

# Brain Metastasis from Dermatofibrosarcoma Protuberans

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Dermatofibrosarcoma protuberans(DFSP) is an uncommon fibrohistiocytic tumor characterized by aggressive local invasion and consequent local recurrence rather than distant metastasis. We present a case of a 51-year-old male patient with a typical cutaneous DFSP, which showed local recurrences and distant metastasis to the central nervous system(CNS) and the lung after 15 years from the initial diagnosis. CNS metastatic lesions recurred in 5 months after surgical resection of the first CNS lesion. These metastatic tumors were treated by open surgery and gamma-knife radiosurgery. Despite continuous medication of oral chemotherapeutic agent, the patient died during 1-year follow-up period.

**KEY WORDS :** Dermatofibrosarcoma protuberans · Brain metastasis.

## Introduction

Dermatofibrosarcoma protuberans(DFSP) is a fibrohistiocytic neoplasm of intermediate-grade malignancy that arises from the dermis and forms dermal or subcutaneous nodular masses<sup>2)</sup>. It often presents during early and middle adult life<sup>2,9)</sup>. The usual location distributed to the trunk, proximal extremities, and head and neck. It grows with infiltrative pattern into surrounding subcutaneous tissue and tends to recur mostly within 3 years after excision<sup>9)</sup>. However, distant metastasis is uncommon<sup>2,9)</sup>. Although there are reports of various sites of systemic metastasis including lung and lymph node, reports of metastasis to the central nervous system(CNS) are extremely rare in the English literature<sup>1,2,9)</sup>. The authors present a patient with DFSP detected on the right thigh, which was followed by local recurrence, distant skin metastases, and eventual multiple metastases to lung and brain.

## Case Report

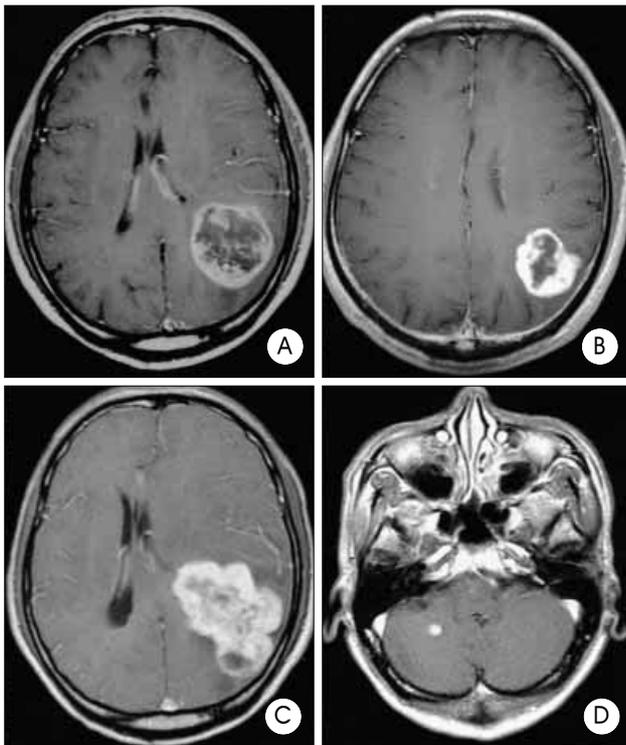
### Clinical course

A 51-year-old man presented with memory disturbance and acalculia. He had a history of a small nodule in the right thigh for which pathological data was unavailable, and had undergone

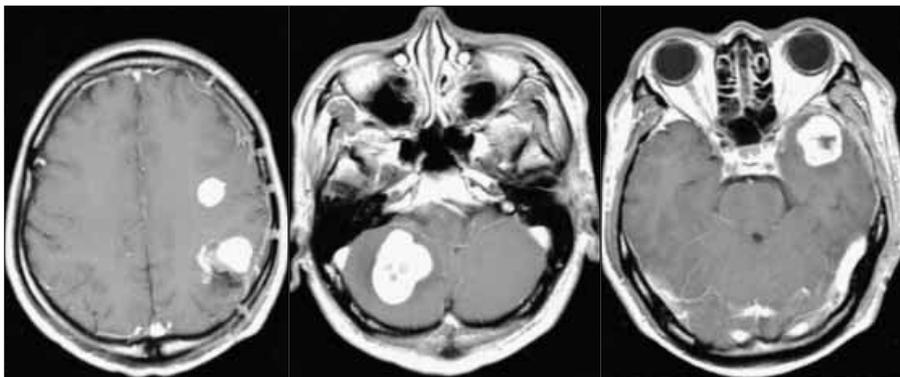
excision 16 years previously. Three years prior to this presentation, a 1cm-sized nodule recurred at the original site in the right thigh and rapidly became enlarged to a 10cm-sized mass. The histological diagnosis after excisional biopsy confirmed DFSP. One year prior to this presentation, he developed fine movement difficulty of the right hand and a tiny nodule was recognized in the right scapular area. Memory disturbance and acalculia then developed slowly with additional skin lesions on the thigh and abdomen. At this presentation, chest computed tomography demonstrated two metastatic lesions in the left upper and the right lower lung fields. Brain magnetic resonance images(MRI) revealed a rim-enhancing 4 × 4 × 5cm-sized mass in the left parietal lobe with peritumoral edema (Fig. 1A). Treatment was started using imatinib mesylate (Gleevec<sup>®</sup>) 400mg qd under the impression of distant metastases of DFSP to lung and CNS. After 2 months of imatinib mesylate therapy, a follow-up imaging study revealed that the parietal mass had shrunk to 3 × 3.5 × 4.6cm and that both lung nodules had decreased slightly (Fig. 1B). However, 2 months after imatinib mesylate therapy, he complained of a severe headache and vomiting. A follow-up brain MRI revealed significant regrowth of the parietal lesion with severe surrounding edema and brain stem compression (Fig. 1C). In addition, a newly-formed tiny enhancing mass was found in the right cerebellar hemisphere

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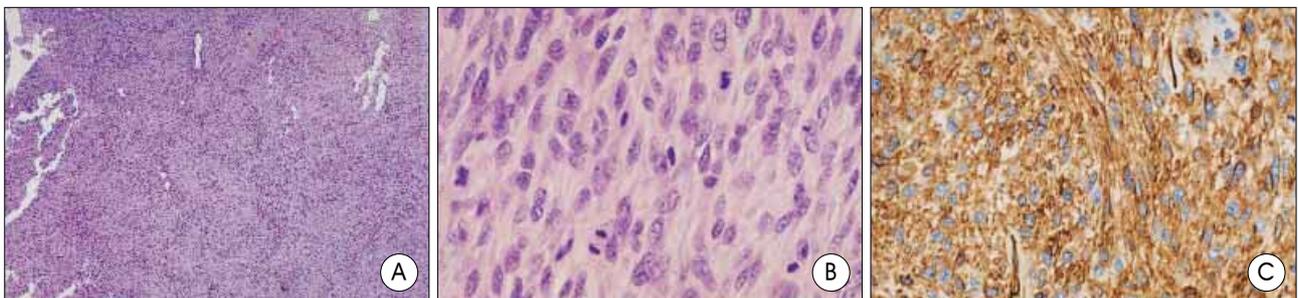
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**Fig. 1.** A rim-enhancing mass with central necrosis is found in the left parietal lobe in the initial brain magnetic resonance image(A). This lesion decreases in size after 2 months of chemotherapy(B), which then enlarges over the following 2 months(C). At this time, a new cerebellar lesion is detected(D).



**Fig. 2.** Multiple metastatic lesions including recurrence of parietal mass, enlarged cerebellar mass and newly developed frontal (two lesions, only one showing) and temporal lobe mass after six months from surgery and chemotherapy.



**Fig. 3.** A : Spindle cells are arranged in a storiform pattern (H & E, ×40). B : Mitoses are observed in the parietal specimen (H & E, ×400). C : Immunostaining for CD 34 shows strong immunoreactivity (×400).

(Fig. 1D). Only the parietal lesion was removed via open surgery. The mass was a hard whitish hypovascular mass, which had penetrated the cerebral cortex. Transient mild right side weakness was observed postoperatively. However, his functional status remained good until he revisited six months after adjuvant chemotherapy with imatinib mesylate for dizziness, motor dysphasia, ataxic gait, and right hand clumsiness. Brain MRI then showed newly-formed masses in frontal, temporal and parietal lobes in addition to enlargement of the previous right cerebellar lesion (Fig. 2). The cerebellar mass was surgically extirpated and the other metastatic lesions were treated by gamma-knife radiosurgery(GKRS). Marginal doses were 16, 20 and 18 and 22Gy to temporal, parietal and frontal (two lesions) metastatic lesions at a 50%-isodose line, respectively. However, he died 4 months later due to a progression of the disease despite continuous imatinib mesylate therapy.

#### The histological findings

The left parietal lesion from the first brain surgery was a hard whitish mass with poor vascularity. Microscopically, the tumor was composed of two distinct regions. In one region uniform spindle cells were arranged in a well-defined storiform pattern, and the other showed myxoid change. Numerous mitoses (as many as 50 per 10 high-power field) and geographic necrosis were seen. An immunostaining for CD34 was strongly positive

in the storiform component (Fig. 3). In addition, immunoreactivities for CD68 and smooth muscle actin (SMA) were focally positive, but epithelial membrane antigen(EMA), desmin and c-kit were negative. The cerebellar mass was histologically and immunohistochemically identical to the previously resected parietal tumor. The proliferative indices of the parietal and cerebellar metastatic tumors using monoclonal MIB-1 antibody against Ki-67 antigen, were both 10%.

## Discussion

**DFSP** is a slow-growing tumor but rapid growth pattern of the tumor is also known<sup>2,9</sup>. Its initial manifestation is a firm, plaque-like lesion of the skin with vertical infiltration to deeper structures. Moreover, the development of a definite nodule indicates conversion to the rapid growth phase<sup>9</sup>. Local recurrence rates are reported variably from 32 to 72%, and may be reduced to 13% in cases of wide excision<sup>6,9</sup>. However, a characteristic infiltrative or web-like growth pattern into adjacent structures makes complete resection of this tumor difficult<sup>9</sup>. Distant metastasis rate of DFSP is as low as 1~6%<sup>5,9</sup>. The lung and the regional lymph nodes are primary sites of distant metastases and metastases to bone, scalp, neck, uvula, pancreas and viscera have been reported<sup>2,3,9</sup>. However, metastasis to the CNS has rarely been reported.

McPeak et al<sup>5</sup> reported a single case of brain metastasis among 86 patients, and Uematsu et al<sup>11</sup> also presented a similar case. In these two cases, a scalp DFSP eroded the skull bone and invaded the brain parenchyma. The latter case was treated with 9 surgical resections, 3 GKRS, and chemotherapy. However, the disease proved refractory to treatment. Compared to these secondary CNS involvements, Auer et al<sup>11</sup> reported a case with three sequential primary CNS metastases at 5, 6, and 12 years after an initial diagnosis of DFSP, which were removed by surgery, but the result of the treatment was unavailable. Thus, the our case adds to the number of published cases of primary CNS metastases in DFSP. In our case, it took 15 years after the initial diagnosis for DFSP to metastasize to the CNS, and this was preceded by multiple skin recurrences, and remote metastasis to the lung. Compared with previous reports which describe chronic progression to CNS metastasis, the present case showed a strikingly aggressive clinical course of CNS metastasis. Rapid progression of the CNS metastasis proved fatal in our patient only 10 months after the detection of the CNS metastasis despite repeated surgical resections, GKRS, and chemotherapy.

DFSP is generally considered a radiosensitive tumor, and radiation therapy has been recommended for large, unresectable tumors or postoperatively for residual tumors<sup>2</sup>, and reported local DFSP control rates achieved by radiation therapy with or without surgery were acceptable<sup>10</sup>. Ten-year local control was achieved in 15 of 18 patients treated by surgery and radiation (15 patients) or radiation alone (3 patients), and the three local failures occurred in 12 patients with positive surgical margins. It is admitted that in general, whole brain radiation therapy lengthens the survival of patients with CNS metastasis or other tumors. However, the efficacy of radiation therapy for metastasis of DFSP to the CNS is unknown. Uematsu et al<sup>11</sup> suggested that GKRS could play a role in inhibiting the

growth of intradural metastatic DFSP. The authors also selected GKRS to treat metastatic masses in the brain. A follow-up brain MRI one month after GKRS revealed transient radiological growth control of the mass. Nevertheless, the disease eventually progressed and the patient died 4 months after GKRS. The efficacy of GKRS for the treatment of metastatic DFSP requires further evaluation. Imatinib mesylate is a selective low-molecular-weight inhibitor of the PDGF receptor tyrosine kinase. It functions by competitively inhibiting the enzyme's ATP-binding site, which inhibits the tyrosine phosphorylation of proteins involved in tyrosine kinase signal transduction<sup>8</sup>. Thus imatinib mesylate controls tumor growth by inhibiting the PDGF-mediated autocrine or paracrine loop of tumor growth<sup>4</sup>. Moreover, beneficial effects of imatinib mesylate have been reported for DFSP and its metastatic lesions<sup>4</sup>. In the present case, the metastatic lung lesions responded to imatinib mesylate therapy, however, the disease progressed despite continuous chemotherapy after CNS metastasis had developed. Further evaluation is needed to evaluate the efficacy of chemotherapy versus the CNS metastasis of DFSP.

The prognostic factors associated with increased local recurrence and distant metastasis have been evaluated. Sasaki et al<sup>7</sup> evaluated 19 DFSP cases, and showed that the mean MIB-1 labeling index of the recurrent tumors ( $11.4 \pm 6.0\%$ , n=10) was significantly higher than that of primary tumors ( $4.4 \pm 3.9\%$ , n=8), and found that DFSP with a higher MIB-1 labeling index had a tendency to recur. The present case had a high MIB-1 labeling index (10%), which concurs with the association between a high MIB-1 labeling index and aggressive behavior mentioned in the previous report.

## Conclusion

**I**t is generally believed that DFSP is a slow-growing but locally invasive tumor. Further, it is regarded that metastasis of DFSP is uncommon and CNS metastasis is rare. However, if CNS metastasis does occur, it is likely to show an aggressive behavior with frequent recurrence and multiple metastasis in the CNS. Surgical excision, GKRS, or chemotherapy using imatinib were applied in the our case to treat CNS metastasis of DFSP, but failed to control the progression of the disease. More experiences and studies are required for the effective treatment of DFSP with CNS metastasis.

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