



Mixed Mesenchymal Chondrosarcoma/Myxoid Round Cell Liposarcoma with Later Recurrence as a Metastatic High-Grade Undifferentiated Round Cell Sarcoma. Report of a Case with Unusual Presentation and Review of the Literature

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Abstract

Mesenchymal chondrosarcomas (MC) are a rare and aggressive neoplasm characterized by primitive mesenchymal cells mixed with well differentiated islands of cartilage. MCs account for 2%-9% of all chondrosarcomas and typically metastasize to bones of the spine, ribs, or jaw with a ten-year survival rate of 27%. MC most commonly occurs in the second and third decades of life. Myxoid round cell liposarcomas (MRCL) are a form of liposarcoma neoplasm which occur in up to 30% of liposarcoma cases. Most MRCL cases occur between the second and third decade of life with a higher percentage of round cells associating with poorer prognosis. Surgical resection of MRCL is the most common treatment, with 14% of cases reoccurring following resection. A higher rate of recurrence is associated with a larger round cell component. 67% of recurrence cases of MRCL are associated with metastasis within 17 months. We report an unusual case of Mixed Mesenchymal Chondrosarcoma/Myxoid Round Cell Liposarcoma with later Recurrence as a Metastatic High-Grade Undifferentiated Round Cell Sarcoma and we review the literature.

ABBREVIATIONS

MC: Mesenchymal Chondrosarcoma; **MRCL:** Myxoid Round Cell Liposarcoma; **ML:** Myxoid liposarcoma; **EMC:** Extraskelatal myxoid chondrosarcoma; **CT:** computerized tomography; **MRI:** magnetic resonance imaging

INTRODUCTION

Mesenchymal chondrosarcoma (MC) is a rare and often aggressive form of sarcoma usually affecting the bones of the spine, ribs, or jaw. MC is a malignant neoplasm known for exhibiting features of primitive mesenchymal cells mixed with islands of cartilage differentiation [1]. Research suggests MC is linked to mutations in the NCOA2 genes and has a female preponderance compared to classical chondrosarcomas which

display a predilection for males. Myxoid liposarcoma (ML) is a neoplasm characterized by myxoid stroma signet ring lipoblasts, regular small round cells and/or a prominent arborizing vascular pattern. ML is characterized by a t(12:16) translocation combining the DDIT3 gene on chromosome 12 with the FUS gene on chromosome 16 [2]. Myxoid liposarcoma represents 30-50% of all liposarcoma cases and usually present with a slow-growing, deep tumor in a lower extremity [3]. An additional characteristic of ML is a round cell component composed of uniform oval-shaped cells and signet-ring cell lipoblasts on a background of myxoid stroma. Presence of the small round cell component in more than 5% of the tumor is indicative of aggressive behavior [4]. When this round cell component is present in more than 5% of the tumor mass, it is called Myxoid Round cell liposarcoma (MRCL), which accounts for approximately 15% of all liposarcomas [4]. MRCL is associated with an unusual pattern of metastasis to bone such as spine and other soft tissues like retroperitoneum, limb, and axilla. We present an unusual case of recurrent sarcoma presented initially as mixed mesenchymal chondrosarcoma/myxoid round cell liposarcoma with prominent small round cell component, which undergone recurrence in form of dedifferentiated small round cell sarcoma.

CASE PRESENTATION

A 41-year-old woman presented with a large 20 x 14 cm right thigh mass, recently enlarging. Imaging studies were compatible with soft tissue sarcoma. The mass was excised, and the pathological examination showed a mixture of histomorphologic features. Some areas displayed biphasic pattern of well differentiated cartilaginous islands distributed among primitive spindle and round cells, typical of histomorphology of a mesenchymal chondrosarcoma (**Figure 1A**). Other areas showed

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lobulated masses formed of numerous signet ring lipoblasts, particularly at periphery of lobules, with mucoid matrix and arborizing vascularity, typical of myxoid liposarcoma (**Figure 1B**). A high grade small round cell component with high mitotic activity was present in more than 25% of the lipomatous tumor (**Figure 1C**). The lipomatous component of the tumor was positive for EWSR1 gene rearrangement, and the non-lipomatous component of the tumor was positive for mutations in the NCOA2 genes. A diagnosis of mixed mesenchymal chondrosarcoma and myxoid liposarcoma with small round cell component was rendered. The excised tumor was present at less than 1 mm from several surgical margins. Post-operative treatment included chemotherapy/radiation.

Two years later, massive metastasis was found around the ovary and omentum, and all over the abdominal cavity. A biopsy from the omental mass showed pathological diagnosis of sarcoma similar to prior sarcoma of the right thigh, but with more dedifferentiated features and predominance of small round cell component. Patient received pre-operative neoadjuvant chemotherapy treatment followed by total excision of the tumor mass. Total excision included the retroperitoneal tumor mass, uterus, right and left ovaries, segment of rectosigmoid colon and the appendix (**Figure 2**). Pathologic examination showed a large hemorrhagic cystic mass measuring at least 8 x 4.5 cm located at

the left para-tubal region infiltrating through the left ovary and extending into the serosal surface of the rectosigmoid colon. A separate retroperitoneal tumor measuring 14 x 12 cm was also excised. Post chemotherapy non-viable tumor was estimated to be 75% of the examined tumor masses (**Figure 1D**). Random samples from different surgical margins were obtained and were negative for tumor. The tumor showed features of a high grade pleomorphic and round cell sarcoma with no specific morphologic differentiation, prominent necrosis was present and mitotic activity exceeded 25 mitosis/10 HPF. A panel of immunohistochemistry studies was performed with the following results; the tumor cells being strongly positive for vimentin, and focally positive for S-100. The tumor cells were negative for pan cytokeratin, EMA, LCA, CD34, Myogenin, Desmin, MDM2, CD56, and CD99.

The tumor was compared with the prior tumor from the thigh and was histomorphologically similar to the dedifferentiated small round cell component of the thigh tumor. The immunohistochemistry pattern was similar in both the primary and the recurrent tumors. Both round cell component of the primary tumor and the recurrent tumor were positive for EWSR1 gene rearrangement, but the recurrent tumor was negative for mutations in the NCOA2 genes. It was concluded that the retroperitoneal metastasis is a recurrent dedifferentiated

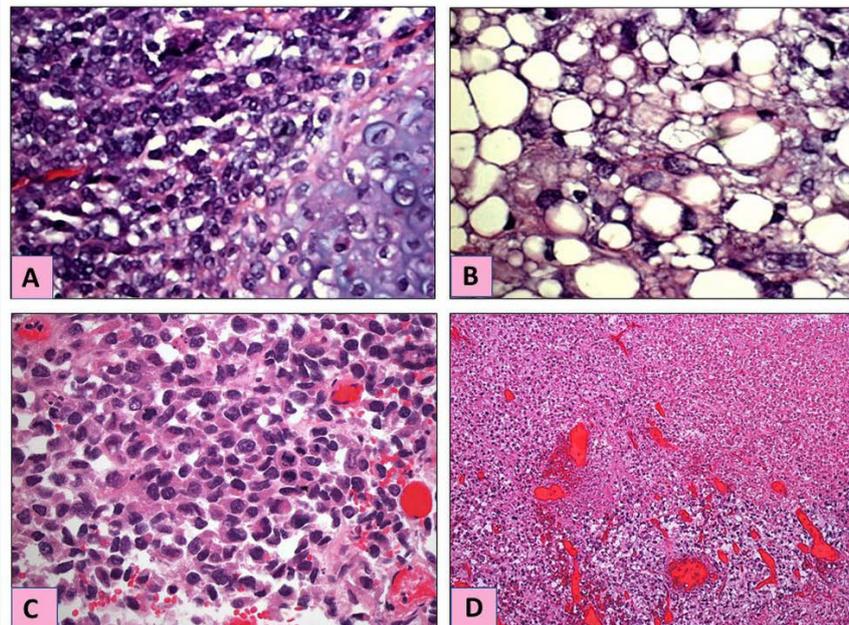


Figure 1 Pathological examination of the tumor.

1A: Primary thigh tumor, well differentiated cartilaginous islands distributed among primitive spindle and round cells, typical of histomorphology of a mesenchymal chondrosarcoma (H&E stain X40).

1B: Primary thigh tumor, lobulated masses formed of numerous signet ring lipoblasts, particularly at periphery of lobules, with mucoid matrix and arborizing vascularity (H&E stain X60)

1C: Primary and recurrent tumors, a high grade small round cell component with high mitotic activity was present in more than 25% of the primary tumor and in the entire recurrent tumor (H&E stain X40)

1D: Recurrent retroperitoneal tumor, post chemotherapy non-viable necrotic tumor was estimated to be 75% of the examined tumor masses (H&E stain X20)

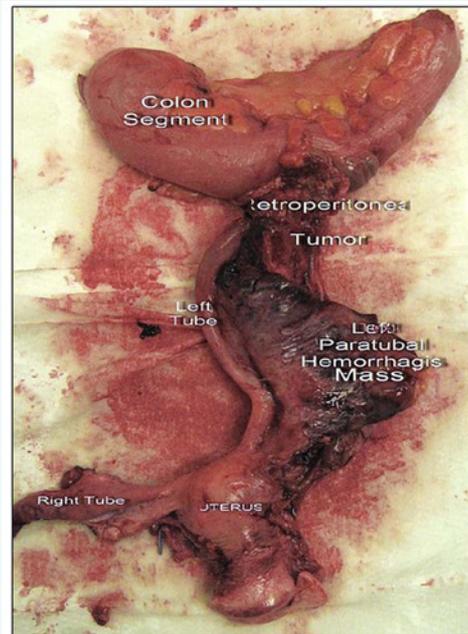


Figure 2 Excised retroperitoneal recurrent metastatic tumor.

form of the original thigh tumor. Post-operative radiation and chemotherapy were administered, and the patient was free of recurrence or metastasis for 6 months after which she expired due to massive metastasis and multiple organ failure.

DISCUSSION

Sarcomas are a rare group of malignancies originating from mesenchymal cells that may arise anywhere in the body [5]. Mesenchymal chondrosarcoma (MC) is a rare malignancy that represents 2% to 9% of all chondrosarcomas and most commonly arises in the second and third decades of life. In comparison to conventional chondrosarcoma, which has a 10-year overall survival rate of 60% to 70%, the mesenchymal subtype is speculated to portend a worse prognosis [6]. Recent meta-analysis of 107 previously reported patients with MC found an overall survival rate at 5 years of 55% and an event-free survival at 10 years of 27% [7]. Recurrence rate in intracranial MC is 63% [8]. Recurrence rate in primary renal MC is unpredictable due to rarity [9]. There is currently minimal data on recurrence rate of generalized MC. Generally, this sarcoma arises from bone, but extra-osseous variants have been known to involve body regions such as visceral organs and meninges. Frequent sites of involvement include the vertebrae, ribs, pelvic bones, and craniofacial bones, with a predilection toward late local and distant recurrences [10]. On unenhanced computerized tomography (CT) lesions indicative of MC appear in homogeneously isodense often with amorphous calcifications or foci of secondary ossifications [11]. On magnetic resonance imaging (MRI) MC appears isointense on T1 Weighted Image (T1WI) and heterogeneously isointense to hypointense on T2 Weighted Image (T2WI). Low signal intensity foci on T2WI appear to correspond to calcifications on CT images [11].

According to a study by Shakked et al. MC biopsies stained positively for vimentin within the mesenchymal component, S100 in the cartilaginous component, and CD99 in the non-cartilaginous component in 100%, 82%, and 67% of cases respectively. In addition, Sox9 may improve diagnostic specificity of MC [12]. The *HEY1-NCOA2* gene fusion is a specific chromosomal aberration for MC and may play a critical role in diagnosis due to its high sensitivity [13]. Physiologically, HEY1 functions mainly as a transcriptional repressor and *NCOA2* encodes a transcriptional coactivator protein for intranuclear receptors. Fusion of HEY1 with *NCOA2* leads to activation of an oncogene specifically associated with MC [14].

The primary treatment for MC is surgical resection. Cesari et al. studied MC patients who achieved complete surgical remission and reported a disease-free survival rate of 76% in those who received chemotherapy and 17% in those who did not receive chemotherapy, suggesting that addition of chemotherapy improves disease-free survival [10]. This notion is further supported by Huvos et al. retrospective study of patients with MC treated with preoperative chemotherapy and which reported that 33% of patients had a complete response, 33% had a partial response, and 3% did not respond [15].

Liposarcomas (LP), the second most common soft tissue sarcomas in adults, arise from adipose tissue [16]. LPs are primarily pure in nature; however, they tend to further dedifferentiate into more sub-categories. They are divided into three different subtypes: well-differentiated, pleomorphic liposarcoma, and myxoid/round-cell liposarcoma [17]. Patients with myxoid liposarcoma (ML) are typically males in their fourth decade of life and present with a slow-growing, deep tumor in a lower extremity [3]. Some MLs can have a round cell



component. ML is described histologically by many different patterns. The classical paucicellular pattern is predominantly myxoid with scant cellularity and arborizing vascularity [18]. Cellular Pattern is defined by layers of uniform round cells which may contain features seen in classical paucicellular. Arborizing, myxoid pattern is noted by a chicken wire appearance of thin-walled vessels throughout the tumor. Signet ring lipoblasts and uniform round cells are hallmarks of myxoid liposarcoma [18]. Immunohistologically, myxoid liposarcomas and MRCL stain with high sensitivity and specificity with cancer testis antigen NY-ESO-1 [23]. Myxoid liposarcoma and MRCL demonstrated 95% immunoreactivity to NY-ESO-1 antigen.

Myxoid/Round cell liposarcoma (MRCL) is understood as a translocation of $t(12;16)(q13;p11)$, leading to the fusion of *FUS*, also known as *TLS*, on chromosome 16 with the entire reading frame of *DDIT3* (also called *CHOP* or *GADD153*) on chromosome 12 [4]. Ultimately, the results of this translocation are still debated. The translocation, however, results in the creation of a fusion protein that is responsible for cell fate decisions which could lead to tumor development. Alternatively, in the “non-instructive” model, only specific cell types are vulnerable to translocation and eventual oncogene activation. In both cases, research shows that secondary events are essential for tumor growth to occur [19]. Three common forms of the *TLS-CHOP* fusion have been described, differing by the presence or absence of *TLS* exons 6–8 in the fusion product. Type I includes *TLS* exon 6 and 7 in the fusion, type II consists of *TLS* exon 1–5 fused to *CHOP* exon 2, and type III fuses *TLS* exons 1–8 to *CHOP* exon 2 [20].

MRCL is one of the most common types of liposarcoma and makes up about 30% of all liposarcoma cases [16]. It is more common in people aged 20 to 40 years old. A significant round cell component is associated with a poorer prognosis. Although these tumors rarely spread, they can recur if not completely removed [21]. In Haniball et al., 12% of patients with MRCL developed a local recurrence at the primary site at a mean of 20 months. The overall risk of recurrence was 12.9% at 5 years and 14.3% at ten years. The risk of local recurrence was also related to the proportion of round cells in the tumour. Of the patients who developed local recurrence, 68% developed metastasis at a mean of 17 months and 91% subsequently died of metastases [22].

Imaging studies showed that some myxoid liposarcomas appear to be cystic at non-enhanced MR imaging, although they enhance similarly to other solid masses at contrast material-enhanced MR imaging [24]. The enhancing areas within the tumor represent increased cellularity and vascularity; the non-enhancing areas represent necrosis, reduced cellularity, and accumulated mucinous material. Gadolinium-enhanced imaging is important in differentiating myxoid liposarcoma from benign cystic tumors. Myxoid liposarcomas exhibit low signal intensity on non-enhanced *T1WI* and high signal intensity on *T2WI* [24]. Histologic characteristics of ML account for the low signal intensity of the lesions on *T1WI*. In contrast, lipomas and well-differentiated liposarcomas typically show high signal intensity secondary to the relatively high fat content. In Sung et al. all but one of 27 myxoid liposarcomas appeared as solid masses with

varying patterns of enhancement at gadolinium-enhanced MR imaging. At non-enhancing imagine, the tumors had a cystic solid mass appearance with intense enhancement [24].

Differentiation from Extraskelatal myxoid chondrosarcoma (EMC) can be also challenging. Nayel Y et al described the considerable challenge in differentiating EMC from myxoid liposarcoma. ML is one of the misleading tumors that are usually on the differential diagnosis resembling EMC and other myxoid tumors, 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, ML is known to be associated with presence of the reciprocal chromosomal translocation $t(12;16)(q13;p11)$ [30]

In ML and MRCL, radiotherapy with or without chemotherapy was associated with a high degree of tumor response. In Chowdhry et al. study, the median percent necrosis for patients who received preoperative radiation therapy was 95%. Necrosis is a direct indicator of pathological response and was inversely associated with histologically intact residual tumor (e.g., 100% necrosis indicates that no histological tumor was left behind) [25]. A complete pathological response was observed in 11.7% of patients. On multivariate analysis, the use of chemotherapy was significantly associated with increased rates of necrosis. However, the addition of chemotherapy did not appear to be associated with improvements in disease-free or overall survival. A current study is investigating treatment with sirolimus and cyclophosphamide on conventional chondrosarcoma, myxoid liposarcoma, mesenchymal chondrosarcoma, and dedifferentiated chondrosarcoma. The results of this study have not been published [26]. In our case, non-viable tumor was estimated to be 75% of the examined tumor masses post chemotherapy/radiation.

Studies have suggested patients with soft tissue sarcoma are at increased risk of developing a second malignancy, most notably of the breast and kidney. Descriptions of patients from families with Li Fraumeni Syndrome may suggest the development of multiple primary sarcomas [27]. Aside from those descriptions, reports on the development of multiple primary sarcomas have been anecdotal [28]. One case reported a neoplasm of mixed mesenchymal and neuroepithelial (glial) origin in a 19-year old man. The combined neoplasm had the gross appearances and microscopic features of giant-cell glioblastoma, giant cell sarcoma, and monstro-cellular sarcoma. This finding suggests that these tumors have a mixed mesenchymal and neuroepithelial component [29].

We present a case of mixed sarcoma with two components including mesenchymal chondrosarcoma and myxoid liposarcoma showing a prominent round cell component greater than 5%. The primary tumor occurred in the thigh and recurred as a wide retroperitoneal metastasis in a purely high-grade round cell form. The primary tumor was positive for mutations in the *NCOA2* genes. Both round cell component of the primary tumor and the recurrent tumor were positive for *EWSR1* gene



rearrangement, but the recurrent tumor was negative for mutations in the NCOA2 genes. Medical literature reporting such mixed sarcoma is limited, and standardized treatment for such tumors is not established yet. We hope that this report drives continued investigation and further development of efficacious diagnosis and safe treatments for improving patient outcomes.

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