CASE REPORT

MEN2B syndrome presenting as an acute respiratory emergency

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SUMMARY

An 18-year-old girl presented to the emergency department with a history of noisy breathing and breathlessness progressively increasing for few days. The patient had stridor and tachypnoea. She was tall with a long thin face, wrist sign and high-arched palate suggestive of marfanoid features. X-ray of the neck revealed critical tracheal narrowing. Emergency tracheostomy was performed as a lifesaving procedure. Non-contrast CT neck revealed extratracheal compression by a mass surrounding it. Contrast-enhanced CT scan of the neck revealed heterogeneous mass arising from the right lobe of the thyroid and tracheal deviation with narrowing. Fine-needle aspiration cytology of the mass revealed medullary carcinoma of the thyroid, positive for calcitonin. Calcitonin levels were raised. Apart from the marfanoid features she had localised swellings over the lips, lower eyelid and the lateral aspects of the tongue, clinically suggestive of neuromas. A clinical diagnosis of multiple endocrine neoplasia type 2B syndrome was made. The patient underwent total thyroidectomy with central lymphnode dissection. This case highlights an unusual presentation of a rare disease.

BACKGROUND

Multiple endocrine neoplasia type 2B (also known as 'MEN2B', 'Multiple endocrine neoplasia type 3' or 'Wagenmann–Froboese syndrome') is a genetic disease characterised by the presence of medullary carcinoma of the thyroid, pheochromocytoma, mucosal neuromas, marfanoid features and multiple skeletal abnormalities such as kyphoscoliosis and pes cavus.¹ It is the most severe type of multiple endocrine neoplasia, differentiated by the presence of benign oral and submucosal tumours in addition to endocrine malignancies. It was first described by Wagenmann in 1922, and was first recognised as a syndrome in 1965–1966 by ED Williams and DJ Pollock. MEN2B syndrome is rarely reported in case reports and its presentation with an acute respiratory emergency was not reported previously as far as the literature could be retrieved.

CASE PRESENTATION

An 18-year-old female patient presented to the emergency department with progressively increasing breathlessness and noise during breathing for the past 5 days. She was in severe respiratory distress when she came to us. There was no history of fever, running nose, cough or orthopnoea. On examination, she had tachypnoea and stridor. The thyroid gland was just palpable. She had a long

thin face, marfanoid features such as high-arched palate, high arm span to height ratio at >1.05, elongated fingers, pes cavus and positive wrist sign which is defined as when the distal phalanges of the thumb and fifth finger overlap on encircling the opposite wrist (figure 1).

INVESTIGATIONS

An emergency X-ray of the soft tissue of the neck revealed critical tracheal narrowing probably due to external pressure (figure 2). An indirect laryngoscopy was also performed which revealed no intralaryngeal lesion but narrowing due to external compression. The patient was stabilised on oxygen therapy and an emergency tracheostomy was performed as a life-saving procedure for her. Non-contrast CT scan of the soft tissue of the neck was also performed which showed extratracheal compression by the mass surrounding it. Her complete blood count was haemoglobin 11.2 g%, total leucocyte counts 4800 cells/mm³, platelet count 1.34 lac/mm³ and erythrocyte sedimentation rate was 11 mm at the first hour. The liver and kidney function tests were within the normal range. Serum calcium was 9.2 mg%, phosphorus was 3.6 mg% and serum alkaline phosphatase was also normal at 53 IU. Posteroanterior view of the chest X-ray was also normal. Serum parathormone was also within normal range. A contrast-enhanced CT (CECT) scan was planned subsequently which revealed a heterogeneously enhancing soft tissue mass lesion arising from the inferior and posterior part of the right lobe of the thyroid gland involving the isthmus and part of the left lobe of the thyroid with tracheal deviation, compression but no lymph node enlargement (figure 3). Fine-needle aspiration cytology of the thyroid mass revealed features suggestive of medullary carcinoma of the thyroid, positive for calcitonin but negative for thyroglobulin. On further evaluation she was found to have localised swelling over the lower lips (mucosal aspect), lower eyelids and lateral aspects of the tongue suggestive of multiple neuromas. A clinical diagnosis of MEN2B syndrome was carried out. The patient was planned for total thyroidectomy. Her vitals were stable with normal blood pressure with no episodic elevation on continuous monitoring. Serum calcitonin levels were very high at 5174 pg/mL (normal levels are considered as less than 5 pg/mL). Serum and urinary catecholamines were normal. 24 h urine vanillyl mandelic acid (VMA) (5.82 mg/g of creatinine with a normal range between 1.5 and 3.6). VMA levels were checked twice and on both occasions they were negative. CECT of the abdomen was also

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Figure 1 Photographs of patient showing multiple mucosal neuromas over lower lip, lower eyelid, lateral aspect of the tongue and positive wrist sign.

performed to rule out pheochromocytoma which revealed normal findings except for the enlarged medial limb of the left adrenal gland. Ophthalmological evaluation and slit-lamp examination revealed thickened corneal nerves. The patient is now in our regular follow-up. A fluorodeoxyglucose-positron emission tomography CT scan was performed to look for residual metastasis but revealed no abnormally active metabolic tissue in the body. Gallium-68 DOTANOC scan was also performed from the other institute but revealed no somatostatin receptor expressing tumour.

DIFFERENTIAL DIAGNOSIS

- ▶ Thymoma causing compression of the trachea
- ▶ Lymphoma as a cause for extraluminal tracheal compression
- ▶ Foreign body obstruction causing acute onset of breathlessness

Figure 2 Chest X-ray posteroanterior view of the patient at the time of presentation showing narrowing of trachea likely due to external compression.

TREATMENT

The patient underwent a total thyroidectomy with central lymph node dissection and temporary tracheostomy. The Preoperative and postoperative periods were uneventful and the patient was stable. Two months after surgery, serum calcitonin levels were repeated and were 4893 pg/mL. Histopathological examination of the thyroid gland revealed that both lobes have features of medullary carcinoma. The tumour shows large area of hyalinisation, foci of amyloid deposition and calcification extending into the thyroid capsule infiltrating into the residual gland and locally into the surrounding skeletal muscle bundle. The rest of the gland showed features of lymphocytic thyroiditis. The patient received three cycles of chemotherapy and three cycles of radiotherapy in the radiotherapy department. The patient was further planned for analysis of rearranged during transfection (RET) proto-oncogene, which could not be performed due to non-availability in our setup and non-affordability by the patient also. The patient had one sibling who was normal with no such features.

OUTCOME AND FOLLOW-UP

The patient is stable and now in our regular follow-up.

DISCUSSION

MEN are autosomal dominant hereditary cancers with their origin in hormone-secreting glands.² These hormones also act as tumour markers that can be used as a screening tool and for follow-up. MEN have been classically described as MEN1 with primary hyperparathyroidism (PHPT), pituitary adenomas and pancreatic islet cell tumours), MEN2A with medullary thyroid carcinoma (MTC), pheochromocytoma and PHPT) and MEN2B with MTC, pheochromocytoma, marfanoid habitus and mucocutaneous neuromas). These syndromes may have overlapping or additional features. Multiple endocrine neoplasia 2 was first described in 1961.³ MEN2B is much less common than MEN2A with the incidence of about one in million, and although its clinical signs have been described in the literature on many occasions

Figure 3 Contrast-enhanced CT neck showing heterogeneously enhancing mass lesion in relation to posterior part of thyroid with marked deviation and narrowing of trachea.

and are highly characteristic, its diagnosis is still too late, except for cases which have familial MEN2B occurrence. It accounts for 5% of cases of MEN2. About 95% of MEN2B are caused due to a specific germline mutation in RET proto-oncogene on chromosome 10q. MEN2B syndrome is usually diagnosed at a mean age of 11.5 years.⁴

Our patient was diagnosed at an age of 18 years. The hallmark of this disease is the occurrence of mucocutaneous neuromas especially on the tongue and subconjunctival areas. In fact, the subconjunctival neuromas are among the earliest manifestations of this disease.⁵ These neuromas are an important clue to underlying MEN2B. Thickened corneal nerves can be appreciated on slit-lamp examination. Intestinal gangliomatosis is found in nearly all the patients.⁶ Our patient did not have this finding on colonoscopy. The next common component is MTC which can have an early onset.⁷ In contrast to MEN2A in which MTC has an indolent course in almost 80% of cases, in MEN2B MTC has a very aggressive course and is rarely completely curable. These tumours are located at the junction of the upper and middle third of the thyroid lobes coherent with the maximum density of the c—cells in this area. It was unusual that our patient of MTC was asymptomatic and diagnosed at the age of 18 years with respiratory complications without having any apparent neck swelling. MEN2B with this presentation was not reported earlier. The diagnosis in our patient was made on purely clinical basis by the presence of marfanoid habitus, multiple submucosal neuromas and MTC. Pheochromocytoma occurs in 50% of the patients with MEN2B.⁸ They present at around 30 years. Our patient did not have pheochromocytoma on imaging study and on biochemical tests which was repeated twice. Furthermore, on regular blood pressure monitoring, there were no fluctuations or any high reading. About half of the tumours are bilateral and >50% of the patients who have had unilateral adrenalectomy develop a pheochromocytoma in the contralateral gland within a decade.

The pheochromocytoma in this syndrome differs from the sporadic and other familial pheochromocytoma in that it secretes predominantly epinephrine. Primary hyperparathyroidism is very rare in MEN2B.⁹ These patients have normal calcium levels. Histologically, in our patient parathyroid glands were normal.

In 1993, germline mutation in RET proto-oncogene that is associated with a missense mutation in methionine residues in exon 16 (codon 918) in the tyrosine kinase receptor domain of RET were found in patients with MEN2B.^{10 11} Clinically useful DNA tests are now available to identify gene carriers so that the affected children can be managed surgically at an early age to reduce metastatic MTC.¹² This test could not be performed in our patient yet but we are planning to get this analysis in our patient and also to screen her siblings as soon as this facility is available in our setup though her siblings are clinically unaffected with any feature of this illness. Furthermore, there was no history of thyroid cancer, phaeochromocytoma or sudden death in the family.

Learning points

- ▶ Multiple endocrine neoplasia type 2B (MEN2B) is a rare entity but should always be kept in mind when there is a high index of suspicion and the clinical features corroborate.
- ▶ MEN2B is a clinical diagnosis.
- ▶ Rarely, but it can present as an acute respiratory emergency in young individuals as in our case.

Contributors PD critically evaluated the patient and was mainly involved in conception and design of the case. AGDM were the treating residents in ward. DD gave expert opinion regarding the diagnosis and further management of the patient.

Competing interests None.

Patient consent Obtained.

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