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Clinicopathological Characteristics of Endometrial Carcinosarcomas: A Single-Center Experience

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Abstract: Endometrial carcinosarcoma (ECS) is epidemiologically and clinically similar to endometrial adenocarcinoma (EA) and is considered an aggressive variant of EA. Considered as carcinomas with sarcomatous and carcinomatous components, these tumors are rare, with a very poor prognosis. The definitive diagnosis of ECS is based on histopathological examination. We aimed to share the clinicopathological characteristics of histopathologically diagnosed ECS cases. We analyzed 26 materials diagnosed as ECS after histopathological examinations that were sent to our department as total abdominal hysterectomy in the last 7 years. The histological type of the carcinoma component was serous carcinoma in 14 cases, and endometrioid adenocarcinoma in 12 cases. The histological type of sarcoma component was endometrial stromal sarcoma in 16 cases, fibrosarcoma in 2, leiomyosarcoma in 2, and chondrosarcoma in 6. According to FIGO staging, 10 of the cases were stage IA, 2 was stage IB, 2 was stage IIIA, 10 were stage IIIC2, and 2 was stage IVB. According to pTNM pathological staging, 10 of the cases were pT1a, 6 were pT1b, 4 were pT3a, 4 were pT3b, and 2 was pT4. Since the sarcomatous component of ECS is unlikely to metastasize, the prognosis is believed to be shaped by the characteristics of the epithelial component. Consistent with the literature, we found all lymph node and distant organ metastases to be consisted of carcinomatous components. ECS is a rare, and extremely aggressive malignancy with poor prognosis. There is still no typical laboratory finding or specific imaging for definitive diagnosis. Thus, the diagnosis of ECS can only be made following histopathological examination. Similarly, FIGO or pTNM staging can only be made after histopathological examination using the appropriate procedure.

Keywords: Endometrial Carcinosarcoma, Malignant Mixed Müllerian Tumor, Histopathology.

1. Introduction

Also called malignant mixed müllerian tumors, endometrial carcinosarcomas (ECS) are extremely rare (1).

Formerly in the uterine sarcoma group, these tumors are now considered as carcinomas with sarcomatous and carcinomatous components and monoclonal

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development (2, 3). Epidemiologically and clinically similar to endometrial adenocarcinomas, ECS is considered an aggressive variant of endometrial adenocarcinoma (4). With a very poor prognosis, ECS accounts for less than 5% of all uterine cancers but is responsible for over 15% of deaths. Similar to endometrial carcinomas, it is associated with obesity, nulliparity, exogenous estrogen, and tamoxifen use. Also, a history of exposure to pelvic radiation is associated with increased ECS risk (5). They often occur in the postmenopausal period. Anemia can be observed in 10% of patients due to vaginal bleeding (6). For over 10% of cases, signs of metastasis can be the first finding (1, 6). Pelvic ultrasonography (USG) is most often the first-line imaging method, although it cannot distinguish ECS from endometrial adenocarcinoma. Using Computed Tomography (CT) or Magnetic Resonance Imaging (MRI), ECS is often detected as a heterogeneous and polypoid mass that extends into the endocervical canal, with an intense increase for a long period of time. These two methods can help detect myometrial invasion depth, lymph node involvement, and metastasis (7). No typical laboratory finding has been associated with the diagnosis of ECS. However, an excessive increase of CA-125 may indicate more advanced disease (8). Still, the definitive diagnosis of ECS is only made after histopathological examination. Here, we aimed to share the clinicopathological characteristics of histopathologically diagnosed ECS cases, a rare malignancy.

2. Material and Methods

We included 26 materials diagnosed with ECS after necessary histopathological examinations that were sent to the Department of Medical Pathology of the Faculty of Medicine at Atatürk University between January 2013 – June 2020 as total abdominal hysterectomy materials. Beside total abdominal hysterectomy, bilateral salpingo oophorectomy and pelvic-paraaortic lymph node dissection were performed in all patients. Hematoxylin-Eosin (H&E) and immunohistochemical preparations and pathology diagnosis reports belonging to each case were obtained from the archives of our department; all cases were re-evaluated by two pathologists. pTNM staging was performed again according to the 8th Edition, Union for International Cancer Control (UICC) and the American Joint Committee on Cancer (AJCC) and clinical staging was performed again according to the International Federation of Gynecology and Obstetrics (FIGO) 2018. The histological type of carcinomatous and sarcomatous components, macroscopic tumor diameters, myometrial invasion depths, the presence or absence of regional lymph node metastasis, survival rates, and the presence or absence of homologous or heterologous components were investigated. Cases with unavailable clinical data or pathology preparation were excluded. Clinical characteristics like age and the year of the case were obtained from the database of our hospital. Approval was obtained from the ethics committee of the Faculty of Medicine at Atatürk University (08-01/10/2020).

3. Results

The patients had a mean age of 59 years, ranging from 51 to 67 years. Mean macroscopic tumoral diameter was 7.3 cm, ranging from 3 to 13 cm. The tumors were invasive to the 1/2 outer part of myometrium in 16 cases and to the 1/2 inner part of myometrium in 10 cases. According to the FIGO staging, 10 cases were stage IA, 2 was stage IB, 2 was stage IIIA, 10 were stage IIIC2, and 2 was stage IVB. According to pTNM pathological staging, 10 cases were pT1a, 6 were pT1b, 4 were pT3a, 4 were pT3b, and 2 was pT4. In 12 patient there was regional lymph node metastasis and in all case it consisted of carcinomatous component metastasis (12 were pN2a and 14 were pN0). Considering distant organ metastasis, 2 was M1 and 24 were M0. Lung metastasis was observed in 2 (8%) patient, and it consisted of carcinomatous component metastasis. Lymphovascular invasion was observed in 24 cases. 10 cases developed from the endometrial polyp floor. Cervical glandular and stromal involvement was observed in 10 cases.

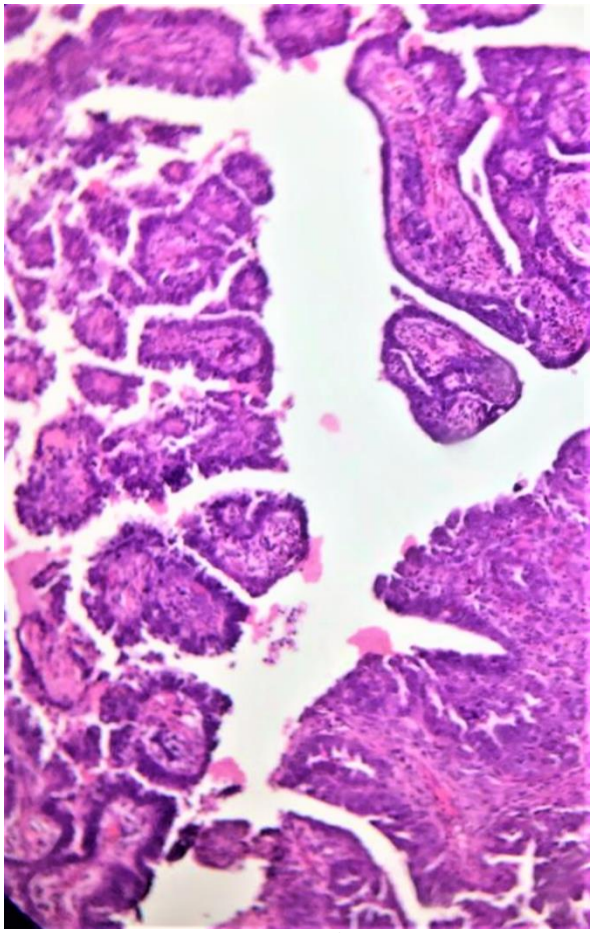

Figure 1: Serous carcinoma areas that form the epithelial component of carcinosarcoma.

The histological carcinoma component was serous carcinoma in 14 cases and endometrioid adenocarcinoma in 12. 6 of our cases were has heterologous sarcomatous components and the sarcomatous component was chondrosarcoma in all 6. 20 of our cases were has homolog sarcomatous components and the sarcomatous component was endometrial stromal sarcoma in 16 cases, fibrosarcoma in 2, leiomyosarcoma in 2. (Table 1 and Figures 1, 2, 3).

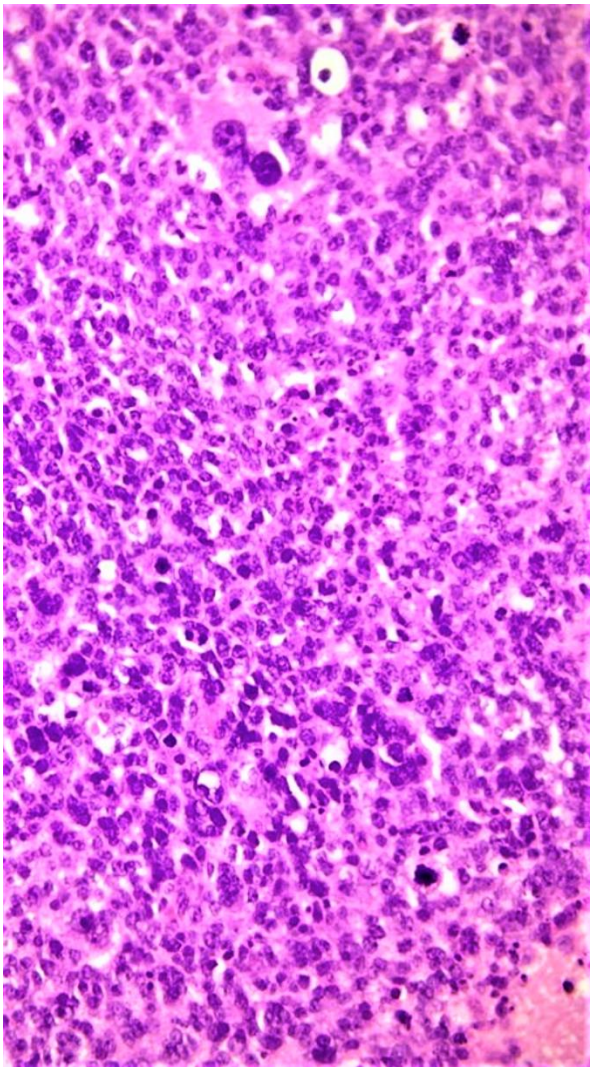

Figure 2: Areas of sarcomatous component of carcinosarcoma.

4. Discussion

ECS is a rare malignancy that often presents with an aggressive clinical picture and poor prognosis. Mean age of incidence has been reported as the seventh decade, with a median age of 62 to 67 years at diagnosis. (9). Bosquet et al. reported 95% of their patients to be in the postmenopausal period, with a mean age of 64.6 years (10). Similar to their findings, all our cases were in the postmenopausal period, with a mean age of 59 years.

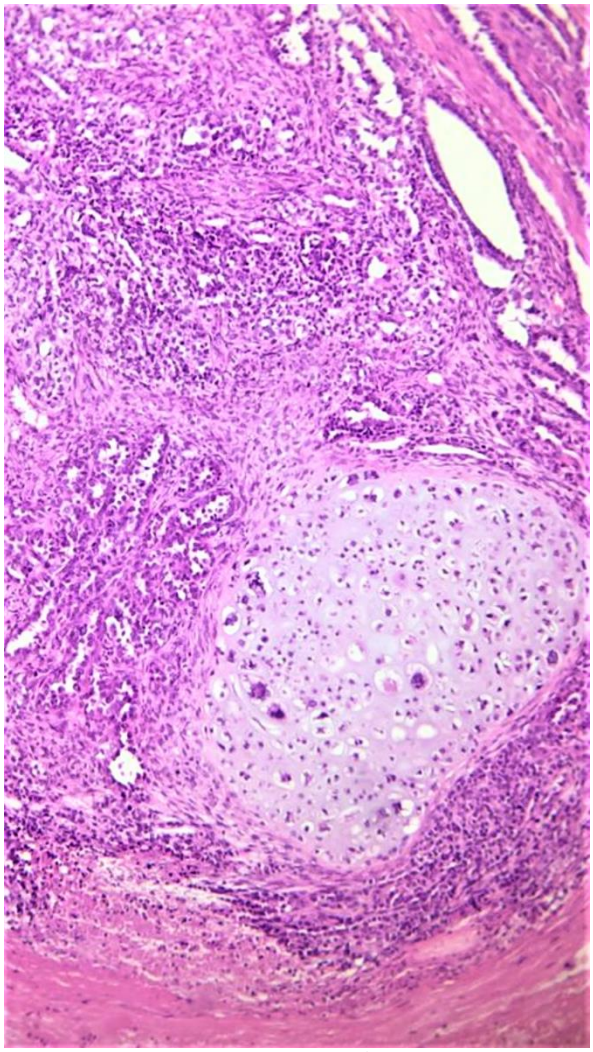

Figure 3: The carcinoma component of carcinosarcoma and the chondrosarcoma area that forms the heterologous element of the sarcomatous component.

ESC has a different biological behavior from other uterine sarcomas. The FIGO 2009 classification has included it among endometrial carcinomas due to similar risk factors and clinical behaviors (11). Recently, however, ECS is believed to develop from the metaplastic transformation of a single neoplastic cell type, arising from the epithelial-mesenchymal transition (12). It is divided into two groups as homologous and heterologous depending on the mesenchymal components (13). Homologous ECS contains mesenchymal components made up of tissues that are normally found in the uterus. On the contrary, heterologous ECS includes sarcomatous components that are not found in the uterus. Most ECS cases have a single sarcomatous component, most commonly high-grade endometrial stromal sarcoma (ESS) in homologous ECS. For heterologous ECS, the most common sarcomatous component is rhabdomyosarcoma (14). In the present study, the sarcomatous component was ESS in 62% of our cases, consistent with the literature. 6 of our cases were

heterologous and the sarcomatous component was chondrosarcoma in all 6, unlike the literature. Recent research reports that most ECS cases only have one carcinomatous component, most commonly high-grade serous carcinoma. In rarer cases, it may be in the form of endometrioid adenocarcinoma or clear cell carcinoma (14). According to our findings, 54% of the carcinoma components were high-grade serous carcinomas, similar to the latest knowledge in the literature.

Table 1: Demographic and Histopathological Features of Cases.

Age	Tumor Diameter (cm)	pT	pN	pM	FİGO Stage	Carcinoma Component	Sarcoma Component
52	8	pT1a	pN0	pM0	IA	Serous Carcinoma	Endometrial Stromal Sarcoma
67	12	pT3b	pN2a	pM0	IIIC2	Endometrioid Carcinoma	Endometrial Stromal Sarcoma
51	3.5	pT1a	pN0	pM0	IA	Endometrioid Carcinoma	Fibrosarcoma
58	5	pT1b	pN2a	pM0	IIIC2	Serous Carcinoma	Endometrial Stromal Sarcoma
65	7.5	pT1b	pN0	pM0	IB	Serous Carcinoma	Endometrial Stromal Sarcoma
56	6	pT3a	pN0	pM0	IIIA	Serous Carcinoma	Leiomyosarcoma
67	8.4	pT4	pN2a	pM1	IVB	Serous Carcinoma	Endometrial Stromal Sarcoma
54	3	pT1a	pN0	pM0	IA	Endometrioid Carcinoma	Chondrosarcoma
55	13	pT1a	pN0	pM0	IA	Serous Carcinoma	Chondrosarcoma
60	3,5	pT1b	pN2a	pM0	IIIC2	Endometrioid Carcinoma	Endometrial Stromal Sarcoma
61	9	pT3a	pN2a	pM0	IIIC2	Endometrioid Carcinoma	Endometrial Stromal Sarcoma
66	12	pT3b	pN2a	pM0	IIIC2	Serous Carcinoma	Chondrosarcoma
52	3.5	pT1a	pN0	pM0	IA	Endometrioid Carcinoma	Endometrial Stromal Sarcoma
66	11	pT3b	pN2a	pM0	IIIC2	Serous Carcinoma	Endometrial Stromal Sarcoma
66	6.5	pT1b	pN0	pM0	IB	Endometrioid Carcinoma	Endometrial Stromal Sarcoma
53	2.4	pT1a	pN0	pM0	IA	Endometrioid Carcinoma	Endometrial Stromal Sarcoma
54	12	pT1a	pN0	pM0	IA	Serous Carcinoma	Chondrosarcoma
54	4.5	pT1a	pN0	pM0	IA	Serous Carcinoma	Fibrosarcoma
56	6	pT1b	pN2a	pM0	IIIC2	Endometrioid Carcinoma	Endometrial Stromal Sarcoma
52	4	pT1a	pN0	pM0	IA	Endometrioid Carcinoma	Fibrosarcoma
62	10	pT3a	pN2a	pM0	IIIC2	Endometrioid Carcinoma	Endometrial Stromal Sarcoma
54	3	pT1a	pN0	pM0	IA	Endometrioid Carcinoma	Chondrosarcoma
59	4.5	pT1b	pN2a	pM0	IIIC2	Endometrioid Carcinoma	Endometrial Stromal Sarcoma
61	8.5	pT3a	pN2a	pM0	IIIC2	Serous Carcinoma	Endometrial Stromal Sarcoma
65	11	pT3b	pN2a	pM0	IIIC2	Endometrioid Carcinoma	Chondrosarcoma
67	9.5	pT4	pN2a	pM1	IVB	Serous Carcinoma	Endometrial Stromal Sarcoma

Like in endometrial carcinomas, metastasis can be observed in regional lymph nodes such as paraaortic and pelvic lymph nodes, peritoneal surfaces, distant organs, and particularly the lungs. Due to the aggressive behavior of ECSs, distant organ metastasis occurs in over 10% of patients at initial diagnosis (1). Similar to the literature, in our study, lung metastasis was observed in 2 (8%) patient, and it consisted of carcinomatous component metastasis. Since the sarcomatous component of ECS is unlikely to

metastasize, the prognosis is believed to be shaped by the characteristics of the epithelial component (1). Here, we observed lymph node metastasis in 12 (46%) cases, all consisting of carcinomatous components, again similar to the literature. In ECS, most of the patients are advanced staged at the time of diagnosis. There were 71 cases of ECS in the studies of Akahira et al. 36 of them (51%) were advanced stage cases (28 at stage I, 7 at stage II, 24 at stage III and 12 at stage IV) (4). Similar to Akahira et al's study in our cases, 14 (54%) were at the advanced stage (2 at stage IIIA, 10 at stage IIIC2, and 2 at stage IVB) and 12 (46%) were at stage I at diagnosis.

Staging should be done with taking into consideration the pathological TNM staging by UICC/AJCC and the clinical staging by FIGO. Although mostly parallel, the pTNM staging and FIGO clinical staging have certain key differences. In clinical staging, the presence of regional lymph node metastasis (presence of pelvic lymph node metastasis–stage IIIC1; presence of paraaortic lymph node metastasis–stage IIIC2) FIGO classifies as stage IIIC (15, 16). Temkin et al. identified the presence of lymph node metastasis in ECS as a poor prognostic factor, highlighting the significance of extensive lymph node dissection (17). Of our cases, 4 with pT1b, 2 with pT3a, and 4 with pT3b based on pathological staging were classified as stage IIIC2 according to FIGO clinical staging due to paraaortic lymph node metastasis. Considering our findings and the findings in the literature, we believe that cases with insufficient lymph node sampling are ineligible for proper FIGO staging and patients cannot benefit from optimal treatment protocols.

It can be difficult to distinguish ECS from uterine sarcoma using a prominent mesenchymal component (sarcomatous overgrowth), which emphasizes the significance of proper pathological-anatomical examination (13). For a correct diagnosis, both components should be observed in the histopathological examination of the uterus (18). Symptoms, imaging methods, and/or laboratory findings cannot distinguish ECS from endometrial carcinoma or uterine sarcoma. Endometrial sampling by endometrial biopsy or curettage is most often performed before surgery. Since ECS has endometrial origins, endometrial sampling is more appropriate for diagnosis. Alas, small biopsy materials that do not reflect the entire lesion are apparently not an accurate test for diagnosing ECS (19). Since the diagnosis of ECS is based on histomorphologically demonstrating carcinomatous and sarcomatous components along with stroma invasion, definitive diagnosis depends on the pathological evaluation of the hysterectomy material.

5. Conclusions

ECS is a rare, and extremely aggressive malignancy with poor prognosis. According to the latest staging guidelines, it is classified among high-grade endometrial carcinomas that include sarcomatous metaplasia. There is still no typical laboratory finding or specific imaging for definitive diagnosis. Thus, the diagnosis of ECS can only be made following histopathological examination. Similarly, FIGO or pTNM staging can only be made after histopathological examination using the appropriate procedure.

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Conflict of Interests
All authors declared that there is no conflict of interest.

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Author Contributions
Ceylan O and Özmen S originally conceived the idea and hypothesis. Özmen S designed the study. Ceylan O made the research organization. Özmen S collected the data. Ceylan O interpreted the results. Ceylan O and Özmen S drafted the manuscript. All authors reviewed and approved the manuscript.

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