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Uterine Leiomyosarcoma (uLMS): A Malignancy in Disguise

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Abstract:

Uterine leiomyosarcoma mimics leiomyoma of the uterus clinically and on ultrasound imaging. The clinical course and prognosis are however markedly different .The entity may commonly present as a pelvic recurrence after initial surgery for unsuspected leiomyosarcoma. The rarity of this clinical entity renders pre-operative diagnosis to be often missed. The staging of this uncommon variant is significantly influenced by the histopathologic diagnosis. Pre-operative suspicion and relevant imaging is needed to improve diagnosis and thereby prognosis through proper surgical staging/sampling and optimal surgical resection as there are no specific tumour biomarkers yet. This is a case report depicting prospectively the outcome of a post-menopausal woman who underwent Total abdominal hysterectomy and bilateral salpingo-oophorectomy for a large fibroid which was confirmed histopathologically as Uterine Leiomyosarcoma(uLMS). After the histologic confirmation of uLMS, the patient was advised Combination chemotherapy, but she declined the adjuvant treatment. After 4 months of primary surgery with no initiation of Chemotherapy , she developed pelvic recurrence with invasion of bladder as detected by CT scan. The patient received 3 cycles of palliative combination Chemotherapy with Inj. Doxorubicin , Inj. Ifosfamide and Inj. Mesna ,Inj. Neukine after the detection of recurrence. She sadly succumbed a few days after completion of the third cycle of chemotherapy. This case report highlights the necessity to suspect the possibility of leiomyosarcoma in a post –menopausal lady with fibroid presenting for surgical management.

Key words: *Leiomyosarcoma, Leiomyoma, surgical management*

Introduction:

Uterine leiomyosarcoma is an aggressive tumour biologically and a relatively chemoresistant disease. Uterine sarcomas are of four main types: Uterine Leiomyosarcoma, Endometrial stromal sarcoma (Low grade and High grade), Malignant mixed Mullerian tumour and Undifferentiated Sarcoma. Most of the leiomyosarcoma that occur in the uterus are presumed to be fibroid because they look like fibroid on imaging scan. These uncommon malignant neoplasms are thought to arise from the myometrium or endometrial stromal precursor cells, rather than from leiomyomas. In contrast to leiomyomas, leiomyosarcomas have complex, highly variable karyotypes that frequently include deletions. Like leiomyomas, a subset contains MED12 mutations, a genetic aberration that appears to be virtually unique to uterine smooth muscle tumors. Leiomyosarcomas occur both before and after menopause, with a peak incidence at 40 to 60 years of age. These tumors often recur following surgery, and more than half eventually metastasize haematogenously to distant organs, such as lungs, bone, and brain. Dissemination throughout the abdominal cavity is also encountered. The overall 5-year survival rate is about 40%, but the anaplastic lesions have a 5-year survival rate of only 10% to 15%.[1]

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Case Report:

A 54 year old grand multi-para lady (P: 7) presented with lower abdominal pain for 3 months in the Gynaecology Out-patient Department of Bangladesh Medical College Hospital. She was menopausal for 10 years. She was suffering from essential hypertension; on medication with Tab. Atenolol 50 mg one tablet daily. On general examination, her Body Mass Index (BMI) was 20.3 kg/m^2, Height 148 cm, Weight 44.5 kg, Body surface area (BSA): 1.34. Abdominal examination revealed a tender uterine enlargement corresponding to 16 weeks size which was re-confirmed by internal examination. The ultrasonography of abdomen revealed: The uterus was enlarged (length 13.1cm x height 6.8 cm x width 8.5 cm & Volume 402 ml) with a large well-defined mixed echogenic area measuring 9.7cm x 6.5 cm x 8.1 cm & volume 270 ml arising most probably from fundus of the uterus . The endometrial thickness was within normal limits and cervix appeared normal with unremarkable ovaries and no fluid collection in the cul- de- sac. The sonographic impression was Fibroid uterus with degenerative change. After routine pre-operative investigations, she underwent Total abdominal Hysterectomy (TAH) with Bilateral salpingo-oophorectomy (BSO) under regional anaesthesia.

The operative findings were as follows: After opening the abdomen by Pfannenstiel incision, uterus was found about 16 weeks size, uniformly enlarged and friable in consistency. Both ovaries and tubes looked healthy. Pouch of Douglas was free. There were few scattered fluid- filled deposits/? seedlings on the surface of the uterus and tubes. Upon application of the clamps on the uterine cornu, the tissue was giving way and the clamps were cutting through very easily. TAH and BSO was performed. Upon bi–halving of the uterus, an approximate 12cm x10 cm heart – shaped compressed intra-cavitary mass was revealed which was apparently separate from the inner wall. There were areas of blackening/ degeneration on the mass. The uterine wall was thinned out. (Figure: 1,2,3) As there was suspicion of malignancy, the parametrium were grossly palpated to reveal no remarkable induration/ thickeing. Histopathology reported atrophic endometrium and myometrium. The intra-cavitary mass revealed features of leiomyosarcoma (LMS) composed of spindle cells with significant

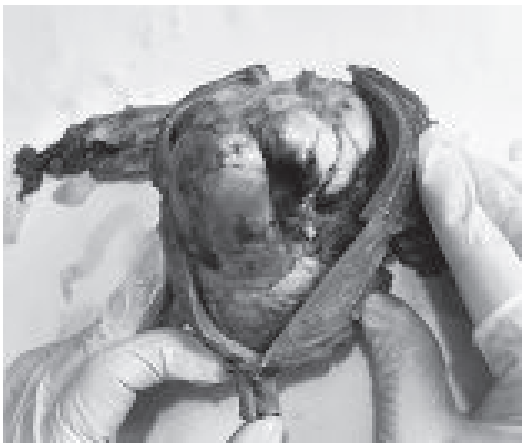

Fig.-1. *The whole resected specimen*

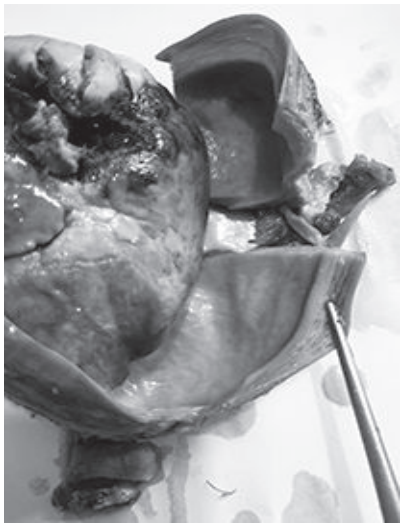

Fig.-2. *The intra-cavitary mass along with the compressed/attenuated uterine wall*

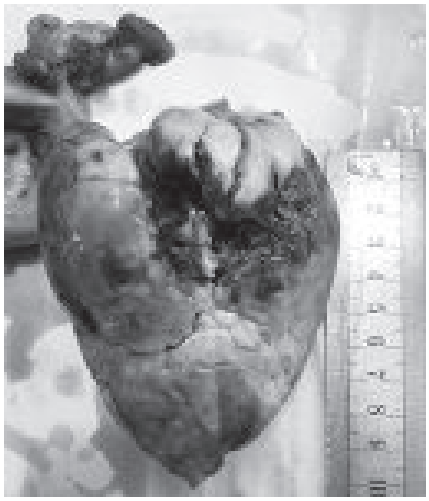

Fig.-3. *The mass with scale demonstrating the actual size*

pleomorphism. Mitotic figures are seen at a rate of 2-3/ HPF with focal areas of haemorrhage and necrosis. (Figure: 4)

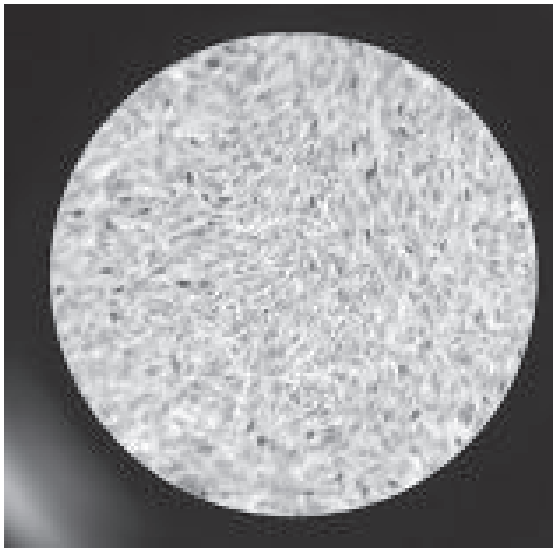

Fig.-4. *The histopathology slide*

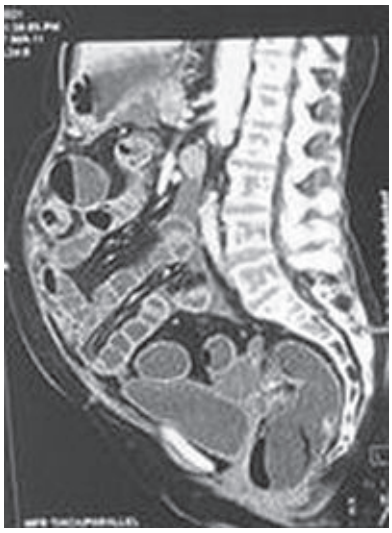

Fig.-5. *CT scan showing pelvic recurrence sagittal view*

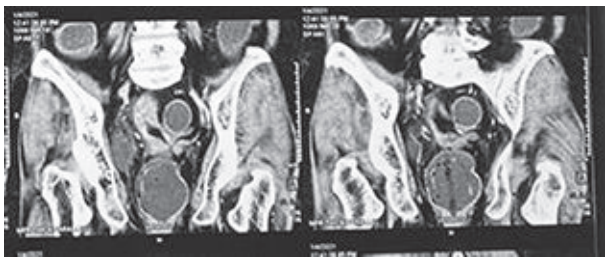

Fig.-6. *CT scan showing pelvic recurrence in coronal view*

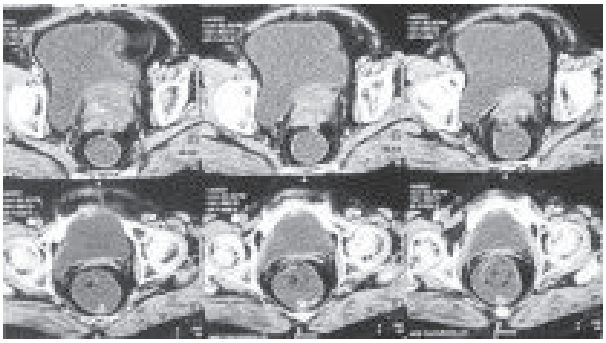

Fig.-7. *CT scan showing pelvic recurrence in transverse view of the pelvis*

The patient had an uneventful post- operative recovery. After the availability of the histopathology report on the 4th post-operative day, she was referred to Oncology Department of our institute. According to the operative findings, the stage was Stage IB (FIGO staging). The decision of chemotherapy as adjuvant treatment was advised along with strict surveillance by a follow-up schedule. Adjuvant Combination Chemotherapy was scheduled at 21 days interval for 6 cycles after 3 weeks of surgery with Inj. Doxorubicin 25 mg D1-3,Inj. Ifosfamide 1500 my D1-4 and Inj. Mesna 1500 mg D1-4,Inj. Neukine 300 mcg D4 .

The patient did not comply with any adjuvant treatment. On 4th January, 2021 four months after the primary surgery, she performed a Computed Tomography scan (CT scan) of the whole abdomen (with IV and rectal contrast) which revealed irregular enhancing solid mass lesion 32 mm x 22 mm x 24 mm in the pelvis with invasion of urinary bladder and vaginal vault as evidenced by loss of intervening fat plane. The mass was superiorly attached to a loculated collection measuring about 55 mm x 40 mm x 20 mm. There was peritoneal metastasis as evidenced by enhancement of the peritoneum in the lateral supra-hepatic region with mild to moderate ascites (Figure: 5, 6, 7).The patient was referred to National Institute of Cancer and Research (NICR), Mohakhali for re-evaluation where she started chemotherapy. She succumbed within few days of completion of the third cycle of palliative chemotherapy on 01/04/2021(3 months of detection of pelvic recurrence and 7 months of the primary surgery) at home with constitutional features of anorexia and difficulty in feeding.

Discussion:

Post – menopausal women with a pelvic mass greater than or equal to 10 weeks size and lacking a previous history of tubal ligation are suspects of uLMS. [2] Our

patient profile quite matches the aforementioned features. Our case was FIGO stage IB and corresponds to American Joint Committee on Cancer TNM staging T1b N0 M0 (The cancer was confined to the uterus and was larger than 5 cm across. There were no palpable lymph node or gross evidence of distant site metastasis, though lymph node sampling was not carried out during surgery). Recurrence – free survival (RFS) was reported to range from 3 months to 42 months.[3] The patient developed pelvic recurrence within 4 months of primary surgery and succumbed by 3 months of detection of pelvic recurrence.

Complete removal of the uterus is obligatory for the surgical management of uLMS. Diagnosis of uLMS after partial uterine resection/myomectomy should prompt instantaneous completion surgery. After a median interval of 6 weeks, 64% have persisting uLMS and in 38% of cases stump recurrence are found. In advanced situations, debulking operation should be attempted. Bilateral salpingo-oophorectomy (BSO) may be considered, depending on menopausal status. Ovaries may be preserved in young patients with tumors confined to the uterus. Fertility preservation in reproductive age should not be recommended, as only limited data is available. FDA recommends in most post- menopausal women to avoid Intra-peritoneal morcellation /endoscopic supracervical hysterectomy or tumor enucleation of fibroid and advocates en block removal of mass because the procedure may increase the risk of spreading cancer if a previously undiagnosed mass is morcellated. It is evidenced that uLMS patients who underwent surgery with tumour disruption resulted in poorer outcomes/ prognosis compared with en block tumor removal, especially those removed by power morcellation. [4] The incidence of pelvic and para-aortic lymph-node metastasis is low; if metastases are palpable, haematogeneous metastasis is likely. Therefore in case of incidental diagnosis after hysterectomy, early re- exploration and surgical staging are appreciated for better prognosis and may alter post- operative management. [5,6] Surgical staging and time to re-exploration are valuable for prognosis in case of incomplete primary surgery such as in case of LSH (Laparoscopic Supracervical Hysterectomy) where cervical stump expiration and trachelectomy may alter post- operative treatment . [5]. Early re-staging means within 30 days of primary surgery and late re-staging includes those performed after 30 days. Re-exploration procedures commonly include resection of abdomino-pelvic mass with BSO (Bilateral Salpingo-oophorectomy) in cases where BSO was not performed at the primary surgery, resection of pelvic mass and appendectomy in the context of Diffuse Peritoneal Carcinomatosis (DPC) or Stage III disease detected at the time of re-exploration. TH (Total Hysterectomy) in case of LM (Laparoscopic Myomectomy), TH with BSO and Omentectomy, Pelvic Lymph Node dissection (PND), Peritoneal washing (PW) and resection of Trocar ports are advocated in case of LM(Laparoscopic Myomectomy) later proven to be uLMS preferably within 30 days of primary surgery to impact prognosis.[6,7] Re-exploration findings in case of laparoscopic morcellation of unsuspected uLMS revealed that 33% of patients with primary power morcellation procedure were in Stage III, whereas there were only 7% on stage III in non-power morcellation group. Total recurrence rate was 58% in power morcellation group and 55.5% in non- power morcellation group. Abdominal recurrence was 100% in power morcellation group. [6] Some studies reported 71% recurrence and 40% mortality rate in the setting of early disease and uterus removed intact.[7,8] In this case, TAH with BSO was performed with en block removal of the mass, though the pelvic lymph node sampling was not performed.

Regarding prognosis, uLMS is a highly aggressive tumor and implies dismal prognosis independent of grading, even if the tumor is confined to the uterus. Consequently, the World Health Organization (WHO) and Gynecologic Oncology Group (GOG) do not recommend grading of uLMS anymore. Relapse rates are reported in between 53 and 71% after 5 years. Norwegian data show a 5-year overall survival (OAS) no better than 51% even in stage I tumors and 25% in stage II. Only early-stage tumors (Stage IA) seem to have a more favourable prognosis, with a 5-year OAS of 76.6%, whereas stage IB tumors are significantly worse with an OAS of 48.4%. Prognostic factors are age, tumor stage, and tumor size. OAS will decrease depending on tumor size: < 5 cm (76.6%), 5-10 cm (52.9%) and > 10 cm (41.9%).In this case, the mass measured 9.7 cm. Involvement of the uterine cervix will reduce OAS to 28.5 vs. 55.3% without cervical involvement. Additional prognostic factors are free margins, mitotic score, and vessel invasion. Morcellation truly contributes to grave prognosis. As pulmonary metastasis is common, a thoracic X-ray image or CT-scan should be considered.[9,10]

Regarding chemotherapy as adjuvant therapy, it has been evidenced that fixed dose regimen Gemcitabine and Docetaxel followed by Doxorubicin in high -grade uLMS with stage I, II and IIIA resulted in higher than

expected Progression –free survival (PFS) rates. Other regimens are: Doxorubicin/ Adriamycin + Ifosfamide, Docetaxel and Dacarbazine(DTIC). [11]

A study to establish method of prognostic prediction for uterine mesenchymal tumor by immune histological biomarkers by Takuma Hayashi mentions that patients with uterine LMS typically present with vaginal bleeding, pain and a pelvic mass with atypical presentations of hypercalcemia and eosinophilia. [12] Defective expression of PSMB9/â1i is likely to be one of the risk factors for the development of human uterine neoplasms, as it is in the PSMB9-deficient mouse. Thus, PSMB9/â1i is useful as a novel diagnostic biomarker for human uterine LMS, and Hayashi's research group have been trying to establish a novel diagnostic biomarker with PSMB9/â1i, which can distinguish the human uterine LMS from other human uterine mesenchymal tumours (including Leiomyoma) under the SIGMA-Aldrich Collaboration Laboratory Project. In recent advancement, Exosomes are being explored which are lipid-bilayer-enclosed extracellular vesicles that contain nucleic acids and proteins.[12] They are secreted from all cells and circulate in the blood. Specific detection and isolation of tumor-cell-derived exosomes in the circulation are currently lacking. Using molecular analyse, cellular factors may be identified in clinical materials derived from patients with ULMS. The molecular experiments demonstrated the differential expression of cyclin E and P27/kIP 1, which regulate cell-cycle G1 arrest via PSMB9/ â1i expression. The discovery of differential expression of factors on a key cell-signalling pathway in the blood may provide new targets for diagnostic approaches and guide therapeutic intervention in uLMS. [12]

Conclusion:

Uterine leiomyosarcoma mimics leiomyoma of the uterus clinically and on ultrasound imaging. The clinical course and prognosis are however markedly different .The entity may commonly present as a pelvic recurrence after initial surgery for unsuspected leiomyosarcoma. The rarity of the case renders pre-operative diagnosis to be often missed. The staging of this uncommon variant is significantly influenced by the histopathologic diagnosis. Pre-operative suspicion and relevant imaging is needed to improve diagnosis and thereby prognosis through proper surgical staging/ sampling and optimal en block surgical resection as there are no specific tumour biomarkers yet.

Reference:

1. Tanitra Tantitamit. GynaecolMinimal Inv.2018, April -June.7(2): 47-55.
2. Juhasz-BössI.a · Gabriel L.a · BohleR.M.b · Horn L.C.c · Solomayer E.-F.a · Breitbach G.-P. Uterine Leiomyosarcoma. Oncol Res Treat 2018; 41: 680-686 .https://doi.org/10.1159/000494299
3. Vinay Kumar Abul Abbas Jon Aster. Robbins & Cotran .Pathologic Basis of Disease, 10e: South Asia Edition, 2 Vol
4. Ramirez PT, Mundt AJ, Muggia FM. Cancers of the uterine body. In: DeVita VT, Hellman S, Rosenberg SA, eds. Cancer: Principles and Practice of Oncology. 9th ed. Philadelphia, Pa: Lippincott Williams & Wilkins 2011: 1345-1362.
5. American Joint Committee on Cancer. Corpus Uteri. In: *AJCC* Cancer Staging Manual. 7th ed. New York, NY: Springer; 2010: 403-409.
6. National Organization for Rare Disorders (NORD) https://rarediseases.org/rare-diseases/uterine-leiomyosarcoma/
7. National Cancer Institute. https://www.cancer.gov/pediatric-adult-rare-tumor/rare-tumors/rare-soft-tissue-tumors/leiomyosarcoma
8. https://jmedicalcasereports.biomedcentral.com/articles/10.1186/1752-1947-4-222
9. Salani R, Backes FJ, Fung MF, Holschneider CH, Parker LP, Bristow RE, Goff BA. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. *Am J Obstet Gynecol*. 2011 Jun; 204(6):466-78.
10. Seidman MA, Oduyebo T, Muto MG, Crum CP, Nucci MR, Quade BJ. Peritoneal dissemination complicating morcellation of uterine mesenchymal neoplasms. *PLoS One*. 2012;7(11):e50058. doi: 10.1371/journal.pone.0050058. Epub 2012 Nov 26.
11. Hensley ML, Ishill N, Soslow R, et al. Adjuvant gemcitabine plus docetaxel for completely resected stages I-IV high grade uterine leiomyosarcoma: Results of a prospective study. *Gynecol Oncol.* 2009;112:563-567.
12. Takuma Hayashi, Miki Kawano, Kenji Sano, Tomoyuki Ichimura, Gal Gur, Pnina Yaish, Dorit Zharhary, Yae Kanai, Susumu Tonegawa, Tanri Shiozawa, Nobuo Yaegashi, Ikuo Konishi.A novel diagnostic biomarker for human uterine leiomyosarcoma: PSMB9/â1i. Vol 6, No 2 (April 2017)