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**Case Report**

# A Pituitary Macroadenoma Cosecreting Prolactin and Growth Hormone in a Patient With Multiple Endocrine Neoplasia Type 4

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## Abstract

Multiple endocrine neoplasia type-4 (MEN4) is a rare form of multiple endocrine neoplasia due to a pathogenic variation in the cyclin-dependent kinase inhibitor 1B (*CDKN1B)* gene. It has a similar presentation to patients with multiple endocrine neoplasia type-1 (MEN1), with primary hyperparathyroidism and pituitary adenomas being the most common features. In this case, we describe a 54-year-old woman presenting with a pituitary macroadenoma cosecreting growth hormone and prolactin and primary hyperparathyroidism. She was initially managed with cabergoline without satisfactory response. Eventually she proceeded to transsphenoidal pituitary resection of the adenoma, and histology revealed appearances consistent with a mixed somatotroph-lactotroph adenoma. Subsequently genetic analysis confirmed the presence of a pathogenic variant in the *CDKN1B* gene (*CDKN1B c.410del*), in keeping with a diagnosis of MEN4. This is the first case of a cosecreting pituitary macroadenoma to be described in a patient with MEN4.

**Key Words:** MEN4, prolactin, growth hormone, pituitary tumor, cosecreting

**Abbreviations:** ACTH, adrenocorticotropin; *CDKN1B*, cyclin-dependent kinase inhibitor 1B gene; IGF-1, insulin-like growth factor-1; MEN1, multiple endocrine neoplasia type-1; MEN4, multiple endocrine neoplasia type-4; MRI, magnetic resonance imagining; MSLA, mixed somatotroph and lactotroph adenoma.

## Introduction

MEN4 is a rare disorder due to a pathogenic variation of the *CDNK1B* gene that was first identified in 2006 [1]. It was initially termed *MENX*, with a change in nomenclature to MEN4 in 2008. Before *CDNK1B* gene testing, patients with MEN4 were diagnosed as having mutation-negative multiple MEN1, based on their clinical presentation [2]. The prevalence of MEN4 in phenotypic MEN1 patients that are negative for a pathogenic variation in the MEN1 gene is less than 1% [3]. With fewer than 100 cases of MEN4 having been reported in the literature, its clinical presentation and genotype-phenotype correlation is still being characterized. To date, it appears that patients with MEN4 present later and with milder symptoms than those with MEN1 [4]. The most common presentation of this condition is the combination of hyperparathyroidism and an adenoma of the anterior pituitary gland, although other features clinical features have been described, including pancreatic neuroendocrine tumors, papillary thyroid carcinoma, adrenocortical tumors, thymic tumors, and renal angiomyolipomas [1, 5]. Nonfunctioning and hormone-secreting pituitary tumors both have been reported. In MEN1 prolactinomas are the most common functioning pituitary adenoma. By contrast, growth hormone– and adrenocorticotropin (ACTH)-producing pituitary adenomas are the most common in MEN4 and prolactinomas are rare. Plurihormonal pituitary tumors are more common in MEN1 than sporadic pituitary tumors [6]; however, to date, they have not been reported in MEN4. Here, we describe the first case of a plurihormonal pituitary tumor in a patient with genetically proven MEN4.

## Case Presentation

In 2003, a 54-year-old woman was admitted to the hospital with epigastric pain, nausea, and vomiting. She also gave a 1-year history of fatigue and headaches. She was 6 years post menopausal. She was taking no medications and had no significant past medical history. She denied galactorrhea or a history of kidney stones. There was no family history of endocrine disorders. On clinical examination she had clinical features consistent with acromegaly, including large hands and feet, coarse facial features, and hirsutism. Laboratory investigations showed a raised insulin-like growth factor-1 (IGF-1) concentration, hyperprolactinemia, and evidence of hyperparathyroidism (discussed later).

## Diagnostic Assessment

At the time of presentation the patient had a plasma IGF-1 concentration of 590 µg/L (SDS > + 5.0) (reference range, 69-246 µg/L), prolactin 12 459 mIU/L (585 µg/L) (reference

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**Table 1. Oral glucose tolerance test (75 g) with glucose and growth hormone measurement**

| Time, min | Glucose mmol/L (mg/dL) | Growth hormone, µg/L |
|---|---|---|
| 0 | 5.6 mmol/L (100 mg/dL) | 4.6 |
| 30 | 9.6 mmol/L (173 mg/dL) | 2.8 |
| 60 | 8.3 mmol/L (150 mg/dL) | 7.1 |
| 90 | 5.5 mmol/L (99 mg/dL) | 4.8 |
| 120 | 5.2 mmol/L (94 mg/dL) | 5.6 |

Normal range for plasma glucose during oral glucose tolerance test: 0 minutes: less than 5.5 mmol/L (100 mg/dL); 120 minutes less than 7.8 mmol/L (140 mg/dL). Normal response of growth hormone is suppression to less than 0.3 µg/L.

range, 102-496 mIU/L [4.8-23.3 µg/L]), cortisol 795 nmol/L (28.8 µg/dL) (reference range, 171-536 nmol/L [6.1-19.4 µg/dL]), free thyroxine 12.1 pmol/L (0.94 ng/dL) (reference range, 10-24 pmol/L [0.77-1.86 ng/dL]), thyrotropin 1.28mIU/L (reference range, 0.5-4.7 mIU/L), follicle-stimulating hormone 44 IU/L (postmenopausal reference range, 20-138 IU/L), luteinizing hormone 11 IU/L (postmenopausal reference range, 15-62 IU/L). The serum calcium level was elevated at 2.82 mmol/L (11.3 mg/dL) (reference range, 2.1-2.6 mmol/L [8.4-10.4 mg/dL]), phosphate 0.81 mmol/L (2.51 mg/dL) (reference range, 0.81-1.55 mmol/L [2.51-4.80 mg/dL]), parathyroid hormone 10.3 pmol/L (97.1 pg/mL) (reference range, 1.6-7.0 pmol/L [15.1-66 pg/mL]), and a 24-hour urine calcium concentration was 7.1 mmol/24 hours (284 mg/24 h) (reference range, 2.5-7.5 mmol/24 h [100-300 mg/24 h]). The serum gastrin concentration was normal at 70 ng/L (reference range, 30-150 ng/L). A 24-hour urinary free cortisol concentration was normal at 379 nmol/24 hours (137 µg/24 h) (reference range, 100-400 nmol/24 h [36-144 µg/24 h]).

A glucose tolerance test was performed indicating failure to suppress growth hormone levels and normal glucose tolerance (Table 1).

A computed tomography scan of the abdomen was normal apart from thickening of the greater curvature of the stomach. Upper gastrointestinal endoscopy revealed grade 3 esophagitis, prominent folds in the body of the stomach, and a large duodenal ulcer. Tests were positive for *Helicobacter pylori*, and biopsies revealed chronic gastritis. Magnetic resonance imagining (MRI) of the pituitary revealed a pituitary macroadenoma measuring $2.3 \times 1.9 \times 1.5$ cm (3.4 $cm^3$) invading the right cavernous sinus (scans no longer available).

The clinical presentation together with the diagnostic tests confirmed a diagnosis of a pituitary tumor secreting both growth hormone and prolactin in a patient with underlying hyperparathyroidism. The patient met the criteria for a clinical diagnosis of MEN1 and proceeded to genetic testing; however, no pathogenic variations in the menin gene were identified.

## Treatment

Initially, the patient commenced a trial of cabergoline therapy. This resulted in normalization of serum prolactin levels; however, the IGF-1 level remained significantly elevated. Eighteen months following diagnosis, cabergoline was discontinued, and she underwent transsphenoidal resection of her pituitary macroadenoma. Pathological examination of the tissue resected revealed appearances consistent with a mixed somatotroph-lactotroph adenoma (Fig. 1).

## Outcome and Follow-up

Initially, following surgery, her IGF-1 level normalized although she remained hyperprolactinemic, suggesting that remnant pituitary tumor tissue was present. An MRI scan 8 months postoperatively revealed the presence of a $2.1 \times 1.5 \times 1.2$ mm (1.97 $cm^3$) pituitary tumor remnant (Fig. 2).

Over the subsequent 2 years her IGF-1 concentration gradually increased and treatment with a somatostatin analogue was reintroduced with normalization of the IGF-1 level. The prolactin level remained elevated at approximately 2600 mIU/L (122 µg/L), and the MRI scan appearances remained unchanged. Her hyperparathyroidism was stable with a serum calcium of 2.7 mmol/L (10.8 mg/dL), and she had not developed any complications of this condition. In 2010 the patient developed gallstones, likely due to somatostatin analogue treatment, and underwent a cholecystectomy.

Repeat genetic testing was performed 9 years post surgery and remained uninformative. Seventeen years after diagnosis, updated testing for the *MEN1* gene and 3 additional genes (*AIP*, *CDC73*, and *CDKN1B*) was performed. This revealed a pathogenic variant in the *CDKN1B* gene (*CDKN1B c.410del*), in keeping with a diagnosis of MEN4. Genetic testing was subsequently offered to her relatives; however, none have pursued this option.

Twenty years following initial presentation, at age 74 years, the patient remains well on monthly somatostatin analogue treatment, with normal IGF-1 levels (161 µg/L SDS +1.3), a prolactin concentration of 2912 mIU/L (137 µg/L), and stable appearances of her pituitary tumor remnant on MRI scan. Her hyperparathyroidism has not progressed (calcium 2.64 mmol/L [10.58 mg/dL]), apart from the development of osteopenia, treated with cholecalciferol. Cross-sectional scanning of the pancreas reveals no abnormalities and both chromogranin A (92 µg/L) and gastrin (79 ng/L) levels are normal.

## Discussion

MEN4 was first described in 2006 in a MEN-like syndrome in the rat and then in a family with mutation-negative MEN1 and is transmitted in an autosomal dominant inheritance pattern [1]. The gene responsible, *CDKN1B*, is on chromosome 12 and encodes the protein p27Kip1 (p27). P27 is a cyclin-dependent kinase inhibitor that acts as a tumor-suppressor by regulating cell cycle progression and consequently cell proliferation. The product of the menin gene appears to modulate the activity of *CDKN1B* gene [7]. Pathogenic variants of the menin gene result in MEN1. This explains the similarity of the clinical presentation of MEN1 and MEN4.

MEN4 is transmitted in an autosomal dominant pattern and has a prevalence of less than one in a million [8]. MEN1 is significantly more prevalent than MEN4. Approximately 10% of patients with the MEN1 phenotype have no pathogenic variations identified in the menin gene and are termed *phenocopies*. In a large French study only 4 out of 5600 (0.07%) MEN1 phenocopy patients were found to have a pathogenic variant of the *CDKN1B* gene [3]. The largest case series of genetically proven MEN4 identified that 53% developed primary hyperparathyroidism and 23.2% developed pituitary adenomas [8]. This compares to 90% to 100% of patients with MEN1 developing primary hyperparathyroidism and 30% to 40% developing pituitary adenomas. Of the patients that develop pituitary tumors with MEN4, the most common

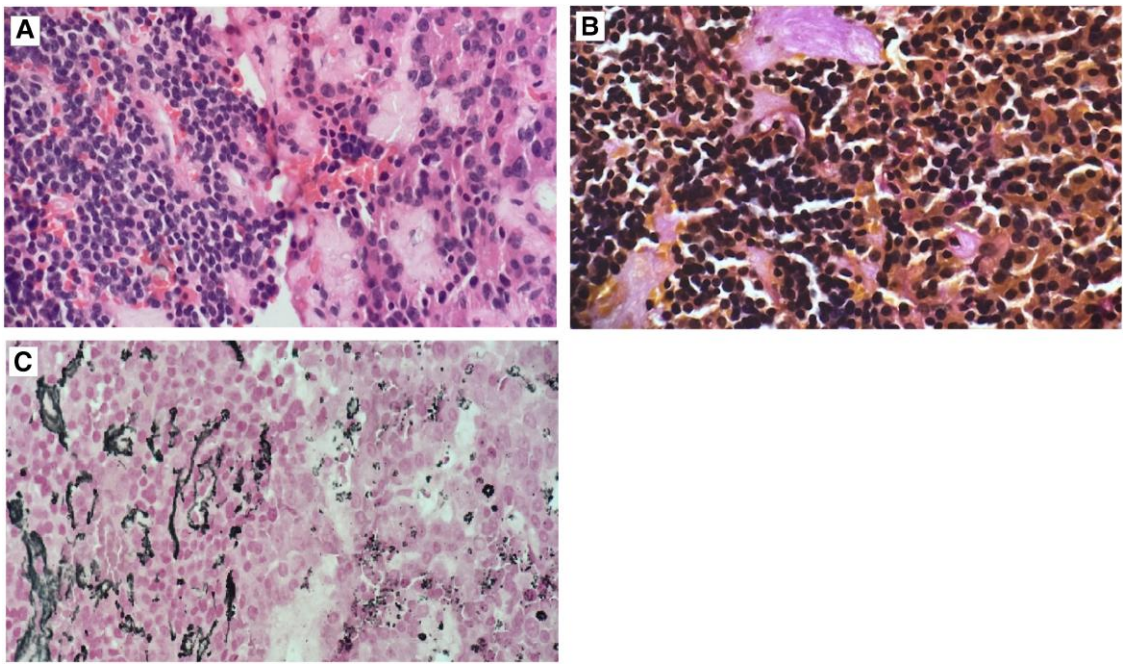


**Figure 1.** Histology showing a mixed pituitary neuroendocrine tumor comprising two distinct cell populations. A, Hematoxylin-eosin (H&E) staining shows a smaller, uniform cell population with scant cytoplasm (left) characteristic of a sparsely granulated lactotroph tumor, and a second population of larger cells with abundant eosinophilic cytoplasm (right) characteristic of a densely granulated somatotroph tumor (H&E, original magnification × 400). B, Periodic acid Schiff–Orange G (PAS-OG) staining highlights the abundant orange acidophilic cytoplasm of the second population of densely granulated somatotroph tumor on the right (PAS-OG, original magnification × 400). C, Both cell populations show a disrupted reticulin network in keeping with their neoplastic nature (reticulin, original magnification × 400).

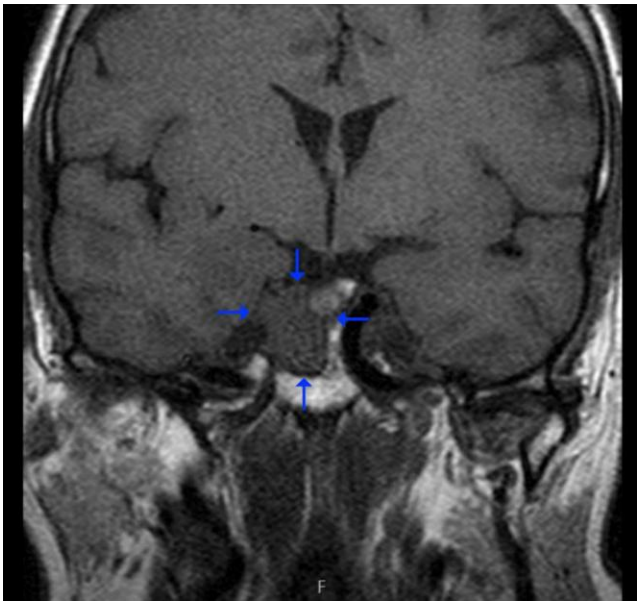

**Figure 2.** Coronal noncontrast T1 image of the right pituitary region postoperatively. Arrows point to the right pituitary mass.

functioning tumors produce growth hormone or ACTH [8]. Only one confirmed case of a prolactinoma in a patient with MEN4 has been reported [9]. This contrasts with MEN1, in which prolactinomas are the most commonly presenting pituitary adenoma. To date, no cases of MEN4 patients with plurihormonal pituitary adenomas have previously been reported.

Plurihormonal pituitary tumors can be found both sporadically and as part of genetic syndromes such as MEN1. Approximately 20% of patients with acromegaly have a pituitary tumor that cosecretes both growth hormone and prolactin [10]. In MEN1 they comprise 7% to 10% of functioning pituitary tumors, with the most common hormones cosecreted being prolactin and growth hormone [11]. With this case, plurihormonal pituitary tumors cosecreting prolactin and growth hormone can now be added to the potential presentations of MEN4.

Plurihormonal tumors producing growth hormone and prolactin can be divided histologically into mammosomatotroph and mixed somatotroph and lactotroph adenomas (MSLAs). These account for approximately 25% of growth hormone–producing adenomas. MSLA tumors are typically larger, have higher preoperative prolactin and IGF-1 levels, and are more invasive with consequently lower cure rates [12].

First-line treatment of acromegaly is surgery with medical therapy reserved for those with persistent disease postoperatively [13]. Somatostatin analogues are generally the first-line medical therapy, with the addition of pegvisomant or dopamine agonist therapy reserved for those who do not achieve biochemical remission with somatostatin analogue therapy alone. A recent report suggests that patients with plurihormonal pituitary adenomas that cosecrete growth hormone and prolactin respond to combination somatostatin analogue and cabergoline treatment as first-line therapy [14].

In conclusion, we report the first case of a patient with genetically confirmed MEN4 presenting with hyperparathyroidism and a plurihormonal secreting pituitary adenoma. This adds to the list of possible pituitary adenoma presentations in this disorder.

## Learning Points

- Plurihormonal pituitary tumors can occur in MEN4.
- MEN1 phenocopy patients that include a plurihormonal pituitary tumor should be screened for MEN4.
- First-line therapy with a combination of a somatostatin analogue and cabergoline can be considered in the management of combined growth hormone and prolactin-secreting pituitary tumors.

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## Contributors

All authors made individual contributions to authorship. P.M. was involved in the diagnosis and management of the patient and manuscript preparation. L.G. and M.S. were involved in literature review, manuscript preparation, editing, and submission. A.B. and A.F. reviewed, prepared, and contributed pathology and radiology components of the case, respectively. All authors reviewed and approved the final draft.

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## Disclosures

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## Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

## Data Availability Statement

Original data generated and analyzed for this case report are included in this published article.

## References

1. Pellegata NS, Quintanilla-Martinez L, Siggelkow H, *et al.* Germ-line mutations in p27Kip1 cause a multiple endocrine neoplasia syndrome in rats and humans. *Proc Natl Acad Sci U S A*. 2006;103(42):15558-15563.
2. Turner JJ, Christie PT, Pearce SH, *et al.* Diagnostic challenges due to phenocopies: lessons from multiple endocrine neoplasia type1 (MEN1). *Hum Mutat*. 2010;31(1):1089-1101.
3. Chevalier B, Coppin L, Romanet P, *et al.* Beyond MEN1, when to think about MEN4? Retrospective study on 5600 patients in the French population and literature review. *J Clin Endocrinol Metab*. 2024;109(7):1482-1493.
4. Ruggeri RM, Benevento E, De Cicco F, *et al.* Multiple endocrine neoplasia type 4 (MEN4): a thorough update on the latest and least known men syndrome. *Endocrine*. 2023;82(3):480-490.
5. Frederiksen A, Rossing M, Hermann P, *et al.* Clinical features of multiple endocrine neoplasia type 4: novel pathogenic variant and review of published cases. *J Clin Endocrinol Metab*. 2019;104(9):3637-3646.
6. Trouillas J, Labat-Moleur F, Sturm N, *et al.* Pituitary tumors and hyperplasia in multiple endocrine neoplasia type 1 syndrome (MEN1): a case-control study in a series of 77 patients versus 2509 non-MEN1 patients. *Am J Surg Pathol*. 2008;32(4):534-543.
7. Thakker RV. Multiple endocrine neoplasia type 1 (MEN1) and type 4 (MEN4). *Mol Cell Endocrinol*. 2014;386(1-2):2-15.
8. Halperin R, Arnon L, Nasirov S, *et al.* Germline *CDKN1B* variant type and site are associated with phenotype in MEN4. *Endocr Relat Cancer*. 2023;30(1):220174.
9. Seabrook A, Wijewardene A, De Sousa S, *et al.* MEN4, the MEN1 mimicker: a case series of three phenotypically heterogenous patients with unique *CDKN1B* mutations. *J Clin Endocrinol Metab*. 2022;107(8):2339-2349.
10. Wang M, Mou C, Jiang M, *et al.* The characteristics of acromegalic patients with hyperprolactinemia and the differences in patients with merely GH-secreting adenomas: clinical analysis of 279 cases. *Eur J Endocrinol*. 2012;166(5):797-802.
11. de Laat JM, Dekkers OM, Pieterman CR, *et al.* Long-term natural course of pituitary tumors in patients with MEN1: results from the Dutch MEN1 study group (DMSG). *J Clin Endocrinol Metab*. 2015;100(9):3288-3296.
12. Lv L, Jiang Y, Yin S, *et al.* Mammosomatotroph and mixed somatotroph-lactotroph adenoma in acromegaly: a retrospective study with long-term follow-up. *Endocrine*. 2019;66(2):310-318.
13. Fleseriu M, Biller BMK, Freda PU, *et al.* A pituitary society update to acromegaly management guidelines. *Pituitary*. 2021;24(1):1-13.
14. Biagetti B, Araujo-Castro M, Torre EM, *et al.* Effectiveness of combined first-line medical treatment in acromegaly with prolactin cosecretion. *Eur J Endocrinol*. 2024;190(6):458-466.