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Fertility-preserving management of an inflammatory myofibroblastic tumor: A case report and review of the literature

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ABSTRACT

Molecular diagnostics have broadened the categorization of mesenchymal tumors of the uterus. Knowledge of the increasing heterogeneity of uterine neoplasms is paramount for the gynecologist as the management and prognosis of these neoplasms differ from those of typical leiomyomas.

In this case, a 26-year-old nulligravid patient underwent hysteroscopic management for an enlarging submucosal neoplasm of the uterus. She was found to have an inflammatory myofibroblastic tumor (IMT) after ALK (anaplastic lymphoma kinase) immunostaining. Upon review of pathologic characteristics, she was treated expectantly with repeat hysteroscopy 12 months later. Ongoing conservative management will entail serial pelvic imaging.

IMTs should be considered in the differential diagnosis of fibroids presenting in young women. Fertility-preserving management in select patients is appropriate after patient counselling.

1. Introduction

Inflammatory myofibroblastic tumors (IMTs) are mesenchymal neoplasms of indeterminate biological potential, first described in the lung in the early 2000s [1]. Recently, they have been described in the uterus and, to date, a total of 125 cases of uterine inflammatory myofibroblastic tumor have been reported [2–8].

Mesenchymal tumors of the uterus are broadly divided into smooth muscle tumors, endometrial stromal and related tumors, and miscellaneous mesenchymal tumors. IMTs are part of the last category. IMTs share many clinical and pathologic features of smooth muscle tumors and can therefore be misclassified as leiomyomas, leiomyosarcomas or smooth muscle tumors of unknown malignant potential (STUMP) [9,10]. The diagnosis of IMTs has been improved in recent years [11] due to the role of anaplastic lymphoma kinase (ALK) immunohistochemistry staining.

In a retrospective analysis of 1747 tumors identified as leiomyomas and 44 tumors identified as leiomyosarcomas, 5 (0.3%) and 1 (2.3%) were respectively re-assigned the diagnosis of IMT after selective immunohistochemistry staining with ALK [10]. Given the frequency of surgery performed for fibroids and increased awareness of this entity, the diagnosis of uterine IMTs will increase in coming years [12].

In this paper, the key diagnostic features for identification of these neoplasms are reviewed and the current evidence for their management and prognosis is presented. Clinical and pathological guidance allowing for fertility-preserving treatment of these patients are provided.

2. Case Presentation

A 26-year-old woman, G0, was referred to gynecology for a 6-month history of increased and prolonged regular menstrual bleeding, which had caused profound anemia requiring blood transfusion. A transabdominal pelvic ultrasound scan (US) revealed an anteverted uterus measuring 70 × 67 × 69 mm with an intramural (FIGO type 3) fibroid measuring 48 × 47 × 48 mm. The patient was treated with ulipristal acetate, tranexamic acid and intravenous iron infusions. Cyclic bleeding remained heavy despite medical treatment. Pelvic magnetic resonance imaging (MRI) was ordered to better delineate the fibroid location in preparation for surgery. The MRI demonstrated a 6.3 × 7.3 × 6.1 cm vascular fundal mass with both submucosal and subserosal components (FIGO type 2–5) and intermediate T2 signaling, suggesting "a possible cellular fibroid, cannot rule out uterine sarcoma" (Fig. 1). In the following days, the patient presented to hospital with acute uterine hemorrhage requiring transfusion. A uterine artery embolization was

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conducted due to the significant ongoing bleeding, followed by a plan for an urgent hysteroscopic surgery.

At hysteroscopy, a large uterine neoplasm arising from the right lateral sidewall (6–7 cm) filled the uterine cavity. A hysteroscopic guided biopsy was performed and a frozen section showed markedly degenerated tissue, for which a diagnosis of leiomyoma was favored. Given the size of the mass and the imaging suggestion of a subserosal component, a diagnostic laparoscopy was conducted and confirmed no subserosal component to the mass. Hysteroscopic resection of the complete mass was undertaken using a combination of a hysteroscopic morcellator (Myosure XL, Hologic Canada) and a hysteroscopic bipolar loop electrode with sterile saline (Olympus Canada).

Pathologic examination revealed a bland spindle cell neoplasm with fascicular growth pattern and sparse lymphocytic inflammatory infiltrate. No nuclear atypia was appreciated, and mitotic activity was low (up 1 mitosis per 10 high-power fields). Degenerative changes with ischemic-type necrosis and focal hemorrhage were present, consistent with the history of uterine artery embolization. By immunohistochemistry, the lesional cells stained diffusely with ALK (anaplastic lymphoma kinase) protein and smooth muscle markers (caldesmon, desmin and smooth muscle actin). An IGFBP5-ALK fusion transcript was detected by RNA sequencing, confirming the diagnosis of inflammatory myofibroblastic tumor (Fig. 2).

The patient had a desire for fertility preservation and was managed expectantly. Repeat hysteroscopy one year later confirmed no tumor recurrence. She will undergo long-term follow-up with yearly pelvic imaging with consideration for completion hysterectomy once childbearing is complete.

3. Discussion

Inflammatory myofibroblastic tumors resemble other uterine neoplasms in both their clinical presentation and their appearance on pathology. They are of indeterminate biological potential and can recur and metastasize. Certain features may be indicative of a more aggressive clinical course. On pathological examination, IMTs show three main morphological patterns: myxoid, fascicular and hyalinized [9], which often overlap with the morphology of smooth muscle tumors. They are characterized by an inflammatory infiltrate of lymphocytes or plasma cells, which can be sparse and focal. They express smooth muscle tumor markers such as SMA (smooth muscle actin), desmin and caldesmon, which further contributes to the diagnostic challenge. They can also exhibit more aggressive features such as tumor cell necrosis, high mitotic activity, and infiltrative borders [9,10].

ALK (anaplastic lymphoma kinase) immunohistochemistry has been shown to be a specific marker for the identification of uterine IMTs. All but one case [13] of uterine IMTs reported to date have demonstrated some degree of ALK immunostaining. Gene rearrangement of ALK on gene 2p23 by RNA sequencing or FISH is thought to be essentially diagnostic of a uterine IMT. A low threshold for performing ALK immunohistochemistry for mesenchymal lesions has been proposed for the correct identification of these rare neoplasms [10].

Clinical features of uterine IMTs reported in the literature include a tendency to arise in younger women, of reproductive age. They appear to predominantly arise as submucosal or pedunculated, polypoid intracavitary masses [10]. An association between IMTs and pregnancy has also been proposed [14,15]. Of 19 neoplasms associated with the placenta in pregnant patients, 2 were subsequently described as IMT (10.53%) after ALK immunohistochemistry [10].

IMTs of all sites combined (lung, digestive tract, urinary tract, peritoneal cavity, uterus) have a local recurrence rate of approximately 25% and a metastasis rate of less than 2% [1]. Three larger case series have described clinical outcomes of patients with uterine IMTs. In the first series, of 10 patients, 1 patient presented with extra-uterine spread to the vagina. No follow-up information was available for this patient. Two patients had recurrence of disease after hysterectomy: the first within 2 months of surgery at the omentum and the second within 2 years from surgery at the left pelvic side wall. All but one of the patients in this series were treated with hysterectomy [5]. Haimes et al. reported 12 cases of uterine IMTs. There were no reported cases of recurrence (one patient with missing information) over a follow-up of 9 to 93 months [16]. Lastly, in the largest series to date, Bennett et al. reported on 23 cases of uterine IMTs. Two of these patients had extrauterine disease on presentation. They both exhibited persistent disease on follow-up. One of them died of disease 35 months after initial diagnosis. The other was alive with disease after 105 months of follow-up. Of the other 21 cases, two additional patients developed disease recurrence, the first at one month after surgery along the bowel and again at 10 months at the ovary. This patient was alive with disease at 11 months. The second patient developed a peritoneal recurrence 116 months after surgery and was alive with disease at 149 months following initial diagnosis [17].

Large tumor size, presence of tumor-type necrosis, high mitotic index and lymphovascular invasion have been proposed as features associated with a more aggressive clinical course [3,5]. Cases of recurrent or metastatic disease have been successfully treated with tyrosine kinase inhibitors such as crizotinib, emphasizing the importance of accurate diagnosis in these patients [4,18].

Of all cases reported in the literature, 21 were treated with fertility-preserving surgery. Where available, follow-up data suggests that outcomes are favorable (Table 1). In the absence of aggressive pathological features, it is unclear if hysterectomy should be offered in all cases of IMT when childbearing is complete and there is limited data to this effect in the literature. In all cases of placenta-associated IMTs, the masses were removed at the time of cesarean section, found incidentally on pathologic examination of the placenta, or expelled spontaneously after vaginal delivery. There have been no reports of recurrent disease in the setting of placenta-associated IMT [10,15,19–21].

In summary, fertility-preserving surgery for the treatment of uterine

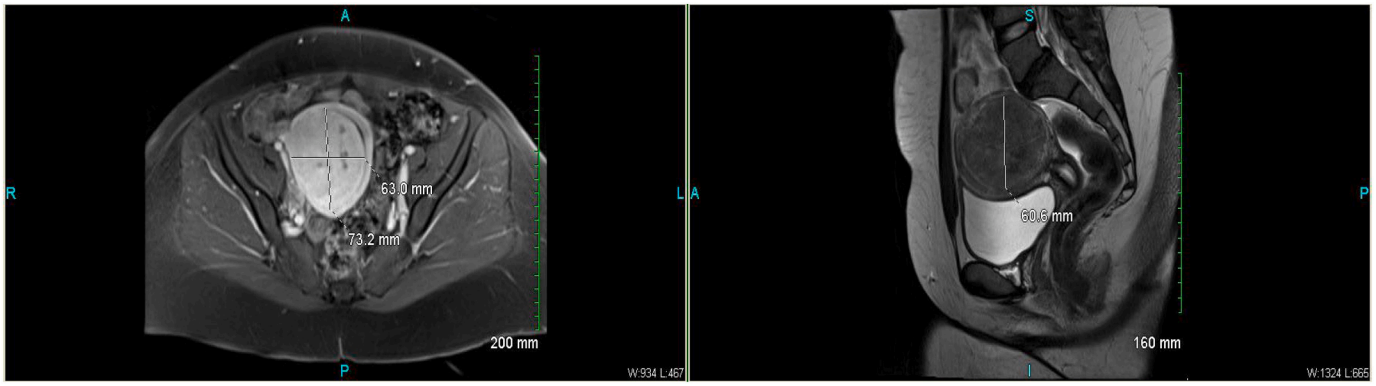

Fig. 1. MRI of the uterine inflammatory myofibroblastic tumor.

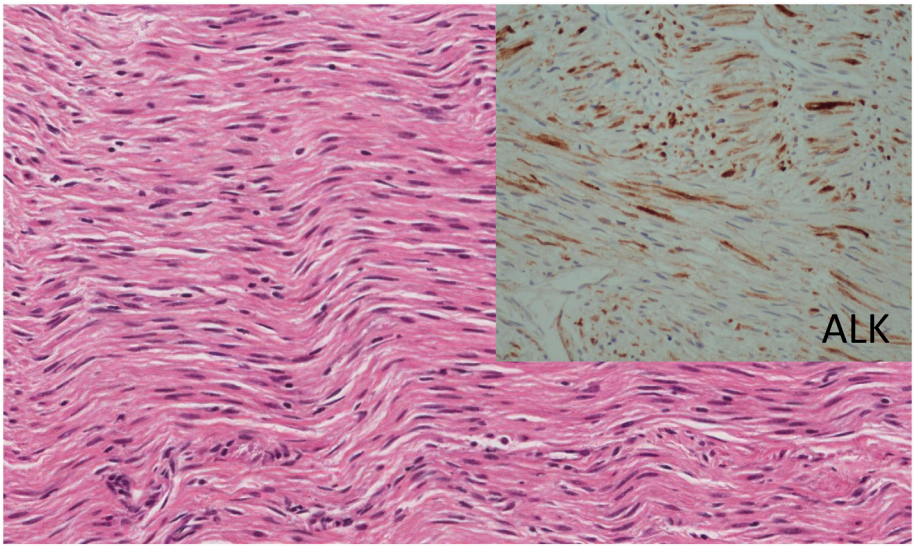

Fig. 2. Histology of the inflammatory myofibroblastic tumor.

Table 1
Fertility-preserving management of uterine inflammatory myofibroblastic tumors reported in the literature.

Author	Year of publication	Age (yrs)	Site	Size (cm)	Surgical management	Follow up
Rabban et al. [22]	2005	25	Uterus	5	Hysteroscopic resection	–
		46	Uterus	3	Hysteroscopic resection	FOD 18 months
		38	Uterus	1	Hysteroscopic resection	FOD 36 months
Olgan et al. [2]	2011	28	Uterus	2	Hysteroscopic resection	FOD 12 months
Gupta et al. [23]	2011	14	Uterus	11	Open myomectomy	FOD 12 months
Fragetta et al. [24]	2015	10	Cervical polyp protruding through vagina	8	No therapy	Metastasis to 2 pelvic lymph nodes, FOD 20 months
Parra-Heran et al. [5]	2015	46	Uterus	–	Endometrial curettage	–
		36	Uterus	1.3	Excision	–
Vasiljovic et al. [25]	2016		Uterus and pelvic side wall	–	Exploratory laparotomy and biopsy	FOD at 24 months (spontaneous regression)
Haimes et al. [15]	2017	59	Uterus	11	Polypectomy	FOD 44 mo
		78	Uterus	3.5	Myomectomy	FOD 35 months
		46	Uterus	8.5	Myomectomy	FOD 36 months
		28	Uterus	5	Myomectomy	FOD 35 months
		24	Uterus	2	Myomectomy	–
Pickett et al. [10]	2017	32	Broad ligamenet	8	Biopsies taken	FOD 69 months
		45	Uterus	4	Curettage	Growth of mass and hysterectomy performed at 2 mo
Bennett et al. [17]	2020	27	Uterus	–	Curettage	–
		35	Uterus	–	Curettage	–
		35	Uterus	–	Curettage	–
		42	Uterus	–	Curettage	–
Etlinger et al. [26]	2020	3.5	Uterus	3 cm	Open myomectomy	FOD 36 months

FOD: Free of disease.

inflammatory myofibroblastic tumors appears reasonable, particularly in the absence of aggressive pathological features and where the tumor is confined to the uterus. As recurrences may present at a time remote from index surgery, long-term imaging follow-up should be offered. A discussion regarding hysterectomy after childbearing completion should be undertaken in light of the risk of recurrence and metastasis.

Contributors

Geneviève Horwood contributed to the conception of the case report, acquiring and interpreting the data, drafting the manuscript, undertaking the literature review and revising the article critically for important intellectual content.

Aurelia Busca contributed to patient care, the conception of the case report, acquiring and interpreting the data, drafting the manuscript, and revising the article critically for important intellectual content.

Sukhbir Singh contributed to patient care, to the conception of the case report, acquiring and interpreting the data and revising the article critically for important intellectual content.

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Patient consent

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This article was not commissioned and was peer reviewed.

Conflict of interest statement

The authors declare that they have no conflict of interest regarding the publication of this case report.

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