10.1053.paor.1999.0149 available online at http://www.idealibrary.com on IDEAL

CASE REPORT

Extraneural Metastasizing Ependymoma of the Spinal Cord

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This paper reports a case of the rare entity of an extraneural metastasizing ependymoma of the spinal cord. The tumor which arose in the conus medullaris and in the cauda equina was first diagnosed in 1956 when a thoracolumbar myeloresection was performed. At autopsy, 40 years after the primary diagnosis, a massive local tumor recurrence with extraneural metastases in the lungs, the pleura, the liver, and the thoracal and abdominal lymph nodes were found. Immunohistochemical stains of the extraneural metastases showed a strong cytoplasmatic expression of glial fibrillary acidic protein (GFAP). Neither the primary tumor nor its metastases showed any of the conventional morphological criteria of malignancy. Reviewing the literature we discuss the possible mechanism of extraneural tumor spread and the incidence of metastases with regard to the tumor type. (Pathology Oncology Research Vol 5, No 1, 56–60, 1999)

Key words: extraneural metastases, intraspinal tumor, ependymoma

Introduction

Ependymomas are glial neoplasms arising in the brain or the spinal cord. Spinal ependymomas are mostly of the myxopapillary type and generally benign with a tendency towards slow growth and local recurrence. Until the late fifties the statement of Bailey and Cushing[1] and later of Willis[36] that gliomas never give rise to metastases outside the central nervous system was generally valid. It is only within the last 40 years that central nervous system tumors with distant metastases have been described and they remain exceedingly rare. Most of these metastasizing tumors arise intracranially and only a very small number are located in the spinal cord. We found only ten previous cases of extraneural metastasizing spinal ependymomas.[6,14,16,18,23,24,29,34,35] This report presents a case of a 54 year old male with a thoracolumbar myeloresection of a well differentiated myxopapillary ependymoma (WHO I) of the conus medullaris and the cauda equina with extraneural metastases 40 years after the primary diagnosis.

Received: Sept 8, 1998; *accepted:* Dec 29, 1998

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Case history

A 15 year old, previously healthy boy, complained of pain in the thoracolumbar region in 1956. In the following 3 months he developed a progressive paraparesis. A myelogram demonstrated a right-sided intramedullary mass, involving the subdural space in the lower part of the spinal cord. The surgeon found a large intramedullary tumor of the conus medullaris with involvement of the cauda equina. The tumor was completely excised and histologically classified as a myxopapillary ependymoma without signs of malignancy (WHO I). After the tumor resection the patient made a complete recovery and remained free of symptoms for 32 years.

At the age of 46 he was readmitted with lumbar pain, obstruction of micturation and defecation and weakness of the legs. Computed tomography (CT) demonstrated a tumor in the lumbar spinal cord with infiltration of the vertebrae bodies L 2–5. Biopsy revealed a recurrence of the myxopapillary ependymoma.

The lower vertebrae and the sacrum were treated with a three-field radiation technique up to 30 Gy in 28 fractions over 41 days.

The patient remained free of symptoms until 1992 when lumbar pain, followed by paraplegia and urinary incontinence recurred. In addition to the neurological symptoms he developed respiratory dysfunction. Chest

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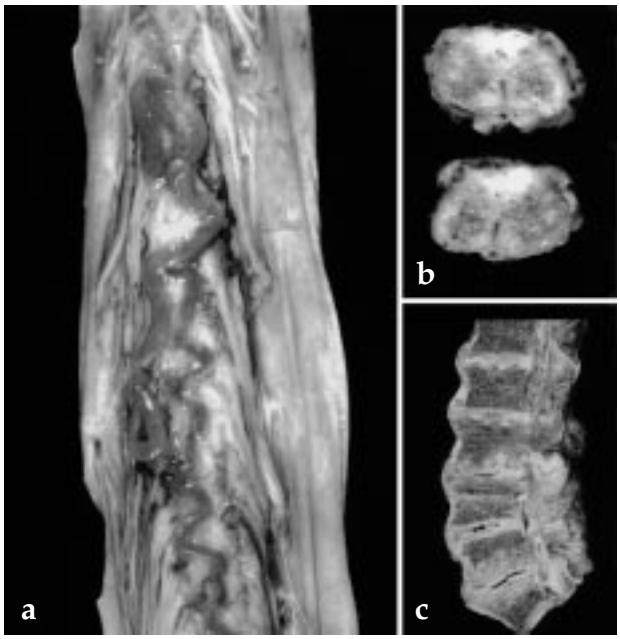

Figure 1. *Lumbar spinal cord, bloated and partially destroyed by a soft tumor (a and b) with extensive tumor vascularisation and infiltration and destruction of the lumbar spinal column (c)*

radiographs showed a few intrapulmonary tumors in both lungs, the greatest 1.5 cm in diameter and a right sided pleural efusion. Microscopically a biopsy of a pulmonary lesion showed a papillary tumor with the same histological pattern as the known spinal ependymoma.

Due to the progress of the pulmonary metastases, three cycles of a multiagent systemic chemotherapy with cisplatin, etoposide and ifosfamide were given There was, however, no evidence of tumor regression. In the remaining two years the lung metastases grew extensively and further metastastic tumors in the liver were noted. At the age of 54 the patient died of respiratory failure, 40 years after the onset of symptoms and the primary diagnosis of a spinal cord ependymoma.

Pathological features

At postmortem examination the lumbar spinal cord and the conus medullaris were bloated by a white-glassy, focally cystic tumor with obliteration of the subdural space *(Figure 1a, b)*. The surrounded dura and vertebrae bodies T12 and L1-5 and parts of the lumbar muscles were infiltrated by the tumor and partially destroyed *(Figure 1c)*. In both lungs, subpleurally and inside the parenchyma numerous well-defined, white-greyish, fleshy nodules up to 2.5 cm in greatest diameter were found *(Figure 2b)*. The tracheobronchial lymph nodes were bilaterally enlarged by white, homogeneous tumor tissue. Further tumor nodules were seen in the liver with a maximum sizes of 4.5 cm *(Figure 2a)*. Metastases were also found in the abdominal lymph nodes.

Microscopic examination revealed a cellular tumor consisting of uniform, ovoid cells in a papillary arrangement with ill defined cytoplasmic borders *(Figure 3a, b)*. These cells were embedded in a myxoid degenerated, fibrovascular matrix and mostly arranged around small, hyanlinized blood vessels, forming pseudorosettes. There was little evidence of cellular pleomorphism and mitotic figures were scanty. Immunohistochemical staining of formalin-fixed, paraffin-embedded tumor tissues *(Figure 3c)* showed strong expression of glial fibrillary acid protein (GFAP) and vimentin and a lack of staining for cytokeratins, S-100 protein, neuron specific enolase, and chromogranin. The histologic appearance and the immunohistochemical data lead to the diagnosis of metastases of the known myxopapillary ependymoma of the spinal cord.

Discussion

Ependymomas are the most common tumors of glial origin of the spinal cord. They often occur in the cauda equina and at this site they are frequently of the myxopapillary type. Although they are usually benign, local tumor recurrence after incomplete removal is often seen.[16,27] Extraneural metastases from spinal cord or primary central nervous system tumors are considered to be a rare event. The majority of the metastasizing tumors are located in the cerebrum, and a very small number arise in the spinal cord.

The first acceptable case of an extraneural metastasizing ependymoma of the cauda equina was described by Weiss et al.[34] in 1955. He reported a 32 year old male with widespread metastases in the lungs, the pleura, the hilar lymph nodes, the liver, and the retroperitoneum, found at autopsy, 10 years after the primary diagnosis. In his paper he established four rigid criteria to diagnose extraneural metastases: (1) the metastatic lesion must be histologically characteristic of a CNS tumor, (2) the clinical history must suggest a CNS tumor as the initial neoplasm, (3) a complete autopsy must be performed to exclude any other primary tumor, (4) the morphologic features of the primary tumor and the metastatic lesion must be identical. Today

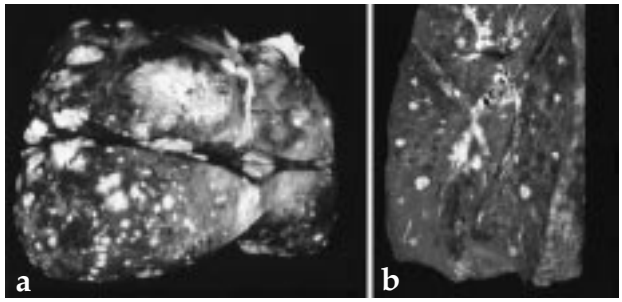

Figure 2. *Widespread metastases in the liver (a) and the lung (b)*

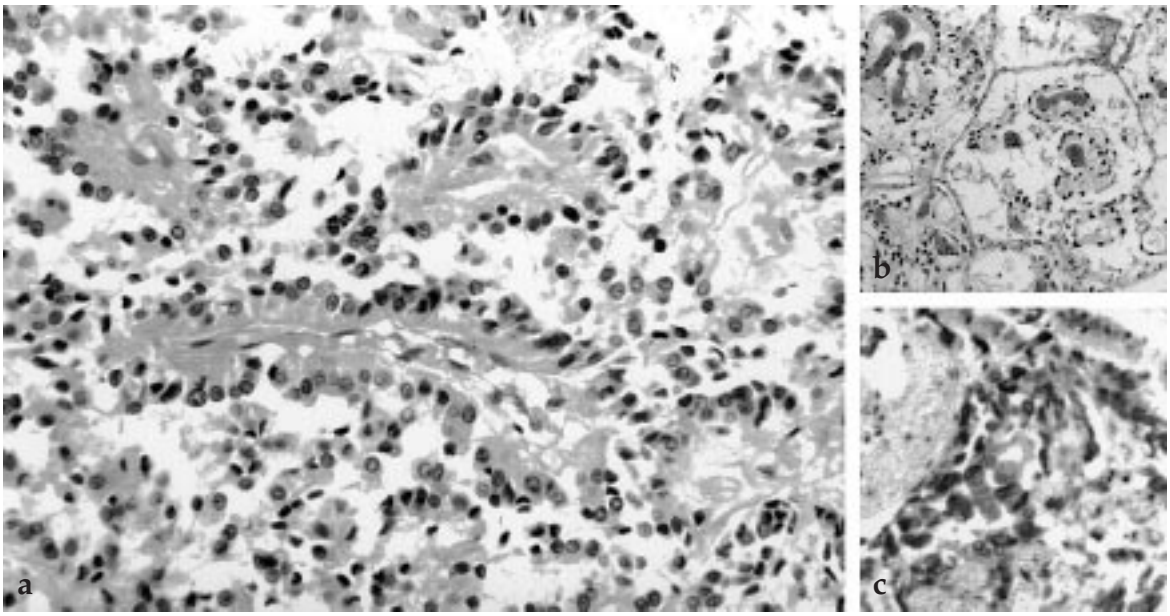

Figure 3. *Histological structure of the pulmonary metastases showing a papillary tumor consist of uniform, ovoid cells arranged around small, hyalinized blood vessels, forming pseudorosettes (a), HE, x300, with intraalveolar tumor spreading (b), HE, x120, and intracytoplasmatic expression of GFAP (c) x360*

these criteria are not generally valid, since cases of extraneural metastases as the first manifestation of a CNS tumor are reported.[4,5] Further, the immunohistochemistry with the use of different antibodies makes it often possible to identify the derivation of a metastases from a nervous system tumor alone by biopsy.

A survey of literature reveals only a few reports of collected cases of different kind of extraneural metastasizing CNS tumors.[8,12] The greatest collection from Hoffman et al.[8] included 282 patients, from whom nearly 60% were adults and 40% were children. In adults the most common metastasizing tumor is the glioblastoma followed by meningeal tumors and medulloblastomas. Ependymomas present only 5% of metastasizing tumors at that age. In children more than 60% of extraneural metastasizing tumors are medulloblastomas, and secondly astrocytomas which present nearly 10%. However, these rates of metastasis rather reflect the general occurence of the tumor type, than indicating the metastasis potential of each entity. Only a few reports exist about the tumor type dependent risk of extraneural metastases in intracerebral neoplasm.[10,25] The incidence of distant metastases in astrocytoma, oligodendroglioma, glioblastoma and meningeal tumors is nearly identical (approximately 0.5%). In ependymomas it is two times higher, while in medulloblastoma it is 12 times higher, corresponding to a metastasis rate of up to 6 % in medulloblastoma.[33] Due to of their rarity, information about the incidence of extraneural metastasizing spinal cord tumors are not available. Jänisch et al[10] listed only 13 cases of intramedullary tumors with distant metastases to 1985, to which 6 further cases have to be added since.[6,18,19,26,28] Most of these cases are ependymomas (n=10), followed by primitive neuroectodermal tumors (n=3) and spinal glioblastomas (n=3). Interestingly, all of the metastasizing spinal ependymomas had four characteristics in common: (1) early onset of disease with a mean age of diagnosis for the primary tumor of 21.1 years, (2) a long, symptomless period from diagnosis to the appearence of metastasis with a mean time of 23.6 years, (3) numerous local operations, and (4) extensive local tumorous progression at the time the distant metastases were noted. The lungs are the most frequent site of metastasis in ependymomas, followed by the pleura, the thoracic and abdominal lymph nodes and the liver. The relevant features of previously published cases are summarized in *Table 1*.

Improvement of care and consequent prolongation of life of paraplegics in recent years may be a factor contributing to remote metastasis.[31] The pathways of extraneural spread of CNS tumor cells have been delineated and related to different factors.[12] The most important factor appears to be surgical manipulation of the tumor with a possible disturbance of tumor cells inside blood vessels. Another route of tumor dissemination is along a cerebrospinal fluid shunt. The use of a microfilter in the shunting system reduces the risk of systemic metastasis.[2] The long time accepted postulate, that glial cells do not invade intact blood vessels, can not be maintained today, because in some cases of extraneural metastases, tumor cells were found in venous blood vessels without a previ-

Table 1. **Reported cases of spinal cord ependymomas with extraneural metastases**

Sex	*Age of onset*	*Site*	*Histology*	*Number of operations*	*Courses of radiotherapy*	*Courses of chemotherapy*	*Site of metastases*	*Survival (years)*	*Reference*
M	22	Cauda equina	Myxopapillary ependymoma	5	2	none	Retroperitoneum liver, pleura, lungs, tracheobronchial lymph nodes, chest wall	10	34
M	29	Cauda equina	Ependymoma	3	yes**	none	Liver, lungs, pleura mediastinum, chest wall	'4	29
F	28	Cauda equina	Myxopapillary ependymoma	3	2	none	Vertebrae, mediastinum, pleura, lung, tracheo-bronchial lymph nodes	17	23
F	17	Cauda equina	Ependymoma	3	5	none	Fourth ventricle, lung pleura, lymph nodes	29	24
M	28	Cauda equina	Ependymoma	2	2	none	Humerus, pleura	31	35
M	7	Cauda equina	Ependymoma	5	2	8	Lungs	29	14
F	10	Cauda equina	Ependymoma	5	2	4	Lungs, right hip	12	17
M	37	Cauda equina*	Myxopapillary ependymoma	3	none	yes**	Lungs, pleura	4	19
M	16	Cauda equina	Myxopapillary ependymoma	2	1	yes**	Abdomen (ventriculo-peritoneal shunt)	18	19
M	23	Thoracolumbar	Ependymoma	1	1	none	Vertebrae, bone marrow	12	6
M	15	Conus medullaris/ Cauda equina	Myxopapillary ependymoma	1	2	3	Vertebrae, lungs, pleura chestwall, liver, abdominal and mediastinal lymph nodes	40	present case

* partially extradural; ** no details

ous surgery or biopsy. This fact makes it likely that the tumor spreads outside the CNS through the venous system after active invasion of intracerebral blood vessel lumina.[4,9,11] Furthermore, a tumor cell separation along the lymphatic system seems to be conceivable since a connection between the liquor space and the lymphatic system has been demonstrated.[15,20,21] Another factor of tumor infiltration and separation depends on cell-cell and cell-matrix interaction via adhesion molecules.[3,32] Regarding migration of brain tumor cells, the adhesion molecules N-CAMs, I-CAMs and the integrins seem to play an important role.[7,13]

Interestingly, the correlation between histological type and differentiation of the ependymoma and metastatic potential is not significant.[8,81] Wight et al[35] reviewed 19 cases of cerebral and spinal ependymoma with extraneural metastases. In more than half of the cases the primary tumor was well differentiated and the metastases also had all the characteristics of benign tumors, like our case.

The therapeutic options for metastasizing nervous system tumors are very restricted. A gentle approach to the tumor and complete resection at the first operation should be the aim.[16,27] In all cases a good response to radiotherapy of the primary tumor has been seen.[30] Intravenous systemic chemotherapy appears to be of limited benefit.[17]

Although distant metastases of cerebral or spinal cord tumors are rare events, an extraneural tumor metastasis should be included to the differential diagnosis, even if the primary tumor was well differentiated and the symptom free interval was long.

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