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## Multiple endocrine neoplasia type 2B in a Chinese patient

### IIB型多發性內分泌腺瘤的一個華人病例

Multiple endocrine neoplasia type 2B syndrome is rarely reported in Chinese patients. A 25-year-old Chinese male presented with full-blown clinical features of this syndrome, including bilateral pheochromocytomas, medullary thyroid carcinoma, and characteristic phenotypic features. One-stage surgical treatment was performed and subsequent genetic analysis confirmed a point mutation at codon 918 in exon 16 of the *RET* proto-oncogene. The mutation was arising de novo as there was no corresponding mutation found in both his parents or younger sister. Data published to date suggest there is no difference in the genetic and pathophysiologic basis, nor clinical characteristics of multiple endocrine neoplasia type 2B in Chinese patients. As the disease can be lethal, early diagnosis by prompt recognition of the characteristic phenotypic features followed by surgical treatment should improve the outcome. Family screening is essential to identify at-risk family members for prophylactic treatment.

IIB型多發性內分泌腺瘤的華人病例非常罕見。本病例報告一名25歲男病者，具有該綜合症所有臨床特徵，包括雙側嗜鉻細胞瘤、髓質性甲狀腺癌以及該症特有的表型特點。患者接受了一次性的手術，其後進行的基因分析發現，*RET*原癌基因外顯子16的密碼918發生點突變。患者的父母和妹妹並沒有出現相應的基因突變，所以斷定患者的基因點突變是原發的。從目前的數據可見，在華人身上發現的IIB型多發性內分泌腺瘤，不論是基因或病理生理學的根據，以至臨床特徵，都與其他病例所見的沒有分別。由於該症可以致命，如能及時確認該症特有的表型特點並施行手術，將可提高療效。此外，也應對患者的家族成員進行檢查，確定患病機會率高的成員，以便及早進行預防性治療。

### Introduction

Multiple endocrine neoplasia (MEN) type 2 syndromes, including types 2A and 2B, are inherited endocrine disorders characterised by the presence of medullary thyroid carcinoma (MTC) and pheochromocytoma. Multiple endocrine neoplasia type 2B is typified by a characteristic phenotype with the occurrence of multiple mucosal neuromas and a marfanoid habitus. Intestinal ganglioneuromatosis, corneal nerve thickening, and skeletal abnormalities are often present. Parathyroid hyperplasia, a common finding in MEN type 2A, is not a feature of MEN type 2B.

Multiple endocrine neoplasia type 2B is rarely reported in Chinese patients. In a review of both the English and Chinese literature, only two Chinese patients with MEN type 2B had been previously reported.<sup>1,2</sup> We report in this case study the surgical treatment of a 25-year-old Chinese man with a full-blown clinical picture of MEN type 2B associated with a de novo germline mutation of the *RET* proto-oncogene gene.

### Case report

A 25-year-old Chinese man studying in Sydney, Australia, presented to a general practitioner with throbbing headache associated with an elevated blood pressure of 240/140 mm Hg. He was referred to the hypertension clinic for investigation of a possible secondary cause. His past health was unremarkable except for on-and-off chronic constipation since childhood. His father had a

#### Key words:

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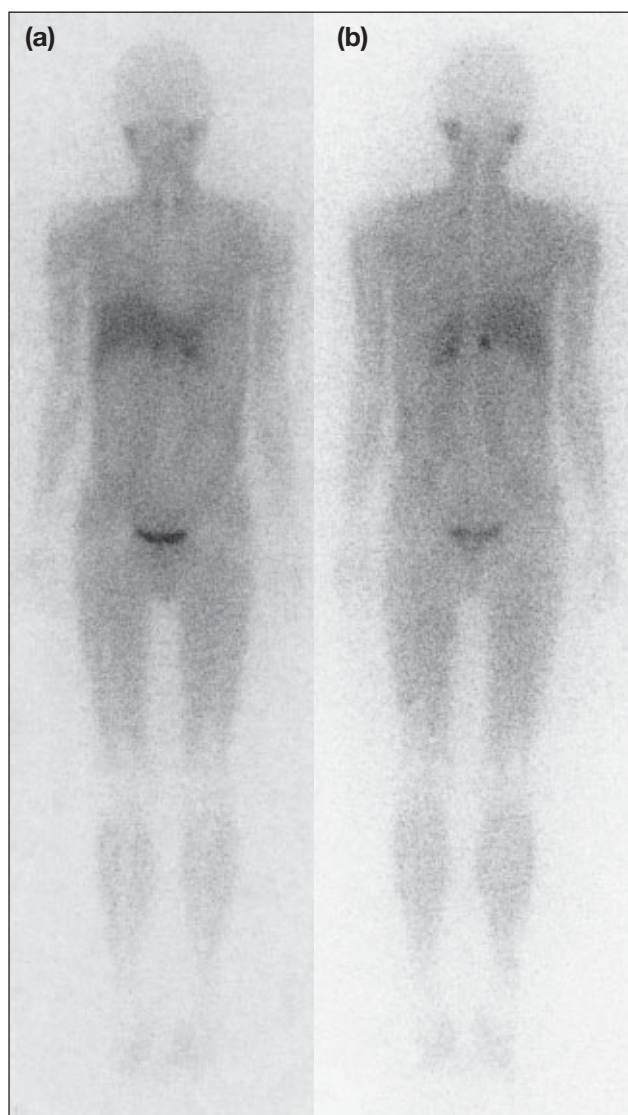
#### 關鍵詞：

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**Fig 1. A small focus of markedly increased metaiodobenzylguanidine uptake demonstrated in the region of the right adrenal gland and also a large focus of irregularly increased uptake in the region of the left adrenal gland as shown in the 24-hour anterior (a) and posterior (b) images post-injection**

history of hypertension requiring antihypertensive medication. Physical examination revealed that the patient, who was tall and had a slender build, possessed features of marfanoid habitus including a long, thin face with prognathism, and long limbs. Multiple nodules were detected in the anterior third of the tongue, buccal mucosa, and lips suggestive of ganglioneuromatosis. There was no sign of congestive heart failure. Examination of the neck showed no palpable lymph node or thyroid mass while abdominal examination showed a distended abdomen with grossly dilated and loaded colon. There was no ascites, hepatosplenomegaly, or ballotable mass. Per-rectal examination was unremarkable.

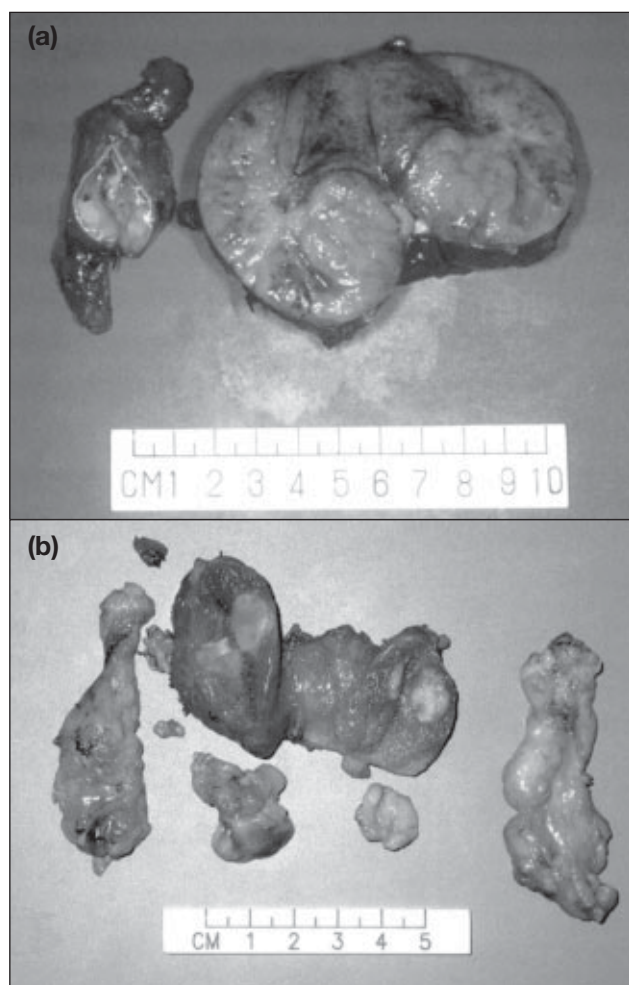
In view of the characteristic phenotypic features and the presence of hypertension, MEN type 2B syndrome was

suspected. A 24-hour urinary collection for fractionated catecholamines showed significantly elevated levels for catecholamines and their metabolites, suggestive of pheochromocytoma. His full blood count, liver and renal function tests including serum calcium level were all normal. Results of his thyroid function test were also normal but the basal calcitonin level was elevated to 29 pmol/L (reference level, <7.5 pmol/L).

Computed tomography (CT) showed a 6-cm mass and a suspicious nodule measuring 1 cm at the left and right adrenal glands, respectively. The ascending and transverse colons were noted to be markedly dilated and loaded with faeces. Metaiodobenzylguanidine scintigraphy confirmed bilateral adrenal involvement and the uptake was more intense on the left side (Fig 1). Ultrasonography and CT scan of the neck showed bilateral thyroid nodules with a mildly enlarged right submandibular lymph node. Ultrasonography-guided fine-needle aspiration of the thyroid nodules confirmed the presence of MTC. However, insufficient aspirate from the submandibular lymph node prevented the confirmation of nodal metastasis. The patient was treated with phenoxybenzamine followed by propranolol to control his blood pressure and as part of the preoperative pharmacological preparation. On receiving a request from the patient to be treated in Hong Kong, the patient was referred to us for definitive surgical treatment.

A one-stage operative procedure with laparotomy and bilateral adrenalectomy followed by cervical exploration was planned. During laparotomy, megacolon measuring almost 10 cm in diameter was noted at the ascending and transverse colon. The pheochromocytomas located at the left and right adrenal glands measured 7 x 6 x 4 cm and 1 cm, respectively. During cervical exploration, tumours measuring 1.5 cm and 1 cm were found at the right and left upper poles of thyroid gland, respectively. Intra-operative frozen section confirmed MTC with metastasis to one lateral cervical lymph node. Total thyroidectomy, and central and bilateral neck dissection were performed (Fig 2). Pathology revealed bilateral pheochromocytomas and multifocal MTC with multiple cervical nodal metastases. The patient recovered well after the operation and was discharged home on postoperative day 8 with thyroxine, cortisol, fludrocortisone, and calcium supplement. Postoperative direct laryngoscopy showed no evidence of cord paresis. Repeated 24-hour urinary levels of catecholamines were all normal. In addition, both his basal and pentagastrin-stimulated calcitonin levels were within the normal range.

Genetic analysis confirmed a point mutation from ATG (Met) to ACG (Thr) at codon 918 in exon 16 of the *RET* proto-oncogene but there was no corresponding mutation found in both his parents or younger sister. Therefore, the mutation was considered as arising de novo.



**Fig 2. (a)** Operative specimens showing a 6-cm and 1-cm pheochromocytoma at the left and right adrenal glands, respectively; **(b)** multiple medullary thyroid carcinomas from 1 to 1.5 cm in size located at the upper pole of thyroid gland as well as the central and bilateral lymphadenectomy specimens

## Discussion

Williams and Pollock<sup>3</sup> first described the association of MTC, pheochromocytoma, and multiple mucosal neuromas, and this syndrome was termed MEN type 2B in 1975 by Chong et al.<sup>4</sup> Multiple endocrine neoplasia type 2B belongs to a family of heritable endocrine diseases that include MEN type 1, MEN type 2A, and familial medullary thyroid carcinoma (FMTC). All MEN syndromes, including MEN type 2B, demonstrate an autosomal dominant pattern of inheritance. As with MEN type 2A and FMTC, MEN type 2B is caused by a defect in the *RET* proto-oncogene, which lies in chromosome 10q11.2 and consists of 21 exons. The *RET* gene is important in signalling for cell growth and differentiation of tissues derived from neural crest cells, such as C-cell of the thyroid gland, the adrenal medulla, the parathyroid gland, and the enteric autonomous nerve plexus. Chinese patients with MEN type 2A have been found to have

germline mutations at a hot site in codon 634.<sup>5,6</sup> For MEN type 2B, mutation at codon 883 has been recently reported in two families<sup>7</sup> but over 95% of patients have a single point mutation in the *RET* gene, with a substitution of threonine for methionine at codon 918 in exon 16. The mutation identified in our patient and in the two previously reported Chinese patients<sup>1,2</sup> is consistent with that reported from western countries.

In MEN type 2 syndrome, there is essentially complete penetrance of the genetic defect but with variable expressivity because not every patient manifests all the characteristics of this syndrome. Medullary thyroid carcinoma is almost always present in all subtypes of MEN type 2 syndrome while pheochromocytoma occurs in 40% to 50% of all patients. Parathyroid hyperplasia is found in 10% to 20% of patients with MEN type 2A but is invariably absent in MEN type 2B. Compared with type 2A, which accounts for 90% of MEN type 2 syndromes, the MEN type 2B is less common, presents at an earlier age, and tends to be more aggressive. The onset of MEN type 2B normally occurs in patients who are in their first or second decade of life. Patients with MEN type 2B also tend to have a poorer prognosis than those with MEN type 2A or FMTC. Genetic inheritance accounts for 80% of MEN type 2A patients, while de novo mutations account for 50% of MEN type 2B patients, including the three Chinese patients reported. Data indicate that patients with MEN type 2B are less likely to reproduce because they die of their disease at an earlier age.

Surgical treatment of patients with MEN type 2B is recommended. Total thyroidectomy with central compartment node dissection is the procedure of choice, preferably on a prophylactic basis at the stage of C-cell hyperplasia before the formation of invasive MTC. Bilateral neck dissection should be performed when the central node shows metastatic involvement because of the high incidence of cervical nodal metastasis. Normocalcemia after calcium and pentagastrin stimulation suggests surgical cure of the MTC. However, thyroidectomy should not be undertaken until co-existing pheochromocytoma has been excluded or treated to avoid catecholamine crisis. The diagnosis of pheochromocytoma in patients with MEN type 2 is not different from that of sporadic pheochromocytoma. Alpha-blockade is preferred for preoperative pharmacological preparation.

Opinions differ with regard to the management of the contralateral adrenal gland in patients presenting with unilateral disease. Bilateral total adrenalectomy at the time of initial surgery is advocated by some clinicians since synchronous tumour or adrenal medullary hyperplasia is almost always seen microscopically in the contralateral gland and the subsequent need for a second surgical procedure can be avoided. The price to

pay for bilateral total adrenalectomy is life-long post-operative replacement therapy with adrenal cortical hormones. Therefore, a selective approach by removing only the affected adrenal gland and closely monitoring the contralateral side through annual measurements of 24-hour fractionated catecholamine is preferred. This is because not all patients will go on to develop a clinically significant contralateral pheochromocytoma. Although laparoscopic adrenalectomy is the preferred surgical approach,<sup>8</sup> open bilateral adrenalectomy was opted in our patient because of the anticipated technical difficulty associated with a limited dissection space caused by the relatively large tumour and the presence of megacolon.

Gastro-intestinal involvement is not uncommon in MEN type 2B. Over 90% of patients report a variety of gastro-intestinal complaints including flatulence, abdominal distension, abdominal pain, constipation, difficulty in swallowing, and vomiting. It has been reported that about 30% of patients with MEN type 2B ultimately need surgery for gastro-intestinal complications.<sup>9</sup> Chronic constipation in patients with MEN type 2B is associated with gastro-intestinal ganglioneuromatosis while concomitant Hirschsprung's disease occurs in patients with MEN type 2A but not 2B syndrome. Our patient had on-and-off chronic constipation with bowel movement every 2 to 3 days. Although his colon was grossly dilated, surgical intervention in the form of subtotal colectomy will not be attempted unless complications arise from his megacolon.

Screening is essential to identify asymptomatic carriers from family members of patients with MEN type 2 syndrome.<sup>10</sup> Genetic screening by blood test is the most cost-effective and least invasive procedure. Genetic analysis is conducted on DNA that has been isolated from peripheral blood leukocytes and amplified using polymerase chain reaction techniques.<sup>10</sup> Direct DNA sequencing can identify specific mutations of the *RET* proto-oncogene. Siblings of patients with MEN type 2B should be screened as early as 1 year of age since C-cell hyperplasia, a precursor of MTC, can be present when the patient is as young as 3 months old. Prophylactic total thyroidectomy before the presence of invasive MTC should be

considered for *RET* proto-oncogene carriers to improve the prognosis.

## Conclusion

Multiple endocrine neoplasia type 2B is rarely reported in the Chinese population compared to the findings in western countries. Based on the published data, there is no difference in the genetic and pathophysiologic basis, or clinical characteristics of MEN type 2B in Chinese patients. As the disease can be aggressive and is associated with a poor prognosis, early diagnosis by prompt recognition of the characteristic phenotypic features followed by an effective surgical treatment should improve the outcome. Family screening is essential to identify at-risk family members for early surgical treatment.

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