An Unusual Oncocytic Sellar Neoplasm in a Patient with Birt-Hogg-Dubé Syndrome

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Abstract

Spindle cell oncocytoma (SCO) is a rare and recently described neoplasm arising from the pituitary adenohypophysis thought to be derived from the folliculostellate cells. Even though SCO has been classified as a distinct World Health Organization (WHO) grade I tumor, sellar neoplasms with an oncocytic appearance are uncommon and have a wide differential diagnosis that includes primary and metastatic lesions. Herein we describe an oncocytic sellar neoplasm of uncertain histiogenesis arising in a 49-year-old man with Birt-Hogg-Dubé (BHD) syndrome. This case is also unusual in that individuals with BHD have a propensity to develop oncocytomas, yet to the best of our knowledge this is the first occurrence of a primary oncocytic neoplasm of the sella in BHD syndrome.

Keywords: Oncocytoma; Spindle cell oncocytoma; Pituitary tumor; Birt-Hogg-Dubé

1. Introduction

Oncocytomas are a group of neoplasms with a distinct eosinophilic and granular appearance due to the intracytoplasmic accumulation of mitochondria. Sellar neoplasms with an oncocytic appearance are uncommon and have a wide differential diagnosis that includes primary and metastatic lesions. Herein we describe an oncocytic sellar neoplasm of uncertain histiogenesis arising in a 49-year-old man with Birt-Hogg-Dubé (BHD) syndrome. Its unusual histology and immunohistochemical profile expands the histologic spectrum of primary sellar oncocytic neoplasms and may represent a variant of spindle cell oncocytoma or a novel entity. This case is also unusual in that individuals with BHD have a propensity to develop oncocytomas, yet to the best of our knowledge this is the first occurrence of a primary oncocytic neoplasm of the sella in BHD syndrome.

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2. Case Report

Clinical Presentation
A 49-year-old man presented with an 18-month history of malaise, decreased libido and hot flashes that was initially diagnosed by his family physician as hypothyroidism secondary to Hashimoto's thyroiditis and an unrelated hypogonadism. Subsequent investigations revealed panhypopituitarism with low testosterone, follicle stimulating hormone (FSH), and luteinizing hormone (LH), and he was referred to endocrinology for further work-up and medical management. His past medical history was significant for dyslipidemia and Birt-Hogg-Dubé syndrome, which was genetically confirmed after he had developed several benign lung cysts. His family history was significant for a multiple members with Birt-Hogg-Dubé syndrome and a first-degree relative with renal cancer.

Physical examination was unremarkable, with normal secondary sexual characteristics and no features of hypothyroidism. Detailed neurological assessment was grossly normal with intact visual function, including full extraocular movements and intact visual fields. Magnetic resonance imaging (MRI) demonstrated a diffusely enlarged, and uniformly enhancing pituitary gland and stalk, with deviation of the stalk (Figure 1), extension into the right cavernous sinus, and mild encasement of the right carotid artery. The initial radiological differential diagnosis included lymphocytic hypophysitis, neurosarcoidosis, lymphoma, and metastatic disease; pituitary macroadenoma was low on the differential. A combined team of surgeons from Otolaryngology and Neurosurgery performed an endoscopic transnasal transphenoidal resection of the pituitary tumor with intraoperative image guidance. The patient had an uncomplicated post-operative recovery.

Fig. 1. Pre-operative T1-weighted MRI with gadolinium. Examination of the patient's T1-weighted MR images (Left: coronal section; Right: sagittal section) revealed heterogeneously enhancing sellar lesion with suprasellar extension causing compression of the optic chiasm (yellow arrows).
Pathological Findings
Histologic exam revealed a hypercellular and moderately pleomorphic neoplasm composed of sheets and trabeculae of cuboidal-to-columnar cells with abundant eosinophilic granular (oncocytic) cytoplasm, and moderate nuclear atypia (Figure 2). In areas, the cells had a columnar morphology and appeared to be lining up around lumina; focal papillary structures and frequent intratumoral aggregates of lymphocytes and histiocytes were also identified. Rare mitotic figures were seen, and Ki67 immunolabeling revealed a moderately elevated proliferative index (approximately 10%). There was no necrosis. A reticulin stain highlighted fibers around vascular structures only, and a periodic acid Schiff stain was negative. Tissue was not available for examination by electron microscopy.

Fig. 2. Histologic examination of hematoxylin and eosin (H&E) stained sections revealed morphologic features of spindle cell oncocytoma. (A) A low power photomicrograph shows a hypercellular lesion composed of a uniform population of cells forming sheets and trabeculae. (B) At higher power, the neoplastic cells have an oncocytic morphology with abundant eosinophilic granular cytoplasm and nuclei with prominent nucleoli. (C) Admixed with the neoplastic cells are scattered aggregates of inflammatory cells composed of lymphocytes and histiocytes. (B and D) This case was unusual in that it showed evidence of epithelial differentiation with the oncocytic cells focally having a columnar appearance and lining up around lumina (black arrows).
Fig. 3. Immunohistochemical studies revealed positivity of the neoplastic cells for (A) vimentin, (B) S100, and (C) epithelial membrane antigen (EMA), characteristic of spindle cell oncocytoma. (D) Negativity for synaptophysin excluded a pituitary adenoma. (E) Positivity for anti-mitochondrial antibody confirmed its oncocytic morphology. (F) Bcl-2 and (G) thyroid transcription factor (TTF)-1 showed positivity, which has also been reported in spindle cell oncocytoma. (H) An unusual finding in this case was positivity for various epithelial markers, including: CAM 5.2 (shown), pooled cytokeratin, cytokeratin 7, AE1-AE3, and beta34E12, which has not previously been reported in spindle cell oncocytoma.
By immunohistochemistry (Figure 3), the neoplastic cells were strongly positive for anti-mitochondrial antigen, vimentin, S100, bcl2, nuclear thyroid transcription factor-1 (TTF-1; SPT24 clone), p53, CD10 and various epithelial markers, including pooled cytokeratin, epithelial membrane antigen (EMA), CAM5.2, cytokeratin 7, AE1-AE3, and β34E12. The neoplastic cells were negative for neuroendocrine markers (synaptophysin, chromogranin, CD56), pituitary hormonal markers (adrenocorticotropic hormone, thyroid stimulating hormone, growth hormone, prolactin, follicle stimulating hormone, and luteinizing hormone), glial fibrillary acidic protein (GFAP), germ cell tumor markers (alpha-fetoprotein, beta-human chorionic gonadotropin, oct 3/4), HMB45, cytokeratin 20, thyroglobulin, PAX8, actin, desmin, and CD34.

Follow-up
Given the diagnostic possibility of a metastatic process (see Discussion below), the patient underwent post-operative imaging, including an ultrasound of the thyroid gland and computed tomography of the chest, abdomen and pelvis, which did not reveal a primary neoplastic process elsewhere.

3. Discussion

The differential diagnosis of an oncocytic sellar neoplasm with epithelioid and papillary features is broad and requires a large panel of immunohistochemical stains to arrive at a definitive diagnosis. Electron microscopy was not performed in this case, but is also a useful adjunct in the workup of primary sellar neoplasms (Roncaroli et al., 2002).

In our case, pituitary adenoma, which is well known to have papillary and oncocytic variants, was excluded early on in the diagnostic workup based on the lack of expression of neuroendocrine and hormonal markers. An oncocytic and papillary neoplasm with extensive cytokeratin and TTF-1 expression also raised the possibility of a metastatic oncocytic papillary carcinoma from an extracranial site such as the thyroid, lung, nasopharynx or salivary gland (Guillen Ponce, Garrido Lopez, Molina Garrido, Munoz Molina, & Carrato, 2007; Matoso et al., 2010; Pineda-Daboin, Neto, Ochoa-Perez, & Luna, 2006). Although not typically TTF-1 positive, a metastatic renal oncocytoma/carcinoma was also considered given that the neoplasm was arising in an individual with BHD (Menko et al., 2009; Oxley, Sullivan, Mitchelmore, & Gillatt, 2007). Clinical imaging did not detect a primary malignancy outside of the sella; however, this does not rule out an occult extra-cranial carcinoma.

Albeit uncommon, there are several primary intrasellar nonendocrine neoplasms that have been described to have oncocytic, epithelioid and/or papillary histologic features, including: spindle cell oncocytoma (Singh et al., 2012), pituicytoma (Ellis et al., 2012), ependymoma (Kleinman, Zagzag, & Miller, 2003; Scheithauer, Swearingen, Whyte, Auluck, & Stemmer-Rachaminov, 2009; Vajtai et al., 2011), meningioma, choroid plexus papilloma (Bian et al., 2011; Diengdoh & Shaw, 1993), and oncocytic neoplasms arising from salivary gland rests in the pituitary (Hampton et al., 1997). A pigmented papillary epithelial neoplasm of the pituitary fossa with oncocytic and papillary regions has also been described (Bian et al., 2011); however our case lacked pigmentation of the neoplastic cells.
The majority of these entities were excluded in our case given that, even in their unusual variants, the diagnosis still requires the presence of their classically described histopathological and/or immunohistochemical features at least focally. Ependymoma has perivascular pseudorosettes with positivity for GFAP and cytokeratin, and negativity for S100. Meningioma typically has its cells arranged in lobules, whorls or syncytial sheets, and apart from secretory meningioma, would not be expected to have cytokeratin positivity. Choroid plexus papillomas should have well-formed papillary structures with PAS positivity and negativity for EMA, and pituicytomas have EMA and cytokeratin negativity with GFAP positivity.

Despite the unusual epithelial and glandular features and a lack of a spindled morphology of our case, the immunohistochemical profile is highly suggestive of a spindle cell oncocytoma. Spindle cell oncocytoma of the adenohypophysis is a rare and diagnostically challenging entity with only twenty-four cases reported in the English literature since the first account in 2002 by Roncaroli et al., (Alexandrescu, Brown, Tandon, & Bhattacharjee, 2012; Borges, Lillehei, & Kleinschmidt-DeMasters, 2011; Borota et al., 2009; Coire, Horvath, Smyth, & Kovacs, 2009; Dahiya et al., 2005; Demssie et al., 2011; Farooq, Bhatt, & Chang, 2008; Fujisawa et al., 2012; Fuller, Scheithauer, Roncaroli, & Wesseling P, 2007; Kloub, Perry, Tu, Lipper, & Lopes, 2005; Matyja et al., 2010; Mlika et al., 2011; Ogawara, Dubner, Shafizadeh, Raizer, & Chandler, 2011; Romero-Rojas et al., 2011; Roncaroli et al., 2002; Singh et al., 2012; Vajtai, Sahli, & Kappeler, 2006). The classical histologic description of SCO is that of a fascicular neoplasm arising from the adenohypophysis and composed of spindled and epithelial oncocytes with immunohistochemical positivity for S100, vimentin, EMA, galectin-3, and antimitochondrial antibodies (Roncaroli et al., 2002). Although typically described as positive in SCO, galectin-3 is generally not useful in the workup of primary sellar neoplasms, as pituicytoma, meningioma, nerve sheath tumors, granular cell tumor, and even metastases have consistently expressed galectin-3 (Rodriguez et al., 2008). The cases in which bcl2 immunohistochemistry has been performed on SCO have largely showed negative expression; however there are two previously reported cases besides our case with immunopositivity for bcl2 (Vajtai et al., 2006; Vajtai, Beck, Kappeler, & Hewer, 2011).

More recently, TTF-1 nuclear positivity has also been described in SCO (Lee, Tihan, Scheithauer, Zhang, & Gonatas, 2009; Mlika et al., 2011; Ogawara et al., 2011; Vajtai et al., 2011); however this is not specific to SCO as TTF-1 is also expressed in other primary brain tumors, and generally those arising in the sellar and third ventricular regions (Kristensen, Nielsen, & Vyberg, 2011; Lee et al., 2009; Zamecnik, Chanova, & Kodet, 2004). It is important to note that these studies have described variable expression of TTF-1 in SCO and other primary brain tumors with both the SPT24 and the 8G7G3/1 clones; in general if positive, the SPT24 clone tends to show stronger expression than the 8G7G3/1 clone.

Pathogenesis of spindle cell oncocytoma
Since the original description of SCO, its immunophenotype and ultrastructural features have led to the speculation that SCO arises from the folliculostellate cells (FSCs) of the adenohypophysis (Roncaroli et al., 2002). FSCs are non-hormone secreting spindle-shaped cells that comprise 5-6% of the normal anterior pituitary and were originally thought to play a supportive role as sustentacular cells. It is now known that they have a multifaceted function with involvement in hormone production, ion regulation, and the immune response, and it has been suggested that they also may act as multipotent stem cells with the capacity to transdifferentiate (Horvath & Kovacs,
2002; Inoue, Mogi, Ogawa, Tomida, & Miyai, 2002; Kloub et al., 2005), including the ability to undergo epithelial transformation in the renewal of endocrine parenchyma. However, the lack of SCO to morphologically recapitulate the various developmental or physiologic states of FSCs has argued against an origin from FSCs (Vajtai et al., 2011). Others have suggested that the clinicopathologic similarities between pituitary adenomas, pituicytomas and SCO indicate a common origin from FSCs, with divergent differentiation occurring during neoplastic transformation (Ulm, Yachnis, Brat, & Rhoton, 2004). More recently, it has been proposed that the finding of diffuse TTF-1 positivity in spindle cell oncocytomas, granular cell tumors, and pituicytoma indicates that these three neoplasms are derived from a common lineage of pituicytes (TTF-1 positive) and not from folliculostellate cells (TTF-1 negative). Non-neoplastic pituicytes are also known to have five distinct ultrastructural variants that could give rise to these three morphologic types of tumors (Lee et al., 2009; Mete, Lopes, & Asa, 2013).

Although the description of SCO includes a variable number of epithelioid cells admixed with the spindled cells, only rare case reports have commented on epithelial differentiation in SCO. One case report described a variant of SCO with focal follicle-like architecture amongst the fascicles of spindle cells, with ultrastructural evidence of follicular lumina lined by specialized epithelial cells with surface microvilli and apical tight junctions. This case also demonstrated immunopositivity for bcl2; however it lacked immunolabeling for cytokeratin markers (Vajtai et al., 2011). A second case also exists of a SCO with spindled and epithelioid cells with ultrastructural evidence of follicular structures identical to pituitary follicles, with features of endocrine differentiation (Coire et al., 2009; Horvath, Coire, Kovacs, & Smyth, 2010). Horvath et al. also described a sellar neoplasm that could not be defined histologically due to extensive radiation-induced fibrosis, but ultrastructurally showed extensive follicular structures recapitulating fetal human pituitary tissue and was thought to represent a tumor of folliculostellate cells (Horvath et al., 2010). Our case may represent an additional variant wherein a trabecular and papillary glandular architecture with cuboidal-to-columnar cytology is seen throughout, with extensive immunolabelling for a variety of epithelial markers. This morphology and immunophenotype have not previously been described before in SCO, and may represent evidence of nonendocrine epithelial transformation in a tumor arising from folliculostellate stem cells or pituicytes.

**Birt-Hogg-Dubé Syndrome & Oncocytoma**

Birt-Hogg-Dubé (BHD) is a rare autosomal dominant hamartomatous syndrome due to a mutation in the folliculin (FLCN) gene. It is typically associated with the development of renal oncocytoma, dermatologic lesions (fibrofolliculomas), multiple lung cysts and spontaneous pneumothorax (Menko et al., 2009). Although extra-renal oncocytomas have been described in BHD patients at various sites including the endocrine organs (thyroid, parathyroid, and adrenal glands) and the salivary glands (Menko et al., 2009), to the best of our knowledge, this is the first case report of an oncocytic neoplasm of the pituitary occurring in a patient with BHD syndrome.

While the pathogenesis of BHD is not fully understood, it is hypothesized that the mutation in FLCN leads to downregulation of folliculin and subsequent dysregulation of mammalian target of rapamycin complex 1 (TORC1), with a predisposition towards renal tumorigenesis. Specifically, patients with BHD are at seven-times increased risk of developing chromophobe and oncocytic renal neoplasms (Zbar et al., 2002). FLCN is ubiquitously expressed in human tissues, and interestingly, Hasumi et al. have recently demonstrated a high level of mRNA expression of FLCN
within the human pituitary (Hasumi et al., 2008). Even more compelling is a study that demonstrated activation of mammalian target of rapamycin complex 2 (mTORC2) and the sonic hedgehog pathway in a SCO of the adenohypophysis (Alexandrescu et al., 2012), indicating a potential link between folliculin deficiency and activation of mTOR in the development of SCO. Interestingly, there is also a case report of a hypothalamic papillary tumor occurring in a patient with tuberous sclerosis, again implicating mTOR activation in the molecular pathogenesis of a neoplasm with an overlapping histologic and immunohistochemical appearance to our case (Hasselblatt et al., 2008).

In general, oncocytomas are a group of tumors that have a distinct eosinophilic and granular appearance due to the intracytoplasmic accumulation of mitochondria, and essentially all neoplasms are capable of accumulating mitochondria. It has long been hypothesized that the morphology of these tumors represents metaplastic transformation of the neoplastic cells due to dysfunction in mitochondrial oxidative metabolism (Chang & Harawi, 1992; Romero-Rojas et al., 2011). Studies have shown increased expression of mitochondrial genes and their transcriptional regulators, as well as mitochondrial DNA rearrangements in renal oncocytomas; taken together it is has been hypothesized that impaired mitochondrial function results in a compensatory increase in mitochondrial expression (Hasumi et al., 2012). Recently, it has been demonstrated in FLCN-knockout mice that FLCN deficiency and the subsequent increased expression of PPARC1A (peroxisome proliferative-activated receptor gamma coactivator-1 alpha) leads to increased mitochondrial function and oxidative metabolism with oncocytic hyperplastic transformation of FLCN-null kidney cells. This evidence suggests that the changes in mitochondrial oxidative metabolism may contribute to tumor initiation and/or progression, with FLCN-null cells having a growth advantage in this metabolic environment (Hasumi et al., 2012). As most studies have involved renal oncocytomas, it is not known whether similar mechanisms are at play in the pathogenesis of extra-renal oncocytomas.

To the best of our knowledge, an oncocytic sellar neoplasm with epithelial and papillary differentiation and an immunohistochemical profile similar to spindle cell oncocytoma has not yet been described in the literature, let alone in an individual with BHD syndrome. Its unusual appearance widens the histologic spectrum of primary sellar neoplasms and may represent a novel entity or a variant of spindle cell oncocytoma. The epithelial/oncocytic differentiation is intriguing and may give credence to further evidence of SCO arising from the differentiation of folliculostellate cells, or possibly even pituicytes. While this case report is not aimed to examine the pathogenesis of BHD nor SCO, this unique case may serve as an impetus to study the possible common pathophysiology of these two rare disorders.

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None

**Conflict of Interest**

None
References


Matyja, E., Maksymowicz, M., Grajkowska, W., Olszewski, W., Zielinski, G., & Bonicki, W. (2010). Spindle cell oncocytoma of the adenohypophysis - a clinicopathological and ultrastructural study of two cases. Folia Neuropathologica / Association of Polish Neuropathologists and Medical Research Centre, Polish
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