

Endometrial stromal nodule: report of 8 cases and literature review

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Summary

Endometrial stromal nodule (ESN) is a rare and benign tumor of endometrial stromal origin that accounts for less than 10% of uterine mesenchymal neoplasms. It is difficult and yet essential to preoperatively differentiate endometrial stromal nodule from other types of mesenchymal malignancies, considering that the therapeutic options and clinical outcomes are totally different. To better guide clinical practice, the authors herein report eight cases diagnosed with endometrial stromal nodule and analyze the clinical and pathological characteristics, and also perform a literature review of endometrial stromal nodule. Authors of the present study conclude that conservative surgery with fertility-sparing is feasible for a suspected diagnosis of endometrial stromal nodule when ultrasonography suggests hypoechoic masses with cystic degeneration or liquefaction and magnetic resonance imaging showed a well circumscribed mass exhibiting isointensity on T1-weighted images, hyperintensity on T2-weighted images, and hyperintensity on diffusion-weighted images.

Key words: Endometrial stromal nodule; Literature review; Magnetic resonance imaging; Fertility sparing; Treatment.

Introduction

Endometrial stromal tumors (EST) are uncommon tumors of endometrial stromal origin that account for less than 10% of uterine mesenchymal neoplasm [1] and less than two percent of all uterine tumors. The World Health Organization recognizes four categories of endometrial stromal tumors based on clinical and pathologic features: endometrial stromal nodule (ESN), low-grade endometrial stromal sarcoma (LG-ESS), high-grade endometrial stromal sarcoma (HG-ESS), and undifferentiated uterine sarcoma (UUS) [2]. These categories are defined by the presence of distinct translocations as well as tumor morphology and prognosis.

Endometrial stromal nodule is a rare benign tumor which commonly occurs in the premenopausal age group, with the average age at diagnosis being 53 years [3]. Additionally, ESN is often asymptomatic and incidentally discovered in hysterectomy specimens performed for other reasons. In other instances, ESN patients may present with non-specific clinical symptoms such as abnormal bleeding or abdominal pain [3, 4]. Utility biomarkers for the diagnosis of ESN are not currently available and it is difficult to differentiate between uterine leiomyoma and ESN on ultrasound, therefore, the diagnosis of ESN relies on pathologic investigations. The most important differential diagnosis includes LG-ESS, HG-ESS, uterine sarcoma, highly cellular leiomyoma (HCL), and other malignancy or diseases with malignant tendency [5]. For these diseases, hysterectomy, and bilateral salpingo-oophorectomy (BSO) is a preferred pro-

cedure, which is a devastating strike for women who desire to retain fertility [6]. On the other hand, rather than total hysterectomy, patients with ESN may undergo conservative treatments such as local excision of the tumor. This method of treatment offers ESN patients the chance to preserve reproductive function [7]. Based on the aforementioned, it is crucial for clinicians to ensure accurate diagnosis of ESN so that informed clinical decisions, particularly relating to treatment could be made, especially for women who desire preservation of reproductive function.

To date, there are only two large ESN cases series. In 1981, Tavassoli and Norris reported on 60 cases of ESN [4] and in 2002, Dionigi *et al.* reported on 50 cases of ESN [3]. The very limited number of studies that have investigated ESN globally have only reported pathological features in ESN patients. Majority of these studies were published before the widespread recognition of the extent to which ESN could be mimicked by highly cellular leiomyomas. Hence the actual number of ESN cases may have been inaccurately estimated. Moreover, the rarity of this tumor also limited the possibility of a large scale study to determine its natural history and clinical characteristics. As a result, preoperative diagnosis of ESN remains a challenge.

There are currently no universal criteria for early diagnosis, treatment, and follow-up strategies for ESN. For these reasons, the authors analyzed eight cases of ESN in a hospital setting and present a review of the literature to compare clinical characteristics of ESN patients with previous studies, with the aim of guiding clinical practice.

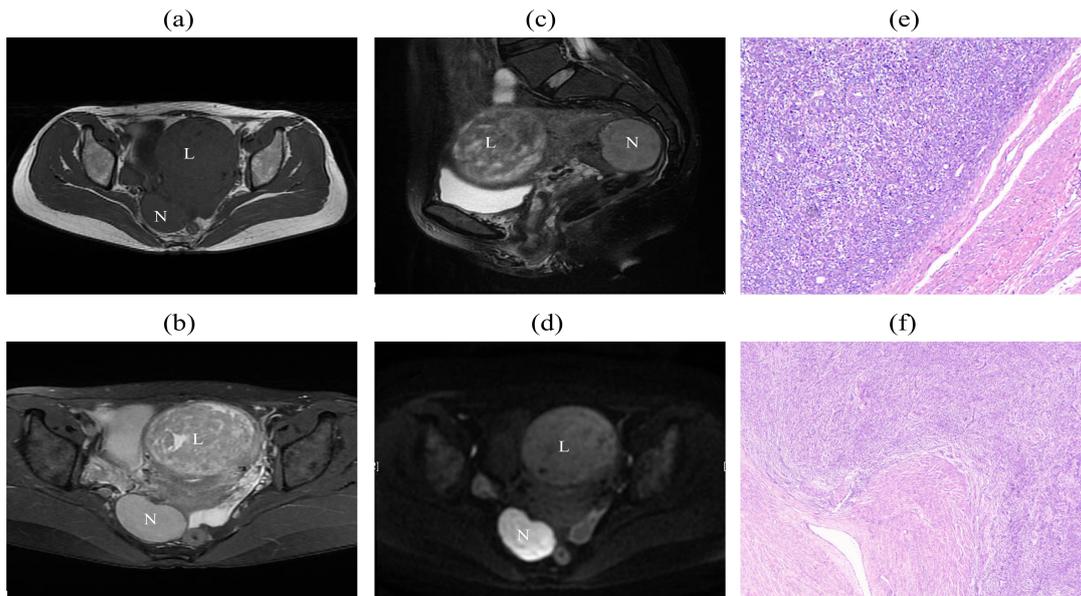


Figure 1. — (a) Axial planes in T1-weighted MRI. The dorsal mass (endometrial stromal nodule, N) and the ventral mass (uterine leiomyoma, L) both show myometrial signal isointensity on T1-weighted images. (b), (c): Axial (b) and sagittal (c) planes in T2-weighted MRI with fat suppression. A heterogeneously hyperintense mass (L) located in the ventral myometrium, and a relative hyperintense mass (N) located in the dorsal myometrium. Both masses have no continuity with the endometrium. (d): Axial plane in diffusion-weighted MRI. The dorsal mass (N) shows higher signal intensity as compared with the surrounding myometrium and ventral mass. (e), (f): Pathological findings of the mass in the dorsal myometrium. Microscopically ($\times 100$), ESN has an expansile, but non-infiltrative border that compresses the surrounding myometrium.

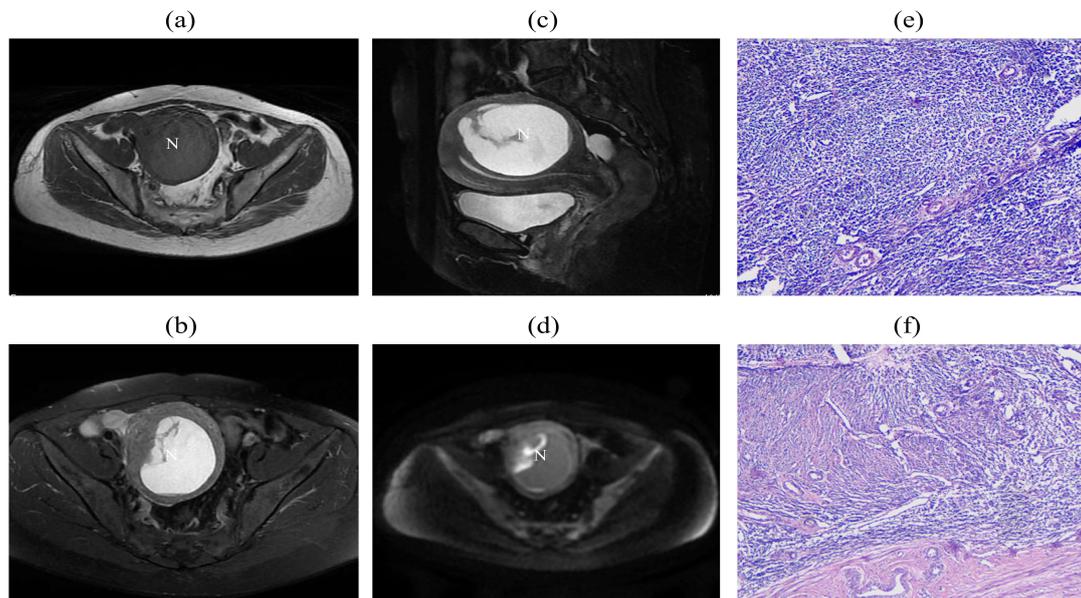


Figure 2. — (a): Axial planes in T1-weighted MRI. The mass (N) shows myometrial signal isointensity on T1-weighted image. (b), (c): Axial (b) and sagittal (c) planes in T2-weighted MRI with fat suppression. A heterogeneously hyperintense mass (N) located in myometrium, and has no continuity with the endometrium. The cystic part shows high signal intensity, while the solid part shows relatively low signal intensity. (d): Axial plane in diffusion-weighted MRI. The solid part of the mass (N) shows higher signal intensity as compared with the surrounding myometrium. (e), (f): Pathological findings of the mass in the dorsal myometrium. Microscopically ($\times 100$), ESN has an expansile, but non-infiltrative border that compresses the surrounding myometrium.

Table 1. — *Clinical characteristics of 8 patients.*

N O.	Age (years)	Meno-pause	G.P.	Symptom	Ultrasonic impression	Magnetic resonance imaging of the mass	Serum biomarker	Treatment	Follow-up	
									Time (month)	Recurrence
1	45	Pre	G3P2	Abnormal bleeding and abdominal pain	Uterine leiomyoma complicated with liquefaction	Isointensity on T1WI; relative hyperintensity on T2WI; hyperintensity on DWI.	WNL	Hysterectomy	12	Non
2	60	Post	G1P1	Abdominal pain	Uterine leiomyoma complicated with liquefaction	Isointensity on T1WI; on T2WI, the cystic part exhibited hyperintensity while the solid part exhibited relatively higher signal; on DWI, the cystic part exhibited isointensity while the solid part exhibited hyperintensity	WNL	Hysterectomy	45	Non
3	43	Pre	G4P1	Menorrhagia and menostaxis	Uterine leiomyoma complicated with cystic degeneration	Isointensity on T1WI; hyperintensity on T2WI; hyperintensity on DWI.	WNL	Hysterectomy	10	Non
4	46	Pre	G1P1	Asymptomatic	Uterine leiomyoma complicated with cystic degeneration	Isointensity on T1WI; on T2WI, the cystic part exhibited hyperintensity while the solid part exhibited relatively higher signal; on DWI, the cystic part exhibited isointensity while the solid part exhibited hyperintensity	WNL	Hysterectomy	6	Non
5	47	Pre	G3P3	Menstrual disorder	Uterine leiomyoma	Isointensity on T1WI; on T2WI, the cystic part exhibited hyperintensity while the solid part exhibited relatively higher signal; on DWI, the cystic part exhibited isointensity while the solid part exhibited hyperintensity	WNL	Hysterectomy	2	Non
6	44	Pre	G1P1	Menorrhagia and menostaxis	Uterine leiomyoma	/	WNL	Hysterectomy	88	Non
7	52	Pre	G2P2	Menstrual disorder	Uterine leiomyoma	/	WNL	Hysterectomy	8	Non
8	29	Pre	G2P1	Vaginal mass	Cervical polyps	/	WNL	Cervical polypectomy+ segmental curettage followed hysterectomy	31	Non

Legend: G.P.: Gravida and para. T1WI: T1-weighted image. T2WI: T2-weighted image. DWI: diffusion-weighted images. Serum biomarkers including CA125, CA153, CA199, SCC, CEA and AFP. WNL: Within normal limits.

Table 2. — Pathological characteristics of patients.

Patient number	Maximum diameter (cm)	Location	Colour	Tumor-myometrium interface	Desmin	Caldesmon	CD10	HMB45	P53	ER	PR	Ki67
1	3.5	Myometrium	Grayish white	Clear	-	++	+++	-	/	+	+++	< 1%+
2	8	Broad ligament	Grayish white	Clear	±	-	+++	/	-	+++	+++	20%+
3	10	Myometrium	Grayish white	Clear	-	++	++	/	/	++	++	10%+
4	5	Myometrium	Grayish white	Clear	-	+	++	-	-	/	+++	10%+
5	4	Myometrium	Grayish yellow	Clear	-	-	++	-	-	++	++	10%+
6	2	Myometrium	Grayish yellow	Clear	++	++	+++	/	++	+	++	< 1%+
7	4	Myometrium	Grayish white	Clear	-	++	+++	-	-	/	/	< 1%+
8	6	Polypoid and projected into the endometrial cavity	Yellow	Clear	±	-	+++	-	+	+++	+++	50%+

Case Report

This study was approved by the ethics committee of Fujian Maternity and Child Health Hospital, Affiliated Hospital of Fujian Medical University. Written informed consent was obtained from the patients to publish case characteristics and accompanying images. A total of eight patients with pathologically confirmed ESN at this institution from January 2011 to July 2018 were included in the present study. All cases were selected from the files of the pathology department and were reviewed and classified on the basis of clinical and morphological characteristics. Representative cases are shown in Figures 1 and 2.

Demographic, clinical, and pathological characteristics of the cases are shown in Tables 1 and 2. There were a total of eight patients with a mean age of 45.8 years at diagnosis. A total of seven (87.5%) patients were premenopausal and only one (12.5%) patient was postmenopausal. Only one patient was asymptomatic which corresponded to 12.5% of patients. The remaining seven patients were initially admitted due to abnormal bleeding, abdominal pain, menorrhagia and menostaxis, menstrual disorder, and vaginal mass. A total of seven (87.5%) patients were diagnosed with leiomyoma by ultrasonography and none of them showed evidence of pelvic lymph node enlargement. Ultrasonic impressions showed uterine leiomyoma with cystic degeneration in two patients, and uterine leiomyoma with liquefaction was observed in another two patients. MRI were performed in five patients, and the masses were all well circumscribed. They seemed to exhibit isointensity on T1-weighted images, hyperintensity on T2-weighted images, and hyperintensity on diffusion-weighted images. Furthermore, when the masses were composed of solid and cystic parts, they seemed to exhibit isointensity on T1-weighted images. The T2-weighted images revealed that the cystic part exhibited hyperintensity while the solid part exhibited relatively higher signal; also, the diffusion-weighted images showed that the cystic part exhibited isointensity while the solid part exhibited hyperintensity. All patients' serum biomarkers including CA125, CA153, CA199, SCC, CEA, AFP were within normal limits. A total of seven patients (87.5%) who initially underwent hysterectomy were diagnosed by pathology confirmation and one patient (12.5%) was diagnosed based on cervical polyp and curettage specimens, further confirmed by hysterectomy specimens. The mean maximum diameter of tumors was 5.31 cm. All tumor boundaries were clear. Tumors were located in the myometrium (submucosal or intramural) in six (75%) patients, broad ligament in one patient and tumor was polypoid and projected into the endometrial cavity in one patient. Immunohistochemical results showed that, CD10 and PR were positive (++, +++) in all tumors. All patients were followed for 2-88 months, the median follow-up time was 12 months, and none of the patients experienced a recurrence. Radiation and chemotherapy were not used in any instance.

Table 3. — Results of the two largest series published to date and the present study.

Study	No of cases	Age (years) Mean (range)	Symptoms (cases)	Clinical findings (cases)	Tumor size (cm) Mean/median (range)	Tumor location (cases)	Treatment (cases)	Follow-up time
Tavassoli and Norris [4]	60	47 (23-75)	Abnormal bleeding and menorrhagia (40)	Uterine enlargement or a uterine mass (37)	Median 4.0 (0.8-15.0)	Within the endometrium (4)	Hysterectomy (54)	Follow-up available for all cases
			Pelvic or abdominal pain (10)			Both the endometrium and the myometrium (19)	Excision of uterine nodules (6)	Range: 0.5 to 16 years
			Asymptomatic (7)			Totally within the myometrium (intramural and subserosal) without any apparent connection to the endometrium (37)		5+ years: 85% (51) of cases
								10+ years: 63% (38) of cases
Dionigi et al [3]	47	53 (31-86)	Abnormal uterine bleeding (23) Abdominal pain (9)	Uterine enlargement or a uterine mass (23)	Mean 7.1 (1.2-22)	Polypoid and projected into the endometrial cavity (16) Submucosal (7) Intramural (14)	Hysterectomy (49) Local excision of the tumor (1)	Follow-up available for 68% (32) of cases Range: up to 214 months (mean 43.5 months)
Present study	8	45.8 (29-60)	Abnormal bleeding and abdominal pain (2) Menstrual disorder (2) Menorrhagia and menostaxis (2) Vaginal mass (1) Asymptomatic (1)	Uterine enlargement or a uterine mass (8)	Mean 5.31 (2.0-10)	Myometrium (submucosal or intramural) (6) Broad polypoid and projected into the endometrial cavity ligament (1) Broad ligament (1)	Hysterectomy (8)	Follow-up available for all cases Range: 2-88 months

Discussion

The rarity of ESN coupled with its overlapping morphological features have contributed to the difficulty for clinicians in recognizing until the initial identification by Norris and Taylor in 1966 [8]. Currently, the total number of ESN cases reported worldwide is no more than 500. Related reports on this disease in China were even fewer, and the number of cases in each report is no more than five cases. Endometrial stromal tumors have been associated with polycystic ovarian disease, estrogen and tamoxifen therapy, and prior radiation [12-14]. In the present study, most patients were premenopausal, and immunohistochemical profiles revealed that all tumors were ER and PR positive, indicating that ESN may be a hormone-dependent disease. However, the pathogenesis of ESN still remains unclear due to the rarity of this tumor and lack of relevant basic experimental research.

The partial results of the two largest series published to date are shown in Table 3. Patients diagnosed with ESN usually present with non-specific symptoms such as abnormal bleeding or abdominal or pelvic pain, which were consistent with findings in the present study. It is noteworthy that evidence obtained from clinical follow-up in previous studies and the present study suggest that these tumors behave in a benign manner.

Therefore, the definitive diagnoses before surgery is important considering that ESN is benign and can be appropriately treated by complete or local lesion excision [2]. Many articles have discussed the differential diagnosis between ESN and LG-ESS, highly cellular leiomyoma and other endometrial tumors with foci of genetic aberrations [15,16] and pathological features such as morphology and immuno-phenotype [17,24]. Even so, definitive diagnosis of ESN before surgery has remained extremely difficult.

In clinical practice, imaging data derived from ultrasonography or MRI and serum biomarkers were useful tools for diagnosing uterine masses. However, the characteristic ultrasonic and MRI appearance of this rare tumor type have only been described in a few cases and have not been established [25,27]. Thus, the present authors report imaging characteristics for five ESN patients, based on ultrasonography and MRI. As shown in the present study (Table 1), transvaginal ultrasonography of ESN usually revealed hypoechoic masses and were misdiagnosed as uterine leiomyoma. Interestingly, ultrasonic impressions seemed to suggest that hypoechoic masses often complicated by cystic degeneration or liquefaction, which deserve the attention of clinicians. Furthermore, when the masses were composed of solid and cystic parts, they seemed to exhibit isointensity on T1-weighted images and the T2-weighted images revealed that the cystic part exhibited hyperintensity, while the solid part exhibited relatively higher signal; also, the diffusion-weighted images showed that the cystic part exhibited isointensity while the solid part exhibited hyperintensity. These findings were similar to those described in the previous reports. For instance, Maruyama *et al.* presented a case of benign ESN that showed high signal intensity in diffusion-weighted images [26] and Ozaki

and Gabata found that the observed hyper-intensity on T2-weighted images, similar to that of the endometrium, and the well circumscribed margin, seemed to suggest an endometrial stromal nodule [27]. Nevertheless, it is disappointing that the present results indicated that serum biomarkers could not provide valid help for clinicians in diagnosing ESN.

Given the limited reports in the literature concerning the clinical management. The appropriate treatment for ESN is a challenge for clinicians. In the present cases, all patients underwent hysterectomy. However, in some cases, hormonal therapy with local excision may be successful. In the series reported by Tavassoli and Norris, the five patients who underwent simple excision of the uterine nodules were followed for 6.2, 6.8, 9.1, and 10 years (two) with no evidence of recurrence [4]. In addition, Schilder *et al.* [7] reported a successful hormonal therapy (leuprolide acetate depot suspension), followed by local excision of the tumor with preservation of reproductive function. Hence, in consideration of ESNs being benign entities, drug therapy or conservative surgery may be a promising treatment strategy for ESNs.

In summary, treatment of ESN should be based on the patient's age, fertility demand, impression of ultrasonography and MRI, and pathological results of curettage specimens. Authors of the current report suggest that a diagnosis of ESN should be suspected when ultrasonography suggests hypoechoic masses complicated by cystic degeneration or liquefaction and MRI shows a well circumscribed mass exhibiting isointensity on T1-weighted images, hyperintensity on T2-weighted images, and hyperintensity on diffusion-weighted images. Meanwhile, for patients with fertility needs or desiring retention of the uterus, complete excision of the uterine nodules is feasible. Although MRI may not be entirely feasible in the differentiation of ESN from LG-ESS [28] and result in misdiagnosis, fertility-sparing treatment is still a viable choice for LG-ESS [29,30]. For postmenopausal women or women without fertility needs, the risk of a poor prognosis may be higher than the wishes for an unwanted pregnancy, hence hysterectomy is recommended. Overall, how to manage these rare tumors and how to ensure patients' benefits with today's precision therapies require further work, especially in women who desire retention of reproductive function. The current study is limited by small number of cases, therefore, randomized controlled trials including large number of cases are needed to be to provide more comprehensive and definitive clinical recommendations, considering the rarity of these tumors.

Author contributions

Conception, design, and writing of the manuscript: Jian An, Guanyu Ruan, Xiaodan Mao, Binhua Dong, Pengming Sun. Acquisition of data: Xiaoyan Xie, Yuequan Shi.

Ethics approval and consent to participate

This study was approved by the ethics committee of Fujian Maternity and Child Health Hospital, Affiliated Hospi-

tal of Fujian Medical University. Written informed consent was obtained from the patients to publish case characteristics and accompanying images.

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Conflict of interest

All authors declare that there is no conflict of interest.

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