

# GROWTH HORMONE–SECRETING PITUITARY CARCINOMA PRESENTING WITH ISOLATED LEPTOMENINGEAL INVOLVEMENT: A CHALLENGING DIAGNOSIS

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## ABSTRACT

**Objective:** To raise awareness of the clinical presentation of growth hormone (GH)-producing pituitary carcinoma and its unique clinical presentation.

**Methods:** A case report of a GH-secreting pituitary carcinoma with predominant leptomeningeal spread presenting as persistent acromegaly post–macroadenoma excision and radiation therapy.

**Results:** A 39-year-old male, diagnosed with a GH-secreting pituitary macroadenoma with acromegaly 3 years prior, presented with persisting acromegalic phenotypic features with associated diabetes mellitus and hypertension. He had undergone an endoscopic transnasal, transsphenoidal adenoma resection, followed 3 months later by conventional cranial irradiation at another center 2 years prior to his current presentation to us. Serum insulin-like growth factor 1 and post 1-hour 100-g oral glucose administration serum GH levels were 1,198 and 393 ng/mL, respectively. Magnetic resonance imaging of the brain with spine screening revealed an empty sella, diffuse enhancing cordal, posterior fossa

and cauda-equina leptomeningeal thickening, suggesting lepto-meningeal spread of a primary neoplastic process. Cytologic examination of cerebrospinal fluid revealed GH-immunopositive malignant cells with pancytokeratin negativity. A diagnosis of GH-secreting pituitary carcinoma with leptomeningeal dissemination was made. He was initiated on intermittent short-acting subcutaneous octreotide and systemic chemotherapy with temozolamide 200 mg/m<sup>2</sup> for 5 consecutive days every 28-days and concomitant skull and spine irradiation (total dose of 36 Grays in 20 fractions). His metabolic parameters improved following 3 cycles of chemotherapy. Interval assessment of disease status is awaited prior to the fourth temozolamide cycle.

**Conclusion:** Pituitary carcinomas are rare. Clinico-biochemical presentation being indistinguishable from that of an adenoma, demonstration of metastasis is essential for diagnosis. Isolated leptomeningeal presentation is a unique presentation of GH-secreting pituitary carcinomas. (AACE Clinical Case Rep. 2017;3:e000-e000)

## Abbreviations:

CSF = cerebrospinal fluid; GH = growth hormone; IGF-1 = insulin-like growth factor 1; MRI = magnetic resonance imaging

## CASE REPORT

A 39-year-old male, diagnosed with acromegaly due to a growth hormone (GH)-secreting pituitary macroadenoma 3 years prior, presented with persisting acromegalic phenotypic features, uncontrolled diabetes mellitus, and hypertension, despite having undergone elsewhere an endoscopic transnasal, transsphenoidal adenoma excision, followed 3 months later by conventional cranial irradiation, in 2012.

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At presentation, he was on oral, 0.5-mg twice-weekly cabergoline and physiologic replacement doses of oral glucocorticoids, levothyroxine, and monthly intramuscular testosterone injections. He denied having had renal stones, recurrent fractures, or progressive weight gain with proximal limb weakness in the past or of similar complaints in his family members.

General physical examination revealed prominent supraciliary arches, prognathism with dental malocclusion, macroglossia, grade 2 acanthosis nigricans, and marked acral enlargement with increased heel pad thickness. Tanner's staging for pubic hair was IV, and testicular volume was 15 mL bilaterally. Ocular examination was significant for visual acuity 6/9 in the left eye, with disc pallor and superior quadrantanopia. Visual acuity was 6/6 in the right eye. Systemic examination was significant for features suggesting left ventricular hypertrophy.

Biochemical investigations indicated optimal glucocorticoid, levothyroxine, and testosterone replacement. Serum insulin-like growth factor 1 (IGF-1) and post 1-hour 100-g oral glucose serum GH levels were 1,608 ng/mL (normal range, 109 to 284 ng/mL) and 302 ng/mL (normal, <0.4 ng/mL), respectively.

Clinical differential diagnoses of residual disease, tumoral recurrence, extrapituitary GH or GH-releasing hormone (GHRH) excess, and rarer possibilities of metastatic pituitary carcinoma were considered.

The excised lesion was confirmed as an atypical, sparsely granulated, GH-producing pituitary adenoma with an mindbomb-1 labeling index of 4% on reviewing the tissue block. Magnetic resonance imaging (MRI) of the brain with dynamic pituitary imaging revealed an empty sella. A whole-body fluorodeoxyglucose-positron emission tomography scan showed metabolically active significant subcarinal and mediastinal lymph nodes.

In this clinical setting, GHRH-secreting non-Hodgkin's lymphoma with residual secondary somatotroph adenoma was considered. An image-guided lymph node biopsy was performed. Histopathologic examination of the biopsied tissue revealed granulomatous inflammation with no features suggestive of lymphoma.

Evaluations for mediastinal lymphadenopathy associated systemic etiologies, including sarcoidosis, Wegener granulomatosis, and tuberculosis, were negative. Additionally, samples of cerebrospinal fluid (CSF), blood, and bone marrow aspirate were negative for bacteria, mycobacteria, and fungi.

The patient was empirically initiated on a weight-based daily antituberculosis therapy regimen. Oral cabergoline was uptitrated to a final dose of 4 mg per week. One month later, the patient presented with an acute worsening of visual acuity and headache. Ocular examination was significant for a visual acuity of 6/9 in the right eye and 6/12 in the left, with bilateral papilloedema. Central nervous system examination was unremarkable.

Clinical differential diagnoses of GH excess-induced benign intracranial hypertension, paraneoplastic cerebral venous sinus thrombosis, and tuberculous meningitis with obstructive hydrocephalus were considered.

Serum IGF-1 and post 1-hour 100-g oral glucose serum GH levels were 1,198 and 393 ng/mL, respectively. Emergency MRI of the brain with spine screening was undertaken. Screening of the spine was prompted by the finding of an empty sella on MRI of the brain. The images were significant for diffuse cordal, posterior fossa, and cauda-equina leptomeningeal thickening with enhancement (zuckerguss sign), suggesting leptomeningeal carcinomatosis or drop metastasis (Fig. 1). Imaging was negative for obstructive hydrocephalus and flow void loss in the cerebral venous sinuses.

CSF opening pressure on lumbar puncture was elevated (50 cm of water; normal, 5 to 18 cm of water). Fluid analysis revealed a marked protein elevation, hypoglycorrhachia, and lymphocytic pleocytosis. CSF GH levels were also elevated (28 ng/mL; normal, <5 ng/mL). Cytologic examination revealed a few clusters as well as singly scattered moderately large cells with irregularly localized round to oval nuclei and abundant cytoplasm (Fig. 2). Occasional binucleated and multinucleated forms were also present. Also on immunohistochemistry, the atypical cells were positive for GH and negative for pancytokeratin (Fig. 3). CSF samples were negative for acid-fast bacilli, and mycobacterial and fungal cultures were sterile.

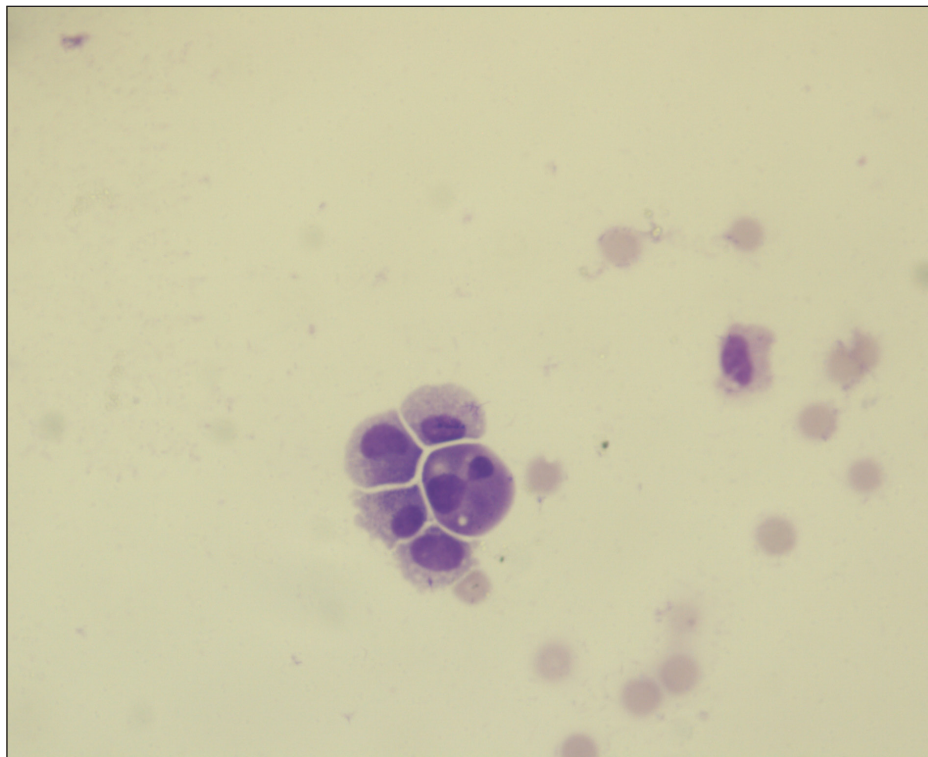
In view of persistently elevated GH and IGF-1 levels postsurgery and radiotherapy, without evidence of residual or recurrent pituitary disease or alternative primary neoplasm, clinico-radiologic features of leptomeningeal dissemination, and GH immunopositive atypical cells in the CSF, a diagnosis of GH-secreting pituitary carcinoma with leptomeningeal dissemination was made.

A lumbar drain was inserted for decompression. The patient was initiated on oral acetazolamide and short-acting subcutaneous octreotide in the dosage of 100 µg three times daily in view of inability to afford long-acting injectable octreotide preparations. He was also started on systemic chemotherapy with temozolamide 200 mg/m<sup>2</sup> for 5 consecutive days every 28 days after ascertaining O<sup>6</sup>-methylguanine-DNA-methyltransferase promoter methylation by methylation-specific polymerase chain reaction. He was also subjected to concomitant skull and spine irradiation (total dose of 36 Grays in 20 fractions) involving the entire area of the spine which was deemed to be affected by metastasis on the MRI.

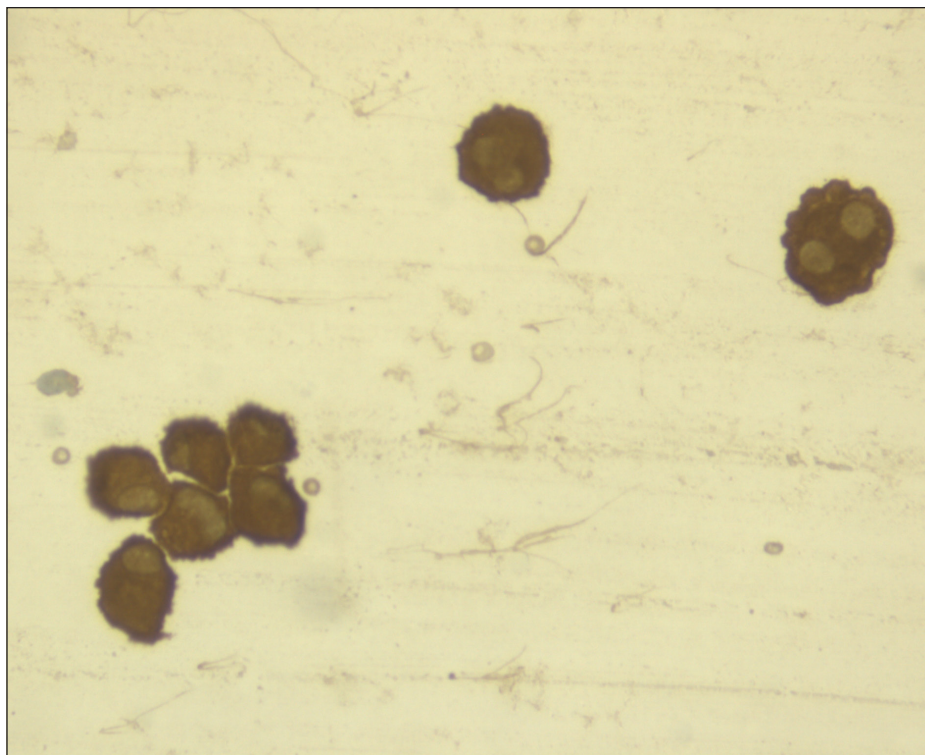
Following decompression, the patient's headache and neck pain improved, while visual acuity remained static. He has received 3 of 12 planned cycles of temozolamide and 7 of 20 planned fractions of skull and spine radiation. Interval assessment of disease status is scheduled prior to the fourth cycle.



**Fig. 1.** Gadolinium enhanced T2-weighted magnetic resonance spine imaging showing marked leptomenigeal enhancement and thickening in the cervicothoracic (*left*) and the thoracolumbar (*right*), respectively.



**Fig. 2.** Photomicrograph of a cytologic preparation of the cerebrospinal fluid sample showing moderately pleomorphic polygonal cells with irregularly localized nuclei and abundant eosinophilic cytoplasm (May-Grunwald-Giemsa stain,  $\times 400$ ).



**Fig. 3.** Photomicrograph of a cytologic preparation of the cerebrospinal fluid sample illustrating growth hormone immunopositivity in the atypical cell cluster shown in Figure 1 (avidin peroxidase stain,  $\times 400$ ).

## DISCUSSION

Defined as distant metastasis of a pituitary neoplasm, pituitary carcinomas are a rare clinical entity, accounting for 0.1% of all pituitary tumours (1,2). The median incidence is between the third and fifth decades (3). The initial lesion is usually a functional macroadenoma. Latency between diagnosis of the pituitary tumor and diagnosis of pituitary carcinoma ranges between 4 months and 18 years (median, 6.6 years) (3). A review of 132 published cases of pituitary carcinoma revealed that while the prolactin and adrenocorticotrophic hormone-secreting subtypes were the most common (47 of 132 [36%] and 39 of 132 [30%], respectively), those producing GH were rare (7 of 132 [5%]) (4).

The clinico-biochemical presentation of GH-secreting pituitary carcinomas is indistinguishable from that of an adenoma. GH-secreting pituitary carcinomas are characteristically unresponsive or partially responsive to standard therapies. Distinction between a GH-secreting carcinoma and adenoma cannot, however, be based on these grounds, since 40% of adenomas fail to respond to standard medical and surgical therapies. Demonstration of metastasis is essential for diagnosis (3).

Pituitary carcinomas may pursue both a systemic hemato-lymphatic and cranio-spinal dissemination. Metastatic sites include the cerebral cortex, cerebellum,

spinal cord, leptomeninges, eyes, heart, lung, cervical and pelvic lymph nodes, pancreas, liver, kidney, ovary, myometrium, and bone (3). Metastatic pituitary carcinoma cells have also been isolated from cerebrospinal and pleural fluids (3). Though GH-secreting carcinomas present more commonly with cerebrospinal metastasis (5), GH carcinomas presenting solely with leptomeningeal spread are uncommon. Our case presents a unique opportunity to understand the clinical and biochemical profiles of patients with isolated leptomeningeal spread of a GH carcinoma.

Given the paucity of clinical pointers in isolated leptomeningeal spread, a high index of suspicion is required for performing whole-spine imaging to identify “drop metastasis,” also demonstrated in our case, and is best guided by symptoms of neck or back pain or in the event of a marked discordance between the sellar tumor volume and biochemical markers (3).

Pituitary carcinomas are associated with poor prognosis. They have a median survival of 12 months in patients with systemic metastasis and 2.6 years in those with exclusive central nervous system disease, despite optimal multimodality therapy (6).

Treatment consists of surgical therapy involving the total or subtotal resection of primary and metastatic tumor tissues, in many cases resulting in immediate compressive symptom relief. Adjuvant irradiation directed to the



sella and to distant metastases prevents significant tumoral regrowth post-subtotal resection and slows growth of metastatic deposits. Whole-brain radiation therapy is reserved for intracranial metastasis. Radiation therapy is limited by the risk of temporal necrosis.

Medical therapy is divided into therapy aimed primarily at controlling hormone secretion and therapy primarily used for an antiproliferative role. Therapy for biochemical hypersecretion does not significantly differ from that used in benign pituitary adenomas, except that higher doses and a combination of agents are required and pegvisomant is contra-indicated.

Temozolamide, a methylating prodrug, is the current first-line antiproliferative agent in various subtypes of pituitary carcinoma. Of four published cases of temozolamide-treated GH-secreting aggressive pituitary tumors (defined as tumors invading contiguous structures with rapid growth), response to temozolamide was observed in one case (7). No published cases of GH-secreting pituitary carcinoma treated with temozolamide were found.

Of the two cases of GH-secreting pituitary carcinomas treated with chemotherapy following surgery and radiotherapy reported in the literature, the patient treated with one cycle of cisplatin, vinblastine, and bleomycin died within 1 month postchemotherapy (8). The other patient, treated with methotrexate and 5-fluorouracil, was alive without recurrence at 24 months (9).

## CONCLUSION

Pituitary carcinoma with isolated leptomeningeal spread is a rare clinical entity, with the GH-secreting subtype being rarer still. Clinico-biochemical presentation being indistinguishable from that of an adenoma, demonstration of metastasis is essential for diagnosis. The rarity of the disease precludes large randomized controlled trials, and present smaller studies suggest that multimodal therapy with surgery, radiotherapy, and chemotherapy—though incapable of cure—can result in disease stabilization.

## DISCLOSURE

The authors have no multiplicity of interest to disclose.

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