A RARE CAUSE OF AN OVARIAN MASS

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ABSTRACT

Multiple Endocrine Neoplasia Type IIB (MEN-IIB) is a syndrome characterised by the presence of medullary thyroid carcinoma (MTC), phaeochromocytomas, neuromas and a marfanoid habitus. The MTC seen in MEN-IIB patients is often more aggressive, and carries a poorer prognosis, than its MEN-IIA or sporadic counterparts. The most common mutation in MEN-IIB patients is a RETMet918Thr substitution, causing overactivity of the oncogene RET tyrosine kinase. We present a rare case of ovarian metastatic spread of MTC in a patient with MEN-IIB.

CASE REPORT:

A 39 year-old ex-chef was diagnosed with MEN-IIB (mutation RETMet918Thr) in 2003. She had previously undergone a left laparoscopic adrenalectomy due to phaeochromocytoma and a total thyroidectomy, laryngectomy and total neck dissection due to metastatic medullary thyroid carcinoma. In addition, she underwent excision of bilateral simple benign paratubal cysts and a benign cystic teratoma of the right ovary in 2003. She presented at the annual surveillance clinic in August 2007 with a 1-month history of nausea, vomiting, palpitation, sweats, muscle weakness and light-headedness. Her medication included thyroxine, alphacalcidol, cyclizine, omeprazole, MST, ibuprofen, codeine phosphate and fluoxetine. There was no relevant family history.

On examination, the patient was cachectic yet comfortable at rest. She was afebrile with a pulse of 112/min and a blood pressure of 104/70. She had a tracheostomy and PEG tube in-situ. Tongue neuromas were present. She had multiple abdominal scars and a lower abdominal mass, which was firm, smooth and dull to percussion. Her blood results were normal except for a slightly reduced corrected calcium level (2.04mmol/L).

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On computed tomography scan, the patient was found to have a 15-17cm in diameter left ovarian multicystic mass, as well as a 1.5cm right adrenal mass (see Fig. 1).

Investigation for possible phaeochromocytoma on hospital admission showed plasma metanephrines to be raised at 3392 pmol/L (normal range: 0-600 pmol/L). After adequate phenoxybenzamine block as well as a restored nutritional and fluid status, this patient underwent a right adrenalectomy, bilateral oophorectomy and hysterectomy in March 2008. Histology revealed that the left ovarian tumour stained positive for calcitonin, synaptophysin and S100, consistent with metastatic spread of MTC.

In summary, we present a 39-year-old lady with MEN-IIb, who has developed metastatic spread of medullary thyroid carcinoma to the left ovary, despite radical thyroid surgery four years previously.
DISCUSSION:

Mechanism of disease:

Medullary thyroid carcinoma in MEN-IIB is an aggressive cancer. Metastatic spread of MTC is common, most commonly to bone, liver and lung. Ovarian spread of MTC is rare with one published case report in a patient without a MEN-II syndrome[1].

There has been significant interest in the mechanism behind the aggressive nature of MTC in MEN-IIB patients. The most common Met918Thr mutation has been shown to stabilize the RET kinase dimer and increase its affinity for ATP[2]. This leads to greater levels of autophosphorylation and hence increased intracellular signaling. Another study [3] suggests that the M918T mutation permits the RET kinase enzyme to autophosphorylate itself without dimerisation, leading to constitutive activation. It is likely these mechanisms coexist to produce the disease state.

In relation to the unusual site of metastasis in this patient, it is likely this occurred by chance. However, it does raise some interesting discussion points regarding the mechanism of metastasis in this type of cancer. There is very little specific evidence in this area and so we can only speculate on the following possibilities.

It is likely that the high metastatic potential of MTC stems from the underlying mechanistic defect. The downstream pathways of RET kinase are evidently complex, but one protein, ‘rac’, is known to be involved with cellular motility. Increased rac activity is associated with increased vascular invasion and metastasis in murine models of melanoma[4], through effects on actin-modulating proteins. As rac is a downstream effector of RET, whose activity is increased in MEN-IIB, this may contribute to the heightened metastatic potential of MTC.

It is known that in papillary thyroid carcinomas there are alterations in the expression of e-cadherin, galectin and CD44[5]. E-cadherin, for example, was found to have a reduced expression level in papillary thyroid cancers that had metastasised to lymph nodes and distant organs, compared to those that had not metastasised. Further studies would be required to elucidate the level of involvement cell adhesion molecules have in metastatic medullary thyroid carcinoma. In particular, studies would be required to identify whether changes in cell adhesion are a contributory factor to the increased aggressiveness of MTC over other thyroid cancers.

A retrospective investigation[6] into the incidence of non-gynaecological metastasis to ovary revealed the most common primary sites are colon and appendix. Other notable sites of primary malignancy included breast, stomach and pancreas. This demonstrates that the ovary does not, as a rule, receive metastases from the thyroid. However, this study is relevant to this discussion in that the route of dissemination was found to be haematogenous,
and not transserosal. This correlates well with the most likely method of spread from thyroid to ovary. This case also allows us to speculate whether the presence of a previous benign teratoma in this patient may have affected the progression of this disease. It is conceivable that the malignant nature of the ovarian mass may have arisen from teratomatous tissue already present in the ovary. Although her right teratoma (removed in 2003) did not contain thyroid tissue, the presence and subsequent malignant transformation of thyroid tissue within an undiscovered left teratoma remains a possibility. Alternatively, metastatic thyroid cells in the blood may be more likely to attach to teratomatous cells than regular ovarian cells, due to changes in the expression of cellular adhesion molecules.

**Risk stratification:**

The genotype-phenotype relationship in MEN-II syndromes has been intensively investigated [7, 8]. This relationship is so precise that the mutation detected in an individual can help guide that patient’s management. One of the most important aspects of management in family members found to have MEN-II mutations is the timing of prophylactic thyroidectomy. The following groups, based on relative risk of malignant disease according to their genotype, have been established.

- **Level 1** mutations (codons 609, 768, 790, 791, 804 and 891) are the least aggressive and age of onset is later. There is some debate as to when these patients should receive thyroidectomy. Suggestions include at 5 years of age, at 10 years of age or postponement until an abnormal C-cell stimulation test is found.

- **Level 2** mutations (codons 611, 618, 620 and 634) are more aggressive, occur at an earlier age and are the major mutations found in MEN-IIA phenotypes. Thyroidectomy is advised before the age of 5.

- **Finally, level 3** mutations are the most aggressive, present the earliest and often lead to a MEN-IIB phenotype. These patients should receive thyroidectomy in the first year of life [7].

Although the age of onset of MTC and aggressiveness of disease are inversely related, Yip et al [8] have shown that the risk group is an independent predictor of disease aggressiveness in these patients.

Further mutation classifications have been made. Machens et al[9] showed differing phenotypes in mutations arising in either the extracellular domain of the RET protein, or the intracellular domain. Extracellular mutations were shown to cause more aggressive disease with an average age of onset of MTC 6.4 years earlier than in individuals with intracellular mutations.

As expected, there is also a correlation between the genotype and development of phaeochromocytomas in MEN-II patients[8]. Mutations in codons 634 and 918 are most commonly found in patients who develop
phaeochromocytomas. This means that patients can be stratified into risk-associated screening groups so as those with a higher potential for phaeochromocytoma development are screened more regularly.

CONCLUSION:

We have presented a complex case involving a rare cause for an ovarian mass. Although the incidence of ovarian spread of MTC is extremely low, a high index of suspicion should be maintained in any MEN-IIIB patient presenting with symptoms of a pelvic mass. Due to the low numbers of affected patients, the precise mechanisms underlying metastatic spread in MEN-IIIB MTC are uncertain. We feel this case highlights the potentially devastating effects of this disease and the need for further investigation.

It has also become possible to predict which MENII patients will develop early aggressive disease. It reflects an interesting and clinically useful feature of the MENII syndromes, whereby genetic analysis can help predict the natural course of the disease, enabling a more individualised management plan.

REFERENCES: