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Case Report

First Case Report of a Uterine Angiolipoleiomyoma With *KRAS* and *KIT* Mutations

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Summary: Angiolipoleiomyoma is a very rare lesion of the uterus. To the best of our knowledge, only 20 cases have been described in the literature. It is an insufficiently defined entity, which is not included in the WHO classification. This lesion may be therefore underdiagnosed and underestimated. We describe here a case of a 58-yr-old woman who underwent routine gynecological examination. Ultrasonography revealed a heterogeneous myometrial mass, while magnetic resonance imaging showed a voluminous corporeal and fundic myometrial mass protruding into the uterine cavity. A total hysterectomy was performed. The macroscopic examination revealed an intramural solitary round mass with a heterogeneous cut-surface. Microscopically, the lesion consisted of an admixture of smooth muscle, adipose tissue, and blood vessels. Desmin was positive, while HMB45 was negative in the tumor. Molecular tests were performed and revealed, for the first time to our knowledge, a case of an angiolipoleiomyoma harboring *KRAS* and *KIT* mutations.
Key Words: Angiolipoleiomyoma—Uterus—KRAS—KIT—HMB45.

Angiolipoleiomyoma (ALM) is a very rare lesion of the uterus. To the best of our knowledge, only 20 cases have been described in the literature. It is an insufficiently defined entity, which is not included in the WHO classification. This lesion may be therefore underdiagnosed and underestimated. Microscopically, it consists of a variable admixture of smooth muscle, adipose tissue, and blood vessels. Here, we report for the first time a case of an ALM harboring *KRAS* and *KIT* mutations.

CASE REPORT

Here we report the case of a 58-yr-old woman who underwent a routine gynecological examination. She had no relevant personal history. Her mother was diagnosed with breast carcinoma. The patient had been in menopause for 6 yr and had a child.

During the gynecological clinical examination, the doctor reported a soft and globular uterus.

Ultrasonographic examination revealed a heterogeneous myometrial mass presenting cystic zones filled with fluid and fibrosis, accompanied by probable calcifications and necrosis. The patient had a normal blood test with no tumor markers detected.

A magnetic resonance imaging was performed and revealed a voluminous myometrial fundic mass in the left antero-lateral part of the uterine wall broadly

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The authors declare no conflict of interest.

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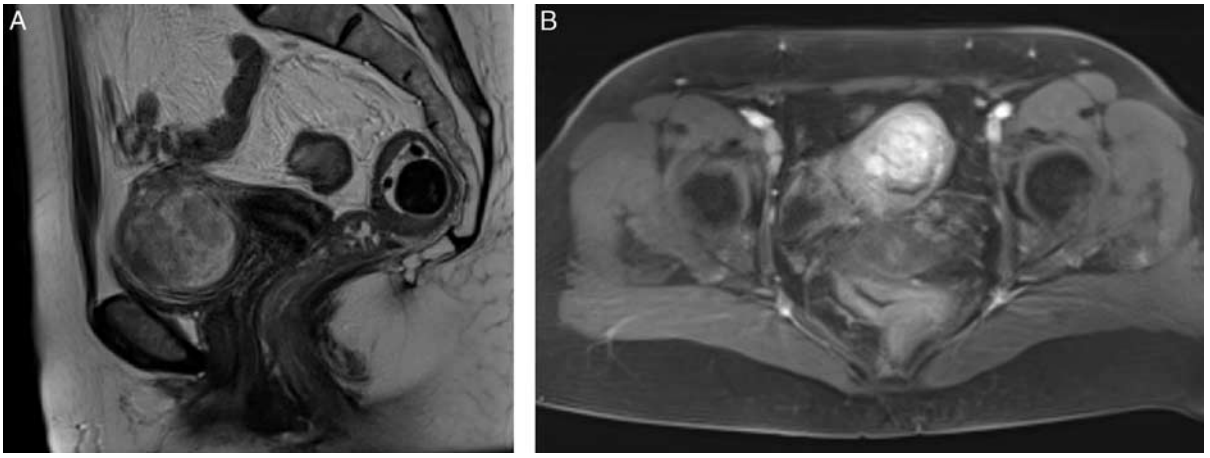

FIG. 1. The MRI revealed a voluminous myometrial fundic mass broadly protruding in the uterine cavity. (A) Sagittal magnetic resonance imaging slice. (B) Axial magnetic resonance imaging slice with contrast.

protruding into the uterine cavity, measuring 52×41×38 mm (Fig. 1). The PET-Scan revealed a very low hypermetabolic mass.

A total hysterectomy with bilateral annexectomy and peritoneal cytology were performed. Follow-up after 2 yr did not reveal any recurrence.

Macroscopically, the uterus was deformed by an intramural solitary round mass, measuring 4×3×3 cm. It was a heterogeneous mass with alternating yellow-tan and white-gray areas on cut surface (Fig. 2). We also described multiple intramyometrial well-circumscribed white firm masses with whorled cut surface, measuring around 1 cm in diameter, whose macroscopic appearance was suggestive of banal leiomyoma.

Microscopically, the heterogeneous lesion was well-circumscribed and consisted of a proliferation of smooth muscle tissue, adipose tissue, and blood vessels, entangled with each other (Fig. 3). No area of necrosis was observed. The leiomyomatous area consisted of intersecting fascicles of spindle cells, with eosinophilic cytoplasm and elongated nuclei with small focal nucleoli. No visible nucleocytoplasmic atypia was observed.

Given the significant cellularity, "cellular leiomyoma" variant was diagnosed. Mitotic count was 1 to 2 mitoses based on the assessment of 10 high power fields (40×). The adipose component of the lesion consisted of a proliferation of mature adipocytes with small elongated eccentric nuclei, frequently located between the spindle cells bundles. The vascular component consisted of predominantly large, noncongested, thick-walled vessels, delineated by a flat endothelium without nucleocytoplasmic atypia.

The lesion presented diffuse cytoplasmic immunohistochemical expression for Desmin [ready-to-use (RTU); clone D33; Agilent] and Caldesmon (RTU; clone hCD; Agilent) in the smooth muscle component, and focally membranous CD10 (RTU; clone 56C6; Agilent) expression, while HMB45 staining (1:100 dilution; clone HMB45; Agilent) was negative in all 3 components (Fig. 3). The CD117 antibody (1:250 dilution; polyclonal antibody; Agilent) highlighted many mast

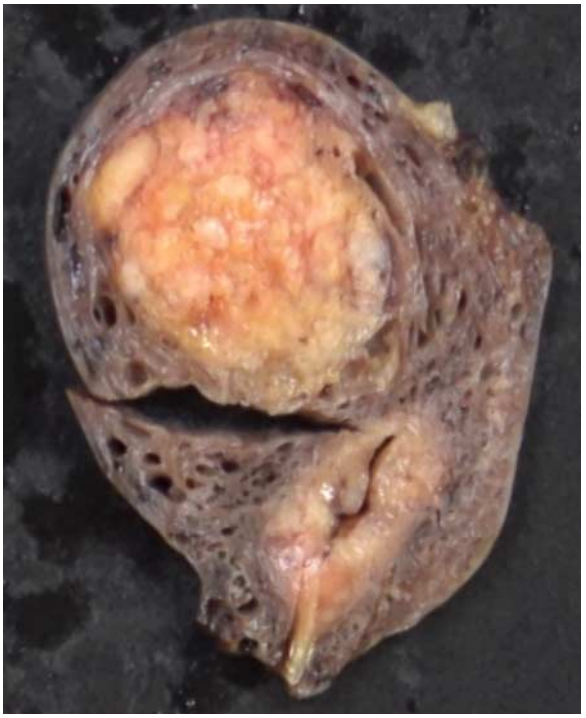

FIG. 2. Uterine body deformed by an intramural round mass, measuring 4×3×3 cm. It appears as a heterogeneous mass with yellow-tan and white-gray areas on cut surface.

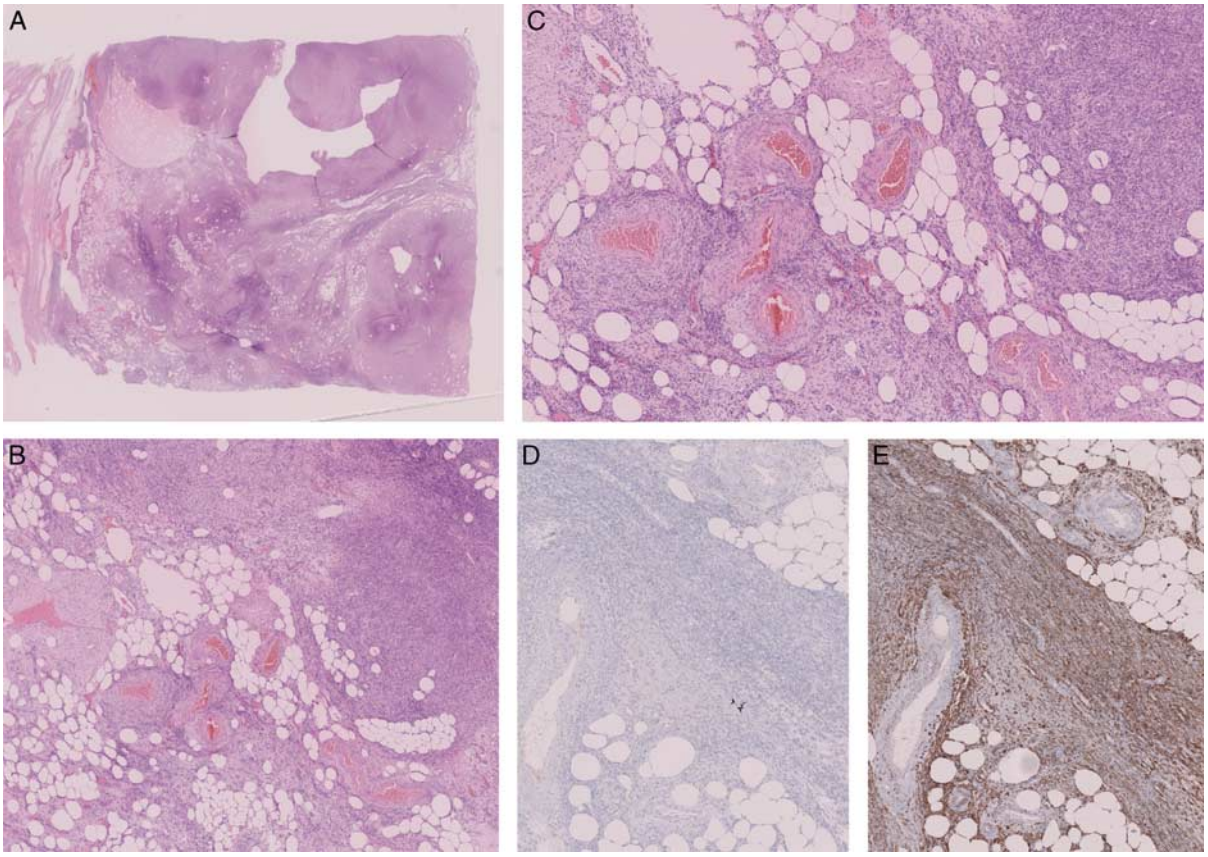

FIG. 3. Visualization of the 3 components of the lesion [A: at low magnification, hematoxylin and eosin (HE) staining; B: HE 2.5×; C: HE 5×]. (D) HMB45 negativity (5×). (E) Desmin positivity (5×).

cells. The other microscopic were those of benign leiomyomas of the myometrium, while fallopian tubes, ovaries, and peritoneal fluid were histologically normal.

A diagnosis of ALM was made.

Molecular tests were performed and revealed *KRAS* G12D and *KIT* V503I mutations. The library construction was performed using a custom Ampliseq panel that targets 16 genes (Supplemental Digitial Content 1, http://links.lww.com/IJGP/A130). Sequencing was performed using the Ion S5 GeneStudio instrument (ThermoFisher Scientific, Waltham, MA).

DISCUSSION

Uterine ALM is a rare benign tumor, with an estimated incidence of 0.06% of the benign uterine lesions (1–3). To the best of our knowledge, the first case was described by McKeithen et al. (4) in 1964. Usually, its onset is in the fourth decade (2,3,5,6), but a case of a 26-yr-old female has already been described (1). The clinical presentation overlaps with leiomyoma and consists of chronic abdominal/pelvic pain, pressure symptoms (urinary incontinence and frequency), vaginal bleeding, menometrorrhagia, and pelvic organ prolapse (1–3). The combination of computed tomography, magnetic resonance imaging, and ultrasonography can allow a preoperative diagnosis (2,3). The median size of the lesion is 8.4 cm, ranging from 2 to 16 cm (1–3). Most commonly, the tumor is localized in the uterine corpus. Other sites include the cervix and lower uterine segment (1–3). The growth pattern is intramural or subserosal (1–3).

Macroscopically, the tumor appears gray, white, or pink on the cut surface, and it is usually encapsulated (1–3). Depending on the predominant component of the lesion, the consistency is firm or soft (1–3). Necrosis and hemorrhage can sometimes be seen (2).

Microscopically, the tumor consists of an admixture of three components in various proportions: adipose tissue, smooth muscle cells, and blood vessels (1–3). The vascular component usually consists of a proliferation of large thick-wall blood vessels (2,3,7), sometimes tortuous and aggregated (1,3,7), and fusing with the stroma (3). The adipose tissue compartment

consists of mature adipocytes with small eccentric nuclei (3), entangled between muscle bundles and blood vessels (1). The muscular component consists of a spindle cell proliferation arranged in fascicles of various thickness (3). The fascicles penetrate between the blood vessels and adipose tissue and surround them (3). Usually, there is no appreciable mitotic activity, anaplasia (3) or necrosis (1).

Given that most cases of ALM were described 40 yr ago, limited information is available on their immunohistochemical profile (3,4). However, when immunohistochemistry was performed (1–3,5), it revealed strong cytoplasmic positivity for smooth muscle actin (SMA), Desmin, and Calponin in the smooth muscle component, but no positivity for HMB45 in any of the 3 components (1–3,5–8).

So far, only 20 cases of ALM have been described in the literature (1–3,5). Moreover, there is no clear definition or classification of ALM up to this point. There may also be macroscopic and microscopic confusion with uterine angiomyolipoma, which has similar clinical and morphologic aspects (9). The angiomyolipoma is composed of epithelioid perivascular cells, and it is classified as PEComa (10). These tumoral cells are also positive for the muscle markers (SMA, Desmin, Caldesmon) (10), but they are especially immunoreactive for HMB45 (10), while the ALM is not (3). For of all these reasons, we suspect that some cases in the literature are misclassified into PEComas, instead of ALM. For example, Yaegashi and colleagues have described some cases of angiomyolipoma, but without positivity for HMB45 (6–8). These cases may be ALM, but without clear or recognized diagnostic criteria, it is difficult to ensure a definitive diagnosis. Moreover, the other ALM cases described before the use of HMB45 may have been misclassified (3,4). Therefore, the total number of ALM, possibly underdiagnosed, is consequently underestimated. TFE3 status can be evaluated by immunohistochemistry or by FISH analysis, and it allows the diagnosis of a special type of PEComa harboring TFE3 translocation. Its presence was not assessed in the previous studies described above. This entity is more often associated with clear cell epithelioid morphology and focal positivity for muscle markers (11).

The histogenesis of the ALM is controversial and not really investigated. The lesion could have the same pathogenesis as adenolipoleiomyoma (12). In this case, its origin is either a benign hamartoma with adipose metaplasia, or a variant of a müllerian mixed tumor (13,14). But the ALM may also have the same development as lipoleiomyoma. In this perspective, it could originate from undifferentiated mesenchymal cells, differentiating into different tissues, composing the lesion (15), or misplaced embryonic fat cells (15) but also lipomatous metaplasia of smooth muscle cells (7).

The particularity of our case is the presence of *KRAS* and *KIT* mutations, which have never been referred before. One study investigated the presence of p53 mutations in renal and hepatic angiomyolipomas without success (16). Others authors, in renal and hepatic angiomyolipomas, studied the immunohistochemical expression of KIT, which was positive in almost all tumor cells (17). Finally, one author described KIT immunohistochemistry positivity in uterine angiomyolipoma (17). Thus, limited molecular information is available for this type of lesion. In the future, it might be interesting to perform molecular tests on ALM, in order to detect if there are recurrent mutations that may allow further characterization of the lesion and develop valid molecular diagnostic criteria.

REFERENCES

1. Paryani N, Shahid R. Unsuspected components of a fibroid uterus: angiolipoleiomyoma. *J Pak Med Assoc* 2020;70:1451–3.
2. Demir-Cendek B, Avsar A, Bostanci-Ergen E, et al. Rarely seen benign tumor of the uterus, angiolipoleiomyoma: a case report. *Med J Bakirkoy* 2018;14:142–5.
3. Ren R, Wu H. Pathologic quiz case: a 40-year-old woman with an unusual uterine tumor. *Arch Pathol Lab Med* 2004;128: e31–2.
4. McKeithen W, Shinner J, Michelsen J. Hamartoma of the uterus. *Obstet Gynecol* 1964;24:231–4.
5. Kajo K, Zùbor P, Krivus S, et al. Angiolipoleiomyoma of the uterus. Case report and literature review. *Ceska Gynecol* 2010;75:54–6.
6. Yaegashi H, Moriya T, Soeda S, et al. Uterine angiomyolipoma: case report and review of the literature. *Pathol Int* 2001;51: 896–901.
7. Shintaku M. Lipoleiomyomatous tumors of the uterus: a heterogeneous group? Histopathological study of five cases. *Pathol Int* 1996;46:498–502.
8. Huang P, Chen J, Ho W. Clinicopathologic analysis of renal and extra- renal angiomyolipomas: report of 44 cases. *Zhonghua Yi Xue Za Zhi (Taipei)* 2000;63:37–44.
9. Wang J, Yang Q, Zhang N, et al. Uterine angiomyolipoma: a clinical analysis of 8 cases and literature review. *Arch Gynecol Obstet* 2021;304:171–7.
10. Kurman RJ, Carcangiu ML, Herrington CS, Young RH, eds. *WHO Classification of Tumours of Female Reproductive Organs*, 4th ed. Lyon: IARC; 2014.
11. Schoolmeester JK, Dao LN, Sukov WR, et al. TFE3 translocation associated perivascular epithelioid cell neoplasm (PEComa) of the gynecologic tract: morphology, immunophenotype, differential diagnosis. *Am J Surg Pathol* 2015;39:394–404.
12. Catteau X, Anaf V, Noël J-C. Adenolipoleiomyoma polyp of the uterus: a case report and review of the literature. *Case Rep Pathol* 2018;2018:5704382.
13. McCluggage W, Hamal P, Traub A, et al. Uterine adenolipoleiomyoma: a rare hamartomatous lesion. *Int J Gynecol Pathol* 2000;19:183–5.

14. Ilhan R, Yavuz E, Iplikci A, et al. Hamartomatous endocervical polyp with heterologous mesenchymal tissue. *Pathol Int* 2001;51:305–7.
15. Cil A, Haberal A, Hucumenoglu S, et al. Angiomyolipoma of the uterus associated with tuberous sclerosis: case report and review of the literature. *Gynecol Oncol* 2004;94:593–6.
16. Bing Z, Yao Y, Pasha T, et al. p53 in pure epithelioid PEComa: an immunohistochemistry study and gene mutation analysis. *Int J Surg Pathol* 2012;20:113–20.
17. Park S, Ro J, Kim H, et al. Perivascular epithelioid cell tumor of the uterus: immunohistochemical, ultrastructural and molecular study. *Pathol Int* 2003;53:800–5.