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Case Report

Extraskeletal Myxoid Chondrosarcomas, a Diagnostically Challenging Uncommon Tumor. Report of a Case and Brief Literature Review

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Abstract

Extraskeletal Myxoid Chondrosarcomas (EMC) are rare low-grade malignant mesenchymal neoplasms of uncertain differentiation characterized by abundant myxoid matrix. EMCs account for almost 3% of all soft tissue sarcomas. This tumor primarily arises from the deep soft tissues of the proximal extremities, trunk, and limb girdles, and is accompanied by a high rate of local recurrence and metastasis. It most commonly occurs in those between the ages of 50-60 years, presenting twice as frequently in males than in females. Current treatment of EMC consists of early wide local resection, or radical surgery with or without radiotherapy or chemotherapy, dependent on the entity's state of metastasis. It is frequent that this type of tumor recurs in the form of a high grade tumor. As a malignant myxoid neoplasm, there is considerable diagnostic challenge to achieve a correct diagnosis of this tumor. We report a case of this uncommon tumor and we review the literature

Keywords: Sarcoma, myxoid, malignant, metastasis, translocation, diagnosis

ABBREVIATION

EMC: Extraskeletal Myxoid Chondrosarcomas, **MLS**: Myxoid Liposarcoma, **MLMS**: Myxoid leiomyosarcoma, **IHC**: Immunohistochemistry

INTRODUCTION

Extraskeletal myxoid chondrosarcomas are considered low-grade sarcomas, characterized by a protracted clinical course. Most reports estimated 10-year survival is 70%, with 48% local recurrence and 46% metastases. Meis et al, in their review of 117 EMCs, concluded that clinical features such as tumor size, tumor site, patient age and metastases, rather than histological features, are significant predictors of survival. It was suggested that high-grade histologic features, such as necrosis, increased cellularity, high mitotic rate, pleomorphism, epithelioid or rhabdoid cells, and spindled foci, do not affect prognosis [15]. Others believe that these histologic features are predictive of an aggressive course and recommend treatment accordingly.

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Microscopically, EMC is characterized by a multinodular architecture, abundant myxoid matrix, and malignant chondroblast-like cells arranged in cords, clusters, or networks [6]. Although the name suggests otherwise, EMCs show no evidence of cartilaginous differentiation [6]; rather, its unique histology and characteristic chromosome translocation, typically t(9;22), distinguishes it from other sarcomas [5,7]. A different translocation, t(9;17)(q22;q11.2), is also seen in EMC, however, it accounts for only a small proportion of neoplasm[5,7]. Current treatment of EMC consists of early wide local resection, or radical surgery with or without radiotherapy, dependent on the entity's state of metastasis [8].

In this paper, we demonstrate the diagnostic process used to identify this type of uncommon tumor and review the literature. Initially the primary tumor showed no evidence of high grade features or necrosis. However, later metastasis to the lung showed the same tumor, but with high grade features. We report this case to contribute to the limited body of work about ECM, to aid in future diagnostic efforts as well as treatment of soft tissue neoplasms.

CASE PRESENTATION

A 57-year-old man presented with a large 12.5 X 6.5 cm soft tissue mass at the anterior aspect of right thigh. The patient noticed the mass only three months ago but reported it was only recently rapidly enlarging with associated pain. A large gauge needle core biopsy was obtained from the mass and submitted for histopathological examination. The core biopsy findings showed lobules of small malignant epithelioid-like cells in background of cartilaginous matrix. The tumor displayed multinodular architecture, abundant myxoid matrix (**Figure 1A**), and malignant chondroblast-like cells arranged in cords, clusters, and scattered networks (**Figure 1B**). The cells showed spectrum of morphology including short, spindle, and oval, with hyperchromatic and vesicular nuclei, and occasionally vacuolated

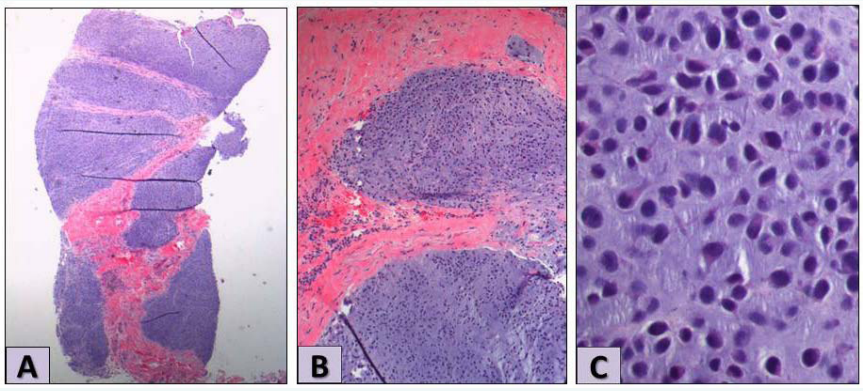

Figure 1 Histopathology examination of the right thigh mass core biopsy.
1A: Core biopsy showing multinodular architecture, and abundant myxoid matrix (H&E stain X20)
1B: Malignant chondroblast-like tumor cells arranged in cords, clusters, and scattered networks (H&E stain X40)
1C: Tumor cells showing spectrum of morphology including short, spindle, and oval, with hyperchromatic and vesicular nuclei, and occasionally vacuolated cytoplasm. Some cells showing rhabdoid-like features (H&E stain X100)

cytoplasm. Some cells showed rhabdoid-like features (**Figure 1C**), but no necrosis present and mitosis < 5 mitosis/10 HPF. Immunohistochemistry (IHC) studies were positive for Vimentin, and focally positive for synaptophysin and S100. The tumor cells were negative for pan cytokeratin, EMA, desmin, SMA, Myogenin, HMB45, and Melan-A. The cytohistomorphologic features, together with the immunohistochemistry profile were consistent with a diagnosis of extraskeletal myxoid Chondrosarcoma (EMC).

FISH studies were performed and the tumor cells were positive for EWSR1 translocation (22q12), a gene rearrangement consistently seen in myxoid Chondrosarcoma. The mass was widely excised with wide safe surgical margins. The tumor did not show high grade features and the mass was adequately excised, so the patient elected not to have post-surgical chemotherapy or radiation. The patient was free of recurrence or metastasis for three years after which several masses were discovered in both right and left lungs. Biopsy of some of lung masses showed metastatic tumor with the same features of original prior tumor, but now with high grade nuclear features and moderate necrosis. Chemotherapy and radiation treatment were started and the patient was disease free of tumor for another two years after which he expired due to massive multiple organs metastasis mainly within the abdominal wall.

DISCUSSION

Extraskeletal Myxoid Chondrosarcoma (EMC) was first described by Stout and Verner in 1953 [9]. However, it was not until 1972 that EMC was histopathologically defined as its own entity [13]: a rare low-grade malignant mesenchymal neoplasm of uncertain differentiation characterized by an abundant myxoid matrix located in the soft tissues [1].

EMC accounts for almost 3% of all soft tissue sarcomas [2], and while it occurs most frequently in the fifth to sixth decades of life [5], rare cases have been reported in adolescent females and children [11,12]. Approximately 64% of these particular tumors originate in the proximal extremities and limb girdles, followed by the 23% in the distal extremities and 13% in the trunk. Unusual locations have included the mediastinum, retroperitoneum, digits, and the intracranial cavity [10]. These tumors classically present as a palpable, often painful mass [13].

Grossly, EMC tumors may present at various stages of development, depending upon their location, and feature a multinodular or nodular configuration, a poorly defined fibrous capsule, and well-defined margins, with diameter at presentation ranging from 6 cm to 13 cm. Grey-white in hue, their structure is gelatinous, and easily friable [3]. Multifocal intramural cysts and hemorrhage may also be present [1].

Histologically, it is characterized by a multinodular architecture, abundant myxoid matrix, and malignant chondroblasts-like cells arranged in cords, clusters, or networks [6]. The cells are short, spindle, or oval in shape, with hyperchromatic or vesicular nuclei, and occasionally vacuolated cytoplasm. Grooved or cleaved nuclei indicative of chondroid differentiation may also be observed [3]. Mitotic activity is low (<2 mitotic figures per 10 high power field) in most cases, and areas of recent and remote tumoral hemorrhage are common. Despite the name, there is no convincing evidence of cartilaginous differentiation [6].

On immunohistochemical staining, vimentin is the only marker consistently expressed in EMC; S100 protein, cytokeratin, and epithelial membrane antigens are expressed in a minority of tumors; if present, they are typically expressed focally [6]. Recent studies have shown EMC to stain positive for neural or neuroendocrine markers such as neuron-specific enolase, protein gene product 9.5, and synaptophysin [3].

The unique characteristic of EMC, differentiating it from other sarcomas, is the entity's chromosomal aberrations and resultant fusion (chimeric) genes [3], typically t(9;22)(q22;q12.2), fusing *EWSR1 to NR4A3* (genes formerly termed *EWS* and *CHN, TEC, or NOR1*, respectively), seen in approximately 70% of cases [5,7]. Another 15% of EMC have the translocation

t(9;17)(q22;q11.2) which results in a *RBP56-NR4A3* fusion gene responsible for alterations in cellular growth and differentiation [7]. It is believed that the remaining 15% of cases could be due to various translocations or gene anomalies still under research, such as TCF12/TEC and TGF/TEC [8]. Ultrastructural studies of EMC have also uncovered evidence of markers of neuroendocrine differentiation such as class III β-tubulin and microtubule-associated protein-2 [7]. These findings argue against a chondrocytic or pre-chondrocytic origin of this malignancy, and further distinguish EMC as a unique entity among sarcomas [7].

Nayel Y et al described the considerable challenge in differentiating EMC from myxoid Liposarcoma (MLS). MLS is one of the misleading tumors that are usually on the differential diagnosis resembling EMC as it arises in the deep tissues of the proximal extremities and limb girdles, and manifests as a deep-seated mass. EMC is most commonly characterized by a balanced translocation, t(9;22)(q22;12), which fuses the EWSR1 gene on Chr. 22 with the NR4A3 gene on Chr. 9. However, MLS is known to be associated with presence of the reciprocal chromosomal translocation t(12;16)(q13;p11) [16].

One other uncommon tumor which may pose a challenge to the diagnosis of EMC is myxoid leiomyosarcoma (MLMS). To differentiate the rare MLMS from other myxoid tumors including Extraskeletal Chondrosarcoma, Afzal IZ. et al proposed an algorithm to assist pathologists in diagnosing MLMS. They recommended that after establishing a malignant diagnosis, the initial step is to identify myxoid stroma content to determine whether the patient has conventional leiomyosarcoma or MLMS or other myxoid malignant neoplasms. Once identified as being over 60% myxoid, studying for capsular and/or lymphovascular invasion would be the next step. Lastly, immunohistochemical staining can be used to assist in diagnosis; HGMA2 expression would be the best sensitive staining test for MLMS and ER/PR positivity can be used in developing a treatment strategy [17]. MLMS was not a diagnostic challenge in our case as IHC muscle markers desmin and SMA were negative.

EMC has a prolonged indolent course with a high rate of local recurrence and distant metastasis, often resulting in late death [13]. This was the case in our reported case. The prognosis and overall survival of the patient is negatively impacted by larger tumor size, older patient age, tumor location in the proximal extremity, and metastasis [5], with tumors >10 cm in size and metastatic disease presumed to have worse prognosis [12]. Due to the tumors' indolent course, patients live for many years after diagnosis, with 5-year, 10-year, and 15-year overall survival rates of 82%, 65%, and 58%, respectively [14].

Current treatment of EMC consists of early wide local resection, or radical surgery with or without radiotherapy or chemotherapy, dependent on the entity's state of metastasis [8]. Some investigators suggested that radiotherapy and chemotherapy use depend on the level of pleomorphism within the tumor [3]. To date, the most efficacious chemotherapy for EMS has yet to be identified, warranting further research in identifying novel target therapies.

It is our hope that this report raises awareness of including this tumor in the differential diagnosis of soft tissue masses presented in the extremities. We also hope that this report will raise the awareness of what remains an unmet need in definitive management of this type of uncommon sarcoma and that continued investigation drives further development of efficacious and safe treatments for improving patient outcomes.

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