International Journal of Research in Medical Sciences
Sarangi PK et al. Int J Res Med Sci. 2016 Oct;4(10):4643-4647
www.msjonline.org
pISSN 2320-6071 | eISSN 2320-6012

DOI: http://dx.doi.org/10.18203/2320-6012.ijrms20163346

Case Report

Multifocal myxoid liposarcoma: a rare and controversial entity-case report with literature review

Pradosh Kumar Sarangi*, Sanjay Kumar Nahak, Sasmita Parida, Jayashree Mohanty, Basanta Manjari Swain

Department of Radiodiagnosis, SCB Medical College and Hospital, Cuttack, Odisha, India

Received: 30 July 2016
Revised: 02 September 2016
Accepted: 07 September 2016

***Correspondence:**
Dr. Pradosh Kumar Sarangi,
E-mail: lipu90sarangi@gmail.com

ABSTRACT

Multifocal soft tissue sarcoma (STS) is a rare and controversial entity, accounting for about 1% of patients with extremity STS and 4.5% of patients with liposarcoma. Multifocal presentation can occur synchronously or metachronously and is defined as the presence of tumor at two or more anatomically separate sites before the manifestation of disease in sites where sarcomas usually metastasize (e.g., lungs, liver, bone). Myxoid liposarcoma is the predominant histological type in multifocal presentation. This matter is debated as to whether this entity represent an unusual pattern of metastasis or multiple separate primary tumors as the differentiation between second primary and metastatic lesions has major clinical consequences. Recent literatures based on molecular biologic analysis of tumor clonal heterogeneity suggest metastatic nature. Multifocal myxoid liposarcoma has an aggressive clinical course with frequent recurrences and poor prognosis. Surgery remains the mainstay of treatment with adjuvant chemo and radiotherapy. Herein we are reporting a case of metachronous multifocal myxoid liposarcoma with multiple tumor sites (bilateral breasts, anterior chest wall, anterior abdominal wall, right shoulder area, left thigh etc.) which developed after one year of lumpectomy of myxoid liposarcoma of left breast. A recent review of literature pertaining to its unusual metastatic character, imaging and pathologic features is made.

Keywords: Myxoid liposarcoma, Multifocal, Metastasis, TLS-CHOP fusion, Metachronous

INTRODUCTION

Myxoid liposarcoma is the second most common type of liposarcoma and represents 20%-50% of all liposarcomas. Some of these myxoid liposarcomas may have multifocal presentation and follow an aggressive clinical course. Multifocal soft tissue sarcoma (STS) is a rare clinical entity occurring in 1% of patients with extremity soft tissue sarcoma and in 4.5% of patients with liposarcoma.[1,2]

Multifocality in STS is defined as the presence of sarcoma at two or more anatomically separate sites before the manifestation of disease in sites where STSs most commonly metastasize such as the lungs.[2,3] The first reported case of multifocal sarcoma dates back to 1934, when Siegmund described a case of multiple primary malignant fatty tumors in a male patient of 65 years in whom the first tumor was noted in the soft tissue of the thigh.[4]

At autopsy, there were numerous individual fatty tumors arising within the pleural cavity, omentum, mesentery, serosa of small and large intestine, along the aorta, surrounding both kidneys, in the soft tissues of the back, thigh and upper arms, the subepicardial fat and in the bone marrow. He interpreted this entity as a systemic malignant disease of the soft tissue and coined the term

"Lipoblastische Sarcomatose". Since then many case studies have been described and controversy exists as to whether this entity represents multiple separate primary tumors or is simply an unusual pattern of metastasis. Recent literatures are in favour of the monoclonal origin of multifocal myxoid liposarcoma, establishing the metastatic nature of distant soft tissue lesions.[1-3,13,14]

A systemic review was done from searching relevant articles from electronic database of medline and google. The database was searched with the terms "multifocal liposarcoma" and "multifocal myxoid liposarcoma". Emphasis was given on recent literature. We found few literatures mostly in the form of clinical case studies. Analysis was done with regard to imaging features, cytogenetics, pathologic features and their characteristic pattern of spread to distant sites. A case report from our institution is also illustrated.

CASE REPORT

A 50 year old female patient presented to our department with a huge lobulated ulcerative growth (20×15 cm) affecting left breast and anterior chest wall of two months duration. She also complained of multiple soft tissue swellings involving anterior abdominal region, left breast, and right scapular region.

She had history of lumpectomy of left breast mass one year back which was found to be myxoid liposarcoma on histopathology. Patient remained asymptomatic for almost ten months thereafter now presenting with multiple soft tissue swellings.

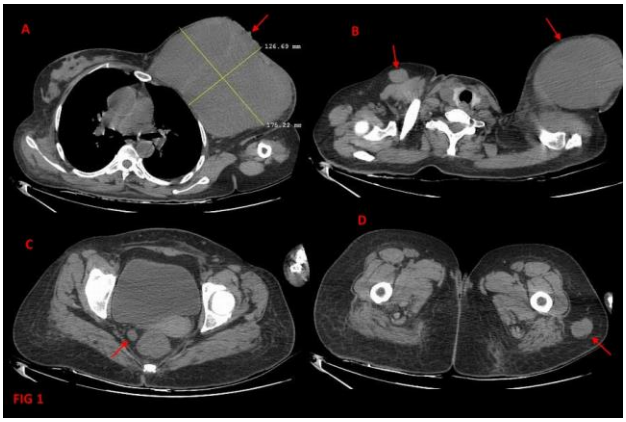

Figure 1: Axial non-contrast CT showing multiple low attenuating lesions in different regions (arrows) with attenuation lower than that of adjacent muscles. Due to high water content of the lesions; the largest one is noted in left breast. There is no intrathoracic extension. No foci of calcification noted.

Punch biopsy of breast lump revealed myxoid liposarcoma. A whole body Computed tomography was done to look for additional sites of tumor. On computed tomography (Figure 1 and 2), the lesions in breast and anterior abdominal wall had slightly lower attenuation to that of muscle and showed peripheral nodular enhancement. Similar looking lesions were found in anterior abdominal wall, left gluteal region, left thigh, left perinephric region, right pericolic region. No hepatic, lung or bone metastases were found. Punch biopsy of right breast lump and one of the anterior chest wall lesions also revealed myxoid liposarcoma. Hence a clinical diagnosis of metachronous multifocal myxoid liposarcoma was made.

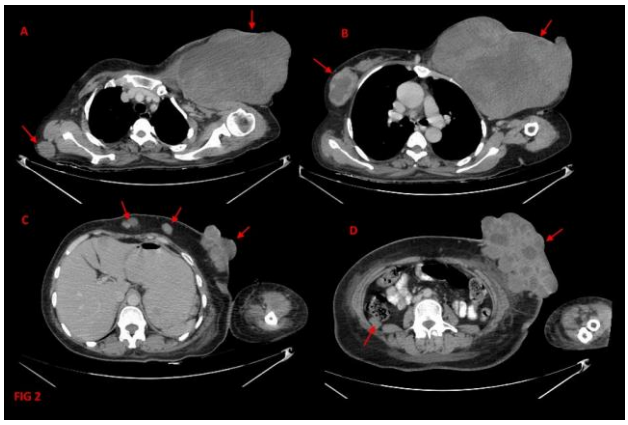

Figure 2: Axial contrast CT showing peripheral nodular enhancement of the lesions (arrows).

Other lesions were assumed to be of same pathology and biopsy of these lesions was not done. Neoadjuvant chemotherapy with 6 courses of ifosfamide 5 g/m^2 and doxorubicin 50 mg/m^2 was started. She is now being planned for bilateral mastectomies. The patient was in good general health throughout treatment course.

DISCUSSION

Liposarcoma represents the second most common type of soft-tissue sarcoma, exceeded only by fibrous and fibrohistocytic malignancies, frequently arising in the superficial and deep soft tissues of the extremities and the retroperitoneum.[5] The World Health Organization classification (2002) categorizes these tumors in five histological types such as well-differentiated, dedifferentiated, myxoid/round cell, pleomorphic, and mixed types.

Myxoid liposarcoma is the second most common type of liposarcoma having intermediate prognosis between between well-differentiated tumors and pleomorphic ones. But multifocal myxoid/round cell liposarcoma is a rare entity having poor prognosis. Myxoid and round cell tumors share the same cytogenetic abnormalities [translocation t (12;16)(q13;p11)], hence considered as a continuum of the same disease with round cell tumors having poor prognosis.[5-8]

No significant differences is seen in sex predilection, age, grade, and depth margins between multifocal and

unifocal disease.[6] The prevalence of apparent multifocal disease in liposarcoma at approximately 10%. The development of multifocal disease can be synchronous or metachronous with metachronous presentation being more common.[2,3,6,7] De Vreeze et al, reported that 12 out of 15 (80%) patients included in their study presented with metachronous multifocal disease and only 3 patients (20%) had synchronous disease.[2]

Cytogenetics

The cytogenetic hallmark of myxoid liposarcoma is the formation of a fusion oncogene FUS-CHOP (also called TLS-CHOP) resulting from t(12; 16)(q13;p11) in at least 95% the cases.

The CHOP gene is implicated in adipocyte differentiation and growth arrest. The presence of TLS-CHOP fusion is highly sensitive and specific of myxoid/round cell liposarcomas. In few cases, a variant chromosomal translocation has been described, t(12;22), resulting in an EWS-CHOP fusion.[1-3,7,14] The TLS-CHOP protein is thought to function primarily as an aberrant transcriptional regulator that interferes with adipocyte differentiation.[3]

The debate – multiple primaries or metastasis?

Less than 50 cases have been reported in the literature since the original description of this disease by Siegmund in 1934, mostly in the form of clinical case studies. The largest series was reported by Enzinger and Winslow in 1962. They found 20 cases of liposarcomas with multifocal presentation from their study of 103 cases of liposarcomas.[1,17]

The debate as to whether this entity represents separate primary tumors or is simply an unusual pattern of metastasis from one primary lesion is not fully resolved. This differentiation has important clinical implications. A resectable second primary tumor would indicate an optimal surgical approach combined with (neo) adjuvant chemoradiotherapy with curative intent, whereas in metastatic disease, the choice of treatment, surgery, radiotherapy, or chemotherapy is made with a limited expectation of ultimate cure with guarded prognosis, predicting other metastases in the near future.[1,2]

A clonal relationship between two tumors proves their common origin in case of metastases. Conversely, the absence of a clonal relationship would suggest a second primary sarcoma.[2,3] The clonality of multifocal disease can't be deduced from histological features alone.

The reason is that tumor foci from different anatomical locations in multifocal presentation may have different histological grades (e.g., low-grade myxoid versus high-grade round cell). So the analysis of the genomic rearrangements of TLS, CHOP, or EWS as clone-specific markers is essential to distinguish true multifocal (multiclonal) sarcoma from a metastatic (monoclonal) sarcoma.

Many authors carried out genetic analysis and confirmed monoclonal origin of multifocal myxoid liposarcoma, hence supported the metastatic nature of multifocal liposarcomas.[2,3,13,14] Still some facts are not fully explained as argued by previous authors. They described these lesions as mutiple primary malignant fatty tumors.[4,11,12]

Previous arguments in favour of multicentric nature

1. There is argument that that detection of the same cytogenetic anomalies(i.e. monoclonality) in different sarcomas cannot be considered indicative of metastatic spread because they propose that this finding could be related with a common etiologic factor, such as a systemic illness or toxicity.[7-10] A parallelism has been drawn between this phenomenon and multiple subcutaneous nodules in patients with neurofibromatosis.[4,17] Ackerman conceptualised that adipose tissue should be considered as a single organ and it is subjected to its own diseases.[11]

According to Tedeschi's concept of "pluri-centric anlage", this might be due to incidental stimulation of undifferentiated mesenchymal cells due to altered lipid metabolism.[12]

2. Secondly the multicentric tumors tend to spare classical metastatic sites of sarcomas like the liver, the lungs or the bones and affect rare and unusual sites like pleura, lymph nodes, retroperitoneum, mesentery and soft tissue of the trunk and glutei.[8-10] This unusual pattern of metastasis might represent an intrinsic property of this subset of myxoid liposarcoma.

3. Thirdly, a long interval between the primary and subsequent tumors would rather support a multicentric origin.[1]

Table 1 summarizes the conclusions drawn by different authors. In the last decade studies involving analysis of the genomic rearrangements of TLS, CHOP, or EWS genes are favouring the metastatic character of this entity. However, there is still certain amount of uncertainty whether the disease is multifocal or metastatic. More studies are needed to reach a consensus about the metastatic nature of this entity.

Imaging features

Myxoid liposarcomas are usually large, well-defined, and multilobulated lesions. The high water content of the lesion leads to predominant low attenuation on CT images, low signal intensity on T1-weighted MR images, and marked high signal intensity on T2-weighted MR images.

Fat may not be appreciable in all cases and typically constitutes only a small volume of the overall mass size (10% of the lesion) and is often seen in septa (lacy or linear pattern) or as subtle small nodules in the lesion. MR imaging is superior to CT in depiction of fat. Myxoid liposarcomas with more prominent round cell components may demonstrate areas of relatively lower water content at CT and MR imaging with attenuation similar to that of muscle on CT scans, and intermediate signal intensity on T1- and T2-weighted MR images. On contrast administration, it shows peripheral nodular (61% of cases), central nodular (44%), and diffuse (17%) type enhancement. Calcification is less common than with well-differentiated liposarcoma.[5]

Table 1: Conclusions drawn by different authors.

Author	Year	Conclusion by authors
Fahr T et al[11]	1925	Metastasis by Fahr, later proposed to be multiple primaries by Nienhuis JH et al
Nienhuis JH et al[11]	1925	Mutiple primary malignant fatty tumors
Siegmund[4]	1934	Mutiple primary malignant fatty tumors
Goormaghtigh et al[11]	1936	Mutiple primary malignant fatty tumors
Ackerman LV[11]	1942	Mutiple primary malignant fatty tumors
Tedeschi CG[12]	1946	Multiple primary tumors
Silva DC et al[7]	1994	Multiple primary tumors
Fernandez-Acenero MJ et al[8]	2007	Unproven
Pearlstone DB et al[9]	1999	Unproven
Blair SL et al[6]	1998	Unproven
Schneider-Stock R et al[14]	1999	Metastasis
Xavier conesa et al[10]	2011	Unproven
#Lopez-Anglada Fernandez E et al[13]	2008	Metastasis
#de Vreeze R et al[2]	2010	Metastasis
#Antonescu CR et al[3]	2000	Metastasis
#Nikolaos S. Salemis et al[1]	2014	Metastasis

carried out by molecular biologic analysis of tumor clonal heterogeneity supported unusual metastatic behavior rather than multifocal character.

Pathologic features

Gross and microscopic appearance depends on relative proportion of myxoid and round cell components. Predominantly myxoid lesions are gelatinous. Lesions with predominant round cell component have a nonspecific, white fleshy appearance similar to that of other soft-tissue sarcomas

Histologically, they are characterised by well-delineated lobules of myxoid tissue and primitive uniform mesenchymal cells with variable numbers of usually monovacuolated and sometimes bivacuolated lipoblasts with scant mitoses. Round cell components have higher mitotic activity, necrosis, increased cellularity and often juxtaposed to myxoid component, hence considered as histologic continuum of same disease.[1,5]

Clinical course and treatment

Though myxoid liposarcoma tends to follow a relatively indolent clinical course, multifocal presentation has aggressive clinical course and poor prognosis. Myxoid liposarcomas are associated with a high tendency for extrapulmonary metastases (three times as common as pulmonary metastasis).[9,16] The most commonly affected sites include the retroperitoneum, abdomen, bones, liver, back soft tissues, pleura, chest wall, and pericardium. So a through clinical examination and complete imaging study (CT scan of thorax, abdomen, pelvis, bone scan) is needed to look for other synchronous or metachronous lesions. Complete tumor resection with clear margins is the treatment of choice which can be combined with chemotherapy (anthracyclines and ifosfamide usually) and radiotherapy.[1,8,10] Despite optimal treatment, multifocal variety has a significantly worse prognosis.[3,6,8,10,13]

The poor prognostic indicators are presence of >5% of round cell component, high-histological grade, presence of necrosis and P53 overexpression.[15,16] Since the recent literatures are favouring metastatic nature of multifocal myxoid liposarcoma, management should be tailored for metastatic disease. Primary curative approach by optional surgical resection combined with radiotherapy for these second tumors would probably not be rational, because the metastatic character of the disease will became clear shortly thereafter.[2]

CONCLUSION

Recent literatures on multifocal myxoid liposarcoma suggest metastatic nature rather than separate primary tumors. However large case series studies are needed to confirm it. Treatment should be tailored as if it is metastatic disease. Multifocal myxoid liposarcomas have aggressive clinical course than unifocal disease.

These tumors have a tendency to spread toward extrapulmonary sites frequently without pulmonary metastasis. Hence a through imaging and clinical examination are necessary to look for other lesions in preoperative evaluation and postoperative follow-up of these patients.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Sarangi PK, Nahak SK, Parida S, Mohanty J, Swain BM. Multifocal myxoid liposarcoma: a rare and controversial entity-case report with literature review. Int J Res Med Sci 2016;4:4643-7.