

CASE REPORT

Rarest of the Rare – Malignant Solitary Fibrous Tumour of the Breast: Case Report and Literature Review

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ABSTRACT

Malignant solitary fibrous tumor of the breast is one of the rarest types of breast malignancy. To the best of our knowledge, only six cases have been reported so far. Here we have presented such a case from India, where a 52-year-old lady presented with a 10 cm x 8 cm breast lump. Diagnosis was achieved with the help of FDG PET, histopathology and immunohistochemistry, which showed nuclear positivity for STAT6. Fluorescent in situ hybridization (FISH) molecular study for SS18-SSX was used to rule out the differential diagnosis of synovial sarcoma. Guidelines for the management of this type of breast malignancy still do not exist. We have done a review of the literature in order to discuss which might be the best management in such cases. Evidence on this very rarest type of breast malignancy is still evolving. The interest in the case described here relies on its rarity, difficulties in achieving diagnosis and formulation of the proper management.

Keywords: cancer, breast, solitary, fibrous, tumor.

INTRODUCTION

Solitary fibrous tumors (SFTs) are rare neoplasms of mesenchymal origin, accounting for <2% of all soft tissue tumors (1). This tumour, previously known as hemangiopericytomas, has been classified as having intermediate biologic potential, characterized by a relatively indolent clinical course with a low risk of metastasis (2). Solitary fibrous tumors were first described as originating

from the pleura by Klemperer and Rabin in 1931 (3), but now has been documented at many extra-pleural sites (1, 2, 4). Breast SFT is rather unique, with less than 50 cases reported in the literature worldwide. In India, till date only one case of breast SFT was reported, which was benign (5). Malignant SFT of the breast is extremely rare, with only six cases worldwide (6-11). Here we have described the clinical presentation, evaluation and management of malignant SFT of the breast in a lady from central India with the

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review of literature for the latest diagnosis and management options. The diagnosis of an extrapleural SFT may be challenging due to its rarity, and requires an integrated approach including, histological, immunohistochemical and even molecular studies. ❑

CASE REPORT

Clinical history

A 52-year-old para 2 living 2 (P2L2) post-menopausal woman presented with a lump in her left breast, which was noticed six months before presentation. It was initially painless and slowly growing, but over the last month it became rapidly progressive with continuous dull aching pain. No skin or nipple-areola involvement was seen. Her past medical history was unremarkable. Also, there were no history of suggestive systemic spread and no significant family or menstrual history. Physical examination (Figure 1) revealed a well-defined lobulated surface with variable consistency, non-tender, freely mobile lump measuring 10 x 8 cm which was involving the upper outer and inner quadrant in the left breast with no nipple discharge, skin or chest wall involvement and with ipsilateral palpable single freely mobile non-tender central axillary lymph node. The contralateral axilla was normal.



FIGURE 1. 10 x 8 cm mass with lobulated surface involving the upper outer and inner quadrant in the left breast

Radiological investigation

Mammography (Figure 2) of both breasts showed a well-defined lobulated dense lesion in the superior lateral and superior medial part of the left breast. No evidence of spiculation or microcalcification was present. Complementary USG showed

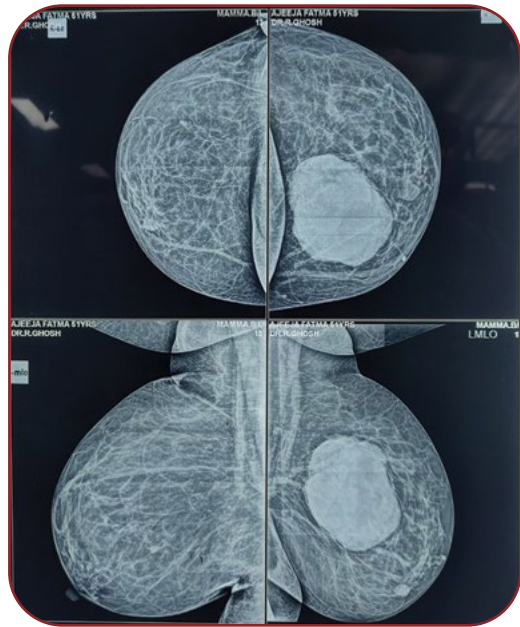


FIGURE 2. Mammography of both breasts showing well-defined lobulated dense lesion in the superior lateral and superior medial part of the left breast - BIRADS IVb

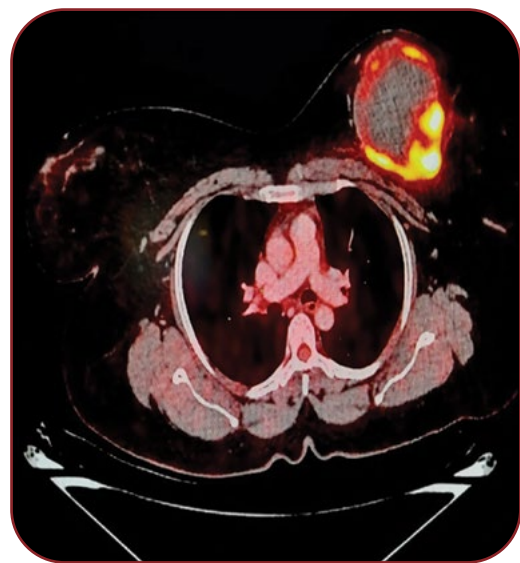


FIGURE 3. FDG PET CT scan showing an FDG avid lesion (SUVmax 22.4) involving all quadrants of the left breast

a large well-defined lobulated solid cystic lesion of 86 x 84 x 63 mm in the left breast at 10/1'0 clock position with foci of internal vascularity in the solid component, which was suggestive of neoplastic etiology – BIRADS IVb.

A PET CT scan (Figure 3) showed an FDG (2-[fluorine 18]fluoro-2-deoxy-d-glucose) avid sizeable soft tissue density mass measuring ap-

proximately 8.4(AP) x 7.6(TR) x 8.8(CC) cm [maximum standardized uptake value (SUVmax) 22.4], which was involving all quadrants of the left breast. There were areas of hypometabolism suggestive of necrosis. Fat planes with the overlying skin and pectoral muscles were maintained. Faint FDG avid left level I and II ipsilateral axillary lymph nodes (SUVmax 1.7) was present – likely reactive. No abnormal FDG uptake in the contralateral breast, bilateral internal mammary and bilateral supraclavicular regions was noted.

Tissue diagnosis

The examined core-needle biopsy sections showed linear cores displaying infiltration by the tumor arranged in fascicles and sheets. Staghorn blood vessel was surrounded by tumor cells with moderate pleomorphism and cytoplasm, predominantly spindle-shaped nuclei and bland hyperchromatic chromatin. Occasional bizarre cells were present. Mitosis was 8/10 HPF. Foci of necrosis were seen.

Immunohistochemistry (IHC) showed tumor cells positive for STAT6 (diffuse nuclear positive), SMA (diffuse positive), MSA (diffuse positive), BCL2 (patchy focal positive) and negative for S100, PanCK, CD117, CD31, Desmin, Caldesmon; CD 34 highlighted blood vessels. Reticulin was used as a special stain, which showed pericellular fibrosis. Provisional impression (as per core needle biopsy): malignant SFTs.

Management

There are no available specific guidelines for managing malignant SFT of the breast in the entire English literature. Hence, after a proper discussion with the patient and considering the tumor size as well as the chance of aggressive behaviour, including recurrence and lymph node metastasis, it was decided to go for modified radical mastectomy (MRM) of the left breast.

The tumor (Figure 4) (7×8×6 cm³) was well-circumscribed and firm, with the complete capsule. The section of the tumor was white-grey with areas of necrosis. Microscopic examination (Figure 5) revealed a well-circumscribed hypercellular tumor comprising fascicles of spindle cells with scant cytoplasm, oval to round prominent hyperchromatic nuclei, vesicular chromatin and prominent nucleoli. Bizarre nuclei were seen. Mitosis 4-5/ HPF and extensive hyalinization and staghorn vessels were noted. Areas of necrosis

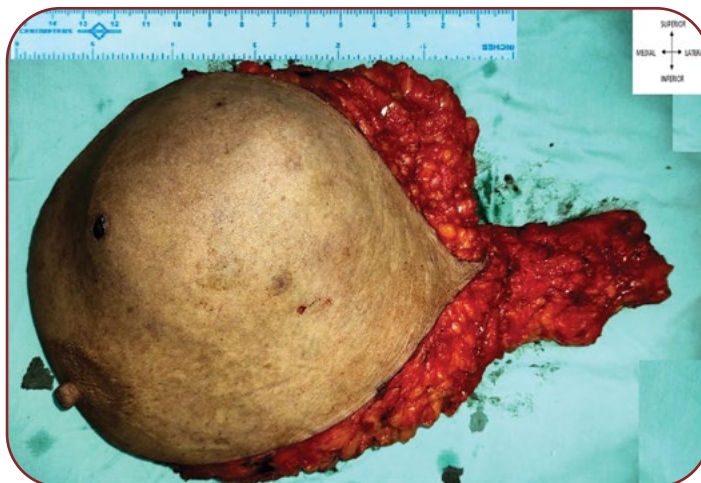


FIGURE 4. Tumor removed by left modified radical mastectomy

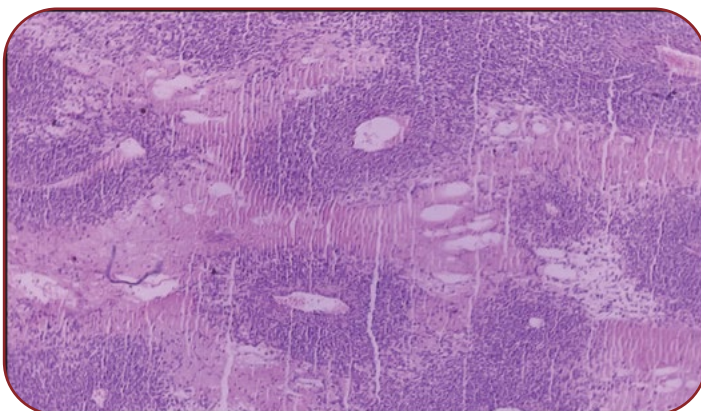


FIGURE 5. H & E, 4X - Perivascular arrangement of tumor cells & necrotic areas.

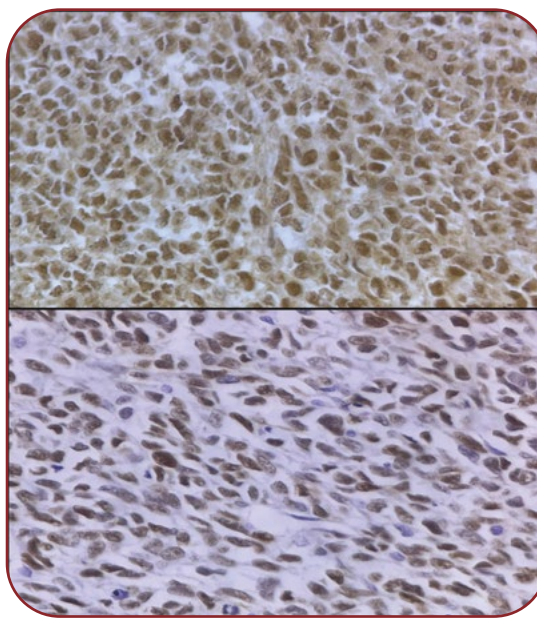


FIGURE 6. Immunohistochemistry 40X showing diffuse nuclear positivity for STAT6 (up) and TLE1 positivity (down)

were also seen. Perivascular arrangement of tumor cells was also noted. Surgical margins were

tumor free. No lymphovascular, perineural or dermal lymphatic invasion were present. No axillary lymph node was positive for micro/macro metastasis. Immunohistochemistry (Figure 6) showed that the tumour was positive for STAT6, TLE1, EMA (focal) and BCL2, but negative for panCK, p63, CD34, CD99, beta-catenin, SOX10, calretinin, myogenin and myoD1.

Diagnostic approach followed

Based on histology, the diagnosis of malignant spindle cell tumor was made and accordingly, immunohistochemistry (IHC) was done. Based on IHC findings, two differential diagnoses were considered: 1) synovial sarcoma (SS) and 2) malignant SFT.

Synovial sarcoma was considered because IHC for TLE1 was positive. Diffuse, moderate to strong nuclear expression of TLE1 is seen in the majority of SS (12), but a minority of SFTs can also express TLE1. Another thing to note, SS is usually positive for EMA, BCL2 and CD99 (13). But in our case, EMA and BCL2 were only focally positive, while CD99 was negative. So, to confirm the diagnosis of SS, the “gold standard” molecular studies (FISH) for SS18-SSX (14, 15) was done, which turned out to be negative. Hence, SS was ruled out.

Solitary fibrous tumor was also considered since IHC for STAT6 had diffuse nuclear positivity. The demonstration of a diffuse and strong STAT6 nuclear staining is beneficial in distinguishing SFTs from other spindle cell mimics arising in the breast (7). Hence, based on diffuse nuclear positivity for STAT6, the diagnosis of malignant SFT was made. ■

DISCUSSION

Classification and epidemiology

The current WHO classification of soft tissue and bone tumors (16) has classified SFT as a fibroblastic/myofibroblastic neoplasm with intermediate (rarely metastasizing) and malignant variants. Although SFTs most commonly occur in the pleura, numerous extra-pleural sites of involvement have been reported mainly in the abdomen, followed by the trunk, head-neck, extremities and intracranial (17). Very few cases of SFTs are described in the breast, with most of them being benign (9), and the literature search shows that to date only there are only six reported cases of ma-

lignant SFT in the breast. The management and prognosis of benign SFTs differ from its malignant variants and its mimics, and correct diagnosis is therefore essential. In general, extra pleural SFTs can present anywhere between the third to seventh decades of life (1, 4, 17), with a peak of incidence in the fifth and sixth decades. Malignant SFT of the breast has been reported in the age group of 38-78 years and all in females (6-11).

Clinical and radiological diagnosis

Solitary fibrous tumors generally present as slowly growing painless masses or may generate symptoms due to mass or pressure effects on adjacent structures. They may also present with paraneoplastic syndromes (1, 17, 18). The radiologic findings of SFTs are non-specific. Most of the available case reports have described breast SFT as a well-circumscribed mass on the mammogram and a hypoechoic mass with vascularity on the sono-mammogram. Our patient had a well-circumscribed mass on the mammogram and a well-defined lobulated solid cystic lesion with foci of internal vascularity on the sono-mammogram with a BIRADS of IVb. Riola-Parada *et al* (11) reported the uptake of 18F-FDG (SUVmax 8.8) in a case of malignant breast SFT on FDG-PET. Our patient had a pathological uptake (SUVmax 22.4) involving all quadrants of the left breast, with areas of hypo-metabolism within the lesion suggestive of necrosis, and therefore suggesting that FDG PET could be valuable in differentiating malignant breast SFTs from benign variant.

Histopathological diagnosis

Histopathological diagnosis of SFT can be challenging and requires an integrated approach, including clinical, histological, immunohistochemical and molecular findings.

Gross pathology and microscopic features

Grossly extra pleural SFTs share the same morphological features as the pleural cases and breast SFTs are similar. Macroscopically, breast SFTs are usually well-circumscribed and often capsulated masses with a firm consistency. There might be areas of infiltration into the surrounding muscle or adipose tissue. Histologically it demonstrates hypercellular spindle shaped tumor cells with “stag-horn” blood vessels and loss of normal ductal and lobular breast architecture. Areas of fibrosis can be present (6, 7, 9, 11).

Immunohistochemistry

To arrive at a specific diagnosis in spindle cell tumors, IHC is essential. On IHC, SFT typically shows a diffuse and strong expression of CD34, BCL2 and CD99 (18). However, many studies have demonstrated the poor specificity of these markers. In our case, BCL2 was focally positive, but CD99 and CD34 were negative. The negativity of CD99 and CD34 might be attributed to the malignant variant in our case, as these might get lost during malignant transformation (18, 19). Recently, it has been demonstrated that NAB2-STAT6 fusion gene was present in almost all cases of SFT, implying that this mutation was a primary and presumably pathogenetic event in SFT development, irrespectively of the anatomic site of origin and morphologic subtype (17, 18, 20). At present, detection of STAT6 on IHC is essential to clinch the diagnosis. Demicco et al demonstrated that STAT6 expression in SFT was exclusively nuclear (21), while other tumors may express this marker in both nuclear and cytoplasmic components. NAB2-STAT6 gene fusion results in strong nuclear expression of STAT6 (22); hence, antibodies against STAT6 can be used as reliable surrogates for the detection of the NAB2-STAT6 fusion gene. The sensitivity and specificity of STAT6 for the diagnosis of SFT was 91% and 75%, respectively (23). G. Magro et al investigated the expression of STAT6 in uncommon spindle cell tumor lesions occurring primarily in the breast parenchyma and confirmed the validity of STAT6 as surrogates in lesions arising from breast parenchyma (24), thereby underscoring the importance of STAT6 in the diagnosis of breast SFTs.

However, it must be kept in mind that STAT6 is not absolutely specific to SFT, since it is very often absent in dedifferentiated forms, while it may be present in other morphologic mimics of SFT, including well-differentiated SSs or dedifferentiated liposarcomas and desmoids fibromatosis (18, 21).

Therefore, other diagnoses must be ruled out based on their specific markers. The expression of GRIA2 and ALDH1 protein is another marker that might be helpful for SFT (20, 23).

Fluorescence in situ hybridization is not useful (20) for demonstrating the NAB2-STAT6 fusion gene because of the constitutional proximity of the two genes, so it can only identify a small fraction of fusion-positive cases. Reverse transcriptase-polymerase chain reaction (RT-PCR) is required, and multiple primer combinations are needed to identify all possible fusion transcripts. Thus, molecular approaches are still of no practical use while immunohistochemical detection of STAT6 nuclear expression shows high specificity and sensibility in addition to cheapness and practicality. But FISH can still play a role in excluding other common differentials like synovial sarcoma (15).

Treatment

For extra-pleural SFTs, wide surgical resection represents the standard therapy for localized disease, while the routine use of adjuvant radiotherapy might improve local control but has not been shown to prolong overall survival (17, 18, 25). Drugs like sunitinib might be promising but need further evaluation (26), while the role of other medications remain questionable (17). There are no specific guidelines for malignant breast SFTs and most cases are reported to have been treated by modified mastectomy or lumpectomy. Therefore, the risk of lymph node metastasis for malignant SFTs is estimated to be < 5% (27) in absence of documented metastasis at the time of presentation, and we believe that resection to negative margins might be adequate particularly for smaller tumors. Our patient had a large tumor which was approached by modified radical mastectomy, and no postoperative adjuvant therapy was given as currently no benefits have been demonstrated for

Serial no.	Reported cases	Patient age (years)	Tumor dimensions (cm)	Surgical management
1	Nitta (6)	78	3.1	Left modified mastectomy
2	Barco (7)	72	2-3	Wide excision
3	Wang (8)	48	25 x 20 x 8	Mastectomy with sentinel lymph node biopsy
4	Jung (9)	75	4.5-5	Surgical resection (left breast)
5	Yang (10)	52	2-3	Lumpectomy
6	Riola Parada (11)	38	5.8	Lumpectomy right breast
7	Our case	52	10 x 8	Left modified radical mastectomy

TABLE 1. Management of malignant solitary fibrous tumors of the breast

the same. The management of malignant breast SFTs reported so far, including the case described by us, is summarized in Table 1.

Prognosis

While the majority of SFTs behave in an indolent manner, the behaviour of SFTs is unpredictable and chance of recurrence and hematogenous or lymphatic metastasis is present (27, 28). Since clinically aggressive classical SFTs cannot be morphologically distinguished from those that will behave indolently, it is crucial that patients with SFTs are followed up on a long-term basis. So far, no recurrences, metastasis or mortality among the cases of malignant breast SFTs have been reported so far. Overall, considering that survival in SFT has been reported to be rather high (17), it can be expected that malignant breast SFTs have better prognosis than other forms of breast cancer.

EG Demicco et al proposed a risk stratification model to predict the outcome of SFT based on patient's age, tumour size, mitotic count (/10 high-power fields) and tumor necrosis, with the total score being used to classify patients into low, intermediate- or high-risk groups for development of metastasis in SFT (2). As per this model, our patient comes under intermediate risk of metastasis.

Our patient had an uncomplicated postoperative course. No chemotherapy or radiotherapy was given as it had no beneficial outcome. She is doing well, without any evidence of recurrence/metastasis eighteen months after surgery. The patient is on regular follow up in an outpatient basis. □

CONCLUSION

Benign SFT of the breast is very uncommon, but its malignant variant is extremely rare, with only six reported cases worldwide to the best of our knowledge. This is the first case report from India. Most patients present with tumor localized in the breast without any axillary spread. There are no pathognomonic imaging findings, and a preoperative diagnosis tissue diagnosis with histological and immunohistochemical analysis is essential for adequate characterization of the lesion. Currently, IHC confirmation depends on the detection of nuclear positivity of STAT6. Molecular studies (FISH) may be required to rule out other differential diagnosis. At present there are no guidelines regarding treatment but resection to negative margins might be adequate if there is no obvious metastasis. In case of larger tumors, mastectomy might be required. The role of radiotherapy and chemotherapy is still evolving. Long term follow-up of this patients is required to monitor for recurrence or metastasis, despite her low risk. □

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