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CASE REPORTS

Noninvasive Polypoid Malignant Mixed Mullerian Tumor of the Uterus: A Case Report and Literature Review

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Abstract

Introduction: Malignant mixed Müllerian tumors (MMMT), also known as carcinosarcomas, are rare and highly aggressive neoplasms of the uterus, accounting for less than 5% of all uterine malignancies. These tumors are biphasic, comprising both carcinomatous (epithelial) and sarcomatous (mesenchymal) components, and are typically associated with poor prognoses due to their rapid progression and high metastatic potential.

In this report, we present a unique case of noninvasive polypoid MMMT of the uterus, highlighting its clinical presentation, diagnostic challenges, and management. We also provide a comprehensive literature review, which enriches our understanding of this case within the broader context of uterine carcinosarcomas.

Results: This is the first documented case in English literature of a polypoid uterine carcinosarcoma without endometrial infiltration. It is significant because it adds to the limited literature on noninvasive polypoid MMMTs, typically aggressive and diagnosed at advanced stages. Uterine carcinosarcomas are generally aggressive, with most cases diagnosed at advanced stages.

Conclusion: Uterine carcinosarcomas are indeed rare, aggressive, and rapidly progressing neoplasms with poor prognoses. It is crucial to include carcinosarcomas in the differential diagnosis of high-grade uterine neoplasms, especially for polypoid tumors. This inclusion is not just essential, but it is the key to ensuring accurate and timely diagnosis, underscoring the significant role of medical professionals in this process.

Keywords: Noninvasive polypoid MMMT, uterine carcinosarcoma, endometrial neoplasms, polypoid uterine tumors,

Introduction

Malignant mixed Mullerian tumors (MMMT), or Carcinosarcomas, are rare biphasic, aggressive malignant tumors with high-grade epithelial and sarcomatous components. Due to metaplasia/transdifferentiation (epithelial to mesenchymal transition), the sarcomatous component can derive from the carcinomatous component. [1] Endometrial Malignant Tumors (EMTs) are most commonly seen in postmenopausal females, with a higher incidence among African lineage.[2]

Regarding the origin of the neoplasm, four theories have been proposed:

1. *Collision theory:* the sarcoma and carcinoma are independent neoplasms;
2. *Combination theory:* both components are derived from a single stem cell that undergoes divergent differentiation early in the evolution of the tumor,
3. *Conversion theory:* the sarcomatous element derives from the carcinomatous component during the evolution of the cancer,
4. *Composition theory:* The spindle cell component is a pseudo sarcomatous stromal reaction to the carcinoma [4].

The Cancer Genome Atlas (TCGA) data supports the conversion and combination theories [5]. The most common epithelial component is adenocarcinoma, but clear cell, mucinous, and papillary serous components can also

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occur, and the most common mesenchymal component is undifferentiated sarcoma in homologous tumors and rhabdomyosarcoma in heterologous tumors [6].

In our case, the patient is a 56-year-old who complained of postmenopausal bleeding and abdominal pain. She had a history of four successful vaginal deliveries and no prior gynecological problems were referred. The patient's symptoms included abnormal vaginal bleeding and lower abdominal pain over the last 3 months.

This patient was diagnosed with a Malignant Mix Mullerian Polypoid Tumor that does not infiltrate the mucosa or the other histologic layers.

To the best of our knowledge in English literature, this is the first case of a polypoid uterine carcinosarcoma without endometrial infiltration. Most uterine carcinosarcomas have an aggressive course and are presented in advanced stages at the time of diagnosis.

Case presentation

A 56-year-old postmenopausal woman presented with a history of abnormal vaginal bleeding and lower abdominal pain in the last 3 months. The patient has successfully undergone four vaginal deliveries (G4P4). No prior gynecological problems were referred, and there was no history of other diseases. In the pelvic exam, normal external genitalia were observed. The cervix was in standard shape and appearance, and the uterus was motile, with mild tenderness in typical dimensions. The fornices were free. The transvaginal ultrasound exam revealed the presence of a 40 mm intracavitary, non-homogenous mass with increased vascularity. The uterus was homogenous, with no signs of myometrial involvement. The ovaries were atrophic, with no evident lesions. No free fluid was noted.

Based on these findings, a hysteroscopic and pathologic examination was recommended. The diagnostic hysteroscopy showed an enlarged, irregular uterine cavity and the presence of a white-gray mass, with increased vascularity, that occupies the uterine cavity (Figure 1 - A).

Several samples were taken for histopathological evaluation, which revealed that the intracavitary mass had highly atypical epithelial and mesenchymal components, raising suspicion for MMMT. Subsequently, the patient underwent an abdominal MRI, which showed a mass in the uterine cavity with no signs of myometrial involvement and without the presence of any other suspicious lesion in other abdominal organs (Figure 1 - B).

Given the diagnostic evidence, it was decided to proceed with surgery for FIGO Stage I – C uterine Carcinosarcoma. The patient underwent a type A - extra fascial total abdominal hysterectomy with bilateral salpingo-oophorectomy and bilateral systematic pelvic lymphadenectomy. The pathologic findings in the final biopsy are as follows.

Macroscopically, we observe the uterus together with the cervix and both adnexa 8 x 9 x 5 cm. A polypoid mass measuring 4 cm in diameter protrudes from the endometrial cavity (Fig.2). The tumor was sectioned carefully in parallel sections on the long axis. Near the center of the cancer, we noticed difficulty in cutting because of the bony, delicate trabecula appearance. The right and left lymph nodes were included after properly dissecting the surrounding fatty tissue.

Microscopically, the tumor reveals a third-grade endometrioid carcinoma and a heterologous sarcomatous component, which consists of osteoid malignant tissue. Cancer presents pronounced necrosis in the areas of attachment to the endometrium through a fragile short, almost 1 mm thick, and 3x4 mm wide peduncle. Neither the endometrium nor the myometrium is invaded in all the circumscribed contact areas of the tumor with the endometrium. Neither lymphatic vascular nor perineural invasion is observed. Twenty-one pelvic lymph nodules were examined, which were reactive without tumor metastasis.

The patient was informed about the diagnosis and the recommended treatment plan. She expressed understanding and consented to the surgery. Post-surgery, the patient was

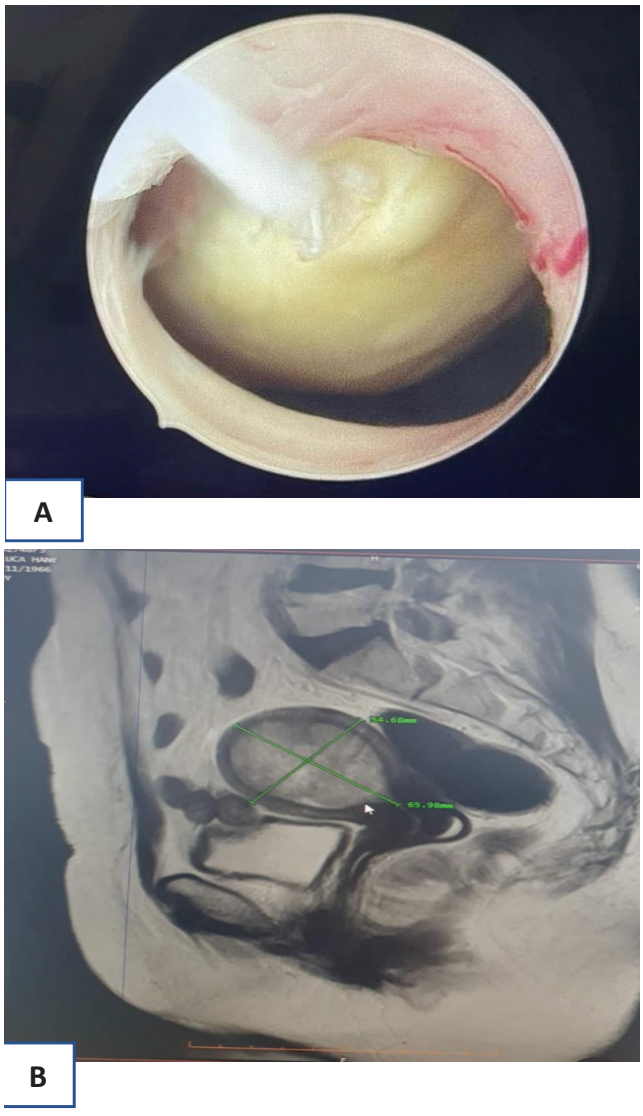

Fig.1 A) Hysteroscopy image B) The MRI imaging

monitored closely and showed a positive response to the treatment, with no signs of recurrence at the last follow-up.

Immunohistochemical exams were performed. Epithelial markers (AE1/AE3) are positive in the epithelial component, while the mesenchymal component exhibited focal positivity for vimentin and smooth muscle actin. Also, ER has a positivity of around 30% in epithelial component, PDL1 scores 0 % in tumoral cells and 80 % in intratumorally inflammatory cells. S100 and Her2 were negative, while p53 was positive in 5% of cells with aberrant expression. Some of the antibodies are shown in the figure 3. Based on the appearance of Hematoxylin Eosin and the Immunohistochemical profile of the tumor, the diagnosis of a Polypoid noninvasive MT of the uterus was established. After multidisciplinary oncologic consultations, it was concluded that the patient should not undergo radiotherapy or chemotherapy because there was no endometrial infiltration, and the stage was T0.

In the follow-up performed every three months for a year, which included an ultrasound examination and a PET scan, the patient had no metastatic lesions, and further routine follow-up was programmed.

Discussion

Uterine carcinosarcoma is a rare, highly aggressive, rapidly progressing neoplasm associated with a poor prognosis that has not significantly improved in the past thirty years despite advances in imaging and adjuvant therapies.[7] Carcinosarcomas, though rare, representing less than 5% of all uterine tumors, account for 16.4% of all deaths caused by a uterine malignancy [8]. Gerhardt reported the first case in 1989, which Meyer confirmed by examining the slides [9]. Women are usually over the age of 50, with most cases

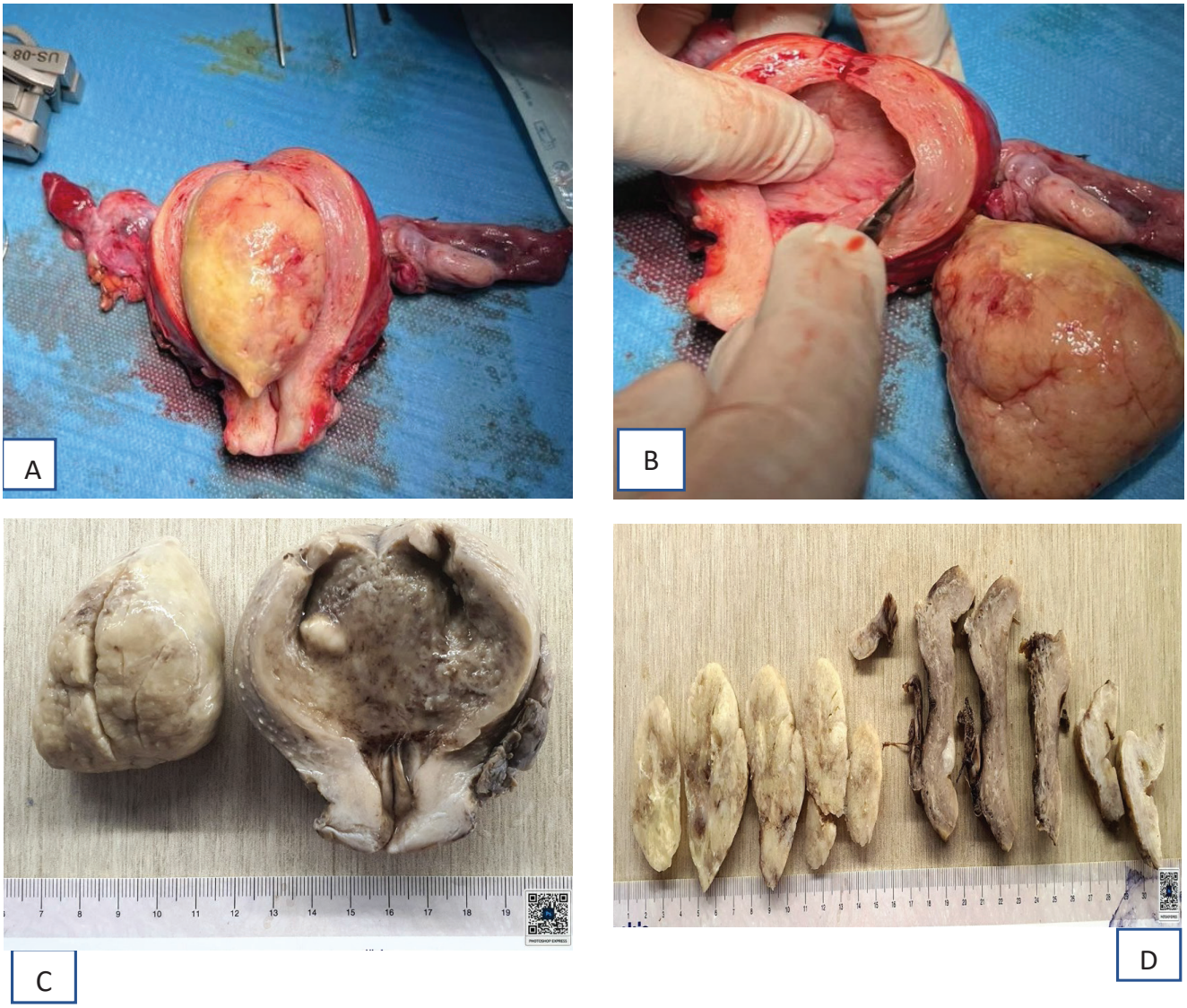

Figure 2. Macroscopically, a polypoid mass measuring 4 cm in diameter. A) The mass immediately after the uterine excision. B) The surgeon removed the mass, and no invasion was observed macroscopically. C) The lesion after the formalin fixation. D) The uterus was cut longitudinally together with the tumor to better evidence the place of insertion of the polypoid mass.

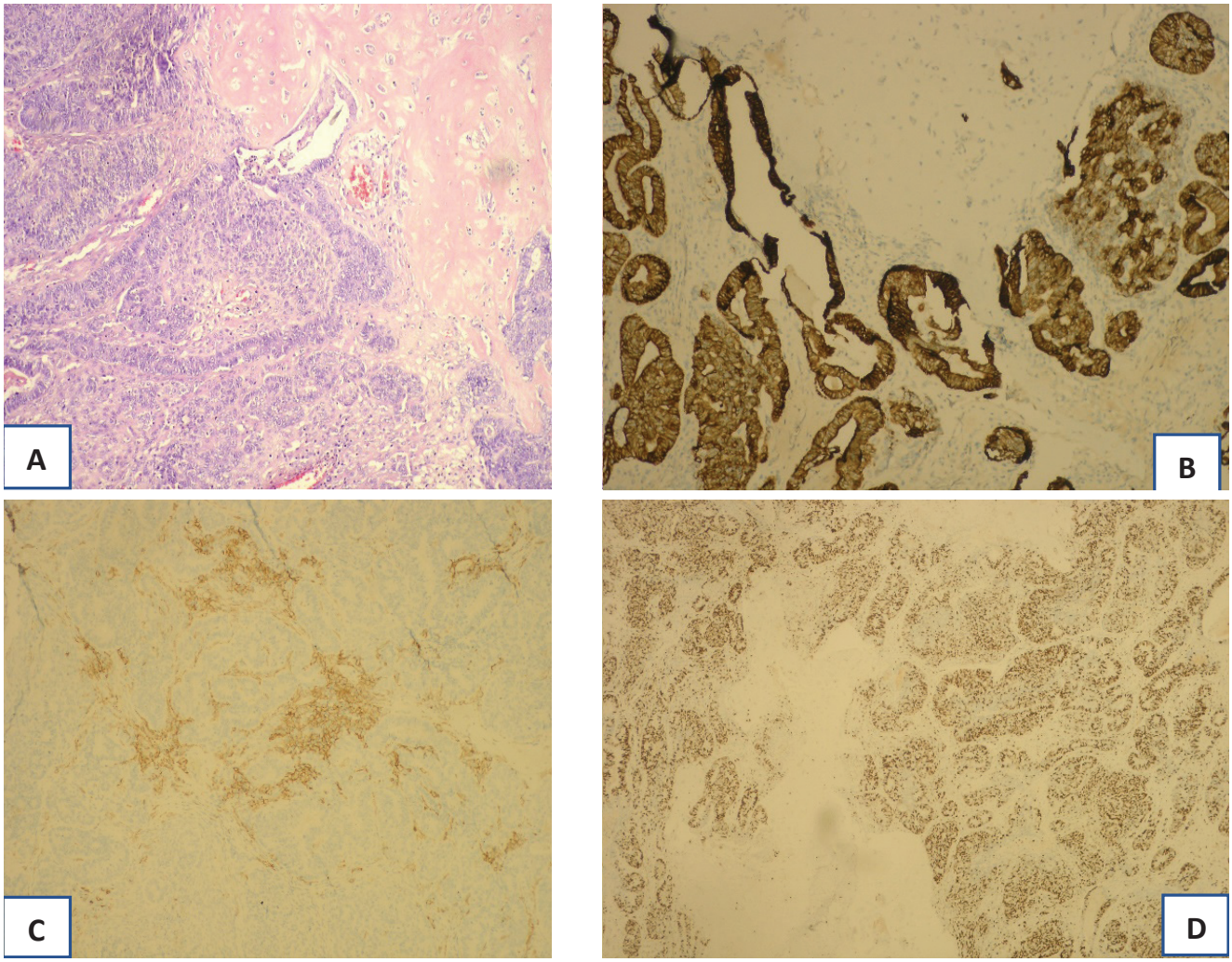

Figure 3. A) Hematoxylin Eosin x20. B) CK7 stain. C) PDL1 stain. D) ER stain.

occurring between the sixth and seventh decade [10], with a median age of 62 years [11]

Cases younger than 40 years old are sporadic. MMMT commonly affects the uterus; however, other parts include the cervix, ovaries, fallopian tubes, vagina, peritoneum, and extra-genital sites [12]. In our case, the patient is 56 years old, which corresponds to the average age of previous studies, and the tumor is located in the back of the corpus uteri.

MMMT has a poor prognosis, and most patients have extrauterine spread at the time of diagnosis [13]. Extension to the pelvis, lymphatic and vascular permeation, distant lymph nodes, and blood-borne metastasis are common [14]. It is crucial to mention that the epithelial component is frequently found at distant metastatic sites. In contrast, the sarcomatous component is linked to the extension of the tumor in the local area [14].

The case we present is unique in the English literature as a T0 case, exclusively polypoid without endometrial infiltration. Other cases in the literature range from at least T1 to stage IV. In a study by Rajshekar SK et al. [15], six patients were in the first stage, four in the second stage, and eight in the third stage. In a clinical case published by Emmanuel D. Morgan et al. [5], the patient was in stage II. Even in other studies or case reports, we did not find a case where the endometrium was not infiltrated by uterine carcinosarcoma.

Analyzing the macroscopic and microscopic findings, we have a previous adenomatous dysplastic endometrial polyp, which was grown sustained by a peduncle to expand the endometrial cavity. Then, malignant transformation occurred, with the subsequent transdifferentiation into the osteosarcoma component.

The symptoms and diagnosis of endometrial carcinosarcomas are vague and generally resemble those of many other types of endometrial cancers. It is challenging to differentiate endometrial carcinosarcoma from different types of uterine tumors based solely on clinical presentation. Clinical signs of uterine carcinosarcoma include vaginal bleeding, abdominal pain, and discharge. [18] Even in our case, the patient presents with postmenopausal bleeding and lower abdominal pain.

For the etiology of MT, nulliparity, diabetes mellitus, obesity, chronic stimulation with estrogen, history of pelvic radiation, and long-term use of tamoxifen are considered predisposing factors. In our case, apart from the fact that she is overweight with a BMI of ~ 25, the patient does not refer to this other predisposing factor. Regarding the treatment, there is no consensus on the gold standard treatment for uterine MT. The optimal treatment remains uncertain, partially because the histogenesis remains controversial. The primary treatment remains surgery with total hysterectomy and pelvic lymph node resection, although the benefits of lymph node resection have not been fully confirmed. A multimodality treatment plan has been suggested, with results indicating that surgery followed by a combination of both chemotherapy and radiation therapy leads to a significantly longer median disease-specific survival (DSS) of 31 months versus surgery alone (DSS = 3 months), radiation therapy alone (DSS = 15 months), or chemotherapy alone (DSS = 14 months). Recently, based on the results of several trials, immunotherapy (with or without tyrosine kinase inhibitor) has emerged as the standard treatment modality after the failure of platinum-based chemotherapy. Around 10% of endometrial carcinosarcomas are MSI-H, 5% are POLE mutated, and 60% show PD-1/PD-L1 immunohistochemical expression; immunotherapy (alone or in combination with tyrosine kinase inhibitor) may be particularly promising in these molecular subgroups. In our case, the patient underwent a total hysterectomy with resection of the pelvic lymph nodes, all of which were found to be reactive. After multidisciplinary oncologic consultations, it was decided that the patient should not undergo radiotherapy or chemotherapy because there was no endometrial infiltration, and the stage was T0. The patient has no metastatic lesions in the follow-up performed every three months for a year with an ultrasound examination and a PET scan.

Regarding the histopathological features, MMMTs express epithelial features through the positivity of epithelial markers such as pan-cytokeratin and epithelial membrane antigen and stromal features through the positivity of stromal markers such as Desmin and S-100. [18] In our case, in the examination with immunohistochemistry, the tumor results in positive CKAE1/AE3, positive Vimentin, and positive smooth muscle actin, supporting the diagnosis and adhering to the histopathological features of uterine carcinosarcomas.

MMMT has a poor prognosis, with extrauterine spread at the time of diagnosis in most of the patients [19]. Extension to the pelvis, lymphatic and vascular permeation, distant lymph nodes, and blood-borne metastasis are common [14]. The patient has no metastases in stages T0 and 12 months after the initial treatment. However, taking into account the aggressiveness of the tumor, it remains to be seen whether it will continue to be without metastases in the future or not. The metastatic spread of MT is similar to high-grade endometrioid carcinoma, and most patients die of local pelvic recurrence or abdominal recurrence. The risk for the advanced stage of the disease and recurrence is closely related to the depth of myometrial invasion. [20]. Moreover, the 3-year disease-free survival rate was 87% for cases with high-grade adenocarcinoma compared to 42% for cases with MMMT [19]. The average 5-year overall survival for patients with MTC was previously to be 21%, and 70%–90% of tumor-related deaths occurred within 18 months of diagnosis [21].

The strength of this case lies in the successful treatment outcome. The fact that the patient, after undergoing surgery without accompanying chemotherapy or radiotherapy, has shown no signs of disease recurrence after 12 months is a testament to the potential for successful treatment of uterine carcinosarcoma.

Conclusion:

Since uterine carcinosarcoma is a rare, highly aggressive, rapidly progressing neoplasm associated with a poor prognosis, it is necessary to include them in the differential diagnosis of uterine high-grade neoplasm. It is essential to make an accurate diagnosis in the cases of polypoid tumors of the uterus. Multiple punch biopsies and deep levels through a hysteroscopic procedure are the only procedures to approach a correct preoperative diagnosis. Considering carcinosarcomas in the differential diagnosis will make treatment more accurate and improve survival. From the clinical and imaging point of view, not all polypoid tumors are benign.

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Authors Contribution: L.K: Conceptualization of the case, revision, the surgeon who made the surgery of this case; L.B: The supervision, investigation, and collection of data; and the pathologist who diagnosed the case.; T.B: Helped in the revision, the collaborator pathologist of the diagnosis.; A.N: The data collection and the article's writing helped structure the article.

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