Maturitas 185 (2024) 107996

Contents lists available at ScienceDirect

Maturitas

journal homepage: www.elsevier.com/locate/maturitas

Original article

Imaging and molecular features of adenomyosis after menopause

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ARTICLE INFO

Keywords:
Post-menopause
Adenomyosis
Transvaginal ultrasound
MRI
Epithelial-mesenchymal transition
Inflammation
Fibrosis

ABSTRACT

Objectives: To explore the imaging features and the molecular characterization of adenomyosis after menopause.
Study design: An observational cross-sectional study was performed in a group of postmenopausal patients undergoing a transvaginal ultrasound (TVUS) ($n = 468$). Among those presenting the US criteria for adenomyosis, also confirmed by magnetic resonance imaging (MRI), previous menstrual symptoms, gynecological and obstetric history were reviewed. In a subgroup undergoing hysterectomy, uterine specimens were analyzed by histology and expression of genes implicated in the epithelial-mesenchymal transition, inflammation and fibrosis, including the sphingosine-1-phosphate (S1P) pathway, was evaluated and compared to matched non-menopausal adenomyosis specimens.
Main outcome measures: Direct and indirect US features of adenomyosis according to Morphological Uterus Sonographic Assessment at TVUS. Molecular characterization of postmenopausal versus pre-menopausal adenomyosis samples.
Results: According to TVUS and MRI, adenomyosis was identified in 49 patients (10.4 %). On US, diffuse adenomyosis was the most common phenotype, whereas internal adenomyosis with diffuse pattern and asymmetric type was the most prevalent on MRI. Molecular analysis showed that adenomyosis lesions express markers of epithelial-mesenchymal transition, inflammation and fibrosis also in postmenopausal women. By comparing the results with those from pre-menopausal samples, the expression of α smooth muscle actin (αSMA), a marker of fibrosis, was significantly greater after menopause, and altered S1P catabolism and signaling were observed.
Conclusions: Adenomyosis may be identified in postmenopausal women by imaging, either TVUS or MRI, and fibrosis is one of the key features on molecular analysis.

1. Introduction

Adenomyosis is a benign gynecological disorder, characterized by the presence of endometrial epithelium (stroma and glands) within the myometrium, surrounded by smooth muscle hyperplasia [1]. The impaired expression of genes related to epithelial-mesenchymal transition, inflammation and fibrosis has been shown in adenomyotic lesions [2–4]. The clinical presentation may include heavy menstrual bleeding (HMB), pelvic pain, dysmenorrhea, infertility and recurrent pregnancy loss [5,6].

According to the International Federation of Gynecology and Obstetrics (FIGO) PALM-COEIN classification, adenomyosis is considered as one of the causes of abnormal uterine bleeding (AUB) [7]. The condition was mainly described after hysterectomy in women with uterine fibroids (UFs) or menstruation-related disorders [8,9]. However, the current use of imaging, both transvaginal ultrasound (TVUS) and magnetic resonance (MRI), is allowing a non-invasive diagnosis of adenomyosis among patients wishing to preserve their uterus [10], opening a new epidemiological perspective [11]. Indeed, several studies have shown that imaging and clinical signs of adenomyosis are observed in young women [12–14]. Nevertheless, there are no description on imaging or molecular aspects of adenomyosis in menopause.

Thus, the aim of the present study was to evaluate in postmenopausal women the imaging aspects of adenomyosis by TVUS and MRI, and in

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https://doi.org/10.1016/j.maturitas.2024.107996
Received 16 December 2023; Received in revised form 27 March 2024; Accepted 9 April 2024
Available online 12 April 2024

cases of hysterectomy, their molecular characteristics.

2. Materials and methods

2.1. Study design, population, and data collection

A group of postmenopausal women referred to the Gynecological Ultrasound Unit from the Menopause Clinic from 2021 to 2022 (n = 468) (mean age 56.9 ± 7.3) at Careggi University Hospital (Florence, Italy) were recruited for an observational cross-sectional study. Menopause was defined as the condition of amenorrhea at least from 12 months. Exclusion criteria were as follows: current AUB symptoms or hormonal replacement therapy (HRT); previous or current diagnosis of endometrial, cervical, ovarian or breast cancer, or endometriosis; iatrogenic menopause.

The evaluation at Menopause Clinic routinely includes the collection of medical history, a physical examination and a TVUS to assess the uterus and adnexa. The US exam is normally performed by a team of gynecologists with expertise in gynecology ultrasound. According to the morphological uterus sonographic assessment (MUSA) criteria [15], the possible presence of signs of adenomyosis was assessed by TVUS in each patient. Those menopausal patients with US features of adenomyosis, confirmed also by MRI (n = 49, 10.4 %) represented the study population. The indications to perform an MRI evaluation, along with adenomyosis, were the presence of ovarian cysts or the mapping of UFs, if multiples. Patients with only TVUS signs of adenomyosis who did not undergo a further investigation with MRI were not included in the study population.

Baseline characteristics were collected: age, body mass index (BMI), presence of systemic comorbidities, parity, menstrual history (regularity, length and amount of menstrual bleeding; if HMB or dysmenorrhea were present, and their severity), infertility history or difficulty to conceive (including use of assisted reproductive technologies - ART), previous and/or current gynecological diseases (UFs, endometrial polyps, ovarian cysts), age at menopause (Table 1).

A subgroup (n = 11) of postmenopausal women with imaging features of adenomyosis among those included in the study underwent hysterectomy for uterine prolapse or concomitant adnexal removal for ovarian cysts. Thus, in these cases also the histological and molecular aspects of adenomyosis were characterized.

2.2. TVUS examination

Ultrasonography was performed by using ultrasound machines (Voluson E8, General Electric, GE) and a transvaginal probe (5–7.5 MHz) with 2-dimensional (2D) and 3D evaluation [16]. During the examination, uterus, adnexa, and pelvic compartments (anterior, posterior) were assessed. In order to accurately report and classify the presence of adenomyosis, uterine fibroids or adnexal mass, and the aspect of endometrium, the Morphological Uterus Sonographic Assessment (MUSA) [15,17], the International Ovarian Tumor Analysis (IOTA) [18] and the International Endometrial Tumor Analysis (IETA) [19] consensus were used. Ultrasound examination was performed by the same expert gynecologist (SV). The MUSA criteria were noted and the diagnosis of adenomyosis was made if at least one of direct features of the disease was present (myometrial cysts, hyperechogenic islands or subendometrial lines or buds). Also the presence of indirect features was noted (globular uterus; asymmetrical myometrial thickening; fan-shaped shadowing; translesional vascularity; irregular junctional zone (JZ); interrupted JZ at 3D ultrasound) [17]. It was also reported the extension of adenomyosis, if diffuse or focal or adenomyoma, and the severity (if mild/moderate/severe) [10]. The ultrasound reports were all standardized and reported the results according to the systematic approach used to study the pelvis.

Table 1
Adenomyosis features at transvaginal ultrasound (TVUS) according to the Morphological Uterus Sonographic Assessment (MUSA) criteria in a group of postmenopausal patients (n = 49).

Adenomyosis DIRECT features	
Myometrial cysts	14(28,5 %)
Echogenic subendometrial lines or buds	14(28,5 %)
Hyperechoic islands	21(42,8 %)
Adenomyosis INDIRECT features	
Uterine wall asymmetry	10(20,4 %)
Fan shaped shadowing	7(14,3 %)
Translesional vascularity	10(20,4 %)
Irregular/interrupted JZ	6(12,2 %)
Type of adenomyosis	
Diffuse	46 (93,8 %)
Focal	3(6,1 %)
Adenomyoma	0
Grade of adenomyosis	
Mild/moderate	45(91,8 %)
Severe	4(8,1 %)

2.3. Pelvic MRI

The MRI imaging protocol included: turbo spin-echo (TSE) T2-weighted sequences on sagittal, coronal and axial planes, and T1 and T1 FS-weighted sequences (non-fat-saturated and fat-saturated). Contrast-enhanced fat-saturated T1 sequences (VIBE) were used in case of T2-weighted atypical features or in case of contemporary presence of other pelvic lesions, such as ovarian cysts [20]. Diffusion-weighted imaging (DWI) allows the mapping of the diffusion process of molecules and it was used as an additional sequence to help differentiating adenomyosis from endometrial or myometrial neoplastic disease, given it is independent from intrinsic vascularization of tissues [21]. The MRI exams were all performed by the same expert radiologist (SG).The following parameters of the myometrium were assessed: the affected area, classified into internal myometrium (internal adenomyosis) corresponding to the inner one-third of the uterine wall or external myometrium (external adenomyosis); the pattern, indicated as diffuse or focal adenomyosis; the size, in cm or categorized into three volumes (<1/3, <2/3, or >2/3 of the uterine wall); the location (anterior, posterior, left-lateral, right-lateral, or fundal); the presence of concomitant pathologies [11]. At MRI direct signs of adenomyosis are represented by tiny cyst (2–9 mm), with low signal intensity (SI) in T1W images and high SI in T2W images, or the presence of an adenomyoma. Indirect signs consist of JZ thickening, JZ focal thickening or large smooth uterus. JZ thickening was defined when: >12 mm, “ratiomax” (ratio between JZ max and the entire myometrial thickness) >40 %, “JZ differential” (the differential in maximal and minimal JZ thickness in both anterior and posterior uterine walls) > 5 mm.

2.4. Histopathology examination and molecular characterization

Among patients with adenomyosis features at imaging, a subgroup (n = 11; average time since menopause 6.5 ± 3.8 years) underwent surgery for uterine prolapse or concomitant adnexal removal for ovarian cysts. After hysterectomy specimens of the uterus were examined by the same expert pathologist (FC). Adenomyosis was histologically defined as the presence of ectopic endometrial tissue (endometrial stroma and glands) within the myometrium. Hematoxylin-eosin staining was performed to visualize the phenotypes of the lesions.

After the sampling was made according to standardized procedures and histopathological examination, the tissues were subjected to RNA extraction. Total RNA was extracted from formalin-fixed paraffin embedded (FFPE) tissue samples (500 ng) using the AllPrep DNA/RNA FFPE kit (Quiagen, Hilden, Germany) and reverse transcribed using the SuperScriptTM IV VILOTM Master Mix (Thermo Fisher Scientific, Waltham, MA, USA), as suggested by the manufacturer. TaqMan gene expression assays (Thermo Fisher Scientific, Waltham, MA, USA) were used to quantify target gene mRNAs in triplicate on a CFX96 Touch Real-

Time PCR Detection System (Bio-Rad, Hercules, CA, USA). The cycling parameters for the polymerase chain reaction were as follows:

1) initial denaturation at 95 °C for 10 min;
2) 40 cycles of denaturation at 95 °C for 15 s;
3) annealing and elongation at 60 °C for 1 min.

The target sequences were amplified alongside the reference gene -actin (ACTB) [22–24]. The $2^{-\Delta Ct}$ method was used to calculate the relative expression of mRNA [25]. The expression of the following genes implicated in adenomyosis pathogenesis was analyzed in adenomyotic lesions and compared to matched premenopausal adenomyosis cases: epithelial-mesenchymal transition (EMT) [(vimentin (VIM), Wilms tumor 1 (WT1), Wnt Family Member 5A (WNT5A)], inflammation [cyclooxygenase-2 (COX2)], extracellular matrix (ECM) remodeling [(metalloproteases 2 and 14 (MMP2- MMP14)] and fibrosis [α Smooth Muscle Actin (αSMA)], Sphingosine 1 Phosphate (S1P) catabolism and signaling. In particular, S1P, a bioactive lipid, key molecule in fibrosis [26], is catalyzed by two different isoforms of sphingosine kinase (SPHK1 and SPHK2). Its degradation is mediated by specific phosphatases (SGPP1 and SGPP2), that catalyze the reversible dephosphorylation of S1P, and by S1P lyase (SGPL), responsible of the irreversible cleavage of S1P. Most of S1P biological actions are mediated by its binding to specific G protein-coupled receptors named $S1P_{1-5}$. The uterine specimens used as controls for molecular analysis were collected after hysterectomy from a group of patients aged 42–48 years, still regularly menstruating, undergoing non-conservative surgical treatment for AUB or HMB resistant to all medical treatments, with histological confirmation of adenomyosis diagnosis.

The institutional review board (protocol no. 13742) approved the study protocol, and all patients gave informed written consent.

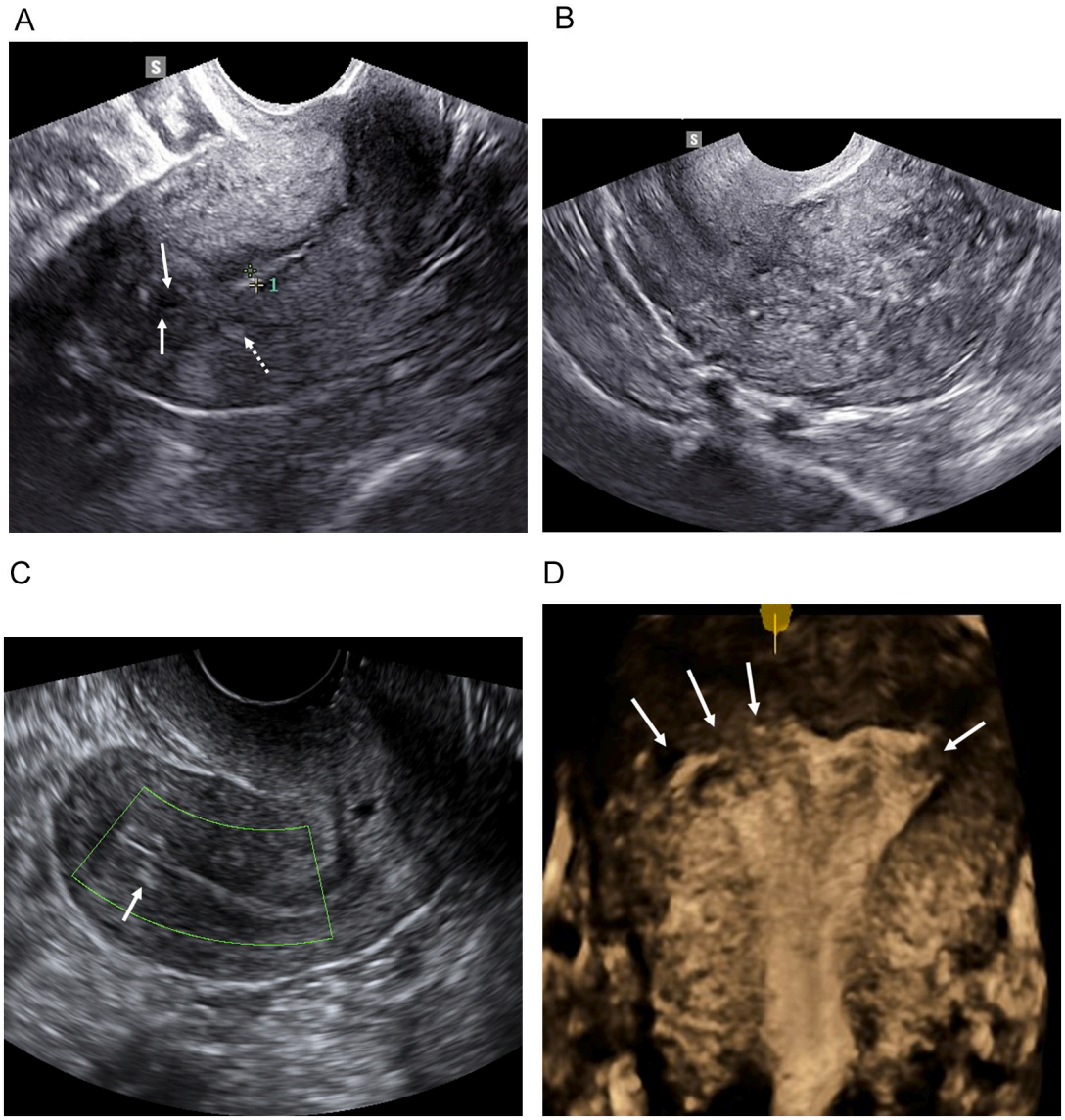

Fig. 1. Ultrasound features of adenomyosis in postmenopause.
A. A myometrial cyst (*white arrow*) and hyperechoic myometrial islands (*dashed arrow*).
B. Multiple hyperechoic myometrial islands with mixed myometrial echogenicity and difficult identification of endometrial lining because of undefined junctional zone.
C. Subendometrial bud (*white arrow*) and multiple hyperechoic myometrial islands (*dashed arrow*).
D. 3D coronal view with interrupted junctional zone (*white arrow*).

2.5. Statistical analysis

Clinical and imaging data, as well as molecular data, were entered in an electronic database and analyzed using the software SPSS (Statistical Package for Social Science) (IBM SPSS Statistics 23, IBM Corporation). A descriptive analysis was conducted with the evaluation of position measures (mean, median) and dispersion indices (standard deviation, range) for the quantitative variables. The binomial variables were described by calculating the absolute and percentage frequencies. Student's *t*-test and Spearman correlation were was used for statistical analysis of molecular data. $P < 0.05$ was considered to be statistically significant. Graphical representations were realized using GraphPad Prism 6.0 (GraphPad Software) (San Diego, CA, USA).

3. Results

The TVUS features of adenomyosis were found in 49 cases (10.4 %), according to direct and indirect signs. Direct signs of the disease, either myometrial cysts, hyperechogenic islands or subendometrial lines or buds were shown, being the presence of hyperechogenic islands the most frequent feature (Table 1). The most common phenotype was the diffuse adenomyosis (Fig. 1). These findings were confirmed in MRI, where internal adenomyosis was the most prevalent with diffuse pattern and asymmetric type (Fig. 2). Regarding menstrual history, this group of patients reported severe dysmenorrhea (32.6 %), HMB (30.6 %) and iron deficiency anemia (IDA) (8.1 %). In their reproductive history, infertility (20.4 %) or recurrent pregnancy loss (22.4 %) were described (Table 2). They reported a systemic comorbidity, such as hypertension, metabolic or autoimmune diseases, in 75.5 % of cases.

In the group of adenomyosis cases evaluated also after hysterectomy, the diffuse form was the most common phenotype, particularly in the corpus and fundus (Fig. 3). In these cases, the pathological diagnosis was evident at gross and microscopic examination. The enlargement of the uterus was mainly the consequence of the myometrial smooth-muscle hyperplasia/hypertrophy that accompanies adenomyosis foci. This hyperplasia grossly appears as areas of hyperfasciculation of the myometrium, with a swirl trabeculated pattern. Regarding microscopic features, the ectopic endometrial tissue (glands and stroma) is present as foci of variable size, haphazardly located in the myometrium. The endometrioid glands were usually inactive, as the basalis glands of the eutopic endometrium. Glands varied in size and configuration, being cystic, filled with cell debris and/or iron-laden macrophages. In some cases, the stroma showed atrophic and some extensive fibrotic changes.

From a molecular point of view, adenomyotic lesions of postmenopausal women showed the expression of genes involved in EMT (VIM, WT1, WNT5a), inflammation (COX2), ECM remodeling (MMP2, MMP14), S1P signaling ($S1P_1$, SGPP2, SGPL) and fibrosis (αSMA) (Fig. 4). SGPP2 and SGPL were significantly more expressed in adenomyotic menopausal samples compared to premenopausal ones ($p < 0.05$) (Fig. 5). In addition, the mRNA levels of $S1P_1$ were significantly lower in menopause adenomyosis than in premenopausal samples ($p < 0.05$); whereas the other genes involved in S1P metabolism and signaling did not show any significant difference. The comparison with adenomyosis samples from menstruating patients showed that αSMA was significantly more expressed in menopausal cases ($p < 0.01$) (Fig. 5), whereas expression of genes involved in EMT, inflammation and ECM remodeling did not show any significant difference between the two groups (results not shown).

4. Discussion

The present study highlighted that adenomyosis may be detected in postmenopausal patients by imaging and confirmed by their molecular features. Despite the absence of current symptoms, given the confirmed menopausal state and related amenorrhea, TVUS showed direct signs of adenomyosis, according to the revised MUSA criteria, then confirmed by

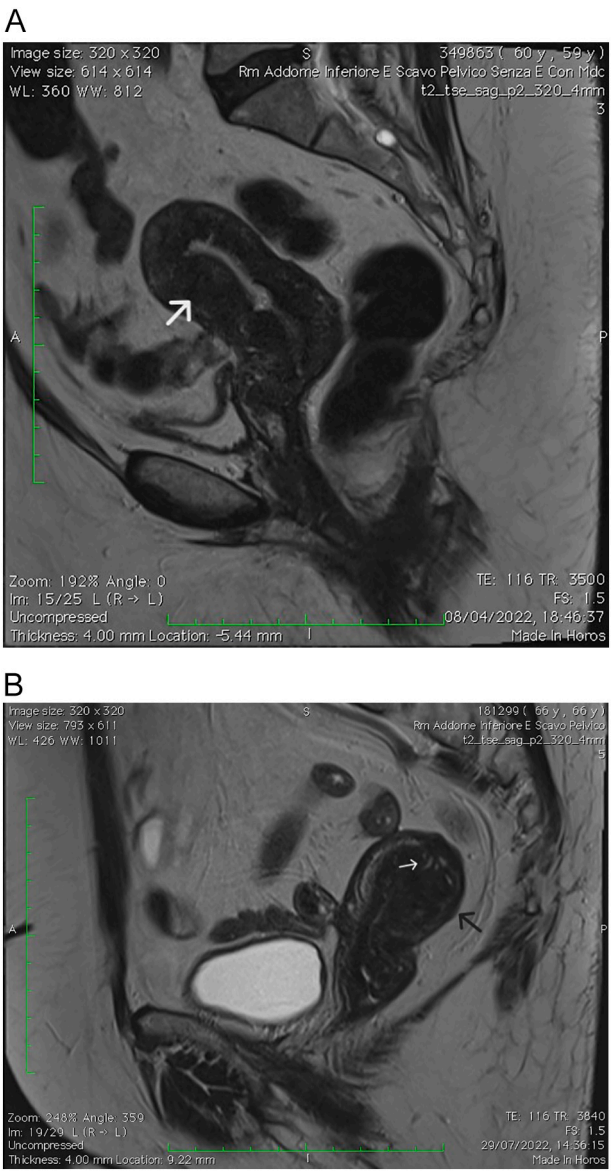

Fig. 2. MRI features of adenomyosis in postmenopause.
A. 60 years. Sagittal TSE T2w: Internal adenomyosis with diffuse pattern, asymmetric type, according to Bazot classification (*white arrow*); JZ thickening with rare small cysts.
B. 66 years. Sagittal TSE T2w: Internal adenomyosis with diffuse pattern, asymmetric type, tiny cysts, and JZ thickening (*black arrows*). The cysts show high signal intensity in TSE T2w images, they are surrounded by a rim of low signal intensity in T2w corresponding to a layer of stroma and hypertrophic myometrium (*white arrow*).

MRI. This observation supports the possible identification of adenomyosis by non-invasive methods also in post-menopause. Additionally, the use of a further imaging methodology, the MRI, which is the gold standard for the non-invasive identification of adenomyosis [11], strengthens the accuracy of diagnosis.

The identification of direct signs of adenomyosis at TVUS, such as myometrial cysts, hyperechogenic islands or subendometrial lines or buds, provides the proof of ectopic endometrial tissue into the myometrium [2,17]. The presence of at least one of these criteria is thought to be a reliable sign of adenomyosis at TVUS [17]. Furthermore, the confirmation of the diagnosis by MRI, especially in those cases where JZ was difficult to be assessed by 3D TVUS because of extremely thin endometrium, resulted very useful [20]. MRI is considered a second-line

Table 2
Baseline characteristics and history of postmenopausal patients with imaging evidence of adenomyosis (n = 49).

Variables	
Age (yrs)	56,9 ± 7,3 (46–64)
BMI	24,2 ± 3,5 (18–32)
BMI ≥ 30	5(10.2 %)
Smoking habit	5(10.2 %)
Systemic comorbidities	37(75,5 %)
Autoimmune diseases	8(16,3 %)
Thyroid diseases	7(14,2 %)
Hypertension	9(18,3 %)
Metabolic diseases	9(18,3 %)
Diabetes	1(2 %)
Gynecological comorbidities	
Uterine fibroids	15(30,6 %)
Ovarian/adnexal cysts	9(18,3 %)
History of uterine surgery	25(51 %)
Myomectomy	3(6,1 %)
Hysteroscopy for endometrial polyp	6(12,2 %)
Cesarean section	13(26,5 %)
Dilatation and curettage (D&C)	7(14,3 %)
Menstrual cycle history	
Age at menarche	12,6 ± 1,3 (9–15)
Cycle regularity	33(67,3 %)
Cycle length (days)	28,2 ± 3,5 (21–45)
HMB	16(32,6 %)
Iron deficiency anemia	4(8,1 %)
AUB before menopause	15(30,6 %)
Severe dysmenorrhea	16(32,6 %)
Dyspareunia	1(2 %)
Parity	
Nulliparous	7(14,2 %)
Recurrent pregnancy loss	11(22,4 %)
Infertility	10(20,4 %)
Age at menopause	50,9 ± 4,5 (45–62)

investigation technique for adenomyosis due to its lower availability and higher cost, even though it has a higher sensitivity (77 %) and specificity (89 %) and a lower operator dependence. Moreover, MRI shows excellent soft-tissue differentiation, which allows the detection of other coexisting gynecologic conditions (e.g., UFs, endometriosis) and a reliable identification of the JZ layer [27]. Indeed, the diagnosis of adenomyosis was confirmed by MRI in each case, otherwise those with only description of TVUS features were excluded.

Previous studies from hysterectomy series reported that adenomyosis prevalence at histology was around 25 %–28 %, higher than in our cohort; however, most of these cases underwent non-conservative surgery for HMB or chronic pelvic pain, either in perimenopause or at least between 40 and 50 years [28,29]. Nowadays the substantial improvement in imaging technologies allows the epidemiologic study of adenomyosis to be extended beyond the population of hysterectomy patients to the general population [6,30]. In reproductive age, the prevalence of adenomyosis at imaging ranges from 25 % to 30 % [13,14], whereas our results shows a 10 % of cases with US signs of adenomyosis in a general menopausal population. On the one hand, the exclusion of patients with history of endometriosis, very frequently associated to adenomyosis [12,31], may explain the low prevalence of the disease found in our study population. On the other hand, the effects of menopausal hormonal changes and related hypoestrogenism may interfere, causing a limited appearance of adenomyosis at imaging, together with the cessation of symptoms such as bleeding and pain. Duration of menopause at the time of enrollment was on average 6 years in our population. However, a limitation should be acknowledged, as the diagnosis of adenomyosis was made for the first time at the TVUS in menopause, which means that was not possible to establish the temporal sequence of adenomyosis appearance. Anyhow, it is likely that the condition was already present in reproductive age, albeit undiagnosed. A larger sample size would be helpful to explore also the association between time duration since menopause onset and potential changes in adenomyosis imaging appearance across time, when already identified in the premenopausal period.

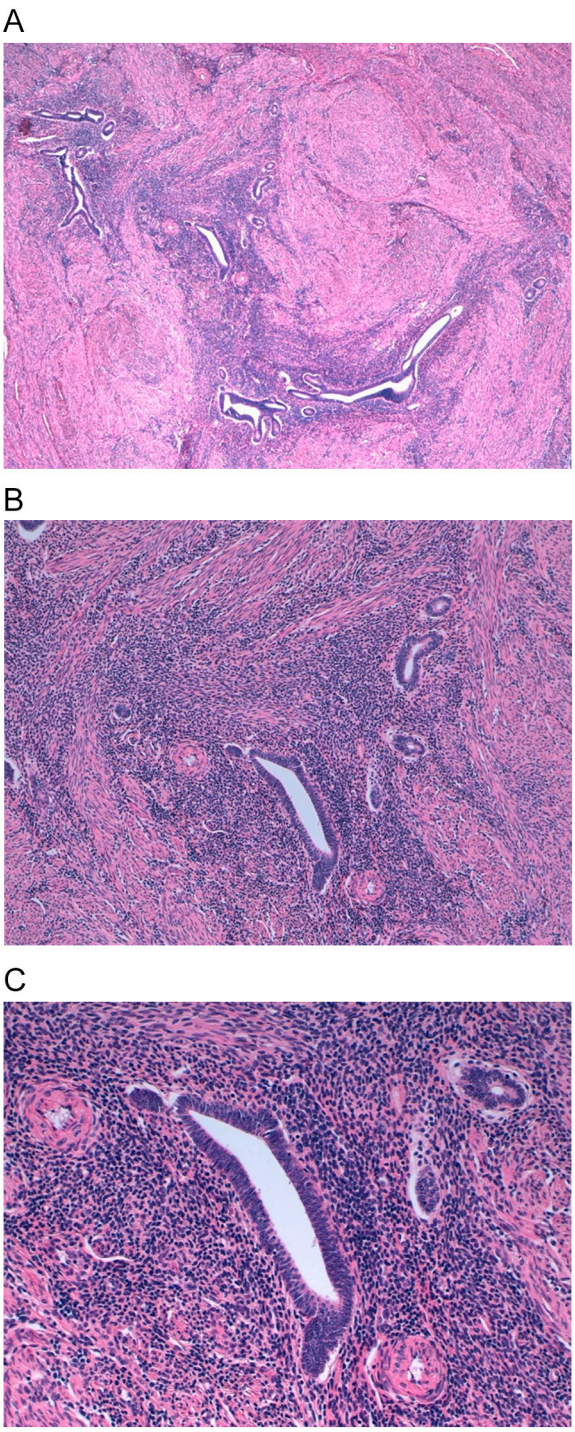

Fig. 3. Histological findings of adenomyosis in postmenopause.
Endometrial glands and stroma are haphazardly distributed within the myometrium. There is no cytological atypia and the gland-to-stroma ratio is preserved. Hematoxylin-eosin staining.
A. 4× magnification. B. 10× magnification. C. 20× magnification.

Furthermore, the menstrual history of these patients in the reproductive years may indicate the clinical presence of adenomyosis in their reproductive life, given the relatively high frequency of severe dysmenorrhea and HMB, which are common symptoms of adenomyosis [10]. However, a recall bias should be considered, as data on reproductive history were retrieved by patients retrospectively. Infertility and

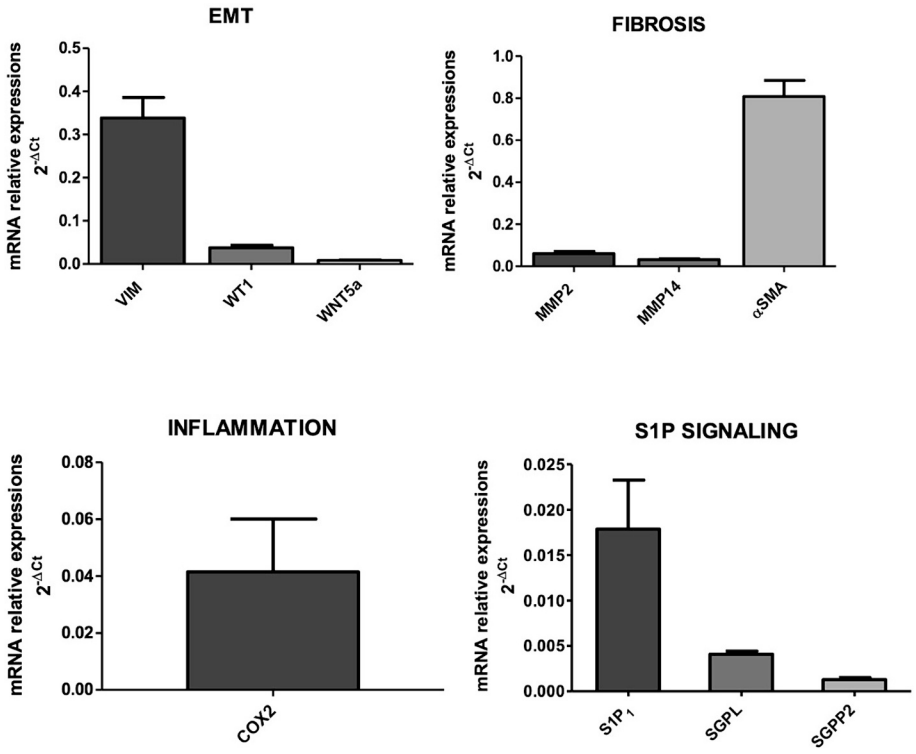

Fig. 4. Molecular characterization of the adenomyotic lesions.
Real-time polymerase chain reaction analysis using TaqMan Gene Expression Assay probes specific for Epithelium-mesenchymal transition (EMT)[(vimentin (VIM), Wilms tumor 1 (WT1), Wnt Family Member 5A (WNT5A)], inflammation [cyclooxygenase-2 (COX2)] and extracellular matrix remodeling (ECM) and fibrosis, [(metalloproteases 2 and 14 (MMP2- MMP14), Smooth Muscle Actin (αSMA), Sphingosine 1 Phosphate (S1P) catabolism and signaling (sphingosine 1-phosphate lyase, SGPL; sphingosine 1-phosphate phosphatase 2, SGPP2). Results were analyzed with the use of the 2−ΔCt method.

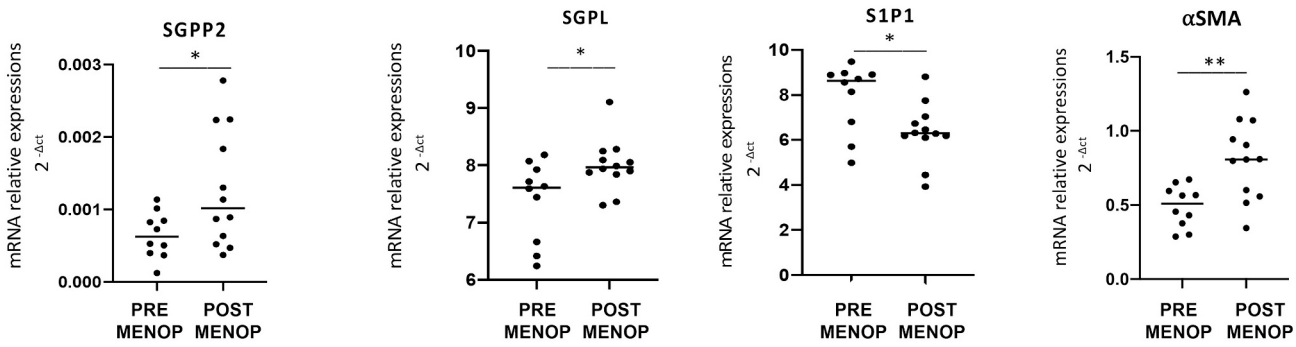

Fig. 5. Molecular characterization of premenopausal versus menopausal adenomyosis
Real-time polymerase chain reaction analysis in lesions of premenopausal adenomyosis ($n = 11$) and lesions of menopausal adenomyosis (n = 11=) using TaqMan Gene Expression Assay probes specific for Sphingosine 1 Phosphate (S1P) catabolism and signaling (sphingosine 1-phosphate phosphatase 2, SGPP2, sphingosine 1-phosphate lyase, SGPL; S1P receptor 1 (S1P1)) and for Smooth Muscle Actin (αSMA). Results were analyzed with the use of the 2−ΔCt method. Differences are statistically significant according to Student's *t*-test (* $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$).

recurrent pregnancy loss were also reported, suggesting again the potential presence of adenomyosis in their reproductive life, even though these conditions may imply additional causes, other than adenomyosis [32].

Anyhow, in all women undergoing hysterectomy, histopathology findings confirmed the diagnosis of adenomyosis and the diffuse was the most common phenotype, with clear evidence of the ectopic foci of endometrial cells and myometrial smooth cells hyperplasia. Furthermore, the molecular characterization of adenomyotic foci in specimens of postmenopausal women are similar to those described in premenopausal patients. The expression of genes related to EMT (VIM, Wnt5a, WT1), inflammation (COX2), ECM remodeling (MMP2, MMP14) and fibrosis (αSMA) was observed. The ectopic endometrium of women with adenomyosis exhibits much higher platelet aggregation and elevated EMT markers [4]. Genes related to inflammation [33,34] are involved in the pathophysiology of adenomyosis, as shown by increased expression of COX-2, corticotropin-releasing hormone (CRH), together with immunological changes [35].

In addition, our results showed that adenomyotic menopausal lesions are characterized by higher expression of enzymes that catalyzed S1P and lower expression of $S1P_1$ receptor, suggesting lower S1P levels in menopausal adenomyosis, as well as a dysregulated S1P signaling linked to this receptor subtype. In a previous study on adenomyosis samples from premenopausal patients, an altered S1P signaling pathway was

found, potentially involved in the fibrosis pathway mediated by αSMA [3]. S1P plays a significant role in adenomyosis in mediating the pro-fibrotic action of TGF [3], which is produced at the site of inflammation by monocytes and lymphocytes. Fibrosis is a crucial mechanism in the pathogenesis of adenomyosis [3], and our histopathological findings confirmed that specimens showed some degree of fibrosis. The higher expression of αSMA in menopausal specimens compared to fertile ones support the fibrotic nature of adenomyosis. On some level, the increase in uterine collagen with fibrosis by the replacement of the stroma with mature collagen and hyalinization may be also one of the age-related changes of aging uterus [36–38]. However, EMT and collagen production are greatly influenced by transforming growth factor (TGF)-signaling, which also causes smooth muscle metaplasia, which in turn causes fibrosis.

In conclusion, the present study showed that adenomyotic features may be found in postmenopausal women by imaging, correlating with their molecular characteristics, being fibrosis a key characteristic. Nevertheless, the natural history of adenomyosis in menopause is yet to be fully clarified, even though a preexisting condition since reproductive age may be hypothesized, albeit undiagnosed. Similarly, the clinical significance and impact of these lesions among menopausal women remains to be elucidated.

Contributors

Silvia Vannuccini contributed to conception and design of the study, collection of ultrasound data, analysis and interpretation of data, and drafted the paper.

Silvia Gabbrielli contributed to collection of magnetic resonance data and interpretation of data.

Francesca Castiglione contributed to collection of histology data and interpretation of data.

Eleonora Nardi contributed to collection of histology data.

Margherita Rossi contributed to molecular analyses.

Gretha Orlandi contributed to collection of clinical data and analysis of data.

Elisa Wu contributed to collection of clinical data and analysis of data.

Francesca Bertoli contributed to collection of clinical data and analysis of data.

Vittorio Miele contributed to collection of magnetic resonance data and manuscript revision for important intellectual content.

Chiara Donati contributed to molecular analyses, interpretation of data, and manuscript revision for important intellectual content.

Felice Petraglia contributed to conception and design of the study, interpretation of data, and manuscript revision for important intellectual content.

All authors saw and approved the final version and no other person made a substantial contribution to the paper.

Funding

The molecular analyses were supported by a grant from the Italian Ministry of Education, University, and Research after the Department was awarded as one of the 180 Departments of Excellence in Italy.

Ethical approval

The institutional review board, the Area Vasta Centro Ethics Committee (CEAVC), reviewed and approved the project (no. 13742) on January 29, 2019. Informed consent was obtained from all individual participants included in the study. Participants provided informed consent for publication imaging pictures.

Provenance and peer review

This article was not commissioned and was externally peer reviewed.

Research data (data sharing and collaboration)

There are no linked research data sets for this paper. Data will be made available only upon specific and motivated request.

Declaration of competing interest

The authors declare that they have no competing interest.

Acknowledgments

The authors took advantage of the newly established Molecular Medicine Facility of the Department of Experimental and Clinical Biomedical Sciences “Mario Serio” at the University of Florence, Italy. The facility was supported by a grant from the Italian Ministry of Education, University, and Research after the Department was awarded as one of the 180 Departments of Excellence in Italy.

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