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REVIEW

Clinical and molecular features of uterine sarcomas

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INTRODUCTION: Uterine sarcomas are rare forms of malignant neoplasm, comprising about 3% of all malignant uterine tumors, representing less than 1% of all gynecologic malignancies. Low cure rates often occur due mainly to distant metastases, usually to the lungs. Aggressiveness, high rates of local recurrence, distant metastasis and poor prognosis with overall two-year survival less than 50% are common features of uterine sarcomas. Despite the low prevalence, these tumors are of great interest because of their multiple morphological and clinical features.

OBJECTIVE: This article will be focused on the uterine sarcomas general aspects, etiology, prognosis, treatment and molecular features.

METHOD: This review was performed using the Pubmed database to search for published articles.

RESULTS: Little is known about the etiology of uterine sarcomas. Some studies have demonstrated the association between genetic events involving mutations in genes of the cell cycle and apoptosis and epigenetic in gynecologic sarcomas. Previous studies showed that chromosomal translocations have been identified, resulting in fusion genes that are constitutive and might involve the activation of transcription factors. Advances in molecular techniques have improved the diagnostic possibilities and allowed an improved understanding of the various pathologies.

CONCLUSIONS: There are several factors that make the study of sarcomas a challenging issue, since those tumors are rare and the cell origin of each histologic type is nor well known Thus, molecular study of the events involved in the development of different types of cancer may lead to new strategies used in the diagnosis and treatment of these tumors.

KEYWORDS: uterine sarcoma; molecular features; prognostic factors.

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INTRODUCTION

Mesenchymal tumors develop in the connective tissue of mesodermal origin and display high histological and cytogenetic heterogeneity.[1–2] Sarcomas are malignant tumors that develop in the soft tissues,[2] may have different origins and can occur in any site within the body.[1–3] They are histologically classified according to tissue differentiation;[3,4] diagnosis is difficult and is based on the histological type and grade of the tumor, as is the treatment.[4]

Uterine sarcomas are uncommon entities that present different histological types. Their histopathological classification and staging were reviewed in 2003 and 2009, respectively. According to the World Health Organization,[5] uterine sarcomas consist of two main groups: mesenchymal tumors and mixed tumors. Pure mesenchymal tumors can be classified into endometrial stromal sarcoma, leiomyosarcoma, and undifferentiated uterine sarcoma. Mixed tumors include carcinosarcoma and adenosarcoma[6].

The carcinosarcoma, also called malignant mixed Müllerian tumors, though previously classified as a sarcoma, has now been redefined as a carcinoma. So its management has also changed to that used for high grade endometrial carcinoma; therefore, it should not be included in a study of uterine sarcomas. However, most retrospective sarcoma studies still include carcinosarcomas.[3–6]

This article will focus on the general aspects, etiology, prognosis, treatment, and molecular methods of study for uterine sarcomas, including some features of carcinosarcomas.

METHODS

The bibliographic search was performed using Pubmed databases for relevant articles dated from January 1, 2000 to march 31, 2014. Six articles published before 2000 were also included because they are specially interesting to the theme.

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The following keywords were used: uterine sarcoma, gynecological tumors, uterine smooth muscle tumors, molecular features and prognostic factors.

RESULTS

After completing the articles search we found a total of 53,006 articles. For uterine sarcoma we found 5,683 reports; for gynecological tumors, 45,851; for uterine smooth muscle tumors, 1,245; molecular features and sarcomas, 36; prognostic factors and sarcomas, 191. We selected for this review 62 studies that include molecular and prognostic features of gynecological sarcomas. They were selected and evaluated by three different researchers and are commented below.

Histological classification of uterine sarcomas

Uterine sarcomas can originate from both endometrial stroma and uterine muscle. When the endometrial stroma undergoes malignant transformation, the resulting tumor is called a high-grade endometrial stromal sarcoma (currently called an undifferentiated endometrial sarcoma).[5,7] An adenosarcoma is characterized by a combination of malignant stromal components and benign epithelial components. Tumors formerly known as low-grade stromal sarcoma are currently known as endometrial stromal sarcoma. Tumors that originate from the malignant transformation of the smooth muscle tissue are known as leiomyosarcoma.[6,7]

Endometrial stromal sarcomas were previously classified into low- and high-grade endometrial stromal sarcomas. Currently, the term "endometrial stromal sarcoma" is restricted to "low-grade" tumors, while high-grade tumors are known as undifferentiated sarcomas. Endometrial stromal sarcomas behave in a relatively indolent manner and present late recurrences; distant metastasis may occur, but long-term survival and cure are possible following the surgical resection of recurrent or metastatic lesions.[5]

The main prognostic factors are the tumor-free resection margin, followed by determination of the malignancy grade, tumor diameter, and menopausal status.[7–11]

An undifferentiated sarcoma is defined as a high-grade malignant tumor of mesenchymal origin. These tumors often exhibit pleomorphic cells with a high mitotic index.[10,11] Stage I patients present a 5 year survival rate of 57%, and all patients in more advanced stages die within 5 years. Vascular invasion is the only statistically significant prognostic factor, with 5 year survival rates of 83% and 17% in the absence and presence of vascular invasion, respectively.[11,12]

Adenosarcomas consist of benign epithelial components and homologous or heterologous mesenchymal sarcomatous components; they are more common in postmenopausal women. However, these tumors can also occur in adolescents and young adults, and they comprise 5.5 to 9.0% of all uterine sarcomas.[12] Usually, adenosarcomas involve only the endometrium, with myometrial invasion regarded as an exception. These rare tumors have low malignant potential; they are polypoid and contain small internal cysts. Most cases present with a low-grade histological diagnosis.[2–8]

Stage I patients show 5 and 10 year survival rates of 76% and 61%, respectively. Tumor cell necrosis is the most important histopathological prognostic factor, although women with overgrowth tumors present similar prognoses to women with carcinosarcoma (> 50% mortality).[13,14]

Leiomyosarcomas develop in the muscle layer of the uterus, the myometrium. Generally, a significant increase in uterine volume is observed, and pain and bleeding may occur in some cases. These tumors spread primarily via a hematogenous route, and metastases occur mainly in the lungs and liver.[3–8] The absence of residual tumors after surgery and the tumor size are the 2 most important prognostic factors for survival among patients with leiomyosarcoma.[12] For tumors smaller than 5 cm in diameter, the overall survival is estimated to be 86%, but survival is reduced to 18% for tumors larger than 10 cm.[15]

Leiomyosarcomas usually occur in the 6th decade of life and, in general, the tumors are large and single, with extensive areas of necrosis. Currently, it is believed that the majority of leiomyosarcomas arise independently, although some investigators believe they transform from pre-existing leiomyomas.[3]

The histological criteria for the diagnosis of a Leiomyosarcoma include high a mitotic index (MI), cellular atypia, and extensive tumor cell necrosis. Patients can be classified into 3 risk groups: low (tumor $<$10 cm in diameter and MI $<$10), intermediate (tumor $>$10 cm in diameter or MI $>$ 10), and high risk (tumor $>$10 cm in diameter and MI $>$10).[12,16] The differential diagnosis is performed in relation to the multiple variants of leiomyomas and the smooth muscle tumors of uncertain malignant potential). It is estimated that 0.2% of leiomyosarcoma cases are diagnosed during fibroid removal surgery. Ganglionic metastases are uncommon and occur in 3 to 9% of cases.[16] Histologically, these neoplasms may present as conventional, epithelioid, or myxoid leiomyosarcoma.[5,6]

Carcinosarcomas have been addressed as epithelial tumors based on molecular aspects and their differing behavior in response to therapy. They tend to be are more aggressive, often spreading to lymph nodes and presenting distant metastases to the liver and lungs.[3,8,12] Affected patients may present increased expression of CA-125.[5]

Clinical, pathological, and molecular evidence indicates that most of the uterine carcinosarcomas are of monoclonal origin and undergo epithelial and mesenchymal differentiation during their development. Some studies suggest that these tumors are indeed carcinomas with sarcomatous metaplasia, where the sarcomatous components were obtained as a result of dedifferentiation.[5,6] The behavior and surgical staging of these tumors is similar to high-grade endometrial adenocarcinomas. Lymph node involvement occurs in 14% to 38% of cases, and they respond better to chemotherapy than sarcomas.[17,18]

There are other types of sarcomas, but they are very rare neoplasias. Embryonal rhabdomyosarcomas are often observed in young patients and can be found in several gynecological location.[19] Angiosarcoma, liposarcoma, rhabdomyosarcoma variants, alveolar soft part sarcoma, osteosarcoma and others are observed in older patients.[6]

Epidemiology and etiology

Uterine sarcomas are rare forms of malignant neoplasms comprising 3 to 9% of all malignant uterine tumors and less than 1% of all gynecologic malignant neoplasms.[4,5,8] Sarcomas comprised approximately 5–6% of the 49,560 cases of uterine cancer occurring in the United States in 2013. The contribution of these cases to the projected 8,190 annual deaths, however, approaches 30%.[20] These tumors mainly affect women aged between 40 and 60 years. Although rare,

these tumors are of great interest due to their multiple morphological and clinical features.[8–20]

Approximately 2,400 new cases of uterine sarcoma were registered in the United States (USA) in 2003, representing less than 10% of new uterine cancer cases diagnosed in the country and 7% of sarcoma cases.[21] According to American Cancer Society, about 52,630 new cases of cancer of the uterine corpus will be diagnosed in 2014, but only about 1,600 of these cases will be uterine sarcomas.[22]

Abeler et al. published a population-based study including a histopathologic review of all uterine sarcomas registered in Norway from 1970 to 2000 using the 2003 WHO classification.[10] After exclusion of carcinosarcoma, the frequencies of the different histological types were as follows: leiomyosarcoma 63%, endometrial stromal sarcoma 21%, undifferentiated uterine sarcoma 6%, adenosarcoma 6%, and other types 5%. As previously mentioned, carcinosarcomas are not currently considered to be sarcomas, but rather metaplastic carcinomas (i.e., type II endometrial carcinoma with areas of sarcomatous metaplasia). Based on the current classification, the most common uterine sarcoma is leiomyosarcoma.[4,5]

Little is known about the etiology of uterine sarcomas. Chromosomal translocations have been identified in a large number of uterine sarcomas, resulting in the fusion of constitutive genes that activate transcription factors.[5] Endometrial stromal sarcomas have specific somatic mutations, while leiomyosarcomas present mutations and overexpression of genes important for cell cycle control. Furthermore, it is assumed that leiomyomas may undergo sarcomatous degeneration at a rate between 0.1 and 0.8%.[23]

The incidence of uterine sarcomas among black women is twice as high as that in white women.[24] Brooks et al. showed that the differences in the incidence of uterine sarcomas between black and white women were restricted to leiomyosarcomas. These authors also observed that 54% of white women and 45% of black women presented with early-stage disease (a significant difference, $p = .001$), and that white women presented an equally significantly higher five-year survival rate (53% vs. 42%, $p = .001$).[21]

A history of previous pelvic radiation was identified as a risk factor for the development of sarcomas.[16] Some evidence indicates that exposure to radiation can increase the risk for carcinosarcoma. Another risk factor for the development of carcinosarcoma and endometrial stromal sarcoma is exposure to estrogen, suggesting similarities in the pathogenesis of these two tumors with endometrial carcinoma.[5,6,25]

Recently, the use of tamoxifen in postmenopausal women was associated with the development of endometrial cancer and other uterine sarcomas.[26,27] An increased incidence of leiomyosarcoma and undifferentiated uterine sarcoma has been described. Thus, it is suggested that patients treated with this drug should be followed up with pelvic examinations and submitted to biopsies if abnormal uterine bleeding occurs.[3,12] Oral contraceptives increase the risk of leiomyosarcoma, and women who have smoked cigarettes present reduced risks of leiomyosarcoma and endometrial stromal sarcoma.[28]

Clinical presentation and prognosis

The most commonly observed symptoms in these neoplasms are abnormal uterine bleeding, abdominal or pelvic mass (uterus with rapid growth), and pain by compression or invasion of adjacent structures. Compared to the most common types of uterine cancer, women with sarcomas have a poor prognosis.[5,6,12]

Uterine sarcomas exhibit fleshy growth with areas of hemorrhage and necrosis. These tumors grow in an exophytic pattern within the endometrial cavity, which may cause uterine bleeding and pain. Leiomyosarcoma may be suspected when increased uterus size is observed in postmenopausal women who are not taking hormone replacement therapy. The frequency of these tumors in patients with uterine fibroids is less than 1%, but it increases with age.[29]

Aggressiveness, high rates of local recurrence, distant metastasis, and poor prognosis, with an overall two-year survival rate less than 50%, are common characteristics of uterine sarcomas.[30] The hematogenous route is the preferred route of metastasis, and metastases to the lungs are the most common. Other sites include the liver, bone, and brain.[12]

In general, uterine sarcomas have a poor prognosis, with estimated five-year survival rates between 17% and 54%, and this has remained unchanged over the past 20 years. Only endometrial stromal sarcomas present a better survival rate (approximately 69%) over 5 years.[8,12] As mentioned earlier, these tumors are characterized by rapid and aggressive growth and frequent lymphatic or hematogenous metastasis. Surgical staging is still the most important prognostic variable.[31]

Other determining factors of the prognosis in patients with uterine sarcoma are histological type, histological grade, and stage of disease. Low-grade sarcomas, such as the endometrial stromal sarcoma, present better clinical outcomes and survival rates.[3–9]

The estimated overall five-year survival rate by type of uterine sarcoma in patients with tumors localized to the uterus is 84% for endometrial stromal sarcoma, 51% for leiomyosarcoma, 76% for adenosarcoma, 57% for undifferentiated uterine sarcoma, and 43% for other types.[10] The cure rate is low, even in localized disease, due to distant metastases, usually to the lungs.[11,12,15]

Clinical diagnosis, staging and treatment of uterine sarcomas

Sarcomas can invade tissues adjacent to the primary tumor and spread to other organs, creating secondary tumors that are similar to the primary tumor. The tumor grade is determined by evaluation of the cancer and abnormal cells, and the degree of malignancy predicts the likelihood that the tumor will grow and how fast it will spread.[33]

Microscopically, sarcomas can be divided into low-grade (G1) and high-grade (G2, G3, and G4) tumors. G1 tumors present well-differentiated lesions, few mitotic figures, few atypical cells, minimal or no necrosis, no vascular invasion, and production of reasonable levels of mature matrix. High-grade tumors are poorly differentiated, present frequent mitoses, a considerable number of atypical cells, necrosis, sparse and immature matrix, and vascular invasion; their cells often spread to other organs of the body.[1,3,4,33] A new staging system for uterine sarcomas was proposed by the International Federation of Gynecology and Obstetrics (FIGO) in 2009.[34]

When a diagnosis of uterine sarcoma is suspected, the pretreatment evaluation should include a history and complete physical examination that includes gynecological and rectal exams. Studies have shown that curettage aided

the diagnosis in 70% of endometrial stromal sarcoma cases but only in 30% of leiomyosarcoma.[3,12]

Transvaginal ultrasound is the standard imaging technique, but magnetic resonance imaging (MRI) of the pelvis optimizes image evaluation of invasion into adjacent structures of the pelvis.[35] Evaluation of the spread of extrapelvic structures should be performed by computed tomography of the thorax and abdomen.[36] The distant spread of sarcomas often involves the lungs. Tomography of the thorax is highly sensitive for the detection of pulmonary metastases. In the case of recurrence, a systemic evaluation to define the approach may be performed by positron emission tomography (PET SCAN) if necessary.[35] Although several features at ultrasonography and magnetic resonance imaging (MRI) can raise suspicion of a uterine sarcoma, there are no pathognomonic features on any imaging technique.[36]

Complete staging includes cytology and a biopsy of any suspicious areas of metastasis, as is the case for other intra-abdominal gynecologic malignancies. The tumor-free resection margin is recommended and has great importance.[15]

The standard procedure for uterine sarcoma treatment is surgery. Currently, hysterectomy with a localized disease resection is the gold standard. A total abdominal hysterectomy with bilateral salpingo-oophorectomy is the standard surgical treatment.[36] Total hysterectomy is essential when a uterine sarcoma is suspected, and it may be curative if the tumor is confined to the uterus. In the case of a preoperative diagnosis of endometrial stromal sarcoma, a radical hysterectomy is recommended due to the frequent involvement of the parametrium, which sometimes only presents invasion in the intravascular space.[15]

The roles of cytoreduction, lymphadenectomy, conservation of the ovaries – in young patients – for the preservation of fertility and adjuvant treatment are controversial in these tumors and vary with histology, staging, and patient age.[37,38]

Because endometrial stromal sarcoma is an estrogen-dependent tumor, similar to type I endometrial cancer, a bilateral salpingo-oophorectomy is recommended, even for premenopausal women presenting stage I disease. High recurrence rates were found among women who preserved their ovaries (50%) compared with those who did not (4%).[39] In leiomyosarcoma, the removal of ovaries does not appear to influence survival, and the preservation of ovarian tissue in premenopausal women does not increase the risk of recurrence.[37,38,40]

Lymph node resection is controversial. For all histological types, suspicious nodules with increased size should be submitted for biopsy. The removal of lymph nodes with microscopic disease apparently has no clinical benefit.[15] The incidence of lymph node metastasis in early stages of leiomyosarcomas, endometrial stromal sarcomas, and adenosarcoma without sarcomatous overgrowth is very low; therefore, resection is not indicated. To date, lymphadenectomy for undifferentiated uterine sarcoma and adenosarcoma with sarcomatous overgrowth is in debate.[41] In general, the lymph nodes are involved in 3 to 9% of leiomyosarcoma cases, and there is no need for routine lymph node drainage because it does not increase disease-free survival.[37] In endometrial stromal sarcomas, lymph nodes are involved in 33 to 45% of the cases. However, the benefit of lymphadenectomy is controversial due to the good prognosis of this tumor.[42,43]

Hoellen et al (2014) published a systematic review of lymphadenectomy impact in uterine sarcomas using data from 51 patients. They showed that women who underwent para-aortic-plus-pelvic or pelvic-alone lymphadenectomy presented better survival.[44]

Uterine leiomyosarcomas showing a disease-free interval of 6 months or more require a different approach. A disease-free interval is an indicator of tumor biology and these uterine leiomyosarcomas might have a less aggressive growth pattern. This subset of tumours is more likely to express hormonal receptors that allow targeted treatment. Hormonal treatment or surgery can, therefore, be considered first instead of chemotherapy.[36]

The effect of optimal cytoreduction on the survival of women with disease presenting extra-uterine spread has only been evaluated in few studies, and the findings are inconsistent. Currently it is not possible to define an optimal cytoreduction for uterine sarcomas.[15] Additional surgical resection should be individualized based on the clinical scenario and the intraoperative findings. Regardless, the tumor-free resection margin without residual disease is the most important prognostic factor for uterine sarcomas.[12]

Treatment options for clinically inoperable patients include pelvic radiotherapy (with or without brachytherapy) and/or chemotherapy, and in some cases such as endometrial stromal sarcoma, hormone therapy).[45] Radiotherapy decreases the local recurrence, but it does not increase survival. These tumors exhibit little response to chemotherapy, with the exception of the most undifferentiated examples; treatment with the adjuvant progestin (medroxyprogesterone acetate or megestrol acetate) appears to be beneficial for endometrial stromal sarcomas.[40–46] Because these sarcomas express both the estrogen and the progesterone receptor, adjuvant targeted hormonal treatment can be considered to reduce recurrence. Progestins or aromatase inhibitors may be considered.[36]

Molecular features of gynecological sarcomas

Similarly to the other tumors, sarcoma development arises from alterations in genes that act in different biochemical and regulatory pathways. These changes can occur at the genomic level (mutation, gene amplification or deletion) or due to epigenetic events (histone acetylation, DNA methylation or miRNA).[47] Molecular analyses of the events involved in the development of different types of cancer have led to new strategies for the diagnosis and treatment of these diseases.[47–49]

These alterations may occur due to DNA polymerase errors during replication of genetic material or injuries that occur in the DNA molecule. Spontaneous DNA lesions are more frequent, the most common of which is the deamination (loss of exocyclic amino group) of nitrogenous bases, particularly of cytosine and 5-methylcytosine, which generates thymine and, consequently, causes a base-substitution mutation.[49,50]

In this context, some sarcomas present specific genetic alterations, while others do not, demonstrating complex karyotype disorganization and severe genetic alterations with high chromosomal instability.[5]

Specific cytogenetic aberrations and molecular alterations characteristic of endometrial stromal tumors have been identified. Recurrent chromosomal rearrangements, loss of heterozygosity in tumor suppressor genes and deregulation

of the Wnt signaling pathway have also been implicated in these neoplasm developments.[3–8]

Previously, our group showed that no gynecological sarcomas may express some particularities and markers. Sarcomas might constitutively show NO and, rarely, inducible iNOS.[51] The expression of genes TOP2A and Survivin can have relevant prognostic roles.[52] Moreover, the genes SNRPD3, MEGF9, SPTAIN-1, AFAP1L2, ENDOD1, SERPIN5, ZWINTAS, UBE2C, ABCF1, MCM2, ARL6IP5 have been found to be markers of aggressiveness and metastasis.[53] Lately, a huge amount of gene profile evaluation has shown a molecular signature for differential diagnosis between leiomyosarcomas and pleomorphic sarcomas, configuring an exclusion diagnosis; the ortholog of the Src gene, SRC is configures as a diagnostic marker.[54,55] Unlike uterine carcinomas, non-uterine sarcomas present with a lack of the GLU-1 protein expression.[56] However these tumors present the same mesodermal origin, and in the uterus, the cells are susceptible to sex steroids action.

Concerning uterine sarcomas, a recent work by our group indicates that Sonic Hedgehog proteins differ between conventional leiomyomas, atypical leiomyomas and leiomyosarcomas (Garcia et al., unpublished data). Additionally, several studies have shown that endometrial stromal sarcomas often carry the translocation[10,14] with the participation of the JAZF1 and JJAZ1 genes, suggesting a genetic basis for tumor development.[47] A recent study showed a review of 49 cases of monomorphic endometrial stromal neoplasm and their histological mimics. The authors performed an evaluation of fluorescent in situ hybridization (FISH) for the JAZF1 and YWHAE breakaparts and their conclusion was that endometrial stromal sarcoma can be differentiated from monomorphic undifferentiated sarcomas by this method.[50] They present immunoreactivity for vimentin, smooth muscle actin, muscle-specific actin, and keratin. They may present diffuse reactivity to α-smooth muscle actin, while desmin and h-caldesmon are usually negative.[47,48,50,57,58]

Expression profiles frequently contain the estrogen and progesterone receptors, PDGFR-α, aromatase, GnRH-R, and WT1. Further studies of JAZF1/JJAZ1, JAZF1/PHF1, and EPC1/PHF1 and their downstream effects are necessary. Similar to uterine leiomyosarcoma, WT1 overexpression in endometrial stromal sarcoma is a potential target for immunotherapy.[36]

It is also believed that abnormalities in chromosomes 1, 7, and 11 may play an important role in the genesis of sarcomas or their progression. Changes in 11q22, the expression of epidermal growth factor receptors (HER-2/neu), p53, and Ki-67 were also described in malignant tumors of the uterus.[59,60]

Recently, some studies have demonstrated an association between genetic events that involve mutations in cell cycle-related genes and apoptosis[59–61] and epigenetic events in gynecologic sarcomas.

Leiomyosarcomas generally express smooth muscle markers, such as desmin, h-caldesmon, smooth muscle actin, and histone deacetylase 8 (HDCA8). Epithelioid and myxoid leiomyosarcomas present lower immunoreactivity for these markers. Immunoreactivity against CD10 and epithelial markers, including keratin and epithelial membrane antigen (EMA or MUC1), may be observed.[5] Studies have demonstrated expression of estrogen receptor, progesterone receptor and androgen receptor in 30 to 40% of the cases evaluated. Overexpression of Ki-67, p53, p21 and p16 has also been reported.[47] Most uterine leiomyosarcomas express the platelet-derived growth factor receptor-alfa (*PDGFR-α)*, Wilms' tumor gene 1 (*WT1*), aromatase, and gonadotropin-releasing hormone receptor (*GnRH-R*). Uterine leiomyosarcomas almost always have absence of epidermal growth factor receptor (*EGFR*) and epidermal growth factor receptor 2 (*ERBB2*) expression.[36] Targets of the estrogen and progesterone receptor have been successful for treating patients with uterine leiomyosarcomas with indolent growth. The PI3K-AKT pathway is also a common point of convergence in signal-transduction networks affected in sarcomas. Monoallelic loss of *PTEN* contributes to tumor growth in the context of other somatic mutations, and PTEN protein concentrations correlate with disease severity. Clinically applicable approaches to counteract the effects of PTEN loss include PI3K, AKT, and mTOR inhibitions.[36,37,50]

A recently research demonstrated that leiomyosarcomas may occur de novo or develop within a preexisting leiomyoma. Apparently, uterine leiomyoma present areas called leyomioma-like that share several molecular features with the malignant cells.[62] There are no other studies in the literature that confirm this transformation.

Undifferentiated uterine sarcomas do not present immunoreactivity for estrogen receptors or progesterone receptors, but they present high immunoreactivity for EGFR. Smooth muscle markers and myogenin or MyoD1 may be useful to exclude leiomyosarcoma or rhabdomyosarcoma as respective diagnoses. Additionally, these tumors are positive for PDGFR-α, androgen receptor and WT1.[36,37]

The mesenchymal component of adenosarcomas exhibit increased proliferation with higher expression levels of Ki-67 and p53. In these cases, the loss of estrogen receptors, progesterone receptors, and CD10 expression is observed. The tumor suppressor gene WT1 is expressed either with or without sarcomatous overgrowth adenosarcomas. Thogether, WT1 and CD10 can be useful for diagnosis of adenosarcoma.[47]

Interesting results were obtained using a high-mobility group A1 gene (HMGA1a) transgenic model too. These mice develop aggressive uterine tumors resembling similar adenosarcoma features.[63] Several studies have reported HMGA1a over expression inducing highly malignant phenotype through the COX-2 upregulation in tumors.[47,48,57,63]

CONCLUSION

In spite of the challenge of sarcoma biology, advances in molecular techniques have improved diagnostic possibilities and allowed for major steps in the understanding of several types of sarcoma. Several factors make the study of sarcomas more complicated because they are rare tumors whose study is possible only in reference centers, and the cellular origins of each of their histological types are unknown. Accordingly, most of the current knowledge on behavior, diagnosis, prognosis, and treatment of these tumors is due to studies conducted using available molecular tools. Knowledge of tumor biology forms the basis for delineating targeted treatment modalities that are currently used, under investigation.

CONFLICTS OF INTEREST AND SOURCE OF FUNDING

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RESUMO

INTRODUÇÃO: Sarcomas uterinos constituem forma rara de neoplasia maligna, composta por cerca de 3% de todos os tumores malignos do útero, o que representa menos de 1% de todas as neoplasias ginecológicas. Baixa taxa de cura muitas vezes ocorre devido a metástases à distância, geralmente para os pulmões. Agressividade, altas taxas de recorrência local, metástases à distância e prognóstico desfavorável com sobrevida global de dois anos em menos de 50% são características comuns aos sarcomas uterinos. Apesar da baixa prevalência, estes tumores são de grande interesse devido às suas múltiplas características morfológicas e clínicas.

OBJETIVO: Este artigo focaliza aspectos gerais dos sarcomas uterinos, etiologia, prognóstico, tratamento e métodos moleculares utilizados em seu estudo.

METODOLOGIA: Esta revisão foi realizada utilizando o banco de dados Pubmed para pesquisar artigos publicados que continham as palavras-chaves: sarcoma uterino, características moleculares, fatores prognósticos.

RESULTADOS: Pouco se sabe sobre a etiologia dos sarcomas uterinos. Alguns estudos têm demonstrado a associação entre eventos genéticos que envolvem mutações em genes do ciclo celular e apoptose e epigenética em sarcomas ginecológicos. Estudos anteriores mostraram que as translocações cromossômicas foram identificadas, resultando em genes de fusão que são constitutivos e podem envolver a ativação de fatores de transcrição. Os avanços nas técnicas moleculares têm melhorado as possibilidades diagnósticas e permitiu uma melhor compreensão de diversas patologias.

CONCLUSÕES: Há vários fatores que dificultam o estudo de sarcomas, pois trata-se de tumores raros e não se sabe a origem celular de cada um de seus tipos histológicos. Assim, o estudo molecular dos fenômenos envolvidos no desenvolvimento dos diferentes tipos de câncer levou a novas estratégias utilizadas no diagnóstico e no tratamento destes tumores.

REFERENCES

1. Gill PG. Sarcoma de partes moles [Soft tissue sarcoma]. (trad. Figueiredo MTA) Manual de Oncologia Clinica. 6th Ed. São Paulo: Fundação Oncocentro de São Paulo; 1999.
2. Cotran RS, Kumar V, Collins T. Robbins Pathologic Basis of Disease. 6th Ed. Philadelphia: Saunders; 1999.
3. Iwamoto Y. Diagnosis and treatment of soft tissue tumors. J Orthop Sci. 1999;4(1):54-65.
4. Kurman RJ, Carcangiu ML, Herrington CS, Young RH. WHO classification of tumours of female reproductive organs. WHO Classification of Tumours. 4th Ed. Lyon: IARC Press; 2014.
5. D'Angelo E, Prat J. Uterine sarcomas: a review. Gynecol Oncol. 2010;116(1):131-9.
6. Di Saia PJ, Creasman WT. Clinical Gynecologic Oncology. 7th Ed. Philadelphia: Mosby Elsevier; 2007.
7. Amant F, Floquet A, Friedlander M, Kristensen G, Mahner S, Nam EJ, et al. GCIG (Gynecological Cancer Inter Group) consensus review for endometrial stromal sarcoma. Int J Gynecol Cancer. 2014 Jul 16, [Epub ahead of print].
8. Denschlag D, Masoud I, Stanimir G, Gilbert L. Prognostic factors and outcome in women with uterine sarcoma. Eur J Surg Oncol. 2007;33(1): 91-5.
9. Chan JK, Kawar NM, Shin JY, Osann K, Chen LM, Powell CB, et al. Endometrial stroma sarcoma: a population-based analysis. Br J Cancer. 2008;99(8):1210-5.
10. Abeler VM, Royne O, Thoresen S, Danielsen HE, Nesland JM, Kristensen GB. Uterine sarcomas in Norway. A histopathological and prognostic survey of a total population from 1970 to 2000 including 419 patients. Histopathology. 2009;54(3):355-64.
11. D'Angelo E, Spagnoli LG, Prat J. Comparative clinicopathologic and immunohistochemical analysis of uterine sarcomas diagnosed using the World Health Organization classification system. Hum Pathol. 2009;40(11):1571-85.
12. Tropé CG, Abeler VM, Kristensen GB. Diagnosis and treatment of sarcoma of the uterus. A review. Acta Oncol. 2012;51(6):694-705.
13. Krivak TC, Seidman JD, McBroom JW, MacKoul PJ, Aye LM, Rose GS. Uterine adenosarcoma with sarcomatous overgrowth versus uterine carcinosarcoma: comparison of treatment and survival. Gynecol Oncol. 2001;83(1):89-94.
14. Kaku T, Silverberg SG, Major FJ, Miller A, Fetter B, Brady MF. Adenosarcoma of the uterus: a Gynecologic Oncology Group clinicopathologic study of 31 cases. Int J Gynecol Pathol. 1992;11(2):75-88.
15. Nam JH. Surgical treatment of uterine sarcoma. Best Pract Res Clin Obstet Gynaecol. 2011;25(6):751-60.
16. Ayham A, Aksan G, Gultekim M, Esin S, Himmetoglu C, Dursun P, et al. Prognosticators and the role of lymphadenectomy in uterine leiomyosarcoma. Arch Gynecol Obstet. 2009;280(1):79-85.
17. Vorgias G, Fostiou S. The role of lymphadenectomy in uterine carcinosarcomas (malignant mixed mullerians tumours): a critical literature review. Arch Gynecol Obstet. 2010;282(6):659-64.
18. Gadduci A, Cosio S, Romaninia A, Genazzani AR. The management of patients with uterine sarcoma: a debated clinical challenge. Crit Rev Oncol Hematol. 2008;65(2):129-42.
19. Baiocchi G, Faloppa CC, Osório CA, Kumagai LY, Fukazawa EM, Cunha IW. Embryonal rhabdomyosarcoma of the uterine cervix in a 47-year-old woman. J Obstet Gynaecol Res. 2011;37(7):940-6.
20. Sutton G. Uterine sarcomas 2013. Gynecol Oncol. 2013 Jul;130(1):3-5.
21. Toro JR, Travis LB, Wu HJ, Zhu K, Fletcher CD, Devesa SS. Incidence patterns of soft issue sarcomas, regardless of primary site, in the surveillance, epidemiology and end results program, 1978-2001: an analysis of 26,758 cases. Int J Cancer. 2006;119(12):2922-30.
22. American Cancer Society. Available at: http://www.cancer.org/acs/groups/content/@research/documents/webcontent/acspc-042151.pdf. Accessed July 26, 2014 Cancer Facts and Figures 2014. Atlanta, GA: American Cancer Society; 2014.
23. Brooks SE, Zhan M, Cote T, Baquet CR. Surveillance, epidemiology, and end results analysis of 2677 cases of uterine sarcoma 1989-1999. Gynecol Oncol. 2004;93(1):204-8.
24. Zelmanowicz A, Hildesheim A, Sherman ME, Sturgeon SR, Kurman RJ, Barrett RJ, et al. Evidence for a common etiology for endometrial carcinomas and malignant mixed mullerian tumors. Gynecol Oncol. 1998;69(3):253-7.
25. Wysowski DK, Honig SF, Beiz J. Uterine sarcoma associated with tamoxifen use. N Engl J Med. 2002;346(23):1832-3.
26. Wickerham DL, Fsher B, Wolmark N, Bryant J, Costantino J, Bernstein L, et al. Association of tamoxifen and uterine sarcoma. J Clin Oncol. 2002;20(11):2758-60.
27. Thomas DB. The WHO collaborative study of neoplasia and steroid contraceptives: the influence of combined oral contraceptives on risk of neoplasms in developing and developed countries. Contraception. 1991;43(6):695-710.
28. Chu CS, Lin LL, Rubin SC. Cancer of the uterine body. In: DeVita VT, Lawrence TS, Rosenberg SA, editors. DeVita, Hellman, and Rosenberg's Cancer Principles & Practice of Oncology. 8th Ed. Philadelphia: Wolters Kluwer/Lippincott Williams & Wilkins; 2008; p. 1543-63.
29. Livi L, Paiar F, Shah N, Blake P, Villanucci A, Amunni G, et al. Uterine sarcoma: twenty-seven years of experience. Int J Radiat Oncol Biol Phys. 2003;57(5):1366-73.
30. O'Neill CJ, McBride HA, Connolly LE, McCluggage WG. Uterine leiomyosarcomas are characterized by high p16, p53 and MIB1 expression in comparison with usual leiomyomas, leiomyoma variants and smooth muscle tumours of uncertain malignant potential. Histopathology. 2007;50(7):851-8.
31. Abbas JS, Holyoke ED, Moore R, Karakousis CP. The surgical treatment and outcome of soft tissue sarcoma. Arch Surg. 1981;116:765-9.
32. Angervall L, Kindblom LG. Principles for pathologic-anatomic diagnosis and classification of soft-tissue sarcomas. Clin Orthop Relat Res. 1993;289:9-18.
33. Prat J. FIGO staging for uterine sarcomas. Inter J Gynaecol Obstet. 2009;104(3):177-8.
34. Brocker KA, Alt CD, Eichbaum M, Sohn C, Kauczor HU, Hallscheidt P. Imaging of female pelvic malignancies regarding MRI, CT and PET/CT: part l. Strahlenther Onkol. 2011;187(10):611-8.
35. Amant F, Coosemans A, Debiec-Rychter M, Timmerman D, Vergote I. Clinical management of uterine sarcomas. Lancet Oncol. 2009;10(12):1188-98.
36. Hensley ML. Uterine/female genital sarcomas. Curr Treat Options Oncol. 2000;1(2):161-8.
37. Kapp DS, Shin JY, Chan JK. Prognostic factors in survival in 1396 patients with uterine leiomyosarcoma: emphasis on impact of lymphadenectomy and oophorectomy. Cancer. 2008;112(4):820-30.
38. Berchuck A, Rubin SC, Hoskins WJ, Saigo PE, Pierce VK, Lewis JL Jr. Treatment of endometrial stromal tumors. Gynecol Oncol. 1990;36(1):60-5.
39. Bodner K, Bodner-Adler B, Obermair A, Windbichler G, Petru E, Mayerhofer S, et al. Prognostic parameters in endometrial stroma sarcomas: a clinicopathologic study in 31 patients. Gynecol Oncol. 2001;81(2):160-5.
40. García-Martínez E, Egea Prefasi L, García-Donas J, Escolar-Pérez PP, Pastor F, González-Martín A. Current management of uterine sarcomas. Clin Transl Oncol. 2011;13(5):307-314, doi: 10.1007/s12094-011-0659-0.
41. Amant F, De Knijf A, Van Caster B, Leunen K, Neven P, Berteloot P, et al. Clinical study investigating the role of lymphadenectomy, surgical

castration and adjuvant hormonal treatment in endometrial stromal sarcoma. Br J Cancer. 2007;97(9):1194-9.
42. Shah JP, Bruant CS, Kumar S, Ali-Fehmi R, Malone JM Jr, Morris RT. Lymphadenectomy and ovarian preservation in low grade endometrial stroma sarcoma. Obstet Gynecol. 2008;112(5):1102-8.
43. Hoellen F, et al. The role of lymphadenectomy in uterine sarcoma: a clinical practical based on restrospective analysis. Anticancer Research. 2014.
44. Greer BE, Wui-Jin-Koh, Abu-Rustun NR, Campos SM, Chan J, et al. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines™), Version I. 2012. Available at: http://www.nccn.org/patients/clinical/default.aspx. Accessed July 26, 2014
45. Riopel J, Plant M, Renaud MC, Roy M, Têtu B. Lymph node metastases in low grade endometrial stromal sarcoma. Gynecol Oncol. 2005;96(2):402-6.
46. Kobayashi H, Uekuri C, Akasaka J, Ito F, Shigemitsu A, Koike N, et al. The biology of uterine sarcomas: a review and update. Molecular and Clinical Oncology. 2013;1:599-609.
47. Erez A, Shchelochkov OA, Plon SE, Scaglia F, Lee B. Insights into the pathogenesis and treatment of cancer from inborn errors of metabolism. Am J Hum Genet. 2011;88(4):402-21.
48. Carvalho KC, Cunha IW, Rocha RM. Molecular tools used in the study of sarcomas. Applied Cancer Research. 2010;30(2):237-9.
49. Stewart CJ, Leung YC, Murch A, Peverall J. Evaluation of fluorescence in-situ hybridization in monomorphic endometrial stromal neoplasms and their histological mimics: a review of 49 cases. Histopathology. 2014 Mar 4, [Epub ahead of print].
50. Cunha IW, Lopes A, Falzoni R, Soares FA. Sarcomas often express constitutive nitric oxide synthases (NOS) but infrequently inducible NOS. Appl Immunohistochem Mol Morphol. 2006;14(4):404-10.
51. da Cunha IW, De Brot L, Carvalho KC, Rocha RM, Fregnani JH, Falzoni R, et al. Prognostication of soft tissue sarcomas based on chromosome 17q gene and protein status: evaluation of TOP2A, HER-2/neu, and survivin. Ann Surg Oncol. 2012;19(6):1790-9.
52. Cunha IW, Carvalho KC, Martins WK, Marques SM, Muto NH, Falzoni R, et al. Identification of genes associated with local aggressiveness and metastatic behavior in soft tissue tumors. Transl Oncol. 2010;3(1):23-32.
53. Silveira SM, Villacis RA, Marchi FA, Barros Filho M de C, Drigo SA, Neto CS, et al. Genomic signatures predict poor outcome in undifferentiated pleomorphic sarcomas and leiomyosarcomas. PLoS One. 2013;8(6):e67643.
54. Villacis RA, Silveira SM, Barros-Filho MC, Marchi FA, Domingues MA, Scapulatempo-Neto C, et al. Gene expression profiling in leiomyosarcomas and undifferentiated pleomorphic sarcomas: SRC as a new diagnostic marker. PLoS One. 2014;9(7):e102281.
55. Carvalho KC, Cunha IW, Rocha RM, Ayala FR, Cajaíba MM, Begnami MD, et al. GLUT1 expression in malignant tumors and its use as an immunodiagnostic marker. Clinics (Sao Paulo). 2011;66(6):965-72.
56. Stewart CJ, Leung YC, Murch A, Peverall J. Evaluation of fluorescence in-situ hybridization in monomorphic endometrial stromal neoplasms and their histological mimics: a review of 49 cases. Histopathology. 2014 Mar, doi: 10.1111/his.12406. [Epub ahead of print].
57. Ballestar E. An introduction to epigenetics. Adv Exp Med Biol. 2011;711:1-11.
58. Murray S, Linardou H, Mountzios G, Manoloukos M, Markaki S, Eleutherakis-Papaiakovou E, et al. Low frequency of somatic mutations in uterine sarcomas: a molecular analysis and review of the literature. Mutat Res. 2010;686(1-2):68-73.
59. Chiang S, Oliva E. Cytogenetic and molecular aberrations in endometrial stromal tumors. Hum Pathol. 2011;42(5):609-17.
60. Popiela A, Gabryś MS, Rabczyński J, Pańszczyk M, Keith G, Baranowski W. Estimation of DNA methylation level in nonendometrial uterus malignancies. Ginekol Pol. 2002;73(11):962-5.
61. Mittal R, Chen F, Wei JJ, Rijhvani K, Kurvathi R, Streck D, Dermody J, et al. Molecular and immunohistochemical evidence for the origin of uterine leiomyosarcomas from associated leiomyoma and symplastic leiomyoma-like areas. Modern Pathology. 2009;22(10):1303-11.
62. Tesfaye A, Di Cello F, Hillion J, Ronnet BM, Elbahioul O, Ashfaq R, et al. The high-mobility group A1 gene up-regulates cyclooxygenase 2 expression in uterine tumorigenesis. Cancer Research. 2007;67(9):3998-4004.