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Mesonephric adenocarcinoma treated with paclitaxel-carboplatin adjuvant chemotherapy: a case report

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Summary

The authors describe a case of a mesonephric adenocarcinoma of the meso-ovarium and meso-salpinx in a 52-year-old woman. The patient underwent total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, followed by adjuvant chemotherapy with paclitaxel and carboplatin for six cycles with three-week intervals in between. The patient remained free of disease for 18 months with good general conditions. They also reviewed the clinical, pathological, and immunohistochemical characteristics of 42 published case reports of mesonephric adenocarcinoma. The most common presentation of the disease was vaginal bleeding, followed by low abdominal pain. Among the 42 cases reviewed, only three patients were given the correct diagnosis preoperatively. A significant portion of them showed positive immunoreactivity for CD10, vimentin, and calretinin. The authors also found that AE1/AE3, CK7, EMA, CD10, and vimentin are typically positive while ER, PR, and CEA are usually negative. Among the cases reviewed, adjuvant chemotherapy was performed in 11 (26.2%) patients while adjuvant radiotherapy was performed in 16 (38.1%) patients. A number of chemotherapeutic regimens have been used but responses to such regimens are still inconclusive. Although further experiences are needed, surgical removal of the mass followed by paclitaxel and carboplatin adjuvant chemotherapy may be considered as a viable option for treatment.

Key words: Mesonephric adenocarcinoma; Hysterectomy; Chemotherapy; Paclitaxel; Carboplatin.

Introduction

Mesonephric adenocarcinoma is one of the rarest tumors of the female genital tract, with only about 40 cases reported in the literature. Data regarding clinical presentation, pathologic characteristics, treatment, and prognosis of the disease are scarce and no standard surgical or medical guidelines for treatment have been established yet. In the present report, the authors describe a case of a mesonephric adenocarcinoma of the meso-ovarium and meso-salpinx in a 52-year-old woman. The patient underwent total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, followed by adjuvant chemotherapy with paclitaxel and carboplatin for six cycles. The patient remained free of disease for 18 months (until the publication of this report). In addition, they reviewed 42 published case reports and summarized the clinical features of the disease.

Case Report

A 52-year-old G2P2A0 post-menopausal woman with no significant past medical history was referred to this institution for evaluation of an exophytic nodule in the uterus that measured about 1.3 centimeters on ultrasonography. The mass was discovered incidentally when she visited her healthcare provider for gynecologic checkup. She did not have any symptoms but ultrasonography was performed as an annual health checkup. The result of the Pap smear performed at the same time did not show any abnormal findings. At the initial discovery of the lesion, the patient was scheduled to be followed up after six months under the impression of uterine leiomyoma. The follow-up ultrasonography showed that the size of the mass increased to 4.1×3.4 centimeters and it was seen with mixed echogenicity with hypervascularity (Figure 1A). The patient was scheduled to be followed up in another three months. When she revisited, the transvaginal ultrasonography revealed atrophic uterus with a 5.8×4.4-centimeter inhomogenous mass lesion with hypervascularity in the right wall with an irregular border (Figure 1B). The endometrium measured 4.0 millimeters while the moderate amount of fluid collection in the posterior cul-de-sac was noted. No significant increases in tumor markers including alpha-fetoprotein (AFP, 1.6 IU/mL), carcinoembryonic antigen (CEA, 0.4 ng/mL), cancer antigen 125 (CA 125, 10.2 U/mL) or cancer antigen 19-9 (CA 19-9, 7.0 U/mL) were observed. Given the rapid growth of the lesion with hypervascularity surrounding the mass, the patient underwent a single-port access laparoscopic mass removal under the presumed diagnosis of rapid growing uterine leiomyoma. The patient did not undergo CT or MRI because the authors usually do not perform such imaging scans for leiomyomas. Despite that the patient did not have any symptoms preoperatively, at surgery, a round ruptured mass about 6 centimeters in diameter was noted in the right lateral side of the uterus with severe adhesions with adjacent adnexal structures (Figures 2A–B). The mass was removed and sent for frozen section, which could not exclude uterine leiomyosarcoma. Therefore, total laparoscopic hysterectomy with bilateral salpingo-oophorectomy were performed. Cytological examinations of peritoneal washing fluid were also performed but did not reveal any evidence of malignancy. On gross examination, the removed mass from the uterus measured 8.0×6.0 centimeters. The cut surface showed whitish to tanned with focal necrotic le-

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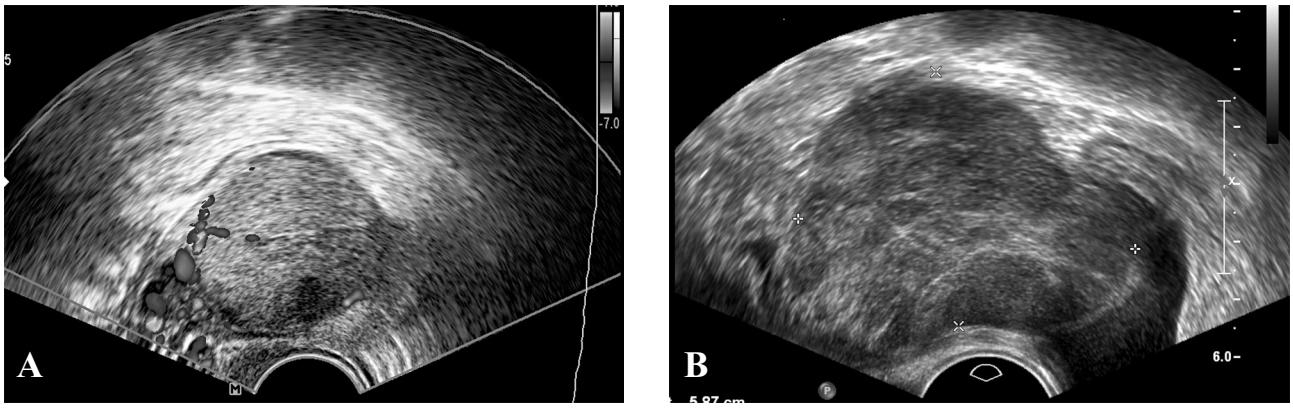

Figure 1. — Ultrasound images (A) taken three months prior to the operation showing 4.07×3.42 cm mixed echogenic mass lesion with hypervascularity surrounding the mass, (B) taken a week before the operation showing inhomogenous mass lesion.

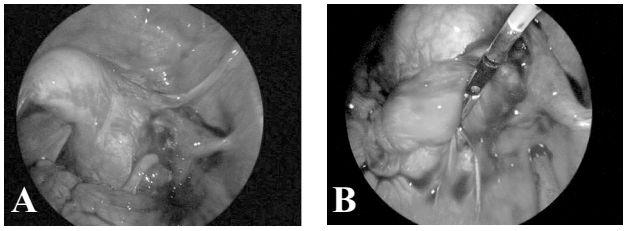

Figure 2. — Operative photo of the lesion (A) with severe adhesion with adjacent structures in the right adnexa and (B) ruptured mass measuring about 6 cm in diameter.

sion and the mass adhered to the right ovary but without cellular invasion. The microscopic findings of the lesion with Hematoxylin and Eosin (H&E) stain revealed both epithelioid and spindle cells growing in sieve-like pattern (Figures 3A–C). In some parts of the tumor, loosely packed small tubules lined by columnar mucin-free cells were identified. Strong positive immunostaining for GATA3, which is a well-known marker for mesonephric origin, resulted (Figure 3D). It also showed positivity for PAX-8, HBME-1, EMA, and focal positivity for calretinin, while negative immunostaining for estrogen receptors (ER), progesterone receptors (PR), WT-1, CD10, inhibin-alpha, and desmin resulted (Figures 4A–E). Macroscopically, the large size tumor with infiltration to the myometrial wall and capsular invasion with rupture strongly suggested its malignant potential. Microscopically, hypercellularity, nuclear pleomorphism, mitotic activity, and geographic necrosis suggested malignancy. Other parts of the uterus were normal except that it had mild chronic cervicitis with atrophy and atrophic endometrium. Although the mass adhered to the right ovary on gross examination, there was no evidence of cellular invasion and both ovaries were normal microscopically. The microscopic findings of the mass with such immunohistochemical stains suggested the diagnosis of mesonephric adenocarcinoma. However, due to the rarity of the reported cases of mesonephric adenocarcinoma, the pathologic samples were sent for additional review by pathologists at another nearby tertiary medical center. Considering the morphologic appearances, the results of the immunohistochemistry, significant nuclear atypia, and mitotic activity seen under the microscope, the final diagnosis of mesonephric adenocarcinoma of the meso-ovarium and meso-salpinx was made. The origin of the tumor seemed to be meso-ovarium and meso-salpinx of the broad ligament rather than the uterine corpus itself. Postoperative recovery was uneventful and the patient was started on adjuvant chemotherapy with paclitaxel (175 mg/m^2, three-hour infusion) and carboplatin (area under the curve, AUC 5) for six cycles with three weeks of intervals in between. Because of the limited data in the literature on chemotherapeutic regimens for mesonephric adenocarcinoma, the present authors chose paclitaxel and carboplatin for her treatment because they are the most commonly used first-line regimens in the gynecologic oncology with the least known toxicities. During the chemotherapeutic treatment, the tumor markers remained within the normal range and the follow-up CT scan, which was performed three weeks after the last cycle, revealing no evidence of disease.

All the authors meet the recommendations for the conduct, reporting, editing, and publication of scholarly work in medical journals provided by the International Committee of Medical Journal Editors. The present study was approved by institutional review board at the corresponding institution.

Discussion

In the present study, the authors report a case of mesonephric adenocarcinoma which was treated with total laparoscopic hysterectomy, bilateral salpingo-oophorectomy, followed by six cycles of paclitaxel and carboplatin adjuvant chemotherapy. Mesonephric adenocarcinoma is a rare tumor of the female genital tract derived from remnants of the paired mesonephric ducts. Such vestigial remnants are usually found in the meso-ovaries, the broad ligament, the lateral walls of the cervix, the vagina, and the corpus uterus [1]. Diagnosing mesonephric adenocarcinoma is challenging because of the absence of specific morphologic and immunohistochemical features of the tumor. To the best of the present authors' knowledge, there have been less than 50 well-documented cases of meso-nephric tumors of the female genital tract in the English literature.

The aim of the present review on the published case reports of mesonephric adenocarcinoma is to provide a summary of the clinical characteristics of this rare type of tumor. Forty-two cases of mesonephric adenocarcinoma that were published between 1972 and 2016 were reviewed (Table 1). The median age of the patients at diagnosis was 54.5 (range: 33–72) years. Of the 42 patients reviewed, 27

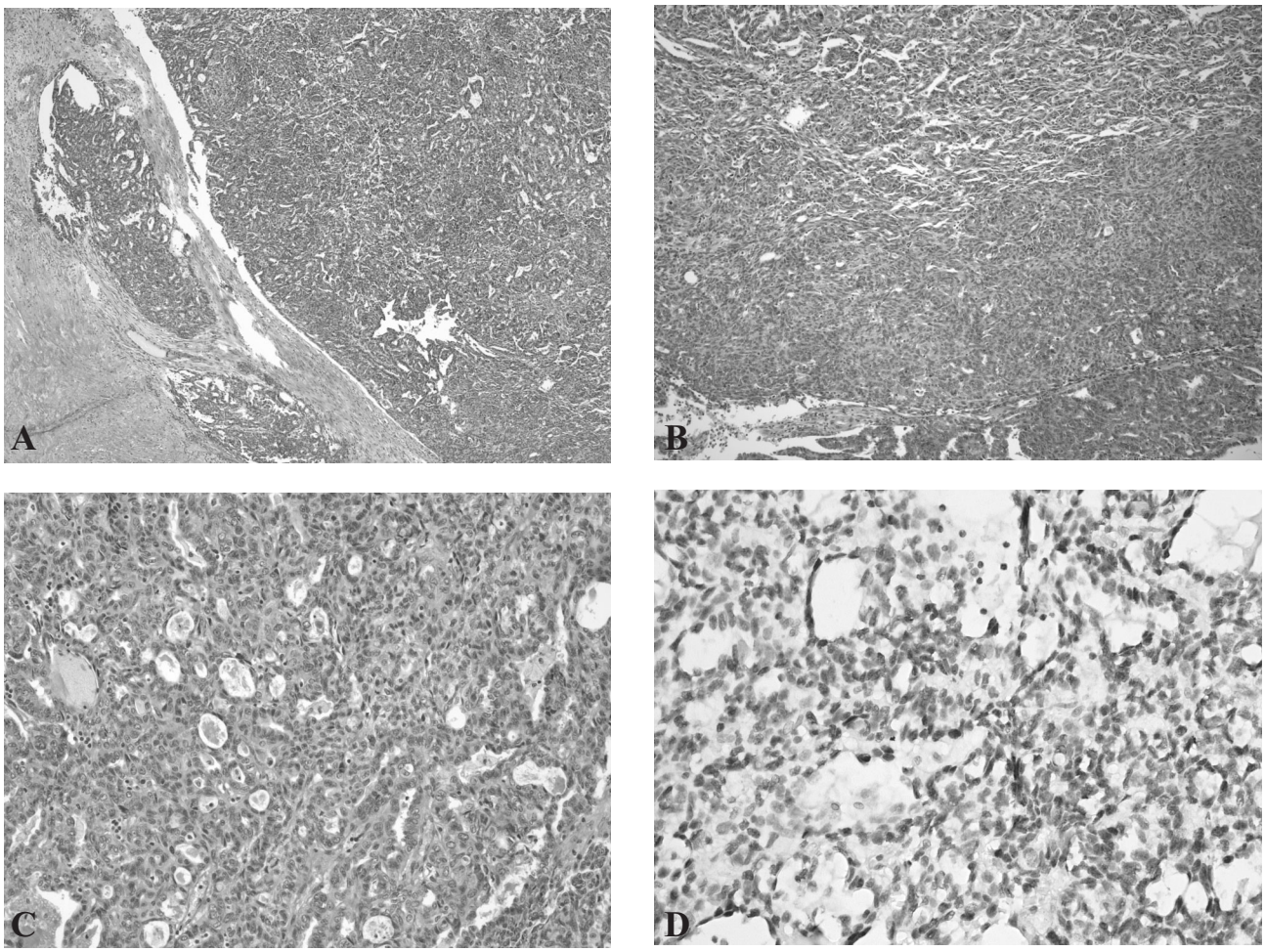

Figure 3. — The microscopic findings of the lesion with hematoxylin and eosin stain showing (A) uterine wall with tumor (Hematoxylin and eosin (HE), magnification x 40), (B) spindle and epithelioid tumor cells (Hematoxylin and eosin (HE), magnification x 100), (C) lesion with sieve-like pattern (Hematoxylin and eosin (HE), magnification x 200), (D) immunostaining of the lesion with GATA3, a well-known marker for mesonephric origin.

(64.3%) patients manifested clinical symptoms. The most common symptom was vaginal bleeding (66.7%), followed by low abdominal pain (19.0%). Among the 42 cases reviewed, only three patients were given the correct diagnosis pre-operatively. Twenty-six (61.9%) patients proceeded to operation without confirmatory diagnosis. Others proceeded to operation with incorrect preoperative diagnoses, most commonly uterine leiomyoma. The stage of the disease at diagnosis varied but most cases were classified between FIGO Stage I and II. Almost all cases had immunohistochemical stainings. A significant portion of them showed positive immunoreactivity for CD10 (61.9%), vimentin (78.6%), and calretinin (57.1%). CD10 and calretinin positivity was especially notable because previous studies have shown consistent CD10 and calretinin staining in a wide range of mesonephric lesions in the upper and lower female genital tract [2]. According to previous studies, AE1/AE3, CK7, EMA, CD10, and vimentin are typically positive while ER, PR, and CEA are usually negative [3-6]. Nonetheless, researchers are in general consensus that the immunophenotypes of paramesonephric and mesonephric structures are not substantially different and that there is no specific marker for the mesonephric structures yet. Therefore, pathologists depend largely on the morphologic appearances on H&E stains to diagnose mesonephric adenocarcinoma.

Owing to the small number of cases with sufficient follow-up periods, no medical or surgical treatment guidelines have yet been established. It seems that surgery should be the initial choice for localized disease, and the role of chemotherapy and radiotherapy remains unclear. Among the cases reviewed in the present study, adjuvant chemotherapy was performed in 11 (26.2%) patients while adjuvant radiotherapy was performed in 16 (38.1%) patients. In the literature, clinicians have tried a number of chemotherapeutic regimens, including paclitaxel plus carboplatin, paclitaxel plus carboplatin plus ifosfamide, cisplatin plus ifosfamide plus bleomycin, cisplatin plus

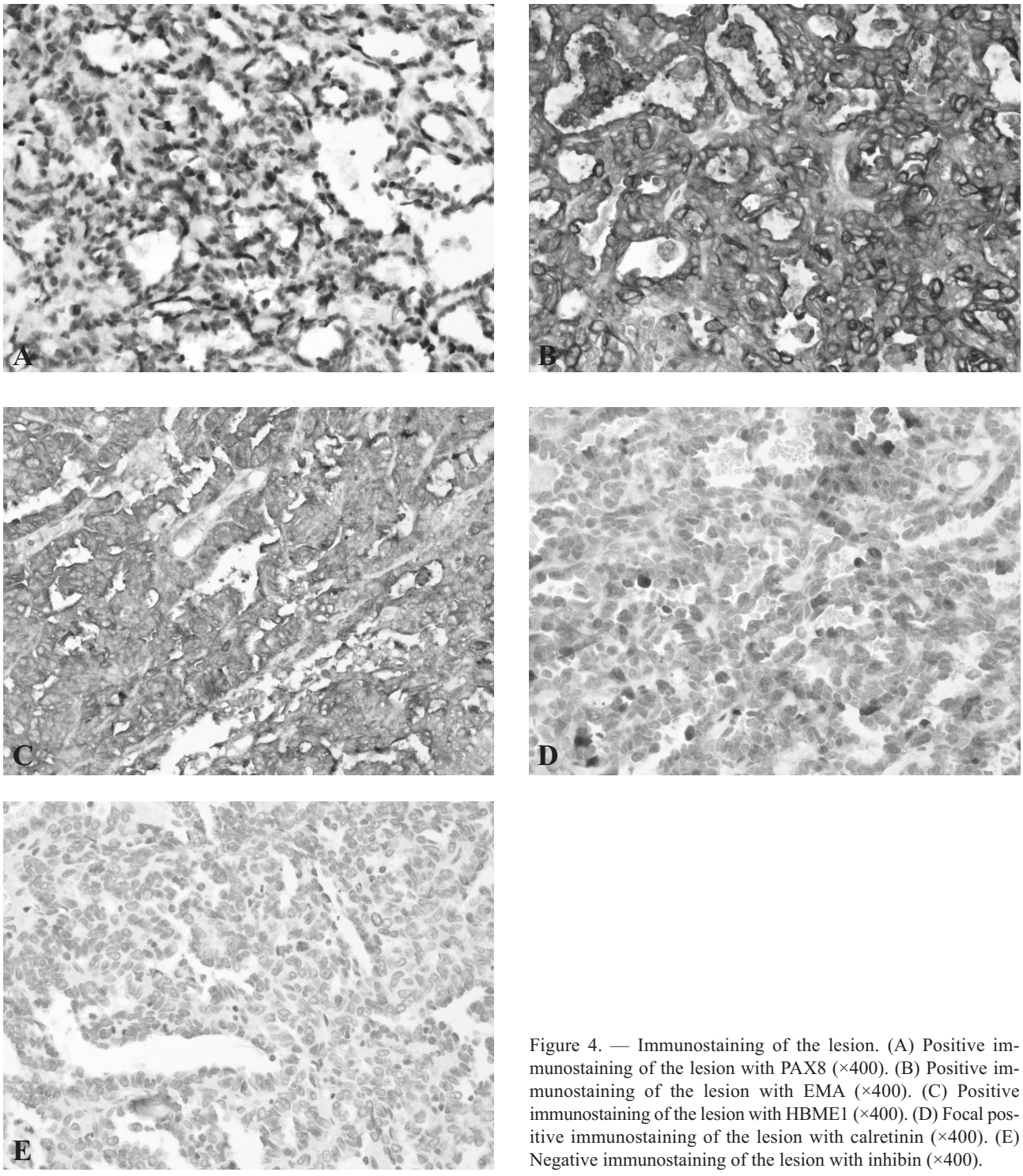

Figure 4. — Immunostaining of the lesion. (A) Positive immunostaining of the lesion with PAX8 (×400). (B) Positive immunostaining of the lesion with EMA (×400). (C) Positive immunostaining of the lesion with HBME1 (×400). (D) Focal positive immunostaining of the lesion with calretinin (×400). (E) Negative immunostaining of the lesion with inhibin (×400).

cyclophosphamide plus doxorubicin and docetaxel plus cisplatin in conjunction with radiotherapy [3, 5, 7, 8]. Responses to such regimens are still inconclusive due to the small number of case reports and the lack of randomized clinical trials systematically comparing different regimens. Among the regimens tried however, paclitaxel and carboplatin may be considered as a feasible option. Montagut *et al.* reported a case of corpus mesonephric adenocarcinoma treated with surgery and local postoperative radiotherapy. The patient, however, developed pelvic-abdominal recurrence and lung metastasis ten months after the initial treatment. Following three cycles of paclitaxel, carboplatin, and

Table 1. — *Clinical data of the mesonephric adenocarcinoma reported between 1972 and 2016.*

Characteristics	Data (n=42)
Median ages in years (range)	54.5 (33–72)
Site – n (%)	
Vagina	9 (21.4%)
Cervix	23 (54.8%)
Uterine corpus	10 (23.8%)
Mean size of the mass in centimeters	5.2 (1.8–14.0)
Symptoms – n (%)	
Asymptomatic	3 (7.1%)
Symptomatic	
Vaginal bleeding	28 (66.7%)
Low abdominal pain	8 (19.0%)
Menorrhagia	6 (14.3%)
Dysmenorrhea	2 (4.8%)
Not described	12 (28.6%)
Elevated tumor marker – n (%)	
CA-125	27 (64.3%)
CA 19-9	23 (54.8%)
CEA	7 (16.7%)
Not mentioned	15 (35.7%)
Preoperative diagnosis – n (%)	
Mesonephric adenocarcinoma	3 (7.1%)
Others	
Uterine leiomyoma or leiomyosarcoma	12 (28.6%)
Endometrial neoplasm	10 (23.8%)
Cervical neoplasm	3 (7.1%)
Uncategorized	26 (61.9%)
Surgery type – n (%)	
Total hysterectomy	36 (85.7%)
Bilateral salpingo-oophorectomy	33 (78.6%)
Pelvic lymphadenectomy	28 (66.7%)
Para-aortic lymphadenectomy	6 (14.3%)
Immunohistochemistry positivity – n (%)	
CD10	26 (61.9%)
Vimentin	33 (78.6%)
Calretinin	24 (57.1%)
Cytokeratin AE1/AE3	4 (9.5%)
Cytokeratin 7	4 (9.5%)
EMA	38 (90.5%)
PAX 8	(19.0%)
p53	2 (4.8%)
TTF-1	1 (2.4%)
Immunohistochemistry negativity – n (%)	
Estrogen receptors	28 (66.7%)
Progesterone receptors	26 (61.9%)
Inhibin	22 (52.4%)
p53	7 (9.5%)
CEA	6 (14.3%)
Cytokeratin 20	2 (4.8%)
Desmin	1 (2.4%)
Calretinin	6 (14.3%)
WT-1	6 (14.3%)
TTF-1	2 (4.8%)
Vimentin	4 (9.5%)
Adjuvant therapy – n (%)	
Chemotherapy	11 (26.2%)
Radiotherapy	16 (38.1%)

CA-125: cancer antigen 125; CA 19-9: cancer antigen 19-9; CEA: carcinoembryonic antigen; CD 10: cluster of differentiation 10; EMA: epithelial membrane antigen; PAX 8: paired box 8; TTF-1: thyroid transcription factor-1; WT-1: Wilms tumor-1.

secondary surgical removal of the lesion, the patient showed partial remission, and complete remission was achieved following three additional courses of chemotherapy with the same regimen [7]. Because effective chemotherapeutic regimens for this rare type of tumor remain unclear, it is reasonable to consider paclitaxel and carboplatin that are most commonly used for treatment in various types gynecologic malignancies.

In conclusion, the authors report a case of mesonephric adenocarcinoma which was treated by surgery followed by paclitaxel and carboplatin adjuvant chemotherapy regimen. Since there is no specific marker for diagnosing mesonephric adenocarcinoma, clinical manifestations of the patients, histomorphologic features, and immunohistochemical staining findings should all be integrated to draw the diagnosis. Although further experiences are warranted to establish the optimal treatment guidelines, surgical removal of the mass followed by paclitaxel and carboplatin adjuvant chemotherapy may be considered as an option for treatment of the disease.

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