CASE REPORT

Multiple endocrine neoplasia 2B: delayed presentation, rapid diagnosis

Karthik Balachandran,¹ Sadishkumar Kamalanathan,¹ S Gopalakrishnan,²
K Murugananadham³

¹Department of Endocrinology, Jawaharlal Institute of Post Graduate Medical Education & Research, Puducherry, India
²Department of ENT, Jawaharlal Institute of Post Graduate Medical Education & Research, Puducherry, India
³Department of Urology, Jawaharlal Institute of Post Graduate Medical Education & Research, Puducherry, India

Correspondence to
Dr Sadishkumar Kamalanathan,
sadishkk@gmail.com

SUMMARY

Multiple endocrine neoplasia (MEN) refers to the synchronous or metachronous development of tumours in two or more endocrine organs. MEN 2B is associated with medullary thyroid carcinoma and pheochromocytoma along with classic morphological features such as marfanoid habitus and mucosal neuromas. Dominantly inherited germline mutations involving the RERanged during Transfection (RET) proto-oncogene are responsible. Affected patients usually present in childhood with thyroid mass or gastrointestinal symptoms. We describe the case of a 28-year-old man who presented to us with metastatic medullary thyroid carcinoma. He lacked the classic marfanoid habitus, but had mucosal neuromas and thickened corneal nerves. Whole-body metaiodobenzyl guanidine scan (MIBG) showed tracer uptake in adrenal and thyroid-confirming pheochromocytoma and medullary thyroid carcinoma. This case exemplifies the late presentation of multiple endocrine neoplasia 2B and emphasises the need to screen all cases of medullary thyroid carcinoma for pheochromocytoma.

BACKGROUND

Multiple endocrine neoplasia type 2B is the rarest of the inherited causes of medullary thyroid carcinoma (MTC). Since MEN 2B is predominantly a disease of childhood, physicians often fail to suspect it in adults with medullary carcinoma. The rarity and lack of familiarity with its lesser-known features (like thickened corneal nerves) compound the problem. Furthermore, the associated pheochromocytoma can be asymptomatic. The failure to diagnose pheochromocytoma in MEN 2B can lead to intraoperative hypertensive crisis during a surgery for MTC. Hence all patients with medullary carcinoma of thyroid should undergo screening for pheochromocytoma to rule out MEN 2B.

Two tests help in rapid confirmation of the diagnosis: Slit-lamp examination and whole-body metaiodobenzyl guanidine scan (MIBG). While slit-lamp examination shows thickened corneal nerves, MIBG scan shows simultaneous tracer uptake in thyroid and adrenal gland—in the presence of MCT and pheochromocytoma. Thus these tests offer a one-step confirmation of MEN 2B.

CASE PRESENTATION

A 28-year-old man presented to us with swelling in front of the neck since 3 years. The patient was apparently asymptomatic till the age of 25 years. The swelling had gradually increased in size and he

had come to us with cosmetic concerns. There was no voice change or difficulty in swallowing. There were no paroxysms of sweating or palpitation. He did not have diarrhoea or any other gastrointestinal symptoms. The patient had no family history of similar neck swelling. After examination, he was found to have firm thyromegaly with enlargement of both lobes of thyroid. No nodules or neck nodes were palpable. The patient also had thick bumpy lips and mucosal neuroma involving the vermilion border of the upper lip (figure 1A). Slit-lamp evaluation showed hypertrophic medullated corneal nerves (figure 1B). He had normal blood pressure during the office visit. The patient was admitted for suspected multiple endocrine neoplasia. During the hospital stay, the patient was found to have labile hypertension.

INVESTIGATIONS

Serum calcitonin level was grossly elevated (1363.2 pmol/l [normal value <48 pmol/l]) and plasma-free metanephrine was 1318.2 pmol/l [normal value <456 pmol/l]) values were elevated. Contrast-enhanced CT adrenal was done which showed a well-defined enhancing lesion in the right adrenal gland, suggestive of pheochromocytoma. MIBG scan was done which showed avid tracer uptake in the right adrenal and thyroid (figure 2). This confirmed the presence of medullary thyroid carcinoma and pheochromocytoma. A diagnosis of multiple endocrine neoplasia type 2 B was made.

DIFFERENTIAL DIAGNOSIS

The clinical profile points to the diagnosis of MEN 2B in this case. The presence of mucosal neuromas and thickened corneal nerves in a case of medullary thyroid carcinoma and pheochromocytoma clinch the diagnosis.

TREATMENT

The patient was started on prazosin (competitive α blocker). He had a paradoxical worsening of hypertension and hence prazosin was changed to phenoxylbenzamine (non-competitive α blockade). Laparoscopic right adrenalectomy was done followed by total thyroidectomy with radical lymph node dissection (clearance of nodes from level II to level V along with central lymph nodes). There was no mediastinal node involvement. Unfortunately, during surgery the tumour was found unresectable as it had involved the right recurrent laryngeal nerve. Hence debulking was done.

To cite: Balachandran K, Kamalanathan S, Gopalakrishnan S, et al. *BMJ Case Rep* Published online: [please include Day Month Year] doi:10.1136/bcr-2013-009185

Figure 1 (A) Figure showing mucosal neuroma.(B) Slit-lamp examination showing thickened corneal nerves.

OUTCOME AND FOLLOW-UP

The patient underwent adjuvant radiotherapy. Adjuvant chemotherapy was not given, as the patient was asymptomatic. He is on regular follow-up, and postoperative calcitonin levels have fallen.

DISCUSSION

Inherited medullary thyroid carcinoma is known to occur in three settings: MEN 2A, MEN 2B and familial medullary thyroid carcinoma (FMT). Among the causes of inherited MTC, MEN 2B is the least common occurring in less than 5% of cases. It is also the earliest to present and has the worst prognosis with an average life expectancy of 30 years. Hence current guidelines recommend DNA analysis of the proband and the kindred for RET

proto-oncogene mutations. All individuals harbouring the RET gene mutation require prophylactic thyroidectomy, while the timing of surgery is dictated by the specific mutation present.¹

In 50% of patients with MEN 2B, pheochromocytoma may be asymptomatic. Failure to recognise concurrent pheochromocytoma can lead to intraoperative hypertensive crisis in a patient operated for medullary thyroid carcinoma.² Thus all patients with medullary carcinoma of thyroid require biochemical screening for pheochromocytoma. An alternative approach is to test these patients for RET proto-oncogene mutations and subject them to pheochromocytoma screening if found positive.

Our patient had mucosal neuromas but lacked marfanoid habitus. He also had thickened medullated corneal nerves, a pathognomonic feature of MEN2B.³ Although certain systemic diseases are associated with thickened corneal nerves, none of them are associated with medullary carcinoma. Hence a slit-lamp evaluation of patients with suspected medullary carcinoma of thyroid offers an easy and rapid way to increase the pretest probability of MEN2B.

Current standard of care for patients with MEN2B dictates the direct DNA analysis of all patients for RET proto-oncogene mutations. If the proband is found positive, genetic screening for all first-degree relatives and children is required. The idea is to detect the disease at the stage of C-cell hyperplasia and hence to prevent mortality due to MTC. However this screening is not commonly available in developing countries and the clinicians often have to make do with biochemical tests. Annual screening with plasma metanephrines and pentagastrin-stimulated calcitonin is another option.²

The prognosis of medullary carcinoma is worst in the setting of MEN2B. However geographical differences exist in this process. A recent review has shown the relatively good prognosis of medullary carcinoma in Japanese patients, leading to the conjecture that Asians with MEN 2B have a better prognosis than the Western population.⁴ However as the disease is rare and that no studies exist, it is difficult to corroborate.

Multiple endocrine neoplasia can be associated with diarrhoea due to high calcitonin level or constipation and abdominal colic due to intestinal ganglioneuromas. Gastrointestinal symptoms are the most common presenting feature in children.⁵ Our patient however did not have any gastrointestinal symptoms.

MIBG scanning is an attractive option for detection of MEN 2B, as other thyroid masses do not show tracer uptake. The simultaneous increased MIBG tracer uptake in both thyroid and adrenal confirms the diagnosis of MEN 2, although the sensitivity is poorer than that for sporadic lesions.⁶ However, it must be borne in mind that biochemical evaluation is the mainstay for the diagnosis of pheochromocytoma and MTC in MEN2, and MIBG corroborates the confirmation.

Figure 2 Metaiodobenzyl guanidine scan showing uptake showing concurrent uptake of tracer by thyroid and adrenal confirming medullary carcinoma and pheochromocytoma.

Learning points

- ▶ All patients with medullary carcinoma of thyroid should undergo biochemical evaluation for pheochromocytoma, regardless of symptoms, blood pressure or age of presentation.
- ▶ Slit-lamp examination to detect thickened corneal nerves offers a simple diagnostic test for multiple endocrine neoplasia 2B.
- ▶ Metaiodobenzyl guanidine scan can simultaneously detect medullary thyroid carcinoma and pheochromocytoma and should be considered if available.

Acknowledgements We acknowledge the Department of Ophthalmology, Nuclear Medicine and Radiotherapy, JIPMER Puducherry for help in the management of the case.

Competing interests None.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

- 1 Kameyama K, Takami H. Medullary thyroid carcinoma: nationwide Japanese survey of 634 cases in 1996 and 271 cases in 2002. *Endocrine J* 2004;51:453–6.
- 2 Longo DL, Harrison TR. *Harrison's principles of internal medicine*. 18th edn. New York: McGraw-Hill, 2012.
- 3 Melmed S, Williams RH. *Williams textbook of endocrinology*. 12th edn. Philadelphia: Elsevier/Saunders, 2011.
- 4 Moline J, Eng C. Multiple endocrine neoplasia type 2: an overview. *Genet Med* 2011;13:755–64.
- 5 Parker DG, Robinson BG, O'Donnell BA. External ophthalmic findings in multiple endocrine neoplasia type 2B. *Clin Exp Ophthalmol* 2004;32:420–3.
- 6 Van der Harst E, De Herder WW, Bruining HA, *et al.* [(123)I] metaiodobenzylguanidine and [(111)In]octreotide uptake in benign and malignant pheochromocytomas. *J Clin Endocrinol Metab* 2001;86:685–93.

Copyright 2013 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow