A Case of Pituitary Apoplexy Following Leuprolide Injection for Prostate Cancer

KANG WOO KIM, BA; SORA CHEE, MD; NAVEENA SUNKARA, MD; MARGARET HAYES BAKER, MD

ABSTRACT

Pituitary apoplexy is a rare but potentially life-threatening complication of androgen deprivation therapy for prostate cancer. We present a case of a 70-year-old African American male with prostate cancer who developed symptoms of pituitary apoplexy, including hot flashes, nausea, vomiting, and cranial nerve III palsy, following the initiation of leuprolide therapy. Imaging revealed a pituitary adenoma with hemorrhage, and prompt multidisciplinary management was initiated. The patient was managed conservatively with improvement in symptoms. This case highlights the importance of recognizing the potential for pituitary apoplexy in patients receiving GnRH agonist therapy. We discuss the clinical presentation of GnRH agonist induced pituitary apoplexy, emphasizing that clinicians should maintain a high index of suspicion and promptly investigate any new neuro-ophthalmic symptoms in this group of patients. Ultimately, prompt diagnosis and treatment are crucial to mitigate the severity of this complication in patients with prostate cancer undergoing androgen deprivation therapy.

KEYWORDS: Prostate cancer, Pituitary apoplexy, Androgen deprivation therapy, Leuprolide, Pituitary adenoma

INTRODUCTION

In 2019, prostate cancer was the second leading cancer related mortality in America and the cancer with the highest incidence, with 112 new cases per 100,000 men.[1] Worldwide estimates report approximately 190,000 new cases with 80,000 deaths each year. About 60% of diagnoses occur in men over the age of 65, with African American men having the highest incidence globally.[2-4] Among medical castration methods used to achieve androgen deprivation, GnRH agonists have been widely accepted across guidelines for initial systemic therapy for regional and advanced prostate cancer. GnRH agonists (GnRHa) have well documented side effects such as fatigue, hot flashes, EKG changes, and a rare association with pituitary apoplexy (PA) in male patients with a pituitary adenoma.[5,6] To date, only 22 cases of induced PA have been described, but it is crucial for healthcare professionals to remain alert to this potentially fatal association for early detection and treatment.

CASE REPORT

A 70-year-old African American male with past medical history significant for hypertension, gout, osteoarthritis, and recently diagnosed prostate cancer presented to the ED with nausea and vomiting. He had been recently diagnosed with metastatic prostate cancer (Gleason 4+5, with pelvic LN involvement on finasteride), and was administered a GnRHa (Leuprolide 7.5 mg subcutaneous 1-month depot injection). Within 3–4 hours after the first injection, the patient began experiencing hot flashes, night sweats, chills, nausea, vomiting, and myalgia. On day 5, he developed diplopia, intermittent headaches, and right eye ptosis. Physical exam findings were significant for isolated cranial nerve 3 palsy. CT Brain and CTA of the head and neck were negative for acute intracranial processes. MRI Brain with contrast revealed a heterogeneous lesion arising from the pituitary fossa and extending into the suprasellar cistern measuring approximately 2.4 cm in the greatest transverse dimension, suggestive of an atypical pituitary adenoma (**Figures 1,2**). Repeat MRI brain with dedicated pituitary protocol was performed

Figure 1. [**A**] Sagittal and [**B**] coronal T1-weighted gadolinium-enhanced MRI.

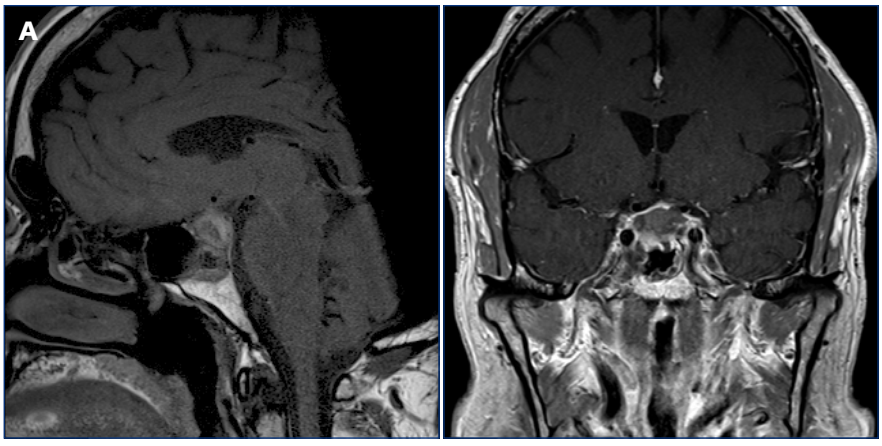

Figure 2. Transverse T2-weighted gadolinium-enhanced MRI.

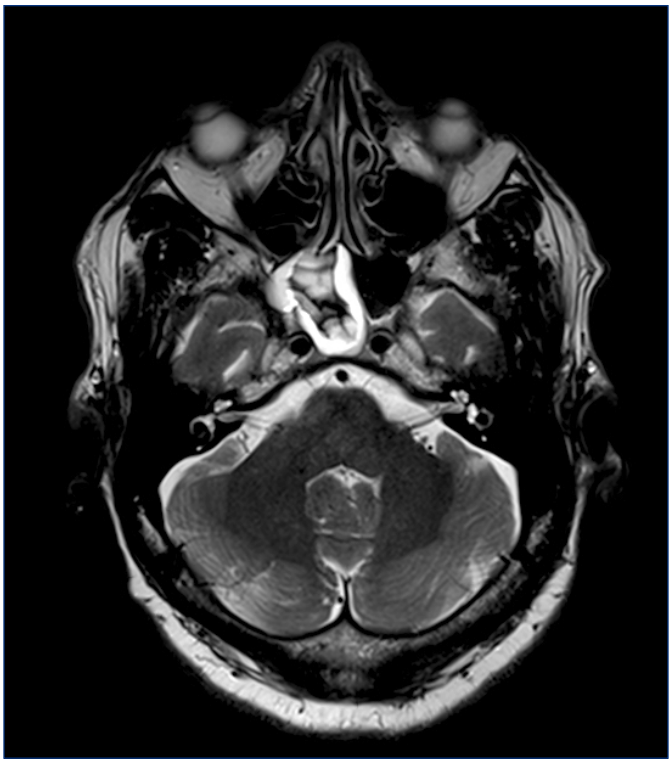

Table 1. Pan-hormone studies relative to post-GnRHa injection date.

	Normal Range	Day 8	Day 27	Day 50
Prolactin	3–20	<0.60	<0.60	0.80
FSH	1–19	1.77	-	0.44
LH	1–9	0.45	<0.07	< 0.07
Cortisol AM	6–28	2.6	3.8	< 1.0
TSH 3rd generation	0.35–5	0.19	0.22	0.36
Free T4	0.6–1.6	1.15	0.78	0.8
ACTH	6–50	<5	<5	<5
T Total	250–1110	8.14	3	3
Sex hormone binding globulin	22–77	—	35	51
Albumin	3.6–5.1	—	4	3.9
T bioavailable	15–150		0.6	0.4
T free	6–73	—	0.3	0.3
PSA	0–4	—	1.43	0.23
Human Growth Hormone	<=7.1	0.1	0.1	—

on day 6 for further clarification, which revealed a new hemorrhage within the pituitary adenoma suggesting pituitary apoplexy. A multidisciplinary team including endocrinology, ophthalmology, neurology, radiology, and neurosurgery was promptly consulted. Further laboratory work up was significant for low ACTH, LH, FSH, prolactin, AM cortisol, and testosterone (**Table 1**). Per the endocrinology team, the patient's AM cortisol was presumed low due to HPA axis suppression from 20 mg prednisone administered a day prior to lab collection and the patient's daily physiologic prednisone dosing as an outpatient regimen for his prostate cancer. Given the absence of clinical signs of adrenal crisis and mineralocorticoid deficiencies alongside stable neurologic exams, the patient was managed conservatively with 5 mg daily prednisone and without indication for urgent surgical management. Within 48 hours of steroid initiation, he had a significant improvement of right eye ptosis, and complete resolution of diplopia with intact extraocular movements. The patient was discharged with endocrinology and surgery follow up for pan-pituitary hormone monitoring and further apoplexy management. Regarding his prostate cancer therapy, leuprolide was discontinued and the patient was scheduled to continue androgen deprivation therapy with degarelix given its GnRH antagonistic effects.

DISCUSSION

Pituitary apoplexy is a rare but potentially life-threatening syndrome encompassing a constellation of symptoms associated with hemorrhage into the gland and surrounding space. Several mechanisms of GnRHa induced pituitary apoplexy have been proposed, including compromised tumor vascularity, increased metabolic activity resulting in perfusion mismatch and mass effect from expanding pituitary hemorrhage leading to pituitary infarct.[7–9]

GnRHa induced PA can present through a wide range of symptoms, most commonly including headache (100%), followed by cranial nerve III/IV/VI palsy (85.7%), and nausea/vomiting (71.4%).[6] Previous reviews have reported that the majority of cases (63%) developed symptoms within 24 hours of receiving a GnRH agonist; however, there has been a case report of symptoms developing as late as 12 months post GnRHa exposure.[6,10] Consistent with previously reported cases, our patient began exhibiting constitutional symptoms including hot flashes, chills, nausea, vomiting within 4 hours after his first leuprolide injection. However, it is important to highlight that he did not develop symptoms more concerning for PA such as cranial nerve III palsy or headache until 5 days following leuprolide administration. This suggests that patients who develop constitutional symptoms several hours after GnRHa injection should be closely examined for neuro-ophthalmic symptoms and be given a higher index of suspicion for PA.

TSH deficiency and decreased prolactin level found in our patient were also consistent with most common central hormone derangements reported in previous literature. Of note, our patient had free T4 levels within normal limits, though there were no values reported in the literature for comparison. Review of prior cases of PA following GNRHa injection demonstrated that levels of LH and FSH can vary widely amongst patients with similar presentations (N=6 normal, N=4 deficient, N=6 elevated, N=5 unknown). Interestingly, our patient had depressed LH and FSH levels

(LH 0.45, FSH 1.77). Our imaging findings demonstrated suprasellar extension which was also consistent with 52.4% of incidence reported.[6]

During his hospital stay, our patient's condition was managed conservatively with a non-stress physiologic dose of daily prednisone, with significant improvement in ptosis and extraocular movements within 48 hours of steroid administration. While there is no gold standard of care for PAs following GNRHa therapy, it is worth noting that two recent cases in the literature treated medically using stress doses of steroids, in contrast to our physiologic dosing.[11,12] Despite this difference, our patient's low AM cortisol was presumed to be due to his daily outpatient steroid dosing for his prostate cancer, thus he was continued on physiologic dosing and his condition improved and was stable for discharge with follow up for surgical planning.

While routine screening MRI prior to ADT initiation is not always practical in the clinical setting, this should serve as a reminder that patients who develop constitutional symptoms after GnRHa injection should be closely followed for further work up including pituitary hormone monitoring and brain imaging. Of note, the presence of a known pituitary microadenoma in patients with prostate cancer is not an absolute contraindication, however requires close evaluation by multidisciplinary team prior to proceeding with GnRHa therapy.[13] It has also been suggested that those who are at risk of developing PA with GnRH agonist use be considered for GnRH antagonist therapy, such as degarelix as part of ADT.[6]

CONCLUSION

While a rare consequence of GnRH agonist treatment, pituitary apoplexy has a major potential for severity and most patients are known to end up with associated hormonal deficiencies with a necessity for long-term replacement therapy.[6,14] Clinicians should be aware of this complication in the management of patients with prostate cancer. With regards to our patient, prior to his onset of ptosis and diplopia, his presenting symptoms were thought to be attributable to the well documented side effect profile of leuprolide injections, and further workup would likely not have been initiated otherwise. It is critical that symptoms such as hot flashes and sweats not be dismissed as common side effects of androgen deprivation therapy and that appropriate workup and treatment be conducted promptly in patients with suspicion for possible GnRH agonist associated pituitary apoplexy.

References

1. Prostate Cancer Incidence by Stage at Diagnosis, United States—2001–2019 | CDC. Accessed June 27, 2023. https://www.cdc.gov/cancer/uscs/about/data-briefs/no34-prostate-cancer-incidence-2001-2019.htm
2. Cancer Statistics Review, 1975-2015 - SEER Statistics. Accessed April 10, 2023. https://seer.cancer.gov/archive/csr/1975_2015/
3. Rawla P. Epidemiology of Prostate Cancer. *World J Oncol*. 2019;10(2):63. doi:10.14740/WJON1191
4. Barbieri CE, Bangma CH, Bjartell A, et al. The Mutational Landscape of Prostate Cancer. *Eur Urol*. 2013;64(4):567. doi:10.1016/J.EURURO.2013.05.029
5. Seidenfeld J, Samson DJ, Hasselblad V, et al. Single-therapy androgen suppression in men with advanced prostate cancer: a systematic review and meta-analysis. *Ann Intern Med*. 2000;132(7):566-577. doi:10.7326/0003-4819-132-7-200004040-00009
6. Raj R, Elshimy G, Jacob A, et al. Pituitary apoplexy induced by gonadotropin-releasing hormone (GnRH) agonist administration for treatment of prostate cancer: a systematic review. *J Cancer Res Clin Oncol*. 2021;147(8):2337-2347. doi:10.1007/S00432-021-03697-1
7. Okuda O, Umezawa H, Miyaoka M. Pituitary apoplexy caused by endocrine stimulation tests: a case report. *Surg Neurol*. 1994;42(1):19-22. doi:10.1016/0090-3019(94)90244-5
8. Korsic M, Lelas-Bahun N, Surdonja P, et al. Infarction of FSH-secreting pituitary adenoma. *Acta Endocrinol (Copenh)*. 1984;107(2):149-154. doi:10.1530/ACTA.0.1070149
9. Li Y, Qian Y, Qiao Y, et al. Risk factors for the incidence of apoplexy in pituitary adenoma: a single-center study from southwestern China. *Chinese Neurosurg J*. 2020;6(1). doi:10.1186/S41016-020-00202-4
10. Elshimy G, Raj R, Jacob A, Correa R. Late onset of pituitary apoplexy following gonadotropin-releasing hormone agonist for prostate cancer treatment. *BMJ Case Rep*. 2022;15(3). doi:10.1136/BCR-2021-248523
11. Tanios G, Mungo NA, Kapila A, Bajaj K. Case Report: Pituitary apoplexy: a rare complication of leuprolide therapy in prostate cancer treatment. *BMJ Case Rep*. 2017;2017. doi:10.1136/BCR-2016-218514
12. Barbosa M, Paredes S, Machado MJ, Almeida R, Marques O. Pituitary apoplexy induced by gonadotropin-releasing hormone agonist administration: a rare complication of prostate cancer treatment. *Endocrinol diabetes Metab case reports*. 2020;2020(1):1-6. doi:10.1530/EDM-20-0018
13. Babbo A, Kalapurakal GT, Liu B, et al. The presence of a pituitary tumor in patients with prostate cancer is not a contraindication for leuprolide therapy. *Int Urol Nephrol*. 2014;46(9):1775-1778. doi:10.1007/S11255-014-0708-Z
14. Muthukumar N. Pituitary Apoplexy: A Comprehensive Review. *Neurol India*. 2020;68(Supplement):S72-S78. doi:10.4103/0028-3886.287669

Authors

Kang Woo Kim, BA, Alpert Medical School of Brown University, Providence, RI.

Sora Chee, MD, Department of Medicine, Brown University, Providence, RI.

Naveena Sunkara, MD, Department of Medicine, Brown University, Providence, RI.

Margaret Hayes Baker, MD, Department of Medicine, Brown University, Providence, RI.

Acknowledgments

The authors thank the patient for consenting to this publication. In accordance with the journal's policy, informed consent was obtained from the patient and family to publish this report.

Financial Disclosure

No author has any financial or proprietary conflict of interest. No financial support was received for this publication.

Correspondence

Margaret Hayes Baker, MD, FACP
VA Internal Medicine Residency Site Director
Associate Chief Hospitalist
Assistant Professor of Medicine
Alpert Medical Schoolof Brown University
401-273-1000
Margaret.baker2@va.gov