

# Transdifferentiation of Neuroendocrine Cells

## Gangliocytoma Associated With Two Pituitary Adenomas of Different Lineage in MEN1

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**Abstract:** Gangliocytomas are rare and benign neuronal cell tumors, mostly found in the hypothalamic and sellar regions. Their histogenesis is still the subject of discussions. Herein we present a unique case of a pituitary gangliocytoma associated with a prolactinoma and a corticotroph adenoma in a patient affected by MEN1. The histologic study revealed shared features between adenomatous and neuronal cells, supporting the etiological hypothesis of a common origin or a phenomenon of transdifferentiation. Furthermore, gangliocytoma could be a new tumor related to MEN1. The clinical and histologic observations are discussed and the literature on the topic is reviewed.

**Key Words:** MEN1, gangliocytoma, pituitary, adenoma, transdifferentiation

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Familial cases of pituitary adenomas (PA) represent up to 5% of all PA, with 2.7% related to multiple endocrine neoplasia type 1 (MEN1) and nearly 2.5% are related to the clinical entity familial-isolated PAs (FIPA). Mutations in the tumor suppressor gene *MEN1* predispose to MEN1, an autosomal dominantly inherited disease that is characterized by the presence of tumors in at

least 2 endocrine tissues. PA occur in ~40% of MEN1 cases with an age of onset between 12 and 83 years (mean 38 y) and a prevalence significantly greater in females than in males. Although PA are larger and more often invasive in MEN1 patients than in sporadic cases, malignant tumors are not more frequent.<sup>1–5</sup> Considering the histopathology of PA associated with MEN1 syndrome, prolactinomas are the most frequent (62%) followed by somatotropinomas (9%), clinically nonfunctioning (15%), and Cushing disease (4%). In 2008, Trouillas and colleagues compared 77 surgically resected MEN1 PA with 2509 unselected non-MEN1 sporadic PA. They concluded that MEN1 tumors occurred in younger patients and were larger, more invasive, and more aggressive tumors. A higher frequency of multiple adenomas (4% vs. 0.1%) and hyperplasia (4% vs. 0%) was also found. The frequency of functional PA was identical in the 2 groups, but the proportion of plurihormonal adenomas was significantly higher in the MEN1 group with very unusual associations of hormones: PRL and adrenocorticotrophic hormone (ACTH) or PRL and FSH or plurihormonal growth hormone (GH) adenomas. PA in MEN1 can therefore be seen as having unusual characteristics as compared with non-MEN1 PA.<sup>6</sup> In the current study, we present the first case of a pituitary gangliocytoma associated with a prolactinoma and a corticotroph adenoma in a patient with genetically proven MEN1 syndrome.

### PATIENT PRESENTATION AND METHODS

In 2003, a 21-year-old man from Cameroon presented with symptomatic severe hypercalcemia (3.11 mmol/L) due to primary hyperparathyroidism (218 pg/mL) caused by parathyroid hyperplasia. He was treated surgically with a subtotal parathyroidectomy and thymectomy. Pathologic examination confirmed hyperplasia of the 4 parathyroid glands suggesting a diagnosis of MEN1 syndrome, which was confirmed by genetic testing. The patient harbored a *MEN1* gene mutation in exon 6 resulting in a 1015 deletion introducing a premature stop codon. On investigation, he also had longstanding symptoms of gastric ulcers and esophagitis since childhood, Zollinger-Ellison syndrome due to a duodenal gastrinoma, a pancreatic neuroendocrine tumor, an

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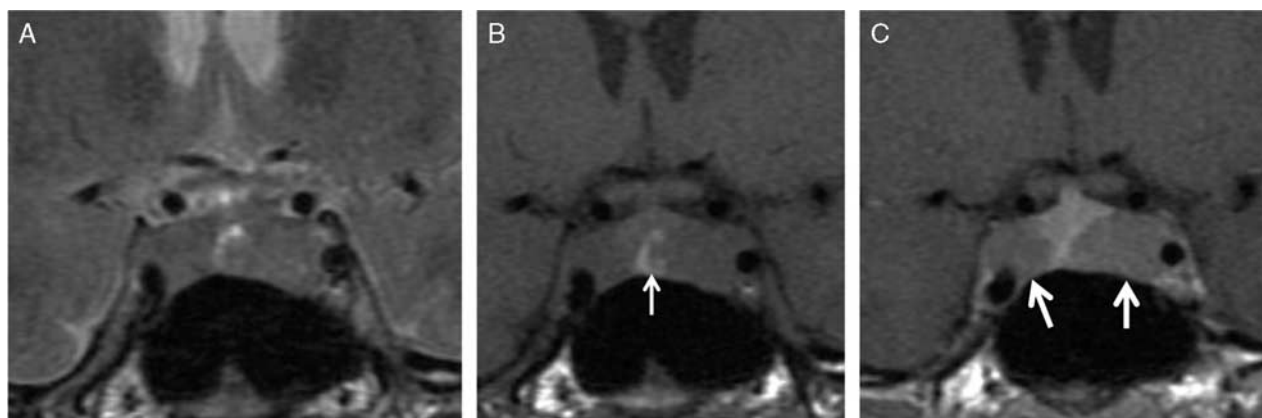
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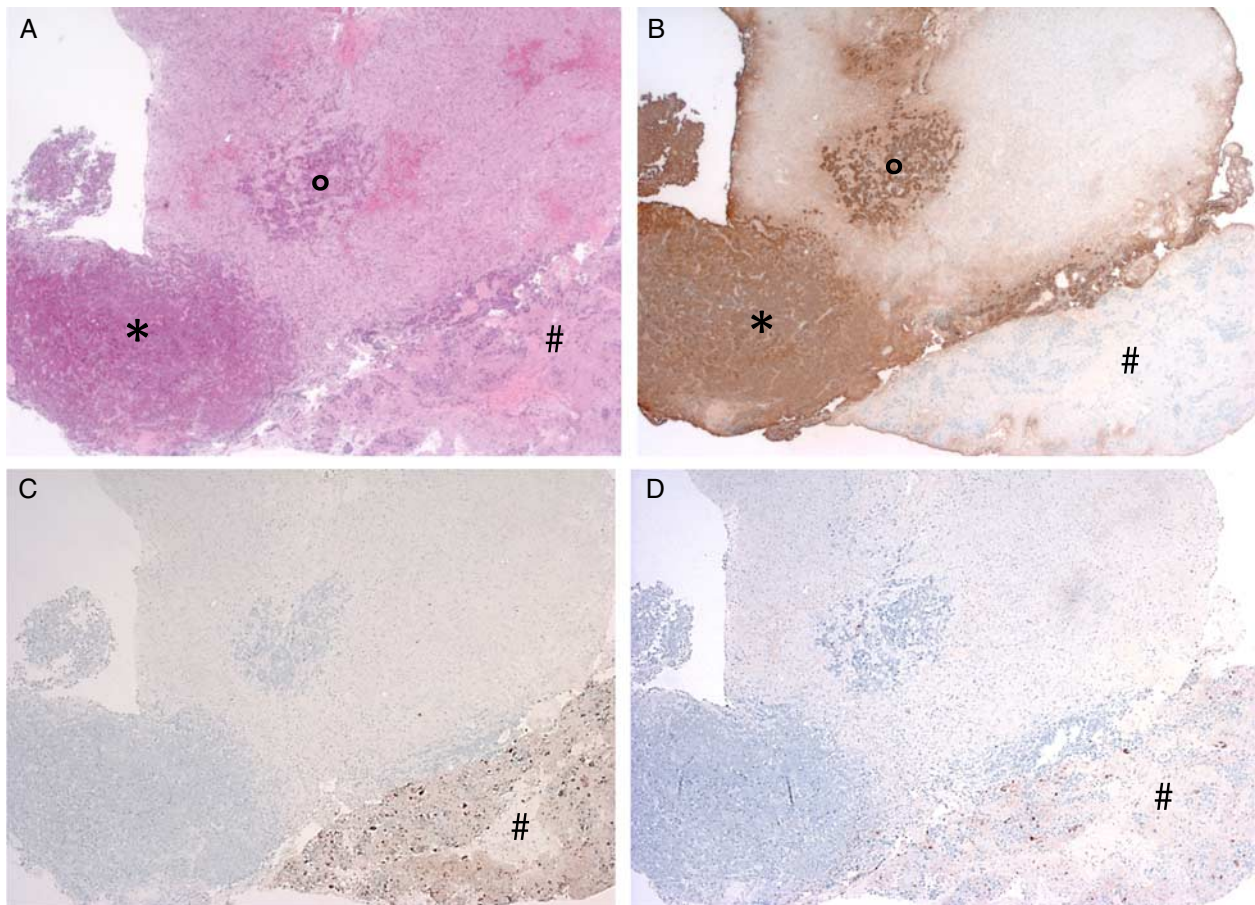
adrenal adenoma, and a double PA with hyperprolactinemia. Urinary catecholamines were normal and there was no hypercortisolism or hyperaldosteronism. Family history was positive; the patient's father had clinical MEN1: a prolactinoma, a pancreatic gastrinoma, and hyperparathyroidism. The patient had 2 brothers in good health. Apart from being overweight (96 kg, body mass index  $30.7 \text{ kg/m}^2$ ), the initial physical examination was normal. In particular there was neither gynecomastia nor galactorrhea and signs of acromegaly or Cushing disease were absent. His sexual development had been unremarkable and he had no erectile dysfunction. He denied headache or visual disturbance. On laboratory testing, his serum prolactin (PRL) level was  $350 \text{ ng/mL}$  (normal  $<20 \text{ ng/mL}$ ), whereas all other hormone levels were normal. His initial magnetic resonance imaging (MRI) scan in 2003 showed a macroadenoma of 12 mm on the right side and a microadenoma of 4 mm on the left. Each of these lesions invaded their respective cavernous sinus (Fig. 1). The patient had bromocriptine and then cabergoline treatment with doses of the latter progressively increasing up to  $2.5 \text{ mg}$  weekly. Serum PRL concentration was reduced but the tumor volumes were unchanged with persistence of the cavernous sinus invasion. The cabergoline treatment was continued to December 2013. Between 2003 and 2010, the patient was asymptomatic with normal PRL and stable pituitary masses. Otherwise, pituitary hormone serum levels remained normal, particularly ACTH and cortisol at 08:00 AM and after a low-dose dexamethasone suppression test. The patient stopped his medical follow-up between 2010 and 2013. In 2013, he came back with a significant weight gain (118 vs. 96 kg, body mass index  $38 \text{ kg/m}^2$ ), with faciotruncal fat distribution. He had developed diabetes mellitus (HBA1c 8.4%). The patient was found to have Cushing disease (free urinary cortisol at  $111 \mu\text{g}/24 \text{ h}$  (normal  $<60$ ), midnight serum cortisol at  $159 \text{ ng/mL}$ , ACTH  $22.4 \text{ pg/mL}$  at 08:00 AM). The Cushing disease was confirmed by petrosal sinus sampling. In December

2013, he underwent transphenoidal surgery to remove the 2 tumors. On postsurgical follow-up after 3 months, the patient's serum PRL level was normal and the serum cortisol level had decreased ( $76 \text{ ng/mL}$  at 08:00 AM). He started to lose weight and blood glucose was well controlled with  $2 \text{ g}$  of metformin per day. The patient is now monitored monthly with a urinary-free cortisol level. On MRI 6 months postoperatively, neither lesion was seen.

On light microscopy, the surgical samples included some fragments of normal adenohypophysis, a fragment of neurohypophysis with "corticotroph basophil invasion." The pars intermedia, immediately in contact with neurohypophysis, appeared enlarged. A basophilic corticotroph microadenoma with strong immunoreactivity for ACTH and cytokeratin (CAM5.2) was observed. Other fragments showed a fibrillary glial/neuropil-like pattern with 2 intermixed cellular populations. These corresponded to a mature neuronal population resembling hypothalamic neurons and another comprising endocrine cells with scant eosinophilic cytoplasm and round nuclei suggestive of PRL-secreting cells. The neuronal component was irregularly distributed, occasionally sparse against a fibrillary background and also occasionally forming clusters. The neurons were variable in shape and size, with binucleation. On immunohistochemistry, the fibrillary background was positive for synaptophysin and neurofilament and negative for glial fibrillary acidic protein; the neurons variably expressed synaptophysin, chromogranin A, and were negative for neurofilament and GH-releasing hormone. The endocrine cells in diffuse arrangement were intermingled with the neuronal component. The majority of cells were strongly positive for PRL and a few were positive for  $\beta$ -FSH (about 5%) and  $\alpha$ -SU ( $<5\%$ ). Pit-1 (mammo-somato-thyrotroph transcription factor) immunostaining showed intense nuclear expression in the PRL-positive cells and also in the nuclei of all neuronal cells. In contrast, corticotroph cells were Pit-1 negative. Neurons were immunoreactive for some anterior pituitary hormones, particularly PRL and rarely



**FIGURE 1.** MRI at the time of diagnosis (2003). Two lesions are identified on either side of the sella turcica. These lesions are ill-defined, isointense on coronal T2-weighted images (A) and coronal T1-weighted images (B). Focal spontaneous T1 hyperintensity (arrow, C) is observed, consistent with hemorrhage. T1 post-gadolinium injection images (C) show 2 well-delimited lesions (arrows) extending to each cavernous sinus.



**FIGURE 2.** Histologic examination ( $\times 40$  magnification). A, H&E stain: on the left of the image (\*) strongly basophil corticotroph microadenoma. In the center of the image (°) neurohypophysis with “basophil invasion” and on the right lower part (#) fibrillar and ganglion cell–rich components of gangliocytoma in collision with nets of endocrine eosinophil cells. B, ACTH immunostaining: on the left of the image (\*) strongly positive corticotroph microadenoma. In the center of the image (°) neurohypophysis with “basophil invasion” strongly positive for ACTH. On the right lower part (#), absence of ACTH expression in gangliocytoma/prolactinoma. C, PRL immunostaining: on the right lower part (#) ganglion cells component of gangliocytoma in collision with nets of endocrine eosinophil cells variably expressing PRL. D,  $\beta$ -FSH immunostaining: on the right lower part (#) ganglion cells component of gangliocytoma variably expressing  $\beta$ -FSH.

for  $\beta$ -FSH and  $\alpha$ -SU (Figs. 2, 3). Overall in both tumor types no mitoses were found and the Ki-67 index was low ( $< 1\%$ ).

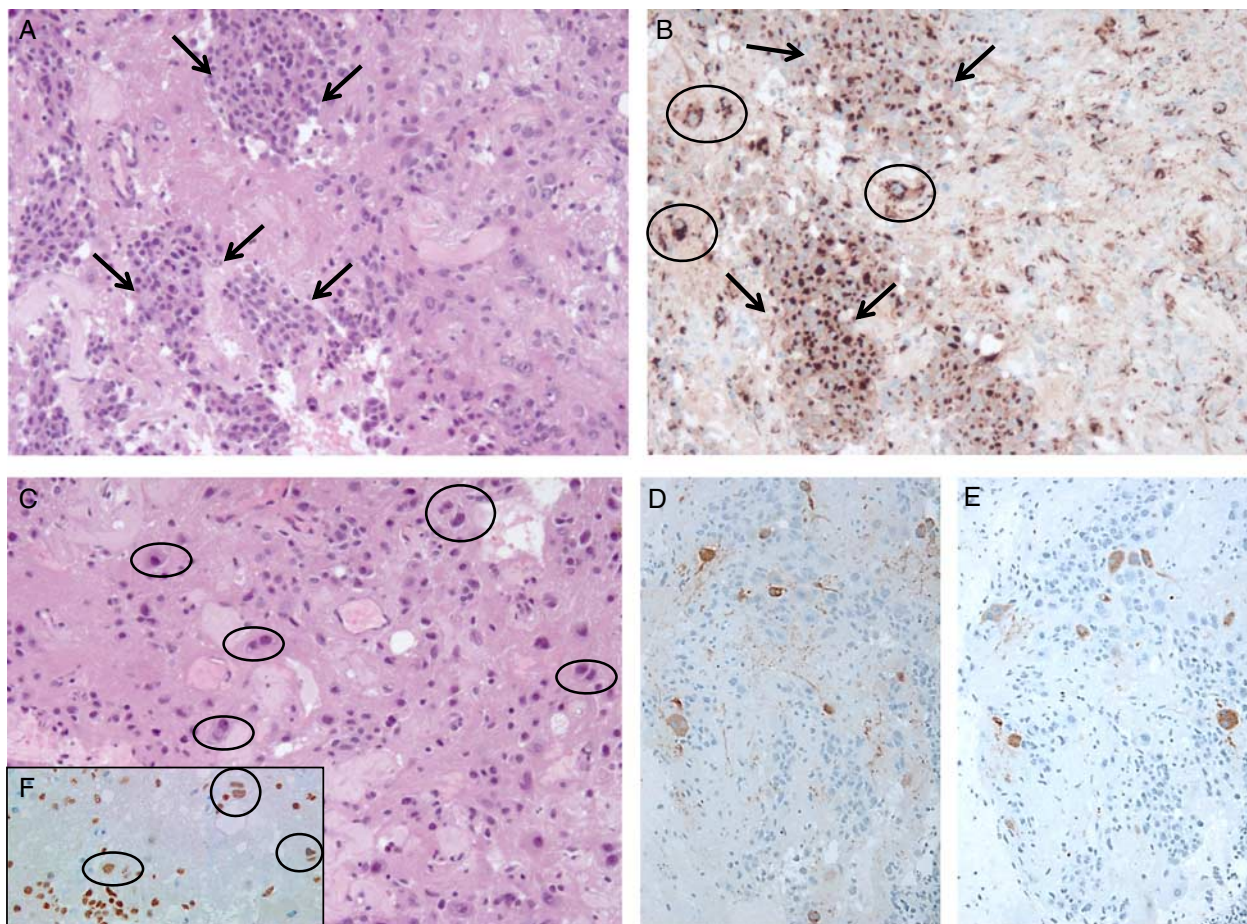
The histologic diagnosis was consistent with a corticotroph microadenoma and a prolactinoma combined with a gangliocytoma.

## DISCUSSION

We report an exceedingly rare case of a patient with a double PA associated with a gangliocytoma in the context of MEN1. Furthermore, the review of the literature revealed no other cases of gangliocytoma reported in MEN1 patients. Clinically, the patient presented with typical MEN1 syndrome with initial symptoms during childhood/adolescence (Zollinger-Ellison syndrome) and a diagnosis of pituitary disease at 21 years old. In some rare cases, a PA is found to coexist with a gangliocytoma.

Worldwide, about 100 cases of PA combined with gangliocytoma have been reported since the first description of this tumor in 1926 by Kiyono and colleagues.<sup>7–9</sup> Gangliocytomas are rare and benign neuronal cell tumors, mostly found in the hypothalamic and sellar regions. Histologically these tumors are composed of mature neuronal cells of variable size, irregular shape (dystrophic appearance), and one or more 1 nuclei (ganglion cells appearance). They are variably immunoreactive for synaptophysin, neuron-specific enolase, and neurofilament protein (suggesting a neural differentiation).<sup>7–9</sup> The neuronal population is accompanied by a fibrillary nontumoral background comprising glial elements and neuropil. Ganglion cells may express hypothalamic factors such as GH-releasing hormone or corticotrophin-releasing hormone, which can stimulate the growth of anterior pituitary cells and eventually promote adenoma formation.<sup>10–13</sup> Hence, most reported





**FIGURE 3.** Histologic examination ( $\times 100$  magnification). A, H&H stain: fibrillar and ganglion cell-rich components of gangliocytoma in collision with nets of endocrine eosinophil cells: the arrows indicate nets of endocrine eosinophil cells. On the right side of the image: ganglion cell-rich component in fibrillary background. B, PRL immunostaining: the arrows indicate nets of endocrine eosinophil cells strongly positive for PRL and the circles show some ganglion cells strongly expressing PRL as cytoplasmic granules. C, H&H stain: fibrillar and ganglion cell-rich components of gangliocytoma with numerous binucleated cells in the circles. D,  $\alpha$ -subunit immunostaining: occasional ganglion cells express  $\alpha$ SU in cytoplasm. E,  $\beta$ -FSH immunostaining: occasional ganglion cells express  $\beta$ -FSH in cytoplasm. F, Pit-1 immunostaining: numerous nuclei of small size are positive for Pit-1, corresponding to PRL-positive cells but also large binucleated ganglion cells strongly expressed Pit-1 (circles).

cases have occurred in the setting of a somatotropinoma causing acromegaly. Similarly, corticotrophin-releasing hormone expression in ganglion cells associated with corticotroph hyperplasia have been described.<sup>14</sup> The association of a gangliocytoma and a prolactinoma is very rare ( $< 10$  cases in the literature). There are also few cases of the association of a gangliocytoma and a mixed PA (GH/PRL). The gangliocytoma may contain some PRL secretagogues such as PRL-releasing peptide.<sup>15–18</sup>

The association between gangliocytoma and PAs is controversial.<sup>19</sup> The most popular hypotheses about the etiology are: (1) hypothalamic-releasing hormone secretion by ganglion neural cells leads to paracrine stimulation and adenomatous cells proliferation as a secondary phenomenon related to high local concentrations of trophic factors<sup>20–22</sup>; (2) ganglion cells result from the transdifferentiation of adenomatous cells or are progenitor cells able to undergo differentiation into either

endocrine or neuronal cells<sup>8,12,13,23,24</sup>; or (3) the 2 cell types occur coincidentally and are unrelated to the development of PA in a preexisting neuronal tumor with the ganglion cell component resulting from the abnormal migration of neurons from hypothalamus.<sup>9</sup> Some studies observed a lack of correlation between the adenoma cell type and the corresponding releasing hypothalamic hormones secreted by ganglion cells.<sup>25–27</sup> Newer perspectives suggest that both neuronal and endocrine cells may originate from the same embryonal pituitary cell rests. These cellular remnants due to the common ectodermic embryonal origin of adenohypophysis and the infundibular region may contain intermediate cells showing features between neuronal and adenohypophyseal elements (as pituitary progenitor or precursor cells). Some authors proposed a reinterpretation of this theory affirming the existence of stem cells in adult pituitary that are capable of multidirectional differentiation.<sup>8,27</sup> In other

endocrine organs such as adrenal gland, a possible pathologic analogue of this, namely pheochromocytoma-ganglioneuroma, has been well characterized and is also described in the setting of MEN2. In vitro studies have reinforced the ability of endocrine neoplastic cells of pheochromocytoma to transdifferentiate into ganglion cells when stimulated with NGF.<sup>28,29</sup> In our case, we describe the association of a gangliocytoma and a double PA in a patient with MEN1. To date, to our knowledge, this is the first case reported in the literature. A high frequency of multiple adenomas and pituitary hyperplasia is seen in MEN1,<sup>6</sup> but in the literature no evidence of coexisting gangliocytoma has been reported. The *MEN1* gene encodes for the protein Menin, which acts as a tumor suppressor, involved in different important cell functions. Menin interacts with many other proteins, including several transcription factors and probably, modulates cell growth, division, and differentiation of endocrine cells. The expression of Pit-1 in both endocrine (PRL) and neuronal cells may suggest a common ectodermal origin for the two components or a phenomenon of transdifferentiation. This feature may also explain the expression of PRL and other anterior pituitary hormones in the cytoplasm of the ganglion cells. Finally, as recently suggested elsewhere,<sup>8,12,13,23,24,30,31</sup> the term gangliocytoma should be limited to hypothalamic tumors and isolated pituitary gangliocytoma without adenoma. A large series to verify the expression of anterior pituitary transcription factors in ganglion cell components associated with PAs is required to validate the hypothesis that the 2 components have the same ectodermal origin.

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