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Carcinoma of the Uterus
(Report of four cases and review of literature)

Uterusun Karsinosarkomu
(Dört olgununu sunumu ve kaynakların gözden geçirilmesi)

Dilek Sema Arıcı Handan Aker

Department of Pathology Cumhuriyet University, School of Medicine, Sıvas/Turkey

Özet: Malign epitelyal ve mezenkimal komponent içeren karsinosarkomlar oldukça nadir ve hızlı seyirli tümörlerdir. Tüm uterus tümörlerinin sadece % 1-3'ünü oluştururlar. Gros olarak büyük polipoid kitle, histopatolojik olarak ise hem karsinomatöz hem sarkomatöz alanlarla karakterlidir. Birden çok sarkomatöz komponent içeren tümörler bildirilmiştir. Ancak aynı tümörde birden çok epitelyal komponent varlığına ait yayın kaynakların gözden geçirilmesi ile saptayamadık. Bu çalışma iki homolog iki heterolog karsinosarkom olgusunu kapsamaktadır. Olgulardan birinde iki malign epitelyal komponent biraradadır. Karsinosarkomların nadir görülen tümör olmaları ve iki malign epitelyal komponentin birarada bulunması nedeni ile bu çalışmada histopatolojik ve immundokukimyasal özellikler değerlendirilerek olgular ilgili kaynaklar eşliğinde tartışılmıştır.

Anahtar Sözcükler: Uterus, karsinosarkom

Summary: *Carcinosarcomas of the uterus, composed of both malignant epithelial and mesenchymal components, are very aggressive and extremely rare tumors. Only approximately 1-3% of all uterine malignancies are carcinosarcomas. These tumors grossly appear as large polypoid masses and histopathologically include both carcinomatous and sarcomatous element. Tumors composed of more than one sarcomatous elements have been reported. However, reviewing the literature, we couldn\rquotet find any paper reporting carcinosarcoma of the uterus composed of more than one malignant epithelial component. This report includes two homologous and two heterologous type carcinosarcomas of the uterus. One of the heterologous type of our case had two different types of malignant epithelial component. This review is performed because of the rarity of carcinosarcoma of the uterus and coexistence of two malignant epithelial components. Histopathological and immunohistochemical features of these cases were evaluated and literature was reviewed.*

Key Words: *Uterus, carcinosarcoma*

Sarcomas of the uterus account for only 3-5% of all uterine malignancies (1-4).Carcinosarcomas (CS), endometrial stromal sarcomas (ESS), and leiomyosarcoma (LMS) are the most common uterine sarcomas (1,5,6). Although CS are more common than others, they constitute less than 3 percent of malignant tumors of the uterus (1,6,7). There have been many theories about the histogenesis of these tumors. The most accepted one is the common embryologic origin of müllerian epithelium and mesencyhme (1,6,8-11).

Designation of the CS have changed several times. In the current classification, carcinosarcoma is synonymous

with the term malignant mixed müllerian tumor or malignant mixed mesodermal tumor. And the term, "CS", has now been adopted by International Society of Gynecological Pathologists and consequently by the World Health Organization (4,6,11). CS are composed of both malignant epithelial and sarcomatous elements. It is usual to subdivide these tumors into homologous and heterologous type depending upon the mesenchymal components. If these components are native to the uterus such as endometrial stroma, muscle or fibrous tissue, they are designated homologous type CS. On the other hand if mesenchymal components are not native to the uterus such as cartilage, bone, striated muscle, they are designated heterologous type CS (1,2,4,6, 12,13). Epithelial component is generally adenocarcinoma. (AC) Squamous cell carcinoma (SCC) is rare except in cervical primaries. In pure form SCC is seen in only 5% of CS (1,2,6,9,12,13).

Reviewing the literature, we couldn't find any tumor consisting of both adenocarcinoma and SCC. Because of their being infrequent malignancies and coexisting two malignant epithelial component, we designed to discuss CS in the light of literature.

Materials and Methods

Four CS diagnosed between January 1988-November 1977 at Pathology Department in Cumhuriyet University Medical Faculty were included in this study. All tumors were studied with routine light microscopy, immunohistochemistry and reticulin staining. Clinical data were obtained from medical records. None of our cases had the history of previous irradiation. We have not been able to follow up the patients and have any prognostic information because the patients were treated in different institutions.

Histopathologically epithelial component was classified as AC and SCC. Mesenchymal component was classified as homologous or heterologous, using established criteria (1). The summary of clinicopathologic data was shown in Table I. Immunhistochemical (IHC) analysis with cytokeratin (K) (Zymed,S. San Francisco, California, USA, ready to use), epithelial membran antigen (EMA) (Biogenex; San Ramon, CA 94583 USA, ready to use), vimentin (V) (Biogenex, San Ramon, CA 94583 USA, ready to use) and desmin (D) (Biogenex, San Ramon, CA 94583 USA, ready to use), was performed to all tissues which were fixed in 10% formalin and embedded in paraffin. The slides were deparaffinized with xylene and endogenous peroxidase activity was blocked with hydrogen peroxide. Peroxidase activity was localized by the avidin biotin complex. IHC results were shown in Table II.

Table I. Clinical and pathological features of four cases.

Case	Clinical Presentation	Gross Pathology	Subtype of CS	Components
1	Abdominal pain, distention	Polypoid	Heterologous	AC, SCC, ESS, RMS, Cartilage
2	Vaginal bleeding	Polypoid	Homologous	AC, FS
3	Vaginal bleeding	Polypoid	Heterologous	SCC,RMS, Osteoid
4	Vaginal bleeding	Polypoid	Homologous	AC, ESS

AC: Adenocarcinoma, SCC: Squamous Cell Carcinoma, ESS: Endometrial Stromal Sarcoma, RMS: Rhabdomyosarcoma, FS: Fibrosarcoma

Table II. Immunhistochemical features of four cases.

Case (n)	Keratin	EMA	Vimentin	Desmin
1	+	+	+	+
2	+	+	+	-
3	+	+	+	+
4	+	+	+	-

EMA: Epithelial Membran Antigen

Case 1: SK, 62 years old female presented with weight loss and abdominal pain. Pelvic mass was found on physical examination. In order to evaluate the primary site of the mass, computerize tomography (CT) was performed. CT revealed a large mass in relation with the uterus. On explorative laparatomy, large necrotic polypoid tumoral mass arising from uterus, occupying abdomen and invading the surrounding structures was defined. The case was evaluated inoperable because of invasion of surrounding tissues. Random biopsies from polypoid tumoral mass were taken. The gross pathologic examination of the 195/1989 numbered biopsy specimen revealed polypoid mass measuring 7x4x3cm in diameter. Histopathologically tumor composed of malignant epithelial and mesenchymal components. Epithelial components consisted of both poorly differentiated AC and SCC (Fig. 1). Mesenchymal part had the appearance of endometrial stromal cells and spindle to round shaped cells with oval

or rounded hyperchromatic nucleus and fibrillar asidophilic cytoplasm some of which mimicked rhabdomyoblast. There were also necrosis and chondroid matrix. IHC revealed diffuse reactivity of the epithelial cells with K and EMA and mesenchymal cells with V. Mesenchymal cells showed focal reactivity with D. Immunreactivity with EMA and K in mesenchymal cells and with V in epithelial cells was also identified. Reticulin stain revealed the presence of dense reticulin around individual mesenchymal cells whereas it was limited to the periphery nests of epithelial cells (Fig. 2). The case was diagnosed as heterologous type CS. Patient was discharged to have subsequent therapy at Oncology Center.

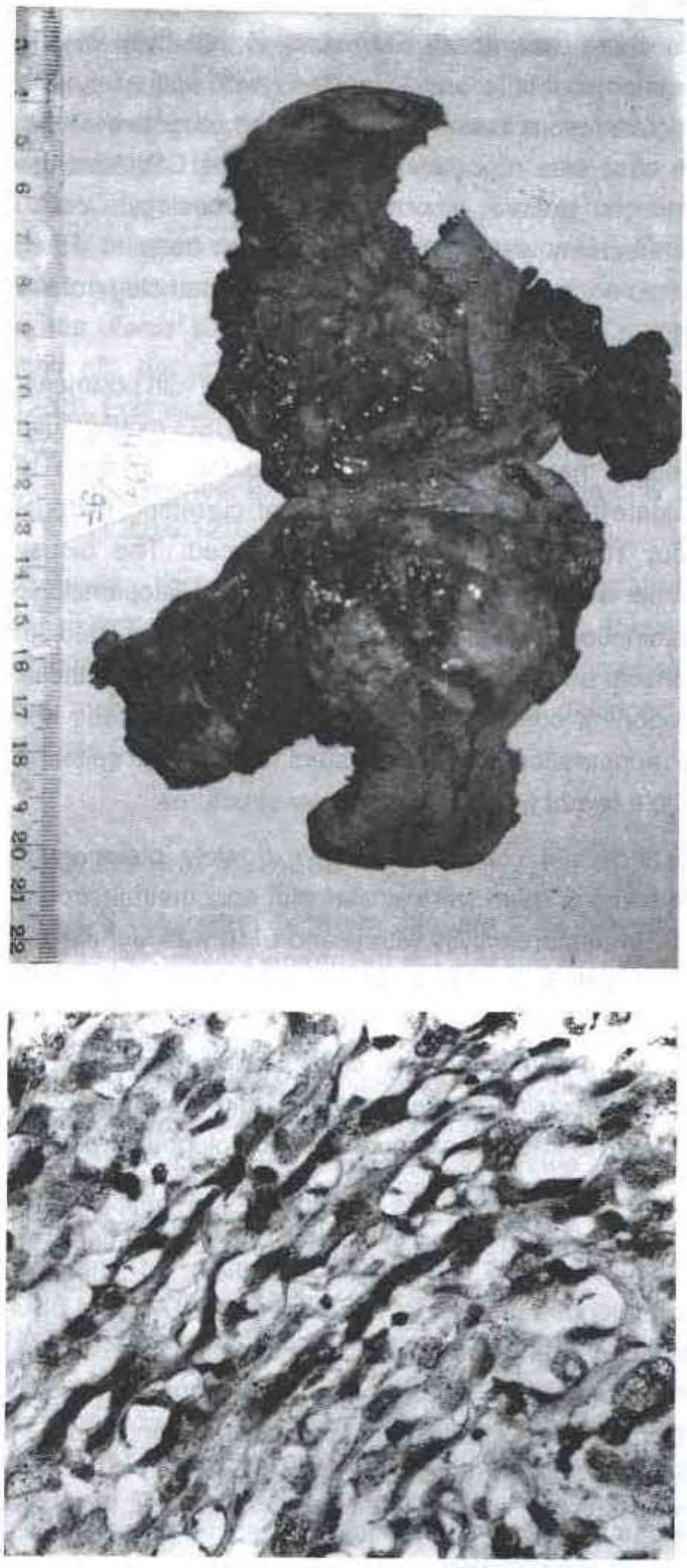
Case 2: FŞ, 53 years old female presented with postmenapousal bleeding of one year}{\f52\lang1033 duration. Pelvic mass was found on physical examination. On explorative laparatomy tumoral mass arising from uterus and invading surrounding tissues was identified. Total abdominal hysterectomy and bilateral salphingoopherectomy (TAH and BSO) was performed. The gross pathological examination of the 450/1990 numbered biopsy specimen revealed polypoid mass located in the posterior wall of the uterus measuring 9x7x3 cm in diameter. Histopathologically a tumor was found in the endometrium and throughout the myometrium.It consisted of both epithelial and mesenchymal components Epithelial components was poorly differentiated AC. Mesenchymal components had the appearance of fibrosarcoma characterized by sheets of spindle or fusiform cells with oval hyperchromatic nuclei and eosinophilic cytoplasm (Fig. 3). IHC revealed diffuse reactivity of epithelial cells with K and EMA, and mesenchymal cells with V. Immunreactivity with D was not identified. Reticulin stain result was the same as the first case. The case diagnosed as homologous type of CS. Patient was discharged to have subsequent therapy at Oncology Center.

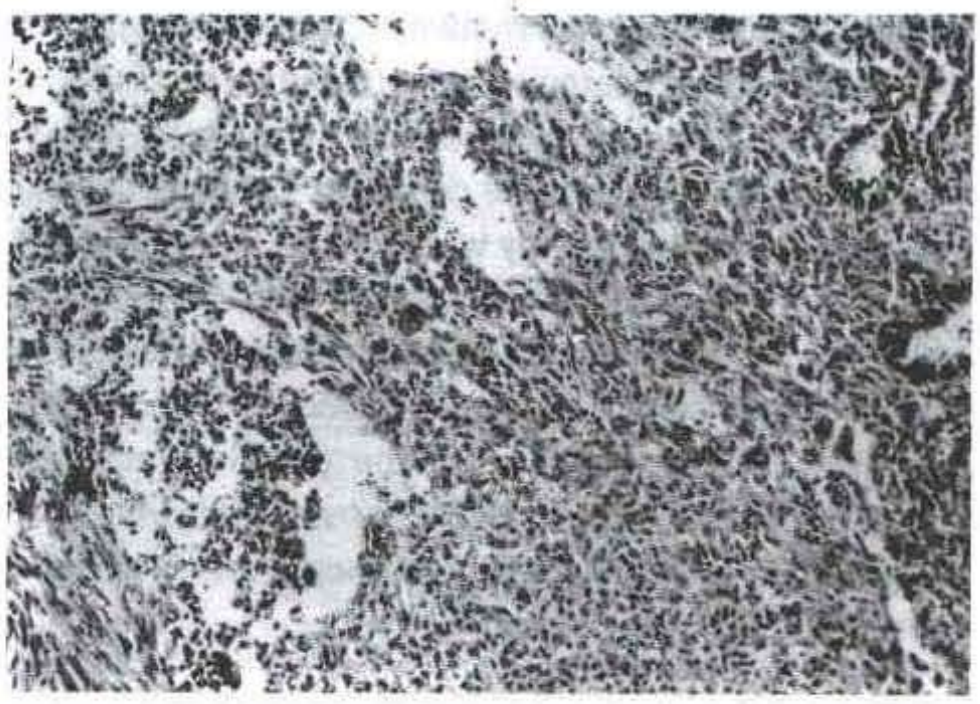
Case 3: NK, 42 years old female presented with abnormal uterine bleeding of 6 months duration. Physical examination revealed exophitic palpable mass located in the cervix. Biopsy specimen measuring 2.5x1x1 and 1x 0.5x 0.3cm in diameter was taken to evaluate the mass. The biopsy number of the specimen was 4307/1994. Histopathologically tumor consisted of epithelial and mesenchymal components. Epithelial component was pure SCC. Mesenchymal cells had the appearance of large round to polygonal cells with abundant fibrillar asidophilic cytoplasm mimicked rhabdomyoblast (Fig. 4). Also, there were myxoid stroma and osteoid formation in some parts of the tumor. Immunoreactivity with K and EMA was identified diffusely in malign epithelial cells. V was identified diffusely in mesenchymal cells but desmin was focally reactive,especially with rhabdomyoblast. Also there was focal EMA and K reactivity in the mesenchymal cells and V reactivity with epithelial cells. Reticulin results were the same as the other two cases. The case was reported as heterologous CS. After the diagnosis, patient was referred to Oncology Center. Hysterectomy was not undertaken in our hospital. Thus, we had not been able to examine gross pathology of the tumor.

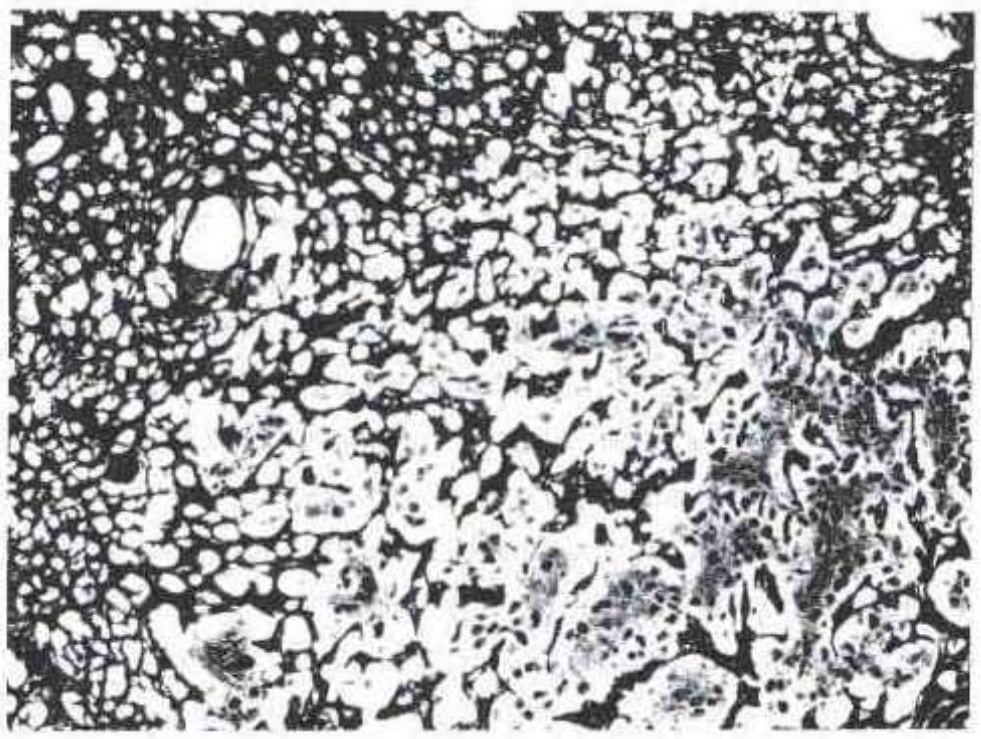
Case 4: GK, 67 years old female presented with postmenapousal bleeding of 6 months duration. USG examination revealed that endometrium had thickened. In order to evaluate this thickness, endometrial curretting material about 10 cc in volume was performed. The biopsy number of the specimen was 4097/1997. Histopathologic examination revealed malignant tumor consisted of epithelial and mesenchymal components. The epithelial component consisted of AC Carcinomatous areas had the appearance of solid clusters of atypical epithelial cells, a few of which had glandular structures.

Mesenchymal component was extremely pleomorphic and some of them were similar with endometrial stromal cells. Immunoreactivity with K and EMA was identified in AC as well as in some cells of sarcomatous areas. V was identified in sarcomatous cells and also it was reactive in some epithelial cells. D was negative in all areas. Reticulin results were the same as the other cases. The case was thought as homologous type CS. But in biopsy specimen, it is difficult to differentiate sarcomas especially homologous types from poorly differentiated AC and ESS. Because of this we recommended the patient to be operated. TAH and BSO was undertaken after 15 days. Gross pathologic examination revealed necrotic polypoid mass measuring 9x5x3cm in diameter located in the posterior wall of the endometrium and involved the myometrium (Fig. 5).

Histopathologically tumor had the same properties as previous endometrial currettings. Furthermore serosal and vascular invasion was noted in the serial section of hysterectomy. Then the case was diagnosed as homologous type CS. The patient was discharged to have subsequent therapy at Oncology Center.







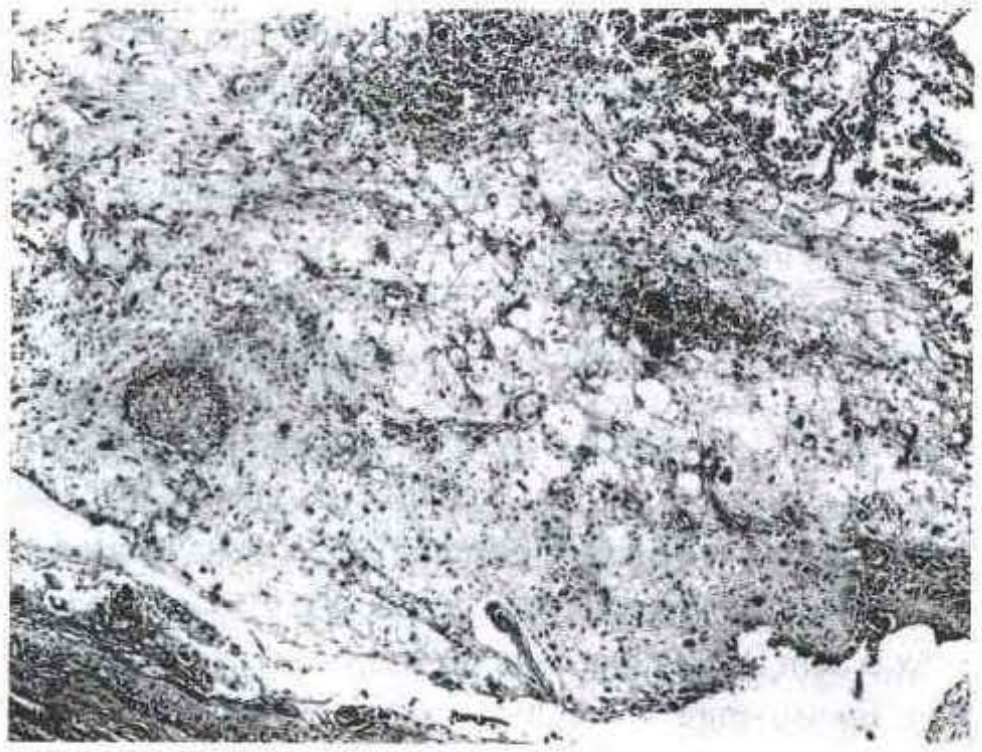


Figure 1. Adenocarcinoma and squamous cell carcinoma components are present together (H+E x10).
Figure 2. The presence of reticulin around individual mesenchymal cells and at the periphery of the nests of epithelial cells (H+E x25)
Figure 3. Adenocarcinoma and fibrosarcoma components of the tumor (H+E x25)
Figure 4. Desmin positive rhabdomyoblast like cells (H+E x100)
Figure 5. Gross pathologic examination of necrotic polypoid mass located throughout the endometrium and myometrium.

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Discussion

CS of the female genital tract are relatively uncommon, aggressive neoplasms that occur more frequently in the endometrium. Tumor classically occurs in the postmenapousal period with median age 62-68 years but also well documented cases have occurred in younger patients (1,5,6,12-14). The tumor presents clinically with abnormal vaginal bleeding, abdominal pain and weight loss. A history of prior pelvic or abdominal irradiation is common in patients with CS (1,2,6,12,13).

We reported three postmenopausal and one young patient. Three of them presented with vaginal bleeding. One of them with abdominal pain and distention and weight loss. None of our cases had pelvic irradiation history.

Gross pathologic examination of CS typically present large poypoid, solitary or multiple masses with a smooth surface. The tumor fills endometrial cavity and extends through cervical canal. The tumor usually invades into the myometrium and spreads beyond the uterine corpus (1,2,4,6,12,14).

We couldn't have opportunity to examine the whole gross pathology of the first case because surgeon had not been able to do hysterectomy because of the invasion to the surrounding tissues. But CT revealed tumoral polipoid mass arose from uterus. Second and fourth case had polipoid appearance and myometrial invasion. In addition, serosal invasion was identified in the last case. Third case had exophitic lesion with polypoid appearance of the cervix uteri and after the diagnosis she had been referred to Oncology Center for subsequent therapy CS are characterized by admixture of carcinomatous and sarcomatous components. AC is by far the most common epithelial component being present in 95% of cases (6,7,9,12). Although squamous epithelium in metaplastic form are common in CS, pure SCC present in only 5percent of the cases. It is more frequent in cervical primaries (4,5,16). More than one epithelial component have not been reported in the literature (1,6,12). Sarcomatous components usually resemble ESS, fibrosarcoma, LMS or undifferentiated sarcoma. If these components are associated with malignant epithelial component tumor is defined as homologous CS. If heterolog components such as striated muscle, cartilage and bone are present, then tumor is defined as heterologous CS. The most common heterolog component is rhabdomyosarcoma. It may be found alone or in combination with other elements. It is accepted that rhabdomyoblasts should be confirmed by immunohistochemical staining using antimyoglobin, or desmin or by phosphotungusticacid (PTAH) staining (1,2,6,12). Cartilage is the second common heterologous component. Cartilage may be mature or immature and it may be seen as chondro sarcoma. Osteoid, bone or osteosarcoma are much less frequent components. More than one heterologous component may also be seen (1,2,4,6,12).

Two homologous and two heterologous CS were reported in this paper. Rhabdomyosarcomatous and cartilaginous areas and osteoid were the heterologous components. One of the presented heterologous case had more than one malignant epithelial component. We identified AC in combination with SCC. Reviewing the literature we couldn't find two malignant epithelial component present in the same tumor. Because Müllerian duct epithelium have the capacity to differentiate to tubal, endometrial and cervical epithelium, our findings provided evidence of this differentiation.

The histogenesis of CS have been continued controversy. There have been different theories. Whether they had a mixture of 2 distinct malignant cell populations or representing a common stem cell origin is not clearly understood (1,6,7,9,10,12,16,17). The possibilities have been investigated by electron microscopy, tissue culture and IHC. IHC studies with K, EMA and V were held in an attempt to gain insight into their nature. Also desmin, S-100 protein, myogobin were performed in order to show heterologous differentiation of the tumor. Many of these studies demonstrated that mesenchymal and epithelial components of these tumors had a significant tendency to coexpress the same antigen. Thus, common cellular origin of the carcinomatous and sarcomatous components have been widely accepted (1,10,12,16).

All of our cases were reactive with K, EMA and V. Desmin reactivity was restricted to rhabdomyoblasts. Also mesenchymal components were reactive with K and EMA as well as epithelial components with V. Our findings provided the common stem cell origin of the tumor.

The differential diagnosis of CS in endometrial currettings or biopsy specimens may be difficult. Especially poorly differentiated AC, high grade ESS and pure sarcomas

are often diagnosed as CS because of inadequate sampling. The accurate distinction is best done with the presence of epithelial and mesenchymal component. Usually there is an abrupt transition from one component to other. Also the presence of reticulin around individual spindle cells or limited to the periphery of nests may be helpful to distinguish two components. The former may support focus as mesenchymal origin, the later as epithelial origin (6,9,12).

In heterologous types we were able to distinguish two different component by H&E. But in the homologous types two components have not been easily recognized by H&E. IHC and reticulin stain were helpful us to distinguish them.

The choice for treatment and prognosis of CS depend on the clinical stage. 30-50% of all cases have invasion beyond uterus. The high rate of unsuccessful therapy was reported in these cases (1,6,12,14). Patients with clinical stage I and II disease without extrauterine disease, TAH and BSO is recommended. It is thought that surgery combined with radiotherapy increases the survival (1,12,14). Although the optimum therapy for stage III and IV is not clear, some reported series favor radiotherapy with or without chemotherapy.

The first and second case had invasion beyond uterus and last case had serosal, vascular invasion. All of three cases have been recommended to refer to on Oncology Center for further treatment.

In summary, the results of this study challenged the traditional view that CS have the common cellular origin. In order to confirm this theory IHK studies could be helpful. Also we could say that more than one epithelial component may coexist in CS as heterologous ones.

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Correspondence address:

Dilek Sema Arıcı
Cumhuriyet University, School of Medicine,
Department of Pathology-58140 SIVAS/TURKEY
Phone: 90 346 2261527
Fax: 90 346 2262162