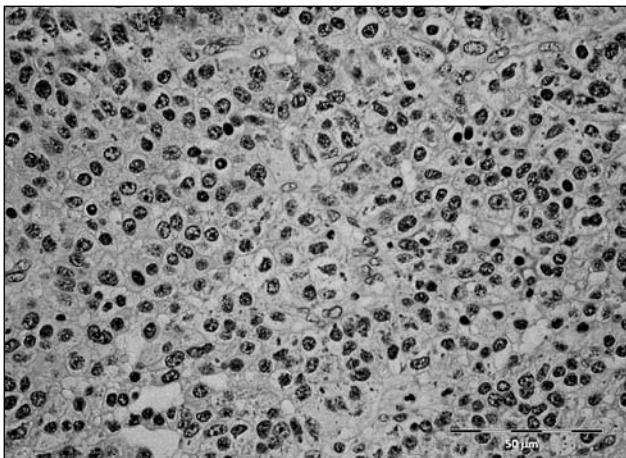


Figure 1: High power view of parathyroid carcinoma showing sheets of cells with abundant, pale, rather granular cytoplasm; central nuclei with anisonucleosis; clumped chromatin and prominent nucleoli. A mitotic count of four mitotic figures per ten high power fields was observed in the tumour (Original magnification: x400)

any family history of parathyroid disorders or MEN. Screening tests to definitively exclude *MEN-1* gene mutations (11q13) were still pending at the time of writing.

Ultrasonography of the neck and technetium-99m-sestamibi scintigraphy with a subtraction thyroid scan using 123-I-iodine both indicated a mass of parathyroid origin while radiography of the left tibia confirmed a lytic bone lesion in keeping with the elevated serum alkaline phosphatase levels. Whole body scintigraphy yielded a metabolic super-scan compatible with a hyperactive parathyroid gland.

The hypercalcaemia was treated with intravenous fluids and hydrocortisone, loop diuretics and pamidronate infusions achieving a serum calcium level of 3.19mmol/l pre-operatively.

Surgery revealed a left-sided parathyroid tumor which was closely apposed to the oesophagus and invading the thyroid veins. The tumor (4 by 5 by 2cm) was excised together with the left thyroid lobe and thyroid isthmus to which it was adherent. Histology showed a parathyroid carcinoma (Fig. 1) infiltrating beyond the parathyroid and into the thyroid gland (Fig. 2). In the immediate postoperative period, serum calcium levels plummeted necessitating high dose oral calcium and vitamin-D supplements which the patient continued to have on discharge.

During the admission, CT scanning of the thorax and abdomen revealed a suspicious ovarian polycystic lesion for which she subsequently underwent a total abdominal hysterectomy. Histology revealed bilateral ovarian endometriosis. Concomitant biopsy of the tibial lesion confirmed a brown tumour of bone which visibly decreased in size and disappeared after the neck surgery relieved hyperparathyroidism and hypercalcaemia.

Six months post surgery, calcium levels began to rise sharply again suggesting the existence of a metastatic focus. CT scanning of the lady's chest in fact showed three well circumscribed right pulmonary lesions which were excised at thoracotomy. Histology confirmed metastatic deposits of parathyroid carcinoma (Fig. 3). Once again there was immediate and significant relief of hypercalcemia postoperatively.

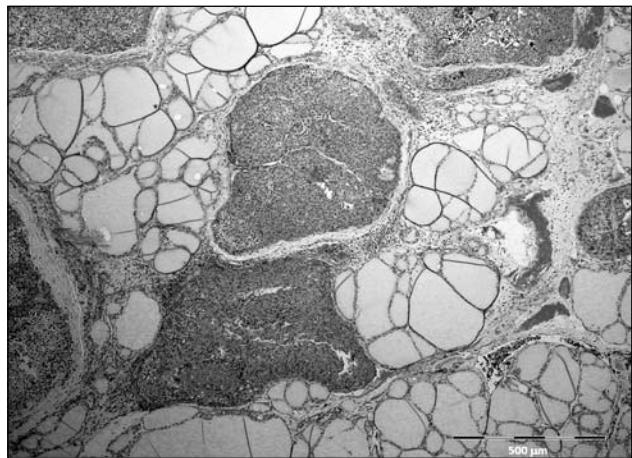


Figure 2: Multiple, partly circumscribed, tumour nodules infiltrating the thyroid parenchyma of the left thyroid lobe. (Original magnification: x100)

The following year, examination of the patient's neck revealed a palpable right upper cervical lymph node. Following radiological studies, a twenty-day course of radiotherapy to the anterior cervical region was administered. During this period she required aggressive management of hypercalcaemia as radiation-induced tumour apoptosis led to parathyroid hormone release. There was an excellent response to radiotherapy with a significant reduction in tumour size and eventual resolution of the hypercalcaemia. At serial follow-up, hypercalcaemia recurred off calcium supplements and serum PTH levels increased to 317.00pg/ml. A CT-thorax disclosed a residual lesion in the right lung which was resected during a second thoracotomy and pulmonary metastasis was again confirmed on histology.

Despite the metastatectomies, the hypercalcaemia failed to settle completely and her requirements for intravenous pamidronate increased. A parathyroid scan showed no abnormal focus of tracer accumulation in the neck, thorax, lung or bones and a thyroid scintigram revealed an enlarged right thyroid lobe with relatively homogeneous tracer uptake throughout. However, approximately five months later, she complained of hoarseness. On examination irregular enlargement of the residual right hemithyroid was palpable and an ultrasound of the neck revealed an enlarged right thyroid lobe containing multiple solid nodules of up to 4cm in diameter. Vocal cord dysfunction was ruled out and the patient referred for surgical neck exploration.

Intraoperatively, metastatic parathyroid carcinoma was seen to involve both anterior jugular veins (Fig. 4), the venous plexus of the right strap muscles, and the veins of tissues anterior to the hyoid bone, thyroid gland, cricoid cartilages and anterior trachea. This entire tissue mass was submitted for histology and infiltration by parathyroid carcinoma was established. Early postoperative hypocalcaemia was treated with oral calcium supplements but within a few weeks hypercalcaemia developed and the patient was commenced on cinacalcet with good effect.

Her hoarseness worsened during the weeks which followed surgery and a CT scan of the neck revealed a soft tissue mass invading

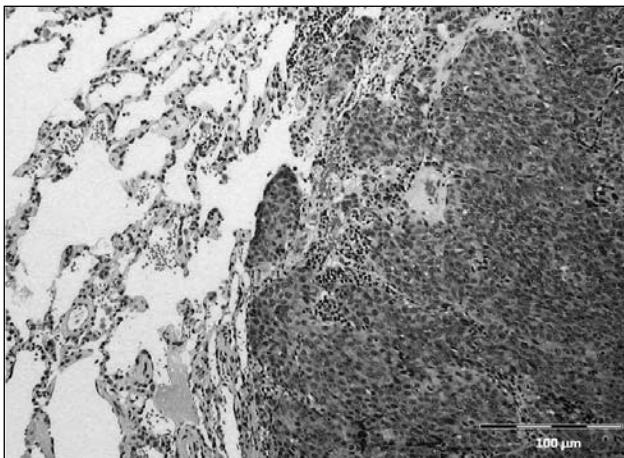


Figure 3: Metastatic parathyroid carcinoma in the right lung. The tumour (right side of image) has a solid growth pattern; some nesting of malignant cells is also observed. (Original magnification: x200)

the larynx (Fig. 5) and the recurrent laryngeal nerve. Eventually she developed significant stridor and laryngoscopy confirmed a right vocal cord paralysis for which an urgent tracheostomy was performed. Meanwhile the oncologist initiated a protracted course of palliative radiotherapy to the neck with good response. Despite the dose of cinacalcet having been increased to 90mgs twice daily, tumour cell apoptosis secondary to radiotherapy has led to the need for repeated sessions of intravenous hydration and pamidronate during the time that she was undergoing radiotherapy. The patient was left with a permanent tracheostomy and continued regular monitoring of her serum calcium levels and medical management as necessary.

Multidisciplinary and multimodality treatment by an endocrine, surgical, ENT and oncology team have enabled this lady to survive an aggressive parathyroid carcinoma for three and a half years.

Discussion

Clinical features

Parathyroid carcinoma classically presents with hypercalcaemia-related symptoms rather than by tumour invasion.⁸ Signs and symptoms of hypercalcaemia include anorexia, lethargy and weight loss, nausea, vomiting, polyuria and polydipsia with our patient demonstrating most of these at presentation. Skeletal involvement is common with features of hyperparathyroid bone disease resulting in bone pain and pathological fractures. Radiological hallmarks include osteitis fibrosa cystica, subperiosteal bone resorption, salt-and-pepper skull and absent lamina dura.

Renal involvement is a frequent feature and renal colic as a consequence of nephrolithiasis is an important presenting complaint. Nephrocalcinosis and impaired glomerular filtration may lead to renal insufficiency in such patients. Pancreatitis and peptic ulcer disease secondary to the relentless hypercalcaemia may complicate the picture further. Our patient did not exhibit any of these symptoms or signs.

There have been isolated reports of nonfunctional parathyroid carcinomas. These often present with metastatic disease and tend to be associated with a worse prognosis.⁹ Serial PTH estimates from the time of presentation to the time of starting cinacalcet confirmed



Figure 4: Parathyroid carcinoma in jugular vein. Tumour (lower right) present in the lumen of the external jugular vein. Part of the muscle wall of the vein is seen on the upper left side of the image. (Original magnification: x200)

that our patient was suffering from a functional parathyroid carcinoma.

Features favouring parathyroid carcinoma as opposed to primary hyperparathyroidism, include the coexistence of renal and/or skeletal involvement,⁴ a palpable neck mass (present in 30-70% of patients with parathyroid carcinoma) and recurrent laryngeal nerve involvement. Hypercalcaemia in parathyroid carcinoma tends to be more severe and recalcitrant to treatment ($>3.5\text{mmol/L}$ in 65-75% of patients). In one study examining the relation between hypercalcaemia and parathyroid carcinoma however, the positive predictive value and sensitivity of hypercalcaemia were found to be 14% and 56% only, respectively. On the other hand, PTH levels and tumour weight emerged as the more reliable surrogate indicators of parathyroid carcinoma. A tumour weight in excess of 2.5g, strongly favours a diagnosis of parathyroid carcinoma over that of adenoma.³ Serum hormone levels tend to hover at about 10.3 times the upper limits of normal in parathyroid carcinomas as was the case in our patient. In contrast, mean PTH levels in benign primary hyperparathyroidism will usually reach 2.6 times the normal values.

Parathyroid carcinoma is slow growing and metastasizes late, with the most frequent sites of deposits being the lung (40%), cervical lymph nodes (30%), and liver (10%). Less commonly, metastases to bone, pleura, pancreas or pericardium may occur.

Diagnosis

The diagnosis of parathyroid carcinoma is often difficult to establish because its clinical features are similar to those of benign primary hyperparathyroidism. Fine needle aspiration is not useful in establishing the diagnosis which is clinched only after confirming infiltration beyond the tumour capsule.

The Schantz and Castleman histological criteria¹⁰ have been used to facilitate differentiation of parathyroid carcinoma from adenoma. Like adenoma, parathyroid carcinoma is usually composed of uniform sheets of cells. Cytologic features of carcinoma include atypical mitotic figures, nuclear pleomorphism and nuclear enlargement. Architectural features of carcinoma include the presence of a thick fibrous capsule, intratumoral fibrous trabeculae

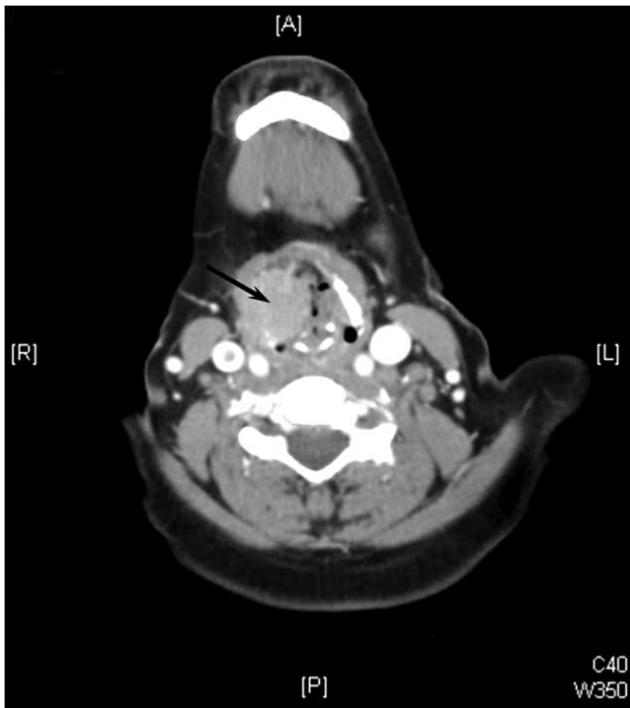


Figure 5: Computed Tomographic scan of the neck in February 2009. There is a solid mass (black arrow) measuring 3-3.5cm on the right extending from the level of the hyoid to the lower margin of the thyroid cartilage. The mass is invading right parapharyngeal region and destroying the right wing of the thyroid cartilage. It is also compressing the pharynx and the proximal part of the trachea

and a trabecular or rosette-like tumour cell arrangement. The criteria upon which a definitive diagnosis of parathyroid carcinoma can be made include capsular invasion, vascular invasion, local invasion of contiguous structures and lymph node or distant metastases.

Bondeson *et al.* noted that the presence of macronucleoli, necrosis and mitotic activity in excess of 5/50 per high power field, generally correlated with more aggressive clinical carcinomas.¹¹ DNA aneuploidy has also been associated with adverse histologic features and a worse prognosis¹² but not invariably, since euploid tumours may also turn out to be clinically aggressive.¹³

Parathyroid carcinomas like adenomas express pancytokeratin and neuroendocrine markers such as chromogranin-A. Histology in our patient showed immunopositivity for these stains. Chromogranin-A or Parathyroid Secretory Protein-1 is a member of the chromogranin/secretogranin (granins) family of neuroendocrine secretory proteins, located in the secretory vesicles of neurons and endocrine cells where it stabilizes the soluble portion of the neurosecretory granules and plays a role in hormonal secretion.¹⁴

Calcitonin and Thyroid Transcription Factor-1 are expressed by medullary thyroid carcinomas but not by parathyroid carcinomas and can serve to tell the two apart.

PTH immunopositivity affirms the parathyroid origin of the tumour whereas proliferation markers serve a limited role in differentiating parathyroid carcinomas from adenomas. Ki-67 is one such marker staining cells which are actively cycling. A higher proportion of Ki-67-positive cells will usually be present

in a carcinoma as opposed to an adenoma because of the higher proportion of proliferating cells in the former, but discrimination between the two on this basis alone is difficult because considerable overlap exists.^{15,16} Cyclin D1 is another proliferation marker which also demonstrates higher expression in carcinomas than adenomas.¹⁷

Immunostaining with Ki-67 was not performed in our patient because evidence of thyroid gland and vascular invasion at the time of presentation had made it already amply clear that the tumour was malignant.

Diagnosis of parathyroid carcinoma also requires radiological investigations such as ultrasonography, CT, MRI and scintigraphy for the purpose of localization and diagnosis.

The low incidence of parathyroid carcinoma means that no American Joint Committee on Cancer staging system has yet been formulated with respect to this disease. Furthermore, neither tumor size nor lymph node status appear to be important prognostic markers for this tumor. It is possible to stratify patients based on whether they have localized or metastatic disease at the time of presentation. Localized disease would involve the parathyroid gland with or without invasion of adjacent tissues while metastatic cancer implies spread beyond the tissues adjacent to the involved parathyroid gland(s).^{18,19}

Molecular pathogenesis

Mutations of several genes have been implicated in the pathogenesis of parathyroid carcinoma, including the Hyperparathyroidism 2 gene (*HRPT2*), the oncogene Cyclin D1 (*CD1*) or Parathyroid Adenoma 1 (*PRAD1*),²⁰ and the tumor suppressor genes Retinoblastoma and *p53*.²¹

CD1 or *PRAD1* is a protooncogene (11q13) whose protein product is a cell cycle regulator.²² *CD1* gene amplification has been implicated in the pathogenesis of numerous tumors with Hsi *et al.* demonstrating that out of 65 patients with parathyroid tumors, over-expression of *CD1* occurred in 18%.²³ Although this study included only three patients with parathyroid carcinoma, two of the these exhibited tumors that stained very strongly for *CD1*, raising the possibility that the frequency of *CD1* over-expression may be greater in carcinoma than previously assumed.

There is increasing evidence to suggest that loss of expression of the *HRPT2* gene (1q21-q32) which customarily encodes the parafibromin protein, is also strongly associated with parathyroid carcinomas. The precise function of parafibromin is still being elucidated but it appears to regulate transcriptional control and inhibit cellular proliferation. Methylation of the *HRPT2* promoter may lead to *HRPT2* gene inactivation potentially giving rise to parathyroid carcinomas.²⁴

Inactivating germline mutations in the *HRPT2* gene give rise to an autosomal dominant type of familial hyperparathyroidism called the Hyperparathyroidism-Jaw Tumor syndrome (HPT-JT).²⁵ These patients are predisposed to mandibular or maxillary ossifying fibromas, cystic and neoplastic renal lesions such as Wilms' tumors, and parathyroid neoplasias such as recurrent parathyroid adenomas with an increased propensity for parathyroid cancer. Importantly, in HPT-JT, all parathyroid glands are at risk for tumor development but the tumors can occur asynchronously over many years.

A subset of patients with sporadic parathyroid cancer may

have clinically unsuspected germline *HRPT2* mutations²⁶ which, if confirmed, would have important therapeutic implications for affected subjects but would also allow for early detection or prevention of parathyroid malignancy in family members. For this reason genetic testing for germline *HRPT2* mutations is clinically indicated in most patients with sporadic parathyroid carcinoma.

Surgical management

The most effective treatment for parathyroid carcinoma is surgical and consists of *en-bloc* resection of the tumor mass with care to avoid rupture of the capsule, as this increases the chance of local seeding.^{1,21} Often, resection of the ipsilateral thyroid lobe and isthmus and dissection of the tracheoesophageal groove may be necessary. The recurrent laryngeal nerve may have to be resected if found to be involved. Locally involved lymph nodes should be excised but radical neck dissection is indicated only when there is spread to the anterior cervical nodes.²⁷

Since the initial intervention offers the best prospect for cure, pre-operative suspicion of parathyroid carcinoma and careful exploration of the four parathyroid glands is key. Frozen section for histology is often resorted to for intra-operative recognition.

One well recognized surgical complication in patients in whom the tumor is completely excised is the development of the "hungry bone syndrome."²⁸ The sudden postoperative withdrawal of PTH induces abrupt cessation of osteoclastic bone resorption without affecting osteoblastic activity. Consequently, an increased bone uptake of calcium, phosphate and magnesium is observed.

Risk factors for the syndrome include: large parathyroid adenomas, age > 60 years, and high pre-operative PTH levels, calcium and alkaline phosphatase. In high risk individuals careful vigilance for clinical symptoms of hypocalcaemia and close follow up of laboratory parameters are warranted during the immediate postoperative period. Treatment is with large doses of oral or intravenous calcium and oral calcitriol, at least initially.

Local recurrence as well as distant metastases occurring due to lymphatic and haematogenous spread may and do occur in parathyroid carcinomas. Since radiotherapy and chemotherapy are generally ineffective,⁶ surgery may also have a role in the palliative management of recurrent or metastatic disease, through the extirpation of lesions in the neck, lungs or liver providing symptomatic relief and reducing serum calcium and hormone levels in most patients.²⁹ The potential morbidity caused by these re-operations must be borne in mind.

Adjuvant therapy

Parathyroid carcinoma is not a radiosensitive tumour and the role of radiotherapy is generally restricted to neck irradiation after surgery for recurrence, in order to prevent re-growth. Use of either radiotherapy or chemotherapy should be considered only when a patient is not a candidate for surgery and hypercalcaemia cannot be controlled.

The role of chemotherapy in the management of parathyroid carcinoma is limited although there are scant reports of success with synthetic oestrogens, 5-fluorouracil, cyclophosphamide and dacarbazine-containing regimes. There have been reports supporting the use of immunotherapy in carcinomas where immunisation with human, modified human and bovine PTH peptides stimulated the

production of autoantibodies against human PTH giving rise to PTH-antibody immune complexes. This strategy has been successful in reducing hypercalcaemia, improving clinical status³⁰ and in one case it was even shown to reduce tumour load.⁶

Control of intractable hypercalcaemia

When the tumor is no longer amenable to surgical intervention, treatment becomes limited to the control of hypercalcaemia through hydration, calcimimetic agents or intravenous bisphosphonates.

Calcimimetics increase the sensitivity of the parathyroid gland calcium-sensing receptor.^{31,32} The longer-acting calcimimetic, cinacalcet (Sensipar®), has been approved by the United States Food and Drug Administration for the treatment of secondary hyperparathyroidism associated with renal failure and hypercalcaemia associated with parathyroid cancer.

Cinacalcet allosterically enhances the action of calcium ions at the parathyroid gland calcium receptors which belong to the superfamily of G protein-coupled receptors. Resulting from the effect at the parathyroid gland calcium receptors, serum levels of calcium decline.³³

Bisphosphonates such as pamidronate (approved by the United States Food and Drug Administration for hypercalcaemia of malignancy) have been reported to improve hypercalcaemia in individual cases of parathyroid carcinoma.^{34,35} One might predict that the more potent zoledronic acid, which is approved for use in hypercalcaemia of malignancy,³⁶ would also be effective in the treatment of hypercalcaemia due to parathyroid carcinoma.

Prognosis

Hypercalcaemia is the principal cause of morbidity and mortality from parathyroid carcinoma. The carcinomas grow slowly in most patients, but can occasionally be aggressive. The disease typically follows one of three courses: one third of patients are cured at initial or follow-up surgery, one third experience a recurrence after a prolonged disease-free survival but may be cured with re-operation, and one third experience a short and aggressive course.³⁷

Parathyroid carcinomas with locoregional extension at initial surgery have potential for recurrence. Aggressive surgical resection of recurrent carcinoma is beneficial for palliation of hypercalcaemia in selected patients. Ki-67 staining may be a valuable prognostic indicator as tumors with indices greater than 10% are more likely to recur in the early postoperative period. In an analysis of several studies, the combined 5- and 10-year survival rates for patients with parathyroid carcinomas varied from 50 to 70 and 13 to 35 percent respectively,¹ with a mean survival time of 6 to 7 years.¹

Conclusion

Albeit the morbidity imparted by the numerous surgical interventions and the more recent tracheostomy, three years since her original diagnosis, a concerted and persistent multidisciplinary effort has meant that our young patient is still capable of enjoying a reasonably good quality of life with her family and children.

Acknowledgements

We would like to thank Dr. Stephen Brincat MRCS, FRCP (Edin), FRCP (Lond), FRCR, Consultant Clinical Oncologist and

Chairman of the Department of Oncology, Sir Paul Boffa Hospital, Malta for his assistance and contribution in this case report.

Disclosure of Potential Conflicts of Interest

The authors declare that they have no financial interests to disclose and no other potential conflict of interest. There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported. This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

References

1. Obara T, Fujimoto Y. Diagnosis and treatment of patients with parathyroid carcinoma: an update and review. *World J Surg.* 1991;15:738-44.
2. Ruda JM, Hollenbeck CS, Stack BC. A systematic review of the diagnosis and treatment of primary hyperparathyroidism from 1995-2003. *Otolaryngol Head Neck Surg.* 2005;132:359.
3. Robert JH, Trombetti A, Garcia A, Pache JC, Herrmann F, Spiliopoulos A, et al. Primary hyperparathyroidism: can parathyroid carcinoma be anticipated on clinical and biochemical grounds? Report of nine cases and review of the literature. *Ann Surg Oncol.* 2005;12:526-32.
4. Levin KE, Galante M, Clark OH. Parathyroid carcinoma versus parathyroid adenoma in patients with profound hypercalcemia. *Surgery.* 1987;101:649-60.
5. Kebebew E, Arici C, Duh QY, Clark OH. Localization and reoperation results for persistent and recurrent parathyroid carcinoma. *Arch Surg.* 2001;136:878-85.
6. Betea D, Bradwell AR, Harvey TC, Mead GP, Schmidt-Gayk H, Ghaye B, et al. Hormonal and biochemical normalization and tumor shrinkage induced by anti-parathyroid hormone immunotherapy in a patient with metastatic parathyroid carcinoma. *J Clin Endocrinol Metab.* 2004;89:3413-20.
7. Shane E. Clinical review 122: Parathyroid carcinoma. *J Clin Endocrinol Metab.* 2001;86:485-493.
8. Anderson BJ, Samaan NA, Vassilopoulou-Sellin R, Ordonez NG, Hickey RC. Parathyroid carcinoma: features and difficulties in diagnosis and management. *Surgery.* 1983;94:906-15.
9. Fernandez-Ranvier GG, Jensen K, Khanafshar E, Quivey JM, Glastonbury C, Kebebew E, et al. Nonfunctioning parathyroid carcinoma: case report and review of literature. *Endocr Pract.* 2007;13:750-7.
10. Schantz A, Castleman B. Parathyroid carcinoma. A study of 70 cases. *Cancer.* 1973;31:600-5.
11. Bondeson L, Sandelin K, Grimelius L. Histopathological variables and DNA cytometry in parathyroid carcinoma. *Am J Surg Pathol.* 1993;17:820-9.
12. August DA, Flynn SD, Jones MA, Bagwell CB, Kinder BK. Parathyroid carcinoma: the relationship of nuclear DNA content to clinical outcome. *Surgery.* 1993;113:290-6.
13. Sandelin K, Auer G, Bondeson L, Grimelius L, Farnebo LO. Prognostic factors in parathyroid carcinoma: a review of 95 cases. *World J Surg.* 1992;16:724-31.
14. Leong SY, Cooper K, Leong FJWM. Chromogranin. Manual of Diagnostic Antibodies for Immunohistology. London: Greenwich Medical Media Ltd, 2003.
15. Farnebo F, Auer G, Farnebo LO, Teh BT, Twigg S, Aspenblad U, et al. Evaluation of retinoblastoma and Ki-67 immunostaining as diagnostic markers of benign and malignant parathyroid disease. *World J Surg.* 1999;23:68-74.
16. Lloyd RV, Carney JA, Ferreiro JA, Jin L, Thompson GB, Van Heerden JA, et al. Immunohistochemical analysis of the cell cycle-associated antigens Ki-67 and retinoblastoma protein in parathyroid carcinomas and adenomas. *Endocr Pathol.* 1995;6:279-87.
17. Vasef MA, Brynes RK, Sturm M, Bromley C, Robinson RA. Expression of cyclin D1 in parathyroid carcinomas, adenomas, and hyperplasias: a paraffin immunohistochemical study. *Mod Pathol.* 1999;12:412-6.
18. Hundahl SA, Fleming ID, Fremgen AM, Menck HR. Two hundred eighty-six cases of parathyroid carcinoma treated in the U.S. between 1985-1995: a National Cancer Data Base report. The American College of Surgeons Commission on Cancer and the American Cancer Society. *Cancer.* 1999;86:538-44.
19. Chow E, Tsang RW, Brierley JD, Filice S. Parathyroid carcinoma--the Princess Margaret Hospital experience. *Int J Radiat Oncol Biol Phys.* 1998;41:569-72.
20. Chung DC. Cyclin D1 in human neuroendocrine: tumorigenesis. *Ann N Y Acad Sci.* 2004;1014:209-17.
21. Lumachi F, Bassi SM, Bassi U. Parathyroid cancer: etiology, clinical presentation and treatment. *Anticancer Res.* 2006;26:4803-7.
22. Temmim L, Sinowatz F, Hussein IW, Al-Sanea O, El-Khodary H. Intrathyroidal parathyroid carcinoma: a case report with clinical and histological findings. *Diagn Pathol.* 2008;3:46.
23. Hsi ED, Zukerberg LR, Yang WI, Arnold A. Cyclin D1/PRAD1 expression in parathyroid adenomas: an immunohistochemical study. *J Clin Endocrinol Metab.* 1996;81:1736-9.
24. Hewitt KM, Sharma PK, Samowitz W, Hobbs M. Aberrant methylation of the HRPT2 gene in parathyroid carcinoma. *Ann Otol Rhinol Laryngol.* 2007;116:928-33.
25. Carpten JD, Robbins CM, Villablanca A, Forsberg L. HRPT2, encoding parafibromin, is mutated in hyperparathyroidism-jaw tumor syndrome. *Nat Genet.* 2002;32:676.
26. Shattuck TM, Valimaki S, Obara T, Gaz RD. Somatic and germ-line mutations of the HRPT2 gene in sporadic parathyroid carcinoma. *N Engl J Med.* 2003;349:1722.
27. Cohn K, Silverman M, Corrado J, Sedgewick C. Parathyroid carcinoma: the Lahey Clinic experience. *Surgery.* 1985;98:1095-100.
28. Farese S. The hungry bone syndrome- an update. *Ther Umsch.* 2007;64:277-80.
29. Wynne AG, van Heerden J, Carney JA, Fitzpatrick LA. Parathyroid carcinoma: clinical and pathologic features in 43 patients. *Medicine (Baltimore).* 1992;71:197-205.
30. Bradwell AR, Harvey TC. Control of hypercalcemia of parathyroid carcinoma by immunisation. *Lancet.* 1999;353:370-3.
31. Collins MT, Skarulis MC, Bilezikian JP, Silverberg SJ, Spiegel AM, Marx SJ. Treatment of hypercalcemia secondary to parathyroid carcinoma with a novel calcimimetic agent. *J Clin Endocrinol Metab.* 1998;83:1083.
32. Silverberg SJ, Rubin MR, Faiman C, Peacock M, Shoback DM, Smallridge RC, et al. Cinacalcet hydrochloride reduces the serum calcium concentration in inoperable parathyroid carcinoma. *J Clin Endocrinol Metab.* 2007;92:3803.
33. Kebig A, Mohr K. Cinacalcet - an allosteric enhancer at the Ca^{2+} receptor. *Dtsch Med Wochenschr.* 2008;113:1681-3.
34. de Papp AE, Kinder B, LiVolsi V, Gupta SM, Stewart AF. Parathyroid carcinoma arising from parathyroid hyperplasia: autoinfarction following intravenous treatment with pamidronate. *Am J Med.* 1994;97:399.
35. Newrick PG, Braatvedt GD, Webb AJ, Sheffield E, Corrall RJ. Prolonged remission of hypercalcemia due to parathyroid carcinoma with pamidronate. *Postgrad Med J.* 1994;70:231.
36. Major P, Lortholary A, Hon J, Abdi E, Mills G, Menssen HD, et al. Zoledronic acid is superior to pamidronate in the treatment of hypercalcemia of malignancy: a pooled analysis of two randomized controlled clinical trials. *J Clin Oncol.* 2001;19:558.
37. Hoelting T, Weber T, Werner J, Herfarth C. Surgical treatment of parathyroid carcinoma (Review). *Oncol Rep.* 2001;8:931.

Erratum

The following case report, published in March 2010, erroneously omitted the acknowledgements below:

Vella C, Pullicino E, Fearne C. Collagenous gastritis: a rare cause of anaemia in childhood. *Malta Medical Journal.* 2010;22(1):34-6.

Acknowledgements

Dr. James Degeatano, Consultant Histopathologist, Department of Pathology, Mater Dei Hospital, Malta for the interpretation of the histology and preparation of the biopsy pictures.

Dr. Ali Safraz, Consultant Histopathologist, St. James' Hospital, Malta for the original histology report and the biopsy specimen.