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Short Communication

Intravenous leiomyomatosis of the uterus: A clinicopathological analysis of nine cases and literature review

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ABSTRACT

Objective: Intravenous/intravascular leiomyomatosis is characterized by intravenous proliferation of a histologically benign smooth muscle cell tumor mass that is non-tissue-invasive. Although benign, intravenous leiomyomatosis may cause remarkable systematic complications, presents significant diagnostic difficulties, and also is characterized by a relatively increased possibility of recurrence. We determine patients' characteristics, and recurrence and treatment of intravenous leiomyomatosis.
Materials and methods: Prognostic factors are analyzed with univariate analysis. Differences in categorical data are evaluated by the X^2 test. A P value below 0.05 is regarded as indicating a significant difference.
Results: The data results accord with the widely held view that complete excision of intravenous leiomyomata achieves favorable prognoses regarding remission. The efficacy of using Gonadotropin releasing hormone agonists to prevent growth or recurrence of tumors in unresected or incompletely resected intravenous leiomyomatosis foci.
Conclusion: If complete surgical resection is not possible, partial resection followed by hormone therapy using gonadotropin-releasing hormone agonists is recommended, which in this study achieved the same favorable prognosis with regard to remission.

Introduction

Uterine fibroids, or smooth muscle leiomyomas, are common uterine tumors. There are a number of variants, all benign. Although benign, some extremely rare conditions of uterine leiomyoma are extremely rare conditions involve the benign smooth muscle tumors extending into the parenchyma of distant organs, such as the great vessels, or the lung [1–3].

Histologically, these variant leiomyoma resemble typical benign uterine leiomyomas at both the gross and microscopic levels, but with different growth patterns, which extend outside the uterus. These include intravenous leiomyomas, disseminated peritoneal leiomyomas, parasitic leiomyomas, and benign metastasizing leiomyomas [2]. Their atypical aggressive growth and expansion present diagnostic dilemmas and have led to controversy regarding their pathogenesis [4].

Among the variations of leiomyomatosis, intravenous leiomyomatosis is characterized by intravenous proliferation of a histologically benign smooth muscle cell tumor mass that is non-tissue-invasive [3,4]. Fewer than 200 cases have been reported in all. Because of its rarity, uterine leiomyomatosis is occasionally misdiagnosed or diagnosed only latterly, leading to improper treatment [5].

In this study, nine cases of intravenous leiomyomatosis are analyzed. All of the cases were confirmed by histopathological evaluation, and treated by gynecologic surgery, including complete or partial myomectomy, hysterectomy, bilateral oophorectomy, and hormone therapy. The characteristics of these intravenous leiomyomatosis cases are described in detail here, to allow the gynecologist to distinguish these uterine leiomyoma variants from the other variants, and from leiomyosarcomas. The literature of these variants of leiomyomatosis is reviewed and referred to with particular comments on histology, differential diagnosis, and treatment.

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Materials and methods

This study combines the data pools from two of the collaborators' hospitals, one in Taiwan and one in China, on a total of 2198 patients diagnosed with uterine leiomyoma who were treated at Chung Shan Medical University Hospital in Taiwan and at the Second Affiliated Hospital of Wenzhou Medical University in China from May 2003 to Oct. 2015. A review of hospital records shows that nine of those patients (0.4%) had pathologically proven uterine intravenous leiomyomatosis (benign smooth muscle extension into uterine blood vessels). They were collected in this study [6,7].

The medical records of each of these patients were reviewed to obtain initial symptoms, clinicopathological findings, types of therapy, and available follow-up information. Pretreatment evaluations included a complete medical history and physical examination, complete blood count, serum electrolytes, chemistry profile, chest X-ray, electrocardiogram, and contrast-enhanced computerized tomography of the abdomen and pelvis. Tumor markers included CA-125, squamous cell carcinoma antigen (SCC) and carcinoembryonic antigen (CEA).

The patients were treated through complete or partial myomectomy, and/or complete or partial hysterectomy. For clarification and verification of the diagnoses, all of the histological material was reviewed by a pathologist. The original tumors were clearly benign. No evidence of primary carcinomas in the uterus could be found, none of the patients had a previous history of carcinoma.

After surgery, therapy with gonadotropin-releasing hormone agonists is optional for premenopausal women and non-castration women. Three patients in this study's case series received that treatment – leuplin depot with gonadotropin-releasing hormone agonists, via a 3.75 mg/vial once a month per half year.

After the completion of therapy, patients were followed up on every three months in the first year. Subsequent follow-ups were every four months for the next three years, and then every six months thereafter.

Prognostic factors were analyzed with univariate analysis. Differences in categorical data were evaluated by a X^2 test. A p-value below 0.05 was regarded as indicating a significant difference.

Table 1
Patient characteristics.

Patient characteristics	No. of patients (n = 9)	Percentage (%)
Age range(y)	32–52	
Mean age	43.3	
Menopause status	1	11.1%
Parous status	8	98.9%
Presenting symptoms		
Abdominal pain	1	11.1%
Vaginal bleeding	2	22.3%
Asymptomatic	6	67%

Table 2
Different treatment methods.

Treatment methods	No. of patients (%)
Hysterectomy & bilateral salpingoophorectomy	4/9 (44.5%)
Hysterectomy without bilateral salpingoophorectomy	1/9 (11.1%)
Subtotal hysterectomy & bilateral salpingoophorectomy	2/9 (22.2%)
Myomectomy without bilateral salpingoophorectomy	2/9 (22.2%)
Post-surgical GnRh-A hormone therapy	3/9 (33.3%)

Table 3
Age and tumor size with respect to recurrence and treatment method.

	No. of IVM patients (n = 9)	Recurrence	P
Age			
<50	8	2 (25.0%)	0.5708
>50	1	0 (0%)	>0.05
Tumor size (cm)			
<8	3	1 (33.3%)	0.6691
8–15	4	1 (25.0%)	>0.05
>15	2	0 (0%)	–
Operation			
Complete resection	4	0 (0%)	0.5708
Incomplete resection	5	2 (40.0%)	>0.05
Myomectomy			
With oophorectomy	7	1 (14.3%)	0.5708
Without oophorectomy	2	1 (50.0%)	>0.05

Results

This study examined nine patients with pathologically proven intravenous leiomyomatosis of the uterus. All of the patients were East Asians - Chinese or Taiwanese. Of them, eight were multiparous, and one was nulliparous. One patient was pregnant. Six of the patients had an abortion history. One patient was a smoker.

The patients' mean age was 42.0 years, with a range from 32 to 52 years. Hypermenorrhea and dysmenorrhea were their predominant symptoms. Among the patients, three presented with symptoms of hypermenorrhea and two presented with symptoms of dysmenorrhea during menstruation onset. One patient had vaginal bleeding, and one patient had urinary frequency symptoms. Three patients remained asymptomatic until latterly and were diagnosed incidentally on imaging. None of the patients presented with constipation. One patient was experiencing menopause [Patient characteristics and treatment methods are listed in Tables 1–3, with details following the tables.].

Four patients with intravenous leiomyomatosis underwent total abdominal hysterectomy and bilateral salpingoophorectomy. One patient underwent abdominal hysterectomy, without salpingoophorectomy. Two patients underwent subtotal hysterectomy and bilateral salpingoophorectomy. The other two patients underwent myomectomy without salpingoophorectomy [Table 2].

During surgery, retroperitoneum involvement was presented in seven of the nine cases (77.8%); colon involvement in one of the cases (11.1%), and bladder involvement in one of the cases (11.1%). After surgery, three pre-menopause patients with no castration (33.0% of the nine cases) received hormone therapy via gonadotropin-releasing hormone agonists.

Through microscopic assessment of these hysterectomized or myomectomized specimens, fibrotic and hyalinized ground tissue, smooth-muscle bundles and scattered single smooth-muscle cells can be seen. Within the larger sample, dilated vascular structures with endothelial lining and well-developed muscular wall layers are found among them.

After five years follow up, seven of the cases (78%) had a prognosis of complete remission. Recurrence of the tumor was documented in two of the cases (22.2%). These two patients were premenopausal women, one of who underwent hysterectomy and one of who underwent myomectomy. Both had incomplete excisions because of bladder and retroperitoneum invasions. The recurrence rate for the incomplete resection group was 66.7% [Tables 3 and 4].

There was no recurrence for the patients who had complete resections [Table 5]. Incomplete resection without hormone therapy using gonadotropin-releasing hormone agonists is a risk factor of recurrence (P = 0.0253) [Table 6].

The two patients with tumor recurrence underwent a second operation. The operations were not completely successful due to extensive retroperitoneum invasion. However, there was a good

Table 4
Incomplete resection vs. complete resection (Number of cases).

	Incomplete resection (Number of cases)	Complete resection (Number of cases)	*P*
Tumor size			
<8	2	1	0.8936
8–15	2	2	
>15	1	1	
Myomectomy			
With oophorectomy	2	4	0.0578
Without oophorectomy	3	0	

Chi-square test, $P < 0.05$.

Table 5
Recurrence vs non-recurrence (Number of cases).

	Recurrence (Number of cases)	Non-Recurrence (Number of cases)	*P*
Age			
<50	2	6	0.5708
>50	0	1	
Tumor size			
<8	1	2	0.6691
8–15	1	3	
>15	0	2	
Operation type			
Complete resection	0	4	0.1515
Incomplete resection	2	3	
Myomectomy			
With oophorectomy	1	5	0.5708
Without oophorectomy	1	2	
Incomplete resection			
With oophorectomy	1	1	0.7094
Without oophorectomy	1	2	
Complete resection			
With oophorectomy	0	4	
Without oophorectomy	0	0	

Chi-square Test, $P < 0.05$.

response to post-surgery gonadotropin-releasing hormone agonist therapy. After five years of follow-up, no recurrence or mortality was noted.

Discussion

Intravenous leiomyomatosis was first described by Birch-Hirschfel in 1896. It is a rare condition in which a smooth muscle cell tumor grows within venous channels in a non-malignant way. However, although it is a histologically benign entity, it can have malignant clinical behavior [1].

There are no reported cases of intravenous leiomyomatosis eventually progressing to malignancy as such. However, intravenous leiomyomatosis can cause considerable systemic complications, can present significant diagnostic difficulties, and also have a relatively high possibility of recurrence [3].

Corroborating other research, which generally reports that intravenous leiomyomatosis affects predominantly premenopausal women in their forties and fifties [3,4], this study also finds that this disorder is seen mostly in premenopausal women (although one post-menopausal woman in this study also experienced intravenous leiomyomatosis).

As with health care issues in general, the crucial issues concerning intravenous leiomyomatosis are what the best therapeutic treatments/approaches are. One of the tradition approaches is the surgical approach. Hysterectomy and bilateral salpingoophorectomy have been proposed as the gold-standard methods of treatment by several studies [5]. Additionally, some studies have

Table 6
Post-surgery GnRh-A hormone therapy vs. Non GnRh-A hormone therapy (Number of cases).

	GnRh-A hormone therapy (Number of cases)	Non GnRh-A hormone therapy (Number of cases)	*P*
Age			
<50	3	5	0.4533
>50	0	1	
Tumor size			
<8	1	2	0.8290
8–15	1	3	
>15	1	1	
Complete resection			
Recurrence	0	2	0.2568
Non Recurrence	3	4	
Incomplete resection			
Recurrence	0	2	0.0253*
Non Recurrence	3	0	
Incomplete resection			
With oophorectomy	1	1	0.7094
Without oophorectomy	2	1	

Chi-square Test, $^{*}P < 0.05$.

argued that more aggressive and radical methods, rather than the total hysterectomy approach, should be considered [6–8,13].

A review of the literature, however, reveals that recurrence rates are very low for simple hysterectomy and bilateral salpingoophorectomy, and even for myomectomy patients.

Given the fact that estrogen and progesterone receptors are present in the leiomyoma cells, bilateral salpingoophorectomy is essential, and exogenous estrogens must be avoided to prevent subsequent growth of microscopic or unresected foci of intravenous leiomyomas. For the non-castration cases, post-surgery hormone therapy should also be considered. Gonadotropin-releasing hormone agonists or antiestrogen therapy have also been used to prevent tumor growth and to reduce the tumor mass but no efficacy has been demonstrated to date [9,10]. This study suggests that gonadotropin-releasing hormone agonists are useful for unresected intravenous leiomyomatosis foci in preventing tumor growth and recurrence. Thus, in the absence of total resection, long-term treatment with gonadotropin-releasing hormone agonists may be useful in preventing recurrence of this disease [11,12,14]. One of the largest series of cases, 18 patients in Du et al. in (2011), shows a recurrence rate of 16.6% for intravenous leiomyomatosis. The current study suggests that young age and size of the initial tumor may be predisposing factors [14]. In this study, the recurrence rate was 22.2%. Incomplete resection without hormone therapy using gonadotropin-releasing hormone agonists seems to be a recurrence risk factor.

Conclusion

Complete resection in cases of intravenous leiomyomatosis has been considered to be essential for a good prognosis regarding remission/recurrence. For cases in which complete surgical resection is not possible, bilateral salpingoophorectomy or hormone therapy using gonadotropin-releasing hormone agonists following surgery have also been recommended, although neither has been thought to be able to result in as good a prognosis as complete resection. In the cases examined in this study, however, incomplete resection followed by gonadotropin-releasing hormone agonists to treat intravenous leiomyomatosis proved to be as effective as complete resection.

Conflict of interest statement

The authors report no conflicts of interest.

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