

Coexisting intracranial tumors with pituitary adenomas: Genetic association or coincidence?

ABSTRACT

The co-occurrence of two or more brain tumors with different histological features is rare. The authors report three rare cases of intracranial tumors associated with pituitary adenomas. Two of the pituitary tumors were functioning adenomas: a prolactinoma and a thyrotropin secreting adenoma. Two of the associated intracranial neoplasms were gliomas and one was a meningioma. Radiological and clinical examination for syndromal association was negative in all cases. We briefly discuss the presentation and treatment options of these cases and review the 19 previous publications in the literature of pituitary tumors occurring in association with other neoplasms and explore the possible links underlying these co-occurring neoplasms. Our three cases represent 0.86% of all pituitary tumors operated at our institute over a 9-year period.

KEY WORDS: Astrocytoma, gliomas, meningioma, MRI, pituitary adenoma

INTRODUCTION

Gliomas constitute 50% of primary intracranial neoplasms, of which 40–50% are glioblastomas and 30–35% are anaplastic astrocytomas. Meningiomas form 15–25% of all intracranial neoplasms and have an annual incidence of 6/100,000.^[1,2] Pituitary adenomas (PA) are reported to co-occur with various grades of glial neoplasms, gliomatosis cerebri, schwannomas, medulloblastomas, and meningiomas.^[1–7] The coexisting pituitary tumor varied from clinically silent lesions to functioning adenomas like prolactinomas and growth hormone (GH)- and thyrotropin (TSH)-secreting tumors.^[1,2,4–6,8] We evaluated the possible tumor induction factors and previously described genetic abnormalities which could link the two unrelated pathologies.

CASE REPORTS

Case 1

A 35-year-old male presented with headache and generalized tonic–clonic seizures (GTCS) of 6 months' duration. He had a right temporal field defect but no other neurological deficits. Magnetic resonance imaging (MRI) revealed a heterogeneous lesion of 3.2 × 2.3 × 2.1 cm size in the sella/suprasellar region. There was another lesion in the right superior frontal gyrus that was hypointense on T1-weighted image (WI) and hyperintense on

T2 WI; it measured 3.8 × 2.1 × 2.2 cm and showed faint contrast enhancement [Figure 1a and b]. Serum T3, T4, and TSH levels were raised [Table 1]. The patient initially underwent a trans-nasal trans-sphenoidal (TNTS) decompression of the PA. Subsequently, a right frontal craniotomy and decompression of the second tumor (a glioma) was performed

Histology of the sellar lesion revealed a PA with positive immunohistochemistry for TSH and prolactin. The frontal lesion turned out to be a low-grade astrocytoma (WHO grade II) [Figure 1c and d]. Immunoreactivity for p53 was demonstrated in both lesions. At 6 months' follow-up the patient had a mildly elevated thyroid hormone profile. There was a residual PA on MRI, but he declined further surgery or octreotide therapy. There was no radiological residual lesion at the site of the glioma surgery.

Case 2

A 53-year old male presented with headache for 2 years and altered sensorium of 2 weeks' duration. Neuroimaging revealed an anterior third parasagittal meningioma, 6 × 5.5 × 5 cm in size. There was also a 3 × 2.5 × 2 cm pituitary macroadenoma [Figures 2a and b]. He underwent TNTS decompression of the non-functioning PA [Table 1] followed by bi-frontal craniotomy and total excision of the meningioma. Histology

Sunil V Furtado,
Prasanna K Venkatesh,
Nandita Ghosal¹,
Alangar S. Hegde

Departments of
Neurosurgery and
¹Pathology, Sri Sathya
Sai Institute of Higher
Medical Sciences,
Bangalore, India.

For correspondence:

Dr. Sunil V Furtado,
Department of
Neurosurgery,
Sri Sathya Sai Institute of
Higher Medical Sciences,
EPIP Area, Whitefield,
Bangalore - 560 066,
India.
E-mail: sunilvf@
gmail.com

DOI: 10.4103/0973-
1482.65246

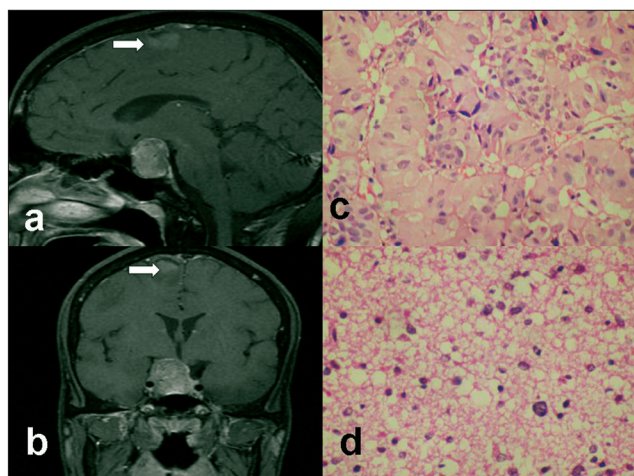


Figure 1: (a) Mid-sagittal and (b) contrast MRI of pituitary adenoma and low-grade glioma (white arrow); (c) paraffin section of pituitary adenoma [(H and E); ×400]; (d) paraffin section of low-grade glioma (H and E; ×400)

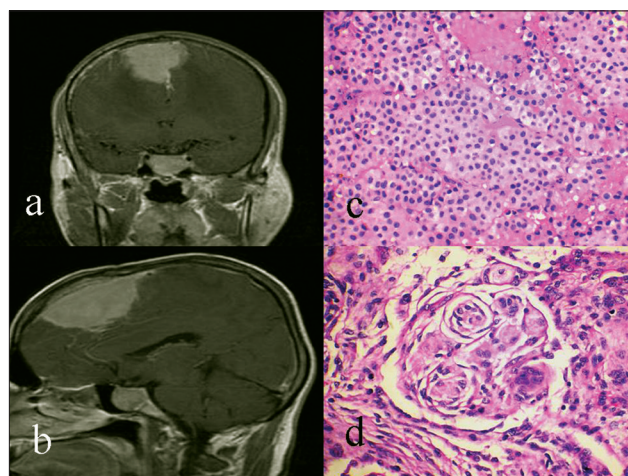


Figure 2: (a) Coronal and (b) mid-sagittal MRI of parasagittal meningioma and pituitary adenoma; (c) paraffin section of pituitary adenoma (H and E; ×400); (d) paraffin section of meningioma showing whorl formation (H and E; ×400)

Table 1: Hormonal assay of patients at first admission

Hormones	Normal range	Case 1	Case 2	Case 3
Total T3 (thyronine)	0.8–1.7 ng/ml	2.63	1.47	1.14
Total T4 (thyroxine)	6–12 µg/dl	20.92	10.69	7.3
Thyroid stimulating hormone	0.3–5 µIU/ml	3.84	2.89	
Prolactin	3–26 ng/ml	28.96	8.05	875
Morning serum cortisol	8–22 µg/dl	11.39	10.26	15.4
Growth hormone	0.004–1.406 ng/ml	0.58	0.73	NA

revealed an acidophil PA and a meningothelial meningioma [Figures 2c and d]. He is presently symptom free, 4 years after surgery, and his MRI shows no residual lesion.

Case 3

A 36-year old lady, who presented in 2000 with irregular menstrual cycles, was diagnosed to have a prolactin-secreting microadenoma [Figure 3a, Table 1]. She was treated with tab. bromocriptine 5 mg twice daily for 5 years. Following treatment her prolactin level returned to normal. She presented in 2008 with GTCS and was diagnosed to have a right frontal parenchymal cyst with a peripheral enhancing solid area measuring 7.5 × 7 × 5 cm [Figure 3b]. MR spectroscopy (MRS) showed increased choline, decreased NAA with lactate doublet [Figure 3c]. She underwent a right frontal craniotomy and decompression of the lesion, which was reported as glioblastoma multiforme [Figure 3d]. She received 57 Gy of radiotherapy followed by tab. temozolomide (150 mg/m²) as cyclic and concomitant chemotherapy. Eight months later she had a recurrence at the corpus callosum for which chemotherapy was restarted and continued for 5 months. Further MRI imaging is awaited.

DISCUSSION

Russel and Rubinstein suggested that the co-occurrence

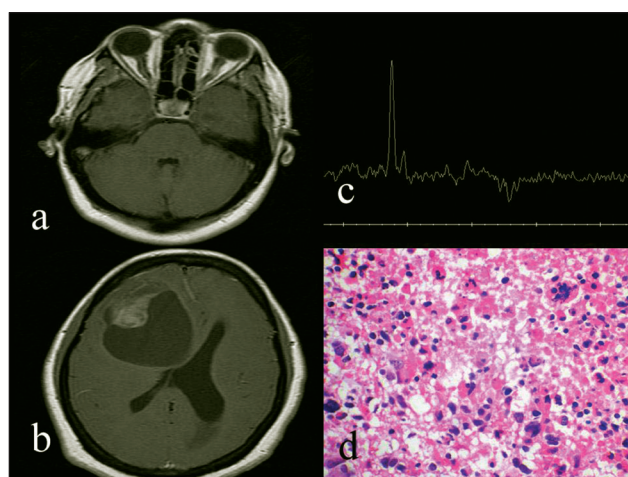


Figure 3: Axial contrast images showing (a) pituitary microadenoma; (b) right frontal glioblastoma; (c) MRS demonstrating increased choline, decreased NAA with lactate doublet; (d) paraffin section of glioblastoma showing necrosis, mitosis, and tumor giant cells (H and E; ×400)

of common primary brain tumors could be attributed to serendipity.^[4] The most common co-occurrence has been of glioma with meningioma, followed by meningioma with PA and neurinoma with meningioma.^[3,4]

The highest incidence of non-syndromal co-occurrence is with gliomas.^[4] There are 13 earlier reports of gliomas occurring with PA, of which details were available for eight patients. Of them, two each were anaplastic astrocytomas and pilocytic astrocytomas, one each were glioblastoma, gliomatosis cerebri, grade II astrocytoma, and oligoastrocytoma.^[4,5,8] There were four non-functioning PAs, two prolactinomas, and one each of GH- and TSH-secreting tumors.^[4]

The presence of a meningioma with a functioning PA such

as GH-secreting adenomas and prolactinomas is ascribed to high circulating levels of GH and IGF-1 receptors in the former and prolactin receptors in the latter.^[1,2,6,8]

PA shows losses for chromosomes 1p, 2q, 4, 5, 6, 11q, 12q, 13q, and 18q and over-representation on 9q, 16p, 17p, 19, and 20q.^[9] Functioning adenomas carry more imbalances than non-functioning tumors, especially deletions on chromosome 4 and 18q and over-representations of chromosomes 17 and 19.^[9] The band 19p13.3 is described as a critical region in human gliomas by loss of heterozygosity studies.^[10] The losses of 19q and retention of 19p are strongly associated with oligodendroglioma and mixed oligoastrocytoma, whereas loss of 19p and retention of distal 19q are associated with astrocytoma.^[10]

Conheim stated that multiple tumors arise from cells of embryonic residua, which later develop neoplastic potential.^[3] Fibroblast growth factor (FGF)-1 receptor and FGF-2 receptor are expressed in human PA, while elevated circulating FGF-like immunoreactivity is found in patients with sporadic PA and MEN-1 and meningiomas.^[3,11] Besides, FGF-1 is mitogenic towards neuroectoderm- and mesoderm-derived cells and is said to have a positive growth effect on neuromas, PAs, and meningiomas through the FGF-1 receptor.^[3,11] The presence of estrogen and progesterone receptors in both PA and glioma tissue was attributed to a common receptor substrate in both tumors.^[5] There is a significant increase in involvement of chromosomes 14 and 22 in estrogen receptor-positive *de novo* meningiomas, when compared with the progesterone receptor-positive meningioma group.^[12] Out of a sample of 30 pituitary adenomas analyzed by Bello, 12 samples had recurrent numerical deviations which involved losses in chromosomes 10, 14, 19, and 22.^[13] Telomeric association involving the short arms of chromosomes 14 and 19 and the long arms of chromosomes 11, 19, and 22 were observed in prolactinomas and non-secreting PAs, respectively.^[14] Proximate genetic alterations shared by two unrelated neoplasms on the same chromosome can possibly explain their co-occurrence.^[4] There may be a significant population of this 'coexisting tumor group' who remain undiagnosed, given the benign and indolent nature of the tumors.

CONCLUSION

Although no definite causative factors are ascribed for the coexistence of these unrelated tumors there may be a common, as yet undetermined, denominator linked to their

origin. The low incidence of the coexisting non-syndromal lesions could point to a common genetic linkage which will help us understand the natural history of their co-occurrence.

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Source of Support: Nil, **Conflict of Interest:** None declared.