CANCER DIAGNOSIS & PROGNOSIS
4: 363-369 (2024) doi: 10.21873/cdp.10333

# Pleomorphic Rhabdomyosarcoma of the Uterine Corpus in an Adult Who Underwent Multi-gene Panel Testing

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**Abstract.** *Background/Aim: Rhabdomyosarcoma (RMS) is the most common malignant soft tissue tumor in children. Adult primary RMS of gynecological origin is a rare condition and uterine RMS is an aggressive malignancy with a poor prognosis. The genetic variants associated with uterine RMS in adults have yet to be fully elucidated, and there is no established therapeutic strategy for rare tumors. Case Report: A 69-year-old Japanese woman was referred to our hospital with abdominal bloating. Imaging examination revealed a tumor with diameter of 85 mm located in the uterus and multiple regional lymph node metastases. Biopsy of the uterine corpus indicated possible uterine carcinosarcoma or RMS. Following debulking surgery, the patient was diagnosed with stage IVB pleomorphic RMS. The patient was treated with two courses of doxorubicin every three weeks and one course of combination chemotherapy with vincristine, actinomycin, and cyclophosphamide. Because of rapid progression of the disease, we decided to perform multi-gene panel testing to determine the most effective therapeutic strategy. However, no therapeutic plan based on genetic information was identified. The patient with chemotherapy-refractory RMS died 11 weeks after surgery. Conclusion: Our patient had advanced uterine RMS with an unresectable tumor that was resistant to chemotherapy, resulting in poor outcomes. Despite conducting multi-gene panel testing, no tailored therapeutic approach based on genetic information was found. This case highlights the challenges in managing uterine RMS in adults and underscores the urgent need for further research to identify effective treatment modalities.*

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Key Words: Multi-gene panel testing, pleomorphic rhabdomyosarcoma, sarcoma, uterine rhabdomyosarcoma.



Rhabdomyosarcoma (RMS) can occur anywhere in the body, including the striated muscles. It mainly arises from the four extremities, urogenital system, and head and neck region in children younger than 10 years. It originates from fetal mesoderm or the mesenchymal tissues that form skeletal muscle in the future or express skeletal muscle differentiation potential after malignant transformation. According to the 2020 World Health Organization classification (1), RMS is categorized into four histological subtypes: embryonal, alveolar, spindle cell/sclerosing, and pleomorphic. Embryonal RMS (ERMS), a tumor mainly originating from the head, neck, and urogenital system, accounts for approximately half of all childhood RMS cases. Although alveolar RMS (ARMS) is common in children, its outcomes are worse than those of ERMS. Pleomorphic RMS (PRMS), which occurs mainly in adults, is high-grade sarcoma associated with poor survival. Some review articles have shown that uterine RMS in adults consists primarily of ERMS and PRMS (1-5). In addition, several reports on uterine PRMS in adults have indicated a high malignant potential and therapeutic inefficiency (3, 5, 6). The treatment strategy for RMS in children is determined based on the tissue type, classification of the pretreatment stage, and postoperative groups based on the presence of residual tumor. In contrast, a therapeutic approach for adult RMS has not yet been established owing to its rarity. Therefore, adult RMS is usually treated in accordance with the management of childhood RMS. Adult RMS is typically managed in the same way that childhood RMS is. However, poor survival in adult RMS may indicate variations in metabolic characteristics and the need for specific therapeutic

strategies. Currently, multi-gene panel testing (MGPT) is widely used to aid in therapeutic decisions. Here, we present a case of PRMS of the uterine corpus in a 69-year-old patient who underwent MGPT.

## Case Report

A 69-year-old postmenopausal Japanese woman (gravida 1, para 1) with complaints of abdominal bloating and rapid increase in abdominal girth was referred to our hospital for further evaluation and treatment of uterine malignancy. The patient reported no vaginal bleeding or abdominal pain. The patient's family history was unremarkable. She was diagnosed with uterine myoma of 50 mm size in the posterior wall and hypertrophic endometrium at the age of 66 years. Endometrial polyps in the resected endometrium were pathologically confirmed using hysteroscopy. Another uterine tumor was detected in the pelvic cavity in addition to the uterine myoma at the age of 66 years, raising suspicions of uterine malignancy. The markedly enlarged uterus was associated with decreased uterine mobility on pelvic examination. Transvaginal ultrasonography revealed a heterogeneous and hypervascular uterine mass, measuring 80×85 mm. Pelvic magnetic resonance imaging showed a huge mass occupying the anterior uterine wall, with greatly enhanced effects and restricted diffusion (Figure 1A-D). There was also a smooth-marginated round tumor, 50 mm in size, in the posterior uterine wall, that displayed low intensity on T1- and T2- weighted imaging, indicating that it was a uterine myoma. Greatly intense $^{18}$F-fluorodeoxyglucose accumulation within the tumor [standardized uptake value (SUV)max, 16.0] and lymph nodes (pelvic nodes, paraaortic nodes, and diaphragmatic crura lymph nodes; SUVmax, 6.2-14.4) was observed on positron emission tomography/computed tomography (Figure 2A-D). Blood examination revealed elevated levels of serum lactate dehydrogenase (2,942 IU/l) and neuron-specific enolase (254 ng/ml), and normal serum levels of carbohydrate antigen 125 (10.8 U/ml) and squamous cell carcinoma antigen (1.1 ng/ml). Endometrial biopsy revealed a cluster of tumor cells with nuclear atypia, resulting in the suspicion of poorly differentiated carcinoma, such as RMS, carcinosarcoma, and neuroendocrine carcinoma.

Although primary cytoreductive surgery was attempted, infiltration of the uterine cervix and parametrium resulted in incomplete surgery; therefore, supravaginal uterine amputation and bilateral salpingo-oophorectomy were performed. In addition, the tumor's high fragility resulted in significant hemorrhage (9,200 ml) and blood-transfusions (red blood cells, 4,480 ml; fresh frozen plasma, 4,080 ml; platelets, 250 ml) were required. The white solid tumor occupied the entire area of the specimen and had macroscopically invaded the surface of the uterine corpus (Figure 3). Histopathological examination revealed that the tumor was mainly composed of necrotic, pleomorphic, suborbicular, and hyperchromatic cells, with a high nuclear-to-cytoplasmic ratio. The tumor cells had invaded the cervical stroma and stump, whereas the endometrial glands were normal. The tumor cells were partially positive for desmin, myogenin, and MyoD1, and showed high Ki-67 expression, as determined using immunohistochemistry (Figure 4A-F). The patient was diagnosed with TNM stage IV and clinical group IV PRMS, according to the Intergroup Rhabdomyosarcoma Study Group staging system (7).

Adjuvant chemotherapy for residual tumors was initiated on postoperative day 19 because of rapid tumor growth. A urethral stent was indwelled 41 days after surgery because the enlarged lymph nodes were responsible for right hydronephrosis after two courses of doxorubicin every three weeks. Moreover, palliative radiotherapy for the para-aortic lymph nodes (20 Gy over five fractions) was performed 56 days after surgery because the back and buttock pain worsened due to multiple regional lymph node metastases. One cycle of combination chemotherapy with vincristine, actinomycin, and cyclophosphamide (VAC) as second-line chemotherapy was administered 68 days after surgery because of the patients' and her family's desire for aggressive treatment. The rapidly progressive disease prompted us to perform multi-gene panel testing (MGPT) (FoundationOne® Liquid CDx, Foundation Medicine, Inc. Boston, MA, USA) to suggest a better therapeutic approach. Although the testing revealed microsatellite stability, low levels of tumor mutational burden (3 mutations/mb), and mutations in *FBXW7, MSH3, RB1*, and *SPOP* genes, no therapeutic strategy based on genetic information was identified. The patient with chemotherapy-refractory RMS died 79 days after surgery.

## Discussion

This is the first report of uterine PRMS in an adult in whom MGPT was conducted to determine an effective treatment. Rapid tumor growth and chemotherapy resistance contributed to a poor prognosis. Although MGPT did not provide a specific therapeutic plan in this case, it has great potential for the treatment of rare malignant tumors in combination with the development of new therapeutic agents.

The prognosis of RMS in children is associated with physiological and clinical characteristics, such as the histological type and the presence or absence of distant metastasis. Multimodal therapies have been developed to improve RMS outcomes in children and adolescents. However, knowledge regarding adult RMS is scarce, and despite worse survival outcomes in adults than in children, therapeutic strategies have not been established because of its rarity (8).

Approximately 140 cases of uterine RMS in adults have been described in literature published in English language.

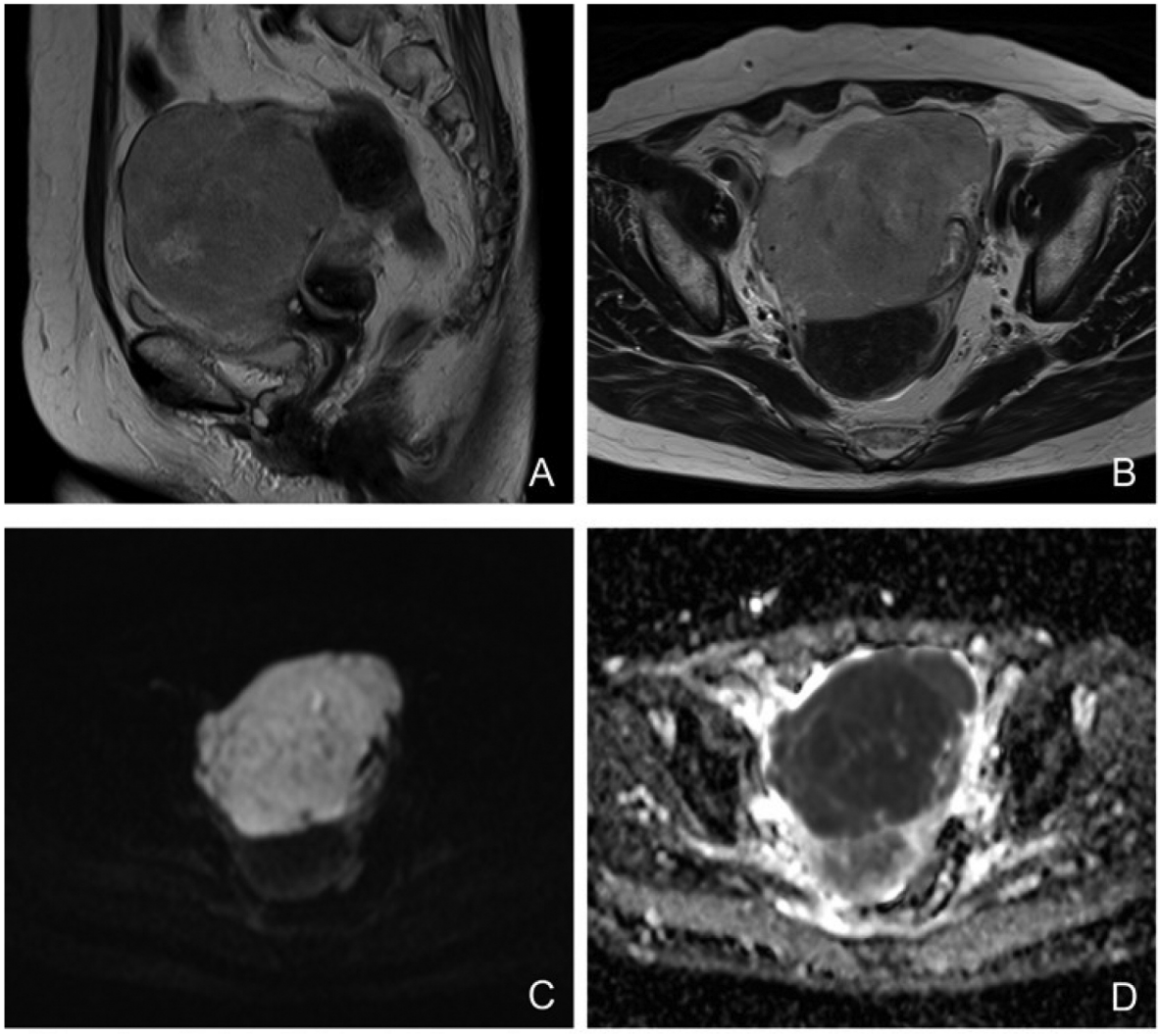


Figure 1. *Pelvic magnetic resonance imaging revealing a mass located in the anterior uterine wall on T2-weighted imaging (A, B). A tumor showing high signal intensity on diffusion-weighted imaging (C) and low signal intensity on apparent diffusion coefficient mapping (D).*

Most patients with uterine RMS experience genital bleeding. Ferguson *et al*. (2) investigated clinical characteristics of 15 women with genital tract RMS, including three cases of uterine corpus RMS and eight cases of cervical RMS, and reported that 70% of patients had abnormal bleeding and 15% had abdominal pain. In a review of 25 reported cases of cervical RMS in adults, Meng *et al*. (9) reported that bleeding was the most frequent symptom, together with vaginal masses or polyps being common. The most common subtype of adult RMS is PRMS, which is associated with unfavorable outcomes (8, 10). Pinto *et al*. (6) estimated that PRMS and ERMS account for 60-70% and 30-40% of uterine RMS in adults, respectively, and ARMS is a rare subtype. However, there seems to be a difference between cervical and corpus RMS in adults. The review of 25 cases (9) with uterine cervical RMS revealed that the median age and tumor size were 20 (range=20-75) years and 6.0 (range=3.3-18.0) cm, respectively. Furthermore, 86% of the patients were diagnosed with stage I RMS and had good outcomes, except for two patients who died within 4 months after surgery. ERMS is the primary subtype of cervical RMS (6). Meanwhile, patients with uterine corpus RMS were found to be older (median age, 65 years; range=21-90 years), with larger tumor sizes (median size, 10.0 cm; range=5.0-20.0 cm) than those with cervical RMS, in a review of 41 cases with uterine corpus RMS (11). The median survival time for patients with uterine corpus RMS was 12.9 months. PRMS accounted for more than half of the uterine corpus

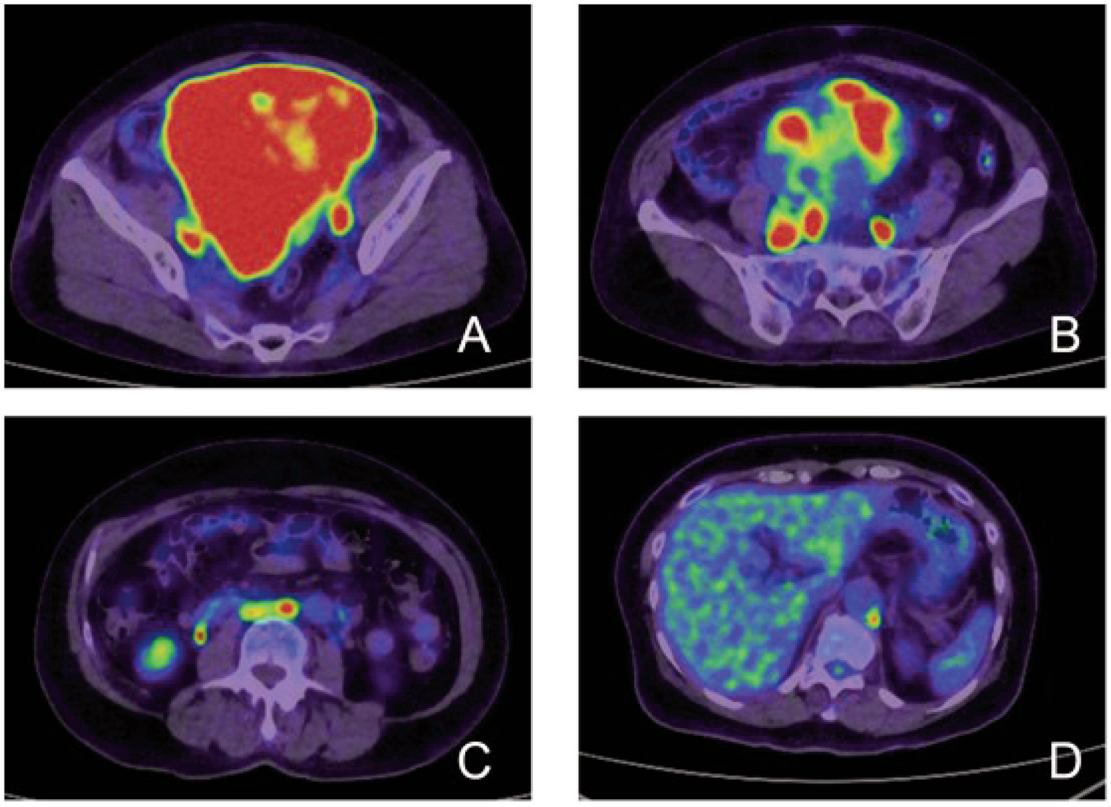


Figure 2. *Whole-body positron emission tomography/computed tomography showing high $^{18}$F-fluorodeoxyglucose accumulation within the uterine tumor (A, SUVmax 16.0), pelvic lymph nodes (B), para-aortic lymph nodes (C), and diaphragmatic lymph nodes (D).*

RMS, and 42.1% of the patients with PRMS died within 6 months after surgery or diagnosis. In contrast, 70% of patients with ERMS, which accounted for 22% of the uterine corpus RMS survived, indicating that uterine PRMS in adults is associated with poor outcomes.

The diagnosis of RMS requires the exclusion of small round cell neoplasms with similar cytological features. Therefore, immunohistochemical studies can contribute to the identification of the origin of the tumor. The use of markers specific to skeletal muscle phenotypes, such as desmin, MyoD1, and myogenin, could lead to an accurate diagnosis (12). The RMS subtype is determined based on the morphological characteristics.

Multimodal therapy consisting of surgery, chemotherapy, and radiation, has also been conducted for uterine RMS in adults as well as children (5, 9, 11). Fertility preservation is a treatment strategy for children with uterine RMS. Complete tumor resection, which may contribute to the improvement of poor outcomes, is recognized as the standard treatment for adults with uterine RMS. Pelvic and/or aortic lymph node dissection has been performed in several cases; however, whether it can improve the outcome of uterine RMS remains unknown. Lymph node excision should be performed with caution because some patients die several days or weeks following surgery (9, 11, 13). Most patients undergo additional therapies, including chemotherapy and/or radiotherapy, after surgery. In a review of 24 adult cases of uterine corpus PRMS, Alavi *et al*. (5) showed that adjuvant therapy improved the outcome of patients with extrauterine spread. Based on pediatric clinical trials conducted by the Intergroup Rhabdomyosarcoma Study Group and the Children's Oncology Group, the gold standard chemotherapy for RMS is VAC therapy. Chemotherapy, including doxorubicin, ifosfamide, platinum, and taxanes, is administered to patients with uterine sarcomas. Furthermore, anticancer agents and molecular-targeted agents, such as trabectedin, eribulin, and pazopanib, are currently available. Most cases of uterine RMS in adults are treated with VAC or chemotherapeutic drugs for uterine sarcoma. There is no English literature on therapy for adult uterine RMS using relatively new agents, such as trabectedin, eribulin, and pazopanib; therefore, further accumulation of cases is needed.

The unfavorable outcomes and rarity of RMS in adults prompted us to seek novel therapeutic strategies focused on

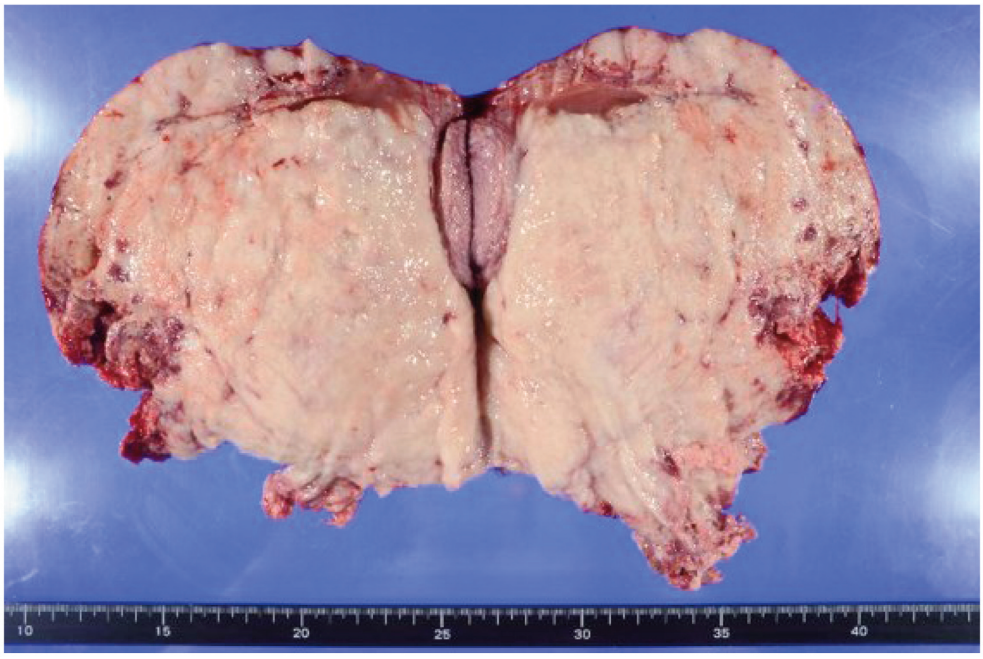


Figure 3. *White solid tumor occupying the entire uterine resection specimen.*

the pathogenesis of RMS. FoundationOne® Liquid CDx is a comprehensive sequencing panel that profiles 324 malignancy-related genes. In this case, we identified mutations in *FBXW7, MSH3, RB1*, and *SPOP*. Moreover, microsatellite stability and low levels of tumor mutational burden were observed. Choi *et al*. (14) demonstrated that both p53 and RB deficiencies in soft tissue sarcomas are related to undifferentiated and high-grade transformation *in vivo*. Many studies have been conducted to identify the molecular pathways attributed to the pathogenesis of RMS in children. Gene fusion (*PAX3-FOXO1* or *PAX7-FOXO1*) has been detected in 70-80% of pediatric ARMS cases (15, 16). *PAX3-FOXO1* fusion contributes to poor prognosis (15, 16). A study of 641 RMS samples from two cohorts investigated 39 target genes previously implicated in RMS using a custom-captured gene panel (17). Mutations in RAS isoforms (*NRAS, KRAS*, and *HRAS*), *BCOR, NF1, TP53*, and *FGFR4* were frequently detected in RMS as well as in female genitourinary RMS. Mutations in *CTNNB1, PIK3CA, MDM2, CDKN2A, FBXW7, MYOD1, CDK4*, and *MYCN* occur in 2-5% of cases. Gene mutations varied with the age of onset; *MYOD1* mutation, and *CDK4* and *MYCN* amplification were elevated in patients older than 10 years, and *HRAS* mutations were elevated in infants under 1 year of age. However, novel therapeutic strategies targeting the molecular pathways underlying the pathogenesis of RMS in children have not yet been discovered. There are few retrospective reports on uterine RMS in adults. Using a 1213 gene-targeted hybrid-capture next-generation sequencing panel, Bennett *et al*. (18) showed that the most frequently mutated genes were *DICER1, TP53, RAS* isoforms, and the PI3K/AKT/mTOR pathway genes in 21 adults with uterine corpus ERMS (18). Somatic *DICER1* mutations were detected in 67% of cases and *FBXW7* mutations were identified in one case. Pinto *et al*. (6) reported the presence of *TP53* and *PIK3CA* mutations in an adult with uterine PRMS who underwent next-generation sequencing. MGPT should be actively investigated to identify novel therapeutic targets because genetic variants associated with the molecular pathogenesis of uterine RMS in adults have not yet been fully identified.

## Conclusion

In conclusion, uterine RPMS in adults, because of its rarity, has no established treatment strategy despite poor prognosis. In our case, the poor outcome was attributed to a tumor with rapid progression and chemotherapeutic resistance. No therapeutic options based on molecular pathways were identified using MGPT. However, genomic information could assist in determining therapeutic decisions regarding rare uterine RMS in adults. MGPT should be actively considered because rapid aggravation and unfavorable prognosis require rapid determination of therapeutic

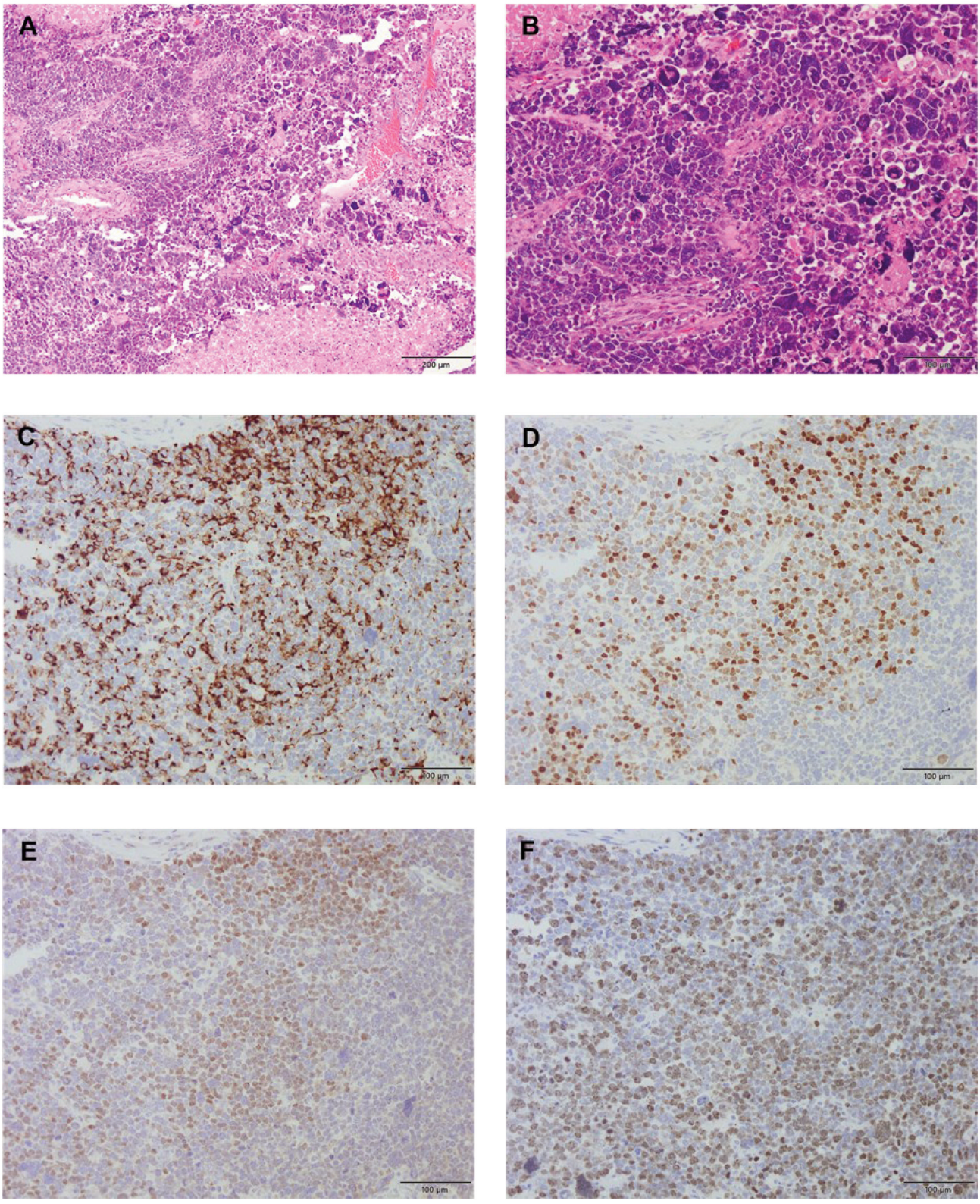


Figure 4. *Histopathology of uterine tumor characterized by hyperchromatic, suborbicular, and remarkably pleomorphic neoplastic cells (hematoxylin and eosin staining; A, 100×; B, 200×), and immunohistochemistry showing partial desmin (C, 200×), myogenin (D, 200×), and myoD1 (E, 200×) positivity and high Ki-67 expression (F, 200×) in tumor cells.*

strategies. Additional studies are needed to advance our understanding of the clinical and clinicopathological features, and molecular genetics of RMS.

## Conflicts of Interest

TO received an unrestricted research grant from Ibaraki Prefecture and the Japan Agricultural Cooperatives of Ibaraki Prefecture. The other authors have no conflicts of interest to disclose.

## Authors' Contributions

TO and NO were responsible for this study. KY and TM were responsible for literature search. KW and NM participated in the supervision. All Authors contributed to reviewing, editing, and approving the final manuscript.

## Funding

No funding was received for this study.

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*Received January 10, 2024*
*Revised February 4, 2024*
*Accepted February 5, 2024*