Localized fibrous tumor of the serosal cavities (localized fibrous mesothelioma) is a generally benign spindle cell neoplasm of uncertain histogenesis. Fourteen histologically similar primary tumors from different mesothelium-lined sites (11 pleural and 1 each in the pericardium, peritoneal cavity, and pouch of Douglas) and 2 recurrences of those tumors (pericardium and pouch of Douglas) were examined histopathologically and by flow cytometry to relate histologic features and DNA ploidy to biologic behavior (follow-up, 48–255 months among 13 patients). All 16 tumors (14 primaries and 2 recurrences) displayed diploid DNA pattern, and none of 13 patients died of disease (1 patient was lost to follow-up). To elucidate the histogenesis, seven primary tumors were examined for vimentin and keratin immunostaining and six primary tumors were assessed by electron microscopy. All cases exhibited spindle-fibroblastic cell proliferation with a prominent hemangiopericytic pattern. All cases so examined had positive results for vimentin and negative results for keratin. Ultrastructurally, the tumor cells showed mesenchymal–fibroblastic features. These results support a mesenchymal origin, most likely from submesothelial fibroblasts. Further, this neoplasm may recur but retain its basic histologic features, diploidy, and benign outcome. (Key words: Fibrous tumor; Serous cavities; Hemangiopericytic pattern; Fibrous mesothelioma; DNA flow cytometry) Am J Clin Pathol 1989;92:561–565

THE SO-CALLED localized fibrous tumor of the serosal cavities was first recognized as a distinct entity by Klemperer and Rabin in 1931. The neoplasm is rare, with an incidence of 2.8 cases per 100,000 tumor registrations at the Mayo Clinic. Nearly all cases arise in the pleura, although occasional cases have been reported in the peritoneum and other serosa-covered surfaces and recently in the lung. Histopathologically, the neoplasm is characterized by varying degrees of spindle cell proliferation in a fibrocollagenous background, with rare mitoses and occasional pleomorphism.

Although many studies of this neoplasm exist, its histogenesis and biologic behavior are still unclear. This uncertainty is reflected in the variety of names given to the neoplasm: localized fibrous mesothelioma; localized fibrous tumor of the pleura, or of the serosal cavities; and submesothelioma, among others. Two principal hypotheses with respect to the histogenesis are currently debated, one considering the origin to be mesothelial and the other postulating a fibroblastic derivation.

Localized fibrous tumors of the serosal cavities are typically benign; however, occasional recurrences and malignant behavior have been reported. Attempts to establish gross and histopathologic features that could predict aggressiveness have been inconclusive, and the suggested parameters are unreliable. Recently, DNA content measurement by flow cytometric analysis has been established as a marker for malignancy and as a prognostic indicator in a variety of human neoplasms. Diploidy has been shown to confirm histologic benignity or signify ameliorated biologic behavior in histologically malignant neoplasms.

To elucidate the histogenesis and biologic outcome of localized fibrous tumor of the serosal cavities, we analyzed the histologic and DNA flow cytometric patterns in 14 primary and 2 of their recurrent neoplasms and reviewed the patients’ charts for follow-up. We also analyzed several of the neoplasms immunohistochemically and ultrastructurally.

Materials and Methods

Fourteen cases of localized fibrous tumor of the serosal cavities, representing 14 primary tumors and 2 recurrent tumors, accessioned at The University of Texas M. D. Anderson Cancer Center between 1959 and 1986, were examined.

The medical records were reviewed for patient age, sex, and follow-up status and tumor size and location. Hematoxylin and eosin–stained slides (3–11 sections, with an average of six slides) were prepared for light microscopic examination.

Immunohistochemical staining was performed in seven tumors. The avidin–biotin–peroxidase complex (ABC) method of Hsu and colleagues was used on formalin-fixed, paraffin-embedded tissue sections, with staining enhancement by trypsinization for 20 minutes at 37 °C (0.1% trypsin in 0.134% calcium chloride, pH 7.8). Tissue
sections were stained with AE-1/3 (Hybritech, Inc., San Diego, CA; 1:200 dilution), a mixture of two mouse monoclonal keratin antibodies, AE-1 and AE-3; and a mouse monoclonal antibody that reacts to vimentin (Lab Systems, Chicago, IL; 1:25 dilution).

The specificity of the immunoreactions was verified by the staining of known positive and negative control tissue sections, and by negative staining when the primary antibodies were replaced with normal serum from the same species in which the primary antibodies were produced.

Electron microscopic examination of six cases was performed, on 2% glutaraldehyde in cacodylate buffer-fixed material. Ultrathin sections were stained with uranyl acetate and lead citrate.

The DNA content was analyzed by flow cytometry in all 14 primary tumors and 2 recurrent tumors. Tissue from formalin-fixed, paraffin-embedded blocks was processed with the use of a slight modification of the method of Hedley and associates.14 In brief, single-cell suspension was obtained by mechanical and enzymatic treatment of two 50 μm paraffin sections of each neoplasm and stained with propidium iodide. The cellular DNA content was measured with the use of a Coulter Profile® Flow Cytometer equipped with an argon-5 laser. Normal human lymphocytes were prepared by Ficoll-Hypaque® separation and stained with propidium iodide to assess the instrument performance and to serve as a normal control. The number of cells in each measurement was at least 2 X 10⁴. The coefficient of variation of the diploid peak ranged from 2.5 to 5.5.

Results

Clinical and Gross Findings

The patients’ ages ranged from 21 to 71 years (mean, 50 years). There were nine men and five women. Primary tumor size, available in 13 cases, ranged from 2.5 to 20.0 cm (mean, 7.1 cm; median, 6.0 cm). Follow-up, available in 13 cases, ranged from 48 to 255 months (mean, 144 months). Primary tumors occurred in the pleura in 11 cases and 1 each in the pericardium, pouch of Douglas, and peritoneum. In four of the pleural tumors, the mass involved the lung parenchyma secondarily.

The local recurrences occurred in the pericardium and pouch of Douglas, 120 and 156 months after initial surgical excision. There were no metastases. Eleven of the patients were alive and well at latest follow-up, and two patients died of unrelated causes.

The tumors were described at surgery as round to oval or irregular masses showing a gray to white cut surface, with a rubbery to firm consistency.

Clinical data and primary tumor size and location are provided by case in Table 1.

Light Microscopic Findings

All neoplasms exhibited a bland spindle cell proliferation in a fibrocollagenous background and showed a prominent hemangiopericytic vascular pattern. This feature was present in all sections examined and all locations. The degree of cellularity varied from mild (nine cases) to moderate (five cases). Cases with mild cellularity showed a striking stromal hyalinization (Fig. 1), but tumors with moderate cellularity revealed a lesser formation of collagenous matrix (Fig. 2). Mitoses were rare in all primary lesions, ranging from none to three per ten high-power fields (HPFs). The two recurrent lesions showed an increased cellularity and more frequent mitoses (five and ten per ten HPFs), compared with their respective primaries, however, the general histologic features, including hemangiopericytic pattern, persisted (Fig. 3). In three cases, the tumor was covered by an overlying mesothelial

Table 1. Clinical and Follow-Up Data

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at Diagnosis (years)</th>
<th>Sex</th>
<th>Diameter of Primary Tumor (cm)</th>
<th>Location of Primary Tumor</th>
<th>Recurrence</th>
<th>Follow-Up (mo)</th>
<th>Most Recent Status</th>
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<tbody>
<tr>
<td>1</td>
<td>42</td>
<td>M</td>
<td>2.5</td>
<td>Pleura</td>
<td>No</td>
<td>227</td>
<td>Alive and well</td>
</tr>
<tr>
<td>2</td>
<td>63</td>
<td>M</td>
<td>9.0</td>
<td>Pleura</td>
<td>No</td>
<td>119</td>
<td>Alive and well</td>
</tr>
<tr>
<td>3</td>
<td>63</td>
<td>M</td>
<td>5.5</td>
<td>Pleura</td>
<td>No</td>
<td>211</td>
<td>Died; unrelated cause</td>
</tr>
<tr>
<td>4</td>
<td>56</td>
<td>M</td>
<td>5.7</td>
<td>Pleura</td>
<td>No</td>
<td>132</td>
<td>Alive and well</td>
</tr>
<tr>
<td>5</td>
<td>69</td>
<td>M</td>
<td>NA</td>
<td>Pleura</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>56</td>
<td>F</td>
<td>13.0</td>
<td>Pericardium</td>
<td>Yes</td>
<td>202</td>
<td>Alive, no further recurrence</td>
</tr>
<tr>
<td>7</td>
<td>64</td>
<td>M</td>
<td>20.0</td>
<td>Pleura</td>
<td>No</td>
<td>255</td>
<td>Died; unrelated cause</td>
</tr>
<tr>
<td>8</td>
<td>62</td>
<td>F</td>
<td>4.0</td>
<td>Pouch of Douglas</td>
<td>Yes</td>
<td>136</td>
<td>Alive, no further recurrence</td>
</tr>
<tr>
<td>9</td>
<td>21</td>
<td>F</td>
<td>6.0</td>
<td>Peritoneum</td>
<td>No</td>
<td>48</td>
<td>Alive and well</td>
</tr>
<tr>
<td>10</td>
<td>33</td>
<td>M</td>
<td>5.0</td>
<td>Pleura</td>
<td>No</td>
<td>79</td>
<td>Alive and well</td>
</tr>
<tr>
<td>11</td>
<td>24</td>
<td>F</td>
<td>7.0</td>
<td>Pleura</td>
<td>No</td>
<td>92</td>
<td>Alive and well</td>
</tr>
<tr>
<td>12</td>
<td>39</td>
<td>M</td>
<td>6.0</td>
<td>Pleura</td>
<td>No</td>
<td>112</td>
<td>Alive and well</td>
</tr>
<tr>
<td>13</td>
<td>71</td>
<td>F</td>
<td>6.5</td>
<td>Pleura</td>
<td>No</td>
<td>188</td>
<td>Alive and well</td>
</tr>
<tr>
<td>14</td>
<td>39</td>
<td>M</td>
<td>2.5</td>
<td>Pleura</td>
<td>No</td>
<td>76</td>
<td>Alive and well</td>
</tr>
</tbody>
</table>

M = male; F = female; NA = not available.

Electron microscopic examination of six cases was performed, on 2% glutaraldehyde in cacodylate buffer-fixed material. Ultrathin sections were stained with uranyl acetate and lead citrate.

The DNA content was measured with the use of a Coulter Profile® Flow Cytometer equipped with an argon-5 laser. Normal human lymphocytes were prepared by Ficoll-Hypaque® separation and stained with propidium iodide to assess the instrument performance and to serve as a normal control. The number of cells in each measurement was at least 2 X 10⁴. The coefficient of variation of the diploid peak ranged from 2.5 to 5.5.

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FIG. 1 (upper, left). Tumor with lower cellularity and significant stromal hyalinization. Note hemangiopericytic vascular pattern. Hematoxylin and eosin (×250).

FIG. 2 (upper, right). Tumor with moderate cellularity and less collagenous matrix. Also, note the presence of the hemangiopericytic vascular pattern. Hematoxylin and eosin (×100).

FIG. 3 (lower, left). Recurrent tumor (case 5). Notice increased cellularity and nuclear size. The tumor, however, retains the hemangiopericytic vascular pattern. Hematoxylin and eosin (×250).

cell surface. In no instance was there transition between mesothelial cells and neoplastic cells.

**Immunohistochemical and Electron Microscopic Findings**

All seven cases examined immunohistochemically showed diffuse cytoplasmic immunoreactivity to vimentin (Fig. 4) and negative staining for keratin. Ultrastructurally, all six cases assessed showed fairly uniform spindle cells with mesenchymal features (Fig. 5). These tumor cells were embedded in the collagenous matrix and contained scanty cytoplasmic organelles (mainly mitochondria), rough endoplasmic reticulum, and rare intermediate filaments. No specific cellular organelles were present. Cell junctions were infrequent and primitive. The nuclei were large and irregular. No evidence of mesothelial cell differentiation, namely, well-formed cell junctions and long, slender microvilli, was identified.

**Flow Cytometric DNA Analysis**

All 14 primary neoplasms and the 2 recurrences exhibited diploid DNA content (Fig. 6), each with a DNA index of 1.0. The proliferative index (S-phase) was low in all lesions, with a mean of 2.0% for the primary tumors and 4.0% for the recurrences.

**Discussion**

Controversy lingers as to the histogenesis of the localized fibrous tumor of the serosal cavities. Ultrastructural and immunohistochemical studies have yielded conflicting observations. In some of these studies, surface mesothelial cell characteristics have been found.\(^5,7,11,17\) Furthermore, a link between this neoplasm and diffuse biphasic mesothelioma has been suggested.\(^11\) On the other hand, similar studies suggest that less-differentiated mesenchymal cells with fibroblastic features are the principal component.\(^6,15,20,23,29\) The histologic, ultrastructural, and immunohistochemical features of the cases examined in the present study support a mesenchymal-fibroblastic origin. We did not observe features characteristic of mesothelial differentiation in any of our cases. Interestingly, we observed a well-formed mesothelial covering in three cases, but in none of these cases, with multiple sections, was there a transition or merging with the underlying neoplastic cells. The occasional mesothelial differentiation observed could have resulted from sampling of entrapped mesothelial cells. Our study highlights the hemangioperi-
cytoma-like pattern of this neoplasm.6,9,12,26,27 This feature was a constant finding, both in primary lesions and recurrences.

As do some others, we do not agree with the suggestion that there is a link between this neoplasm and the sarcomatous component of biphasic mesothelioma. The biologic, histopathologic, immunohistochemical, and ultrastructural findings do not support such a link.8,9 Furthermore, asbestos exposure has not been implicated in any reported cases.8 Although interesting, studies showing mesothelial features in the reparative response of subserosal cells to injury do not establish the histogenesis.3,4 It is not known, for instance, whether the same or different types of subserosal mesenchymal cells that react to injury can give rise to this tumor.

This study is the first, to our knowledge, to apply flow cytometric DNA analysis to this neoplasm. The diploid DNA content displayed in all primary tumors and the recurrences may suggest a less aggressive clinical behavior. Despite the disturbing histologic features in the recurrent neoplasms, they do maintain a diploid DNA content, however, more of these cases with prolonged follow-up are needed to support this observation.

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References