CASE REPORT

MEN-2A syndrome and pulmonary metastasis

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A case of multiple endocrine neoplasia syndrome type-2A (MEN-2A) with primary hyperparathyroidism and medullary carcinoma of thyroid initially treated by surgery is reported. The presence of pulmonary nodules six years after the initial treatment was thought to be related to metastasis of medullary carcinoma, and the increase in serum calcium concentrations was assumed to be caused by persistence of parathyroid adenomatous or hyperplastic tissue. The patient underwent surgery again and the pulmonary nodules were confirmed to be metastases of a parathyroid carcinoma, a very rare entity in MEN-2A syndrome.

Multiple endocrine neoplasia syndrome type-2A (MEN-2A) is an autosomal dominant disorder that comprises medullary thyroid carcinoma and variable prevalences of hyperparathyroidism and pheochromocytoma. Hyperparathyroidism is usually caused by parathyroid hyperplasia and, rarely, parathyroid adenoma. Sporadic parathyroid carcinoma often presents as local invasion or recurrence, and a severe hypercalcaemia may be caused by distant metastases, particularly in the lung.¹

CASE REPORT

A 49 year old man was admitted because of acute myocardial infarction. Serum total calcium concentration was 3.6 mmol/l,

phosphorus 0.58 mmol/l, creatinine 168 μ mol/l, and intact parathyroid hormone (PTH) 370 ng/l (normal range 10–55). Primary hyperparathyroidism was diagnosed. Cervical ultrasonography showed an image compatible with a parathyroid adenoma and a surgical neck exploration was performed. The left upper parathyroid gland was removed, and the pathological study revealed a 12.5 g parathyroid adenoma. Intraoperative biopsy of the inferior left gland showed the absence of fatty tissue; the upper right gland had a normal appearance and the lower right gland was not identified. After surgery, the calcium concentration was 2.67 mmol/l and PTH 118 ng/l.

Twelve months after surgery the patient underwent repeat cervical surgery for a thyroid nodule casually found in an ultrasonographic study. No pathological parathyroid tissue was found and a right hemithyroidectomy was performed. The pathological study showed a medullary carcinoma and the thyroidectomy was completed. Therefore, the patient was diagnosed with MEN-2A. Calcitonin was 75.8 ng/l (normal range 23–71) after surgery and 57 ng/l 17 months later. Metanephrines and vanillylmandelic acid concentrations were normal. Genetic study did not reveal any known mutation in the MEN-2A gene. Figure 1 shows calcaemia and PTH over time.

The patient didn't have a known familial history of hypercalcaemia or any thyroid or adrenal neoplasia, but after this

Abbreviations: MEN-2A, multiple endocrine neoplasia syndrome type-2A; PTH, parathyroid hormone

Figure 1 Concentration of serum total calcium during follow up. Dots represent PTH concentration. Normal range for calcium is represented between dotted lines. Arrows represent surgical procedures. (A) Upper left parathyroid gland removal. (B) Right hemithyroidectomy. (C) Total thyroidectomy. (D) Pulmonary segmentectomies.

diagnosis his son was studied and a primary hyperparathyroidism was discovered. A subtotal parathyroidectomy and total prophylactic thyroidectomy were performed. Pathology of the thyroid showed hyperplasia of C cells.

Six years after the initial diagnosis, chest radiography showed multiple nodular images; the largest was 10 mm in size. Carcinoembryonic antigen was 9.4 µg/l (normal <3) and calcitonin was undetectable. A diagnosis of metastatic medullary thyroid carcinoma was then assumed. No additional treatment was administered.

Ten years after the initial diagnosis, serum calcium was 3.77 mmol/l, phosphorus 0.84 mmol/l, alkaline phosphatase 365 U/l (normal range 56–119), and PTH 1399 ng/l. The patient developed a severe osteitis fibrosa cystica. It was thought that this was caused by a growth of hidden parathyroid adenomatous or hyperplastic tissue, and image techniques were performed. A ^{99m}Tc-sestamibi scan showed mediastinic activity compatible with an ectopic parathyroid gland. Magnetic resonance imaging confirmed this finding and showed an increase in the size of the pulmonary nodules. The patient underwent surgery again to remove the pathological parathyroid tissue and as much metastatic medullary thyroid carcinoma tissue as possible, at which time mediastinic fat was removed and seven pulmonary segmentectomies were performed. A meticulous pathological study of the mediastinic fat could not find any parathyroid tissue, but both an enlarged lymphatic node and the pulmonary lesions showed parathyroid carcinoma metastasis. Immunohistochemistry was positive for PTH and negative for calcitonin in pulmonary samples. Postsurgical serum calcium fell to 2.0 mmol/l, PTH to 588 ng/l, carcinoembryonic antigen to 4.7 µg/l, and alkaline phosphatase to 154 U/l.

DISCUSSION

To our knowledge, this is the second reported case of MEN-2A associated parathyroid carcinoma.² We misdiagnosed the pulmonary nodules because no signs of malignancy were found in the pathological study of the original parathyroid samples and because parathyroid carcinoma in MEN-2A is exceedingly rare. This unusual presentation, with high levels of carcinoembryonic antigen, and the possibility that low basal calcitonin was a false negative result,³ supported the diagnosis of metastatic medullary thyroid carcinoma. The rise in calcium concentrations was attributed to growth of parathyroid adenomatous or hyperplastic tissue. Synthesis of carcinoembryonic antigen is well known in medullary carcinoma,⁴ but has not been reported in parathyroid carcinoma, although it is a very unspecific marker.

Another interesting issue in this case was the initial serum calcium level. Usually MEN-2A associated hyperparathyroidism is mild and develops after the diagnosis of medullary

Learning points

- MEN-2A is an autosomic dominant disorder which comprises medullary thyroid carcinoma and variable prevalences of hyperparathyroidism and pheochromocytoma.
- Hyperparathyroidism is usually caused by parathyroid hyperplasia and, rarely, parathyroid adenoma. The presence the parathyroid carcinoma in MEN-2A is very unusual.
- Parathyroid carcinoma often presents as a local invasion or recurrence, and a severe hypercalcaemia may be caused by distant metastases, particularly to the lung.

thyroid carcinoma. The discordance between high PTH and normal calcium level after surgery in our patient may suggest a low bioactivity of the PTH molecule.

If we had suspected the real diagnosis we would have operated on the patient when the pulmonary nodules were discovered, to remove parathyroid tissue and avoid or delay the bone disease. We think physicians need an open mind and should be aware that sometimes a patient can be "special".

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