Primary Fat-forming solitary fibrous tumor with focal atypical features of the breast. A case report and literature review

Yufei Liu (402762573@qq.com)
China Three Gorges University
Mingjie Zhang
China Three Gorges University
Xiaoli Shui
China Three Gorges University
Daizhong Wang
Hubei University of Medicine
Chunyu Cao
China Three Gorges University Medical college
Zhi Yao
Yichang Central People's Hospital
Junlong Pan
Yichang Central People's Hospital

Case Report

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Abstract

Background: Primary solitary fibrous tumor (SFT) in breast is rare, while breast fat-forming solitary fibrous tumor (FFSFT) is even more rare in clinic. Here we reported a case of FFSFT with focal atypical features of the left breast, and present the clinicopathological features, molecular features and pathological diagnosis.

Case presentation: A 51-year-old female patient underwent breast surgery in clinic of our hospital with a 6 month of a palpable painless left breast mass. Imaging examination of the breast revealed a 3.4 cm ×1.9 cm ×1.7 cm solid mass originating from her left breast. Then the patient underwent left breast lumpectomy in the tumor area, and postoperative pathological result confirmed the diagnosis of FFSFT with focal atypical features deriving from breast. The additional treatment such as chemotherapy or radiotherapy were not provided. The patient remains with no evidence of disease recurrence or metastasis in 3 months of follow-up.

Conclusion: Primary breast FFSFT is very rare and easy to be confused with other soft tissue tumors. The definitive diagnosis of primary breast FFSFT should base on histopathological morphology, immunophenotype and molecular detection.

Background

Solitary fibrous tumor (SFT), which was described for the first time by Klemperer and Rabin in 1931, is rare mesenchymal neoplasm that have been known to mainly affect the pleura and mediastinum. Since its initial description, SFT has been reported at almost every anatomic site [1], but rarely reported in breast. To date, only 32 cases of breast SFT have been reported as single cases or small case series in English literatures (summarized in Table 1) [2–27]. Here, we presented a rare case of breast fat-forming solitary fibrous tumor (FFSFT) with focal atypical features and discussed its clinicopathological features, diagnosis and differential diagnosis. To our knowledge, FFSFT originating in the breast have not been reported in English literatures.

Case Presentation

A 51-year-old chinese woman went into breast surgery with a 6-month history of a palpable painless left breast mass. The histories of chronic disease, including tumor, breast trauma and the family history of breast or ovarian cancer, or other malignancy were denied. On physical examination, there was a soft mass at the 12 o'clock position (about 3 cm from the nipple) of the left breast with a maximum diameter of 3.4 cm. No skin change or nipple dischargewas observed, nor there were any palpable axillary or supraclavicular lymph nodes.

The patient underwent breast ultrasonography (US) examination and demonstrated a 3.4-cm-sized oval, well-circumscribed, hypoechoic solid mass at 12 o'clock of the left breast. Color Doppler US showed some peripheral and internal color flow signals (Fig. 1a). The mass was not contiguous with the pectoralis major muscle. Considering its morphology, the mass was classified as BI-RADS 4A. Magnetic resonance imaging (MRI) showed a focal lobulated solid nodular lesion with a maximum diameter of 3.4 cm at the 12 o'clock positionof the left breast, with geographical enhancement and no architectural distortion (Fig. 1b). The lesion was classified as BI-RADS 4B. As the mass was highly vascularized, and considering the wishes of the patient, core needle biopsy was not attempted, The patient underwent left breast lumpectomy in the tumor area, and surgical margins were tumor-free.

Grossly, the tumor removed and sent for pathological examination was a well-defined solid nodule without capsule measuring 3.4 cm ×1.9 cm ×1.7 cm, the cut surface of the tumor was brown-gray, with slightly tough texture; no necrosis or hemorrhage was evident (Fig. 2). Microscopically, the mass was well circumscribed. Neverthelsee, focal infiltration into the surrounding breast tissue was identified (Fig. 3a). In the periphery of the tumor, the normal histological features of normal mammary gland could be observed. But the amianthoid fibers or entrapped mammary ducts/lobules were absent in the tumor. The tumor showed patternless proliferation of ovoid to short spindle-shaped cells intermingled with fibrillary collagen fibers and alternating hypercellular and hypocellular areas (Fig. 3b). Small blood vessels could be seen in some areas of the tumor, and some of which were staghorn-like branching pattern (Fig. 3c). Many mature adipocyte cells were also observed (Fig. 3d). At

higher magnification, tumor cells showed mild to moderated cytological atypia without obvious pleomorphism and necrosis. The mitotic figure was unremarkable in most areas, but high mitotic activity (up to 4/10HPFs) could be counted in focal area of the hypercellular areas with diminished branching vasculature, and atypical mitotic figures were not observed.

We performed immunohistochemistry (IHC) staining for actin, Bcl-2, calponin, CD34, CD99, CDK4, Cytokeratin(AE1/AE3), HMB45, MDM2, Melan-A, RB1, STAT6, SMA, S100 and Ki67. Both ovoid to short spindle-shaped cells and adipocytes showed diffuse strong positive for STAT6 (Fig. 4a) and Bcl-2; positive for CD34, CD99 and RB1; negative for actin, calponin, CDK4, Cytokeratin(AE1/AE3), HMB45, MDM2, Melan-A and SMA. S100 was expressed in some dipocyte cells (Fig. 4b), and S100 and STAT6 were co-expressed in some adipocytes (Fig. 4c). The Ki67 labelling index was less than 10% in most areas of the tumor, whereas it was about 20% in the hypocellular area with increased mitosis (Fig. 4d). For further analysis, we performed fluorescence in situ hybridization (FISH) to identify the amplification of *MDM2* gene and detected no amplification of *MDM2* gene with MDM2:CEP12 ratio of 0.98. In order to further study the molecular genetic features of this case, a next-generation sequencing (NGS) platform was employed to detect *NAB2-STAT6* fusion variants at the RNA level, and a *NAB2*exon6-*STAT6*exon2 fusion gene transcript was identified. The result of NGS was further verified by Sanger sequencing (Fig. 5).

Base on the above morphological, immunohistochemical and molecular findings, the lesion was diagnosed as breast FFSFT with focal atypical features. Although this case has increased mitotic activity, it fitted into the low risk class for distant metastasis according to Demicco et al's refined stratification model [28].

Treatment and follow-up

The patient underwent left breast lumpectomy with clear margins in the tumor area. Postoperatively, additional therapies such as chemotherapy or radiotherapy were not provided. The patient was alive and in well situation, in which without evidence of recurrence or metastasis at 3 months after operation.

Discussion

The FFSFT is an uncommon variant of SFT and is composed of typical or cellular SFT with mature adipose tissues. Nielsen et al reported three cases, composed of hemangiopericytomas and adipose tissues in 1995 and referred to them as lipomatous hemangiopericytoma for the first time [29]. Guillou et al reported that lipomatous hemangiopericytoma shared the similar clinical course, pathological features, ultrastructural features and IHC staining with SFT, except for the presence of mature adipocytes [30].Therefore, the lipomatous hemangiopericytoma was regarded to be a subgroup of SFT. This tumor has been classified as a variant of SFT in the 4th World Health Organization (WHO) classification of Soft tissue and Bone Tumors. SFT is now reported in all anatomical sites, remaining a rare entity in the breast. But when it comes to FFSFT of the breast, no case has been reported in English literatures.

In the cases of breast SFT, including this case, except that a very small number of cases were accidentally found on routine mammography, most cases showed palpable masses of varying sizes, ranging from 0.6 cm to 10 cm with a mean of 3.29 cm and a median of 2.85 cm. Most of them were painless masses, and some cases were accompanied by pain [10, 20, 22]. Except that 8 cases did not mention the side, the side of breast involved in the reported cases was roughly similar, with 12 cases in the left and 12 cases in the right breast. The age of patients ranged from 38 to 88 years with a mean age of 61.6 and a median age of 62.5 years. There were 8 males and 24 females, male: female = 1:3, and the incidence rate of female was higher than that of male, but this discordant prevalence may be attributed to the judgment as to the epicenter of SFT [7]. The radiologic findings of SFTs are nonspecific [18]. Breast SFT often presents as a hypoechoic or inhomogeneous echoic hypervascular mass with benign features at the radiological work-up, such well-defined margins and smooth echostructure [5]. The elastography on US is not hard [2]. Breast SFT can be shown as a relatively well-defined mass without calcifications on mammography [8, 18]. While malignant solitary fibrous tumors (MSFTs) often present at least focal lobulated appearance [2, 5, 20], and it often be classified as BIRADS category 4C by radiologists [2, 5, 20].

Grossly, the surgical specimen consisted of a well-defined solidmass with clear boundary. The cut surface of the tumor was gray-yellow, and often without bleeding and necrosis. In cases of breast MSFT, focal invasive margins can sometimes be seen

[5, 8, 20]. As with SFTs from other anatomic locations, Breast SFTs are characterized by a well-defined mass composed of bland oval to spindle cells arranged in a haphazard “patternless” pattern, alternating with hypercellular and hypocellular areas. Sometimes tumor cells are arranged in sheet-like, storiform, fascicular, and even a herringbone patterns. In the hypocellular areas, there is a characteristic hemangiopericytic vascular pattern, the so-called “staghorn” vessels, in a rich, collagenous stroma with ropy collagen. However, non-classical SFT have also been documented, such as SFT with extramedullary hematopoiesis (EMH) [31]. Breast MSFT is extremely rare, and only 4 cases have been reported so far. In addition to the morphological characteristics of classical SFT, the reported 4 cases showed mild to moderate cytological atypia and high mitotic activity(≥ 4/10HPFs) [2.5,8,20]. Of which, 3 cases showed infiltrative margins at least in the local area [5, 8, 20] and 2 cases were significantly hypercellular and showed tumor necrosis [5, 20]. In only one case, the diameter of the tumor was greater than 5 cm [20]. As the histological diagnostic criteria of MSFT are not very clear, so the diagnosis of MSFT requires a comprehensive evaluation based on the morphological criteria proposed, rather than making the diagnosis only according to a single index such as mitotic activity.

As to our case, in addition to the typical morphological characteristics of SFT, there were some mature adipocytes in the tumor tissue. The morphological characteristics were consistent with the FFSFT reported in the literatures. Although there was no pleomorphic and necrosis, the tumor was hypercellular and the tumor cells had mild atypia. In addition, the mitoses in the hot spot reached 4/10HPFs. Therefore, it presented some atypical characteristics in morphology. However, our case did not meet most of the histological diagnostic criteria of MSFT, so it could not be diagnosed as MSFT.

A combination of CD34, CD99 and Bcl-2 has been widely used to diagnose SFT. Although these IHC markers are highly sensitive and usually show diffuse and strong expression in approximately 90% cases, whereas the specificity of both these markers is low [1]. Since a wide variety of mesenchymal tumors can express these markers, especially when the tumor and SFT show overlap in morphological changes, the value of these markers in differential diagnosis has great limitations. In recent years, fusion genes of *NAB2-STAT6* has been identified as a hallmark of SFT, and IHC staining shows that the diffuse nuclear expression of STAT6 is highly consistent with the fusion of *NAB2-STAT6* gene. The diffuse nuclear expression of STAT6 is highly sensitive (97% − 100%) and specific (97.5% − 100%) for the diagnosis of SFT [1, 32]. It should be noted that the expression of STAT6 is generally reduced or not expressed in dedifferentiated SFTs [33]. However, in a few cases, STAT6 expression also occurs in other non SFTs [1]. In particular, this marker can be expressed in a small subset of well-differentiated liposarcomas (WDLPSs)/dedifferentiated liposarcomas (DDLPSs), which is usually focal positive [1, 32, 34]. This phenomenon is considered to be the over-expression caused by *STAT6* gene amplification [34], while other CD34 positive or negative spindle cell tumors that need to be differentiated from SFT have no positive STAT6 nuclear expression.

The adipocytic component of the FFSFTs reported in the literatures was mostly mature adipocytes [1, 35, 36], as showed in our case. Of note, multivacuolated lipoblasts and/or atypical lipomatous tumor-like areas can be observed in some cases, closely mimicking WDLPS [35]. In our case, no *MDM2* gene amplification was found, and the *NAB2*exon6-*STAT6*exon2 fusion gene transcript was detected by NGS, which confirmed that this case was FFSFT rather than liposarcoma. There are few previous studies on STAT6 IHC staining in FFSFT. Yoshida et al reported the expression of STAT6 in 49 cases of SFT, of which only 1 case was FFSFT. STAT6 was expressed in spindle tumor cells, and negative in adipocytes [32]. Creytens et al. evaluated the expression of STAT6 in 6 cases of FFSFT, and spindle tumor cells in 6 cases were diffusely moderately to strongly positive for STAT6 [36], but their article did not mention whether adipocytes expressed STAT6. Florian found that spindle cells in FFSFTs expressed STAT6, and some adipocytes also expressed STAT6 [37]. In this case, STAT6 IHC staining showed that the spindle cells and adipocytes in the tumor were positive, some adipocytes expressed S100, and a small number of adipocytes co-expressed STAT6 and S100, which indicates adipogenesis due to tumor differentiation rather than fat deposition due to degeneration. The interaction of STAT6 with genes regulating adipocyte differentiation, such as peroxisome proliferator activated receptor-γ(PPARγ), may provide a possible explanation for inducing adipocyte differentiation in FFSFT [37].

The differential diagnosis of breast FFSFT mainly include phylloides tumor (PT), myofibroblastoma, spindle cell lipoma (SCL), ASLT and DDLPS. □PT is composed of epithelium and stroma. The stroma can have adipose components and adipoblasts, but the proliferative fibrous stroma often compresses the epithelium into fissures, and the fibrous stroma often expresses SMA and desmin, while SFT has no epithelial component and often does not express SMA and desmin. □myofibroblastoma is

circumscribed tumor composed of intersecting fascicles of bland spindle shaped myofibroblastic cells with intervening collagen bundles and mature adipocytes in different proportions. It often occurs in the breast and its morphology can be similar to FFSFT, but it always lacks the change of cell density and hemangiopericytoma like growth pattern. Although tumor cells demonstrate variable expression of CD34, Bcl-2 and CD99, but desmin and actin are always positive. This tumor is characterized by 13q14 and 16q deletion, resulting in partial or complete inactivation of *RB1* and *FoxO1* genes and subsequent loss of RB1 protein expression. Therefore, about 90% of myofibroblastomas shows loss of nuclear expression of RB1 protein. SCL often occurs in the head and neck dermis or subcutaneous tissue. It often has a complete capsule and exhibits bland spindle cells, ropy collagen bundles and mature adipose tissue and expresses CD34 immunostain [1]. This tumor also has *RB1* gene deletion, resulting in the loss of RB1 protein expression. ASLT is common in adults and has a wide incidence site, with more than half of it located in the limbs or extremities. Most of the manifestations are slow growing masses or bulges under the skin or fascia. The tumor often has no capsule, and about 35% of it can infiltrate the surrounding tissue. Histologically, ASLT consists of different numbers and proportions of atypical spindle cells and adipocytes including adipoblasts at different stages of differentiation distributed in mucoid and fibrous stroma. In most cases, singular multinucleated giant cells can be seen scattered. It often expresses S100, CD34 and desmin in varying degrees, but does not express STAT6, SMA, MDM2 and CDK4; About 57% of the cases shows loss of RB1 expression, which can be identified. DDLPS exhibit a wide variety of histological features which resemble low- and high-grade sarcomas. It can resemble malignant FFSFT [1], In addition, another pitfall is that 11%-14% of DDLPSs can partially show STAT6 nuclear expression [1, 32, 34]. Notwithstanding immature adipoblasts are commom seen in DDLPS. In addition, the positive expression for MDM2, CDK4 and p16 IHC stains and the amplification of *MDM2* gene detected by FISH helps in establishing the diagnosis of DDLPS [1].

Due to their rarity and lack of randomized control trials, there is no global consensus on treatment of breast SFTs. Complete excision with clear margins, a long-term follow-up and a multidisciplinary team approach are therefore recommended for treatment and management of these cases because of the unpredictable clinical behavior in some cases without malignant morphological features. Although our case showed the increased mitotic activity, but lacked other malignant histological features and the risk of metastasis was low. Therefore, adjuvant therapy was not given because there was no evidence that radiotherapy or chemotherapy did not actually increase any benefits. The patient was instructed to attend regular controls every 3 months. There was no recurrence and metastasis after 3 months of follow-up. The patient is still being followed up.

Conclusions

In summary, we reported a rare case of breast FFSFT with focal atypical features. The correct identification and diagnosis of SFT is needed for its' appropriate treatment and management. Only with comprehensive pathologic diagnosis with proper sampling, full awareness of the similarities and differences between SFT and mimicking lesions, as well as appropriate ancillary testings including STAT6 immunostain and molecular detection of the *NAB2-STAT6* fusion gene, could an accurate diagnosis of SFT be established.

Abbreviations

ASLT: Atypical spindle cell lipomatous tumor; BI-RADS: Breast Imaging and Reporting Data Systems; Bcl-2: B-cell lymphoma 2; CD: cluster of differentiation; CDK4: cyclin-dependent kinase 4; CK: cytokeratin; DDLPS: Dedifferentiated liposarcoma; EMH: Extramedullary hematopoiesis; FFSFT: Fat-forming solitary fibrous tumor; F: female; FISH: fluorescence in situ hybridization; HPF: highpower fields; IHC: Immunohistochemistry; Lt: left; M: male; MSFT: malignant solitary fibrous tumor; MRI: magnetic resonance imaging; MDM2: murine double minute2; NGS: next-generation sequencing; NA: not available; NAB2: NGFI-A binding protein 2; Rt: right; RT-PCR: Reverse transcription polymerase chain reaction; RB1: retinoblastoma 1; SFT: solitary fibrous tumor; STAT6: signal transducer and activator of transcription 6; SMA: smooth muscle actin; SCL: spindle cell lipoma; US: ultrasonography; WHO: World Health Organization; WDLPS: Well differentiated liposarcoma; +: positive; −: negative.

Declarations

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Authors'contributions

Yufei Liu and Mingjie Zhang contributed equally to the writing of the manuscript. Yufei Liu made the final diagnosis of this disease and wrote the manuscript. Mingjie Zhang collected the clinical data and wrote part of the manuscript. Xiaoli Shui helped to perform immunohistochemical examination and collected follow-up data. Daizhong Wang performed the FISH analysis. Chunyu Cao reviewed and edited the manuscript. Zhi Yao and Junlong Pan collected the US and MRI data. The author(s) read and approved the final manuscript.

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Availability of data and materials

There are no additional supporting data available.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Yichang Central People's Hospital.

Consent for publication

Not applicable.

Competing interests

The authors declare that no conflict of interests exists.

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Table

Table 1
Summary of breast SFTs reported in the English literatures

Author	Sex/Age(years)	Side/Size	Symptom	Key IHC markers					Diagnosis
				STAT6	CD34	Bcl-2	CD99	S100	
This case	F/51	Lt/3.4 cm	palpable painlessmass	+	+	+	+	+	FFSFT
Nitta el al.	F/78	Lt/3. 1 cm	mass	+	+	+	NA	NA	MSFT
Dubois el al.	F/63	Lt/0.6 cm	Incidentally found (initial), and slowly growing mass (after 3 year)	+	+	NA	NA	-	SFT
Naso el al.	F/52	NA/1.1 cm	Nontender, mobile, mass incidentally found on routine mammography	+	+	NA	NA	NA	SFT
Barcoel al.	F/72	Rt/2.7 cm	Palpable mass with growing steadily for 2 months	+	+	+	+	-	MSFT
Choel al.	F/57	Rt/3.2 cm	Incidentally found mass on routine mammography	+	+	NA	NA	-	SFT with EMH
Jung el al.	F/75	Lt/4.4 cm	Palpable mass for 3 months	+	+	+	NA	-	MSFT
Salemis el al.	F/42	Rt/3 cm	Palpable mass for 6 months	NA	+	NA	NA	-	SFT
Song et al.	M/64	Lt/5 cm	Palpable mass for 10 years	NA	+	NA	NA	-	SFT
Brenes et al	F/38	Rt/6 cm	Nontender and painful lump for 4 months	NA	+	+	+	-	SFT
Magro et al.	F/62	NA/1 cm	Incidentally found	+	+	+	+	-	SFT
	F/58	NA/1.5 cm	NA	+	+	+	NA	-	SFT
	M/81	Rt/3 cm	Palpable mass	+	+	+	+	-	SFT
Park et al.	F/63	Rt/8.9 cm	Recurrent lesion at 6 months after the first occurrence of SFT	NA	NA	+	NA	-	SFT
Tsai et al.	F/41	Rt/3 cm	Palpable mass for 5.5 years	NA	NA	NA	NA	NA	SFT
Rhee et al.	M/53	Lt/2.3 cm	Palpable mass for 2 years	NA	+	NA	NA	-	SFT

Author	Sex/Age(years)	Side/Size	Symptom	Key IHC markers					Diagnosis
				STAT6	CD34	Bcl-2	CD99	S100	
Han et al.	F/50	Lt/2.5 cm	NA	+	+	+	+	NA	SFT
Yang et al.	F/52	Lt/10 cm	Incidentally found (initial), and Painful palpable mass (after 1 year)	NA	+	+	+	-	MSFT
Rovera el al.	M/49	Rt/3 cm	Palpable mass	NA	+	NA	NA	-	SFT
Meguerditchian et al.	M/79	Lt/1.2 cm	Tender mass	NA	+	+	NA	-	SFT
Falconieri et al.	F/58	Rt/9 cm	Palpable mass	NA	+	-	NA	NA	SFT
	F/62	Rt/2.5 cm	Palpable mass	NA	+	+	NA	NA	SFT
	F/64	Lt/3 cm	Palpable mass	NA	+	-	NA	NA	SFT
Bombonati et al.	F/88	Lt/0.6 cm	Incidentally found during follow-up mammography for breast cancer	NA	+	NA	NA	-	SFT
Salomao et al.	F/64	NA/NA	NA	NA	+	NA	NA	-	SFT
	F/79	NA/NA	NA	NA	+	NA	NA	-	SFT
	F/77	NA/NA	NA	NA	+	NA	NA	-	SFT
	F/71	NA/NA	NA	NA	+	NA	NA	-	SFT
Khalifa et al.	F/53	Rt/1.5 cm	Mass	NA	+	NA	NA	-	SFT
Damiani et al.	M/63	Lt/2 cm	Palpable mass	NA	+	NA	NA	NA	SFT
	M/68	Rt/2 cm	Palpable mass	NA	-	NA	NA	NA	SFT
	M/45	NA/2.5 cm	Palpable mass	NA	+	NA	NA	NA	SFT

Figures

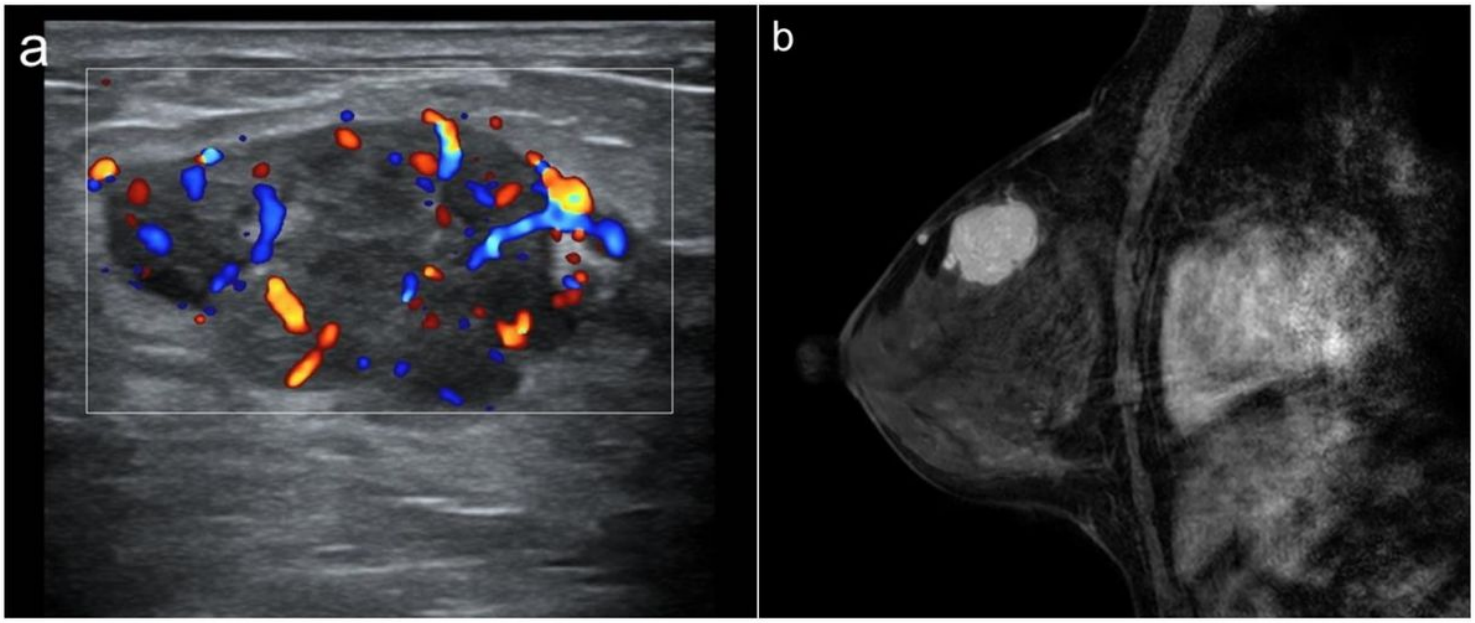

Figure 1

Imaging findings. a Color Doppler sonography showed some peripheral and internal color flow signals in the solid mass of the left breast. b MRI showing a well-defined, focal lobulated, solid nodular lesion with a maximum diameter of 3.4 cm in the 12 o'clock direction of the upper quadrant of the left breast, with geographical enhancement and no architectural distortion.

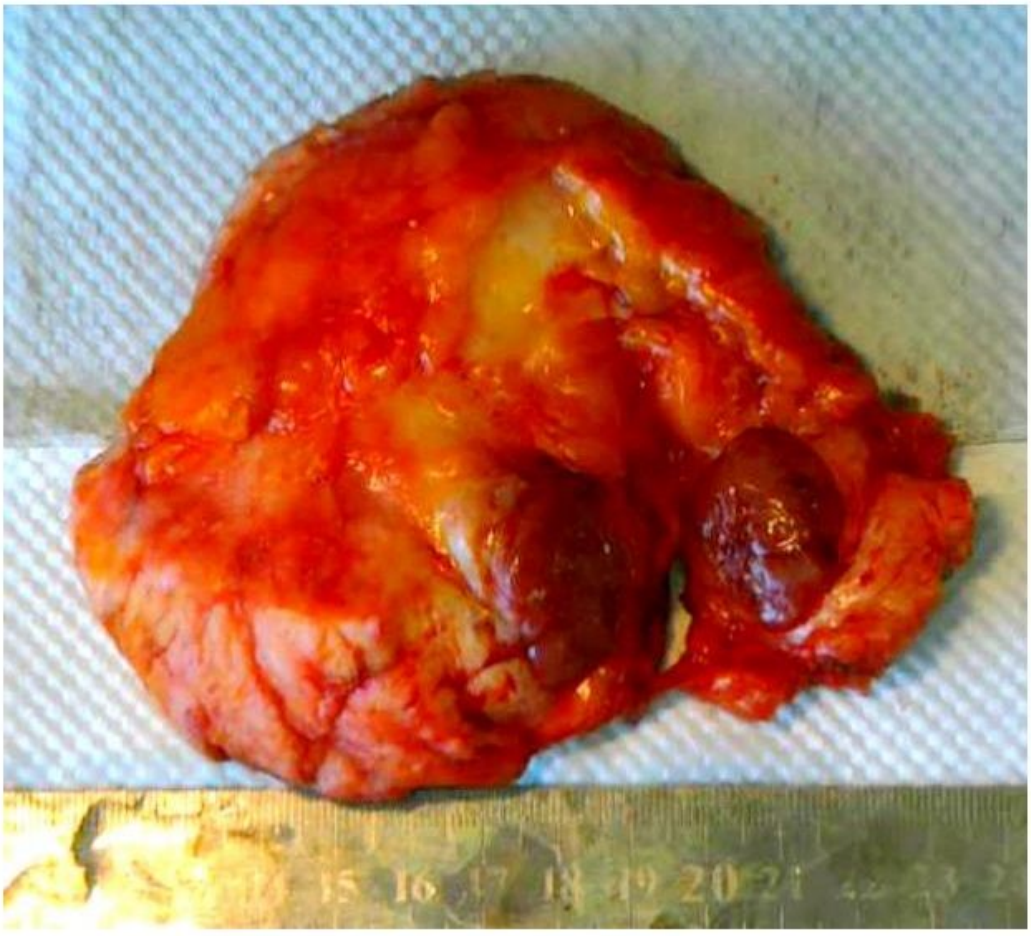

Figure 2

Gross examination of the resected specimen.

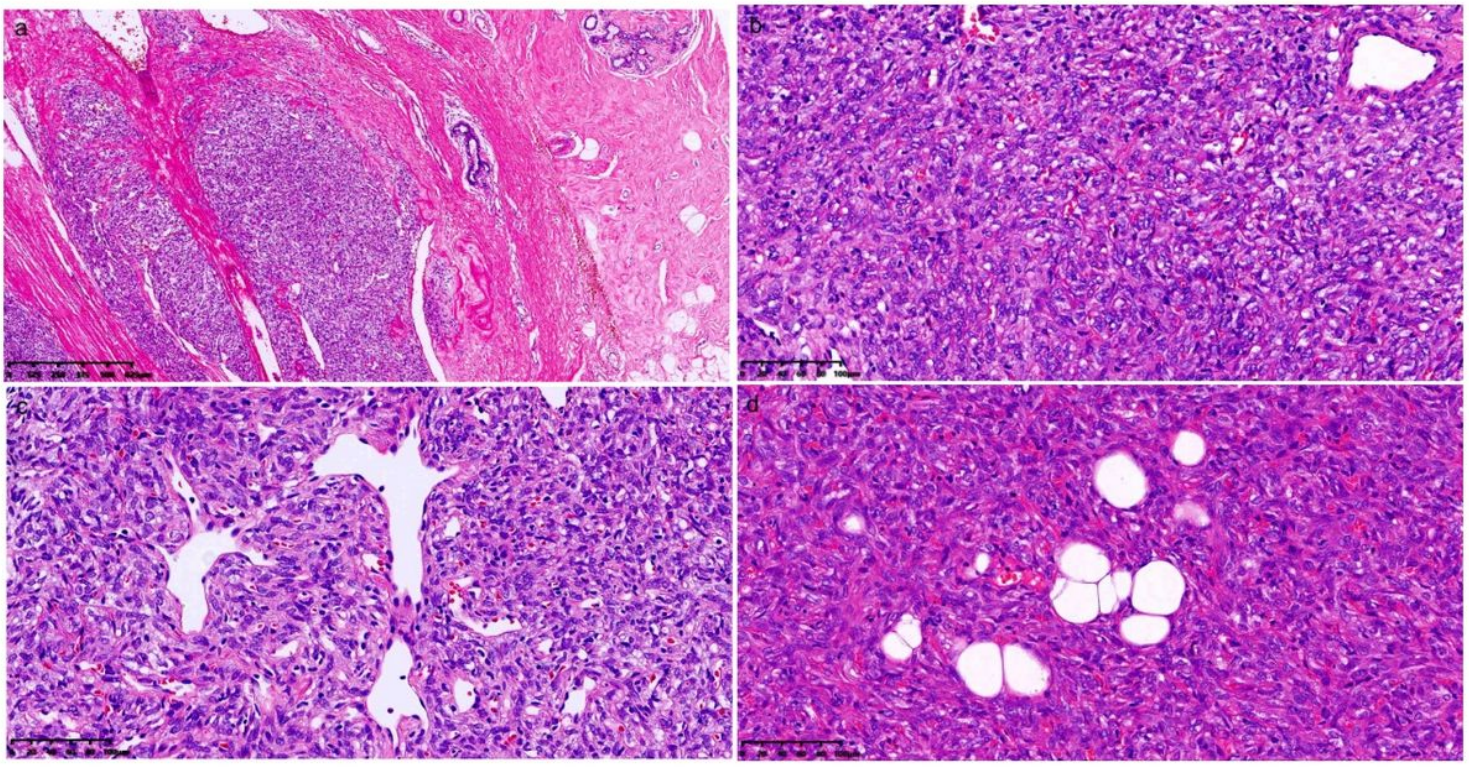

Figure 3

Pathologic findings (hematoxylin and eosin staining). a Focally, the margins of the tumor infiltrated into the surrounding breast tissue (original magnification×40), b The tumor showed patternless proliferation of ovoid to short spindle-shaped cells intermingled with fibrillary collagen fibers and alternating hypercellular and hypocellular areas (original magnification×200), c Some of small blood vessels were staghorn-like branching patter (original magnification×200), d Many mature adipocyte cells were observed (original magnification×200).

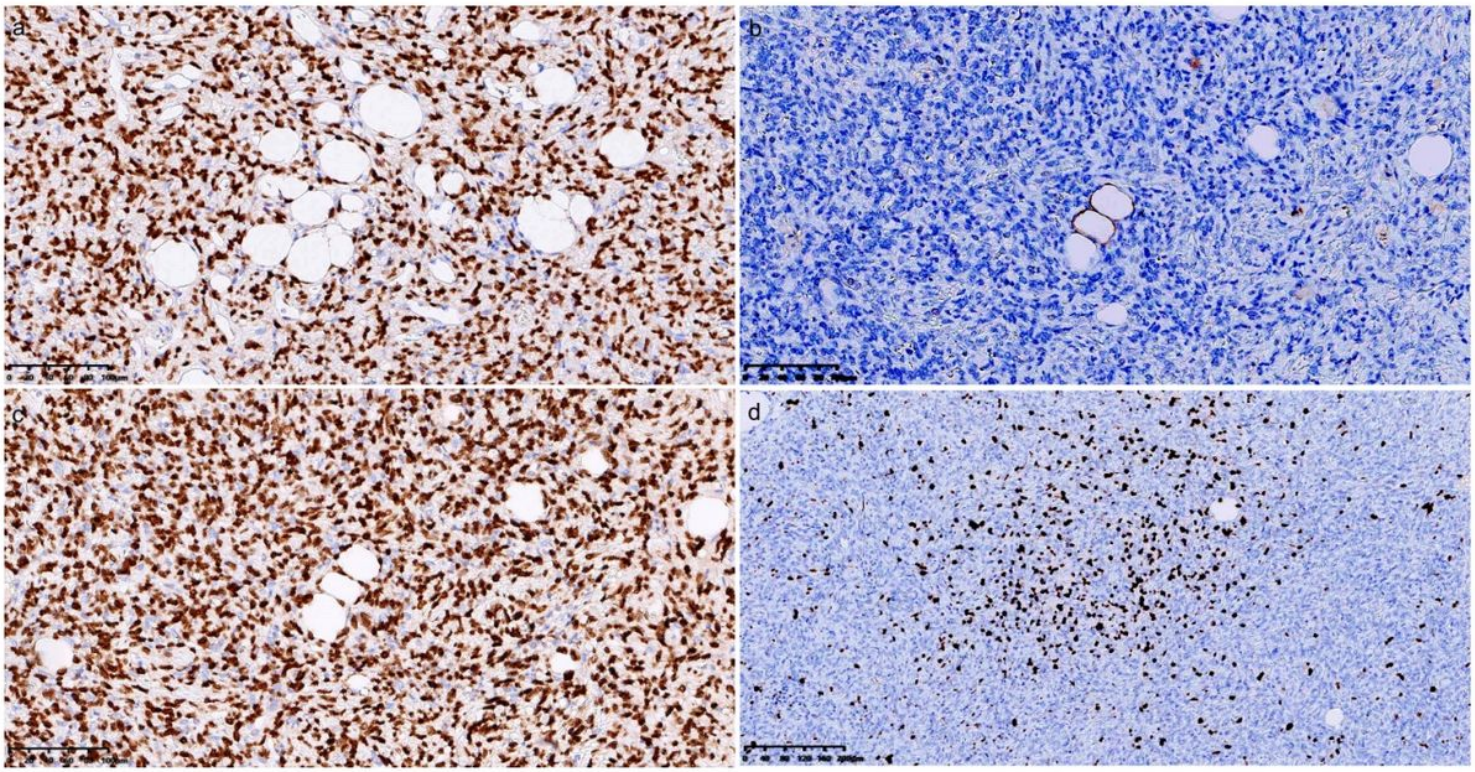

Figure 4

Immunohistochemical findings. a Strongly and diffusely positive STAT6 staining (original magnification×200), b Positive S100 staining in adipocyte cells (original magnification×200), c STAT6 was co expressed in a small number of adipocyte cells (original magnification×200), d Ki67 proliferation index was about 20% in the hypocellular area with increased mitosis (original magnification×100).

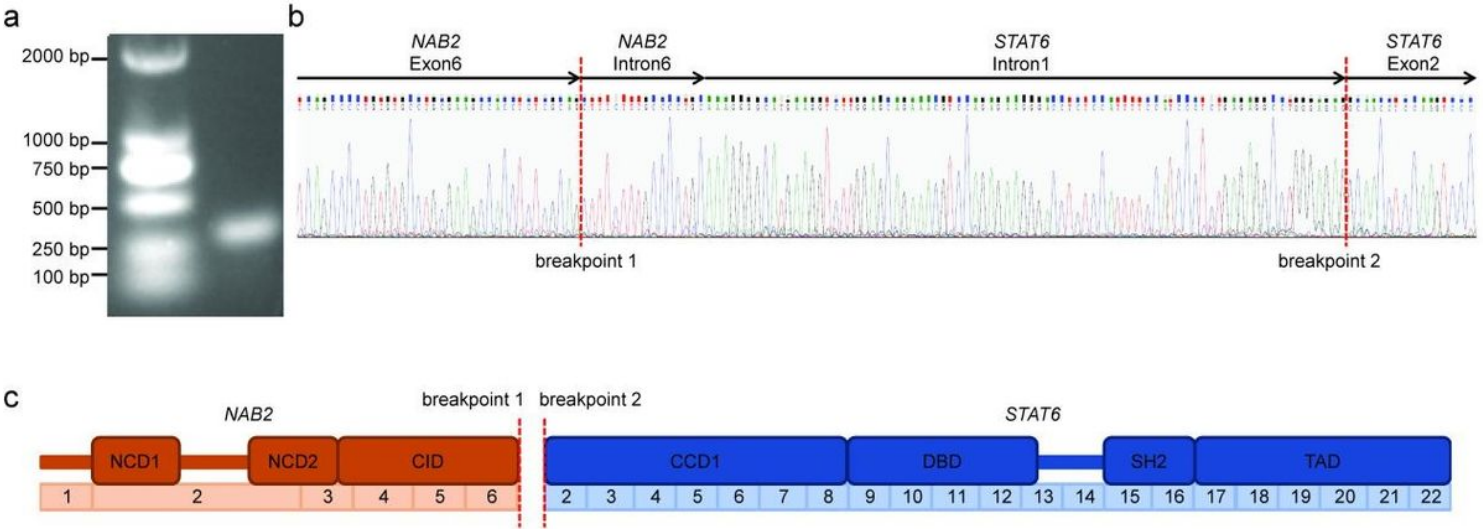

Figure 5

NAB2-STAT6 fusion gene status. a Agarose gel separation of a NAB2-STAT6 fusion-specific RT-PCR product (NAB2 exon6/STAT6 exon2) from this case. b Sanger sequencing chromatogram of a NAB2/STAT6 fusion-specific RT-PCR product. c Protein domains retained in the NAB2/STAT6 fusion.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Fig.MDM2FISH.jpg