A rare case of ovarian adenomyoma mimicking primary invasive ovarian cancer with a contralateral serous borderline ovarian tumor: A case report and review of the literature

Viola Liberale, Alessandra Surace, Lorenzo Daniele, Luca Liban Mariani

1. Introduction

An extraterine adenomyoma is a circumscribed, nodular aggregate of smooth muscle, endometrial glands and endometrial stroma originating outside the uterus. This rare type of benign tumor has been described in pararectal spaces, ovaries, broad ligament, peritoneum, cornus medullaris, bowel and liver [1, 2]. The ultrasound appearance is typically that of malignant ovarian tumors due to the prevalent solid component and atypical vascularization. Herein, we describe a clinical case of an ovarian adenomyoma in a symptomatic woman without a previous history of pelvic endometriosis and we provided a review of the inherent literature.

2. Case

A 40-year-old woman para 0000 was referred to our Institution for a pelvic pain irradiated to the left flank. Her medical history was unremarkable and she did not assume regular medications. She did not report any general surgical procedure except for a cesarean section in 2015 for breech presentation. Her family history for gynecological malignancies was negative. At admission, she denied dyspepsia, bowel or urinary habits changes and she had regular menses. The pelvic pain onset was intermittent and persistent over the previous three weeks.

Vital parameters were regular and the patient was afebrile. Clinical examination revealed a left iliac firm and painful mass with tenderness exacerbated by bimanual mobilization. On palpation the uterus and right adnexa appeared physiological and no blood nor atypical vaginal discharge was recorded. Blood tests were all in normal ranges. Alpha-fetoprotein, carcinoembryonic antigen, CA-19.9, CA-15.3, were all negative. Serum cancer antigen-125 was elevated, reaching 680.8 UI/ml.

Transvaginal scan was performed by using a 5–7 MHz transvaginal transducers (Affiniti 70 - Philips). IOTA (International Ovarian Tumor Analysis) terms and definitions were adopted to describe the ovarian lesion. The ultrasound (US) examination confirmed the presence of an irregular dishomogeneous solid mass of $63 \times 62 \times 60$ mm, arising from the left ovary, with two hypoechoic cysts and regular margins (Figure 1).

The operator attributed a color score of 4 (highly vascularized) due to the presence of a single dominant vessel crossing the central part of the mass with multiple branches distributing to the periphery and surrounding the cystic areas (Figure 2, video 1).
A positive sliding sign was present between the uterus and the pelvic sidewall. Furthermore, the right adnexa appeared to have an increased volume (55 × 31 mm) with an inner hemorrhagic area and an adjacent unilocular cystic lesion with irregular borders, multiple papillary structures and color score 3 (Figures 3 and 4, video 2); the bigger papillary projection measured 11 × 11 mm. The ultrasound aspect was presumed suggestive for at least a serous borderline ovarian tumor (sBOT). The uterus had an irregular myometrial-endometrial junction with hyper-echoic areas dispersed in the myometrium, a mild and diffuse ultrasound beam absorption, overall suggesting the presence of adenomyosis. No abnormalities of the bladder, ureters in the pelvic tract, or kidneys were detected. No free fluid was detected in the Douglas pouch. The overall features of the left ovarian lesion, were highly suspicious for an invasive epithelial ovarian cancer. This result was also supported by ADNEX model analysis [3] retrieving a risk of ovarian cancer of 90.1% with a risk of II - IV stage of 73.3% for the left ovary mass (Figure 5).

An overall staging was completed with thorax and a whole abdominal computed tomography (CT), which confirmed the finding of an inhomogeneous adnexal solid-cystic left mass with an irregular contour, high contrast enhancement and a smaller contralateral solid-cystic lesion. No additional lesions were reported in the remaining abdomen nor in the thorax.

Upon gross examination, the left ovary lesion was greyish, lobulated, with a smooth surface, an irregular shape and had solid-elastic consistency. On the cut section, the mass showed a prevalent solid component.
with gray cystic areas filled with brown-chocolate fluid. Microscopy revealed the presence of two endometriotic cysts surrounded by a variable thickness of smooth muscle layers lined with endometrial glands and stroma without nuclear atypia resembling normal uterine myometrium and endometrium. These findings were consistent with uterus-like extrauterine adenomyoma associated with ovarian endometriomas (Figures 6, 7, 8 and 9). In the same ovary a cystic-hemorrhagic corpus luteum was also found. On the cut section, right ovary mass showed a prevalent cystic component filled with clear fluid and projecting papillary structures. The diagnosis of right atypical proliferative serous tumor (according to the last WHO classification of ovarian neoplasm) was established. [5] All other specimens were negative for premalignant or malignant cells. The patient was discharged from hospital 4 days after surgery in good condition. Informed consent for scientific publication was obtained from the patient.

3. Discussion

An extrauterine adenomyoma is a rare type of benign tumor, mainly located in ovaries. Since it was first described by Cozzutto et al. in 1981 [6] subsequent cases were reported with various names as “uterus-like mass”, “extrauterine adenomyoma” and “endomyometriosis”. The pathogenesis behind extrauterine proliferation of adenomyomas is not yet well understood.

Figure 5. ADNEX model of left ovary mass.

Figure 6. Adenomyoma with uterine-like features. Endometrial cyst cavity with blood inside is lined by typical endometrial glandular epithelium and stroma surrounded by hypertrophied smooth muscle resembling that of the myometrium.

Figure 7. Microscopic analysis revealing the interface between hyperplastic smooth muscle layer and epithelial capsule of endometriotic cyst. The multiple vessels interspersed in the muscular layer account for high vascularization observed on ultrasound examination.

Figure 8. The thickened muscular layer is composed of normal, organized myometrial-type smooth muscle. The differential diagnosis is between the typical endometriomas which may also show some degree of smooth muscle metaplasia and extrauterine leiomyoma where the muscular layer is predominant with only few endometrial-type glands and stroma inside.

Cozzutto in his paper, proposed the theory in which adenomyomas could originate after a process of metaplastic transformation of endometriotic cells into smooth muscle, but this theory could not explain whole cases published later. Four other theories, from Rosai, Redman, Batt and Belmarz, have been proposed for explaining the pathophysiology of extrauterine adenomyomas and are described below.
Rosai [7] suggested the theory of defective müllerian duct fusion. This theory explains cases of extrauterine adenomyoma accompanying congenital urogenital abnormalities like renal agenesis and double excretory system associated with anomalies of the genital tract. Abnormalities of the uterus, such as rudimentary horn or uterine duplications, could lead, after a process of detachment, to an implant of a uterus-like mass in the abdominal cavity [1, 25, 52]. Since some extrauterine adenomyomas responded to hormonal treatment, in 2005 Redman et al. [25, 32, 33] suggested the theory of sub-coelomic mesenchymal metaplasia according to which multipotent cells, contained below the mesothelial layer of the peritoneum, could differentiate and grow under estrogen impulse, leading to the formation of a supernumerary müllerian uterus-like structure.

Batt et al. [8, 9] proposed the theory of mullerianosis which states that a heterotrophic organoid structure of embryonic origin composed of müllerian cell rests may get incorporated into normal organs at the time of organogenesis. The müllerianosis’ theory was particularly suitable for providing an explanation for extrauterine lesions that occurred in unusual sites outside the pelvic and lower abdominal cavities. Newsworthy Belmaz et al. [54] in 2019, describing a patient with leiomyomatosis peritonealis disseminata and extrauterine adenomyomas, shed light on the possibility of a similar pathogenetic theory. Both of these pathologies could arise by deposits of iatrogenic dropped cells within the abdomen and pelvis during hysterectomy or myomectomy.

Most patients with ovarian adenomyoma had a presumptive ultrasound diagnosis of ovarian endometrioma. Moreover, most ovarian adenomyomas arise in the left ovary according to our case report. Several Authors [10, 11, 12] observed higher frequency and/or more severe pelvic endometriotic lesions on the left pelvic side due to the presence of sigma causing an anatomical distortion for the refluxing menstruation. The back-flow hypothesis may therefore, be suitably applied to ovarian adenomyoma in patients with a concomitant endometriotic lesions reinforcing Cozzutto’s theory [6]. Guerriero et al. defined typical ultrasound features of ovarian endometriomas as unilocular, ground-glass cyst, with or scarce vascularity (color score 1 and 2, respectively) [13]. More recently Van Holsbeke [14] revised the previous definition reporting that most endometriomas are premenopausal, 1-4 loculi, ground glass cysts with or without papillary projections, not vasculated. It is noteworthy that ovarian endometriomas may change their ultrasound appearance across different ages. Indeed as age increases, multiocular cysts and cysts with papillations and other solid components become more common, while the typical ground glass echogenicity of cyst fluid and tender mass on an ultrasound scan become less common [15]. These morphological changes are typically found during the fourth and fifth decades. This observation accounts for the confusion with other benign ovarian lesions or with ovarian malignancy [16]. In our case the prevalent solid component and the high and atypical vascularity (single dominant vessel with multiple branching) oriented towards a malignant lesion. Additional misleading factors were no history of pelvic endometriosis nor infertility. Moreover, ultrasound examination did not find any sign indicative or suspicious for endometriosis (i.e. uterine adenomyosis, kissing ovaries, ground glass ovarian cyst, pelvic adhesions with negative sliding signs) [17].

Notwithstanding the patient complained of pelvic pain which is a symptom often associated with endometriosis and a parameter introduced in LR1 (Logistic Regression) model of IOTA group to identify benign ovarian masses [18, 19]. The suspicious ultrasound features appear to stem from the microscopical analysis of ovarian adenomyoma as opposed to endometriomas. Indeed, several Authors depicted primary ovarian adenomyoma as a mass with central cavities lined by endometrial-type glands and stroma surrounded by well-formed and thick smooth muscles layers [20, 21]. In the present case, the final aspect of the left ovary mass was even more misleading due to the concomitant presence of endometriomas and a suspicious lesion contralaterally.

In 2018, a review of literature of extraterine adenomyoma was published by Paul [1] and our analysis supplements Paul’s review with the last published literature (Table 1). To the best of our knowledge only 42 cases of primary ovarian adenomyoma, including our case report, were published.

Analyzing the past medical history reported, we could classify each case report basing on pathogenesis: Mullerianosis’ theory was respected in 52% of cases (22/42), Belmaz’s theory (previous gynecological surgery) in 33% of cases (14/42), Cozzuto’s theory (coexistence of endometriosis) in 19% of cases (8/42), subcoelomic mesenchymal metaplasia’s theory (pelvic treatment response) in 9.5% of cases (4/42) and Rosai’s theory (genito-urinary anomalies association) in 2.4% of cases (1/42).

In nearly one-fifth of cases (8/42), no theory fits with the past medical history and the clinical presentation of each case reported. Due to the lack of data on this rare pathology, no theory is able to globally explain the pathogenesis of extra-uterine adenomyoma so far and more cases collection is needed.

Analyzing the characteristic of extrauterine adenomyoma, abdominopelvic pain is the most common clinical sign at presentation. Endometriosis was reported in the medical history of eleven out of forty-two patients (26%), substantially according to the previous literature review [22] in which endometriotic cyst were identified in the residual ovarian parenchyma of overall 21% of cases. Interesting, slightly more than half of patients (52%) had a previous history of gynaecological surgery for benign pathologies such as hysterectomy, myomectomy or ovarian cystectomy.

Surgical management was the treatment approach in all cases of extra-uterine adenomyomas but only in 2 cases out of 42 a diagnosis of extra-uterine adenomyoma was correctly suspected in the preoperative phase by imaging. Ultrasonography was the most common imaging modality adopted as single diagnostic procedure (66% of the cases, 28/42); more than one radiological staging technique (such as US, CT and MRI) was used in 50% of the cases (21/42).

In sixteen cases out of 42 a preoperative diagnosis was postulated, according to radiological findings or preoperative biopsies: malignancies in 7/16, ovarian thecoma/fibroma in 1/16, ovarian mass torsion in 1/16, myoma in 2/16, endometrioma in 2/16, serous cystadenoma in 1/16, leiomyomatosis peritonei/carcinomatosis in 1/16, and inguinal adenopathy in 1/16. Preoperative biopsies were performed in two cases, reporting extrauterine adenomyoma in one case and a suspect of adenomyosis versus endometriosis in the other one.

Including our presented case, 4 cases (9.7%) were associated with malignancy. Torres et al. [44] reported clear cell adenocarcinoma in a case of broad ligament adenomyoma. Ullm et al. [45] reported focal endometrioid adenocarcinoma in extrauterine endometrioma (round ligament) with concurrent stage 1 uterine endometrioid adenocarcinoma. Rahilly et al. [23] reported a concurrent occurrence of ovarian adenomyoma with ovarian endometrioid carcinoma and uterine endometrial cancer.
Table 1. Description of extrauterine adenomyomas. RIF- Right iliac fossa, TAH with BSO- Total abdominal hysterectomy with bilateral salpingo-oophorectomy, HRT-Hormone replacement therapy, CT-Computerized tomography, USG-Ultrasoundography, IVP-Intravenous pyelography, MRI-Magnetic resonance imaging, IVU-Intravenous urography, TLH with BSO-Total laparoscopic hysterectomy with bilateral salpingo-oophorectomy, PID-Pelvic inflammatory disease, LSO-Left salpingo-oophorectomy, RSO- Right salpingo-oophorectomy, DUB- Dysfunctional uterine bleeding, GnRH- Gonadotropin releasing hormone, SCH-Supracervical hysterectomy, C- Cozzutto’s theory, R- Rosai’s theory, S- sub-coelomic mesenchymal metaplasia, M-mullerianosis’s theory, B- Belmarez’ theory. Courtesy of Paul et al.

| Sr.n | Study (Year) | Size and location | Age | Past history | Presenting complaints | Imaging modalities | Suspected pre-operative diagnosis | Surgical intervention | Pathogenic Theory |
|------|--------------|-------------------|-----|--------------|-----------------------|-------------------|---------------------------------|----------------------|------------------|
| 1    | Rahilly et al. [23] | 5 cm, right ovary | 38  |  | RIF and pelvic pain | IVP | TAH with BSO | - | |
| 2    | Horie et al. [24] | 14 × 11 cm, small bowel mesentery | 59  |  | Lower abdomen mass | not reported | Surgical excision | M | |
| 3    | Redman et al. [25] | 5 cm, pararectal | 50  |  | TAH with BSO + HRT | Dysuria, suprapubic and pelvic pain | CT, USG, IVP | Excision + left ureteric stenting | B, M | |
| 4    | Bayar et al. [26] | 7.5 cm, left ovary | 38  |  | Gonaladotropin treatment | Infertility and pelvic pain | USG | Laparoscopic excision | - | |
| 5    | Choudhrie et al. [27] | 0.8 cm, left ovarian ligament | 57  |  | Lump lower abdomen and pelvic pain | USG, IVU | TAH with BSO | M | |
| 6    | Kim et al. [28] | 10.5 × 9.5 cm, pararectal | 42  |  | Lower abdominal pain | CT | Surgical excision | M | |
| 7    | Menn et al. [29] | 6 × 4 cm, right broad ligament | 37  |  | Myomeotomy and polypectomy | Right quadrant pain and intermenstrual spotting | USG, MRI | TAH | B | |
| 8    | Kaufman et al. [30] | 7 × 5 cm, right pelvic wall | 39  | Subfertility, PID | Dysmenorrhea, pain and menorrhagia | USG, CT | Laparoscopic excision | R | |
| 9    | Kaufman et al. | 10.5 × 9 cm, right pelvic wall | 57  | | RSO, TAH + LSO for wall endometriosis + HRT | RIF pain, suprapubic pain and backache | USG, CT, IVP | Laparoscopic excision + oral medroxyprogesterone | M, C, S | |
| 10   | Stewart et al. [31] | 6 × 4.5 cm, left paravesicular mass | 40  |  | TAH for DUB | Left iliac fossa pain | USG | Laparoscopic excision | - | |
| 11   | Stewart et al. | 6.3 × 4 cm, right parametrial mass | 65  | PID, breast cancer | Pelvic mass | USG | Hysterectomy with BSO with mass excision | - | |
| 12   | Carinelli et al. [32] | 10 cm sigmoid, 6 cm pelvic, 4 cm ileal, 1 cm paraileal and paravesical | 46  |  | Myomeotomy | Abdominal pain and constipation | USG, CT | Excision, hysterectomy with partial colectomy and Meckel diverticulum resection + GnRH agonist | M, B | |
| 13   | Carinelli et al. | 3 cm sigmoid, 3.5 cm right ovary endometriosis | 39  |  | Left ovariectomy for ovary endometriosis | Dysmenorrhea, chronic abdominopelvic pain | USG, CT, MRI | Laparoscopic excision. Partial colectomy with colostomy 7 days later + GnRH agonist for relapse | M, C, B | |
| 14   | Liang et al. [33] | 4 cm, left broad ligament | 17  |  | Mesosalpinx cystectomy | Dysmenorrhea and pelvic pain | USG, CT | Excision | - | |
| 15   | Sinodja et al. [34] | 5.5 × 5.3 cm, right ovarian ligament | 56  |  | Dyusiria, lower abdominal pain, vaginal bleeding | USG, IVP | TAH with BSO | - | |
| 16   | Moon et al. [35] | 7 × 6 cm, pararectal | 41  | SCH and right salpingectomy | USG, MRI | Excision and LSO | M, B | |
| 17   | Seki et al. [36] | 3.8 × 2 cm, left inguinal region | 44  |  | Left oophorectomy, Endometriosis | Abdominal pain | USG, MRI | Surgical excision | M | |
| 18   | Takeda et al. [37] | 3.8 × 3.7 cm, left ovarian ligament | 39  |  | Pain lower abdomen | CT, MRI, IVP | Laparoscopic excision | - | |
| 19   | Moghadamfalahi et al. [38] | 6 cm, pararectal; 7.5 cm, upper abdomen | 39  |  | SCH, cervical myomeotomy, endometriosis | Abdominal pain and rectal bleeding | CT | Surgical Excision | M, C | |
| 20   | Carvalho et al. [39] | Few mm to 50 mm, pelvic and abdominal peritoneum and omentum, left ovary | 32  |  | Hysteroscopic myomeotomy | USG, CT, MRI | Excision + Goserelin + Anastrazole | M, S | |

(continued on next page)
| Sr.n | Study (Year) | Size and location | Age | Past history | Presenting complaints | Imaging modalities | Suspected pre-operative diagnosis | Surgical intervention | Pathogenic Theory |
|------|--------------|-------------------|-----|--------------|-----------------------|-------------------|---------------------------------|----------------------|-------------------|
| 21   | Carvalho et al. Case 2 | Few mm to 20 mm, pelvic and abdominal peritoneum and omentum | 41 | | Dysmenorrhea and pelvic pain, proctalgia | | LSO with partial excision of nodules + Medroxy progesterone acetate | | M, S |
| 22   | Kim et al. [21] | 2 × 1.5 cm, appendix | 46 | | Supracervical hysterectomy | USG, CT | Surgical excision | | B |
| 23   | Huanwen et al. [40] | 3.6 × 2.6 cm, liver | 29 | | Myomectomy | USG, CT | Surgical excision | | B, M |
| 24   | Bulut et al. [41] | 5–10 cm, bilateral broad ligament, ectopic adrenal tissue | 56 | | Menorrhagia and pelvic pain | USG, MRI | Large necrotic leiomyoma without an exclusion of malignancy | TAH with BSO and excision of intraligamentary masses | M |
| 25   | Na et al. [42] | Caecum, descending colon and mesocolon | 39 | | Total hysterectomy with LSO, RSO for endometriosis | USG, CT | Ovarian endometriosis | Colonoscopic and laparoscopic resection | M, B, C |
| 26   | Ulm et al. [43] | 3 cm, right round ligament | 49 | | Metromenorrhagia | CT | Inguinal adenopathy | TAH with BSO and lymph node dissection | M |
| 27   | Torres et al. [44] | 4 cm, right broad ligament | 58 | | Post menopausal bleeding | USG, CT | Malignancy | Total Robotic hysterectomy with bilateral salpingo-oophorectomy | M |
| 28   | Sopha et al. [45] | 1.4 cm, liver | 47 | | RS0 for teratoma, SCH + HRT | CT | | Laparoscopic excision biopsy | S, B |
| 29   | Ko et al. [46] | 4 cm, right adnexa | 64 | | Recurrent thigh sarcoma | MRI | | Laparoscopic BSO | |
| 30   | He et al. [2] | 7 × 4.6 cm, left broad ligament | 43 | | Acute lower abdominal pain and hypomenorrhea | USG | Pelvic mass torsion | Surgical excision | M |
| 31   | Khurana et al. [47] | 13 × 9 cm, abdominopelvic | 47 | | Subtotal Hysterectomy for fibroids, bilateral oophorectomy for endometriosis | CT | Leiomyosarcoma | Surgical excision | C, B |
| 32   | Tandon et al. [48] | 6 × 4.5 cm, liver | 50 | | Laparoscopic hysterectomy with unilateral salpingectomy, endometriosis | CT | Cystic malignancy, metastatic disease or abscess (CT); endometriosis/adenomyosis (liver biopsy) | Surgical excision | M |
| 33   | Sampaio et al. [49] | 5 cm, abdominal wall | 70 | | Melanoma | CT | Leiomyoma (CT); extravasation adenomyoma (biopsy) | USG guided core biopsy | M |
| 34   | Goswami et al. [50] | 20 cm, right broad ligament | 46 | | Swelling and pain abdomen | USG, CT | Serous cystadenoma | TAH + BSO | M |
| 35   | Paul et al. [1] Case 1 | 10 cm, pararectal | 3 | | Laparoscopic right ovarian cystectomy 2 years back, endometriosis | USG | Heavy menstrual bleeding, mid-cycle pain and difficulty in initiating micturition | TLH, right oophorectomy, left ovarian cystectomy and excision of pararectal mass | C, B |
| 36   | Paul et al. Case 2 | 3 cm, right round ligament | 45 | | Laparoscopic left ovarian cystectomy 20 years back, SCH 12 yrs back and laparoscopic RS0 and left salpingectomy 4 years back, endometriosis | USG | Right lower quadrant pain | Laparoscopic left oophorectomy and excision of the round ligament mass | C, B |
| 37   | Paul et al. Case 3 | 6 cm, pararectal mass; 3 cm, ovarian mass | 37 | | Laparoscopic myomectomy 5 years back, endometriosis | USG | Subfertility, intermenstrual spotting, dysmenorrhea, constipation | Laparoscopic excision and left ovarian cystectomy | C |
Table 1 (continued)

| Surgical pre-operative | Pathogenic Theory |
|------------------------|-------------------|
| Total abdominal hysterectomy, B | Endometriosis |
| Laparoscopic salpingo-oophorectomy, B | Endometriosis |
| Left salpingectomy, right salpingo-oophorectomy, B | Endometriosis |
| Peritoneal dialysis, tubal salpingo-oophorectomy, B | Endometriosis |
| Peritoneal dialysis, tubal salpingo-oophorectomy, B | Endometriosis |

4. Conclusion

Extrauterine adenomyoma is still a major challenge. The data available so far bring out the difficulties to correctly diagnose this rare entity preoperatively, due to the lack of a typical ultrasonographic pattern of presentation. This type of ovarian lesion may appear in middle aged women with no previous history of pelvic pain suggestive for endometriosis. The case herein presented shed light on the possibility that ovarian adenomyoma associated with endometriotic cysts may resemble the ultrasound features of ovarian malignancy according to validated IOTA models. The lack of knowledge of this rare entity may eventually lead to unnecessary diagnostic procedures and improper surgical approach.

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