CASE REPORT

Symptomatic Rathke's cleft cyst with a co-existing pituitary tumor; Brief review of the literature

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ABSTRACT

Pituitary adenomas and Rathke's cleft cysts (RCCs) share a common embryological origin. Occasionally, these two lesions can present within the same patient. We present a case of a 39-year-old male who was found to have a large sellar lesion after complaints of persistent headaches and horizontal nystagmus. Surgical resection revealed components of a RCC co-existing with a pituitary adenoma. A brief review of the literature was performed revealing 38 cases of co-existing Rathke's cleft cysts and pituitary adenomas. Among the cases, the most common symptoms included headache and visual changes. Rathke's cleft cysts and pituitary adenomas are rarely found to co-exist, despite having common embryological origins. We review the existing literature, discuss the common embryology to these two lesions and describe a unique case from our institution of a co-existing Rathke's cleft cyst and pituitary adenoma.

Key words: Adenoma, development, neoplasm, pituitary, Rathke's cleft cyst, sella, tumor

Introduction

Rathke's cleft cysts (RCCs) are thought to originate from Rathke's pouch, an epithelialized rostral invagination of the stomadeum. The Rathke's pouch has an anterior and posterior wall in addition to a central embryonic cleft. The anterior pituitary and the pars tuberalis arise from the anterior wall, while the posterior portion develops into the pars intermedia. The central lumen becomes the Rathke cleft, and normally regresses. However, this structure may persist and enlarge, resulting in the formation of a cyst. As the anterior pituitary lobe may at times clonally expand to form a pituitary adenoma, RCCs and these tumors have a common embryologic ancestry.[1] Very rarely, pituitary adenomas may occur concurrently with an RCC. We present a case of a symptomatic pituitary adenoma associated with a RCC and discuss the origin, histological findings, clinical presentation, imaging and management of these combined tumors. We also review the literature of existing cases.

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Case Report

A 39-year-old male presented to his primary care physician with a severe headache, fever and chills. The patient subsequently presented to the Emergency Department of an outside hospital due to worsening symptoms and the onset of substernal chest pain. His electrocardiogram was normal although the cardiac biomarkers were significantly elevated. In addition to working up the patient's cardiac compliant, computed tomography of the head was obtained due to the patient's persistent headache and the presence of horizontal nystagmus on exam. This scan revealed a large sellar mass. To further characterize this mass, a brain magnetic resonance imaging (MRI) was obtained. This revealed a 3.3 cm × 2.9 cm × 3.1 cm cystic mass in the sellar region [Figure 1]. He was then transferred to our institution for further management of his non-ST elevation myocardial infarction and sellar mass. Endocrine labs were obtained and were found to be significant for hypogonadotropichypogondism, with a total serum testosterone level of 23 ng/dL (normal range, 175-780 ng/dL), with all other pituitary labs within normal limits.

The patient subsequently underwent minimally invasive endoscopic transnasaltransphenoidal pituitary resection. Once the pituitary was exposed, an incision was made into the gland, releasing a large amount of fluid from the cyst. After removal of the lining of the cyst cavity, the wound was closed with a septal flap. The patient had an uneventful post-operative course and was discharged in a stable condition.

Histological examination of the mass showed adenohypophyseal tissue with focal monomorphic proliferation consistent with an adenoma [Figure 2a]. Also seen was

cytokeratin-immunopositive cuboidal epithelium consistent with an RCC [Figure 2b]. Immunohistochemical studies demonstrated tumor cells immunopositive for chromogranin, synaptophysin and human chorionic gonadotropin. However prolactin, adrenocorticotrophic hormone (ACTH) and growth hormone were seen to be negative.

Discussion

Origin and histology

RCCs were first described by Luschka in 1860, and are thought to arise from the remnants of Rathke's pouch.[2] During the third or fourth week of development, this structure is formed by the infolding of the roof of the stomodeum.[3] Between the anterior and the posterior walls that form the lobes of the pituitary gland is a central lumen known as Rathke's cleft. During normal development, this structure is obliterated. However, this cleft may persist, resulting in the formation of a cyst due to the secretion of products from the epithelial cells lining the intermediate lobe.[4-7] As the Rathke's pouch forms the craniopharyngeal duct, it has been proposed that RCCs and craniopharyngiomas represent a continuum of ectodermally derived epithelial lesions.[8] This is supported by papillary craniopharyngiomas having foci of ciliated and mucin-producing epithelia similar to that found in Rathke's cleft. However, despite pituitary adenomas and RCCs having a common embryologic ancestry, their co-existence may be coincidental.

Pituitary adenomas are thought to occur due to a variety of factors. As most of these tumors are monoclonal, tumor development likely occurs through genetic mutations that lead to cell transformation and further progression due to hormonal and growth factor stimulation.[9,10] Genetic defects have been shown to occur in a variety of genes controlling cell cycle progression, growth factor receptor expression and signal transduction pathways.[11]

Evidence supporting the link between pituitary adenomas and RCCs is based on pituitary adenomas occasionally containing both elements of the fetal Rathke's pouch and differentiated adenohypophyseal cells. It has been thought that these tumors were derived from "transitional" cells between the lining of Rathke's cleft and the glandular cells of the anterior pituitary.[12] Kepes referred to these tumors as transitional cell tumors of the pituitary gland as they contained squamous cells, mucin-producing cells and cells of the anterior lobe of the pituitary. However, it has been shown that the cysts within the pituitary adenomas differ from those found in the embryonic stage of the pituitary; therefore, making it unlikely that the tumors originate from the epithelium of RCCs.[13] Also, some of these tumors may occur due to the differentiation of folliculostellate or marginal cells.[1,14] As the origin of these tumors is unclear, they should be classified as mixed tumors that have both pituitary adenoma and RCC elements.[15]

Clinical presentation

RCCs have been found incidentally in 11-33% of post-mortem examinations, and were associated with 1.7% of the pituitary adenoma cases in a study involving 464 patients.[1,3] However, symptomatic RCCs associated with pituitary adenomas occur more rarely, having only been described in less than 40 cases [Table 1].[16-27] These cysts are typically less than 3 mm in diameter and remain intrasellar. However, one-third of the RCCs may have suprasellar extension leading to compression of the adjacent structures and increased intracranial pressure.[1,4,7,28-30] Vision loss may occur due to impingement of the optic chiasm and optic nerve, while pressure on the cavernous sinus may result in extraocular muscle palsy or ptosis due to cranial nerve dysfunction. Headaches, such as those that occurred in our patient, may occur due to leakage of the contents of the cyst and resulting irritation

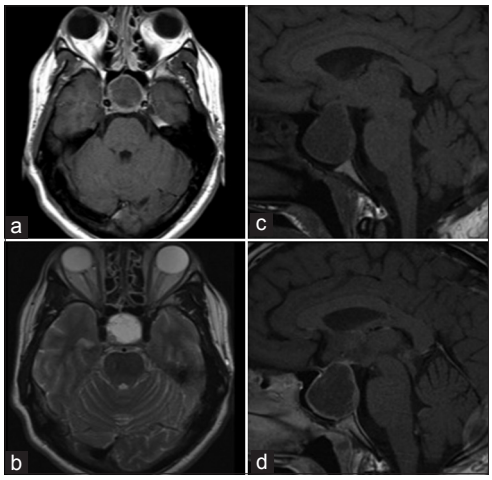

Figure 1: Magnetic resonance imaging (MRI) images of a cystic sellar lesion found to be a combined Rathke's cleft cyst with pituitary adenoma. (a) Axial T1-weighted MRI, (b) axial T2-weighted MRI, (c) sagittal T1-weighted MRI and (d) sagittal T1-weighted post-contrast MRI showing peripheral enhancement

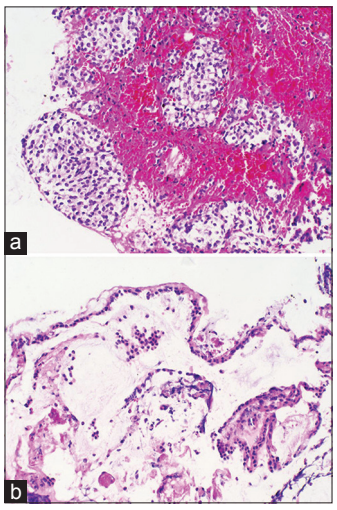

Figure 2: (a) Pituitary adenoma is present among hemorrhage, (b) Cuboidal epithelial lining was immunopositive for cytokeratin and is consistent with a Rathke cleft cyst component (a and b hematoxylin and eosin, ×20)

Table 1: Characteristics and clinical presentation of patients with a pituitary adenoma and *Rathke's cleft* cyst

Patient	Author, year	Sex	Age	Hormone Produced	Symptoms		
					Headaches	Visual	Hormonal
1	Bader, 2004 (2)	F	47	GH	Y	Binasal field defect	Acromegaly, carpal tunnel
2	Hiyama, 1986 (7)	F	35	Prolactin	N	Bitemporal hemianopsia	Amenorrhea, galactorrhea
3	Ikeda, 1987 (10)	F	31	Prolactin	Y	Yes	Amenorrhea, galactorrhea
4	Ikeda, 1992 (9)	M	50	GH	N	LU temporal quadrantanopsia	Acromegaly, libido loss
5	Kaku, 2005 (12)	M	42	None	Y	Bitemporal hemianopsia	None
6	Kepes, 1978 (16)	F	79	NS	NS	NS	NS
9	Matsumori, 1984 (18)	F	28	Prolactin	N	Bitemporal hemianopsia	Amenorrhea, galactorrhea
10	Miyagi, 1993 (21)	M	44	None	N	None	None
11	Nakasu, 1989 (23)	F	21	Prolactin	N	None	Amenorrhea
12	Nishio, 1995 (25)	M	44	GH	N	None	Acromegaly, libido loss
13		F	35	GH	N	Enlargement of blind spot	Menstrual irregularity
14	Nishio, 1987 (26)	F	21	Prolactin	Y	None	Amenorrhea, galactorrhea
15		F	23	Prolactin	N	None	Amenorrhea, galactorrhea
16		F	24	Prolactin	N	None	Amenorrhea, galactorrhea
17		F	25	Prolactin	N	None	Amenorrhea, galactorrhea
18		F	29	Prolactin	N	None	Irregular menses
19		F	30	Prolactin	N	None	Amenorrhea, galactorrhea
20		F	31	Prolactin	Y	None	Amenorrhea, galactorrhea
21		M	31	Prolactin	N	None	Galactorrhea, decreased libido
22		F	34	Prolactin	N	None	Amenorrhea, galactorrhea, lethargy
24	Sumida, 2001 (32)	F	67	GH	NS	None	Acromegaly
25		M	42	ACTH	NS	None	Cushing's disease
26		F	44	GH	NS	None	Acromegaly
27		M	18	GH	NS	None	Gigantism
28		M	46	GH	NS	None	Acromegaly
29		F	56	GH	NS	None	Acromegaly
30		M	39	ACTH	NS	None	Cushing's disease
31		M	48	GH	NS	None	Acromegaly
32	Swanson, 1985 (33)	F	34	None	Y	Yes	Amenorrhea
33	Trokoudes, 1978 (34)	F	38	Prolactin	N	None	Amenorrhea
34	Vancura, 2006 (35)	M	70	None	N	Diplopia	None
35	Noh, 2007 (27)	F	62	GH	N	None	Acromegaly
36	Radhakrishnan, 2011 (29)	F	16	None	N	Bitemporal hemianopsia	Amenorrhea
37	Koutourousiou., 2010 (17)	F	42	ACTH	NS	NS	Cushing's disease
38		M	76	None	NS	NS	None
39	Karavitaki, 2008 (14)	M	54	ACTH	N	None	Cushing's disease
40	Present report	M	39	None	Y	Horizontal nystagmus	None

*NS – not specified

of the meninges.[31] This may cause aseptic meningitis or hypophysitis.

Compression of the pituitary stalk by RCCs may impair dopamine transport to the anterior pituitary, resulting in hormonal abnormalities such as hyperprolactinemia.[32] This presents with galactorrhea, amenorrhea and hypogonadism.[33] However, the cause of this hyperprolactinemia may be unclear when a pituitary mass is present as it may also be due to a prolactin-secreting adenoma. Generally, prolactin-secreting adenomas result in a

serum prolactin concentration >200 ng/mL, whereas values below this indicate pituitary stalk compression as the more likely cause.[34] RCCs have also been reported to occur with adenomas secreting ACTH and growth hormone.[2,13,15,31,35,36] As untreated subclinical hypopituitarism may result in adverse effects on sexual function, skeletal integrity and cardiovascular function, the hypothalamic–pituitary axis should always be evaluated when a pituitary mass is present.[37]

Imaging

MRI is the recommended modality for visualization of the pituitary gland and parasellar regions. Because of the diverse composition of RCCs, MRI features are variable.[31] These cysts may contain mucinous fluid, mucopolysaccarhides and hemosiderin deposits, affecting their appearance on MRI. The presence of hemorrhage or mucopolysaccarhides within the cyst causes high T1-weighted image intensity, whereas the presence of cerebrospinal fluid-like fluid causes a low intensity on T1-weighted images.[38] Also, mucinious fluid may have a high- or iso-intense appearance on T1-weighted images depending on the viscosity of the fluid. Despite the inconsistent features of RCCs, it has been suggested that a hallmark of these cysts is a lack of post-contrast enhancement on MRI.[14] As a result, pre-operatively diagnosing a pituitary adenoma and concomitant RCC is rare as differentiation from a cystic pituitary, craniopharyngioma, arachnoid cyst or pars intermedia cyst is difficult. Although imaging studies with clinical and laboratory data may narrow the differential diagnosis, a histological analysis of the mass is the only way to reach a definitive diagnosis.

Management

Treatment for pituitary masses typically includes normalization of the hormonal abnormalities and alleviation of mass effect. Surgical therapy is recommended for hormone-secreting tumors resistant to medical therapy, acute hemorrhage and masses impinging on the surrounding structures. Operative management of pituitary adenomas and suspected RCCs involves transsphenoidal resection. This approach is minimally invasive and has been proven to safely excise these masses completely, allowing for the restoration of pituitary function. However, the recurrence rates for pituitary tumors such as GH-secreting adenomas are significant, ranging from 5.4% to 10%.[31] Therefore, adjuvant therapy such as radiosurgery may be indicated. On the other hand, the risk of recurrence of RCCs is low, with further treatment rarely necessary, although suprasellar extension, large cyst size and packing of the sella are risk factors for recurrent cyst formation.[29] Post-operative care includes monitoring of hormone levels, surveillance MRI scans and neurophthalmologic testing.

Conclusion

We present a report of a patient with a pituitary adenoma in combination with a symptomatic RCC. This rare combination is thought to occur due to the common embryological ancestry of these lesions. These combined tumors are difficult to diagnose pre-operatively due to the variable signal intensity and position of the RCCs. However, the presence of a non-enhancing cyst with a pituitary adenoma suggests the possibility of an accompanying RCC. Treatment of these lesions involves surgical resection to decrease mass effect and medical management to normalize hormonal imbalances.

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