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Case Report

WHO Grade I Meningioma Metastasis to the Lung 26 Years after Initial Surgery: A Case Report and Literature Review

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Metastases from meningioma grade I are especially rare. We describe a case of a 65-year-old male with meningioma WHO grade I with a history of local recurrence and distant metastasis to the lung 26 years after the initial surgery. The original tumor was localized at the occipital low convex and invaded into the venous sinus and posterior cranial fossa; it was resected. About 15 years later, the tumor recurred in the posterior cranial fossa and γ-knife radiosurgery was performed. About 4 years later, the recurred tumor was resected at our hospital. Another 7 years later, the tumor recurred in the same area and right middle cranial fossa. All tumors except that inside the venous sinus were excised. All specimens obtained were classified as meningioma WHO grade I. Preoperative examination of the third operation revealed a nodule in the lower lobe of the right lung. The nodule grew gradually. Four months after the third surgery, partial resection of the right lung was performed. Histology indicated meningioma WHO grade I. The two lesions in the cranium and lung lesions were subjected to fluorescence *in situ* hybridization of the NF2 gene, and the three specimens had similar findings, genetically confirming them to be metastases of the intracranial meningioma. A literature review of past cases of meningioma progression revealed that the mean duration to metastasis is 12.5, 6.8, 3.7 years for grades I, II, and III, respectively. The current case therefore has an extended time frame.

Keywords: meningioma, extracranial metastasis, WHO grade I, lung, sinus invasion

Introduction

Intracranial meningiomas are the most common tumors of the central nervous system, accounting for 13–26% of all primary intracranial tumors;[1)] they are typically solitary and benign. Despite being pathologically benign, there are rare cases of metastases to extracranial sites, which take a course of malignancy.[2–6)] Distant metastasis of a meningioma is extremely rare, at 0.15%,[7)] but this may be an underestimation.[8)] Because of the rare nature of extracranial metastases, no standard management protocol has been established and the prognosis for these patients is unknown.[9,10)] Most meningiomas are WHO grade I and about 7–15% and 2–4% of meningiomas are WHO grade II and III, respectively.[11,12)] In metastatic cases, there are more cases of grades II and III. We describe a case of WHO grade I meningioma that had metastasized to the lung and reviewed the relevant literature.

Case

The patient was a 65-year-old male who, 26 years previously, had undergone surgery (at a previous hospital) for occipital low convexity meningioma that had invaded the transverse sinus, sigmoid sinus, jugular vein, and posterior cranial fossa. Part of the tumor in the sinus was left untouched, the remainder of the tumor was excised and a subtotal resection was performed. The tumor was diagnosed as fibrous meningioma. Sixteen years after the operation, the tumor recurred in the posterior cranial fossa and γ-knife radiosurgery was performed at another hospital. A further 3 years later, the tumor recurred and the patient came to our hospital for a second surgery. The second operation was performed and the tumor was completely excised (Figs. 1A and 1B). Histological sections showed a proliferation of spindle cells with oval and elongated nuclei arranged in fascicular or whorl-like arrangements. No atypical features were detected and WHO grade I meningioma was considered (Fig. 1C). Seven years after the second operation, the patient suffered headaches and nausea. Magnetic resonance imaging (MRI) revealed a recurring tumor (size: 6.5 × 5.7 × 5.9 cm) in the location of the previous operation; there was also another tumor in the middle cranial fossa (5.0 × 4.7 × 3.8 cm) where the first operation had been executed (Figs. 2A and 2B). A third operation was scheduled and the preoperative examination was performed. A chest X-ray revealed a nodule shadow in the right middle lung field. In a chest computed tomography (CT), a 2 cm nodule was seen in the lower lobe of the right lung (Fig. 3A). At this time point, treatment for the intracranial tumor was performed which included embolization of the feeding artery and tumor resection (Simpson grade II; Figs. 2C and 2D). There was no macroscopically visible tumor infiltration into the bone, and no histological examination of tumor infiltration was performed. Histologically, the sections showed proliferation of meningothelial tumor cells with oval or elongated nuclei arranged in

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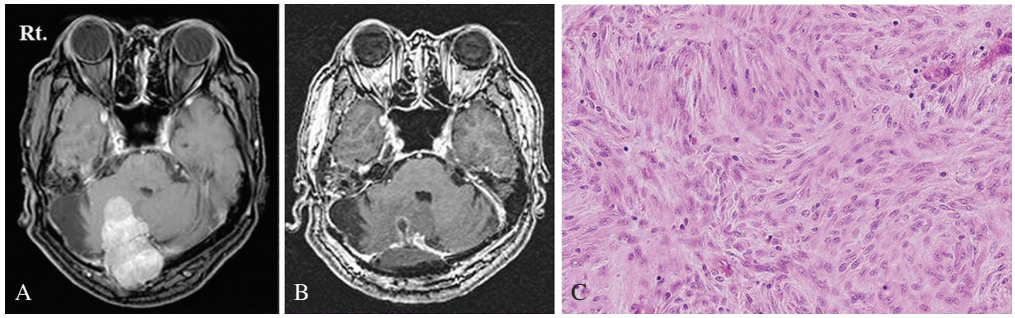

Fig. 1 (A) Pre-second operation. A tumor recurred in the posterior cranial fossa. (B) Radiologically, the tumor was completely resected. (C) The section shows proliferation of spindle cells with oval and elongated nuclei arranged in fascicuuli (hematoxylin and eosin, 200×). Atypical features were not evident.

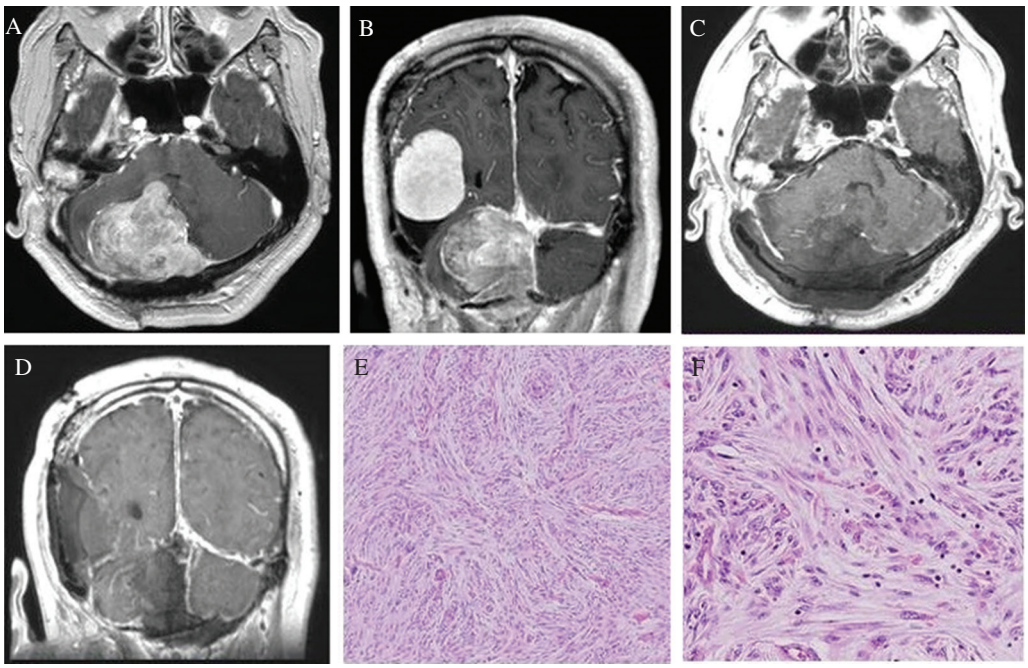

Fig. 2 (A and B) Pre-third operation. The tumor recurred in the same place (6.5 × 5.7 × 5.9 cm) as for the previous operation and additionally, it expanded from the ridge of the resected site to the middle cranial fossa (5.0 × 4.7 × 3.8 cm). (C and D) Tumors were excised for Simpson grade II. (E and F) The sections show proliferation of meningothelial tumor cells with oval or elongated nuclei arranged in intersecting short fascicles or small whorl-like structures [hematoxylin and eosin, (E) 100×, (F) 200×].

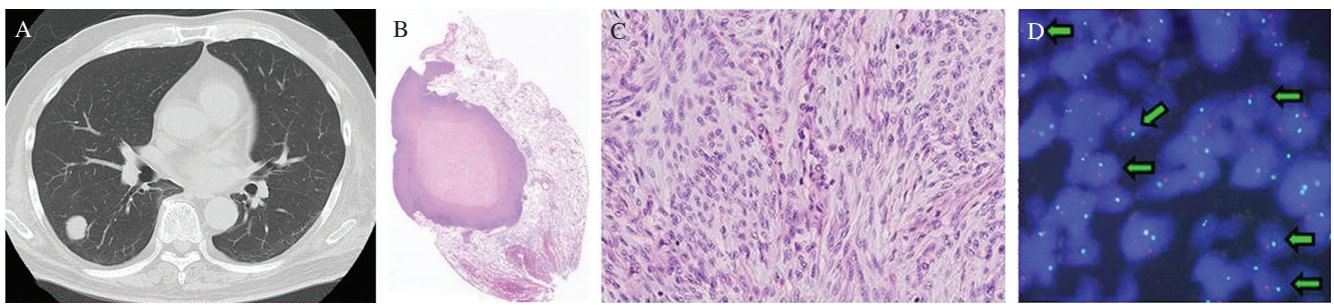

Fig. 3 (A) In the chest CT, a 2 cm nodule was seen in the right lower lobe. (B and C) The section showed proliferation of spindle shaped tumor cells with round to oval nuclei forming intersecting short fascicles [hematoxylin and eosin, (C) 200×]. Necrosis was seen in the center of the tumor, but no other atypical features were evident. (D) NF2 gene fluorescence *in situ* hybridization (FISH) image. NF2 FISH predominantly demonstrated a single pair in the lung tumor. Arrows show one pair of red and green signals per cell. Red signal, NF2 (22q, 12.2); Green (FITC) signal, chromosome 22 centromere.

intersecting short fascicles or small whorl-like structures (Figs. 2E and 2F). No high mitotic figures were found (1 < 10 high power fields). Although a small focus of necrosis was seen in the posterior fossa specimen, it was considered to be an effect of vascular embolization. These findings were consistent with WHO grade I meningioma. Ki-67(MIB-1) labeling index of the posterior fossa and temporal lesions were 4.8% and 5.1%, respectively, making them slightly high. Since there is a tendency for tumorous lesions in the lung to expand, a thoracoscopic partial resection of the right lower lobe was performed 2 months after the third cranial surgery. Histologically, the section showed proliferation of spindle shaped tumor cells with round to oval nuclei forming intersecting short fascicles (Fig. 3C). Although, necrosis was seen in the center of the

tumor, no other atypical features were evident (Fig. 3B). We performed fluorescence *in situ* hybridization (FISH) to reveal the presence or lack of heterozygosity of the NF2 gene (22q 12.2) in both the resected lung tumor and the intracranial tumor. Probes for NF2 assessment included a Fluorescein isothiocyanate (FITC, green) – labeled chromosome 22 centromeric (CEP22q) probe and Texas Red-labeled, locus-specific NF2 probe (Abnova, Walnut, CA, USA). Results revealed that both these tumors had loss of heterozygosity of the NF2 gene (Fig. 3D). These findings were consistent with metastasis of meningioma WHO grade I. No adjuvant therapy was performed. The patient is alive 12 months after surgery of the pulmonary lesion without recurrence of the lung and head lesions.

Discussion

Meningioma was found in the patient's lung, 26 years after the first surgery. The lesion was histologically similar to the intracranial lesion, and pulmonary metastasis of the meningioma was suspected. Distant metastases of grade I meningioma are rare. Despite this rarity, primary meningioma may occur in the lung. In order to confirm the genetic identity of these tumors, FISH was performed, and it was found that the NF2 gene (22q 12.2) was deleted to the same degree in both intracranial and lung lesions (Table 1). Thus, we confirmed genetically and morphologically that the intracranial lesions and the pulmonary lesion were identical.

The higher the tumor grade, the higher the incidence of distant metastasis. The incidence of distant metastases in grades II and III are 5% and 30%, respectively.[13] The route for distant metastases includes hematogenous metastasis via the internal jugular vein system and paraspinal venous plexus, lymphogenous metastasis, and cerebrospinal fluid dissemination.[14] As far as we are aware, there has been no report summarizing the time period until the occurrence of distant metastases or the course after distant metastasis for each grade. To examine these, we reviewed the English-language literature published since 2007 using the PubMed search engine with the terms ("meningioma" AND "metastasis"). This search was performed on January 31st, 2018. We excluded cases in which metastases were found first or where simultaneous primary tumor and metastasis were identified. Cases of suspected drop metastasis or cerebrospinal fluid dissemination were also excluded. We reviewed 35 articles and 48 (present case included) cases of meningioma metastasized to extracranial sites.[2,4,8–10,13–42] The median age of the extracranial metastases was 61.5 years (range 3–82 years) with a female predominance (30 females, 17 males, and not described in one case). Regarding the WHO grade of the primary tumor, 19 (39.6%) cases were grade I, 14 (29.2%) cases were grade II, 12 (25%) cases were grade III, and 3 (6.3%) cases were not described. Regarding metastatic tumor grading, 12 (25%) cases were grade I, 15 (31.3%) cases were grade II, 19 (39.6%) cases were grade III, and two (4.2%) cases were not described. In 13 cases, pathological upgrade was confirmed at the time of distant metastasis from initial surgery. With regard to the time of upgrading, 10 cases were at the time of local recurrence, three cases were metastasis, and one case showed local recurrence and metastasis simultaneously.

Table 1 Comparison of NF2 deletion pattern with FISH in lung and brain meningioma

	Lung (%)	Posterior fossa (%)	Temporal fossa (%)
Single pair	80.3 (94/117)	59.0 (85/144)	62.7 (77/123)
FITC signal one only	19.7 (23/117)	20.8 (30/144)	21.1 (26/123)
Normal	0 (0/117)	11.8 (17/144)	13.0 (16/123)
Homozygous deletion	0 (0/117)	3.5 (5/144)	1.6 (2/123)
Heterozygous deletion	0 (0/117)	4.9 (7/144)	1.6 (2/123)

FISH: fluorescence *in situ* hybridization, NF2: neurofibromatosis type 2, single pair pattern: one pair of red and green signal, FITC signal one only: only single green signal was detected, Normal: two pairs of red and green signal, Homozygous deletion: no red signals and two green signals were observed, Heterozygous deletion: single red signal was deleted, and two green signals were preserved.

The period of primary tumor operation to metastasis varied depending on the tumor grade. The mean period until metastasis in grades I, II, and III was 11.0, 5.4, and 2.0 years, respectively. The period until metastasis in our case was 26 years; this was fairly long compared with the mean period. Prognosis after metastasis was examined, and it was different depending on each grade. For grade I, there was one case of death with an unknown survival time, but there were no other deaths within the observation period in other cases. In grades II and III, the mean survival times were 3.3 and 0.98 years, respectively. Median survival period was 4 years and 1 year, respectively. Data indicate that when the tumor of a distant metastasis reached a high grade, the survival period was significantly shortened.

Known risk factors for metastasis and local recurrence are histopathological signs of malignant behavior. But this does not explain why grade I meningiomas metastasize. The pathophysiology leading to distant metastases may be a hematogenous spread originating from tumor invasion into the venous sinuses. In fact, 75% of patients with extracranial metastases of meningioma show an invasion of the venous sinus.[43] In our review, five cases did not reveal any relationship between the sinus and tumor from the description and two cases were spinal meningioma. These seven cases were excluded when considering the association with the venous sinus. Invasion or contact with the venous sinus was observed in 60.1% (25/41) of cases. In this group, grade I accounted for 11/25 cases (44%). Grades II and III were 7/25 (28%) and 5/25 (20%), respectively. Not described was 2/25 (8%). In each grade, where an association with the sinus venosus was observed, the association was as follows: grade I, 61%; grade II, 54%; and grade III, 62.5%. These results indicate that contact with the venous sinus has the potential to develop extracranial metastases. In addition, in recent years, there are reports that CD90 becomes highly expressed in meningioma metastasis, and that chromosomal instabilities such as deletion of chromosomes 22 and 1 are associated with distant metastasis.[2,44]

Our case was histologically WHO grade I but the MIB-1 labelling index was slightly high. At the time of first surgery,

the tumor had already made extensive infiltration into the venous sinus and jugular vein. These factors may have contributed to meningioma WHO grade I metastasized to the lung.

Conclusion

We experienced a case of meningioma WHO grade I that had metastasized to the lung 26 years after initial surgery. Confirmation was made morphologically and also genetically. However, despite the histological features indicating WHO grade I, sinus invasion may be associated with metastasis. Our review shows that the histological grading of the primary tumor was related to the period to metastasis. Furthermore, grading of the distant metastasized tumor was related to survival time.

Limitation

In this case study, we considered the lung disease to be a metastasis, but we could not fully eliminate either metastasis or both primary. Because the somatic NF2 loss of heterozygosity was not examined, the possibility of meningiomatosis cannot be discounted.

Conflicts of Interest Disclosure

All authors declare no conflicts of interest.

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