

Case Report

Diplopia Presenting in a Case of Pineal Metastasis of Pulmonary Sarcomatoid Carcinoma Refractory to Treatment

Abstract

A 42-year-old male presented with diplopia, headache, and nausea. Magnetic resonance imaging (MRI) of the brain showed pineal tumor, and chest computed tomography (CT) demonstrated a lung tumor. Disorientation developed, with occurrence of hydrocephalus, and we performed neuroendoscopic surgery for biopsy of the pineal tumor and third ventriculostomy. The lung tumor was biopsied under bronchoscopic and CT guidance, and based on the pathological results, we diagnosed pineal metastasis of pulmonary sarcomatoid carcinoma (cT3N1M1b Stage IVA). Stereotactic radiotherapy for the metastatic pineal tumor and systemic chemotherapy (carboplatin + pemetrexed) were pursued, but hemorrhage of the tumor occurred, hydrocephalus worsened, and neoplastic meningitis was diagnosed by MRI. Therapy was switched to nivolumab, but without effect, and the patient succumbed. Even among lung tumors, sarcomatoid carcinoma is rare. There are also few reports of lung tumors metastasized to the pineal gland. Our case report of pineal tumor regarded as metastasis of pulmonary sarcomatoid carcinoma also includes a discussion of the literature.

Keywords: Endoscopic biopsy, metastasis, pineal gland, sarcomatoid carcinoma, third ventriculostomy

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Introduction

In the WHO Classification of Tumors of the Lung, Pleura, Thymus, and Heart (2015 edition), sarcomatoid carcinoma of the pulmonary origin is a generalized term for pleomorphic carcinoma, spindle cell carcinoma, giant cell carcinoma, carcinosarcoma, and pulmonary blastoma, representing minimally differentiated, nonsmall cell carcinomas including sarcoma or sarcomatoid component. Pineal metastasis is a rarity as a metastatic site for lung cancer. We report the clinical course from our experience of a case of pineal tumor regarded as metastasized, sarcomatoid carcinoma of the pulmonary origin.

Case Report

Male, age 42 years

Chief complaints: Diplopia, headache, and nausea.

Prior history/familial history: None noteworthy.

Smoking history: 30 cigarettes/day, 22 years.

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Present illness history

Emergency outpatient treatment was received for complaints of sudden diplopia, headache, and nausea in the late February 2019. Parinaud's syndrome was observed, but additional, distinct, atypical findings of neurological nature were not observed. In computed tomography (CT) brain, a 1.9 cm × 1.5 cm × 1.9 cm neoplastic lesion was observed in the pineal gland. In contrast magnetic resonance imaging (MRI), the entire tumor demonstrated an enhancement; gradient recalled echo imaging showed intratumoral hemorrhage. Chest CT also demonstrated a 5 cm × 4.5 cm × 3.5 cm pulmonary lesion at D1/2 level on the right [Figure 1a]. Laboratory findings on admission included tumor markers CEA (13.8 ng/ml), CYFRA (1.4 ng/ml), and ProGRP (23.1 pg/ml). The cerebrospinal fluid (CSF) cytology was Class I, and CSF testing showed levels of 3.6 ng/ml ACTH, 15.4 ng/ml CEA, and less than 1 HCGβ [From April to September for 6 months].

After admission, disorientation and urinary incontinence developed gradually, and

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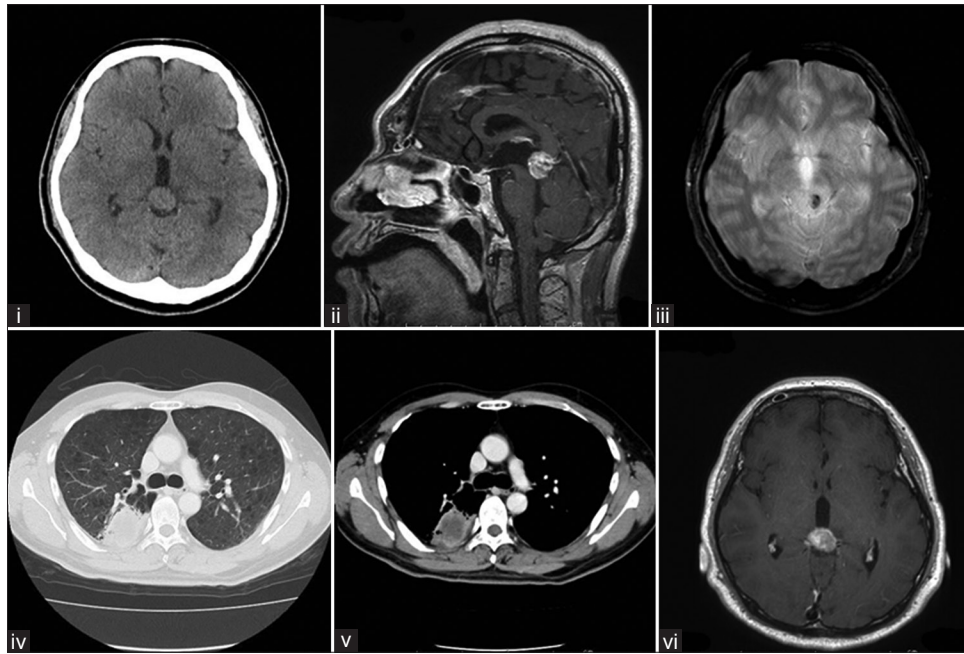


Figure 1a: (i) Head computed tomography demonstrated a 1.9 cm × 1.5 cm × 1.9 cm pineal lesion. (ii and vi) Contrast magnetic resonance imaging demonstrated a contrast enhancement in the pineal lesion. (iii) Gradient recalled echo imaging showed intratumoral microhemorrhage. (iv and v) Chest computed tomography demonstrated a 5 cm × 4.5 cm × 3.5 cm pulmonary lesion at D1/2 level on the right

head CT demonstrated hydrocephalus with aqueduct stenosis [Figure 1b]. In order to confirm pathological findings of both pineal and pulmonary lesions in deciding the treatment strategy, first, we performed surgery that Releasing of hydrocephalus which is a cause of Consciousness disorder and pathological diagnosis of pineal lesions. In the surgery, an 11-Fr transparent sheath was inserted into the anterior horn of the lateral ventricle with neuronavigational assistance; a flexible scope (Visera ventricular videoscope, VEF Type V) was inserted through the foramen of Monro to the point of the third ventricle; and after the tuber cinereum was punctured by forceps, an expanding balloon catheter was inflated to confirm CSF interchange. Next, we ascertained a tumor occluding the aqueduct entrance at the posterior end of the third ventricle and collected a portion with biopsy forceps [Figure 1c]. The tumor was hemorrhagic, but hemostasis was achieved by the recirculation of artificial CSF. After biopsy, the surgery was completed by visualized confirmation of hemostasis and placement of a ventricular drain to evaluate intracranial pressure (ICP). After surgery, ICP was monitored in our intensive care unit. Postoperative neurological observations showed residual disturbance of ocular motility but improvement in headache, nausea, and disorientation.

The pineal tumor biopsy demonstrated a mass of atypical cells and was positive for AE1/AE3 and CAM5.2. No mucicarmine-positive mucous was observed, and in immunostaining, the majority of cells were positive for Ki67 and P53. Results were negative for CK5/6, CK7, CK20, CEA, TTF1, napsin-A, P40, S100, GFAP,



Figure 1b: Head computed tomography demonstrated hydrocephalus with attendant aqueduct stenosis

chromogranin, synapsin, and CD56. No papillary structures were observed, and the specimen was deemed a minimally differentiated epithelial tumor. No disposition was noted toward differentiation into glands, squamous epithelium, or other such tissues [Figure 2a]. The specimen was deemed a minimally differentiated epithelial tumor not consistent with a pineal primary tumor.

Positron emission tomography-CT demonstrated FDG accumulation in the right upper lobe lesion and hilar lymph nodes [Figure 3]. The lung tumor was difficult to approach by bronchofiberscope and was therefore biopsied with CT guidance. Biopsy of the lung tumor demonstrated a mass of spindle cells. Mucicarmine-positive mucous was not

observed, and the specimen was positive for AE1/AE3 and P53 and negative for TTF1, P40, EGFR, ALK, and ROS1. PD-L1 expression showed tumor proportion score (TPS) <1%. No disposition was noted toward differentiation into glands, squamous epithelium, or other such tissues, and the specimen was regarded as a carcinoma derived from sarcomatoid pyramidal cells [Figure 2b].

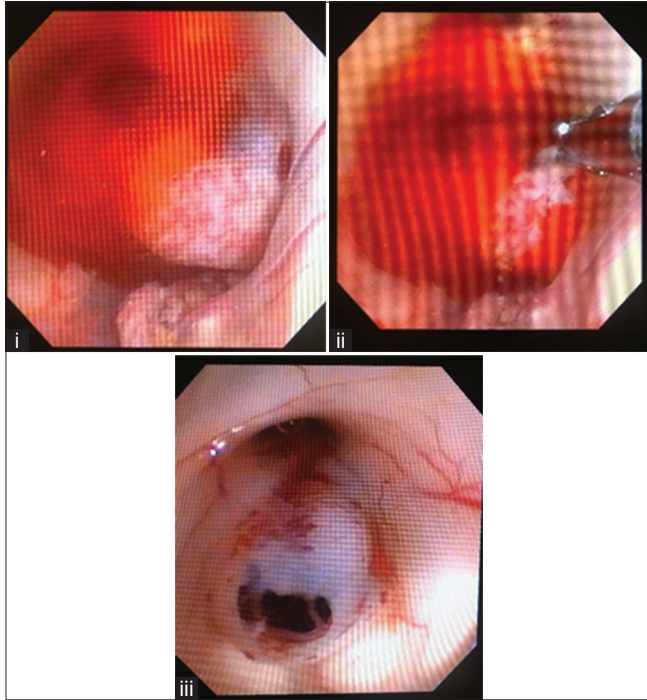


Figure 1c: (i and iii) Neuroendoscopic findings included tumor with gross hemorrhage and bleeding when grasped with forceps. (ii) The tuber cinereum was fenestrated, and cerebrospinal fluid interchange was observed

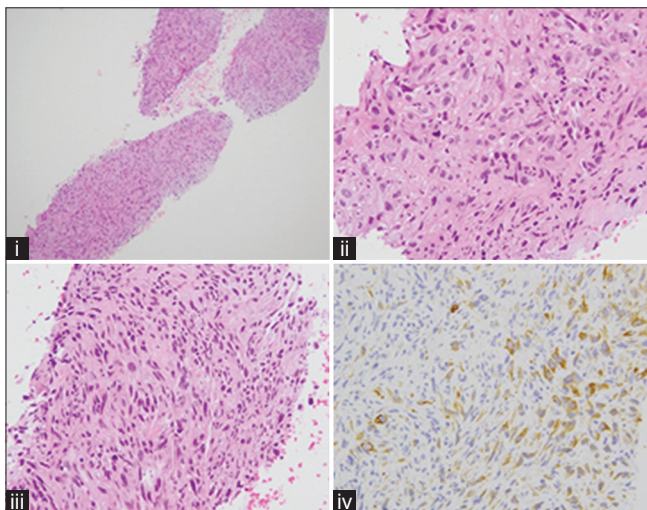


Figure 2b: (i-iii) Lung tumor pathology findings (H and E stain): Spindle cells replicating densely into bundled/figured mat form. One area showing notable cylindroid and multiform cells. No apparent disposition toward differentiation into glandular cavity/papillary structures. (iv) Immunostaining: AE1/AE3-positive

According to the JLCS Rules for Lung Cancer Management, 8th edition,^[1] confirmative diagnosis is possible only through a biopsied partial histology specimen or cytology, but pineal metastasis of sarcomatoid carcinoma regarded as spindle cell carcinoma was diagnosed by additional imaging studies and clinical observations. Approximately 1 month after the head surgery, stereotactic radiotherapy was pursued for the pineal tumor at a dosage of 35 Gy/5 Fr.

At the same time, chemotherapy was also initiated by the case pulmonologist. The lung cancer stage was cT3N1M1b Stage IVA, and the first-line treatment implemented was six courses of carboplatin + pemetrexed (PEM). During the first-line treatment, tumor hemorrhage occurred two times [Figure 4a]. MRI after the second incident of tumor hemorrhage showed slight growth of the pineal tumor and enlargement of the lateral ventricle, but

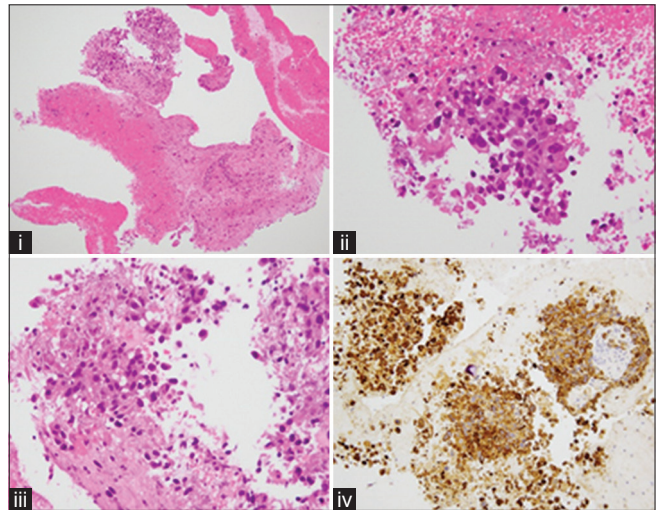


Figure 2a: (i-iii) Pineal tumor pathological findings (H and E stain): Atypical cells form a nearly solid cellular nest. No apparent disposition toward differentiation into glandular cavities/papillary structures. (iv) Immunostaining: AE1/AE3-positive (D). Regarded as minimally differentiated epithelial tumor not consistent with pineal primary tumor



Figure 3: Positron emission tomography-computed tomography: FDG accumulation observed in right upper lobe lesion and hilar lymph nodes

selective inversion recovery (IR) pulsing in MRI demonstrated CSF interchange at the fenestration in the third ventricular base [Figure 4b], and because nausea was also improved by dexamethasone treatment, continuation of chemotherapy was prioritized. In chest CT 1 month after the first-line treatment, the lung tumor showed a growth trend, but even at such time, CSF cytology detected no tumor cells. Nonetheless, MRI demonstrated aggravation of hydrocephalus and contrast enhancement of areas including the ventricular wall proximal to the left hypothalamus and the cerebellar fissure, suggesting meningeal dissemination.

The pineal metastatic focus was also refractory to radiotherapy, and additional whole-brain irradiation was not performed [Figure 5a]. Due to apparent resistance to the first-line chemotherapy, treatment was switched to nivolumab as the second-line option. On MRI 1 month after initiation of the second-line treatment, hydrocephalus had not progressed, but a contrast-enhancement effect was noted in the hypothalamus walls bilaterally and within the left-sided hypothalamus, and the basal portion of the tumor had progressed to the fourth ventricle [Figure 5b].

Due to the lack of deterioration in higher cognitive function testing from the time of initial admission, and to avoid interruption of chemotherapy, we elected to observe progress without additional efforts to manage hydrocephalus, such as ventriculoperitoneal (VP) shunt or Ommaya reservoir.

After this 3-week period, bodily movement became impaired, nausea and diminished consciousness level, and head CT demonstrated increased hydrocephalus and hemorrhage from the tumor to the pons and cerebellum [Figure 4c]. Given the reduction in performance status and a lack of desire for treatment on the part of the family, nivolumab was also discontinued after three courses. Consciousness level declined gradually after admission, resulting in an outcome of death 2 weeks after the repeat hemorrhage. The family did not provide consent for autopsy.

Discussion

Metastases of cancer to the pineal region are rare. From 1984 to 2000, there were 37 cases of metastasis to the pineal region among 10,489 reported cases of metastatic

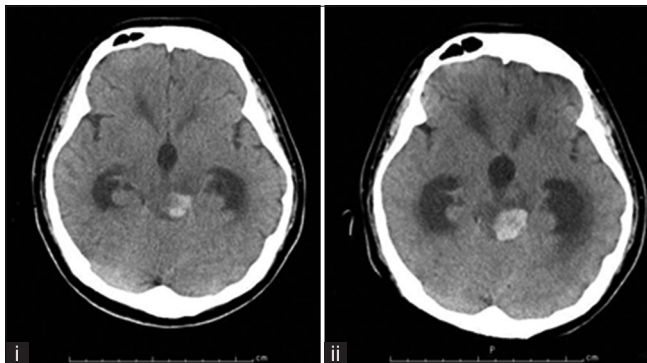


Figure 4a: (i and ii) Intratumoral hemorrhage occurring on 6/2 and 7/20. Notable ventricular enlargement and periventricular lucency due to hydrocephalus

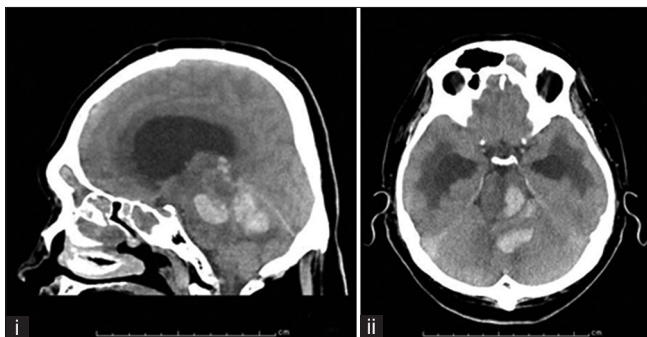


Figure 4c: (i and ii) Head computed tomography on 9/4: Increased hydrocephalus and hemorrhage extending inside/outside tumor to pons and cerebellum

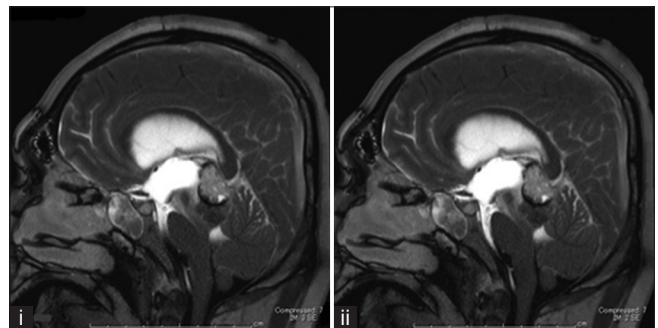


Figure 4b: (i and ii) 3T-magnetic resonance imaging: Cine-imaging of cerebrospinal fluid using selective IR pulsing demonstrated cerebrospinal fluid interchange at fenestration

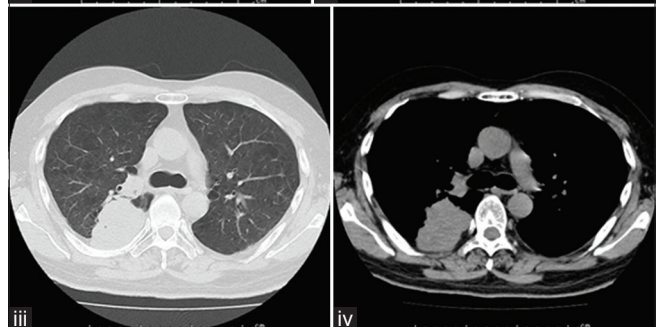
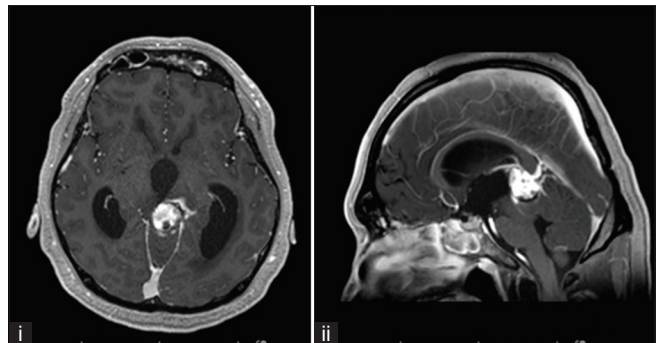


Figure 5a: (i and ii) Contrast-enhanced magnetic resonance imaging of head after tumor hemorrhage on 7/20: Notable aggravation of hydrocephalus and contrast enhancement of areas including ventricular wall of left hypothalamus and cerebellar fissure. (iii and iv) Chest computed tomography: Pattern of enlargement in lung tumor

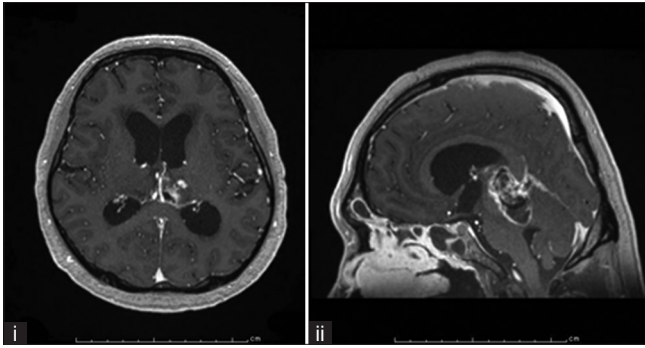


Figure 5b: (i) Contrast-enhanced head magnetic resonance imaging on 8/13: No progression of hydrocephalus, but notable contrast-enhancement effect in hypothalamus walls bilaterally and within left-sided hypothalamus. (ii) Tumor progression to fourth ventricle

brain tumor, a mere 0.4% rate of metastatic brain tumor.^[2] Reports state that the most frequent primary focus of tumors which metastasize to the pineal body is lung cancer, and among these, the most frequent by histological type is small cell cancer.^[3] The majority of metastatic pineal tumor cases are asymptomatic and are often diagnosed by autopsy.^[4,5] When accompanied by symptoms, reports cite frequent headache or nausea accompanied by increased ICP.^[6] Intervention for pineal tumors is considered on a case-by-case basis. Pyramidal cell cancer is another rare tumor,^[1] comprising only spindle cells. According to the report of Mainwaring *et al.*, this cancer is extremely rare, occurring in only 0.2%–0.3% of primary lung cancers, and its prognosis is reportedly poor, with a 2-year survival rate of 10%.^[7] However, these statistics also include tumors demonstrating squamous epithelium, and there are additional reports of pleomorphic cancer and reports which categorize cancer type.^[8] The specimen tissue in our case report also represented only a portion of the entire tumor, which may have been a pleomorphic cancer, but we believe that it lay in the category of sarcomatoid carcinoma.

Treatments such as chemotherapy and radiotherapy also have little effect on spindle cell, pleomorphic, and other such cancers.^[9,10] Even when treated with cisplatin + PEM,^[11] which has a high reported response rate of 42% against brain metastasis of solid cancers, the effect of chemotherapy or radiotherapy was poor not only on the primary focus but also on metastatic foci in the pineal region, where there is no blood–brain barrier.

Even when a pineal tumor is detected, investigation is needed to determine whether it is metastatic or primary to the pineal body, since treatment must conform to its histological type. The localization of these tumors often poses difficulties for complication-free removal, and opinions also diverge as to timing and necessity.

Neoplastic meningitis occurs in approximately 5% of solid cancers, and the median survival is reportedly 6–8 weeks.^[12] For solid cancers, positive rates in CSF cytology are reportedly 50% in the first test and

approximately 80% in the second test and are barely increased at all in the third and subsequent tests.^[13] When CSF cytology is negative, means such as CEA or other such biological markers can provide adjunct diagnosis, but there is no consensus as to cutoff values. Contrast-enhanced T1 or FLAIR diagnostic imaging is known to provide a high signal in the cerebellum or occipital lobe in 25%–35% of CSF cytology-positive patients,^[14] while impaired absorption is known to represent occurrence of hydrocephalus. In the current case, CSF cytology was negative, but selective IR-pulsed MRI allowed diagnosis of meningeal dissemination after demonstrated CSF interchange at the third ventriculostomy, concomitant with aggravated hydrocephalus, and contrast enhancement of areas, including the ventricular wall of the left hypothalamus and the cerebellar fissure. VP shunt was also considered; however, given the possibility of peritoneal dissemination and the fact that chemotherapy would have been delayed until healing of the wound, we prioritized chemotherapy. For hydrocephalus, ICP can be monitored,^[15] symptoms of elevated ICP can be controlled by external drainage,^[16] and in the event of observations suggesting dissemination, intraventricular CSF cytology allows simple follow-up. In this light, and once time frames are considered, we believe that the placement of an Ommaya reservoir is another alternative.

Conclusion

We reported the clinical course of a pineal tumor representing a suspected metastasis of primary pulmonary sarcomatoid carcinoma. We also discussed intervention through placement of an Ommaya reservoir when aggravation of hydrocephalus is observed despite third ventriculostomy, and neoplastic meningitis is suspected. Although control of metastatic brain tumors is a challenging issue in the development of cancer drug therapy, including development of molecular-targeted drugs, these drugs had little effect in the case of sarcomatoid carcinoma that we report. Further case collection is needed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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