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Pathologic and molecular features of uterine carcinosarcomas

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Uterine carcinosarcomas (UCSs), formerly known as malignant mixed müllerian tumors, are uncommon neoplasias that account for <5% of uterine malignancies. Traditionally, UCSs have been considered a subtype of sarcoma and the staging system and adjuvant oncological treatments used have been similar to those used for high-grade uterine sarcomas. However, there is now enough clinical, pathologic, and biological evidence to consider UCSs more closely related to high-grade endometrial carcinomas. Thus, these tumors should be staged based on the surgicopathologic staging system used for endometrial carcinomas. Morphologically, UCSs are heterogeneous biphasic tumors composed of an admixture of malignant (endometrioid and nonendometrioid) epithelial and (homologous and heterologous) mesenchymal elements in different proportions. UCSs predominantly metastasize as carcinomas and they are associated with a poor prognosis. Although stage is a consistent prognostic factor, the significance of several histopathological features, such as myometrial invasion, lymphovascular space involvement, type of carcinomatous component, extent of the sarcomatous component, and the presence of heterologous elements, remains controversial and probably differs among different stages. Although the diagnosis of UCS is not difficult in most cases, the differential diagnosis may include entities such as undifferentiated or dedifferentiated carcinoma, endometrioid adenocarcinoma with spindle cell elements, sarcomatous overgrowth in a low-grade müllerian adenosarcoma, and pure malignant mesenchymal tumors. Genetic and molecular studies have confirmed the clonal origin of most UCSs and have shown these tumors to be similar to those observed in high-grade/nonendometrioid carcinomas, with p53 mutations being the most common molecular alteration. Finally, from a biological standpoint, the process by which epithelial malignant cells of UCS transdifferentiate to malignant mesenchymal cells could be considered a true example of epithelial mesenchymal transition in human neoplasias.

Introduction

Uterine carcinosarcomas (UCSs), formerly known as malignant mixed müllerian tumors, are uncommon neoplasms accounting for <5% of uterine malignant tumors that arise most commonly in the uterine corpus, but also rarely in the uterine cervix. Although traditionally classified among sarcomas, during recent years clinical, pathologic, and biological evidence has indicated that they are closely related to high-grade endometrial carcinomas.[1,2] UCSs represent a heterogeneous but aggressive group of neoplasms associated with poor prognosis. Immunohistochemical and molecular genetic studies support the monoclonal nature of carcinosarcomas in general and UCSs in particular, supporting the hypothesis that UCSs in fact represent metaplastic car-

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cinomas. Cell lines established from carcinosarcomas are able to differentiate into either epithelial, mesenchymal components or both.[3,4] Furthermore, immunohistochemical studies have documented the expression of epithelial markers in the sarcomatous components of a large proportion of cases.[5] More recently, chromosome X inactivation studies,[6] gene mutation analyses, and loss of heterozygosity (LOH) studies have all indicated that carcinomatous and sarcomatous elements share common genetic alterations in most of these tumors.[7-9]

From a biological point of view, the process by which epithelial malignant cells of UCS transdifferentiate to malignant mesenchymal cells could be considered a true example of epithelial mesenchymal transition (EMT) in human neoplasia.[10] Indeed, EMT is a process of cellular transdifferentiation in which epithelial cells lose polarity and cell–cell contacts, reorganize their cytoskeleton, acquire expression of mesenchymal markers, and manifest a migratory phenotype. EMT can be induced by different signals and pathways, such as those mediated by transforming growth factor β (TGF-β), tyrosine kinase receptors, and/or Wnt, depending on the specific cellular context.[11] Activation of one or more of these pathways frequently converges in the activation of a group of transcription factors such as Snail1, Slug, ZEB1, ZEB2, E47, E2-2 and Twist, most of them with the ability to repress E-cadherin, a master regulator of cell adhesion and polarity.[12,13] The rarity of UCSs along with its pathologic heterogeneity renders the analysis of molecular alterations particularly challenging in this type of tumors. Moreover, the genetic and/or epigenetic changes that function as the main driving forces in the initiation and progression of UCS remain unknown.

Clinical features

Although patients with UCSs tend to be elderly, postmenopausal women (median age of 65 years), they may occur in younger women or rarely in young girls.[14] According to data from the Surveillance, Epidemiology and Result Program, the adjusted rate of UCSs is 0.6/100,000, although a higher incidence (2.2-3) has been reported among African American women.[15-17] Risk factors associated with the development of UCSs are similar to that reported in endometrial carcinoma, such as obesity, nulliparity, and exogen estrogen use.[18,19] In addition, an association between long-term tamoxifen therapy and the development of these neoplasias has been described.[20-22] Occasional cases have been related to a history of pelvic postirradiation.[14] The most frequent presentation, similar to other endometrial cancers, is abnormal vaginal bleeding, although some patients present with an abdominal mass, pelvic pain, or abnormal Pap smear. Another typical presentation is as a mass that protrudes through the cervix because these tumors are often polypoid.[14]

Morphologic features

Gross examination typically reveals polypoid, bulky, and necrotic masses that fill the entire endometrial cavity and usually invade the myometrium, often extending beyond the uterus. Occasional tumors arise in the cervix and secondarily involve the uterine corpus. Tumors at this location are also typically polypoid or pedunculated.[23-25] They have a soft to firm and tan cut surface with extensive areas of necrosis and hemorrhage (Figure 1). Polypoid tumors often protrude through the cervix, simulating a cervical neoplasm. If either cartilage or bone represents a significant proportion of the tumor, they may have a hard consistency. Occasionally, they are confined to benign endometrial polyps.[14] Carcinosarcomas are biphasic tumors composed of an admixture of malignant epithelial and mesenchymal elements.[14] Typically, carcinomatous and sarcomatous components are easily identified and should be clearly demarcated one from another. In some cases, one of the elements may represent a very minor component of the neoplasia and require exhaustive sampling so as not to misclassify the tumor either as a pure epithelial or mesenchymal malignancy. Although most UCSs show an intimate admixture of carcinoma and sarcoma (but with no transition; Figure 2A), some tumors have two completely separated elements resembling a collision tumor (Figure 2B). In the series by Ferguson et al,[26] a significant percentage of UCSs (approximately 14%) displayed a low-power microscopic pattern of growth resembling a low-grade müllerian adenosarcoma with a phyllodes-like appearance; however,

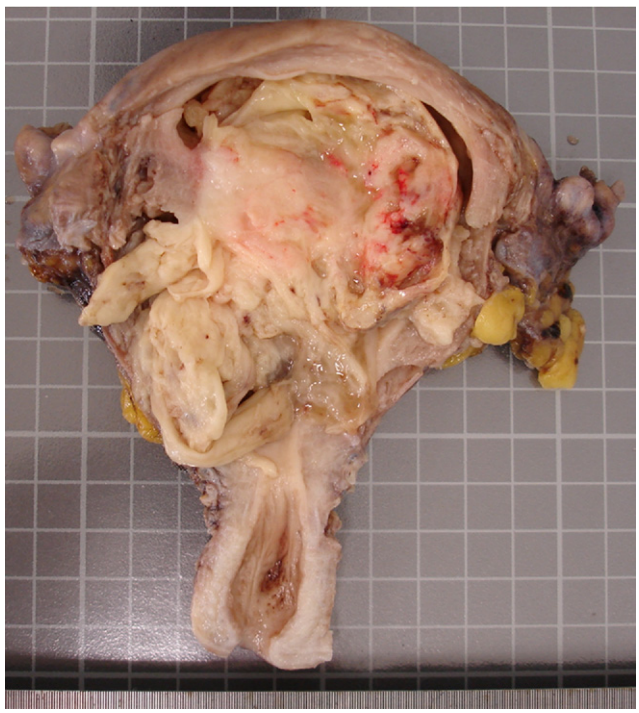

Figure 1 Uterine carcinosarcoma. The tumor is polypoid distending the endometrial cavity and shows focal areas of hemorrhage.