

Extraskelatal myxoid chondrosarcoma of the thigh with a t(9;17) translocation

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Abstract. Extraskelatal myxoid chondrosarcomas (EMC) are relatively rare. We report a case of EMC of the thigh. A 41-year-old man presented with a tumor history of more than 4 months. Following open biopsy, wide resection of the tumor was performed. Histopathologically, the tumor had a multinodular architecture consisting of myxomatous areas demarcated by fibrous septa. Proliferation of uniform, round tumor cells with oval nuclei was observed. Well-formed hyaline cartilage and rhabdoid-like cells were not visible. Immunohistochemically, the tumor cells were positive for vimentin and S-100. The composite karyotype was 46,XY,t(9;17)(q22;q11),t(9;21)(q21;p13), and the diagnosis of EMC was made. No recurrence of the mass or metastasis was observed during a follow-up period of 4 years and 7 months. Only 50 cytogenetic cases of EMC, including our case, have been reported in the English literature thus far. Clinical presentation, radiological features and histopathological and cytogenetic findings are described, and the relevant literature is reviewed.

Introduction

The concept of extraskelatal myxoid chondrosarcoma (EMC) was described by Enzinger and Shiraki in 1972 (1). As cartilaginous areas are not common despite the name 'EMC', making a diagnosis based solely on histopathological findings is often difficult. At present, the number of reported cytogenetic studies of EMC remains small due to the rarity of the tumor (2-21). We report an additional case of EMC and review the literature on cytogenetic studies. This study was conducted following a clinical research review by our ethics committee. The patient was informed that data from the case would be submitted for publication and gave his consent.

Case report

A 41-year-old man presented with more than a 4-month history of a tumor in the left thigh. No history of disease or trauma was noted. The size of the tumor was 5x10 cm. The surface was smooth with no signs of inflammation, but the borders were unclear. Radiological studies revealed an expansion of the soft tissue, but no bony changes or calcifications.

Magnetic resonance imaging (MRI) revealed a low-intensity lesion with T1-weighted imaging and a high-intensity lesion with T2-weighted imaging (Fig. 1A and B). The tumor exhibited enhancement following intravenous administration of gadolinium. The inside was heterogeneous, and the border was ill-defined (Fig. 1C). ⁶⁷Ga scintigraphy did not show abnormal uptake. Chest radiography and computed tomography showed no evidence of lung metastasis. Laboratory findings were normal.

Open biopsy was performed. Uniform round- to spindle-like tumor cells proliferated with myxomatous stroma. Well-formed hyaline cartilage and rhabdoid-like cells were not observed. The specimen was submitted for cytogenetic analysis. Karyotype analysis was performed with the G-banded method. Karyotypes were described using the International System for Human Cytogenetic Nomenclature (22). The composite karyotype was 46,XY,t(9;17)(q22;q11),t(9;21)(q21;p13)[16]/46,XY[4] (Fig. 2). The diagnosis of EMC was made based on the histopathological and cytogenetic findings.

Wide resection of the tumor was performed in July, 2006. The tumor was completely resected along with a portion of the rectus femoris, tensor fascia latae and the fascia of vastus lateralis. The tumor was contained within a pseudo-capsule and was multinodular and yellowish in color (Fig. 3). Histopathologically, the tumor had a multinodular architecture consisting of myxomatous areas demarcated by fibrous septa. Each lobule was composed of proliferating tumor cells and showed a lace-like appearance with an abundant myxoid matrix (Fig. 4A). The proliferation of uniform, round tumor cells with oval nuclei was observed (Fig. 4B). Mitoses were rare. Immunohistochemically, tumor cells were positive for vimentin and S-100, and negative for epithelial membrane antigen. Chemotherapy and radiotherapy were not performed. No masses recurred during the follow-up period of 4 years and 7 months.

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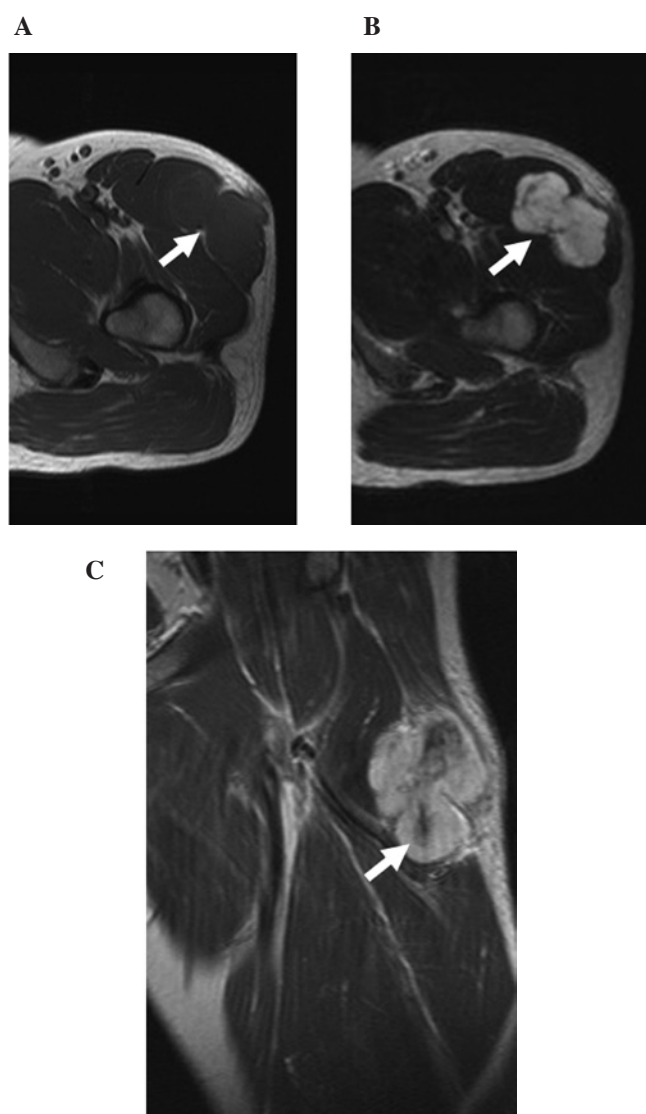


Figure 1. MRI findings. (A) T1-weighted axial imaging; (B) T2-weighted axial imaging. MRI shows an intramuscular, low signal intensity mass located in the rectus femoris and tensor fascia latae (arrow). (C) T1-weighted frontal MRI image after contrast enhancement shows a multinodular, heterogeneous, high signal intensity mass (arrow).

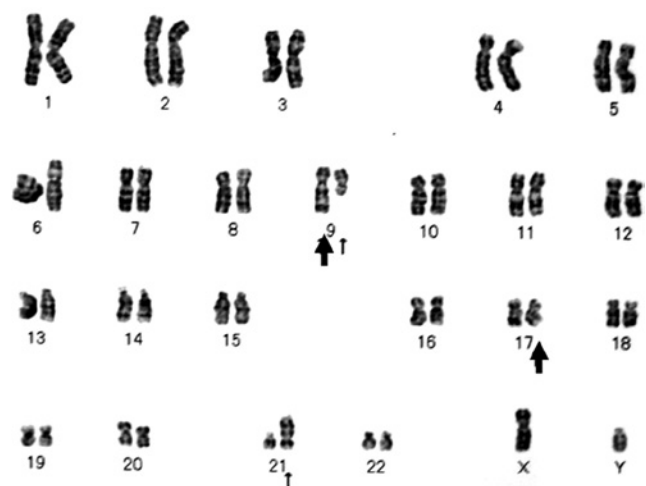


Figure 2. G-banded karyotype. The translocation t(9;17)(q22;q12) was identified (large arrows). The translocation t(9;21)(q21;p13) was also observed in this case (small arrows).

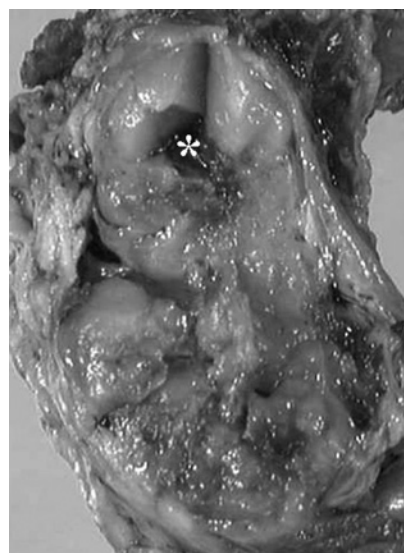


Figure 3. Gross appearance of surgical specimens. The tumor was encased by a thin capsule and divided into multiple gelatinous nodules by fibrous tissue. The hemorrhagic area is shown (asterisk).

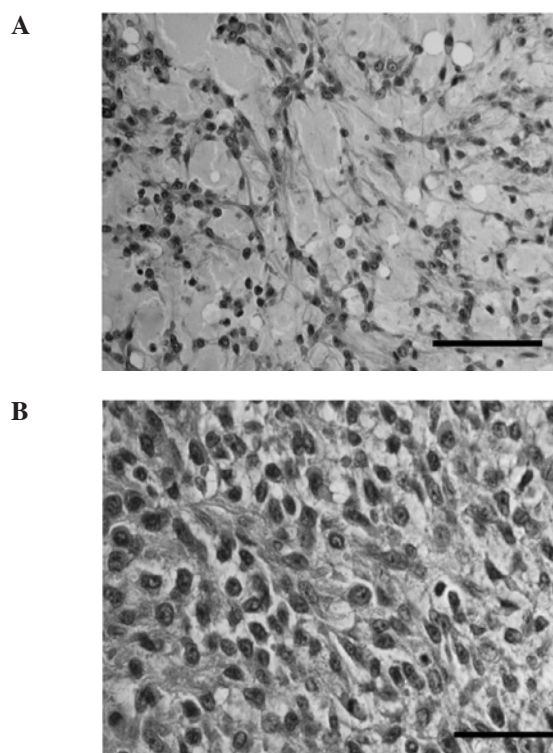


Figure 4. Histological appearance of surgical specimen. (A) Lace-like appearance with an abundant myxoid matrix is shown (hematoxylin and eosin; scale bar, 200 μ m). (B) Diffuse proliferation of small, uniform, round cells with hyperchromatic nuclei is observed. Mitoses are rare (hematoxylin and eosin; scale bar, 50 μ m).

Discussion

EMC is a rare tumor, accounting for less than 3% of primary soft tissue sarcomas (23) and most commonly affecting individuals older than 35 years of age (1). Males are affected approximately twice as often as females. EMC arises in the

deep soft tissues of proximal extremities. Patients with EMC tumors have long survival and prolonged follow-up, but EMC leads to a high disease-associated mortality rate (24,25). Local recurrence and metastasis each occur in approximately half of cases. Meis-Kindblom *et al* (24) reported 5-, 10-, and 15-year survival rates of 90, 70, and 60%, respectively. Therefore, EMC should be considered an intermediate-grade rather than a low-grade malignant tumor, and long follow-up is necessary.

Based on histopathological and immunohistochemical findings, EMC is difficult to distinguish from myxoid tumors including myxomas, myxofibrosarcomas (also known as myxoid malignant fibrous histiocytomas), and myxoid liposarcomas. Myxomas exhibit a similar paucity of vascular structures, but are less cellular. Myxofibrosarcomas have a similar fibrous septum and myxoid stroma but show a broad spectrum of cellularity and pleomorphism. Most myxofibrosarcomas are negative for S-100. Myxoid liposarcomas exhibit a marked plexiform vascular pattern and contain lipoblasts. S-100 positivity is found in approximately 40% of myxoid liposarcomas (26) and 50% of EMCs (27). Thus, S-100 does not help distinguish myxoid liposarcomas from EMC. Therefore, we performed a cytogenetic examination. The karyotype was t(9;17)(q22;q11), and the diagnosis of EMC was made in this case.

At present, only 50 cytogenetic cases of EMC, including our case, have been reported in the English language literature (2-21). Cytogenetic findings of EMC are occasionally complex (12%). In addition, a diploid or near-diploid chromosomal complement has been observed. Recurrent chromosomal aberrations in EMC include t(9;22)(q22;q12), t(9;17)(q22;q11), and trisomies 7, 8, 12, 18, 19 and 22. t(9;22)(q22;q12) is the most specific chromosomal aberration in EMC and was observed in 29 cases (58%). t(9;22)(q22;q12) results in the fusion of *NR4A3*, located at 9q22, to *EWSR1*, located at 22q12, to form the abnormal fusion gene *EWSR1/NR4A3*, which is thought to play a primary role in the causation and development of EMC (9).

t(9;17)(q22;q11) is less common than t(9;22)(q22;q12), but is a specific chromosomal aberration in EMC. Of the 50 cases, t(9;17)(q22;q11) was observed in nine cases (18%). t(9;17)(q22;q11) results in the fusion of *TAF15*, located at 17q11, to *NR4A3*, located at 9q22, to form the abnormal fusion gene *TAF15/NR4A3* (15,19,27). t(9;22)(q22;q12) and t(9;17)(q22;q11) have not been found in any other tumors. t(9;15)(q22;q21), which results in the *TCF12/NR4A3* fusion gene (16,27), and t(3;9)(q12;q22), which results in the *TFG/NR4A3* fusion gene (28), were reported in only one case each. It is unclear whether the fusion genes identified in EMC are associated with particular morphological features and clinical significance.

We reviewed the site, size and prognosis of tumors with t(9;22)(q22;q12) and t(9;17)(q22;q11). EMC tumors with t(9;17)(q22;q11) tended to be larger than those with t(9;22)(q22;q12). However, we did not observe a significant difference due to the small number of cases. In our case, t(9;17)(q22;q11) and t(9;21)(q21;p13) were observed. t(9;21)(q21;p13) has not previously been reported in EMC or any other tumor. A number of genes located at 9q21, including *ALDH1A1*, *NTRK2* and *GAS1* were identified, but tumor-related genes located at 21p13 have not yet been identified.

EMC usually lacks overtly cartilaginous areas. Therefore, EMC was provisionally classified as a tumor of uncertain

differentiation in the revised version of the World Health Organization classification of tumors of soft tissue and bone (29). Although a possible association between t(9;17)(q22;q11) and neural differentiation has been suggested (30), the number of cases examined is insufficient to draw any conclusions. Comprehensive studies examining the nature of the tumor and biological properties are required in EMC.

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