

# Pituitary Apoplexy After Intravitreal Injection of Vascular Endothelial Growth Factor Inhibitor: A Novel Complication

Rebecca A. Kasl<sup>1</sup> Heather M. Kistka<sup>1</sup> Justin H. Turner<sup>2</sup> Jessica K. Devin<sup>3</sup> Lola B. Chambless<sup>4</sup>

<sup>1</sup>Department of Neurosurgery, Vanderbilt University Medical Center, Nashville, Tennessee, United States

<sup>2</sup>Department of Otolaryngology-Head and Neck Surgery, Vanderbilt University School of Medicine, Nashville, Tennessee, United States

<sup>3</sup>Division of Diabetes, Endocrinology and Metabolism, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, United States

<sup>4</sup>Division of Neurological Surgery, Department of Neurosurgery, Vanderbilt University Medical Center, Nashville, Tennessee, United States

Address for correspondence Rebecca A. Kasl, MD, Department of Neurosurgery, Vanderbilt University Medical Center, T4224 Medical Center North, Nashville, TN 37232, United States (e-mail: rebecca.a.kasl@vanderbilt.edu).

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## Abstract

Pituitary adenomas are common in the general population. They can be complicated by intratumoral hemorrhage, otherwise known as apoplexy, which frequently presents with neurologic deficits that may necessitate urgent surgical decompression. Many risk factors for pituitary apoplexy have been suggested in the literature. We present a case of symptomatic apoplexy in a woman following the intravitreal administration of the vascular endothelial growth factor (VEGF) inhibitor ranibizumab. Ophthalmoplegia resolved and visual acuity significantly improved following gross total resection of the tumor via an endoscopic endonasal surgical approach. The association between intravitreal injection of a VEGF inhibitor and pituitary apoplexy has not been previously described, but physicians performing these procedures should be aware of this potential complication.

## Keywords

- ▶ pituitary apoplexy
- ▶ hemorrhage
- ▶ vascular endothelial growth factor inhibitor
- ▶ ranibizumab

## Introduction

Pituitary adenomas may present with a gradual decline in vision, cranial nerve palsies, or change in endocrine function. Less commonly, an average of 2% of surgically treated pituitary adenomas present acutely with intratumoral hemorrhage, termed *apoplexy*.<sup>1,2</sup> Previously described triggers of this rare presentation include trauma, antithrombotic therapy, coagulopathy, recent surgical intervention, dopamine agonists, and essential hypertension.<sup>3–7</sup> Clinically, apoplexy is characterized by vision loss, ophthalmoplegia, headache, or nausea, and it often warrants urgent surgical intervention.<sup>1</sup>

Vascular endothelial growth factor (VEGF) is an important regulator of tumor angiogenesis. Increased VEGF expression is associated with hemorrhage in pituitary adenomas.<sup>8,9</sup> Due to the critical role of VEGF in tumor growth, intravenous infusion of VEGF inhibitors is increasingly used in neuro-oncology to treat refractory high-grade neoplasms.<sup>10,11</sup> Data from these patients have revealed an increased risk of intratumoral hemorrhage with this treatment.<sup>12</sup> VEGF inhibitors are also used in ophthalmology to treat a variety of conditions believed to stem from increased angiogenesis including diabetic retinopathy, macular degeneration, and central serous chorioretinopathy.<sup>13,14</sup> Intraocular hemorrhage after intravitreal injection of VEGF inhibitors has been described.<sup>15,16</sup>

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We present the first reported case of pituitary apoplexy after intravitreal injection of the VEGF inhibitor ranibizumab. Prompt recognition of this event and urgent surgical resection of the lesion in this case provided this patient with an excellent functional outcome.

## Case Report

### History

A 74-year-old woman presented to neurosurgical attention with acute left-sided unilateral vision loss and complete left oculomotor nerve palsy. She had received an intravitreal ranibizumab injection and fluorescein angiography 2 days prior for a new diagnosis of central serous retinopathy.

The patient initially presented to the ophthalmology clinic with a few months of worsening blurry vision in her left eye. Her ophthalmologic history was significant for cataracts, hyperopia, and astigmatism requiring eyeglasses. There was no history of trauma, ocular surgery, or pituitary tumor. She had no prior intracranial imaging. Her medical history was notable for primary hypothyroidism and essential hypertension managed with levothyroxine and verapamil. In the clinic, her corrected visual acuity was significantly worse in her left eye (20/200) than in her right (20/30), and intraocular pressures were normal. Neurologic examination was unremarkable with equal, round, and reactive pupils bilaterally, intact extraocular movements, and full visual fields to confrontation. Slit lamp examination was normal. Her fundal examination was only notable for a 1.5-mm left choroidal nevus. Optical coherence tomography demonstrated chronic idiopathic central serous chorioretinopathy (left more than right).

Intravitreal injection of ranibizumab was recommended to treat central serous chorioretinopathy. The treatment was administered by a retinal specialist in the clinic later that day. Prior to the ranibizumab injection, fluorescein corneal angiography was performed without complication. Ranibizumab was then injected at the 4:00 site on the left eye. The patient tolerated the procedure well and went home in stable condition.

Forty-seven hours later, the patient was seen emergently in the ophthalmology clinic. She relayed a history of diffuse headache and neck stiffness beginning the day after the procedure. Symptoms progressively worsened, peaking on the morning of presentation when she awoke with left ptosis, diplopia, persistent headache, and nausea. Upon examination in clinic, she was alert and oriented. Her right eye examination was unchanged, but her left visual acuity had acutely worsened from 20/200 to 20/400 with normal intraocular pressure. She demonstrated left ptosis and a fixed and dilated left pupil at 6 mm. Her left eye was laterally and inferiorly deviated with impaired medial adduction and impaired left consensual response when exposed to light on the right. Slit-lamp and dilated fundus examinations were unchanged. She was emergently transferred to the emergency department (ED) with a diagnosis of acute left oculomotor nerve palsy.

In the ED, a noncontrast computed tomography (CT) scan of the head revealed a sellar mass with leftward hemorrhagic

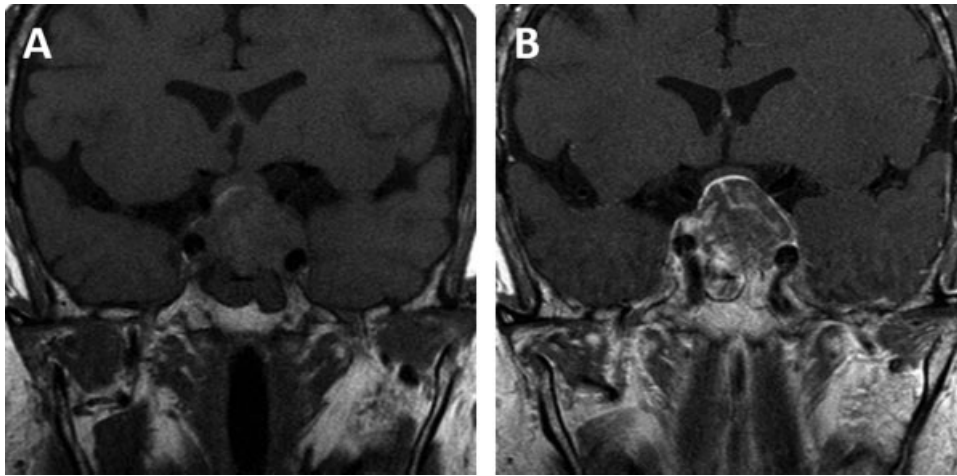
expansion and bony erosion (►Fig. 1). CT angiography was negative. Follow-up magnetic resonance imaging (MRI) exhibited acute hemorrhage within a 17 × 25 × 25 mm mass compressing the optic chiasm and invading the left cavernous sinus consistent with pituitary apoplexy (►Fig. 2). Pituitary function tests demonstrated central hypothyroidism superimposed on preexisting primary hypothyroidism (thyroid-stimulating hormone [TSH] 0.128 mIU/L, free thyroxine [FT4] 0.88 ng/dL), and central hypogonadism in a postmenopausal woman (luteinizing hormone [LH] 0.4 mIU/mL, follicular-stimulating hormone [FSH] 3.7 mIU/mL). Prolactin was normal at 6.0 ng/mL. After neurosurgical evaluation and endocrine consultation, the patient was administered dexamethasone and scheduled for urgent endoscopic transsphenoidal resection.

### Operation

The patient was placed under general anesthesia, positioned supine, and administered preoperative dexamethasone and antibiotics. A neurosurgeon and rhinologist collaborated for the procedure, and the BrainLAB (Munich, Germany) stereotactic navigation system guided their approach. Bilateral endoscopic sphenoidotomies and a posterior septectomy were performed to create a common cavity. The sella turcica was opened widely to expose the dura, which was incised in a cruciate fashion. Hemorrhagic pituitary tumor was recognized immediately and resected circumferentially. Numerous specimens were obtained and sent for permanent pathology. An intraoperative cerebrospinal fluid leak was noted and repaired with a Durepair (Medtronic, Minneapolis, Minnesota, United States) underlay graft and free mucosal overlay graft harvested from the left middle turbinate. The repair was supported with dry Gelfoam (Pfizer, New York, United States) and gloved Meroceel (Medtronic, Minneapolis, Minnesota,



**Fig. 1** Noncontrast computed tomography of the head demonstrating hemorrhage within the sella with surrounding bony erosion consistent with pituitary apoplexy.



**Fig. 2** (A) Precontrast and (B) postcontrast T1-weighted magnetic resonance imaging of the brain demonstrating a  $17 \times 25 \times 25$  mm pituitary mass with evidence of hemorrhage, chiasmatal compression, and cavernous sinus invasion.

United States) sponges. The patient awoke from anesthesia without difficulty and was taken to the neurologic intensive care unit in stable condition.

### Pathologic Findings

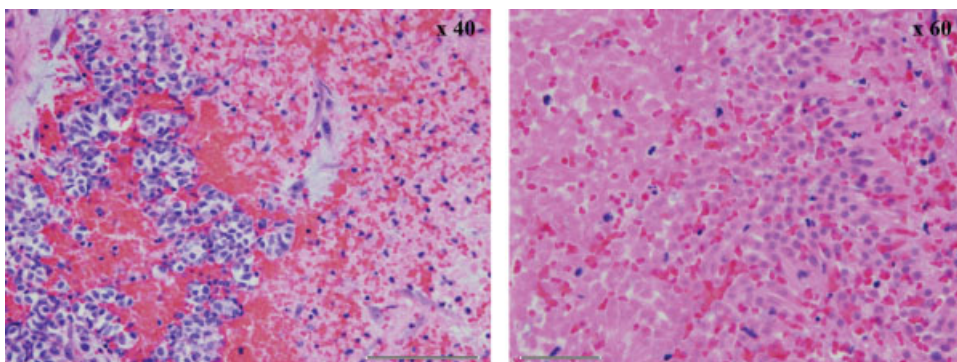
Histologic sections showed small foci of viable pituitary adenoma characterized by cells with monomorphic round-to-ovoid nuclei arranged in perivascular palisades. Large regions of tumor demonstrated incipient cell death with loss of nuclear detail and increased cytoplasmic eosinophilia, and areas of frankly necrotic tumor were observed. Abundant hemorrhage and an acute inflammatory infiltrate were seen. Tumor cells showed immunoreactivity for synaptophysin, FSH, and LH. This pathologic description was consistent with a silent gonadotroph, or nonfunctioning, pituitary adenoma (► Fig. 3).

### Postoperative Course

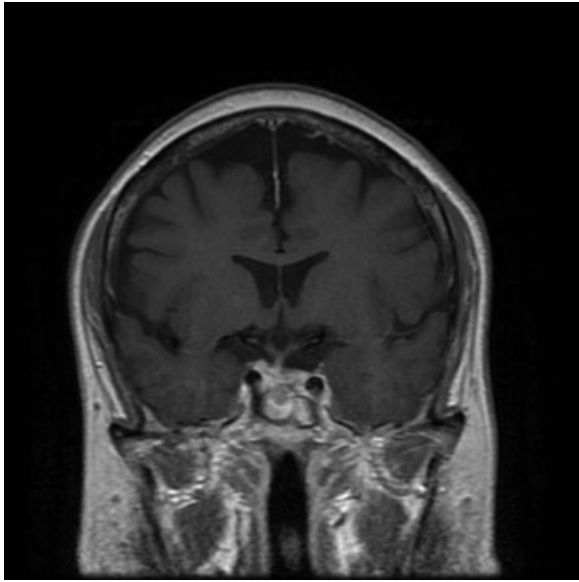
On postoperative day (POD) 1, the patient's subjective vision had notably improved. Her corrected left eye visual acuity was

tested and noted to be 20/100. By POD 2, her vision was 20/30 and 20/25 with correction in the left and right eyes, respectively. Her intraocular pressure was normal, and pupils were reactive bilaterally. Left-sided ptosis and ophthalmoplegia were improved, but some diplopia persisted. She did not experience any disorders of water metabolism, including diabetes insipidus or hyponatremia, in the postoperative period. Perioperative corticosteroids were tapered to a physiologic replacement dose of 5 mg prednisone daily until her endocrine follow-up appointment. Her levothyroxine dose was optimized following a low normal FT4 laboratory result. She was discharged to home on POD 3, by which point her ptosis and ophthalmoplegia had nearly recovered.

Her follow-up period was uneventful. At her 6-week follow-up appointment, MRI illustrated gross total resection with complete decompression of the optic apparatus and no evidence of recurrent tumor (► Fig. 4). She had complete resolution of her oculomotor nerve palsy and believed her vision was better than it had been in years. Her endocrine laboratory evaluation confirmed panhypopituitarism



**Fig. 3** The pathologic specimen at  $\times 40$  and  $\times 60$  magnification. At  $\times 40$ : A small focus of viable neoplasm (left side of image) is surrounded by hemorrhage, necrosis, and infiltrating leukocytes (hematoxylin and eosin [H&E], original magnification  $\times 400$ ; scale bar = 100 microns). At  $\times 60$ : Spectrum of adenoma cell death with loss of nuclear detail and cytoplasmic hypereosinophilia (right side of image) progressing to frank necrosis (left) (H&E, original magnification  $\times 600$ ; scale bar = 50 microns).



**Fig. 4** A 6-week postoperative postcontrast T1-weighted magnetic resonance imaging of the brain demonstrated surgical decompression of the optic apparatus and infundibulum without evidence of residual tumor.

(baseline adrenocorticotrophic hormone 6 µg/dL and cortisol 2.4 µg/dL with a stimulated cortisol of 13.9 µg/dL 1 hour after 250 µg Cortrosyn, TSH 0.246 mIU/mL, FT4 1.17 ng/dL, LH 1.4 mIU/mL, and FSH 4.6 mIU/mL). She remains on treatment for central adrenal insufficiency and hypothyroidism. Postoperative neuro-ophthalmology examination demonstrated 20/20 and 20/70 corrected vision in the right and left eyes, respectively, with full and equal peripheral vision via Goldmann visual fields. The examination confirmed a visually significant cataract in her left eye and concomitant macular degeneration. Because delayed recurrence following apoplexy is not uncommon, she will be followed with annual pituitary MRIs to monitor for any evidence of tumor recurrence.<sup>17</sup>

## Discussion

Pituitary adenomas are common intracranial tumors.<sup>18</sup> They are typically benign, and a third are nonfunctional. Although nonfunctional tumors lack hormone production, they often stain positively for LH and FSH.<sup>19,20</sup> Given the endocrine inactivity, their course is typically occult until a macroadenoma becomes large enough to compress neighboring structures such as the optic chiasm and surrounding pituitary tissue. As such, the most common symptomatic presentation includes gradual onset of vision loss, hormonal deficiencies, or headache.

Pituitary apoplexy is defined as acute hemorrhage or infarction of the pituitary mass causing rapid expansion of the sella turcica. Pituitary apoplexy can be a challenging diagnosis because patients frequently have no history of an adenoma. The classic acute clinical presentation of apoplexy involves headache (63–100%), visual deficits (40–100%), and nausea/vomiting (59–78%).<sup>1,21–23</sup> Laboratory work-up usual-

ly demonstrates hypopituitarism (88%),<sup>1,21</sup> and the diagnosis is confirmed by intracranial imaging.

Although the precise pathophysiologic mechanism for apoplexy has not been ascertained, rapid tumor growth exceeding or compressing the vascular supply as well as primary hemorrhagic or ischemic events has been proposed.<sup>1,24</sup> As a tumor grows, so does its vascular supply. In fact, the pituitary gland's robust vasculature contributes to a 5.4-fold greater chance of hemorrhage when compared with other central nervous system tumors.<sup>25</sup> Additionally, non-functional adenomas and prolactinomas carry a higher incidence of apoplexy.<sup>26</sup> Thus our patient's large nonfunctioning macroadenoma possessed several risk factors for hemorrhage including tumor size and type, essential hypertension, and recent surgical intervention.

Pituitary apoplexy following injection of an intravitreal VEGF inhibitor has not been previously described in the literature. VEGF is a protein that promotes angiogenesis. As such, overexpression of VEGF is associated with tumor growth and retinal vascular disease progression. Inhibitors of VEGF, such as the monoclonal antibody bevacizumab (Avastin) and antibody derivative ranibizumab (Lucentis), have an evolving therapeutic role in retinopathy by targeting the neovascularization and vascular permeability processes inherent to the disease pathogenesis.<sup>27</sup>

VEGF upregulation also has a proposed role in pituitary hemorrhage.<sup>9</sup> Elevated VEGF expression has been reported in hemorrhagic pituitary tumors, regardless of an apoplectic clinical presentation.<sup>8,28,29</sup> This patient received localized therapy, yet intravitreal injections of VEGF have demonstrated widespread complications indicating systemic distribution of the drug.<sup>30,31</sup> One hypothetical pathophysiologic mechanism behind apoplexy is the medication-induced apoptosis of endothelial cells.<sup>32</sup> VEGF is known to maintain endothelial stability.<sup>33</sup> The acute perturbation in the endothelial lining could precipitate hemorrhage or hemorrhagic infarction in a pituitary adenoma, a tumor type known for its hypervascularity. Although the role of VEGF in spontaneous apoplexy is not fully understood, the VEGF inhibitor ranibizumab likely triggered apoplexy in our patient, which may suggest that her preexisting level of VEGF could have been a significant factor.

Treatment for pituitary apoplexy is surgical resection or conservative therapy. In either case, initial management is to stabilize the patient whose propensity for hormone deficiencies may compromise a surgical intervention. A conservative method often involves high-dose corticosteroids, dopamine agonists for prolactinomas, or radiotherapy.<sup>22,34,35</sup> Expectant management is considered appropriate for patients without severe visual compromise or altered mental status.<sup>2,26,36</sup>

Preserving vision is the primary goal of surgical intervention for pituitary apoplexy, and outcomes depend on symptom severity and time until intervention.<sup>2,37</sup> Patients presenting with monocular blindness have a better visual recovery rate than those with binocular blindness.<sup>2</sup> No difference in visual recovery for patients who underwent surgery within the first day of apoplexy versus 2 to 7 days has been demonstrated.<sup>2,38</sup> However, early surgery within a week of

the sentinel event produces better visual outcomes.<sup>23,39</sup> Our patient's apoplectic attack included severe monocular visual decline; thus urgent surgical management was appropriately pursued. The attack's estimated onset was 1.5 days prior to presentation and 2.5 days prior to surgical intervention. Therefore, her timely presentation to medical care increased her likelihood for visual recovery after tumor resection. Our patient's vision improved quickly to 20/25 and 20/30 in the right and left eyes, respectively, by POD 2.

Even when vision is saved, pituitary apoplexy is commonly complicated by long-term hypopituitarism. After surgical intervention, hormone replacement is required in 82% of patients who present with apoplexy.<sup>1</sup> Diabetes insipidus is a transient complication in 10 to 18% of cases.<sup>1,40</sup> On average, long-term glucocorticoids, thyroid hormone, and gonadal steroids are required in 75%, 75%, and 95% of patients, respectively.<sup>1</sup> Our postmenopausal patient continued to require corticosteroids and thyroid hormone 4 months after her initial presentation.

## Conclusions

We describe a case of pituitary apoplexy after intravitreal injection of a VEGF inhibitor in a 74-year-old woman. A VEGF inhibitor triggering an apoplectic event has not been previously described in the literature. Physicians performing intravitreal VEGF inhibitor injection should be aware of this potential complication because immediate recognition of apoplexy may be key to preserving vision. Although pituitary adenomas are less common than retinopathy in the elderly population, nonfunctional tumors should be considered during evaluation of progressive vision loss. Furthermore, an acute change in vision or focal neurologic deficit warrants rapid imaging. Our patient demonstrated remarkable visual recovery after expeditious surgical intervention with minimal visual acuity deficits and no cranial nerve deficits at 6-week follow-up. Rapid assessment, diagnosis, and treatment were paramount to her recovery.

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