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CASE REPORT

Atypical Polypoid Adenomyoma in a Patient with Hyperprolactinemia: a Novel Case and Systematic Review of the Systematic Reviews

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ABSTRACT

Background: *A 34-year-old nulligravid lady was referred to the outpatient gynecology department with the symptoms of abnormal menstrual bleeding and mild anemia. A transvaginal ultrasound (TVS) revealed the presence of a hyperechoic lesion measuring 9.5x4.5 mm in the uterine cavity at the level isthmus (lower uterine segment), suggestive of an endometrial polyp. Consequently, a diagnostic hysteroscopy was performed. Transcervical hysteroscopic resection (TCR) and diagnostic curettage (D&C) were accomplished. A macroscopic analysis of the specimen exhibited a white, pale polypoid formation measuring 1x1 cm with a hard consistency. Histology analysis confirmed the diagnosis of an atypical polypoid adenomyoma (APA). All these findings were explained to the patient and the risk of potential progression to endometrial carcinoma was discussed in detail. A multidisciplinary meeting (MDT) was held and conservative management with levonorgestrel coil insertion or Methoxy progesterone administration* per os, *along with frequent hysteroscopies every three months, was offered. The patient decided to undergo a hysterectomy with preservation of the ovaries, despite the lack of childbearing. A laparoscopic-assisted vaginal hysterectomy with preservation of adnexa was performed. The pathology analysis confirmed the diagnosis of APA with coexistence of well-differentiated (low-grade) endometrioid carcinoma of the endometrium, stage Ia.*

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Methods: *We performed a systematic review of systematic reviews with APA and quality assessment of the included studies. Furthermore, a flow-chart guideline for the management of APA in premenopausal and postmenopausal women is offered.*

Conclusions: *Atypical polypoid adenomyoma is a rare clinical entity. It occurs mainly during the reproductive period of a woman. It is associated with abnormal vaginal bleeding, infertility, nulliparity, obesity, metabolic syndrome, hyperprolactinemia and hyperestrogenism. It is a risk factor for the development of endometrial hyperplasia and subsequent endometrial cancer. Preoperative diagnosis is extremely difficult; there are no specific imaging landmarks in ultrasound and magnetic resonance imaging (MRI) assessment. In patients with a desire for fertility, the management is complicated and should be based on a four-step hysteroscopic transcervical resection of the lesion. Hysterectomy is the right option for post-menopausal women and for women not wishing to conceive.*

Keywords: Atypical polypoid adenomyoma, endometrial cancer, hysteroscopy, transcervical resection, hyperprolactinemia, hysterectomy.

BACKGROUND

The term atypical polypoid adenomyoma (APA) has been suggested by Mazur *et al* (1) to describe endometrial polypoid lesions occurring in premenopausal women characterized by irregular atypical glands with squamous metaplasia and a cellular, smooth muscle stroma.

Atypical polypoid adenomyoma contains an architecturally complex and cytologically atypical glandular component that could be confused with well-differentiated adenocarcinoma but was distinguished from invasive endometrial carcinoma by its occurrence in younger patients and by the presence of a cellular, mitotically active smooth-muscle stroma (2). Nevertheless, current literature indicates that these uterine proliferations are occasionally associated with endometrial adenocarcinoma, suggesting that APAs are not a benign entity (3). Atypical polypoid adenomyoma is a rare clinical entity that remains to be established.

Moreover, APA was initially viewed as being a benign disease that should be differentiated from cancer, but in recent years, cases that have progressed from APA to cancer and cases with coexisting cancer have been reported and quite a few situations have also been encountered in which there has been great concern about its clinical management (4).

Treatment of APAs depends on both clinical and microscopic factors of this disease and women's desire to preserve their fertility. Younger women with a lesion characterized by low architectural index or mild to moderate atypia can be managed conservatively, whereas older women or patients with a lesion characterized by high architectural index or severe atypia consistent with adenocarcinoma in situ should undergo hysterectomy (5).

Herein we present an incidental novel case of atypical polypoid adenomyoma which progressed to endometrial carcinoma. We discuss the diagnosis and the management of this rare clinical entity; in addition, we perform a systematic review of the published systematic reviews.

CASE REPORT

A 34-year-old nulligravid lady was referred to the outpatient gynecology department of Rea Maternity Hospital in Athens, Greece, with the symptoms of abnormal menstrual bleeding and mild anemia. She had irregular menstrual periods for six years. She reported that she was trying to conceive, but without success, despite frequent sexual intercourse.

Her physical examination was unremarkable; pap smear revealed ASCUS (atypical squamous cells of undetermined significance).

A transvaginal ultrasound (TVS) revealed the presence of a hyperechoic lesion measuring 9.5x4.5 mm in the uterine cavity at the level isthmus (lower uterine segment), suggestive of an endometrial polyp (Figure 1). Transvaginal ultrasound enhancement with color Doppler flow did not reveal any flow or a feeding vessel within the polyp.

An intramural myoma measuring 5x4 cm was also revealed. Consequently, a diagnostic hysteroscopy with a 4 mm rigid hysteroscope with an

oblique vision of 30° was performed; transcervical hysteroscopic resection (TCR) and diagnostic curettage (D&C) were accomplished. A macroscopic analysis of the specimen exhibited a white pale polypoid formation measuring 1x1 cm with hard consistency (Figure 2). Histology analysis confirmed the diagnosis of an atypical polypoid adenomyoma (APA) (Figure 3). The diagnosis was confirmed by two experienced pathologists according to the World Health Organization (WHO) pathological classification (2020). The patient was subjected to blood analysis of Ca-125, Ca 19.9 and Ca 15.3 tumor marker levels, which appeared to be within the normal range. Hormone levels showed an increase in levels of E2 estrogen (700 pg/mL) and prolactin (40 ng/mL). She also had an increased insulin tolerance test and a body mass index (BMI) of 25. Her high density lipoprotein (HDL) concentration was < 1.2 mmol/L (Table 1). In addition, a blood sample was obtained from the patient and a whole genome sequence technique was performed to provide karyotyping to exclude possible genetic abnormalities; the results were normal.

All these findings were explained to the patient and the risk of potential progression to endometrial carcinoma was discussed in detail. She underwent a second hysteroscopy after three months; a hysteroscopic resection and D&C were performed and the pathology analysis revealed a de novo APA of the uterus. Magnetic resonance imaging (MRI) of the pelvis was performed; the imaging did not reveal pathology from the uterine cavity. A multidisciplinary meeting (MDT) was held and conservative management with levonorgestrel coil insertion or methoxyprogesterone administration per os, along with frequent hysteroscopies every three months, was offered. The patient decided, after being informed, to undergo a hysterectomy with preservation of the ovaries, despite the lack of childbearing. A laparoscopic-assisted vaginal hysterectomy with two ports of 5 mm with preservation of adnexa was performed. Total operation time was 150 minutes and total blood loss was 60 cc. The postoperative period was unremarkable and the patient was discharged the next day with no complaints.

The pathology analysis confirmed the diagnosis of APA with coexistence of well-differentiated (low-grade) endometrioid carcinoma of the endometrium, stage Ia by the International Federation of Gynecology and Obstetrics (FIGO). The patient

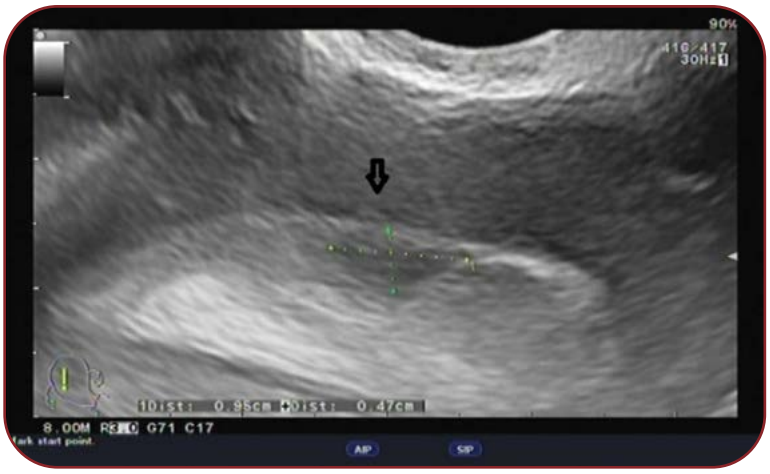

FIGURE 1. Transvaginal ultrasound exhibiting the location of the atypical polypoid adenomyoma within the uterine cavity

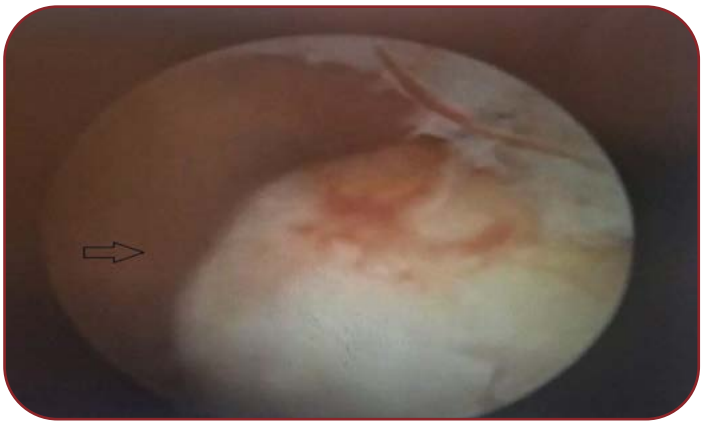

FIGURE 2. Hysteroscopic view of the atypical polypoid adenomyoma located in the isthmus of the uterus, revealing a white pale polypoid formation 1x1 cm

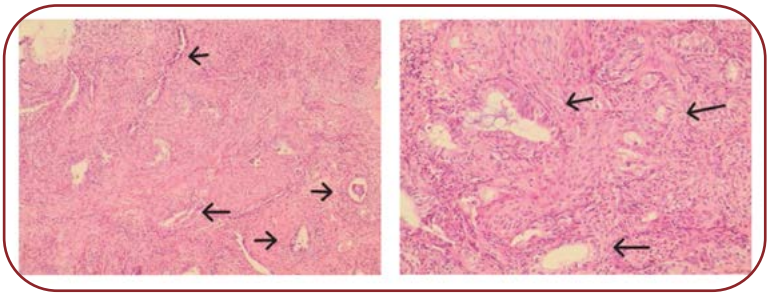

FIGURE 3. Histology specimen revealing irregular atypical glands with squamous metaplasia and a cellular smooth muscle stroma (Hematoxyline Eosine) ob 10 x

TABLE 1. Variables at patient admission

Variables	Ca-125 (U/mL)	Ca 19.9 (U/mL)	Ca 15.3 (U/mL)	E2 (pg/mL)	Prolactin (ng/mL)	ITT (mmol/L)	BMI (kg/m^2)	HDL (mmol/L)
Normal range	0-35	0-37	0-30	30-400	3-27	0.026-0.085	18-25	>1.3
On admission	25	2	HDL: high density lipoprotein 1.095				25	<1.2

E2: estradiol; ITT: insulin tolerance test; BMI: body mass index; HDL: high density lipoprotein

has been followed up for five years with no evidence of disease. This case report was designed in agreement with CARE guidelines for writing a case report https://www.care-statement.org/ (6).

Aim and objectives of the systematic review

The aim of our systematic review was to report a novel case of atypical polypoid adenomyoma in a patient with hyperprolactinemia, which progressed to endometrial cancer. Furthermore, we systematically reviewed the systematic reviews in patients with APA.

MATERIALS AND METHODS

Data sources, search strategy and study selection

We performed an electronic search on the following databases: MEDLINE-Ovid (1950–May 2025), Google Scholar (1980-May 2025). The following Specific Medical Subject Headings (MeSH) and/or text words were applied with combinations: atypical [All Fields] AND polypoid [All Fields] AND ("adenomyoma" OR "Adenomyofibroma" OR Adenomyomas OR Adenomyofibromas[All Fields]) AND «Systematic reviews" OR "Systematic review" AND "Reviews" OR "Review" Full search strategy is available upon request.

Inclusion criteria

In the present systematic review we included all previous systematic reviews regarding women diagnosed with APA.

Exclusion criteria

Narrative reviews; observational studies, case series and case reports; experimental studies *in vitro*; and studies not providing evidence about search strategy and with lack of clinical data were all excluded.

Study selection and data extraction

The selected studies were examined by two reviewers (PP and DS). The abstracts and full text of the studies were scrutinized. The references of the studies were assessed to retrieve further studies that were not identified by the initial search. From each study, we obtained the following clinical data: author and year of publication; country and city of publication; electronic databases that were searched; flowchart and meta-analysis in case they were utilized; number of studies; number of patients; the type of studies that were reviewed; the mean age of the patients and the range of years; quality of systematic reviews if it was performed; main outcomes of the studies; the conclusions of the studies. All collected clinical data were double-checked and tabulated on an Excel 2024 spreadsheet. The systematic review methodology adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines, version (7).

Quality assessment of the systematic reviews

The methodological quality of the included systematic reviews was evaluated using a measurement tool to assess systematic reviews, AMSTAR 2, which is a critical appraisal tool that consists of 16 items defining the quality criteria for the evaluation of systematic reviews (https://amstar.ca/Amstar_Checklist.php) (8).

The quality rating criteria are divided into four categories, according to the assessment of the 16 items, as follows: 1) high (zero or one non-critical weakness) – the systematic review provides an accurate and comprehensive summary of the results of available studies that address the question of interest; 2) moderate (more than one non-critical weakness) – the systematic review has more than one weakness, but no critical flaws, and it may provide an accurate summary of the results of the available studies that were included in the review; 3) low (one critical flaw with or without non-critical weaknesses) – the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest; and 4) critically low (more than one critical flaw with or without non-critical weaknesses) – the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies.

RESULTS

Study selection

The electronic search of the databases yielded 7048 studies from two different sources (MEDLINE and Google Scholar). Further assessment of the selected studies led to the selection of 3500 articles. Examination of the selected articles and extraction of non-relevant data resulted in 40 studies. The extracted studies were assessed and hand-searched for additional studies not identi-

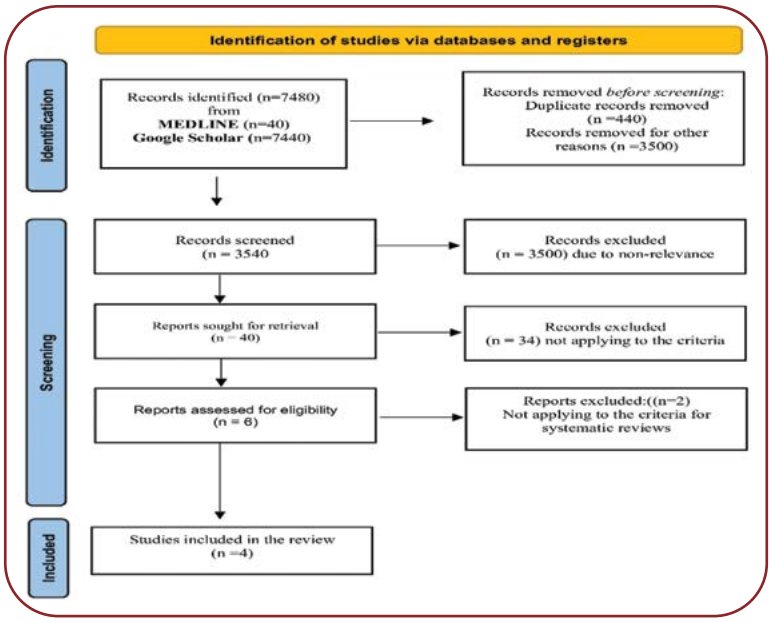

FIGURE 4. Flowchart diagram of the study selection according to PRISMA guidelines

fied by the initial search. Finally, four articles written in English and published between 2019 and 2020 were included in the present systematic review (9-12). The flowchart diagram according to PRISMA guidelines is exhibited in Figure 4.

Characteristics of systematic reviews

In total, we included four systematic reviews, with their main characteristics being exhibited in Table 2. The systematic reviews were conducted in the UK (9), Greece (10) and Italy (11, 12). All four studies were derived from University Hospital settings. The most frequently searched electronic database was MEDLINE (9-12), followed by SCOPUS (9, 11, 12). A flowchart diagram was utilized in two studies (10, 12) and a meta-analysis was performed in three studies (10-12). Meta-analysis with the utilization of forest plot diagrams was reported in one study (12). The four systematic reviews comprised a total patient population of 1349 women diagnosed with APA and a total number of studies, including case reports, case series and observational studies, of 202 (9-12). The mean age of patients included in the four systematic reviews was 38 years (35-39.9 years), with an age range of 17-73 years (9-12). Quality assessment of studies was performed only in three studies (10-12).

One study (10) was registered in the PROSPERO database of reviews & meta-analysis (No CRD42018080003) (https://www.crd.york.ac.uk/prospero/). Risk of bias was assessed with the assistance of the methodological Index for Non-Randomized Studies (MINORS) (13) in one study (11). Methodological quality was assessed with the aid of CARE guidelines in another study (12). The main outcome of the studies was the risk of endometrial cancer development, which was reported in four studies and ranged from 8.8% (9) to 10.1% (10), 11% (12) and 16 % (11). Also, the risk of endometrial hyperplasia development was reported in three studies: 6.7% (10), 5.5% (11) and 5.9%, respectively (12).

Recurrence of atypical polypoid adenomyoma of 35.1% (10), 28.9% (11) and 44% (12) was reported in three studies. Recurrence rate after transcervical resection was 10% (9) and 22% (12). Conservative treatment with medroxyprogesterone acetate (MPA) was reported to offer a response rate of 77% (9). Pregnancy rates after APA management of 60% (10) and 79% (12) were reported in two studies. One study reported the coexistence of adenomyosis in 18 % of patients with APA (12).

The main conclusions of the four systematic reviews were focused on the four-step transcervical resection of APA, which was reported to provide a decreased recurrence rate in cases where fertility was desired (9-12). In addition, the conservative treatment with MPA was considered not an adequate choice because it did not reduce the possibility of APA relapse APA (12). All studies concluded that hysterectomy was the gold standard of treatment in cases when childbearing was not desirable (9-12).

Quality of systematic reviews

Quality assessment of the four systematic reviews using AMSTAR 2 tool showed that one study was graded as "critically low quality" (9), two studies as "moderate quality" (10, 11), and one study as "high quality" (12). The results are summarized in Table 3. The study by Habiba *et al* (9) did not fulfil the criteria for 11 items and the study by Mikos (10) and Raffone (11) did not meet the criteria for two items. The study by Biasoli *et al* (12) fulfilled the criteria in all items; therefore, the quality was graded as "high".

Strengths and limitations of the study

The strength of this current study is the presentation of a novel case of atypical polypoid adenomyoma according to the guidelines of CARE (6).

Author Year	Country	Databases	Flowchart Meta-analysis	(N)=studies	(N)=patients	Type of studies	Mean age/range yrs	Quality assessment	Main outcomes	Conclusions/outcomes
Habiba [9]	UK	PubMed	No	82	466	45 case reports	39.9 yrs	No	Coexistence with	Minimal invasive approach
2019		MEDLINE	No			7 observational	25-72 yrs		endometrial cancer	Of a 4-step transcervical
		SCOPUS				30 case series			(17-23 %)	resection is related
									Recurrence rate	with decreased
									in conservative	recurrence rate
									treatment (8.8 %)	Conservative treatment
									Risk of endometrial	with Megestrol acetate
									cancer (8.8 %)	160 mg daily for 6
									Hysteroscopic	months is related
									resection	with increased cure
									recurrence (9%)	rate and possible
									Medroxyprogesterone	future pregnancies
									acetate(MPA) gives a	
									response rate (77,8 %)	
Mikos [10]	Greece	MEDLINE	Yes	63	350	Case reports	39.7 yrs	Yes	Recurrence rate of APA (35.1%)	Transcervical resection
2019		Web of Science	Yes			Observational	29-55 yrs		Concurrent endometrial	is related with decreased
		Cochrane				Case series			hyperplasia rate (7.2%)	recurrence rate and
									Concurrent endometrial	increased cure rate
									cancer rate (4.2%)	APA treatment should be
									Subsequent endometrial	individualized for each
									hyperplasia rate (6.7%)	patient.
									Subsequent endometrial	Hysterectomy is the
									cancer rate (10.1%)	appropriate treatment
									Pregnancy rate (60%)	
									Live birth rate (56.4)	
Raffone [11]	Italy	MEDLINE	No	11	237	Observational	37.7 yrs	Yes	Coexistence with atypical	4-step transcervical
2019		EMBASE	Yes				17-73 yrs		hyperplasia (5.5%)	resection is considered
		Web of Science							Coexistence with endometrial	the best option for
		SCOPUS							cancer (59 %)	fertility preservation
		Clinicaltrial.gov							Risk of recurrence (28.9%)	Hysterectomy is advised
		Ovid							Risk of endometrial cancer (16.6%)	when fertility is not
		Google Scholar							4-step transcervical resection	desirable
		Cochrane							showed lower progression (p=0.0002)	
									and recurrence rate (p=0.013)	
Biorioli [12]	Italy	MEDLINE	Yes	46	296	36 case reports	35 yrs	Yes	APA-relapse-(44%)	Operative hysteroscopy
2020		SCOPUS	Yes			10 case series			(CI:35 33-57%)	reduces the risk of
									Coexistence with	recurrence and improves
									endometrial cancer- (16%)	the accuracy of diagnosis
									(CI:95 9-29%)	of carcinoma or hyperplasia
									Risk of endometrial	MPA does not reduce the
									hyperplasia 59.91%	risk of recurrence of APA
									(CI.95: 28.54-77.19%)	
									Pregnancy success	
									15/19 (79%) in cases	
									of personal desire	
									Adenomyosis rate- (18%)	

APA: atypical polypoid adenomyoma; MPA: medroxyprogesterone acetate

TABLE 2. Main characteristics and outcomes of the four published systematic reviews

Author Year	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	AMSTAR-2 Rating
Habiba [9] 2018	No	No	No	Partial Yes	No	No	No	Partial Yes	NA	Yes	No	No	No	No	No	Yes	Critically low
Mikos [10] 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial Yes	Partial Yes	Yes	Yes	No	No	Yes	Yes	Yes	Moderate
Raffone [11] 2019	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial Yes	Partial Yes	Yes	Yes	No	No	Yes	Yes	Yes	Moderate
Biorioli [12] 2020	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Partial Yes	Partial Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	High

TABLE 3. Quality assessment of the included systematic reviews

Furthermore, it is the first study in the international literature that has performed a systematic review of the available systematic reviews with an additional quality assessment of these publications. The quality assessment has shown that only one systematic review was of "high quality". This

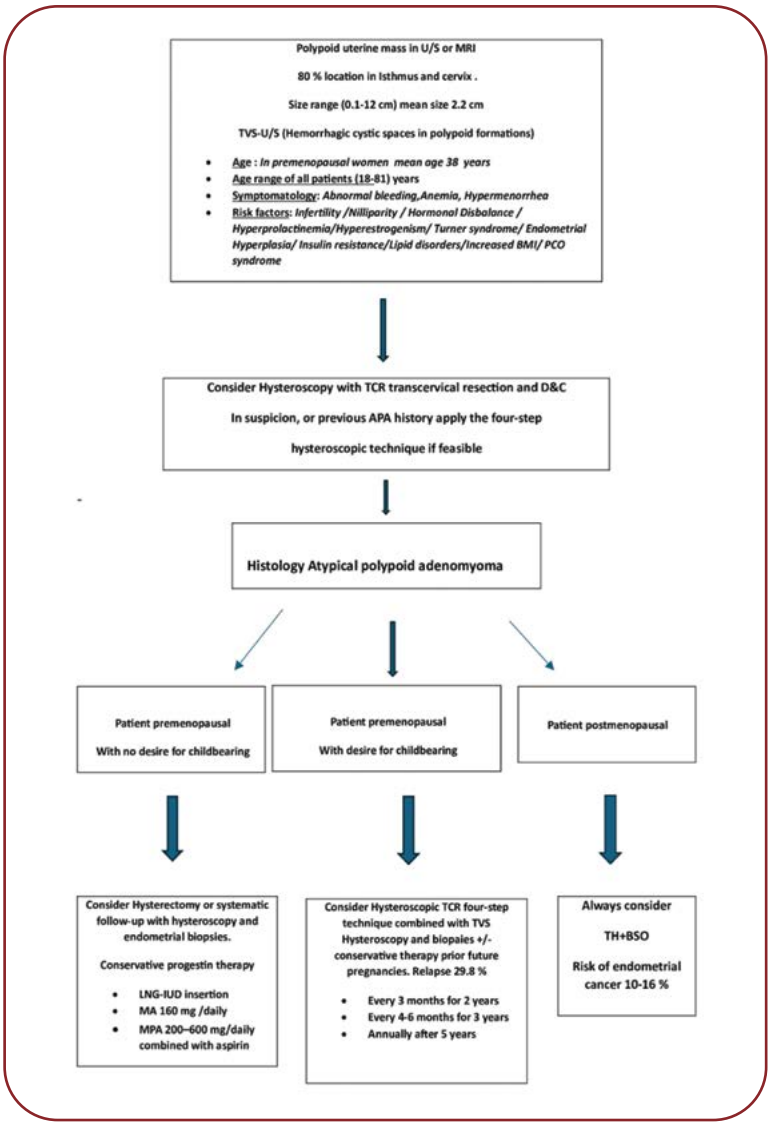

FIGURE 4. Flowchart guideline for the management of atypical polypoid adenomyoma (APA) in premenopausal and postmenopausal women. Report on the most frequent location of lesion, on size range and mean size of the lesion, mean age at diagnosis and overall age range; report on risk factors that are associated with the development of APA; step-by-step management in each three categories of women diagnosed with APA; TCR-four step technique: 1) lesion excision of lesion; 2) excision of the underlying endometrium; 3) excision of myometrium beneath the lesion; and 4) random adjacent hysteroscopic biopsies and D&C
U/S: ultrasound; MRI: magnetic resonance imaging; TVS: transvaginal scan; PCO: polycystic ovarian syndrome; BMI: body mass index; TCR: transcervical resection; D&C: diagnostic curettage; APA: atypical polypoid adenomyoma; LNG-IUD: levonorgestrel intrauterine device; MA: megestrol acetate; MPA: medroxyprogesterone acetate; TH-BSO: total hysterectomy and bilateral salpingoophorectomy.

evidence is supported by the fact that the systematic review by Biasioli *et al* (12) is the only one that has performed an analytical meta-analysis with a forest plot illustration. The three remaining systematic reviews did not meet most of the AMSTAR-2 criteria, and therefore, their quality was lower (9-11). The lower quality of these studies is based on the lack of randomized trials and the lack of homogeneous studies. Atypical polypoid adenomyoma is a rare clinical entity and the creation of studies with a randomized design is a difficult task. Randomized trials would be a reality in the presence of large studies with multicentric design enrolling a large cohort of patients.

Following the available clinical evidence, we strived to create a guideline-flowchart for the management of uterine APA in premenopausal and postmenopausal women. The aim is to provide valuable assistance and guidance to the clinicians regarding this rare clinical entity. The flowchart is exhibited in Figure 5.

In cases diagnosed with APA, the patients should be informed about the possibility of developing endometrial hyperplasia and subsequent endometrial cancer. In patients with a desire for childbearing, the four-step transcervical resection should be applied, followed by endometrial biopsies every three months for two years, then every 4-6 months for three years, and annually for five years after the initial follow-up. Total hysterectomy should be considered in cases of non-desirable childbearing and in post-menopausal women. Conservative progestin therapy may be offered with the administration of a levonorgestrel intrauterine device, oral megestrol acetate (MA) 160 mg daily, or MPA 200-600 mg daily, combined with aspirin.

DISCUSSION

Atypical polypoid adenomyoma is a rare disease, with fewer than 500 cases reported in the international literature, and therefore, it is difficult to estimate its incidence. The origin for the majority of APA cases (80%) is located at the cervical/isthmus level, but it can develop from any part of the uterus (11, 12). The diameter of the lesion may vary from 0.1 to 6 cm, with 12 cm being the largest recorded tumor. In general, the mean size of the majority of the clinical cases was reported to be 2.2 cm (10-12). In our case presentation, the lesion was also located in the isthmic region and it had a mean size of 1 cm.

Rare examples of APA have been described in patients with Turner syndrome who have been prescribed unopposed estrogens (11, 12). We ob-

served that our patient had elevated estrogen and prolactin levels. Similarly, Nasu *et al* (14) described the diagnosis and management of an APA in a 23-year-old patient with hyperprolactinemia. The authors postulated that the ovarian dysfunction caused by hyperprolactinemia was a risk factor for the development of APA.

Wang *et al* (15) reported that there is a positive association between elevated HOMA-IR (> 2.2) and lower serum HDL (< 1.2 mmol/L) in patients diagnosed with APA who developed endometrial cancer and/or endometrial hyperplasia. Homeostatic model assessment (HOMA) is a method used to quantify insulin resistance. In our patient with APA, we diagnosed low serum HDL and increased insulin resistance as well.

Due to the rarity of the neoplasm, the diagnostic approach is restricted. The preoperative diagnosis of atypical polypoid adenomyoma of the uterus remains challenging in contemporary clinical practice. Given the rarity of APA, no prospective trials have been designed and the management of patients has never had the so-called "gold standard". As a result, there is no official consensus on the optimal treatment and follow-up of APA (12).

Clinical imaging of APA is a difficult task. It is not extensively documented in many cases and it offers the impression of the existence of prolapsed leiomyomas or malignancies. Interesting evidence is the presence of hemorrhagic cystic spaces within a prolapsed uterine tumor. This should prompt suspicion of the possible diagnosis of polypoid adenomyoma. Such blood-filled cystic spaces are atypical and uncommon in leiomyomas and malignancies (15, 16). In our case, the ultrasound imaging was suggestive of an endometrial polyp; hysteroscopic examination also exhibited a polypoid formation.

Some studies reported magnetic resonance imaging (MRI) findings of APA. When closely examined, polypoid adenomyomas do not show significant differences from ordinary endometrial polyps. However, on MRI imaging, they present well-defined intracavitary uterine masses and can extend into the lower uterine segment, endocervix, or uterine corpus. On T1-weighted images, these lesions exhibit isointense characteristics. The signal intensity on the T2-weighted images may vary depending on the size and the presence of glands within the tumor (17). Our patient underwent a MRI imaging; however, the formation was not noticed due to the previous hysteroscopic resection.

One study reported that the tumor markers CA125 and CA19.9 did now show alterations and ranged within the normal levels. Similarly, we observed that tumor markers were normal and their application did not provide useful clinical information. The necessity for the implementation of specific tumor markers, which will assist the diagnosis of APA and distinguish it from endometrial hyperplasia, is noted by Raffone *et al* (12).

The diagnosis of APA is primarily based on a histological examination. Often, it is an extremely difficult task to distinguish it macroscopically from entities like endometrial polyps, submucous myomas, or adenofibromas. The complex biphasic histological pattern can resemble adenocarcinoma invading the myometrium or malignant mixed Müllerian tumors, adding to the diagnostic difficulty of APA (15).

Immunohistochemistry does not provide substantial assistance in distinguishing between APA and the myometrium infiltrated by carcinoma. One potentially useful marker is CD10, as it tends to be absent in the stromal component of APA. H-caldesmon is expressed in the myometrial smooth muscle invaded by the endometrioid adenocarcinoma, while in cases of APA is typically absent (18).

In cases where there is a desire for fertility preservation, minimally invasive treatment with the assistance of operative hysteroscopy is often considered to be the best management choice. The following four-step technique for managing atypical polypoid adenomyoma has been proposed, involving a hysteroscopic transcervical resection (TCR) of the lesion and a careful follow-up: 1) resection of APA; 2) resection of the adjacent endometrium surrounding the lesion; 3) resection of the underlying myometrium beneath the lesion; and 4) random endometrial biopsies obtained with diagnostic curettage or hysteroscopic resection. The aforementioned technique is often used as a fertility-sparing approach for early-stage endometrial cancer and atypical endometrial hyperplasia (11, 12). Despite the undisputed advantages of a TCR, it is essential to note that there is still a recurrence risk of (29.8%) and a progression risk of (10.8%), even after this procedure (11, 12). Transcervical hysteroscopic resection alone is considered to be an efficient and safe surgical option, with an initial response seen in 98.7% of operated

women. The outcomes for a TCR alone include a progression rate of 10.8%, a final complete response rate of 77.3%, a recurrence rate of 29.8% and a pregnancy rate of 21.1% (9, 10). It is essential to mention that a long-term follow-up is recommended. This follow-up includes dilation and curettage or a hysteroscopic biopsy, combined with transvaginal ultrasonography, every three months for the first two years, then close monitoring every 4–6 months for three years and annually thereafter (11).

Medroxyprogesterone acetate medical treatment for APA can be a reasonable alternative option. However, there is evidence that recurrence may occur even after complete remission with the MPA treatment. The recurrence rate following TCR is lower than that after D & C. This difference can be attributed to the advantage of a TCR in detecting the lesion and decreasing the possibility of residual disease. Nevertheless, even with the MPA therapy or the megestrol acetate therapy, recurrence rates of 10–33% have been reported (19). Additionally, the use of a levonorgestrel intrauterine device (IUD) has been suggested as a form of maintenance therapy for young women who wish to preserve their fertility (19). Nomura *et al* (20) administered MPA (200-600 mg) daily in patients with APA, combined with low doses of aspirin 100 mg daily to prevent eventual thrombosis from progestin therapy.

Systematic reviews are a powerful tool for synthesizing evidence; their level is based on the type and quality of the studies included. In our systematic review or also known as an umbrella review, we concluded that one systematic review was graded as "high quality" (12), two systematic reviews as "medium quality" (10, 11) and the remaining one as "critically low quality" (9).

Systematic reviews provide a level of evidence that is important for clinical practice. According to the classification of levels of evidence for systematic reviews, three studies (10-12) have provided a level of evidence of 3a, which accounted for systematic reviews of homogeneous case-control studies. The level of evidence 3a suggests the so-called level of recommendation B, which indicates that the findings of a systematic review are consistent in general. In addition, it supports the fact that clinicians should follow a recommendation but should remain alert to new information and sensitive to patient preferences (21). ❑

CONCLUSION

Atypical polypoid adenomyoma is a rare clinical entity. It occurs mainly during the reproductive period of a woman. It is associated with abnormal vaginal bleeding, infertility, nulliparity, obesity, metabolic syndrome, hyperprolactinemia and hyperestrogenism. It is a risk factor for the development of endometrial hyperplasia and subsequent endometrial cancer. Preoperative diagnosis is extremely difficult; there are no specific imaging landmarks and points of reference in ultrasound and MRI assessment. Only pathology confirms the diagnosis. In patients with a desire for fertility and childbearing, the management is complicated and should be based on a four-step hysteroscopic transcervical resection of the lesion from an experienced gynecologist. Hysterectomy is the right option for post-menopausal women and for women not wishing to conceive. Conservative treatment with progestins only is associated with relapses of APA. Larger multicentric studies with randomized character and numerous patients are necessary to offer stable clinical evidence. ❑

Availability of data and materials: The original contributions presented in this study are included in the article. Further inquiries can be directed to the corresponding author.

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