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Cystic Degeneration within Non-functioning Pituitary Macroadenoma: Pathogenesis, Differential diagnosis and Surgical outcome with representative Case Illustration

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Abstract

Background: Cystic pituitary adenomas constitute diagnostic as well as therapeutic challenges in terms of accurate preoperative diagnosis, per operative incomplete removal, CSF leakage and recurrence. Thereby, understanding the pathogenesis of cyst formation, neuroimaging criteria of the cysts in different cystic sellar masses are important in preoperative counselling, operative strategy and predicting outcome.

Aim of this work: We report two cases of Cystic pituitary adenomas and reviewed the relevant literature to explain the pathogenesis of cystic degeneration, differential diagnosis of cystic sellar mass, impact of cystic changes on operative decision, operative results and outcome.

Case series: Our 1st case was a 16 years old male, presented with headache and dimness of vision. Fundoscopy revealed early changes of primary optic atrophy. 2nd case was a 46 years old female having similar presentation. However, her visual acuity restricted to hand movement and counting finger. Fundoscopy showed primary optic atrophy. In both of our cases, we went for endoscopic endonasal transsphenoidal removal of the tumor. Resolution of headache and improvement of visual function were observed. There was no recurrence at 2 years follow up.

Conclusion: Understanding the basic pathophysiology, preoperative prediction about the diagnosis and timely intervention are the key factors for optimum outcome in case of Cystic Pituitary Adenomas.

Keywords: Cystic pituitary adenoma, Cystic degeneration

Abbreviations: CP: Craniopharyngioma; CPA: Cystic Pituitary Adenoma; CSF: Cerebrospinal Fluid; CSM: Cystic Sellar Mass; CT: Computed Tomography; DCE: Dynamic Contrast Enhanced; DI: Diabetes Incipidus; MRI: Magnetic Resonance Imaging; POD: Post Operative Day; RCC: Rathke's Cleft Cyst; VEGF: Vascular Endothelial Growth Factor

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Introduction

Pituitary adenomas are the most common lesion in the sellar and suprasellar region. Considering their location, growth pattern, mode of angiogenesis and metabolic features, they are more prone to infarction or haemorrhagic changes in comparison to other intracranial tumors.[1] Though many sellar and suprasellar lesions are distinguished by their neuroimaging characteristics, it is not always easy to make a differential diagnosis when the lesion occupies both sellar and suprasellar region, having both solid and cystic characteristics. Apart from Cystic Pituitary Adenoma, other differentials include Rathke's cleft cyst (RCC), craniopharyngioma (CP), dermoid and epidermoid cyst and pituitary abscess.[2,3] The characteristics of cystic changes of these differentials often creates a diagnostic dilemma which possesses a great impact upon surgical decision making, preoperative counselling of the patient and/ or guardian, necessity of the adjuvant therapy and outcome. Thereby, the Authors report two cases of CPA, describes their neuroimaging characteristics, surgical outcome and beside this, they give special emphasis on the pathophysiology of the cystic degeneration, angiogenesis of Pituitary adenoma, exclusion of the differentials from neuroimaging and surgical strategy.

Case Series

Case 1

History and clinical examination

A 16 years old boy, with apparently having no medical illness admitted into our facility with the complaints of headache and dimness of vision for four months. Neurological examination demonstrated his visual acuity on both eyes were 6/36. He had bitemporal hemianopia on visual field analysis and fundoscopy showed early changes of primary optic atrophy. His growth pattern and school performances were within normal limit.

Investigations

MRI of the brain demonstrated a mixed intensity lesion, having both solid and cystic components occupying both sella and suprasellar region with significant compression on the optic chiasm Figure 1. Floor of the third ventricle was compressed and displaced upwards. After administration of the contrast, there was multiple, irregular, complete rim enhancement Figure 2. Complete hormone analysis showed growth hormone and testosterone below than the normal physiological limit.

Operative management and outcome

With all aseptic precaution, patient underwent endoscopic endonasal transsphenoidal approach and complete removal of the tumor. Biopsy was taken from the lower most solid part at the very beginning, followed by decompression of the large cystic part. There was coffee coloured fluid, signified it as previous haemorrhage. There was no visible CSF leakage, even after giving Valsalva maneuver. Sellar floor was reconstructed with fat, fascia lata and fibrin glue. Patient developed post-operative DI which had been corrected at 3 months follow up. There was improvement of headache and visual function recorded at 1st POD. Follow up CT scan showed complete removal of the tumor Figure 3. Histopathological findings were consistent with Pituitary Adenoma.

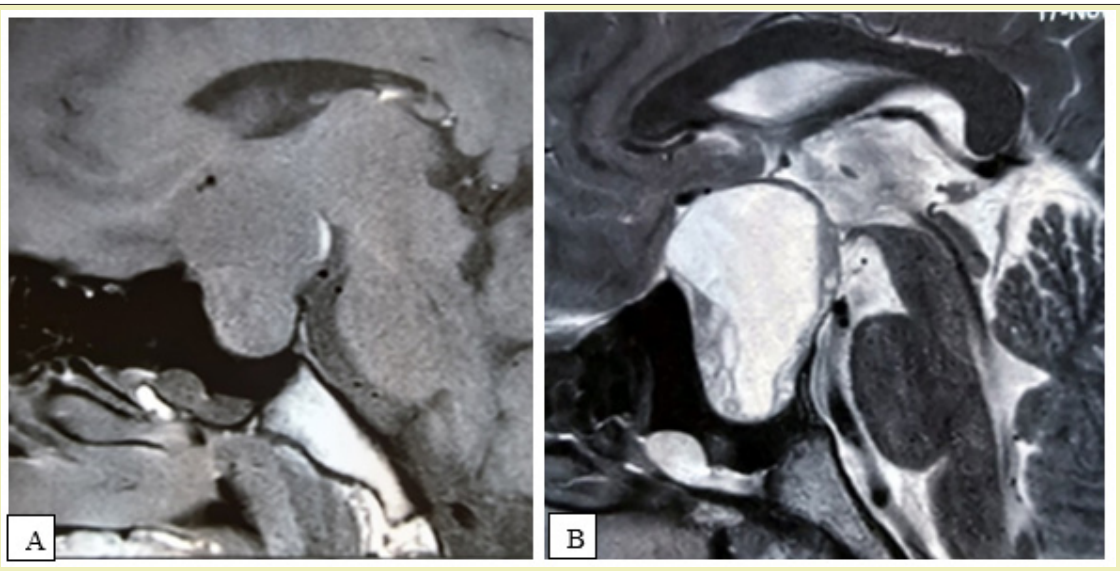

Figure 1: MRI of the brain, sagittal section T1WI (A) and T2WI (B) demonstrated that a lesion occupies the sellar region having suprasellar extension. The lesion is isointense on T1WI and heterogeneously hyperintense on T2WI. Pituitary gland is displaced postero-superiorly.

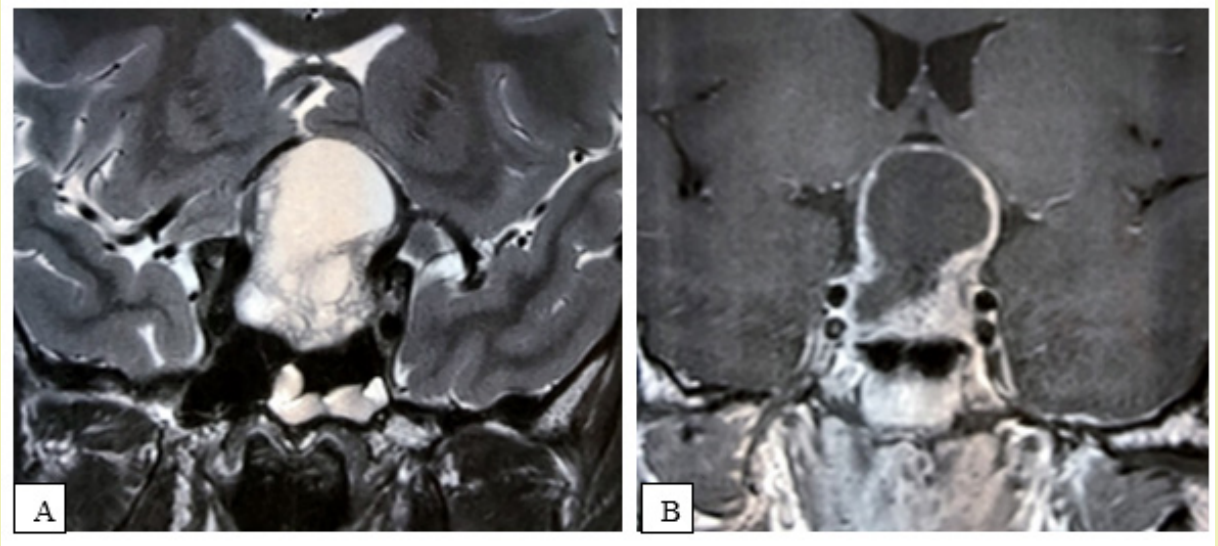

Figure 2: MRI of the brain, coronal section, T2WI (A) and post contrast (B) demonstrated that, optic chiasm is compressed and displaced upwards. Third ventricle is also compressed. After administration of contrast, there is heterogenous rim enhancement. However, no encasement of the cavernous segment of internal carotid artery noted.

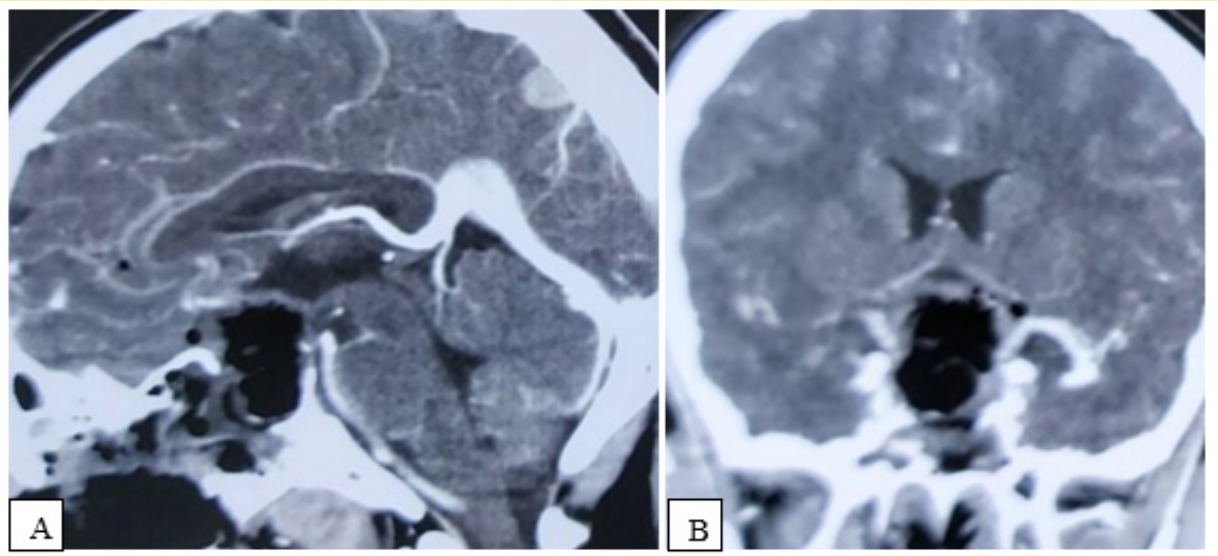

Figure 3: Follow up CT scan of brain with contrast, sagittal (A) and coronal (B) showed complete removal of the tumor.

Case 2

History and clinical examination

A 42 years old female presented with the complaints of headache and dimness of vision for ten months. She was amenorrhic for 1 year; although no history of milk secretion even after squeezing of nipple. Neurological examination demonstrated her visual acuity on both eyes were 6/60 with no improvement on pinhole. She had complete blindness in right eye and temporal hemianopia in left eye on visual field analysis and fundoscopy showed primary optic atrophy in both eyes.

Investigations

MRI of the brain demonstrated a predominantly hyperintense lesion occupying both sella, suprasella and left parasellar extension, multilobulated, having a fluid fluid level with significant compression on the optic chiasm and optic nerve Figure 4A,4B). Floor of the third ventricle was compressed and displaced upwards. After administration of the contrast, there was complete rim enhancement Figure 4C. Complete hormone analysis showed cortisol and leutinizing hormone below than the normal physiological limit.

Operative management and outcome

With all aseptic precaution, patient underwent endoscopic endonasal transsphenoidal approach and complete removal of the tumor. Decompression of the cystic part done initially. Fluid was motor oil like, signified it as late subacute haemorrhage. Sellar floor was reconstructed with fat, fascia lata and fibrin glue. There was no post-operative DI. Patient noticed improvement of headache as well as visual function in her left eye. Follow up CT scan showed complete removal of the tumor Figure 5. Histopathological findings showed neoplasm consists of round polygonal cells; present in a delicate fibrovascular stroma which were consistent with Pituitary Adenoma Figure 6.

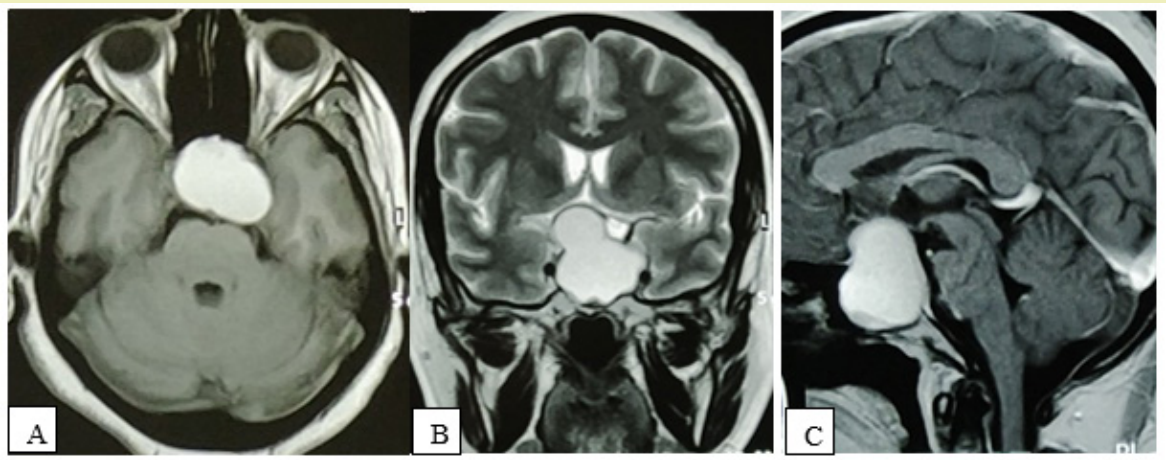

Figure 4: MRI of the brain with contrast, T1WI axial (A), T2WI coronal (B) demonstrated a well demarcated hyperintense, multilobulated lesion in sella, suprasella and left parasellar region with severe compression on the optic chiasm. Post contrast, sagittal section (C) showed a indistinct fluid fluid level in the bottom.

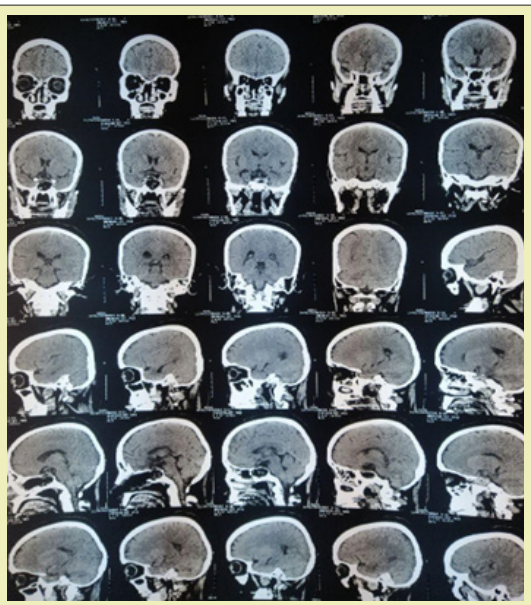

Figure 5: Plain CT scan of the brain, coronal and sagittal section demonstrated complete resection of the tumor.

Discussion

Incidence

Sella turcica is anatomically confined space where numerous pathologies, like-neoplastic, infective, inflammatory lesion occur. Among them, Pituitary Adenoma is the most common lesion. When it become large enough to occupy the suprasella and /or parasellar region, its more prone to undergo infarction or hemorrhage, considering its nature of blood supply and metabolic feature of the adenoma cell. The reported rate of PA bleeding is about 20%-30%, which is 5.4 times to the other intracranial tumors whereas rate of necrosis followed by cystic degeneration rate is about 5%-18%.[1,2]

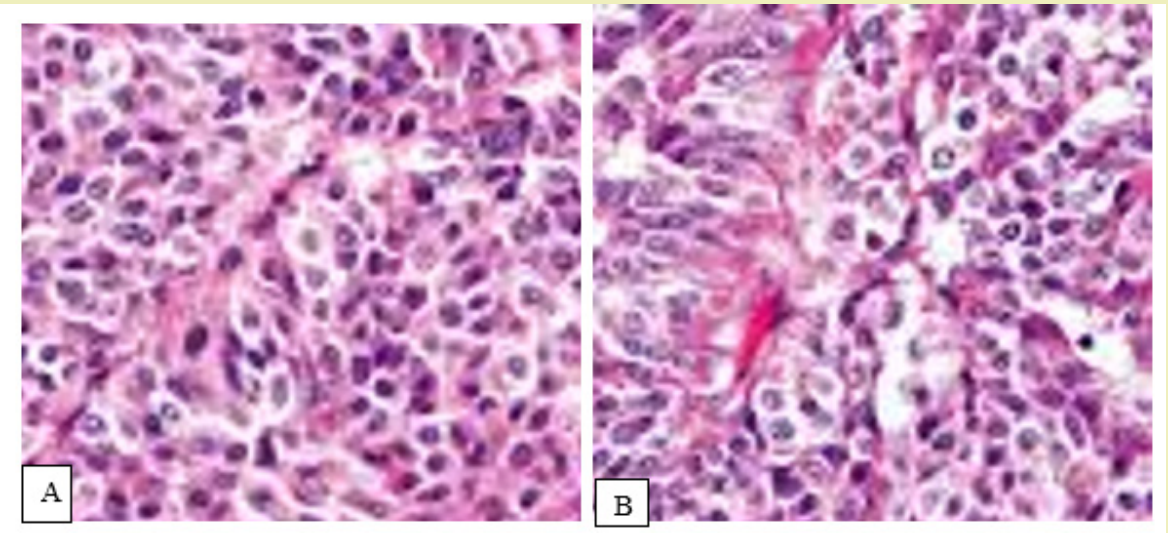

Figure 6: Photomicrograph of the pathological specimen with hematoxylin and eosin staining (A and B) showed a neoplasm consists of polygonal cells in a delicate fibrovascular stroma; consistent with pituitary adenoma.

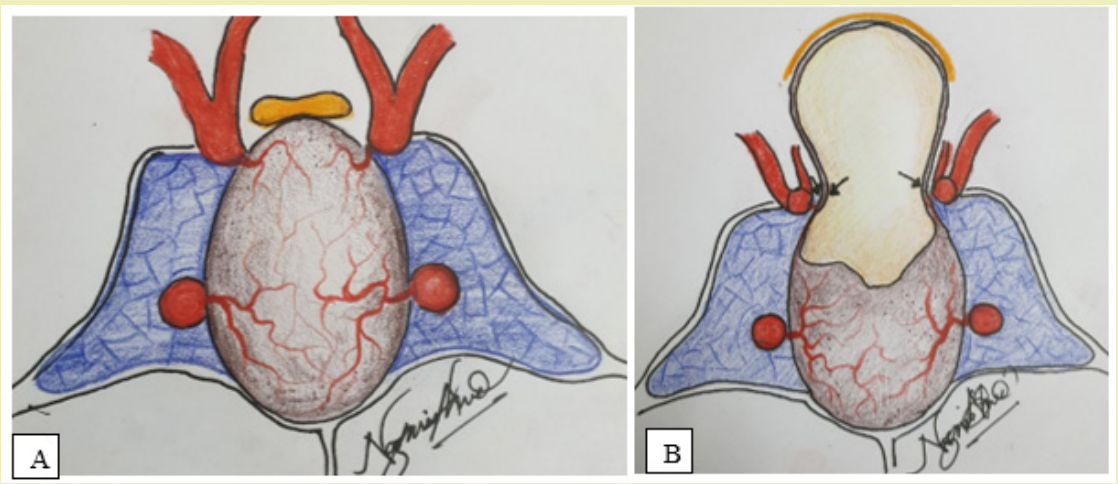

Figure 7: Schematic picture (A and B) demonstrated the blood supply of pituitary adenoma and pathogenesis of cystic degeneration. With progressive growth towards suprasellar region, superior portion deprived of its blood supply. Furthermore, Diaphragma sellae compressed the adenoma (drawn by black arrow) to increase the pressure in the intrasellar portion which further leads to ischemic changes.

Pattern of angiogenesis within the pituitary adenoma

Blood supply of the pituitary gland predominantly originates from superior hypophyseal arteries. However, the caudal region get nourishment from meningo-hypophyseal trunk. Both of them are the branches of internal carotid artery. In normal pituitary gland, superior hypophyseal artery is predominant supply to the gland.[3,4] However, study on the blood supply of pituitary macroadenoma showed that blood supply of the tumor mainly originated from the meningo-hypophyseal trunk in the caudal part.[3] Therefore, as pituitary adenoma continues to grow to occupy the suprasellar region, upper region of tumor becomes increasingly distant from the source of blood supply. With the course of time, the suprasellar part become vulnerable to undergo ischemic changes. Beside this, current research has determined the additional features of blood vessels inside the adenoma cells. The diameters of blood vessels are less than 300-micron, irregular with incomplete basement membrane together leads to blood flow stasis and finally leading to hemorrhagic changes inside the tumor.[5] Moreover, with further growth of the PA, hypophyseal portal system gets compressed at the seller septal foramen which further reduces the blood perfusion at the upper region of the pituitary adenoma.[5]

Pathogenesis of cystic degeneration

There are currently two main hypotheses proposed for the formation of cystic change of pituitary adenoma:

1) Ischemia and necrosis of the adenoma tissue leads to cystic change,[6]

2) Cystic change are secondary to intratumoral hemorrhage.[7,8]

Both hypotheses are pointing towards that the cystic change of PA is related to its insufficient blood supply. Beside this, Zhang. proposed the additional hypothesis of uneven distribution of regional blood supply inside the adenoma is the trigger point of pituitary adenoma infarction. Moreover, existing research already suggests that pituitary adenoma is more prone to infarction than other intracranial tumors considering its anatomical location, metabolic nature of the tumor, peculiarity of the blood vessels and pattern of angiogenesis. Regarding tumor location, diaphragm sellae limits the suprasellar extension. So, when tumor growth continues, the intrasellar pressure steadily increases and consequently reduces the adenoma perfusion.[9-10] Beside this, hypermetabolic nature of the adenoma has been already confirmed by PET scan and tumor cell culture experiments.[11] In comparison with their metabolic demand, angiogenesis of the pituitary adenoma is not syncronus.[12] In addition, Zayour. in their study showed that VEGF expression in the pituitary adenoma was almost similar to that of normal pituitary tissues.[13] In summary, growing adenoma becomes relatively deprived of its required blood supply because of the above reasons.[14] When there is already evident of relative hypoxia, certain conditions, like-hypotension or vasoconstriction are triggering factors lead to ischemia followed by infarction. With the course of time, cystic cavity forms replacing the area of infarction. However, Zhang detected regional differentiation of blood supply inside the tumor with increased tumor growth.[15] Blood supply at the upper part of pituitary adenoma is significantly poorer than on lateral and lower regions. Meanwhile, we also found that cystic change of pituitary adenoma was more likely to be in the upper region in both of our cases, which matched the poor blood supply in this location. This, from another perspective, explained why the trigger point of pituitary adenoma infarction was mostly in the upper region of the tumor.

Differential diagnosis of cystic sellar lesion with suprasellar extension; how to differentiate them from neuroimaging

From neuroimaging, it is quite challenging to distinguish Cystic pituitary adenoma from craniopharyngioma, RCC, pituitary abscess and germ cell tumors.[3] Thereby, several studies focused on some special neuroimaging criteria to differentiate them preoperatively.[16-22] In 2010, Goel suggested that, fluid fliud level is one of the reliable criteria to differentiate CPA from other lesions in the similar region.[21] They hypothesized that, cystic fluid material in pituitary tumors appears to have a special proteinaceous content that makes it prone to fluid-fluid levels. Other studies have suggested that fluid-fluid level within a fluid cavity is induced by the sedimentation of blood products at the subacute or chronic stage, as well as the separation of unclotted blood as opposed to serous fluid.[20-22] The signal intensity varies depends upon the age of blood products. The supernatant hyperintense areas demonstrated xantho chromic fluid and the subnatant hypointense areas demonstrated dark-red liquefied hematoma.[22,23] Xiao showed in his study that, fluid-fluid levels were detected in 55.13% of cystic pituitary adenoma cases;[22] however, they were rarely observed in RCC, craniopharyngioma and pituitary abscess. Furthermore, multiple fluid level phenomenon was only observed in pituitary adenomas. Though in our cases, we observed this fluid level in one case only. As our reported case displayed hyperintensity both in T1WI & T2WI which signifies late subacute hemorrhage; this fluid level was the result of blood breakdown products in the bottom with supernatant fluid in the top. Therefore, the identification of fluid-fluid levels may be beneficial in diagnosing cystic pituitary adenomas and distinguishing them from other sellar-suprasellar lesions. Additionally, hemorrhage within pituitary adenomas is common in patients with non-functioning adenomas and prolactinomas.[24,25] These findings were observed in both of our cases as they were nonfunctioning macroadenomas. The cystic degeneration without fluid-fluid level formation are also observed in neuroimaging. When the hematoma is in acute or chronic stage and if cystic cavity forms as a consequence of infarction, then fluid-fluid level is absent.

RCC and craniopharyngioma are also common lesions in the sellar and suprasellar regions. On MRI, RCC is typically exhibited as an intrasellar cystic lesion with suprasellar extension that is ovoid or kidney shaped, well demarcated, having no calcification, sometimes presence of intracystic nodules. After administration of contrast, there is thin regular rim enhancement.[26] In our second case, most of the neuroimaging criteria goes in favour of RCC, though this case was histologically proven as Pituitary adenoma.

Craniopharyngiomas are typically presented as sellar-suprasellar heterogeneous lesions, with mixed solid and cystic characteristics, presence of calcification, reticular enhancement of the solid portion, and third ventricle compression by superior tumor extension.[26-28] Apart from calcification, our first case fulfill all of the neuroimaging criteria of CP. Beside this, there was no fluid fluid level in this case and patient's age was goes in favour of CP. However, histopathological findings were in consistent with pituitary adenoma. In various previous studies, intracystic nodules have been regarded to have diagnostic value for RCC.[27,28] However, it may be difficult to distinguish the intracystic nodule of RCC from acute hemorrhage observed in pituitary apoplexy. The pathogenesis is different. The nodule formed by protein concretions and appear in the bottom of the cyst whereas the fluid-fluid level is due to the sedimentation of blood products and often appears in the suprasellar portion of the tumor.[28] Beside this, presence of T2WI hypointense rim, internal septation, and an off midline location mostly goes in favour of pituitary adenoma rather than RCC.[29] Very rarely, collision sellar

pathology; like co-existence of PA and RCC may mimic other cystic sellar pathology. In that case, definitive diagnosis can only be possible after histopathology.[30]

Surgical strategy and outcome

The tumor resection is relatively easy to carry out by endoscopic endonasal transsphenoidal approach even if the tumor is quite large to occupy the suprasella and parasellar region. Depends upon the Knosp grading, sometimes extended endoscopic approach may be necessary for complete removal. CPA have a propensity to adhere to the pituitary stalk, and occupy redundant spaces in distended sellar diaphragm, leading to compromised surgical visualization, difficult complete resection, CSF leakage and incomplete cyst wall removal.[31] The rate of intra-operative CSF leak in lesions with suprasellar extension was nearly double that in lesions without extension. Though we did not encounter per operative CSF leakage but due to their propensity to adhere with surrounding structures and recommendations from previous studies.[21,31,32] we used of a lumbar drain and reconstructed the sellar floor with fat, fascia lata and fibrin glue. In this study[3] it was shown that the cystic degeneration PA was rich in blood supply, and the adhesion degree of tumor with surrounding structures of cystic degeneration with fluid-fluid level was more serious and the borders were often unclear. Therefore, to the patients with cystic degeneration with fluid-fluid level, more patience and careful attention were needed during the operation to decrease bleeding, improve the resection rate and reduce the occurrence of cerebrospinal fluid leakage.

However, when the tumor was closely adhered to the sellar diaphragm, the medial wall of the cavernous sinus, the pituitary stalk or other surrounding structures, total resection should not be suggested according to the specific situation. If blindly seeking total resection of tumor, it was easy to cause surgical site bleeding and cerebrospinal fluid leakage, or cause the suprasellar vascular rupture hemorrhage, optic nerve injury, increased pituitary stalk pulling, postoperative polyuria and diabetes insipidus.[4-6] As for the tumor residual, suitable long-term follow-up was necessary and a trial radiosurgery or reoperation was needed during recurrence. Sometimes a small amount of the tumor tissue was appropriate to retain, which, could avoid the occurrence of disastrous consequences.[33-36]

Conclusion

CPAs are a heterogeneous group of intracranial lesions that demonstrate significant overlap in their clinical presentation and imaging findings. Thereby, preoperative differentiation is helpful in operative planning, counselling of the patient and necessity of adjuvant therapy. Careful observation of the cystic criteria can act as a valuable guide for the neurosurgeons for the diagnosis and management.

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Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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