

# Cauda Equina Paranglioma with Ependymoma-Like Histology: A Case Report

## *Kauda Ekuinada Yerleşmiş Ependimoma Benzeri Histoloji Gösteren Paranglioma: Bir Olgu Sunumu*

Ahmet MIDI<sup>1</sup>, Arzu Nese YENER<sup>1</sup>, Aydın SAV<sup>3</sup>, Rahmi CUBUK<sup>2</sup>

<sup>1</sup>Maltepe University, Faculty of Medicine, Department of Pathology, Istanbul, Turkey

<sup>2</sup>Maltepe University, Faculty of Medicine, Department of Radiology, Istanbul, Turkey

<sup>3</sup>Acibadem University, Faculty of Medicine, Department of Pathology, Istanbul, Turkey

Correspondence address: Ahmet MIDI / E-mail: ahmetmidi@yahoo.com

### ABSTRACT

Paranglioma affecting the cauda equina region is very rare and can be misinterpreted as an ependymoma which is more common at this site. A 38-year-old woman with a paranglioma in the cauda equina is presented. MRI revealed a well-circumscribed, intradural, extramedullary tumor nodule with the dimensions of 2.5x1x1 cm. The patient underwent L3 laminectomy and total excision of the tumor. The tumor was diagnosed as ependymoma and the patient was decided to undergo adjuvant radiotherapy. The patient applied to our medical center for a second opinion. Histopathologically, her tumor was found to be a paranglioma with ependymal features. Therefore no adjuvant therapy was applied. There is no evidence of recurrence or metastases for 15 months after her operation. Paranglioma in the cauda equina/ filum terminale is very rare and can be misdiagnosed as ependymoma especially when it exhibits ependymoma-like histology. This rare form of paranglioma behaves like a WHO grade I tumor of CNS like classic paranglioma. No recurrence or metastasis is expected when it is totally resected. Morphology can be misleading hence immunohistochemistry and/or ultrastructural study is necessary for correct diagnosis.

**KEYWORDS:** Paranglioma, Ependymoma-like histology, Filum terminale, Immunohistochemistry, CD 99

### ÖZ

Kauda ekuina yerleşimli paranglioma oldukça nadir olup, bu lokalizasyonda daha sık görülen ependimoma ile karışabilir. Bu çalışmada kauda ekuina yerleşimli, ependimoma benzeri histoloji gösteren paranglioma olgusunu sunmayı amaçladık. 38 yaşındaki bayan hastaya, MR yöntemi ile saptanan 2,5x1x1 cm boyutlarda, intradural-ekstramedüller yerleşimli, iyi sınırlı kitle nedeniyle bir başka merkezde L3 laminektomi ve kitle eksizyonu uygulanmıştır. Burada tümör, ependimoma olarak rapor edilmiştir ve hastaya adjuvan radyoterapi verilmesi kararı alınmıştır. Hasta, tanı ve tedavisi konusunda ikinci bir görüş almak üzere merkezimize başvurmuştur. Merkezimizde yapılan patolojik inceleme ve immünohistokimyasal boyamalar sonucu, tümörün ependimoma benzeri histoloji gösteren paranglioma olduğu rapor edilmiştir. Bunun üzerine hastanın ek tedavi almamasına karar verilmiştir. Hastanın, ameliyatından sonraki 15 aylık izlemi sonucunda nüks ya da metastaz bulgusu izlenmemektedir. Kauda ekuina/filum terminale yerleşimli paranglioma oldukça nadir olup özellikle ependimoma-benzeri histoloji gösteren olan olgular, ependimoma ile karışabilmektedir. Bu tür olgularda klinik seyir, SSS tümörleri-WHO Sınıflamasında yeralan derece I tümörlerdeki gibi olup, tedavide kitlenin total eksizyonunun yapılması yeterlidir. Morfolojik bulgular yanıltıcı olabileceği için immünohistokimyasal ve/veya ultrastrüktürel yöntemler, kesin tanı için gereklidir.

**ANAHTAR SÖZCÜKLER:** Paranglioma, Ependimoma-benzeri histoloji, Filum terminal, İmmünohistokimya, CD99

### INTRODUCTION

Paranglioma (PG) is the neoplasm of dispersed neuroendocrine system that affects a variety of anatomic sites mainly head and neck, mediastinum and retroperitoneum (10). PGs of the central nervous system (CNS) are uncommon and usually arise from the cauda equina/filum terminale region (18) or less commonly from the spinal nerve roots (14,20). These are WHO grade I neoplasms and the prognosis is excellent when totally resected (18). Ependymoma, a histologically WHO grade II-III glial neoplasm is also well documented in the cauda equina region and it may cause a diagnostic confusion.

We report a PG of the filum terminale featuring ependymoma-like areas within the tumor. The case was initially misdiagnosed as ependymoma at another medical center. We emphasize the microscopic similarity of the PG and ependymoma and the importance of employing the appropriate immunohistochemistry to make an accurate final diagnosis.

### CASE REPORT

#### *Clinical findings*

A thirty eight-year-old woman applied to a neurosurgery clinic with a 9-month history of progressive left-sided leg pain with difficulty in ambulation. Magnetic resonance imaging

(MRI) of the lumbosacral spine demonstrated an intradural, extramedullary well-circumscribed, tumor nodule with the dimensions of 2.5x1x1 cm which revealed homogenous contrast enhancement in the region of the left filum terminale (Figure 1A, B). The patient underwent L3 laminectomy followed by total microsurgical excision of the lesion.

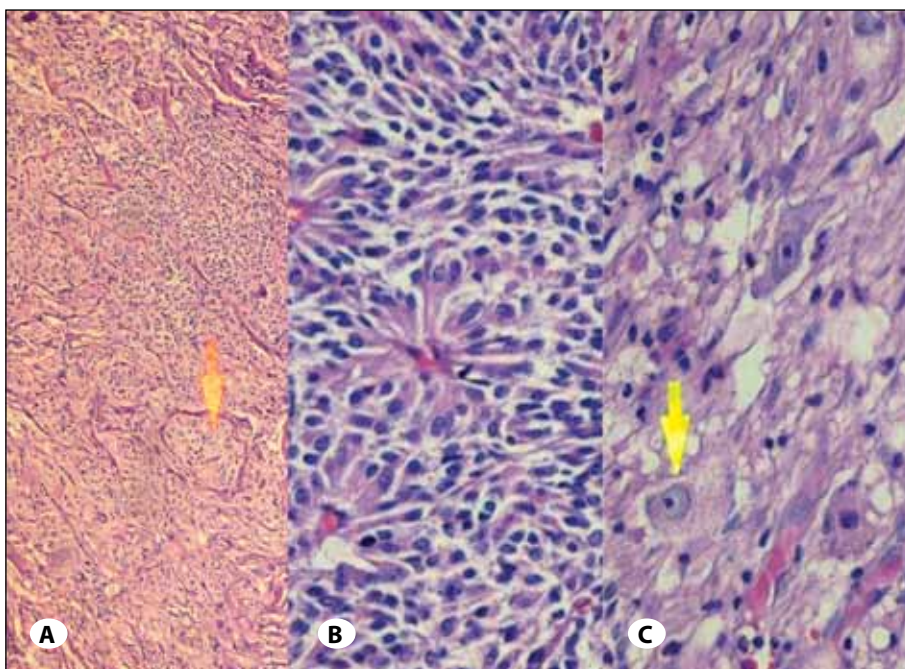
### Pathology findings

The specimen was prepared and evaluated at the department of pathology in that medical center. Gross inspection revealed a grayish-white tumor with dimensions of 2.5x1x1 cm and

that was moderately hard in consistency. Based on the histopathological findings and focal immunohistochemical expression of GFAP, the case was diagnosed as ependymoma and the patient was decided to undergo adjuvant radiotherapy. At this point, she needed to have a second opinion for her pathology. All paraffin blocks from the patient's tumor were sent to us to be reviewed. Her sent-in material to our institute showed two distinct morphologies, consisting of PG-like areas and ependymoma-like areas. The former pattern was represented with lobules and nests of uniform chief cells encompassed by flattened layer of sustentacular cells



**Figure 1A, B:** Axial/ Sagittal T2/T1-weighted images show well circumscribed intradural mass with contrast enhancement at L3-L4 level.



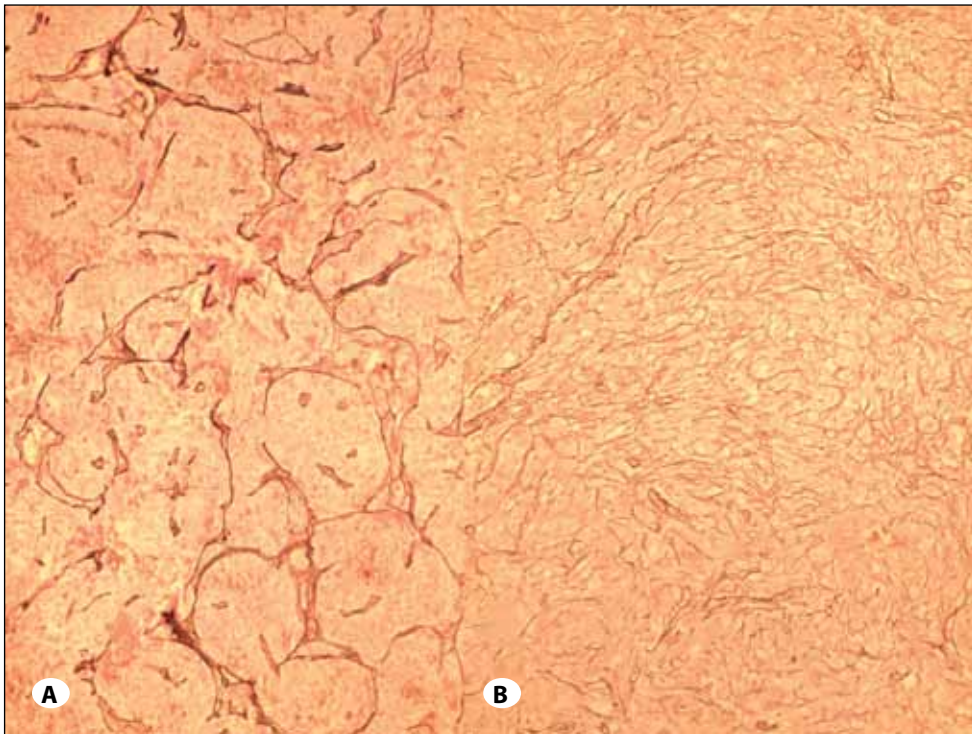
**Figure 2:** **A)** Typical “Zellballen” and surrounding fibrovascular stroma, characteristic of PG (H&E 200x), **B)** Ependymoma-like areas representing with pseudorosette formation (H&E 200x), **C)** Ganglionic cells in the paraganglionic areas (H&E 400x).



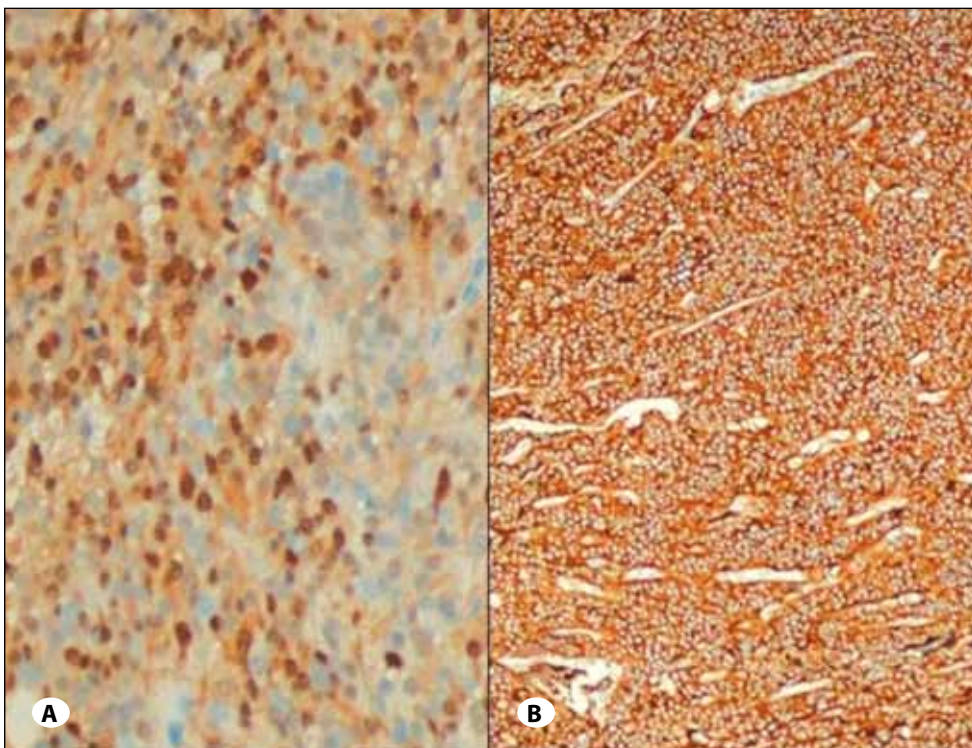
(Figure 2A). The latter pattern consisted of ependymoma-like areas with typical pseudorosettes (Figure 2B). There were also numerous ganglionic cells within the tumor (Figure 2C). Gomori / Wilder's reticulin stain showed septate delineating Zellballen (Figure 3A, B). An immunohistochemistry panel was applied.

#### **Immunohistochemical Markers and Staining Method**

Immunohistochemical staining was performed using the peroxidase-anti-peroxidase technique using the following antibodies; glial fibrillary acidic protein (GFAP; Dako, N1506), S100 protein (Novocastra, RTU-S100p), epithelial membrane



**Figure 3: A)** Gomori reticulin stain showing septate delineating Zellballen in typical paraganglionic areas (200x), **B)** Gomori reticulin staining in areas with ependymoma-like histology (200x).



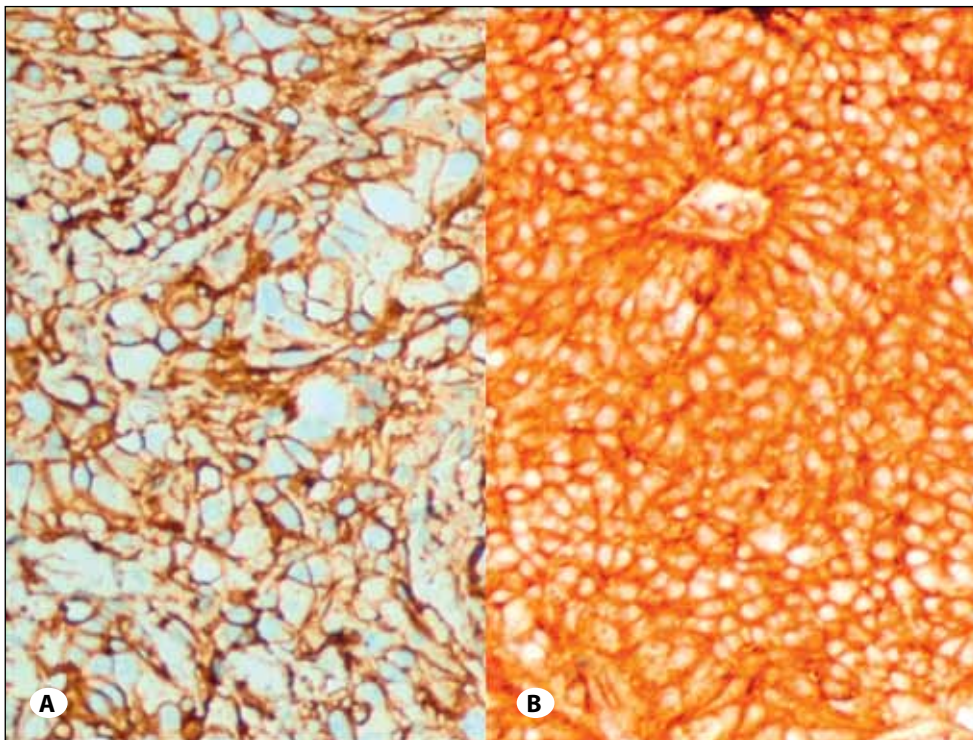
**Figure 4: A)** Nuclear and cytoplasmic staining for S100 (400x), **B)** Positivity for SYN (200x).



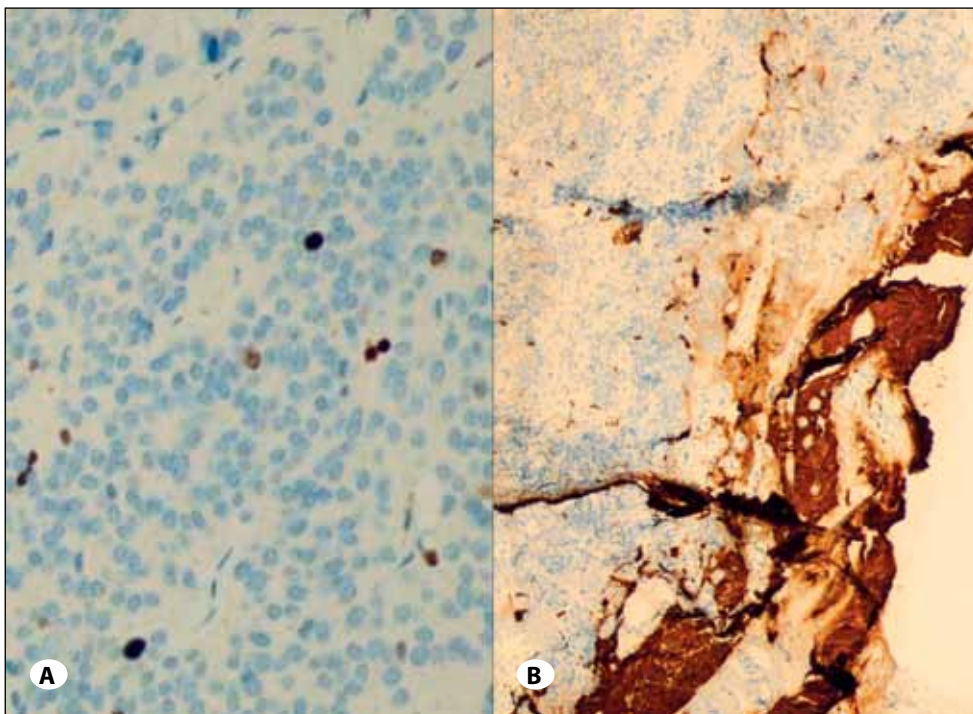
antigen (EMA; Dako, N1504), neuron filament protein (NFP; Dako, N1591), synaptophysin (Novocastra, RTU-SYNAP-299), vimentin (BioGenex San Ramon, CA), Chromogranin A (Novocastra, RTU-CHROM), CD99 (Dako, N1593) and Ki-67 (RTU, Neomarkers, RM-9106-R7).

### Immunohistochemistry findings

The chief and ganglionic cells expressed synaptophysin (SYN) (Figure 4B) and chromogranin A (CGA) whereas sustentacular cells were positive for S100 protein in PG areas (Figure 4A). Strong biphasic expression of CD99 in two above-mentioned parts of the tumor was observed



**Figure 5: A)** CD99 positivity in typical paraganglionic areas (x400),  
**B)** CD99 positivity in ependymoma-like areas (400x).



**Figure 6: A)** Ki67 labeling index was 3% (200x),  
**B)** GFAP immunoreactivity in normal glial tissues surrounding the tumor (40x).

(Figure 5A,B). Ki-67 labeling index was 3% throughout the lesion (Figure 6A). Immunohistochemistry (IHC) repeated twice with external positive controls was negative for GFAP except for focal immunoreactivity in normal glial tissues surrounding and in a few flattened sustentacular cells (Figure 6B). IHC stains negative were EMA, NFP and pancytokeratin. Immunohistochemical staining results are shown in Table II. With the histological and immunohistochemical findings, we diagnosed the case as "paraganglioma with ependymal morphology". She did not undergo any adjuvant therapy and has been doing well for the last 15 months after her operation.

## DISCUSSION

Paragangliomas of the CNS are relatively rare neoplasms which usually present as spinal intradural tumors (18). They usually arise in the cauda equina/filum terminale region comprising 3.5 % of all cauda tumors (17,18,20) and in the lumbar region as well (14). Only fifteen cases in the thoracic region (18, 22) and two in the cervical region have been reported to date (18).

Radiographically, cauda equina PGs lack specific features. MRI shows a sharply circumscribed mass that is hypo- or isointense to the spinal cord on T1-weighted images and markedly contrast enhancing and hyperintense on T2-weighted images. They therefore appear similar to other cauda equina tumors such as ependymoma (18,22). Occasionally, MRI may reveal serpentine, congested, ectatic vessels and a low signal intensity rim ("cap sign") on T2-weighted images which are considered diagnostically helpful clues, given the vascularity of PGs compared to that of other cauda equina tumors (18). We did not observe these clues in our case and she was operated on with preoperative diagnosis of well circumscribed intradural, extramedullary tumor without having any further distinction.

As elsewhere in the body, PGs are well-differentiated tumors composed of chief cells (type I) with eosinophilic and finely granular cytoplasm in nests or lobules (Zellballen), surrounded by an inconspicuous, single layer of sustentacular cells (type II). The Zellballen are surrounded by a delicate capillary network (18). Nuclear pleomorphism is generally mild and scattered mitotic figures can be seen. Besides their classical alveolar pattern (Zellballen), they sometimes exhibit a variety of histological features with spindle cells (14), ganglionic cells (21) or with melanotic, carcinoid tumor-like growth patterns (20) which may cause a diagnostic problem.

Histopathological similarity between PGs and ependymomas in the cauda equina region may lead to diagnostic confusion especially when a tumor shows both paraganglionic and ependymal differentiation (2) or when the lesion contains areas with ependymoma-like morphology but still revealing PG-like immunohistochemistry. The latter condition is quite rare and to our knowledge, only a few cases of PGs with ependymoma-like histology have been reported to date (17,19,20). This rare entity should be kept in mind to avoid any misdiagnosis of ependymoma which is known to have a more aggressive course.

Immunohistochemistry and/or ultrastructural study should be done to give an accurate diagnosis. The markers mainly expressed in chief cells in PG are NSE, SYN and CGA whereas in sustentacular cells they are S100 and occasionally GFAP (18). In our case, we observed coexistence of strong positivity for NSE and SYN and weak to moderate positivity for CGA in chief cells and strong positivity for S100 in sustentacular cells. GFAP was also expressed weakly in the latter and also in the surrounding glial tissues. Such a weak positivity of GFAP may have lead the former pathologist to think the tumor as an ependymoma. We took into consideration that the ependymal tumors are far more common in this region than PGs with the incidence rate of roughly fifty percent of all ependymomas located at the spine levels (16). However, ependymomas exhibit their glial heritage in the form of GFAP immunoreactivity mainly in pseudorosettes (16). GFAP is diffusely expressed in 90-100% of axial (5,15) and 83% of extra-axial ependymomas (5). Alternatively ependymoma cells may sometimes be nonreactive for GFAP both in classic (9) or in anaplastic ependymoma (12). In our case, ependymoma-like areas consisted of WHO grade I histological features without having any anaplasia criteria. We still considered the histological findings with all the IHC findings as a whole. Histopathological and immunohistochemical features of PG and ependymoma are given in Tables I, II.

Ganglion cells, present in nearly half of paragangliomas affecting the CNS (20), are fully mature elements that lie in clusters within a connective tissue matrix or are intra-acinar and in transition to chief cells (1,18,21). They were also scattered throughout the lesion in our case.

CD99, a product of MIC2 gene which encodes for a transmembrane glycoprotein has been less extensively studied in ependymal neoplasms (3,11) and PGs (4,7). This marker is expressed in a variety of human tissues including all leukocytes mainly cortical thymocytes, Ewing's sarcoma/PNET cells, granulosa cells of the ovary, Sertoli cells of the testis and the CNS ependymal cells. Although CD99 was suggested as a marker to differentiate between EP and non ependymal tumors, its usefulness is still under debate. Mahfouz et al reported weak or moderate positive CD99 staining in non ependymal CNS tumors (11). Similarly, Choi et al studied this marker in non ependymal tumors mainly consisting of astrocytic, oligodendroglial and choroid plexus neoplasms and they found a variety of staining patterns such as incomplete membranous staining, focal or diffuse staining (3).

Since we observed strong membranous CD99 positivity throughout the tumor in our case, we considered of Ewing's sarcoma/PNET in differential diagnosis. The cauda equina is an extremely rare location and only about 5 cases of primary cauda equina Ewing's sarcoma/PNET have been reported to date (6,13). However, it is a tumor with highly malignant features, high MIB-1 proliferative index and with small round cell pattern which is quite different from the morphologic features of the PG.

**Table I:** Comparison of Histopathological Features of Paraganglioma and Ependymoma (1,18)

	Paraganglioma	Ependymoma
Histological pattern	Nests or lobules (Zellballen)	Gloma-like loose texture with pseudorosettes and sometimes true ependymal rosettes
Cytopathological features		
Nucleus	(Chief cells) uniform, round or polygonal shape, located centrally.	Less uniform than chief cells of PG, monomorphic, round-to-oval shape
Chromatin	Finely stripling	Salt and pepper speckling
Cytoplasm	Eosinophilic, faintly granular	Fibrillar processes
Mitotic activity	Occasional mitoses	Rare or absent
Necrosis	Focal hemorrhagic necrosis (±)	Occasional, non-palisading, geographic necrosis (±)
Electron microscopy	Typical dense core (neurosecretory) granules	Ependymal cell-like features like having cilia, blepharoblasts and microvilli

**Table II:** Comparison of Immunohistochemistry of Paraganglioma and Ependymoma

Immunohistochemical marker	Paraganglioma CC/SC	Our case CC/SC	Ependymoma
GFAP	-/rarely + *(18) or -/-	-/+	+, rarely - *(9)
S100	-/+	-/+	-
Synaptophysin	+/-	+/-	-
Chromogranin A	+/-	+/-	-
Ki-67 labeling index	variable	3%	variable
Vimentin	+/+	+/+	+
Neuron filament protein (NFP)	-/-	-/-	+
Epithelial membrane antigen (EMA)	-/-	-/-	+
CD99	variable *(4,7)	+/-	+

**Abbreviations:** **CC:** chief cells, **SC:** sustentacular cells. \*The numbers in parantheses refer to the references given at the end.

Of interest, a case of PG with strong CD99 positivity throughout the lesion was reported (7). This was a case of PG with malignant transformation simulating Ewing's sarcoma/PNET in the nasal cavity and the diagnosis was supported by gene translocation study which failed to show an essential step for definitive diagnosis of Ewing's sarcoma/PNET (7). On the other hand, a rare paratesticular PG with CD99 negativity was also described (4).

According to all these data above, it seems that CD99 is still far from being a reliable marker to differentiate classic ependymoma and classic PG. However, ependymal cells have been described as neural stem cell in origin in rodents (8). Although highly speculative, any transdifferentiation hypothesis regarding ependymal and neuroendocrine/neuronal cells in humans may exist. In this context, CD99 immunoreactivity in our case may in a way give a clue for the histogenesis of this rare morphology in PG. Another speculation on the histogenesis of this tumor was made as it might have originated from elements normally found in the cauda equina/filum terminale such as ependymal cells, ganglionic neurons and neuroblasts (2). These authors

reported a unique tumor located in the cauda equina which showed features of both ependymal and paraganglionic differentiation within the same lesion.

It should also be kept in mind that rare ependymoma cases with neuronal differentiation does also exist (15). However, this is more often in the form of focal immunorexpression of neuronal markers such as SYN, CGA and Neu-N than at the histological level. It is concluded that immunohistochemistry with multiple, reliable neuronal markers should be coupled with the convincing ultrastructural features of neuronal differentiation to support "glioneuronal" differentiation in otherwise typical ependymoma (15). In our case, we observed SYN and CGA reactivity, however constant GFAP negativity lead us to think that we are not facing a tumor of glial origin.

**CONCLUSIONS**

The diagnosis of a cauda equina tumor should not be based solely on conventionally stained sections. Histopathological similarity between ependymomas and paragangliomas may lead to a diagnostic confusion especially when a paraganglioma exhibit ependymoma-like histology. Since



ependymomas are more common tumors than paragangliomas at this location, this condition may easily be overlooked on conventionally stained sections resulting in unnecessary, or even harmful adjuvant radiotherapy of patient. Immunohistochemistry batteries consisting of a variety of antibodies and/or ultrastructural analyses are essential to make an accurate diagnosis.

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