CASE REPORT

Uncommon association of cerebral meningioma, parathyroid adenoma and papillary thyroid carcinoma in a patient harbouring a rare germline variant in the *CDKN1B* gene

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Accepted 28 December 2015

SUMMARY

Multiple endocrine neoplasia type 4 (MEN 4) is a novel form of multiple endocrine neoplasia caused by mutations in the *CDKN1B* gene. Its clinical presentation includes MEN 1-related tumours such as parathyroid and anterior pituitary tumours in possible association with gonadal, adrenal, renal and thyroid tumours as well as facial angiofibromas, colagenomas and meningiomas. We describe the case of a patient with meningioma, papillary thyroid carcinoma, parathyroid adenoma and, additionally, Hürthle cell adenoma, cholesteatoma and uterine leiomyomas. Considering that this association could represent a MEN 4-like phenotype, we looked for germline mutations in the *CDKN1B* gene. A rare heterozygous single nucleotide substitution c.397C>A was identified. Its role as a susceptibility factor remains to be established.

BACKGROUND

The association of cerebral meningioma (CM), parathyroid adenoma (PA) and papillary thyroid carcinoma (PTC) was first reported in 1991 by Cagnano *et al*[1] in a patient with lymphangioleiomyomatosis, multiple soft-tissue tumours, fibrous tumour of the lung, cavernous haemangioma of the liver and nodular stromal hyperplasia of the ovary. In 2000, Yamakita *et al*[2] described the second case of this association along with thyroid follicular adenoma, temporal astrocytoma, haemangioma of the external auditory meatus and oral papilloma. Caliumi *et al*[3] reported a third case, in 2006.

Hyperparathyroidism may be part of familial syndromes such as multiple endocrine neoplasia type 1 (MEN 1) or MEN 2A. Hyperparathyroidism occurs in more than 90% of MEN 1 patients whereas it occurs in only 10–30% of MEN 2A patients. Meningiomas, occasionally, have been reported in patients with MEN 1.

Assuming a genetic predisposition for the triad CM, PA and PTC, Yamakita *et al*[2] and Caliumi *et al*[3] looked for mutations in the *MEN 1* and *RET* genes responsible for MEN 1 and MEN 2, respectively. No mutations were found in their patients.

MEN 4 is a novel form of multiple endocrine neoplasia including MEN 1-related tumours such as parathyroid and anterior pituitary tumours in possible association with gonadal, adrenal, renal and thyroid tumours as well as facial angiofibromas, colagenomas and meningiomas. It is caused by mutations in the *CDKN1B* gene.[4]

CASE PRESENTATION

A 56-year-old woman was referred to our department after being submitted to a total thyroidectomy plus central and right lateral neck dissection at a different institution. The histological diagnosis was of multifocal PTC (largest diameter 2 cm) with areas of classic pattern, follicular pattern and, additionally, of follicular oncocytic pattern; there was evidence of extrathyroidal extension and lymph node metastases; pT3(m)pN1b, a coexisting Hürthle cell adenoma (largest diameter 1.5 cm), was also identified. Routine postoperative blood tests disclosed high levels of serum calcium. Further tests favoured the diagnosis of primary hyperparathyroidism: serum calcium 12.7 mg/dL (normal: 8.5–10.2), serum phosphorus 2.2 mg/dL (normal: 2.7–4.6) and PTH 148 pg/mL (normal: 10–65). Neck ultrasonography and a sestamibi scan were concordant and suggested enlargement of the left inferior parathyroid. Medical treatment for hypercalcaemia was started with hydration and *bisphosphonates* in order to proceed to adjuvant ^{131}I treatment. Later, a surgery aimed at resection of the left inferior parathyroid was performed and the histological diagnosis was of PA.

The patient's medical history revealed atypical meningioma (grade II), cholesteatoma and uterine leiomyomas.

INVESTIGATIONS

We looked for germline mutations in the *MEN 1*, *RET* and *CDKN1B* genes. A heterozygous single nucleotide substitution c.397C>A was identified in the *CDKN1B* gene.

OUTCOME AND FOLLOW-UP

At last observation (28 months after thyroid surgery and 12 months after parathyroid surgery), the patient was in remission of thyroid cancer, and serum calcium and PTH were normal.

DISCUSSION

This is the fourth report, over a 24-year period, of the association between CM, PA and PTC. The type of tumours and the coexistence of other components differed from patient to patient, consistent with the hypothesis of a MEN 4-like syndrome despite non-familial presentation.

Germline mutations of the *CDKN1B* gene, which encodes the 196 aminoacid cyclin-dependent

To cite: Bugalho MJ, Domingues R. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2015-213934

kinase inhibitor $p27^{kip1}$, have been implicated in the development of MEN 4 in humans. The heterozygous variant documented in the patient reported here—c.397C>A—directing a Pro133Thr substitution in the translated p27 protein, was already observed in germline DNA of a patient with an apparently sporadic PA.[5] Whether this variant is a mutation or a rare polymorphism is uncertain. The allele A frequency is estimated at <0.01 in the National Center for Biotechnology Information (NCBI) and Ensembl databases. It is predicted to be tolerated by *in silico* analysis using SIFT and PolyPhen software. However, its functional consequences remain to be fully established.

Learning points

- Hyperparathyroidism may be part of different familial syndromes such as multiple endocrine neoplasia type 1 (MEN 1), MEN 2A and MEN 4.
- MEN 4 is a novel form of multiple endocrine neoplasia with features that overlap the clinical features of the MEN 1 syndrome.
- Germ line mutations in *MEN1*, *RET* and *CDKN1B* genes are the underlying cause of MEN 1, MEN 2 and MEN 4, respectively.

The triad—CM, PA and PTC—was associated, for the first time, with a rare germline variant in a gene known to be responsible for the MEN 4 syndrome.

Contributors MJB was involved in the conception, design, interpretation of data, drafting, revision and final approval. RD was involved in the molecular analysis, revision and final approval.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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