

Review

Ubiquitin-specific Peptidase 6 (*USP6*)-associated Fibroblastic/Myofibroblastic Tumors: Evolving Concepts

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Abstract. *Ubiquitin-specific peptidase 6 (USP6) is a hominoid-specific gene residing on chromosome 17p13 and serves as a deubiquitinating enzyme with a diverse set of functions including intracellular trafficking, inflammatory signaling, cell transformation and protein turnover. USP6 rearrangements were first identified in aneurysmal bone cysts, resulting in promoter swapping and over-expression of wild type USP6. Several morphologically overlapping fibroblastic/myofibroblastic tumors are known to harbor USP6 rearrangements, including nodular fasciitis, cellular fibroma of tendon sheath, myositis ossificans and fibro-osseous pseudotumor of digits. Over the past few years, fusions involving the USP6 gene and various partner genes have been described in these neoplasms. The current World Health Organization Classification of Tumors of Soft Tissue suggests that USP6-rearranged lesions are typically benign and usually self-limited in their growth. This review provides an updated overview of the clinical, histological and molecular genetic features of USP6-associated fibroblastic/myofibroblastic tumors and discusses how these lesions should be best classified.*

Ubiquitin-specific peptidase 6 (*USP6*), located on chromosome 17p13, is a hominoid-specific gene primarily expressed in testicular tissue and encodes a deubiquitinating

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enzyme that plays critical roles in diverse cellular processes such as intracellular trafficking, inflammatory signaling, cell transformation and protein turnover (1, 2). *USP6* was initially cloned from transfected DNA of human Ewing sarcoma cells (3). *USP6* rearrangements were first identified in a primary aneurysmal bone cyst (ABC) (4). Subsequently, various fusion partners for *USP6* were discovered in ABC (5). These alternative gene fusions induce tumorigenesis by a promoter-swapping mechanism that drives transcriptional up-regulation of *USP6*. It was also shown that *USP6* induces expression of matrix metalloproteinase through activation of the classical nuclear factor-kappaB pathway (6). Furthermore, recent studies demonstrated that *USP6* promotes tumorigenesis through multiple pathways, including Wnt, Jak1-STAT3 and c-Jun (7-9).

The new fifth edition of the World Health Organization Classification of Tumors of Soft Tissue was published in early 2020. Several benign fibroblastic/myofibroblastic tumor subtypes are characterized by certain morphologies or distinctive anatomical distributions, including nodular fasciitis, cellular fibroma of tendon sheath, myositis ossificans and fibro-osseous pseudotumor of digits. Most notably, these benign tumors usually harbor *USP6* rearrangements (10-13). In this review, we present an updated overview of the clinical, histological and molecular genetic features of *USP6*-associated fibroblastic/myofibroblastic tumors and discuss their relationships to one another. The corresponding clinico-pathological and molecular characteristics are summarized in Table I.

Nodular Fasciitis

Nodular fasciitis is a benign self-limited fibroblastic/myofibroblastic neoplasm of unknown etiology. It equally affects males and females and occurs in all age groups but more often in young adults (20 to 40 years of age). The upper extremities are most frequently affected, followed by trunk and

Table I. Clinicopathological and molecular characteristics of *USP6*-associated fibroblastic/myofibroblastic tumors.

Entity	Clinical features	Histological features	<i>USP6</i> fusion partners
Nodular fasciitis	Third to fourth decades; Equal male and female incidence. Most cases involve the subcutaneous tissue and underlying fascia.	Circumscribed or infiltrative lesion, composed of plump (myo)fibroblasts in a myxoid or collagenous stroma with a tissue culture-like growth pattern; Extravasated erythrocytes, lymphocytes and osteoclast-like giant cells are common.	<i>MYH9</i> , <i>RRBP1</i> , <i>CALU</i> , <i>CTNNB1</i> , <i>MIR22HG</i> , <i>SPARC</i> , <i>THBS2</i> , <i>COL6A2</i> , <i>SEC31A</i> , <i>EIF5A</i> , <i>COL1A1</i> , <i>COL1A2</i> , <i>PAFAH1B1</i> , <i>SERPINH1</i> , <i>COL3A1</i> and <i>PPP6R3</i>
Cellular fibroma of tendon sheath	Third to fifth decades; Male predominance. Most cases attach to the tendon (sheath).	Increased cellularity compared with classical fibroma of tendon sheath; Well-circumscribed lesion, composed of spindled (myo)fibroblasts in a collagenous stroma. Slit-like vessels are present at the periphery.	<i>MYH9</i> , <i>COL1A1</i> , <i>COL3A1</i> , <i>PKM</i> , <i>RCC1</i> and <i>ASPN</i>
Myositis ossificans	Second to third decades; Equal male and female incidence. Most cases occur in the skeletal muscle.	Well-delineated lesion; Zoning phenomenon with immature bone at the center and mature bone at the periphery. Early (<6 weeks) lesion demonstrates a close resemblance to nodular fasciitis.	<i>COL1A1</i>
Fibro-osseous pseudotumor of digits	Second to fourth decades; Female predominance. Most cases occur in the subcutaneous tissue.	Less well-delineated lesion compared with myositis ossificans; Most cases have myositis ossificans-like histological features, composed of (myo)fibroblastic/osteoblastic cells in a collagenous to myxoid stroma. Zoning phenomenon may or may not be evident.	<i>COL1A1</i>

USP6: Ubiquitin-specific peptidase 6; *MYH9*: myosin heavy chain 9; *RRBP1*: ribosome binding protein 1; *CALU*: calumenin; *CTNNB1*: catenin beta 1; *MIR22HG*: MIR22 host gene; *SPARC*: secreted protein acidic and cysteine rich; *THBS2*: thrombospondin 2; *COL6A2*: collagen type VI alpha 2 chain; *SEC31A*: SEC31 homolog A; *COPII*: coat complex component; *EIF5A*: eukaryotic translation initiation factor 5A; *COL1A1*: collagen type I alpha 1 chain; *COL1A2*: collagen type I alpha 2 chain; *PAFAH1B1*: platelet activating factor acetylhydrolase 1b regulatory subunit 1; *SERPINH1*: serpin family H member 1; *COL3A1*: collagen type III alpha 1 chain; *PPP6R3*: protein phosphatase 6 regulatory subunit 3; *PKM*: pyruvate kinase M1/2; *RCC1*: regulator of chromosome condensation 1; *ASPN*: asporin.

head and neck. Most cases involve the subcutaneous tissue and underlying fascia. Nodular fasciitis typically grows rapidly and reaches its final size within a few weeks. Mild pain or tenderness may be present. The lesion usually measures 2 to 3 cm in diameter. Several subtypes of nodular fasciitis are recognized on the basis of the anatomical location, including intravascular fasciitis and cranial fasciitis (14).

Histologically, nodular fasciitis consists of a proliferation of spindle-shaped cells in a myxoid or collagenous stroma. The neoplastic cells are typically slender and delicate, mimicking the appearance of fibroblasts in tissue culture and are arranged in whorls, short fascicles or haphazardly (Figure 1A). Mitotic activity is easily identified but atypical mitoses are not observed. Extravasated erythrocytes, lymphocytes and osteoclast-like giant cells are frequently identified (14). Occasionally, osseous metaplasia may be present as seen in myositis ossificans and fibro-osseous pseudotumor of digits

(13). Immunohistochemically, the neoplastic cells are usually positive for smooth muscle actin (SMA) (Figure 1B) and muscle specific actin (MSA). Focal desmin expression is occasionally found.

Clonal chromosomal aberrations were detected in five cases of nodular fasciitis (15-19). Rearrangements involving 3q21 and 15q22-q26 were identified in a small subset of nodular fasciitis.

In 2011, *USP6* rearrangements were detected in 44 of 48 (92%) cases of nodular fasciitis (20). In that study, myosin heavy chain 9 (*MYH9*), located on chromosome 22q12.3, was identified as a novel fusion partner and it was shown that increased expression of *USP6* could induce formation of a tumor clinically and histologically similar to human nodular fasciitis in xenograft models. Since then, various *USP6* fusion partners were discovered in nodular fasciitis and its subtypes, including ribosome binding protein 1 (*RRBP1*), calumenin

(*CALU*), catenin beta 1 (*CTNNB1*), MIR22 host gene (*MIR22HG*), secreted protein acidic and cysteine rich (*SPARC*), thrombospondin 2 (*THBS2*), collagen type VI alpha 2 chain (*COL6A2*), SEC31 homolog A, COPII coat complex component (*SEC31A*), eukaryotic translation initiation factor 5A (*EIF5A*), collagen type I alpha 1 chain (*COL1A1*), collagen type I alpha 2 chain (*COL1A2*), platelet activating factor acetylhydrolase 1b regulatory subunit 1 (*PAFAH1B1*), serpin family H member 1 (*SERPINH1*) and collagen type III alpha 1 chain (*COL3A1*) (21-27). Some fusion partners appear to be shared across neoplasms (5, 24). These molecular studies indicate that the most frequent fusion partner of *USP6* is *MYH9* in nodular fasciitis. Wang *et al.* (24) suggested that the *MYH9-USP6* fusion is not related bone formation. Furthermore, a protein phosphatase 6 regulatory subunit 3 (*PPP6R3*)-*USP6* fusion with gene amplification was detected in two cases of nodular fasciitis with malignant behavior (28, 29). It is suggested that this fusion and/or *USP6* amplification may be associated with malignant condition. However, further studies with a large number of cases are needed to better understand the correlation between certain gene fusions and distinct biological behavior.

Cellular Fibroma of Tendon Sheath

Fibroma of tendon sheath is a benign fibroblastic/myofibroblastic neoplasm that is usually attached to a tendon (sheath) of the fingers. It may occur at any age but has a peak incidence in the third to fifth decades of life, with a male predominance. Fibroma of tendon sheath typically presents as a firm, small (usually less than 3 cm), slow-growing, painless mass (30). A cellular variant of this neoplasm has been described as having morphological overlap with nodular fasciitis (31).

Histologically, fibroma of tendon sheath consists of bland spindle cells in a dense collagenous stroma (Figure 2A). Cytological atypia is not observed and mitotic activity is low. There are characteristic slit-like thin-walled vessels or clefts at the periphery of the lesion. Degenerative features such as myxoid change, osseous metaplasia and pleomorphism may be present (30). Cellular fibroma of tendon sheath is generally defined as a tumor having areas of increased cellularity and a nodular fasciitis-like appearance as well as identifiable histological features of classical fibroma of tendon sheath (Figure 2B). Immunohistochemically, the neoplastic cells are often positive for SMA (Figure 2C). Expression of desmin, S-100 protein and FOS-like antigen 1 is absent (32).

Clonal chromosomal alterations were detected in four cases of classical fibroma of tendon sheath (33-36). These cytogenetic studies suggest that 11q rearrangement may be characteristic of classical fibroma of tendon sheath. It is of interest that this chromosomal rearrangement has also been observed in desmoplastic fibroblastoma (32), which can show

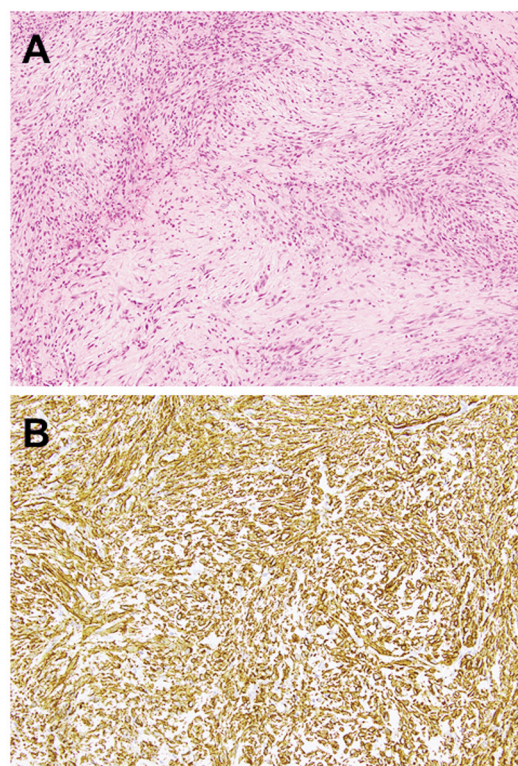


Figure 1. Histological and immunohistochemical features of nodular fasciitis. A: Nodular fasciitis consists of plump spindle-shaped cells with a vague fascicular and storiform pattern. Extravasated erythrocytes and lymphocytes can be observed (hematoxylin and eosin staining, original magnification $\times 100$). B: The neoplastic cells are diffusely positive for smooth muscle actin (original magnification $\times 200$).

morphological overlap with classical fibroma of tendon sheath.

Cellular fibroma of tendon sheath appears to be genetically distinct from classical fibroma of tendon sheath. *USP6* rearrangements were detected in 6 of 9 (67%) cases of cellular fibroma of tendon sheath but not in classical fibroma of tendon sheath (37). In 2020, various *USP6* fusion partners were discovered in a subset of cellular fibroma of tendon sheath, including pyruvate kinase M1/2 (*PKM*), regulator of chromosome condensation 1 (*RCC1*), asporin (*ASPN*), *COL1A1*, *COL3A1* and *MYH9* (24, 38). In view of the similar morphological and molecular genetic features, a subset of cellular fibroma of tendon sheath may in fact be tenosynovial nodular fasciitis.

Myositis Ossificans and Fibro-Osseous Pseudotumor of Digits: Are they Related?

According to the current World Health Organization Classification of Tumors of Soft Tissue, myositis ossificans and fibro-osseous pseudotumor of digits belong to the same neoplastic spectrum, with definite bone-forming capacity (39).

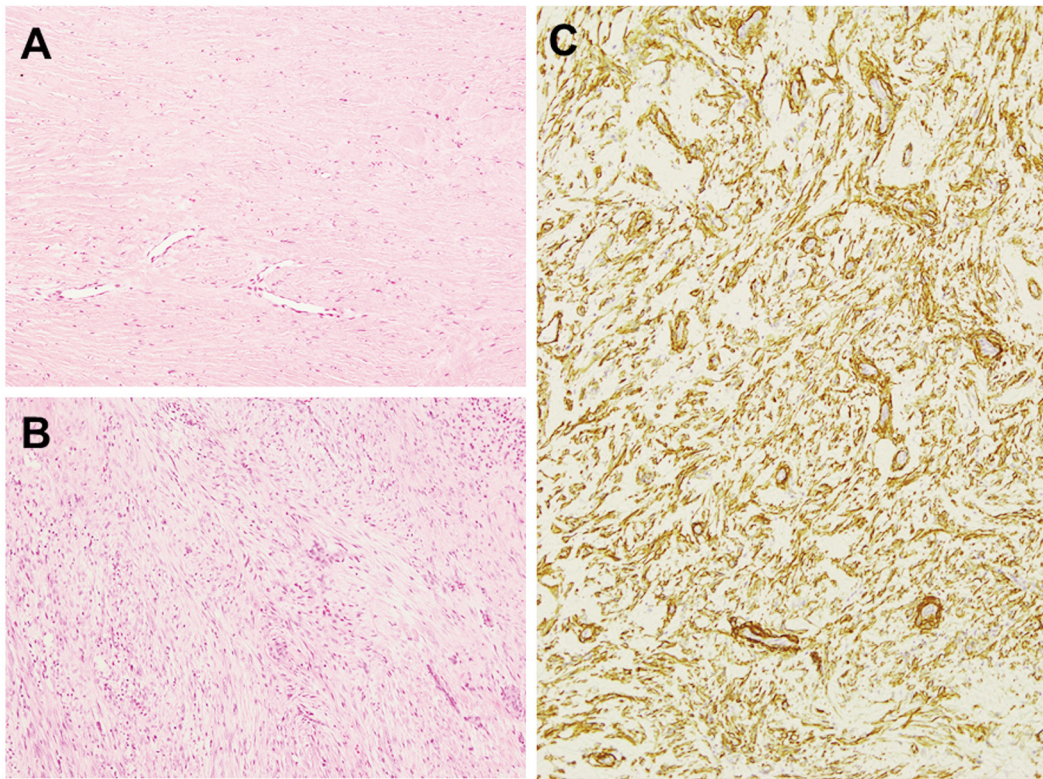


Figure 2. Histological and immunohistochemical features of classical and cellular variants of fibroma of tendon sheath. A: Classical fibroma of tendon sheath consists of bland spindle cells in a dense collagenous stroma. Slit-like vessels can be seen (hematoxylin and eosin staining, original magnification $\times 100$). B: Cellular fibroma of tendon sheath contains areas of increased cellularity composed of spindled-to-stellae cells arranged in a vague fascicular pattern (hematoxylin and eosin staining, original magnification $\times 100$). C: The tumor cells are positive for smooth muscle actin (original magnification $\times 100$).

Myositis ossificans is a benign self-limited fibroblastic/myofibroblastic neoplasm typically occurring within the skeletal muscle. A history of trauma is sometimes absent, and the lesion may be an incidental finding. It equally affects males and females and usually occurs in physically active adolescents and young adults. Although myositis ossificans can occur anywhere in the body, the most common locations are the thigh, lower leg and buttock. Deep-seated lesions may involve both muscle and underlying periosteum. The clinical features depend on the phase; in the early phase (1-2 weeks), the involved area is swollen and painful. Eventually, it evolves into a firm, rapidly growing, painless mass (Figure 3A). The diameter ranges from 2 to 12.5 cm (median of 5 cm) (40).

Histologically, myositis ossificans is characterized by the presence of a distinct zonal pattern with a peripheral rim of mature bone and a central cellular area composed of (myo)fibroblasts and immature bone (Figure 3B and C). In the early phase, myositis ossificans demonstrates a close resemblance to nodular fasciitis, with a highly cellular proliferation of (myo)fibroblasts within a variably myxoid stroma. The constituent (myo)fibroblasts display a mild degree

of cellular pleomorphism and rather prominent mitotic activity. In the late phase, on the other hand, myositis ossificans consists almost entirely of mature lamellar bone. Woven bone rimmed by uniform osteoblasts is present throughout the lesion. Entrapment of atrophic muscle fibers is often observed. Necrosis is usually absent. Immunohistochemically, the neoplastic cells may express SMA and MSA, suggesting myofibroblastic differentiation.

In 2008, *USP6* rearrangements were identified in 2 cases with radiological and histological features consistent with myositis ossificans (41). These cases were at that time considered to be the early phase of soft-tissue ABC rather than myositis ossificans. In 2018, Bekers *et al.* (42) confirmed the presence of *USP6* rearrangements in 8 of 9 (89%) cases of myositis ossificans. Recently, *COL1A1* was detected as a fusion partner of *USP6* in a subset of myositis ossificans (24, 43, 44). It is of interest that this gene fusion has also been found in soft-tissue ABC (24, 45, 46). These findings suggest that myositis ossificans and soft-tissue ABC are closely related entities.

Fibro-osseous pseudotumor of digits is a rare benign self-limited neoplasm usually occurring in the subcutaneous tissue

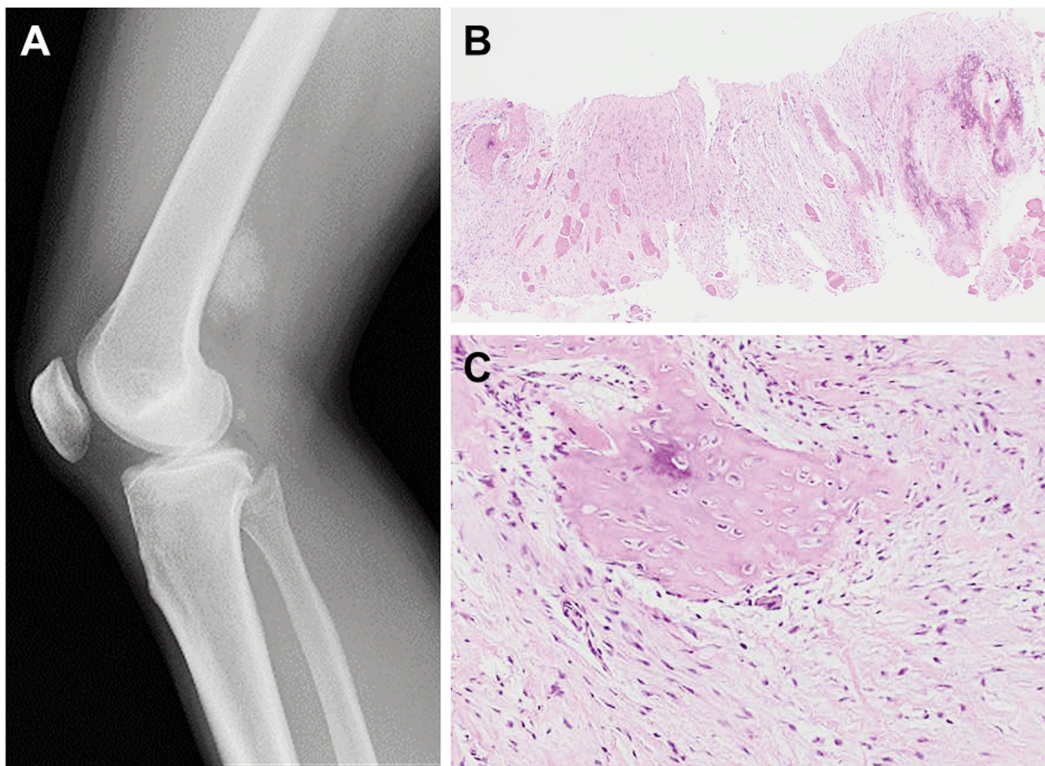


Figure 3. Radiographical and histological features of myositis ossificans. A: Lateral radiograph shows a densely mineralized mass in the posterior aspect of the distal thigh. B: Myositis ossificans shows a distinct zonal pattern with a central spindle cell proliferation surrounded by a peripheral bone formation. Skeletal muscle is entrapped (hematoxylin and eosin staining, original magnification $\times 20$). C: Myositis ossificans is composed of (myo)fibroblasts and foci of osteoid formation (hematoxylin and eosin staining, original magnification $\times 100$).

of the digits (Figure 4A). The etiology of this neoplasm remains unclear. It predominantly affects young to middle-aged adults, with a female predominance. The index finger appears to be a preferential location. Fibro-osseous pseudotumor of digits typically grows rapidly and the clinical features evolve over time. In the early phase, there is a variably painful fusiform swelling (47). Eventually, it becomes firm and well-demarcated. The diameter ranges from 0.2 to 5 cm (median of 1.5 cm) (48).

The histological features of fibro-osseous pseudotumor of digits are very similar to those of myositis ossificans. Minor histological differences are believed to be related to the different location of involvement (40). Fibro-osseous pseudotumor of digits shows an irregular multinodular growth pattern and is histologically composed of a mixture of (myo)fibroblasts, osteoblasts and bony trabeculae with various stages of maturation (Figure 4B and C). Like myositis ossificans, the zonal pattern may be seen (48). Mitotic activity may be high but abnormal mitotic figures are not observed. Immunohistochemically, the neoplastic cells may express SMA. No immunoreactivity has been reported for desmin, S-100 protein and CD34 (49).

In 2018, *USP6* rearrangements were detected in 4 of 5 (80%) cases of fibro-osseous pseudotumor of digits (50). Recently, *COL1A1* was detected as a fusion partner of *USP6* in a significant number of fibro-osseous pseudotumor of digits (24, 44). Intriguingly, almost all of bone-forming *USP6*-rearranged neoplasms adopt *COL1A1* as the fusion partner, including myositis ossificans, fibro-osseous pseudotumor of digits and soft-tissue ABC. We suggest that these bone-forming soft tissue lesions belong to the same spectrum of *USP6*-induced neoplasms in light of their overlapping, occasionally indistinguishable morphology.

Molecular Diagnostics

In current practice, molecular genetic assays can serve as a useful diagnostic adjunct for soft tissue tumors (10). Notably, the development of next-generation sequencing has advanced our knowledge of molecular genetics in soft tissue tumors (22, 51).

Because of its rapid growth, high cellularity and high mitotic activity, nodular fasciitis can be misdiagnosed as a malignant soft tissue tumor such as low-grade fibrosarcoma

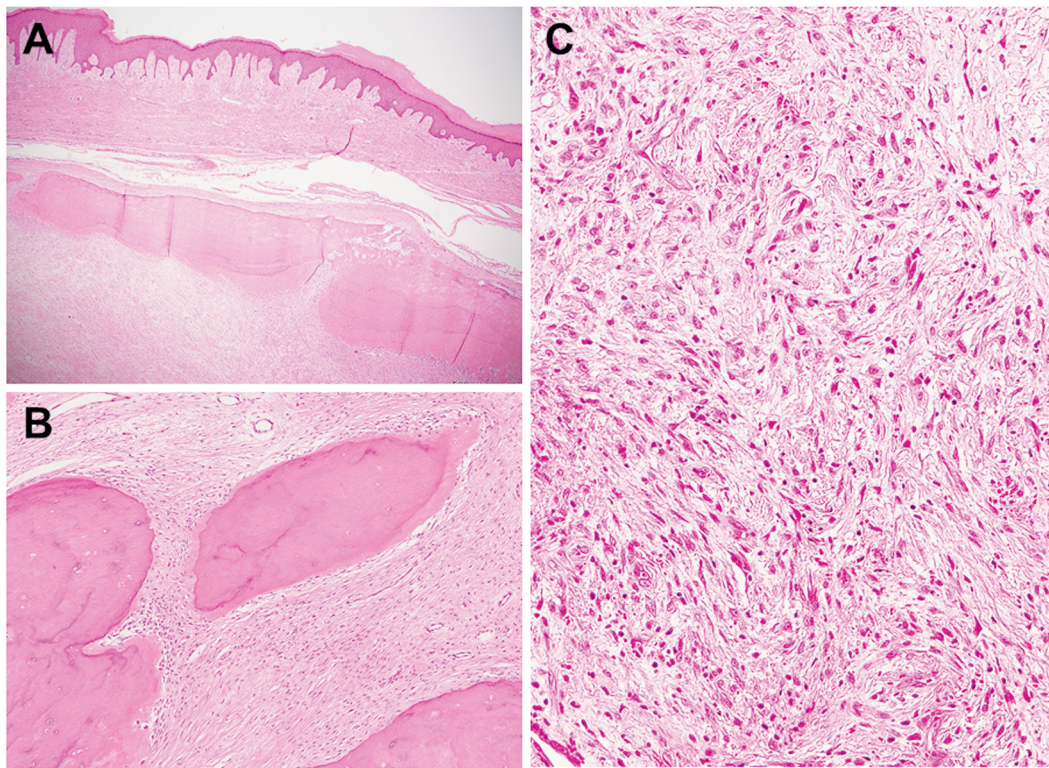


Figure 4. Histological features of fibro-osseous pseudotumor of digits. A: Fibro-osseous pseudotumor of digits involves the subcutaneous tissue. Mature bone is present at the periphery of the lesion (hematoxylin and eosin staining, original magnification $\times 20$). B: Fibro-osseous pseudotumor of digits shows a (myo)fibroblastic proliferation and mature woven bone formation (hematoxylin and eosin staining, original magnification $\times 100$). C: The central portion is composed of (myo)fibroblasts with a storiform pattern, resembling nodular fasciitis (hematoxylin and eosin staining, original magnification $\times 200$).

or low-grade myxofibrosarcoma, often leading to unnecessarily aggressive treatment. Similarly, myositis ossificans and fibro-osseous pseudotumor of digits can be easily confused with extraskeletal or parosteal osteosarcoma. Cellular fibroma of tendon sheath may be histologically confused with low-grade fibromyxoid sarcoma and low-grade myofibroblastic sarcoma. It is of interest that the most important differential diagnoses do not show *USP6* rearrangements. Therefore, the detection of *USP6* rearrangements and/or *USP6* fusions would be useful for the diagnosis of these benign fibroblastic/myofibroblastic neoplasms, especially in small biopsy specimens.

Behavior and Treatment

In our experience, conservative treatment is a reasonable first-line approach for benign self-limited neoplasms such as nodular fasciitis and myositis ossificans. In bone-forming cases, repeated radiographical examinations should be obtained during the follow-up period to document the maturation of the lesion and the absence of destructive growth.

Nodular fasciitis is a benign self-limiting process. Spontaneous regression is well documented and simple excision without attention to margins is sufficient. Local recurrence is very uncommon and typically cured by simple re-excision. Although extremely rare, malignant clinical behavior has been described in the literature (28, 29).

Simple excision is the treatment of choice for fibroma of tendon sheath but local recurrence is seen in 5-10% of cases (30). Recurrence is not aggressive and typically respond to simple re-excision. No cases of malignant transformation have been reported. There is no relationship between morphological variants and different clinical outcomes.

Undoubtedly, myositis ossificans and fibro-osseous pseudotumor of digits are benign self-limiting conditions similar to nodular fasciitis. Simple excision is the treatment of choice for these lesions and prognosis is excellent. Malignant transformation in myositis ossificans, usually into osteosarcoma, has been described (52) but it is exceptionally rare. On the other hand, there is no evidence of malignant transformation of fibro-osseous pseudotumor of digits.

Conclusion

Almost all of *USP6*-associated fibroblastic/myofibroblastic tumors have a benign clinical course. Over the past decade, a number of novel fusions involving the *USP6* gene have been identified in nodular fasciitis, cellular fibroma of tendon sheath, myositis ossificans and fibro-osseous pseudotumor of digits. These fusion partners act as an ectopic promoter leading to transcriptional activation of *USP6*. A subset of cellular fibroma of tendon sheath are probably in fact tenosynovial variants of nodular fasciitis. Myositis ossificans and fibro-osseous pseudotumor of digits may represent a morphological spectrum of the same biological entity, related to and sometimes indistinguishable from soft-tissue ABC. Further studies are required to determine whether different fusion partners are associated with distinct morphological features and biological behavior of *USP6*-induced neoplasms.

Conflicts of Interest

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

Authors' Contributions

SN researched the literature and drafted the article. JN collected the data and was a major contributor to writing the article. MA, KK and KN performed the histological evaluations. TY reviewed the article. All Authors read and approved the final article.

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