Author's response to reviews

Title: Isolated Sixth Cranial Nerve Palsy as the Presenting Symptom of a Rapidly Expanding ACTH Pituitary Adenoma: Case Report

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Author's response to reviews: see over
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To Whom It May Concern:

Thank you for the instructive feedback on the submitted manuscript. Below please find a point-by-point response to the reviewers’ comments. The responses are in italics and are in order of reviewer. Changes have been made to the original manuscript as necessitated by reviewer feedback and are highlighted in the revised manuscript. All editorial requests have been fulfilled. We hope that all concerns have been addressed satisfactorily and once again look forward to your consideration.

Sincerely,

Elizabeth Kaplow

Responses to Reviewer 1

1. It would be interesting to know if this patient with sarcoidosis had been taking steroids before her diagnosis, and if steroids had been discontinued or the dose had been changed. Did her sarcoidosis worsen after the tumor was treated?

_The patient was not receiving steroids for her sarcoidosis prior to the diagnosis and no changes in her sarcoidosis have been noted throughout the diagnosis and treatment period of the pituitary tumor. The manuscript has been revised to reflect this information._

2. Were preoperative and postoperative ACTH and/or cortisol levels available? It is unclear if this is a hormone secreting or "silent" corticotroph adenoma; there is some evidence that "silent" corticotroph adenomas are associated with a more aggressive clinical course as compared with nonfunctioning adenomas. A few references could be cited in the Discussion section.

_ACTH and cortisol levels were scheduled but could not be completed before the patient was rushed to emergent surgery. Postoperative levels were not obtained. There is indeed some evidence of a more aggressive course associated with silent adenomas, as discussed in the last paragraph of the discussion, beginning on line 4. A more thorough_
discuss the topic is now provided; further information on this topic can be found in references 16-19.

3. What visual loss did the patient have preoperatively? Loss of acuity and/or visual fields, or just ophthalmoplegia?

Immediately preoperatively, the patient experienced significant clinical deterioration. She developed left sided ptosis, proptosis, complete ophthalmoplegia, and decreased visual acuity. Visual field testing was not repeated at this time. The manuscript has been revised to reflect this more detailed description of the patient’s preoperative visual loss.

4. What were the intraoperative findings? Even if there was no hemorrhage, did the tumor appear necrotic, which might be an explanation for the rapidly progressing symptoms? Was there extension into the cavernous sinus?

Intraoperative findings demonstrated clinical extension of the tumor into the cavernous sinus. This information has been added to the manuscript. Although there was question of a possible hemorrhagic or necrotic appearance to the tumor intraoperatively, absolutely no evidence of hemorrhage or necrosis was found on pathological examination.

Responses to Reviewer 2

Major Compulsory Revisions:

1. In background section line 8 the authors described the adenoma as “…rapidly expanding ACTH secreting tumor without apoplexy.” However I could not find any clinical description or any hormonal profile regarding Cushing’s disease in the paper. Therefore the authors should include the following important details in the manuscript.
   A) Did the patient have any clinical features of hypercortisolemia?
   B) Did the authors perform any hormonal test (ACTH level, cortisol level, 24 hours urinary cortisol level, dexametasone suppression test etc…) for the diagnosis of Cushing’s disease?
   C) If there is no clinical and/or hormonal evidence of hypercortisolemia the authors have to describe the pituitary adenoma as “ACTH positive silent adenoma” instead of “ACTH secreting adenoma”.

No signs or symptoms of hypercortisolemia were found on history and physical exam. Hormonal testing, including ACTH, was scheduled but the patient was rushed to surgery before testing could be completed. This statement has been added to the manuscript. As pointed out, without this information and without any signs or symptoms, the pituitary tumor must be considered to be silent, not secreting. Thus, the description of the adenoma has been revise to reflect this point.
2. The title also need to be revised as"… ACTH positive pituitary adenoma..” instead of “..ACTH adenoma…."

*The title has been revised to reflect the point that this was ACTH positive, though not secreting. The title is now reads “Isolated Sixth Cranial Nerve Palsy as the Presenting Symptom of a Rapidly Expanding ACTH Positive Pituitary Adenoma: A Case Report.”*

3. In case presentation section the authors did not mention the pituitary hormone status of the patient. The preoperative values of thyroid function, prolactin, IGF-I levels are warranted to comment on the functional status of pituitary adenoma.

*Laboratory testing (including prolactin and IGF-1) to evaluate the hormone status of the patient was scheduled, however the patient was rushed to surgery before workup could be initiated. However, the patient reported no symptoms that would indicate that the tumor had involved any of these hormonal axes. This point has been added to the manuscript.*

4. What about the menstrual history of the patient? If the patient is postmenopausal FSH/LH levels are the only way to understand gonadotropin deficiency due to adenoma compression to the normal gland.

*At the time the patient was not yet postmenopausal and did not report any menstrual abnormalities. Despite this, FSH/LH levels were scheduled, but could not be completed prior to emergent surgery. The manuscript now reflects this information.*

Discretionary Revisions:

1. If possible it would be better to add the final enlarged dimensions of the pituitary adenoma before surgery.

*Initial MRI prior to surgery demonstrated a 1.5 x 1.9 x 1.4 cm mass. Non-contrast head CT at the time of clinical deterioration demonstrated a 1.5 x 1.3 x 2.4 cm mass, which is an overall enlargement of the tumor. This information has been added to the manuscript.*

2. In discussion section it would be better to add the clinical and radiological differences of pituitary apoplexy and rapidly growing adenoma.

*A definition of pituitary apoplexy, based on clinical and radiologic findings has been added to the background section (beginning on line 6). The discussion section has been amended to explain that the characteristic radiological findings of pituitary apoplexy were not found on imaging and confirmed by pathologic examination.*