

## Case Report

## Orbital metastasis of pituitary growth hormone secreting carcinoma causing lateral gaze palsy

Rohan R. Lall, Stephen F. Shafizadeh, Kyung-Hwa Lee<sup>1</sup>, Qinwen Mao<sup>1</sup>, Minesh Mehta<sup>2</sup>, Jeffrey Raizer<sup>3</sup>, Bernard R. Bendok, James P. ChandlerDepartment of Neurological Surgery, <sup>1</sup>Department of Pathology, <sup>2</sup>Department of Radiation Oncology, <sup>3</sup>Department of Neurology, Northwestern University McGaw Medical Center, Chicago, ILE-mail: Rohan R. Lall - [rohan@northwestern.edu](mailto:rohan@northwestern.edu); Stephen F. Shafizadeh - [stephen.shafizadeh@gmail.com](mailto:stephen.shafizadeh@gmail.com); Kyung-Hwa Lee - [kyunghwa-lee@fsm.northwestern.edu](mailto:kyunghwa-lee@fsm.northwestern.edu); Qinwen Mao - [q-mao@nmff.org](mailto:q-mao@nmff.org); Minesh Mehta - [mmehtha@nmff.org](mailto:mmehtha@nmff.org); Jeffrey Raizer - [jraizer@nmff.org](mailto:jraizer@nmff.org); Bernard R. Bendok - [bbendok@nmff.org](mailto:bbendok@nmff.org);\*James P. Chandler - [jchandler@nmff.org](mailto:jchandler@nmff.org)

\*Corresponding author

Received: 03 February 13 Accepted: 25 March 13 Published: 18 April 13

**This article may be cited as:**Lall RR, Shafizadeh SF, Lee K, Mao Q, Mehta M, Raizer J, et al. Orbital metastasis of pituitary growth hormone secreting carcinoma causing lateral gaze palsy. *Surg Neurol Int* 2013;4:59.Available FREE in open access from: <http://www.surgicalneurologyint.com/text.asp?2013/4/1/59/110658>

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**Abstract****Background:** Although pituitary adenoma is one of the most common intracranial tumors, it rarely progresses secondarily into a metastatic carcinoma. Commonalities in reported cases include subtotal resection at presentation, treatment with radiation therapy, and delayed metastatic progression. Pathologic descriptions of these lesions are varying and inconsistent.**Case Description:** A 52-year-old male was diagnosed with acromegaly and pituitary tumor in 1996. He underwent four subtotal resections and five courses of stereotactic radiosurgery over 14 years. He developed left eye lateral gaze palsy, and was found to have a distant orbital metastasis with involvement of the left lateral rectus and lateral orbital wall. He underwent left orbital craniotomy via eyebrow incision for resection of this lesion. Pathologic evaluation showed a markedly elevated Ki67 level of 30%.**Conclusion:** While overall incidence of metastatic progression of pituitary adenoma after radiotherapy appears to be low, it appears to be a possible complication, and could be more likely in patients receiving multiple doses of radiotherapy. Our review of reported cases showed that 45/46 (97.8%) of patients developing carcinoma had prior radiation exposure. These patients may also have more aggressive pathologic characteristics of their lesions.**Key Words:** Acromegaly, orbital metastasis, pituitary carcinoma, stereotactic radiosurgery**Access this article online****Website:**  
[www.surgicalneurologyint.com](http://www.surgicalneurologyint.com)**DOI:**  
10.4103/2152-7806.110658**Quick Response Code:****INTRODUCTION**Although pituitary adenomas are very common, accounting for 25% of intracranial tumors, metastatic progression to pituitary carcinoma is very rare.<sup>[40,46]</sup> Progression to carcinoma has been previously described inall subtypes of adenomas.<sup>[9,11,16,19,23,41]</sup> Common themes in published accounts include early use of radiation therapy and subtotal resection, although this is not established as a causative factor, and may represent the more frequent use of radiotherapy in more clinically aggressive lesions.<sup>[5,8,13,17,19,25,39,51]</sup> Because of the close proximity

of the cavernous sinuses and critical neurovascular structures, subtotal resection with follow up radiation therapy is a fairly common clinical scenario.<sup>[1,12,13,20,31,58]</sup> Conventional radiotherapy is extensively utilized and yields excellent local rates of control.<sup>[30,54,55,57]</sup> Increasingly, radiosurgery has begun to gain favor as a modality producing similar control rates with possibly earlier secretory control, especially for GH-secreting adenomas. No direct comparison has been carried out, and typically smaller lesions further from the optic chiasm are treated with radiosurgery, while larger lesions with poorly defined margins, or those close to the optic apparatus, are treated with fractionated radiotherapy.<sup>[7,15,42,49]</sup>

Progression to pituitary carcinoma is not a pathologic diagnosis, but a clinical one. Regardless of pathologic features, progression to pituitary carcinoma is singly defined by the presence of metastases. And while atypical pathologic features in pituitary adenoma has been linked to aggressive local invasion, a consensus has not been reached regarding common pathologic features in pituitary carcinoma.<sup>[61]</sup> Reports of Ki67 and MIB1 levels in pituitary carcinoma range from low levels to those consistent with atypical features, or even higher.<sup>[24,38,46,52,53]</sup>

We report here on the clinical course of a patient treated with multiple courses of resection and radiosurgery for growth hormone secreting pituitary adenoma, who subsequently developed delayed lateral gaze palsy related to an orbital metastasis. Although sixth nerve palsy has been described in pituitary adenoma due to involvement of the cavernous sinus, our case illustrates a novel cause of lateral gaze palsy. We describe the pathologic findings of the case, and perform a review of previous published pathologic descriptions in pituitary carcinoma. We also review the radiation and surgical exposure described in published cases of pituitary carcinoma.

## CASE REPORT

A 52-year-old male was initially diagnosed with acromegaly and pituitary tumor in 1996 at a local community hospital. He underwent subtotal resection through a transphenoidal approach at that time. He subsequently had radiographic progression of disease and spikes in his IGF1 level, which were resistant to aggressive medical therapy, prompting stereotactic radiosurgery in 1998, 2000, 2006, and 2008 under the guidance of his first neurosurgeon. The patient transferred his care to another medical center, where he underwent endoscopic debulking operations in 12/08, and 6/09, followed by fractionated stereotactic radiosurgery (Cyberknife) in 08/09. All surgeries were performed endonasally, and no violation of the subarachnoid space occurred during these surgeries.

In November 2010, he developed severe, intractable epistaxis due to a ruptured Left Cavernous internal

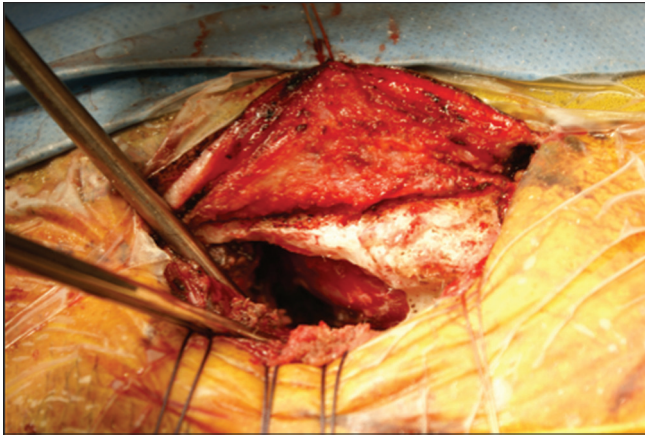
carotid artery (ICA) pseudoaneurysm, and was transferred to our hospital for further management. We had extensive discussions with the patient about his treatment options, specifically in regard to our concerns for leaving an exposed metallic stent sheath in close proximity to the tumor. He agreed to undergo Hunterian Ligation of the Left ICA with Superficial Temporal Artery-Middle Cerebral Artery (STA-MCA) bypass on December 2. He unfortunately developed a subgaleal abscess 3 weeks postoperatively, requiring washout and craniectomy. He returned for follow-up 1 month later with left gaze palsy. He underwent a follow-up brain magnetic resonance imaging (MRI), which showed a new lesion in the left orbit and lateral rectus muscle [Figure 1]. The mass was demonstrated clearly to be a distinct lesion, with a significant distance from the parasellar tumor burden, no intradural extension, and with osseous invasion. Initial radiographic review was described as concerning for radiation-induced meningioma or metastasis from a systemic cancer.

We chose to combine resection of the left orbital lesion with a cranioplasty procedure. We first performed an incision starting within the left eyebrow [Figure 2]. We came through the frontalis muscle, exposing the roof of the orbit, and laterally removed the periosteum down to the zygoma. The temporalis muscle was then taken down to expose the lateral wall of the orbit, where infiltrative tumor was directly visualized. We carefully removed the lateral wall of the orbit, skeletonizing the tumor. The borders of the tumor were identified, and the tumor was completely removed. The tumor was completely external to the subarachnoid space, and no spinal fluid was encountered during this surgery. We then opened the previous incision to complete the cranioplasty in a separate procedure. The patient tolerated the procedure very well, and was discharged home on excellent condition. Postoperative imaging showed gross total resection of the metastatic lesion. He also had an excellent cosmetic outcome related to the supraorbital incision, and experienced resolution of his lateral gaze palsy. Postoperative pathology showed pituitary adenoma with atypical features, further described below.

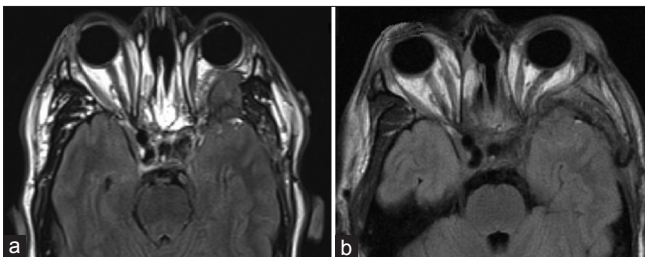
## Pathology

Preoperative laboratory work-up showed pan-hypopituitarism, with marked elevation of growth hormone and IGF1. The prolactin level was 1.28 (with absent Hook effect), Growth hormone was 126.0, insulin-like growth factor 1 (IGF1) was 907, follicle-stimulating hormone (FSH) was 0.4, luteinizing hormone (LH) was 0.1, Cortisol was 0.3, and adrenocorticotrophic hormone (ACTH) was <5. He was receiving replacement therapy for thyroid function, testosterone, and cortisol hormone replacement. Postoperatively, growth hormone dropped to 31.6, IGF1 dropped to 499, and prolactin dropped to 0.3.

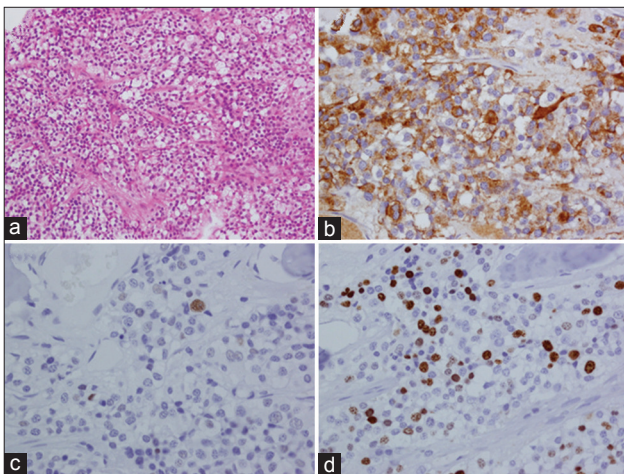
Microscopic examination of the current biopsy showed sheets of monomorphic cells infiltrating bone marrow between bone trabeculae [Figure 3]. The neoplastic cells had chromophobic or mildly acidophilic cytoplasm, coarse chromatin, and prominent nucleoli. There were occasional



**Figure 1:** Intraoperative image from eyebrow incision and orbital craniotomy



**Figure 2:** (a) Preoperative and (b) Postoperative images demonstrating resection of lateral orbital lesion



**Figure 3:** (a) The tumor is composed of monomorphic neoplastic cells with chromophobic or mildly acidophilic cytoplasm, coarse chromatin, and prominent nucleoli (H and E, magnification  $\times 100$ ). (b) The neoplastic cells are weakly to moderately immunopositive for growth hormone (GH) (immunohistochemistry, magnification  $\times 200$ ). (c) There are occasional p53-immunopositive nuclei (immunohistochemistry, magnification  $\times 200$ ). (d) The Ki-67 proliferation index approaches 30% in the most densely labeled area (immunohistochemistry, magnification  $\times 200$ )

mitoses up to 2 per 10 high-powered fields (HPFs). Some of the adenoma cells were weakly to moderately immunopositive for GH. Immunostaining was negative in all adenoma cells for prolactin, FSH, LH, TSH, and ACTH. There were scattered p53-immunopositive nuclei. The Ki-67 labeling index approached 30% in the most densely labeled area. Although the original biopsy was not available for review, the unusual features for pituitary adenoma in the current biopsy including high Ki-67 proliferation index, increased mitotic activity, and p53-positivity are consistent with atypical pituitary adenoma proposed in the literature.

## DISCUSSION

Pituitary carcinoma remains a clinically rare and elusive entity. The natural history and biology of pituitary carcinoma remains poorly defined. Due to the high incidence of pituitary adenoma and very low incidence of metastatic progression, clinicians typically have a very low index of suspicion. Also, the end organ of metastasis is highly variable, ranging from numerous locations on the craniospinal axis to distant solid organs including the skeleton, liver, ovaries, lymphatic spread, or in this case, the orbit.<sup>[8,13,17-19,22]</sup> Common themes in the case reports existing in the literature include early subtotal resection, radiation therapy, and delayed progression of metastasis.<sup>[5,8,9,11,13,16,17,19,23,25,39,41,51]</sup>

Recent reports have demonstrated excellent rates of long-term control of progression in pituitary adenomas after stereotactic radiosurgery (83-98%).<sup>[7,15]</sup> These rates are similar to those achieved with fractionated radiotherapy, but hormonal secretion appears to undergo more rapid resolution after radiosurgery. Specifically, a review of stereotactic radiosurgery in growth hormone-secreting adenomas quoted tumor growth control in 37-100% of patients, with 17-82% of patients experiencing normalization of hormonal levels.<sup>[49]</sup> This prompted some authors to recommend stereotactic radiosurgery as first line therapy for growth-hormone secreting adenomas that are not amenable to surgery, and have a suitable size for radiosurgery.<sup>[42]</sup>

We performed a review of published cases of pituitary carcinoma to highlight commonalities and risk factors [Table 1]. The review was performed via a Pubmed search of all cases of pituitary carcinoma with

**Table 1: Review of published adult cases of pituitary carcinoma**

# of Patients	Previous radiation treatment	Previous Stereotactic Radiosurgery	Previous external fractionated radiation	Mean Delay to Metastatic Progression
46	45 (97.8%)	8 (17.3%): Mean 1.13 treatments	40 (87.0%): Mean 1.11 courses	5.96 years

the following inclusion criteria: Adults, English language, and a clear description of clinical course. A total of 45 of 46 (97.8%) published cases described utilizing radiation therapy prior to metastatic progression were reviewed.<sup>[1-5,8-14,16,17,19-23,25-27,29,31-37,39,41,44,45,47,48,50,51,56,58-60,62]</sup> Eight patients had undergone stereotactic radiosurgery (Mean: 1.13 treatments) prior to progression. Forty patients underwent external radiation therapy (Mean: 1.11 treatments). The average time to metastatic progression from first dose of radiation was 5.96 years (Range: 1 month to 23 years).

Our case report features the novel presentation of lateral gaze palsy caused by direct invasion of the lateral rectus muscle, as opposed to sixth nerve palsy in the cavernous sinus. We speculate that five courses of radiosurgery within 12 years could potentially have contributed to the metastatic progression, particularly given the aggressive pathologic features. Additionally, the development of a carotid pseudoaneurysm and subsequent hemorrhage are suggestive of radiation injury. Past studies have questioned the role of radiation therapy in metastatic progression of pituitary carcinoma, and our case may represent another cautionary story.<sup>[36]</sup>

Nevertheless, the relationship of the numerous courses of radiotherapy to the ultimate metastatic progression remains a correlation in this case, and cannot be formally proven. Radiation-induced neoplasm has become a widely published and controversial entity, with rates of secondary neoplasm being related to dose, type of radiotherapy, and region of the initial neoplasm.<sup>[28]</sup> Cahan's criteria for radiation-induced neoplasm correlate in this case 1) The second neoplasm must be in the radiated field; 2) A latent period of several years must exist; 3) There must be evidence of nonmalignancy prior to radiation; and 4) The second tumor must be different from the first tumor.<sup>[6]</sup> These criteria cannot be strictly applied to this case, however, because the progression to malignancy in pituitary carcinoma is not a pathologic diagnosis, but a clinical one.

### Pathology discussion

According to the 2004 World Health Organization (WHO) classification, adenomas with robust p53 immunoreactivity, MIB-1 proliferative index greater than 3%, and elevated mitotic-index fall under the category of "atypical adenomas" to signify their potentially aggressive behavior.<sup>[61]</sup> The incidence of atypical pituitary adenoma ranges from 2.7% to 15%.<sup>[43,61]</sup> The term pituitary carcinoma is exclusively applied to adenohypophysial tumors with cerebrospinal and/or systemic metastasis.<sup>[61]</sup> Primary pituitary carcinomas are very rare, representing approximately 0.2% of all operated adenohypophysial neoplasms.<sup>[38]</sup>

Separation of pituitary adenoma from a carcinoma based on morphologic features is not possible within current

definitions.<sup>[24]</sup> There is no diagnostic combination of histological features for carcinoma. General histologic indications for malignant tumor such as invasion, cellular pleomorphism, nuclear abnormalities, mitotic activity, and necrosis may be noted in nonmetastasizing adenomas in varying degrees.<sup>[46]</sup> Proliferative activity and cytological atypicality, however, increase with aggressive behavior.<sup>[46]</sup> One study found mitoses in 3.9% of noninvasive adenomas, 21.4% of invasive adenomas, and 66% of carcinoma deposits, although there was considerable overlap.<sup>[52]</sup> Ki-67 expression correlates with invasiveness and probably prognosis.<sup>[52,61]</sup> Thapar *et al.* demonstrated that mean Ki-67 labeling index in noninvasive adenomas, invasive adenomas, and carcinomas was 1.37, 4.66, and 11.91%, respectively.<sup>[52]</sup> The WHO criteria adopted these authors' suggestion of a 3% labeling index as a threshold for distinguishing invasive from noninvasive adenomas. Another study by Thapar *et al.* reported p53 expression in benign adenomas, invasive adenomas, and carcinomas to be 0, 15.2, and 100%, respectively.<sup>[53]</sup> An additional study by Pernicone *et al.* reported p53 expression in 57% of primary tumors and 88% of metastases.<sup>[38]</sup> Interestingly, there is a direct correlation between high Ki-67 labeling and high p53 immunopositivity.<sup>[53]</sup> Pituitary carcinomas are usually endocrinologically functional, most often prolactin or adrenocorticotrophic hormone producing.<sup>[38]</sup> In contrast, the most common atypical tumor subtypes were growth hormone secreting, null-cell, and silent ACTH adenomas.<sup>[43,61]</sup> Immunostaining was negative for prolactin, making this tumor less likely to be a mammosomatotroph, a commonly very aggressive tumor subtype, although some postoperative decrease in the prolactin level was noted on serum blood work.

### CONCLUSION

We present a novel case of a male presenting with lateral gaze palsy in the setting of known growth hormone secreting adenoma, caused by metastasis to the lateral rectus muscle. Metastatic progression occurred in a much delayed fashion after numerous courses of stereotactic radiosurgery and subtotal resections. We recommend awareness of potentially unusual clinical presentations of metastatic progression of pituitary tumors, particularly in the setting of past radiation treatment.

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