



Extraskelatal Myxoid Chondrosarcoma in Comparison to Myxoid Liposarcoma - Case Report of a Challenging Diagnosis and Brief Review of the Literature

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Abstract

Extraskelatalmyxoidchondrosarcoma is an uncommon soft tissue sarcoma that can resemble a much more common sarcoma, myxoidliposarcoma, leading to misdiagnosis. This has important clinical implications as these pathologies differ in treatment, recurrence rates, and metastasis. Here, we present a case of a 29-year-old man, who presented with a large soft tissue mass at the front of the left ankle. This case presented a diagnostic challenge based on histomorphology and IHC studies alone. Molecular testing was essential for definitive diagnosis due to lack of agreement among soft tissue pathology experts. Reporting cases of EMC is imperative in order to bridge the gap between the known pathological features of this tumor and the consideration of this neoplasm in differential diagnoses.

Abbreviations

ML: Myxoid Liposarcoma; EMC: Extraskelatal Myxoid Chondrosarcoma; IHC: Immunohistochemical

Introduction

Liposarcoma, a tumor of lipoblasts, is the most common soft tissue sarcoma in adults involving deep soft tissues. Among other sites, it can be found in the retroperitoneum and popliteal fossa [1]. One genetically distinct variant of liposarcoma, myxoidliposarcoma (ML), is characterized by a t(12:16) translocation combining the DDIT3 gene on Chr. 12 with the FUS gene on Chr. 16 [2]. ML represents 30-50% of all liposarcoma cases [3]. It mostly occurs in the lower extremities and has a propensity to metastasize to non-pulmonary soft tissues, such as bone or the contralateral limb [3]. A characteristic of ML is a round cell component composed of uniform oval-shaped cells and signet-ring cell lipoblasts on a background of myxoidstroma. The presence of this small round cell component in more than 5% of the tumor mass is indicative of an aggressive behavior [4].

An additional sarcoma with a similar round cell component is extraskelatalmyxoidchondrosarcoma (EMC), which on clinicopathological findings is similar to ML [5]. First described by Stout and Verner in 1953 [6], this sarcoma accounts for less than 2.5% of all soft tissue sarcomas [7]. The rare occurrence of EMC, along with its similar presentations to ML, often leads to misdiagnosis and underrepresentation of EMC due to the lack of its consideration as part of the differential diagnosis [8]. EMC has specific pathological features, immunohistochemical (IHC) profile, and is characterized by a specific genetic translocation that can aid in a proper diagnosis [9]. We present a case of EMC that presented a diagnostic challenge on the basis of histomorphology and IHC studies alone and highlights the importance of molecular studies that were essential for definitive diagnosis.

Case Presentation

A 29-year-old male presented with a large soft tissue mass measuring 6.5 X 3 cm at the front of the left ankle. Magnetic resonance imaging (MRI) revealed a soft tissue tumor mass with an isointense signal at the front of the lower part of the left tibia (Figure 1A). A small core biopsy was performed, but the diagnosis was inconclusive. The mass was excised, and gross findings showed a relatively well demarcated tumor mass encased by a pseudocapsule. It divided into multiple gelatinous nodules by fibrous septa. Multifocal intramural cysts and hemorrhage were also seen (Figure 1B). Microscopic examination revealed a large, relatively well-demarcated, multinodular tumor contained by a pseudo fibromembranous capsule. The tumor consisted of myxoid areas containing cords and cellular aggregates of mesenchymal cells demarcated by dense fibrous septa. The cellular component displayed a spectrum of histomorphology. The cells predominantly formed linear cords and small aggregates, and some areas showed a complex cribriform appearance. Rhabdoid-like cells with eccentric hyaline globules were occasionally found within the tumor. The tumor showed focal cellular areas composed of large cells with vesicular nuclei and deeply

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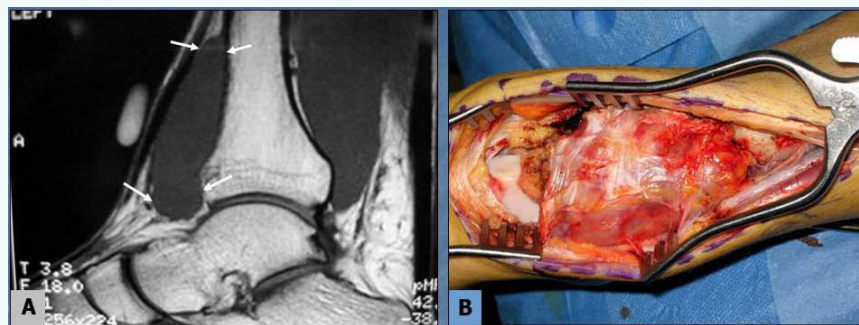


Figure 1 Imaging studies and the excised specimen.

A- Magnetic resonance imaging (MRI) revealed a soft tissue tumor mass with an isointense signal at the front of the lower part of left tibia.

B- A relatively well demarcated tumor mass encased by a pseudocapsule and divided into multiple gelatinous nodules by fibrous septa. Multifocal intramural cysts and hemorrhage were also seen.

eosinophilic cytoplasm. Mild pleomorphism, minimal necrosis (< 5 %), but unusually high mitotic activity (>10 mitosis/10 HPF in the cellular areas) were also displayed (Figure 2 C-F). These initial gross and microscopic findings led to a differential diagnosis including Myxoid Liposarcoma (ML), Myxoid Malignant Fibrous Histiocytoma, Malignant Myoepithelioma, Parachordoma, Extraskeletal Myxoid Chondrosarcoma (EMC), or Clear Cell Sarcoma of Soft Parts.

IHC studies showed positive staining of the tumor cells with Vimentin (strong), and S-100 (focal, but strong in the cellular areas). The tumor cells were negative for HMB45, Cytokeratin AE1/AE3, Calponin, P63, EMA, E-Cadherin, SMA, NSE, Desmin, and GFAP. Based on the initial histomorphological findings and IHC studies, a diagnosis of EMC was rendered with a recommendation of molecular testing for confirmation and to rule out possible ML.

Due to lack of agreement among soft tissue pathology experts, molecular testing was essential. Chromosomal analysis and karyotyping of the tumor cells showed a t(9:22) confirming the diagnosis of EMC with an unusual and highly atypical small round cell component in more than 10% of the tumor mass.

The mass was completely excised with adequate safe surgical margins. Post-operative treatment included external beam radiotherapy and adjuvant anthracycline-based chemotherapy. Patient was under close follow up for five years with no evidence of recurrence or metastasis. After 5 years, local recurrence was found in the form of a 3.8 cm mass at the same location. The mass was excised with adequate safe surgical margins with repeated post-operative radiation and chemotherapy treatment. Patient was closely followed up for another 3 years with no evidence of recurrence or metastasis, after which he was lost for follow up.

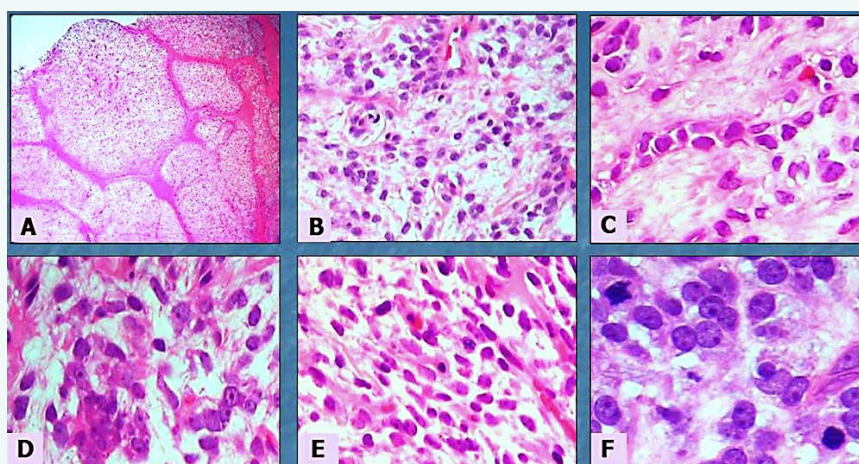


Figure 2 Microscopic examination of the tumor mass showing spectrum of histomorphologic features.

A- Lobulated cellular aggregates of mesenchymal cells, demarcated by dense fibrous septa (H&E, x20)

B- Tumor cells showing delicate cellular networks in a myxoid background (H&E, x40)

C- Tumor cells predominantly showing linear cords and small aggregates (H&E, x60)

D- Some tumor cells showing complex cribriform appearance (H&E, x60)

E- Tumor cells showing spindling and large eosinophilic cytoplasm (H&E, x60)

F- Tumor cells with frequent mitosis (H&E, x100)



Discussion

Sarcomas are a rare group of malignancies originating from mesenchymal cells that can arise anywhere in the body [10]. Statistics from the American Cancer Society show that around 12750 new cases of soft tissue sarcomas are diagnosed each year, with males sharing a larger burden [11]. Liposarcomas, the most common soft tissue sarcomas in adults, arises from adipose tissue [1]. They are divided into three different subtypes: well-differentiated (including de-differentiated liposarcoma), pleomorphic liposarcoma, and myxoid/round-cell liposarcoma [12]. Patients with myxoidliposarcoma (ML) are typically males in their fourth decade of life and present with a slow-growing, deep tumor in a lower extremity [10].

MLs can undergo further de-differentiation. The majority are pure MLs, which are the second most common type of liposarcoma [13]. On the other hand, MLs can also de-differentiate and have a round cell component. When this round cell component is present in more than 5% of the tumor mass, it is called Myxoid/Round cell liposarcoma, which account for approximately 15% of all liposarcomas [13]. Myxoid/Round cell liposarcoma is characterized by translocation t(12;16)(q13;p11), which fuses FUS (also called TLS) on chromosome 16 with the entire reading frame of DDIT3 (also called CHOP or GADD153) on chromosome 12 [14].

Histopathologically, ML most commonly reveals a myxoid-type tumor with bland fusiform to ovoid cells in a myxoidstroma with a prominent plexiform capillary network and scattered signet-ring lipoblasts [15]. The diagnosis of ML is usually not difficult when these characteristic features are identified [15]. However, the variability within these tumors is great and due to the abundance of unusual variants it is relatively easy to be misled [5]. This is especially the case when a biopsy specimen reveals an unusual morphologic variant [15], such as ML with a round cell component.

One of the misleading tumors that are usually on the differential diagnosis with ML is extraskeletal myxoid chondrosarcoma (EMC) [15]. EMC is a rare malignant mesenchymal neoplasm of uncertain differentiation, which affects adults around the age of 50 and has a male to female ratio of 2:1 [7]. Resembling ML, EMC arises in the deep tissues of the proximal extremities and limb girdles, and manifests as a deep-seated mass, yet EMC accounts for less than 3% of soft tissue sarcomas [7,16]. Also similar to ML, 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 [17]. Characteristic features of EMC neoplasms are a multinodular growth pattern, cords of eosinophilic chondroblast-like cells, and an abundant myxoid matrix, which on gross and microscopic findings can look similar to ML [16].

Differences can be seen in their recurrence rate, metastasis rates, metastasis location, and survival rates. For ML, local recurrence was seen in 9% of patients, who were treated with limb-sparing surgery and risk-adapted radiation therapy [3]. On the other hand, EMC has a much higher rate of local recurrence at 37-48% [18]. The development of metastatic disease differs

between the two sarcomas. ML has a distinct pattern of non-pulmonary metastatic disease and it is advised that patients with high-risk extremity ML should undergo imaging studies of the chest, abdomen, spine and pelvis [3]. Of patients with ML, 10% will develop metastatic disease [22]. This differs from EMC where the risk is increased to 50% and is usually pulmonary [18]. For ML, survival rates are 81% after 5 years and 72% after 10 years [3]. EMC survival rates after 5 and 10 year are 82-90% and 65-70%, respectively [18,19]. Although survival rates are almost similar, it is important to differentiate between the two sarcomas due to their differences in metastatic disease rates and location, and recurrence rates.

Even though ML and EMC share similarities, the treatments of the two neoplasms differ drastically. Surgery, radiation, and systemic therapies are all used in the treatment of ML [10]. This multi-modality therapy with radiation, chemotherapy, and surgery decreases the likelihood of local recurrence and allows for a greater percentage of limb-salvage surgery compared to surgery alone in soft-tissue sarcomas [20]. ML's have been found to be much more radiosensitive than many other types of soft tissue tumors [21], therefore surgery for ML is combined with neoadjuvant or adjuvant radiation [22]. The addition of radiation therapy to surgery has led to a clear increase in local control with a large decrease in metastatic rate [23]. Adjuvant chemotherapy is considered in ML only in patients with high-risk soft-tissue sarcomas [10]. So far, no evidence exists to prefer neoadjuvant over adjuvant chemotherapy; therefore adjuvant therapy is most widely used, except in cases where neoadjuvant therapy is chosen to reduce the size of the tumor to allow for limb salvage surgery [10]. The anthracycline, doxorubicin, has been the standard chemotherapeutic drug used for metastatic soft-tissue sarcoma [10]. However, in 2015, trabectedin, a marine alkaloid, was FDA-approved for ML following disease progression with anthracycline-based chemotherapy [24]. Future directions of chemotherapeutic treatment for ML are exploring the effects of PPAR-gamma agonists as the FUS-CHOP fusion caused by translocation t(12;16) in ML results in a transcriptional program that inhibits differentiation and is associated with suppression of PPAR-gamma activity [25].

On the other hand, the standard treatment for primary, localized EMC is surgery, but patients with advanced disease need medical treatment with drugs [26]. The role of radiation therapy in EMC has largely been unidentified, yet a study published by Kemmerer et al. in 2018 suggests that external beam radiotherapy is associated with a cancer specific survival benefit in localized EMC and should be used along with aggressive local therapy [27]. Additionally, anthracycline-based chemotherapy, which is the first-line regimen used in soft-tissue sarcoma like ML, has low activity in this sarcoma subtype [28]. In contrast to anthracycline-based chemotherapy, retrospective evidence of sunitinib antitumor activity in advanced EMC has driven novel research into the use of antiangiogenic drugs as an option for EMC treatment [29]. A recent study published in July 2019 by Stacchiotti et al., shows that Pazopanib has clinically meaningful antitumor activity in patients with progressive and advanced EMC, and could be considered a suitable option after failure to respond to first-line anthracycline-based chemotherapy [26].



Considering that the two neoplasms have different metastasis rates, recurrence rates, and survival rates and are both treated differently, it is therefore imperative to clearly distinguish EMC from ML to ensure optimal patient management. In a study conducted on 18 cases of EMC, immunohistochemical analysis showed that the tumors were immunoreactive for vimentin (89%), synaptophysin (72%), epithelial membrane antigen (28%), and S-100 protein (17%) [9]. For ML, immunohistochemical analysis shows that S100 stains mature fat cells and lipoblasts but is rarely of diagnostic use [30]. CD34 stains are negative or stain rare small cells and MDM2 and CDK4 generally negative [30]. Therefore, as there is not a single stain to clearly differentiate between ML and EMC, chromosomal analysis is essential for diagnosing challenging cases. EMC is characterized by a balanced translocation, t(9;22) [17], and translocation t(12;16) is characteristic for ML [14]. Rare cases of ML may have a translocation involving DDIT3 from ML and EWSR1 from EMC, therefore the finding of a rearrangement involving the EWSR1 gene without a rearrangement involving DDIT3 would support the diagnosis of EMC [31].

This case highlights a difficult diagnosis of EMC as the histomorphologic features and immunohistochemistry profile were similar to ML. Molecular testing was essential for definitive diagnosis due to lack of agreement among soft tissue pathology experts. It is our hope that this report raises awareness of what remains an unmet need in definitive diagnosis and 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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