Endocrinology, Diabetes & Metabolism CASE REPORTS

M Barbosa and others | Rare complication of prostate cancer treatment

ID: 20-0018; June 2020
DOI: 10.1530/EDM-20-0018

Pituitary apoplexy induced by gonadotropin-releasing hormone agonist administration: a rare complication of prostate cancer treatment

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Summary

Gonadotropin-releasing hormone (GnRH) agonists, currently used in the treatment of advanced prostate cancer, have been described as a rare cause of pituitary apoplexy, a potentially life-threatening clinical condition. We report the case of a 69-year-old man with a known pituitary macroadenoma who was diagnosed with prostate cancer and started treatment with GnRH agonist leuprorelin (other hormones were not tested before treatment). Few minutes after drug administration, the patient presented with acute-onset severe headache, followed by left eye ptosis, diplopia and vomiting. Pituitary MRI revealed tumor enlargement and T1-hyperintense signal, compatible with recent bleeding sellar content. Laboratory endocrine workup was significant for low total testosterone. The patient was managed conservatively with high-dose steroids, and symptoms significantly improved. This case describes a rare phenomenon, pituitary apoplexy induced by GnRH agonist. We review the literature regarding this condition: the pathophysiological mechanism involved is not clearly established and several hypotheses have been proposed. Although uncommon, healthcare professionals and patients should be aware of this complication and recognize the signs, preventing a delay in diagnosis and treatment.

Learning points:

- Pituitary apoplexy (PA) is a potentially life-threatening complication that can be caused by gonadotropin-releasing hormone agonist (GnRHa) administration for the treatment of advanced prostate cancer.
- This complication is rare but should be taken into account when using GnRHa, particularly in the setting of a known pre-existing pituitary adenoma.
- PA presents with classic clinical signs and symptoms that should be promptly recognized.
- Patients should be instructed to seek medical care if suspicious symptoms occur.
- Healthcare professionals should be aware of this complication, enabling its early recognition, adequate treatment and favorable outcome.

Background

Pituitary apoplexy (PA) is a potentially life-threatening clinical syndrome characterized by sudden onset of headache, vomiting, visual impairment and decreased consciousness, caused by bleeding and/or infarction of the pituitary gland, usually within a tumor (1). Androgen deprivation therapy, including gonadotropin-releasing hormone agonists (GnRHa), is administered as primary systemic therapy for regional or advanced prostate cancer

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and as neoadjuvant/concomitant/adjuvant therapy in combination with radiation in localized or locally advanced disease (2). GnRHa administration for prostate cancer has been reported to induce PA in patients with a concurrent pituitary adenoma, but there are only 21 cases described in the literature to date (3, 4, 5, 6, 7, 8, 9, 10). Although it is a rare complication, and since diagnosing PA requires high suspicion index, healthcare professionals should be aware of this association in order to enable an early recognition and adequate treatment.

Case presentation

A 69-year-old man with past medical history significant for diabetes, hypertension, dyslipidemia, Parkinson disease and cerebral falx meningioma had a pituitary macroadenoma (11.5 × 10.9 × 9 mm) incidentally detected in 2016 during workup for the meningioma – Fig. 1. An endocrinology evaluation was requested but the patient failed to attend and was lost to follow-up. He was diagnosed with prostate cancer in 2017 and underwent retropubic prostatectomy; two years later there was evidence of histologic prostate tumor progression and he started on a GnRHa – a s.c. injection of leuprorelin 45 mg every 6 months. A few minutes after the first injection, the patient presented with acute-onset severe persistent headache, followed by left eye ptosis 2 days later, diplopia and vomiting. He was observed by a neurosurgeon on the emergency department who confirmed left third cranial nerve palsy, with no other neurologic abnormalities. Remaining physical exam was unremarkable.

Investigation

Head CT with angiography showed pre-existing lesions: the tumor in the sellar region and the cerebral falx meningioma. Brain MRI was performed for further clarification and revealed sellar tumor enlargement and a heterogeneous T1-hyperintense signal, compatible with recent bleeding sellar content, with extension to the left cavernous sinus (Knosp grade II) – Fig. 2. Laboratory workup was significant for total testosterone 72.1 ng/dL (86.5–788.2), with no other relevant abnormalities on pituitary cell lines or blood electrolytes as the sample was collected after steroid administration - Table 1.

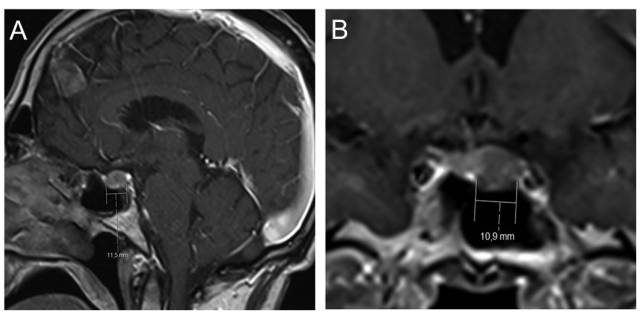

Figure 1
Gadolinium-enhanced T1-weighted pituitary MRI images with sagittal (A) and coronal (B) sections showing macroadenoma before apoplexy.

Treatment

High-dose steroids – a 10 mg dexamethasone i.v. bolus followed by 5 mg of dexamethasone every 8 h – were started, with significant improvement of all clinical signs and symptoms, reason why the non-surgical approach was maintained. On discharge, the patient had complete resolution of the third nerve palsy, presenting with normal extraocular movements and no further headaches or vomiting. Dexamethasone was switched to methylprednisolone with tapering dose over 4 weeks and then replaced by hydrocortisone (15 mg/day).

Outcome and follow-up

At two-month follow-up evaluation, the patient remained asymptomatic and biochemical workup revealed adrenocorticotrophic hormone 8.4 pg/mL (<46), cortisol 7.3 ug/dL (4.3–22.4) (sample collected 24 h after last hydrocortisone administration) and total testosterone 20 ng/dL (86.5–788.2), with no other biochemical remarks. He was maintained on hydrocortisone 15 mg/day. A pituitary MRI was performed 4 months later that revealed tumor volume reduction, with T1-isointense signal, but heterogeneous features reflecting different stages of previous bleeding and reduced extension to the left

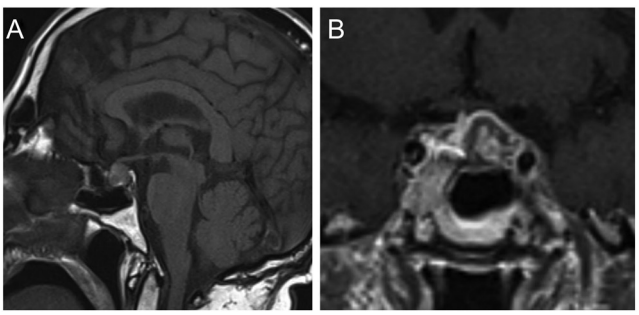

Figure 2
Non-contrast T1-weighted sagittal section (A) and gadolinium-enhanced T1-weighted coronal section (B) of pituitary MRI at presentation demonstrating sellar tumor enlargement and heterogeneous hyperintense signal compatible with pituitary apoplexy.

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Table 1 Laboratory workup at admission (*after steroids administration*).

Laboratory test	Result	Reference range
Cortisol, µg/dL	1.6	4.3–22.4
ACTH, pg/mL	10.8	<46
TSH, µUI/mL	0.3	0.4–3.7
FT4, ng/dL	0.9	0.8–1.5
Prolactin, ng/mL	0.5	2.1–17.7
GH, ng/mL	0.8	<3
IGF-1, ng/mL	147	37–219
FSH, mUI/mL	3.5	
LH, mUI/mL	4.3	
TT, ng/dL	72.1	86.5–788.2
Sodium, mmol/L	139	136–145
Potassium, mmol/L	3.8	3.5–5.1
Creatinine, mg/dL	0.9	0.7–1.2
CRP, mg/L	25	<3

ACTH, adrenocorticotropic hormone; CRP, C-reactive protein; FSH, follicle-stimulating hormone; FT4, free thyroxine; GH, growth hormone; IGF-1, insulin-like growth factor-1; LH, luteinizing hormone; TSH, thyroid-stimulating hormone; TT, total testosterone.

cavernous sinus (Knosp grade I) – Fig. 3. Meanwhile, he was started on radiation therapy for prostate cancer.

Discussion

Prostate cancer is a prevalent disease, with an estimate of 174 650 new cases in the United States to be diagnosed in 2019, accounting for 20% of new cancer cases in men.

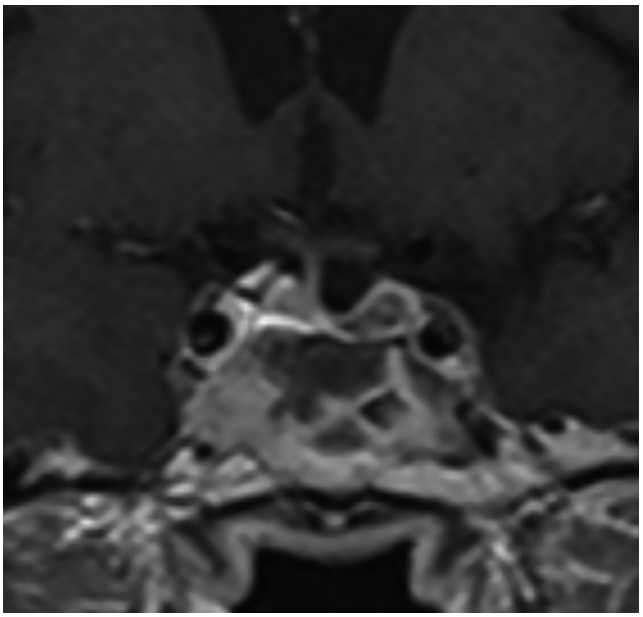

Figure 3
Gadolinium-enhanced T1-weighted coronal pituitary MRI image showing tumor volume reduction and isointense signal 4 months after apoplexy.

Hormonal therapy including GnRHa is an important modality of treatment in selected cases (2). Increasing use of GnRHa therapy has revealed a rare adverse drug reaction, the development of apoplexy in a pre-existing pituitary adenoma. We report a case of PA occurring minutes after the administration of leuprorelin in a patient with prostate cancer and a previously diagnosed pituitary macroadenoma.

The first case recording this condition was reported by Ando *et al*. in 1995 and since then 20 other cases have been published (3, 4, 5, 6, 7, 8, 9, 10) – Table 2. Literature analysis of these reports revealed clinical features consistent with PA, highlighting pituitary MRI as the gold standard for diagnosis. Treatment decision on how to manage those patients – conservatively or with surgery – should be assessed by a multidisciplinary team (1). There are no randomized controlled trials and no evidence-based criteria to justify the clinical decision between a conservative approach and neurosurgical intervention. According to United Kingdom guidelines, patients with PA who are without any neuro-ophthalmic signs or mild and stable signs can be considered for conservative management with careful monitoring and frequent neurological assessments. On the other hand, patients with severely reduced visual acuity, severe and persistent or deteriorating visual field defects or deteriorating level of consciousness should be considered for surgical management (performed by an experienced pituitary surgeon and preferably within the first 7 days of symptoms onset). They emphasize that ocular paresis in the absence of visual field defects or reduced visual acuity is not in itself an indication for immediate surgery (resolution will typically occur within days or weeks) (1). Also, it is important to keep in mind that acute secondary adrenal insufficiency is seen in approximately two-thirds of patients with PA and is a major source of mortality. Therefore, initiating early glucocorticoid therapy is crucial in patients with PA and hemodynamic instability, altered consciousness level, reduced visual acuity, severe visual field defects or confirmed hypocortisolism. According to the literature, an i.v. bolus of hydrocortisone 100–200 mg is appropriate followed either by 2–4 mg/h continuous i.v. infusion or by 50–100 mg i.m. injection every 6 h (1). Dexamethasone is not favored as a glucocorticoid replacement option, although it may be used to reduce edema as part of nonsurgical strategy for PA treatment, as occurred in the case we report.

Review of the documented cases evidenced a mean age of 69.8 years (ranging from 60 to 85 years) at the event time. The majority of reported cases (11) occurred

Table 2 Summary of reported cases of pituitary apoplexy induced by gonadotropin-releasing hormone agonists.

Year	Reference	Patient age	GnRH agonist, dose	Time of onset	Symptoms/signs	Pathological findings	Treatment
1995	(11)	83	Goserelin, 3.6 mg	9 days	Headache, nausea/vomiting, altered mentation, diplopia, fever and hyponatremia	–	Medical
1995	(12)	78	Triptorelin, 3.75 mg	a few min	Headache, postural dizziness and left partial ophthalmoplegia	–	Medical
1996	(13)	74	Leuprolide, 7.5 mg	15 min	Headache, nausea/vomiting, left ophthalmoplegia, altered mentation, generalized weakness and visual disturbances	Stain FSH +, LH +, GH +	Surgical
1997	(14)	62	Leuprorelin, 3.75 mg	4 days	Headache, left ophthalmoplegia and papilledema	Stain FSH +, LH +	Surgical
2001	(15)	67	Goserelin, 3.6 mg	4 h	Headache, nausea/vomiting, visual disturbances, altered mentation and hypertension	Stain FSH +, LH +	Surgical
2002	(4)	74	Leuprolide, -	–	Headache and nausea/vomiting	–	Medical
2003	(16)	69	Leuprolide, -	<4 h	Headache, visual disturbances and diabetes insipidus	Stain FSH +	Surgical
2006	(17)	68	Goserelin, 3.6 mg	4–6 h	Headache, nausea/vomiting, altered mentation, diplopia and right ptosis	–	Surgical
2006	(18)	61	Leuprolide, 30 mg	a few hours	Headache, nausea/vomiting, diplopia and ophthalmoplegia	Stain FSH +	Surgical
2006	(19)	70	Leuprolide, 11.25 mg	10 days	Visual disturbances, diplopia and right ptosis	Stain FSH +	Surgical
2007	(20)	60	Leuprolide, 22.5 mg	4 hs	Headache, nausea/vomiting, altered mentation, visual disturbances, left ophthalmoplegia and diplopia	Stain LH +	Surgical
2010	(5)	71	Goserelin, -	8 weeks	Headache, nausea/vomiting and visual disturbances	Stain FSH +, LH +	Surgical
2010	(10)	60	Leuprolide, -	a few hours	Headache, left ophthalmoplegia and visual disturbances	Stain LH +	Surgical
2011	(6)	78	Goserelin, 3.6 mg	9 days	Headache, left ophthalmoplegia and visual disturbances	Stain FSH +	Surgical
2013	(9)	77	Leuprorelin, 3.75 mg	a few hours	Headache, nausea/vomiting and left ophthalmoplegia	–	Surgical
2014	(7)	60	Leuprolide, -	a few hours	Headache, nausea/vomiting, diplopia and left ptosis	Stain LH +, TSH +	Surgical
2015	(21).	62	Leuprolide, 11.25 mg	10 min	Headache, nausea/vomiting and right ophthalmoplegia	Stain FSH +, LH +	Surgical
2015	(8)	77	Triptorelin, 22.5 mg	1 h	Headache, nausea/vomiting, diplopia and right ptosis	–	Surgical
2016	(22)	67	Triptorelin, -	14 days	Headache and right ptosis	Stain FSH +, LH +	Surgical
2016	(23)	63	Leuprolide, 11.25 mg	3 days	Headache, visual disturbances and altered mentation	–	Medical
2017	(3)	85	Leuprolide, 45 mg	4 h	Headache and nausea/vomiting	–	Medical

FSH, follicle-stimulating hormone; GH, growth hormone; LH, luteinizing hormone; TSH, thyroid-stimulating hormone.

with leuprolide, whereas goserelin was implicated in five cases, triptorelin in three cases and leuprorelin in tw cases. The most variable parameter was time of symptom onset, occurring within minutes to several days after GnRHa administration. In 13 cases, symptoms developed within hours; the remaining patients presented clinical features 3 to 14 days after the injection, and in one case delayed PA was diagnosed 8 weeks after treatment. Headache was the predominant symptom, described in 95.2% of cases ($n=20$), followed by nausea/vomiting in 61.9% ($n=13$), ophthalmoplegia and visual disturbances in 42.9% ($n=9$), diplopia in 33.3% ($n=7$) and altered mentation status in 28.6% ($n=6$). Regarding treatment, surgical approach was conducted in 76.2% of cases ($n=16$). As mentioned previously, while many patients with PA require surgical intervention, selected patients may be managed conservatively. In fact, our patient, despite the presence of a neuro-ophthalmic deficit, presented an

excellent outcome with only medical treatment, possibly due to prompt evaluation and management. Histological findings with adenomatous tissue immunohistochemical staining were available in only 13 reports, all of them compatible with gonadotrophinomas (six positive for both luteinizing hormone (LH) and follicle-stimulating hormone (FSH), four positive for FSH and three positive for LH) (3, 4, 5, 6, 7, 8, 9, 10).

The exact pathophysiologic mechanism involved is this association is not clearly established. Multiple factors have been implicated in the increased risk of pituitary bleeding: larger size of the tumor, elevated intrasellar pressure and intrinsic vasculature abnormalities (9). Guerra *et al*. proposed a biphasic phenomenon, hypothesizing that PA induced by GnRHa can occur through an acute and a subacute phase (10). This concept of dual pathophysiology can reconcile the different features described in reported cases, especially concerning the timing of symptom onset. In cases where the condition occurred a few minutes or hours after drug administration (acute phase), a combination of cell degranulation/shrinking and metabolic hyperactivity in a poorly perfused adenomatous pituitary tissue (abnormal capillarity system) would explain the event. On the other hand, in the group of patients with a later start of symptoms (subacute phase), it was suggested that the stimulation of LH secretion leading to cell growth and protein synthesis could have an effect on tumor size and intrasellar pressure, promoting generalized ischemia and consequent bleeding (8, 10). Moreover, it has also been proposed that gonadotroph adenomas are the most common adenomas associated with the occurrence of PA. GnRHa binding to GnRH receptors on pituitary gonadotropin-secreting cells causes levels of LH and FSH to increase dramatically and this hormonal stimulation of gonadotrophs may be related to tumor growth, perpetuating tissue infarction (3). In fact, to our knowledge, only gonadotrophinomas were reported (both functioning and non-functioning (10)), despite co-staining for growth hormone (GH) in one case and thyroid-stimulating hormone (TSH) in another (3, 7).

Attending to the frequency of pituitary adenomas in the general population and the widespread use of GnRHa in prevalent diseases such as prostate cancer, along with the fact that pre-treatment pituitary hormone tests or imaging evaluation are probably not cost-effective, it is essential to draw attention to this possible complication (7, 8). In patients with a known pituitary adenoma, Babbo *et al*. recommended a thorough clinical evaluation and discussion by a multidisciplinary team including endocrinologists and neurosurgeons: in macroadenomas, surgical resection of the tumor prior to GnRHa therapy may be appropriate (given the higher likelihood of apoplexy in larger tumors), while in microadenomas, it may be suitable to cautiously proceed with GnRHa therapy (7). Nonetheless, regardless of the presence or absence of a known pituitary adenoma, both physicians who prescribe these drugs and patients should be informed and vigilant to the warning, clinical signs and act accordingly.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent
Written informed consent was obtained from the patient for publication of the submitted article and accompanying images.

Author contribution statement
All authors contributed to the case report and were included in the medical team that assisted the patient. Material preparation, data collection and literature review were performed by Mariana Barbosa. The first draft of the manuscript was written by Mariana Barbosa and all authors commented on previous versions, read and approved the revised and final manuscript.

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Received in final form 8 April 2020
Accepted 6 may 2020