

# Prophylactic oophorectomy and aromatase inhibitors for premenopausal deep angiomyxoma: A case report and literature review

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**Abstract.** Deep angiomyxoma is a rare, infiltrative, hormone-dependent, benign-mesenchymal neoplasm that occurs in the deep soft tissues of the perineal regions. In total, 33% females with newly diagnosed deep angiomyxoma will typically relapse within 5 years after the standard treatment of radical resection. Postoperative hormone therapy is frequently administered to prevent recurrence, but the role of prophylactic oophorectomy in premenopausal women remain to be fully elucidated. In the present report, a 42-year-old Japanese woman was referred for a refractory Bartholin's cyst that is 14 cm in diameter. Based on the results of imaging (unenhanced CT and MRI) and histopathology, deep angiomyxoma was suspected, but no definitive diagnosis was possible. Tumor resection and bilateral salpingo-oophorectomy were performed before the postoperative diagnosis was confirmed to be deep angiomyxoma. The patient received an aromatase inhibitor (2.5 mg letrozole daily) as adjuvant hormonal therapy. There was no evidence of recurrence at the 1-year postoperative follow-up. In conclusion, prophylactic oophorectomy and postoperative adjuvant therapy with aromatase inhibitors may be a promising treatment option for deep angiomyxoma to optimize the outcome of surgical treatment. Long-term follow-up is required to monitor for the late and/or local recurrence of deep angiomyxoma and possible adverse effects of adjuvant hormonal therapy.

## Introduction

Deep angiomyxoma (DAM), which was first described by Steeper and Rossi in 1983, is a rare, infiltrative, hormone-dependent, benign and mesenchymal neoplasm that typically occurs in the deep soft tissues in the perineal region (1,2). Clinically, DAM mimics more common gynecological conditions, such as Bartholin's cyst, lipoma and hernia, rendering it frequently misdiagnosed (3). In addition, DAM is histologically a hypocellular and hypervascular tumor with a mucinous stroma, containing cytologically pale stellate or spindle-shaped cells with consistent nuclear immunoreactivity for estrogen receptors (ER) and progesterone receptors (PgR) (4). High mobility group AT-hook 2 immunohistochemical staining is also a useful auxiliary marker, but it lacks specificity (5). The standard treatment method for DAM is normally surgical resection followed by histological diagnosis, which relieves the mass effect (4). However, the relatively high recurrence rate, ranging from 30 to 40%, remains an unsolved problem (4). Furthermore, the radicality of surgery (negative or positive surgical margins) has no statistically significant impact on the progression-free interval (6).

Therefore, hormone therapy is frequently used in combination with surgery to prevent recurrence (7). The majority of the drugs used for DAMs are gonadotropin-releasing hormone agonist (GnRHa) preparations, though there have been various reports of the use of aromatase inhibitors or selective ER modulators (SERMs) (7). In addition, since DAM tends to be more common in premenopausal females, recurrence after the completion of GnRHa therapy has been frequently reported (7). However, the role of prophylactic oophorectomy has remained poorly understood (8).

The present report documents a case of a premenopausal woman who underwent DAM tumor resection and prophylactic oophorectomy followed by adjuvant hormonal therapy with an aromatase inhibitor to prevent recurrence.

## Case report

A 42-year-old Japanese female (gravida 4, para 2) first visited the Plastic Surgery Department of Oita University Hospital

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*Abbreviations:* DAM, deep angiomyxoma; ER, estrogen receptor; PgR, progesterone receptor; GnRHa, gonadotropin-releasing hormone agonist; SERM, selective estrogen receptor modulator

*Key words:* aromatase inhibitors, deep angiomyxoma, hormone manipulation, mesenchymal neoplasms, prophylactic oophorectomy

(Oita, Japan) in January 2021, complaining of a refractory Bartholin's cyst persisting for 2 months. The patient had a medical history of lumbar disc hernia (timing of disease was unclear). On clinical examination, the patient's left labium majus was determined to be enlarged and saddled. Subcutaneous tissue hyperplasia due to chronic inflammation was suspected after examination by transperineal ultrasonography (the ARIETTA 50 ultrasound machine; Hitachi, Ltd.; 2-10 Hz resolution transvaginal ultrasound probe). Unenhanced pelvic CT (Aquilion ONE/PRISM Edition; Canon Medical Systems; tube voltage, 120 kilovolt peak; field of view, 398.44 mm<sup>2</sup>; scan speed, 0.5 rotation/sec; pitch factor, 0.813; helical pitch, 65.0; reconstruction software algorithm, Advanced intelligent Clear-IQ Engine Body sharp mild; slice thickness, 1.0 mm; dose index, 8.6 mGy) indicated a low-density, irregular pelvic mass, suggesting DAM or angiofibrosarcoma. Pelvic MRI (3.0T MRI MAGNETOM Skyra VE11C; Siemens AG; scan time, 2:42; repetition time, 4,000 msec; echo time, 90 msec; turbo factor, 15; band width, 302 Hz/px; slice thickness, 3 mm; field of view, 25x25 cm; matrix size, 0.6x0.6 mm; Parallel Imaging, GRAPPA 2) indicated a nodular, structured tumor with a maximum diameter of 14 cm (Fig. 1A). The tumor, which had a swirled and layered pattern according to T2-weighted MRI, extended from the left vulva subcutaneously to the paravesical space (Fig. 1B). DAM was therefore suspected. The patient was thereby referred to the Gynecology department, where a transperineal tumor biopsy was performed. Pathological examination results strongly suggested DAM. Therefore, considering all clinical findings, DAM was finally diagnosed. Contrast-enhanced CT of the chest and pelvis revealed no metastatic lesions.

The patient underwent bilateral ureteral stent placement, followed by transabdominal and transperineal tumor resection and bilateral salpingo-oophorectomy (BSO), performed by trained gynecological oncologists and urologists. Intraoperatively, the tumor extended from the left vulva to the anterior surface of the bladder and the retroperitoneal space on the left side of the uterus. The tumor was resected *en bloc* without any adjunct organ injuries and weighed 480 g (Fig. 1C). Macroscopically, the resected tumor was not well-defined, elastoplastic and soft with a glistening and gelatinous surface (Fig. 1D). The excised specimens were fixed using neutral-buffered 10% formalin, dehydrated in a series of ethanols and embedded in paraffin. Serial sections of 4-μm thickness were made and then subjected to hematoxylin-eosin staining. Immunohistochemical staining was performed with a Ventana automated immunostainer (Ventana Medical Systems, Inc.) using an UltraView Universal DAB Detection Kit (Ventana Medical Systems, Inc.). Pathological diagnosis indicated DAM against a background of sparse connective tissue with a mucous matrix (Fig. 2A) and mildly atypical spindle-shaped cell proliferation (Fig. 2B). The tumor cells exhibited diffuse positive immunoreactivity for ER (cat. no. 790-4325; dilution, 1:1; Ventana Medical Systems, Inc.; Fig. 2C), PgR (cat. no. 790-4296; dilution, 1:1; Ventana Medical Systems, Inc.; Fig. 2D) and desmin (cat. no. PA0033; dilution, 1:1; Leica Microsystems GmbH; Fig. 2E). The tumor was partially positive for α-smooth muscle actin (cat. no. PA0943; dilution, 1:1; Leica Microsystems GmbH; Fig. 2F) and CD34 (cat. no. PA0212; dilution, 1:1; Leica Microsystems GmbH; Fig. 2G). However, it was negative for cyclin-dependent kinase 4

staining (cat. no. AHZ0202; dilution, 1:40; Invitrogen; Thermo Fisher Scientific, Inc.). The patient's postoperative course was uneventful. At 1 month postoperatively, a follow-up MRI confirmed no residual tumor. The patient started receiving oral letrozole treatment (2.5 mg/day), an aromatase inhibitor, 1 month after surgery. A follow-up CT scan after 1 year confirmed no recurrent lesion. Currently (June 2022, 1 year after surgery), the patient is continuing with letrozole treatment. Mild menopausal symptoms (hot flashes and tiredness) associated with oophorectomy and aromatase inhibitor therapy were observed, but the general condition was good.

Written informed consent was obtained from the patient to publish anonymized data in the present case report. In addition, the patient was informed and consented to all the benefits and risks of this new treatment (prophylactic oophorectomy and aromatase inhibitor) in advance.

## Discussion

The present case demonstrates two important clinical issues. First, a multidisciplinary team approach enabled the wide local resection of the DAM without permanent sequelae. Furthermore, prophylactic oophorectomy was performed for premenopausal DAM and an aromatase inhibitor was administered as postoperative adjuvant therapy.

The standard treatment strategy for DAM is surgery with R0 resection (negative resection margin) (6). However, R0 resection is technically difficult because DAM frequently infiltrates adjacent soft tissues and organs and is poorly circumscribed (6). Therefore, R1 resection or fractional resection is acceptable when a high risk of morbidity due to extensive surgery is anticipated (9).

Whether surgical radicality affects clinical outcomes in DAM remains controversial. Chan *et al* (6) previously reviewed 73 reported cases of patients with DAM who underwent surgery and observed that 34 (47%) had recurrence. In addition, there was no significant difference in the recurrence rate between the patients with positive and negative resection margins. It should be noted that there was no information in this previous report (6) regarding hormone manipulation therapy. Furthermore, Zou *et al* (10) reviewed the data of 27 patients who underwent surgery performed by a single surgeon at a single university hospital over 15 years. They determined that a clear surgical margin was an independent prognostic factor for the disease-free interval (10). It may be speculated that a radical multidisciplinary surgical approach with greater invasiveness performed by skilled surgeons may contribute to more favorable outcomes in patients with DAM.

Given that DAM occurs predominantly during premenopausal periods or the fourth decade of life (11), reported rapid growth during pregnancy (12) and stains positive immunohistochemically for ER and PgR, it is highly likely that DAM is hormone-sensitive (13). Therefore, hormonal therapy with ovarian-derived estrogen, progesterone and non-ovarian-derived estrogen, is frequently used in combination with surgical resection.

Hormonal therapy for DAM has been used in both primary and recurrent settings with agents, such as GnRHa, aromatase inhibitors and SERMs (7). In particular, GnRHa has been actively used as an adjuvant therapy for

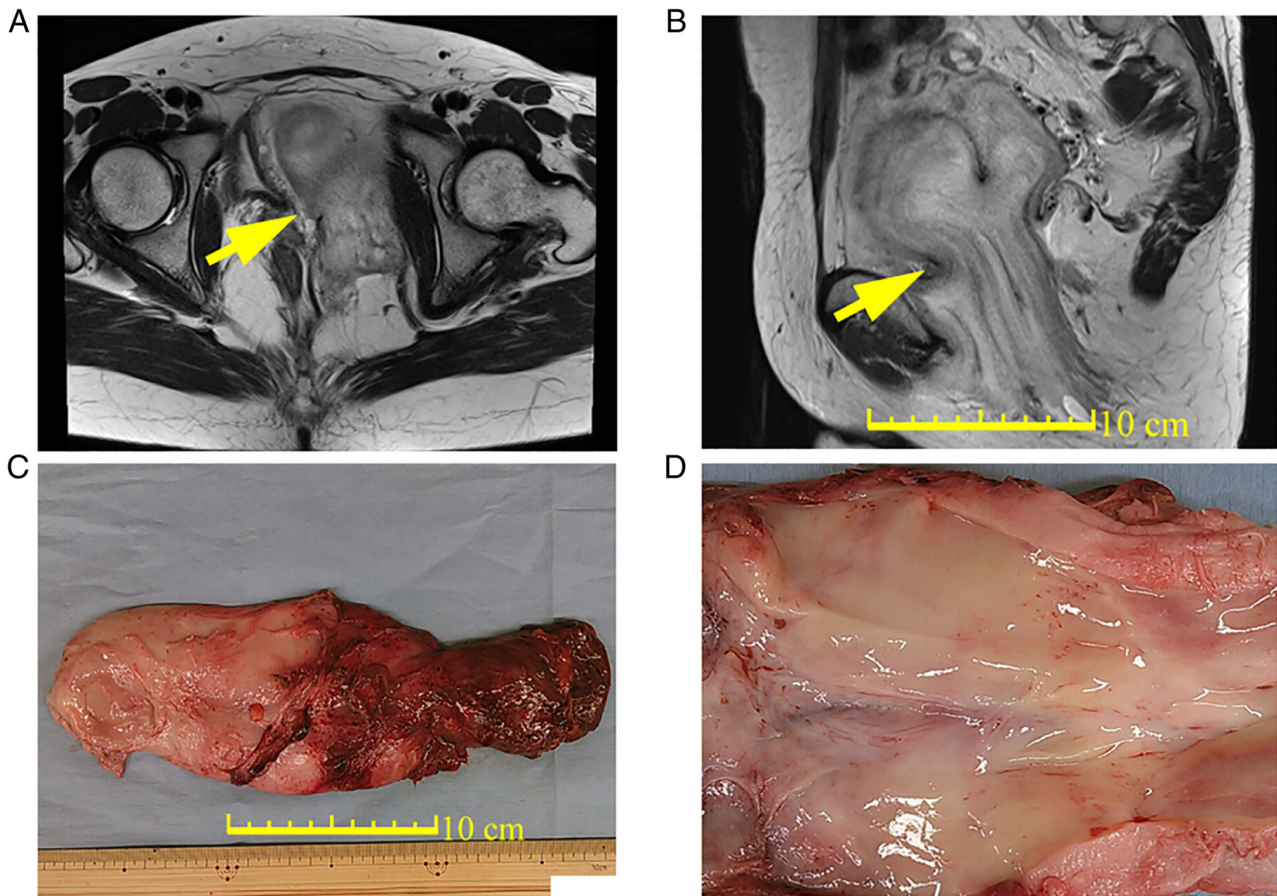


Figure 1. Imaging and gross pathology of the deep angiomyxoma. (A) Axial, enhanced, T2-weighted MRI scan indicating a high-signal intensity tumor displacing the pelvic organs to the right (arrow). (B) Sagittal, enhanced, T2-weighted MRI scan indicating a 14-cm in the longest axis, nodular, structured tumor extending from the vulva to the paravesical space with swirled and layered strands of lower signal intensity (arrow). (C) The gross appearance is elastoplastic and soft, with a glistening and gelatinous surface. (D) Close-up of C.

premenopausal DAM. However, in premenopausal women, recurrence and enlargement of the lesions after completion of hormone therapy has been frequently observed due to the residual ovaries (7). Artificial menopause with prophylactic oophorectomy may have a longer-lasting effect compared with GnRHa for preventing recurrence, since it permanently depletes ovarian-derived estrogen and progesterone. Table I summarizes seven premenopausal patients with DAM who underwent prophylactic oophorectomy and radical resection. None of the patients had any recurrence after bilateral salpingo-oophorectomy was performed.

DAM causing death is a rare phenomenon (14). The present study also focused on non-ovarian-derived estrogen to minimize the recurrence risk of DAM. Non-ovarian-derived estrogen is synthesized by aromatase from androstenedione derived from adipose tissue and adrenal glands (15). In postmenopausal females (whether natural or artificial), non-ovarian-derived estrogen requires strict control. Aromatase inhibitors and SERMs inhibit estrogen synthesis and receptors, respectively, to reduce the recurrence of aggressive angiomyxomas more effectively compared with GnRHa. Fucà *et al* (7) previously reported that hormonal therapy with aromatase inhibitors and SERMs tended to result in longer progression-free survival. Reported cases of patients receiving aromatase inhibitors or SERMs are summarized in Table II. Of the 12 patients, including one

male patient, who underwent surgery and anti-estrogen therapy (including GnRHa), three had stable disease, six had partial response and three had a complete response. The effects of aromatase inhibitors and SERMs were independent of sex, age, menopausal status and surgical treatment (7). Therefore, it was necessary to use aromatase inhibitors or SERMs to suppress the levels of non-ovarian derived estrogen. Since SERMs act as agonists or antagonists of estrogen on an organ-by-organ basis, an aromatase inhibitor was selected in the present report. Furthermore, similar treatment options may be effective for other hormone-sensitive soft tissue tumors, such as leiomyoma and adenomyosis. Mizoguchi *et al* (16) and Nasu *et al* (17) reported that a combination of prophylactic oophorectomy and adjuvant aromatase inhibitors is effective for premenopausal patients with intravenous leiomyomatosis and benign metastasizing leiomyoma, respectively. In addition, combined ovarian ablation and aromatase inhibition were effective for metastatic breast cancer in premenopausal women (18). Oophorectomy also improved primary cancer incidence and mortality in women with *BRCA* mutations (19,20). Advantages of BSO include preventing recurrence due to permanent hormone deficiency and avoiding long-term GnRH administration (7). By contrast, disadvantages include the possibility of hormone deficiency symptoms such as menopause and osteoporosis. The advantage of aromatase inhibitors is that they can inhibit recurrence by



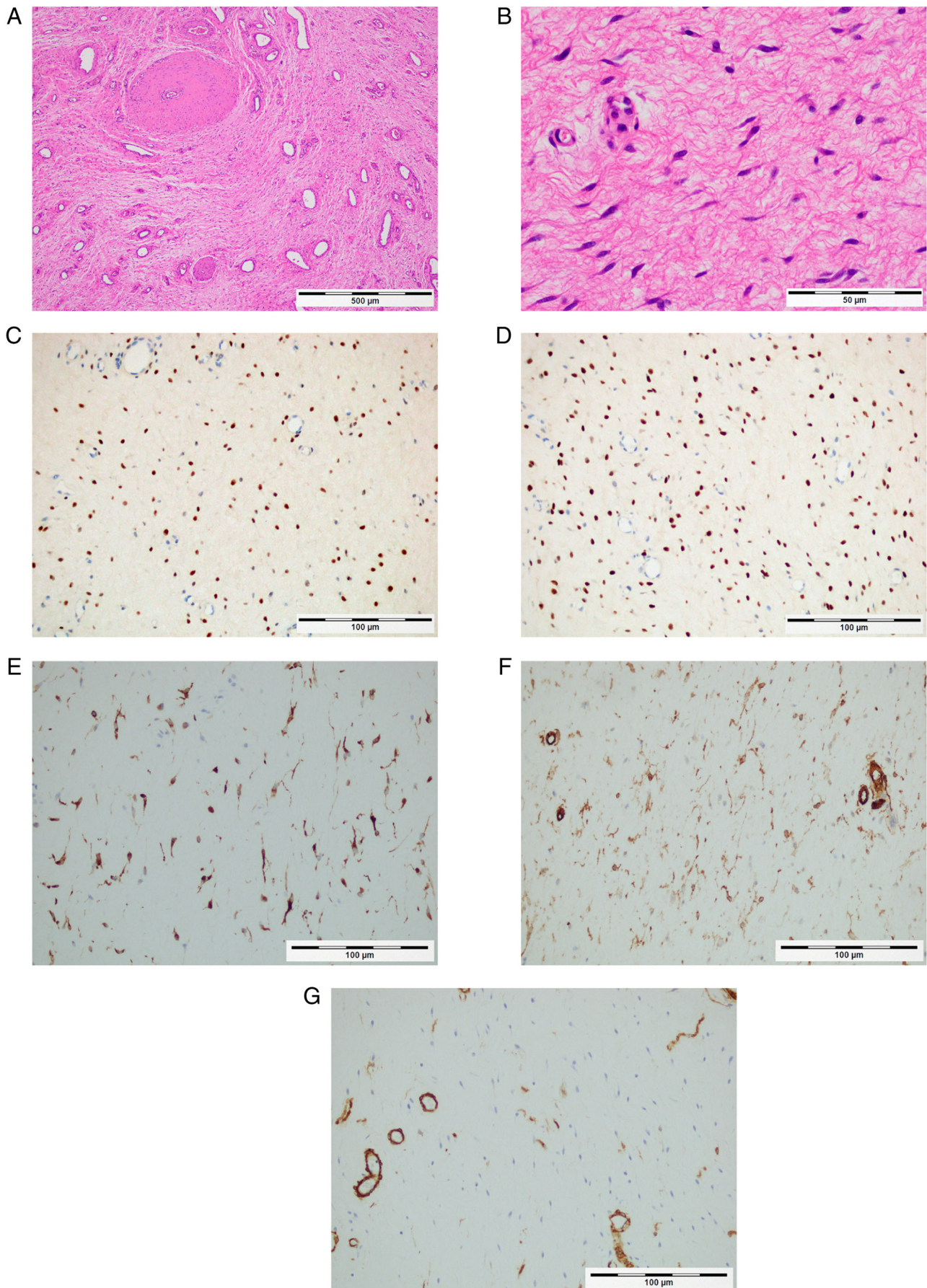


Figure 2. Tumor pathology and hormone receptor expression. (A) The tumor is comprised loose fibromyxoid stroma, fine collagen fibers and prominent vessels, according to H&E staining (original magnification, x4; scale bar, 500  $\mu$ m). (B) High-power photomicrograph indicates the proliferation of mildly atypical spindle-shaped cells according to H&E staining (original magnification, x40; scale bar, 500  $\mu$ m). Immunoreactivity for (C) estrogen receptor (D) progesterone receptor is positive, (E) desmin, (F)  $\alpha$ -smooth muscle actin and (G) CD34 (original magnification, x20; scale bar, 100  $\mu$ m).

Table I. Reported cases of prophylactic oophorectomy for premenopausal deep angiomyxoma.

First author, year	Age, Years	Relapses, n	History/neoadjuvant therapy	Concurrent surgeries with radical resection	Adjuvant therapy	Follow-up, months	Outcome	(Refs.)
Fetsch, 1996	35	1	Local resection	TAH + BSO	Radiation	91	NED	(11)
Lourenço, 2013	47	2	Two local resections	TAH + BSO	None	12	NED	(9)
Sirasagi, 2014	45	0	None	TAH + BSO	None	NA	NA	(22)
Beuran, 2017	45	5	Four local resections	TAH + BSO + Ureter resection	None	12	NED	(23)
Song, 2017	49	0	Fulvestrant + goserelin	TAH + BSO + Anterior exenteration	None	15	NED	(24)
Gaurav, 2020	45	0	None	Lap-BSO	None	NA	NA	(25)
Tonai, 2022 <sup>a</sup>	42	0	None	Abdominal BSO	Letrozole	12	NED	

<sup>a</sup>Present case. BSO, bilateral salpingo-oophorectomy; Lap, laparoscopic; NA, information not available; NED, no evidence of disease; TAH, total abdominal hysterectomy.

Table II. Clinical outcomes of patients treated with aromatase inhibitors or selective estrogen receptor modulators.

First author, year	Sex	Age, years	Tumor resection	BSO	Type of hormone therapy	Therapy response	(Refs.)
Fucà, 2019	Female	61	Yes	No	Anastrozole	SD	(7)
Fucà, 2019	Male	63	Yes	No	Letrozole	SD	(7)
Fucà, 2019	Female	40	No	No	Tamoxifen	PR	(7)
Fucà, 2019	Female	35	Yes	No	Raloxifen	PR	(7)
Fucà, 2019	Female	45	Yes	No	Leuporelin + tamoxifen	CR	(7)
Fucà, 2019	Female	43	Yes	No	Triptorelin + tamoxifen	PR	(7)
Fucà, 2019	Female	54	Yes	No	Anastrozole	SD	(7)
Fucà, 2019	Female	37	Yes	No	Triptorelin + letrozole	CR	(7)
Fucà, 2019	Female	48	Yes	No	Triptorelin + letrozole	PR	(7)
Lee, 2019	Female	44	No	No	Leuprolide + anastrozole	PR	(20)
Giles, 2008	Female	78	No	No	Exemestane	PR	(21)
Tonai, 2022	Female	42	Yes	Yes	Letrozole	CR	Present case

BSO, bilateral salpingo-oophorectomy; CR, complete response; PR, partial response; SD, stable disease.

suppressing non-ovarian derived estrogen, whilst disadvantages include the requirement for long-term medication and possible side effects, such as menopausal symptoms, liver dysfunction, osteoporosis and lipid metabolism abnormalities (21).

A literature search was conducted in MEDLINE/PubMed (<https://pubmed.ncbi.nlm.nih.gov/>) and Google Scholar (<https://scholar.google.co.jp/schhp?hl=ja>) for cases of prophylactic oophorectomy with the administration of aromatase inhibitors as a potential treatment for DAM. The English-language literature was searched using the terms ‘aggressive angiomylaplasty’, ‘deep angiomylaplasty’ and ‘oophorectomy’, with no publication date filter. Cases in which therapeutic oophorectomy was performed were excluded. To the best of our knowledge, the present study was the first to report prophylactic oophorectomy followed by treatment using an aromatase inhibitor as a strategy for DAM.

A limitation of the present report is the short follow-up period. In addition, the criteria for cases that should receive hormone therapy remain controversial. Since DAM has a high postoperative recurrence rate (30-50%) (4), it may be suggested that hormone therapy (prophylactic oophorectomy or an aromatase inhibitor) should be actively introduced. Case accumulation and long-term follow-up on this treatment strategy for DAM is required in the future.

In conclusion, surgical resection with minimal invasiveness is preferred for premenopausal women with DAM, but radical surgery with greater invasiveness should be used if necessary. Prophylactic oophorectomy and adjuvant hormone therapy with aromatase inhibitors, as well as GnRH agonists, may be promising treatment options to optimize the outcome of surgical treatment. Furthermore, this treatment strategy may also



apply to hormone-sensitive mesenchymal tumors. Long-term follow-up is required to confirm late and local recurrence of DAM, along with the side effects of adjuvant hormonal therapy.

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## Availability of data and materials

All data generated or analyzed during this study are included in this published article.

## Authors' contributions

NT and MY drafted the manuscript and made substantial contributions to the conception and design of the study, as well as the acquisition, analysis, interpretation of data. NT and MY confirm the authenticity of all the raw data. MS, KK and MN made contributions to the acquisition, analysis and interpretation of data. KN and YK made contributions to the analysis and interpretation of data, as well as reviewing and editing of the manuscript. All authors read and approved the final manuscript.

## Ethics approval and consent to participate

Not applicable.

## Patient consent for publication

Written informed consent was obtained from the participant for participation in the study and the publication of the data. The patient consented to the images being taken for research and also consented to their publication.

## Competing interests

The authors declare that they have no competing interests.

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