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Müllerian adenosarcoma of the uterine cervix with sarcomatous overgrowth: A case report of aggressive disease in a young patient

David A. Morales F. [a,*], Monica L. Medina R. [a], Lina M. Trujillo [a], Maria I. Beltrán [b], Isabel C. Dulcey [b]

[a] Department of Gynecologic Oncology, National Cancer Institute of Colombia (INC), Bogotá D.C., Colombia
[b] Department of Pathologic Oncology, National Cancer Institute of Colombia (INC), Calle 1 # 9-85, Bogotá, Colombia

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ABSTRACT

INTRODUCTION: Müllerian adenosarcoma of the cervix with sarcomatous overgrowth and lymphovascular invasion is a rare and aggressive disease. We report a case of a young patient with Müllerian adenosarcoma with sarcomatous overgrowth in the uterine cervix and pelvic lymph node involvement. The patient received radical surgery but not adjuvant treatment, and the disease was aggressive with rapid relapse.
PRESENTATION OF CASE: A 39-year-old woman was diagnosed with Müllerian adenosarcoma of the cervix with sarcomatous overgrowth, International Federation of Gynecology and Obstetrics (FIGO) stage IB2. She underwent abdominal radical hysterectomy and resection of the left external iliac lymph nodes for suspected metastatic involvement detected during surgical exploration but undetected via imaging. She refused adjuvant treatment, and the disease recurred 8 months after primary oncologic surgery, with rapid local, regional, and bone relapse.
DISCUSSION: Our report suggests that sarcomatous overgrowth, a high mitotic index, a rhabdomyoblastic component, and lymphovascular compromise are risk factors for aggressive recurrence. Positron emission tomography-computed tomography (PET-CT) was used to identify relapse locations in addition to those detected via clinical examination of the vaginal vault. However, whether PET-CT is indicated for the initial detection of lymph node and bone metastases in FIGO stage IB tumors with surgical indication is unclear.
CONCLUSION: A young woman with Müllerian adenosarcoma of the cervix with sarcomatous overgrowth presenting the risk factors for its recurrence experienced a rapid relapse after receiving radical surgery but not adjuvant therapy. Control of this aggressive disease via sequential radiotherapy and chemotherapy are recommended.

1. Introduction

Müllerian adenosarcoma with sarcomatous overgrowth typically occurs in the uterine corpus, to a lesser extent in the ovaries, and rarely in the cervix. The average age at presentation is 60 years in uterine corpus cases and 41 years in cervical cases. Müllerian adenosarcomas are mixed tumors: they consist of an epithelial glandular component and a mesenchymal component, with the latter presenting at various stages of dedifferentiation and containing homologous or heterologous tissue. Herein we describe an interesting and unusual case of a Müllerian adenosarcoma with sarcomatous overgrowth in the cervix and pelvic lymph node involvement that was not detected via imaging. Abdominal radical hysterectomy was performed along with resection of the pelvic lymph nodes that were suspected for metastatic involvement during surgical exploration. The patient refused adjuvant treatment, and the disease aggressively recurred.

2. Presentation of case

A 39-year-old woman presented with a history of pelvic pain and bleeding over a 6-month period and a rapidly growing mass protruding through the uterine cervix. Based on the histopathology of a previous tumor biopsy, the final diagnosis was Müllerian adenosarcoma of the cervix with a heterologous component.

Thoracic computed tomography did not identify any lesions. Magnetic resonance imaging (MRI) of the abdomen and pelvis revealed a polypoid lesion with heterogeneous T2 signal intensity with hyperintense signal predominance originating in the left side of the cervix. The lesion measured $59 \times 64 \times 60\,mm$
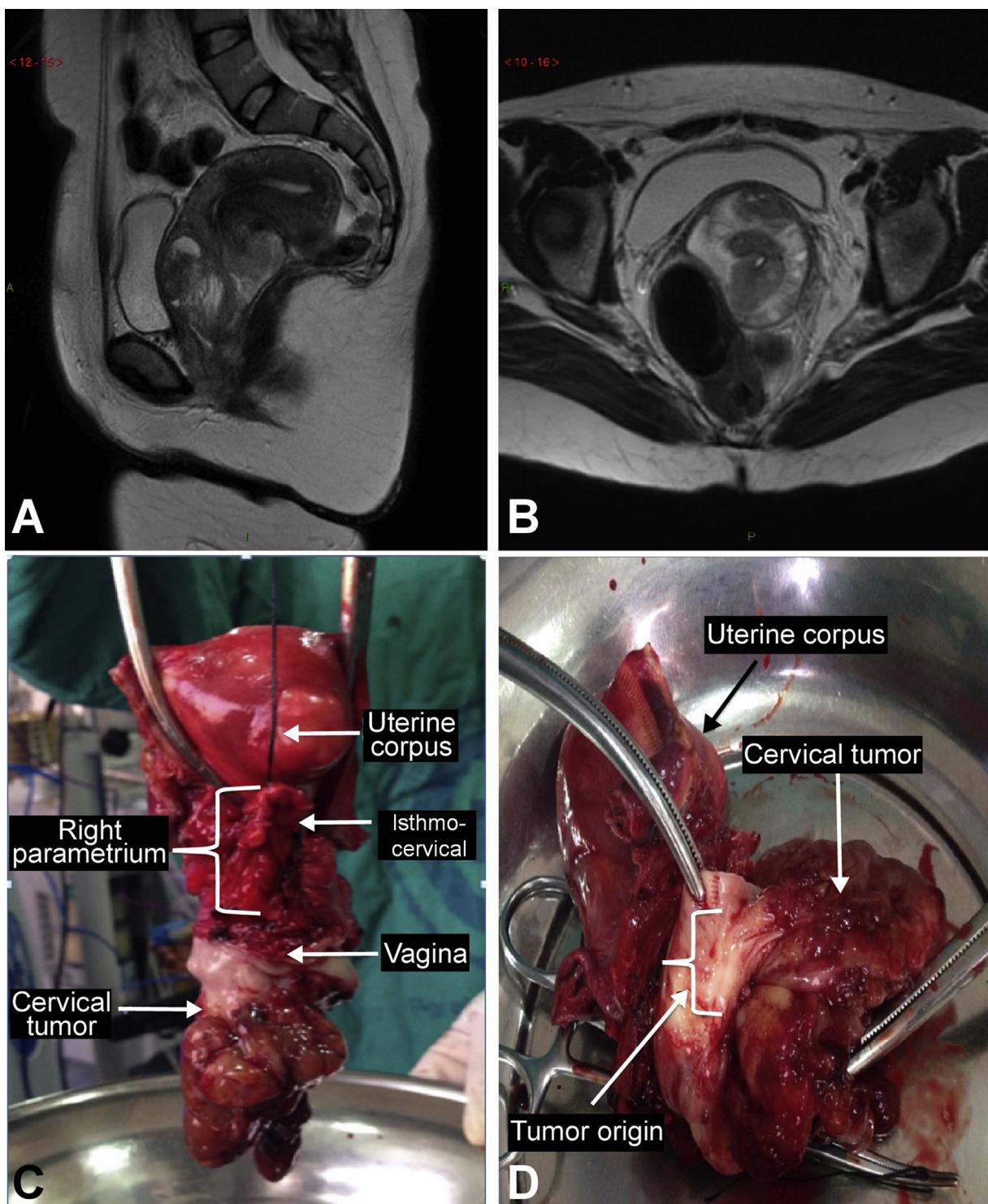
Fig. 1. (A) Magnetic resonance imaging (MRI) shows a normal endometrium and myometrium with a mass originating in the cervix. (B) MRI shows a cervical tumor without parametrial compromise. (C) A radical hysterectomy specimen. (D) Cervical tumor (7 cm) with a clear origin in the cervix.

(width × depth × length) and extended into and occupied the vaginal cavity (Fig. 1A and B). Retroperitoneal lymph nodes were not identified.

The patient was subsequently taken to surgery with a clinical preoperative diagnosis of Müllerian adenosarcoma of the cervix, International Federation of Gynecology and Obstetrics (FIGO) stage IB2. Abdominal radical hysterectomy was performed along with resection of the left external iliac lymph nodes that were suspected

for metastatic involvement during surgical exploration of the pelvic and para-aortic regions (Fig. 1C and D).

Histopathology revealed an exophytic, friable mass. Macroscopically, it appeared to originate in the cervical wall and protrude through the external cervical ostium, compromising the anterior and posterior aspects and the endocervical canal, with the uterine cavity free of lesions. Microscopically, the lesion was a Müllerian adenosarcoma of the cervix with stromal overgrowth greater than 25% and a heterologous component (cartilage and rhabdomy-
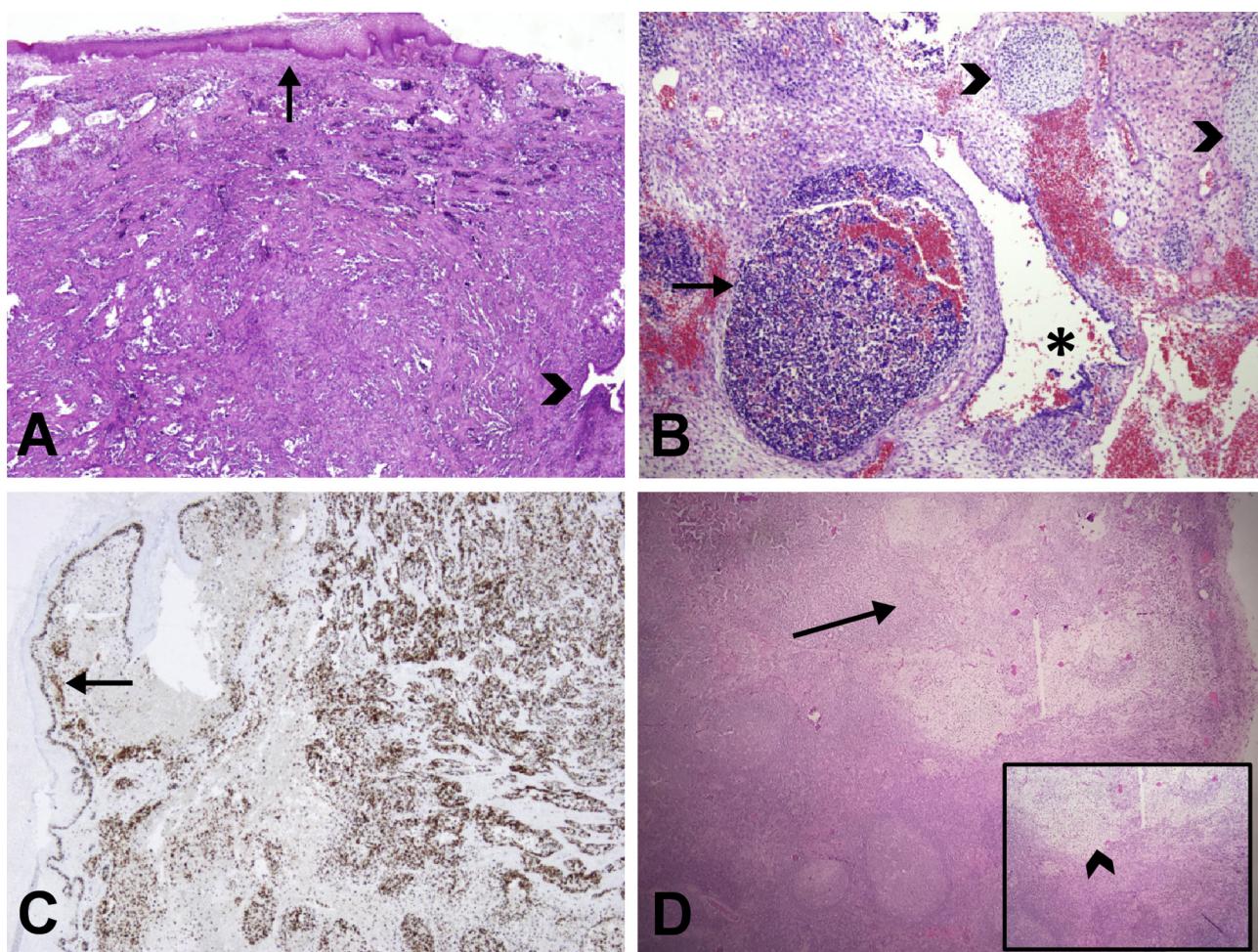
Fig. 2. (A) Cervical stroma highly infiltrated by the sarcoma. The exocervical (arrow) and endocervical (head of arrow) epithelia are histologically normal (20× magnification, hematoxylin & eosin). (B) Close-up of the areas of mesenchymal overgrowth (arrow) associated with the areas of cartilage in the heterologous component (head of arrow) and benign glands (asterisk) (20× magnification, hematoxylin & eosin). (C) The proliferation index as determined via Ki67 staining was 60%, with normal reactivity in the basal layer of the exocervix (arrow) (20× magnification, Ki67 immunostaining). (D) Lymph node metastasis at 4× (arrow) and 20× (arrowhead) magnification.

oblasts); the maximal tumor size was 7.5 cm in diameter (Fig. 2A and B).

The tumor exhibited CD10 focal positivity, S100 positivity in the cartilaginous component, myogenin positivity in the rhabdomyoblastic component, and cytokeratin cocktail and estrogen receptor positivity in the superficial epithelial and glandular components. The proliferation index as determined via Ki67 staining was 60% (Fig. 2C). Lymphovascular invasion was present; 1 left iliac lymph node displayed tumoral compromise (Fig. 2D), whereas parametrium and proliferative endometrium did not.

Adjuvant ifosfamide chemotherapy and pelvic radiotherapy plus high-dose intracavitary brachytherapy were recommended, but the patient refused owing to personal beliefs and having been asymptomatic after a successful postoperative course. She returned to our hospital 8 months after surgery with light bleeding and pelvic pain radiating to the lower right limb, for which we performed a complete physical exam and positron emission tomography-computed tomography (PET-CT) and MRI of the thoracic and lumbosacral spine. We observed local and regional tumor regrowth in the form of an exophytic mass 6 cm in diameter originating in the vaginal vault (Fig. 3A). There was also a conglomeration of right pelvic lymph nodes, each 7 cm in diameter. These lesions were visualized clearly via PET-CT, as was a metastatic lesion in the right pubic ramus (Fig. 3B, C and D).

To treat the patient's pelvic recurrence and pelvic bone metastasis, external pelvic radiation (conformational technique) was delivered to the surgical site and margins in fractions of 2 Gy/day up to 50 Gy/day (planning target volume 1), with posterior reinforcement over the nodal conglomeration and vaginal vault until the total dose reached 60 Gy. High-dose-rate intracavitary brachytherapy of 2.1 Gy was also administered. After receiving 2.3 Gy of external pelvic radiation, the patient was once again asymptomatic, with a significantly improved clinical status and a 95% reduction in vaginal tumor volume (Fig. 4A). Owing to the excellent pelvic clinical response and the high functional status of the patient (Eastern Cooperative Oncology Group 0), palliative chemotherapy consisting of ifosfamide and cisplatin was administered to manage the metastases.

MRI revealed osteolytic lesions with diffuse infiltration of the T11, T12, L1, and L2 vertebral bodies with a compression fracture of T12, left spinal infiltration, and medullary canal compromise (Fig. 4B and C). Hence, the patient received pelvic radiotherapy and conventional external radiotherapy at a total daily dose of 30 Gy in the thoracolumbar spine. The objectives of palliation were achieved, and there were no new signs of disease progression. A total of 21 months elapsed between surgery and the writing of this report.

Table 1
Sequentially 1995–2016 cases of Müllerian adenosarcoma of the cervix with sarcomatous overgrowth and other risk factors.

Reference	Age	PAP/HR-HPV	Surgery	TS	Heterologous	MI	SO	M × 10 HPF	LVI/NODAL	ADJUV	Follow-Up
Jones and Lefkowitz [14]	33	No	TAH	40 mm	N	N	Yes	28	NA/NA	No	WD 163 m
Park et al. [11]	37	No	TAH + BSO + PL	20 mm	N	N	Yes	20	N/N	No	WD 9 m
Manoharan et al. [15]	28	No	RH	60 mm	Striated muscle	N	Yes	>10	P/NA	Ifosfamide, doxorubicin, Pelvic Rt, BRT	WD 48 m
Comunoğlu et al. [20]	60	No	TAH + BSO + PL	125 mm	N	N	Yes	10	N/N	No	WD 14 m
Gallardo and Prat [6]	52	No	TAH	NA	Rhabdomyosarcoma	NA	Yes	6	NA/NA	No	DWD 35 m
Duggal et al. [16]	15	No	TAH + BSO + Omentectomy	60 mm	Chondrosarcoma, myxoid liposarcoma, leiomyosarcoma, rhabdomyosarcoma	N	Yes	24	NA/NA	6 cycles chemotherapy, Rt	DWD 12 m
Patrelli et al. [17]	72	No	TAH + BSO + PL + Omental biopsy + Appendectomy	60 mm	Rhabdomyosarcoma	Yes	Yes	10	N/N	Pelvic Rt 45 Gy, ifos-famide + cisplatin)	WD 3 m
Charfi et al. [18]	26	No	TAH	60 mm	Rhabdomyosarcoma, cartilage	NA	Yes	25	NA	No	Lost to follow-up
Seagle et al. [19]	54	No	RH + BSO + PL + PAL	80 mm	N	N	Yes	<1	N/N	BRT 25 Gy iridium-192 + 6 cycles doxorubicin	WD 66 m
Present study	39	P/N	RH + PNSR	75 mm	Cartilage, rhabdomyoblastic	N	Yes	52	P/P	Rt, ifos-famide + cisplatin	AWD 21 m

PAP: Papanicolaou; No: Not performed; N: Negative; P: Positive; HR-HPV: high risk human papilloma virus; NA: Not applicable or not evaluated; TAH: Total abdominal hysterectomy; RH: Radical hysterectomy; BSO: Bilateral salpingo-oophorectomy; PL: Pelvic lymphadenectomy; PAL: Para-aortic lymphadenectomy; PNSR: Pelvic nodes suspicious removed; TS: Tumor size (maximal diameter); MI: Myometrial invasion; SO: Sarcomatous overgrowth; M × 10 HPF: Mitoses per 10 high-power fields (number of mitoses in the stromal component); LVI: Lymphovascular invasion; ADJUV: Adjuvant management; Rt: Pelvic radiotherapy; BRT: Brachytherapy; WD: Without disease; AWD: Alive with disease; DWD: Dead with disease; m: months.
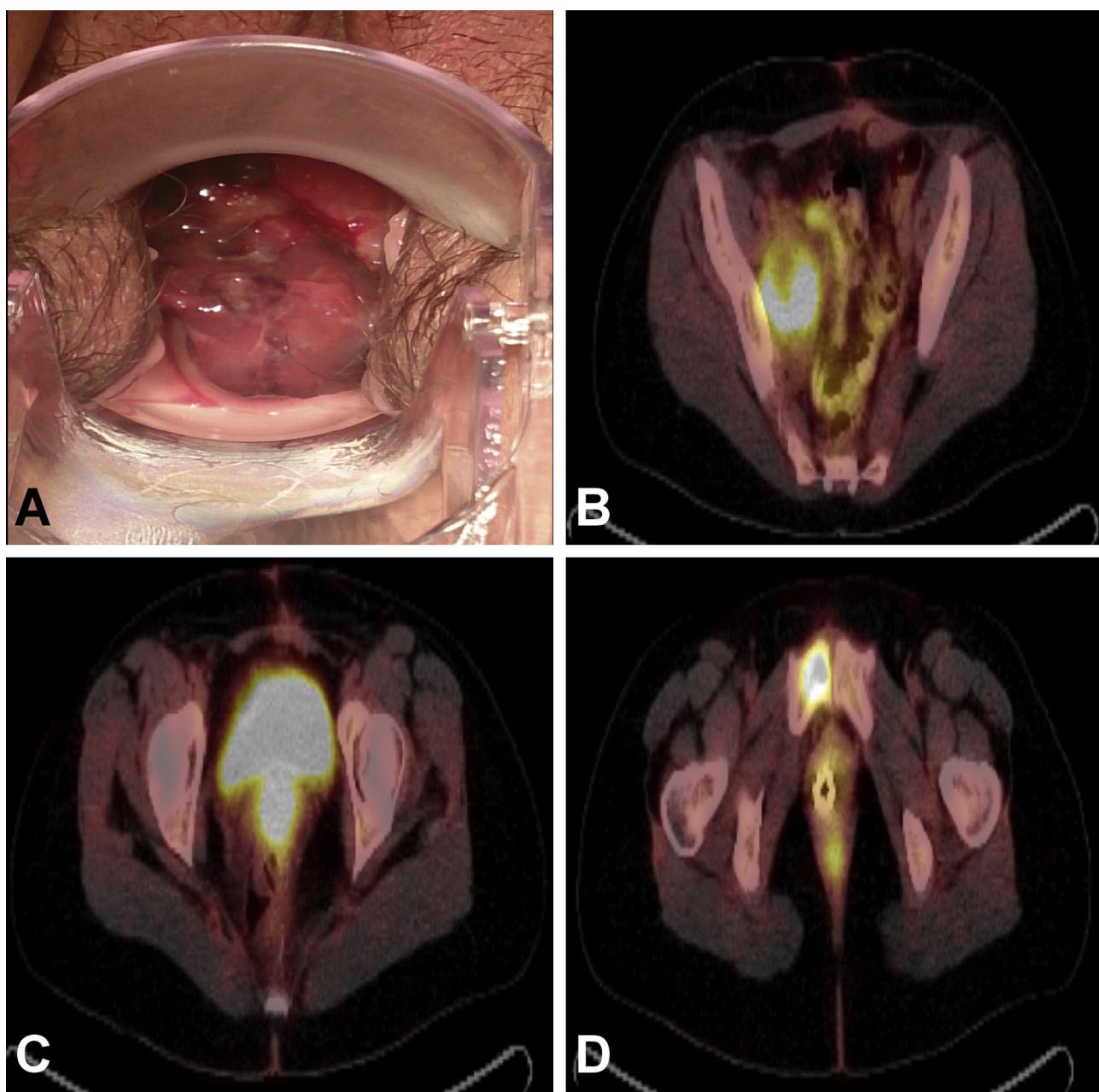
Fig. 3. (A) Speculoscopy shows local tumor regrowth in the vaginal vault. (B) Positron emission tomography-computed tomography (PET-CT) shows intense capture of 18-fluorodeoxyglucose in the right iliac nodal conglomeration, which measured $44 \times 53 \times 57$ mm. (C) PET-CT shows hypermetabolic vaginal vault regrowth and a tumor measuring 76×39 mm. (D) PET-CT shows bony recurrence in the right pubic ramus.

3. Discussion

Müllerian adenosarcoma of the cervix is relatively rare, accounting for approximately 2% of uterine adenosarcomas [1]. It is exceptionally rare for patients with this disease to present with sarcomatous overgrowth and a heterologous component (present in 20% of cases), as well as lymph node involvement [2].

The risk factors for diseases of cervical origin are unresolved. Whether radiotherapy is a risk factor for cervical adenosarcoma is also unclear owing to inconsistent data [3]. No high-risk human papilloma viruses (HR-HPVs) were detected via hybridization techniques or polymerase chain reaction (PCR) in the 9 cases of Müllerian adenosarcoma examined by Mumba et al. [4] In our case, PCR was used and HR-HPV DNA was not detected, thus excluding HPV involvement in tumor development.

In previous cases and case series, total abdominal hysterectomy was the most frequently performed surgery in patients with tumors of cervical origin. However, we recommend radical hysterectomy aimed at obtaining sufficient tumor-free margins, because most clinically evident lesions are FIGO stage IB1 or IB2 [5]. As consistently reported, recurrence is more likely when less radical surgical procedures (e.g., polypectomies that preserve fertility) are performed. This is particularly true among adolescents, and the time to recurrence varies from 3 to 11 years [6,7]. Bilateral oophorectomy has been widely used to manage Müllerian adenosarcomas of the uterine corpus. However, for tumors of cervical origin, the indications for oophorectomy are difficult to establish owing to the infrequency of these tumors [8].

Myometrial invasion is a significant histopathological prognostic factor for adenosarcomas of the uterine corpus. More
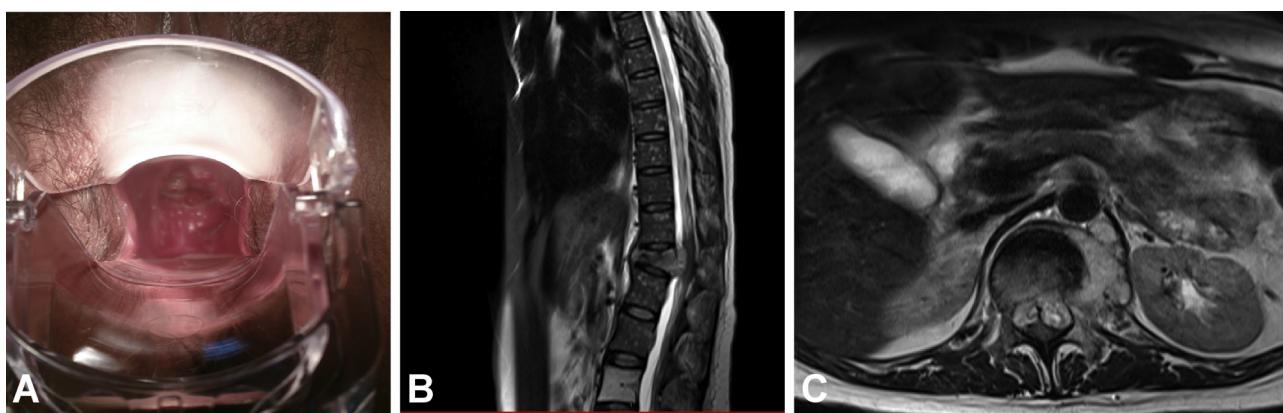
Fig. 4. (A) Posterior speculoscopy at the start of external pelvic radiotherapy shows a clear reduction in tumor volume. (B) Magnetic resonance imaging (MRI) in the sagittal plane of the dorsal spine shows vertebral body metastasis with pathological fracture of the T12 vertebra. (C) MRI at the T12 level shows infiltrative metastatic compromise of the medullary canal.

recurrences and lower survival rates have been reported in cervical adenosarcomas with myometrial invasion ranging from the internal third to the deep region compared with those with lesser or no invasion [9].

Lymphovascular or nodal compromise in Müllerian adenosarcoma of the cervix with sarcomatous overgrowth is poorly described. In a study of 60 patients with 9 cases of adenosarcoma of the uterine corpus, 4 had local relapse and 3 exhibited stromal overgrowth; however, there was no lymphovascular compromise in the 6 cases in which it was assessed [10]. In the case of a tumor with sarcomatous overgrowth described by Park et al., pelvic lymphadenectomy ruled out retroperitoneal nodal compromise, and the outcome was good [11].

It is possible that tumors without risk factors for recurrence and progression [e.g., sarcomatous overgrowth, high mitotic index, heterologous (rhabdomyoblastic) component, lymphovascular compromise, and myometrial invasion] have better outcomes without adjuvant management, as suggested by others [9,12–14]. However, we recommend adjuvant chemotherapy consisting of ifosfamide and platinum and pelvic radiotherapy for tumors with histopathological findings indicating a high risk of recurrence, as in the case reported by Manoharan et al. [15] In the study by Tanner et al., Müllerian adenosarcomas of the uterus with sarcomatous growth (n = 5) had much lower progression-free survival and global survival rates (both 20%) than did those without sarcomatous overgrowth (both 100%). Recurrence developed in 4 of the 5 (80%) patients with sarcomatous growth, 3 of whom presented with myometrial invasion [13]. Table 1 lists the cases of Müllerian adenosarcoma of the cervix with sarcomatous overgrowth and other risk factors that have been reported in the English literature [16–20].

Reports of PET-CT as a preoperative procedure for Müllerian adenosarcoma of the cervix or in cases of recurrence are rare. Choi et al. described a Müllerian adenosarcoma with sarcomatous overgrowth in the uterine corpus whose disease staging and diagnosis of progression were achieved via PET-CT [21]. In our study, PET-CT was used to identify relapse locations in addition to those detected via clinical examination of the vaginal vault. However, whether PET-CT is indicated for the initial detection of lymph node and bone metastases in FIGO stage IB tumors with surgical indication is unclear.

4. Conclusion

This case illustrates the need for sequential pelvic radiotherapy (external and brachytherapy) and chemotherapy for the treatment of patients with cervical Müllerian adenosarcomas presenting risk factors for recurrence. Radiotherapy and ifosfamide and platinum chemotherapy may aid recurrent disease control.

Conflict of interest

There is no conflict of interest.

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Ethical approval

None.

Consent

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Author contributions

The author contributions are as follows. David A. Morales F., Mónica L. Medina R., and Lina M. Trujillo, all of whom belong to the gynecologic group, designed and performed the clinical study of the patient, reviewed the literature, and critically revised the manuscript. Isabel C. Dulcey and Maria I Beltrán, who belong to the pathologic oncology group, made the diagnosis and wrote and reviewed the pathology section of the manuscript. David A. Morales F. also contributed to data acquisition and drafted the manuscript.

Guarantor

David A. Morales F.

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