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Case Report

Pazopanib-mediated Long-term Disease Stabilization after Local Recurrence and Distant Metastasis of Primary Intracranial Leiomyosarcoma: A Case Report on the Efficacy of Pazopanib as a Salvage Therapy

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Primary intracranial leiomyosarcoma (LMS) is an extremely rare tumor of the central nervous system. Only sporadic case reports have been published, and therefore data regarding long-term prognosis remain scarce. A 76-year-old woman presented with a right parietal mass, which had grown rapidly in the month prior to admission. Neuroimaging showed a resemblance to intraosseous meningioma. Gross total resection of the tumor was achieved, and histological diagnosis confirmed LMS. Because positron emission tomography (PET) with fluorodeoxyglucose (FDG) just after the resection showed no abnormal uptake, we diagnosed the tumor as primary intracranial LMS. Follow-up PET at 16 months after treatment showed two foci of FDG uptake in the bilateral lungs. Histological diagnosis by surgical resection identified the lesions as lung metastases of LMS. In addition, follow-up head magnetic resonance imaging (MRI) at 31 months showed local recurrence, and we conducted salvage therapy using CyberKnife system (Accuray incorporated) and pazopanib. To date, for 15 months after local recurrence, she is alive with intracranial recurrent disease remained inactive.

Keywords: leiomyosarcoma, lung metastasis, local recurrence, pazopanib

Introduction

Leiomyosarcoma (LMS) is a malignant tumor that can originate from smooth muscle cells anywhere in the body, such as the uterus, gastrointestinal tract, and subcutaneous tissue.[1,2] In contrast, primary intracranial LMS is extremely rare, and only a few case reports have been published.[3,4] Paulus et al. reported that LMS constitutes only 0.012% of primary intracranial tumors.[5] Data regarding long-term prognosis of primary intracranial LMS are scarce and no standardized therapy has been established. Although some authors have suggested that prognosis is relatively favorable,[6,7] others have reported relatively poor outcomes once recurrence or progression occurred.[8–10]

The oral tyrosine kinase inhibitor pazopanib was the first molecular-targeted agent approved for the treatment of advanced soft tissue sarcoma. Pazopanib is an oral multityrosine kinasae inhibitor of vascular endothelial growth factor (VEGFR)-1, -2, and -3; platelet-derived growth factor (PEGFR)-α, and –β; and c-Kit receptor.[11] In the PALETTE trial, it has been demonstrated to improve progression-free survival, compared with placebo.[12] Here we report a case of intracranial LMS with local recurrence and lung metastases treated with pazopanib, which led to stable disease control.

Case Report

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from the participant included in this study. A 76-year-old woman with a prior history of appendicitis, torsion of the ovarian cyst pedicle, and myoma uteri presented with a right parietal mass behind the ear. The lesion had been growing rapidly in the month before admission. There were no neurological symptoms and no symptoms suggestive of other sites of involvement. Complete blood counts and metabolic panel were normal. Viral serology was negative for both human immune deficiency virus and Epstein-Barr virus. A non-contrast computed tomography (CT) scan of the brain demonstrated a 5-cm mass involving the meninges with invasion of the parietal bone (Fig. 1a). A magnetic resonance imaging (MRI) scan with gadolinium showed a heterogeneously enhanced mass in the right parietal region (Fig. 1b). A cerebral angiography showed that the tumor was vascularized and was supplied by the middle meningeal artery. Thus, a clinical diagnosis of osteoblastic meningioma was made. The differential diagnosis included

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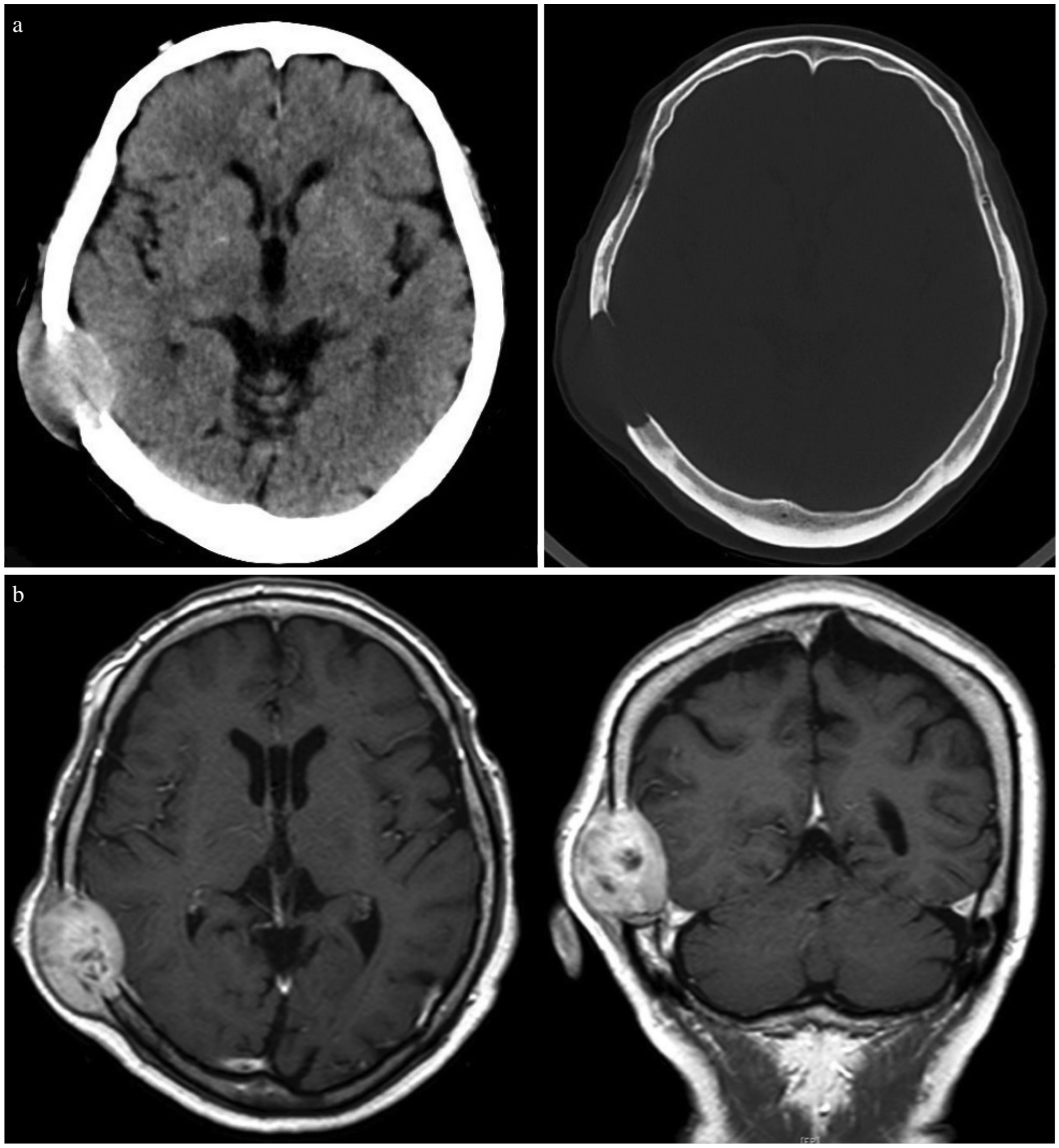

Fig. 1 (a) Head CT scan shows a hyperdense lesion in the right parietal area. CT scan with bone window shows remarkable bone destruction of the right parietal skull. (b) Gd-enhanced MRI shows a heterogeneously enhanced lesion, adjacent to the mastoid air cell.

primary lymphoma, metastasis, and sarcoma. The patient underwent a surgical resection of the tumor following endovascular embolization of the feeding middle meningeal artery using platinum coils. At surgery, the scalp was easily removed from the tumor, which had caused destruction of the skull and had extended extradurally without any intradural involvement. The tumor and surrounding bone with about a 1-cm margin were removed, followed by bone reconstruction. Histology showed a malignant spindle cell neoplasm (Fig. 2a) with positive immunostaining for α-smooth muscle actin, vimentin, and desmin (Fig. 2b). Immunohistochemical staining for Epstein Barr virus was negative. Pathological interpretation was a malignant spindle cell neoplasm consistent with high-grade LMS. Postoperative complications included chronic mastoiditis due to cerebrospinal fluid leakage. Staging CT scan of the lung and abdomen and whole body positron emission tomography (PET) scan were negative for extra cranial involvement. Pelvic MRI showed a 4-cm myoma uteri on the anterior wall of the uterine corpus, which has not been growing and PET-negative throughout the follow-up period. The patient underwent local field radiotherapy (45 Gy in 25 fractions with a boost to the tumor bed). Follow-up brain MRI at 26 months showed no evidence of local recurrence. FDG-PET scan at 16 and 26 months after the treatment showed two small foci of abnormal uptake in the bilateral lungs, which had been growing slowly. The maximum tumor standard uptake value was 3.3 and 6.35 at 16 and 26 months, respectively. Chest CT at 26 months showed a 9-mm nodular lesion in the right lung and a 6-mm nodular lesion in the left lung. Chronological changes in size and uptake values suggested lung metastasis of the LMS. The lesions were separately removed, and histology of the surgical specimens confirmed them to be metastatic LMS. Although postoperative recovery was uneventful, follow-up MRI at 31 months showed local recurrence mainly in the mastoid air cell

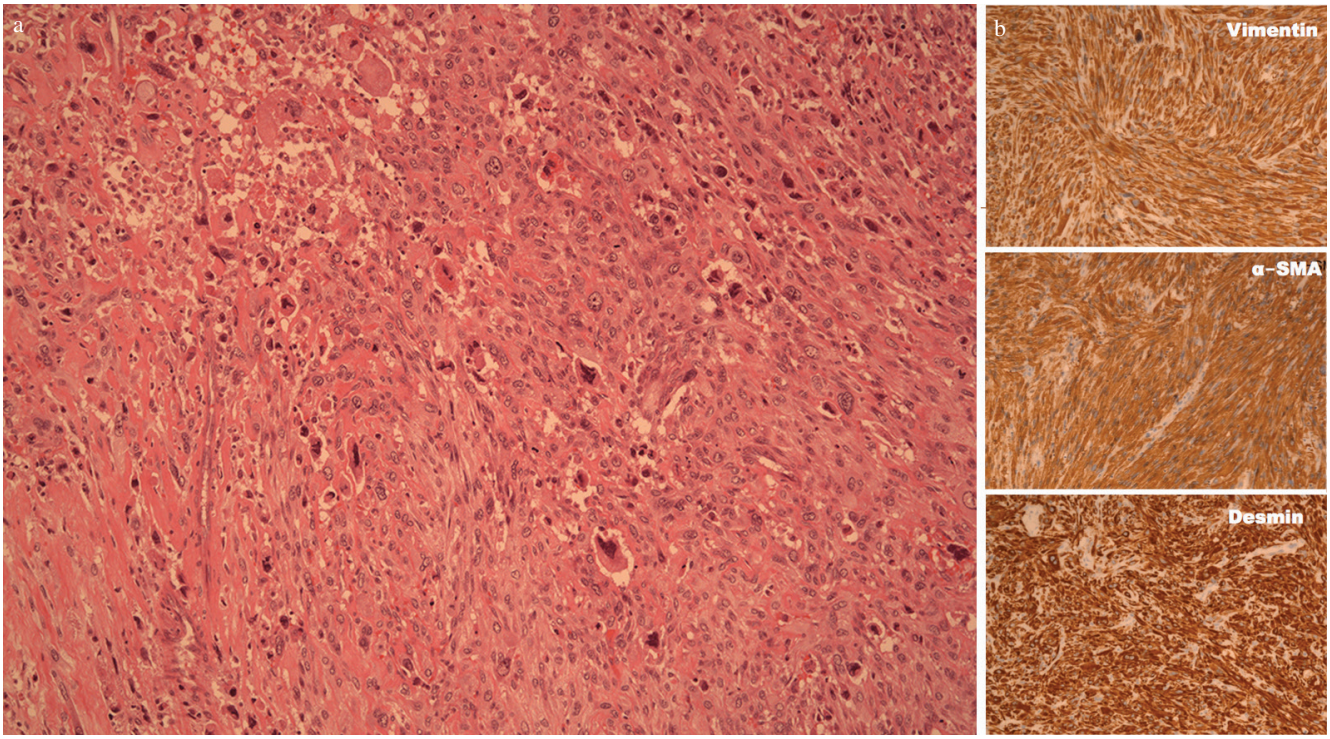

Fig. 2 (a) Light microscopy shows high-grade sarcoma with poorly differentiated and highly proliferative atypical spindle shaped cells. (b) Immunochemistry revealed staining for vimentin, α-smooth muscle actin, and desmin.

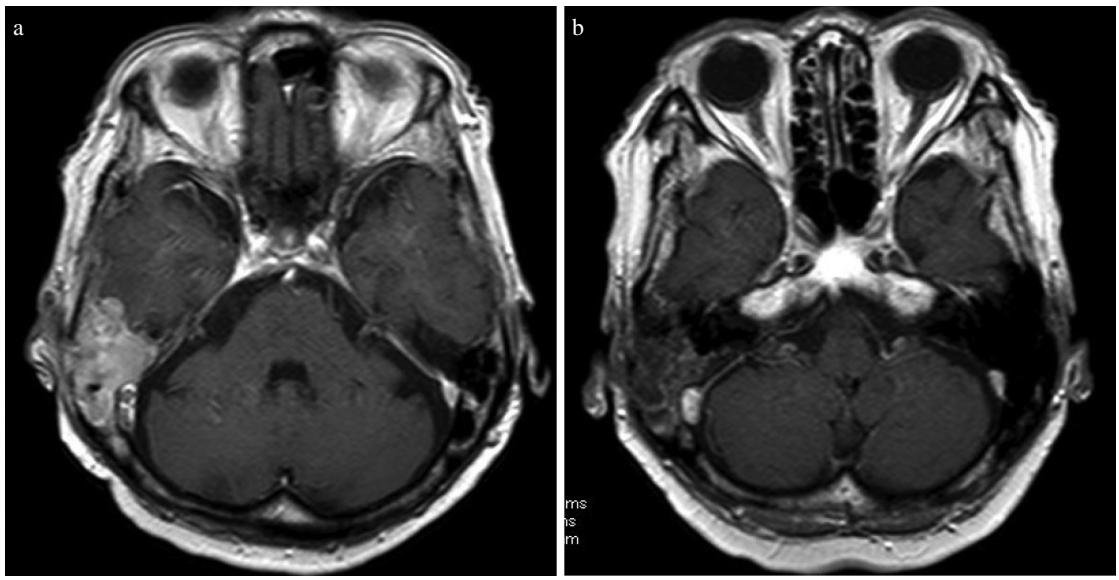

Fig. 3 (a) Follow-up head MRI at 31 months showed local recurrence in the right mastoid air cell. (b) Follow-up head MRI at 45 months showed cystic degeneration of the recurrent lesion.

(Fig. 3a), which was probably caused by cancer cell dissemination through cerebrospinal fluid leakage. Local recurrence was treated by salvage therapy using CyberKnife system (Accuray incorporated) at the prescription dose of 36 Gy and pazopanib. Pazopanib administration at 800 mg/day was started, but was discontinued after 2 weeks because she had grade 1 of appetite loss according to the common terminology criteria for adverse events (CTCAE) version 4.0.[13] It was then restarted at the reduced dose of 600 mg/day after one month, further reduced to 400 mg on alternate weeks after 2 months, and finally reduced to 200 mg on alternate weeks after 4 months due to appetite loss and general fatigue. She also experienced an adverse event of hypertension, and eight mg of candesartan was prescribed after 3 months. Follow-up MRI at 45 months showed cystic degeneration of the local recurrent lesion (Fig. 3b), and she is doing well in spite of hearing loss of the right ear.

Table 1 Summary of patients with primary intracranial leiomyosarcoma ever reported in the literature

Author, year	Sex	Age	Location	Number of lesions	Medical history	Extent of resection	Adjuvant therapy	Recurrence (months)	Follow-up (months)	Outcomes
Anderson, 1980[24]	male	35	sellar and suprasellar region	single	none	partial	Rad(+)		32	alive
Sieben, 1980[14]	male	57	foramen jugulare	single	radiation therapy, syringomyelia	none	Rad(+)		n.a.	dead
Asai, 1988[25]	male	73	dura	single	none	complete	Rad(+)		n.a.	n.a.
Louis, 1989[26]	female	72	intraventricle	single	none	complete	none		6	alive
Skullerud, 1995[27]	male	33	pineal region	single	teratoma of the pineal area	complete	Rad(+)		24	alive
Niwa, 1996[7]	male	51	sella, cavernous sinus, and sylvian fissure	single	pituitary adenoma, radiation therapy	partial	none	L	8 years	dead
Lee, 1997[28]	male	8	extra-axial	single	none	complete	CTx(+), Rad(+)		20	alive
Mierau, 1997[29]	female	14	temporal lobe	single	genetic immunodeficiency	complete	none		18	alive
Murakami, 1997[30]	male	38	frontal lobe	single	fibrillary astrocytoma, radiation therapy	partial	CTx(+), Rad(+)		n.a.	n.a.
Litofsky, 1998[18]	male	50	dura	single	AIDS	complete	none		8	alive
Kleinshmidt-DeMasters, 1998[31]	female	14	dural sinus	single	AIDS	complete	none		21	alive
Bejjani, 1999[32]	male	38	dura	single	HIV positive	complete	none		12	alive
Brown, 1999[33]	female	34	pontine cistern	multiple	AIDS	partial	none	L(12)	12	alive
Blumenthal, 1999[34]	male	43	cavernous sinus	n.a.	AIDS	n.a.	CTx(+)		24	alive
Merimsky, 2000[6]	male	33	temporo-occipital lobe	single	n.a.	complete	Rad(+)	M(111)	111	alive
Yeh, 2002[35]	male	42	brainstem	single	ganglioglioma, radiotherapy	complete	none		n.a.	n.a.
Kaphan, 2003[21]	male	45	cavernous sinus	single	renal transplantation	biopsy	CTx(+), Rad(+)	L	18	dead
Eckhardt, 2004[36]	male	13	temporoparietal	single	none	partial	CTx(+), Rad(+)	L+LD	15	dead
Suankratay, 2005[10]	female	43	tentorium cerebelli	multiple	AIDS	complete	CTx(+), Rad(+)		4	dead
Suankratay, 2005[10]	female	34	tentorium cerebelli	single	AIDS, HBV(+)	complete	Rad(+)		8	alive
Hussain, 2006[37]	male	26	extra-axial	single	none	complete	Rad(+)	L(5)+M(5)	7	dead
Toh, 2007[38]	female	40	intradural and extradural	single	pituitary adenoma, radiation therapy	partial	none		1.5	dead
Jhas, 2009[39]	male	14	temporal lobe	single	neurofibromatosis type 1	complete	CTx(+), Rad(+)		24	alive
Mathieson, 2009[3]	male	5	frontal lobe	single	chronic subdural hematoma	partial	CTx(+), Rad(+)		18	alive
Fujimoto, 2011[8]	female	45	cerebellopontine angle	single	prior neurofibroma	partial	Rad(+)	L+LD	10	dead

Table 1 Continued

Author, year	Sex	Age	Location	Number of lesions	Medical history	Extent of resection	Adjuvant therapy	Recurrence (months)	Follow-up (months)	Outcomes
Almubaslat, 2011[40]	female	47	frontoparietal lobe	single	none	complete	none		21	alive
Aeddula, 2011[41]	male	58	temporal lobe	multiple	adenocarcinoma	complete	none		3 weeks	dead
Sivendran, 2011[19]	male	43	frontal lobe	single	AIDS	complete	none		20	alive
Kelley, 2012[9]	male	2	intra-axial and extra-axial	multiple	none	partial	none	LD	3	dead
Zhang, 2012[4]	female	26	the genu of corpus callosum	single	none	partial	Rad(+)		3	dead
Alijani, 2013[42]	male	19	extra-axial	single	none	complete	Rad(+)		18	alive
Takei, 2013[23]	male	27	frontal lobe	single	concurrent Hodgkin lymphoma	complete	CTx for HL		24	alive
present case, 2015	female	76	extra-axial	single	none	complete	Rad(+)	M(16)	46	alive

AIDS: adult immunodeficiency syndrome, HBV: hepatitis B virus, CTx: chemotherapy, Rad: radiotherapy, L: local recurrence or progression, LD: leptomeningeal dissemination, M: metástasis, n.a.: not available, HL: Hodgkin lymphoma.

Discussion

LMS is a malignant tumor that can originate from smooth muscle cells anywhere in the body. The most frequent site is the uterus, but the other sites include the gastrointestinal tract, retroperitoneum, lung, and heart.[1,14–16] The myoma uteri in this case has been dormant and negative on PET-CT scan throughout the follow-up period, and considered unrelated to intracranial lesion. The differential diagnosis for intracranial LMS includes meningiomas and schwannomas,[8,17] which are more prevalent. Thus, clinical experience in treating intracranial LMS is limited and the long-term prognosis is unknown, especially in terms of recurrence or metastasis. The prognosis of intracranial LMS can be underestimated because it is sometimes associated with immunosuppression, such as human immunodeficiency virus infection,[10,18–20] transplantation,[21,22] and malignancies.[23] However, the prognosis for intracranial LMS was reported to be relatively fair: a recent review by Zhang et al. showed that the 5-year survival rate was as high as 70%.[4]

Summary of reported LMS cases is shown in Table 1.[3,4,6,8–10,14,18,19,24–42] In literature, local recurrence or progression was observed in seven patients, and leptomeningeal dissemination was observed in three patients. Six of 7 patients who had local recurrence or progression died after a median of 12.5 months (4–96 months), and all the three patients with leptomeningeal dissemination died after a median of 10 months (3–10 months). Although five incidences of local recurrence or progression (45%) were observed in 11 patients (in whom partial resection or biopsy was performed), only one local recurrence (5%) was observed after complete resection ($P < 0.05$, Fisher's exact test). In addition, leptomeningeal dissemination was exclusively observed in three patients (9.1%) after partial resection. Intracranial LMS has to be resected as much as possible, preferably with a safety margin, to prevent local recurrence. Although the most common sites of distant metastasis from LMS include lung, liver, kidney, bone, spine, and brain[1,19,43,44] few data exist about the metastatic potential of intracranial LMS. Extracranial metastasis was observed in three patients (9.1%), including our case. One patient had both a local recurrence and systemic metastases at 5 months after complete resection of the tumor, and died at 6 months.[37] The other patient had malignant pleural effusion at 111 months after the treatment, but the details were not known.[6] Thus, it can be said that the prognosis should be poor once local recurrence, dissemination, or metastasis occur.

Pazopanib is a multi-targeted tyrosine kinase inhibitor that impairs angiogenesis. The most common adverse events with pazopanib were fatigue, diarrhea, nausea, weight loss, and hypertension. Randomized controlled trial showed pazopanib prolonged median progression-free survival compared with placebo in patients with metastatic soft-tissue sarcoma.[12] It is small enough to penetrate the blood brain barrier, and phase II trial was performed for patients with recurrent glioblastoma.[45] Inoue et al. also reported a case report to show the efficacy of pazopanib for metastatic brain tumor in a patient with advanced uterine LMS.[46] However, our case was the first to show the long-term stable disease control using pazopanib

combined with stereotactic radiosrugery after local recurrence and lung metastasis of intracranial LMS. Thus, it cannot be determined whether pazopanib should be similarly effective even if without combined therapy of stereotactic radiosurgery. However, it can be said that pazopanib can be effective not only to control local recurrence but also distant metastasis on which stereotactic radiotherapy should have no effect.

Conclusions

Local recurrence or distant metastasis can occur even after complete resection of intracranial LMS. Pazopanib combined with stereotactic radiosurgery is effective as a salvage therapy for a recurrent or metastatic disease of intracranial LMS.

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Conflicts of Interest Disclosure

We have nothing to disclose regarding this manuscript. All authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

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