Dedifferentiated Extraskeletal Myxoid Chondrosarcoma of the Masticator Space — A Case Report —

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Received: October 25, 2010
Accepted: November 23, 2010

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Extraskeletal myxoid chondrosarcoma (EMC) is a rare malignant soft tissue sarcoma, distinguished from its skeletal counterpart by cytogenetic and histologic features. EMC was first described as a distinct pathologic entity in 1953, although its clinicopathologic features, defined in 1972, showed that it was a distinctive type of soft tissue sarcoma characterized by a protracted clinical course despite high local recurrence and metastasis rates. EMC usually develops in the deep soft tissues of the extremities in middle-aged adults. Conventional EMC is characterized by uniform round to oval cells forming cords or clusters and abundant myxoid stroma. In up to 30% of patients, however, EMC may contain cellular foci reminiscent of chondroblastoma, Ewing's sarcoma, synovial sarcoma, and fibrosarcoma, and may have rhabdoid features. Dedifferentiated EMC is rare; to our knowledge, only three patients have been described in the English language literature. We describe here a dedifferentiated EMC that arose in the left masticator space of a 69-year-old woman.

CASE REPORT

A 69-year-old woman presented with an 8-month history of a painful firm mass palpable on the left buccal area. She had a previous history of tuberculosis and leg fracture but was otherwise healthy. Her laboratory findings were unremarkable. Both computed tomography and magnetic resonance imaging revealed a 5-cm sized mass in the left masticator space. Histologically, the tumor consisted of two distinct areas. The less cellular area was a low-grade extraskeletal myxoid chondrosarcoma, composed of strands or cords of uniform spindle cells and abundant myxoid stroma. The more cellular, dedifferentiated area corresponded to a high grade myxofibrosarcoma, consisting of anaplastic tumor cells in myxoid stroma and geographic necrosis. The tumor cells of the former area were positive for S-100 protein, microtubule-associated protein-2 (MAP-2) and class III β-tubulin, but negative for cytokeratin, smooth muscle actin, and desmin. The tumor cells in the latter, pleomorphic area showed MAP-2 and β-tubulin immunoreactivity with a high Ki-67 labeling index. Based on its histologic and immunohistochemical features, the tumor was considered a dedifferentiated extraskeletal myxoid chondrosarcoma.

Key Words: Extraskeletal myxoid chondrosarcoma; Cell dedifferentiation; Masticator space
Fig. 1. T2-weighted magnetic resonance imaging demonstrating a well demarcated 5-cm sized ovoid mass (arrows) in the masticator space of our patient.

Fig. 2. Gross features of the lesion, showing a well-demarcated, ovoid 4.9 × 3.9 × 3.8 cm sized mass (arrows) adjacent to the mandibular bone. The cut surface of the mass is heterogeneous, grayish yellow and gelatinous, with some areas showing geographic necrosis.

Fig. 3. Histologic features of the tumor. (A) The less cellular area consists of strands or cords of oval and spindle cells embedded in abundant myxoid stroma. (B) The tumor cells in the less cellular area have relatively uniform, spindle and oval nuclei and a moderate amount of cytoplasm. (C) The cellular, dedifferentiated area is pleomorphic sarcoma with myxoid stroma, corresponding to high-grade myxofibrosarcoma. (D) The tumor cells in the more cellular area have pleomorphic oval to spindle shaped nuclei and moderate to ample amounts of eosinophilic cytoplasm.
form, spindle and oval nuclei, with dense, evenly dispersed chromatin, and a moderate amount of eosinophilic cytoplasm that was often finely vacuolated. Mitotic figures were rare (Fig. 3A, B). The more cellular area was a pleomorphic myxoid sarcoma consisting of pleomorphic tumor cells with occasional rhabdoid features and geographic necrosis (Fig. 3C, D). In the less cellular area, the tumor was positive for S-100 protein (1:1,000, Zymed, San Francisco, CA, USA), microtubule-associated protein-2 (MAP-2; 1:200, clone AP18, Neomarkers, Fremont, CA, USA), class III β-tubulin (1:200, clone TU-20, Genetex, Irvine, CA, USA), focally positive for epithelial membrane antigen (1:25, Dako, Glostrup, Denmark) and negative for cytokeratin (CK; 1:250, Zymed), smooth muscle actin (1:200, Dako), synaptophysin (1:100, clone sp11, Neomarkers) and desmin (1:200, Dako), supporting the conclusion that there had been neural-neuroendocrine differentiation. The Ki-67 (1:100, clone 7B11, Zymed) labeling index was very low (less than 1%). The tumor cells in the pleomorphic area were strongly positive for MAP-2 and class III β-tubulin with a high Ki-67 labeling index (40-50%) (Fig. 4), but the remaining markers were all negative. Based on its histologic and immunohistochemical features, the tumor was diagnosed as a dedifferentiated EMC. Fluorescence in situ hybridization (FISH) on formalin-fixed, paraffin-embedded tissue samples using dual-color, break-apart rearrangement probes (Vysis) to assess Ewing’s sarcoma (EWS) gene breakage showed no evidence of EWS rearrangements. The patient underwent adjuvant radiotherapy. Her post-operative course was unremarkable, with no evidence of recurrence at 3 months.

DISCUSSION

EMC is a rare but clinicopathologically well-characterized soft tissue sarcoma. However, the line of differentiation of EMC cells remains unclear. EMCs consist of primitive mesenchymal

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**Fig. 4.** Immunohistochemical findings of the tumor. The tumor cells in the less cellular, differentiated area are positive for S-100 protein (A) and class III β-tubulin (B). The tumor cells in the dedifferentiated area are negative for S-100 protein (C) and positive for class III-β-tubulin (D).
cells with the potential for multidirectional differentiation. Despite being described as a chondrosarcoma, discernible chondrocytic differentiation is unusual. Therefore, the 2002 World Health Organization (WHO) classification has provisionally categorized EMCs as tumors of uncertain differentiation.\(^8\)\(^9\) Indeed, high percentages of cellular foci of these tumors have been found to show diverse histologic features, resembling the features of other tumors such as chondroblastoma, EWS, synovial sarcoma, and fibrosarcoma, as well as having rhabdoid features.\(^4\) Some EMCs, so-called ‘cellular’ variants, consist of diffusely cellular areas with minimal to absent myxoid stroma.\(^1\) In addition, EMCs have been found to show ultrastructural and immunohistochemical characteristics of neuroendocrine differentiation, including neurosecretory granules and positivity for neuroendocrine markers such as synaptophysin, S-100 protein, and PGP9.5.\(^10\) Recently, expression of microtubule-related proteins, class III β-tubulin, and MAP-2 has been demonstrated in EMCs, supporting neural-neuroendocrine differentiation of the tumor cells.\(^11\)

Most EMCs have a bland-looking or low-grade morphology, with dedifferentiated EMCs rarely being described. To our knowledge, only three such cases have been reported in the English language literature.\(^5\)\(^7\) Dedifferentiated EMCs have been observed in older individuals, aged 65 to 85 years (mean, 72.7 years). The affected site appears to vary, although the number of patients is too small to be conclusive. Tumor diameters have ranged from 4.9 to 15 cm. Follow-up information is available for three of the four patients, including the one described in this report, with two of these patients showing tumor recurrence within 1 year postoperatively. Although our patient did not show evidence of disease recurrence, the postoperative follow-up time was too short (3 months) to draw firm conclusions. The clinicopathologic findings of these 4 patients are summarized in Table 1. EMCs have been reported in unusual sites such as the retroperitoneum, mediastinum, fingers, and intracranial cavity, as well as the head and neck area.\(^12\)\(^13\)

Although the biologic behavior of EMCs was initially considered less aggressive, patient prognosis is not as good as previously thought. Multivariate analysis has shown that older patient age, larger tumor size, and tumor location in the proximal extremity or limb girdle were significant, independent adverse prognostic factors. In contrast, the prognostic significance of tumor histologic features, such as tumor grade and high-grade morphology, has not yet been established.\(^12\)\(^13\) Patients with an EMC eventually die of this disease because of the high rates of recurrence and metastasis. Therefore, long-term follow-up is mandatory in patients with EMC. The estimated 10 year survival rate is 70%.\(^1\) Chemotherapeutic agents currently in use have not shown satisfactory results in these patients, making early wide local resection with or without radiation for localized disease the only curative option for patients with EMC.\(^13\)

Besides their distinct histologic features and biologic behavior, EMCs harbor characteristic cytogenetic changes. Approximately 75% of tumors have the t(9;22)(q22;q12) translocation, resulting in a fusion of the 5’ part of the EWS gene at 22q12 to the NR4A3 gene at 9q22. Although the function of EWS/NR4A3 fusion transcript.\(^14\)\(^15\) The t(9;17)(q22;q11) translocation occurs less frequently (~15%), generating the RBP56/NR4A3 fusion transcript.\(^16\) Importantly, this fusion protein is detected exclusively in EMCs, and, theoretically, its presence may be diagnostic of EMC. Although we performed dual-color break apart FISH analysis for EWS, the result was negative. The rates of cytogenetic abnormalities, however, suggest that at least 25% of EMCs are negative for EWS rearrangement. EWS is involved in a broad variety of mesenchymal lesions, including EWS/peripheral neuroectodermal tumor, desmoplastic small round cell tumor, clear cell sarcoma, anaplastic fibrous histiocytoma, EMC, and a subset of myxoid liposarcomas.\(^17\) Therefore, analysis of the NR4A3 rearrangement would be helpful in the diagnosis of EMCs with atypical features. Evaluation of NR4A3 rearrangements in EMCs showed that these rearrangements

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Reference</th>
<th>Age (y)</th>
<th>Gender</th>
<th>Location</th>
<th>Size (cm)</th>
<th>Histology</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ramesh et al.(^5)</td>
<td>65</td>
<td>F</td>
<td>Gluteal region</td>
<td>15</td>
<td>Fibrosarcomatous differentiation</td>
<td>Surgery only</td>
<td>Recurrence after 8 mo</td>
</tr>
<tr>
<td>2</td>
<td>Antonescu et al.(^6)</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td>High grade spindle cell sarcoma</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>3</td>
<td>Reid et al.(^7)</td>
<td>85</td>
<td>M</td>
<td>Upper arm</td>
<td>7</td>
<td>High grade spindle cell sarcoma with rhabdoid, epithelioid, and pleomorphic areas</td>
<td>Surgery followed by radiation</td>
<td>Two recurrences after 10 and 13 mo</td>
</tr>
<tr>
<td>4</td>
<td>Present case</td>
<td>68</td>
<td>F</td>
<td>Masticator space</td>
<td>4.9</td>
<td>High grade myxofibrosarcoma</td>
<td>Surgery followed by radiation</td>
<td>NED during 3 mo follow-up</td>
</tr>
</tbody>
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F, female; NS, not specified; M, male; NED, no evidence of disease.
were present in two tumors not carrying any EWS breakpoint region 1 (EWSR1) rearrangements. In summary, dedifferentiated EMCs are extremely rare and may be confused with other benign or malignant tumors due to their rarity and diversity of histologic features. Diagnosis of conventional EMCs may help in the diagnosis of dedifferentiated EMCs. Moreover, ancillary immunohistochemical studies, such as staining for the S-100 protein and microtubule-related proteins, and cytogenetic analysis are recommended to confirm the diagnosis.

REFERENCES