INTRODUCTION

Radiation therapy is an integral part of the locoregional treatment of many cancers, particularly carcinoma of the breast. Whole breast irradiation, frequently with additional radiation or “boost” to the tumor bed, is a standard adjuvant treatment after breast-conserving surgery. In combination with systemic chemotherapy, chest wall and regional nodal irradiation after mastectomy reduces breast cancer mortality and is indicated in patients with large primary tumors or multiple positive lymph nodes [8, 34]. However, radiotherapy is also considered a risk factor in breast cancer patients for the development of soft-tissue and bone sarcoma [1, 14, 23, 36]. The postirradiation sarcoma (PIS) that develops in the irradiated breast is a rare iatrogenic complication of these tumors. Nonetheless, with new indications for radiotherapy and increased screening of breast cancer, the number of post-radiation sarcoma will increase in the future.

Reported PIS of the breast include angiosarcoma, osteosarcoma, fibrosarcoma, and malignant fibrous histiocytoma (MFH) [1, 14, 36]. Only a few sporadic MFHs located in the breast region have been reported in the English literature [6, 7, 18, 22, 24, 26, 32, 33, 35]. We report a case of MFH of the breast occurring 7.8 years after radiation treatment for infiltrating duct carcinoma. Our aim is to highlight this rare
clinicopathologic entity to both general surgeons and to pathologists. Its extremely low incidence has precluded clinicians from gaining experience concerning appropriate management of these tumors.

CASE REPORT

A 37-year-old female patient presented to our hospital with one mass lesion over right axillary area that limited her range of motion of right shoulder. She had received right lumpectomy and axillary lymph node dissection for a 1.5 cm infiltrating duct carcinoma on October 16, 1995. Metastatic duct carcinoma was present in one of eleven axillary lymph nodes. The patient was then referred to our department for postoperative radiotherapy with 5040 cGy to right residual breast tissue and right supraclavicular lymph node region, 5940 cGy to a cone down field, which included the surgical scar on the right breast. Adjuvant chemotherapy with CMF (cyclophosphamide, methotrexate and 5-fluorouracil) regimen was administered twice after completion of radiotherapy. The patient was regularly followed up at our hospital with no evidence of tumor recurrence.

Ninety-two months postoperatively, the patient was evaluated for a firm, fixed mass measuring 4 × 5 cm at the site of radiation exposure. Computed tomography scan of neck and chest demonstrated a lesion of solid tissue density with ring-enhancement involving the right side of the axillary area (Figure 1). A plain chest radiograph was negative for metastatic disease. The abdominal ultrasonography results were normal, and there was no suggestion of distant metastasis. To discriminate tumor recurrence over lymph node or second malignancy, the patient underwent incisional biopsy on July 22, 2003 and spindle cell sarcoma was impressed. A wide excision of the irregularly shaped, hard tumor with latissimus dorsi muscle flap reconstruction and split thickness skin graft was performed one week later. Macroscopically, the tumor was multilobular and 5.5 cm in diam-

Fig 1. Computed tomography scan of neck. Tumor is seen in right axillary region (arrow).

Fig 2. Malignant fibrous histiocytoma of the axilla. (a) There is one well-defined whitish whorl mass measuring 5.5 cm in diameter with intact skin. (b) Spindle cell or pleomorphic giant cells with storiform or fascicle pattern are apparent with infiltration into deep subcutaneous soft tissue. (Hematoxylin and eosin; original magnification x 100)
eter with intact skin. In cut sections there is one well defined whitish whorl mass (Figure 2a). Microscopically, the tumor consisted of spindle cell or pleomorphic giant cells with storiform or fascicle pattern, infiltrating into deep subcutaneous soft tissue (Figure 2b). Immunohistochemical staining of this tissue indicated the presence of vimentin and the absence of cytokeratin. The final diagnosis was malignant fibrous histiocytoma. The surgical margins were free of tumor. The patient is alive and well without evidence of recurrent disease 8 months after the surgery.

**DISCUSSION**

Radiation therapy plays a major role in the treatment of breast cancer. Approximately 60% of patients with cancer receive irradiation at some time in the course of their disease. There is an abundance of data to indicate that radiation can induce cancer in the human. Indeed, radiation has been described as a “two-edged sword” because, when it is a major modality for the treatment of cancer, it can also be the cause of cancer. With improvements in therapeutic modalities, steady progress in treatment has been achieved. Today, nearly 50% of patients with cancer are alive 5 years after the initial diagnosis of their disease [12]. Although most long-term survivors have a tumor-free life, a few patients suffer from a second malignancy in the irradiated field. Compared with other radiation-induced malignancy, reports describing PIS are few in number [18]. The exact incidence of postirradiation sarcomas of the breast is difficult to determine.

Large single-institution retrospective studies have estimated cumulative incidence rates for breast cancer patients receiving radiation at about 2 per 1,000 at 10 years. The Gustave Roussy Institute reported 11 radiation-induced sarcomas identified in 6,919 patients followed for more than 1 year [31]. Cumulative incidences of 0.2% at 10 years, 0.43% at 20 years, and 0.78% at 30 years were reported. Remarkably similar rates of radiation-associated sarcoma have been reported in different institutional studies. Pierce et al. [28] found three in-field sarcomas in 1,624 patients at the Joint Center for Radiation Therapy and calculated a crude incidence of 0.18%. Hatfield and Schulz [10] estimated a rate of 0.22% based on 5 radiation-induced sarcomas in 2,250 patients, and Philips and Sheline [27] found a similar rate of 0.22% with 1 sarcoma out of 445 patients. Doherty et al. [4] described 4 in-field bone sarcomas for 3,199 patients with 18 to 28-year follow-up (0.26% percentage risk). Zucali et al. [37] reported 3 cases of soft-tissue sarcoma among 3,295 patients (2 out of 3 were angiosarcoma). Kurtz et al. [17] found 2 out of 2,850 patients with in-field soft-tissue sarcoma among patients treated with breast conservation therapy in Marseilles. In our current study, estimated cumulative incidence of PIS at 10 year was about 0.97% from one in-field MFH among 129 patients who received postoperative radiotherapy. The higher cumulative incidence might be due to relatively smaller population in our study.

Previous population studies indicate that breast cancer patients who do not receive radiotherapy are also at increased risk of second malignant sarcoma. Both the data from Denmark [5] (n = 54,964, 1943-1980) and from Connecticut tumor registry [9] (n = 41,109, 1935-1982) suggested a relative risk of about 2.1 to 2.3 for second malignant sarcoma in all breast cancer survivors. For patients receiving radiotherapy, the relative risk of sarcoma was approximately doubled, although in-field and out-of-field occurrences could not be distinguished. Karlsson et al. [14] reported 19 sarcomas vs. 8.7 expected for the Swedish Cancer Registry data (1960-1980, n = 13,490). Recently, a total of 263 subsequent sarcomas were identified within 274,572 breast cancer patients identified from the SEER data [36]. For
patients receiving radiotherapy, the cumulative incidence of second malignant sarcoma was 3.2 per 1,000 at 15 years compared to 2.3 per 1,000 in patients not receiving radiotherapy. Risk factors for second malignancy in unirradiated patients may be related to underlying genetic susceptibility, environmental exposures, chemotherapeutic agents, or to surgically treatment-related sequelae.

The interval time from start of radiation therapy of the first primary tumor to the first PIS diagnosis is between 2 and 65 years (mean latency period between 10 and 15 years) in several large single-institution retrospective and population-based studies [18, 25, 28, 30, 31, 35, 36]. While some reports failed to demonstrate any difference between the latency periods for post-radiation soft tissue and bone sarcoma [13], others have shown that the latency period may be longer for bone [26] and that there may be a bimodal distribution for soft-tissue sarcoma [16]. Latency period appears inversely related to radiation dose, i.e., a shorter latency period with a larger radiation dose [10, 35], although there are reports to the contrary [3, 11, 15]. The latency period may also be affected by the age at the time of radiotherapy [13, 16, 19, 21]. There is some evidence to suggest that megavoltage radiotherapy [18, 29] or higher doses [18, 35] may be associated with a shorter latency, but it is not conclusive [10, 35].

The first reports on clinical PIS were generally of bone lesions, and the first criteria for PIS of bone were proposed by Cahan et al. in 1948 [2]. Laskin et al. modified these criteria for PISs of soft tissue origin [18]. These modified criteria are a prior history of radiation, development of a sarcoma in the field of radiation, a latency period of at least 2 years between radiation and the appearance of the sarcoma, and proof that the sarcoma is histologically different from the radiated primary. In our current study, the patient had received radiation for infiltrating duct carcinoma of the right breast. After 7 years of latency, she developed a histologically proven MFH in the irradiated field.

MFH has been one of the most common defining types of PIS. Fibrous stromal configuration is often characteristic of MFH. However, this so-called storiform stromal pattern may not be the predominant histopathologic background in all MFHs. Myxoid, inflammatory, and pleomorphic predominance may also occur. Although there are no clear histopathologic differences between radiation induced and spontaneously occurring MFHs, the lack of a typical storiform pattern and the abundance of dense and sclerotic connective tissue stroma found in one third of the post irradiation MFH is meaningful [18]. Negative staining result for cytokeratin excludes the possibility of a sarcomatoid carcinoma. A spindled morphology and numerous bizarre tumor cells in conjunction with the immunohistochemical findings support the diagnosis of MFH. Tumors exhibiting the storiform pattern and the myxoid variants are considered to have rather good prognoses and respond well to local wide surgical therapy. In contrast, the inflammatory and the pleomorphic variants behave aggressively, and local surgical therapy alone is not sufficient in treating these forms.

The PIS should be treated with a radical aim, and wide radical surgical excision should be the first choice in operable patients. Adjuvant radiation therapy and/or chemotherapy should also be considered. In addition, clinical and radiologic examinations had not revealed any lymphadenopathy. Adjuvant therapeutic modalities were also not considered.

Our review of the literature suggests that the risk of postirradiation MFH in the breast is extremely low (Table 1). Compared with risks of surgery, anesthesia, and chemotherapy, the risk of PIS after radiation therapy does not appear to be appreciably worse. We believe that this risk can be successfully managed with wide surgical excision. Given these objectives and the large number of patients who can be treated with radi-
Table 1. Postirradiation Malignant Fibrous Histiocytosis (MFH) of Breast Cancer Patients

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patient number</th>
<th>&quot;Age,&quot;</th>
<th>Dose (cGy)/Energy Source</th>
<th>Site of MFH</th>
<th>Latency (yrs)</th>
<th>Follow-up</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laskin et al. [18]</td>
<td>1</td>
<td>&quot;49, F&quot;</td>
<td>NA</td>
<td>R. Shoulder</td>
<td>6</td>
<td>1</td>
<td>Died (NAS)</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>&quot;37, F&quot;</td>
<td>4200/Mega</td>
<td>L. Subscapula</td>
<td>10</td>
<td>1</td>
<td>Died (NAS)</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>&quot;55,F&quot;</td>
<td>5400/Mega</td>
<td>Chest wall</td>
<td>9</td>
<td>4</td>
<td>Alive (WS)</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>&quot;31,F&quot;</td>
<td>NA</td>
<td>L. Clavicle</td>
<td>24</td>
<td>1</td>
<td>Alive</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>&quot;49,F&quot;</td>
<td>4500/Mega</td>
<td>R. Breast</td>
<td>6</td>
<td>1</td>
<td>Alive (NAS)</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>&quot;42,F&quot;</td>
<td>5000/Mega</td>
<td>R. Breast</td>
<td>7</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>7</td>
<td>&quot;42,F&quot;</td>
<td>5000/Mega</td>
<td>L. Axilla</td>
<td>5</td>
<td>10</td>
<td>Alive (NAS)</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>&quot;58,F&quot;</td>
<td>5000/Mega</td>
<td>R. Axilla</td>
<td>12</td>
<td>2</td>
<td>Alive (NAS)</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>&quot;34,F&quot;</td>
<td>NA</td>
<td>L. Axilla</td>
<td>9</td>
<td>1</td>
<td>Died (WS)</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>&quot;65,F&quot;</td>
<td>3200/Mega</td>
<td>Chest wall</td>
<td>7</td>
<td>1</td>
<td>Died (WS)</td>
</tr>
<tr>
<td>Wiklund et al. [35]</td>
<td>11</td>
<td>&quot;56,F&quot;</td>
<td>NA</td>
<td>Neck of Scapula</td>
<td>3.4</td>
<td>0.3</td>
<td>Died (WS)</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>&quot;66,F&quot;</td>
<td>NA</td>
<td>Subcutis of Humerus</td>
<td>15.8</td>
<td>3.9</td>
<td>Died (WS)</td>
</tr>
<tr>
<td>Pendlebury et al. [26]</td>
<td>13</td>
<td>&quot;37,F&quot;</td>
<td>5400/Ortho</td>
<td>Humerus</td>
<td>15.7</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Vera-Sempere et al. [33]</td>
<td>14</td>
<td>NA</td>
<td>5400/Mega</td>
<td>Breast</td>
<td>5</td>
<td>1</td>
<td>Died (WS)</td>
</tr>
<tr>
<td>Tsuneyoshi et al. [32]</td>
<td>15</td>
<td>&quot;52,F&quot;</td>
<td>2500/Mega</td>
<td>R. Breast</td>
<td>11</td>
<td>9</td>
<td>Alive (NAS)</td>
</tr>
<tr>
<td>Hardy et al. [7]</td>
<td>16</td>
<td>&quot;40,F&quot;</td>
<td>6500/Mega</td>
<td>R. Axilla</td>
<td>8</td>
<td>0.2</td>
<td>Died (WS)</td>
</tr>
<tr>
<td>Goette et al. [6]</td>
<td>17</td>
<td>&quot;45,F&quot;</td>
<td>NA</td>
<td>L. Scapular Skin</td>
<td>27</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Luzzatto et al. [20]</td>
<td>18</td>
<td>&quot;43,F&quot;</td>
<td>5000/Mega</td>
<td>L. Breast</td>
<td>2</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Mason et al. [22]</td>
<td>19</td>
<td>&quot;43,F&quot;</td>
<td>5000/Mega</td>
<td>L. Inframammary</td>
<td>5</td>
<td>4</td>
<td>Alive (NAS)</td>
</tr>
<tr>
<td>Meunier et al. [24]</td>
<td>20</td>
<td>&quot;45,F&quot;</td>
<td>4500/Mega</td>
<td>Parasternal</td>
<td>17</td>
<td>8</td>
<td>Alive (NAS)</td>
</tr>
<tr>
<td>Liu et al. [Current study]</td>
<td>21</td>
<td>&quot;29,F&quot;</td>
<td>5940/Mega</td>
<td>R. Axilla</td>
<td>7.8</td>
<td>0.8</td>
<td>Alive (NAS)</td>
</tr>
</tbody>
</table>

Mega: megavoltage radiation.
Ortho: orthovoltage radiation.
WS: with sarcoma.
NAS: no active sarcoma.
NA: not available.
L.: left.
R.: right.
Postirradiation malignant fibrous histiocytoma

Postirradiation, the possibility of PIS after radiation therapy should not impede the planning of treatment for patients with breast cancer.

REFERENCE

放射治療術後引發乳房惡性纖維組織細胞瘤病例報告與文獻回顧

劉岱瑋１ 許文林１ 許永祥２ 李文星１３ 夏錫生１ 蔡恩霖１ 蘇怡如１ 吳紹縈１

佛教慈濟綜合醫院 １ 放射腫瘤科 ２ 藥理科
佛教大林慈濟綜合醫院 ３ 放射腫瘤科

放射治療術後引發之肉瘤為一罕見但已廣為確定之癌症治療晚期效應。一位 37 歲婦女於 7.8 年前因乳癌接受放射線治療後，於右側腋下發生惡性纖維組織細胞瘤。由於其腫瘤位置、組織病理及免疫組織化學表現，最初治療結果至發病時間間隔等特性分析，此惡性纖維組織細胞瘤可能與先前之放射治療有密切關係。由於放射治療術後引發肉瘤之機率甚低，因此不應列入乳癌病人接受放射治療與否之主要參考因素。對於惡性纖維組織細胞瘤之後續處理，廣泛性之手術切除是目前相當然有效之方法。

[ 放射治療與腫瘤學 2004; 11(2): 119-126 ]

關鍵詞：乳癌、放射治療、放射治療術後引發肉瘤、惡性纖維組織細胞瘤