CASE REPORT

Pituitary apoplexy: a rare complication of leuprolide therapy in prostate cancer treatment

Georges Tanios, Nicolas Andrews Mungo, Aaysha Kapila, Kailash Bajaj

Internal Medicine, East Tennessee State University, Johnson city, Tennessee, USA

Correspondence to
Professor Kailash Bajaj,
BAJAJK@mail.etsu.edu

Accepted 29 May 2017

SUMMARY

Gonadotropin-releasing hormone agonists, used widely in the treatment of metastatic prostate cancer and hormone receptor-positive breast cancer, are associated with a rare but potentially fatal outcome of pituitary apoplexy (PA). An 85-year-old man presented with sudden onset of headache, left eye pain, sensitivity to light, nausea and vomiting. The symptoms started 4 hours after initiation of leuprolide therapy for treatment of recently diagnosed metastatic prostate carcinoma. Radiological imaging of the brain demonstrated a heterogeneously enlarged pituitary gland measuring 19×16×13 mm and T1-hyperintense signal compatible with pituitary haemorrhage. Hormone function tests were indicative of panhypopituitarism, confirming the diagnosis of PA. Due to age, the patient was started on hormonal replacement therapy and eventually symptoms improved.

BACKGROUND

Physicians should be aware of the rare association of pituitary apoplexy (PA) with the use of Gonadotropin-releasing hormone (GnRH) analogue. Though our patient was fortunate, lack of recognition of this condition has the possibility of a life-threatening outcome to patients. PA has been well documented with usage of various medications including oestrogen, bromocriptine, anticoagulants, carbamazepine and isosorbide dinitrate. There are a few case reports of GnRH agonist-induced PA. Extensive literature review revealed only 15 previously documented cases to date.^{1–17} There are no recommendations on pretreatment evaluation of the patients receiving hormonal therapy. Thus, it is important to recognise this condition because if left untreated, it can have long-term implications.

CASE PRESENTATION

An 85-year-old man, recently diagnosed with prostate cancer (Gleason score=9), presented with a sudden onset of severe, dull and pulsating frontal headache that started 4 hours after administration of the first dose of leuprolide, 45 mg subcutaneously. The patient complained of left eye pain, photophobia, nausea and vomiting. His medical history was significant for diabetes, hypertension, coronary artery disease, benign prostate hypertrophy and migraine headaches. His home medications included: amlodipine, isosorbide dinitrate, fosinopril, promethazine, finasteride, tamsulosin and sumatriptan. On physical examination, the patient

seemed to be in apparent distress with normal vital signs. The physical examination was unremarkable with normal extraocular movements, normal visual field confrontation and an insignificant neurological examination.

INVESTIGATIONS

Laboratory workup was significant for thyroid-stimulating hormone (TSH) 0.131 mIU/mL (0.46–4.6 mIU/mL), cortisol 2.5 µg/dL (4.5–22.7 µg/dL), blood glucose 141 mg/dL (75–110 mg/dL), adrenocorticotrophic hormone 6.2 pg/mL (7.2–63.3 pg/mL), insulin-like growth factor (IGF) 78 ng/mL (37–182 ng/mL), free testosterone 3.33 ng/dL (5–21 ng/dL), prolactin 2.7 ng/mL (4–15.2 ng/mL), arginine vasopressin <0.8 pg/mL (0.0–4.7 pg/mL), sodium 129 mEq/L (135–145 mEq/L) with normal follicle-stimulating hormone (FSH), luteinising hormone (LH), growth hormone and free T4. CT of the head demonstrated a 9 mm soft tissue is visualised in the suprasellar cistern. MRI of the pituitary confirmed the presence of an enlarged gland measuring 19×16×13 mm, with a suprasellar component that abuts and slightly uplifts the optic chiasm, and a heterogeneous partially T1-hyperintense signal compatible with pituitary haemorrhage, probably within a pre-existing adenoma (figure 1).

DIFFERENTIAL DIAGNOSIS

Our initial differentials included subarachnoid haemorrhage, optic neuritis, aneurysmal rupture, bacterial meningitis, stroke and PA. Based on the imaging studies, laboratory workup and clinical presentation, a diagnosis of PA was established.

TREATMENT

Considering our patient's age and symptoms, a conservative non-surgical approach was adopted. The patient was started on hormonal replacement treatment including hydrocortisone, 100 mg intravenously one dose followed by 100 mg every 6 hours. On discharge, he was instructed to take hydrocortisone 20 mg in the morning and 10 mg in the evening along with dexamethasone 4 mg/mL intramuscular injection for symptoms suggesting adrenal insufficiency, acute drop in blood pressure, nausea, weakness or fatigue.

CrossMark

To cite: Tanios G, Mungo NA, Kapila A, et al. *BMJ Case Rep* Published Online First: [please include Day Month Year]. doi:10.1136/bcr-2016-218514

Figures 1 Sagittal (A) and coronal (B,C) sections: Non-contrast pituitary MRI illustrates enlarged pituitary gland (white arrow) measuring 19x16x13 mm, T1-hyperintense signal compatible with pituitary haemorrhage indicative of pituitary apoplexy.

OUTCOME AND FOLLOW-UP

On follow-up in the endocrinology clinic, our patient reported to be doing well. The hydrocortisone dose was decreased to 15 mg in the morning and 5 mg in the evening. He was educated to continue using dexamethasone injection in situations indicative of adrenal insufficiency. An MRI of the brain had been scheduled in 6 months.

DISCUSSION

Prostate cancer is the most frequently diagnosed cancer in men and is the second leading cause of cancer death preceded by lung cancer.¹⁸ Prostate cancer has an incidence of affecting one in seven men, which has increased in the early 1990s as result of the introduction of prostate-specific antigen (PSA) testing. Additionally, the mortality rate in the USA has diminished by 3.5% per year from 2003 to 2012. Various treatment modalities may be attributing to this diminished mortality rate, including observation, surgery, radiation, hormonal therapy, chemotherapy and the recent introduction of sipuleucel-T immunotherapy.¹⁹ Hormonal therapy including LH-releasing hormone (LHRH) agonists or antagonists are an important modality of treatment for advanced prostate cancer. They are used when surgery or radiation therapy is not possible or preceding radiation in metastatic disease.

Leuprolide acts as an agonist that binds to pituitary GnRH receptors. It acts via desensitisation, downregulating FSH and LH production and ultimately decreasing testicular and ovarian steroidogenesis.²⁰ Initial administration leads to transient stimulation of the pituitary which leads to elevated FSH and LH levels and increased production of oestrogen and testosterone in the first week, with eventual downregulation of the overall pathway.²⁰ Major side effects of these agents include impotence, hot flashes, reduced or absent libido and osteoporosis. A rare complication is the development of apoplexy in a pre-existing pituitary adenoma. Per extensive literature review, there have only been 15 reported cases of PA in patients undergoing treatment for prostate cancer since its implementation.^{1–17} The first case of PA was reported in 1995 by Ando *et al* in a patient receiving a GnRH analogue for treatment of prostate cancer.⁷

LHRH agonists such as leuprolide are not exclusively in use for men with prostate cancer. These agents have also been commonly used in premenopausal women with hormone receptor-positive breast cancer, where it reduces the risk of early-stage breast cancer recurrence after surgery or other treatments. Adjuvant GnRH analogue treatment has demonstrated a survival benefit in premenopausal patients with endocrine responsive breast cancer.^{21 22} Male breast cancer is relatively rare and there is less known about the optimal treatment for male hormone

receptor-positive breast cancer, though cases have been reported of leuprolide use in these men.²³ About 40 610 women in the USA are expected to die in 2017 from breast cancer, though death rates have been decreasing since 1989.²⁴ These decreases are thought to be the result of earlier detection in combination with advancements in treatment, such as leuprolide. It is therefore necessary to report the uncommon complication of PA associated with GnRH analogue administration for prostate cancer therapy given the additional concern for the development of this side effect in all utilisations of GnRH analogue class drugs.

PA is a syndrome characterised by sudden severe headache mimicking subarachnoid bleeding associated with visual impairment, headache, vomiting and ophthalmoplegia, which per literary review has been consistent in previous case reports. Acute multihormonal pituitary failure results when the anterior lobe is destroyed, leading to serious medical conditions including adrenal failure, hypothyroidism, diabetes insipidus and rarely death.²⁵ PA has been associated with a wide range of pathologies from sudden head trauma, major surgery (especially coronary artery bypass grafting), arterial hypertension, transient elevation of intracranial pressure, diabetes mellitus, thyrotropin-releasing hormone, anticoagulation, bromocriptine, isosorbide dinitrate, chlorpromazine, oestrogen, pregnancy, obstetrical haemorrhage, dynamic pituitary function testing, radiotherapy and GnRH analogues.^{25 26}

The mechanism relating GnRH analogue administration with PA is not clearly understood. It is believed that the initial pituitary stimulation by leuprolide administration causes increased metabolic activity of the underlying adenoma which outgrows its blood supply, thus developing ischaemic necrosis and subsequent haemorrhage. A second hypothesis is compression of the superior hypophyseal and infundibular vessels against the diaphragm sellae may explain infarction in the non-adenomatous gland.^{4 25} Our patient received the intramuscular form of leuprolide that reaches maximum serum concentration in 4 hours, coinciding with the onset of symptoms. This is consistent with 12 out of the 15 previous cases documented, as shown in table 1 summarising all previous case reports.

Underlying gonadotroph adenomas are the most common adenomas associated with the occurrence of PA because the hormonal stimulation accelerates the growth of the adenoma and perpetuates infarction that causes apoplexy.^{3 6} The prevalence of pituitary adenomas has been reported to be 16.7%, with prevalence of macroadenomas being 1 in 600.²⁷ There is a high likelihood that these functional or non-functional adenomas will not be recognised until they are detected by imaging or autopsy. However, 65% of cases of PA occur in patients with previously undiagnosed non-functioning pituitary adenomas with 17% of

Table 1 Summary and organised current and all previously reported cases of pituitary apoplexy induced by GnRH analogues

Year	Author	Age of patient	GnRH agonist	Drug dose	Time of onset	Pathological findings	Signs/symptoms	Ultimate treatment
1995	Ando <i>et al</i> ⁷	83	Goserelin	3.6 mg	9 days	No biopsy, CT imaging showed suprasellar mass	Headache, nausea, vomiting, altered mentation, hyponatraemia, diplopia	Medical management
1995	Chanson <i>et al</i> ¹³	78	Triptorelin	3.75 mg	<4 hours	No biopsy, CT imaging showed suprasellar mass	Headache, dizziness, partial ophthalmoplegia	Medical management
1996	Morsi <i>et al</i> ⁶	74	Leuprolide	7.5 mg	<4 hours	Pituitary adenoma, Stain FSH+, LH+	Headache, nausea, vomiting, generalised weakness, altered mentation, ophthalmoplegia	Surgical removal
1997	Reznik <i>et al</i> ¹²	62	Leuprolide	?	<4 hours	Pituitary adenoma, Stain LH+, FSH+	Sudden intracranial hypertension	Surgical removal
2001	Eaton <i>et al</i> ¹¹	67	Goserelin	3.6 mg	4 hours	Pituitary adenoma, Stain LH+, FSH+	Headache, nausea, vomiting, visual disturbances, altered mentation, hypertension	Medical management
2003	Hernandez <i>et al</i> ⁵	69	Leuprolide	?	<4 hours	Pituitary adenoma, Stain FSH+	Headache, visual disturbances, diabetes insipidus	Surgical removal
2006	Blaut <i>et al</i> ¹⁰	68	Goserelin	3.6 mg	4–6 hours	Pituitary adenoma	Headache, nausea, vomiting, altered mentation, diplopia, ptosis	Surgical removal
2006	Davis <i>et al</i> ⁴	61	Leuprolide	30 mg	<4 hours	Pituitary adenoma	Headache, nausea, vomiting, ptosis, diplopia, ptosis, CNIII palsy	Surgical removal
2006	Massoud <i>et al</i> ⁹	70	Leuprolide	11.25 mg	10 days	Pituitary adenoma	Visual disturbances, diplopia, intracranial hypertension, ptosis	Surgical removal
2007	Hands <i>et al</i> ³	60	Leuprolide	22.5 mg	4 hours	Pituitary adenoma, Stain LH+, FSH-, PRL-	Headache, nausea, vomiting, altered mentation, ptosis, CNIII, IV, VI paralysis, diplopia	Surgical removal
2010	Guerra <i>et al</i> ²	60	Leuprolide	?	<4 hours	Pituitary adenoma, Stain LH+	Headache, blurry vision, ptosis, ophthalmoplegia	Surgical removal
2013	Huang <i>et al</i> ⁸	77	Leuprolide	3.75 mg	<4 hours	Necrotic debris	Headache, nausea, vomiting, ophthalmoplegia	Surgical removal
2015	Sasagawa <i>et al</i> ¹⁵	62	Leuprolide	11.25 mg	<4 hours	Pituitary adenoma, Stain LH+, FSH+	Headache, nausea	Surgical removal
2016	Keane <i>et al</i> ¹⁶	67	Triptorelin	?	10–14 days	Pituitary adenoma, Stain LH+, FSH+	Headache, ptosis, CNIII palsy	Surgical removal
2016	Fabiano <i>et al</i> ¹⁷	63	Leuprolide	11.25 mg	3 days	No biopsy, MRI showed haemorrhage	Headache, blurry vision, loss of consciousness	Medical management
2017	Tanios <i>et al</i>	84	Leuprolide	45 mg	<4 hours	Pituitary adenoma	Headache, photophobia, nausea, vomiting	Medical management

CN, cranial nerve; FSH, follicle-stimulating hormone; LH, luteinising hormone; PRL, prolactin.

the cases occurring in patients with a known pituitary adenoma.²⁸ Although potentially fatal, this complication remains rare; thus, pretreatment evaluation is not necessary especially when the majority of these adenomas are non-functioning.²⁹

MRI is currently the gold standard for diagnosing PA; therefore, an urgent MRI or dedicated pituitary CT if MRI is contraindicated or unavailable should be performed in all patients with suspected PA. Empiric steroid therapy of 100 mg intravenous bolus, followed by 2–4 mg/hour continuous infusion or 500–1000 mg every 6 hours via intramuscular route should be initiated once blood work for the baseline endocrine, kidney and renal function has been collected.²⁶ Pituitary function should be evaluated via Free-T4 (FT4), TSH, LH, FSH, IGF1, cortisol, growth-hormone (GH), estradiol in women and testosterone in men at the time of admission then 4–8 weeks after the event plus annual evaluation if required.²⁶ The decision to manage conservatively or with surgical intervention should be made carefully through a multidisciplinary team composed of an endocrinologist, ophthalmologist and pituitary surgeon. Preferably, a pituitary surgeon should perform a trans-sphenoidal surgery within 7 days of onset of symptoms in patients with visual problems, altered consciousness or cranial nerve involvement.²⁶ All these factors combined will potentially improve the outcome of this possibly life-threatening condition. Patients without neuro-ophthalmic signs or mild and stable signs can be considered for conservative management with close monitoring.³⁰

All patients with PA should have an endocrine evaluation at 4–8 weeks following the event. Both conservatively and surgically treated patients require close radiological follow-up and, if residual tumour or recurrence is detected, additional treatments such as radiotherapy or additional surgery should be considered.³⁰ It is important that patients are educated about the various side effects of leuprolide therapy in order to recognise the signs and symptoms of pituitary failure. Healthcare professionals additionally must be vigilant regarding the rare but possibly fatal consequence of GnRH analogue administration in prostate and breast cancer patients. Early recognition could be life altering and would result in a better prognosis.

Learning points

- ▶ Pituitary apoplexy (PA) is a rare but potentially fatal medical emergency associated with use of Gonadotropin-releasing hormone (GnRH) analogues in a patient with advanced prostate cancer and hormone receptor-positive breast cancer.
- ▶ PA can mimic subarachnoid haemorrhage.
- ▶ No pretreatment evaluation is indicated in non-functioning pituitary adenomas.
- ▶ MRI or dedicated pituitary CT should be performed in all patients with suspected PA.
- ▶ Clinicians should be familiar with this complication that could prevent a delay in diagnosis and thus help in a better outcome.

Contributors All persons who meet authorship criteria are listed as authors, and all authors certify that they have participated sufficiently in the work to take public responsibility for the content, including participation in the concept, design, analysis, writing or revision of the manuscript. GT was instrumental in the initial diagnosis, management of the patient and of the acquisition of data for this report. AK was instrumental in the planning, design and reporting of data for this report. She was also instrumental in the review of the write up. NAM was instrumental in the write-up, design, analysis and interpretation of the data in the report. He additionally constructed the table provided in the report summarising similar cases to date. KB was instrumental in the acquisition and analysis of the data as well as review of the write-up. Furthermore, each author certifies that this material or similar material has

not been and will not be submitted to or published in any other publication before its appearance in The British Medical Journal.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

© BMJ Publishing Group Ltd (unless otherwise stated in the text of the article) 2017. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

- 1 Sinnadurai M, Cherukuri RK, Moses RG, *et al.* Delayed pituitary apoplexy in patient with advanced prostate cancer treated with gonadotrophin-releasing hormone agonists. *J Clin Neurosci* 2010;17:1201–3.
- 2 Guerra Y, Lacuesta E, Marquez F, *et al.* Apoplexy in non functioning pituitary adenoma after one dose of leuprolide as treatment for prostate cancer. *Pituitary* 2010;13:54–9.
- 3 Hands KE, Alvarez A, Bruder JM. Gonadotropin-releasing hormone agonist-induced pituitary apoplexy in treatment of prostate cancer: case report and review of literature. *Endocr Pract* 2007;13:642–6.
- 4 Davis A, Goel S, Picoles M, *et al.* Pituitary apoplexy after leuprolide. *Pituitary* 2006;9:263–5.
- 5 Hernandez Morin N, Huet D, Hauteceuvre M. Two cases of non-functional gonadotroph adenoma pituitary apoplexy following GnRH-agonist treatment revealing gonadotroph adenoma and pseudopituitary apoplexy after GnRH administration. *Ann Endocrinol* 2003;64:227–31.
- 6 Morsi A, Jamal S, Silverberg JD. Pituitary apoplexy after leuprolide administration for carcinoma of the prostate. *Clin Endocrinol* 1996;44:121–4.
- 7 Ando S, Hoshino T, Mihara S. Pituitary apoplexy after goserelin. *Lancet* 1995;345:458.
- 8 Huang TY, Lin JP, Lieu AS, *et al.* Pituitary apoplexy induced by Gonadotropin-releasing hormone agonists for treating prostate cancer-report of first asian case. *World J Surg Oncol* 2013;11:254.
- 9 Massoud W, Paparel P, Lopez JG, *et al.* Discovery of a pituitary adenoma following treatment with a gonadotropin-releasing hormone agonist in a patient with prostate cancer. *Int J Urol* 2006;13:87–8.
- 10 Błaut K, Wiśniewski P, Syrenicz A, *et al.* Apoplexy of clinically silent pituitary adenoma during prostate Cancer treatment with LHRH analog. *Neuro Endocrinol Lett* 2006;27:569–72.
- 11 Eaton HJ, Phillips PJ, Hanieh A, *et al.* Rapid onset of pituitary apoplexy after goserelin implant for prostate cancer: need for heightened awareness. *Intern Med J* 2001;31:313–4.
- 12 Reznik Y, Chapon F, Lahlou N, *et al.* Pituitary apoplexy of a gonadotroph adenoma following gonadotrophin releasing hormone agonist therapy for prostatic cancer. *J Endocrinol Invest* 1997;20:566–8.
- 13 Chanson P, Schaison G. Pituitary apoplexy caused by GnRH-agonist treatment revealing gonadotroph adenoma. *J Clin Endocrinol Metab* 1995;80:2267–8.
- 14 Huang TY, Lin JP, Lieu AS, *et al.* Pituitary apoplexy induced by Gonadotropin-releasing hormone agonists for treating prostate cancer-report of first Asian case. *World J Surg Oncol* 2013;11:254.
- 15 Sasagawa Y, Tachibana O, Nakagawa A, *et al.* Pituitary apoplexy following gonadotropin-releasing hormone agonist administration with gonadotropin-secreting pituitary adenoma. *J Clin Neurosci* 2015;22:601–3.
- 16 Keane F, Egan AM, Navin P, *et al.* Gonadotropin-releasing hormone agonist-induced pituitary apoplexy. *Endocrinol Diabetes Metab Case Rep* 2016;2016:160021.
- 17 Fabiano AJ, George S. Pituitary apoplexy after Initial Leuprolide injection. *World Neurosurg* 2016;95:616.e7–9.
- 18 American Cancer Society Cancer Facts & Figures. 2016 <http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2016/index> (accessed 12 Sep 2016).
- 19 Kantoff PW, Higano CS, Shore ND, *et al.* Sipuleucel-T immunotherapy for castration-resistant prostate cancer. *N Engl J Med* 2010;363:411–22.
- 20 Micromedex Solutions. <http://www.micromedexsolutions.com/micromedex2/librarian#> (accessed 12 Sep 2016).
- 21 Shiba E, Yamashita H, Kurebayashi J, *et al.* A randomized controlled study evaluating safety and efficacy of leuporelin acetate every-3-months depot for 2 versus 3 or more years with tamoxifen for 5 years as adjuvant treatment in premenopausal patients with endocrine-responsive breast cancer. *Breast Cancer* 2016;23:499–509.
- 22 Kurebayashi J, Toyama T, Sumino S, *et al.* Efficacy and safety of leuporelin acetate 6-month depot, TAP-144-SR (6M), in combination with tamoxifen in postoperative, premenopausal patients with hormone receptor-positive breast cancer: a phase III, randomized, open-label, parallel-group comparative study. *Breast Cancer* 2017;24:161–70.
- 23 Zhu J, Davis CT, Silberman S, *et al.* A role for the androgen receptor in the treatment of male breast cancer. *Crit Rev Oncol Hematol* 2016;98:358–63.
- 24 US Breast Cancer Statistics. http://www.breastcancer.org/symptoms/understand_bc/statistics (accessed 6 Apr 2017).
- 25 Randeva HS, Schoebel J, Byrne J, *et al.* Classical pituitary apoplexy: clinical features, management and outcome. *Clin Endocrinol* 1999;51:181–8.

- 26 Vanderpump M, Higgins C, Wass JA. UK guidelines for the management of pituitary apoplexy a rare but potentially fatal medical emergency. *Emerg Med J* 2011;28:550–1.
- 27 Ezzat S, Asa SL, Couldwell WT, *et al.* The prevalence of pituitary adenomas: a systematic review. *Cancer* 2004;101:613–9.
- 28 Wakai S, Fukushima T, Teramoto A, *et al.* Pituitary apoplexy: its incidence and clinical significance. *J Neurosurg* 1981;55:187–93.
- 29 Faustini-Fustini M. Pituitary apoplexy after leuprolide administration for carcinoma of the prostate: what's new? *Clin Endocrinol* 1997;46:378.
- 30 Rajasekaran S, Vanderpump M, Baldeweg S, *et al.* UK guidelines for the management of pituitary apoplexy. *Clin Endocrinol* 2011;74:9–20.

Copyright 2017 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <http://group.bmj.com/group/rights-licensing/permissions>.
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- Submit as many cases as you like
- Enjoy fast sympathetic peer review and rapid publication of accepted articles
- Access all the published articles
- Re-use any of the published material for personal use and teaching without further permission

For information on Institutional Fellowships contact consortiasales@bmjgroup.com

Visit casereports.bmj.com for more articles like this and to become a Fellow