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Malignant transformation of uterine leiomyoma: suggested by clinical, imaging, histological, and genetic findings

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Summary

The authors describe a case of uterine leiomyosarcoma, in which clinical, radiological, histopathological, and genetic findings suggested malignant transformation of uterine leiomyoma as the cause of the disease. A 37-year-old woman receiving follow-up care for a uterine leiomyoma detected six years ago presented with lower abdominal pain. Sequential magnetic resonance imaging scans indicated the development of uterine leiomyosarcoma in the same location as the preexisting uterine leiomyoma. Histopathological examination of the excised tumor revealed uterine leiomyosarcoma with a component of uterine leiomyoma. Concordant mediator subcomplex 12 gene mutation status was observed in both components. This report supports the possibility of malignant transformation of uterine leiomyoma to uterine leiomyosarcoma.

Key words: Malignant transformation; Uterine leiomyoma; Uterine leiomyosarcoma.

Introduction

The possibility of malignant transformation of uterine leiomyoma (UL) to uterine leiomyosarcoma (ULMS) remains debatable. ULMS is extremely rare, karyotypically highly complex, and genetically unstable relative to UL, and is therefore not considered to originate from UL [1, 2]. Gene expression profiling findings also indicate that UL rarely progresses to ULMS [3]. In contrast, several case reports and series [4-7] have advocated the possibility of malignant transformation merely on the basis of the presence of a histopathological UL component in some cases of ULMS. Mittal *et al.* [8] further examined genetic aberrations in six ULMS cases with UL component using high-density oligonucleotide array-comparative genomic hybridization. They reported that most of the genetic aberrations in the UL components were preserved in the corresponding ULMS components, and additional genetic aberrations, involving several tumor suppressor genes, were found in the ULMS components.

Recently, Matsubara *et al.* [9] examined four cases of ULMS with UL components with respect to mediator subcomplex 12 gene (*MED12*) mutations, which have been recently discovered in various uterine smooth muscle tumors, including a majority (37−85%: mean 64%) of UL cases and a small proportion (2−30%: mean 14%) of ULMS cases [10, 11]. All four cases had a concordant *MED12* mutation status in both ULMS and UL components, in which two cases harbored the identical *MED12* mutation, while the remaining two cases did not. Their results made the present authors realize that the *MED12* mutation status could be used to determine the clonal origins of both ULMS and UL components. Herein, they report a possible case of malignant transformation of UL, on the basis of clinical, radiological, histopathological, and genetic findings.

Case Report

A 37-year-old gravida 1, para 1, woman was referred to this hospital with a growing abdominal mass. She was receiving follow-up care for a UL, which was detected during pregnancy six years ago (Figure 1A) and then showed considerable regression after pregnancy (Figure 1B).

Upon arrival, she complained of a three-month history of dull pain in the lower abdomen. Abdominal examination revealed a tense mass in the lower abdomen. An ultrasound examination revealed a solid mass with mixed echogenic components (120×105 mm). MRI showed a large and well-circumscribed mass in the pelvic cavity located immediately dorsal to two small leiomyomas (Figure 1C) on the right side of the lower uterine segment (Figure 1D). The solid mass consisted of two components with intermediate and high intensity on T2-weighted imaging (Figures 1C, D). Both components contained high intensity spots on T1-weighted imaging (Figure 1E) and exhibited diffuse high intensity on diffusion-weighted imaging (Figure 1F). Positron emission tomography-computed tomography showed intense fluorodeoxyglucose uptake predominantly on the component showing intermediate intensity on T2-weighted imaging (standardized uptake value max: 23.6, Figure 1G). The corresponding MRI scans taken during pregnancy six years prior (Figure 1A) demonstrated a large and well-circumscribed mass showing low intensity with a speckled

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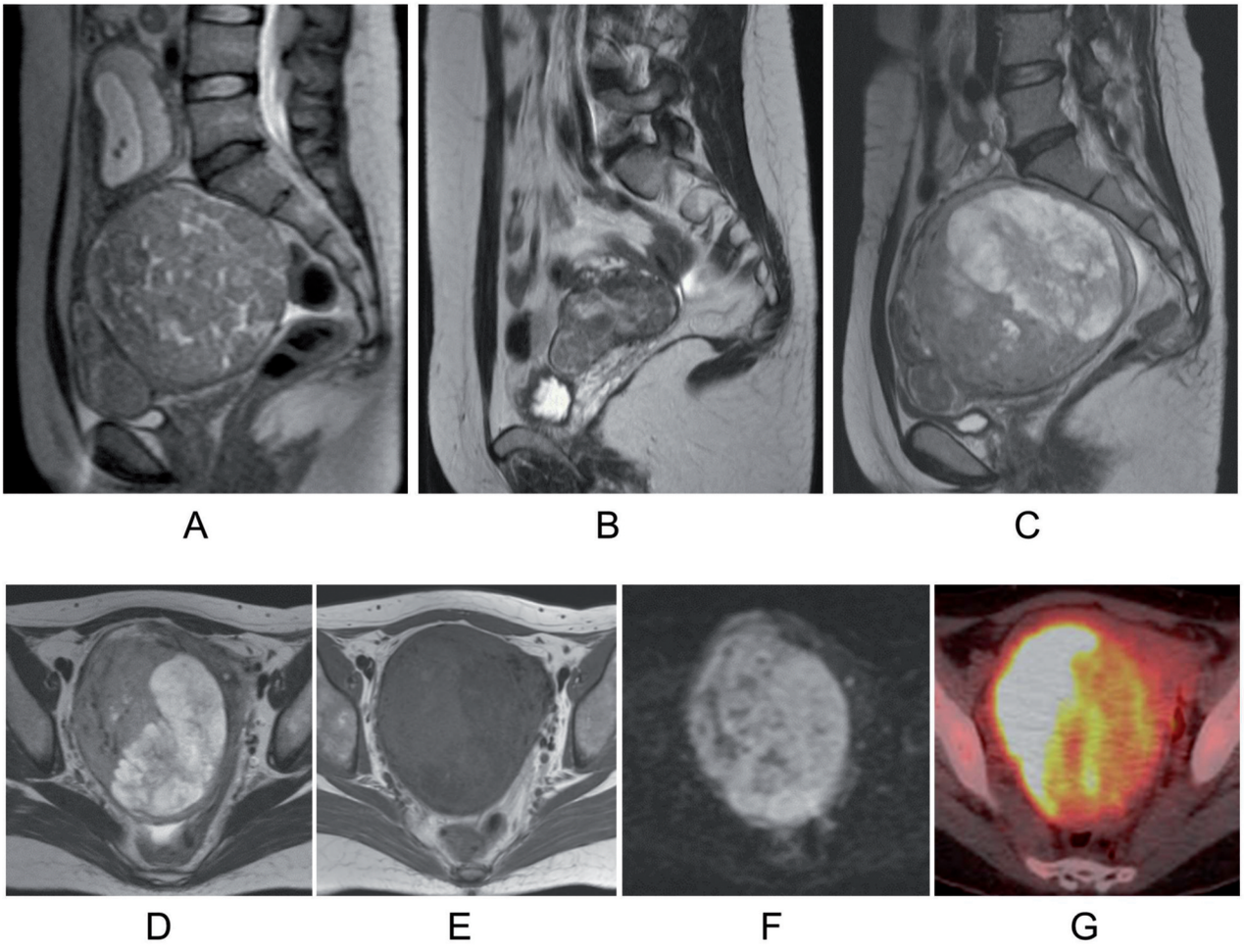

Figure 1. — (A) T2-weighted sagittal MRI scans obtained during pregnancy six years ago and (B) two years prior to referral show that a large mass with typical imaging of uterine leiomyoma, located immediately dorsal to two small leiomyoma, regressed dramatically after pregnancy. (C) T2-weighted sagittal MRI scan obtained after referral shows a well-circumscribed mass, located immediately dorsal to two small leiomyoma in the same position as the regressed uterine leiomyoma. (C, D) The mass consists of two components with intermediate and high intensity on T2-weighted imaging, with (E) small areas of high intensity on T1-weighted imaging (arrows), and exhibits (F) diffuse high intensity on diffusion-weighted imaging. (G) Positron emission tomography-computed tomography image showing intense fluorodeoxyglucose uptake (standardized uptake value max: 23.6).

appearance on T2-weighted imaging, which was a typical imaging finding of UL, exactly at the same position. The mass regressed dramatically on the follow-up MRI taken after pregnancy (two years prior to referral, Figure 1B). Laboratory data were unremarkable except for mild leukocytosis (10,770 cells/μL) with a left shift (neutrophils: 77.7%) and moderate elevation of the C-reactive protein level (7.0 mg/dL). Lactate dehydrogenase and cancer antigen 125 levels were close to the lower limit of the normal range (121 IU/L and 9 U/mL, respectively).

Based on the aforementioned clinical and radiographic findings, the authors considered a uterine malignancy (ULMS) originating from the preexisting UL. During the laparotomy, they found a hard, smooth mass originating from the lower region of the uterine corpus along with enlarged lymph nodes in the right pelvic and para-aortic regions. The patient underwent simple hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy.

The uterus weighed 674 grams, and the gross appearance indicated focal necrosis and hemorrhage (Figure 2A). Histopathological examination revealed bundles of spindle-shaped cells with irregular and hyperchromatic nuclei and multiple mitotic figures (Figure 2C) along with areas of myxoid change and coagulative tumor necrosis (Figure 2D). Immunohistochemically, tumor cells were positive for α-smooth muscle actin, and negative for desmin. The Ki-67 labeling index was 20%. In addition, UL areas with scattered markedly enlarged atypical cells (Figure 2E) were seen adjacent to the ULMS areas (Figure 2B). The dissected lymph nodes were negative for metastasis. Based on the above findings, a pathological diagnosis of ULMS (pT1bN0M0: WHO 2014) was made. The patient's postoperative course was uneventful, and no recurrence was detected at 20 months after surgery.

Because the histopathological UL component was found adjacent to the ULMS area (Figure 2B), the authors further examined the *MED12* mutation status in the ULMS and UL components, and confirmed a concordant mutation status, in which both components did not harbor the *MED12* mutation (Figure 3). The fre-

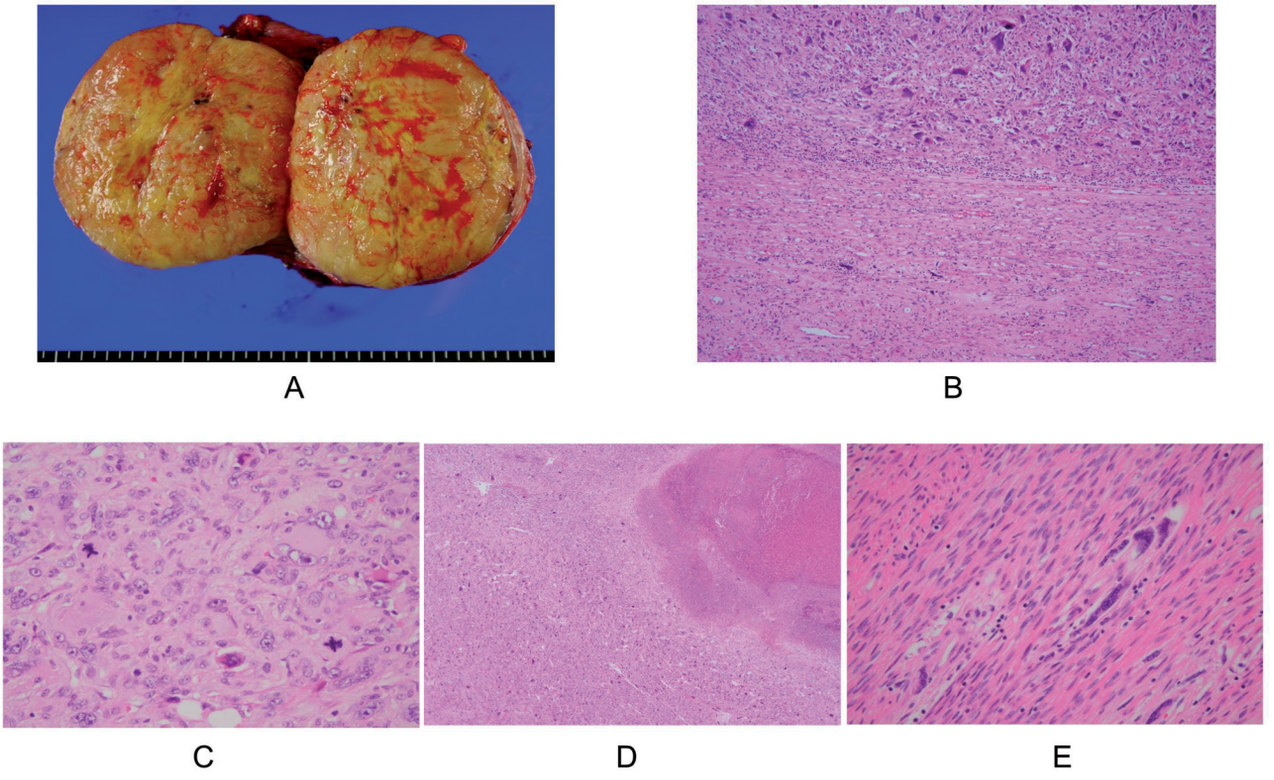

Figure 2. — (A) Gross examination of the tumor. (B) Photomicrograph showing a transition area between the leiomyosarcoma (upper half) and leiomyoma (lower half) area. (C) Bundles of spindle-shaped cells with irregular and hyperchromatic nuclei and mitotic figures are seen in the leiomyosarcoma area. (D) In the leiomyosarcoma area, coagulative tumor necrosis was also observed. (E) Scattered markedly enlarged atypical cells are seen in the uterine leiomyoma area.

quently mutated region of *MED12*, spanning intron 1 to exon 2, was analyzed by Sanger sequencing as previously described [9].

The patient provided written informed consent to publish her medical information.

Discussion

The present findings are remarkable in terms of the clinical course and sequential MRI evidence obtained > 6 years before the ULMS was detected. The images clearly showed that the UL regressed after pregnancy and was located in the very same position that the ULMS was subsequently detected in. The clinical course and images also showed that the apparently benign tumor varied drastically over time. Although it is possible that the ULMS originated from normal uterine smooth muscle and invaded the adjacent preexisting UL, it is unlikely because only the area that contained the UL was affected.

In addition to the clinical and radiographic findings, histopathological examination revealed the presence of UL areas adjacent to the ULMS area. Recent studies reported that UL areas in ULMS are detected more commonly than previously thought [8, 9]. Mittal *et al.* [8] and Matsubara *et al.* [9] reported detection rates of 69% (18/26), and 33% (4/12), respectively. Thus, re-evaluation of the histopathological findings of ULMS cases with particular attention to the presence of UL areas is recommended, as these areas might have received less attention than the areas with malignant features. Furthermore, concordant *MED12* mutation status, in that both components did not harbor the *MED12* mutation, was found in the present case. Given the reported incidence of *MED12* mutations (64% in UL and 14% in ULMS) [11], the concordance rate for *MED12* mutation status is approximately 40% (9% for both positive and 31% for both negative UL and ULMS components). Therefore, in combination with four cases with concordant *MED12* mutation status from a previous report [9], there is only a 1% chance (0.4*0.4*0.4*0.4*0.4*100) that all five cases of ULMS with benign UL areas show a concordant *MED12* mutation status. In other words, the absence of discordancy in *MED12* mutation status in all five examined cases suggests that the presence of UL areas adjacent to the ULMS area indicates their monoclonal origin. Along with the high prevalence of UL areas adjacent to the ULMS area reported in recent literatures [8, 9], the malignant transformation of UL may even play a significant role in the pathogenesis of ULMS.

At present, only one study has described the clinical char-

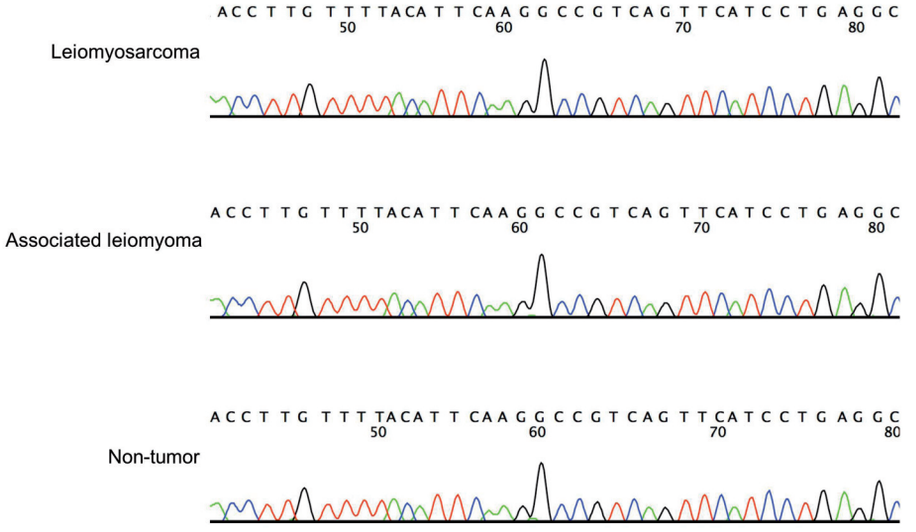

Figure 3. — Mediator subcomplex 12 gene mutation status in the uterine leiomyosarcoma and leiomyoma components. Neither of the components harbor the mutation.

acteristics of ULMS with UL areas. Yanai *et al.* [7] reviewed ten such cases including four of their own, and reported that the tumors were detected at a relatively early stage, and these patients had a relatively favorable prognosis, indicating that the presence of UL areas might serve as a new prognostic marker of ULMS. Herein, the authors described convincing evidence for a case of ULMS with UL areas on the basis of clinical, radiological, histopathological, and genetic findings, all of which suggested malignant transformation of UL as the most probable cause of the disease. Further studies focusing on identifying UL areas in ULMS cases and further accumulation of clinical information on this group of patients are needed to develop a better understanding of the clinicopathological features of ULMS.

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