

Ectopic adrenal cortical adenoma in the spinal region: Case report and review of the literature

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Abstract

Ectopic adrenal cortical neoplasms are extremely rare; few involve the central nervous system (CNS). We report a 17-month-old girl with spinal adrenal cortical neoplasms. She was unable to crawl or stand and was irritable at night. Her appearance was asymmetric; her face on the right side and her lower right leg were enlarged. In addition, she manifested hyperplasia of the thymus, fibrous hyperplasia of the bladder, and hamartoma in the liver. However, all abnormalities were asymptomatic. Magnetic resonance imaging (MRI) revealed well-circumscribed masses within the dura mater at the Th12 - L1 and L3 - L4 level. Histology disclosed that the lesions were composed of sheets and nests of round and polygonal cells with mostly round regular nuclei; eosinophilic to clear cytoplasm was abundant. Immunohistochemically, the tumor cells were strongly positive for inhibin alpha, positive for synaptophysin and vimentin, and negative for GFAP, EMA, S-100, NSA, and chromogranin A. In addition, the nuclei stained positive for steroidogenic factor 1 (Ad4BP/SF-1), which is involved in adrenal steroidogenesis. This case confirms the occurrence of adrenocortical adenoma in the CNS. We suggest that this tumor

should be considered in the differential diagnosis of CNS tumors.

Introduction

The adrenal gland arises from primordial mesenchyme in the wall of the dorsal coelom adjacent to the dorsal mesentery and urogenital structures ^{1,2}.

Therefore, most ectopic adrenocortical tissue is found along the path of embryonic migration within the urogenital tract. The most common sites include the celiac axis (32%), the broad ligament (23%), the adnexa of the testis (7.5%), and the spermatic cord (3-8%) ³. Adrenocortical tumors, both benign and malignant, can also arise at ectopic sites, presumably from ectopic adrenal rests ^{4,5}.

A unique anatomic region for ectopic cortical tumors is the lower spinal region ⁶⁻¹¹. We report an unusual patient with ectopic adrenocortical tumors in the spinal region and several systemic anomalies such as hyperplasia of the thymus, fibrous hyperplasia of the bladder, hamartoma in the liver, and asymmetry of the face and lower extremity.

Case Report

The mother of this 17 month-old girl noted that she was unable to crawl

or stand and that she was irritable at night. Both parents were healthy and had no history of congenital disease. A cystic region in the liver had been diagnosed on ultrasound performed at 28 weeks of gestation; it was monitored and found to be enlarging gradually. As the membrane ruptured at 34 weeks of gestation the infant was delivered by Caesarean section; the Apgar score was 8. Her birth weight was 2,306 g. Laboratory examination disclosed anemia and hypoglycemia. Her face and lower extremity were asymmetrical; her right cheek and right lower leg were enlarged. Contrast-enhanced abdominal CT led us to suspect that the cystic mass in the liver was a hamartoma. At this time, there were no obvious neurological deficits.

She was carefully monitored in our pediatric outpatient department. At 7 months, CT revealed enlargement of the thymus. A specimen obtained by open biopsy yielded a histological diagnosis of hyperplasia. The cystic mass in the liver gradually decreased under observation. At 15 months, her mother found a soft mass protruding through the urethra. Ultrasound identified a solid mass in the bladder; it was removed through the urethra. The histologic

diagnosis was fibrous hyperplasia without evidence of malignancy.

Subsequently her mother noted her inability to crawl or stand up and irritability at night. On neurological examination there was decreased movement of her lower extremities attributable to back pain. Bowel and bladder dysfunction were noted. On magnetic resonance imaging (MRI) scans, well-circumscribed masses were located within the dura mater at the Th12 - L1 and the L3 - L4 level. The rostral mass was hypointense on both T1- and T2-weighted images with homogeneous enhancement (Fig. 1). The caudal mass was slightly hyperintense on T1- and very hypointense on T2-weighted images with faint enhancement, findings suggestive of intratumoral hemorrhage (Fig. 1). The brain, upper spinal cord, abdomen, and specifically the adrenal glands were unremarkable on MRI. Based on the location of the masses and their MRI characteristics, they were thought to be myxopapillary ependymoma. Our preoperative differential diagnosis also included Schwannoma and meningioma.

We performed Th12 - L4 laminectomy for resection of the masses under

spinal cord monitoring. The vertebral level was reconfirmed by X-ray before proceeding with the operation. Upon opening the dura mater and arachnoid membrane, 2 encapsulated masses were noted (Fig. 2). One mass was yellowish-brown, the other was dark red. They were entirely intradural and extramedullary. The rostral tumor was attached to the conus medullaris and nerve roots but readily separated from these structures. The caudal tumor also attached to the nerve roots and contained an old hematoma. Both tumors were well-circumscribed and showed no invasion of surrounding tissue. Gross total resection was successful, her postoperative course was uneventful and she was able to resume activities normal for her age and to stand with support.

Pathological findings

Formalin-fixed, paraffin-embedded tissue sections obtained at surgery were submitted for hematoxylin and eosin (H&E) staining and immunohistochemistry. The primary antibodies to synaptophysin (DAKO, 1:50), vimentin (DAKO, 1:400), cytokeratin (NICHIREI, 1:2), CD138 (DAKO,

1:100), CD56 (NOVOCASTRA, 1:50), S-100 (NICHIREI, 1:2), epithelial membrane antigen (EMA) (DAKO, 1:100), chromograninA (DAKO, 1:100), neuron-specific enolase (NSE) (NICHIREI, 1:2), glial fibrillary acidic protein (GFAP) (DAKO, 1:2500), SF-1 (Ad4BP) (Perseus Proteomics, 15 µg/ml), inhibin alpha (DAKO, 1:50), and Ki-67/MIB-1 (DAKO,1:50) were used.

Histologically, the specimen was composed of sheets and nests of round and polygonal cells with mostly round regular nuclei and abundant eosinophilic to clear cytoplasm (Fig. 3). Mitoses of 7/20 HPF in the rostral tumor and 4/20 HPF in the caudal tumor were found. The caudal tumor contained hemorrhagic and necrotic foci. Our differential diagnosis included paraganglioma, adrenal cortical carcinoma or adenoma, and oncocytic neoplasm.

Immunohistochemically the tumor cells were strongly positive for inhibin, positive for synaptophysin and vimentin (Fig. 4a-c, Fig. 5a), and focally positive for cytokeratin and CD138. In contrast, they were negative for S-100, EMA, chromogranin A, NSE, and GFAP. The proliferation index for Ki67

(MIB-1) was 15.0% in the rostral and 14.4% in the caudal tumor (Fig. 4d). In addition, the nuclei stained positive for steroidogenic factor 1 (Ad4BP/SF-1) (Fig. 5b), which is involved in adrenal steroidogenesis.

Our findings indicated that the tumor was oncocytic with an immunoprofile of an adrenal cortical adenoma. Although there was some mitotic activity (MIB-1 15.0 and 14.4%), the absence of invasion into surrounding tissues and the patient's clinical history ruled out adrenocortical carcinoma. Follow-up MRI study performed 2 years after resection yielded no evidence of tumor recurrence.

Discussion

Ectopic adrenocortical tumors in the nervous system are rare; only a few cases have been documented ⁶⁻¹¹. A summary of previously-reported cases of spinal adrenocortical adenoma is presented in the table. Ectopic adrenocortical tumors in the nervous system seem to locate exclusively in the lower spinal region; the median patient age is 21.5 years and there is a strong female predominance (7:1). Of 8 such tumors 2 were intramedullary and the

other 6, including ours, were intradural and extramedullary.

The MRI features of spinal adrenocortical adenomas are non-specific; they share signal characteristics with common spinal tumors such as ependymoma, Schwannoma, meningioma, and metastasis. According to Harrison et al. ³ they may appear hypo- or hyperintense on T1- and slightly hypointense on T2-weighted images. In our patient the rostral tumor was hypointense on both T1- and T2-weighted images and manifested homogeneous enhancement. The appearance of the caudal tumor was affected by intra-tumoral hemorrhage. In the absence of reports on spinal adrenocortical adenomas with hemorrhage, it was difficult to reach a differential diagnosis based on radiological findings.

Histologically, the differential diagnosis of spinal adrenocortical tumors is broad and includes myxopapillary ependymoma, oncocytic meningioma, and paraganglioma of the filum terminale. Microscopic examination revealed an eosinophilic neoplasm with tumor cells clustered in lobular and nest patterns. In immunohistochemical studies, the positive expression of steroidogenic factor

1(SF-1/Ad4BP), inhibin-alpha, and synaptophysin has been used to diagnose adrenocortical adenomas. These findings and the negative immunostaining for chromogranin, S-100, EMA, and GFAP led to our diagnosis. Our case lacked the typical features of paraganglioma, i.e. the zellballen architecture, chromogranin expression, and S-100 positive sustentacular cells. Oncocytic meningiomas express EMA and usually exhibit typical meningothelial features. Myxopapillary ependymoma is characterized by glial cells radiating around vascular structures in papillary configurations within a mucoid stroma. The cells are GFAP-positive and should not be immunohistochemically positive for inhibin and SF-1/Ad4BP. The immunohistochemical evaluation for SF-1/Ad4BP, a transcription factor of all steroidogeneses, can aid in rendering a differential diagnosis because nuclear immunoreactivity for this transcriptional factor is relatively specific to steroid-producing cells¹².

While the origin of spinal adrenal tumors is not clear, they are thought to derive from ectopic adrenocortical tissue. Adrenal remnants may persist along the embryonic migration path in the spermatic cord, adnexa of testes,

groin, and retroperitoneal space^{13,14}. Karikari et al.⁷ who encountered a case associated with a tethered cord and lipoma speculated that premature separation of ectoderm from neuroectoderm before the completion of neurulation permits invasion of the neural groove by mesodermal tissue committed to the formation of adrenocortical tissue. In extramedullary adrenocortical tumors lacking an association with dysraphism, retroperitoneal adrenal rests gaining intradural access by way of exiting nerves or entering vessels, has been postulated⁸.

Our case is unique in that it featured several abnormalities including asymmetry of the face and lower extremity, hyperplasia of the thymus, hamartoma in the liver, and fibrous hyperplasia in the bladder. These findings suggest some genetic abnormality although there was no significant family history of malignant diseases.

Our understanding of molecular alterations underlying the pathogenesis of adrenocortical tumors has been advanced by high-throughput molecular techniques¹⁵⁻¹⁹. Comparative genomic hybridization showed that aberrations

in chromosomes 1p, 4q, 5, 11, 12, and 17 are common in individuals with these neoplasms. Sidhu et al.¹⁸ reported that specifically gains in chromosomes 5 and 12 and losses in chromosome regions 1p and 17p are more closely associated with carcinoma than adenoma. Furthermore, loss of heterozygosity at 9p21, the locus for the tumor suppressor gene p16, is more frequent in adrenocortical carcinomas than adenomas²⁰. Studies are underway in our laboratory to examine genetic aberrations in our patients to gain a better understanding of the pathogenesis of her tumors.

In summary, we reported a primary adrenocortical adenoma in the spinal regions of an infant. Gross total resection appeared to be curative. Immunohistochemical studies that include inhibin-alpha, synaptophysin, S-100, chromogranin, and SF-1/Ad4BP were useful in the rendering of an accurate diagnosis.

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Figure Legends

Figure1:

Magnetic resonance imaging (MRI) revealed well-circumscribed masses at the Th12 - L1 and the L3 - L4 level. The rostral mass was hypointense on both T2- (a) and T1-weighted images (b) with homogenous enhancement (c, d). The caudal mass was hypointense on T2- (a) and slightly hyperintense on T2-weighted images (b) with faint enhancement (c, d).

Figure2:

Operative view of the tumors. Both rostral (arrow head) and caudal masses (arrow) were entirely intradural and extramedullary.

Figure 3:

Hematoxylin and eosin staining of rostral (a, b) and caudal (c, d) tumors show sheets and nests of round and polygonal cells with mostly round regular nuclei and an abundance of eosinophilic to clear cytoplasm at low- (x 40; a, c) and high power (x 200, b, d) magnification.

Figure 4:

Immunohistochemical staining of samples from the rostral tumor. The tumor cells were positive for synaptophysin (x 200; a), inhibin alpha (x 200; b), and vimentin (x 200; c). The proliferation index for Ki67 (MIB-1) was 15% (d).

Figure 5:

Immunohistochemical staining of samples from the caudal tumor. The tumor cells were positive for inhibin alpha (x 200; a) and steroidogenic factor 1 (SF-1/ Ad4BP) (x 200; b).

Table1: Ectopic spinal adrenocortical adenoma

	Age/Sex	Lesion location	Symptoms
Kepes et al. ⁸	8/F	Extramedullary, L2	Pain
Mitchell et al. ⁹	16/F	Extramedullary, L2	Pain
	63/F	Extramedullary, cauda equina	Pain
Cassarino et al. ⁶	27/M	Intramedullary, conus medullaris	weakness, hypoesthesia
Karikari et al. ⁷	27/F	Intramedullary, L2	pain
Schittenhelm et al. ¹⁰	44/F	Extramedullary, L1	Pain
Rodriguez et al. ¹¹	5mo/F	Extramedullary, Th10-L2	pain, irritability
Present case	1/F	Extramedullary, Th12/L1, L3/4	pain, bladder and rectal disturbance