Estrogen and progesterone expression of vessel walls with intravascular leiomyomatosis; Discussion of histogenesis

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Summary

We report seven cases of intravenous leiomyomatosis. Growth beyond the uterus occurred in two of the seven cases in the broad ligament. One 21-year-old patient is one of the youngest reported cases in the literature. Five patients had total abdominal hysterectomy with removal of the adnexa and two patients underwent myomectomy. One of the myomectomy cases had abdominal hysterectomy and bilateral salpingo-oophorectomy one year later due to recurrence. The other one was disease free six months after the operation. Vessel walls harboring intravascular tumor were investigated immunohistochemically for Factor VIII, CD 34, estrogen and progesterone receptors with the hope of making the histogenesis of intravenous leiomyomatosis clear. Immunohistochemical analyses of estrogen receptors, progesterone receptors, vimentin, desmin, smooth muscle actin, CD 10 and h-caldesmon were performed on intravascular tumor cells.

Endothelial and subendothelial cells expressed none to scant, very weak progesterone and estrogen receptor positivity. Intravascular tumor cells showed weak (10%) to strong (70%) progesterone receptor positivity and weak (10%) to strong (60%) estrogen receptor positivity.

These results do not support the hypothesis of a vessel wall origin for intravenous leiomyomatosis.

Key words: Intravenous leiomyomatosis; Uterus.

Introduction

Intravenous leiomyomatosis (IVL) is a rare neoplasm characterized by nodular masses of histologically benign smooth muscle cells growing within the uterine and extrauterine venous system [1]. More than 150 cases have been reported in the English literature [1-14]. Most cases are associated with leiomyoma within the uterus. Histologically benign IVL may extend into the inferior vena cava, right-sided cardiac chambers and even the pulmonary artery, which can be fatal [6-9, 15].

Although it presents few diagnostic problems, its histogenesis is unclear and origins from both the venous wall and from a pre-existing leiomyoma have been proposed [1].

We report seven cases of IVL with emphasis on immunohistochemical analyses of estrogen and progesterone receptors (ER; PR) in the walls of vessels with intravascular tumor. Immunohistochemical ER and PR analyses of vessel walls have not been reported previously in cases with IVL. We also performed immunohistochemical staining on intravascular tumor cells for ER, PR, vimentin, smooth muscle actin, CD 10 and h-caldesmon

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Material and Method

Seven cases of IVL from the Zeynep Kamil Maternity Hospital were reviewed for this study. Clinical records, gross descriptions and gross photographs were available. The number of paraffin-embedded blocks of tissue ranged from 8 to 15 with an average of 12 per case. One paraffin block per centimeter of the greatest tumor diameter was obtained to ensure adequate tumor sampling. The tumors were evaluated as IVL conforming to the Norris and Palmley criteria [1]. Histologic features studied included the degree of mitotic activity and the degree of cellular atypism within the tumor.

Intravascular tumors and walls of the vessels with intravascular tumor were analysed for ER , PR, Factor VIII and CD-34 immunohistochemically. Staining intensity was graded as weak (+), moderate (++) and strong (+++). We also noted the percentage of positively reacting cells. In addition, immunohistochemical studies with vimentin, desmin, smooth muscle actin, CD 10 and h-caldesmon (DAKO, ready to use) were performed on intravascular tumors by the peroxidase-antiperoxidase method.

Results

Clinical Features

Median age of the patients was 41 [21-47]. Four women were premenopausal and three were postmenopausal. Presenting symptoms of the patients were abnormal vaginal bleeding, pain and vague pelvic discomfort. A pelvic mass which was thought to be an enlarged uterus was detected in all cases by pelvic examination. A prospective diagnosis of IVL had not been

Table 1. — *Clinical and pathological features of cases with intravenous leiomyomatosis of the uterus.*

Case	Age	Presentation	Extrauterine extension	Therapy	Proportion within vessels	Follow-up
1	27	Menometrorrhagia, pelvic pain	None	Myomectomy	10%	Due to pelvic recurrence, 12 months later TAH & BSO
2	21	Pelvic pain, pressure, menorrhagia	Left broad ligament	Myomectomy, removal of br.lg.tm+GnRH agonist	20%	NED but 6 months later TAH & BSO
3	46	Pelvic pain menorrhagia	None	TAH & BSO	10%	NED, 18 months
4	39	Menorrhagia, pelvic pressure	Bilateral broad ligament	TAH & BSO, removal of br. lg. tm	30-40%	NED, 6 months
5	41	Pelvic pain, pressure	None	TAH & BSO	< 10%	NED, 33 months
6	47	Menorrhagia, pelvic pain	None	TAH & BSO	10-20%	NED, 24 months
7	42	Pelvic pain, pressure	None	TAH & BSO	20%	None

NED: No evidence of disease, Br.lg.tm.: Broad ligament tumor.

made in any of the patients. Five patients underwent hysterectomy and bilateral sapingo-oophorectomy (TAH & BSO). At surgery, an enlarged uterus was found in all patients and in two cases an extrauterine tumor was found within the broad ligament. Surgeons were not suspicious about IVL in any case.

Two patients had myomectomy alone due to reproductive concerns. One did not receive hormonal or radiotherapy. She underwent TAH & BSO one year after the initial diagnosis due to recurrence. The other patient received gonadotropin releasing hormone agonist (GnRH-a) treatment for six months. She was disease-free at the sixth month after the operation.

Gross Features

Macroscopic examination of enlarged uteri revealed solitary or multiple intramural and submucosal leiomyomas measuring up to 7 cm in diameter. Most of the masses were well demarcated from the surrounding myometrium. The sectioned surfaces of the masses were typically lobulated with tan to gray color. In three cases wormlike plugs were identified within the myometrial vessels. Extrauterine masses with a gross appearance similar to that of the uterine masses were identified within the broad ligament in two cases (Figure 1). These broad ligament masses measured 1-5 cm in diameter with a multilobulated cut surface.

Leioyomas of two patients undergoing myomectomy were 6 and 9 cm in diameter with a significant amount of surrounding myometrium. Wormlike plugs were seen within the surrounding myometrium. One also had a 1 cm intravenous tumor within the broad ligament resembling the uterine tumor grossly and histologically. A hysterectomy performed one year later revealed a 6 cm leiomyoma with extension into the myometrial vessels.

Microscopic features

All cases were characterized by the presence of endothelium-covered proliferations of cytologically benign smooth muscles within the lumens of the myometrial veins (Figure 2). Most of the vessels were identified as veins, although some may have been lymphatics. It was occasionally difficult to distinguish intravenous growth from tumor within artefactual spaces due to retraction.

Examination of sections stained for endothelial antigens (Factor VIII and CD- 34) was performed to exclude such artefactual retraction (Figure 3).

The estimated proportion of tumor that was intravascular ranged from 5% to 30%. The intravascular tumor had a smooth and round contour. In each case intravascular tumors were unattached to the vessel wall and free floating. In all cases the intravascular tumors resembled each other. These tumors were composed of densely cellular proliferations of uniform oval-spindle shaped cells and were usually arranged in intersectioning fascicles. No more than one mitotic figure/10 high power fields and mild atypia was seen in any case.

Immunohistochemical studies showed that the intravascular tumor cells in all cases were diffusely and strongly positive for vimentin, smooth muscle actin, desmin and h-caldesmon and negative for CD 10, cytokeratin and epithelial membrane antigen. Intravenous tumor cells

Table 2. — *Immunohistochemical analysis of intravascular tumor cells.*

Case	ER	PR
1	< 10%, +	30%, ++
2	60%, +++	70%, +++
3	30%, ++	90%, +++
4	50%, ++	60%, ++, +++
5	10-20%, +	50%, ++
6	10%, +	60%, +++
7	< 10%, +	10%, +

Table 3. — *Immunohistochemical analysis of vessel walls with intravascular tumor.*

Case	ER	PR
1	None	None
2	None	< 10%, +
3	None	None
4	< 10%, +	10%, +
5	None	< 10%, +
6	None	None
7	None	None

Fig. 1

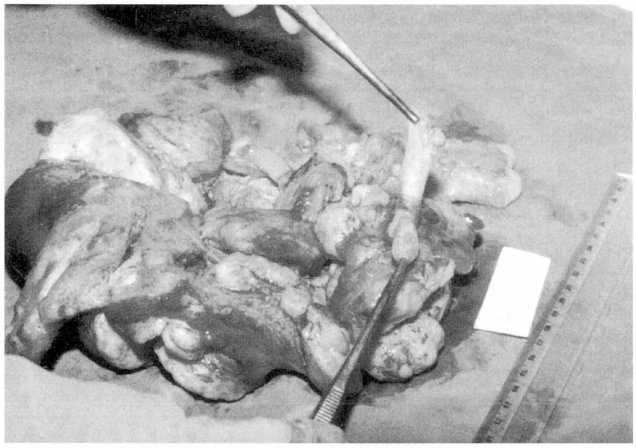


Fig.

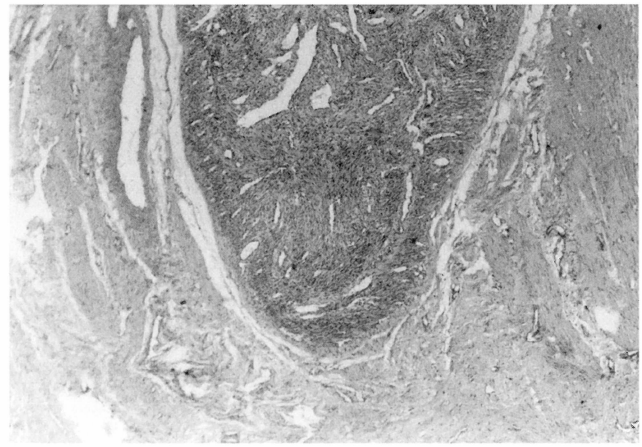


Fig. 3

Fig.

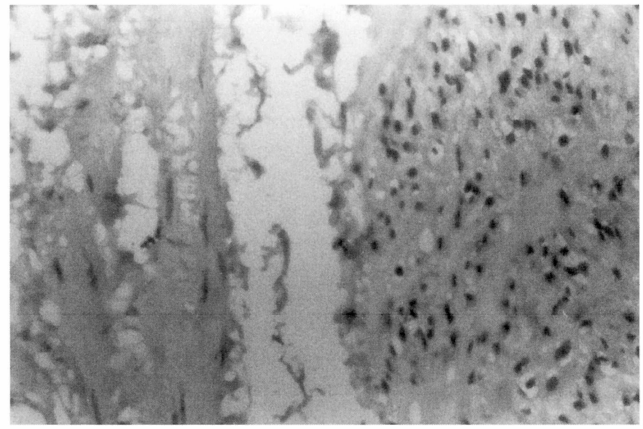
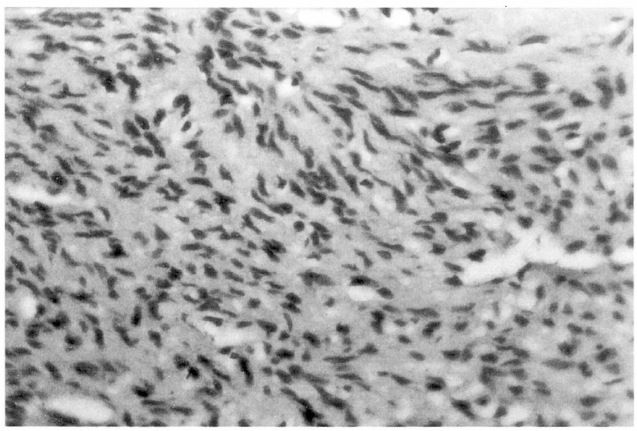


Fig. 5



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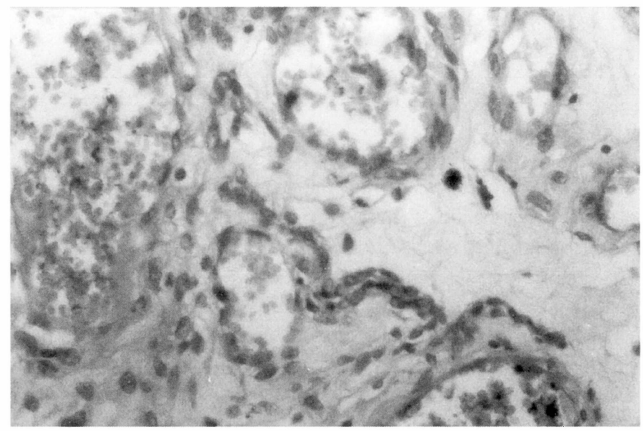

Figure 1. — Extrauterine worm-like masses identified within the broad ligament.
Figure 2. — Endothelium-covered proliferations of cytologically benign smooth muscles within the lumens of myometrial veins (HE x 40).
Figure 3. — Endothelial cells were stained for Factor VIII (HE x 40).
Figure 4. — Intravenous tumor cells show strongly diffused PR positivity (on the right side). Endothelial and subendothelial cells express none to weak-scant PR positivity (on the left side) (HE x 400).
Figure 5. — Spindle-shaped cells arranged in intersecting fascicles (cellular variant) (HE x 400).
Figure 6. — Intravascular tumor containing numerous blood vessels (angiomatoid pattern) (HE x 400).

showed weak (10%) to strong (70%) PR positivity and weak (10%) to strong (60%) ER positivity (Table 2) (Figure 4). Endothelial and subendothelial cells expressed none to weak (10%) PR positivity, none to weak-scant-ER positivity (Table 3) (Figure 4).

Discussion

The diagnosis of IVL is usually encountered after the operation during the sectioning of the surgical specimen by the pathologist. IVL incidence is more common than the number of reported cases because the diagnosis is overlooked by pathologists. One problem is failure to recognize the intravascular location of the tumor especially in those cases in which no extrauterine extension of tumor is noted intraoperatively by the gynecologist and where there is inadequate sampling of uterine tumors by the pathologist [1].

The post-hysterectomy status of IVL patients is well known [1-12]. There have been a few reported cases who died after hysterectomy due to extension of tumor up to the heart [2].

The status of patients treated with myomectomy alone is unknown. There are few reported cases who had been treated only by myomectomy [3, 5]. In Mulvany *et al.'s* report [3], one of two patients with IVL treated by myomectomy alone had an abdominal hysterectomy two years later demonstrating a 5 cm IVL involving the veins of the right broad ligament. The other one was disease free at the end of the second postoperative year. No chemotherapy or radiotherapy was instituted as adjunctive treatment. Heironen *et al.* [5] published a case of a 34-year-old woman treated by myomectomy. Four years later, due to pelvic recurrence, total abdominal hysterectomy and right salpingo-oophorectomy were performed.

Two of our patients underwent myomectomy. One of them had TAH & BSO one year later which revealed IVL involving the veins of the myometrium. She had no hormonal treatment, chemotherapy or radiotherapy. In the other patient who did not have a hysterectomy, a vascular tumor involving the area of the right uterine cornu and adjacent broad ligament was completely resected. She received only GnRH-a treatment and was disease free six months after the operation.

In the literature there are several IVL reports with a highly variable histologic appearance [1-3]. Five of our cases had the appearance of typical leiomyoma with spindle-shaped cells arranged in intersecting fascicles (cellular variant) (Figure 5). In the remaining cases, intravascular tumor contained numerous blood vessels, at least some of which were large and thick-walled (angiomatoid pattern) (Figure 6) [1-3].

IVL, particularly the cellular variant, may be confused with endometrial stromal sarcoma (ESS). ESS usually has a more uniform histologic appearance than IVL, characterized by a diffuse pattern and network of small thin-walled vessels throughout the tumor [2]. In a retrospective study Clement *et al.* reported that ESS was the initial diagnosis in several of their IVL cases [13]. CD 10 and h-caldesmon are useful markers in the discrimination of cellular leiomyomas and ESS [16-19]. We performed immunohistochemical analysis for CD 10, h-caldesmon, smooth muscle actin, and desmin.

The histogenesis of IVL is unclear. Origins from both the venous wall and from a pre-existing leiomyoma have been proposed [1]. Review of the existing literature provides arguments for both possibilities.

Although the largest series [1-4] proves both theroies as the correct origin with equal numbers of cases for each alternative, most of the publications are no more than case reports associated with pre-existing leiomyomas. Despite these observations, there is still evidence for a venous origin in some cases of IVL where no leiomyoma has been found grossly [1]. The presence of intraluminal vena cava leiomyomas also supports this hypothesis [21]. Further support for a venous wall origin stems from the fact that intimal proliferations are triggered by sex steroids [22], hormones that are well known to be capable of differentiating smooth muscle from the different types of stem cells present within and outside the female genital tract [23]. There are also reports indicating the presence of ER and PR in intravascular smooth muscle proliferations [5, 10, 11, 24, 25]. Recently there have been studies in the field of cardiology demonstrating the presence of ER and PR in the vascular smooth muscle cells of large arteries [26-29]. Most of these studies used polymerase chain reaction instead of immunohistochemistry.

We performed immunohistochemical analysis for ER and PR at the walls of vessels with intravascular tumor which is the first report up to our Pubmed search. We found very low levels of ER and PR expression in endothelial and subendothelial cells compared to high levels of expression of intravenous tumor cells which does not support the histogenesis of vessel wall origin. In only one case which harbored a higher proportion of tumor within the vessel, expression of weak to scant ER and weak to 10% PR positivity was noted in the endothelial and subendothelial cells of the vessel wall.

In our cases a higher percentage of the tumor was outside the vessels; according to this and immunohistochemical data, we concluded that IVL was unlikely to have arisen from the smooth muscle of the vessel wall. Instead it might have originated from a pre-existing leiomyoma. This conclusion does not necessarily invalidate the theory of venous origin. It would be more logical and meaningful to conduct studies investigating ER and PR at the vessel walls of cases with high intravascular components.

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