CASE REPORT

An unusual presentation of MEN2A

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ruthcasey232@gmail.com**SUMMARY**

A 35-year-old woman presented with non-specific symptoms of fatigue and weight loss. Radiological investigations diagnosed a metastatic process and large bilateral adrenal masses. Histology from a liver biopsy and skin biopsy confirmed a diagnosis of metastatic medullary thyroid cancer. Further biochemical investigations revealed a positive 24-h urinary metanephrine collection and evidence of primary hyperparathyroidism. Genetic testing confirmed a mutant RET oncogene, confirming our clinical suspicion of multiple endocrine neoplasia type 2 (MEN2A) syndrome. The patient had no family history of endocrine disease and presented with widespread metastatic disease, making this an unusual presentation of MEN2A syndrome. Furthermore cutaneous metastases are rarely encountered in conjunction with metastatic medullary thyroid cancer. This case draws attention to the importance of genetic counselling in first-degree relatives of patients with confirmed MEN2A. This allows for timely diagnosis and reduced morbidity and mortality.

BACKGROUND

Multiple endocrine neoplasia type 2 (MEN-2) is a complex hereditary disorder which confers a predisposition to the development of endocrine tumours. MEN-2 occurs owing to a germline mutation in the rearranged during transfection (RET) proto-oncogene¹ that is transmitted in an autosomal dominant pattern. MEN2A, MEN2B and familial medullary thyroid cancer (FMTC) comprise the MEN-2 syndrome. The MEN2A complex comprises FMTC, pheochromocytoma and primary hyperparathyroidism. MTC is usually the initial presenting feature of this complex and the prognosis of MEN2A is dependent on the stage of FMTC at diagnosis.² Reported cases of MEN-2 have been identified in 500–1000 families and the prevalence is estimated to be 1 in 30 000.³ The specific RET codon mutation correlates with phenotype and can help predict disease variant, the age of onset of FMTC and how aggressive the FMTC will behave. Therefore genetic testing of first-degree relatives at an early age is essential in guiding major management decisions such as the timing of prophylactic thyroidectomy.⁴

CASE PRESENTATION

A 35-year-old woman presented to her general practitioner with fatigue and an unintentional weight loss. At this time she was 9 months post-partum following the birth of her first child. Routine blood tests revealed deranged liver function tests and an outpatient liver ultrasound revealed multiple irregular nodules and masses,

consistent with a metastatic process. Her medical history was significant for low-grade hypertension and she was not taking any regular medications. There was no family history of malignancy or endocrine disorders. On observation, the patient was cachectic, visibly anxious and vital signs showed a persistent tachycardia and low-grade hypertension. Clinical examination revealed axillary and cervical lymphadenopathy, a palpable irregular liver edge and a 1.5 cm cutaneous nodule on the right shoulder. Examination of her thyroid gland yielded no clinical findings.

INVESTIGATIONS**Laboratory**

Investigations on admission revealed deranged liver function tests and evidence of primary hyperparathyroidism. A number of tested tumour markers were elevated, with the most significant elevation being with calcitonin (table 1).

A 24 h urinary collection showed elevations in urinary metanephrines and catecholamines (table 2).

Imaging

Contrast-enhanced CT of the thorax, abdomen and pelvis showed innumerable bilateral pulmonary nodules, nodules throughout both lobes of the liver, large bilateral adrenal masses (figure 1) and extensive low-grade retroperitoneal lymphadenopathy. A non-specific 1.8 cm nodule in the right lobe of the thyroid gland was also noted. An isotope bone scan revealed no evidence of osteoblastic bone lesions.

Pathology

An ultrasound-guided percutaneous liver biopsy showed liver parenchyma infiltrated by a metastatic medullary thyroid carcinoma (figure 2). Immunohistochemistry showed strong positivity to Ttf1, CD56, calcitonin (figure 3) and synaptophysin, confirming the presence of a metastatic deposit of FMTC. The cutaneous nodule was excised and showed a metastatic deposit of FMTC (figure 4).

Genetics

The patient was subsequently screened for the RET gene mutation. Genetic testing confirmed a C.19000T (p.CYS634Arg) heterozygous pathogenic mutation in exon 11 of the RET gene. This is the most common mutation of codon 634 on the RET gene and is associated with the development of pheochromocytoma and primary hyperparathyroidism.⁵ First-degree relatives were screened with serum calcitonin, serum calcium level, thyroid function tests, liver function tests, thyroglobulin level, parathyroid hormone level, carcinoembryonic

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Table 1 Investigations performed on admission

Serum investigations	Results	Reference range
Sodium	141.00 mmol/l	136–145 mmol/l
Potassium	4.90 mmol/l	3.3–5.1 mmol/l
Chloride	100.00 mmol/l	98–106 mmol/l
Glucose	7.70 mmol/l	3.0–7.8 mmol/l
Urea	3.70 mmol/l	2.5–6.4 mmol/l
Creatine	47.00 µmol/l	44–80 µmol/l
Calcium	2.77 mmol/l↑	2.17–2.51 mmol/l
Inorganic phosphate	1.16 mmol/l	0.87–1.45 mmol/l
Total protein	81.00 g/l	64–83 g/l
Albumin	44.00 g/l	39–51 g/l
Total bilirubin	13.00 µmol/l	1–19 µmol/l
Alkaline phosphatase	394.09 U/l↑	35–104 U/l
Alanine Aminotransferase	261.00 U/l↑	0–40 U/l
γ-Glutamyl transpeptidase	533.00 U/l↑	6–42 U/l
Free T4	17.10 pmol/l	10.5–22.0 pmol/l
Thyroid-stimulating hormone	2.66 Miu/l	0.27–4.20 Miu/l
Lactate dehydrogenase	264.00 U/l↑	135–214 U/l
Intact parathyroid hormone	130.90 ng/l↑	15–65 ng/l
Carcinoembryonic antigen	42.10 ng/ml↑	0–3.4 ng/l
CA 19-9	100.00 U/ml↑	0–27 U/ml
CA 125	63.00 U/ml↑	0–35 U/ml
Calcitonin	1533.00 ng/l↑	0–10 ng/l
α-feto protein	4.50 ng/ml	0–7 ng/ml
White cell count	15.800 ×10 ⁹ /l↑	4–10 ×10 ⁹ /l
Haemoglobin	11.800 g/dl↓	12–15 g/dl
Haematocrit	0.361 l/l	0.36–0.46 l/l
MCV	88.10 fl	84–96 fl
Platelet count	306.00×10 ⁹ /l	150–400×10 ⁹ /l

antigen (CEA) levels and thyroid ultrasound, but there were no positive results. RET gene molecular genetic testing should be offered to all first-degree family members of patients in whom a germ-line RET mutation has been diagnosed. Genetic testing of the RET gene predicts disease-causing mutations in 98% of individuals with MEN2A, more than 98% of individuals with MEN2B, and in about 95% of families with familial MTC.⁶ In keeping with the wishes of the family, neither the patient's child nor her first-degree relatives have been genetically tested to date.

OUTCOME AND FOLLOW-UP

After consultation with oncology, chemotherapy was started after α-blockade. The patient's clinical course was complicated with sepsis and a catecholamine crisis. Despite maximum support in the intensive care unit, the patient developed liver and respiratory failure and died. Her death occurred within

Table 2 Twenty-four hours urine collection result

Investigation	Result	Reference range
Total volume of urine	2050 ml	
Noradrenaline	21 308 nmol/24 h↑	0–900 nmol/24 h
Adrenaline	37 003 nmol/24 h↑	0–230 nmol/24 h
Dopamine	5719 nmol/24 h↑	0–3300 nmol/24 h
Total normetanephrine	31 693 nmol/24 h↑	0–2800 nmol/24 h
Total metanephrine	110 208 nmol/24 h↑	0–1800 nmol/24 h

Figure 1 Contrast-enhanced CT of the thorax, abdomen and pelvis showing bilateral adrenal metastases (arrows).

3 months of her initial presentation. Postmortem examination confirmed the presence of a 26 mm FMTC of the right thyroid lobe and a separate 6 mm tumour of identical histology in the left thyroid lobe. Multiple pulmonary and hepatic nodules were sampled confirming metastatic deposits of FMTC.

DISCUSSION

Rare cases of MEN2A have been attributed to mutations in the intracellular portion of RET⁷ and somatic mutations in RET have been identified in 50% of cases of sporadic FMTC.⁸ These mutations are not genetically acquired but are present on the tumour cells of the individual. Unlike many other onco-genetic mutations, mutations in RET result in a hyperfunctional state.⁷

FMTC is usually the first manifestation of MEN2A. In known familial MEN2A, the biochemical manifestations of FMTC usually become apparent between the ages of 5 and 25 years.⁹

These biochemical manifestations include elevated basal calcitonin levels and pentagastrin-stimulated elevations in calcitonin.^{5–9} Serum calcitonin is a useful tumour marker for FMTC and remains the most sensitive marker for the early diagnosis of

Figure 2 Light microscopy of liver biopsy with H&E staining showing liver parenchyma with infiltration of tumour cells displaying large anaplastic nuclei and amorphous cytoplasm surrounded by vascularised stroma (arrow).

Figure 3 Immunohistochemistry of liver biopsy showing positivity (arrows) for calcitonin (A; brown staining with polyclonal rabbit anti-human antibody, 1:400, Dako), CD56 (B; brown staining with monoclonal mouse anti-human antibody, clone 4KB 5, 1:100, Leica) and Ttf1 (C; brown staining with monoclonal mouse antibody, clone 8G7G311, 1:100, Leica).

FMTC. Recently the role of CEA as a prognostic marker in FMTC has been assessed and has been reported to be a more sensitive predictor of metastatic FMTC than serum calcitonin.¹⁰ If presymptomatic screening is not performed, FMTC typically presents as a neck mass or neck pain at about age 5–20 years. Over 50% of this patient group will have cervical lymph node metastases.¹¹

Testing for RET mutations is recommended in first-degree relatives of patients with identified MEN2A syndrome, and should be considered in patients with sporadic FMTC. There has been a surge in data regarding the genotype–phenotype correlation in patients with MEN-2 complex, which has led to improvements in earlier detection rates and screening.¹² Genetic screening is recommended even in those cases where first-degree relatives are asymptomatic.¹³ DNA testing for RET gene can be performed from a simple blood test, allowing for early identification. The aggressiveness of the FMTC, which dictates prognosis in MEN2A, also correlates with specific genotypes, allowing for identification of patients and family members who require aggressive management. The recognition of this genotype–phenotype correlation prompted a risk stratification system (highest, high, intermediate and low) to predict the most appropriate timing for prophylactic thyroidectomy in children with a RET mutation.^{14 15} The risk stratification was categorised A–D, with category A carrying the highest risk and category D carrying the lowest risk. In this particular case the genetic mutation in exon 11 would place the patient's child into risk category B. The advice for patients, who fall into

category B is for genetic testing for RET mutations before the age of 3 and, if positive, prophylactic thyroidectomy before the age of 5.^{13 14}

Learning points

- ▶ This case highlights an atypical presentation of a rare genetic syndrome as the patient had no family history of endocrine disease and presented with widespread metastatic disease.
- ▶ The diagnosis of medullary thyroid cancer (MTC) warrants further investigations to rule out the presence of multiple endocrine neoplasia type 2A syndrome.
- ▶ Definitive treatment of pheochromocytoma to be considered first prior to treatment of MTC if the medical condition of the patient permits.
- ▶ Genetic counselling and screening of first-degree relatives is essential to reduce morbidity and mortality associated with this inherited genetic syndrome.

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Competing interests None.

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Figure 4 Light microscopy of cutaneous nodule with H&E staining showing soft tissue and fat replaced by metastatic carcinoma (arrow) and vascular invasion (A). Immunohistochemical staining of cutaneous nodule showing strong positivity (arrow) for calcitonin (B; polyclonal rabbit anti-human antibody, 1:400, Dako).

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