Sclerosing Rhabdomyosarcoma
A Clinicopathologic and Immunohistochemical Study of Five Cases
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Key Words: Rhabdomyosarcoma; Sclerosis; Soft tissue tumor; Immunohistochemistry

Abstract
We report 5 cases of sclerosing rhabdomyosarcoma. The patients included 4 adults and 1 adolescent. In the 5 cases, 3 tumors occurred in the head and neck region and 2 in an extremity. Histologically, all 5 tumors were characterized by the presence of abundant extracellular hyaline matrix, mimicking osteoid or chondroid tissue. They were composed mostly of primitive small round cells that displayed diverse growth patterns. In 2 cases, focal areas suggestive of spindle cell rhabdomyosarcoma were present. Typical features of embryonal or alveolar rhabdomyosarcoma were not noted; however, rare strap rhabdomyoblasts were identified in 1 case. Immunohistochemically, all 5 cases showed diffuse immunoreactivity for MyoD1, with varied expression of myogenin, desmin, muscle-specific antigen, and α-smooth muscle actin. All patients underwent surgery, combined with adjuvant radiation therapy or chemotherapy. Of 4 cases with follow-up, recurrence was found in 2. Sclerosing rhabdomyosarcoma represents a special variant of rhabdomyosarcoma and is possibly related to embryonal rhabdomyosarcoma.

Rhabdomyosarcoma is the most common malignant soft tissue tumor of childhood and adolescence.1 Rhabdomyosarcoma is relatively rare in adults older than 45 years.2 Based on the morphologic features and molecular analysis, the current World Health Organization classification categorizes rhabdomyosarcoma into 3 main subtypes: embryonal (encompassing the botryoid, spindle cell, and anaplastic variants), alveolar (including the solid variant), and pleomorphic.3 Although embryonal rhabdomyosarcoma and alveolar rhabdomyosarcoma typically affect children younger than 15 years, they can be occasionally encountered in adults.4 In comparison, pleomorphic rhabdomyosarcoma arises almost exclusively in adults,5 with very few cases reported in children.6

In 2000, Mentzel and Katenkamp7 reported a peculiar type of adult rhabdomyosarcoma characterized by prominent hyaline sclerosis and a pseudovascular growth pattern. They called it sclerosing, pseudovascular rhabdomyosarcoma. In 2002, Folpe et al8 described 4 additional cases with similar features, and they proposed to designate the lesion as sclerosing rhabdomyosarcoma. Because of the presence of heavily hyalinized collagenous matrix and occasional pseudovascular growth pattern, sclerosing rhabdomyosarcoma is frequently misdiagnosed as chondrosarcoma, osteosarcoma, or angiosarcoma at initial evaluation. The relationship between sclerosing rhabdomyosarcoma and the conventional rhabdomyosarcomas remains uncertain, although cytogenetic studies suggest a link with embryonal rhabdomyosarcoma.9 To increase the recognition of this rare entity, we describe 5 new cases of sclerosing rhabdomyosarcoma.
Materials and Methods

All 5 cases were retrieved from the consultation files of the Department of Pathology, Cancer Hospital, Fudan University, Shanghai, China. None was identified before 2000. Clinical data were obtained from patients’ medical records. Follow-up information was obtained from clinicians or by contacting the referring pathologists when possible. The referring diagnoses included mass without an exact diagnosis; extraskeletal osteosarcoma; rhabdomyosarcoma, not otherwise specified; rhabdomyosarcoma vs sclerosing epithelioid fibrosarcoma; and neurofibroma and malignant triton tumor. All specimens were fixed in 4% buffered formalin and routinely processed. We reexamined 4-µm-thick H&E-stained sections. Each case was evaluated for the border of the tumor, stromal hyalinization, growth pattern of the tumor cells, presence of rhabdomyoblasts, mitotic figures, and necrosis.

Immunohistochemical staining was performed on paraffin-embedded sections by the standard EnVision (DAKO, Carpinteria, CA) technique using a panel of antibodies, including vimentin (V9, dilution 1:200; DAKO), desmin (D33, dilution 1:200; DAKO), α-smooth muscle actin (1A4, dilution 1:200; DAKO), muscle-specific actin (HHF35, dilution 1:100; DAKO), myogenin (F5D, dilution 1:50; DAKO), MyoD1 (5.8A, dilution 1:50; DAKO), CD31(JC/70A, dilution 1:100; DAKO), CD34 (QBend10, dilution 1:100; DAKO), pankeratin (AE1/AE3, dilution 1:50; DAKO), osteonectin (NCL-O-NECTIN, dilution 1:100; Novocastra, Newcastle upon Tyne, England), osteopontin (NCL-O-PONTIN, dilution 1:50; Novocastra), and S-100 protein (polyclonal, dilution 1:300; DAKO). Appropriate positive control samples were used throughout.

Results

The clinical features of the 5 patients are summarized in Table I. There were 3 females and 2 males. The age at initial examination ranged from 12 to 54 years (mean, 35.6 years). Three tumors were located in the head and neck region, including 1 on the right cheek, 1 on the right side of the face, and 1 in the right nasal cavity. Two tumors involved the extremities, with 1 on the left wrist and 1 on the right thigh. Initial symptoms included swelling, rapidly growing mass, aching teeth and difficulty in opening the mouth and speaking, palpable facial mass, and nasal swelling and obstruction. The duration before excision varied from 3 months to 1 year. Imaging studies (computed tomography or magnetic resonance imaging) revealed soft tissue masses of homogeneous density with an irregular shape Image II. All 5 patients underwent surgery as the initial treatment. After surgery, they received adjuvant

<table>
<thead>
<tr>
<th>Case No./Sex/Age (y)</th>
<th>Year</th>
<th>Site</th>
<th>Size (cm)</th>
<th>Symptoms</th>
<th>Referring Diagnosis</th>
<th>Treatment</th>
<th>Follow-up (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/54</td>
<td>2000</td>
<td>Left wrist</td>
<td>2.5</td>
<td>Rapidly growing mass</td>
<td>None</td>
<td>Resection; radiotherapy</td>
<td>NA</td>
</tr>
<tr>
<td>2/F/52</td>
<td>2003</td>
<td>Right thigh</td>
<td>6</td>
<td>Swelling</td>
<td>Extraskeletal osteosarcoma</td>
<td>Resection; radiotherapy</td>
<td>AWD, 36</td>
</tr>
<tr>
<td>3/F/20</td>
<td>2005</td>
<td>Right side of face</td>
<td>5</td>
<td>Palpable facial mass</td>
<td>Rhabdomyosarcoma, NOS</td>
<td>Tumor debulking; chemotherapy</td>
<td>AWD, 26</td>
</tr>
<tr>
<td>4/M/40</td>
<td>2006</td>
<td>Right cheek</td>
<td>6 × 5</td>
<td>Teeth ached; difficulty opening mouth</td>
<td>Rhabdomyosarcoma; sclerosing epithelioid fibrosarcoma</td>
<td>Wide local excision; radiotherapy</td>
<td>AWD, 16</td>
</tr>
<tr>
<td>5/F/12</td>
<td>2007</td>
<td>Right nasal cavity</td>
<td>4</td>
<td>Nasal swelling, obstruction</td>
<td>Neurofibroma</td>
<td>Simple excision</td>
<td>Recurred, 3</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Malignant triton tumor</td>
<td>Wide local excision; chemotherapy</td>
<td>AWD, 5</td>
</tr>
</tbody>
</table>

AWD, alive without disease; NA, not available; NOS, not otherwise specified.

Image II Maxillofacial computed tomography scan showing an expansile mass in the right muscle of mastication.
radiotherapy and/or chemotherapy. Follow-up information was available for 4 patients with an interval ranging from 5 months to 3 years (mean, 20.8 months). Of the 4 patients, 2 experienced local relapse and 2 are free of disease. No case in this series had evidence of metastasis.

Grossly, the tumors were described as ill-defined masses of intermediate to hard consistency. They measured from 2.5 to 6.0 cm in maximum dimension (mean, 4.7 cm), and the cut sections were gray to white.

At low power, tumors were all deeply seated and showed extensive infiltration to the surrounding normal structures, especially striated muscles. All 5 tumors had abundant hyalinizing matrix that varied from eosinophilic to basophilic and closely resembled primitive osteoid or chondroid tissue Image 2A and Image 2B. The tumors were composed predominantly of primitive round to ovoid cells with hyperchromatic nuclei. They were arranged in diverse growth patterns, including small nests or fascicular, cord-like, single file-like strands and trabecular, microalveolar, or pseudovascular structures Image 2C, Image 2D, and Image 2E that were embedded in or surrounded by the sclerosing matrix. “Spider cells” or wreath-like multinucleated giant cells were absent in all cases, but scattered strap rhabdomyoblasts were identified in 1 case (case 3) Image 2F. In 2 cases (cases 3 and 5), besides the primitive small round cells, elongated spindle-shaped cells were also observed. These spindle-shaped cells
were arranged in long fascicles, reminiscent of a spindle cell rhabdomyosarcoma. Mitotic figures were readily encountered in all 5 cases, with an average of 5 per 10 high-power fields (range, 2-19 per 10 high-power fields). Except for the recurrence in 1 case (case 2), coagulative necrosis was not a prominent feature in this series.

Immunohistochemically, tumor cells in all 5 cases showed diffuse immunostaining for vimentin and MyoD1. Of the 5 cases, 4 (90%) were positive for muscle-specific actin. Of 3 cases, 2 (67%) also showed strong positivity for α-smooth muscle actin. Focal expression of desmin (4/5 [90%]) and myogenin (2/4 [50%]) was observed. S-100 protein was generally negative in the 2 cases tested, but in 1 case (case 5), nonspecific cytoplasmic staining was observed. Results for the remaining stains, including osteonectin, osteopontin, AE1/AE3, CD31, and CD34, were all negative.

**Discussion**

Rhabdomyosarcoma consists of a heterogeneous group of entities that share skeletal muscle differentiation but differ in clinical, morphologic, and molecular aspects. Categorization of rhabdomyosarcoma is important not only to the diagnosis but also to prognostic prediction and therapeutic protocols, including prospective genetic treatments. Sclerosing rhabdomyosarcoma, a recently described entity
of rhabdomyosarcoma, however, is difficult to categorize in the current rhabdomyosarcoma classification systems.

Sclerosing rhabdomyosarcoma represents a rare entity. To our knowledge, only 27 cases have been reported in the literature.7-14 Of these 27 cases, 12 (44%) occurred in the extremities, 11 (41%) in the head and neck region, 2 (7%) in the sacrum, and 1 each (4%) in the scrotum and retroperitoneum. The tumors measured from 0.3 to 11.8 cm, with a median size of approximately 6 cm.

Early reports showed that sclerosing rhabdomyosarcoma occurred exclusively in adults; however, recent studies have indicated that the tumor also has occurred in young children and adolescents.10-12 In a retrospective study, Chiles et al10 identified 13 cases with features of sclerosing rhabdomyosarcoma among 1,207 pediatric rhabdomyosarcoma cases accessioned by the Intergroup Rhabdomyosarcoma Study Group. To date, 9 were diagnosed as alveolar rhabdomyosarcoma, 3 as embryonal rhabdomyosarcoma, and 1 as spindle cell rhabdomyosarcoma. Taking the pediatric group into account, the overall median and average ages of patients with sclerosing rhabdomyosarcoma at diagnosis are 16 and 26.6 years, respectively (range, 0.3-79 years). There was a slight male predilection.

Symptoms varied with respect to the tumor site. Tumors of the extremities typically manifested with a rapidly growing soft tissue mass or swelling accompanied with no or slight pain. Tumors arising from the head and neck region could cause facial swelling, dysphagia, difficulty in opening the mouth and speaking, nasal obstruction, and articulation disorder. Imaging studies usually revealed an irregular, expansive soft tissue mass of homogeneous density, which was revealed to be highly infiltrative by pathologic examination.

Histologically, sclerosing rhabdomyosarcoma is characterized by the production of abundant extracellular hyalinizing matrix that imitates primitive chondroid or osteoid tissue. The sclerosing stroma can cause 40% to 70% of the tumor bulk. Therefore, sclerosing rhabdomyosarcoma may easily be misdiagnosed as hyalinizing chondrosarcoma or osteosarcoma at initial evaluation without immunohistochemical studies. Because sclerosing rhabdomyosarcoma can occasionally exhibit a pseudovascular growth pattern or assume a single-file cell arrangement, the lesion may also be mistaken for angiosarcoma, sclerosing epithelioid fibrosarcoma, or infiltrating carcinoma.

Another distinct feature of sclerosing rhabdomyosarcoma is the presence of a microalveolar structure, which might resemble alveolar rhabdomyosarcoma. However, sclerosing rhabdomyosarcoma lacks the large alveolar pattern separated by fibrovascular septa in alveolar rhabdomyosarcoma and the wreath-like giant cells. On the other hand, spindle-shaped cells observed in some sclerosing rhabdomyosarcomas are not features of alveolar rhabdomyosarcoma. Moreover, 11 cases of sclerosing rhabdomyosarcoma have been tested thus far by reverse transcription–polymerase chain reaction or fluorescence in situ hybridization to detect the alveolar rhabdomyosarcoma–associated PAX3/7-FKHR fusion genes resulting from t(2;13)(q35;q14) or t(1;13)(p36;q14).8-14 The results showed that except for 1 case that expressed the PAX3/FKHR fusion transcripts due to t(2;13) translocation,10 the majority were negative for alveolar rhabdomyosarcoma–specific fusion transcripts, indicating no link between sclerosing rhabdomyosarcoma and alveolar rhabdomyosarcoma.

Instead, several aspects suggest that sclerosing rhabdomyosarcoma might be closely related to embryonal rhabdomyosarcoma. First, small foci of rhabdomyoblastic strap cells were observed in a few cases of sclerosing rhabdomyosarcoma.7,8,12 Second, some cases of sclerosing rhabdomyosarcoma also contained a spindle cell component,7,10,12 which could have a close resemblance to spindle cell rhabdomyosarcoma, a variant of embryonal rhabdomyosarcoma. To date, 1 of the 13 cases reported by Chiles et al10 was initially diagnosed as spindle cell rhabdomyosarcoma. In the present series, 2 cases (cases 3 and 5) also showed focal areas suggestive of spindle cell rhabdomyosarcoma. On the other hand, according to the recent studies by Nascimento and Fletcher15 and Mentzel and Kuhnen,16 sclerosing and pseudovascular features could also be observed in focal areas of spindle cell rhabdomyosarcoma. Third, cytogenetic analysis in some cases of sclerosing rhabdomyosarcoma has shown complex abnormalities, especially a hyperdiploid karyotype, including +2, +7, +8, +9, +11, +12, +14, +16, +19, and +2110,12,13 overlapping with embryonal rhabdomyosarcoma. Comparative genomic hybridization analysis has been performed in only 1 case, which demonstrated a sharply delineated −10q22, −Y, and +18, indicating sclerosing rhabdomyosarcoma to be a distinct subtype of rhabdomyosarcoma.14

Although sharing skeletal differentiation with conventional rhabdomyosarcomas, sclerosing rhabdomyosarcoma demonstrates a distinctive immunophenotype. Sclerosing rhabdomyosarcoma is characterized by diffuse, strong positivity for MyoD1 but usually focal expression of desmin and myogenin. The latter 2 markers could be negative in a few cases of sclerosing rhabdomyosarcoma, which may result in potential pitfalls in interpretation. Besides MyoD1, some cases of sclerosing rhabdomyosarcoma also express actins, which may be helpful in establishing the final diagnosis. Ultrastructural studies in sclerosing rhabdomyosarcoma are limited. The case described by Kuhnen et al14 showed disorganized intracytoplasmic fibrils; however, well-formed Z bands could not be detected. The abundant tumor matrix was characterized ultrastructurally by densely arranged collagen bundles.

With regard to the biologic behavior of sclerosing rhabdomyosarcoma, 7 (25%) of 28 cases with follow-up information experienced local recurrence, and 5 (18%) cases
developed distant metastases; 4 patients (14%) died of the disease. There is no consensus on the treatment of sclerosing rhabdomyosarcoma. However, similar to conventional rhabdomyosarcoma, radical excision combined with adjuvant chemotherapy and/or radiotherapy remains the mainstay for most cases of sclerosing rhabdomyosarcoma.

We describe 5 new cases of sclerosing rhabdomyosarcoma. Familiarity with the characteristic features and immunophenotype of sclerosing rhabdomyosarcoma is helpful for recognizing this special variant of rhabdomyosarcoma. Besides occurring in adults, sclerosing rhabdomyosarcoma can also occur in children and adolescents. Our study suggests that sclerosing rhabdomyosarcoma is likely related to embryonal rhabdomyosarcoma.

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References