Spindle cell oncocytoma of adenohypophysis: Cytogenetics and \(\beta\)-catenin findings with pathology differential diagnosis and review of the literature

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**Abstract**

Spindle cell oncocytoma (SCO) is an extremely rare neoplasm arising in the anterior pituitary. We report comprehensive pathological description of a case of SCO in a 60-year-old male who presented with nausea, vomiting and severe hyponatremia, and pan hypopituitarism. Magnetic resonance imaging (MRI) showed a 3.1 \(\times\) 2.3 \(\times\) 2.0 cm homogeneously enhancing bilobed mass within the sella turcica and suprasellar cistern. Intraoperative frozen section and touch imprint cytology showed cohesive spindle cells with abundant oncocytic cytoplasm. Histologic sections revealed the tumor was composed of interlacing fascicles of compact spindled cells with abundant dense oncocytic cytoplasm. There was no mitosis or necrosis present. Ki-67 index varied in areas, with an average of 3%. By immunohistochemistry (IHC), the tumor cells were negative for Cam5.2, AE1/3, neuron, synaptophysin, and strongly positive for vimentin, TTF-1 and EMA. S-100 showed focal weakly positivity. By electron microscopy (EM), the cytoplasm of the spindle cells contained numerous abundant, back-to-back, uniform, round, normal-sized mitochondria with long and lamellar cristae. Beta-catenin showed diffuse membranous and partial cytoplasmic positivity. Cytogenetic analysis showed extra copies of chromosome 1 (74%, up to 8 copies), and loss of chromosome 2 (35%). The histogenesis, classification and differential diagnosis are discussed.

**Keywords:**
Spindle cell oncocytoma, Adenohypophysis, Immunohistochemistry, Differential diagnosis, Pathogenesis, Chromosomal abnormality

1. Background

Spindle cell oncocytoma (SCO) of the adenohypophysis is a rare neoplasm of the anterior pituitary. It was first reported as a new central nervous system neoplasm in 2002 \([1]\). To date, there are 26 cases reported in the literature \([2,3]\). Although the folliculo-stellate cell (FSC) origin had been proposed, the exact tumor histogenesis is controversial \([4]\) and the pathogenesis of the neoplastic process has yet to be studied. We describe comprehensive pathological description of a case study of SCO\(^1\) with the first report of cytologic findings, along with additional immunohistochemistry (IHC) and electron microscopy (EM), and fluorescent in-situ hybridization (FISH) studies.

2. Report of a case

2.1. Clinical characteristics

The patient was a 60-year-old male who presented a two-week history of nausea, vomiting, fatigue and syncopal episodes. Laboratory findings revealed severe hyponatremia (sodium level of 112 mmol/L), and endocrine investigation revealed panhypopituitarism \([3]\). Magnetic resonance imaging showed a 3.1 \(\times\) 2.3 \(\times\) 2.0 cm, homogeneously enhancing and bilobed mass within the sella turcica and suprasellar cistern, with a mass effect on the optic chiasm but no cavernous sinus extension. Endoscopic endonasal transphenoidal surgical resection revealed a very vascular whitish-yellow mass with soft consistency, and there was extensive intraoperative bleeding. There has been no evidence of tumor recurrence on serial brain imaging after 18 months of follow up after surgery \([3]\).

2.2. Cytologic and surgical pathology findings

Intraoperative frozen section and touch imprint cytology showed cohesive spindle cells with abundant oncocytic cytoplasm (Fig. 1). Histologic sections demonstrated the tumor was composed of interlacing fascicles of moderately compact spindle cells with a minimal stromal component. The spindle cells had abundant dense and granular eosinophilic cytoplasm. The nuclei were oval to elongated and centrally located with fine chromatin. Some of the nuclei contained a single centrally located nucleolus. In some areas, the nuclei were large and pleomorphic, and there were scattered multinucleated or binucleated cells (Fig. 1).

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There was no evidence of mitosis or tumor necrosis. Scattered intercellular microcyst-like open spaces, as well as intracytoplasmic vacuoles were present. There were abundant microvasculatures within the tumor parenchyma outlined by CD31 immunohistochemical staining (Fig. 2). There was no reactive lymphocytic infiltration or other inflammatory response. The MIB-1 positivity varied, but was higher in the areas with more cellular pleomorphism. The average of MIB-1 index was approximately 3% (Fig. 2).

2.3. Immunohistochemical findings

The neoplastic spindled cells were negative for Cam5.2 and AE1/3 and strongly positive for EMA and vimentin. S-100 was focally and weakly positive. TTF-1 staining demonstrated strong nuclear positivity (Fig. 3). The neoplastic cells are also negative for NF, NeuN, GFAP and synaptophysin. β-catenin showed diffuse membranous and partial cytoplasmic positive staining (Fig. 4).

2.4. Electronic microscopic findings

By electron microscopy, the cytoplasm of the spindle cell contained abundant back-to-back uniform and round normal-size mitochondria, having long and lamellar cristae in parallel array. Lysosomes were identified in the cytoplasm. The spindle neoplastic cells had reduplicated basal lamina, and intercellular tight junctional apparatus. There were no cytoplasmic neurosecretory particles, intermediate filament or other organelles (Fig. 5).

2.5. Fluorescent in-situ hybridization findings

Fluorescent in-situ hybridization (FISH) analysis was performed by using probes for chromosomes 1, 2, 7, and 17 respectively. Specifically, the probes included a chromosome 1 centromeric probe (D1Z5), a probe for the ALK gene at 2p23, a centromeric and q arm probe on chromosome 7 (D7Z1 and D7S522), and a centromeric and q arm probe on chromosome 17 (D17Z1and HER-2/neu). One hundred cells with each probe were scored. All probes showed some degree of aneuploidy (both loss and gains of chromosomes). There were loss and gain of chromosome 1, 2, 7, 17. The most noteworthy findings was the high percentage of extra copies of chromosome 1 (74%, up to 8 copies), and the high percentage of loss of chromosome 2 (35%) (Fig. 6, Table 1).

3. Discussion

Spindle cell oncocytoma is a rare pituitary neoplasm with only a few previous case reports [1,4–15]. Patients with SCO are most commonly middle aged to older adults, with no apparent gender predilection. Patients present with a pituitary mass lesion that is clinically indistinguishable from a pituitary adenoma, and symptoms are due to tumor extension to the pituitary causing hypopituitarism, or mass extension to surrounding structures [10].

Histologically, most of the reported cases had tumor cells which were bland and devoid of nuclear atypia. Most of the reported cases had no or rare mitotic activity accounting for less than one mitotic figure per 10 high-power fields and a Ki-67 index was less than 5%. A recent study evaluated four SCO cases by exome sequencing and revealed that these tumors have low mutation rate and copy-neutral profile [16]. These results support low-grade neoplasm classification of SCO. However, there were some cases reported with nuclear atypia and pleomorphism, demonstrated by slight hyperchromasia, coarse chromatin, and solitary eosinophilic nucleoli [1]. Furthermore, in a few reports, the Ki-67 indices were higher than 5%, ranging from 7% to 20%. The higher mitotic rates and Ki-67 indices were associated with larger tumors [12] and with tumor recurrence [12,15]. This raises the question as to whether some of the large
spindle cell oncocytoma with high Ki-67 index, should be classified as atypical spindle cell oncocytoma, in a fashion that is similar to atypical meningioma, and classified as a WHO grade-2 tumor that benefit from more aggressive treatment such as post-surgery chemotherapy or radiation treatment. Robust MAPK activity in SCO has been recently described as evidenced by strong phospho-ERK staining in SCO. This suggests that MAPK signaling pathway could serve as a potential therapeutic target for aggressive tumors refractory to surgical resection [16].

There was abundant well-organized capillary vasculature within the tumor parenchyma demonstrated by CD31 immunohistochemistry. The above result is consistent with previous reports noting that the tumor appeared to have abundant vasculature [13], resulted in the extensive intraoperative bleeding [6,11], which was also present in our case.

There are several tumors in the sella and suprasellar region which enter into the differential diagnosis of spindle cell oncocytoma. These include pituicytoma, granular cell tumor, paraganglioma, schwannoma and meningioma. Pituicytoma is a glial cell neoplasm, with a spindled architecture and fibrillary background, and is GFAP positive. Granular cell tumor has an abundant eosinophilic cytoplasm similar to SCO. However, the cytoplasm of the granular cell tumor has prominent granularity, with distinct cell borders and nuclei that are often small and round. The most distinct histological feature of paraganglioma is the “zellballen” architecture and nuclear chromatin with a “salt and pepper” quality. Although the histologic features in each neoplasm discussed above can help in suggesting the correct diagnosis, the definitive diagnosis often is dependent on immunohistochemistry. The panel could include chromogranin, epithelial membrane antigen, GFAP, synaptophysin, TTF-1, and vimentin. The dual positivity of TTF-1 and EMA supports diagnosis of spindle cell oncocytoma for a sellar tumor only when oncocytic cytoplasm features are clearly present, since there was a recent study revealed that the presence of dual positivity of TTF-1 and EMA can also be seen in some cases of granular cell tumor and pituicytoma [4]. Therefore, cytologic and histologic correlation with the IHC finding is important, and ultrastructural examination could provide additional information for the correct final diagnosis.

The Folliculo-stellate cell (FSC) was proposed to be the precursor of the spindle cell oncocytoma of the adenohypophysis, because the tumor cells have the features that are seen in the normal FSC, such as positive stain for S100 and EMA, and electron microscopic evidence of desmosomes and intermediate junctions. FSC is a star-shaped, follicle-forming cell in the anterior pituitary gland that was first identified by electron microscopy (EM) as non-endocrine agranular cells. FSC is known to be positive for S-100 protein [17], and therefore was thought to act as sustentacular elements similar to those observed in other endocrine organs. However, one case showed the spindle cells forming cohesive clusters that was indistinguishable from pituitary follicles, and another reported case revealed that a minority of tumor cells exhibited endocrine differentiation evidenced by the presence of prominent Golgi complex and some secretory granules with electron microscopy [12]. Recently, a study demonstrated that the tumor cells expressed neuronal differentiated markers such as SMI-311, CD44 and nestin, suggesting a neuron precursor origin of SCO [5].

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**Fig. 3.** Immunohistochemical staining patterns of spindle cell oncocytoma. The spindle cells are diffusely and strongly positive for vimentin (A) and EMA (B), locally weak positivity for S-100 (C) and diffuse and strong positivity for TTF-1, with unstained endothelial spindle nuclei in the background (D).

**Fig. 4.** Immunohistochemistry of β-catenin shows membranous and partial cytoplasmic staining, but nuclear staining is absent.
Fig. 5. Ultrastructure features of spindle cell oncocytoma. Prominent nucleoli and marked accumulation of mitochondria in the cytoplasm (A); Serial degenerated mitochondria and osmium-rich membrane rolls (B); intercellular tight junctional apparatus (C); reduplicated basal lamina of the cellular membrane (D); lysosomes (E).

Fig. 6. Extra copies of chromosome 1 and loss of chromosome 2. Fluorescent in-situ hybridization analysis was performed by using a chromosome 1 centromeric probe (D1Z5), and a probe for the ALK gene at 2p23. The result showed that the tumor cells gained extra copies of chromosome 1 up to 8 copies (A) and loss of chromosome 2 (B). The chromosome 1 centromeric probe and ALK probe are red, CEP probe is green. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)
There was a recent study which proposed that spindle cell oncocytoma and granular cell tumors of the pituitary are all variants of pituicytoma, since they are positive for TTF-1, sharing a common lineage [4]. In the most recent WHO classification and the pituicytoma, since they are positive for TTF-1, sharing a common origin oncocytes and granular cell tumors of the pituitary are all variants of pituicytoma. In one of seven cases of spindle cell oncocytomas and one of three cases of granular cell tumors in a series study [4]. In our case, GFAP is negative. We favor that spindle cell oncocytoma, pituicytoma and granular cell tumor may all arise from multipotent stem cells, such as a progenitor cell of FSCs in the pituitary.

Our cytogenetic study showed that the pituitary tumor had a high percentage of extra copies of chromosome 1 and a high percentage of loss of chromosome 2. This finding has not been previously reported in oncocyotic neoplasms of other sites. It is well established that oncocytomas in such as kidney have characteristic loss of chromosome 1 [18]. This suggests that the spindle cell oncocytoma of the adenohypophysis is not a typical oncocyto of the chromosomal level. Extra copies of chromosome 1 maybe a distinctive chromosomal abnormality of the spindle cell oncocytoma and have diagnostic utility, and potentially provide evidence in the histogenesis of this neoplasm [4] which warrant further investigation.

As a spindle cell neoplasm, SCO has architectural and cytological features of mesenchymal differentiation with the strong IHC positivity for vimentin as seen in this case. Although the tumor is negative for cytokeratin, the tumor cells maintain intercellular tight junctional apparatus as demonstrated by EM. It is well known that TGF-β signaling and β-catenin play a significant role in the transdifferentiation of epithelial cells into mesenchymal cells [19], therefore, we performed β-catenin IHC and demonstrated diffuse positivity with a cell membrane pattern and partial cytoplasmic positivity, with absence of nucleus staining. The membrane and cytoplasmic expression of β-catenin in spindle cell oncocytoma suggests that SCO is an epithelial neoplasm with mesenchymal differentiation.

Table 1

<table>
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<th>Chromosome</th>
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