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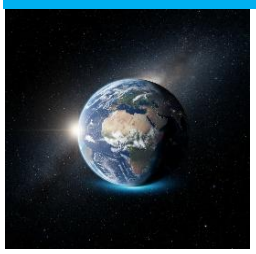

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Biphasic tumor of uterine origin – a case report and literature review

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Abstract

Background: Uterine carcinosarcoma represents a rare subtype of the primary tumors of the uterus, consisting of less than 5% of uterine neoplasms. The most common symptom is abnormal vaginal bleeding. Most frequently, this type of cancer occurs in women over the age of 70.

Aim: The aim of the paper is to present the significance of early diagnosis and treatment of uterine carcinosarcoma and to compare treatment methods among patients with different stages of this type of cancer.

Materials and methods: This paper presents a case report of a 56 yeras old patient who was admitted to the hospital due to postmenopausal bleeding. During examination, an echogenic heterogeneous tumor was spotted in the uterine cervix. The materials obtained during the uterine dilation and curettage (D&C) revealed sarcoma stromale. During the second admission, laparoscopic hysterectomy was performed. Histopathological analysis of the material

recognised neoplasm as carcinosarcoma not otherwise specified (NOS). According to the decision made during consultation, the patient was qualified for chemotherapy (6 cycles), followed up with radiotherapy.
Results: Uterine carcinosarcoma is characterized by its unique, bi-phasic structure, aggressive, high-grade character and poor prognosis, which all create diagnostic and therapeutic difficulties. Due to its rare occurrence, precise histopathological examination is crucial in the diagnostic process and further treatment administration.
Conclusions: Carcinosarcoma is an uncommon and distinctive form of uterine tumor. Its unusual morphology can complicate the diagnostic process and histopathological evaluation, potentially delaying the final diagnosis. Furthermore, because of its biphasic nature, its treatment approach differs from that used for more typical uterine cancers.

Keywords: uterine neoplasm; uterine carcinosarcoma; gynecological malignancy.

Introduction

Uterine carcinosarcoma represents a rare subtype of the primary tumors of the uterus, consisting of less than 5% of uterine neoplasms [1, 2]. It is characterized by its unique, bi-phasic structure, aggressive, high-grade character and poor prognosis [3]. It consists of epithelial and mesenchymal components, in which the sarcoma element has de-differentiated from the carcinoma element [4, 5, 6]. Despite its rare occurrence USC is characterized by a higher mortality rate and worse prognosis than other uterine neoplasms, resulting in around 15% of deaths caused by all uterine tumors [7, 8, 9, 10]. This unfavorable statistics stems from the highly malignant nature of the tumor and the major clinical difficulties. Most challenges come in the form of lowered chemo-sensibility and limited treatment options due to lack of hormone dependency in the majority of documented cases. The recommended treatment consists of surgical removal followed by adjuvant chemoradiation [11, 12].

Case Report

A 57 years old female was admitted to hospital on 2021-12-21 due to postmenopausal bleeding. Dilation and curettage (D&C) of cervix and corpus of the uterus was performed. In USG examination of uterus and adnexa an 41x37 mm echogenic heterogeneous tumor in uterine cervix with high central and peripheral vascularization was detected. Histopathological

examination of the acquired biological material revealed the tumor as adenosarcoma of mesenchymal origin of mixed components. Benign epithelial component and malignant mesenchymal component were recognised as sarcoma stromale. Simultaneously adenomatous and germinal cords differentiation as well as necrosis were visible.

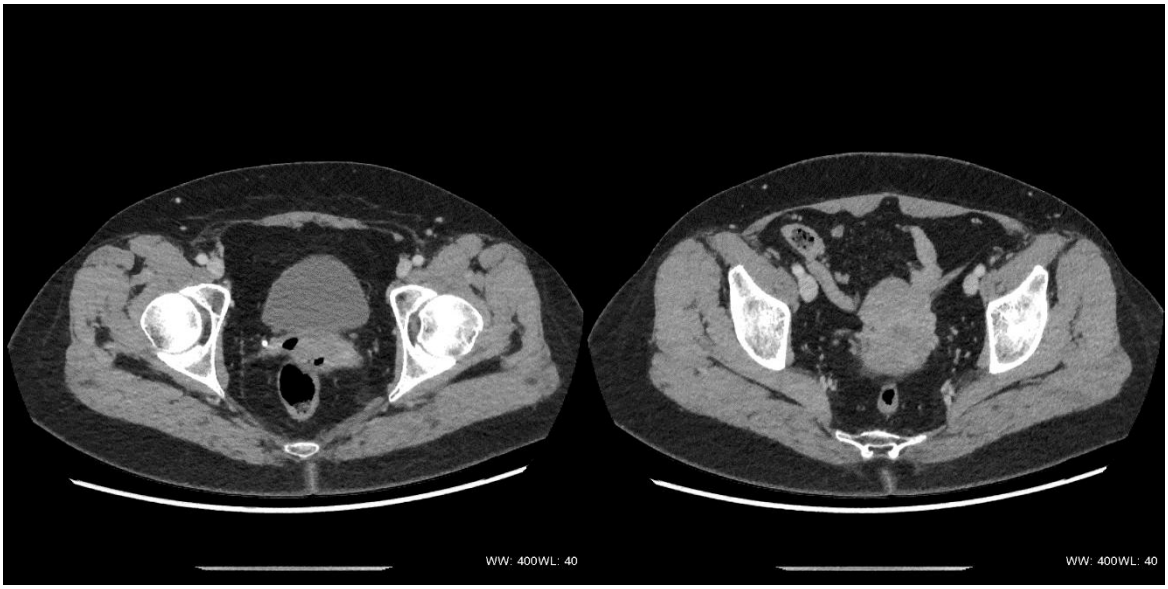

Figure 1. CT scans from January 2022

On 12.01.2022 the patient was admitted to the oncology ward and on 13.01.2022 her oncologic diagnostics and treatment cart (DILO) was created. Same day laparoscopic hysterectomy with adnexa was performed, along with greater omentum removal and per vaginal drainage. In macroscopic examination a gray, solid, 25x20x15mm mass was found on the verge of cervix and corpus of the uterus. Neoplasm was infiltrating more than ½ of the thickness of myometrium of both cervix and corpus of uterine, crossing radical line of resection in places. Infiltration of carcinomatous cells included less than 50% of thickness of myometrium and entire thickness of uterine cervix stroma and serosa. Neither angioinvasion nor perinervous infiltration were identified. Additionally 15x 10x 5 mm polyp of the uterine cavity was spotted. Neoplasm was diagnosed as carcinosarcoma NOS in histopathological examination. Tissues were built in 50% from epithelial component corresponding to serous adenocarcinoma of solid structure and homological mesenchymal component of high-grade sarcoma non-other specified (NOS) morphology (Table1). IHC staining was positive for CKAE1/AE3+, EMA+, foccaly for CD10+ and in epithelial component for CK7+. Staining for desmin, progesterone receptors (PGR), estrogen (ER) receptors and mucicarmine were negative. Ki67+ index was revealed positive in 40% of epithelial component and 25% of mesenchymal component (Table 2).

Table 1. Histopathological diagnosis of the components

Component type	**Histopathological diagnosis/ Cancer characterization**
Epithelial component	serous adenocarcinoma of solid structure
Mesenchymal component	high-grade sarcoma non-other specified (NOS)

Table 2. IHC staining status of the examined material

IHC staining	**Staining status**
CKAE1/AE3+	positive
EMA+	positive
CD10+	positive foccaly
CK7+	positive in epithelial component
desmin,	negative
progesterone receptors (PGR),	negative
estrogen receptors (ER)	negative
mucicarmine	negative

Table 3. Ki-67+ status

Ki-67+ status	
in epithelial component	positive in 40%
in mesenchymal component	positive in 25%

Tumor has been qualified as pT3a pN and type IIIa in FIGO scale.
CT scan performed on 22.02.2022 showed no visible metastatic changes, including brain tissues and bones.
According to the decision made during consultation, the patient was qualified for 6 cycles of chemotherapy consisting of paclitaxel and carboplatin. Pharmacological treatment was followed up with radiotherapy consisting of 28 cycles in a dose of 1,8 Gy reaching 50,4 Gy total. After the radiotherapy brachytherapy in the area of the vaginal stump in 2 cycles of 7,5 Gy - 15 Gy total. The tolerance of the administered treatment was good.

Discussion and literature review

Uterine carcinosarcoma belongs to the primary neoplasm of the uterus, previously known as Mullerian mixed type tumor [13, 14, 15]. The unusual morphology caused the previous classification of the neoplasm as a subtype of uterine sarcoma [16]. Recent findings however strongly suggest the thesis of second dedifferentiation of the tumor from primarily carcinomatous cells of uterine origin [4, 5, 6].

The typical clinical presentation of carcinosarcoma of the uterus includes heavy bleeding, which aligns with our clinical experience [12, 17, 18, 19, 20]. Highest prevalence of this neoplasm is shown in elderly women, mostly in their 7th decade or later [21,22]. Since early 2000 slight change in demographics was noted with an increased incidence rate in the younger population - women in their 60's and less prominent rise of patients between 50-59, within which falls our patient [23]. To the risk factors associated with USC among others belong increased body mass present in our patient bordering between overweight and obesity [24, 25, 26, 23, 27, 28].

Ultrasonographic examination revealed characteristics mostly typical for reported cases of USC - heterogeneous appearance and high vascularisation of the lesion [27, 29, 30]. Atypical placement of the lesion in USG examination in uterine cervix, macroscopic localization of the tumor on the verge of cervix and corpus of the uterus in material acquired during hysterectomy correlate with histopathological findings. Neoplasm represents serous adenocarcinoma as epithelial component - more typical for extrauterine UCS and homologous sarcomatoid component of non-other specified sarcoma, both of which are frequently found in UCS [30].

Lack of positive staining for hormone receptors (ER, PGR) correlates with commonly found phenotype in uterine carcinosarcoma subtype, with expression of aforementioned receptors detected in less than 40% of cases [31]. This causes yet another clinical disadvantage in managing USC as hormone targeted therapy is unavailable for the majority of patients and achieves little response in treated patients.
Recent reports are inconsistent in regard to factors relevant to survival and prognosis, mostly agreeable on the role of heterologous tissue, majority of sarcomatous component in the tumor, lymph node metastasis and clinical stage III and IV [9, 23, 29, 31, 32, 33, 34, 35, 36, 37, 38]. Our patient lacks most of the characteristics linked to poor prognosis in reviewed publications: increased tumor size (over 5cm), heterologous sarcomatous component, presence of a rhabdomyosarcoma component deep myometrial infiltration, lympho-vascular space, late diagnosis, gross residual disease, previous pain or uterus enlargement, invasion of local lymph nodes, adnexa and extrauterine tissues [9, 23, 34, 36]. According to An and Wang OSucs analysis prevalence of hypertension, III or IV clinical stage along with lack of response as clinical outcome and heterologous differentiation are predictive for the disadvantageous prognosis and worse OS [33]. The history of hypertension, classification of tumor as IIIa in FIGO scale, invasion of half of the myometrium in both uterus and cervix, along with a sarcomatoid component in 50% of the neoplasm tissue and negative hormone receptor staining

implies the intermediate malignancy of the tumor in our case [24,31]. Neither local nor distant metastasis were found in control/ initial CT scans performed, what is atypical for USC [23] .

Clinical experience and survival analysis shows notably better overall survival in groups treated with chemoradiotherapy as adjuvant treatment following surgical resection in comparison to surgical removal, chemotherapy or radiotherapy only [34, 38, 39, 40, 41, 42, 44]. Moreover multimodal treatment and chemoradiation is considered as positive predictor marker [36, 40, 45]. Radiotherapy has been linked to lowered recurrence rate [46]. According to clinical trial results and current National Comprehensive Cancer Network practice guidelines the combination of carboplatin/paclitaxel, administered in our patient, is deemed as favored systemic treatment with better PFT and OS. [47] The area of molecular therapies used in UCS is still underdeveloped as neoplasms are of extremely rare occurrence.[11] It is highly probable that strong expression of EMT signature in most USC screened is directly linked with low response rate and aggressive nature of the tumor [5, 48, 49]. Considering high expression levels of PD-L1 in researched UCS reaching around 60% and strong connotations between heightened EMT expression, heightened TMB score and better ICI response in other tumors, checkpoint inhibitor immunotherapy may be promising therapy in USC [45].

Conclusions

Carcinosarcoma is a rare, unusual type of uterine neoplasm. Its atypical morphology may cause difficulties during diagnostic process and histopathological examination, therefore prolong time of final diagnosis. Due to its biphasic structure, the treatment management also differs from the more common types of uterine cancers. The therapeutic process in the described patient is inconclusive and requires further research due to short treatment time.

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