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INTRAVENOUS LEIOMYOMATOSIS – AN UNUSUAL VARIANT OF LEIOMYOMA- A REPORT OF TWO CASES AND REVIEW OF LITERATURE

Pathology

Sindhuja Prakasam	Assistant Professor, Department of Pathology, Institute of Obstetrics & Gynaecology, Egmore, Chennai
Revathy Mahendran	Assistant Professor, Department of Pathology, Institute of Obstetrics & Gynaecology, Egmore, Chennai
Seethalakshmi K	Professor, Department of Obstetrics & Gynaecology, Institute of Obstetrics & Gynaecology, Egmore, Chennai
Madurai Padmanabhan Kanchana*	Professor & Head, Department of Pathology, Institute of Obstetrics & Gynaecology, Egmore, Chennai. *Corresponding Author

ABSTRACT

Leiomyomas of the uterine wall is a common entity affecting 30% of women above 35 years. However intravenous leiomyomas are a rare variant of leiomyomas which represents intraluminal growth of smooth muscle into either venous or lymphatic channels outside the uterine wall. Despite being a benign lesion, invasion into large vessels and cardiac extension occurs and can be fatal. We present here two cases of intravenous leiomyomas among 5765 patients diagnosed by histology following hysterectomy. The aim of the study is to highlight the rarity of the variant (i.e 0.00034%) and to investigate all possible treatment strategies including follow-up to diagnose early recurrences.

KEYWORDS

Intravenous leiomyomas, hysterectomy

BACKGROUND:
Leiomyomas are probably one of the most common benign tumours in the female uterine tract with an average incidence ranging from 5.4% to 77%. They occur in women of reproductive age and is characterized by benign smooth muscle neoplasms in the uterine wall [1]. There occurs an entity often referred to as leiomyomas beyond uterus (LBU) which is defined as tumourous smooth muscle cells which present outside the uterus. LBU is sub classified into intravenous leimyomatosis (IVL), benign metastasizing leiomyomas (BML), diffuse peritoneal leimyomatosis (DPL), retroperitoneal leiomyomas and parasitic leiomyomas[2]. Birsch-Hirschfeld first reported IVL in 1896. it is characterized by benign smooth muscle proliferation within vascular spaces of the venous system[3-5]. The incidence of IVL among those who present with uterine fibroids is around 0.25% to 0.40% [6]. Till date , around 300 cases of intravenous leiomyomas have been reported in literature.

We hereby present two cases of IVL from our institution over a period of 10 years on detailed analysis of 5765 patients who were diagnosed with fibroids of the uterus. The incidence was 0.00034% which explains why only 300 cases have been reported worldwide till date.

Case 1 :
A 42 year old female patient presented with heavy menstrual bleeding for one year. On examination she was found to have a palpable mass per abdomen corresponding to 24 week gestation. Radiographs of the chest were normal. Patient underwent total abdominal hysterectomy with bilateral salphingoophorectomy. Macroscopic analysis revealed a subserosal 4 cm mass with endometrial thickness of 0.1 cm. Myometrium showed a solitary poorly defined nodule about 6 cm in diameter. On cross section, it appeared grey tan in colour with soft consistency and finger like extensions projecting from the mass into dilated smooth walled blood vessels(Fig.2). The rest of the myometrium showed multiple worm like nodules(Fig.1) confined to the vascular spaces. Microscopic examination revealed IVL without mitosis, cellular atypia and necrosis(Fig.3 & 4). Immunohistochemistry exhibited CD 34 positivity in the vessels surrounding the smooth muscle tumour confirming the diagnosis. The postoperative period was uneventful. The patient is currently under follow-up with our Institution.

Case 2 :
A 48 year old female patient admitted with abdominal pain and distension for over a year and urinary retention for a month. She was diagnosed to have a posterior wall fibroid on ultrasonogram. On examination, she was found to have a 18 week sized palpable mass per abdomen. Patient underwent total abdominal hysterectomy + Bilateral salphingoophorectomy. Intra-operative diagnosis was a broad ligament fibroid of size 12X10X7 cm. Macroscopically , cut surface of the fibroid showed multiple nodules with cleft like spaces. On further dissection, finger like projections were noted extending into the vascular spaces of the myometrium. Microscopy confirmed the diagnosis of IVL.

Review of literature :
Pathogenesis :
The exact etiopathogenesis of IVL still remains an enigma to many pathologists. However experts in the fields have forwarded two theories regarding the pathogenesis. Knauer postulated that IVL develops from the smooth muscles of the venous system of the uterus which undergo metaplastic changes[30]. This theory was refuted by Ma et al who found no evidence of endothelial markers such as CD10, CD31 or CD 34. The second theory was put forth by Steinmetz et al who thought that IVL results from progressive growth of preexisting leiomyoma which subsequently invades vascular lumen.

Histological characters and genetics dysregulation:
Under a high power microscope, IVL resembles a typical uterine myoma in staining positively for actin, desmin and caldesmon which are positive markers for muscle tissue. The cells also are positive for estrogen and progesterone receptors but exhibit a low mitotic rate. [7]. However there were differences observed at the molecular level such as dysregulation of HOXA13 which is a specific gene for embryonic growth and cell differentiation [8] and MED12 mutation which is pivotal in RNA polymerase II transcription [9]. A new protein – High mobility group AT-hook 2 (HMGA 2) which plays a role in mesenchymal differentiation is also suspected in IVL transformation[10].

To arrive at an accurate diagnosis, sampling is very important and must include the tumour and smooth muscle component[11].

Clinical features
IVL though conventionally described as a benign lesion exhibits malignant behaviour and spreads unilaterally by the venous system of the uterus either through the uterine veins to the IVS through the iliac veins or from the ovarian veins directly into the IVC.IVL characteristically never shows either complete occlusion of the vascular lumen or vascular adhesion [12,13,14].The presenting symptoms can range from non specific pain to more serious symptoms such as chest pain, dyspnoea or even cardiac arrest when the tumour invades the cardiac chambers[7]. Previous surgical procedures such as myomectomy or hysterectomy are often risk factors for the development of IVL[1]. The differential diagnosis includes thrombus, soft tissue sarcoma, lymphoma, cardiac myxoma, Wilm's tumour or metastasis[15,16-18].

Radiological investigations
Radiological investigations such as MRI, CT and ECHO all have a specific role in the diagnosis of IVL. [19-21]. Echocardiography plays a pivotal role in IVL with cardiac extension wherein multiple stripe-like hyperechogenic lines, filled with colored blood flow are visualized. CT is often the modality of choice compared to MRI or US in mapping the full extent of tumour spread.[19]. Surgical staging of the lesion is done by MRI/CT and the treatment is often chalked out by a multi-disciplinary team.

Staging :
IVL is staged reflecting the tumour progression before the surgery into

Stage I: Tumor penetrates the uterine venous wall but confined to the pelvic cavity

Stage II: Tumour extension into the abdominal cavity but not into renal vein

Stage III: Extension into renal vein and IVC till right atrium but not into pulmonary arteries

Stage IV: Extension into pulmonary arteries and lung metastases.

Treatment
Surgery is the mainstay of treatment [22], although there is no uniform consensus on the optimal approach[23]. The current recommendations are surgical resection by total hysterectomy irrespective of stage. The only exceptions are the young patient who desire preserving their fertility. In these patients a simple myomectomy have been attempted. The consensus between the open versus laparoscopic techniques is still unclear with no clear difference noted between the two surgical techniques [4,7]. Few have advocated Bilateral salpingoophorectomy followed by hormone therapy to be a better treatment package[24]. Tamoxifen, GNRH agonists, medroxyprogesterone and other drugs are used due to their anti-estrogenic effects. The basis of their use is to control residual tunour or reduce tumour growth and reduce tumour volume. The use of such drugs has also found benefit for those who are poor surgical candidates and those who refuse surgery or for non-castration cases

In those patients who present with more advanced stage of the disease, complex single or double procedures are often recommended with inputs from cardiothoracic and general surgical team. If cardiac extension is noted, then sternotomy followed by laparotomy seems to be the norm [22]. Recently there has been a shift towards a single stage approach due to better understanding of the disease[24,25]. Cardiopulmonary bypass with complete circulatory arrest is currently the norm but it is possible to perform the same with a beating heart as well[26,27]. The potential advantages of the single stage approach is reduced risk of tumour embolism, tumour spread and repeat surgery[22,23]. Statistically, complete tumour resection with total hysterectomy and bilateral salphingo-ooporectomy had lower recurrence rates (i.e 7.6%) when compared to those who underwent more conservative procedures such as preservation of adnexa (25%) or simple myomectomy(75%).

The complications reported in literature are death, haemorrhage, infections, embolism and the conventional post-operative complications as with any major surgical procedure[28,29]. Pre-operative embolization is often done to reduce intra-operative bleeding [22].

Follow-up :
Recurrence of leiomyomatosis has been shown in 30% of patients followed up for 7 months to 15 years[30]. Hence long term monitoring of such patients is important to identify earlier recurrences and institute appropriate treatment. Some of the risk factors for increased risk of recurrences are age, size of the initial tumour and multiparity. The recommended follow-up intervals are every 6 months with chest and abdominal CT scans and in some rare scenarios with MRI -venography and/or pelvic ultrasound and echocardiography.

CONCLUSION :
With the current available newer diagnostic modalities, IVL is no longer a rare entity as was once perceived to be. However its still not that common to warrant screening before every myoma surgery. To conduct a randomized controlled trial to assess the same is also very difficult due to limited number of patients in the group.

IVL should be considered as a differential for giant pelvic masses, a broad ligament myoma or in patients whose radiology shows "snakeheads" or "walking stick heads". The aim of surgery should be complete resection to minimize the risk of recurrence. Adjuvant therapies like hormonal treatments are to be balanced with their side effects and clinical benefits. Like every tumour management, treatment should be individualized depending on location, hormonal status, age and the initial tumour size. We recommend regular follow-ups and patients should be informed about the signs and symptoms of early recurrence.

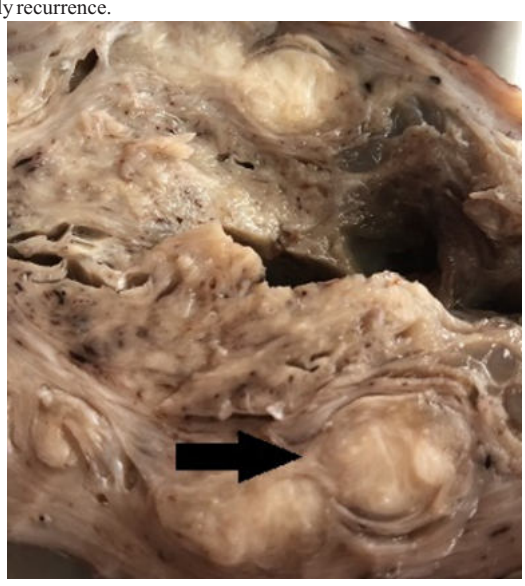

Fig.1. : Gross section showing multiple worm like nodules confined to vascular spaces

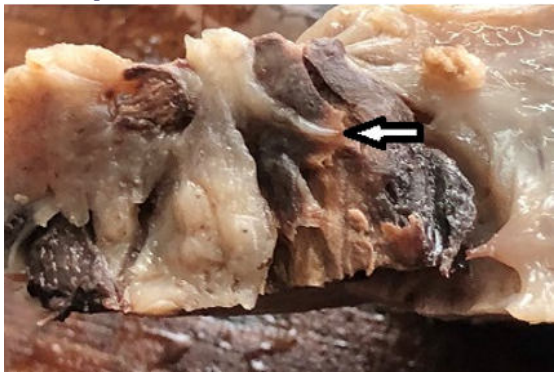

Fig. 2. : Finger like extensions projecting from the nodules into the dilated blood vessels seen along with a thrombus

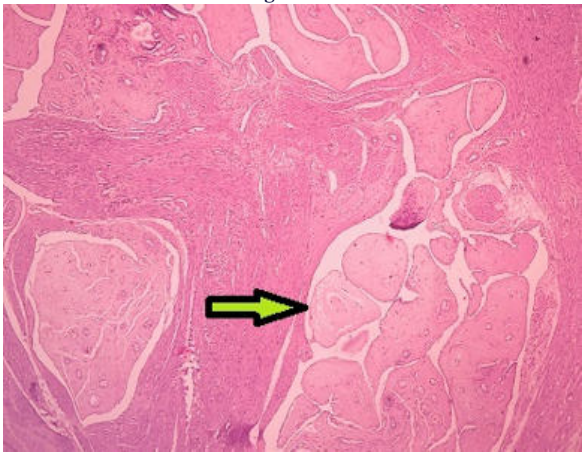

Fig.3 : Benign smooth muscle tumour seen within the dilated thin walled vascular spaces surrounded by endothelial cells. H&E at 10X

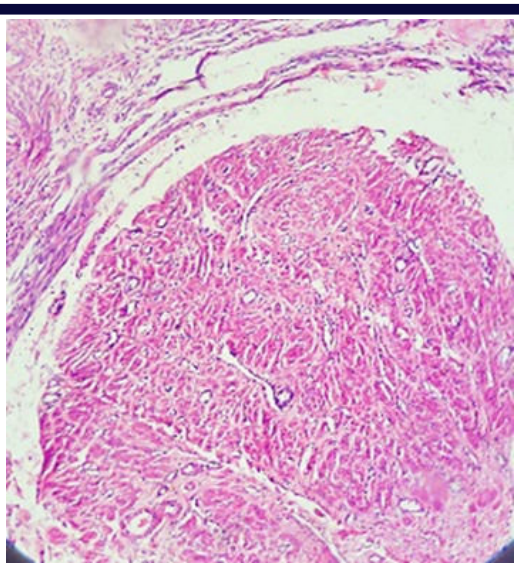

Fig.4: HPE 40X magnification showing endothelium lined vessel enclosing smooth muscle neoplasm with no atypia or necrosis

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