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Case Report

Management dilemmas in a rare case of pituitary apoplexy in the setting of dengue hemorrhagic fever

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Abstract

Background: Pituitary apoplexy occurs due to infarction or hemorrhage, within a pituitary adenoma or a nontumorous pituitary gland and can have catastrophic consequences. Dengue hemorrhagic fever (DHF) is a severe manifestation of the spectrum of dengue virus infection and is characterized by high-grade fever, thrombocytopenia, hemorrhagic tendencies, and increased vascular permeability. Cases of incidentalomas complicated by DHF and presenting with apoplexy are extremely rare.

Case Description: We describe the case of a 45-year-old gentleman who suffered an attack of pituitary apoplexy while being treated for DHF. The issues pertaining to the management of hydrocephalus, timing of surgical intervention, and treatment of electrolyte imbalances encountered in the dual setting of DHF and pituitary apoplexy are discussed with reference to the outcome in our case.

Conclusion: Although patients suffering from DHF harbor multiple factors, which may be precipitants of pituitary apoplexy, the association between these two conditions is rare and only few case reports document their coexistence. We review the pertinent literature and discuss the management dilemmas faced by us while dealing with these dual pathological states.

Key Words: Dengue hemorrhagic fever, hydrocephalus, pituitary apoplexy, surgical management, thrombocytopenia

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INTRODUCTION

Pituitary apoplexy (PA) is an acute clinical syndrome characterized by sudden headache, vomiting, visual disturbances, ophthalmoplegia, and/or altered consciousness, secondary to infarction or hemorrhage within a pituitary tumor or nontumorous pituitary gland.[5,6] PA may occur spontaneously or as a result of several precipitating factors; one such factor being thrombocytopenia.[1,2,5] Dengue hemorrhagic fever (DHF) is characterized by fever, hemorrhagic tendencies, thrombocytopenia, and increased vascular permeability.[7] PA occurring in the setting of DHF with thrombocytopenia has been described earlier but is extremely rare.[3,4,8,10] We report the occurrence of PA

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in a patient of DHF with thrombocytopenia presenting to the emergency with hydrocephalus. In this short report, we delve on the management issues pertaining to the management of hydrocephalus, timing of surgical intervention, and treatment of electrolyte imbalances encountered in the dual setting of DHF and PA.

CASE REPORT

Clinical presentation

A 45-year-old man presented with a history of high-grade fever of 7-day duration. He was evaluated at a general hospital, and was noted to have NS1 IgM positive serology for Dengue infection and low platelet counts. Patient was diagnosed as DHF in view of severe thrombocytopenia and was managed accordingly with resuscitative measures. On the 7th day of the fever, the patient developed severe headache, multiple episodes of vomiting, and altered sensorium. Electrocardiograph (ECG) showed sinus bradycardia and computed tomography (CT) scan of the brain showed sellar and suprasellar hemorrhagic lesion with obstruction of the foramen of Monro, leading to hydrocephalus [Figure 1a]. The patient was referred to our tertiary neurosurgical center for further management. At presentation, he was drowsy, disoriented, but obeying to commands. The pupils were equal in size and reacting to light. Visual acuity and complete neurological status could not be tested due to the patient's altered sensorium.

Course in the hospital and surgical management

The management issues in this patient were treatment of hydrocephalus and the surgical management of PA in the setting of severe thrombocytopenia. The patient's platelet count at admission was 27000/mm^3. Serial platelet transfusions were instituted. While his hematological dysfunction was being corrected, patient deteriorated in sensorium (E1M4V2), was immediately intubated, and a right frontal external ventricular drain (EVD) was placed. Cerebrospinal fluid (CSF) was under high pressure. Patient did not improve in sensorium following EVD and repeat CT brain showed persistent left lateral ventriculomegaly. A left frontal EVD was placed. Following bilateral EVD placement, patient improved in sensorium to drowsy, obeying, and disoriented status.

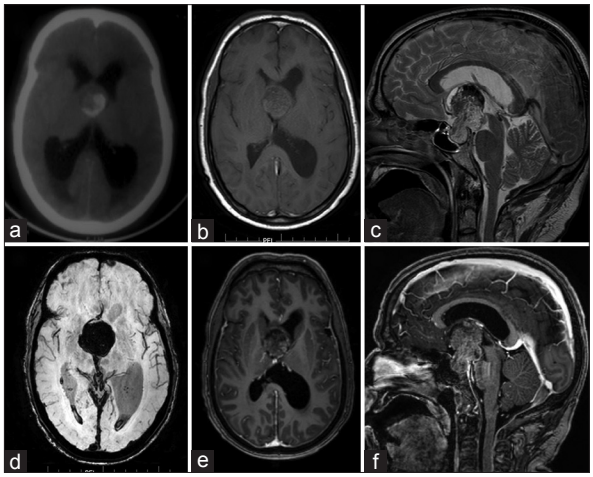

Figure 1: (a) Computed tomography (plain) of the brain at presentation showing the hemorrhagic lesion in the third ventricle obstructing the foramen of Monro and causing hydrocephalus; magnetic resonance imaging demonstrating [(b) T1-weighted axial, (c) T2-weighted sagittal, (d) Susceptibility-weighted Imaging (SWI) axial, (e) contrast-enhanced T1-weighted axial, and (f) contrast-enhanced T2-weighted sagittal images] a pituitary macroadenoma with suprasellar extension with evidence of apoplectic change

A magnetic resonance imaging (MRI) of the brain showed a sellar suprasellar lesion extending into the third ventricle up to the foramen of Monro. The lesion was T1 isointense, T2 hyperintense with areas of T2 hypointensity, and was heterogeneously enhancing on contrast [Figure 1b-f]. On susceptibility-weighted images (SWI), intratumoral hemorrhage was clearly documented [Figure 1c]. Hormonal profile revealed normal serum hormonal levels (Growth Hormone (GH) = 0.48 ng/mL; Luteinizing Hormone (LH) = 4.05 IU/L; Prolactin (PRL) = 5.42 ng/mL; Cortisol = 42.94 nmol/L; Follicle Stimulating Hormone = 2.68 IU/L; T3 = 0.573 ng/dL; Thyroxine (T4) = 6.02 micro-g/dL; Thyroid Stimulating Hormone (TSH) = 1.060 mIU/L). Following multiple platelet transfusions, the platelet count was raised to 143,000/mm^3, patient was hemodynamically stable and was planned for surgery. He underwent endoscopic endonasal transsphenoidal decompression of the pituitary adenoma. After entering sella and opening the dura, a gush of blood was noted. The tumor was decompressed carefully and hemostasis was obtained. Postoperative CT brain showed small residual tumor.

Histopathology

Histopathology sections showed fragments of an endocrine neoplasm composed of sheets, lobules, and papillaroid clusters of round-to-polyhedral cells having moderate amphophilic cytoplasm and a regular round-to-oval nucleus [Figure 2a and b]. Intratumoral hemorrhage was evident. Increased vascularity with delicate branching vessels was noted. The tumor was ACTH-positive and negative for all other IHC markers [Figure 2c and d].

Postoperative course and follow-up

The patient had a stormy postoperative course. He developed diabetes insipidus with serially rising sodium levels and high urine output. The intravascular volume status was monitored with central venous pressure (CVP) recordings. Patient was managed with hypotonic fluids and subcutaneous pitressin (5 units BD and 5 units in excess if urine output for two consecutive hours was more than 250 ml). The patient was managed with strict hourly input-output monitoring and eighth hourly electrolyte levels. This intensive CVP, input-output, and electrolyte level monitoring was essential in the setting

of hypothalamic–hypophyseal dysfunction (in view of pituitary apoplexy) and increased vascular permeability (in view of DHF). On postoperative day 4, the patient regained consciousness. Sequential EVDs were removed with serial CTs not showing evidence of ventriculomegaly after EVD blockade. On discharge, the patient was conscious with visual acuity of 6/36 in both eyes, and fundus examination showing bilateral temporal pallor. At 6-month follow-up, the patient is doing well with only residual bitemporal hemianopia and MRI brain revealed minimal residual lesion [Figure 3a and b]. He has been started on hormonal supplementation in view of hypothyroidism, hypocortisolism, and hypogonadism.

DISCUSSION

PA (hemorrhage or infarction of a pituitary adenoma or nontumorous pituitary gland) may occur spontaneously or as a result of several precipitating factors such as head trauma, dynamic tests to evaluate pituitary function, surgery (mainly cardiac surgery), coagulation disorders, medications including aspirin, estrogens, heparin, and dopamine agonists, and some conditions such as chronic systemic hypertension, diabetes mellitus, and radiotherapy.[2,5,6] The precipitants of PA can be classified into 4 categories: (1) reduced blood flow into the pituitary adenoma, resulting in infarction; (2) acute increase in blood flow to the pituitary gland from the hypothalamus portal system because it may increase the intra-sellar pressure; (3) stimulation of the pituitary gland, as occurs in any stress-inducing states; and (4) thrombocytopenia because of increased risk of bleeding.[1,2]

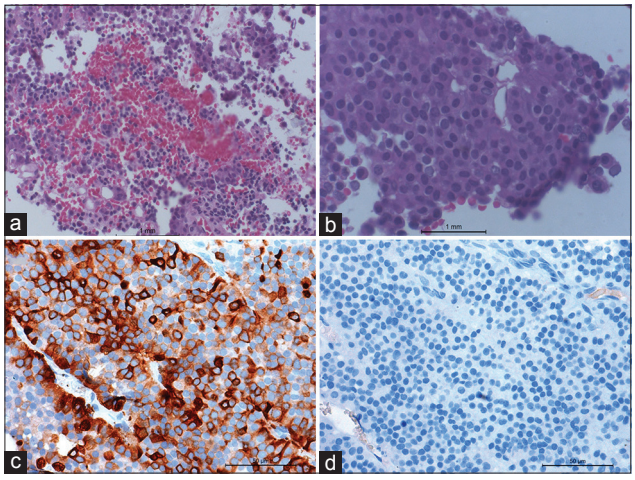

Figure 2: (a) Microphotograph showing fragmented bits of a cellular neoplasm with hemorrhage (hematoxylin and eosin ×100). (b) Microphotograph showing an endocrine neoplasm with cells arranged in organoid nests and conglomerate acinar, solid clusters (hematoxylin and eosin ×400). Note the uniform cells and regular nuclei with homogenous chromatin; (c) Microphotograph showing cells positively stained for ACTH immuno-stain (ACTH-IHC ×400) (d) Microphotograph showing cells negatively stained for growth hormone immunostain (GH-IHC ×400)

Thrombocytopenia can be caused by various conditions, infections being one among them. Dengue fever is endemic in tropical countries and can range from a nonspecific febrile illness to DHF, which is characterized by high-grade fever, marked thrombocytopenia (<100,000/μL), and increased vascular permeability.[7] In DHF, patients may have episodes of hypotension and hypovolemia, leading to oscillations in blood pressure.[7] Because it is an acute systemic illness, there is an increased demand on the pituitary gland and pituitary stimulation. In addition, DHF is characterized by severe thrombocytopenia and increased hemorrhagic tendencies. All these factors combined may have a compounding effect on the risk of PA in a pre-existing pituitary adenoma. However, the association of DHF and PA is exceedingly rare and only few case reports document their co-occurrence.[3,4,8,10] The review of literature pertaining to the incidence of pituitary apoplexy in the setting of DHF revealed five previously reported cases. The summary of these cases along with their comparative features has been described in Table 1.

In our case, the first challenge was the management of hydrocephalus. Initially, as the patient was maintaining a conscious status, it was decided to correct thrombocytopenia, perform imaging and hormonal evaluation, and then plan transsphenoidal decompression of the tumor. When the patient deteriorated in sensorium, raised ICP due to hydrocephalus or the apoplectic lesion compressing on the hypothalamus were considered to be the cause. A calculated risk of placement of EVD in the setting of severe thrombocytopenia had to be taken. While the EVD placement can resolve the hydrocephalus, it also could result in intraventricular/parenchymal hemorrhage adding to the complexity of the condition.

The second dilemma was timing of the the definitive surgery. After ICP control and stabilizing the

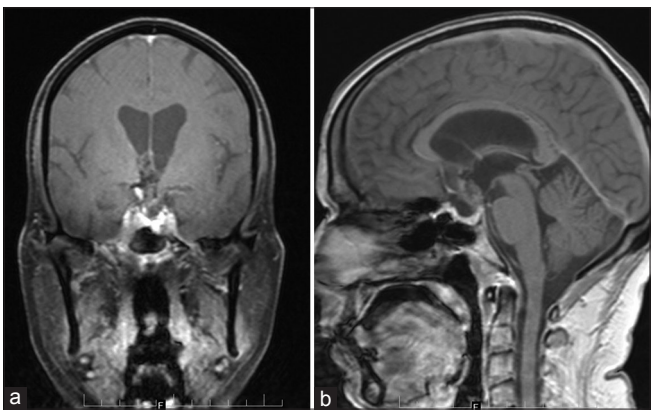

Figure 3: Magnetic resonance imaging [(a) contrast-enhanced T1-weighted coronal and (b) contrast-enhanced T2-weighted sagittal images] at 6-month follow-up exhibiting near total resection of the pituitary adenoma

Table 1: Summary of cases presenting with pituitary apoplexy during an episode of dengue hemorrhagic fever

Reference	Age/ Sex	Clinical features	Hormonal Profile	Platelet Count	MRI findings	Management	Follow-up
Kumar *et al*. (2011)[3]	31/F	Vision loss, H/A, vomiting	Hypothyroid, rest of the hormonal profile normal	Low (45000/mm^3)	Pituitary macroadenoma (16×22 mm) with acute bleed	Endoscopic endonasal decompression of the tumor	Residual bitemporal field defects at 3-month F/U
Wildenberg *et al*. (2012)[10] Case 1	40/M	H/A, vomiting, acromegalic features	Acromegaly; Hypogonadotropic hypogonadism	Mildly decreased (98000/mm^3)	Intrasellar lesion s/o – pituitary apoplexy	Transsphenoidal surgery 20 days after apoplexy	Acromegaly persists; other hormones normal
Wildenberg *et al*. (2012)[10] Case 2	38/M	Prolactinoma on medical Mx, presents with visual field deficits	Hypogonadism; Prolactin decreased on medical management	Mildly decreased (79000/mm^3)	Pituitary mass with areas of bleed	Urgent transsphenoidal surgery	Visual field defects improved. Hormonal deficits persist
Tan *et al*. (2014)[8]	53/M	Acute-onset Lt third, sixth nerve palsy, Rt temporal hemianopia	Hyperprolactinoma; thyrotropin and gonadotropin deficiency	Low (16000/mm^3)	37×24×31 mm hemorrhagic pituitary adenoma with B/L cavernous sinus extension	Underwent transsphenoidal surgery for decompression (two surgeries)	Prolactin normal, anterior pituitary deficits and right eye visual defects persist
Mishra *et al*. (2015)[4]	43/M	Decreased vision, H/A, vomiting	Normal hormonal profile	Low (47000/mm^3)	23×21×20 mm sellar and suprasellar mass with bleed	Urgent transsphenoidal decompression of tumor	Visual acuity improved. Residual visual field deficits persist
Present Case (2016)	45/M	Severe H/A, vomiting and LOC	Normal hormonal profile	Low (27000/mm^3)	Pituitary apoplexy (sellar and suprasellar lesion) and obstructive hydrocephalus	EVDs to manage HCP; followed by endoscopic endonasal decompression	Vision normal. Anterior pituitary deficits present

H/A: Headache, Rt: Right, Lt: Left, LOC: Loss of consciousness, EVD: External ventricular drainage, HCP: Hydrocephalus, Mx: Management

hemodynamic parameters and the serum electrolytes, the patient improved in sensorium to a drowsy conscious state. The options of VP shunt followed by delayed surgery at a later date or decompression in the present admission were considered, weighing the risks/benefits of both the options. Management of PA in the setting of thrombocytopenia can be very challenging because the benefit of early intervention has to be carefully weighed against the risk of bleeding during and immediately after surgery.[8,10] After consideration of all the factors, platelet levels were corrected to >100,000/mm^3 with successive single donor platelet transfusions, and we decided to perform the surgery. The patient underwent surgical tumor decompression in a controlled setting without intraoperative complications.

The patient had a stormy postoperative course, and management of his fluid and electrolyte disturbances was the third demanding task. The impact of the pituitary stalk and hypothalamic dysfunction was compounded by the increased vascular permeability seen in DHF. In addition, hyponatremia (serum sodium level <130 mEq/L) is commonly found in dengue patients and has been hypothesized to be a consequence of salt depletion, excess water from increased metabolism, decreased renal excretion, transient inappropriate antidiuretic hormone, or the influx of sodium into the cells as a result of dysfunction of sodium potassium pump seen in the setting of dengue fever.[9] Because it was difficult to predict which phenomenon was influencing the fluid-electrolyte disturbances, our patient was treated in the neurointensive care unit with close monitoring of the consciousness level, input-output calculations, and corrections as per the central venous pressure (CVP) monitoring and every twelfth hourly serum electrolyte levels. This enabled us in detecting and appropriately managing the triphasic pattern of diabetes insipidus, seen in the postoperative period, with fluid balance and subcutaneous pitressin injections. We emphasize the importance of managing such patients in neurointensive care units with multidisciplinary team approach in order to achieve a good postoperative outcome.

CONCLUSION

An occurrence of pituitary apoplexy in the background of DHF raises multiple complexities in the management. An awareness of the detailed pathophysiology of both the conditions and their interplay at hemodynamic and endocrine levels is essential for the treating physician

to actively manage the problem. The management of raised ICP secondary to hydrocephalus, importance of the correct timing of surgical intervention and active intervention to maintain fluid, and electrolyte balance are paramount to achieving a good outcome in the combined setting of pituitary apoplexy and DHF.

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Conflicts of interest
There are no conflicts of interest.

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