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Clinical Study

Paragangliomas in the cauda equina region: clinicopathoradiologic findings in four cases

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Summary

Paragangliomas of the cauda equina are rare neuroendocrine tumors. Four cases of nonsecreting paraganglioma of the cauda equina, preoperatively misdiagnosed as neurinoma, are presented with an emphasis on the correlation between magnetic resonance imaging findings and pathological features. Although it is difficult to correctly diagnose paraganglioma preoperatively for intradural extramedullary tumors, especially in the cauda equina, paraganglioma should be included in differential diagnoses.

Abbreviations: CSF – cerebrospinal fluid; GFAP – glial fibrillary acid protein; GTR – gross total removal; LBP – low back pain; MIBG – metaiodobenzyl guanidine; MR – magnetic resonance; NSE – neuron specific enolase

Introduction

Extra-adrenal paragangliomas are rare neuroendocrine tumors, which can occur throughout the body. In the head and neck, they occur most commonly (more than 90% of cases) in the carotid bodies and in the jugular glomus. Paragangliomas of the central nervous system are very rare, and occur almost exclusively in the cauda equina of the spinal cord. The first description of paraganglioma of the cauda equina was made by Lerman et al. in 1972 [1]. Here we present four cases of pathologically proven paragangliomas of the cauda equina with an emphasis on magnetic resonance imaging (MRI) findings correlated vs. pathological features.

Materials and methods

We retrospectively reviewed the data collected from 703 patients with spinal cord tumors treated surgically at our hospital between 1973 and 2001. Among these, four patients were diagnosed as having a paraganglioma, all of which occurred in the cauda equina. These paragangliomas comprised 1.5% of intradural extramedullary spinal tumors (4/268 cases) and 3.8% of lumbar spinal tumors (4/104 cases). We analyzed clinical data, including medical and radiological records, and the histopathological findings of these four cases. The clinical data is summarized in Table 1.

Case 1 (Figure 1)

This 49-year-old man was transferred to our hospital with a 3-year history of intermittent low back pain. Neurological examination revealed normal power and muscular tone, no sensory or sphincter abnormality and normal reflexes. MR images of the lumbar spine demonstrated an intradural extramedullary tumor at the L3 level. Preoperatively, this lesion was misrecognized as a neurinoma. At surgery, a pinkish well-circumscribed tumor measuring $1.0 \times 1.3 \times 1.8$ cm was located intradurally with attachment to a nerve root. A significant vascular pedicle, not visualized in MR images, was also detected. Microscopic examination showed that a pseudocapsule separated the tumor into two parts. However, the pathological findings found no difference between these two parts. The tumor showed old hemorrhage, which included hemosiderin-laden macrophages, dilated vessels, Gamna–Gandy bodies and inflammation. Hemosiderin pigmentation was detected in the pseudocapsule and multiple feeding arteries were found around the tumor; these were invisible by MRI. Postoperatively, the patient's pain disappeared, and no signs of recurrence were evident after 33 months of follow-up.

Case 2 (Figure 2)

This 63-year-old woman was admitted with a 3-month history of increasing pain in the low back and posterior thigh bilaterally. A physical examination showed no significant neurological abnormalities. MR images of the lumbar spine revealed a well-demarcated intradural extramedullary mass, almost filling the entire spinal canal, at the L4-5 level, and an extratumoral cyst in the upper and lower portions of the tumor. At surgery, a soft cherry-red spherical tumor, $1.1 \times 1 \times 0.6$ cm in size, was completely excised from the filum terminale. Many vessels surrounded the tumor. Microscopically the tumor was a biphasic, densely cellular area alternating with microcystic degenerated regions containing hyalinized vessels. In the degenerated region, the cellularity

Table 1. Clinical features of the four cases

Case	Sex/age (year)	Symptom	Duration (month)	Site	Preoperative diagnosis	Size	Treatment	Follow-up (month)
1	M/49	LBP, sciatica	36	L3	Neurogenic tumor	1 × 1.3 × 1.8 cm Nerve root	GTR	33
2	F/63	LBP, sciatica	3	L4-5	Neurogenic tumor	1.1 × 1 × 0.6 cm Filum terminale	GTR	40
3	F/71	LBP, sciatica	24	L4	Neurogenic tumor	2.2 × 1.4 × 1.4 cm Nerve root	GTR	24
4	F/52	LBP, sciatica, motor weakness	10	L3	Neurogenic tumor	2.2 × 1.6 × 1.2 cm Filum terminale	GTR	71

M – male; F – female; LBP – low back pain; GTR – gross total removal.

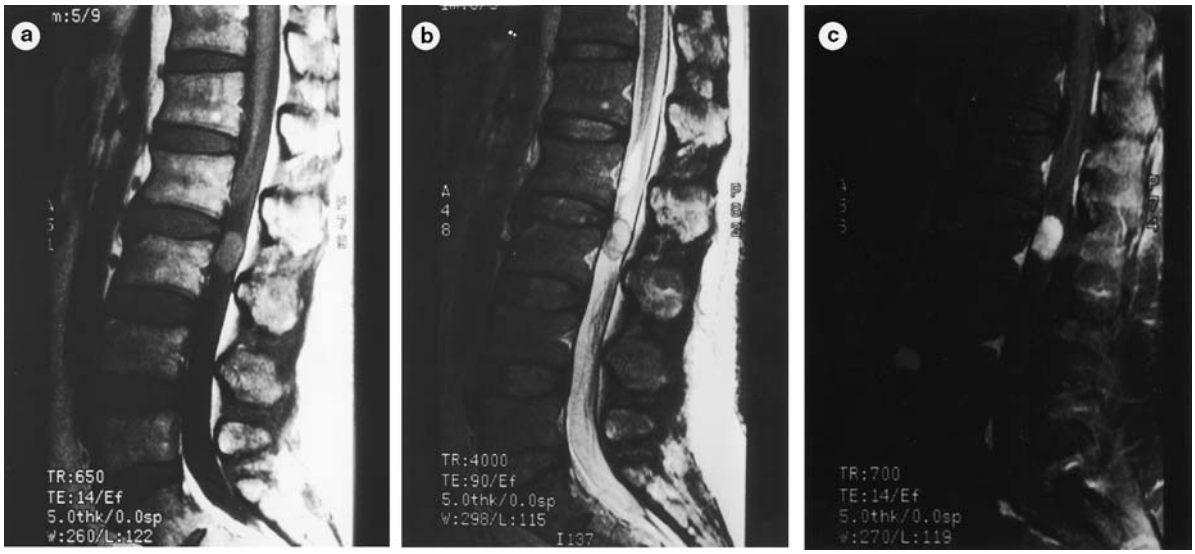

Figure 1. Sagittal T1-weighted (a), T2-weighted (b), and contrast-enhanced T1-weighted (c) MR images showing a well-defined intradural extramedullary mass at the L3 vertebral body level. There was no intratumoral cyst but an extratumoral cystic lesion irrelevant to the tumor at the L2 vertebral body level. A portion of the anteroinferior pole of the tumor was slightly hypointense vs. the remainer of the tumor on T1- and T2-weighted images. The tumor shows strong homogeneous enhancement, except for the intermediately enhancing anteroinferior portion.

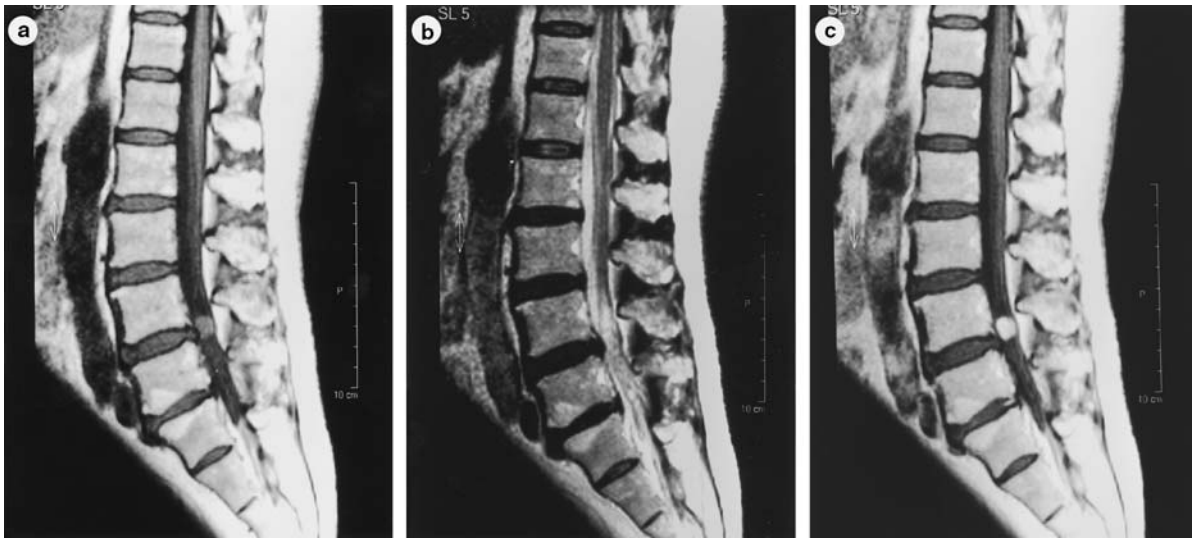

Figure 2. Sagittal T1-weighted (a), T2-weighted (b), and contrast-enhanced T1-weighted (c) MR images revealing a well-demarcated intradural extramedullary mass at the L4-5 vertebral body level. The peripheral rim of the mass shows hypointense but the central region of the mass hyperintense on T2-weighted images. The tumor reveals strong homogeneous enhancement. Extratumoral cysts are present in the upper and lower portions of the tumor.

of tumor cells decreased but fibrous tissue increased. Her pain subsided after the operation, and no signs of recurrence were evident at the 40-month follow-up.

Case 3 (Figure 3)

A 71-year-old woman presented with a 10-year history of low back pain and a 2-year history of a radiating pain in the right thigh. Neurological examination revealed neither motor nor sensory changes, whilst an urodynamic study revealed underreactive detrusor activity. Electromyography showed radiculopathy of the right L5 and S1 nerve roots. MR images of the lumbar spine showed an intradural extramedullary tumor at the L4 level. At surgery, a bluish-gray tumor, $2.2 \times 1.4 \times 1.4$ cm in size, was found to be covered with a whitish capsule, and to have originated from a nerve root. Old blood gushed out from the cystic component in the ventral portion of the hypervascular tumor. There was a significant feeding artery. The tumor was completely excised from the root. Microscopically hemosiderin was found to be present in the pseudocapsule at the lower margin of the tumor, in accord with the hypointense margin on the T2-weighted images. Multiple cystic lesions were detected. The patient had an uncomplicated recovery and was symptom-free at 24 months.

Case 4 (Figure 4)

This 52-year-old woman was admitted with a 10-month history of low back pain and a radiating pain in both legs and neurogenic claudication. On physical examination, left big toe weakness was recognized at dorsiflexion. MR images of the lumbar spine revealed a round oval intradural extramedullary tumor at the L3 vertebral body level. At surgery, a well-encapsulated hypervascular grayish mass, $2.2 \times 1.6 \times 1.2$ cm in size, was found to be densely adhered to the filum terminale. Microscopically the mass was more hypervascular than in the other cases. No intratumoral cyst was seen despite its large size. A postoperative I-123 MIBG scan showed no evidence of metastasis. The patient made a good postoperative recovery, and has remained symptom free for 71 months.

Results

Radiological findings

In all cases, MR images obtained after the administration of contrast material showed tumor enhancement. The MR images of the tumors were generally nonspecific, showing isointensity with the spinal cord on T1-weighted images and hyperintensity on T2-weighted images. In all cases, heterogeneous signal intensity was observed on T2-weighted images. The tumor margins were hypointense on T2-weighted images in three cases. In one case, serpiginous flow voids were noted in the tumor, which may have been caused by tumor hypervascularity or compression of veins by the mass. The radiological findings of each case are shown in Table 2.

Surgical and pathological findings

Grossly all of the tumors, located in the intradural, extramedullary space, were well encapsulated, red-black in color, very soft or friable, and bled easily. Two cases were adherent to the nerve roots and the others to the filum terminale. All cases were adherent to a vascular pedicle or a richly vascular network. The cut surfaces of the tumors showed identical features, showing a whitish gray solid appearance with focal hemorrhage. Histopathologically (Figure 5), each tumor had the typical

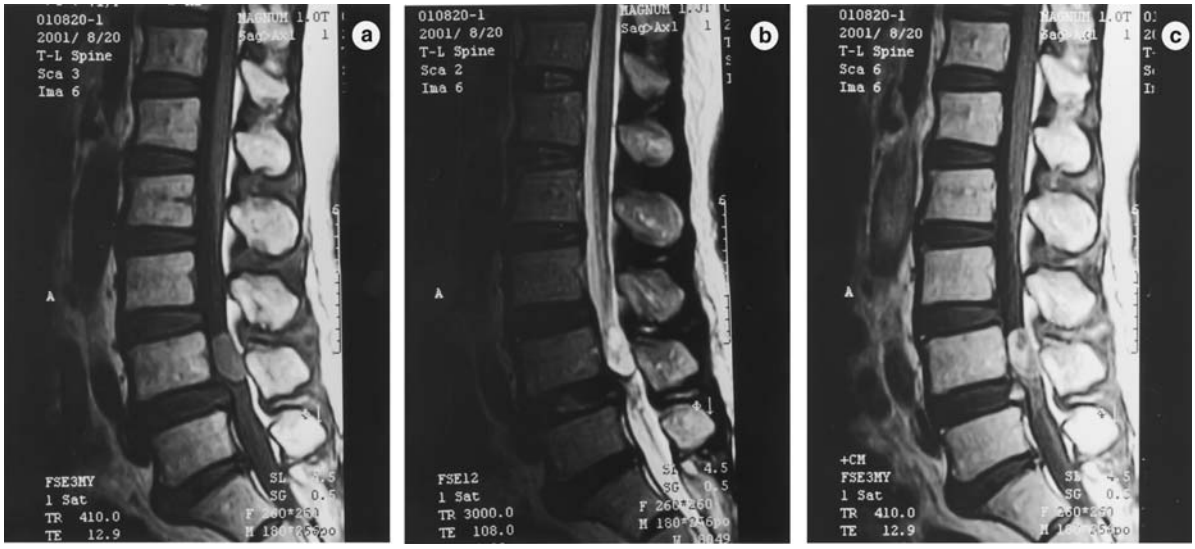

Figure 3. Sagittal T1-weighted (a), T2-weighted (b), and contrast-enhanced T1-weighted (c) MR images showing an intradural extramedullary tumor at the L4 vertebral body level. The lesion is hyperintense vs. the CSF, and has a cystic component with septations at both poles and is slightly hyperintense or isointense, relative to cord, solid component on the T2-weighted image. Tumor were generally isointense on the T1-weighted images and sharply defined by a band of a low signal intensity in all sequences. The tumor shows homogeneous enhancement except for the cystic component.

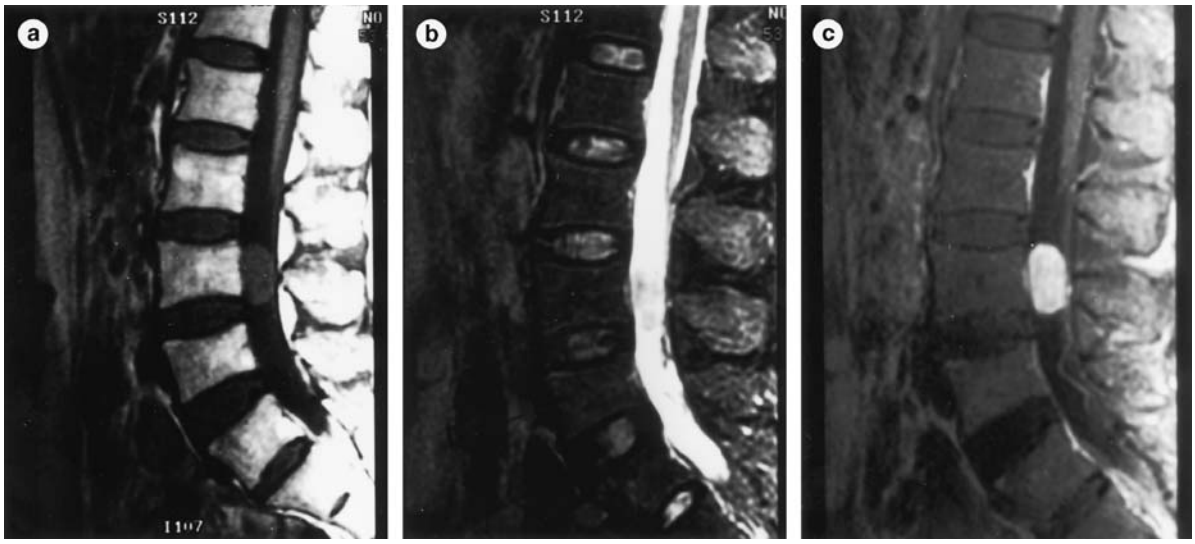

Figure 4. Sagittal T1-weighted (a), T2-weighted (b), and contrast-enhanced T1-weighted (c) MR images revealing a round oval intradural extramedullary tumor at the L3 vertebral body level. The mass is isointense on T1-weighted and hyperintense relative to the spinal cord on T2-weighted images. The mass showed inhomogeneous signal intensities with dendritic low signal intensity on axial T2-weighted image (d).

Table 2. The findings of magnetic resonance image and feature about four cases

	T2-weighted image	T1-weighted image	Contrast enhanced	Features
Case 1 M/49	Slightly hypointense	Slightly hypointense	Strong except less enhancing part	Different signal between two portions Extratumoral cyst Peripheral rim: hypointense on T2-WI
Case 2 F/63	Hyperintense	Slightly hyperintense	Strong except less enhancing part	Degenerated portion Extratumoral cyst Peripheral rim: hypointense on T2-weighted image
Case 3 F/71	Isointense: solid Hyperintense: cyst	Isointense: solid and cyst	Strong heterogeneous	Intratumoral hemorrhagic cyst Peripheral rim: hypointense on T2-weighted image
Case 4 F/52	Hyperintense Stippled Focal hypointensity	Isointense Stippled Focal hypointensity	Strong heterogeneous	Intratumoral dendritic hypointensity

M – male; F – female.

appearance of a paraganglioma, being composed of an organoid or 'zellballen' arrangement of polyhedral and argyrophilic cells, circumscribed by a richly vascular stroma. Tumor cells were arranged around small vessels reminiscent of pseudorosettes. In addition, papillary epithelial structures were present in areas resembling ependymal tubules. Areas of characteristic cell nesting forming 'zellballen' were present in all four tumors. More magnified images showed that the nuclei were uniformly round to oval in shape with a regular chromatin pattern. Nucleoli were observed and the cytoplasm was finely granular. No mitosis was present in any of the four cases. Immunohistochemical results are summarized in Table 3. Immunohistochemical examination showed positivity synaptophysin, chromogranin, vimentin, and neuron specific enolase (NSE) in all cases. Glial fibrillary acid protein (GFAP), cytokeratin, and neurofilament protein was not expressed in the tumor cells. Sustentacular cells in all cases were immunoreactive for S100 protein.

Discussion

Spinal paragangliomas are rare tumors, which exclusively occur in the cauda equina. More than 70 cases have been reported since 1972 [2]. The age of patients ranges from 12 [3] to 71 [4] (mean: 48 years), with a male predominance: $M/F = 1.54/1$ [5]. Spinal paragangliomas are believed to be predominantly of the sympathetic type, but the majority of paragangliomas in the carotid and jugular bodies are parasympathetic in type [6]. The most frequent clinical presentation is lumbar pain and sciatica accompanied by sensory or motor deficit in the lower extremities and occasionally in the bladder, bowel and erectile function [4]. No symptomatic differences

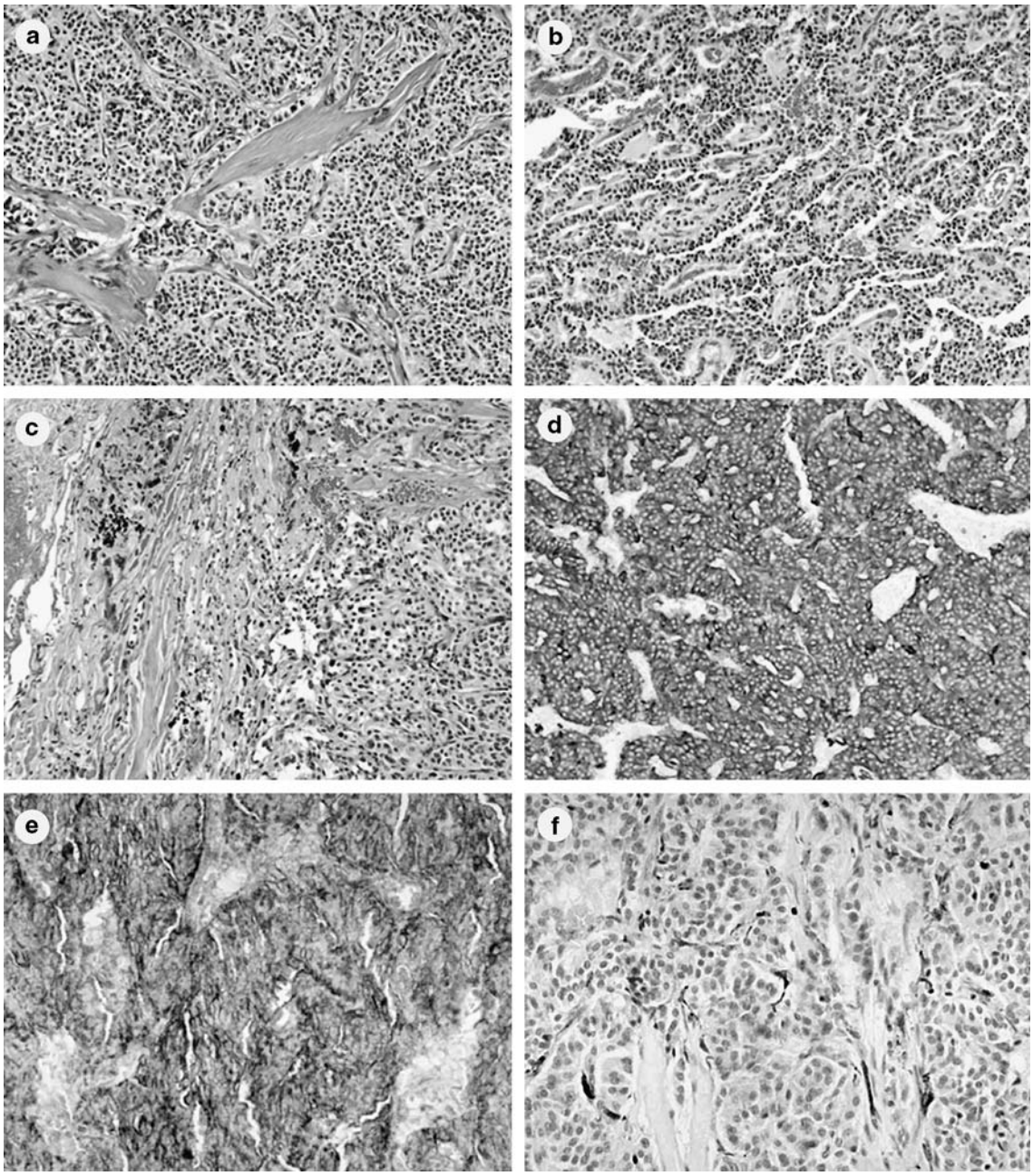

Figure 5. (a) Photomicrograph of a tumor showing a zellballen pattern with thick trabeculae (H&E, ×200). (b) The tumor partly shows a pseudopapillary configuration of monotonous round to oval cells (H&E, ×200). (c) The capsule of the tumor shows fibrous tissue with a hemosiderin deposit (H&E, ×200). (d, e) Immunohistochemically, the neoplastic cells expressed synaptophysin and chromogranin A, diffusely and strongly (d: synaptophysin immunostaining, ×200, e: chromogranin A immunostaining, ×200). (f) By S100 immunostaining, scattered S100 protein immunoreactive sustentacular cells were evident (S100 protein immunostaining, ×200).

were observed between our four cases like other reported ones. Pathologically, these are solid, highly vascularized, slow growing and well-encapsulated tumors, which usually originate from the proximal filum terminale. In our cases, the tumors were attached to the filum terminale in two cases and to a nerve root of the cauda equina in the other two cases. Aghakhani et al. [2] summarized attachment in 79 cases of previously reported paragangliomas of the cauda equina, and reported a filum to nerve root attachment ratio of 39:15. Paragangliomas of the cauda equina generally show features resembling those of other tumors arising in the spinal cords. Since there is no specific symptom or sign of spinal paragangliomas, it is essential that paragangliomas should be suspected during the course of diagnosis, based on the radiological findings. For these reasons, spinal paragangliomas are hardly diagnosed or are misrecognized before the pathological confirmation. Complete surgical resection is considered curative and subtotal resection often leads to recurrence. Moreover, postoperative radiation therapy for patients with incomplete excision has no effect on recurrence prevention [4]. For these reasons, treatment outcome may depend upon the preoperative diagnosis. The differential diagnoses of spinal paraganglioma include myxopapillary ependymoma, schwannoma, meningioma,

Table 3. Immunohistochemical results of four cases of paraganglioma in cauda equina region

	F/52	F/71	F/63	M/49
Synaptophysin	+	+	+	+
NSE	+	+	+	+
Chromogranin A	+	+	+	+
Vimentin	+	+	+	+
S100[a]	+	+	+	+
GFAP	−	−	−	−
Cytokeratin	−	−	−	−
Neurofilament	−	−	−	−
Epithelial membrane antigen	−	−	−	Not performed

[a] Positive in sustantacular cells; +: positivity; −: negativity.

metastatic tumors, and dermoid tumor or lipoma; the latter two are easily excluded by their signal patterns in MR imaging [6]. The review of our cases and of the literature permitted us to analyze clinical and radiological presentations, surgical aspects, and pathological and immunohistochemical findings. Such findings should help us differentiate spinal paraganglioma from other spinal tumors.

Clinical presentation

Despite their neuroendocrine origin, we found only two cases of paraganglioma of the cauda equina with functional hormonal activity in the literature, which was not detected in our cases: one of them had flush like attacks, without paroxysmal hypertension, but with abnormal urine noradrenaline concentration. In contrast, the other one presented hyperadrenergic symptoms, immediately preoperatively and intraoperatively while the tumor was manipulated [2,7]. Biochemical and immunohistochemical analyses of the spinal paraganglioma revealed that 5-hydroxytryptamine was present in paraganglioma at higher levels than catecholamines, and that up to 75% of spinal paraganglioma showed immunoreactivity to 5-hydroxytryptamine [4,8]. The lack of paroxysmal hyperadrenergic states in spinal paraganglioma may have two reasons: the inability of tumor cells to secrete the stored substances or the inability of these substances to provoke a clinical syndrome [9].

Cerebrospinal fluid (CSF) analysis is nonspecific; protein content is usually markedly increased, as in any intradural tumor. Occasionally, a 'bloody tap' is obtained, when a hypervascular paraganglioma is punctured.

Radiological features

In a few cases, heterogeneous signal intensity has been observed on T2-weighted images. Hypointense tumor margins on T2-weighted images, suggesting paramagnetic effects from hemosiderin as is commonly observed on gradient echo imaging, were present in three of our cases and a number of cases in the literature [2,10–13]. Pathologically, hemosiderin pigmentations, suggesting previous trivial bleeding of hypervascular tumors, were detected in the pseudocapsule of Cases 1 and 3.

The hypervascular nature of paragangliomas results in punctuate areas of flow void interspersed in a matrix of increased signal intensity caused by slow flow and tumor cells. This produces a salt-and-pepper appearance on T2-weighted images, which is considered as a characteristic of paragangliomas of the head and neck, and has also been described in lesions arising in the cauda equina. However, this pattern was not observed in our cases [14]. Serpiginous defects were found around the tumors, suggestive of dilated serpentine vessels. Focal intratumoral dendritic low signal intensities and multiple signal voids around the tumor were likely to be findings of dilating vessels, based on the pathologic findings in Case 4. Araki et al. [10] suggested that this sign is a major clue to the diagnosis of a highly vascular lesion. These findings are also sometimes noticed in hemangioblastoma, which is also a hypervascular tumor, but they are unusual in ependymoma and schwannoma.

The extratumoral cysts seen in Cases 1 and 2, and which were more hyperintense than the CSF, were located above the tumor and separated from it. Spinal cord cysts associated with the tumor were hyperintense, and resulted from elevated proteins within the cystic fluid was considered a loculated CSF space, but this was not proven pathologically. Faro et al. [15] proposed two hypotheses. One is that normal CSF flow might be blocked inferiorly by the tumor, thus creating a pressure differential and forcing fluid into the spinal cord with subsequent cysts creation. The other is that a cyst might be created by fluid extravasated from abnormal tumor vessels into the interstitial space in the spinal cord. We supported the notion that cysts may be attributed to a blockage in the CSF circulation. The difference between our cases and cases in the literatures concerns lesion location. However, in Case 3, the fluid in the intratumoral cyst was due to hemorrhage. In the literature, high signal intensity had been observed in the CSF beneath the lesion, probably secondary to a blockage of the CSF circulation, an elevation of CSF protein or a reduction in CSF pulsations [16].

In our four cases, such findings were found in part and these correlated with pathologic findings. Putting these various radiological findings together, it is said that radiological findings not only are seen infrequently in MR imaging but may also help to diagnose spinal paraganglioma.

Pathological findings

The primary histological features of paraganglioma are 'zellballen', or a nesting of cell groups, and trabecular cords of cells within thin fibrovascular stroma. The predominant cell type is the chief cell, which is round to oval in shape with abundant eosinophilic granular cytoplasm. The second cell type is the sustentacular or supporting cell. The loss of normal paraganglionic architecture in paragangliomas has been associated with a more aggressive or malignant behavior. The paucity or absence of sustentacular cells in paraganglioma has also been found to be an indicator of an aggressive or malignant nature [17,18]. The myxopapillary

ependymoma is characterized by perivascular pseudorosettes, i.e., radially oriented cell groups surrounding small vessels. The histological differentiation of paragangliomas from ependymomas on routine staining can be very difficult when none of the above pathognomonic patterns is present or when surgical artifacts are present. Immunohistochemical staining for chromogranin, NSE, and synaptophysin, which is positive for paraganglioma, is most commonly used for differential diagnosis, whereas GFAP is negative in neoplastic cells. NSE although a sensitive marker of chief cells lacks specificity, but synaptophysin and chromogranin are sensitive and reliable [4,18]. Differential diagnosis from ependymoma can be made by GFAP positivity in ependymal tumors. Ependymoma may also show positivity for mucin and S100 protein in tumor cells rather than in sustentacular cells of paraganglioma. In our cases, immunohistochemical staining was typical. Generally, a pseudopapillary pattern was observed with thick hyalinizing fibrous trabeculae, which caused confusion with myxopapillary ependymomas; this feature is seen in all four cases. Therefore, the pseudopapillary pattern might be characteristic a feature of cauda equina paraganglioma.

No functional hormonal activity in our four cases made it unnecessary to study immunohistochemical staining for catecholamines. Also in the literature review catecholamines have been studied biochemically, but no immunohistochemical analysis was found [5].

Conclusion

Spinal paraganglioma is seldom considered in preoperative differential diagnosis due to its rarity and nonspecific imaging features. However, when well-demarcated, heterogeneously enhancing masses with a hypointense tumor margin, intratumoral hemorrhagic or cystic changes, intratumoral focal low signal intensity, and peritumoral loculated CSF spaces are observed in the intradural extramedullary space, especially in the cauda equina, paraganglioma should be included in the differential diagnoses.

Acknowledgements

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References

1. Lerman RI, Kaplan ES, Daman L: Ganglioneuroma – paraganglioma of the intradural filum terminale. Case report. J Neurosurg 36: 652–658, 1972
2. Aghakhani N, George B, Parker F: Paraganglioma of the cauda equina region – report of two cases and review of the literature. Acta Neurochir (Wien) 141: 81–87, 1999
3. Park DH, Park YK, Oh JI, Kwon TH, Chung HS, Cho HD, Suh YL: Oncocytic paraganglioma of the cauda equina in a child. Case report and review of the literature. Pediatr Neurosurg 36: 260–265, 2002
4. Sonneland PRL, Scheithauer BW, LeChago J, Crawford BG, Onofrio BM: Paraganglioma of the cauda equina region: clinicopathologic study of 31 cases with special reference to immunocytology and ultrastructure. Cancer 58: 1720–1735, 1986
5. George CM, Athanassios PK, Konstantinos SP: Cauda equina paraganglioma: a review. J Neurooncol 65: 177–190, 2003
6. Sundgren P, Annertz M, Englund E, Strömblad LG, Holtås Ś: Paragangliomas of the spinal canal. Neuroradiology 41: 788–794, 1999
7. Böker DK, Wassmann H, Solymosi L: Paragangliomas of the spinal canal. Surg Neurol 19: 461–468, 1983
8. Pigott TJD, Lowe JS, Morrell K, Kerslake RW: Paraganglioma of the cauda equina. Report of three cases. J Neurosurg 73: 455–458, 1990
9. Gould VE, Valaitis J, Trujillo Y, Chejfec G, Gruhn JG: Neuroendocrinoma of the jejunum: electron microscopic and biochemical analysis. Cancer 46: 713–717, 1980
10. Araki Y, Ishida T, Ootani M, Yamamoto H, Yamamoto T, Tsukaguchi I, Nakamura H: MRI of paraganglioma of the cauda equina. Neuroradiology 35: 232–233, 1993
11. Levy RA: Paraganglioma of the filum terminale: MR findings. Am J Roentgenol 160: 851–852, 1993
12. Taira H, Takasita M, Yoshida S, Takita C, Tsumura H, Torisu T: MR appearance of paraganglioma of the cauda equina. Case reports. Acta Radiol 41: 27–30, 2000
13. Wolansky LJ, Stewart VA, Pramanik BK, Heary RF, Cho ES, Schulder M, Pak J: Giant paraganglioma of the cauda equina in adolescence: magnetic resonance imaging demonstration. J Neuroimaging 6: 54–56, 1996
14. Olsen WL, Dillon WP, Kelly WM, Norman D, Brant-Zawadzki M, Newton TH: MR imaging of paragangliomas. Am J Roentgenol 148: 201–204, 1987
15. Faro SH, Turtz AR, Koenigsberg RA, Mohamed FB, Chen CY, Stein H: Paraganglioma of the cauda equina with associated intramedullary cyst: MR findings. Am J Neuroradiol 18: 1588–1590, 1997
16. Berenguer J, Bargallo N, Sanchez M, Bravo E, Cardenal C, Mercader JM, Munoz J: Magnetic resonance imaging of paraganglioma of the cauda equina. Can Assoc Radiol J 46: 37–39, 1995
17. Kliewer KE, Wen DR, Cancilla PA, Cochran AJ: Paragangliomas: assessment of prognosis by histologic, immunohistochemical, and ultrastructural techniques. Hum Pathol 20: 29–39, 1989
18. Kliewer KE, Cochran AJ: A review of the histology, ultrastructure, immunohistology, and molecular biology of extraadrenal paragangliomas. Arch Pathol Lab Med 113: 1209–1218, 1989

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