

Two Cases of Medullary Thyroid Carcinoma

M Jong,*^{MB Bch (Hons Belf), MRCP (UK)}, F X Sundram,**^{FAMS, MSc (Nucl Med), DMRT}

Abstract

Introduction: Medullary thyroid carcinoma (MTC) is a rare thyroid malignancy but accounts for a significant mortality. We present 2 cases of MTC and review the literature regarding its management and genetic screening. **Clinical Picture:** Patient 1 presented after a routine health screening and subsequently was found to have a germline mutation for MEN 2A. Patient 2 presented with sweating irritability and a thyroid mass which illustrates the progressive relentless nature of the disease and highlights current imaging practice. **Treatment:** Both patients underwent extensive surgery and received postoperative ablative dose of radioactive iodine. Patient 2 also had a large dose I-131 MIBG therapy and further surgery. **Outcome:** In Patient 1, postoperative calcitonins remained elevated indicating residual disease. Patient 2 underwent further radioguided surgery; however, his postoperative calcitonins remained elevated. **Conclusion:** MTC can be relentless. Routine genetic screening of all patients with MTC, Tc-99m pentavalent (V) DMSA imaging, near total thyroidectomy with routine central neck dissections and removal of all lymph nodes in the central neck compartment should be performed.

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Case Reports

Patient 1

A 44-year-old Indian man was found to have a raised carcinoembryonic antigen (CEA) (49.5 µg/L) [normal range <5.1 µg/L] detected on routine medical examination in February 2000. His past medical history included asthma, chronic anal fissure and haemorrhoids, cervical spondylosis and mild hypercholesterolaemia. He had undergone many investigations to trace the source of this raised CEA at his referring hospital. Oesophago-gastro-duodenoscopy, barium enema, colonoscopy, ultrasound of the abdomen and computed tomographic (CT) scan of his abdomen and pelvis were all essentially non-contributory. His prostate specific antigen (PSA) was also normal at 0.5 µg/L (normal <2.6 µg/L). It was only then that a thyroid mass was noted. An ultrasound scan of the thyroid revealed a hypoechoic mass in both thyroid lobes with punctate calcifications within. A CT scan of the chest and neck showed left cervical lymphadenopathy with no evidence of lung or mediastinal lymph nodes. An open biopsy of one of these nodes revealed medullary thyroid carcinoma (MTC). Tc-

99m pentavalent (V) DMSA scan was performed, which revealed a small focus of increased tracer at the lower right lobe and the upper left lobe as well as tracer uptake in the left cervical lymph node chain, suggestive of a MTC particularly involving the left lobe and cervical lymph nodes.

Preoperatively, his intact parathyroid hormone (PTH) was 36.5 pg/mL (normal range 12.0 to 72.0 pg/mL) and calcitonin was >800 pg/mL (normal range <20 pg/mL).

On balance, his 24-hour urinary catecholamines were deemed to be normal. Adrenaline 0.19 mmol/24 hours (normal range 0.02 to 0.10 mmol/24 hours), noradrenaline 0.16 µmol/24 hours (normal range 0.20 to 0.44 µmol/24 hours), dopamine 3.91 µmol/24 hours (normal range 1.0 to 3.7 µmol/24 hours), metanephrine 1.14 µmol/24 hours (normal range <1.79 µmol/24 hours) and normetephrine 2.26 µmol/24 hours (normal range <4.13 µmol/24 hours).

Two months after his initial health screen, he underwent a total thyroidectomy, bilateral functional neck dissection and central compartment clearance. Division of the left accessory nerve was necessary because of the fibrous

* Registrar in Endocrinology
Department of General Medicine
Tan Tock Seng Hospital

** Head and Senior Consultant
Department of Nuclear Medicine
Singapore General Hospital

Address for Reprints: Dr Michelle Jong, Registrar in Endocrinology, Department of General Medicine, Tan Tock Seng Hospital, 11 Jalan Tan Tock Seng, Singapore 308433.

E-mail: michelle_jong@notes.ttsh.gov.sg

scarring from a previous open biopsy. The nerve was re-anastomosed. Histopathology showed multiple foci of MTC in the thyroid with jugular nodes, left and right paratracheal nodes as well as level 2 to 5 nodes being positive for tumour. He was placed on thyroxine replacement.

Despite having no family history of note, he was screened and found to have a germline RET-proto-oncogene mutation in codon 634. His relatives are yet to be screened as the cost is prohibitive to them.

Two months postoperatively, his repeat urinary catecholamines were normal but his calcitonin remained elevated at 36.9 pg/mL (normal range 3.0 to 26.0 pg/mL).

Patient 2

A 44-year-old Sikh man presented in November 1996 to his company doctor with complaints of weight loss, sweaty palms and irritability. He was noted to have a thyroid mass and was diagnosed as having a thyroid malignancy. Preoperative Tc-99m sestamibi and Tc-99m (V) DMSA scans (Figs. 1 & 2) showed nodes in the mediastinum. He underwent a total thyroidectomy and right neck node dissection was done in December 1996; unfortunately, the mediastinal nodes were not removed at the time. Histology revealed MTC with lymph node involvement from level 1 to 5. His calcitonin remained at >79 pg/mL (normal range 3.0 to 26.0 pg/mL). He was given an outpatient ablative dose of radioactive iodine. He was commenced on 200 mcg of thyroxine. Further Tc-99m sestamibi and Tc-99m (V) DMSA scans postoperatively (Figs. 3 & 4) showed residual nodal disease in the mediastinum. Hence, in September 1997, he underwent excision of the nodes in the mediastinum. Histology confirmed MTC in 8 nodes. Further Tc-99m sestamibi whole scan revealed two mediastinal nodes and the serum calcitonin still elevated at >79 pg/mL, indicating that the patient still had residual disease. The patient declined radiotherapy or CT post procedure. Repeat scans from 1998 to 2000, with Tc-99m (V) DMSA and I-131 MIBG, showed progression of disease. Hence, he was admitted for a large dose I-131 MIBG therapy. The scans revealed disease in the neck and mediastinum. His serum calcitonin remained elevated at >500 pg/mL.

In view of the residual disease in the thorax, a thoracic surgeon operated on the patient in December 2000 4 hours after an injection of scan dose of Tc-99m (V) DMSA. The scan done preoperatively helped to localise the disease. The nuclear medicine physician was also in the operating theatre with a gamma-probe to guide the surgeon to the sites of the disease in the thorax (radioguided surgery). A postoperative Tc-99m (V) DMSA scan showed no residual disease in the chest (Fig. 5). Subsequently, from April to

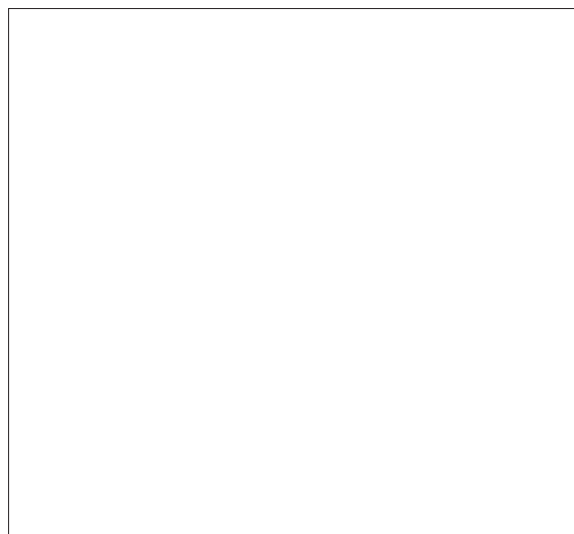


Fig. 1. Case 2—preoperative Tc-99m sestamibi scan shows disease in the chest and neck.



Fig. 2. Case 2—preoperative DMSA (V) scans shows disease in the chest and neck but more intense tracer uptake as compared to Figure 1.

June 2001, the patient was given a course of external beam radiation to the lower neck and mediastinum in order to prevent local recurrence. Although the patient remained clinically well, the serum calcitonin was still elevated at 600 pg/mL (normal range 3.0 to 26.0 pg/mL).

The patient finally consented to be screened for a RET mutation. The results showed a silent mutation in codon 769 (exon 13, CTT to CTG) coding for leucine.

Discussion

Although MTC is a rare thyroid malignancy, it accounts for significant mortality.¹⁻³ It arises in the thyroid C cells which produce both CEA as well as calcitonin. CEA can be demonstrated within the C cells through all stages of

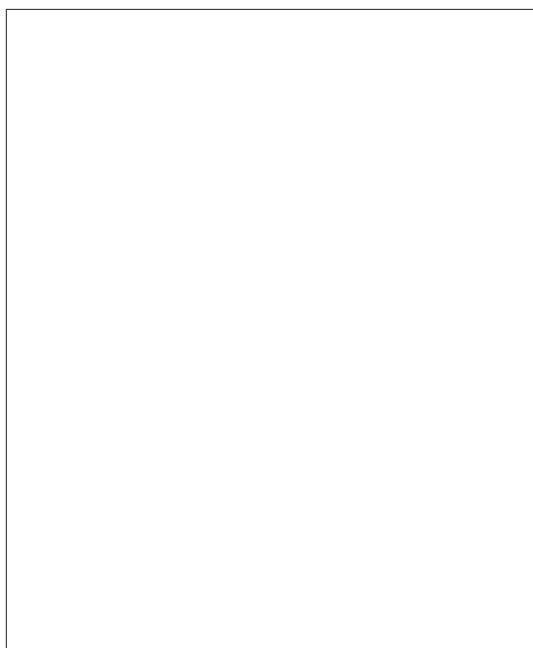


Fig. 3. Case 2—postoperative Tc-99m sestamibi scan.

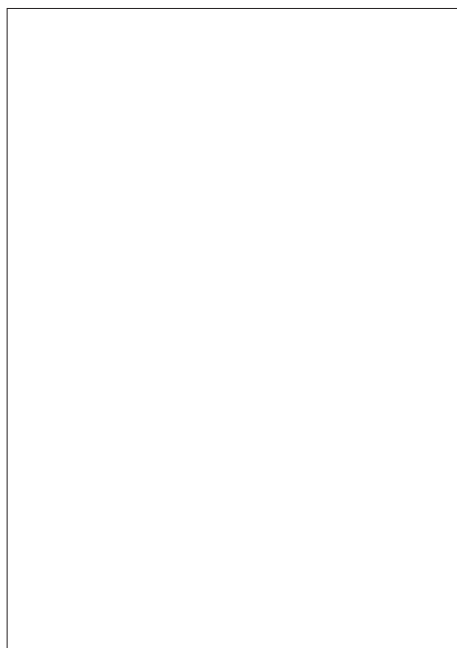


Fig. 5. Case 2—most recent DMSA (V) scan done after recent surgery showing clearance of the tumour from the thorax (slight increase in tracer in the midline is reflective of recent surgery).

progression of MTC,⁴ yet it does not readily come to mind when faced with a raised CEA on routine screening during medical check-ups in otherwise asymptomatic individuals, as demonstrated in Patient 1. Calcitonin and CEA have similar homogenous distribution, being present among cells in the medullary carcinoma.

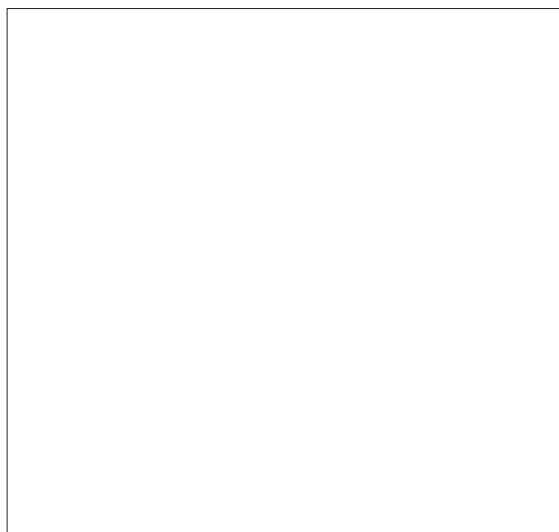


Fig. 4. Case 2—postoperative DMSA (V) scans.

Once the diagnosis of MTC has been made, the importance of surgery cannot not be overemphasised, as it represents the only accepted method for a potentially curative treatment of MTC. The extensive excision that these patients underwent should be routine, as the recognition of high rate of regional nodal involvement has led to routine central and bilateral functional neck dissection with central compartment clearance being strongly recommended for patients undergoing thyroidectomy of MTC.^{5,6} Patients who have had total thyroidectomy with cervical lymph node clearance require fewer difficult re-operations for persistent or recurrent MTC.⁷⁻⁹ Systematic lymphadenectomy, using compartment orientated microdissection of cervico-mediastinal lymph nodes, is thought to decrease recurrence and increase the chances of normalisation of postoperative calcitonin levels.^{10,11} Still, patients with MTC often have to undergo repeated operations as demonstrated in Patient 2. Radioguided surgery with Tc-99m (V) DMSA scan can detect metastases with a size of 5 mm in diameter and this can be employed in patients with recurrent MTC by means of an intraoperative gamma probe examination which is able to localise over 30% more tumour lesions when compared to conventional preoperative imaging modalities and surgical findings.¹² This technique has indeed been proven useful in Patient 2.

Imaging modalities have changed over the years. It has been recognised that while I-131 is poor at identifying disease and its metastases, sestamibi is a great improvement to I-131. However, we used the Tc-99m pentavalent (V) DMSA scan which contributes specificity to diagnose MTC of thyroid and metastatic lesions^{13,14} and is clearly superior to MIBI in the follow-up of patients with MTC.^{15,16} Comparison of scans taken pre- and postoperatively with

sestamibi and DMSA showed better “pick up” of metastases by the DMSA scans. Improved imaging techniques help us to deal with the problem of persistent hypercalcaemia post primary surgery. If the scans show more metastases, further surgery will be offered. If the scans are clear and hypercalcaemia is asymptomatic, then the patient should just be observed.¹⁷

Patient 1 highlights the exciting developments that have taken place in the changing practices of this condition since the identification of the RET gene in 1993. This segregated the disease phenotype in MEN 2, familial medullary thyroid carcinoma (FMTC) and sporadic. Patient 1 did not have any significant family history which would have led us to suspect that he would have a germline mutation. However, among the “sporadic” MTCs, up to 6% of cases may be unsuspected familial cases.¹⁸ Germline mutations in the RET proto-oncogene, which code for a receptor tyrosine kinase, cause MEN 2.¹⁹ Mutations in 1 to 5 cysteine codons (609, 611, 618 and 620 in exon 10 and 634 in exon 11), which encode part of the extracellular cysteine-rich domain, are found in the majority of families with FMTC and MEN 2A.¹⁸ Codon 634 mutations, as found in Patient 1, are by far the most common mutation associated with MEN 2A occurring in 85% MEN 2A families with RET mutations.¹⁸

As Patient 1 bears the mutation at codon 634, there is a strong likelihood that he will develop pheochromocytomas and hyperparathyroidism.¹⁸ Mutations of the RET proto-oncogene have been identified in the majority of MEN 2 families (92% and more) and can now serve both as clinical confirmation of the clinical diagnosis of and the predictive test for the syndrome.¹⁸ Previous biochemical screening protocols, such as serum calcitonin levels as a measure of increased C cell bulk or occult MTC, provided adequate diagnostic information but false positive and negative have been well documented.^{20,21} In a known MEN 2 family, individuals at risk of the disease including first degree relatives of a RET mutation positive should undergo DNA testing before any surgical intervention is considered.¹⁸ Although screening for a pheochromocytoma proved negative in Patient 1, he remains at risk for developing this at a later stage and therefore the need for continuous monitoring and screening. There is sufficient data to estimate that the probability of a RET-germline-mutation-negative individual with MTC representing a MEN 2 case is 0.5%.¹⁸

Patient 1 has 2 children who may be at risk and may have in effect “missed the boat” with regards to a “cure”, as we know that families with the MEN 2A syndrome have an earlier, more aggressive form of MTC, which has led to the recommendation for a thyroidectomy by 5 years of age.²² In fact, MTC has been found to be present in gene-positive patients as early as the age of 2 years.²³ In one series, all

MEN gene carriers revealed C-cell hyperplasia and almost all of them developed multifocal MTC.²⁴ Patient 2 showed a RET mutation at Leu 769 (CTT CTG) in exon 13. This is likely not to be significant as previous studies have shown it to be present in up to 40% of healthy individuals.²⁵

Screening for mutations to detect occult MEN 2 families²⁶ and early treatment (total thyroidectomy with central neck lymph node clearance) have nearly a 100% cure rate.^{7,27,28}

Both our patients have to be classified as having a poorer prognosis as the age of presentation and TNM (tumour, node and metastasis) staging are independent predictors of survival.^{7,29} Bone metastases were correlated with a worse prognosis than distant metastases to soft tissues. As MTC is a relatively slow-growing tumour, there is an excess of mortality even after 10 years of diagnosis of MTC.²⁹ Three groups whose risk after 10 years did not exceed that of the general population include:

- 1) those whose MTC is detected through genetic screening as an at risk member,
- 2) those whose tumour size is <1 cm, or
- 3) those with early stage of the disease at the time of diagnosis.³⁰

Both our patients presented with extremely high preoperative calcitonin levels plus lymph node involvement in more than 2 compartments, thus predicting a failure for postoperative normalisation.^{8,20} Patients with postoperative hypercalcaemia without clinical or radiological evidence of residual tumour after apparently curative surgery may enjoy long-term survival but have occult MTC.⁷

In conclusion, routine genetic screening, imaging with Tc-99m pentavalent (V) DMSA, total thyroidectomy with bilateral functional neck dissection and central compartment clearance, with an aim to reduce the significant mortality, should ideally be performed on all patients found to have MTC.

REFERENCES

1. Gilliland F D, Hunt W C, Morris D M, Key C R. Prognostic factors for thyroid carcinoma: a population based study of 15,698 cases from surveillance. Epidemiology and end results surveillance program 1973-1991. *Cancer* 1997; 79:564-73.
2. Hundahl S A, Fleming A M, Menck H R. A national cancer database report on 53,856 cases of thyroid carcinoma treated in the US 1985-1995. *Cancer* 1998; 83:2638-48.
3. Marsh D J, Leoroy D L, Robinson B G. Medullary thyroid carcinoma; recent advances and management update. *Thyroid* 1995; 5:407-20.
4. Mendelsohn G, Wells S A Jr, Baylin S B. Relationship of tissue carcinoembryonic antigen and calcitonin to tumour virulence in medullary thyroid carcinoma. An immunohistochemical study in early, localized, and virulent disseminated stages of the disease.

- Cancer 1984; 54:657-62.
5. Randolph G W, Maniar D. Medullary thyroid carcinoma of the thyroid. *Cancer Control* 2000; 7:253-61.
 6. Bi L, Lu B. Advances in the diagnosis and management of thyroid neoplasms. *Curr Opin Oncol* 2000; 12:54-9.
 7. Kebebew E, Ituarte P H G, Siperstein A E, Duh Q Y, Orlo H C. Medullary thyroid carcinoma. Clinical characteristics, treatment, prognostic factors and a comparison of clinical staging. *Cancer* 2000; 88:1139-48.
 8. Cohen R, Campos J M, Salaun C, Heshmati H M, Kraimps J L, Proye C, et al. Preoperative calcitonin levels are predictive of tumour size and postoperative normalization in medullary thyroid carcinoma. *J Clin Endocrinol Metab* 2000; 85:919-22.
 9. Fleming J B, Lee J E, Bouvet M, Schultz P N, Sherman S I, Sellin R V, et al. Surgical strategy for the treatment of medullary thyroid carcinoma. *Ann Surg* 1999; 230:697-707.
 10. Burh H J, Kallinowski F, Raue F, Frank-Raue K, Herfarth C. Microsurgical neck dissection for metastasizing medullary thyroid carcinoma. *Eur J Surg Oncol* 1995; 21:195-7.
 11. Dralle H, Damm I, Scheumann G F, Kotzerke J, Kupsch E, Geerlings H, et al. Compartment-orientated microdissection of regional lymph nodes in medullary thyroid carcinoma. *Surg Today* 1994; 24:112-21.
 12. de Labriolle-Vaylet C, Cattani P, Sarfati E, Wioland M, Billotey C, Brocheriou C, et al. Successful surgical removal of occult metastases of medullary thyroid carcinoma recurrences with the help of immunoscintigraphy and radioimmunoguided surgery. *Clin Cancer Res* 2000; 6:363-71.
 13. Shikare S, Bashir K, Menon P S, Bapat R D, Tilve G H. Detection of medullary thyroid carcinoma with liver metastases using 99m Tc DMSA (V) scintigraphy. *J Postgrad Med* 1995; 41:12-3.
 14. Adelet I, Kocak M, Oguz H, Alagol F, Cantez S. Determination of medullary thyroid carcinoma metastases by 201TI, 99Tcm (V) DMSA, 99T-MIBI and 99T-tetrafosmin. *Nucl Med Commun* 1999; 20:353-9.
 15. Ugur O, Kostakglu L, Guler N, Caner B, Uysal U, Elahi N, et al. Comparison of 99m Tc(V)-DMSA, 201TI and 99m-Tc-MIBI imaging in the follow-up of patients with medullary thyroid carcinoma. *Eur J Nucl Med* 1996; 23:1367-71.
 16. Yen T C, King K L, Yang A H, Liu R S, Yeh S H. Comparative radionuclide imaging of metastatic insular carcinoma of the thyroid; value of Tc-99m(V) DMSA. *J Nucl Med* 1996; 37:78-80.
 17. Learoyd D L, Delbridge L W, Robinson B G. Multiple endocrine neoplasia. *Aust N Z J Med* 2000; 30:675-82.
 18. Wohllk N, Cote G J, Bugalho M M. Relevance of RET proto-oncogene mutations in sporadic medullary thyroid carcinoma. *J Clin Endocrinol Metab* 1996; 81:3740-5.
 19. Eng C, Clayton D, Schuffenecker I, Lenoir G, Cote G, Gagel R F, et al. The relationship between specific RET proto-oncogene mutations and disease phenotype in multiple endocrine neoplasia type 2. *JAMA* 1996; 276:1575-9.
 20. Lips C J, Landsvater R M, Hoppener J W, Geerdink R A, Blijham G, van Veen J M, et al. Clinical screening as compared with DNA analysis in families with multiple endocrine neoplasia type 2A. *N Engl J Med* 1994; 331:828-35.
 21. Marsh D J, McDowall D, Hyland V J, Andrew S D, Schnitzler M, Gaskin E L, et al. The identification of false positive responses to the pentagastrin stimulation test in RET mutation negative members of MEN 2A families. *Clin Endocrinol* 1996; 44:213-220.
 22. Gill J R, Reyes-Mugica M, Iyengar S, Kidd K K, Touloukian R J, Smith C, et al. Early presentation of metastatic medullary carcinoma in multiple endocrine neoplasia, type IIA: implications for therapy. *J Pediatr* 1996; 129:459-64.
 23. van Heurn L W, Schaap C, Sie G, Haagen A A, Gerver W J, Freling G, et al. Predictive DNA testing for multiple endocrine neoplasia 2: a therapeutic challenge of prophylactic thyroidectomy in very young children. *J Pediatr Surg* 1999; 34:568-71.
 24. Hinze R, Holzhausen H J, Gimm O, Dralle H, Rath F W. Primary hereditary medullary thyroid carcinoma. *Virchows Arch* 1999; 433:203-8.
 25. Ceccherini I, Hofstra R M, Luo Y, Stulp R P, Barone V, Stelwagen T, et al. DNA polymorphisms and conditions for SSCP analysis of the 20 exons of the ret proto-oncogene. *Oncogene* 1994; 9: 3025-9.
 26. Huang C N, Wu S L, Chang T C, Huang S H, Chang T J. RET proto-oncogene mutations in patients with apparently sporadic medullary thyroid carcinoma. *J Formos Med Assoc* 1998; 97:541-6.
 27. Krueger J E, Maitra A, Albores-Saavedra J. Inherited medullary microcarcinoma of the thyroid. A study of 11 cases. *Am J Surg Pathol* 2000; 24:853-8.
 28. Girelli M E, Bellastella A, Colantuoni V. Germline and somatic mutations of the RET proto-oncogene in apparently sporadic medullary thyroid carcinomas. *Mol Cell Endocrinol* 1998; 135: 51-7.
 29. Girelli M E, Nacamulli D, Pelizzo M R, De Vido D, Mian C, Piccolo M, et al. Medullary thyroid carcinoma: clinical features and long-term follow-up of 78 patients treated between 1969-1986. *Thyroid* 1998; 8:517-23.
 30. Bergholm U, Berstom R, Ekblom A. Long term follow-up of patients with medullary thyroid carcinoma of the thyroid. *Cancer* 1997; 79:132-8.