

## Multiple endocrine neoplasia type 2A



**Department of Medicine, Division of Endocrinology and Metabolism, Johannesburg Hospital**  
**A M Klisiewicz, MB BCh, FCP (SA), MMed (Int Med)**  
**F J Raal, FRCPC, FCP (SA), MMed (Int Med), PhD**

**Department of Chemical Pathology, Johannesburg Hospital**  
**J Paiker, MB BCh, FCPATH, DipPEC**

**Division of Anatomical Pathology, School of Pathology, University of the Witwatersrand and National Health Laboratory Service, Johannesburg**  
**S J Naylor, BSc, MB BCh, FCPATH (SA), MMed (Anat Path)**

Multiple endocrine neoplasia type 2A (MEN-2A) is an autosomal dominant genetic syndrome consisting of medullary thyroid carcinoma, pheochromocytoma and hyperparathyroidism. A germline mutation in the RET proto-oncogene which codes for tyrosine kinase receptors expressed in neural-crest derived cells of the thyroid, the parathyroid, adrenal medulla and enteric autonomic plexus results in this syndrome. Genetic testing for mutations in the RET proto-oncogene should now be the standard of care for the diagnosis and screening of families with MEN-2A. This report describes a 34-year-old Congolese man with newly diagnosed MEN-2A.

### Case report

A 34-year-old Congolese man presented to the endocrine clinic at Johannesburg Hospital in February 2007 complaining of a 3-month history of headaches, nervousness and vomiting. He was admitted into a medical ward with a hypertensive crisis. The history and clinical symptoms were suggestive of the diagnosis of pheochromocytoma. His past medical history included a recent diagnosis of sickle cell anaemia. He was unaware of other family members with this disorder.

Examination revealed a healthy looking young man with no palpable thyromegaly or neurocutaneous manifestations. The only positive findings were a cataract in the right eye with band keratopathy and grade II hypertensive changes in the left fundus. He was admitted to an endocrine ward for investigation of pheochromocytoma as a cause of his hypertension. He was commenced on an alpha-blocker followed by a beta-blocker and remained normotensive on treatment.

### Investigations and results

The following investigations were performed:

1. Blood biochemistry revealed normal serum electrolytes, urea, creatinine, and glucose. However, persistently elevated levels of the following serum

analytes were found: corrected calcium (2.97 mmol/l, reference range (RR) 2.05 - 2.56), parathyroid hormone (19.3 pmol/l, RR 1.2 - 8.4) and calcitonin (168 ng/l, RR <8.4).

2. Measurement of the 24-hour urine catecholamines revealed metnoradrenaline 56 176 nmol/24 h (RR 480 - 2 424) and metadrenaline 5 504 nmol/24 h (RR 264 - 1 729), with a metnoradrenaline/creatinine ratio of 3 725 nmol/mmol (RR 28 - 158).
3. Computed tomography (CT) showed an inhomogeneous mass originating from the left medial limb of the adrenal gland and hypodensities in the liver.
4. A I-123 meta-iodobenzylguanidine (MIBG) scan was in keeping with a secreting neuro-endocrine tumour of the left adrenal but the inhomogeneous uptake in the liver was inconclusive.
5. Magnetic resonance imaging (MRI) confirmed a left adrenal lesion and benign liver cysts.
6. A parathyroid sestamibi scan showed no evidence of parathyroid adenoma.
7. A thyroid pertechnetate scan revealed a 'cold' nodule in the lower pole of the right lobe and 'hot' nodules in both lobes medially.

The provisional diagnosis of multiple endocrine neoplasia type 2A (MEN-2A) was made based on the presence of thyroid, parathyroid and adrenal pathology, and with the patient's consent arrangements were made for genetic testing. The

phaeochromocytoma was treated by means of a laparoscopic left adrenalectomy.

## Histological examination

Histological examination confirmed a left adrenal paraganglioma with no evidence of malignancy. The tumour cells stained positively with pan-neuroendocrine markers (neuron-specific enolase, synaptophysin and chromogranin A). The patient subsequently underwent total thyroidectomy with central node dissection and parathyroidectomy. Histological examination of the thyroid gland revealed multifocal medullary thyroid carcinoma. The medullary carcinoma cells were strongly positive for calcitonin and amyloid. Parathyroid hyperplasia was also noted.

## Genetic testing

Following genetic counselling, genetic testing confirmed a mutation in exon 11 of the RET gene (C634R).

The postoperative course was uneventful, with normalisation of the corrected calcium, parathyroid hormone, calcitonin and 24-hour urine catecholamine levels. Arrangements were made for the patient's baby to be assessed by the paediatric endocrine team in order to consider the most appropriate therapy for the child in view of the patient's RET mutation. It was also advised that his extended family in Congo undergo genetic testing for MEN-2A. The patient was last seen in December 2007 and remains well.

## Discussion

Since the chance autopsy observation by John Sipple in 1961 that led to the first association of thyroid carcinoma and phaeochromocytoma, much has been learnt about MEN-2. The RET proto-oncogene, which encodes a tyrosine kinase receptor, was first discovered in 1985, and was subsequently mapped to the chromosome 10 locus in 1987. In 1993 mutations of this gene were first reported.<sup>1</sup> Preventive genetic testing is now a standard form of care for family members of patients with MEN-2A,<sup>2</sup> helping to reduce the morbidity and mortality associated with this disease.

Medullary thyroid carcinoma (MTC) is present in all patients with MEN-2A. It is usually bilateral, multifocal and multicentric with C-cell hyperplasia as a precursor lesion. The tumour produces calcitonin and in rare instances may be associated with ectopic adrenocorticotrophic hormone (ACTH) syndrome. The tumour may display an aggressive course with early metastases in 5 - 10% of cases, but in 80% of cases it pursues an indolent course. Phaeochromocytoma develops in 50% of genetic carriers. Paragangliomas in MEN-2A are usually adrenal, multicentric, and rarely malignant. Plasma normetanephrine and

metanephrine are sensitive tests for detecting phaeochromocytoma in patients with MEN-2A, and unlike this patient, most patients with MEN-2A are characterised by an adrenergic phenotype which may be due to expression of phenylethanolamine N-methyltransferase (PNMT) which converts norepinephrine to epinephrine.<sup>3</sup> It is important to recognise that measurement of vanillylmandelic acid may not always be useful for detection of phaeochromocytoma in these patients, and 24-hour urine collection for fractionated catecholamines or plasma metanephrines are the recommended tests.

Hyperparathyroidism occurs in 15 - 20% of patients with MEN-2A. Hyperplasia is the presenting pathological condition in the majority of patients, and only rarely do adenomas occur. Clinical features are similar to sporadic hyperparathyroidism.

The importance of genetic testing is emphasised in the clinical management of MEN-2A patients and their families. Thyroidectomy is recommended for all patients confirmed to have the RET mutation to prevent medullary carcinoma. The timing of the surgery is dependent on the nature of the mutation, with some carrying a higher risk than others. It is recommended that in patients with high-risk mutations a prophylactic thyroidectomy be performed before the age of 6 months, while with lower-risk mutations, thyroidectomy is performed before the age of 5 years. Similarly emerging data suggest codon-specific, age-related development of phaeochromocytoma in RET gene carriers.<sup>4</sup> Information on RET genotype may therefore also help to improve effectiveness of treatment and screening of phaeochromocytoma.

## Conclusion

This case illustrates the value of genetic testing in the diagnosis and management of patients with MEN-2A as well as for their family members. MEN-2A is still under-diagnosed in many areas of the world. Genetic testing has significantly improved the ability of physicians to diagnose and treat patients suffering from this disease and has resulted in dramatically lower mortality rates.<sup>5</sup> However, it is not freely available in South Africa and is restricted to isolated specialist laboratories. It is hoped that in the near future greater access to genetic testing for this disease will become available.

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