Case Report
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A Review on Solitary Fibrous Tumor Behavior in Pregnancy: A Case Report and Literature Review

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Abstract

A solitary fibrous tumor (SFT) of the pleura is a rare chest wall mesenchymal neoplasm which usually arises from CD34-positive sub-mesothelial mesenchymal cells of visceral pleura. It is rare, accounting for less than 5% of all pleural neoplasms. Recently, steroid hormone receptors were recognized in the cells of extra-pleural SFT. Progesterone may participate as a growth factor in many CD34 (+) stromal neoplasms. During pregnancy, the amount of plasma progesterone gradually increases. As a result, it could promote the development of cancers that rely on progesterone. However, the link between SFT and pregnancy has not yet been established. There are only six extra-thoracic SFT-reported cases with accelerated growth during pregnancy, on the literature. Hence, we reported an interesting case of SFT which is the first reported case of thoracic SFT presenting during pregnancy. Moreover, we attempted to clarify the mechanism of this tumor's rapid growth by examining its hormonal receptors status in the cells of this tumor.

Keywords: Pleural neoplasms, Rapidly-Growing Mass, Diagnosis, Receptors, Steroid, Immunohistochemistry

Introduction

Solitary fibrous tumors (SFT) of the pleura are uncommon mesenchymal tumors of the chest wall that often develop from sub-mesothelial mesenchymal cells that are CD34 positive in the visceral pleura.[1] Less than 5% of pleural neoplasms are this uncommon condition. The cells of extra-pleural SFT have recently been shown to have steroid hormone receptors. In particular, progesterone may participate as a growth factor in many CD34 (+) stromal neoplasms which express these receptors. The level of progesterone in the body steadily rises during the pregnancy. Therefore, it may enhance the growth of progesterone-dependent tumors. There is no known associated genetic or environmental risk factor for SFT.[2] SFTs preferentially arise in serosal membranes, such as pleura,

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pericardium, the dura of the meninges (formerly known as hemangiopericytoma), peritoneal membrane (visceral fascia), and deep soft tissues of trunk and extremities (somatic fascia). Although SFT was initially described in the thoracic cavity (including pleura, lungs, and mediastinum), 50 to 70% of SFTs arise in extra-thoracic regions. Extra-pleural SFTs are presented at 30% in the central nervous system, 30% in the peritoneal cavity, retroperitoneal soft tissue, and pelvis, 20% in the head and neck, and the remaining 20% in deep soft tissues of the trunk and extremities, or occasionally in bone (periosteum).[3] The clinical course is usually indolent, and most of the patients are asymptomatic and respiratory symptoms are the most common in symptomatic patients. Extra-thoracic manifestations (paraneoplastic syndromes) are presented in 25% of cases, including hypoglycemia (IGF-2 secretion), osteoarthropathy and clubbing (hyaluronic acid or cytokines secretion). Malignant SFTs of the pleura (SFTP) are two times (70% for malignant histology vs. 35% for benign histology) more likely to be symptomatic (non-specific pulmonary

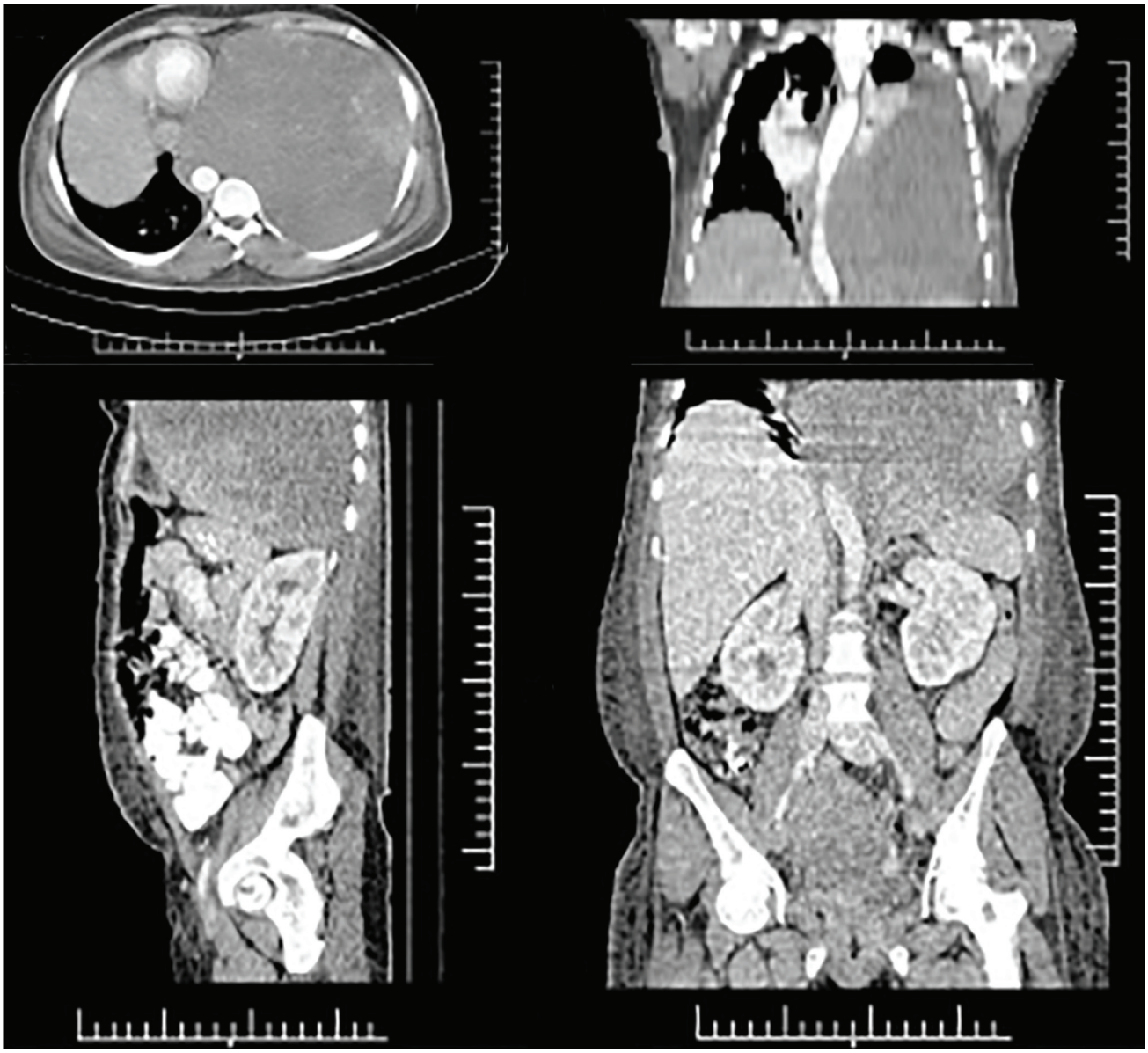

Figure 1. Initial contrast-enhanced chest and abdominopelvic computed tomography scan image showed a huge homogeneous, sharply defined mass in the left pleural cavity, compressing the heart and the descending thoracic aorta, with pressing the left hemi-diaphragm downward against the spleen and stomach.

Table 1. Patient characteristics and the overview of study characteristics for comparative assessment in the patients with rapidly growing SFT in pregnancy

Author -Year	Patient Age – G P	Gestational Age	Anatomical Site	Diameter	Ki-67	PR	ER	AR
Current Study	31 y – G3P2	33 w	Left Pleura	19 cm	< 1%	40% positivity	3-4% positivity	15% positivity
Hyde -2018[13]	32 y - G?P?	Second trimester	Orbit	2.2 cm	< 5%	Strong positivity	Focal positivity	ND positivity
Acosta Gonzalez – 2016[14]	40 y – G3P1	2-months post-delivery	Liver	16 cm	< 10%	Focal positivity	Focal positivity	ND positivity
Peksa -2011[15]	24 y – G?P?	20 w	Retroperitoneal	25cm	ND	Negative	Negative	ND
Morris – 2011[16]	23 y – G1P0	14 w	Liver	27 cm	ND	ND	ND	ND
Das – 2009[17]	32 y – G?P?	12 w	Orbit	4 cm	ND	ND	ND	ND
Bongiovanni – 2000[18]	23 y - G?P?	22 w	Left adrenal gland	9 cm	< 6%	Focally positive	Negative	ND

G: Gravida; P: Para; ND: Not determined; AR: Androgen receptor; ER: Estrogen receptor; PR: Progesterone receptor; SFT: Solitary fibrous tumor

symptoms e.g., cough, chest pain, and dyspnea) and usually present with larger tumors. Pleural SFTs can reach a huge size, while remaining asymptomatic. SFTs tend to displace rather than invade surrounding tissues. Consequently, symptoms brought on by mechanical compression from big tumors that are not discovered by chance (e.g., of the inferior vena cava, causing lower extremity edema, or of the heart). Rarely, hemoptysis and obstructive pneumonitis, which have been linked to airway obstruction.[4] Typically, the lesions are incidentally discovered as an asymptomatic mass on a chest radiograph carried out for an unrelated reason. Sometimes, imaging may also be able to determine whether the mass is arising from the pleura or from the mediastinum.[5] Nevertheless, a definitive diagnosis requires histologic confirmation. Virtually all SFTs share a recurrent NAB2-STAT6 fusion, regardless of anatomic location. In SFT, the adjacent genes NAB2 and STAT6 (on chromosome 12q13) are fused by a chromosomal inversion. NAB2-STAT6 fusion induces the expression of EGR1 target genes. SFTs expressed high levels of both EGR1 target genes, including NAB2, NAB1, IGF2, FGF2, and PDGFD, and tyrosine kinase receptors, such as FGFR1 and NTRK1.[6] Each case should be discussed in a multidisciplinary tumor board with all relevant specialties. Complete en-bloc surgical resection to negative margins is the mainstay of therapy for all localized SFTs.[7] There is no proof that totally resected SFTs benefit from adjuvant radiation or chemotherapy (even with malignant histology). It is advisable to make case-by-case decisions during multidisciplinary team meetings about the use of adjuvant radiotherapy or chemotherapy for incompletely resected or recurring SFTs.[8] Long-term follow-up is recommended because local and distant relapse is possible, even with benign-appearing tumors. VEGF targeted therapy and other tyrosine kinase-targeted therapy (bevacizumab, sunitinib and

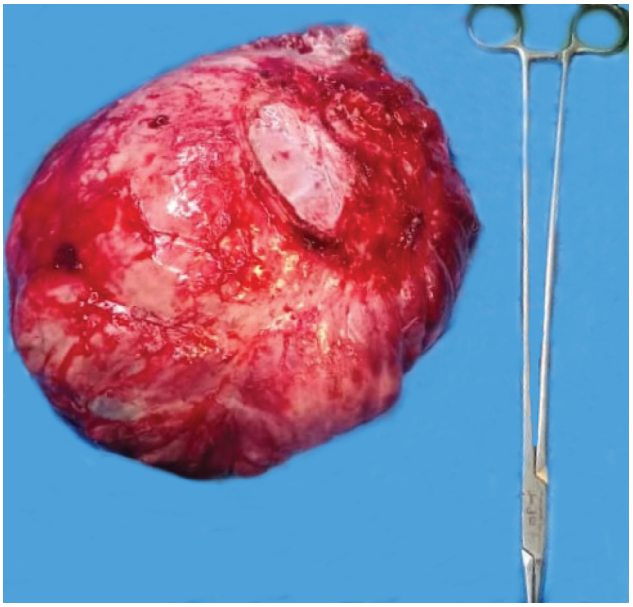

Figure 2. Intraoperative and pathologic finding. Posterolateral thoracotomy revealed a large encapsulated mass measuring 19 × 16 × 8 cm that weighed 1,720 g.

pazopanib), disrupt the blood supply to the tumor, and are currently being investigated for the treatment of advanced SFTs.[9]

Moreover, SFT was rarely described in association with pregnancy. The association of SFT with pregnancy has not been recognized, yet. After reviewing the current literature using PubMed and Google, we found that only six extra-thoracic SFT cases with accelerated growth during pregnancy were reported in the English-written literature, up to May 2021. Hence, this report is the first case of thoracic SFT of the pleura presenting during pregnancy.

Case Presentation

A 31-year-old woman, Gravida 3 Para 2, at 33 weeks of gestation presented to an outpatient clinic with worsening dyspnea, dry cough, and pleuritic chest pain over the preceding two weeks. Her past medical history was only significant for hypothyroidism which was diagnosed once she had become pregnant, about 7 months earlier.

On physical examination, there were noteworthy findings including symmetrical upper limbs with minor pitting edema, raised jugular venous pressure, unilaterally and markedly reduced left side breath sounds, and frequent mild tachycardia to 104. As the dyspnea was progressive in nature and was exacerbated by exertion, the patient's obstetrician felt that dyspnea was unusually severe for the patient. Electrocardiogram (ECG) demonstrated sinus tachycardia. Laboratory studies, including complete blood count and biochemical analysis were unremarkable except for mild hypoglycemia (FBS: 70 mg/dl).

Computed tomography of the chest revealed a large mass in the left pleural cavity with a mediastinal shift to the right. The mass was inhomogeneous with peripheral enhancement. There was mild pleural effusion on the left side (Figure 1).

Soon after, our medical oncologists and surgeons were brought in to consult for specialized advices and a percutaneous ultrasound-guided biopsy was conducted to establish an initial diagnosis of suspected malignancy. Immunohistochemical examination showed a tumor with fibroblast-like (spindle) cells in the collagenous background with some dilated blood vessels. It was negative for S-100 and positive for CD 34 and Bcl-2. Furthermore, mitosis, atypia, pleomorphism, necrosis, and hemorrhage were absent. These features were highly characteristics of benign SFTP.

1) After the multidisciplinary team fully discussed the patient, a decision on treatment options was made, and the patient was managed as follows: The patient was scheduled for delivery by cesarean section at 34 weeks of gestation, 7 days after admission. The infant was healthy and weighed 2350 g.

2) Three weeks thereafter, the patient underwent planned en-bloc resection of the chest wall mass via the left posterolateral thoracotomy

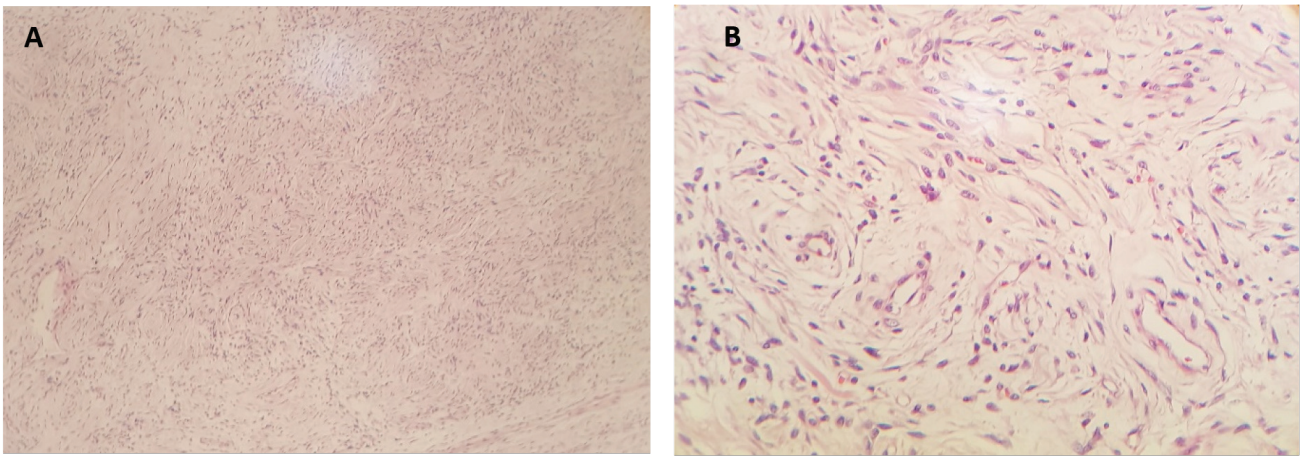

Figure 3. Microscopic findings, included solid proliferation of spindle-shaped fibroblastic cells in a less pattern. (Hematoxylin and eosin; magnification (A) 40 × and (B) 200 ×).

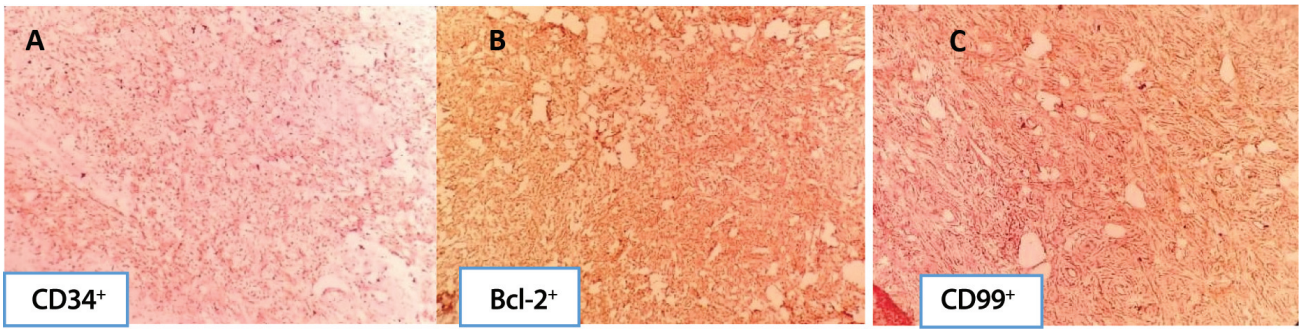

Figure 4. Immunohistochemical stains (40×) showing tumor cells strong and diffusely positive for CD34 (A) and BCL-2 (B) and CD99 (C).
CD: The cluster of differentiation (CD), BCL-2: B-cell lymphoma 2

through the sixth intercostal spaces.

Intraoperatively, the large mass was adhered to the adjacent lung, chest wall as well as the diaphragm. The seventh rib was removed to provide better access to the diaphragm. There was no evidence of invasion of the surrounding tissue; thus, en bloc resection of the tumor with the adjacent small portion of the diaphragm was done. The tumor was measured 19.0 × 16.0 × 8.0 cm and weighed 1720 g (Figure 2). Postoperative course was uneventful and the patient was discharged on postoperative day 4th. The histopathologic examination of the surgical resection specimen confirmed the SFTP (Figure 3, Figure 4). Immunohistochemical Markers of SFTP such as CD34, Bcl-2 and CD 99 were positive and immunohistochemical markers of mesotheliomas such as Calretinin, WT1, Cytokeratin 5/6 were negative (Figure 5). In addition, Ki-67 proliferative index was positive in < 1% of tumor cells (Figure 6). The margins of resection were microscopically clear of disease. The left lung completely expanded and pulmonary function recovered to the normal level after the removal of giant tumor. Her postoperative course was uneventful and she has been doing well for the first year after the surgery without any evidence of recurrence or metastasis.

Immunohistochemical staining analysis for the expression of the hormonal receptors revealed moderate positivity for progesterone receptors (PR: 40%), and weak positivity for estrogen receptors (ER: 3-4%) and androgen receptor (AR: 15%). The increase of SFTP in the example described here is thought to have been more likely impacted by progesterone than by androgen or

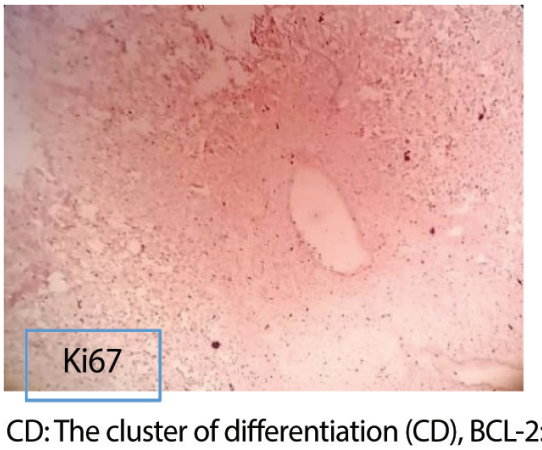

Figure 5. Ki-67 immunostaining (40×) showing occasional nuclear staining, and very low proliferation rate with ki-67. [The Ki-67 nuclear antigen is associated with cell proliferation. It is found throughout the cell cycle that includes the G1, S, G2, and M phases; but not the (G0) phase.]
Ki-67: Antigen KI-67 known as Ki-67 or MKI67 (Marker Of Proliferation Ki-67) is a protein that in humans is encoded by the MKI67 gene (antigen identified by monoclonal antibody Ki-67); G1: Growth phase-1; the first of four phases of the cell cycle; S: Synthesis phase; the second of four phases of the cell cycle, in which DNA is replicated, occurring between G1 phase and G2 phase; G2: Growth phase-2; the third subphase of interphase in the cell cycle directly preceding mitosis

estrogen; however, it is unknown which of the three hormones, if any, was at play.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Iran University of Medical Sciences (code: IR.IUMS.FMD.REC.1400.635) and is in accordance with guidelines laid down by the latest version of Helsinki Declaration.

Discussion

Steroid hormone-dependent tumors

There are some kinds of tumors (including; breast, ovarian, endometrial, prostate and testicular cancer, etc.), that need hormones to grow and develop. As a result, hormone stimulation may contribute to either their initial development or recurrence. In these situations, whether a patient may benefit from anti-hormone therapy or not depends on whether the tumor cells have hormone receptors or not.[10] The most commonly used hormone therapy drugs for hormone receptor-positive tumors are; anti-estrogens (such as tamoxifen) for breast carcinoma, and anti-androgens (such as flutamide) for prostate cancer. Anti-progesterone medications (such as mifepristone) have been recently used as hormonal therapy for patients with unresectable meningiomas.[11]

Steroid hormone receptor expression in SFTs

SFTs are rare masses of CD34-positive mesenchymal cells origin. There is no identified risk factor for SFTs.[12] However, there are some reports describing the rapid growth of SFTs during pregnancy which might show an association between SFTs and steroid hormones. Positive immunohistochemical staining of tumor cells for PR, ER, and AR may indicate hormonal stimulation as a driver of neoplastic cell proliferation.

Only six extra-thoracic SFT instances have, to our knowledge, been documented in the literature. Only four of the six reported SFTs linked to pregnancy underwent immunohistochemistry for ER and PR; three of these individuals had positive nuclear staining for PR. While positive nuclear staining for ER was observed in two of these patients.[13-18] Patient characteristics and an overview of these studies are shown in table1.

Moreover, almost all these cases of rapidly growing SFTs during pregnancy were histologically benign (Table 1).

In an immunohistochemical review of 4 malignant cases of SFTP, Liu et al. reported all the cases had been negative for ER and PR expression.[19] This finding may reflect receptor mutations with antigen loss and heterogeneous tumor populations within malignant tumor cells.

In another review of 32 patients of pleural SFTs with ki-67 less than 7% (Benign SFTs), 8 out of 32 expressed PR (25%), while none expressed ER or AR, suggesting that progesterone may have a role in the growth of some benign SFTs.[20]

Based on the individual receptor status for primary and recurrent illness, individuals with SFTs could benefit from hormone treatment. A possible role for hormonal stimulation, particularly

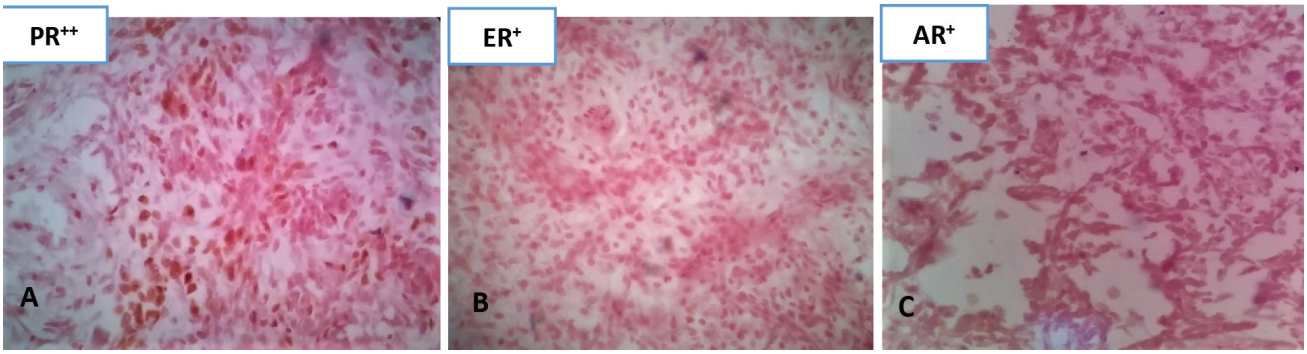

Figure 6. PR, ER, and AR immunostaining (40×) showing; moderately positive staining for PR (40% of tumor cells) (A), and weakly positive staining for ER (3-4% of tumor cells) (B), and AR (15 % of tumor cells) (C).
PR: Progesterone receptor; ER: Estrogen receptor; AR: Androgen receptor

progesterone, as a driver of tumor cell proliferation in SFTs has been suggested by the positive staining for PR, ER, and AR in our instance (Figure 5).Unfortunately, the patient had no chest imaging prior to her pregnancy to compare the current imaging with the previous one. Furthermore, we can not determine whether the tumor has started developing before or during pregnancy. But one thing for sure, the patient could not have been remained asymptomatic with such a large mass and simultaneous mediastinal shift, even prior to pregnancy. Thus, even if the tumor had begun developing before pregnancy, its growth must have been enhanced following pregnancy.

It seems this patient was a case of Doege-Potter Paraneoplastic syndrome (large SFT with dimensions greater than 20 cm) characterized by hypoglycemia and aggressive clinical behavior and is resolved by surgical resection of the lesion) which is associated with producing a form of IGF2 by these tumors. IGF2 is uniformly overexpressed in SFT. IGF2 is imprinted on the paternal allele in most adult tissues; Overexpression of IGF2 and consequent activation of the insulin receptor may also explain why a subset of SFT patients presents with hypoglycemia.[21]

Conclusion

In conclusion, SFT is a tumor which should be part of the differential diagnosis in a chest wall tumor of rapid growth during pregnancy. Prompt diagnosis and management of SFTP during pregnancy are important because it is potentially curable. Furthermore, proper antenatal assessment, a multidisciplinary team approach, and appropriate discussion with the patient are important determinants to achieve the best clinical outcomes for the mother and baby.

Pregnancy could be considered a potential precipitating factor in the presence of PRs in SFTs. Our case expressed moderately positive staining for PR, and weakly positive staining for ER and AR, a finding which deserves further investigations in a much larger series of SFTs.

Availability of Data and Materials

The datasets during and/or analyzed during the current study available from the corresponding author on reasonable request.

Informed Consent

Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

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Conflict of Interest

None declared.

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