



# Metastatic Uterine Leiomyosarcoma in a Nullipara with Primary Infertility: A Case Report

Okechukwu B. Anozie<sup>\*1,2</sup>, Johnbosco I. Nwafor<sup>1</sup>, Chidi U. Esike<sup>1,2</sup>, Chukwuemeka I. Ukaegbe<sup>1,2</sup>, Richard L. Ewah<sup>3</sup>, Emeka O. Onwe<sup>4</sup>, Justus N. Eze<sup>1,2</sup>, Sunday U. Asogwa<sup>1</sup>

<sup>1</sup>Department of Obstetrics and Gynaecology, Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Ebonyi State, Nigeria

<sup>2</sup>Department of Obstetrics and Gynaecology, Ebonyi State University, Abakaliki, Ebonyi State, Nigeria

<sup>3</sup>Department of Anaesthesia, Federal Teaching Hospital, Abakaliki, Ebonyi State, Nigeria

<sup>4</sup>Department of Paediatrics, Alex Ekwueme Federal University Teaching Hospital, Abakaliki, Ebonyi State

\*Corresponding Author: Dr. Okechukwu Bonaventure Anozie; okayanoziey2k@yahoo.com

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## Abstract

Uterine leiomyosarcoma accounts for 1-2% of uterine cancers. It is an extremely aggressive malignancy associated with a poor prognosis. Women affected may vary in age, but are most common between 4<sup>th</sup> and 7<sup>th</sup> decades of life. Presenting symptoms mimic uterine leiomyoma. Preoperative diagnosis of uterine leiomyosarcoma is difficult and often made at time of surgical resection. We report a case of Mrs A.E, a 40 year old nullipara with history of primary infertility of 20 years duration, who presented with abdominal swelling of 3 years and vaginal bleeding of 7 weeks duration. Abdominopelvic ultra-sonography done at presentation was suggestive of leiomyoma. She was scheduled for myomectomy and subsequently had total abdominal hysterectomy and omentectomy following intra-operative findings of features suggestive of leiomyosarcoma with evidence of metastasis to omentum. These findings were confirmed on histology of the specimen. She received one cycle of combination chemotherapy but was lost to follow up. Uterine LMS is an aggressive tumour, therefore, a high index of suspicion is needed especially for huge uterine nodules and such patients must be closely monitored for adequate management.

**Keywords:** *Metastatic uterine leiomyosarcoma, nullipara, primary infertility.*

## Introduction

Uterine leiomyomas are the most common gynaecologic tumours of the uterus.<sup>[1]</sup> These benign tumors arise from overgrowth of smooth muscle and connective tissue within the uterus and are frequently diagnosed in childbearing years.<sup>[1]</sup> Leiomyomas can undergo various degenerative changes, however malignant transformation is rare.<sup>[1]</sup>

Uterine leiomyosarcoma (ULMS) is a malignancy of smooth muscle origin whose incidence is only 1 per 1000 that of leiomyoma.<sup>[1]</sup> It accounts for 1 - 2% of uterine malignancies.<sup>[2]</sup> The U.S. Food and Drug Administration (FDA) estimates the rate of uterine LMS in surgical procedures performed for presumed benign fibroids to be 1 in 498.<sup>[3]</sup> Other estimates of the risk of encountering an unexpected ULMS following surgery for presumed benign uterine leiomyoma range from 1 in 300 to 1 in 5000.<sup>[4]</sup> Women with ULMS are on average more than a decade older (age above 50 years) than those with leiomyomas.<sup>[5]</sup>

The presenting symptoms of ULMS are the same as those of leiomyoma.<sup>[6]</sup> This characteristic hinders a prompt suspicion and diagnosis before any surgical intervention. Signs and symptoms

frequently associated with uterine LMS are abnormal uterine bleeding, pelvic pain and a rapidly enlarging fibroid.<sup>[6]</sup>

Currently, even though morphological features (margins, necrosis, haemorrhage, vascularity, calcifications and heterogeneity) and especially diffusion-weighted magnetic resonance imaging can help to characterize large uterine lesions, we are unable to accurately predict the presence of malignancy based solely on individual imaging features in any available imaging studies.<sup>[7]</sup>

Uterine leiomyosarcoma is diagnosed using the Stanford histologic criteria: coagulative necrosis, cellular atypia, elevated mitotic rate of greater than 10 mitotic figures per 10 high power field.<sup>[8]</sup> Most cases of ULMS arise de novo with limited reports of ULMS arising in leiomyoma.<sup>[8]</sup>

The standard of care in this disease is en bloc total hysterectomy, with bilateral salpingo-oophorectomy not well established in premenopausal women.<sup>[9]</sup> Adjuvant pelvic radiotherapy may help to reduce the local recurrence rates, but have little or no impact on overall survival. Similarly, the clinical benefit of combination chemotherapy versus single-agent chemotherapy is still under investigation.<sup>[10]</sup> Most uterine leiomyosarcomas are large and are advanced when detected.<sup>[10]</sup>

They are usually fatal despite combinations of surgery, radiation therapy, and chemotherapy. Five-year survival is about 25%.<sup>[11]</sup> Overall, ULMS carries a poor prognosis even when it is confined to the uterus.<sup>[11]</sup>

Herein we report a case of 40 year old nullipara with history of primary infertility of 20 years duration that was managed for uterine leiomyosarcoma at Alex Ekwueme Federal University Teaching Hospital, Abakaliki, South-east, Nigeria.

### **Case report**

A case of Mrs A.E, a 40 year old nullipara with history of primary infertility of 20 years duration, who presented with abdominal swelling of 3 years and vaginal bleeding of 7 weeks duration. The abdominal swelling was gradual in onset and progressively increased in size. It was associated with abdominal discomfort, early satiety and waist pain. Vaginal bleeding was initially mild in form of spotting and later became profuse 2 days prior to presentation. The bleeding consisted of flank red blood and came in clots. It was contained with 4 well soaked perineal pads per day. It was associated with dizziness and fainting spells. For the above symptoms, she presented to the accident and emergency department of our facility for care. There was history of loss of appetite and weight loss.

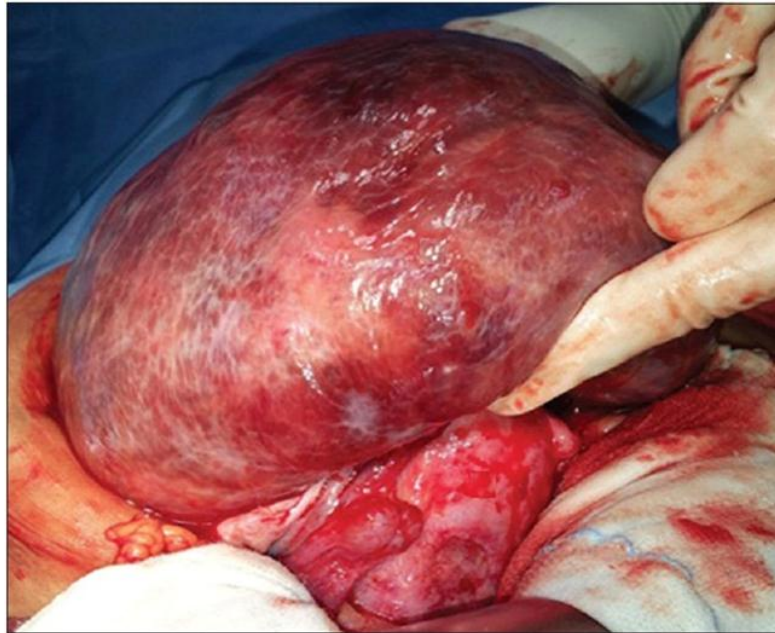
She had 3-day menstrual flow in a regular 28-day menstrual cycle prior to onset of symptoms. There was history of dysmenorrhea and menorrhagia. She was aware of Pap smear but had not been screened. She was not a known hypertensive or diabetic. She was a civil servant, with Bachelor's degree in Geology, married in a monogamous setting to a legal practitioner.

On examination, She was in no obvious distress, not dehydrated, afebrile (temperature = 36.6oC), pale and anicteric. There was no pedal oedema nor peripheral lymphadenopathy. She weighed 107 kg and her height was 1.64 meters. Her BMI was 39.8 kg/m<sup>2</sup>. Her pulse rate was 92 beats per minute and blood pressure was 120/70 mmHg. The first and second heart sounds were heard. There were no murmurs. Her lung fields were clinical clear. The abdomen was distended and moved with respiration. There was no area of tenderness. There were multiple firm nodular masses in the abdomen with boundaries difficult to delineate. There were difficulties in palpating intra-abdominal organs due to the presence of intra-abdominal masses. There was no ascites. Pelvic examination showed vulva smeared with blood. There was no active vaginal bleeding. Speculum examination showed a health-looking cervix. Bimanual examination revealed multinodular uterus of 40 cm Symphyseal Fundal height (SFH) by abdominal palpation. The anterior posterior diameter by ultrasonography also showed 150mm uterine size. The adnaexa could not be felt because of multiple abdominal masses and tenderness. The pouch of Douglas was free. A provisional clinical diagnosis of symptomatic uterine leiomyoma with degenerative changes was made.

Investigation results showed haemoglobin concentration of 5.7 g/dl. Complete blood count, serum electrolytes, urea and creatinine, liver function test, chest x-ray and ECG results were normal. Abdomino-pelvic ultrasound showed bulky uterus with multiple roundish hypoechoic masses. The uterus measured 150 mm in antero-posterior diameter. The adnexae were normal. Pouch of Douglas was empty. The liver, gall bladder, pancreas, spleen and kidneys showed normal sonographic features. No ascites was seen.



**Fig.1. Abdomino-Pelvic Ultrasound image of Mrs. A.E,**



**Fig.2. Uterine Mass on Laparotomy**

Clinical diagnosis of abnormal uterine bleeding secondary to uterine fibroid was made. The clinical findings and the diagnosis were explained to her. She was admitted into the emergency department. She received 5 units of blood. The post-transfusion haemoglobin concentration was 10.2 g/dl. She was commenced on tablets Norethisterone enantate 10 mg daily for one week. She was counseled on myomectomy with possibility of hysterectomy depending on intra-operative findings. She gave consent for the procedure. She subsequently had total abdominal hysterectomy and omentectomy. The intra-operative findings were enlarged uterus about 40 weeks pregnancy size, multiple uterine fibroids of subserous, intramural, submucous, and pedunculated types, no clear delineation of uterine muscles from fibroid masses, cheesy-looking uterine muscles, friable and haemorrhagic mass on the inferior aspect of the omentum, healthy-looking fallopian tubes and ovaries. The specimens were sent for histology. She was transfused with 2 units of whole blood during surgery.

Following surgery, she was commenced on intravenous fluid, antibiotics and analgesic. She subsequently made uneventful recovery. The histology result was retrieved on day 9 post-operation and showed leiomyosarcoma with metastasis to the omentum. She was counseled on the diagnosis and the need for chemotherapy. She was subsequently commenced on intravenous doxorubicin 75 mg/m<sup>2</sup> weekly and intravenous ifosfamide 5 g/m<sup>2</sup> weekly for 3 weeks. She received 1<sup>st</sup> course of chemotherapy and was discharged home on day 25 post-operation for follow up at gynaecological clinic. She was lost to follow-up.

## Discussion

Uterine leiomyosarcoma is an uncommon malignancy accounting for approximately 1- 2% of uterine cancers.<sup>[10]</sup> Studies done by Adesiyani in Kano<sup>[10]</sup>; Ogunbiyi in Ibadan<sup>[11]</sup> and Seleye-Fubara in Port Harcourt<sup>[12]</sup>, Nigeria and other parts of Africa show that ULMS is a rare tumour<sup>[13]</sup>.

Uterine leiomyosarcoma typically occurs in women between 4<sup>th</sup> and 7<sup>th</sup> decades of life.<sup>[14]</sup> Mrs A.E was 40 years old and falls within the age bracket for ULMS. However, a case of 14-year old, thin, African female, gravida 0, with abdominal discomfort and increased abdominal circumference and ruptured uterus secondary to ULMS was once seen in Istanbul, Turkey.<sup>[15]</sup> Also, Vaz, et al

reported a case of ULMS within a prior myomectomy site in a 16-year old Hispanic female in U.S.A.<sup>[16]</sup> This shows that ULMS can occur in different age groups. It also confirms that the epidemiological profile of the patients does not identify any unique characteristic that defines the group diagnosed with the disease, making screening in a selected group of patients almost impossible.

Although leiomyosarcoma can occur elsewhere in the pelvis, including the cervix and urinary bladder, it is more commonly found in the uterus<sup>[16]</sup> as seen in our case.

Women with ULMS usually present with abnormal vaginal bleeding, palpable uterine mass and sign and symptoms resembling leiomyoma.<sup>[16]</sup> Our patient presented with complaints of abdominal swelling and abnormal vaginal bleeding, which are the usual presentations of the lesion as seen in most studies. However, our patient had primary infertility of 20 years duration. Adesiyani in Zaria, Nigeria reported a case of ULMS in a woman with background history of infertility.<sup>[11]</sup> It is not known whether undiagnosed ULMS may be associated with infertility as seen in our patient.

Diagnosis is often challenging before histopathologic analysis as no imaging modality can reliably distinguish ULMS from leiomyoma.<sup>[17]</sup> Abdomino-pelvic ultrasonography done for our patient was suggestive of huge leiomyoma with degenerative changes; this is the usual presentation seen. Harry et al. reported that the most common presentation of uterine LMS was an incidental finding at the time of surgery.<sup>[17]</sup> In France, Leung et al. studied a 1,297-patient cohort who were hysterectomised for probable uterine leiomyomas, and found three patients with the final diagnosis of LMS (0.23%).<sup>[18]</sup> Our patient, Mrs A.E was scheduled for myomectomy for uterine leiomyoma. However, intraoperative findings raised suspicion for ULMS which necessitated performing abdominal hysterectomy and omentectomy. This highlights difficulty in making preoperative diagnosis of ULMS.

Management of ULMS remains controversial.<sup>[19]</sup> Most experts offer total abdominal hysterectomy. Following hysterectomy, the role of oophorectomy and lymph node sampling for ULMS is unclear as metastases to these organs occur in only a small percentage of cases.<sup>[19]</sup> Some physicians may recommend bilateral salpingo-oophorectomy due to the concern that oestrogen and progesterone may drive the risk of recurrence. Our patient had

total abdominal hysterectomy and omentectomy without bilateral oophorectomy. Even though total hysterectomy has been established as the safest surgical procedure for cases where the diagnosis is reached during the histological examination after a myomectomy, Gadducci et al. have reported successful cases of survival free of disease in Italy, including some with future pregnancies, when conservative surgery was requested.<sup>[20]</sup> Also, Yanque in Peru reported cases of two patients who were treated by myomectomy, and pathological analysis after surgery revealed the diagnosis of ULMS. These patients, after counselling, opted not to have hysterectomies, and were kept under clinical and radiological follow-up, and showed no recurrence of the disease. One of these patients had two subsequent pregnancies.<sup>[21]</sup> These findings showed that in premenopausal patients with an incidental finding of uterine LMS, conservative management can be successful with close follow-up. This option was not adopted for our patient because she had advanced disease with macroscopic evidence of metastasis to the omentum. Besides, she had poor health seeking behaviour and was unlikely to adhere to follow-up.

Adjuvant therapy for early stage disease remains controversial as multiple clinical trials have failed to demonstrate benefit on overall survival.<sup>[21]</sup> However, there are a variety of adjuvant therapies that can be offered to women with advanced and metastatic ULMS, including radiotherapy, hormone therapy and chemotherapy.<sup>[21]</sup> Pelvic radiotherapy is not a common treatment for ULMS patients as it has not been shown to significantly improve survival.<sup>[21]</sup> There have been no prospective studies on the impact of hormone therapy in the adjuvant setting for ULMS patients.<sup>[22]</sup> However, because a significant percentage of ULMS expresses oestrogen and/or progesterone receptors, hormonal blockade is used empirically by some clinicians. Recently, postoperative chemotherapy regimens have been tested with the hope of preventing recurrence and increasing overall survival.<sup>[22]</sup> However, due to the rarity of uterine LMS, no conclusive evidence has been found. In 2013, a phase II trial by Hensley et al. showed that adjuvant therapy of fixed-dose-rate gemcitabine-docetaxel followed by doxorubicin in high-grade ULMS patients with stage I, II, and IIIA disease resulted in higher than expected progression-free survival (PFS) rates.<sup>[23]</sup> Unfortunately, the subsequent phase III trial was prematurely closed due to slow accrual.<sup>[23]</sup> However, a National Cancer Database Study showed that adjuvant chemotherapy is associated with 8.5 months increased survival of women with metastatic uterine leiomyosarcoma.<sup>[24]</sup> While there is no conclusive evidence on overall survival benefit from utilizing adjuvant chemotherapy for ULMS, there was evidence of metastasis to the omentum at the time of initial resection in our patient and the entire pelvis was at risk for disease recurrence. Given the risk of recurrence, a multimodality adjuvant approach was used. The available multi-modality regimens including ifosfamide and doxorubicin were utilized. She received one cycle of chemotherapy before discharge from the hospital and was scheduled for gynaecological clinic appointment. The patient was eventually lost to follow-up.

Recurrence is common up to 70%. Survival rate is dependent on the stage of the disease at diagnosis. Five-years survival rate is 50-55% for stage 1, 8-12% for stage 2-4. Overall, 5-years survival rate, for all stages ranges from 30-50%.<sup>[24]</sup>

## Conclusion

In conclusion, malignant transformation of a leiomyoma to a ULMS is rare. We report a unique case of metastatic ULMS in a 40-year old nullipara with history of primary infertility. Therefore a

high index of suspicion even at an early age is key in early diagnosis and proper management of the disease condition.

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