# A Perplexing Case of the Adrenal Insufficiency

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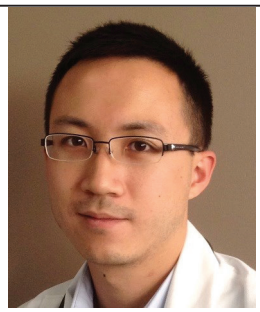

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## ABSTRACT

We report an unusual clinical presentation of adrenal insufficiency. A 54-year-old post-menopausal woman with well-controlled hypertension presented with 1 month of progressive anorexia and intermittent low-grade fever. She underwent extensive initial investigations that included computed tomography (CT) of the head, chest, and abdomen; gastroscopy; infectious and autoimmune workups; all of which were unrevealing. The head CT did not demonstrate any hyperintense or space-occupying lesion. When she represented to hospital, we noticed an empty sella on the initial CT. This prompted a magnetic resonance imaging study that revealed pituitary apoplexy, leading to eventual diagnosis of secondary adrenal insufficiency (morning cortisol 81 nmol/L and ACTH 1 pmol/L). Her symptoms resolved within 24 hours of glucocorticoid replacement. Diagnosis was elusive due to patient's atypical presentation – she did not have visual symptoms or cranial nerve deficits to suggest pituitary apoplexy, and also did not have any objective findings such as hypotension or electrolyte abnormalities to suggest adrenal insufficiency.

## Résumé

Nous rapportons ici un tableau clinique inhabituel en matière d'insuffisance surrénale. Une femme de 54 ans, ménopausée, dont l'hypertension est bien contrôlée, souffre depuis un mois d'anorexie progressive et d'une fièvre légère intermittente. Elle a subi de nombreux examens, notamment de tomodensitométrie (TDM) de la tête, du thorax et de l'abdomen; une gastroscopie; ainsi que des investigations techniques sur les plans infectieux et auto-immuns. Tous ces examens ont été vains. La TDM de la tête n'a montré aucune lésion hyperintense ou étendue. Lorsque la patiente s'est présentée de nouveau à l'hôpital, une relecture de la TDM initiale indiqua une selle turcique vide. Cela nous a incité à effectuer un examen d'imagerie par résonnance magnétique, qui révéla une apoplexie hypophysaire et nous mena finalement à un diagnostic d'insuffisance surrénale secondaire (taux de cortisol matinal de 81 nmol/L et ACTH de 1 pmol/L). Les symptômes se sont résorbés dans les 24 heures qui suivirent l'administration de glucocorticoïdes. C'est en raison du tableau atypique des symptômes de la patiente que le diagnostic a été difficile à cerner – il y avait absence de symptômes au niveau des yeux et absence de déficits au niveau des nerfs crâniens, ce qui aurait pu indiquer une apoplexie hypophysaire. De plus, il y avait absence de signe objectif comme de l'hypotension ou des anomalies électrolytiques indiquant une insuffisance surrénale.

## Case Presentation

Mrs. X was a 54-year-old woman who presented to the hospital with a 1 month history of persistent anorexia, generalized fatigue and weakness. Her past medical history entailed migraine headaches and hypertension for which she was on hydrochlorothiazide. She took no other medications and denied any history of alcohol or substance use.

For the previous 4 weeks, Mrs. X complained of being "unable to keep down solid foods" due to a lack of appetite, dysphagia, and nausea. She reported intermittent fever (maximum documented axillary temperature in hospital was 38.4° C). When prompted, she recalls an episode of sudden onset frontal headache a month prior to her presentation, lasting minutes and associated with nausea. She did not find this unusual given her history of migraines. She presented to a community hospital, where she underwent extensive investigation including whole body imaging. Non-contrast computed tomography (CT) of the head did not show any abnormal enhancement suggestive of intracranial hemorrhage, or any space-occupying lesion, and the ventricles were normal in size. CT of the thorax, abdomen, and pelvis were unrevealing. Abdominal ultrasound showed fatty liver and gallstones, without any sign of cholecystitis. Gastroscopy demonstrated normal anatomy, no signs of infection or inflammation, and gastric emptying was deemed normal. Transthoracic echocardiogram showed normal heart function. Infectious workup including pan-cultures and viral serologies (hepatitis, human immunodeficiency virus, Epstein-Barr virus, cytomegalovirus, parvovirus) were negative, as were serologies for connective tissue diseases. She remained hemodynamically stable, normotensive, and afebrile during her hospitalization. Patient was normotensive during her admission, and she was advised to discontinue her hydrochlorothiazide. No clear diagnosis was found and Mrs. X was discharged home with plans for outpatient Internal Medicine follow up.

One week later, Mrs. X represented to our university hospital with persistent inability to tolerate oral intake and progressive weakness. At this point, she was unable to keep down either solids or liquids, and as a result had lost 10 pounds in the last month. This time, she denied any dysphagia or odynophagia. She also denied any new headache, focal neurological symptoms, vertigo, dysarthria, or incoordination that would otherwise suggest a central cause. On examination, she was afebrile with heart rate of 98, blood pressure of 120/84 and she was breathing comfortably on room air. Neurological examination demonstrated normal visual fields, normal extraocular movements, and no upper motor neuron or lateralizing neurological findings. Cardiopulmonary and abdominal exams were unremarkable. Admission blood work including cell count, electrolytes, renal function, liver function, and thyroid stimulating hormone were within normal limits. Inflammatory markers were found elevated (ESR 73, CRP 29, platelets 602).

On careful review of the non-contrast head CT obtained during patient's initial admission 2 weeks previous, the authors noticed that the sella appeared empty. This prompted a dedicated

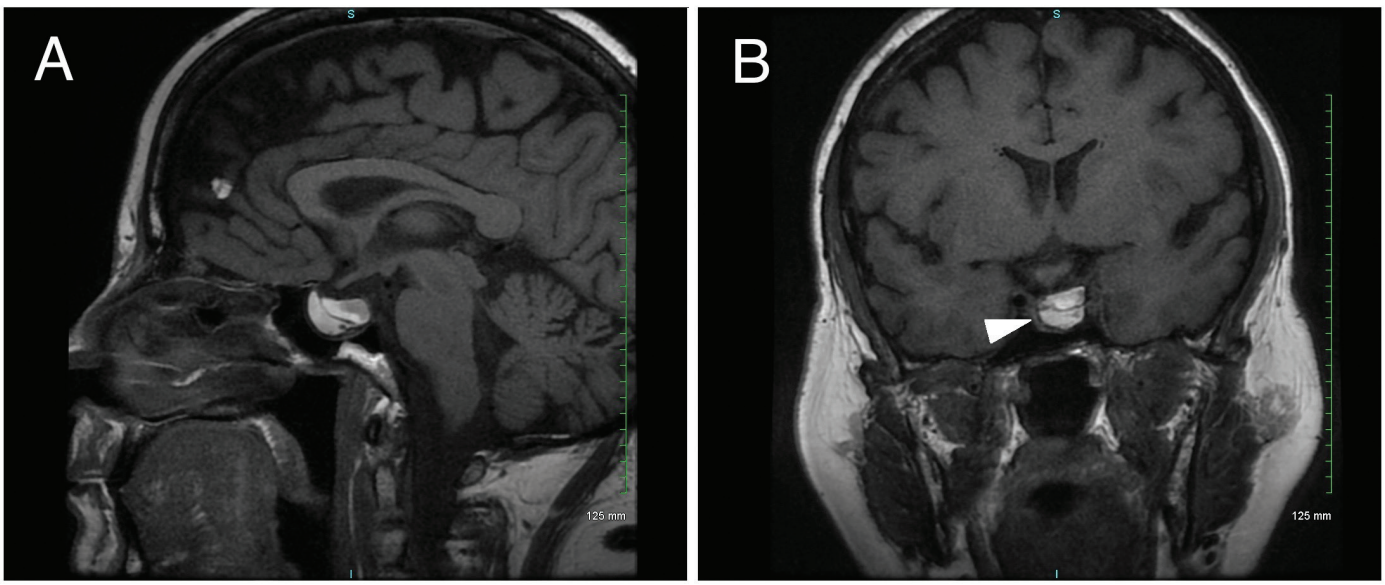


Figure 1. MRI of sella turcica in saggital (A) and coronary (B) views showing hyperintense T1 signal present in the pituitary gland, which measures 1.2 × 1.5 × 2 cm. A thin rim of normal pituitary tissue is seen in the right side of the hemorrhagic component (white arrow). There is mild deviation of the pituitary stalk to the right, and no compression of the optic nerves or optic chiasm.

MRI of the sella turcica which revealed pituitary apoplexy in the background of a normal pituitary tissue (Figure 1). There was no compression of the optic nerves or optic chiasm. Subsequently, adrenal workup showed morning cortisol level of 81 nmol/L and ACTH level of 1 pmol/L, in keeping with secondary adrenal insufficiency. Other pituitary axis hormones were within normal limits: TSH 1.93 mIU/L, free T3 5.5 pmol/L, free T4 9.9, FSH 7.1 IU/L, LH 0.5 IU/L, estradiol 73 pmol/L, prolactin 14 ug/L, and progesterone 1.5 nmol/L. Patient was promptly started on hydrocortisone 100 mg IV q8h, and her symptoms subsided the next morning and resolved completely within 36 hours. She was discharged home on physiologic replacement dose of glucocorticoid, and with outpatient endocrinology and neurosurgery follow up.

## Discussion

Pituitary apoplexy is a rare, but potentially life-threatening condition that can develop secondarily to acute hemorrhage or infarction of the pituitary gland. This uncommon condition is usually associated with underlying pituitary adenoma (0.6–7% of pituitary adenomas) or pregnancy.[1] The anterior pituitary gland is perfused by the hypophyseal portal system that courses down the hypophyseal stalk, and it is thought that this unusual blood supply renders it more susceptible to bleed. Pituitary tumours are approximately 5.4 times more likely to bleed than other intracranial tumours.[2,3] Symptoms arise from the mass effect within sella turcica causing compression of adjacent parasellar structures.

### Clinical Manifestations

The classic presentation of pituitary apoplexy consists of acute onset headache, visual change, altered level of consciousness and hypopituitarism. Headache is thought to be due to meningeal irritation, dura stretching and trigeminal nerve involvement inside the cavernous sinus.[4] Visual change is caused by suprasellar extension of the expanding pituitary mass compressing the optic chiasm and optic nerves. Visual field deficits, such as the classic bitemporal hemianopsia, may progress to include the nasal fields and the central vision. Lateral involvement of cavernous sinus results in third, fourth, fifth, and sixth cranial nerve palsies.[5,6] Anterior pituitary hormone dysfunction is present in around 80% of patients at initial presentation.[7–9] The most critical deficiency is adrenocorticotroph hormone (ACTH), seen in around 70% of cases.[9] Up to 20% of pituitary apoplexy cases may be sub-clinical but with radiological and pathological evidence of hemorrhagic infarction.

Precipitating factors for pituitary apoplexy include: hypotension, hypertension, major surgery, coronary bypass surgery, clotting disorder, anticoagulation, pituitary stimulation tests, dopamine agonists, estrogen therapy, head trauma, radiotherapy and pregnancy.[9–11] In many cases there is no clear precipitant or a known history of pituitary adenoma. A study in 2009 investigated predisposing factors in 83 patients with pituitary apoplexy, and found presence of precipitating factors in 48% of patients.[12]

### Diagnosis and Treatment

Management of pituitary apoplexy comprises of urgent neuroimaging, treatment of adrenal insufficiency, and neurosurgical consultation. Dedicated MRI of sella is the modality of choice. Compared to CT, MRI sella is superior in detecting tumour and hemorrhage/infarct as well as superior and lateral extension of bleed, especially in subacute and chronic stages of apoplexy.[7,13] Acute adrenal insufficiency is the main source of morbidity and mortality, and thus stress dose glucocorticoids should be promptly administered intravenously.[15] Although our patient did not have hypothyroidism, management of pituitary apoplexy should entail evaluation for and treatment of potential thyroid hormone deficiencies. Debate continues as to the benefit versus risk of neurosurgical management. If there are signs of mass effect on the brain, optic chiasm or cranial nerves, early surgical decompression is recommended. All patients with pituitary apoplexy should have long-term follow up to assess for tumour growth and apoplexy recurrence.[8,14,15]

Mrs. X had no known pituitary adenoma and there were no precipitant factors other than history of mild hypertension. She presented with headache, nausea, and vomiting that lasted minutes, followed by gradual development of anorexia and nausea over weeks due to secondary adrenal insufficiency. Aside from headache, which was comparable to her usual migraine headaches, she displayed none of the classic symptoms of pituitary apoplexy (such as visual field deficit, cranial nerve palsy or altered mental status). She also lacked any findings, such as hypotension or hyponatremia, to suggest adrenal insufficiency. The only subtle diagnostic clue for adrenal insufficiency was the empty sella on her non-contrast CT head, which was initially overlooked. Neuroimaging studies often do not detect pituitary apoplexy early on in the course of the condition and serial neurological examinations and imaging are required.[16]

## Conclusion

This case illustrates that pituitary apoplexy, which is a rare, but life-threatening diagnosis, is a condition that can wear many different hats. In particular, recognition of symptoms of adrenal insufficiency such as fatigue, weakness, anorexia and nausea is key. Common conditions that may mimic pituitary apoplexy include meningitis and subarachnoid hemorrhage with overlapping symptoms of headache, fever, and altered level of consciousness.[17,19] In this case report, pituitary apoplexy

presented as an insidious onset of adrenal insufficiency in the absence of any focal neurological symptoms or any of its classic findings, eluding its early diagnosis. Regardless of its cause once a diagnosis of pituitary apoplexy is made, it is critical to promptly treat adrenal insufficiency and monitor neurological status closely. Emergency surgical decompression may be indicated in cases where there are signs of mass effect on optic chiasm or cranial nerves.[8,14,15]

Given continuous improvements in detection and treatment of pituitary apoplexy, mortality is approximately 5%. Around 50% of patients with this condition will require long-term hormone replacement therapy.[18,19] Thus, routine reassessment of the pituitary hormones, as well as adrenal and thyroid function is recommended.[19]

## Competing Interests

None

## Funding

None

## Ethical Approval

Written informed consent to publication has been obtained from the patient.

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