

A Single-Centre Experience on the Management of Adenosarcoma: A Successful Report of an Integrated Medical and Surgical Approach

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Margherita Nannini¹ , Giulia Dondi², Donatella Santini³,
Antonio De Leo³, Angelo Paolo Dei Tos^{4,5}, Claudio Zamagni⁶,
Maristella Saponara¹ , Lidia Gatto¹, Concetta Nigro¹, Paola Bertaccini⁷,
Maurizio Zompatori⁷, Pierandrea De Iaco², Anna Myriam Perrone^{2*}
and Maria Abbondanza Pantaleo^{1,8*}

¹Department of Specialized, Experimental and Diagnostic Medicine, S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy. ²Gynecologic Oncology Unit, S. Orsola-Malpighi Hospital, Bologna, Italy. ³Pathology Unit, S. Orsola-Malpighi Hospital, Bologna, Italy. ⁴Department of Pathology, Azienda ULSS 2 Marca Trevigiana, Treviso, Italy. ⁵Department of Medicine, School of Medicine, University of Padua, Padua, Italy. ⁶SSD Oncologia Medica "Addarii," S. Orsola-Malpighi Hospital, Bologna, Italy. ⁷Radiology Unit, Cardio-Thoracic-Vascular Department, S. Orsola-Malpighi University Hospital, Bologna, Italy. ⁸"Giorgio Prodi" Cancer Research Center, University of Bologna, Bologna, Italy.

ABSTRACT: Adenosarcomas are the rarest form of uterine sarcomas, and clinical experience with their management is still limited. Here, we reported 7 patients with uterine adenosarcoma referred to our institution, focusing on main pathologic features, their medical history, and long-term follow-up. Among these patients, we provided a detailed description of the medical history of a 49-year-old woman with advanced uterine adenosarcoma with sarcomatous overgrowth who presented a brilliant radiologic and pathologic response after 3 cycles of epirubicin and ifosfamide, ultimately achieving an extraordinary long-term outcome through an integrated surgical and medical approach. Our single-centre experience would suggest that aggressive uterine adenosarcomas with sarcomatous overgrowth are sensitive to standard epirubicin and ifosfamide and that an integrated approach, both medical and surgical, could be considered in clinical practice, again emphasizing the relevant role of multidisciplinary management for this extremely rare disease.

KEYWORDS: Adenosarcoma, epirubicin and ifosfamide, multidisciplinary management, sarcomatous overgrowth, endometriosis, biphasic tumours

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CORRESPONDING AUTHOR: Margherita Nannini, Department of Specialized, Experimental and Diagnostic Medicine, S. Orsola-Malpighi Hospital, University of Bologna, Via Massarenti 9, 40138 Bologna, Italy. Email: margherita.nannini@unibo.it

Background

Adenosarcomas are the rarest form of uterine sarcomas, accounting for approximately 5% of all uterine sarcomas and having a peak incidence in the fifth to sixth decades.¹ Most adenosarcomas arise from the uterus, but they can also originate in the ovaries and, more rarely, in the cervix, vagina, fallopian tubes, and omentum.^{1,2} Adenosarcomas are biphasic tumours and are typically characterized by a benign glandular epithelial component and a malignant mesenchymal component.^{3,4} Even if in most cases the mesenchymal component is low grade, in approximately 10% to 25% of rhabdomyoblasts, sex cord-like stromal, chondrosarcoma, liposarcoma, or smooth muscle-derived elements have been described.⁵ The presence of a sarcomatous overgrowth defined as pure sarcoma comprising more than 25% of the tumour is widely recognized as the most significant prognostic marker in adenosarcoma, and its frequency increases with the increasing stage of disease.^{6–10}

* Both are co-last authors.

Adenosarcomas are most commonly seen in conjunction with extra-ovarian endometriosis, but a definitive causal link has not yet been established.¹¹ DNA damage resulting from persistent oxidative stress induced by endometriosis-dependent haemorrhage has been suggested as a possible cause.¹² Additional potential risk factors for adenosarcoma include previous pelvic irradiation, prolonged oestrogen exposure, and exposure to other selective oestrogen receptor (ER) modulators.¹

Total hysterectomy is the mainstay of treatment for localized uterine adenosarcoma, whereas the role of bilateral salpingo-oophorectomy in the case of uterine and cervical adenosarcoma is still debated.¹³ Although ovarian metastases are rare, removal of the ovaries could be of potential benefit to patients, given the frequent positivity of oestrogen and progesterone receptors (PRs) in adenosarcoma. However, that benefit should be weighed against the age of the patient and the cost of surgical menopause.¹³ Approximately one-third to one-half of adenosarcoma patients will develop recurrences over a period



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of 10 years.¹ Likewise, the role of chemotherapy in this disease, supported by only small retrospective series and case reports, is still not well defined, and its place in an integrative approach to surgical cytoreduction is still questioned.^{6,14–20}

We report here a case series of adenosarcoma referred to our institution from 2009, focusing on surgical and medical treatment, pathologic features, and outcome.

Patients and Methods

We performed a retrospective analysis of all patients diagnosed with uterine adenosarcoma who received surgical and medical treatment at S. Orsola-Malpighi Hospital of Bologna. Patients were identified from a prospectively maintained institutional database. We excluded patients presenting only for consultation. All medical records were reviewed for age at diagnosis, sites of metastatic disease, surgical procedures performed, tumour grade, and other pathologic risk factors, including deep myometrial invasion, the presence of sarcomatous overgrowth, and the type of medical treatments received. This study was approved by the local institutional ethical committee of S. Orsola-Malpighi Hospital (approval number: 164/2017/O/Oss).

Results

From June 2005 to November 2014, 7 patients were diagnosed with uterine adenosarcoma at our institution. All patient characteristics are listed in Table 1. Median age at diagnosis was 53.5 years (range 38–76 years). Primary tumour site was the uterus in 5 patients and the ovary in 2 patients. Six patients presented with a localized disease, whereas only 1 presented with advanced disease (peritoneal involvement) at diagnosis. Lymph node status was negative in all 5 patients who underwent lymphadenectomy. For primary surgery, laparotomy was performed in 6 cases and laparoscopy in only 1 case (#6). Six patients underwent total hysterectomy and bilateral salpingo-oophorectomy, and 1 patient (#3) underwent hysterectomy and right salpingo-oophorectomy because left salpingo-oophorectomy had been already performed in the past for benign disease. Two patients underwent pelvic lymphadenectomy, whereas 2 other patients underwent both pelvic and para-aortic lymphadenectomy. Lymph node status was negative in all 4 cases. Omentectomy was performed in 4 cases, peritoneal washing in 4 cases, peritoneal random biopsies in 3 cases, and pelvic peritonectomy in 2 cases (in case #3 due to pelvic adhesions for endometriosis and in case #7 because of neoplastic infiltration). Appendicectomy was performed only in 1 case (#3) due to the presence of pelvic adhesions for endometriosis.

Intestinal resection was performed in 2 cases; both required an ileal resection with a latero-lateral anastomosis and a resection of the sigmoid colon with an end-to-end anastomosis due to the presence of severe pelvic and abdominal adhesions for endometriosis in case #1 and for previous surgery and neoadjuvant chemotherapy in case #7. Both patients needed a protective ileostomy, which was closed 1 year and 4 months after surgery,

respectively. Except for case #7, who presented wide peritoneal involvement, surgical margins were negative in all cases.

Concerning pathologic features, 4 patients had low-grade tumours, whereas 3 patients had high-grade tumours, defined as the presence of sarcomatous overgrowth associated with morphologically “high-grade” stromal elements. Sarcomatous overgrowth, defined as the presence of pure sarcoma (without any epithelial component) comprising at least 25% of the tumour, was present in 3 cases (cases #2, #5, and #7). Among the patients with localized uterine adenosarcoma, myometrial invasion was assigned a status of M1 (infiltration of the inner half of myometrium) in 2 cases and M2 (infiltration of the outer half of myometrium) in 3 cases. No cases presented heterogeneous elements or rhabdomyosarcomatous differentiation.

For the medical history, 5 patients presented with abnormal uterine bleeding, whereas in 2 patients, a suspected ovarian lesion was found during routine gynaecologic control. None of the patients received radiotherapy; 1 patient received adjuvant anastrozole for 18 months, and 1 patient (case #2), due to high grade and the presence of sarcomatous overgrowth, received adjuvant doxorubicin for 4 cycles.

At the last follow-up, all patients were alive without recurrence, with a follow-up ranging from 32+ to 91+ months. Except for case #7, who presented with advanced disease at the time of diagnosis, only 1 patient (case #2) developed a lung recurrence after 26 months from the primary surgery and thus underwent pulmonary atypical resection.

Herein, among all these patients, we provide a detailed description of the medical history of case #7 because of the interest for clinicians.

Case #7 history

In November 2013, a 49-year-old woman came to the gynaecologic emergency room for acute abdominal pain. A computed tomographic (CT) scan showed a huge pelvic mass of 14 cm × 10 cm × 13 cm with prominent colliquative aspects (Figure 1A to C). She underwent emergency laparotomy for an acute abdomen: surgical abdominal exploration revealed a 20-cm, easily bleeding mass that adhered strictly to the pelvic peritoneum, sigma-rectum, ileal loops, and omentum. Haemoperitoneum was present. The mass apparently was not connected to the uterus, which appeared of greater volume, or to the ovaries. Simple hysterectomy, peritoneal biopsies, asportation of the pelvic mass, and of the pelvic peritoneum, which was involved in the neoplastic process, were then performed. There was no macroscopic disease at the end of surgery (R0).

At macroscopic examination, the entire uterine cavity was filled by a polypoid mass of 3.5 cm in diameter. Microscopic examination showed a biphasic tumour composed of benign epithelial elements and a sarcomatous stroma. At low power magnification, the tumour had a “phyllodes-like” architecture with leaf-like projections lined by a variety of benign Müllerian-type

Table 1. Patients' characteristics.

| PATIENT | #1 | #2 | #3 | #4 | #5 | #6 | #7 |
|---------------------------------|--|-------------------------------------|---|----------------------------|---------------------------------------|----------------------|--|
| <i>Clinical data</i> | | | | | | | |
| Age | 38 | 50 | 57 | 76 | 66 | 39 | 49 |
| Year of diagnosis | 2014 | 2014 | 2009 | 2013 | 2005 | 2014 | 2013 |
| Primary site | Ovary | Uterus | Ovary | Uterus | Uterus | Uterus | Uterus |
| Distant metastases at diagnosis | No | No | No | No | No | No | Yes |
| Lymph node status | Negative | Negative | NA | Negative | NA | Negative | Negative |
| Peritoneal involvement | Absent | Absent | Absent | Absent | Absent | Absent | Present |
| <i>Surgical data</i> | | | | | | | |
| Type of surgery | Laparotomy: HBSO, ileal resection, resection of sigmoid colon, ileostomy, PLND, PALND, omentectomy, WP | Laparotomy: HBSO, PLND, omentectomy | Laparotomy: hysterectomy and right salpingo-oophorectomy Pelvic peritonectomy appendicectomy, omentectomy, peritoneal biopsies, WP | Laparotomy: HBSO, PLND, WP | Laparotomy: HBSO, peritoneal biopsies | Laparoscopy HBSO, WP | Laparotomy: TAH, pelvic mass asportation, pelvic peritonectomy Laparotomy: BSO, omentectomy, PLND, PALND, peritoneal biopsies, ileal resection, resection of sigmoid colon, ileostomy |
| Surgical margins status | NED | NED | NED | NED | NED | NED | Macroscopic NED |
| <i>Pathologic data</i> | | | | | | | |
| Tumour size, cm | NA | NA | 12 | 10 | 8.5 | NA | 3.5 |
| Myometrial invasion | Not applicable | M2 | Not applicable | M1 | M1 | M2 | M2 |
| Lymphovascular invasion | No | No | No | No | No | No | No |
| ER/PR status | Positive | Negative | NA | NA | NA | NA | Positive (only on the primary) |
| Grade | Low | High | Low | Low | High | Low | High |

(Continued)

Table 1. (Continued)

| PATIENT | #1 | #2 | #3 | #4 | #5 | #6 | #7 |
|----------------------------------|-----------------------|---|-----------------------|-----------------------|-----------------------|-----------------------|---|
| Sarcomatous overgrowth | Absent | Present | Absent | Absent | Present | Absent | Present |
| Mitotic activity | <10/10 HPF | >10/10 HPF | <10/10 HPF | <10/10 HPF | >10/10 HPF | <10/10 HPF | >10/10 HPF |
| Necrosis | No | No | No | No | Yes | No | Yes |
| FIGO stage | IIIC | IC | IA | IB | IB | IC | IIIB |
| <i>Medical history</i> | | | | | | | |
| Radiotherapy | No | No | No | No | No | No | No |
| Hormone therapy | Anastrozole | No | No | No | No | No | No |
| Adjuvant chemotherapy | No | Doxorubicin (75mg/m ²) | No | No | No | No | No |
| Chemotherapy | No | Gemcitabine (900 mg/m ²) and docetaxel (75mg/m ²) | No | No | No | No | Epirubicin (60 mg/m ² d1,2)/ifosfamide (1800 mg/m ² d1-5) |
| Recurrence | No | Yes | No | No | No | No | Yes |
| Site of recurrence | — | Lung | — | — | — | — | Abdomen |
| Surgery of relapse | No | Yes | No | No | No | No | Yes (twice) |
| <i>Follow-up data</i> | | | | | | | |
| Disease status at last follow-up | Alive without disease | Alive without disease | Alive without disease | Alive without disease | Alive without disease | Alive without disease | Alive without disease |
| Follow-up duration, mo | 33 | 32 | 91 | 55 | 84 | 40 | 44 |

Abbreviations: ER, oestrogen receptor; HBSO, hysterectomy and bilateral salpingo-oophorectomy; NA, not available; NED, no evidence of disease; PALND, para-aortic lymphadenectomy; PLND, pelvic lymphadenectomy; PR, progesterone receptor; TAH, total abdominal hysterectomy; WP, peritoneal washing.

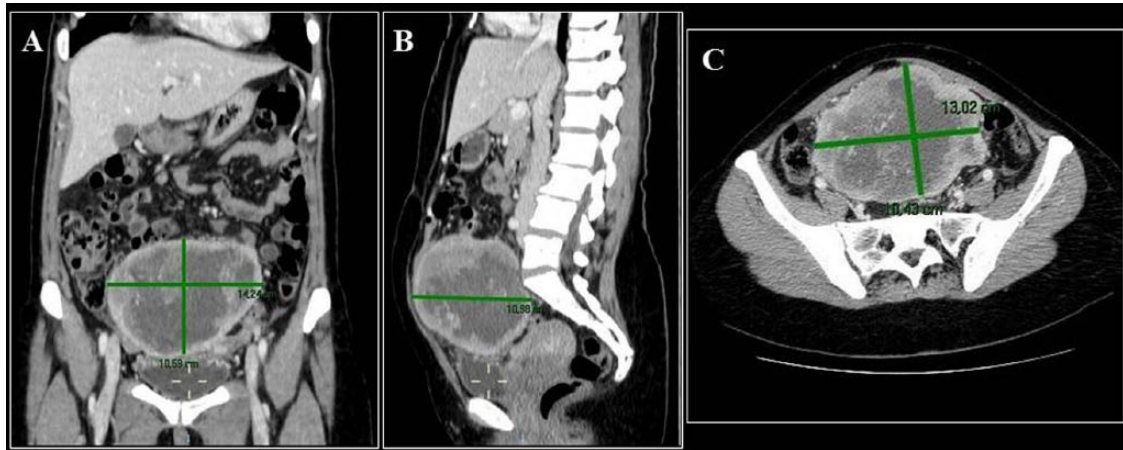


Figure 1. (A) Coronal sequence, (B) axial sequence, (C) lateral sequence (November 2013): A computed tomographic scan revealed a huge pelvic mass of 14 cm × 10 cm × 13 cm with prominent colliquative aspects and heterogeneous contrast enhancement uptake.

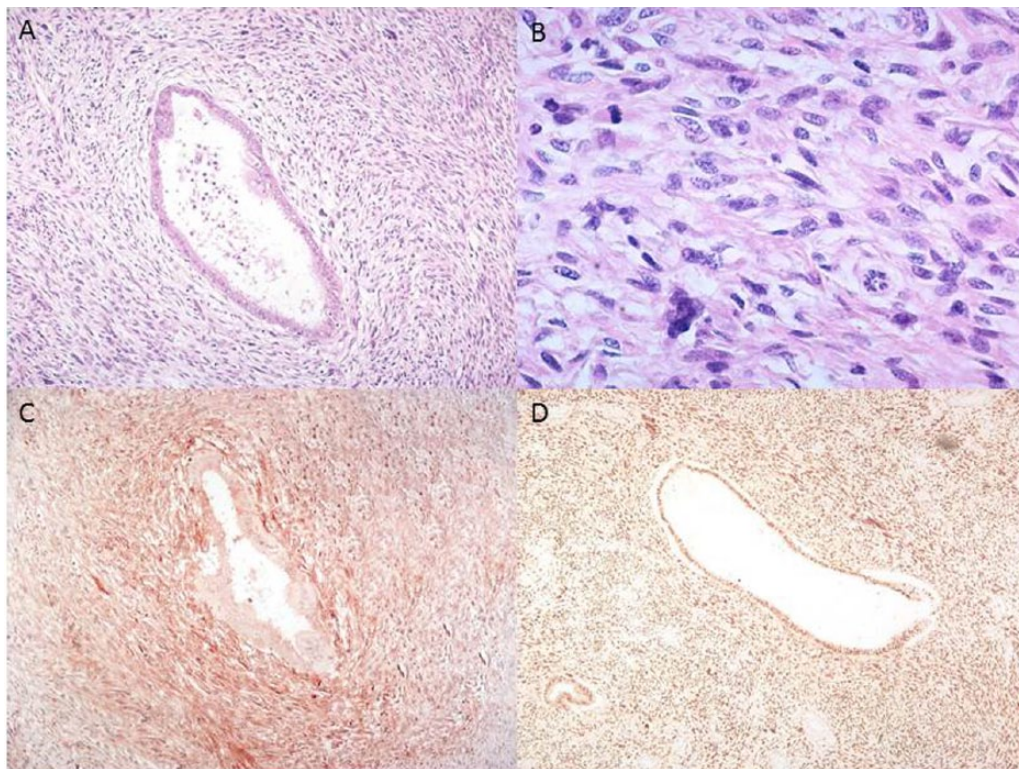


Figure 2. (A) Adenosarcoma with periglandular stromal condensation (Hematoxylin and Eosin, 100 x), (B) sarcomatous overgrowth with significant stromal pleomorphism (Hematoxylin and Eosin, 400 x), (C) the tumour cells show a heterogeneous immunoreactivity for CD10 (100 x), and (D) diffuse positivity for oestrogen receptor (100 x).

epithelia. The stromal component arose from the endometrial stroma and was admixed with areas of pleomorphic cells with high mitotic figures (up to 15/10HPF). Necrosis and haemorrhage were abundant. The tumour had invaded into the outer half of myometrium. These morphological features were all characteristic of adenosarcoma and were confirmed by an appropriate immunohistochemical panel. As is well known, in adenosarcomas the stromal component has an immunophenotype similar to that of a normal endometrial stroma expressing an ER, a PR, and CD10. In areas of high-grade sarcoma and of sarcomatous overgrowth, the mesenchymal component may lose the

expression of the cell differentiation markers. In the present case, immunohistochemistry revealed a multifocal expression of CD10 in the stromal compartment highlighting the typical periglandular cuffing. A strong positivity for ER and PR, both in the glandular and stromal components, was seen. Mesenchymal markers, such as smooth muscle actin, desmin, CD34 and cytokeratins, were negative. Immunohistochemical expression of mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2) was preserved (Figure 2A to D).

The subsequent CT scan evaluation showed mesenteric multiple hyperdense solid lesions of 23 mm, 33 mm, and 20 mm in

diameter, respectively; these were suspected of being peritoneal implants, and they increased substantially and became confluent in a lobed mass after few weeks (Figure 3). Thus, in December 2013, a first-line treatment with epirubicin ($60\text{ mg/m}^2\text{ d1,2}$) and ifosfamide ($1800\text{ mg/m}^2\text{ d1-5}$) was started. After 1 cycle, the patient presented with an acute abdominal pain and positive Blumberg sign. An emergency CT scan revealed a prominent increase in the pelvic mass ($16\text{ cm} \times 10\text{ cm} \times 6\text{ cm}$ of diameter), with intra-lesional heterogeneous colliquative features and irregular and thick septa, suggestive of early radiologic response, according to Choi criteria (Figure 4A and B). She completed the planned treatment, and in January 2014, after 3 cycles, the CT scan evaluation showed a marked shrinkage of the pelvic mass ($8.6\text{ cm} \times 3.3\text{ cm} \times 3.3\text{ cm}$ in diameter), which was largely necrotic and had heterogeneous aspects, together with a relevant clinical benefit (Figure 5A and B). Therefore, in March 2014, she underwent laparotomy for suspected pelvic residual disease. Severe abdominal adhesions involving the ileal loops, ovaries, sigmoid colon, and bladder were found. The ovaries were of normal size but were involved in the neoplastic process, and the Douglas pouch was obliterated. The patient underwent bilateral

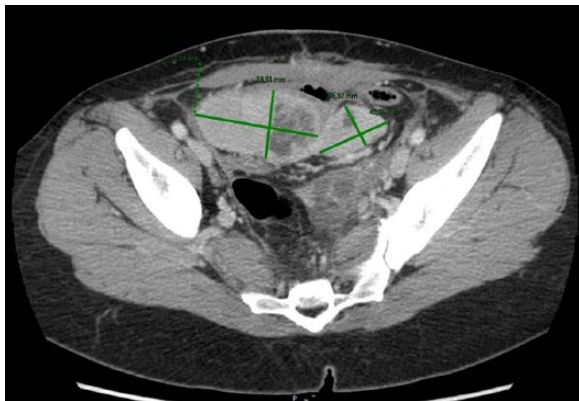


Figure 3. December 2013: A post-operative computed tomographic scan revealed multiple peritoneal implants, confluent in a lobated mass with colliquative aspects.

salpingo-oophorectomy, omentectomy, pelvic and para-aortic lymphadenectomy, and peritoneal biopsies. Ileal resection, latero-lateral ileal anastomosis, resection of the sigmoid colon, termino-terminal colorectal anastomosis, and protective ileostomy were performed. The residual disease was absent after the end of surgery. The histologic examination revealed a complete pathologic response, with no evidence of residual tumour and with an extensive hyalinization and fibrosis (constituting 100% of the lesion) associated with haemosiderin deposition, foamy macrophages, calcifications, and inflammation.

In June 2014, the patient underwent closure of the protective ileostomy without complications.

The subsequent clinical and instrumental follow-up was negative until March 2015, when a CT scan revealed a pelvic solid mass, $6\text{ cm} \times 3\text{ cm} \times 4\text{ cm}$ in diameter, suggestive of relapse (Figure 6A and B). Given the long disease-free interval and the single localization, we decided on the surgical approach. Therefore, the patient underwent a third laparotomy for the resection of the pelvic relapse, which was a nodule of approximately 5 cm connected to the ileal loops, bladder, and rectum. Adhesiolysis, ileal resection with latero-lateral ileal anastomosis, and resection of the pelvic nodule were performed. There was no residual disease at the end of surgery (R0). The histologic examination and immunohistochemical features confirmed an ileal localization of high-grade sarcoma compatible with a relapse of the sarcomatous component of the previous adenosarcoma (Figure 7A and B).

The patient continued the surveillance programme every 6 months, and the last CT scan performed in July was negative for disease relapse.

Discussion

Adenosarcomas are rare tumours with generally low malignant potential, except in cases with myometrial invasion, sarcomatous overgrowth, and lymphovascular invasion, conditions that are already recognized as the most important pathologic predictors of outcome.⁶⁻¹⁰ In addition to this clinical variability,

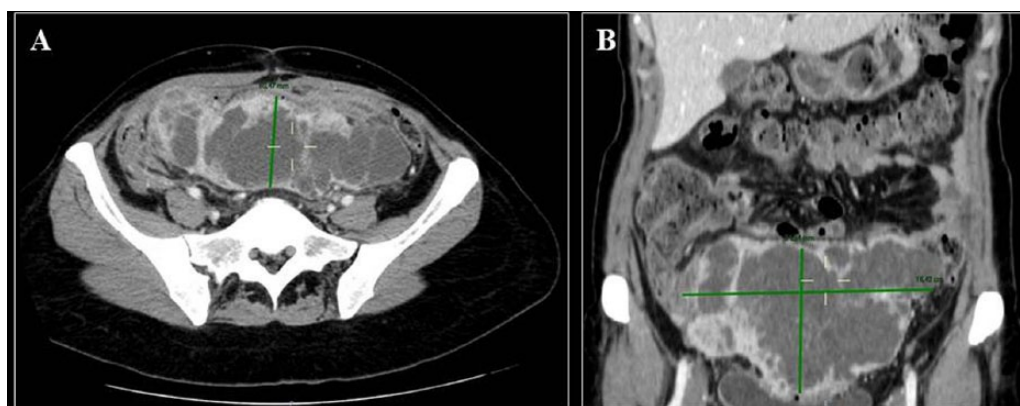


Figure 4. (A) Axial sequence, (B) coronal sequence (December 2013): A computed tomographic scan evaluation after 1 cycle of epirubicin and ifosfamide, performed earlier due to sudden onset of abdominal pain, showed a prominent increase in the pelvic mass ($16\text{ cm} \times 10\text{ cm} \times 6\text{ cm}$ in diameter), with intra-lesional heterogeneous colliquative features and irregular and thick septa.

the molecular landscape of adenosarcoma seems to be heterogeneous, with a divergence between adenosarcoma with and without sarcomatous overgrowth or between high-grade and low-grade adenosarcoma, according to the presence of a high-grade stromal component.^{21–23}

In the largest series of patients with adenosarcoma, secondary cytoreduction has been shown to favourably impact the median overall survival and median survival time from the date of recurrence, with values of 58.4 and 16.1 months, respectively.⁶ However, the role to be played by medical treatment in an integrative approach to cytoreduction is still a question, given the rarity of this subtype of sarcoma, together with its known biological and clinical variability. In fact, the role of medical

treatment for patients with advanced or recurrent disease is still undefined and only supported by limited reports.^{6,14–20}

Currently, given the extreme rarity of this of this subtype of sarcoma, specific clinical guidelines are lacking, and the management of adenosarcoma does not differ from that of all other gynaecologic sarcomas.²⁴

We are aware that our case series is too limited to provide a definitive suggestion on adenosarcoma clinical management. However, among our 7 cases of adenosarcoma, we have provided a detailed description of the medical history of a 49-year-old female patient with advanced uterine adenosarcoma with sarcomatous overgrowth, who presented a brilliant radiologic and pathologic response after 3 cycles of epirubicin and ifosfamide, achieving an extraordinary long-term outcome by an integrated surgical and medical approach.

This clinical case, despite its singularity due to the rarity of this disease, could be a relevant report for clinical practice for several reasons. First, it showed the efficacy of standard anthracycline-based therapy for aggressive uterine adenosarcoma with sarcomatous overgrowth, in line with the small amount of data found in the literature. This likely may be due to the presence of the sarcomatous overgrowth component that could confer more sensitivity to cytotoxic treatments.

Second, an integrated medical and surgical approach could be considered in clinical practice for advanced or recurrent adenosarcoma in selected cases, suggesting that multidisciplinary management may play a relevant role for this rare disease in the setting of recurrence. Third, the long survival of 44 months from the primary surgery and 27 months from the

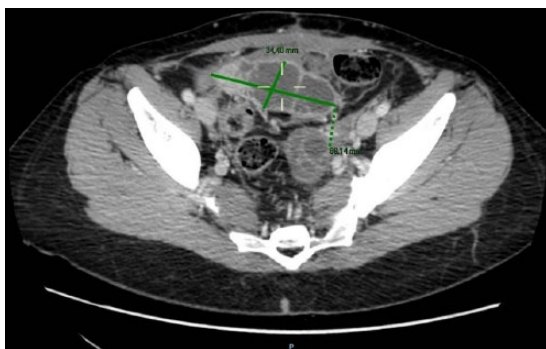


Figure 5. January 2014: A computed tomographic scan evaluation after 3 cycles of epirubicin and ifosfamide showed a marked shrinkage of the pelvic mass (8.6 cm × 3.3 cm × 3.3 cm in diameter), largely necrotic and with heterogeneous aspects (axial sequence).

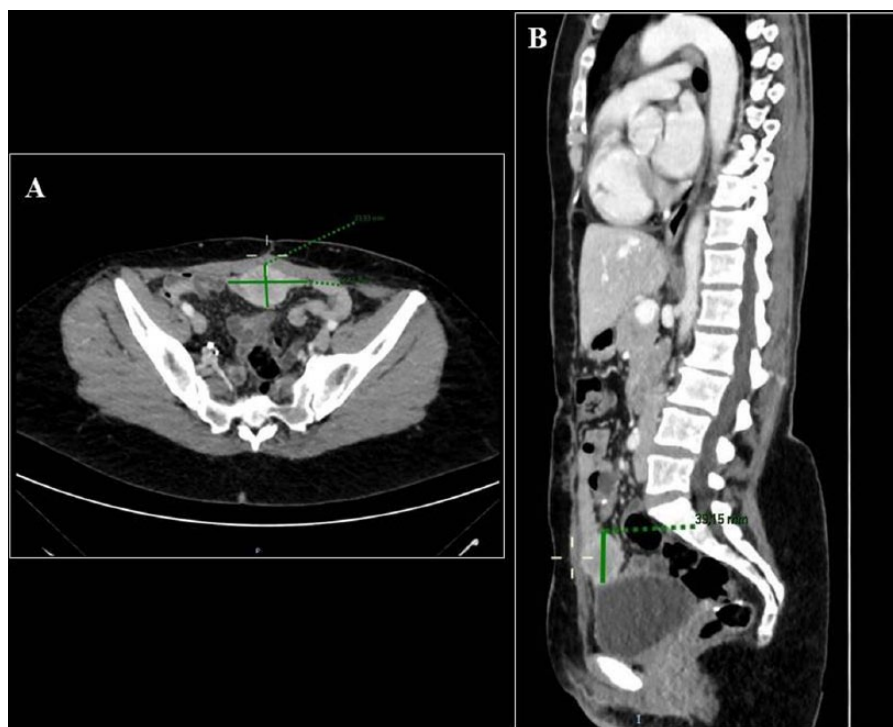


Figure 6. (A) Axial sequence, (B) lateral sequence (March 2015): During a regular surveillance programme, a computed tomographic scan evaluation showed a pelvic solid mass, 6 cm × 3 cm × 4 cm of diameter, suggestive of relapse.

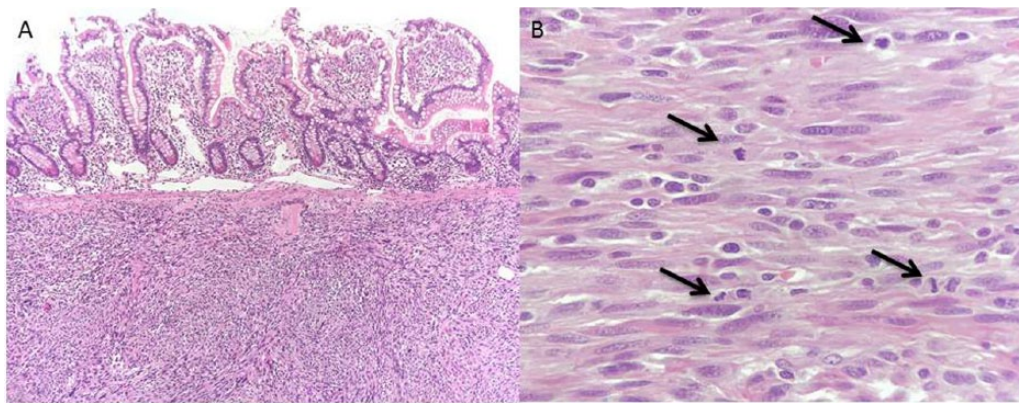


Figure 7. (A) March 2015: ileal relapse of high-grade sarcomatous component of adenosarcoma with high mitotic count (Hematoxylin and Eosin, 50 x), (B) magnification of the high mitotic count highlighted by black arrows (Hematoxylin and Eosin, 400 x).

date of secondary surgical cytoreduction in a patient with advanced uterine adenosarcoma deserves to be highlighted and suggests that, according to what has been reported by Carroll et al,⁶ primary and secondary cytoreduction can favourably impact on overall survival.

Moreover, it is interesting to emphasize the differential ER and PR statuses between primary tumour and peritoneal sites of disease, suggesting the existence of a biological heterogeneity within the tumour and a likely inverse correlation between ER and PR positive staining and the histologic evolution to sarcomatous overgrowth.²⁵

Finally, looking at our case series in full, 3 of the 7 patients had a medical history positive for endometriosis, and 1 had also undergone 2 consecutive in vitro fertilization-embryo transfers, and 1 patient had received tamoxifen for 9 years due to breast cancer, all of which suggested cause, in line with the data reported in the literature.^{26–34}

In conclusion, aggressive uterine adenosarcomas with sarcomatous overgrowth are sensitive to standard epirubicin and ifosfamide, and an integrated approach – medical and surgical – could be considered in clinical practice, again emphasizing the relevant role of multidisciplinary management for this extremely rare disease.

Author Contributions



MN: has made substantial contributions to conception of the study, and drafted the manuscript; GD: has provided surgical data, helped to draft and revised the manuscript; DS: has been involved in revising the manuscript critically for important intellectual content and have given final approval of the version to be published; ADL: has provided the pathological data; APDT: has contributed on pathological data; CZ: has been involved in revising the manuscript critically for important intellectual content and have given final approval of the version to be published; MS: has helped to draft and revised the manuscript; LG: has helped to draft and revised the manuscript; CN: has helped to draft and revised the manuscript; PB: has provided the radiological data; MZ: has been involved in revising the manuscript critically for important intellectual content and

have given final approval of the version to be published; PDI: has been involved in revising the manuscript critically for important intellectual content and have given final approval of the version to be published; Myriam AP: have made substantial contributions to conception of the study and drafted the manuscript; Maria AP: have made substantial contributions to conception of the study and drafted the manuscript.

Informed Consent Statement

The patient provided written informed consent.

ORCID iDs

Margherita Nannini  <https://orcid.org/0000-0002-2103-1960>
Maristella Saponara  <https://orcid.org/0000-0003-0715-171X>

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