RECURRENT PITUITARY APOPLEXY IN AN ADENOMA WITH SWITCHING PHENOTYPES

Teresa V. Brown, DO¹; Kalmon D. Post, MD²; Khadeen C. Cheesman, MD¹

ABSTRACT

Objective: To describe an unusual presentation of a patient with recurrent pituitary apoplexy of an adenoma that switched phenotypes from a nonfunctioning, or silent gonadotroph adenoma (SGA), to a silent corticotroph adenoma (SCA). We discuss the potential etiologies of both recurrent pituitary apoplexy and phenotype switching of pituitary tumors.

Methods: The presented case includes clinical and biochemical findings, surgical outcomes, and pathologic reports related to the treatment of our patient who presented with recurrent pituitary apoplexy.

Results: A 56-year-old man presented for evaluation of decreased libido and was found to have a low testosterone level. A pituitary magnetic resonance image demonstrated an 8-mm pituitary adenoma. He underwent transsphenoidal surgery (TSS) to remove the tumor and pathology demonstrated an SGA immunopositive for luteinizing hormone and follicle-stimulating hormone with evidence of apoplexy. Eight years later, the patient underwent another TSS after developing acute-onset headache, vomiting, and a cranial nerve palsy. Pathology at this time showed a necrotic tumor consistent with apoplexy with negative immunostains for all pituitary tumors. Three years after this, the tumor recurred and after another TSS the tumor stained positive for adrenocorticotropic hormone but was negative for luteinizing hormone and follicle-stimulating hormone with hemorrhage consistent with apoplexy. A few years afterward, he again developed acute-onset headache and cranial nerve palsies and had another TSS. On pathology, the tumor demonstrated extensive necrosis consistent with apoplexy and again stained positive for adrenocorticotropic hormone. The patient was then referred for radiation therapy and was subsequently lost to follow up.

Conclusion: Recurrent pituitary apoplexy in the same patient has only been described 3 times in the literature. There have been no case reports of a pituitary adenoma that switched phenotypes from an SGA to SCA. We suggest that pituitary apoplexy may recur multiple times due to a tumor with particularly fragile vessel walls and increased vascularization. We review the literature that suggests clinical and molecular similarities between SGAs and SCAs. Further studies are needed to determine the etiologies of recurrent apoplexy and pituitary adenomas with switching phenotypes. (AACE Clinical Case Rep. 2020;6:e221-e224)

Abbreviations:
ACTH = adrenocorticotropic hormone; FSH = follicle-stimulating hormone; GH = growth hormone; LH = luteinizing hormone; MRI = magnetic resonance imaging; SCA = silent corticotroph adenoma; SGA = silent gonadotroph adenoma; TSH = thyroid-stimulating hormone; TSS = transsphenoidal surgery; VEGF = vascular endothelial growth factor
INTRODUCTION

Pituitary apoplexy is a neurosurgical and endocrine emergency. Prompt recognition and treatment can significantly improve outcomes. Although there is debate on the optimal definition, it was originally defined as the sudden onset of visual impairment, headache, vomiting, ophthalmoplegia, and altered consciousness that occurs in response to the rapid expansion of the contents of the sella turcica, most commonly from spontaneous hemorrhage or necrosis of a preexisting adenoma (1-3).

Pituitary apoplexy that is recurrent in the same patient is not a well-described phenomenon; there are only 3 such cases described in the literature (4,5). In addition, while “collision sellar lesions,” or 2 morphologically different tumors attached to each other, have been described (6) there is scarce literature regarding pituitary tumors with switching phenotypes. Though most pituitary tumors are monoclonal in origin, the possibility of new clones developing during the progression of an adenoma has been suggested (7). There have been case reports of metamorphoses of non-functioning pituitary adenomas to Cushing disease (8-11), although all of the tumors in these series initially either stained negative for all hormones or initially stained for adrenocorticotropic hormone (ACTH) in the absence of clinical or biochemical hypercortisolism. Only later they progressed to secreting tumors that caused clinical and biochemical hypercortisolism.

Our patient initially presented with pathology consistent with a silent gonadotroph adenoma (SGA), but subsequent pathology showed a silent corticotroph adenoma (SCA) without immunohistochemical positivity for follicle-stimulating hormone (FSH) or luteinizing hormone (LH), an instance of a phenotype switch. To our knowledge, we are the first to report a case of a patient with recurrent apoplexy of a pituitary tumor with switching phenotypes. We aim to review the literature on the pathogenesis of pituitary apoplexy and to discuss the possible pathogenesis of recurrent pituitary apoplexy. We will also discuss possible mechanisms for how a pituitary tumor could change from an SGA to an SCA.

CASE REPORT

A 56-year-old man with a past medical history of primary hyperparathyroidism status post parathyroidectomy and subtotal thyroidectomy who was on thyroid hormone replacement presented with a few months of decreased libido. Other than thyroid hormone replacement, the patient was not on any other medications including aspirin or anticoagulants.

This prompted an endocrine workup which revealed a low testosterone of 153 ng/dL (reference range is 260 to 1,000 ng/dL) and inappropriate normal gonadotropins with an LH of 3.1 mIU/mL (reference range is 1.5 to 9.3 mIU/mL) and an FSH of 5.2 mIU/mL (reference range is 1.4 to 18.1 mIU/mL). Prolactin levels were 26 and 34 ng/mL (reference range is 2 to 18 ng/mL). No dynamic pituitary testing was performed. A magnetic resonance image (MRI) of the pituitary gland revealed an 8-mm sellar lesion on the right side consistent with an adenoma.

The patient was given the option to monitor the lesion conservatively or have it removed. He opted for surgical management and underwent transsphenoidal surgery (TSS) performing an adenomectomy in March of 2002. Pathology showed extensive hemorrhage and was consistent with a silent gonadotroph tumor that stained weakly positive for FSH and LH. The proliferation index by labeling with the antibody MIB-1 was approximately 10%. Postoperatively, he was maintained on synthroid, hydrocortisone, and androgel and monitored closely.

Approximately 8 years later, in October of 2009, a routine MRI showed tissue in the suprasellar region which was consistent with recurrent tumor and measured 1.8 cm × 2.5 cm. It did not approach the optic chiasm or optic nerves. Due to very little difference between the 2009 scan and a previous scan from 2004, as well as the fact that the recurrent tumor was not threatening the optic chiasm, he was followed conservatively.

In April of 2010, he presented with sudden-onset headache, nausea, vomiting, and a right third nerve palsy. MRI showed a large suprasellar region with blood and necrotic tumor. He was taken back to the operating room and was found to have a necrotic tumor with hemorrhage filling the expanded sella and sphenoid sinus typical of apoplexy. Pathology showed necrotic tissue suggestive of apoplexy. Immunostains for pituitary hormones including ACTH, growth hormone (GH), prolactin, FSH, LH, and TSH were negative or weakly immunopositive.

More than 3 years later, in September of 2013, he was taken back to the operating room due to an enlarging mass in the sphenoid sinus which measured 1.9 cm × 4.0 cm × 2.7 cm. Pathology now showed an ACTH cell type adenoma with focal proteinaceous debris suggestive of a mucocle with a MIB-1 index of 3 to 5% and a p53 index of <1%. The tumor cells were nonreactive for prolactin, GH, FSH, LH, and TSH. The patient was not screened for Cushing disease because he had no signs or symptoms of the disease.

In July of 2015, he again presented with a sudden-onset headache associated with photophobia, nausea, and partial third and sixth nerve palsies. MRI scan showed a pituitary adenoma measuring 1.8 cm × 1.6 cm × 1.3 cm with probable apoplexy (Fig. 1). Intraoperative findings were consistent with a cheesy looking recurrent tumor and pathology again revealed an ACTH adenoma with extensive necrosis consistent with pituitary apoplexy. MIB-1 index was 30% and p53 index was 15%. Again, immunostains for prolactin, GH, FSH, LH, and TSH were negative. Postoperatively, he was referred for radiation therapy. He
received 5 days of cyber knife treatment in 2015 and has been lost to follow up since. At his last visit he was on levothyroxine and hydrocortisone.

DISCUSSION

The pathogenesis of pituitary apoplexy is likely multifactorial. Typically, pituitary tumors are thought to rapidly outgrow their blood supply resulting in ischemia and necrosis or compression of arteries such as the superior hypophyseal artery against the diaphragmatic notch leading to ischemia and necrosis (12). In the setting of an adenoma that is not a macroadenoma, however, as in the case of our patient’s initial tumor, these theories are less likely. Some authors have proposed that pituitary adenomas in general have an intrinsic vasculopathy with fragile blood vessels making them more susceptible to hemorrhage (2). The vessels of pituitary adenomas have been shown to have signs of poor fenestration and incomplete maturation with basal membranes that are ruptured. Furthermore, vascular endothelial growth factor (VEGF) has been found to correlate with a risk of pituitary hemorrhage and it has been shown that VEGF is overexpressed in pituitary adenomas (13-15).

SCAs represent about 20% of all corticotroph adenomas and 5% of nonfunctioning adenomas (16,17). They are non-secreting tumors without biochemical hypercortisolism or clinical evidence of Cushing disease, but stain positive for ACTH. SCAs behave in a more aggressive manner than other corticotroph adenomas and both are at increased risk for recurrence and hemorrhage (17). Clinically nonfunctioning adenomas are null cell tumors that either are not immunopositive for any pituitary hormones or gonadotroph adenomas which stain for but do not secrete FSH or LH.

Cooper et al (18) studied the clinical and cellular characteristics of SCAs in relation to nonfunctioning SGAs and found them to behave and express cellular proteins in a manner that is more similar to SGAs than to functioning corticotroph adenomas despite staining positive for ACTH. In particular, they found SCAs to express DAX-1, alpha GSU, and SF-1, cellular proteins typically expressed in gonadotroph adenomas. They also found SCAs to have honeycomb golgi and increased mitochondrial density, 2 characteristics of SGAs. This group suggested a common corticotroph and gonadotroph pituitary progenitor cell and proposed a reclassification of SCAs and SGAs to silent corticotroph gonadotroph adenomas.

Langlois et al (19) compared SCAs to SGAs and found that SGAs and SCAs have some similar clinical characteristics with similar tumor size and invasiveness. This group did, however, find that SCAs had a threefold higher likelihood of recurrence than SGAs. Despite the strong correlation that has been suggested between these 2 adenoma subtypes both clinically and from a molecular standpoint, a switch of an adenoma phenotype from an SGA to an SCA or vice versa, has not been described in the literature.

Interestingly, our patient had a hemorrhagic tumor despite the fact that it was only 8 mm. In the absence of the patient being on anticoagulants or aspirin, and without other risk factors for apoplexy, this suggests that his particular tumor likely had a fragile endothelium and perhaps may have had increased VEGF expression as most tumors that undergo apoplexy are macroadenomas that are hypothesized to have outgrown their blood supply. Unfortunately, the pathologic block was not available for VEGF staining. The high MIB-1 index of the initial tumor, which was approaching 10%, was suggestive that this adenoma might recur and be more aggressive in nature, but there is no published literature to date regarding the correlation of the MIB-1 index with the likelihood of a tumor undergoing recurrent apoplexy. Nonfunctioning adenomas or gonadotroph adenomas are the most common pituitary adenoma subtype to undergo apoplexy, but there is no available literature regarding whether these tumors are more likely to undergo apoplexy multiple times. In addition, it may be a selection bias that these tumors are more likely to undergo apoplexy as they are the most common type of pituitary adenomas (20).

CONCLUSION

We suggest that the pathophysiology of recurrent pituitary apoplexy may be due to particularly fragile blood
vessel walls of an adenoma together with overexpression of genes and growth factors related to vascularization such as VEGF. We further propose that there is a potential common corticotroph and gonadotroph pituitary progenitor cell and that new clones may develop during the course of a pituitary adenoma. Further studies need to be done to elucidate the mechanisms by which both recurrent pituitary apoplexy and phenotypic switching of a pituitary adenoma may occur.

DISCLOSURE

The authors have no multiplicity of interest to disclose.

REFERENCES