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Case Report

Extraskeletal Myxoid Chondrosarcomas of the Ankle, Case Report of Uncommon Tumor and Brief Review of the Literature

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Abstract

Extraskeletal myxoid chondrosarcoma (EMC) is an uncommon form of sarcoma that typically localizes to the limbs. It is considered a neoplasm of uncertain differentiation, and accounts for fewer than 3% of all sarcomas. EMC is twice as common in males as it is in females, and most commonly occurs around the age of 50. Since EMC does not have specifically characteristic findings in terms of clinical presentation, pathology, or imaging, differentiation from other neoplasms can be challenging. However, immunohistochemistry studies and molecular analysis aid in its definitive diagnosis. Current treatment guidelines of EMC include total resection of the primary tumor with a wide safe surgical margin. Post-operatively the patient should be closely followed-up due to the high possibility of metastasis and recurrence. Here we report a case of this challenging tumor and include a brief review of the literature.

Keywords: Chondrosarcoma; Myxoid; Malignant; Amputation

Abbreviation

EMC: Extraskeletal myxoid chondrosarcoma; **CS**: Chondroid sarcoma; **IHC**: immunohistochemistry

Introduction

Chondroid sarcoma (CS), also known as extraskeletal myxoid chondrosarcoma (EMC), is a relatively rare but well described tumor that usually arises in the deep soft tissues of the extremities [4]. EMC has a male to female ratio of 2:1, with the peak occurrence in the sixth decade of life. Although more common in the lower extremities, cases of EMC of the orbit, shoulder and upper extremities have been reported [3].

Extraskeletal myxoid chondrosarcoma has the potential for multiple differentiations and was traditionally classified as a low-grade malignancy [2]. 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 [7].

Irrespective of EMC localization, pre-operative clinical diagnosis may be challenging, and thus definitive diagnosis is carried out based on the results of tissue biopsy, followed by the evaluation of histological features and immunohistochemistry (IHC) profile of the tumor tissue [8]. Furthermore, EMC does not have specific clinical, imaging, or pathological characteristics, which makes it difficult to differentiate between EMC and other myxoid tumors. However, EMC has a rare gene fusion, EWS RNA binding protein 1-nuclear receptor subfamily 4, group A, member 3 (*EWSR1-NR4A3*), which is useful in confirming the diagnosis [5]. Microscopically, EMC is characterized by a multinodular architecture, abundant myxoid matrix, and malignant chondroblast-like cells arranged in cords, clusters, or networks [20].

The treatment of patients with localized EMC should include primary tumor excision with a wide surgical margin [3]. Due to its rarity, protracted clinical course and prolonged survival of patients with EMC, long-term follow-up is recommended for early detection of local recurrence and distant metastases. Although EMC has been reported to have a relatively good prognosis, a high potential for metastasis, particularly to the lungs, regional lymph nodes and bones should be expected. [3]

Case Presntation

A 29-year-old man presented with a large soft tissue mass in his left ankle, which was recently enlarging in size. Patient reported no significant medical history. Clinical examination showed tender large soft tissue fullness in the anterior aspect of the left ankle measuring 7 x 4 cm. Axial T2 fat-saturated MRI demonstrated a large lobulated T2 hyperintense mass with T2 hypointense internal fibrous septa.

Tissue biopsy was performed and microscopic examination showed cellular tumor with multinodular architecture, abundant myxoid matrix, and malignant appearing chondroblast-like cells arranged in clusters and elongated cords. The cells were short, spindle, and oval in shape, with hyperchromatic vesicular nuclei,

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prominent nuclei, increased mitotic activity, and occasionally vacuolated cytoplasm. Grooved and cleaved nuclei suggestive of chondroid differentiation were also observed (**Figure 1 A-B-C**). IHC studies were performed to determine cellular differentiation. The tumor cells were positive for Vimentin, Synaptophysin, Cytokeratin AE1/AE3 (**Figure 1E**), CD34 (**Figure 1D**) and focally positive for S-100 and EMA, while negative for HMB45, CD30 and CD45. Molecular analysis showed translocation t(9;22) involving the EWS gene (22q12). The histomorphology, IHC studies and molecular testing confirmed the diagnosis of EMC.

A staging chest CT and 99mTc bone scan were performed showing no evidence of metastatic spread and a curative procedure was planned. Imaging studies confirmed wide diffuse spread of the tumor throughout the knee joint. A multidisciplinary tumor board meeting recommended left below the-knee amputation as the limb determined not to be salvaged. Histological examination of the amputation specimen revealed a synovium-based tumor with same features of the original biopsy. No post-operative treatment was administered.

The patient was followed with for 2 years with no recurrence or metastasis after which he was lost to follow up.

Discussion

Extraskeletal myxoid chondrosarcoma is a rare malignant soft tissue tumor with an indolent course but with high risk of local recurrence and metastasis. Various reports demonstrated an indolent but resilient course with late metastatic progression and local recurrence in the vast majority of patients [11,20]. EMC is a misnomer insofar as the tumor is actually of uncertain differentiation with no convincing evidence of cartilaginous origin. In reality it is an infrequent tumor of soft tissues, forming around bones [10]. Extraosseous myxoid chondrosarcomas can grow to large sizes and compress other tissues and organs, causing restriction of movement and pain at local site. They can present with complications such as damage to vital nerves or vessels, damage to the underlying bone, or lung or lymph node metastasis [10].

EMC has a reported overall survival rate at 5 years of 82%, at 10 years of 65%, and at 15 years of 58% [11]. In an analysis of 23 cases by Oliveria et al, the tumors were located in the lower extremities (19 cases, 83%), upper extremities (two cases), anterior chest wall (one case), and paravertebral area (one case). Among the tumors located in the lower extremities, the thigh was the most common anatomical location (nine cases), followed by the ankle (four cases), foot (three cases), knee (two cases), and leg (one case) [12]. There is no racial predilection; however, EMC affects males twice as often as females and is most prominent in the sixth decade of life [3, 13].

The histogenesis of EMC is still a subject of controversy. However, chondroblastic differentiation has been supported by

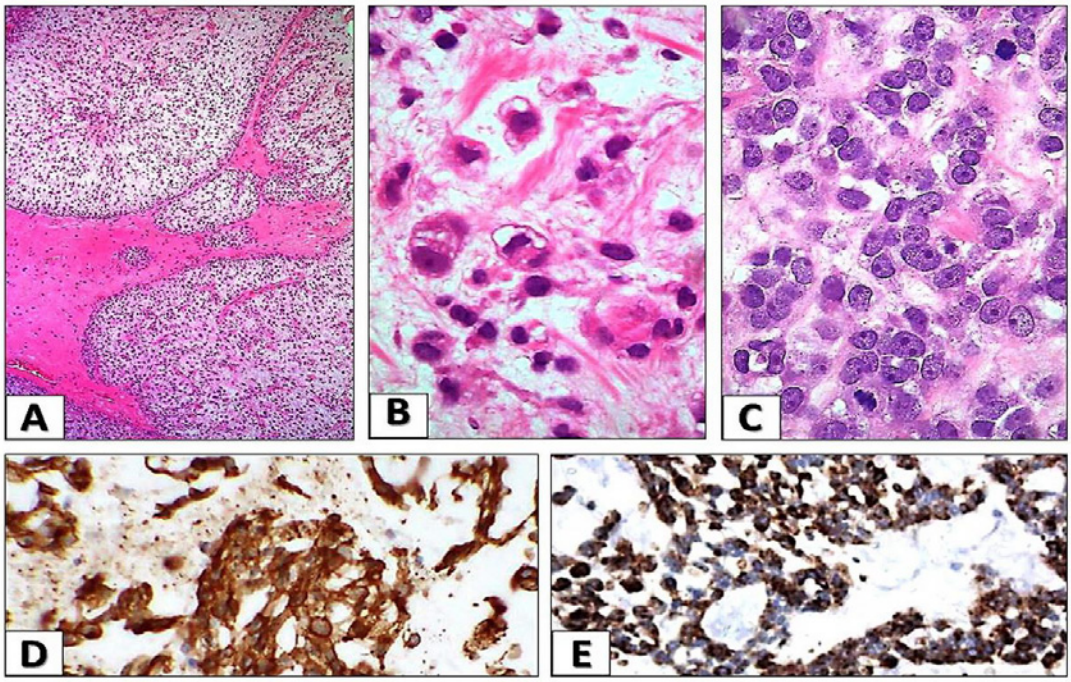

Figure 1 Pathological examination of extraskeletal myxoid chondrosarcoma biopsy
1A: Cellular tumor with multinodular architecture, and abundant myxoid matrix (H&E stain x20)
1B: Malignant appearing chondroblast-like cells arranged in clusters and elongated cords. (H&E stain x60)
1C: Spindle, and oval cells, with hyperchromatic vesicular nuclei, prominent nucleoli, increased mitotic activity, some with vacuolated cytoplasm (H&E stain x60)
1D: Tumor cells positive for CD34
1E: Tumor cells positive for cytokeratin AE1/AE3

ultrastructural and histochemical studies. 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. Multifocal intramural cysts and hemorrhage may also be present [7, 19].

Histologically, it is characterized by a multinodular architecture, abundant myxoid matrix, and malignant chondroblast-like cells arranged in cords, clusters, or networks. 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 [15].

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 [20]. 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 [12].

In addition, cytogenetic and molecular analyses have shown that EMC is a distinct entity with the characteristic translocation t(9;22) involving the *EWS* gene (22q12) and the *TEC* gene (9q22) in a majority of the cases [20]. It remains to be defined whether EMC is composed of a homogenous tumor or heterogeneous tumor groups [14].

In an analysis of 23 cases by Oliveria et al, a trend to decreased overall survival was observed with high mitotic activity, male sex, and older age, but these features did not reach statistical significance [12]. Another study evaluating EMC by Jackson et al showed that 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, with tumors >10 cm in size and metastatic disease presumed to have worse prognosis [5].

One potential differential diagnosis for EMC is a hemangioma. As discussed in Wyke, hemangiomas that occur in the oral and maxillofacial area account for 60% of all hemangiomas in the body. They are mostly located on the facial skin, subcutaneous tissue and oral mucosa, such as the tissues of the tongue, lips and floor of the mouth, while a few cases have been reported in the jaw or deep tissues. Cavernous hemangioma is a slow-growing soft mass with no subjective symptoms. When the head is in a low position, the tumor expands due to hyperemia, and if the head returns to the normal position, the shape of the tumor is restored. Superficial tumors produce a blue-purple color on the skin surface or mucous membranes. The skin color is normal when the tumor is located deeper. The tumor is soft on palpation, with no clear boundary and no tenderness. The tumor size is decreased by extrusion and returns to the original size after the pressure is released. The histopathological characteristics of the tumor include the presence of irregular cavities in the lower part of the dermis and the subcutaneous tissue, which contains red blood cells and fibrous tissue. The cavity wall is a monolayer of endothelial cells. Endothelial cell hyperplasia may be observed in the larger vascular compartment, resulting in a thickened wall [15].

Another differential diagnosis is fibrosarcoma, which is common in young adults. Tumors located in the mouth and jaw are usually found in the gum and the surface of the jaw, have a spherical or lobulated shape and exhibit a purple-red color, often with ulceration and hemorrhage. Invasion of the surrounding tissue may lead to bone destruction and loosening of the teeth or tooth loss. Peripheral type tumors may present as a local mass in the early stage, followed by pain. On histopathological examination, the tumor is composed of spindle fibroblasts and most skin fibrosarcomas are well-differentiated, with few mitoses, no obvious spiral structures and reduced fiber generation. When these phenomena are present, they indicate that the tumor is invasive, and the prognosis is poor [16].

Mesenchymal chondrosarcoma is another differential diagnosis in the case of EMC. Ultrastructural studies have revealed additional differences between EMC and mesenchymal chondrosarcoma, which showed that intracytoplasmic glycogen of EMC cells is abundant, while mesenchymal chondrosarcoma is devoid of intracytoplasmic glycogen. The stroma of mesenchymal chondrosarcomas is rich in collagen fibrils. EMC does not share this characteristic [9].

Nayel Y, et al described the considerable challenge in differentiating EMC from myxoid liposarcoma (ML). ML is one of the diagnostically challenging tumors that are usually on the differential diagnosis of EMC and other myxoid tumors. ML 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, ML is known to be associated with presence of the reciprocal chromosomal translocation t(12;16)(q13;p11) [17].

One uncommon tumor that would also be included in the list of differential diagnoses alongside EMC is a Myxoinflammatory Fibroblastic Soft Tissue Sarcoma (MIFS). MIFS typically presents grossly as gray-white or yellow and has a consistency between firm and myxoid. MIFS most commonly presents in the subcutaneous region and tends to involve the dermis as well as other surrounding structures. It consists of cells with nuclear atypia that range between spindle and epithelioid shape. It also includes other neoplastic cells that appear like ganglion cells and are large. MIFS stains positive for vimentin and CD68 and shows variable expression of other markers such as cytokeratin and CD34. It has two different genetic associations; one is a reciprocal translocation t(1;10)(p22;q24) and the other is the amplification of certain genes on chromosome 3 [18].

Another 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 [21].

Current treatment of EMC consists of early wide local resection, or radical surgery with or without radiotherapy or chemotherapy, considering absence or presence 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 investigations to identify novel targeted therapies.

Wide surgical resection is currently the preferred treatment for EMC, and incomplete tumor resection is considered a major cause of recurrence [2]. Kawaguchi et al, performed univariate analysis of 42 patients and found that inadequate initial surgery was significantly associated with decreased recurrence-free survival. None of other variables (including age, gender, tumor size, depth and site of the tumor, and histologic grade) showed significant association with disease-free, metastasis-free, or recurrence-free survival [14]. These findings are in support of the role of wide tumor excision in local control of EMC. Consistent literature data supports the use of radiotherapy in combination with surgery, in both the adjuvant and the neoadjuvant setting. EMC patients who received surgery alone showed significantly higher local recurrence rates than patients treated with a combination of surgery and radiotherapy [11].

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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