JCEM Case Reports, 2025, **3**, luaf072
https://doi.org/10.1210/jcemcr/luaf072
Advance access publication 18 April 2025
Case Report

Pituitary Complications of Enchondromas Due to Maffucci Syndrome

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Abstract

Maffucci syndrome (MS) is a congenital disorder caused by a gain-of-function variant in isocitrate dehydrogenase-1 (*IDH1*) or isocitrate dehydrogenase-2 (*IDH2*) genes on chromosomes 2 and 15, respectively. Common manifestations include the development of multiple enchondromas, chondrosarcomas, and intracranial tumors such as pituitary adenomas. Endocrinological conditions are less frequently associated with MS. We present a patient with MS with complete anterior pituitary insufficiency with central hypothyroidism, adrenal insufficiency, and hypogonadotropic hypogonadism, which may be related to the mass effect of her intracranial enchondromas. With hormonal treatments including thyroid hormone replacement, hydrocortisone, and cabergoline, the patient's symptoms of fatigue and cold intolerance improved. We highlight the importance of endocrinological evaluation in patients with neurological tumors related to MS.

Key Words: Maffucci syndrome, hypopituitarism, hyperprolactinemia, anterior pituitary insufficiency

Introduction

Maffucci syndrome (MS) and Ollier disease are 2 of the 7 subtypes of enchondromatosis syndrome [1]. MS is a rare, nonhereditary congenital disorder characterized by the development of multiple cartilaginous tumors (enchondromas) and spindle cell hemangiomas. In contrast, Ollier disease leads to multiple enchondromas but is not associated with vascular hemangiomas [1-3]. MS is attributed to somatic mosaicism of the isocitrate dehydrogenase-1 (*IDH1*) or isocitrate dehydrogenase-2 (*IDH2*) genes, which leads to the production of tumor metabolite 2–hydroxyglutaric acid [4-6]. This is believed to restrict cell differentiation by inhibiting the activity of chromatin–modified histones and deoxyribonucleic acid demethylation [2]. As a result, MS enchondromas most commonly arise in the metaphysis of bones.

Frequent manifestations of MS include extremity swelling, gait disturbance, pathological fractures, vascular anomalies, and an increased risk of malignancies. Most malignancies associated with MS are chondrosarcomas, gliomas, and spindle cell hemangiomas [7]. Several associated central nervous system tumors have been identified, including pituitary adenomas and olfactory neuroblastomas [7, 8].

MS is a rare condition with fewer than 300 cases reported globally and even fewer reported associations with endocrinologic disorders [2]. Prior case studies by Hao et al and Ranger et al identified the presence of pituitary adenomas while Nemoto et al discussed a patient with primary hyperparathyroidism; to our knowledge, panhypopituitarism has been reported only once in patients with MS [8-10]. Our case study highlights the importance of understanding and screening for endocrine conditions in patients with MS, including those that may develop iatrogenically.

Case Presentation

Our patient was a 32-year-old female at the time of her first endocrinology assessment at our facility. Her medical history included MS and multiple surgical resections of enchondromas on her extremities and intracranially. She was wheelchair-bound but could walk short distances and took nonopioid medications to manage chronic pain due to her numerous enchondromas. The patient had good insight into her condition and enjoyed reading as a hobby. However, she rarely left her home during the winter, electing to see her physicians only in the summer due to her severe cold intolerance and fatigue.

At the time of presentation, she was in a wheelchair and wrapped in blankets despite her visit occurring in the middle of summer. She reported low energy, dry skin, sensitivity to heat and cold, intermittent headaches, and amenorrhea.

In the preceding years, she had undergone several surgeries including resections of oral hemangiomas, extremity chondrosarcomas, vascular malformations of various extremities, and spindle cell hemangioendotheliomas. At the age of 29, she developed progressive vision loss and was noted on computed tomography imaging of the brain to have a large right skull base enchondroma. Her brain magnetic resonance imaging with and without contrast revealed a large mass involving the right mid-skull base consistent with an enchondroma; there was projection of the lesion into the sellar and suprasellar region (Figs. 1 and 2). She underwent a right frontotemporal craniotomy and superficial temporal artery to middle cerebral artery bypass due to an aneurysm in addition to ventriculoperitoneal shunt placement.

Received: 6 January 2025. **Editorial Decision:** 24 March 2025. **Corrected and Typeset:** 18 April 2025

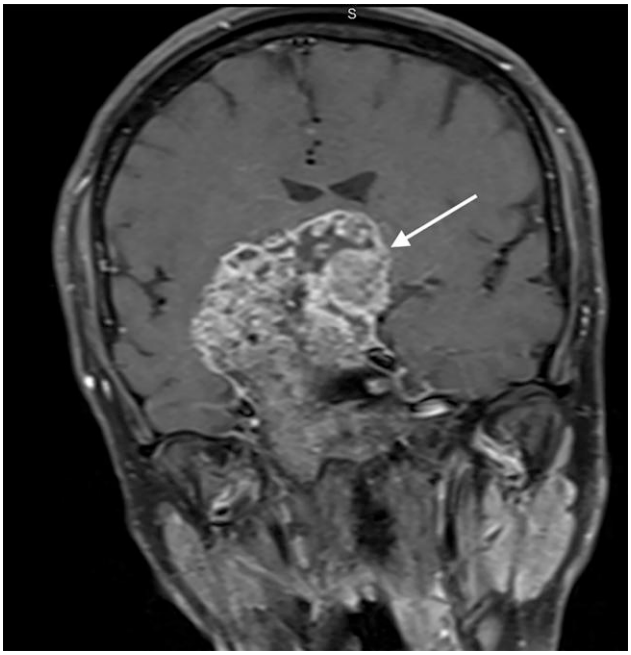

Figure 1. Magnetic resonance imaging of the brain (T1-weighted coronal view) demonstrating a large skull base mass, concerning for an enchondroma, with invagination into the brainstem, including into the pons and to the level of the middle cerebellar peduncle. The size of the mass is approximately 4.7 cm × 5.5 cm. There is mass effect upon the inferior right basal ganglia and inferior frontal lobes.

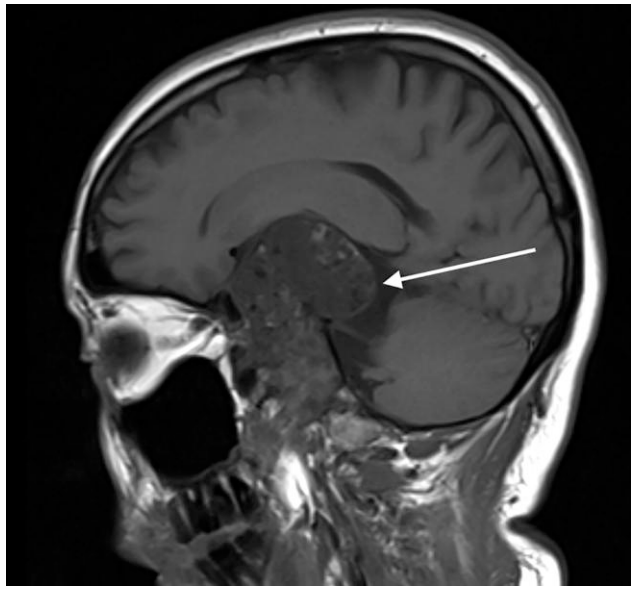

Figure 2. Magnetic resonance imaging of the brain (T1-weighted sagittal view) demonstrating the large skull base mass as described in Fig. 1. The mass appears to destroy the sella turcica and extends into the suprasellar area.

Diagnostic Assessment

Due to the patient's frequent and lengthy hospitalizations, testing including for ACTH, total cortisol, and IGF-1 was delayed until approximately 14 months after initial presentation to the endocrine clinic. The hormone evaluation performed upon presentation, summarized in Table 1, was suggestive of hypopituitarism with central hypothyroidism, hypogonadotropic hypogonadism, and central adrenal insufficiency (Table 1). She was also noted to have hyperprolactinemia.

Treatment

Levothyroxine was initiated and gradually increased over the next 18 months to achieve normal free thyroid levels of 1.6 ng/mL (20.59 pmol/L) (reference range, 0.9-1.8 ng/dL [11.58-23.17 pmol/L]) and free T3 of 2.1 pg/mL (0.03 pmol/L) (reference range, 2.3-4.2 pg/mL [3.53-6.45 pmol/L]). She was also referred to a gynecologist for her low total estrogen and began estrogen replacement therapy. Clinically, her symptoms improved; in particular, her cold intolerance significantly lessened. With treatment, she was able to leave her home in the fall and spring and attend in-person doctor's appointments for the first time in years.

Following the diagnosis of central adrenal insufficiency just over a year after treatment with levothyroxine, she began hydrocortisone 10 mg in the morning and 5 mg at noon. For her secondary amenorrhea, she was started on cabergoline 0.5 mg twice weekly. With hydrocortisone and cabergoline therapy, she had further improvements in her symptoms. Three months after the initiation of hydrocortisone and cabergoline, her ACTH was 8 pg/mL (1.76 pmol/L) (reference range, 6-58 pg/mL [1.32-12.77 pmol/L]) and total cortisol was 2.8 µg/dL (77.25 nmol/L) (reference range, 4.3-22.4 µg/dL [118.62-617.93 nmol/L]); her hydrocortisone dose remained stable, but her cabergoline was gradually decreased given her undetectable prolactin levels of <0.1 ng/mL (<0.10 µg/L) (reference range, 2.8-29.2 ng/mL [2.8-20.2 µg/L]).

Outcome and Follow-up

Our patient has at times been switched from hydrocortisone to dexamethasone upon her neurosurgeon's recommendations for neurosurgical periprocedural necessity or to reduce severe pain or swelling of her intracranial enchondromas. Imaging performed approximately 6 years after the initial imaging demonstrated a continued mass effect of the skull base lesions and continued extension of the mass into the sella turcica and suprasellar area (Figs. 3 and 4). Otherwise, she remains on a stable dose of her levothyroxine and cabergoline.

Discussion

MS is a rare disorder characterized by benign bone tumors that arise in high frequency, often leading to significant physical limitations. Several case reports have identified a possible association between MS and the development of tumors such as central nerve system gliomas and pituitary adenomas, which immunohistochemically demonstrated IDH1 pathogenic variance [7, 8, 11]. Two case studies by Schnall et al and Nemoto et al reported an association between MS and parathyroid adenoma [10, 11]. Miki et al reported on 1 individual with panhypopituitarism related to multiple intracranial tumors including pituitary adenoma and tuberculum sellae enchondroma [12]. While tumors of the skull are common, endocrinological disorders associated with the condition appear to be uncommon.

We report a case of complete anterior pituitary insufficiency concurrent with MS. Our young female patient had an insidious onset of hypopituitarism that initially presented with

Table 1. Hormone evaluation prior to initiation of treatment

Hormone tested	Value	Normal range
TSH	**5.76 μIU/mL (mIU/L)**	0.27-4.20 μIU/mL (0.27-4.20 mIU/L)
Free T4	**0.3 ng/mL (3.86 pmol/L)**	0.9-1.8 ng/dL (11.58-23.17 pmol/L)
Free T3	2.3 pg/mL (0.04 pmol/L)	2.3-4.2 pg/mL (0.04-0.06 pmol/L)
Prolactin	**69.3 ng/mL (69.3 μg/L)**	2.8-29.2 ng/mL (2.8-29.2 μg/L)
Total estrogen	**14.8 pg/mL (14.80 ng/L)**	Early follicular: 30.0-250.0 pg/mL (30.0-250.0 ng/L) Late follicular: 200.0-650.0 pg/mL (200.0-650.0 ng/L) Luteal: 50.0-350.0 pg/mL (50.0-350.0 ng/L)
FSH	**1.3 mIU/mL (1.30 IU/L)**	Follicular: 2.5-10.2 mIU/mL (2.50-10.20 IU/L) Midcycle: 3.4-33.4 mIU/mL (3.40-33.40 IU/L) Luteal: 1.5-9.1 mIU/mL (1.50-9.10 IU/L)
LH	**0.4 mIU/mL (0.40 IU/L)**	Follicular: 1.9-12.5 mIU/mL (1.90-12.50 IU/L) Midcycle: 8.7-76.3 mIU/mL (8.70-76.30 IU/L) Luteal: 0.5-16.9 mIU/mL (0.50-16.90 IU/L)
ACTH	8 pg/mL (1.76 pmol/L)	6-58 pg/mL (1.32-12.76 pmol/L)
Morning total cortisol	**2.0 μg/dL (55.18 nmol/L)**	4.3-22.4 μg/dL (118.63-617.97 nmol/L)
IGF-1	**55 ng/mL (7.21 nmol/L)**	83-280 ng/mL (10.87-36.68 nmol/L)

Abnormal values are bolded. International System of Units are included within parentheses.

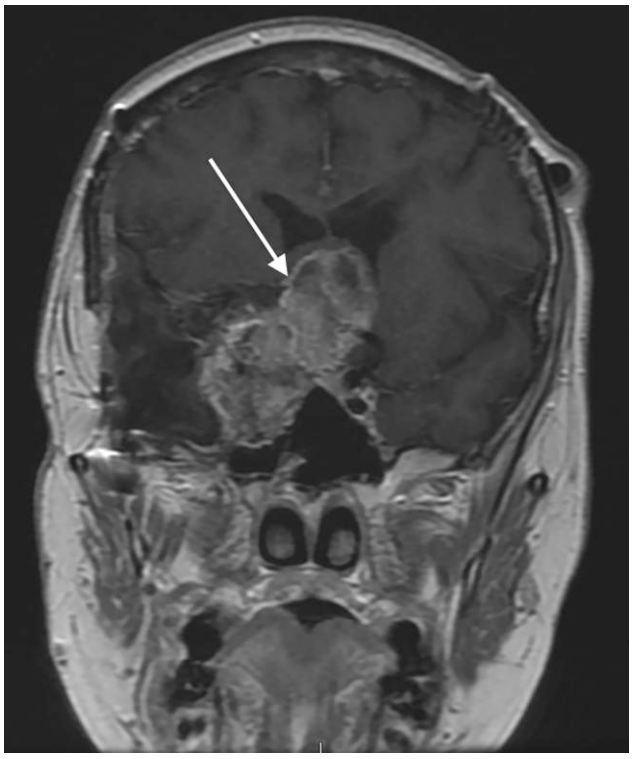

Figure 3. Gadolinium-enhanced magnetic resonance imaging of the brain (T1-weighted coronal view), performed 5 years after the imaging in Figs. 1 and 2, showing a calcified mass on the skull base that extends into the cavernous sinus and sella turcica and leads to mass effect onto the suprasellar area.

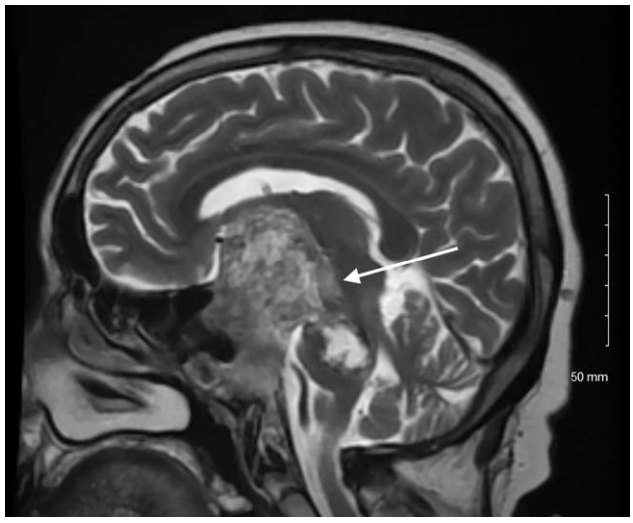

Figure 4. Magnetic resonance imaging of the brain (T2-weighted sagittal view) with increased size of the ventricular system. There is no clear differentiation between the pituitary gland and the skull base mass.

hypothyroidism and subsequently was identified as central adrenal insufficiency in the setting of complete anterior pituitary insufficiency and hyperprolactinemia. Considering the enchondroma identified on magnetic resonance imaging in the sellar region, the pituitary hyposecretion is presumed to be due to a mass effect while the hyperprolactinemia may be secondary to damage of the pituitary stalk section during 1 of her numerous neurologic procedures (Figs. 3 and 4).

Although the progression of our patient's hypopituitarism could not be directly correlated with the enchondroma mass effect, it was presumed to be the most likely etiology of her hormonal hyposecretion. She was initiated on levothyroxine, cabergoline, and hydrocortisone for hormonal replacement, and her symptoms significantly improved.

Although our patient carried a high burden of disease and significant physical limitations, hormonal supplementation resulted in marked subjective improvement. Given the association with MS and the development of gliomas that may require medical or surgical treatment, clinicians may consider close monitoring of endocrine conditions to ensure prompt treatment of intracranial pathologies that affect hormonal balance.

Learning Points

- Individuals with MS require individualized monitoring due to the varied nature of its conditions.
- Patients with neurological masses and symptoms attributable to endocrinological disorders should have a thorough hormonal evaluation.
- Endocrine disorders may present concurrently, such as anterior pituitary insufficiency with hyperprolactinemia as in our patient.

Contributors

All authors made individual contributions to authorship. N.M., R.F., and M.M. contributed to the writing of the manuscript. M.M. evaluated, diagnosed, and managed the patient's ongoing medical conditions. N.M., R.F., and M.M. were involved with manuscript preparation and submission. All authors reviewed and approved the final draft.

Funding

No public or commercial funding.

Disclosures

The authors have no disclosures to state.

Informed Patient Consent for Publication

Signed informed consent was obtained directly from the patient.

Data Availability Statement

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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