Case Report

Pituitary oncocytoma presenting as Cushing’s disease

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ABSTRACT

A 19-year-old girl presented with classical features of Cushing’s syndrome. Endocrinal evaluation was consistent with pituitary source of ACTH; but imaging showed normal pituitary. Bilateral inferior petrosal sinus sampling confirmed the diagnosis. A successful remission was achieved after adenomectomy by transphenoidal route. Histopathological examination was consistent with pituitary oncocytoma and immunohistochemistry was positive for synaptophysin, chromogranin, neuron specific enolase, S-100, ACTH, prolactin, and GH.

Key words: Cushing’s syndrome, pituitary oncocytoma

INTRODUCTION

Pituitary adenomas comprise a family of tumors with diversified histopathological and hormonal phenotypes. Oncocytoma is essentially a subtype of null cell tumor and does not produce hormone and has the additional feature of oncocytic changes on light microscopy and substantial number of mitochondria in the cytoplasm under the electron microscope. As no hormone is produced by null cell adenomas and oncocytomas, they are not associated with clinical manifestations resulted from hormone over production. However, one case of prolactin secreting oncocytoma presenting as galactorhea–amenorrhea syndrome and another with Cushing’s syndrome have been reported. Here we report a case of pituitary oncocytoma presenting as Cushing’s syndrome in a young girl.

CASE REPORT

A 19-year-old girl presented with complaints of weight gain, hypertrichosis, menstrual irregularities of 2 years and hypertension of 4 months duration. She also gave history of easy bruisability, broad violaceous striae over abdomen and thighs, recurrent vaginal candidiasis. Her height was 154 cm, weight 77 kg, BMI of 32 kg/m2, and waist hip ratio 0.95 on examination. She was normotensive on antihypertensive medications. There was thinning of scalp hairs, mooning of face, facial plethora, hypertrichosis over face, increased supraclavicular and dorsocevical fat pad thickness, violaceous abdominal striae, thinning of skin over dorsum of hands, and proximal muscle weakness. There was no neurological deficit including visual fields. OGGT detected IFG (fasting plasma glucose 102 mg/dl) and IGT (postglucose load 156 mg/dl). Her bone mineral density estimation by DXA revealed osteopenia. Her hormonal evaluation revealed normal basal ACTH levels (38.7 pg/ml) in the presence of basal cortisol levels of 21.3 μg/dl (8 am) and evening cortisol of 23 μg/dl (4 pm). Serum cortisol levels remained unsuppressed following overnight (18.6 μg/dl) and low dose (15.7 μg/dl) dexamethasone suppression test. However, it decreased by 73% on high dose dexamethasone suppression test (5.8 μg/dl). MRI brain did not reveal any pituitary abnormality. Since neurosurgeons were reluctant to operate without localization and also to find source of ACTH, bilateral inferior petrosal sinus sampling (BIPSS) was planned with vasopressin stimulation due to nonavailability of CRH and desmopressin. The central to peripheral ACTH ratio on the right side was 28/1 and 32/1 in basal and postvasopressin respectively (normal <2 and <3 respectively). The interpetrosal...
sinus gradient was also significant (right IPS/left IPS = 13; normal <1.5) suggesting pituitary microadenoma on the right side of adenohypophysis. The patient was diagnosed as having Cushing’s disease caused by an ACTH-secreting pituitary adenoma, which was extirpated (adenomectomy) by transphenoidal surgery. The sixth postoperative day basal Cortisol level was 0.33 μg/dl, suggestive of possible remission of disease. She was discharged on replacement doses of hydrocortisone with advice on stress dosing and she is planned for gradual tapering of hydrocortisone doses.

Histopathological examination on light microscopy showed more than 95% of cells arranged in a large sheet of polyhedral cells with eccentric nuclei and moderate amount of bright eosinophilic, granular cytoplasm consistent with oncocytes, which confirmed the diagnosis of oncocytoma [Figure 1]. These cells were arranged in diffuse, solid, and sinusoidal pattern [Figure 2]. These cells were strongly positive for ACTH [Figure 3]; prolactin; GH; S100; neuron specific enolase; chromogranin A; and synaptophysin on immunohistochemical staining and displayed a bright brown positivity universally. Phosphotungstic acid hematoxylin (PTAH) staining revealed dark blue oncocytic cytoplasm [Figure 4].

**DISCUSSION**

Oncocytes are rounded, swollen, granular cells, which are found in the parotid, thyroid, parathyroid glands, kidney and hypophysis; first described by Hemperal.[6] Oncocytoma of the pituitary was first described by Kovacs et al[7] and Landolt et al.[8] Oncocytoma is essentially a subtype of null cell tumor and does not produce hormone and has the additional feature of oncocyic changes on light microscopy and substantial number of mitochondria in the cytoplasm under the electron microscope.[1,2] The incidence of pituitary oncocytomas are 6% among pituitary tumors.[5] Oncocytomas are more common observed in

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**Figure 1:** H and E-×20: Tumor cells distinct sinusoidal and nested pattern

**Figure 2:** H and E-×40: Polyhedral tumor cells with bright pink eosinophilic granular cytoplasm with eccentric nuclei

**Figure 3:** IHC – ×40: Tumor cells showing diffuse strong positivity for ACTH monoclonal antibodies (similar pattern were seen for GH, prolactin, S100, neuron specific enolase, chromogranin A and synaptophysin)

**Figure 4:** PTAH – ×40: Tumor cells showing diffuse strong dark blue cytoplasm suggestive of oncocytoma
elderly patients with peak incidence in the sixth decade of life and has a strong predilection for males. It is uncommon in patients older than 70 and younger than 40 years of age.\(^{[9-12]}\) Our case was of 19 year of age. Other authors have reported secreting oncocytoma in 19-year and 27-year-old women.\(^{[13,14]}\) To the best of our knowledge, this is the youngest case of secretory pituitary oncocytoma.

As no hormone is produced by oncocytomas, they are not associated with clinical manifestations resulted from hormone overproduction. Hence, oncocytomas usually present after they are of considerable size, causing symptoms of mass effect such as visual loss, headaches, and hypopituitarism.\(^{[10]}\) Our case has presented with classical clinical features of Cushing’s syndrome, which was on hormonal evaluation consistent with diagnosis of Cushing’s disease. Moreover, though imaging was negative for pituitary tumor, surgery has confirmed it to be a microadenoma. Gjerris et al.\(^{[19]}\) reported a patient that had invasive pituitary oncocytoma associated with Cushing’s disease. However, their case presented with abducens nerve paresis and hormonal parameters revealed only loss of diurnal variation of cortisol before operation. Clinical features of Cushing’s syndrome appeared 4 months after surgery. They have not performed immunohistochemistry on the tumor to document ACTH staining of the tumor cells, which has been documented in our case. The present case achieved remission after surgery, which further confirms ACTH secreting pituitary tumor. Some oncocytomas have prominent endoplasmic reticulum, which may help them to secrete hormones.\(^{[13]}\)

Oncocytic changes in over 50% of the adenoma cells having oncocytic features are required for diagnosis of oncocytoma, but some investigators require complete transformation before a diagnosis of oncocytoma is made.\(^{[14,15]}\) On light microscopy more than 95% of cells were oncocytes, which confirmed the diagnosis of oncocytoma in our case. The cells were arranged in diffuse, solid, and sinusoidal pattern in our case, but also reported in pseudopapillary pattern, rosette formation, and other patterns. The oncocytic cytoplasm stains dark blue with PTAH. As the oncocytic changes produces bright eosinophilic cytoplasm, PTAH is rarely needed for its detection; however, we have also documented this in our case. Under the electron microscope, the cytoplasm of oncocytoma is filled with mitochondria.\(^{[1,3,10,11]}\) However, it could not be done in our case due to unavailability.

The spectrum of pituitary tumors includes the commonest pituitary adenomas, craniopharyngiomas, meningiomas, oncocytomas, and granular cell tumors.\(^{[9]}\) Among these the pituitary adenomas with oncocytic change can simulate oncocytomas histologically. They are differentiated by positivity to neuroendocrine markers due to the presence of mitochondria. The granular cell tumor shows positivity only to S-100 protein and not other neuroendocrine immunohistochemical stains. The meningiomas do not display the oncocytic change, but when spindled may need differentiation from spindle cell oncocytomas. Granular cell tumors are the closest mimics histologically. The cytologic features are similar to granular tumors arising in other parts of the body. In common, they are composed of solid sheets of polygonal cells with a granular cytoplasm and bland nuclei. Although the cytoplasm is granular, they are not as brightly eosinophilic as in pituitary oncocytoma.

On periodic acid-Schiff (PAS) stain, cytoplasm of granular cell tumors is strongly positive. Positive immunoreactivity for S100 protein and GFAP has been described in some but not all granular tumors.

Although, no hormone production is usually detected by immunostaining in both null cell adenomas and oncocytomas, immunostaining for thyrotropin stimulating hormone, follicle stimulating hormone, luteinizing hormone, prolactin, growth hormone, and/or alpha-subunit of glycoprotein hormones have been reported in a few scattered cells. Our case differed from this commonly believed feature, in that it was strongly positive for ACTH, prolactin and GH on immunohistochemistry. Oncocytomas show positivity with neuron-specific enolase, chromogranin A, and synaptophysin.\(^{[15-18]}\) Oncocytoma in our case was positive for all these.

### Conclusion

We have presented a case of pituitary oncocytoma presenting as microadenoma and Cushing’s disease, which was contrary to generally held belief about oncocytoma in literature. Genetic analysis and variability of such tumor may unravel pleomorphic nature of these tumors in future.

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