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Primary intraosseous ganglioneuromatous paraganglioma of the sacrum with immunopositivity for cytokeratin

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Abstract. – BACKGROUND: Paragangliomas are derived from neurosecretory cells believed to be of neural crest origin. A spinal location of paraganglioma is rare and usually presents as an intradural mass.

PATIENT AND METHODS: A primary intraosseous paraganglioma of sacrum is extremely unusual, and only 6 cases were reported. In this study, we report a rare case of a 44-year-old man with the complaint of low back pain and lower extremity weakness. Imaging workup, including computerized tomography (CT), and magnetic resonance imaging (MRI) presented an intraosseous sacral lesion with invasion of sacrum in the S1-S3 vertebrae, and extension to L4-L5 spinal canal. The patient underwent subtotal tumor resection, followed by radiation therapy.

RESULTS: The morphological and immunohistochemical studies revealed a composite tumor of paraganglioma and ganglioneuroma components, with immunopositivity for cytokeratin.

CONCLUSIONS: To the best of our knowledge, this is the first report in the literature demonstrating an intraosseous sacral paraganglioma with these 2 pathological features.

Key Words:
Paraganglioma, Ganglioneuroma, Cytokeratin, Intraosseous, Sacrum.

Introduction

Paragangliomas are derived from neurosecretory cells believed to be of neural crest origin. These lesions tend to occur in a variety of locations normally rich in paraganglionic tissue, with about 90% of paragangliomas arising in the adrenal tissue, and 10% outside of the adrenal system, such as carotid body and jugular glomus. Paragangliomas have also been reported to occur in locations where paraganglia are not normally found, such as gastrointestinal tract, urinary bladder, and central nervous system. A spinal location of paraganglioma is rarely found and usually presents as an intradural mass. A primary intraosseous paraganglioma of sacrum is extremely unusual, with only 6 cases reported in the literature[1-6]. In this report we described a rare case of paraganglioma arising in sacrum with extradural extension. And the immunohistochemical findings, which involve ganglioneuromatous component and immunopositivity of tumor cells for cytokeratin, make this case even rarer. To the best of our knowledge, this is the first report in the literature demonstrating an intraosseous sacral paraganglioma with these 2 pathological features.

Case Report

A 44-year-old man presented with a history of increasing low back pain and lower extremity weakness for 5 years. The patient had a blood pressure of 130/82 mmHg. There was percussion pain over the L5, S1, S2 vertebrae and paravertebral muscles. Lower extremity examination indicated reduced strength in the shank muscles, with decreased sensation in the posterior shank and the planta. There was hypoesthesia in the perineal region and defect in erectile function and bowel control.

Preoperative computed tomography (CT) of the lumbosacral spine revealed erosion of the sacrum in the midline, flake residual bone and a large expanding mass in the lumbosacral spine (Figure 1). Magnetic resonance imaging (MRI)

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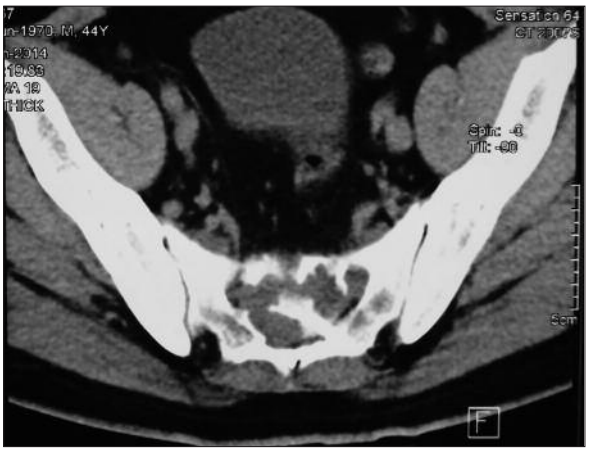

Figure 1. ***A, B,*** Preoperative transverse computed tomography (CT) at S1-S3 revealed an expansile mass and erosion of the sacrum.

demonstrated a lobulated mass that was isointense to paravertebral muscles on T1-weighted MRI and hyperintense on T2-weighted MRI with irregular borders, invasion of sacrum in the S1-S3 vertebrae, and extension to L4-L5 spinal canal. Heterogeneous enhancement of the lesion with Gd-DTPA, non-enhanced cystic areas with fluid, and tree-like tubular and round signal void structures were observed (Figure 2). CT scan of the spinal cord, brain, chest, abdomen, and pelvis showed no evidence of other lesions, indicating a primary intraosseous tumor of sacrum.

Surgical excision was performed through a posterior midline incision exposing L4 to S3. A highly vascular encapsulated tumor invading lamina of vertebrae was encountered just below the musculature. After laminectomy, an irregular, soft, and friable tumor was exposed. The tumor was located in the extradural space and pushed the dural sacs dorsally, encroaching upon the S1 and S2 nerve roots. An intraoperative frozen section was examined with a suggestive diagnosis of ependymoma. Subtotal tumor excision was performed with decompression of the nerve roots, followed by stabilization and arthrodesis from L5 to the ilium. Postoperatively, adjuvant radiotherapy was performed with a total dose of 50Gy in 25 fractions during a 5-week treatment course. The patient had definite recovery of motion, sensation and autonomic function. Follow-up at 1 year showed no evidence of disease progression or metastasis.

Sections of paraffin-embedded tissue were stained with hematoxylin and eosin. The histological examination revealed that the tumor consisted of 2 main components: paraganglioma areas and ganglioneuroma areas, with the paraganglioma leading the dominant proportion of the tumor volume (Figure 3a). The paraganglioma element was composed of uniform cells with faintly eosinophilic cytoplasm, a single round nucleus, and an indistinct nucleolus. These epithelioid chief tumor cells were clustered in tight nested organoid (Zellballen) (Figure 3b) and pseudorosette arrangement (Figure 3c), separated by scattered spindle-like sustentacular cells. Mild cellular pleomorphism was present but only very rare mitoses were seen. In ganglioneuromatous component, ganglion cells with eccentric vesicular nuclei, large conspicuous nucleoli and eosinophilic cytoplasm were arranged irregularly in a neurofibromatous background (Figure 3d). These 2 compo-

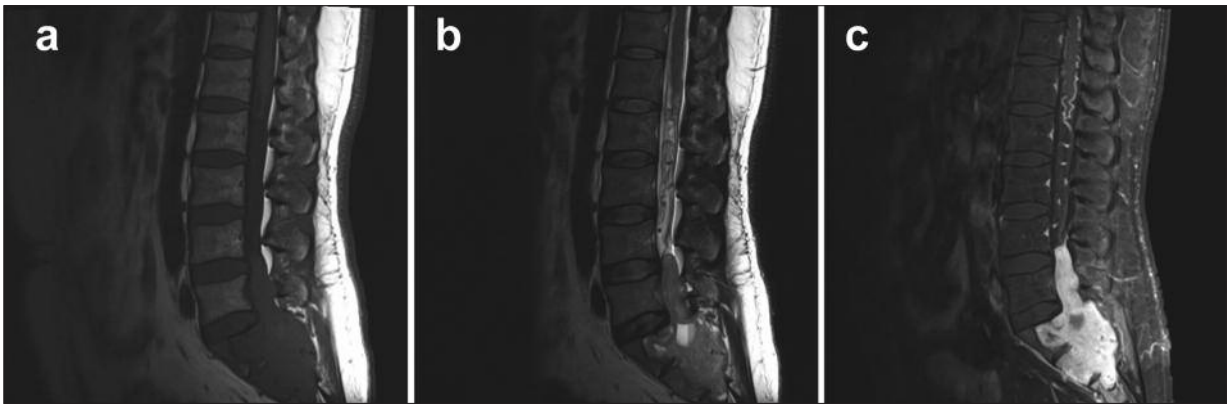

Figure 2. ***a,*** Sagittal plain T1-weighted, ***(b)*** plain T2-weighted, ***(c)*** T1-weighted with contrast MRI of the lumbosacral spine showed a sacral tumor isointense to paravertebral muscles on T1-weighted MRI and hyperintense on T2-weighted MRI with heterogeneous enhancement.

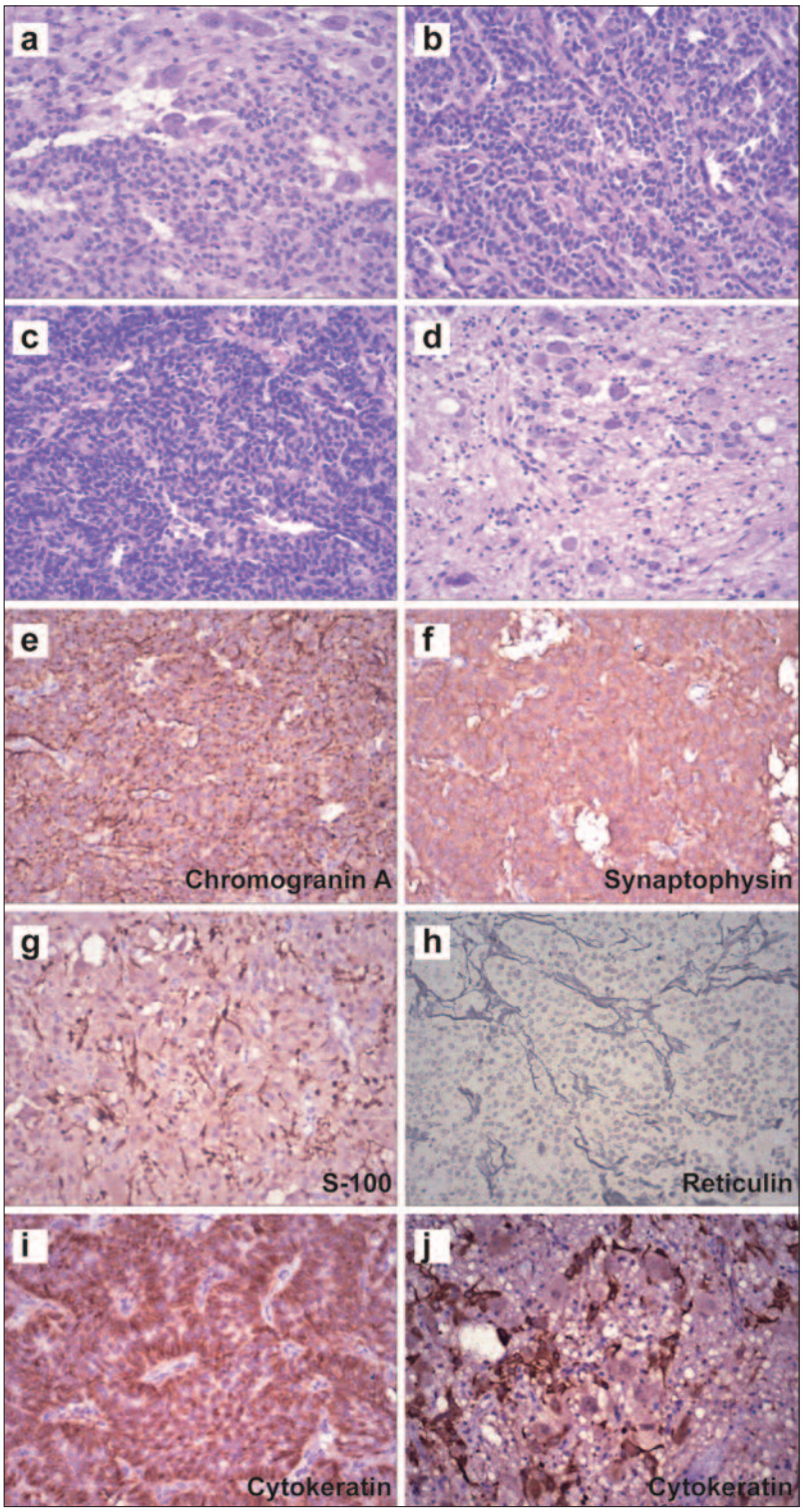

Figure 3. ***a,*** Composite tumor with paraganglioma and ganglioneuroma areas. ***b,*** Paraganglioma component with chief cells clustered in tight nested organoid (Zellballen) arrangement. ***c,*** Paraganglioma component with chief cells arranged in a pseudorosette pattern. ***d,*** Ganglioneuromatous component with ganglion cells arranged irregularly in a neurofibromatous background. The chief paraganglioma cells strongly expressed ***(e)*** chromogranin A and ***(f)*** synaptophysin. ***g,*** Scattered S-100 positive sustentacular cells were identified within the paraganglioma component. ***h,*** The Zellballen was surrounded by a delicate fibrous network. ***i,*** Strong expression of cytokeratin was observed in chief paraganglioma cells. ***j,*** Cytokeratin expression of ganglion cells was weak (400×).

nents existed separately or merged into each other. Especially, ganglion cells were scattered among chief paraganglioma cells in certain areas as in a gangliocytic paraganglioma.

Immunohistochemical studies were performed with commercially available antibodies. The chief paraganglioma cells strongly expressed chromogranin A (Figure 3e), synaptophysin (Figure 3f), and neuron-specific enolase, and were negative for glial fibrillary acidic protein. In addition, strong expression of cytokeratin was observed in chief cells, which was unexpected (Figure 3i). Scattered S-100 positive sustentacular cells were identified (Figure 3g). The Zellballen was surrounded by a delicate fibrous network (Figure 3h). In ganglioneuromatous element, ganglion cells were also immunoreactive for chromogranin A and synaptophysin, but the cytokeratin expression was weak (Figure 3j). Neurofilament staining highlighted the axons within the ganglioneuromatous component. Mitotic activity was low and ranged from 0 to 1 mitosis per 10 high-power fields in both two components.

Discussion

Paragangliomas used to be classified according to the chromaffin reaction and functional activity. However, the fact that chromaffin reaction is neither specific for catecholamine-secreting function nor relevant to the disease biological behavior made us reevaluate the paraganglioma classification. As suggested by Glenner and Grimley, [7] it is rational to classify the paragangliomas according to the anatomic site, which is more related to the disease biological features and prognosis. The spinal location of paragangliomas is rare. Most of these have been reported as intradural extramedullary lesions in the lumbosacral region, while extradural spinal paragangliomas were found mainly in the thoracic spine[8]. Only 6 cases of paraganglioma originating primarily in sacrum have been reported. Most of these lesions presented as an intraosseous mass with extradural extension, with typical pathological findings of paraganglioma. This case is the first report of an intraosseous sacral paraganglioma with 2 pathological features: ganglioneuromatous component and immunopositivity of tumor cells for cytokeratin.

The hypothesis of the mechanisms for paragangliomas originating in unusual anatomic sites like bone involves more extensive distribution of paraganglia than normal in fetus or neonate. Neural crest cell migration and differentiation during the embryonic development may lead to the rare occurrence of paragangliomas[9].

Ganglion cell differentiation has never been reported in intraosseous sacral paragangliomas, while its existence in duodenum and cauda equina lesions is common[10]. A composite tumor with both paraganglioma and ganglioneuroma components is even more unusual[11]. In this case, we can see intimately admixed components of paraganglioma and ganglioneuroma, a diagnosis of composite ganglioneuromatous paraganglioma was made. As suggested by Pytel et al[11], these composite tumors suggest the common origination of tumor cells, and help understanding the neural crest cell development and differentiation.

Unlike the paragangliomas arising in adrenal gland, tumors in lumbosacral region more commonly show immunoreactivity for cytokeratin[11]. However, in the reviewed studies, most of these reported tumors are located in intradural space, with none of these implicating an intraosseous sacral paraganglioma. As for this intraosseous case, the fact that not only the chief paraganglioma cells but also the ganglion cells are positive for cytokeratin supports the hypothesis that these two components may have common origination.

Most of the spinal paragangliomas are considered as benign and slow-growing tumors. Compared to pathological features, clinical findings involving tumor location, recurrence or metastasis are more valuable for indicating the malignancy. Nevertheless, a loss of normal paraganglionic architecture and paucity of sustentacular cells in paragangliomas have been associated with more aggressive behavior. In the 6 cases of intraosseous sacral paragangliomas, none of these tumors were evaluated as malignant, consistent with our report.

The differential diagnosis of osteogenic tumors of sacrum includes primary chordomas, giant cell tumors, cavernous hemangiomas, osteoid osteomas, metastatic lesions, etc. A minority of sacral neoplasms develops in the sacral spinal canal, and the differential diagnosis should include myxopapillary ependymomas, schwannomas, neurofibromas, meningiomas, etc. In our study, both the intraoperative and postoperative pathological studies exhibited some ependymoma-like areas representing with pseudorosette formation. Differential diagnosis

from ependymoma can be made by the positivity for glial fibrillary acidic protein, and the negativity for chromogranin A and synaptophysin of ependymal tumors. Considering the immunopositivity for cytokeratin, differential diagnosis should include metastatic tumors, which are the most common sacral neoplasms, with lung, breast, and prostate carcinomas being the most frequent tumors of origin.

Given the fact that some malignant tumors involved in the differential diagnosis of paragangliomas have a more aggressive course, presurgical diagnosis with either open or CT-guided fine needle aspiration biopsy or intraoperative biopsy is essential to avoid unnecessary destructive operation[5]. Gross total removal should be the goal of surgery to achieve surgical cure in patients with paragangliomas, and radiation therapy can be used in cases with incomplete resection[12]. However, local recurrence and distant metastasis have been reported even after macroscopic total excision[13]. Thus, total tumor excision and postoperative follow-up study are recommended.

Conclusions

In spite of the rarity, the possibility of paragangliomas should be kept in mind to avoid any misdiagnosis of sacral tumors. Immunohistochemical studies consisting of a variety of antibodies are essential to make an accurate diagnosis.

Acknowledgements

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Conflict of Interest

The Authors declare that there are no conflicts of interest.

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