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Dermatofibrosarcoma Protuberans Metastasizing to Cavernous Sinuses and Lungs: a Case Report

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Dermatofibrosarcoma protuberans (DFSP) is a locally aggressive tumor with a low potential for distant metastases. We report a 22-year-old female patient with a typical cutaneous DFSP who developed five local recurrences followed by left cavernous sinus metastasis at the eighth year and right cavernous sinus and lung metastases at the ninth year. In each local recurrence the tumor showed histological signs of progression as being more cellular, having higher mitotic index and being aggressively invasive through the underlying soft tissues. The histopathological evaluation of the metastatic tumor resected from the left cavernous sinus revealed dedifferentiation from low-grade DFSP to higher grade fibrosarcomatous morphology. Immunohistochemical studies of the primary tumor and also the recurrent and metastatic tumors showed diffuse CD34 positivity in all specimens and p53 positivity was detected in the metastatic tumor resected from left cavernous sinus.

Key words: dermatofibrosarcoma protuberans – cranial and lung metastases

INTRODUCTION

Dermatofibrosarcoma protuberans (DFSP) is a locally aggressive fibrohistiocytic tumor of intermediate malignancy with a great potential for local recurrences and a small risk of distant metastases (1). It has been reported that multiple operations for recurrences precede the appearance of metastases (1). In this paper we report a patient with DFSP on the forehead who developed a metastatic tumor to the left cavernous sinus followed by subsequent right cavernous sinus and lung metastases.

CASE REPORT

A 22-year-old female patient with a 3 × 3 cm cutaneous mass located on her forehead was referred to Hacettepe University hospital in October 1990. The mass was totally excised and pathological examination showed an unencapsulated tumor, a myxoid DFSP located in the dermis. The lesion was composed of uniform, cytologically bland spindle cells in myxoid matrix (Fig. 1a). A vague storiform pattern was present in some areas. Immunohistochemically, neoplastic cells gave a negative reaction with anti-cytokeratin, S-100, smooth muscle actin (SMA), desmin and HMB-45 antibodies but they were diffusely positive for vimentin and CD34 (Fig. 1b). Five years later, in January and August 1995, two local recurrences were subtotally excised. Light microscope examination in both cases demonstrated the neoplasm carrying the same morphology as the primary, but this time more cellular (Fig. 2a). The storiform pattern was prominent throughout. The mitotic index was high (1 mitotic figure/high power field). Neoplastic cells continued to express CD34 (Fig. 2b). Pleomorphism was absent and the tumor invaded the surrounding adipose tissue and skeletal muscle. The deep surgical margins were positive for lesion in both recurrences. After surgical excision in August 1995, a total dose of 50 Gy with 6 MeV electron beams to the tumor bed with a 3 cm safety margin was applied. During the following 2 years, three local recurrences were widely resected and the operative defects were covered with skin grafts. The diagnosis of DFSP was confirmed after all excisions.

In October 1998, the patient was readmitted with a complaint of diplopia. Physical examination revealed ptosis in the left eye with hyperaesthesia in the left second, third, fourth, fifth and sixth cranial nerve areas. Cranial MRI showed a 4 × 3 × 2 cm mass located in the left cavernous sinus. A sarcoma secondary to radiation was out of consideration since radiotherapy to the forehead was applied with low-energy electron beams. The provisional diagnosis was a metastatic tumor of DFSP and the patient was consulted for palliative cranial irradiation without an attempt for histological confirmation. Since metastases of DFSP to the brain has been reported to be extremely rare and no other metastatic focus could be distinguished at that time,

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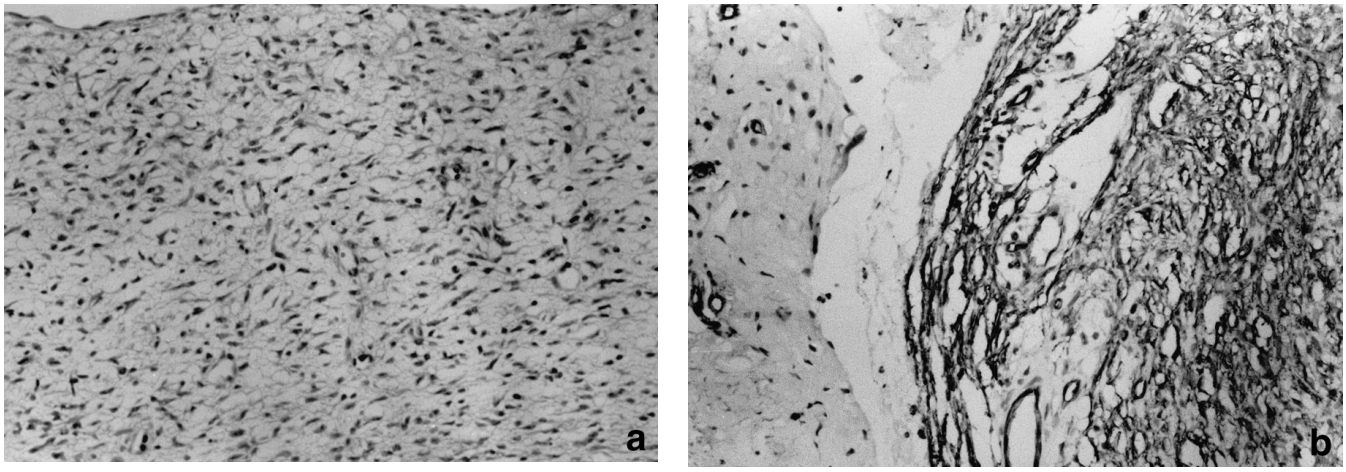

Figure 1. (a) Tumor composed of loosely arranged fusiform cells in myxoid stroma. Mitotic figures are rare (<1/10 high-power field) (H&E, ×200). (b) The border between DFSP and neoplastic tissue. Tumor cells are strongly CD34 positive (IHC, primary anti-CD34 antibody, ×200).

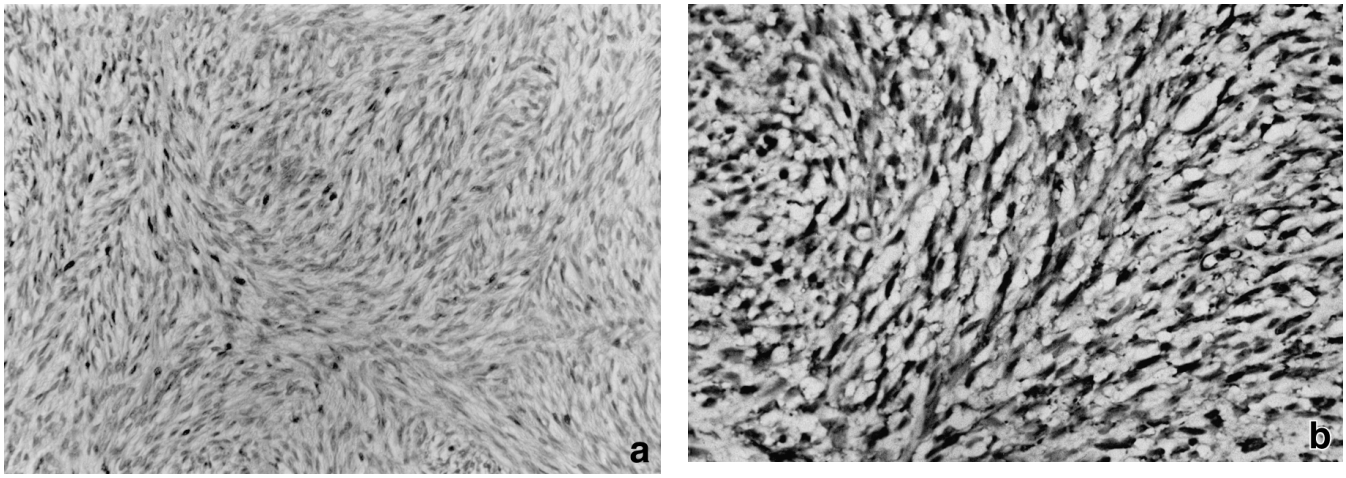

Figure 2. Recurrent tumor. (a) Increased cellularity in comparison with the primary lesion (H&E,×200). (b) CD34 expression by the tumor (IHC, primary anti-CD34 antibody, ×400).

surgical intervention was decided to exclude the possibility of a second primary tumor. In February 1999, orbitofrontozygomatic craniotomy and gross total tumor excision were performed at another institution. The pathological diagnosis was an undifferentiated malignant mesenchymal tumor. Triple-dose contrast cranial MRI and thorax CT revealed nothing abnormal except the tumor located in the left cavernous sinus. The tumor was considered as a second primary and a course of radiotherapy with 6 MV photon beams with the three-field technique encompassing the cranial tumor bed with a 2 cm safety margin in conventional daily fractions to a total dose of 60 Gy was applied. In October 1999, another 6.5 × 5 cm tumoral mass located in the right cavernous sinus extending to the nasopharynx and middle cranial fossa was detected (Fig. 3). Thorax CT revealed metastatic nodules (Fig. 4) in the left and right lung parenchyma. After detecting the other distant metastatic foci, the pathological slides of the tumor located on the left cavernous sinus were re-examined retrospectively together with the other primary and recurrent tumor specimens by a single pathologist and histopathology revealed a metastatic tumor to the left cavernous sinus rather than a second primary. Morphological features were similar except for the storiform pattern being less striking (<50% of the sampled tumoral area). More often, spindle cells formed cellular streams intersecting one another at acute angles with a herring-bone appearance reminiscent of classic fibrosarcoma. However, expression of CD34 by the tumor cells was still found positive (Fig. 5a). Pleomorphism was still lacking but mitotic figures were frequent (Fig. 5b). No tumor necrosis was identified. The proliferative activity in the primary, recurrent and metastatic tumors by immunohistochemistry using monoclonal MIB-1 antibody against Ki-67 antigen was studied and it was found that the cellular proliferation rate progressively increased from primary to metastatic DFSP (Fig. 6). The Ki-67 labeling index was calculated by determining the percentage of positive nuclei in the area of the highest staining density (i.e. ratio of positive cells to all nuclei). It was 2% in the primary tumor and changed to ~15–20% in recurrences and to 70% in

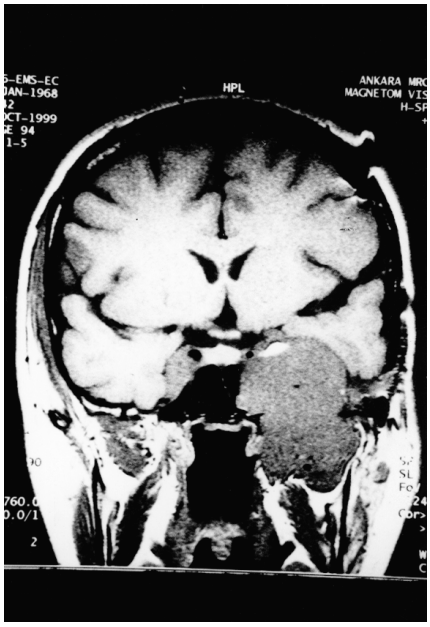

Figure 3. A coronal MRI section of the tumoral mass located in the right cavernous sinus.

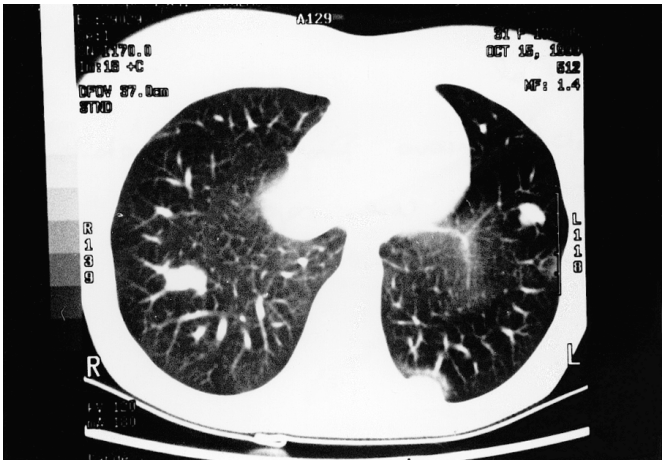

Figure 4. Thorax CT revealing lung metastases in the left and right lung parenchyma.

metastasis. Negative p53 protein expression was found in the primary and the recurrent tumors, but >10% of neoplastic cells were found to overexpress strongly nuclear p53 in the metastatic lesion (Fig. 7). Systemic chemotherapy was applied without any apparent benefit and the patient died with progressive lung metastases and a right cavernous sinus mass in May 2000 at the age of 32 years. An autopsy was not performed.

DISCUSSION

DFSP is a so-called fibrohistiocytic neoplasm that commonly arises on the lower extremities and trunk and forms dermal or subcutaneous nodular masses. The neoplastic cells are uniform plump fibroblasts and they typically exhibit a 'storiform' or 'cartwheel' growth pattern. A special type is the Bednar tumor, the pigmented form of DFSP, which contains heavily melanin-loaded dendritic cells. Rarely DFSP contains areas that are indistinguishable from a fibrosarcoma or malignant fibrous histiocytoma with more pleomorphism and mitotic activity. The primary lesion in our case was the myxoid variant of DFSP which contained large amounts of myxoid stroma. The storiform pattern was less distinct.

The metastatic capacity makes DFSP a true sarcoma, although the rate of metastases is <5% (1). Resection is the treatment choice and local recurrence rates range up to 53% depending on the adequacy of excision and margin status (2). Distant metastases usually occur only after multiple local recurrences (2,3). It has been proposed that any manipulation in the form of inadequate excision, which cuts through tumor and simultaneously opens vascular channels, may be essential

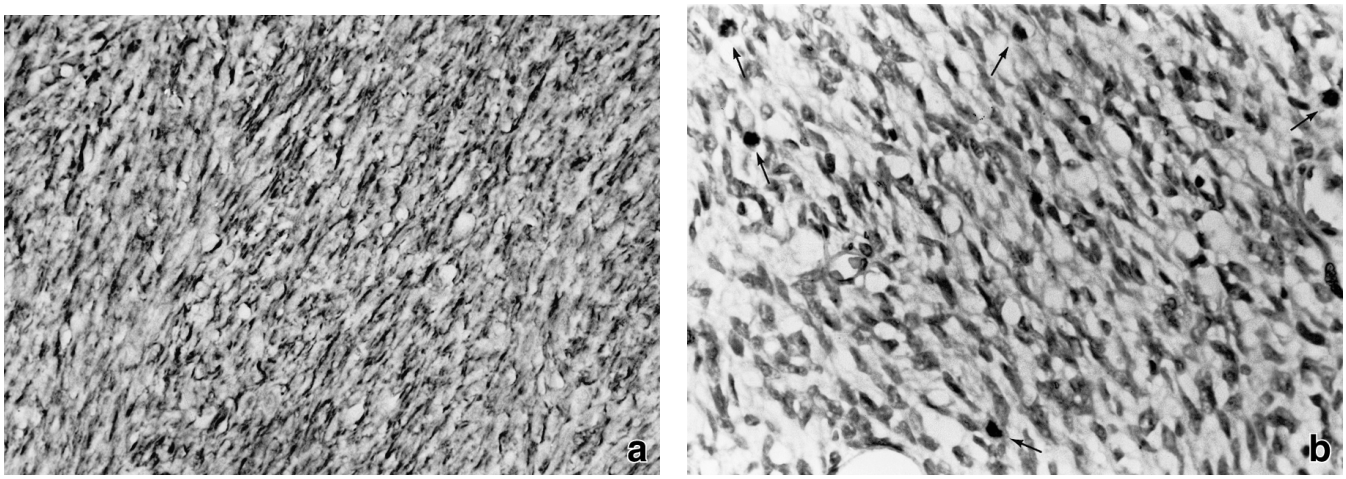

Figure 5. Metastatic tumor. (a) Persistent CD34 expression (IHC, primary anti-CD34 antibody, ×200). (b) A microscope field containing a high number of mitotic figures (arrows). (H&E, ×400).

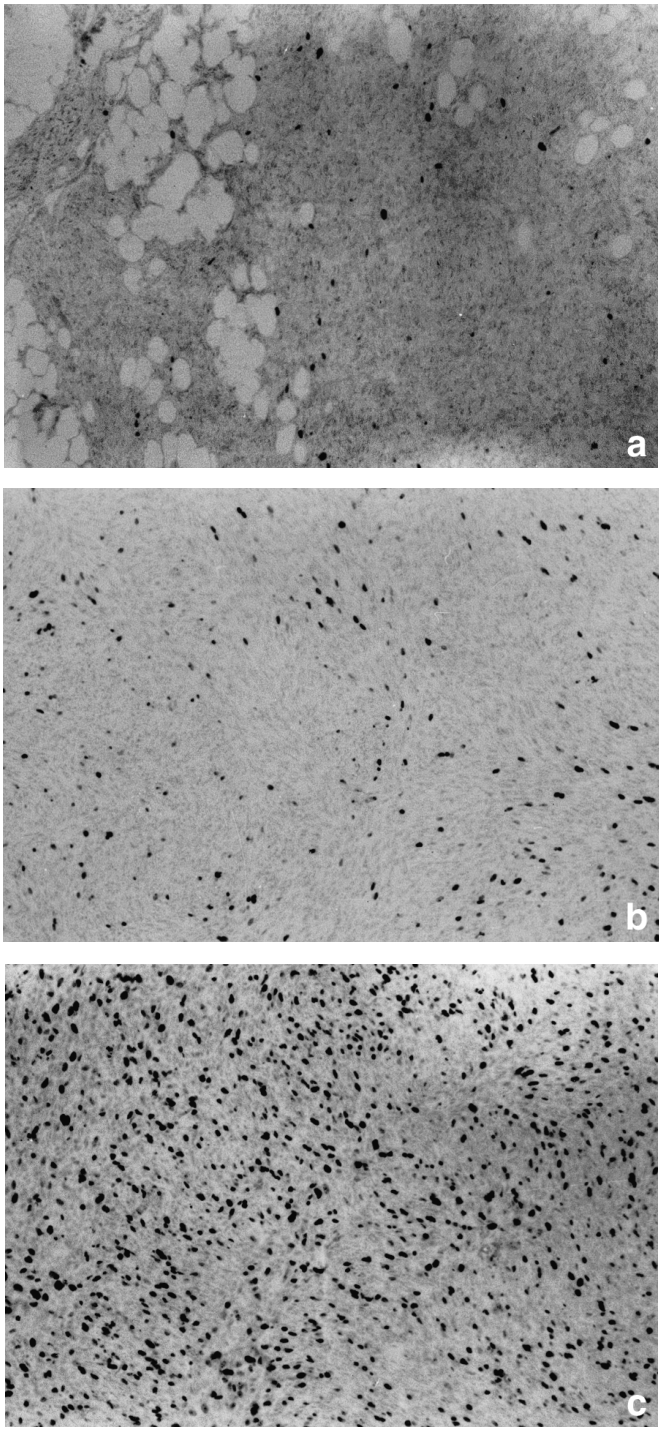

Figure 6. Gradual increase in the proliferative activity of tumor cells detected by MIB-1 labeling. (a) Primary tumor (IHC, anti MIB-1 antibody, ×100). (b) The first recurrence (IHC, anti MIB-1 antibody, ×100). (c) Metastasis (IHC, anti MIB-1 antibody, ×100).

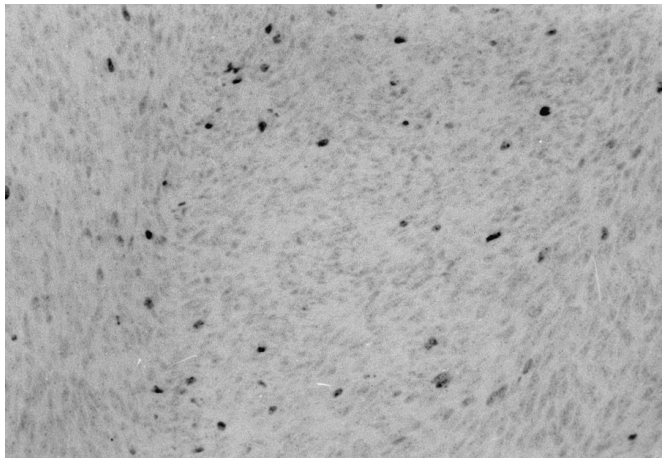

Figure 7. p53 expression: intense nuclear positivity in >10% of tumor cells in metastasis (IHC, primary anti-p53 antibody, ×200).

for metastases to develop (1). The neoplasm in our case started as a 3 × 3 cm mass located on the forehead. Morphologically it was a DFSP with myxoid stromal changes. It recurred several times, the first being 5 years after the primary and metastasized at the end. In each recurrence the tumor showed histological signs of progression as being more cellular, having higher mitotic index and being aggressively invasive through the underlying soft tissues. Deep surgical margins were positive in all recurrences. Dedifferentiation from low-grade DFSP to higher grade fibrosarcomatous morphology was noted in the metastatic tumor resected from the left cavernous sinus. Immunohistochemistry studies of the primary, recurrent and metastatic tumors by using monoclonal MIB-1 antibody against Ki-67 antigen showed that the cellular proliferation rate progressively increased from primary to metastatic DFSP.

It is well known that DFSP shows slow but persistent growth over several years. Unfortunately, there are no solid prognostic criteria to determine the more aggressive forms. Among the histological subtypes, it has been suggested that DFSPs having fibrosarcomatous areas (DFSP-FS) may exhibit an increased chance of an adverse outcome. DFSP-FS have tended to have a higher proliferative activity than DFSPs that do not have an FS area. It has been proposed that an altered p53 pathway may have a potential role in tumor progression and p53 mutation may correlate with aggressiveness in DFSP. The overexpression of p53 varies widely between 4 and 71% in different reports (4–6). Sasaki et al. (4) detected immunohistochemical p53 overexpression in three out of their 19 cases of DFSP, which also showed higher proliferative activity and aneuploidy. The positive staining rate of mutated p53 protein was reported to increase with increase in malignancy of the neoplasm (5). Li (5) found the positive staining rates in fibroma, DFSP, fibrosarcoma and malignant fibrous histiocytoma to be 0, 4, 37.5 and 62.5%, respectively. The fibrosarcomatous component in our case was not present in the primary or recurrent lesions, but appeared in the metastasis. The immunohistochemical studies revealed negative p53 protein expression in the primary and the recurrent tumors, but >10% of neoplastic cells were found to overexpress strongly nuclear p53 in the metastatic lesion.

Onoda et al. (7) described a similar case to ours. In that particular autopsy case, a 45-year-old patient with a tumor of DFSP located on the right upper arm developed two local

recurrences followed by skin, lung and brain metastases during an 8-year clinical course. The recurrent and metastatic tumors in that case lacked both melanin production and a storiform arrangement and instead revealed fibrosarcomatous change with a herringbone or interlacing pattern of growth. The clinical and histopathological surveillance of our case and the case reported by Onoda et al. led us to think that although considered as low grade, these tumors have the ability to change their biological behavior to a more aggressive form, which may be a true sarcoma if treated inadequately and such transformation involves p53 mutation.

It has been reported that distant metastases occur predominantly to lung or to lymph nodes (8). In a retrospective study by McPeak et al. (1), five out of 86 patients with DFSP developed distant metastases, one of which showed brain metastases in addition to lung and bone metastases. Left cavernous sinus metastasis in our case developed first after multiple local recurrences and was followed by right cavernous sinus and lung metastases.

DFSP has been proposed to be a relatively radiosensitive tumor and radiation at doses of 50–60 Gy should be considered as an adjuvant to resection if margins are positive (9–12). In a retrospective analysis by Haas et al. (9), of the 21 patients treated surgically, all with negative resection margins, seven recurred, which makes a local control probability of 67%. Combined modality treatment with surgery and radiotherapy in that analysis was given to 17 patients who experienced 33 local recurrences prior to radiotherapy and only three recurrences were detected, which makes a local control probability of 82%. In our case, radiotherapy was added to surgery after the second local recurrence and a total dose of 50 Gy was applied with low-energy electron beams. Postoperative radiotherapy in our case seems to be ineffective since three local recurrences were detected in the following 2 years. We think that the ineffectiveness of adjuvant radiotherapy may be due to the inadequate energy and total dose.

In conclusion, it is usually believed that DFSP is very invasive locally but almost never metastasizes (13). Since it is generally regarded as a low-grade or borderline neoplasm, treatment is frequently too conservative. Our patient and the other cases reported in the literature led us to think that a proportion of these tumors, although small, have a definite metastatic potential especially after multiple inadequate surgical resections. Every attempt should be made for total excision with negative margins and in the case of positive margins or where repeated surgery may cause mutilation or functional impairment, radiotherapy should be added without any delay.

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