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Uterine Fibromyoma and Intravascular Thrombosis—Eight Cases

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Abstract

Objectives: We present eight cases of vascular thrombosis of the pelvic vessels and deep venous thrombosis (DVT) of the lower limb, secondary to compression of the pelvic vessels by the uterine fibroid, managed over a span of twelve years from 2001 to 2013. We discuss the mean size of the leiomyoma, the prediliction for DVT of the left lower limb, the role of oral contraceptives when used in women with large fibroids, to increase the risk of DVT and present a brief literature review. Results: Age, the mean age of our patients was-41.12 yrs, range-18 yrs to 50 yrs. Parity and Menopausal Status: Seven were parous women. One was unmarried, nulligravid. Seven were premenopausal and one was postmenopausal. Vascular Thrombosis: In one it was arterial thrombosis and in seven it was venous thrombosis. DVT was on the left side in -6/8 - 75%. Clinical Complaints: The presenting complaints were heavy menstrual bleeding in three, severe dysmenorrhoea and heavy bleeding in one, mass per abdomen in one, heavy menses and abdominal mass in one, no complaints apart from DVT in one. Uterine Enlargement: The size of the uterus was between 12 to 26 weeks. The mean size was 20 weeks. It was a single fibromyoma in six and multiple, two in two. Use of Oral Contraceptives: OC pills were used to control heavy menstrual bleeding in three cases—3/8, 37.5%. Discussion: The DVT was on the left side in six of our cases, 75% were on the left side in our series. Menstrual problems like heavy bleeding can be secondary to fibromyoma. Three of the eight-37.5%, women used OC pills to control menorrhagia. One developed DVT after one cycle of use of OC pills; the second developed arterial thrombosis of the pelvic vessels after four cycles of OC pill use; the third used OC pills for a longer period, on and off.

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The woman who developed arterial thrombosis was using OC pills with 50 mcgs of oestrogen and 0.5 mg norgestrel. Conclusions: Uterine leiomyoma can cause vascular thrombosis secondary to compression of the pelvic vessels. The mean size of the uterine enlargement by the fibromyoma was 20 weeks and in 6/8, it was a solitary fibromyoma. DVT was on the left side in 75% of our cases. Use of OC pills in women with an enlarged uterus with leiomyoma can increase the risk of DVT.

Keywords

Fibroid; Leiomyoma; DVT; Intravascular Thrombosis; IVL; Intravenous Leiomyomatosis; PTE

1. Introduction

Deep vein thrombosis (DVT) of the pelvic and femoral veins has been reported in association with uterine fibromyoma [1]-[16]. In women presenting with acute pulmonary thromboembolism, the possibility of uterine leiomyoma causing DVT of the pelvic vessels should be entertained [17]-[25]. Acute PTE secondary to a large uterine leiomyoma without DVT of the lower extremities has also been reported [26]. Multiple cerebral emboli due to foramen ovale and uterine fibromyoma have been reported [27]. Chronic non healing leg ulcer secondary to compression of the pelvic veins by the fibromyoma, leading to venous insufficiency in the leg veins, resolution and complete healing after hysterectomy has been reported [28]. Acute abdomen due to mesenteric vein thrombosis secondary to compression by a large fibroid [29] and claudication due to compression of the right iliac artery by the fibroid have been reported [30].

Association of deep venous thrombosis with fibromyoma has been described in cases of intravenous leio-myomatosis also [31] [32].

Intravenous leiomyomatosis (IVL), showing unusual growth patterns of uterine leiomyoma, is a rare neoplasm characterised by intravascular proliferation of a histologically benign looking smooth muscle tumor mass, but not invading the tissue.

The criteria for the diagnosis of IVL should take into account one of the following circumstances [33]:

- 1) Multiple uterine fibroids with pathologic changes involving parauterine tissues and annex, especially when worm like or cable like invasive tumors are found in the blood vessels under the microscope.
- 2) Patients have a history of uterine fibroids or uterine surgery, accompanied by one of the following: the right atrium tumor, right heart dysfunction, inferior venacava obstruction syndrome, Budd Chiari syndrome or deep vein thrombosis.

There is a need to increase the awareness regarding the assosciation between DVT due to compression of the pelvic vessels by a large fibroid and intravenous leiomyomatosis with fibromyoma, among gynaecologists, vascular surgeons and cardiologists for proper early diagnosis and management.

We present eight cases of vascular thrombosis of the pelvic vessels secondary to compression of the pelvic vessels by the uterine fibroid, managed over a span of twelve years from 2001 to 2013.

2. Material & Methods

2.1. Case One—2001

Mrs. C, 50 yrs, para-1, live-1, abortion-1, last child birth was 27 yrs ago, attained menopause 10 years ago, presented with deep vein thrombosis of left lower limb in the year 2001. Doppler venous study, duplex & real time ultrasonography confirmed left ilio femoral thrombosis. Therapeutic anticoagulation with unfractionated heparin was initiated and the patient was referred to the gynaec department of Government maternity hospital, Hyderabad, from the medical ward of Nizams institute of medical sciences. On gynaecological examination a firm mass corresponding to 24 weeks gestation was detected and a provisional diagnosis of uterine fibromyoma was made. She had no menstrual problem prior to menopause and no postmenopausal bleeding per vaginum. She had no problem related to micturition. There was no evidence of pelvic malignancy. CA-125 levels were normal. Pap. smear was normal.

Transvaginal ultrasonography and doppler blood flow to the mass were done, endometrium was thin (3 mm), endocervical canal was normal. Ectocervix was healthy. Other investigations were normal. Total abdominal hysterectomy and bilateral salpingo-oophorectomy were performed two months after anticoagulation, when doppler venous study revealed partial recanalisation of the thrombosed iliofemoral veins.

The patient who was on oral anticoagulant after DVT, was given preoperatively and postoperatively low molecular weight heparin and later again switched to oral anticoagulantion. Postoperative period was uneventful. Histopathology confirmed fibromyoma. **Figure 1** shows the specimen of uterus enlarged to 20 weeks size due to a solitary fibromyoma—case one.

2.2. Case Two-2001

Miss S, 18 yrs, unmarried adolescent presented with mass per abdomen, swelling and pain over left lower limb, difficulty in walking and fever of one week duration. She gave history of mass per abdomen, gradually increasing in size since one year. She did not have any menstrual disturbances. Gynaecological examination revealed a 24 weeks size fibromyoma uterus. Duplex venous ultrasonography showed extensive thrombus extending from saphenous vein in mid thigh upwards into femoral, external iliac and common iliac veins. A provisional diagnosis of a large fibromyoma uterus causing DVT was made on 7.12.2001. She was on LMW Heparin from 17.12.01 till 8.01.02 and later on, oral anticoagulant was started.

Repeat doppler studies on 11.01.02 and 29.01.02 revealed partial DVT, good collateral veins and absent thrombus in common iliac vein. She underwent Myomectomy on 7.02.2002. She was transfused three units of whole blood preoperatively and two units postoperatively. She was kept on oral anticoagulants for two months and discharged to attend the out patient department.

2.3. Case Three—2010

A 45 years woman, para 3, live 3, all three vaginal deliveries, presented to Kamineni hospital with abdominal pain and heavy menstrual bleeding of two months duration, was admitted on 18.05.2010. Clinical examination revealed the uterus to be enlarged to 26 weeks size, due to a large fibromyoma. Past history: She had deep venous thrombosis in the left lower limb six years ago, she was on anticoagulants at that time. Though she was advised surgery for fibroid, did not heed advise.

Venus doppler study on 18.05.2010 demonstrated partial chronic thrombosis of femoral vein, saphenous vein and complete thrombosis of popliteal veins, incompetent left sapheno femoral junction with dilated great saphenous vein and varicosities. She had TAH + BSO on 20.05.2010, received prophylactic anticoagulation, for four days postoperatively. She was advised screening for thrombophilia conditions.

2.4. Case Four—2011

A 49 years premenopausal woman was admitted with DVT of the left lower limb. Therapeutic intravenous



Figure 1. Solitary uterine fibromyoma—case one.

anticoagulation was initiated. Gynaecological examination revealed the uterus enlarged due to a fibromyoma, confirmed by vaginal sonography, a solitary fibroid was detected and she was advised regarding the need to undergo hysterectomy at the time of discharge. But she did not report to us for surgery, must have had it elsewhere.

2.5. Case Five—2012

Mrs. N, 45 yrs, para 2, live 2, both normal vaginal deliveries, last childbirth was 22 yrs ago, tubectomy done, presented with heavy menstrual bleeding and severe dysmenorrhoea of one year duration. She was hypothyroid on 100 mcgs. Of tab Eltroxin since four years, known hypertensive using drugs since three years. She had DVT in the rt. lower limb in July 2012, was on LMWH and changed over to oral anticoagulant. While on anticoagulants she had heavy vaginal bleeding and progesterones were given to arrest the bleeding episode. Uterus was enlarged to 14 to 16 weeks size, sonography revealed two fibroids of sizes 58×49 mm in fundus and 28×24 mm in the anterior wall of uterus. Dobutamine stress echo was negative for inducible ischaemia, 2D ECHO was normal, cardiology fitness taken for surgery. On venus doppler of rt. lower limb on 13.09.12, there was no evidence of DVT. TAH + LSO were performed. Bicornuate uterus with two fibroids and a small polyp in the left cornua were noted on cut section.

2.6. Case Six-2012

Mrs R, 42 yrs, P2 L1 D1 A2, presented with history of heavy menstrual bleeding of three years duration. She used oral contraceptives (OC) for controlling menorrhagia for one month, as per the gynaecologist advise. Developed deep venous thrombosis of left lower limb three years ago. Sonography confirmed the presence of uterine fibroids. She postponed hysterectomy for three years and was on anticoagulants. Uterus was enlarged to 24 weeks size with multiple fibroids. She had chronic rheumatic heart disease, moderate mitral stenosis, mild mitral regurgitation. She had hypertension. She was admitted on 5-03-2012 for severe anaemia and palpitations. Two units of packed cells were transfused and oral haematenics given. Underwent total abdominal hysterectomy on 26-3-2012.

2.7. Case Seven—2013

A 49 yrs, Mrs. S, P2, L2, had tubectomy, consulted for menorrhagia since four months and on hormonal therapy (Ovral G) to control heavy bleeding. She had pain in the right lower limb, painful blisters over the right little toe two months ago. She was taking treatment for diabetes mellitus since two months and for hypertension since 15 years. Examination revealed moderate pallor, BP = 150/100 mm of Hg, on speculum examination, cervix and vaginal mucosa were healthy, bleeding through the os was noted and vaginal examination noted the uterus enlarged to 12 weeks size, fixed and not tender. Her haemoglobin was 8.6 gms, sonography revealed intramural fibroid uterus, $98 \times 48 \text{ mm}$ size, in the posterior wall.

CT-Angiogram was done, thrombosis in the right superficial femoral artery, popliteal, posterior tibial and profunda femoris arteries was identified. Vascular surgeon was consulted. Because of menorrhagia an emergency hysterectomy was planned as the first step. So emergency TAH + BSO was done under spinal anaesthesia, on 2nd Jan. 2013. Anti-coagulation, low molecular weight heparin, Inj. Clexane 40 mg SC, BD, started 12 hours after surgery. Histopathology reported as fibromyoma. Right transfemoral thrombectomy was done on 10th Jan. 2013. Tab. aspirin 150 mg OD and tab. warfarin 5 mg OD started from 11th January.

2.8. Case Eight—2013

Mrs. R.S. 31 yrs. P2, L2, both lscs, tubectomy done, had last child birth, three and a half years ago. She was on oral anticoagulants when she consulted at care hospital in March 2013 for DVT of external iliac and femoral veins of left lower limb. There was associated marked left hydronephrosis & left hydroureter and mild rt. hydronephrosis, which was considered secondary to extraneous pressure effect by the mass. The uterus was enlarged to 24 weeks size, non mobile and tender on examination. She had MRI and CT abdomen done in addition to doppler. TAH was done on 8 03 13, a large mass stony hard in consistency, from the cervical region filling the entire pelvis was noted with no plane of cleavage to enucleate the fibromyoma. With difficulty the mass had to be removed in pieces, unlike the enucleation of a fibroid. There was suspicion whether it was an adenomyoma. There could have been small pieces left behind which could not be removed. The ovaries were healthy and conserved. Histopathological examination confirmed uterine fibromyoma. Later after one month, renal

function tests revealed the left kidney found to be non functional (95%). Rt. ureter stenting was done. On 8.08 2013, cystoscopy and rt. ureter stenting, laparoscopic left nephroureterectomy were performed. Exploratory laparotomy and removal of the mass remnants and bilateral oophorectomy were performed at the same sitting. Histopathology report was, adenomyoma, secretory endometrium, hydronephrosis and chronic pyelonephritis. ovaries—corpus luteal cyst rt ovary, follicular cyst lt ovary.

3. Results

3.1. AGE

The mean age of our patients was—41.12 yrs, range—18 yrs to 50 yrs.

3.2. Parity and Menopausal Status

Parity: Seven were parous women. One was unmarried, nulligravid.

Seven were premenopausal and one woman was ten years postmenopausal.

3.3. Vascular Thrombosis

In one it was arterial thrombosis and in seven it was venous thrombosis.

DVT was on the left side in -6/8 - 75%, and involving the right lower limb in -2/8 - 25%.

3.4. Clinical Complaints

The presenting complaints were heavy menstrual bleeding in three, severe dysmenorrhoea and heavy bleeding in one, mass per abdomen in one, heavy menses and abdominal mass in one, no complaints apart from DVT in one.

3.5. Uterine Enlargement

The size of the uterus was between 12 to 26 weeks. The mean size was 20 weeks. It was a single fibromyoma in six and multiple, two in two.

3.6. Use of Oral Contraceptives

OC Pills were used to control heavy menstrual bleedig in three cases—37.5% and T. Medroxy progesterone acetate was used in one to control HMB, after DVT while she was on anticoagulants.

3.7. DVT to Surgery Interval

The interval between DVT and surgery was, two months in three cases, one month in one, 3 years in one, 6 years in one and emergency hysterectomy in one, among the seven operated cases.

3.8. Comorbid Conditions

Comorbid conditions were diabetes mellitus and HTN in one, hypothyroidism and HTN in one and chronic rheumatic heart disease in one.

3.9. Surgical Details

Surgery: Hysterectomy was done in one case, myomectomy was done in one, hysterectomy with bilateral salpingo-oophorectomy in four and TAH + LSO in one. One patient did not report to us for surgery.

A second surgical procedure five months later was needed in one, to remove the residual mass and ovarian removal, combined with left nephroureterectomy.

The clinical profile, hormonal use and surgical management are shown in Table 1.

3.10. Histopathology

Histopathology reported as fibromyoma in six cases, fibromyoma and adenomyosis in one case.

Table 1. Fibromyoma & vascular thrombosis, clinical profile and surgical management of eight cases—2001 to 2013.

special features	10 yrs. Postmenpausal	unmarried, nulligravid	using OC pills on & off	not operated by us	used progesterone after DVT	used anticoagulants for 3 yrs.OC pills one cycle	anaemia+.Arterial thrombosis, OC pills x 4 cycles	Had second surgery 5 months later. left nephroureterectomy + BSO + removal of residual mass
co-morbid conditions	NIL	NIL	NIL	NIL	HTN, HYPOTHYROID	CRHD,HTN	HTN, DIABETES	LT. KIDNEY- nonfunctional
Presenting complaints	ÏÏ	Mass abdomen	HMB, pain abdomen	NA	HMB, dysmenorrhoea	HMB	HMB	Pain abdomen
surgery	TAH+BSO	myomectomy	TAH + BSO	NA	TAH + BSO	ТАН	TAH + BSO	TAH + BSO
Fibroid	single	single	single	NA	two	multiple	single	single
Uterine sizeweeks	24	24	26	12	41	24	12	24
OC pill use	0	0	irregular	0	prog-1cycle	1 cycle	4 cycles	0
Duration of DVT	2 months	2 months	6 years	NA	2 months	3 years	emergency	1 month
DVT lowerlimb	left	left	left	left	right	left	right	left
para, live abortion	PILIAI	unmarried	P3L3	NA	P2L2	P2L1A2	P2L2	P2L2
AgeYrs	50	18	45	49	45	42	49	31
Case-no Year Hospital AgeYrs	ВМН	ВМН	2010 Kamineni	CARE	CARE	CARE	CARE	CARE
Year	2001	2001	2010	2011	2012	2012	2013	2013
Case-no	Case-1	Case-2	Case-3	Case-4	Case-5	Case-6	Case-7	case-8

NOTE: 1. TAH+BSO-Total abdominal hysterectomy & bilateral salpingo oophorectomy. 2. HMB-Heavy menstrual bleeding. 3. OC pill-Oral contraceptive pill. 4. CRHD-Chronic rheumatic heart disease.

4. Discussion

During pregnancy, the enlarging uterus impeding blood flow in the pelvic venous system and the passage of fetal head through the birth canal causing trauma to the pelvic veins are two reasons mentioned, along with other hemostatic changes, to explain the greater occurrence of venous thromboembolism in pregnancy [34]. In a similar manner an enlarged uterus with fibromyoma can cause impedence to blood flow in the pelvic veins predisposing to thrombus formation.

The mean age of our eight cases was 41 years, range 18 to 50 years, which is in agreement with other reports.Riat R. reported the mean age at presentation of their nine cases of fibroids with thrombosis was 41 years, range (33 - 51 years) [35]. The mean size of the fibroid uterus was 20 weeks, range between 12 to 26 weeks and it was a solitary fibromyoma in 6/8 in our study. The incidence of DVT was found to be higher in cases where uterine weight was 1000 gms, or higher [8].

The DVT was on the left side in six of our cases, and on the right side in two, 75% were on the left side in our series. DVT were in the left leg in 81.9% during pregnancy [36]. Deep venous thrombosis occurred in the left lower extremity in 76% of the pregnant and 47% of the postpartum women [34]. In pregnant women with deep venous thrombosis, involvement of the left leg was reported in 82% and in 71% thrombosis was restricted to the proximal veins without involvement of the calf veins [37]. There is a greater predeliction for iliofemoral deep vein thrombosis on the left side, this may be as a consequence of the rt. iliac artery crossing the left iliac vein and compression of the left iliac vein by the gravid uterus [37].

One of the main presenting complaints in women with uterine fibromyoma is heavy menstrual bleeding. Menstrual problems like heavy bleeding can be secondary to fibromyoma. Hormonal preparations are used to control heavy menstrual bleeding when mefenamic acid and tranexamic acid are unsuccessful. Three of the eight women used OC pills to control menorrhagia. One developed DVT after one cycle of use of OC pills, the second developed arterial thrombosis of the pelvic vessels after four cycles of OC pill use, the third used OC pills for a longer period, on and off. The woman who developed arterial thrombosis was using OC pills with 50 mcgs of oestrogen and 0.5 mg norgestrel. Medroxy progesterone acetate was used to control heavy menstrual bleeding in a woman on anticoagulants after she developed deep venous thrombosis.

Currently available oral contraceptives still have a major impact on thrombosis occurrence and many women do not use the safest brands with regards to the risk of venous thrombosis [38]. The risk of venous thrombosis with the current oral contraceptives is fivefold compared with nouse and the risk differed with the type of progestogen and dose of oestrogen. The risk of venous thrombosis in oral contraceptive users was fourfold with levonorgestrel progestogen, 5.6 fold for gestodene, 7.3 fold for desogestrel, 6.8 fold for cyproterone acetate and 6.3 fold for drospirenone, compared to nonusers [38].

Women taking third generation oral contraceptives have a 1.7 fold increased risk of venous thrombosis compared with those taking second generation oral contraceptives [39]. Second and third generation oral contraceptives increase the risk of venous thromboemblolism in carriers of factor V Leiden mutation by 3.3 fold and 4.2 fold respectively [40]. Factor V leiden may be important here since APC resistance has been reported in 30% of oral contraceptive pill associated thrombosis. Women using oral contraceptives with drospirenone are at similar risk of venous thromboembolism to those using oral contraceptives with desogestrel, gestodene or cyproterone and higher than those using oral contraceptives with levonorgestrel [41]. The risk of VTE was not reduced by using 20 mcg oestrogen instead of 30 mcg oestrogen in oral contraceptives with drospirenone [42]. Roberts L. N. have reported that deep venous thrombosis in association with leiomyoma was more common in women of Afro Caribbean descent and also that most women would not have thrombophilic disorders [43]. The prevalence of DVT amongst Indians was significantly higher as compared to whites and blacks [44]. Amongst the known thrombophilia markers, only homocysteine was significantly higher in males compared with females (P = 0.006) [44]. A study on common thrombophilia markers and risk factors in Indian patients with primary DVT revealed that the commonest were elevated fibrinogen and APC-resistance (17.9% each) followed by low protein S (16.6%) [45] [46]. Thrombophilia was noted in 20% - 50% of women who experience VTE during Pregnancy [47]. Our women, though advised did not get the screening tests for thrombophilia. Thrombophilia screening in women having DVT with fibromyoma would enable us to understand better the role of fibromyoma and thrombophilias in the occurrence of DVT.

Oral contraceptives, estrogen alone, estrogen plus progestin and progestin with or without estrogen are independent VTE risk factors [48]. As per the WHO medical eligibility criteria for contraceptive use 2009, OC pills

can be safely advised to women with uterine fibroids without any fear of increase in the size of the fibroid, category-1 [49]. If large fibroids are accepted as an independent risk factor for DVT, then use of OC pills in such women would compound the risk, as seen in our study.

In one of our cases the tumor could not be removed in toto, she underwent a second surgical procedure, five months later in August 2013, to resect the residual mass in the pelvis, bilateral oophorectomy was performed to prevent recurrence and she had left laparoscopic nephroureterectomy as the left kidney was non functional.

A two stage operation was performed, hysterectomy for uterine leiomyoma followed by arterial thrombectomy ten days later in one of our cases.

In cases of IVL a cytogenetic characterization of the disease has more recently been described, consisting of the karyotype, 45, XX,der(14)t(12;14) (q15;q24),-22. These chromosomal aneusomies have been detected at different tumor sites and in different cases of intravascular and uterine leiomyomatosis, in separate patients, implying that the pathogenesis of both is closely related [50]. Cytogenetic studies would help to differentiate between fibroids causing DVT due to compression and intravenous leiomyomatosis causing DVT, in addition to histopathology.

5. Conclusions

A greater awareness regarding the uterine fibroids which are considered benign tumors and complications like DVT, IVL, ICL leading to life threatening emergency situations is necessary among gynaecologists, vascular surgeons and cardiac surgeons.

From these eight cases we conclude that a uterus enlarged to 20 weeks gestation size by a fibromyoma would fill the capacity of the pelvis, leading to compression of the vessels, stasis and predisposes to deep venous thrombosis.

In the cases of IVL and uterine myomas, oophorectomy has to be considered in special situations of incomplete resection of the tumor mass [33]. Antiestrogen therapy has been used in the cases of residual tumor mass being left behind [33].

Use of OC pills, especially with high dose estrogens and third generation progestins in patients with an enlarged uterus with leiomyoma can increase the risk of DVT. Indiscriminate use of oral contraceptives without knowledge about the dose of oestrogen and the type of progestogen to control heavy menstrual bleeding needs to be curbed.

It is necessary to educate the public regarding the need for surgery, when the fibroids cause the uterus to be enlarged to 16 to 18 weeks size, without procrastination, lest life threatening complications like pulmonary thromboembolism may occur.

Regarding the use of oral contraceptives in women with large uterine fibromyomas, keeping the risk of vascular thrombosis in mind, whether the WHO medical eligibility criteria should be revisited or modified is for the learned to muse.

Deep venous thrombosis is also seen in women with intravascular leiomyomatosis, in addition to leiomyoma causing deep venous thrombosis, whether these two are two distinct entities or not, the cytogenetic studies may clarify.

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