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Recurrent dedifferentiated retroperitoneal liposarcoma complicating pregnancy

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Abstract:

Retroperitoneal liposarcoma is an uncommon tumor both in the pregnant and nonpregnant state. Its exact incidence is unknown because of its rarity. Due to its propensity for local recurrence, prognosis depends on histologic subtype and negative margins of resection. Surgery remains the mainstay of treatment, and timing is critical in terms of finding a surgically resectable lesion while balancing fetal risks. This report describes tumor recurrence in a pregnancy with a prior history of surgery for an atypical lipomatous tumor presenting as a retroperitoneal mass. After discussion with the multidisciplinary team, as well as with the patient's consent, the plan was to defer surgery until 34 weeks, followed by scheduled tumor removal 2 weeks postpartum. She delivered abdominally to a baby girl with a good outcome. Histopathology showed dedifferentiated liposarcoma with a positive tumor margin. The patient has survived at 6-month follow-up and completed four cycles of chemotherapy with doxorubicin, ifosfamide, and mesna. However, surveillance imaging again showed tumor recurrence.

Keywords:

Dedifferentiated liposarcoma, recurrent liposarcoma, retroperitoneal liposarcoma in pregnancy

Introduction

The most common cancers in pregnancy include breast cancer, cervical cancer, lymphoma, ovarian cancer, and melanoma.[1] In contrast, soft-tissue sarcomas are typically uncommon even in the nonpregnant state, comprising <1% of all malignancies.[2] The most common variant is liposarcoma, often found in the extremities and rarely in the retroperitoneum, where it contributes to half of all retroperitoneal tumors.[2] The setting of pregnancy and tumor recurrence adds further rarity to the case, with no published cases of retroperitoneal liposarcoma in pregnancy in the Philippines.

These tumors usually present in the mid-fifties, although they may occur at any age, including reproductive years.[2] They are often large at presentation due to the expansive nature of the retroperitoneum, which lacks bony boundaries. Although slowly growing, clinical manifestations only present when the tumor is large enough to cause pressure symptoms. In addition, symptoms may also overlap those of normal pregnancy, such as nausea, vomiting, abdominal pain, and enlargement, further contributing to its delayed diagnosis. Definitive treatment consists of complete tumor removal. However, they are highly associated with recurrence. This report describes a case of retroperitoneal liposarcoma presenting as a recurrence during pregnancy.

Case Report

JM, a 23-year-old Gravida 2 Para 1 (1001), was referred to our institution due to a recurrent abdominal mass during pregnancy.

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A year before pregnancy, the patient consulted due to a breast mass. Incidentally, she was noted to have a globular abdomen by her breast surgeon. Abdominal computed tomography (CT) scan showed intraperitoneal, well-defined, large, fat-attenuated masses with consideration of liposarcoma. She underwent exploratory laparotomy, peritoneal fluid cytology, enterolysis, excision of intraabdominal tumor with retroperitoneal extension, right salpingo-oophorectomy, and appendectomy. Intraoperatively, there was an irregularly shaped, intraperitoneal lipomatous mass extending to the retroperitoneum measuring 36 cm × 35 cm × 35 cm. It was also densely adherent to a suspicious mass measuring 6 cm × 4 cm × 3 cm, subsequently identified as the normal right adnexa and appendix on microscopy. Histopathology of the abdominal mass, however, showed mesenchymal neoplasm favor atypical lipomatous tumor with negative tumor margins.

The patient was subsequently lost to follow-up. In the interim, neither constitutional symptoms nor masses were noted.

She became cognizant of pregnancy at 9 weeks age of gestation. A slightly globular abdomen was noted, which was attributed to pregnancy. Due to a prior history of surgery, a whole abdominal ultrasound was requested, which showed a large abdominopelvic solid mass with minimal internal vascularity and internal calcification. The consideration was tumor recurrence.

Abdominal magnetic resonance imaging (MRI) at 19 weeks age of gestation showed an intraperitoneal mass measuring 20.2 cm × 14.8 cm × 15.3 cm, heterogeneous with soft tissue, fat, and cystic components with varying degrees of restricted diffusion and intralesional thin and thick septations situated at the right hemiabdomen [Figure 1].

She was subsequently referred to our institution at 20 weeks age of gestation via telehealth for further management. Unfortunately, face-to-face consultations were initially difficult due to frequent lockdowns during the COVID-19 pandemic.

A review of slides from her previous surgery showed atypical lipomatous tumor. A multidisciplinary conference was carried out consisting of surgical oncology, neonatology, thoracovascular surgery, urology, and anesthesiology. As the mass was rapidly enlarging resulting in structural crowding of the tumor and the ongoing pregnancy, the consensus was to do a two-step procedure – abdominal delivery at 34 weeks followed by elective tumor removal after 2 weeks.

The prenatal course was unremarkable. After completion of steroids for fetal lung maturity, she underwent elective low-segment cesarean section. Intraoperatively, the gravid uterus was pushed to the left hemiabdomen, with the fundus occupying the left flank. There was a huge lobulated mass, predominantly solid, with cystic components occupying the entire right hemiabdomen. The bowels were displaced to the left upper quadrant and were grossly normal. No tumor implants were noted.

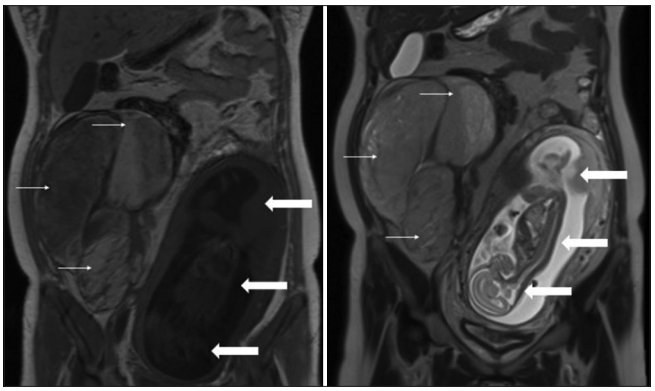

Figure 1: Abdominal magnetic resonance imaging at 19 4/7 weeks showing a well-defined, multilobulated, intraperitoneal mass lesion (thin arrows) measuring 20.2 cm × 14.8 cm × 15.3 cm, heterogeneous with soft tissue, fat, and cystic components exhibiting predominantly T1-hypointense (left image) and T2-iso to hyperintense signals (right image). The gravid uterus is displaced to the left (block arrows)

She delivered a baby girl weighing 2200 g, with Apgar score 9, 9, 34 weeks by pediatric aging, appropriate for gestational age. Adhesions were encountered between the omentum and anterior abdominal wall, as well as the right lower uterine segment and the inferior portion of the mass. A tributary of the right uterine artery was injured during adhesiolysis. The right adnexa were surgically absent. The left fallopian tube and ovary were grossly normal.

The estimated blood loss was 1.8 L. Correction of anemia was done postoperatively, after which she was subsequently discharged. Etonogestrel subdermal implant was inserted for contraception.

CT scan done 1 day postoperatively showed a large, well-defined, lobulated, mixed soft-tissue and fat-containing mass occupying the right hemiabdomen measuring 29.2 cm × 27.1 cm × 28.8 cm [Figure 2]. Neither lung metastases nor pleural effusion were present.

The patient subsequently underwent cystoscopy, preoperative right ureteral stenting, adhesiolysis, and wide excision of retroperitoneal tumor recurrence at 2 weeks postpartum. Intraoperatively, there was a huge, encapsulated, lobulated, cystic mass with solid areas measuring 35 cm × 25 cm × 22 cm with a 5 cm long discontinuation at the medial portion of the capsule. The mass was attached to the right retroperitoneum and extended intraperitoneally due to its size [Figure 3]. On the cut section, it consisted of predominantly fatty tissues with areas of hemorrhage [Figure 4]. There was a bony

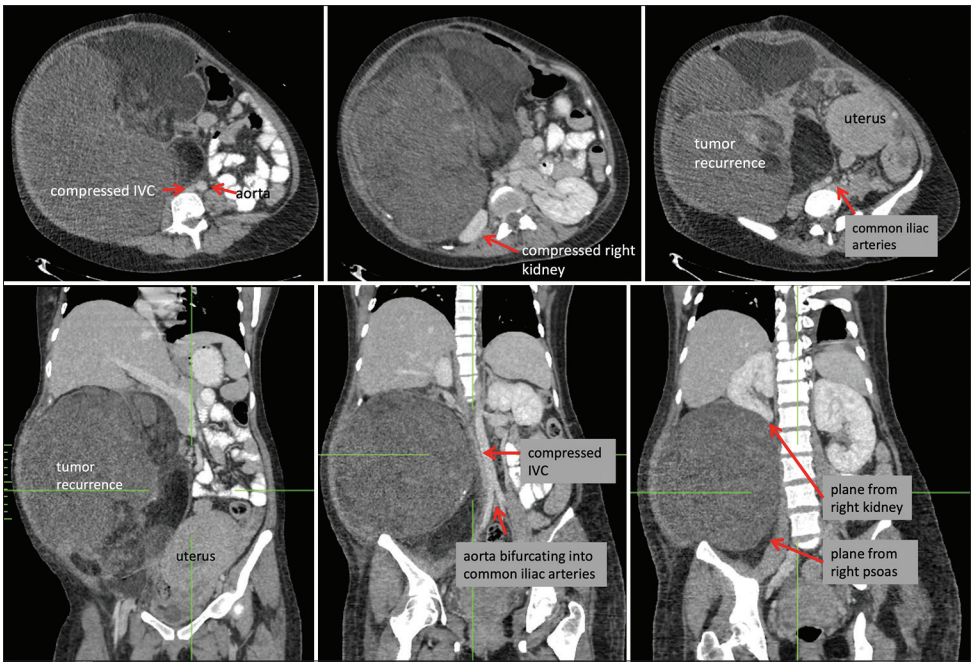

Figure 2: Abdominal computed tomography scan done 1 day postpartum showing a large, well-defined, lobulated, mixed soft tissue and fat-containing tumor occupying the right hemiabdomen measuring 29.2 cm × 27.1 cm × 28.8 cm and its relationship with nearby structures. IVC: Inferior vena cava

component measuring 8.5 cm × 7.5 cm × 5.5 cm near the inferior portion of the mass.

There were also adhesions to the surrounding small bowels. The inferior vena cava, bifurcation of the iliac vessels, and right ureter were intact. There were no gross tumor remnants.

The estimated blood loss was 3 L, for which correction of anemia was done. She had an otherwise unremarkable postoperative course.

Histopathology showed dedifferentiated liposarcoma with a positive tumor margin at the medial side [Figure 5].

The patient was classified as stage IIIB (T4N0M0G2) based on the American Joint Committee on Cancer TNM system. Adjuvant chemotherapy was advised because of the positive tumor margin. Postpartum, she was advised to refrain from breastfeeding on initiation of chemotherapy due to potential excretion through breast milk. Hence, she was also advised to seek breast milk donors. She had completed four cycles of doxorubicin, ifosfamide, and mesna. However, surveillance imaging at 6 months posttumor removal showed recurrence at the right pelvic region. The patient is for reassessment for possible tumor resection and radiotherapy.

Discussion

Liposarcomas are categorized using the World Health Organization classification of soft-tissue tumors. In terms of malignant potential, they may either

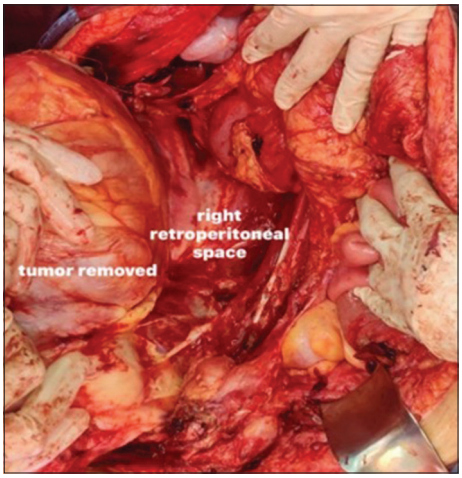

Figure 3: Intraoperative findings on the second operation showing the tumor as it is being removed from its attachment at the right retroperitoneal space

be benign, intermediate (locally aggressive), or malignant.[2] Histologically, the four major subtypes include well-differentiated, which is synonymous with atypical lipomatous tumor; dedifferentiated; myxoid; and pleomorphic liposarcoma. Among these, the well-differentiated and dedifferentiated types are most common in the retroperitoneum.[2] Atypical lipomatous tumors are considered tumors with intermediate malignant potential and locally aggressive, while dedifferentiated liposarcomas are considered malignant.[2] In terms of tumor grade, well-differentiated and myxoid types fall under low-grade tumors, while dedifferentiated and pleomorphic types are considered high grade.[2]

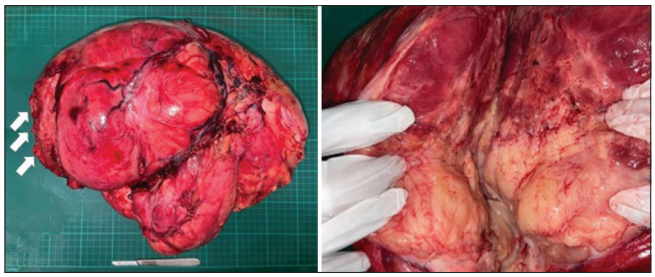

Figure 4: Left image: Excised retroperitoneal mass measuring 35 cm × 25 cm × 22 cm encapsulated, lobulated soft to hard with a 5 cm long area of rupture at the left/medial side (block arrows). Right image: Cut specimen of the tumor showing fatty tissues with areas of hemorrhage

The etiology of liposarcoma is not entirely clear but is thought to involve genetic changes and exposure to radiation or chemical substances.[3]

Dedifferentiated liposarcoma is characterized by nonlipogenic components arising from a well-differentiated liposarcoma that confers metastatic potential. This histologic type often grows *de novo* in more than 90% of cases or as a recurrence in <10%.[2] The mechanisms behind dedifferentiation are not fully understood but may involve pathways like c-Jun N-terminal kinase leading to peroxisome proliferator-activated receptors gamma inactivation, affecting adipocytic differentiation.[2]

Imaging studies often provide a characteristic appearance of liposarcomas, making pretreatment biopsies sometimes unnecessary, especially if the mass is resectable. Hence, biopsy was not considered in this case.

Surgery is the mainstay of treatment, and the goal should be to complete resection as much as possible. It is difficult, however, to obtain a wide negative tumor-free margin among retroperitoneal tumors owing mostly to its large size, deep location, and proximity to vital structures. This results to locally recurrent disease, which constitutes 75% mortality among cases.[4] High-grade dedifferentiated tumors, however, have higher recurrence risk and systemic spread and, hence, are unlikely to benefit from extensive surgery.[5]

During pregnancy, surgery is usually deferred to the second trimester whenever possible due to increased rates of miscarriage if done in the first trimester.[1] If performed after 24 weeks, continuous fetal monitoring should be done along with preparations for a possible emergent delivery.[1]

Unfortunately, the patient was only seen during the mid-second trimester of pregnancy, and due to the complexity of the case, immediate action cannot be taken without thorough preparation, including a multidisciplinary consultation. This is especially

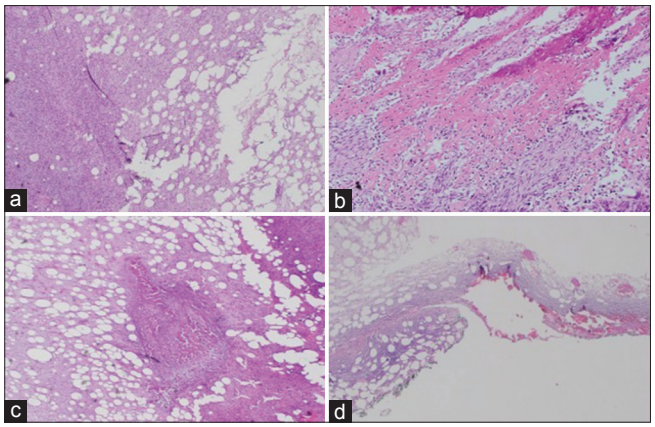

Figure 5: (a) Interphase between the well-differentiated and dedifferentiatied components. The right side of the image shows lipocytes of varying sizes, which is characteristic of well-differentiated liposarcoma. An abrupt transition is noted toward the left side of the image, which is predominantly occupied by hyperchromatic spindle cells. (b) microscopic image of the solid portion of the mass showing bone formation, consisting of osteoblasts and osteoclasts occupying the nonlipogenic areas of the mass. (c) central area of necrosis showing loss of architecture and cellular details, which is surrounded by lipocytes of varying sizes with intervening stroma. (d) tumor margin at the medial portion of the mass showing tissues containing lipocytes protruding out of the margin with no visible capsule. This is in contrast to other areas which show an intact fibrous capsule

crucial among the COVID-19 pandemic, during which lockdowns were frequently implemented. At that point of her pregnancy, surgery poses risk for prematurity brought about by preterm labor or nonreassuring fetal status. Hence, it must be performed at a time that emergent delivery can be carried out in the event of nonreassuring fetal status. One option was to proceed with surgery to avoid further enlargement of the mass but at the expense of obstetrical risks such as preterm delivery. The other option was to delay surgery up to an acceptable age of gestation, where there is a good chance for fetal survival in case delivery should be necessary.

Case reports were gathered as summarized in Table 1.[6-11] Similar to the study of Oh *et al.* in 2014, the consensus for this case was to perform a 2-staged procedure – scheduled delivery followed by elective tumor removal.[6] Considering the background of a prior atypical lipomatous tumor, which has intermediate malignant potential although with a 10% chance of dedifferentiation, the decision, in this case, was to postpone surgery. The multidisciplinary team agreed that the best time to carry out a successful preterm delivery was at 34 weeks after completion of antenatal corticosteroids for fetal lung maturity. Tumor excision was elected 2 weeks postpartum to ensure complete tumor removal while preventing excessive blood loss brought about by pregnancy.

Though not an outright indication for cesarean delivery, the abdominal route was chosen in order to avoid the possibility of tumor rupture and for a more controlled environment.

Table 1: Summary of gathered case reports on retroperitoneal liposarcoma in pregnancy

	AOG at diagnosis	Intervention	AOG at delivery	Outcome
Oh *et al.*, 2014[6]	28 2/7 weeks 35 cm × 26 cm × 17 cm mass atretroperitoneal area	Cesarean section and tumor removal at two different stages Prevent excess blood loss For complete tumor removal	29 weeks	BW 1180 g Apgar score 4, 6 Dedifferentiated liposarcoma Chemoradiation Survived at 6 months follow-up
Jeng *et al.*, 2005[7]	12 weeks AOG History of well-differentiated sarcoma 9.3 cm × 6.0 cm and 6.7 cm × 6.3 cm, right adnexa and cul-de-sac	The patient opted to continue pregnancy Radical excision of the retroperitoneal tumor, multiple peritoneal biopsies, bilateral pelvic lymphadenectomy, PALS, IO	36 weeks 25 cm × 20 cm	BW 2558 g, Apgar scores 9, 10 Well-differentiated retroperitoneal myxoid liposarcoma with local metastases Tumor recurrence after 4 months Debulking surgery with radiotherapy Myxoid liposarcoma with focal mixed round cells Tumor persistence, excision done Poorly differentiated myxoid liposarcoma
De Jaco *et al.*, 2014[8]	34 weeks 20 cm retroperitoneal complex mass	Cesarean section followed by resection of retroperitoneal mass	36 weeks	BW 1850 g Apgar scores 6, 8 High-grade myxoid liposarcoma Died 8 months postsurgery
Rousková *et al.*, 2007[9]	Metastatic abdominal liposarcoma during the third trimester of the pregnancy	Induced vaginal delivery, palliative surgery and one cycle of systemic combination chemotherapy	Unspecified	Died of progressive disease 1 month after diagnosis High-grade pleomorphic liposarcoma arising from the retroperitoneum with liver and lung metastases
Lopes *et al.*, 2009[10]	First trimester	Complete surgical resection at 13 weeks AOG 22 cm × 20 cm × 20 cm retroperitoneal mass	37 weeks	Well-differentiated liposarcoma
Huo *et al.*, 2015[11]	16 weeks left retroperitoneal tumor, 16 cm × 9 cm	Surgery at 20 weeks AOG	Elective cesarean section at 37 weeks	Low-grade myxoid liposarcoma No recurrence 6 months postoperatively

*De Jaco P, Giorgio M, Zantedeschi B, Mazzoleni G, Marabini A. A case of retroperitoneal liposarcoma in pregnancy. Acta Obstet Gynecol Scand 1993;72:122-4, †Rousková L, Melichar B, Nikolov DH, Cerman J Jr., Havel E, Megancová J, *et al.* Fulminant course of metastatic liposarcoma after delivery – Case report. Eur J Gynaecol Oncol 2007;28:67-8, ‡Lopes RI, Machado M, Paz C, Santos AC, Rezende WW. Successful outcome of a surgically treated giant retroperitoneal liposarcoma during pregnancy. Arch Gynecol Obstet 2009;280:1067-9, §Huo D, Liu L, Tang Y. Giant retroperitoneal liposarcoma during pregnancy: A case report. World J Surg Oncol 2015;13:145. AOG: Age of gestation, BW: Birthweight, PALS: Para-aortic lymph node sampling, IO: infracolic omentectomy

Based on imaging studies conducted on such tumors, the mean tumor volume doubling time is around 100 days.[12] In our case, from an initial tumor volume of 20.2 cm × 14.8 cm × 15.3 cm based on abdominal MRI done at 19 weeks and CT done 1-day postpartum showing tumor enlargement to 29.2 cm × 27.1 cm × 28.8 cm, there was five times tumor enlargement in 104 days indicative of the aggressive nature of the disease.

Age, size, resectability of the mass, histology, grade, nodal disease, and distant metastasis are all contributory factors that influence the overall prognosis of these tumors.[13] Distant metastasis is largely dependent on the tumor grade. Well-differentiated tumors are not considered aggressive but are associated with local recurrence.[5] Dedifferentiated tumors, on the other hand, are highly aggressive and are associated with metastasis and recurrence.[5]

Well-differentiated tumors have a 90% 5-year survival rate, while dedifferentiated tumors have only a 75% 5-year survival rate.[12] Approximately 10% of retroperitoneal liposarcoma are metastatic at presentation, often found in the lungs or liver.[14] The presence of distant metastases is an adverse prognostic factor, with a poor overall survival of 13 months once found.[13]

Although distant metastasis is rare, local recurrence is common.[2] Their large size, deep location, and involvement of adjacent vital structures may sometimes preclude complete resection. Local recurrence within 5 years occurs in 41%–50% of patients who had a complete resection.[2] Pregnancy does not seem to affect overall maternal survival.[7]

Managing recurrent retroperitoneal liposarcoma in pregnancy involves several ethical principles. Beneficence focuses on promoting the well-being of the patient and the fetus, while nonmaleficence involves avoiding harm to both. The decision to defer surgery aims to balance the benefits of tumor removal with the risks of surgery during pregnancy, such as preterm labor, fetal distress, or surgical complications. By delaying surgery until the fetus is more developed, the team aims to maximize the chances for a better fetal outcome while minimizing harm to the mother due to the delay in definitive treatment. Finally, the principle of autonomy is upheld by respecting the patient's choice, providing her

with comprehensive information about her condition, treatment options, and potential risks and benefits.

Adjuvant radiation therapy is a valuable treatment option to improve local control of liposarcoma, especially in the presence of positive tumor margins or high-grade tumors. However, there is a paucity of studies regarding its role in retroperitoneal liposarcomas due to the rarity of these tumors. Although they are generally radiosensitive,[14] the use of radiotherapy is complicated by treatment-related toxicities to visceral structures that have low radiation tolerance, such as the liver, kidney, bowels, and spinal cord. Postoperatively, the bowels tend to occupy the tumor bed and may become fixed by adhesions, which adds to difficulty in the delivery of radiotherapy to the resection site.

The role of adjuvant chemotherapy, on the other hand, remains controversial. Although randomized trials suggest benefit from adjuvant chemotherapy for extremity sarcomas, there are only limited studies on its role in retroperitoneal liposarcomas. Previous studies show limited benefit of chemotherapy with response rates of <12%.[15] This has been challenged by more recent studies.

Chemotherapy was administered as adjuvant treatment for our patient due to the iatrogenic rupture at the medial side of the tumor. Doxorubicin, ifosfamide, and mesna (AIM protocol) are the preferred regimen for systemic adjuvant treatment for soft-tissue sarcoma.[16]

Radiotherapy was not immediately given to our patient for several reasons. As no gross tumor was left intraoperatively, clips were not left in the tumor bed, which could have served as a guide for postoperative radiotherapy. Furthermore, the tumor bed is large and is likely already occupied by bowels. Hence, radiotherapy was not employed as first-line adjuvant treatment due to possible adverse effects on nearby structures. Given the potential hematogenous spread of dedifferentiated liposarcoma, chemotherapy was administered to address both this risk and the potential for micrometastatic spread.

Follow-up is necessary due to the high propensity for recurrence. Based on the latest National Comprehensive Cancer Network[16] guidelines for soft-tissue sarcoma, follow-up physical examination with imaging is recommended every 3–6 months for 2–3 years, then every 6 months for the next 2 years, and then annually.[16]

Conclusion

Retroperitoneal liposarcoma, though rare, may occur in the reproductive age and consequently during pregnancy as well. Although rarely metastatic at presentation, it is locally aggressive with a high propensity for local recurrence. There should be a high index of suspicion for patients who present with a prior history of a retroperitoneal mass. Surgery remains the mainstay of treatment. However, timing should be discussed by the multidisciplinary team while balancing the risks between maternal and fetal survival.

Authorship contributions

Jemimah T. Cartagena - Lim, MD) - Involved in the conceptualization, writing of the original draft, review and editing.

Kristine Therese Elises-Molon, MD - Involved in the conceptualization, review of the draft and supervision.

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Conflicts of interest

There are no conflicts of interest.

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