A case of extremely chemoresistant pure pleomorphic rhabdomyosarcoma of the uterus associated with a high serum LDH level

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Summary

Background: Pleomorphic rhabdomyosarcoma (RMS) of gynecologic origin is an exceedingly rare, highly malignant tumor. Only a few cases have been reported in the last decades. *Case report:* A 60-year-old postmenopausal woman presented with a high LDH level of unknown origin. Ultimately, she was diagnosed with pleomorphic RMS. She underwent total hysterectomy, bilateral salpingo-oophorectomy, left pelvic and paraaortic lymphadenectomy and partial omentectomy. Surgery was followed by systemic chemotherapy and pelvic irradiation. Unfortunately, the patient did not respond to treatment. Her disease course correlated with the fluctuation of plasma LDH levels. Ultimately she died within 20 months of the diagnosis. *Conclusion:* It is important to have better insight and to set a standard multimodal treatment for adult RMS. In addition, plasma LDH levels can be considered as a prognostic marker for RMS, particularly in advanced stage.

Key words: Uterine sarcoma; Uterine rhabdomyosarcoma; Lactate dehydrogenase.

Introduction

Pleomorphic rhabdomyosarcoma (RMS) has clinicopathological characteristics that set it apart from other types of RMS. It presents as an aggressive, predominantly spindle-cell tumor expressing myogenic differentiation. It is defined by the presence of large, pleomorphic tumor cells, which show, at least focally, immunophenotypic or ultrastructural sarcomeric muscle differentiation. This subtype of RMS occurs almost exclusively in adults while the embryonal and alveolar varieties are more common in children and adolescents. It is highly malignant, and patients frequently present with extrauterine spread. Chemoresistance, coupled with early metastatic recurrence make this tumor highly lethal [1]. In adults, RMS usually occurs as a heterologous component of a malignant mixed mesodermal tumor [2]. In the last decades, however, few pure RMS cases have been reported [2, 3]. Here, we describe a rare case of pleomorphic RMS in an elderly, asymptomatic postmenopausal woman whose diagnosis was incidental to the evaluation of a high LDH level. Her disease course paralleled the fluctuation in blood LDH levels. Despite multimodal treatment, the patient never entered remission and died 20 months after diagnosis. The rarity of this histologic variant of RMS, its uncommon presentation and extremely chemoresistant behavior make this case notable.

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Case Report

The patient, a 60-year-old postmenopausal woman, was noted to have a high LDH level at a routine physical exam in December 2004. A pelvic ultrasound (US) exam demonstrated no abnormalities, and other causes of a high LDH level were ruled out. Her LDH level continued to rise rapidly, and eventually, the patient developed abdominal discomfort secondary to a rapidly growing abdominal mass. She had no prior history of vaginal bleeding or pain. Physical examination and repeat US revealed a large abdominal mass which appeared to be arising from the pelvis and extending towards the umbilicus. On computed tomography (CT) scan, the mass measured 7 x 10 x 12 cm on the posterior wall of the uterus and enlarged paraaortic lymph nodes were noted (Figures 1A/B). There was no increase in endometrial thickness on US. In addition, endometrial biopsy ruled out the possibility of endometrial carcinoma. T2-weighted magnetic resonance imaging (MRI) showed a heterogeneous hyperdense abdominal mass with slightly high signal intensity (Figures 1C/D). This suggested uterine sarcoma. Tumor marker blood levels were CA19-9 29 U/ml, CA125 10 U/ml, and CEA 2.6 ng/ml. Exploratory laparotomy demonstrated a large, irregularly shaped uterine mass extending beyond the pelvis, and enlarged pelvic and left paraaortic lymph nodes (Figure 2). There was no invasion either into the bladder or intestine. A small amount of serous ascites was noted. Total hysterectomy, bilateral salpingo-oophorectomy, left pelvic and paraaortic lymphadenectomy and partial omentectomy were performed on March 3, 2005. The resected specimen weighed 690 g and measured 17 x 12 x 7 cm. The final histopathological diagnosis was pure pleomorphic RMS originating from the uterus.

On April 11, 2005, the patient was readmitted for back pain. A repeat CT scan revealed multiple lung and liver metastases along with cervical, paraaortic and pelvic lymph node enlargement. We planned to begin treatment with combined chemoradiation using the Intergroup Rhabdomyosarcoma Study regimen. Chemotherapy began with four courses of an IE regimen consisting of ifosfamide (1.8 g/body weight (wgt) daily

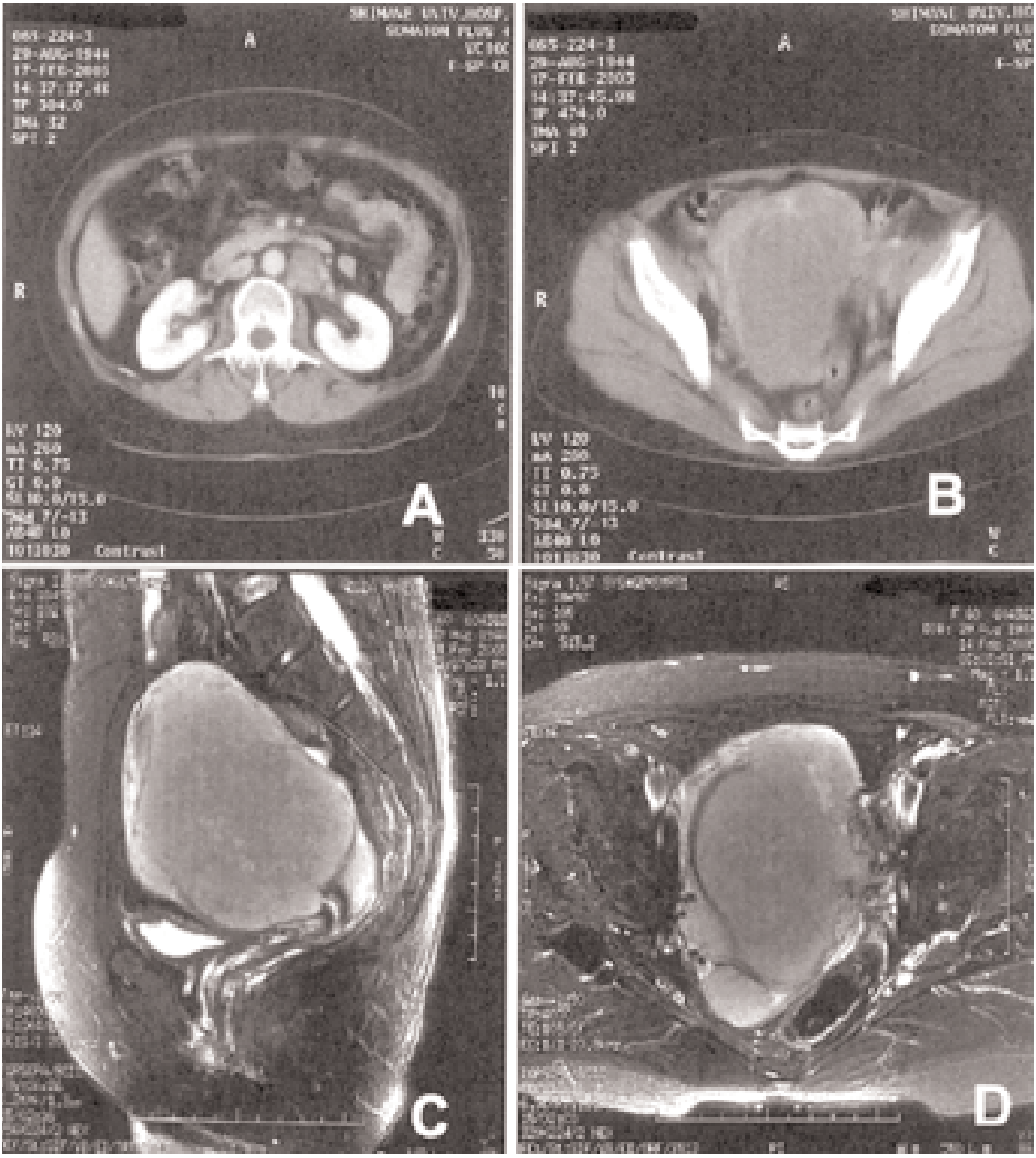

Figure 1. — A/B) CT showing a homogeneous hyperdense mass in the abdomen arising from the pelvis and enlarged paraaortic lymph nodes. C) MRI, a hypodense mass on T1-weighted images D) MRI, a hyperdense mass on T2-weighted images.

for 5 days) and etoposide (75 mg/body wgt daily for 5 days). Initially, chemotherapy was effective in decreasing the sizes of the metastatic nodules in the lung, liver and lymph nodes on CT scan and lowering the blood LDH level. IE therapy was followed by two courses of a VAC regimen containing vincristine (2 mg/body wgt once weekly for 3 weeks), actinomycin D (0.015 mg/day/body wgt for 5 days), and cyclophosphamide (2.29 g/body wgt). The CT scan at this time suggested metastasis. Positron emission tomography confirmed the presence of residual disease in the lungs, lymph nodes and pelvis. Prior to the next course of chemotherapy the patient received radiotherapy, a total of 45 Gy. Despite these measures, her LDH level began to rise. Chemotherapy was continued with VAC (vincristine 2.0 mg/body wgt 1/wk x 3), Actinomycin D (0.015 mg/body wgt x 5 days) and cyclophosphamide (2.2 g/body wgt x 75% = 1.6 g/body wgt). Unfortunately, her disease pro-

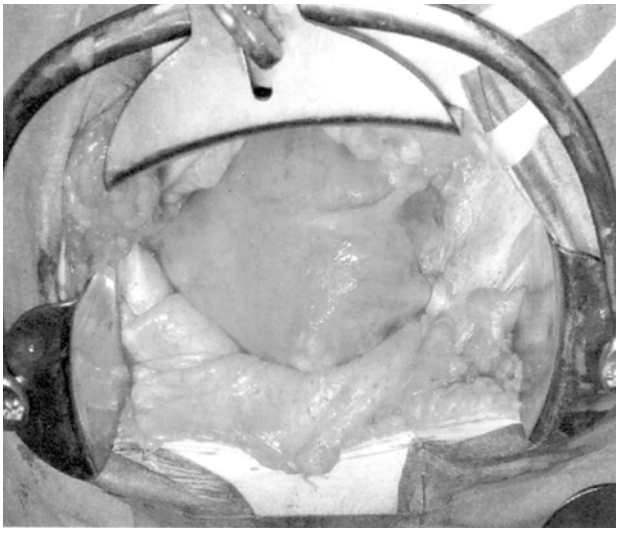

Figure 2. — Markedly enlarged uterus containing the tumor.

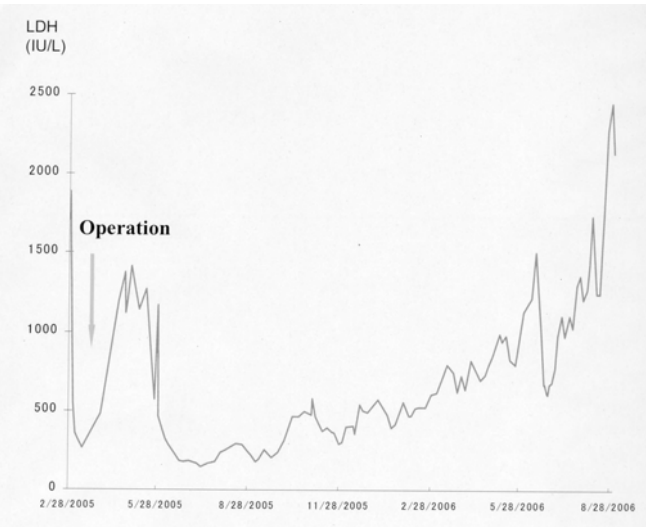

Figure 3. — Fluctuations in plasma LDH level.

gressed, as evidenced by further elevation of her LDH level (Figure 3) and multiple lung and lymph node metastases were detected by CT scan. Chemotherapy was changed to the CAP regimen containing carboplatin (75 mg/body wgt), adriamycine (30 mg/body wgt) and cyclophosphamide (500 mg/body wgt).

Despite a variety of employed chemotherapy regimens, the patient failed to respond further and had widespread tumor dissemination in the lungs, liver and bone marrow.

Over the course of treatment the patient suffered from several chemotherapy-induced side-effects including grade 3 and 4 neutropenia, severe anemia and infection. These were treated with G-CSF and antibiotics. Her bone metastases caused severe back pain that was managed with opioid analgesics. Ultimately, she had permeation of her kidneys by the tumor and died of renal failure on September 13, 2006.

Histology and immunohistochemistry

The tumor was composed of poorly differentiated spindle-shaped cells with abundant eosinophilic cytoplasm and eccentric nuclei (Figures 4A/B). Phosphotungstic hematoxylin acid (PTHA) staining showed cross striation of the rhabdomyoblasts (Figure 4C). Immunohistochemistry revealed positive immunoreactivity for myosin and desmin (Figures 5A/B) but no reactivity for p53. The tumor was negative for estrogen and progesterone receptors (Figures 5D/E), indicating that it was hormone independent. The proliferation index was very high, around 25 to 30 mitoses per 10 high power fields. This was confirmed by a high Ki-67 labeling index (Ki-67 LI: 60) (Figure 5C).

Discussion

Soft tissue sarcomas are a group of tumors comprised of a wide variety of subtypes. Sarcomas account for 6% of pediatric and 1% of all adult malignancies. The most common subtypes originating in the female genital tract are uterine leiomyosarcomas and endometrial stromal sarcomas. RMS is one of the rarest subtypes of gynecological sarcomas and accounts for only 3% of all adult malignancies [4]. It is more frequent among children and adolescents. Therefore, most of the studies regarding treatment and outcome are from the pediatric literature.

Sarcomas of the uterus were originally classified into pure, mixed and malignant mixed Müllerian tumors. Recently, however, mixed Müllerian tumors have been reclassified as carcinomas [5]. Pure sarcomas are of two categories: pure homologous and pure heterologous. Pure homologous uterine sarcomas originate from tissues that are normally present in the uterus. The pure heterologous variety includes those derived from tissues not normally present in the uterus. Examples include rhabdomyosarcomas, liposarcomas, chondrosarcomas and osteosarcomas.

Rhabdomyosarcomas are divided into three major morphologic categories: embryonal, alveolar and pleomorphic. The most common is the embryonal subtype which accounts for 70-75% of all RMS cases. It is followed by the alveolar (20-25%) and pleomorphic types (5%). The embryonal and alveolar subtypes are most frequently seen in children. In contrast, the pleomorphic category is found almost exclusively in adults and is currently not used for pediatric RMS subtyping [6]. RMS occurs throughout the body including in the head and neck, orbita, extremities, trunk, genitourinary and retroperitoneal regions. Although RMS in the genital tract most frequently occurs in children, it is extremely rare in adults [7]. All three types of RMS have been reported in the uterus. The most common site for uterine RMS is the cervix followed by the corpus [8]. RMS originating from the female genital tract is mostly either embryonal or botryoid type occurring more frequently in children and adolescents.

Pleomorphic RMS, first described by Stout in 1946, is a rare tumor. Whether it was a distinct entity was controversial until immunohistochemistry confirmed its myogenic potential. It is a high-grade rare malignant neoplasm occurring most frequently in adults over 45 years of age. Most patients present with a rapidly growing, painful mass or unusual vaginal bleeding. Imaging reveals lesions which are isodense to skeletal muscle on T1 weighted images, heterogeneous on T2 images, and may or may not have necrotic foci. Grossly the tumor is

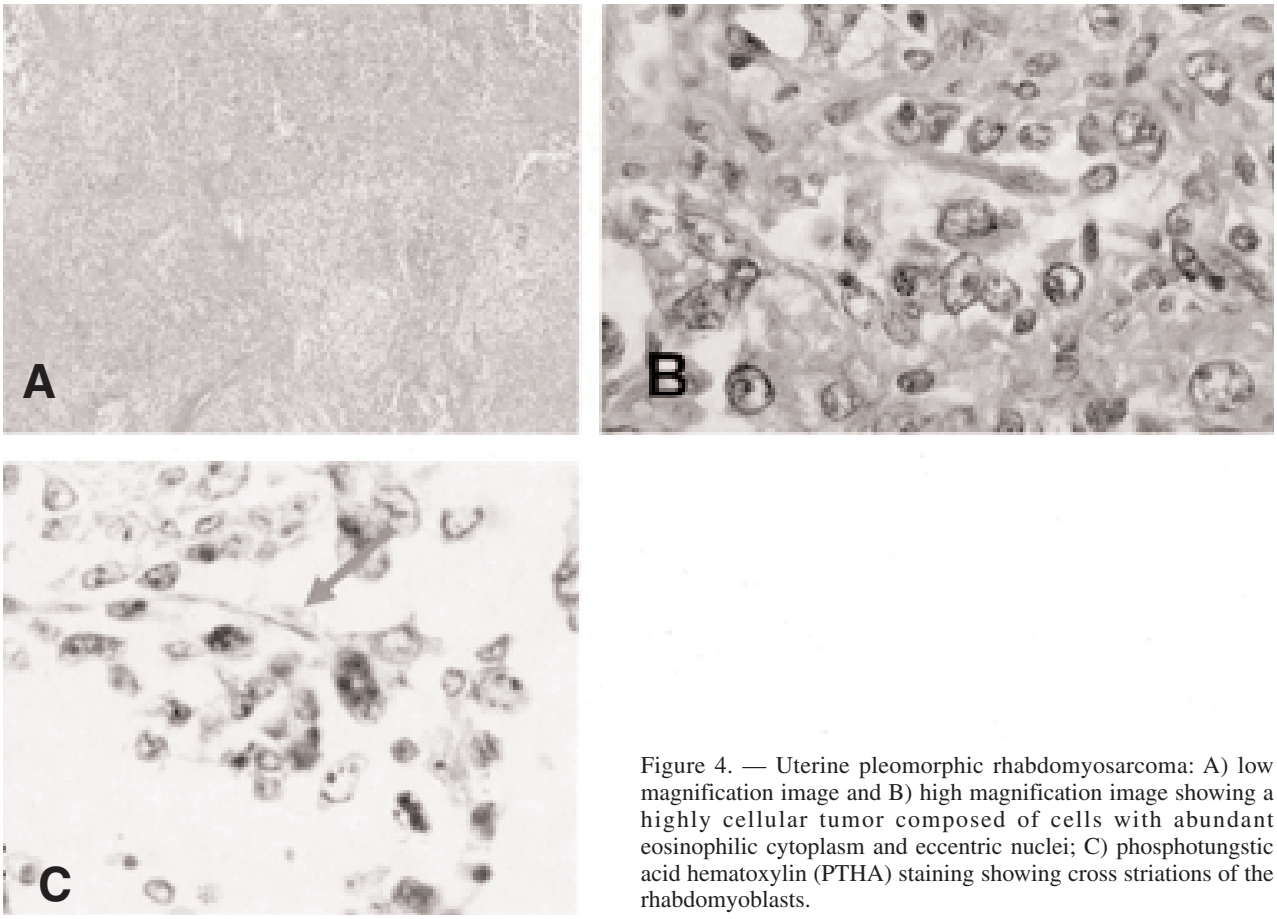

Figure 4. — Uterine pleomorphic rhabdomyosarcoma: A) low magnification image and B) high magnification image showing a highly cellular tumor composed of cells with abundant eosinophilic cytoplasm and eccentric nuclei; C) phosphotungstic acid hematoxylin (PTHA) staining showing cross striations of the rhabdomyoblasts.

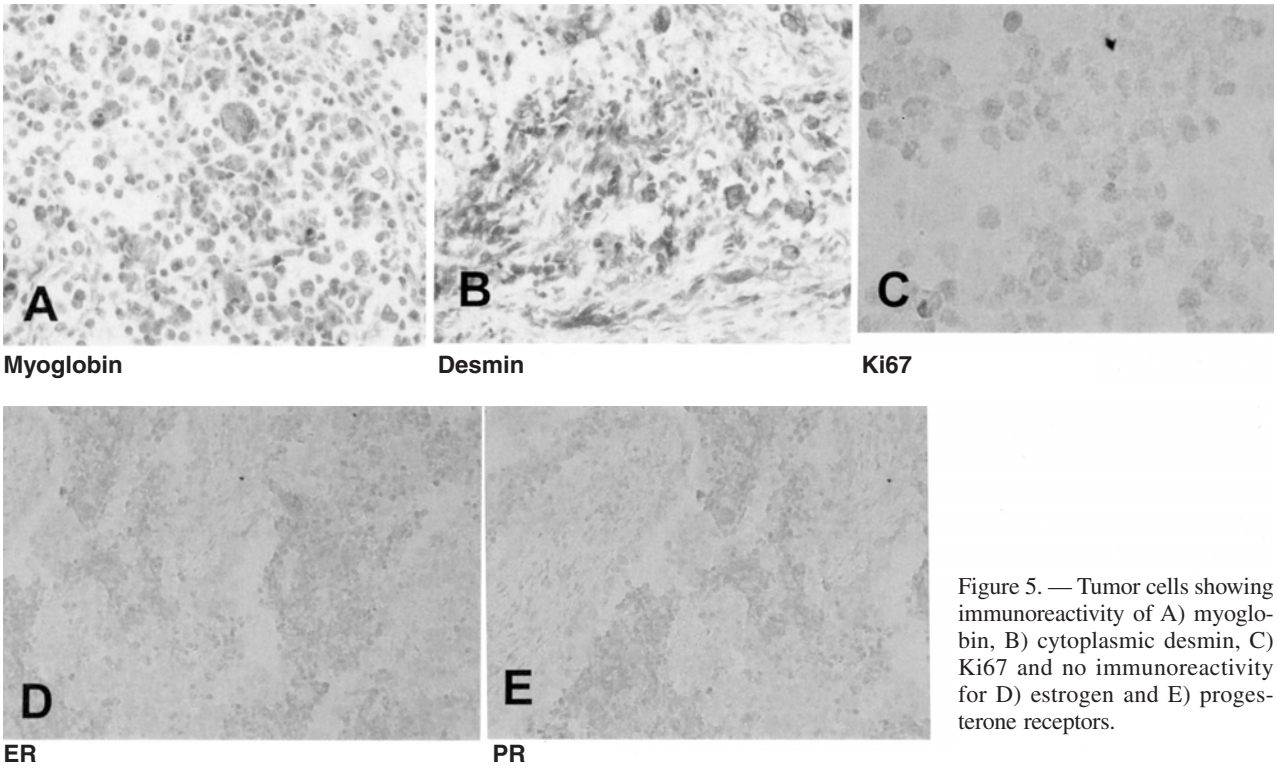

Figure 5. — Tumor cells showing immunoreactivity of A) myoglobin, B) cytoplasmic desmin, C) Ki67 and no immunoreactivity for D) estrogen and E) progesterone receptors.

quite large and occasionally surrounded by a pseudocapsule. Cut surfaces are whitish and firm with variable hemorrhagic necrosis. Diagnosis is made on the basis of hematoxylin-eosin staining of the pathological slide. The presence of undifferentiated, round to spindle shaped cells with eosinophilic cytoplasm and eccentric nuclei, expressing at least one skeletal muscle-specific marker (myoglobin, MyoD1, fast skeletal muscle myosin, or myf4) by immunohistochemistry, is required for diagnosis. In addition nonspecific muscle markers (desmin, MSA, SMA, myf3) may also be present [6]. For diagnostic purposes, the most widely used antibodies are against desmin, muscle-specific actin, and myoglobin. RMS is uniformly aggressive, and prognosis is affected by age and stage at diagnosis, anatomic site of disease and the histologic variant of the tumor. Among all histologic varieties of adult RMS, the nonembryonic variety is the rarest. It is particularly aggressive, has often spread beyond the uterus at the time of diagnosis, and has the worst prognosis [9].

Currently there is no standard treatment regimen for RMS in adults. To date, clinical trials have focused on pediatric patients. However, the cytogenetics, outcome and response to chemotherapy differ between adult and pediatric populations. The alveolar and pleomorphic varieties are more common in adults, are inherently more aggressive and progress more rapidly than embryonal RMS [10]. In adults, the overall survival is 40% at five years compared to 85% in children with RMS in the reproductive tract [8]. There is significant controversy regarding the disparity in outcome. One viewpoint is that adult RMS is a distinct biologic entity, that behaves more like other adult soft tissue sarcomas that are inherently insensitive to chemotherapy [11]. Others argue that there is no fundamental difference between adult and pediatric patients and that similar treatment modalities are suitable for both groups [4].

According to the intergroup rhabdomyosarcoma study, an IE (ifosfamide, etoposide) containing regimen showed a better response rate [12]. Patients who responded well to IE therapy were then switched to 12 weeks of VAC therapy. This study was conducted in patients younger than 21 years of age, and this IE regimen has not been trialed in adults. There have been reports of response to other regimens. For example, there is one case report of uterine RMS that demonstrated a good response to doxorubicine-based chemotherapy and was still in complete remission one year later [3]. Though our patient initially responded to IE therapy, the effect was short-lived and she failed to respond to any subsequent regimens.

A number of tumor markers and specific antibodies have been reported in RMS. Philip *et al.* reported one case of RMS with a high CA125 level [12]. However, to our knowledge, there is no report suggesting the association between the elevated LDH and RMS in adults. However, Moritake *et al.* described such a correlation in three children with advanced alveolar RMS [13]. Our patient's clinical course coincided completely with the fluctuation of serum LDH levels. This finding suggests that LDH may be a potential marker for diagnosis, prognosis and follow-up for RMS, particularly in advanced stage.

Since RMS in adults is very rare, no large, randomized, double-blinded multicenter studies have been undertaken to compare different treatment modalities and outcome of RMS in the adult age group. Therefore, results concerning treatment, long-term outcome and prognosis of adult RMS are conflicting. The aggressive nature of this tumor in adults calls for more intensive treatment comprising surgical excision with wide margins, appropriate chemotherapy and adequate radiotherapy. Because of the rarity of adult gynecological RMS and the complexity of its clinicopathological features and treatment, the management of patients with gynecological sarcomas should be handled by multidisciplinary teams experienced in the treatment of this entity. Thus, collaboration is needed to establish a standard protocol for adult RMS to optimize patient survival.

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