Extracranial Metastases of Malignant Ependymoma

—Case Report—

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Abstract

A case of malignant ependymoma with extracranial metastases is reported. A 59-year-old male was admitted to our hospital with vomiting and ataxia. Following computed tomographic (CT) scanning indicating a ring-like enhanced mass in the cerebellum, the tumor was subtotally removed in December, 1985. Histological diagnosis was malignant ependymoma. A second operation was performed in February, 1987, due to recurrence of the tumor in the fourth ventricle. Postoperative radiation therapy at a total dose of 7780 rads was given over 2 years. Eleven months after radiation therapy was completed, he reported cough and multiple skin metastases. Chest x-rays showed metastases at the right hilus. Repeated CT scans revealed separate frontal cerebral metastatic tumors. He died of respiratory insufficiency. Extracranial metastases of infratentorial ependymoma to the skin and lung are rare pathological entities.

Key words: malignant ependymoma, extracranial metastases

Introduction

Extracranial metastases of primary intracranial tumors are extremely rare. One clinicopathological study³²⁾ revealed that such metastases occurred in only 0.4–0.5% of all primary intracranial tumors. In this report, we present a case of malignant ependymoma originating in the fourth ventricle and metastasizing to the lung and skin.

Case Report

A 59-year-old male with complaints of headache, vomiting, and ataxia was admitted to our department on December 5, 1985. Neurological examination revealed dysarthria and truncal ataxia. A chest x-ray disclosed no abnormalities. A computed tomographic (CT) scan showed a ring-like enhanced mass in the cerebellum adjacent to the fourth ventricle (Fig. 1A). Left vertebral angiograms revealed no tumor staining. A suboccipital craniectomy performed on December 17 encountered a cystic tumor with hemorrhagic nodules extending into the vermis. The

Fig. 1 A: Postcontrast CT scan taken in December, 1985, shows a ring-like enhanced mass in the right cerebellar hemisphere adjacent to the fourth ventricle. B: Postcontrast CT scan taken in February, 1987, shows a homogeneously enhanced mass in the fourth ventricle.

tumor was subtotally removed, some tissue around the pons and the bulbar dorsal point being left. Histological diagnosis was malignant ependymoma (Fig. 2). The tumor cells were negative for glial fibrillary acidic protein. Radiation therapy at a total dose of 4840 rads was administered after surgery.

Fig. 2 Photomicrographs of the first surgical specimen, show papillary growth of tumor cells with hyperchromatic nuclei. Cellular pleomorphism, mitotic figures, and endothelial proliferations can be seen. No necrotic foci are observed. HE stain, A: $\times 100$, B: $\times 200$.

The postoperative course was uneventful and he was discharged on February 22, 1986, returning to a normal life.

In January, 1987 he again began to experience ataxic gait. He was readmitted on February 12, for severe vomiting. A CT scan showed a tumor recurrence in the original location, appearing as a homogeneously enhanced mass lesion (Fig. 1B). The angiographic findings were the same as before. On February 17, a second operation was performed and the tumor appeared as a hemorrhagic mass with distinct boundaries and no cysts. Dissection of the tumor from the ventricular wall was not difficult, but the fibrous part of the mass at its lower boundary near the obex was difficult to distinguish from normal tissue; therefore, some tumor tissue was left at the site. The results of histological analysis were the same as for the first surgical specimen. Following the second operation, he received radiation therapy at a total dose of 2940 rads, applied to the posterior fossa and superior cervical vertebrae. At the same time, 10^5 IU of human interferon (INF)- β was administered once a week. On March 27, 1987, he was discharged with no neurological deficit.

In January, 1988, he began to experience coughing with sputum. He was readmitted on February 27. Chest x-rays showed an abnormal shadow in the right hilus pulmonis (Fig. 3A). On admission, two subcutaneous tumors 2–3 cm in size were discovered in the left thoracic area and in the right abdomen. No neurological symptoms were observed. A ^{67}Ga citrate scan demonstrated an abnormal tracer accumulation in the right mediastinum. A biopsy of the hilus taken with a bronchofiberscope revealed the presence of tumor tissue (Fig. 4A). In view of his

Fig. 3 A: Chest x-ray taken on the day of the third admission, shows a round, soft tissue mass at the right hilus, with pleural effusion in the right costophrenic angle. B: Chest x-ray taken on the 21th day of the third hospitalization, shows increased pleural effusion.

clinical course, the tentative diagnosis of ependymoma metastasized to the lungs was made. A radionuclide bone scan remained normal, but a CT scan showed new metastases to the right frontal lobe, with no recurrence of the cerebellar tumor.

On March 10, chemotherapy using cyclophosphamide, adriamycin, and etoposide was commenced. Repeated chest x-rays revealed increased pleural effusion (Fig. 3B). Cisplatin was given at 2–3 week intervals, and in late June, chest x-rays indicated some improvement. However, skin metastases occurred in additional sites of the right chest (4×4 cm), left axilla (2×2 cm), and left abdomen (2×2 cm). On June 20, partial extirpation was performed by a dermatologist, because of his complaints of pain and enlargement of the tumors. Microscopic ex-

Fig. 4 A: Photomicrograph of biopsy specimen obtained *via* the bronchofiberscopy. Malignant cells are scattered about the bronchial surface and surrounding tissue, with cells observed in clusters (arrows). HE stain, $\times 100$. B: Photomicrograph of the metastatic skin tumor, shows cell proliferation similar to that of the cerebellar tumor. HE stain, $\times 100$.

Fig. 5 Postcontrast CT scan, shows high-density areas in the bilateral frontal lobes and a recurrence of the cerebellar tumor. The fourth ventricle is not compressed.

aminations of the specimen disclosed that malignant ependymoma cells had metastasized into skin layers, from the corium to subcutaneous tissue. In the subcutaneous tissue, cells were clumped in comparatively complete clusters, with evidence of epithelial funicular series and perivascular pseudorosettes. Ependymal rosettes were also present in some places. The shape of the cell nuclei was the same as that of the cerebellar tumor (Fig. 4B). He gained a temporary remission and was discharged on July 3, but he continued to receive INF- β once a week as an outpatient.

On August 29, he was readmitted for pain from skin metastases to the right (2×2 cm) and left (3×4 cm) abdomen and left axilla (1×2 cm).

Chest x-rays taken in November revealed a fluid accumulation in the pleural cavity. Skin metastases had appeared on seven sites in total. A CT scan showed a slightly enhanced tumor in the cerebellum and markedly enlarged high-density areas in the left and right frontal lobes (Fig. 5). He died of respiratory insufficiency on November 20. No autopsy was obtained.

Discussion

According to the literature, since Meredith's report in 1951²¹⁾ there have been only 29 cases of ependymoma with extracranial metastases.^{1-3,5-8,10-12,16,18-21,23-27,30-36)} In this country, only four such cases have

Table 1 Summary of reported cases of intracranial ependymoma with extracranial metastases

Case No.	Author (Year)	Age/ Sex	Location of primary tumor	No. of opera- tions	Radia- tion therapy	Dura- tion*	Site of metastases	Autopsy	Diagnosis
1	Meredith and Sahyoun (1951) ²¹⁾	21/F	frontal lobe	2	+	7 mos	dura, skull	—	ependymoblastoma
2	Feigin and Volk (1951) ⁶⁾	29/M	frontal lobe	3	+	2 yrs	scalp	+	malignant ependymoma
3	Mastragostino (1952) ²⁰⁾	44/M	lateral ventricle	1	—	6 yrs	lung, subpleura	+	ependymoma
4	Maass (1954) ¹⁸⁾	27/M	occipital lobe	3	+	30 mos	scalp, cervical lymphnodes	—	ependymoblastoma
5	Sherbaniuk and Shnitka (1956) ³¹⁾	16/F	parietal lobe	3	+	13 yrs	dura, scalp, lung	+	ependymoma, grade I
6	Wen and Barrows (1957) ³⁵⁾	9/M	frontal lobe	1	+	15 mos	scalp, lung, axillary and hilar lymphnodes	+	ependymoma
7	Perry (1957) ²⁶⁾	39/M	parietal lobe	2	+	6 yrs	liver, femur	+	ependymoma
8	Breslich (1957) ³⁾	11/M	occipital lobe	2	+	2 yrs	dura, lung, pleura, mediastinal and hilar lymphnodes	+	ependymoma, grade III
9	Perrin (1958) ²⁵⁾	2/F	cerebellum	2	+	7 mos	lungs, mediastinum	+	ependymoblastoma
10		4/F	thalamus	1	+	14 mos	skull, spine, femur, ilium	+	ependymoblastoma
11	Nigogosyan <i>et al.</i> (1962) ²³⁾	15/F	parietal lobe	3	+	4.5 yrs	lung	+	ependymoma, grade II
12	Glasauer and Yuan (1963) ¹⁰⁾	2/M	parieto-occipital lobe	3	+	14 mos	dura, lung, hilar lymphnodes	+	ependymoblastoma
13	MacMahon and Urista (1964) ¹⁹⁾	3/M	lateral ventricle	2	+	15 mos	dura, lung, pleura, mediastinal lymphnodes	+	malignant ependymoma
14	Hesselvik and Tygstrup (1965) ¹¹⁾	2/M	parietal lobe	3	+	12 mos	dura, skull, scalp, lung, subpleura	+	ependymoblastoma
15	Wentworth and Birdsall (1966) ³⁶⁾	2/M	parieto-occipital lobe	2	+	5 mos	dura, hilar lymphnodes, lung	+	ependymoblastoma
16	Fragoyannis and Yalcin (1966) ⁸⁾	22/M	occipital lobe	2	+	13 mos	dura, vertebra, cervical lymphnodes	—	ependymoma, grade III
17	Robinson and Sharkey (1967) ²⁷⁾	14/M	third ventricle	1	+	22 mos	lungs, pleura, mediastinum, mediastinal lymphnodes	+	ependymoma, grade IV
18	Braun and Tzonos (1968) ²⁾	6/F	frontal lobe	1	+	5 mos	scalp	—	ependymoma
19	Smith <i>et al.</i> (1969) ³²⁾	31/M	parietal lobe	2	+	8 yrs	lung, cervical and mediastinal lymphnodes	+	ependymoma
20	Højgaard and Joransen (1970) ¹²⁾	13/M	fourth ventricle	2	+	9 mos	lung, liver, kidney	+	malignant ependymoma
21	Schuster <i>et al.</i> (1976) ³⁰⁾	13/F	frontoparietal lobe	1	—	7 mos	preauricular lymphnodes	—	ependymoma, grade II
22		7/M	parietal lobe	2	+	31 mos	dura, scalp, cervical lymphnodes	+	ependymoma, grade II
23	Tamura <i>et al.</i> (1980) ³³⁾	22/F	frontal lobe	1	+	23 mos	dura, lung, liver	+	ependymoblastoma
24	Duffner and Cohen (1981) ⁵⁾	9/F	parietal lobe	3	+	45 mos	lung, pleura, bone, hilar lymphnodes	+	ependymoma
25	Panyathanya and Chantarakul (1982) ²⁴⁾	38/F	lateral ventricle	1	—	1 mo	heart	+	melanotic ependymoma
26	Andoh <i>et al.</i> (1984) ¹⁾	28/F	parietal lobe	3	+	5 yrs	scalp, lungs, spine, hilar and axillar lymphnodes	+	ependymoma
27	Ferracini <i>et al.</i> (1984) ⁷⁾	30/F	temporal lobe	2	+	17 mos	cervical lymphnodes	—	malignant ependymoma
28	Wakabayashi <i>et al.</i> (1986) ³⁴⁾	19/M	frontal lobe	4	+	2.4 yrs	lung, bone, cervical and hilar lymphnodes, dura	+	malignant ependymoma
29	Liote <i>et al.</i> (1988) ¹⁶⁾	27/F	occipital lobe	6	+	14 yrs	lung, pleura	—	ependymoma, grade IV
30	Present case	59/M	fourth ventricle	2	+	3 yrs	lung, skin	—	malignant ependymoma

*From diagnosis to death.

been reported,^{1,33,34)} including the case reported here. We summarized these cases in Table 1, excluding cases with dissemination to the spinal cavity and with metastases *via* shunts, but including cases with tumor tissue permeation to the scalp through the dura mater. Ages ranged from 2 to 59 years and there were only 15 children 15 years of age or younger, so that it cannot be said that metastases of ependymoma most frequently occur in children. The case reported here is the oldest.

The male-to-female ratio is 17:13. Overall median survival time is 36 months, but 11 months for children 5 years of age or younger. Primary tumors were located supratentorially in 27 cases and infratentorially in only three, demonstrating the overwhelming frequency of supratentorial origin. Locations of metastases are the lungs and pleura in 19 cases, the scalp, skull, and dura mater in 17, the lymphnodes in 15, and the skeletal system, kidneys, or heart occasionally. This is the first report of an adult with ependymoma originating in the fourth ventricle and metastasizing to the skin outside the scalp.

There are a number of theories of the mechanism of distant metastasis.^{7,8,10,17-19,30)} It is generally thought that the dissemination of tumor tissue results from invasive surgery such as craniotomy, in which tumor cells penetrate the scalp and gain access to the blood or lymph system. Table 1 includes 13 cases in which a clear invasion of tumor cells into the dura mater or scalp was observed. However, there are many other cases in which such invasion of tumor cells could not be demonstrated, or in which there is no clear description in this regard. In these cases, some possible routes and mechanisms of dissemination were suggested: tumor cells move along nerve roots until they reach the lymph system, then metastasize from there; tumors directly permeate the neurovascular system and metastasize *via* the blood; or tumor cells circulate within the spinal fluid causing multiple metastases and finally metastasize to sites unrelated to the original tumor. In the cases with metastases to the cervical lymphnodes, the cervical lymphatics were considered to be the most probable route of dissemination.

For each case listed in Table 1, surgery was performed on 1-6 occasions, on average 2.2 times; 27 of 30 cases received radiation therapy. In some cases, multiple operations, including craniotomy and shunts, or radiation therapy were thought to be factors encouraging metastasis,^{17,23,26,31)} but considering the very low incidence of metastasis outside the skull, this theory cannot be considered to be fully substantiated. Hematogenous dissemination may have occurred in the case reported here. This case is

highly unusual in two points: metastases to the lungs and skin occurred without marked worsening of the original tumor, and the metastatic tumors, not the original tumor, were the eventual cause of death.

Concerning the histological characteristics of the original tumor, degree of malignancy varies as shown in Table 1. One reason for this extreme variety is that definitions for use of the term "ependymoma" are still not established, and there are numerous classifications, especially for the undifferentiated types of ependymoma.

The Kernohan's classification¹⁴⁾ of astrocytic gliomas based on anaplastic features is recognized to be useful in predicting the outcome.⁹⁾ For ependymoma, however, there has been a lot of discussion.²⁸⁾ Many authors have reported a generally favorable outcome for differentiated types of ependymoma.⁴⁾ However, even in cases whose histological malignancy is extremely high, prognoses are not necessarily poor.^{13,15)} In 1970, Rubinstein²⁹⁾ made a comprehensive study of the histological characteristics of ependymoblastoma, elaborating clearer definitions based on the varying histological and pathological features, then in 1989,²⁸⁾ again emphasized the importance of differentiation between malignant ependymoma and ependymoblastoma, from the standpoint of correlation of histological features and outcome. In our case, all the characteristics of malignant ependymoma described by Rubinstein were evident, including extremely dense and irregular tumor architecture involving numerous giant and multi-nucleated cells, markedly abundant mitotic figures, vascular endothelial proliferation, and ependymal rosettes.

There are marked differences between malignant ependymoma and ependymoblastoma even in clinical terms. Most ependymoblastomas are seen in children 5 years of age or younger, and locate supratentorially. Outcome is extremely poor (median survival time, 12-18 months), and a widespread invasion through the cerebrospinal subarachnoid space is frequently shown.^{22,29)} Outcome in cases of malignant ependymoma vary greatly, however, their overall malignancy are much less severe than those supposed from histological characteristics. One-third of reported cases suffer poor outcome due to tumor recurrence (median survival time, 3.2 years), but another two-thirds enjoy good outcome (median survival time, 7.6 years). It is still unclear what accounts for this discrepancy.²⁸⁾

Table 1 also shows the relationship between the age at tumor onset and outcome. Five of the six cases 5 years of age or younger were diagnosed as ependymoblastoma and showed an extremely poor

outcome, but in adult cases, the relationship between survival time and histological characteristics varied considerably. The authors find special interest in this in the light of the relationships between outcome and histological types of malignant ependymoma described by Rubinstein.

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