

Case Report Paper

Long survival in patients with metastatic leiomyosarcoma of the uterine corpus: A report of 2 cases

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Leiomyosarcoma of the uterus is relatively uncommon in Ahmadu Bello University Teaching Hospital, Zaria – Nigeria and generally has a poor prognosis. A report of palliative treatment for invasive leiomyosarcoma of the uterine corpus with pulmonary metastases in 2 women is presented. Both patients presented with advanced bulky locoregional and metastatic disease. The patients had palliative care using multimodality approach with surgery, chemotherapy and radiotherapy. 2 years after treatment, the patients were alive without evidence of locoregional disease, with one patient having residual pulmonary metastasis. Despite evidence of metastasis, it is possible to have long survival, effective palliative care and improvement in quality of life with multimodality and multidisciplinary collaboration.

Key words: Leiomyosarcoma, uterine corpus, pulmonary metastasis.

INTRODUCTION

Uterine corpus sarcoma is a rare malignant tumour and it accounts for less than 1% of all gynaecological malignancies and 2 - 5% of all uterine malignancies (Harlow et al., 1986; Harris et al., 2005). Of the uterine sarcomas, carcinosarcoma is the commonest (50%), followed by leiomyosarcoma LMS (30%) and endometrial stromal sarcoma (15%) (Silverberg et al., 1990) Uterine sarcomas arise primarily from the mesenchymal or muscle elements of the uterus. They may be comprised of pure mesenchymal elements or of mixed mesenchymal and epithelial elements (Harris et al., 2005). The incidence of LMS of the uterus in Nigeria is unknown but from the cancer registry of Ahmadu Bello University Teaching Hospital, Zaria – Nigeria, it accounted for 2.8% (2000 – 2007) of all leiomyosarcoma, irrespective of sites. The incidence of this sarcoma in America is about 0.67 per 100,000 women (Quinn et al., 1997). LMS may arise from the uterine myometrium *de novo* or may be transformed

formed from a preexisting benign leiomyoma and the risk factors for development of sarcoma of uterine corpus have not been completely elucidated. The incidence of sarcomatous transformations in benign uterine leiomyoma is between 0.13 and 0.81% (Berchuck et al., 1988). We discuss the clinico - pathological findings, response to palliative treatment and long survival in two Nigerian patients with invasive leiomyosarcoma and pulmonary metastases.

CASE 1

A 54 - year old housewife referred from Gynaecology clinic of Ahmadu Bello University Teaching Hospital (ABUTH) Zaria, to Radiotherapy and Oncology Clinic (ABUTH) as a case of leiomyosarcoma of the uterus, presented with history of lower abdominal pain, spontaneous and post coital vaginal bleeding and vaginal discharge for about 48 months. Per vaginal bleeding requires an average of 4 - 5 pads per day with associated dizziness. The review of other systems was not contributory. Married twice, second marriage was 4 years ago in to a

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polygamous family. She is Para⁷⁺², 5 alive; last child birth was 23 years ago, all the children were delivered at home. She attained menopause more than 10 years ago. She neither smoke cigarette nor ingest alcohol. No family history of any malignancies.

Examination revealed an obese, elderly woman, pale; other aspects of general examination were not remarkable. Abdominal examination revealed a grossly distended abdomen, with tender, globular, immobile mass in the suprapubic area arising from the pelvis about 18 weeks size and the abnormal finding on vaginal examination was creamy yellow discharge and bleeding from cervical os. Laboratory data showed a low packed cell volume (PCV) of 26% and no abnormality in serum urea, creatinine, sodium, potassium, chloride and bicarbonate concentrations. A liver function test was also within normal limits. Chest x-ray revealed multiple nodules of different sizes in both lung fields but no pleural effusion. Abdomino - pelvic ultra-sound revealed an enlarged uterus with an anterior wall myoma measuring 8 x 6 x 5 cm in size. Both ovaries appear normal. After optimization of patient and blood transfusion, Total abdominal hysterectomy and bilateral Salpingo - oophorectomy, without lymphadenectomy was performed. Intra - operative findings are those of a huge retroverted uterus with right hydrosalpinx, normal left adnexal and necrotic friable tumour on the uterus, with extrauterine infiltrating of the pelvic peritoneum anteriorly but the cervix is free. Histopathology report confirmed leiomyosarcoma of the uterus corpus. Microscopic description revealed ovoid spindle shaped cells with vesicular nuclei with prominent nucleoli. Mitosis (10 - 12) per high field (phf) was seen with areas of necrosis. The endometrium was atrophic with normal fallopian tubes and cervix. A diagnosis of leiomyosarcoma of uterine corpus with pulmonary metastasis was made (stage IV disease).

She was commenced on Chemotherapy CYVADIC regimen (intravenous Cyclophosphamide 500 mg/m²; Vincristine 1.5 mg/m²; Doxorubicin 50 mg/m² and Dacarbazine 750 mg/m², all on Day 1, cycle repeated every 3 weeks). She had 6 courses of chemotherapy followed by radiotherapy to the pelvis. She had pre-medication with intravenous dexamethasone, hydrocortisone, granisetron and maxolon followed by oral maxolon. She had alopecia and nausea during treatment. She received 5400 cGy in 27 fractions over 5.5 weeks. Presently, 3 -years after surgery and chemoradiotherapy, she is doing well without evidence of locoregional relapse or distant metastasis. No radiological evidence of pulmonary metastasis.

CASE 2

A 35 - year old business woman referred from a private specialist hospital, to radiotherapy and oncology center of Ahmadu Bello University Teaching Hospital (ABUTH)

Zaria, as a case of leiomyosarcoma of the uterus, presented with 12 months of excessive menstrual flow (menorrhagia) warranting the use of at least 4 – 5 pads per day for about 10 days every month, suprapubic mass and progressive swelling of both lower limbs for 2 months. She has a background history of recurrent fibroids for which she had myomectomy twice. She is Para⁰⁺², attained menarche at age of 13 years and married once; she neither smoke cigarette nor ingest alcohol. No family history of any malignancies.

On examination, significant findings were dyspnoea, pallor, bilateral pedal oedema extending to the thighs, Karnofsky performance status of 70. Systemic examination revealed crepitations in both lung fields and a bulky palpable uterus of 16 weeks size. Digital vaginal examination revealed an offensive sausage - like mass protruding through the cervical os that could be felt in the vagina.

Other abnormal findings were on chest x-ray which showed widespread cannon balls opacities of different sizes in both lung fields, and ultrasound of abdomen and pelvis revealed a large solid irregular uterine mass measuring 8.7 X 8.6 cm infiltrating the pelvic side walls and extending to inguinal regions. Intravenous urography (IVU) revealed a displaced left ureter to the right with the urinary bladder markedly compressed. Her low packed cell volume (PCV) was corrected with blood transfusions. At laparotomy, there was significant haemoperitoneum that appears to have been sourced from a bizarre looking node of fibroids. The left parametrium was difficult to access because of significant bleeding from there. The paraaortic and the internal iliac lymph nodes were enlarged but no histological confirmation of lymph nodes metastases. Myomectomy was effected and histology confirmed leiomyosarcoma. Microscopic description shows a cellular tumour composed of sheets of spindle to oval cells. These have dark nuclei and coarse chromatin. There are 4 - 5 mitosis PHF and necrosis noted. A diagnosis of leiomyosarcoma of uterine corpus with pulmonary metastasis was made (stage IV). She was commenced on chemotherapy CYVADIC regimen (intravenous Cyclophosphamide 500 mg/m² Day1; Vincristine 1.5 mg/m² Day 1; Doxorubicin 50 mg/m² Day1 and Dacarbazine 250 mg/m², on Days 1 - 5, cycle repeated every 4 weeks). She had 8 courses of chemotherapy due to residual lung metastases, followed by radiotherapy to the pelvis. She received 5400 cGy in 27 fractions over 5.5 weeks. After 8 cycles, no clinical and radiological evidence of pulmonary metastases and chemotherapy was stopped.

During evaluation, 1 year after completion of treatment, she has no locoregional disease except for residual lung metastases evident on chest x - ray although remarkably reduced. She was scheduled for second line chemotherapy using Ifosfamide based chemotherapy. She absconded from clinic for 8 months only to resurface cannon balls metastases of various sizes involving the

whole lungs, with destruction of the 6th - 9th ribs on the right. She was optimized and recommenced on chemotherapy but her performance status was poor and the lungs were markedly compromised and as such she could not receive further chemotherapy. She died from the complication of lung metastases. Overall survival was 30 months.

DISCUSSION

These cases highlight the problems of late presentations, advanced disease, prevailing poverty and lack of histological pre-operative diagnosis and the role of effective palliative care in prolonging survival and improving quality of life with multimodality and multidisciplinary management. LMS may arise from the uterine myometrium *de novo* or may be transformed from a preexisting benign leiomyoma and the risk factors for development of sarcoma of uterine corpus have not been completely elucidated (Singh et al., 2006).

Application of radiation therapy to the pelvis has been considered to have an impact on the development of carcinosarcoma of the uterine corpus (Singh et al., 2006) although none of these patients had radiation therapy in the past prior to onset of leiomyosarcoma. The average age of women with leiomyosarcoma is 40 - 50 years (Vasiljevic et al., 2008). Our patients were 35 and 55 years of age, outside the age range. The reason for this is unknown and only one of the patients had a history of leiomyoma for about 3 years. Benign leiomyomas occur commonly in the uterus; however, LMS is believed to arise independently, and malignant transformation of a leiomyoma is considered exceedingly rare (Harris et al., 2005). Because of the background history of leiomyoma in case 2, which was histologically confirmed, the leiomyosarcoma in this patient could be a malignant transformation of existing leiomyoma and in case 1, it arises *de novo*.

The disease symptoms are not specific and usually include an enlarged uterus, vaginal haemorrhage, and pelvic pain from pressure. Our patients had all of the above symptoms due to late presentations. There was menstrual irregularity, menorrhagia, per vaginal discharge and a palpable irregular mass in the pelvis. In case 2, there was lymphoedema. The pattern of presentation is same as documented in literature especially in those presenting late with advanced disease. LMS is typically a solitary lesion that irregularly permeates the adjacent myometrium, and may show areas of haemorrhage and necrosis (Harris et al., 2005). These were evident in both patients at surgery and from the pathology report. Histologically, the tumours are densely cellular and are composed of bundles of spindle cells. The degree of smooth muscle differentiation is variable. Nuclear and cellular pleomorphism, nuclear hyperchromasia, and multinucleate giant cells are common. In

approximately 27% of cases, LMS metastasizes to the lymph nodes, and 50% of cases recur, with lung the most common site of metastasis. Although only one patient had lymph node evaluation, the reason why this patient never had lymph node metastases despite presence of lung metastasis is unknown but may support the findings that lungs is the most common site of distant metastasis (Harris et al., 2005; Goff et al., 1993).

In about 80% of cases the diagnosis is established upon hysterectomy by histological analysis of the uterine tissue (Quinn et al., 1997). The diagnosis in these patients was made by histological analysis of the surgically removed uterine tumour, since the preoperative diagnosis had been uterine myoma. One of these patients had 2 previous surgeries in which leiomyosarcoma could not be established. This is not surprising since to differentiate LMS from benign leiomyoma, the following factors should be considered: patient age, tumour size and gross appearance of the tumour, invasiveness of the tumour margins, vascular invasion, cytologic atypia, tumour cell necrosis, and mitotic activity (Goff et al., 1993). A lot of these are seen in both leiomyoma and leiomyosarcoma. In establishing the diagnosis of uterine sarcoma pre-operatively, a significant role belongs to uterine curettage, ultrasonography, magnetic resonant imaging and computed tomography. Uterine curettage is only useful in sub mucosa mass. Because of prevailing poverty, MRI and CT scan were not done in these patients as it is out of reach of most patients.

According to literature approximately 50 - 75% of all patients present with clinical stage I disease compared to our environment where 80% of patients presents at stages III and IV (Vasiljevic et al., 2008). In our patients, it was metastatic disease of the uterine corpus with pulmonary metastases, stage IV, thus indicating late establishment of the disease diagnosis. This is the norm in our environment irrespective of tumour type; presentation is usually late. (Adewuyi et al., 2008). In these patients, there was no histological confirmation of metastatic changes in the pelvic and paraaortic lymph nodes. In patients with stages I and II of the disease, ovarian metastases were found in 2.8% of cases, while there were no metastases in the lymph nodes. In advanced stages of the disease with extrauterine disease, the percentage of ovarian metastases was about 5.4%, and in the lymph nodes about 8.1% (Leitao et al., 2003).

In both cases presented, there was no evidence of ovarian metastasis. At present no uniform consensus exists regarding the best treatment strategy for effective and adequate palliative care but therapy typically requires a multimodality and multidisciplinary team approach. Adding radiation therapy in treating metastatic disease significantly improves local control and quality of life over surgery alone (Livi et al., 2003; Chauveinc et al., 1999). Even in early stage disease, local control however does not govern overall survival as most patients who die from

Table 1. Selected cytotoxic drugs trials in uterine sarcoma (Burke et al., 1997).

Series	sarcoma type	Drug	Patients	CR + PR	Endpoints or comments
Omura et al. (1983)	All	DOX	80	5 + 8	Median survival 7.7 months; response 25% for LMS
		VS			
Muss et al. (1985)	All	DOX + DTIC	66	7 + 9	Median survival 7.3 months; response 30% for LMS
		DOX	26	5	Median survival 11.6 months
		VS			
		DOX + CTX	26	5	Median survival 10.5 months
Sutton et al. (in press)	LMS	DOX + IFX	27	1 + 9	
Thigpen et al. (1986)	LMS	CDDP	10	0 + 1	Prior treatment; less responsive than MMT
Sutton et al. (1992)	LMS	IFX	35	0 + 6	No prior treatment; less responsive than MMT
Thigpen et al. (1992)	LMS	CDDP	33	0 + 7	No prior treatment; less responsive than MMT
Slayton et al. (1987)	MMT	VP-16	28	1 + 2	No prior treatment
Currie et al. (1996)	LMS	HED	39	2 + 5	
Slayton et al. (1987)	MMT	VP-16	31	0 + 2	Both had prior response to DOX
Thigpen et al. (1992)	MMT	CDDP	63	5 + 7	No prior treatment
Thigpen et al. (1986)	MMT	CDDP	28	5	Prior treatment

CR, complete response; PR, partial response; DOX, doxorubicin; LMS, leiomyosarcoma; DTIC, di - methyl triazenoimidazole carboxamide; CTX, cyclophosphamide; IFX, ifosfamide; CDDP, cisplatin; MMT, mixed mullerian tumour; VP-16, etoposide; HED, hydroxyurea + etoposide + dacarbazine.

their disease do so from distant metastases (Knocke et al., 1998; Major et al., 1993). The main indication for chemotherapy in these patients is the metastatic stage of the disease as stage is the most significant predictor of outcome for patients with uterine sarcomas (Tore et al., 1990; Benoit et al., 2005). Most sarcomas do not respond to hormonal therapy and because there was no evidence of receptor positivity on the tumours, these patients were never considered for any form of hormonal therapy (Harris et al., 2005; Wade et al., 1994).

Differences in the management of metastatic uterine leiomyosarcoma with respect to systemic chemotherapy, response rates and survival are emerging (Table 1). The impact of such chemotherapies in advanced stages of disease remains uncertain. Doxorubicin was shown to be an effective drug against LMS arising in the uterus. Unfortunately, the addition of dacarbazine to doxorubicin failed to improve the survival of patients with metastatic uterine sarcomas beyond that obtained with doxorubicin alone but response rates were however; significantly better in the doxorubicin plus dacarbazine arm (Tore et al., 1990; Benoit et al., 2005). Single agent chemotherapy using cisplatin, etoposide, mitoxantron had negative result when used alone in patients who had failed doxorubicin and in untreated patients. The ideal chemotherapeutic agent has yet to be established but common chemotherapeutic drugs used include doxorubicin, Ifosfamide, cyclophosphamide, dacarbazine, cisplatin and vindesine in different combinations regimens (Table 1). The readily available, less toxic and affordable combination chemotherapy regimen in this environment is the CYVADIC regimen (combination of cyclophosphamide, vincristine, doxorubicin and dacarbazine) which is very old, but still effective. It is very affordable, and side effects

are mild and manageable. A multidisciplinary approach to palliative treatment of patients with metastatic uterine sarcoma is crucial for long survival and optimal palliation in view of late presentation and high risk of haematogenous and lymphatic spread. Surgical treatment depends on resectability and the performance status of the patient. Disease prognosis is generally poor but there is need for an effective treatment in controlling local disease and improving quality of life. Tumour size more than 5 cm, high mitotic indices, cellular atypia, presence of anaplasia and tumour necrosis are signifi-cant indicators of tumour prognosis (Giuntoli et al., 2003; Evans et al., 1988). These poor prognostic factors are seen in our patients. Even though Survival of patients with uterine leiomyosarcoma is 20 - 63%, five - year survival for patients with stage I disease is approximately 50% and for other stages 0 - 20% (Dusenbery et al., 2004). One of the patients died after 2 - years and the other is still alive at 3 years. Thus we have a 2 - year overall survival of 100% although this is just 2 patients. In this environment, due to the rarity of these tumours and the different characteristics and prognosis of the various histological subtypes optimum treatment strategy has not yet been defined. The impact of radiotherapy on local control especially in old patients in controlling symptoms and improvement in overall survival with chemotherapy has been demonstrated in these patients.

Conclusion

The prognosis of LMS is generally poor. A multimodality and multidisciplinary approach would be a logical treatment of these aggressive tumours since these tumours

have a poor prognosis and the majority of patients die because of distant metastases. Therefore, for long survival and effective palliation, radiotherapy should be employed to control local disease and chemotherapy to treat or prevent metastases. Efforts should be made to encourage early presentation, collaboration amongst specialists and availability of modern effective and less toxic chemotherapy drugs at affordable price.

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