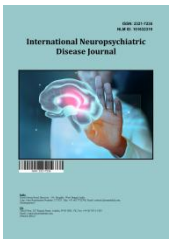

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An Unexpected Headache: Pituitary Apoplexy in a Patient Admitted with Diabetes Ketoacidosis (DKA)

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Background: Pituitary apoplexy is a clinical problem resulting from abrupt pituitary ischemia or hemorrhage. A small proportion of pituitary adenomas manifest as an apoplectic crisis, with pan hypopituitarism, vomiting, nausea, headache, ophthalmoplegia, and visual impairment being the most common symptoms.
Case Report: A 32-year-old diabetic Asian male presented to the emergency department with symptoms of polyuria, polydipsia, persistent vomiting, and diffused abdominal pain. He also reported a recent fever and severe headache, as well as self-limited episodes of blurring of vision

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and diplopia three months prior. Upon admission, his vitals were stable and he was fully conscious and oriented, though irritable and anxious. On examination, he was found to have third cranial nerve palsy and a dilated pupil with no light reflex. Laboratory tests revealed diabetic ketoacidosis (DKA). A CT scan of the brain revealed a possible invasive pituitary macro adenoma and the patient was referred for further evaluation. He also tested positive for COVID-19. Treatment for DKA was initiated and an MRI scan was scheduled for further evaluation. However, the patient's condition worsened and he was transferred to the ICU, where he was intubated and an MRI indicated a hemorrhagic mass in the pituitary gland. The patient was diagnosed with pituitary apoplexy, and he also received treatment with antibiotics and antiviral medication for suspected encephalitis.

Conclusion: Pituitary apoplexy is a serious condition that requires immediate evaluation and treatment. It can cause permanent damage or death if left untreated. Treatment options include surgery and conservative management with frequent monitoring.

Keywords: Pituitary apoplexy; adenomas; diabetic ketoacidosis; third nerve palsy; encephalitis.

1. INTRODUCTION

This case highlights the increased risk of pituitary apoplexy. As apoplexy is often the first presentation of an underlying pituitary adenoma, consideration of this as a possible diagnosis for acute onset severe headache and/or visual disturbance is important. Pituitary apoplexy in the case of a tumor seems to be favored by a reduced intratumor vascularization with inherent vascular fragility along and rapid tumor growth. Precipitating factors in 10—40% of cases include major previous surgery, brain trauma, endocrinological dynamic testing, angiographic procedures, bleeding disorders, and some drugs (e.g antiplatelet, anticoagulants, and dopamine and/or gonadotrophin agonists) [1].

Symptoms of pituitary apoplexy include severe frontal or retro-orbital headaches, as seen in 80% to 90% of cases. Acute visual abnormalities as a consequence of mass effect in 47% to 68% of those diagnosed [2]. Cranial nerve palsies (III, IV, and VI) feature in 39% to 52% of cases, with palsy of the third cranial nerve being the most predominant [3].

Reduced consciousness presents in up to 42% of patients. Nausea, vomiting, and photophobia may also occur, mimicking meningitis [4]. There is a presence of secondary adrenal insufficiency in 45% to 70% of cases.

2. CASE PRESENTATION

A 32-year-old Asian male with a history of type 2 diabetes mellitus attended the emergency, complaining of polyuria and polydipsia which was followed by vague diffused abdominal pain and persistent vomiting. He was taking pre-mixed insulin twice daily (15 units before breakfast, 20 units before dinner) and had skipped his insulin dose four days prior to this**.** Three days before admission, he developed a high-grade fever associated with an on-and-off frontal headache which progressively increased in severity. Three months before admission, the patient had experienced self-limited episodes of blurring of vision and diplopia in his right eye. He did not consult any physician for these visual symptoms. He denied any previous medical problems apart from his diabetes mellitus. He gave no history of head injury or fall. He has no history of smoking, alcohol consumption, or substance abuse. He has no history of a “running nose”, ear discharge, or intolerance to light or sound.

Upon admission, the patient’s vital signs were as follows: blood pressure was normal at 144/77 mm Hg, heart rate 113/minute, saturation of 100% on room air, respiratory rate of 19 breathings per minute, and an oral temperature of 37°C.

On examination, he was fully conscious and oriented, though irritable and anxious. A CNS examination revealed palsy of the third right cranial nerve, with a dilated right pupil with no light reflex. There was no evidence of meningeal irritation.

Laboratory test results revealed serum Na 120 mmol/L (136—145), K 6 mmol/L (3.5---5.10), Urea 15 mmol/L (2.10---7.10), Creatinine 119 umol/L (71—115), RBG 30mmol/l. urine ketones +3. Arterial blood gas on admission: PH =7.06, HCO3 = 7.0. An electrocardiogram showed a normal sinus rhythm. The laboratory reports supported a diagnosis of DKA (Diabetic Ketoacidosis) causing dehydration contributed to by vomiting and reduced fluid intake. He was

admitted to the Male Medical ward and treatment for DKA was started as per hospital protocol.

In view of the persistent headache upon admission and associated symptoms, an urgent non-contrast CT Scan brain was performed which revealed a space occupying lesion (SOL) at the sellar region with a large suprasellar component which was reported as a possible Invasive pituitary macro adenoma. An MRI with contrast was recommended for further evaluation.

On the second day, the patient developed irritability and agitation so the MRI was postponed. He was referred to psychiatry with a history of agitation, irritability, and abnormal behavior. Haloperidol was started and received a partial response.

On day three after admission, he received a positive COVID-PCR result, so was moved to an isolation room, though he remained in DKA and the DKA treatment was continued. His blood glucose was monitored closely.

Neurologist and the ophthalmologist opinions were requested. The neurosurgeon advised an MRI of the brain after the patient recovered from DKA. The ophthalmologist recommended that a proper assessment of his vision that could be done only after his condition improved.

On day four, the patient was confused and unable to communicate. Occasional spontaneous eye opening was observed. His pupils were dilated and reactive. He had a fever and tachycardia. His vital signs were as follows; temperature 37.8'c, Spo2 99% on room air, Tachypnea RR >30, acidotic breathing, and regular pulse rate of 143/m. Venous blood gas showed no acidosis and labs revealed leukocytosis WBC 13X109, high CRP 140, and acceptable CK, lactic acid, mineral, and renal profiling. Repeated ECGs reveled sinus tachycardia. In view of his deterioration, he was shifted to the ICU, where he continued to be hydrated and was started on empirical antibiotics while culture reports were awaited. A neurologist was consulted who suggested the possibility of meningoencephalitis and started the patient on empirical Acyclovir. He also suggested an MRI scan with contrast after an improvement in his condition.

On the day five, the patient was very confused and could not communicate. An urgent MRI brain scan was conducted after intubating the patient. The MRI scan revealed a hemorrhagic mass occupying sellar and suprasellar areas, measuring 3.8x2.3x3.6 cm in axial dimension, extending superiorly and obliterating the suprasellar cistern. The radiologist proposed two possibilities: a ruptured thrombosed giant supra clinoid Internal carotid intracranial aneurysm or pituitary apoplexy associated with vascular complication. He was referred to and examined by the neurosurgeon who did not recommend any intervention at the time. Labs revealed serum Na 181 mmol/ (136—145). A diagnosis of central diabetes insipidus was considered in view of his polyuria and hypernatremia.

Hormone assays of the pituitary gland and other hormones were done and the reports were as follows:

IGF-1 489 ng/ml (high), basal cortisol 624 & 749 nmol/L (Normal), FT4 8.4 pmol/L(suppressed), TSH 0.29 mu/L (suppressed), ACTH 5 ng/L(low), Prolactin 23.40 mu/L (low), LH 1.19 u/L(low), FSH 3.17IU/L(low), (NR, 2–11), LH 1.1mU/mL (NR, 0.4–5.7), total testosterone 10pg/mL (NR, 181–772), basal cortisol 11.8µg/dL (NR, 6.2–26).

A state of panhypopituitarism was diagnosed and he was started on pituitary hormone replacements including hydrocortisone, levothyroxine, and nasal desmopressin.

The patient condition worsened rapidly. He stopped making any voluntary respiratory efforts and had to be ventilated. No eye opening or motor responses were observed. Pupils measured at 4 mm, equal but not reacting.

The neurosurgeon reviewed him and concluded that neurosurgical intervention would not help due to his low GCS and fixed dilated pupils. Brain death was confirmed.

3. CHALLENGES WE HAD TO FACE AT DIFFERENT STAGES OF PATIENT MANAGEMENT

There were challenges in diagnosing the case. We requested a CT-brain scan upon admission. Blood products are initially hyperdense making it an ideal imaging option at least acutely (<6 hours from symptoms onset), though hyperacute blood can be isointense and infarction may be difficult to discern. At presentation, the initial CT- brain was showing a huge sellar and suprasellar mass but no bleeding.

For the pituitary MRI in the acute phase, blood can be difficult to characterize in the presence of deoxyhemoglobin because blood is isointense on T1 and bright on T2 in the hyperacute stage.

Within 24 to 48 hours, T1 hyperintensity signal usually increases and persists from 7 to 28 days. For our case, we performed the pituitary MRI on day five due to lack of evidence of bleeding on the initial brain CT and the patient had become agitated and uncooperative. He was later intubated and the pituitary MRI was performed which showed evidence of bleeding, supporting the diagnosis of pituitary apoplexy on top of giant pituitary macroadenoma.

We faced the second challenge when we started the treatment with glucocorticoid replacement followed by the thyroid hormone replacement, levothyroxine. However, once the patient was stabilized, subsequent optimal management remained uncertain and the neurosurgical opinion did not support surgical intervention. The patient was then intubated and started on a minimum dose of noradrenaline to maintain his blood pressure. In addition, the coexistence of two critical conditions – DKA Diabetic ketoacidosis, which resolved on day three, and Pituitary apoplexy – his positive Covid-19 status creating the need for isolation, and his rapid deterioration meant that investigations like a timely MRI and neurosurgical intervention were prevented. This meant our patient was treated conservatively.

Conservative management has increased studies comparing surgical vs non-surgical treatment for pituitary apoplexy.

Singh et al. [5] J Neurosurgery 2015: of 87 patients with pituitary apoplexy 20% were managed conservatively and 48% had no visual complaints at all.

Shepard et al. [6] J Neurosurgery 2021: of 64 patients with pituitary apoplexy, 74% managed conservatively and 15 % required surgery within three months [6].

There is no evident difference in visual field or acuity between the conservative and surgical groups.
Cranial nerve palsy was lower with surgery though recovery time was longer.

The pituitary apoplexy score (PAS) for our case was seven (Glasgow coma scale <8 = four points, reduced unilateral visual acuity = one point, unilateral visual field defect = one point, and unilateral third nerve palsy = one point).

Surgical cases are selected carefully; patients who have surgery are inherently different at presentation and have a higher PAS score. This is often interpreted as meaning that those with a PAS score of fur or more should have surgery, as well as patient who have more optic chiasmal compression, larger tumors, and worse visual acuity. Outcomes are not stratified according to the severity of the presentation.

When we applied the pituitary apoplexy score (PAS) to our patient, we will find his score was seven, putting him at high risk and making him a candidate for surgical intervention [7]. Regardless of treatment modality, approximately 75% will need at least one axis replaced following pituitary apoplexy [8].

Some studies note low prolactin as associated with no or decreased pituitary hormonal axis recovery (<20, 10%recovery, >20, 47 % recovery) [8].

Another challenge was finding an expert pituitary surgeon, if the patient was fit for neurosurgery intervention. The question is whether there is a downside of surgery when performed by an experienced team. Study showed less complications if neurosurgical intervention is performed by the experienced team. (Overall less than a 5% risk and less than a 1% of severe complications):

- Cited risk for surgery: CSF leak <1% in experienced teams for pituitary tissue resection (direct visualization in the endoscopic era, preserved).
- Hypopituitarism in addition to possible deficits at presentation.
- Diabetes insipidus.
- Other complications such as carotid artery injury are very rare.

Another challenge regarding the time for surgical intervention is that most authors who reported cases of pituitary apoplexy agree that surgery should be performed within 24—72 hours of presentation. Surgery should be offered as soon as possible if there is an experienced surgical team available or transfer to an institution with an experienced team is possible. The recommendation, in cases of mild symptoms such as pituitary insufficiency or headache or for patients who are high risk, is conservative treatment with frequent monitoring.

4. RADIOLOGY IMAGES

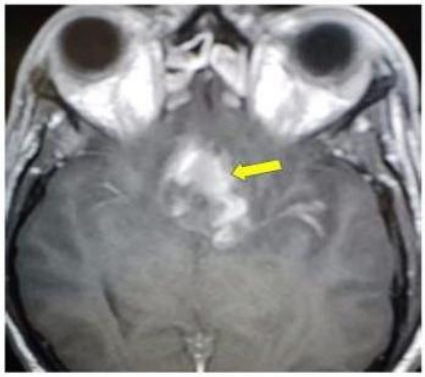

Fig. 1. Seller and suprasellar mass

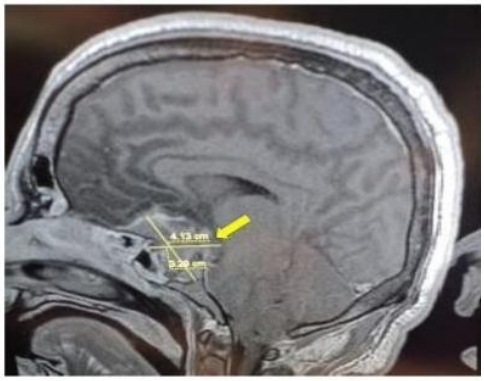

Fig. 2. The mass is encroaching on the Suprasellar cistern and optic chiasma

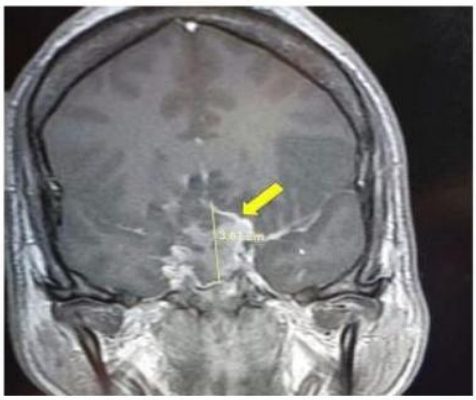

Fig. 3. The encorching both thalami, part of Globus

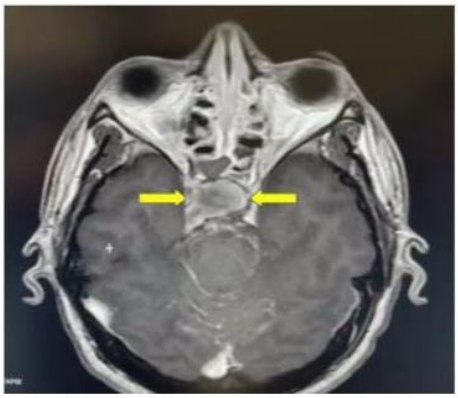

Fig. 4. Associated oedema in pallidus and lateral ventricle. both thalami, Globus pallidus and part of basal ganglia

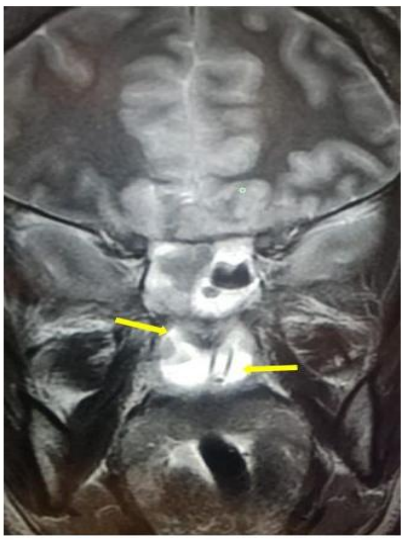

Fig. 5. Brain edema

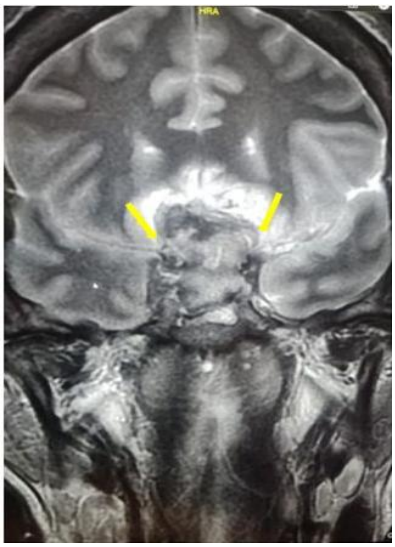

Fig. 6. Brain edema ,3" ventricle and lateral ventricle not clear

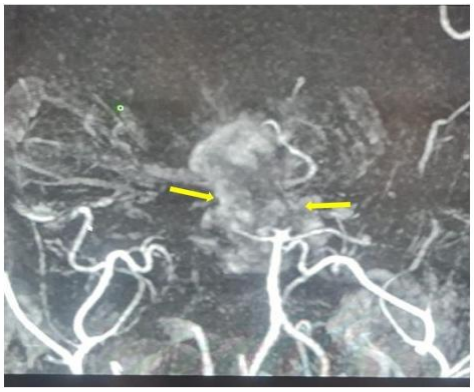

Fig. 7. MRA: Circle of Wills engulfed by the mass

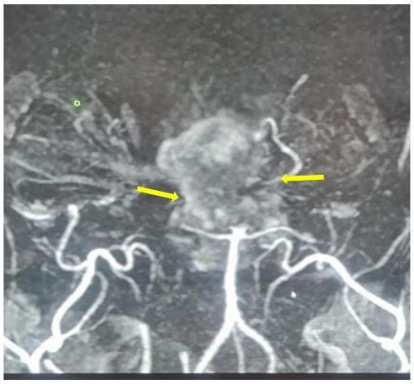

Fig. 8. Basilar artery can be seen, internal carotid artery and bifurcation of middle cerebellar artery obliterated by the mass

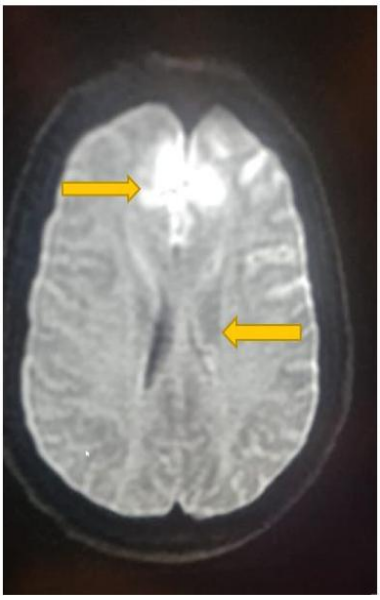

Fig. 9. Diffusion image: frontal lobe ischemia and mass effect on the lateral

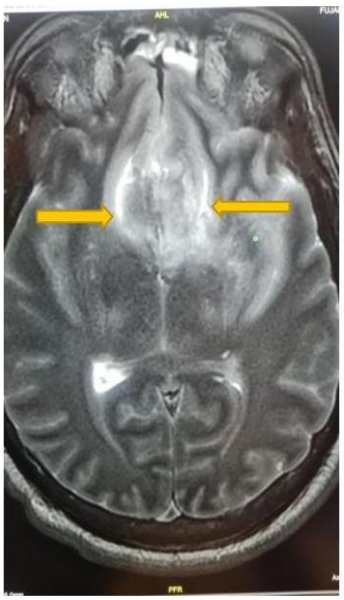

Fig. 10. Frontal lobe ischemia

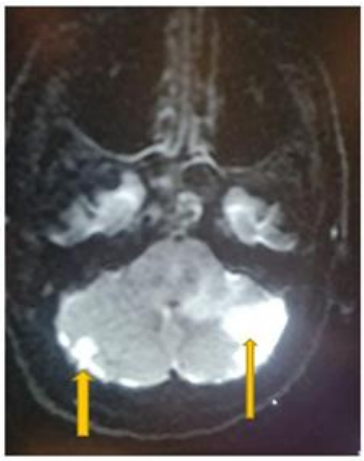

Fig. 11. Bilateral hemisphere ischemia

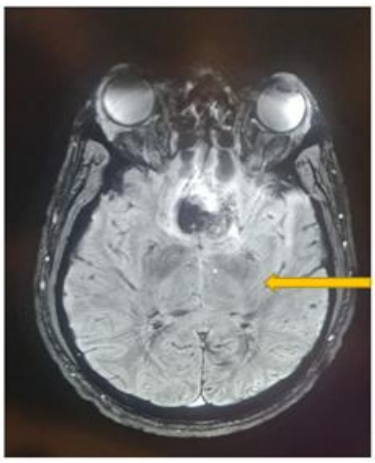

Fig. 12. Haemorrhagic mass

5. DISCUSSION

- Pituitary apoplexy is a rare condition and there is a lack of randomized trials regarding surgical versus medical treatment. Studies looking at the role of conservative versus surgical management of apoplexy with regard to visual loss all suffer from selection bias and a lack of appropriately matched patients. When pituitary apoplexy score was applied (as is done in only one of these studies – Bujawa Bujawansa and colleagues), there was a clear discrimination between conservative and surgical cohorts (1.8 v3.8) [3].
- The chance of pituitary function improvement ranges from 12% to 23%, depending on time of assessment [3].
- The study outcome showed 45 patients were included in this retrospective study and that transient diabetes insipidus occurred in nine (20%) patients. Two (4.4%) required long-term hormonal replacement. The mean follow-up was 25 months [9].
- Baseline visual improvement was achieved in 39 (86.7%) patients. There was complete recovery from ocular cranial nerve palsy in 17 (77.2%) patients. Endocrine follow-up showed that the 11 (24.4%) patients with panhypopituitarism failed to recover [9].
- In our case, recovery from third nerve palsy and panhypopituitarism was uncertain if neurosurgical intervention was performed.
- In some cases of pituitary apoplexy, surgery is not performed, especially for patients with severe comorbidities who are at risk with general anesthesia and patient with severe blood dyscrasias that cannot be reversed efficiently, such as severe thrombocytopenia not responsive to transfusion.
- Agitation and non-cooperation could have been a part of the electrolyte disturbances and pituitary-related complication, though we could not state it conclusively because of the lack of access to imaging during the deterioration.
- Deterioration was attributed to the possibility of meningoencephalitis – the neutrophilic leukocytosis suggesting bacterial infection and the altered consciousness and behavior disturbance suggesting the possibility of viral etiology. The patient was given empirical antibiotics and antiviral Acyclovir.
- An MRI done on day five, when the patient could not even communicate, revealed pituitary apoplexy. This was supported by the presence of diabetes insipidus indicated by persisting polyuria and polydipsia, despite controlling diabetic ketoacidosis and hypernatremia. Low levels of many pituitary hormones (TSH, Prolactin, FSH, LH, ACTH) supported a diagnosis of panhypopituitarism. He was promptly started on Hydrocortisone, followed by levothyroxine and nasal Desmopressin.

  Does surgical intervention have a better outcome than conservative management?
- Reports of spontaneous improvement of neurological complications, regression on MRI, and resolution of hypersecretion [10].
- High-dose glucocorticoids (Dexamethasone IV 2—16 mg) for all patients with surgery whose mental status or vision failed to improve.
- 7/12 could be managed conservatively. Visual disturbance resolved in six cases and improved in one. 5/12 had surgery-prompt neurologic and visual improvement in all. However, this was complete in only one case, partial in one, and minimal in two.

  Gruber et al BR J Neurosurg 2006 (n=30) [11].
- The surgical group (n=10) had more visual deficits, while the conservative group (n=20) had more ophthalmoplegia.
- Similarly, Kim et al (world Neurosurgery 2017) assessed 41 patients who had trans sphenoidal surgery TSS for pituitary apoplexy. The severity of visual impairment score was the only risk factor for post-operative neurological sequelae [12].
- Comparing surgery and conservative measures, most studies report no difference in visual field, visual acuity, or cranial nerves palsies
- Significant recovery of visual field defect (or 0.32 95% CI 0.10—0.97).
- Significant recovery of cranial nerve palsy (OR 0.17 95% CI 0.03—0.79) [13].

  No difference in visual acuity or hormonal recovery. Meta-analysis included 14 studies (457 cases) spanning 1988 to 2018 [14].

There was no recorded difference in visual field defect, visual acuity, or cranial nerve palsies. Almeida et al performed pooled analysis of 11 studies with similar results: Tu et al J Neurol Sci 2016, Goshtabsi et al. World Neurology, Almeida et al. 2019. Budohoski et al. 2022, Caralli et al. 2021, Nakheleeh et al. 2021, Shepherd et al 2021 [15].

- Rapid deterioration in general condition meant neurosurgery was not an option which added to the already complicated situation [16].

6. LEARNING POINTS

- Pituitary apoplexy may be the first presentation of an underlying tumor and has widely varied symptomatology—it should be considered a differential diagnosis for headaches, visual disturbances, or symptoms of hypopituitarism. Changes in visual acuity and field are due to the rapid growth of pituitary adenoma. Pituitary adenoma can expand laterally into the cavernous sinus which compresses the third, fourth, and sixth cranial nerves, like in our case, or upwards, compressing the optic chiasm. Our patient had third nerve cranial nerve palsy.
- An earlier MRI study of the pituitary could have been helpful but could not be performed as the patient was very aggressive. As the pituitary macroadenoma in our patient was large and aggressive and he had apoplexy, his condition deteriorated rapidly. The presence of diabetic ketoacidosis is known to trigger apoplexy and this might have been a complicating factor in this case. Though the preferred emergency treatment for pituitary apoplexy is surgery, our patient did not get the opportunity to be referred for neurosurgery intervention due to multiple associated factors – poor general condition, despite his rapid recovery from DKA and mild symptoms of COVID-19 and being on inotropic support, intubated and connected to ventilator support. However, he was managed conservatively with the medical treatment of panhypopituitarism (including the stress doses of hydrocortisone), but still, dexamethasone could have been a better option in the presence of cerebral oedema and the absence of primary adrenal insufficiency in this case.
- A diagnosis of pituitary apoplexy should be considered in all patients who have acute severe headaches, if accompanied by nausea and vomiting, as it is the most common and earliest manifestation.
- Clinicians may choose to consider COVID-19 a risk factor for pituitary apoplexy and adjust the management of these patients accordingly.

7. CONCLUSION

Pituitary apoplexy is a life-threatening condition consisting of intra-pituitary hemorrhage and/or infarction that, in the vast majority of cases, occurs in the presence of a pituitary tumor. Left unrecognized or inadequately treated, it has been associated with irreversible morbidity or death. Hypopituitarism is an important complication of apoplexy and may be missed if not carefully scrutinized for. Pituitary apoplexy should be evaluated emergently by an endocrinologist and neurosurgeon when vision, ophthalmopathy, or loss of consciousness are present. Surgery should be offered as soon as possible if there is an experienced surgical team available or transfer to an institution with an experienced team is possible. If symptoms are mild such as pituitary insufficiency or headache, or the patient is high risk, conservative treatment with frequent monitoring is an option. Conservative management has become increasingly common over time and a regimen of glucocorticoids need to be standardized.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Biagetti B, Simò RJIJOMS. Pituitary apoplexy: Risk factors and underlying molecular mechanisms. 2022;23(15):8721.
2. Pyrgelis ES, Mavridis I, Meliou M. Presenting symptoms of pituitary apoplexy. 2018;79(01):052-9.
3. Barkhoudarian G, Kelly DF. Pituitary apoplexy. 2019;30(4):457-63.
4. Suri H, Dougherty C. Reports H. Presentation and management of headache in pituitary apoplexy. 2019; 23(9):1-4.
5. Singh TD, Valizadeh N, Meyer FB, Atkinson JL, Erickson D, Rabinstein AA. Management and outcomes of pituitary apoplexy. 2015;122(6):1450-7.
6. Shepard MJ, Snyder MH, Soldozy S, Ampie LL, Morales-Valero SF, Jane JA. Radiological and clinical outcomes of pituitary apoplexy: comparison of conservative management versus early surgical intervention. 2021;135(5):1310-8.
7. Cavalli A, Martin, A, Connolly DJ, Mirza S, Sinha SJB. Pituitary apoplexy: how to define safe boundaries of conservative management? Early and long-term outcomes from a single UK tertiary neurosurgical unit. 2021;35(3):334-40.
8. Taweesomboonyat C, Oearsakul TJWN. Factors Predicting neuroendocrine recovery following transsphenoidal surgery in pituitary apoplexy patients. 2022; 159:e40-e7.
9. Galal A, Ahmed OEF. Determinants of visual and endocrinological outcome after early endoscopic endonasal surgery for pituitary apoplexy. Surg Neurol Int. 2022;13:433.
   Published 2022 Sep 23.
   DOI:10.25259/SNI_642_2022.
10. Pelkonen R, Kuusisto A, Salmi J, Eistola P, Raitta C, Karonen SL, et al. Pituitary function after pituitary apoplexy. 1978;65(5):773-8.
11. Gruber A, Clayton J, Kumar S, Robertson I, Howlett T, Mansell P. Pituitary apoplexy: retrospective review of 30 patients—is surgical intervention always necessary? 2006;20(6):379-85.
12. Kim YH, Cho YH, Hong SH, Kim JH, Kim MS, Khang SK, et al. Postoperative neurologic outcome in patients with pituitary apoplexy after transsphenoidal surgery. 2018;111:e18-e23.
13. Goshtasbi K, Abiri A, Sahyouni R, et al. Visual and endocrine recovery following conservative and surgical treatment of pituitary apoplexy: A meta-analysis. World Neurosurg. 2019;132:33-40.
    DOI:10.1016/j.wneu.2019.08.115
14. Donegan D, Erickson D. Revisiting pituitary apoplexy. J Endocr Soc. 2022;6(9): bvac113. Published 2022 Jul 26.
    DOI:10.1210/jendso/bvac113
15. Almeida JP, Sanchez MM, Karekezi C, Warsi N, Fernández-Gajardo R, Panwar J, et al. Pituitary apoplexy: results of surgical and conservative management clinical series and review of the literature. 2019;130:e988-e99.
16. Garni Barkhoudarian, Daniel F. Kelly. Pituitary apoplexy, neurosurgery clinics of North America. 2019;30(4):457-463.
    ISSN 1042-3680, ISBN 9780323681681,
    DOI:https://doi.org/10.1016/j.nec.2019.06.001.

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