

Review

## An Update on Clinicopathological, Imaging, and Genetic Features of Angioleiomyoma

MIKIRO KOGA<sup>1\*</sup>, JUN NISHIO<sup>2\*</sup>, TAKAMASA KOGA<sup>3</sup>, KAORI KOGA<sup>4</sup>, SHIZUHIDE NAKAYAMA<sup>1</sup> and TAKUAKI YAMAMOTO<sup>1</sup>

<sup>1</sup>Department of Orthopaedic Surgery, Faculty of Medicine, Fukuoka University, Fukuoka, Japan;

<sup>2</sup>Section of Orthopaedic Surgery, Department of Medicine, Fukuoka Dental College, Fukuoka, Japan;

<sup>3</sup>Koga Orthopaedic Clinic, Fukuoka, Japan;

<sup>4</sup>Department of Pathology, Faculty of Medicine, Fukuoka University, Fukuoka, Japan

**Abstract.** Angioleiomyoma is a benign, pericytic (perivascular) neoplasm that primarily occurs in the subcutis or dermis of the extremities. The lesion typically presents as a small, firm, slow-growing, painful nodule. Magnetic resonance imaging reveals the lesion to be a well-defined, round to oval mass with signal intensity similar to or slightly hyperintense to that of skeletal muscle on T1-weighted sequences. A dark reticular sign on T2-weighted sequences appears to be a characteristic feature of angioleiomyoma. Prominent enhancement is usually seen after intravenous contrast. Histologically, the lesion consists of well-differentiated smooth muscle cells with many vascular channels. Based on vascular morphologies, angioleiomyoma is classified into three subtypes: solid, venous, and cavernous. By immunohistochemistry, angioleiomyoma is diffusely positive for smooth muscle actin and calponin and variably for h-caldesmon and desmin. Conventional cytogenetic studies have demonstrated relatively simple karyotypes characterized by one or few

structural rearrangements or numerical aberrations. In addition, metaphase comparative genomic hybridization analyses have revealed recurrent loss of 22q and gain of Xq. Angioleiomyoma can be successfully treated with simple excision, with a very low recurrence rate. Knowledge of this peculiar neoplasm is important because it can mimic a variety of benign and malignant soft-tissue tumors. This review provides an updated overview of the clinical, radiological, histopathological, cytogenetic, and molecular genetic features of angioleiomyoma.

Angioleiomyoma, also known as vascular leiomyoma, is a distinctive, relatively common, benign soft-tissue tumor originating from the smooth muscle layer of blood vessels. It belongs to the pericytic (perivascular) tumor group according to the 2020 World Health Organization Classification of Soft Tissue Tumors (1). The etiology of angioleiomyoma remains unknown. Angioleiomyoma can show a morphological overlap with a variety of benign and malignant soft-tissue tumors, including angiomyolipoma, myopericytoma and leiomyosarcoma. In our extensive experience, it is often difficult to diagnose angioleiomyoma preoperatively and this lesion may not be recognized as the cause of pain for some time. Advances in knowledge of the imaging, histopathology, and genetics of angioleiomyoma are leading to more accurate diagnosis and appropriate treatment. This review highlights the clinical, radiological, histological, immunohistochemical, cytogenetic and molecular genetic features of angioleiomyoma.

\*These Authors contributed equally to this study.

Correspondence to: Jun Nishio, MD, Ph.D., Section of Orthopaedic Surgery, Department of Medicine, Fukuoka Dental College, 2-15-1 Tamura, Sawara-ku, Fukuoka 814-0193, Japan. Tel: +81 928010411, Fax: +81 928010735, e-mail: nishio@fdcnec.ac.jp

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### Clinical Features

Angioleiomyoma has a peak incidence in the fourth to sixth decades of life. The solid type is more common in females, whereas the venous and cavernous types show a slight male predominance (1). It typically presents as a solitary, firm, well-

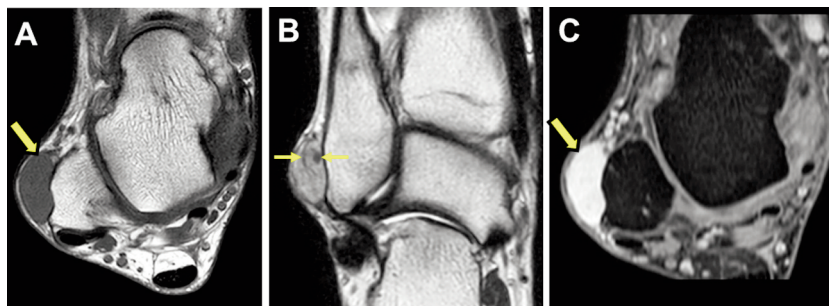


Figure 1. Magnetic resonance images of angioleiomyoma of the ankle in a 60-year-old man. (A) T1-weighted sequence shows a well-defined subcutaneous mass (yellow arrow) with signal intensity similar to that of skeletal muscle. (B) T2-weighted sequence shows that the mass has high signal intensity. A dark reticular sign (yellow arrows) can be seen. (C) Contrast-enhanced fat-suppressed T1-weighted sequence reveals prominent homogeneous enhancement throughout the mass (yellow arrow).

circumscribed, slow-growing, subcutaneous nodule, which is often painful. Angioleiomyoma shows a wide anatomic distribution but most frequently occurs in the extremities, particularly the lower leg. The diameter ranges from 0.2 to 4.3 cm (usually less than 2 cm) (2). Simple excision is the treatment of choice and prognosis is excellent. It is recommended that patients are followed up for one year after excision (3).

### Radiologic Features

Various imaging modalities have been applied for the detection of angioleiomyoma. The radiographic and computed tomographic (CT) features of this neoplasm are not specific but ultrasonographic and magnetic resonance imaging (MRI) features are relatively characteristic. It is important to be familiar with the key imaging features of angioleiomyoma for its appropriate management.

Radiographs may be normal or reveal only a nonspecific soft-tissue mass. In such cases, it is often not possible to establish a meaningful differential diagnosis. Calcification may be seen in acral regions (4-6) and has been interpreted as degenerative in nature, probably related to repetitive minor trauma (6). CT reveals a well-defined soft-tissue mass with tissue attenuation similar to that of skeletal muscle. Ultrasound shows a solid, ovoid, well-defined mass with a relatively homogeneous, hypoechoic echotexture (7). Color doppler examination demonstrates prominent hyper-vascularity and may display associated feeding vessels. However, echogenicity and vascularity can be variable for angioleiomyoma based on the histological subtypes (8). On MRI, the lesion is well-defined and displays isointense or slightly hyperintense relative to skeletal muscle on T1-weighted images (Figure 1A) and variable heterogeneous signal intensity on T2-weighted images (9-12). A peripheral rim of low signal intensity can be seen on both T1- and T2-weighted images (10). A dark reticular sign on T2-weighted images appears to be a characteristic feature

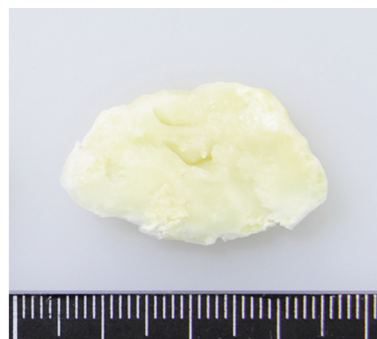


Figure 2. Gross appearance of angioleiomyoma showing a well-circumscribed mass with a gray-white, gritty cut surface.

of angioleiomyoma (Figure 1B) (11). Contrast-enhanced MRI demonstrates prominent homogeneous and heterogeneous enhancement (Figure 1C). The presence of an adjacent tortuous vascular structure has also been reported after intravenous contrast (10). The vascular nature of the lesion may be identified on Tc-99m red blood cell perfusion and blood-pool scintigraphy (13).

### Histological and Immunohistochemical Characteristics

Grossly, angioleiomyoma is an ovoid, well-circumscribed, rubbery nodule with a gray-white or brown cut surface. The lesion with calcification can appear gritty on sectioning (Figure 2). An attached blood vessel wall may be identified (1). Histologically, the lesion is composed of well-differentiated smooth muscle cells with intervening vascular channels (Figure 3A). In addition, adipocytic metaplasia, hyalinization and calcification may be seen (Figure 3B). Mitotic figures are absent. Based on vascular morphologies, angioleiomyoma is

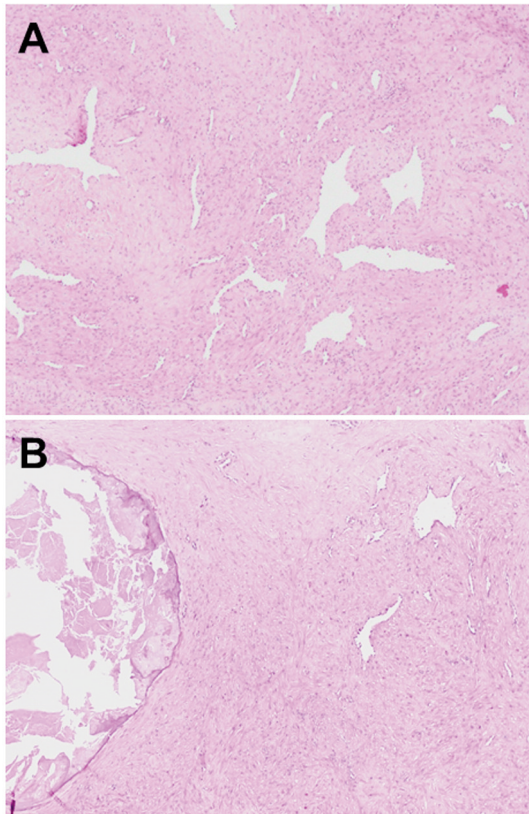


Figure 3. Histological features of angioleiomyoma. (A) The tumor is composed of well-differentiated smooth muscle cells with intervening vascular channels. (B) Calcification can be seen. (hematoxylin and eosin staining, original magnification  $\times 100$ ).

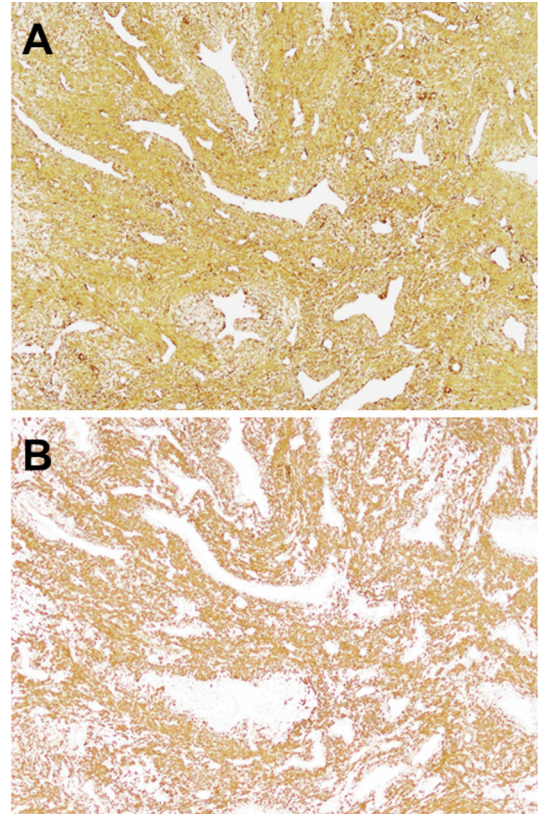


Figure 4. Immunohistochemical features of angioleiomyoma. The tumor cells are diffusely positive for smooth muscle actin (A) and h-caldesmon (B) (original magnification  $\times 100$ ).

subclassified into the three histological subtypes: solid, venous, and cavernous (1). The solid type has closely compacted smooth muscle cells with intervening thin-walled, slit-like vascular channels. The venous type shows thick muscle-coated blood vessels with intervacular smooth muscle bundles. The cavernous type is characterized by dilated vascular channels with attenuated walls of smooth muscle cells. In the largest series of 562 cases of angioleiomyoma, Hachisuga *et al.* reported that the solid type was the most common (66%), followed by the venous (23%) and cavernous (11%) types (2). Immunohistochemically, the tumor cells are diffusely positive for smooth muscle actin (SMA) (Figure 4A), muscle-specific actin (MSA) and calponin and variably for h-caldesmon (Figure 4B) and desmin (14). Immunostainings for S-100 protein and HMB45 are typically negative.

### Cytogenetic and Molecular Genetic Features

Only six cases of angioleiomyoma have been cytogenetically characterized in the literature (15-19) (Table I). Angio-leiomyoma displays mostly simple karyotypes

characterized by one or few chromosomal rearrangements or numerical aberrations. Previously, we identified the presence of DNA copy number changes involving one or two chromosomes in 8 (35%) of 23 cases of angioleiomyoma (20). The most common recurrent change was a loss of 22q11. Recurrent gain of Xq was also observed. Recently, Notch Receptor 2 (*NOTCH2*) gene rearrangements have been detected in a very small subset of angioleiomyomas (21). Further studies are needed to better understand the correlation between certain genomic alterations and distinct biological behavior.

### Differential Diagnosis

The differential diagnosis for angioleiomyoma is broad and includes both benign and malignant entities such as schwannoma, glomus tumor and synovial sarcoma (11, 22). In our opinion and experience, the most significant differential diagnosis is synovial sarcoma, and its small, well-circumscribed mass may give the wrong impression of a benign lesion by clinical examination and imaging.



Table I. Chromosomal changes in angioleiomyoma.

Case	Age/Sex	Location	Karyotype	Reference
1	29/F	Supraclavicular fossa	46,XX,del(6)(p21p23),del(21)(q21)	Heim <i>et al.</i> (15)
2	73/M	Gluteal region	46~47,XY,-13,+1~2mar	Nilbert <i>et al.</i> (16)
3	58/F	Finger	46,X,t(X;10)(q22;q23.2)	Sonobe <i>et al.</i> (17)
4	41/F	Uterus	46,X,t(X;11)(p11.4;p15)/46,idem,inv(2)(p15q13),t(5;20)(q13;q13.2)	Hennig <i>et al.</i> (18)
5	63/F	Ankle	45,XX,t(4;5)(p12;q33),der(13;15)(q10;q10)	Welborn <i>et al.</i> (19)
6	24/M	Thigh	46,XY,del(6)(q13q23),add(8)(q24),del(19)(q10),+mar	Welborn <i>et al.</i> (19)

F: Female; M: male.

Schwannoma is an almost invariably slow-growing neoplasm that may present as a painful mass, often less than 5 cm in size. It can occur at any age but has a peak incidence in the fourth and sixth decades of life (23). Radiographs are frequently normal. In rare cases, a fusiform soft-tissue mass with surrounding fat may be seen. Calcification is uncommon. Ultrasound typically shows a well-defined hypoechoic mass with variable posterior acoustic enhancement (24). An entering and exiting nerve sign and a polar blood supply sign on color doppler flow imaging can be seen (25). Ogata *et al.* reported that several ultrasonographic features including maximum diameter, tumor localization and continuity with the nerve were significantly different between schwannoma and angioleiomyoma (26). On MRI, the lesion usually displays intermediate or low signal intensity on T1-weighted images and high signal intensity on T2-weighted images. A target sign is one of the characteristic imaging features of schwannoma (27) and may be helpful to distinguish it from angioleiomyoma (28). A fascicular sign and a split-fat sign may also be observed. The histological hallmark of schwannoma is the pattern of alternating Antoni A and B areas. Immunohistochemically, the tumor cells are diffusely positive for S-100 protein (23).

Glomus tumor is a rare pericytic neoplasm that typically presents as a small, red-blue, painful nodule in the distal extremities, particularly the subungual region. It occurs in all age groups but more often in young adults (29). Radiographs may be normal or reveal a small soft-tissue mass related to the nail bed. Extrinsic erosion of the bone, often with a sclerotic margin, may be seen in subungual glomus tumor (30). Ultrasound usually reveals a solid, well-defined hypoechoic mass with prominent vascularity on color doppler examination (31, 32). On MRI, the lesion displays intermediate or low signal intensity on T1-weighted images and high signal intensity on T2-weighted images (32). Contrast-enhanced MRI demonstrates prominent homogeneous enhancement (32, 33). Histologically, the lesion consists of uniform, round cells with sharp cellular borders. Immunohistochemically, the tumor cells are positive for SMA, MSA and h-caldesmon (29). In 2015,

we reported the first case of glomus tumor with a t(1;5)(p13;q32) translocation (33). The discovery of *NOTCH1/2/3*-MicroRNA 143 (*MIR143*) fusion genes has recently led to more precise diagnosis of glomus tumor (21).

Synovial sarcoma is a malignant mesenchymal neoplasm that usually presents as a slow-growing, painful mass in the extremities, particularly around the knee. The duration of symptoms is quite variable. It most commonly affects adolescents and young adults (34). Radiographs may be normal or reveal a well-defined or lobulated soft-tissue mass. Calcification, often eccentric or at the periphery of the lesion, is seen in one-third of cases (35). Adjacent bone involvement (periosteal reaction, osseous remodeling, or frank bony invasion) may be seen. CT shows a heterogeneous soft-tissue mass with tissue attenuation similar to or slightly lower than that of skeletal muscle. Contrast-enhanced CT reveals heterogeneous or nodular enhancement in almost all cases (36). Ultrasound reveals a focal, nodular, round, or lobulated, solid but hypoechoic soft-tissue mass suggestive of a more indolent, less aggressive process (37). On MRI, the lesion is relatively well-defined and appears isointense or slightly hyperintense relative to skeletal muscle on T1-weighted images and displays prominent heterogeneous signal intensity on T2-weighted images. A triple signal pattern on T2-weighted images is often seen (38). Contrast-enhanced MRI typically demonstrates prominent heterogeneous enhancement (36). However, small lesions (less than 5 cm) may have a predominantly homogeneous appearance on all MR images (39). Histologically, synovial sarcoma can be classified as monophasic or biphasic. Monophasic synovial sarcoma is composed of fascicles of relatively uniform spindle cells with sparse cytoplasm and hyperchromatic nuclei with regular granular chromatin and inconspicuous nucleoli. Biphasic synovial sarcoma has epithelial and spindle cell components (40). Immunohistochemically, the tumor cells are positive for epithelial membrane antigen (EMA) and cytokeratins. A large majority of synovial sarcomas are positive for BCL2 and CD99. Notably, transducin-like enhancer of split 1 (TLE1) staining is highly sensitive for synovial sarcoma (34). Synovial sarcoma is characterized by the presence of a unique

t(X;18)(p11;q11) translocation, resulting in a fusion of SS18 subunit of BAF chromatin remodeling complex (*SS18*) (18q11) and *SSX* family member (*SSX*) (Xp11) (34). Identification of the *SS18-SSX* fusion would be helpful diagnostically for synovial sarcoma in more difficult cases.

## Conclusion

Angioleiomyoma is a distinct, benign, pericytic neoplasm and simple excision is usually curative. A diagnosis of angioleiomyoma can be formed on a routine microscopic assessment in a typical clinical setting. Angioleiomyoma should be considered a possible diagnosis when a well-demarcated oval or round subcutaneous mass with T1-isointense-to-slightly high signal, T2-high signal intensity, hypointense rim and intense enhancement is seen in the soft tissue of the extremities. Rearrangements of 22q and Xq are prominent in this peculiar neoplasm. Further studies are required to determine the biological consequences of these genomic alterations in angioleiomyoma.

## Conflicts of Interest

The Authors declare no conflicts of interest associated with this article.

## Authors' Contributions

MK collected the data, searched the literature, and drafted the article. JN was a major contributor to writing the article. KK performed the histopathological evaluations. TK, SN and TY reviewed the article. All Authors read and approved the final article.

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