Virchows Arch (2004) 444:459–464
DOI 10.1007/s00428-004-0991-7

CASE REPORT

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Malignant solitary fibrous tumor of the meninges

Received: 20 January 2004 / Accepted: 5 February 2004 / Published online: 10 March 2004

Abstract Increasing numbers of solitary fibrous tumors (SFTs) in the meninges have been reported since this entity was first recognized. While most cases previously reported were considered to be benign, the malignant potential of extrathoracic SFTs has not been excluded. The authors report a rare case of a meningeal SFT with malignant behavior occurring in a Japanese female patient, initially resected when she was 44 years old and recurring in the same place four times during a 26-year follow-up period. A metastatic tumor to the right lung arose 25 years after the resection of the first meningeal tumor and focal invasion into the cerebellum was also observed with her last (5th) meningeal tumor. Immunohistochemical analysis showed all tumors to be diffusely positive for CD34 and negative for EMA, with a so-called "patternless" histological pattern, featuring thin collagen fibers between tumor cells. A focal "staghorn" vascular pattern was also observed. Ki67 (MIB-1) labeling indices and mitosis rates were 3.1±1.2% and less than 1/10 high power fields (HPF) in the first meningeal tumor and 16.1±6.4% and 6/10HPF in the last (5th) one, respectively. Thus, the present case suggests that meningeal SFTs possess malignant potential so that careful long-term follow up is required.

Key words Solitary fibrous tumor · Meninges · Metastasis

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Introduction

The solitary fibrous tumor (SFT) is an uncommon spindle-cell neoplasm, first described as a pleural lesion in 1931 [17]. Extrathoracic SFTs [31] have also been increasingly recognized, including examples in the meninges [1, 2, 4, 5, 7, 8, 10, 15, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30]. Characteristic histological and immunohistochemical features of SFTs in any region are a "patternless" growth pattern, with spindle cells and keloid-like hyalinization, the lesions being intensely and diffusely positive for CD34 antigen and negative for EMA antigen [16]. In the meninges, fibrous meningioma and hemangiopericytoma (HPC) have been recognized as major tumors requiring differential diagnosis from SFTs [5, 10, 24, 29]. Most fibrous meningiomas are positive for EMA antigen, and HPCs are generally only focally and weakly positive for CD34 antigen [24]. The majority of extrathoracic SFTs, including those of meningeal origin, have been described as benign tumors. However, among about forty reported cases of meningeal SFTs, local recurrence was found in six [5, 22, 29, 30], including one case complicated with metastases to the lung and soft tissue [22]. We present here a case of malignant meningeal SFT which progressed after a very long (26 years) and indolent course featuring frequent recurrence and ultimate metastasis to the lung (Table 1). To our knowledge, this is only the second case in the English or Japanese literatures of a meningeal SFT which developed distant metastasis.

Materials and methods

All surgically resected tissues were routinely fixed in 10% formalin, embedded in paraffin and prepared for histological observation. Immunohistochemical analyses were performed by the

Table 1 Sequential changes of the histology and proliferation potential

Year, month	Age	Region (size, ∅ cm)	p53 (%)	Necrosis	Cellularity (/cm^2)	Ki67 (%)	Mitosis (/10 HFP)
1976, June	44	Meninges (3[a])	2.1±0.4	–	94.9±24.0	3.1±1.2	<1
1984, Nov	52	Meninges (1.5[a])	1.1±0.3	+	122.2±5.7	8.0±0.3	5
1995, April	63	Meninges (3)	7.1±1.9	–	93.5±6.3	5.3±1.4	<1
1999, Sept	67	Meninges (3)	13.6±2.4	–	114.0±9.5	8.4±2.1	2
2001, Jan	69	Right upper lung (1.8)	1.3±0.3	+	90.8±12.2	9.8±2.3	5
2002, Aug	70	Meninges (3)	13.2±3.2	–	84.0±18.3	16.1±6.4	6

[a] Tumor size was retrospectively estimated from the pathological specimen

avidin-biotin-peroxidase complex technique using a Vectastain ABC Elite Kit (Vector Laboratories Inc., Burlingame, CA) and diaminobenzidine for visualization of binding. The following antibodies were employed: anti-keratin (AE1/AE3, DakoCytomataion, Glostrup, Denmark, 1:50, with heat-pretreatment), anti-EMA (Zymed Laboratories Inc., South San Francisco, CA, 1:1), anti-vimentin (Ventana Medical Systems, Tucson, AZ, 1:1, with protease-pretreatment), anti-CD34 (Nichirei, Tokyo, Japan, 1:50), anti-Leu-7 (CD57, Ventana, 1:1, with heat-pretreatment), anti-S-100 protein (Dako, 1:400, with trypsin-pretreatment), anti-CD99 (12E7, Dako, 1:100), anti-CD99 (O-13, Santa Cruz Biotechnology Inc., Sant Cruz, CA, 1:40), anti-p53 (CM1, Novocastra Laboratories Ltd., Newcastle upon Tyne, UK, 1:100) and anti-Ki67 (MIB-1, Novocastra, 1:3000, with heat-pretreatment). Labeling indices for p53 and Ki67 and cellularity were generated from counts under a light-microscope in three randomly selected areas (with scale on the ocular, 0.25^2 mm×3 sights, which covered totally 1500~2000 cells) of each tumor, then expressed as mean values with standard deviation.

Case Report

This 70-year-old Japanese woman has been followed up as suffering from repeated local recurrence of atypical meningiomas in her left tentorial area and treated by repeated excision since 1976, when she was 44 years old (Table 1). To date, she has undergone six surgical resections of tumors, including five operations in the left tentoreal area (1976, 1984, 1995, 1999, 2002) and one in the lung (2001) (Fig. 1). Specimens from the last excision of the recurrent meningeal tumor showed histological and immunohistochemical characteristics of SFT, and, therefore, all of the previous slides of meningeal and pulmonary tumors were reviewed histologically and immunohistochemically. The immunohistochemical analyses demonstrated the lesions to be CD34 positive and EMA negative, suggesting a SFT rather than a meningioma. Histologically, a so-called patternless pattern was recognized, with focal staghorn-like vascular channels and no whirl formation, in line with the diagnosis as SFT. The pulmonary lesion was diagnosed as a metastatic tumor.

Clinical history

In 1976, when the patient was 44 years old, she first visited a hospital with the complaint of headache persisting from 2 years previously. At that time, she walked with a shift to her right side and demonstrated an elevation of intra-cranial pressure (over 200 mmH_2O), congestion of the retinal papilla and hemorrhage in her eyeground. A solid tumor, estimated to be 3 cm in diameter, was evident in her left tentorium on computed tomography (CT) scanning. Total resection of the tumor was performed and then histopathological diagnosis of a meningioma with immature features was given. The second meningeal tumor in the same region was noted 7.5 years later when she was 52 years old and again was totally resected. With continuous follow-up and magnetic resonance imagine (MRI) examination, the third (Fig. 1a) and fourth (Fig. 1b) local recurrent tumors were found when she was 63 years and 67 years old, respectively, and resected when they became 3 cm in diameter. She expressed only slight headaches before the operations. When she was 69 years old, a fifth tumor was apparent as a round and well-bordered abnormal shadow in the upper lobe of her right lung on chest X-rays, and CT and MRI confirmed the presence of a 1.8-cm diameter lesion (Fig. 1c). With histological observation of frequent mitosis and atypia indicative of malignancy in frozen sections, the right upper lobe was removed. The sixth tumor in her left sub-occipital region was resected 20 months later, when she was 70 years old (Fig. 1d).

Pathological findings

As shown above and in Fig. 2 and Fig. 3, all six tumors showed basically the same histological character, consisting of moderately hypercellular spindle cells with a "patternless" growth pattern, without apparent whirled cell arrangement or psammoma bodies. The tumors had thick collagen bundles with a hyaline appearance and intercellular collagen (Fig. 2a) and a reticulin network recognized with silver staining. Staghorn-like vascular channels were focally evident (Fig. 2b). Immunohistological analysis (Fig. 2c and d) showed the tumor cells to be completely negative for keratin and EMA and diffusely positive for vimentin and CD34. S-100 protein was negative and Leu-7 was positive. The staining results with anti-CD99 antibodies were contradictory, being positive with the 12E7 clone but negative with the O-13 clone. The lung tumor also had similar histological features with more apparent necrosis, with no attachment to the pleura.

Sequential changes in malignant and/or proliferative features are summarized in Table 1. Focal cysts and/or necroses were more or less observed in all the tumors. The second meningeal tumor and the lung metastatic tumor had larger areas of necrosis (Fig. 3c). All tumors were well demarcated but the last meningeal tumor slightly invaded into the cerebellum (Fig. 3e). Cellularity was mildly high from the first tumor but the Ki67 index and mitosis index were low in the first and third tumors and higher in the later lesions (Table 1 and Fig. 3b, d, f). Labeling indices for p53 protein varied considerably.

Discussion

We have presented here a case of meningeal malignant SFT, which locally relapsed four times, metastasized to the lung and invaded in the cerebellum over a period of

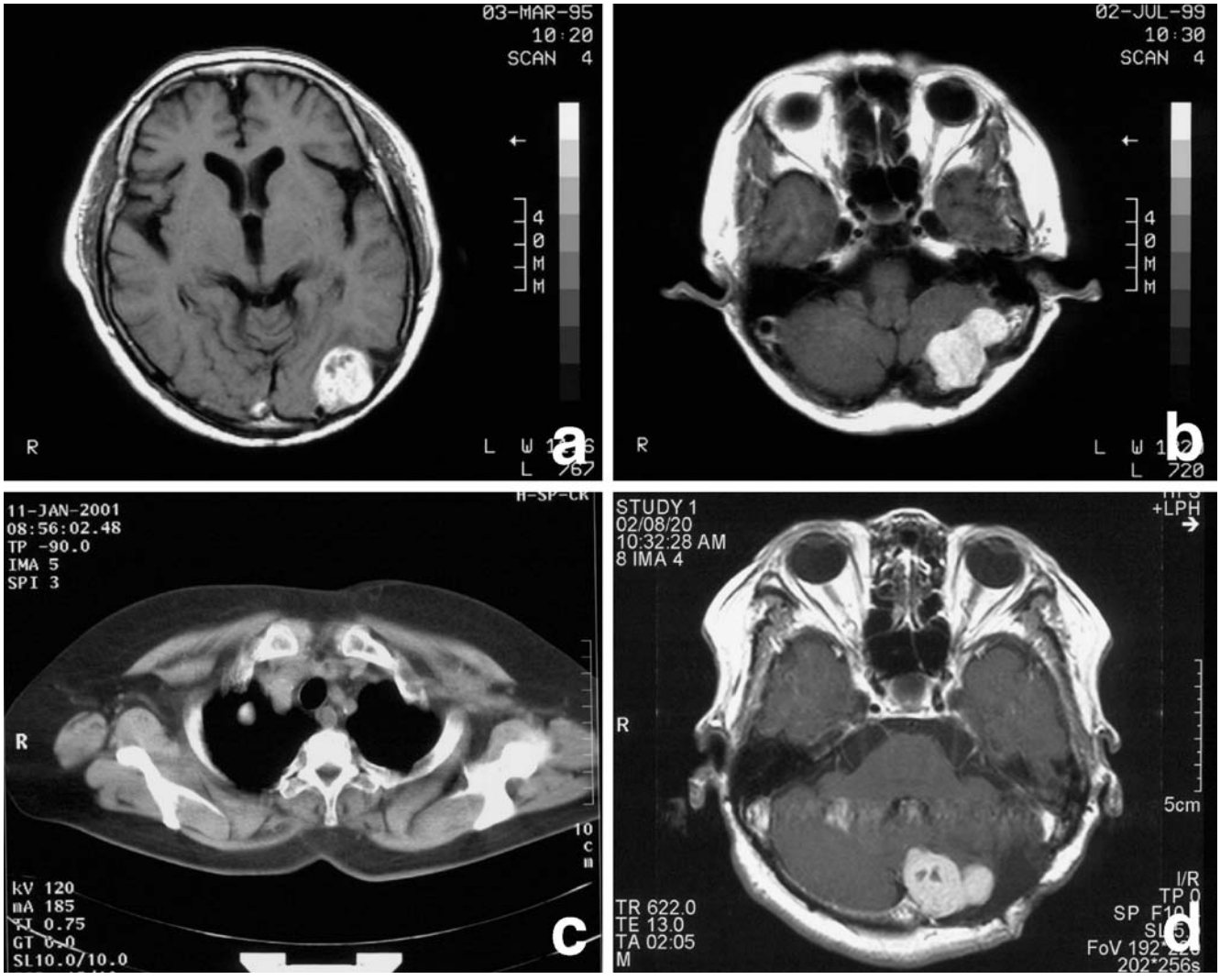

Fig. 1 Magnetic resonance imaging (MRI) observation of the meningeal and lung tumors. **a** Third meningeal tumor found in left tentorium area in 1995. **b** Fourth meningeal tumor found in the same area in1999. **c** Lung metastatic tumor in the right upper lobe in 2001. **d** Fifth meningeal tumor of the left suboccipital region in 2002

26 years. The histopathological and immunohistochemial features of the tumors fit those for SFTs described in previous literature [31], including examples originating in the meninges [5, 24]. Since the first report by Carnerio and co-workers in 1996 [5], retrospective reviews of pathology files of meningioma and/or HPC of the meninges revealed that approximately 30 cases should be reclassified as SFT [5, 29, 30], and overall more than 40 cases have now been reported [1, 2, 4, 5, 6, 7, 8, 10, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30]. Of these, only one case showed metastasis to other organs (lung and soft tissue) [22]. In terms of the biological behavior of SFT, the pathological criteria for determining malignant potential are of obvious clinicopathological interest for pathologists.

Histological features associated with local or distant recurrence of intrathoracic SFTs are reported to include high cellularity, mitotic activity (>4/10 HPF), nuclear pleomorphism, and necrosis [13, 31, 33]. In extrathoracic SFTs, such as those occurring in the abdomen/pelvis, retroperitoneum, groin, trunk, and upper arm, these factors are associated with, but are not by themselves predictive of, aggressive clinical behavior [31]. It seems that there is no strict correlation between morphology and biology [14, 15, 19, 31]. The results of a recent karyotyping study showing tetrasomy 8 to be associated with malignant behavior in the SFT of the pleura [11] might provide a new solution to this issue. In the present case, the first tumor showed hypercellularity and some mitoses. Therefore, according to the histological criteria mentioned above, the tumors had an aggressive nature and malignant potential from the beginning. Of importance is the very long duration between surgical removal of the first tumor and the second tumor occurrence, and between the first tumor and lung metastasis (7.5 years and 25 years, respectively). The mitotic index and the Ki67 labeling

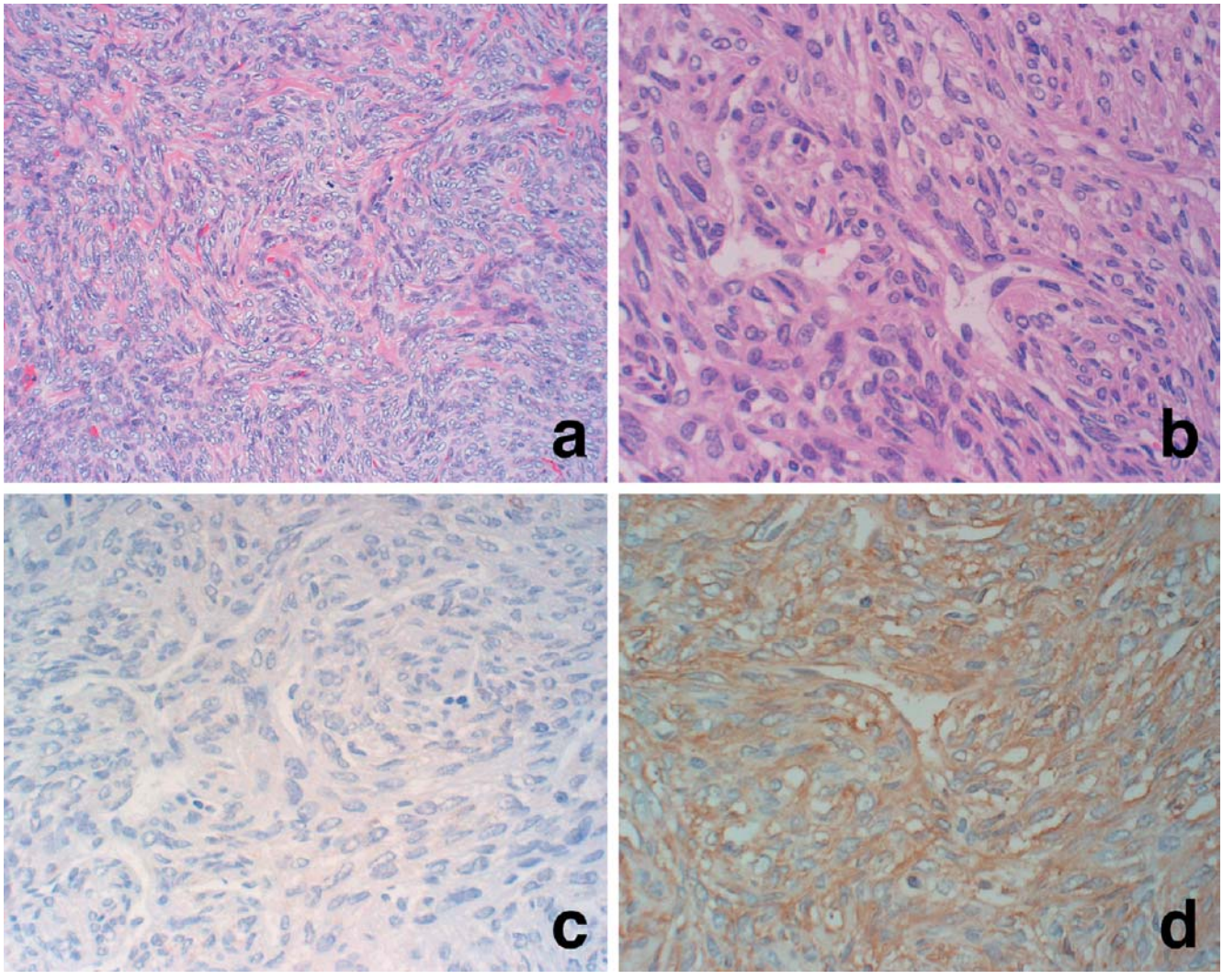

Fig. 2 Histopathological and immunohistochemical findings for the fifth meningeal tumor. **a** Collagen bundles with a hyaline appearance are evident. **b** Staghorn-like vascular channels are focally present. **c** Tumor cells are negative for EMA. **d** Tumor cells are diffusely positive for CD34

index were medium in the first tumor and tended to gradually increase with shortening of the interval before recurrence. However, the patient is now (2003, 2 years after surgical excision of the metastatic tumor in the lung) clinically free from distant metastasis. This might mean that the biological nature of meningeal SFT is very indolent, even when atypical histological features are evident. However, meningeal SFT cases with malignant features are very low in number, and the follow-up duration has not been sufficiently long in most cases. Therefore, further clinicopathological analyses are required for clarification.

The confusion surrounding the relationship between the SFT and the HPC may be particularly due to the fact that both show "staghorn" sinusoidal vessels and CD34 positive immunoreactivity, even though HPCs react less strongly and diffusely for CD34 than do SFTs [24]. The tissue patterns of the two lesions appear to coexist in occasional cases, and the border between them is blurred [14]. It is the present consensus that small foci of HPC-like tissue can be accepted in SFT, but the histological overlap is not yet clear. Moreover, while not observed in the present case, not only intrathoracic but also extrathoracic HPC [3, 9] as well as SFT [12] may be sources of hypoglycemia due to the production of an insulin-like growth factor. Intracranial HPCs are reported to have a relatively high rate of recurrence (60–83%) and metastasis (23–28%) [18, 30] and it is difficult to predict malignant potential from cell proliferation indices such as Ki67 or PCNA [32]. Further comparative analysis of links between the presence of HPC-like tissue in a meningeal SFT and malignant behavior is necessary. Another tumor to be differentiated from meningeal SFT is fibrous meningioma but this can generally be achieved on the basis of its positivity for EMA and only weak or negative CD34 staining.

In conclusion, we have experienced a case of SFT derived from the meninges with malignant potential. In

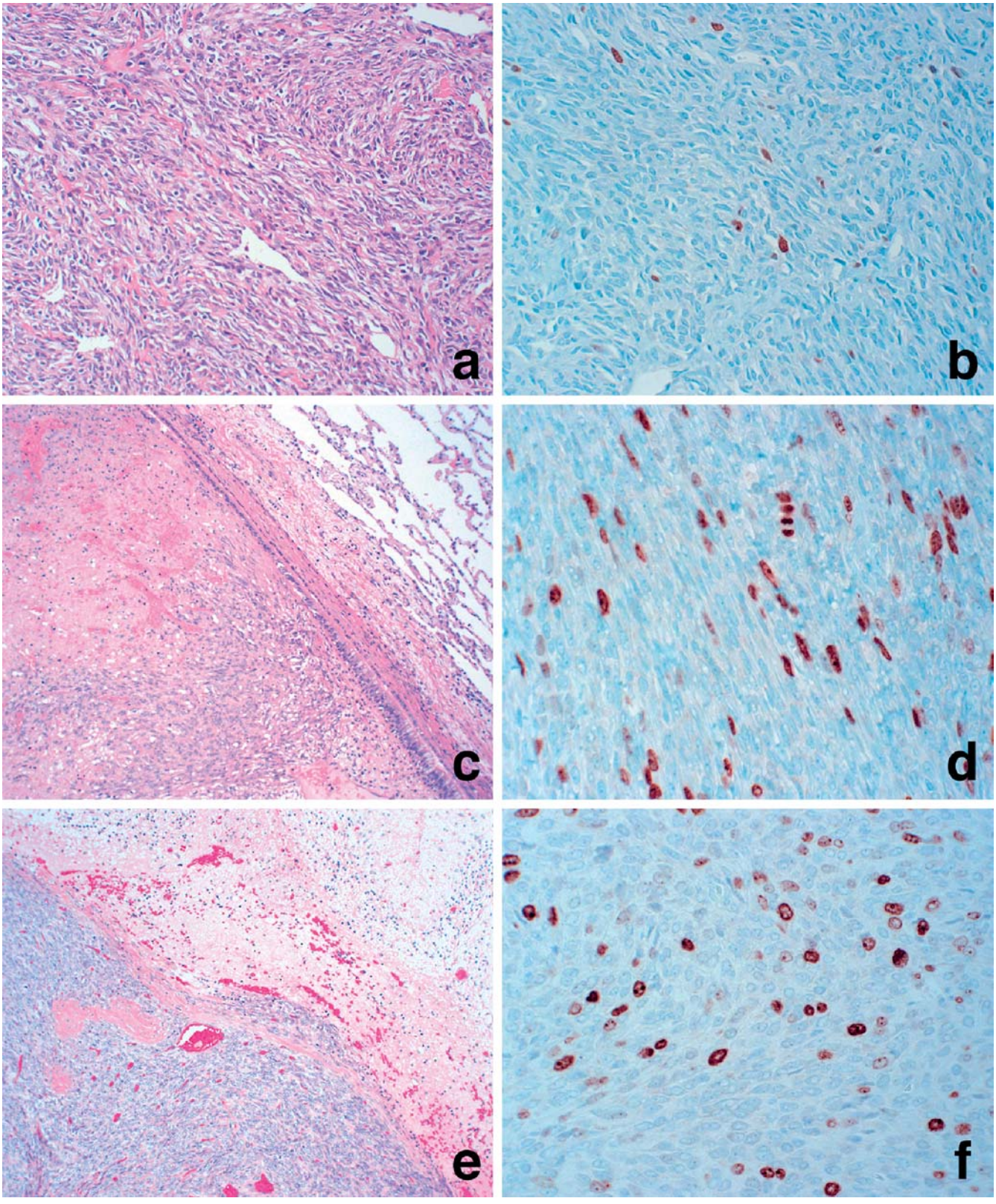

Fig. 3 Histological findings of the sequentially resected tumors (**a**, **c**, **e**; HE staining and **b**, **d**, **f**; anti-Ki67 immunohistochemical staining). **a**, **b** The primary meningeal tumor resected in 1976. Note the hypercellular fibrous nature with a "pattern-less" pattern and a few Ki67 positive cells. **c**, **d** The metastatic tumor found in left lung in 2001. The lesion demonstrates necrosis and pressure on the surrounding lung tissue with many Ki67 positive cells. **e**, **f** The fifth meningeal tumor resected in 2002. Partial invasion into the cerebellum and many Ki67 positive cells are apparent

such lesions, even mitotic and Ki67 indices are quite low, caution and careful follow-up are therefore needed. Regarding meningeal SFTs in the previous literature, so far one case having both recurrence and metastasis to the soft tissues and lungs [22] and five cases having local recurrence [5, 29, 30] have been reported. Considering that the first recurrence was observed 7 years after resection of the primary tumor in the present case, it is conceivable that follow-up in some of the previous cases may not have been long enough to allow the conclusion that they did not recur.

Acknowledgements We appreciate the valuable comments of Dr. Christopher D.M. Fletcher, Brigham and Women's Hospital, Harvard Medical School. This work was supported in part by a grant from the Society for Promotion of Toxicological Pathology of Nagoya, Japan.

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