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Massive Lung Metastasis from Cerebellar Medulloblastoma: a Report on One Case and Review of Literature

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Cerebellar medulloblastoma with massive lung metastasis in a 10-year-old girl was studied histopathologically and immunohistochemically. She was treated twice by operation and had bilateral lung metastases appearing 13 months after the second operation. The autopsy revealed that the bilateral lungs were almost replaced by the medulloblastoma, and that the residual tumor cells in the primary focus could only be seen at the level of light microscope. The primary and metastatic tumor cells did not show any differentiation immunohistochemically. While researching the literature between the years 1960 to 1996, 114 cases of all ages having medulloblastomas with extracranial metastases were found. The metastatic spread of the tumors occurs at the rate of 3.9% (114/2,925). This is an invaluable report which clearly shows the massive lung metastasis of medulloblastoma, based on the detailed review of literature.

Key words: extracranial metastasis; reviewing literature; lung metastasis; medulloblastoma; immunohistochemistry

It is well known that extracranial metastasis of primary brain tumors is an unusual occurrence. Some authors attribute the rarity of remote metastases of primary brain tumors to an inability of tumor cells to proliferate in other organs during the short postoperative life span of the patient (Winkelman et al., 1952; Perry, 1957). In a series of 8,000 cases of central nervous system (CNS) tumors of neuroectodermal origin, only 35 patients developed extracranial metastases (Smith et al., 1969). Approximately 200 cases of extracranial metastases have been reported in the literature in patients of all ages with brain tumors (Smith et al., 1969; Liwnicz and Rubinstein, 1979; Kleinman et al., 1981). As for the incidence of extracranial metastases in children with primary brain tumors, a clinical and pathologic review of brain tumors (917 cases in a 62-year period) identified only 21 cases (2.3%) with systemic metastases, and this included 15 cases of medulloblastoma (1.6%) (Campbell et al., 1984). We report a child patient having medulloblastoma with massive metastasis to the bilateral lungs appearing 13 months after the second resection of the cerebellar medulloblastoma, whose lungs are almost replaced by the medulloblastoma. In addition, we provide a detailed review of the literature of the medulloblastomas with extracranial metastases.

Abbreviations: ABC, avidin-biotin-immunoperoxidase complex; BSA, bovine serum albumin; CNS, central nervous system; CSF, cerebrospinal fluid; CT, computed tomography; GFAP, glial fibrillary acidic protein; H&E, hematoxylin and eosin; NSE, neuron specific enolase; PBS, phosphate-buffered saline; pNFP, phosphorylated neurofilament protein; PTAH, phosphotungstic acid-hematoxylin

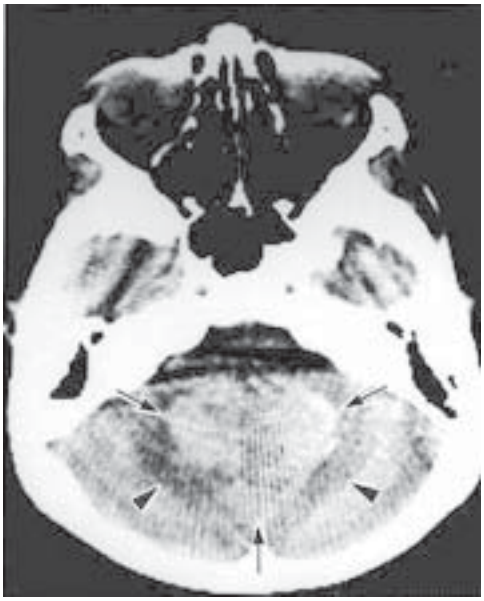

Fig. 1. Contrast enhanced computed tomography scan of the brain shows a high density mass (arrows) with perifocal edema (arrowheads) in the cerebellar vermis.

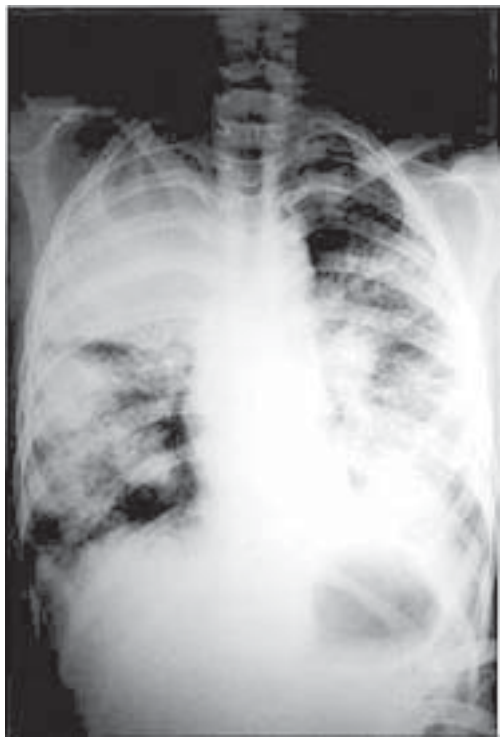

Fig. 2. Chest radiograph demonstrates multiple radiopaque lesions in the bilateral lung fields and almost complete opacity in the superior lobes on the right side.

Materials and Methods

Patient

An 8-year-old female child was admitted to Matsue Municipal Hospital with a 1-month history of loss of consciousness on January 26, 1990. At the time of admission she was in good general health and was afebrile. An contrast enhanced computed tomography (CT) scan of the brain demonstrated a high density mass with perifocal edema in the cerebellar vermis (Fig. 1). The chest radiograph showed no abnormalities. Suboccipital craniectomy was performed on February 1, 1990. The tumor in the cerebellar vermis was totally resected under direct vision. Radiotherapy (total dose of 40 Gy) was given on over a period of 4 weeks. The postoperative and postradiation state was uneventful. She became able to walk by herself and was discharged on April 3, 1990.

On February 5, 1991, she suffered from unconsciousness again and was readmitted. A second operation was performed on February 7, 1991, and the recurrent tumor in the cerebellar vermis was subtotally removed. The chest radiograph before the second operation showed no abnormality. The second postoperation course was relatively smooth until she complained of dyspnea 13 months after the second operation. X-Ray films of the chest demonstrated multiple radiopaque lesions in the bilateral lung fields and almost complete opacity in the superior lobe on the right side (Fig. 2). Her dyspnea progressed and her general condition deteriorated gradually, and she died of respiratory insufficiency at the age of 10, on April 23, 1992. A postmortem examination was performed 16 h after her death.

Histopathology and immunohistochemistry

After being fixed in 10% buffered formalin for 2 weeks, the specimens were embedded in paraffin, and cut into 6 μm-thick sections. The brain, spinal cord and lungs as well as lymph nodes were stained by the following routine methods: hematoxylin and eosin (H&E), Klüver-Barrera, Holzer, Bodian, reticulin, phosphotungstic acid-hematoxylin (PTAH) and Bielschowsky stains. The sections of the visceral organs were stained with H&E. Representative paraffin sections were used for immunohistochemical tests.

The avidin-biotin-immunoperoxidase complex (ABC) method (Hsu et al., 1981) was employed for glial fibrillary acidic protein (GFAP), synaptophysin, phosphorylated neurofilament protein (pNFP) and neuron specific enolase (NSE). Sections were deparaffinized, endogenous peroxidase activity was quenched by incubation for 30 min with 0.3% H_2O_2, followed by washing with phosphate-buffered saline (PBS). Normal horse serum served as a blocking reagent. Mouse monoclonal antibodies against GFAP (ready-to-use, BioGenex Laboratories, San Ramon, CA), synaptophysin [1:100 in 1% bovine serum albumin (BSA)-containing PBS, Boehringer-Mannhaim Biochemica, Germany], pNFP (1:5,000 in BSA-PBS, Sternberger Monoclonals Inc., Baltimore, MD) and NSE (ready-to-use, BioGenex Laboratories) were used. Tissues sections were incubated with the antibodies for 18 h at 4˚C. PBS replaced the antibody in the controls. The horse anti-mouse IgG Vectastain ABC kit (Vector Laboratories, Burlingame, CA) was used to detect each bound antibody. 3,3'-Diaminobenzidine tetrahydrochloride was the final chromogen. Hematoxylin was used to counterstain some sections while other sections were not.

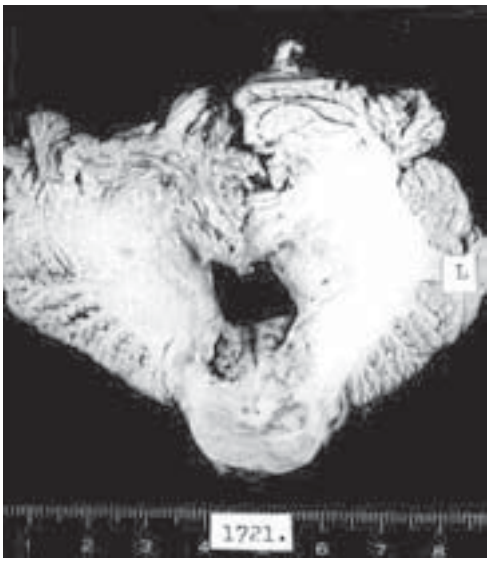

Fig. 3. Transverse section of the cerebellar vermis (primary focus), cerebellar hemisphere and pons. Although the cerebellar vermis shows an operative defect, an apparent tumor mass is not seen macroscopically.

Results

Autopsy findings

The brain weighed 1,080 g. At autopsy, the tumor infiltrating into the spinal cord lesions, especially the thoracic segments, were identified externally. However, the cerebellar vermis showing the operative defect had no apparent tumor tissue macroscopically (Fig. 3). The tumors in the spinal cord were soft, rather fragile and moderately demarcated from the normal tissues. The tumor-cut surfaces were greyish with small necrotic foci. The lungs on the bilateral sides were almost replaced by the greyish tumors. Sections of the lung tumors were greyish in color, associated with hemorrhage and necrosis. The normal lung area not involved by tumors was only one-tenth of the whole lung, showing an advanced edema and congestion (Fig. 4). The lymph nodes were swelling in the hilus of the lung as well as in the areas adjacent to the esophagus, thoracic aorta and trachea. Cross sections of these areas showed an outline of fused nodes with tiny necrotic foci. Other abnormalities of the visceral organs included bilateral pleural effusion.

Histopathology and immunohistochemistry

Although the cerebellar vermis showed no apparent tumor tissue macroscopically, tumor cells were observed at the level of a light microscope. The tumors of the brain, spinal cord, lungs and lymph nodes had essentially the same aspects. One feature of the tumors showed high cellularity. Every field was packed with small cells in which the cytoplasms were scanty and poorly defined, and the nuclei were round or oval, variable in size and highly hematoxyphilic on account of their abundant coarse chromatin (Fig. 5). Mitotic figures were abundant and necrotic foci were occasionally seen. In many fields there were no special architectural arrangements of the cells: they simply formed irregular masses and sometimes they were supported by a tenuous stroma of blood vessels and collagenous tissues. The formation of rosettes of the Hormer Wright type was not observed in the examined tumor areas. PTAH-positive fibers were not observed in the tumors. Argyrophilic neurites in the tumors were also not seen. The tumor of the thoracic segments was characterized by a dense intercellular network of reticulin and collagen fibers, and had reticulin-free islands. This finding was compatible with a so-called desmoplastic

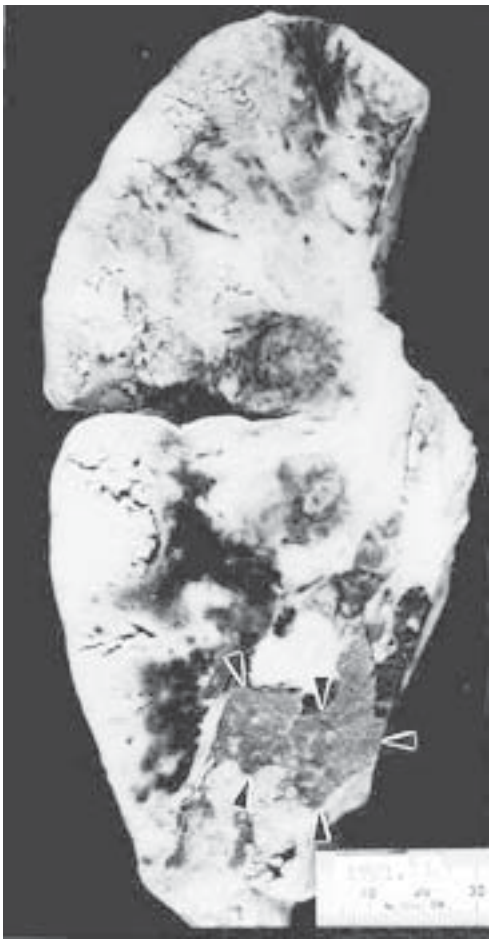

Fig. 4. Section of the left lung. The lung is almost replaced by the greyish tumor in association with hemorrhage and necrosis. The normal lung area not involved by tumors is approximately only one-tenth of whole lung, showing an advanced edema and congestion (arrowheads).

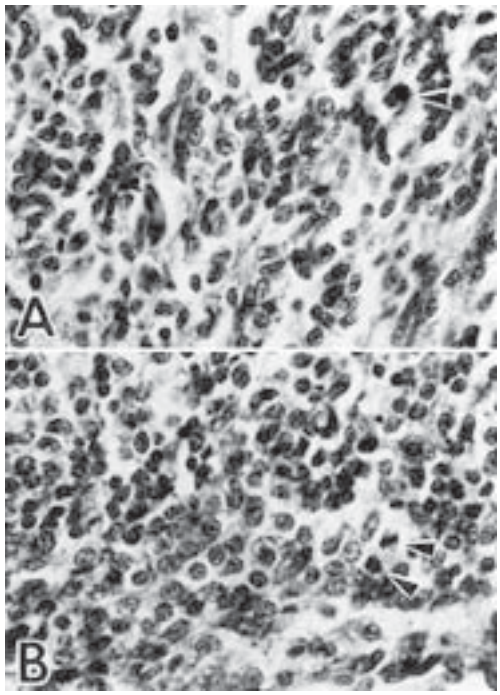

Fig. 5. Light micrographs of the cerebellar vermis (**A**, primary focus) and the lung tumor (**B**, metastatic lesion). The tumors of the cerebellum and lung have the same aspect: tumors are composed of small undifferentiated cells in which the cytoplasms are scanty, and the nuclei are oval and highly hematoxyphilic on account of their abundant coarse chromatin. Mitotic figures are seen (arrowheads in **A** and **B**). Hematoxylin and eosin (H&E). **A**, **B**: × 421.

change. However, the other tumor areas did not show a desmoplastic change. Immunohistochemistry revealed that the tumor cells in the CNS, lungs and lymph nodes were not stained by the antibody against GFAP (Fig. 6) and did not have a glial differentiation. The tumor also did not show a neuronal or neuroblastic differentiation because the tumor cells did not express the epitopes of synaptophysin, pNFP and NSE, immunohistochemically. The final diagnosis was undifferentiated medulloblastoma. Microscopic distribution of the medulloblastoma in the CNS is illustrated in Fig. 7.

Discussion

The medulloblastoma is a neoplasm composed largely of small undifferentiated cells and most of them originate in the cerebellar vermis (Russell and Rubinstein, 1989; Burger et al., 1991). The incidence of the medulloblastoma is highest during the first two decades of life, declining sharply during adulthood (Hubbard et al., 1989). A slight male predominance appears statistically valid (Caputy et al., 1987; Hughes et al., 1988). Our medulloblastoma was also composed of small undifferentiated cells and its primary focus was the cerebellar vermis. Immunohistochemistry demonstrated that the present medulloblastoma showed neither glial nor neuronal differentiation. Tumor-disseminating thoracic segments demonstrated a desmoplastic change as a result of its arachnoid involvement. The patient was a 10-year-old female child. Therefore, our case was one of typical medulloblastomas in terms of age, primary region and morphology.

The present case showed a massive metastasis to the bilateral lungs and dissemination along the cerebrospinal fluid (CSF). As for the dissemination, in 1930 Bailley demonstrated

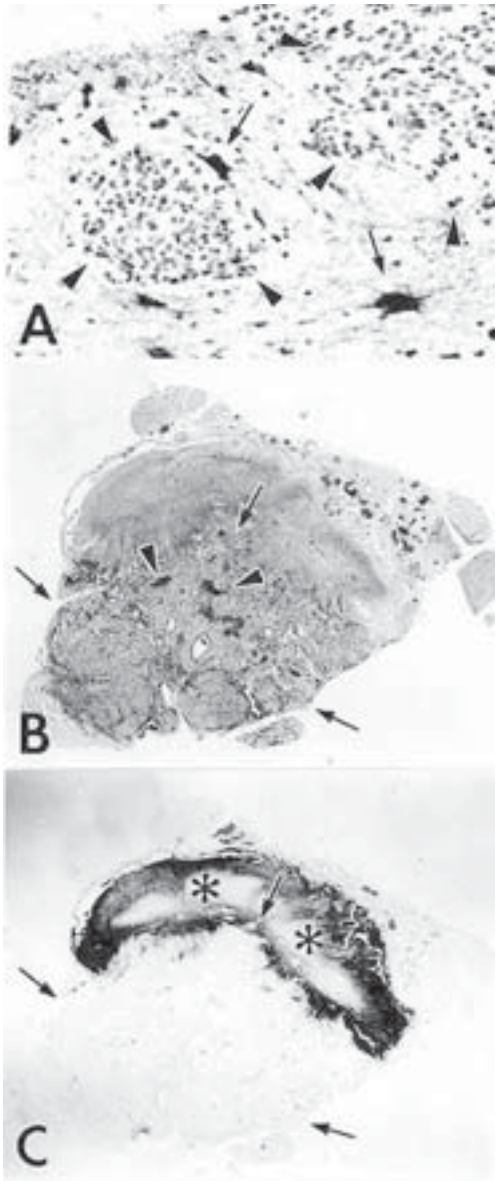

Fig. 6. A: Immunostaining with antibody against glial fibrillary acidic protein (GFAP) in the tumor of primary focus in the cerebellar vermis. This section is counterstained with hematoxylin. Tumor cells are not stained with the antibody to GFAP (arrowheads), while the reactive astrocytes around the tumor are intensely positive (arrows). **B, C:** Serial sections of a thoracic segment in the spinal cord involved by the tumor, stained with H&E (**B**) and the antibody against GFAP without counterstain (**C**). The tumor infiltrating into the spinal cord (arrows in **B**) is not stained by the antibody to GFAP (arrows in **C**). However, a GFAP-positive reaction is seen in the normal spinal cord tissue compressed by the tumor (asterisks in **C**). There are small necrotic foci in the tumor (arrowheads in **B**). **A:** $\times 100$, **B, C:** $\times 6$.

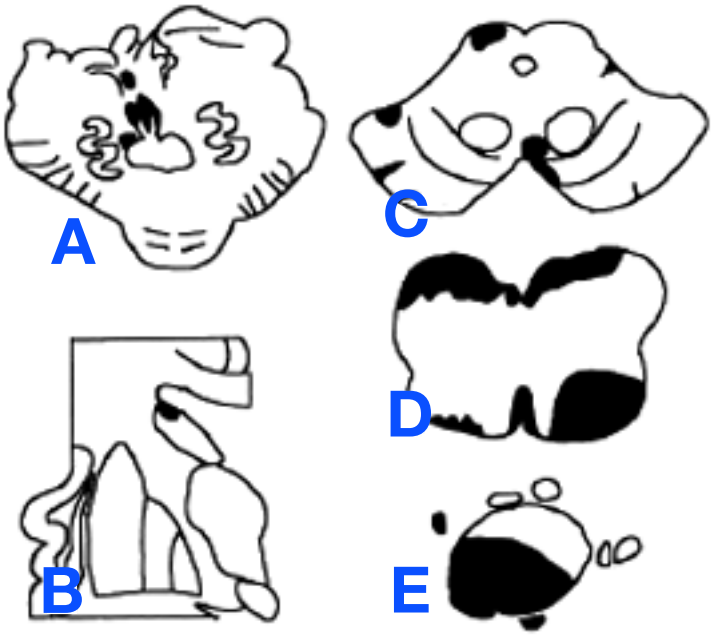

Fig. 7. Microscopic distribution of the tumor cells in the central nervous system. The shaded areas show the microscopic presence of the tumor cells. **A:** Transverse section of the cerebellar vermis (primary focus), cerebellar hemisphere and pons. As seen in Fig. 3, the cerebellar vermis shows no apparent tumor evidence macroscopically. As indicated by Figs. 5A and 6A, tumor cells are, however, observed at the level of a light microscope. **B:** Coronal section of the basal ganglia in the cerebrum at the level of mamillary body. **C:** Midbrain. **D:** Medulla oblongata. **E:** Thoracic segment of the spinal cord indicated by Figs. 6B and 6C.

that medulloblastomas tended to seed along CSF pathways, and in the same year Wohlvill (1930) was the first to draw attention to the occurrence of systemic metastasis of medulloblastoma. Since then, metastases within the CNS have been found in one-third to one-half of cases where a careful search of the brain, spinal cord and nerve roots was carried out (Abbott and Kernohan, 1943; Ingreham et al., 1948; Strang, 1962). Metastases outside the craniospinal axis, however, are much rarer. A review of the pediatric literature quoted 21 cases of extracranial metastases from 917 cases of primary intracranial tumors (Campbell et al., 1984). This included 15 cases out of 152 medulloblastomas; 1 case each out of 555 gliomas, 100 ependymomas and ependy-

Table 1. Frequency of medulloblastomas with extracranial metastases

Authors		No. of cases of medulloblastomas	No. of cases of extracranial metastases
Paterson	(1961)	35	7
Friborský	(1963)	6	1
Dexter and Howell	(1967)	93	3
Bloom et al.	(1969)	82	2
Aron	(1969)	24	1
McFarland et al.	(1969)	1,360	0
Chatty and Earle	(1971)	201	4
Smith et al.	(1973)	43	3
Hoffman et al.	(1976)	44	6
Brown et al.	(1977)	14	1
Das and Dalby	(1977)	22	3
Schnitzler et al.	(1978)	28	4
Jackson and Graham	(1978)	100	1
Raimondi and Tomita	(1979)	51	0
Naruse et al.	(1979)*	197	3
Paillas et al.	(1979)	17	3
Komatsu et al.	(1980)*	100	6
McComb et al.	(1981)	34	6
Campbell et al.	(1984)	152	15
Kasantikul and Shuangshoti	(1986)	35	1
Nakamura et al.	(1987)*	243	32
Farwell and Flannery	(1987)	44	12
Total		2,925	114 (3.9%)†

*Literature in Japan.
†( ), percentage of medulloblastoma with extracranial metastasis.

Table 2. Location of medulloblastomas with extracranial metastases

Authors	Rochkind et al. (1991)			Nakamura et al. (1986)			Komatsu et al. (1980)	Wakamatsu et al. (1972)
Sex	M	F	Total	M	F	Total	Total	Total
No. of cases	21	8	29	21	5	26	55	63
Organ								
Lung	4	1	5	3	2	5	8	2
Bone	21	7	28	13	2	15	44	47
Lymph node	5	5	10	6	1	7	23	7
Liver	3	1	4	8	2	10	7	2
Pleura	1	1	2	2	1	3	3	2
Diaphragm	0	0	0	3	1	4	0	0
Spleen	0	0	0	1	0	1	0	0
Kidney	0	0	0	2	0	2	0	0
Pancreas	1	1	2	2	0	2	3	0
Adrenal	0	0	0	2	0	2	0	0
Mesentery	0	0	0	3	0	3	0	0
Uterus	1	0	1	0	0	0	0	0
Bladder	0	0	0	1	0	1	0	0
Retroperitoneum	0	1	1	3	0	3	0	0
Skin, muscle and soft tissue	0	0	0	0	0	0	5	3

M, male; F, female.

moblastomas, and 43 pineal tumors; and an additional 3 cases out of 67 other miscellaneous types of brain tumors. In searching the literature from the years 1960 to 1996, 114 cases of medulloblastomas with extracranial metastases of all ages were found (Table 1). The metastatic spread of the tumor occurs at the rate of 3.9%. Although the present case was female, a marked overall male predominance is evident from the literature, with a 5:2 male/female ratio in foreign countries (Rochkind et al., 1991 in Table 2) and a 4:1 male/female ratio in Japan (Nakamura et al., 1986 in Table 2). Although remote metastases from intracranial tumors could be found in almost all parts of the body, our case showed that the target organs of the distant metastases from cerebellar medulloblastoma were lungs and lymph nodes. The literature (Table 2) demonstrates that the bone was the most frequent site for extracranial metastases (58–97%). Lymph node metastases were the second in frequency with an incidence of 11–42%. Lung metastases (3–17%) were slightly less frequent in comparison with liver metastases (3–38%).

Even so, the great rarity of extracranial metastasis of primary brain tumors is still not clearly understood. The absence of cerebral lymphatics (Elvidge et al., 1937; Dubois-Ferriere, 1940), early occlusion of venous channels by tumor compression (Smith et al., 1969), immunoresponse to the tumor cells by other organs (Kato et al., 1995), and the significant short postoperative life span in comparison with the clinical detection of the metastatic foci (Alvord, 1976) have all been regarded as significant factors. Russell and Rubinstein (1989) have documented in their textbook that resistance of the endothelium to invasion by glioma, resistance of the lung to grow medulloblastomas, inability of glioma to induce stroma, and immunological factors have also been considered to be important factors. By comparison, it is believed that surgical procedures play a major role in the entrance of tumor cells into extracranial blood vessels and lymphatics (Yokoyama et al., 1985). Direct lymphatic spread is impossible because true lymphatics are not present in the CNS. However, it is possible that the spread of tumors in continuity

along nerve roots may lead to the invasion of lymphatics (Das and Dalby, 1977), and indeed Oberman and colleagues (1963) have reported the presence of tumor cells in peripheral lymphatics. Russell and Rubinstein (1989) conjectured that small veins might be the routes of extracranial dissemination because tumor cells penetrating blood vessels, tumor invasion of dural veins, or direct extension to the cranium or to the operation site, were almost always encountered. By now, the hematogenous route of spread is accepted by most authors (Rochkind et al., 1991). Therefore, our case with massive lung metastasis is thought to be the result of the hematogenous route because of operation maneuvers, and lymph-node metastasis might be a secondary lymphatic spread from the tumors in the lung.

It is most conspicuous in the present case that almost all areas of the bilateral lungs were replaced by the medulloblastoma, appearing only 13 months after operation. As Russell and Rubinstein (1989) pointed out, the lungs have a resistance to the growth of medulloblastomas. Table 2 demonstrates that the incidence of lung metastases of medulloblastomas is rarer in comparison with those of the bone or lymph node. One report (Komatsu et al., 1980) has documented that only a 2 cm tumor focus of medulloblastoma in the upper lobe of the right lung was detected at autopsy, and that no clinical manifestation of the lung metastasis was observed. The responsibility for death in the present case was respiratory failure due to massive medulloblastoma infiltration into the bilateral lungs. To our knowledge (Tables 1 and 2), there is no literature of the medulloblastoma with massive lung metastasis except for the present case. Although the present medulloblastoma was undifferentiated and was thought to have a great growth potential, the reason why the medulloblastoma showed a rash proliferation in the lungs in comparison with the CNS including the cerebellum, brain stem and spinal cord is still unknown.

After the Packers' report on medulloblastoma treatment (1991), mainstream therapy supports irradiation plus adjuvant chemotherapy. Therefore, if this patient could have been treated with additional chemotherapeutics after the first operation, a short duration recurrence of the medulloblastoma in the cerebellum and/or a massive lung metastasis might not have occurred.

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