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Calcifying Aponeurotic Fibroma

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Abstract: *Calcifying aponeurotic fibroma is a rare, slow-growing, poorly circumscribed fibroblastic tumor. It may represent the cartilage analogue of fibromatosis. Initially described in children and adolescents, the tumor has now been recognized to occur over a wide age range, at various anatomical sites and to exhibit a large variety of clinical manifestations. Although the histological features include an ill-circumscribed fibroblastic proliferation, with foci of calcification and chondroid differentiation, the lesion may not be associated with definite calcification, while, on the other hand, the presence of calcification is not pathognomonic of the tumor. The findings of computed tomography and magnetic resonance imaging are usually nonspecific. The latter may be suggestive of potential malignancy due to the local invasion of the lesion. An accurate diagnosis may only be secured on the histopathological findings following excisional biopsy. Local recurrence after surgical resection is quite common because of the locally infiltrative nature of the tumor. Recurrences are not destructive and simple removal is usually the only indicated treatment of the recurrent lesion. The purpose of this editorial is to review the clinical, imaging and histological findings of three patients treated at our institution and to review the relevant publications.*

Keywords: *Calcifying, juvenile, aponeurotic, fibroma.*

EDITORIAL

Keasbey in 1953 named as juvenile aponeurotic fibroma a rare benign soft tissue tumor that was previously designated as a fibroma of the palms and soles in young children [1]. Since then, more than 150 cases have been documented in the world English and non-English literature [2-11]. The lesion was termed 'the cartilage analogue of fibromatosis' by Litchenstein and Goldman [12]. The tumor was also named calcifying juvenile aponeurotic fibroma, juvenile aponeurotic fibromatosis and juvenile nodular aponeurotic fibroma. Considering the wide age range of the reported patients, the term of the lesion was changed to aponeurotic fibroma and calcifying aponeurotic fibroma (CAF) [13, 14]. The term aponeurotic recalls, apart from the aponeurotic origin of the lesion, to the histiogenesis of ligaments, fascia, aponeurosis and tendon as they insert into bone through Sharpey fibers [15-17]. A fibroblastic or myofibroblastic origin has been suggested in the pathogenesis [18].

The lesion is benign, but it has a high incidence of nondestructive recurrence after surgical excision [1, 19-21]. There is no evidence of a familial or racial prevalence [19]. The lesion has also been detected in animals [22]. Its molecular basis is unknown. Chromosome banding analysis, fluorescence in situ hybridization, mRNA sequencing, RT-PCR (Reverse transcription-polymerase chain reaction), and immunohisto-chemistry have been used to characterize a series of CAFs. High-level expression of the entire FN1 (Fibronectin 1) gene in CAF suggests that strong FN1 promoter activity drives inappropriate expression of the biologically active portion of EGF (Epidermal growth factor), which was detected immuno-histochemically in 8 out of 9 cases.

The FN1-EGF fusion, which has not been observed in any other neoplasm, appears to be the main driver mutation in CAF. Although further functional studies are required to understand the exact pathogenesis of CAF, the composition of the chimera suggests an autocrine/paracrine mechanism of transformation [23].

The tumor has a predilection for the male sex and juvenile age. The reported age range in the literature is from birth to 69 years, while the mean age at diagnosis is about 12 years of age [18, 21, 24-27].

Localization is nearly exclusively in the hand and foot, with over three fourths of the cases occurring in the hands. The palm is a well-known site of involvement (approximately half of the cases), as well as the fingers and wrist. The toes are an unusual site, since most cases involving the foot occur in the plantar and ankle regions [28, 29]. Exceptionally, the tumor has been found originating in various other sites such as subungually, in the arms, legs, back, chest or abdominal wall and head or neck [16, 21, 30-43]. An intramuscular localization has also been reported [41]. The lesion has also been detected surrounding a joint [20] or invading into the adjacent joint mimicking gout or calcium pyrophosphate dehydrates deposition disease [44]. Rarely the nodules are multiple in the same area [45] or the lesion appears in association with other neighboring soft tissue lesions [46].

Patients usually complain of a deep musculofascial or paraskeletal mass, occasionally subcutaneous, with ill-defined boundaries, mobile or immobile and firm on palpation. It is painless, slowly growing and it is usually attached to tendon or aponeurosis. Painful lesions have also been reported [16, 21, 47, 48]. Intratendinous lesions have rarely been reported [28, 32, 49]. It does not usually reach a large size (rarely more than 3 cm in diameter), with the exception of tumors arising in sites outside the hands and feet. Rapidity of growth seems to slow down, while tumor calcification appears to increase with age. Older lesions tend to become harder and more sharply circumscribed. Despite its infiltrative attitude and high degree of cellularity, the tumor has limited growth and it does not cause important local disorders [50-52].

Radiographic features are also not patho-gnomonic. No calcification or only smudge-like radiopacities may appear initially. However, lesions that have been present for years may exhibit large calcified areas [53, 54]. Signs of bone involvement, such as extrinsic erosion of the adjacent bone [20, 30, 32, 54-61] and adjacent bone thickening [62] may be seen. Ultrasound examination excludes the more likely diagnosis of a ganglion indicating a solid mass mainly fibrous with foci of calcification. A computed tomography also reveals a calcified rather than ossified lesion with a visible cleavage plane from bone, which may lead to the diagnosis of panniculitis ossificans and extraskeletal or parosteal chondroma [18, 32, 53, 59].

A high-resolution magnetic resonance imaging may indicate a heterogeneously enhancing soft tissue mass with subcutaneous distribution, ill-defined appearance, and a tendency to infiltrate into or adhere to the surrounding tissues. The low to intermediate intensity or isointensity on T1-weighted images may be attributed to the fibrous component, the degree of cellularity and the presence of calcification. The variability of signal intensity on the T2-weighted images is thought to depend on the degree of hypocellularity and the amount of collagen and calcification within the tumor.

Most of the lesions, exhibiting hypocellularity, abundant collagen and calcification, showed isointensity to low signal intensity on the T2-weighted images. However, homogeneous or heterogeneous high signal intensity has also been reported [44, 50, 60].

The appearance of hyperintense areas on T1 and T2-weighted imaging, appearing in old lesions, may represent signals from fatty tissues in the site of calcification [63].

The lesion usually demonstrates intense heterogeneous enhancement in postcontrast T1-weighted images, with fat suppression and intravenous gadolinium enhancement [18, 21, 36, 39, 41, 55, 44, 58, 64]. Definite diagnosis is always based on histological findings and sometimes on immunohistochemical tests [65] and ultrastructural studies, due to its wide cytoarchitectural pattern [14, 32, 41, 66, 67].

The histological examination reveals a dense fibrous stroma that surrounds nodules which may have a center composed of cartilage. On gross examination, the pathological tissue is compact; the cut surface appears gray-white and may feel gritty. The lesion is permeating and surrounding the tendons, muscular fascicles, lobules of fat, vessels and nerves, without precise boundaries. At a later stage, the lesion tends to become more nodular, better demarcated and more densely fibrous, possibly speckled by calcific granules. The lesion may invade the subcutis, and adhere to the adjacent periosteum and joint capsule.

At low magnification, the typical case presents a unique pattern of multiple cellular nodules of fibromatosis-like spindle-shaped fibroblasts oriented in circular, parallel rows of cells. The nodules are surrounded by dense, often paucicellular fibrous tissue and may have a central punctuate area of calcium or cartilage.

At higher magnification, the fibroblasts tend to run in the same direction, in columns or palisade

as they circle around the areas of calcification and the nests of cartilage. They may be accompanied by more rounded epithelioid cells [18]. Rays of fibrous tissue extend from the main lesion into the surrounding tissue and may infiltrate muscle or nerves. The surrounded muscular cells, adipose cells, tendons, vessels and nerves are not invaded or destroyed. The fibroblasts have distinctive plump, round-oval, well-strained nuclei, and rather abundant and vesicular cytoplasm.

Calcification is present in the centre of the nodule except in lesions removed from infants and very young children. The pattern of calcium deposition varies from amorphous masses to granular elongate lines. Nuclei are often present within the calcified areas. Occasionally, multinucleated giant cells, reminiscent of tenosynovial giant cell tumor, are encountered [66]. Toward the centre of some nodules, the stroma may take on a chondroid appearance, and sometimes mature cartilage with variable degrees of calcification is present. The cellularity varies from lesion to lesion and within the same lesion. Areas adjacent to the cartilage and calcium are usually cellular, while those away from these centers are paucicellular. Mitotic figures are low and ossification is not usually evident [47].

Rarely, the calcified component may be composed of mature bone exhibiting focal areas of hematopoiesis [18, 38]. Transformation of the histological features of the lesion to a more mitotically active cellular lesion, identical to fibrosarcoma, has been observed, but it is extremely rare.

The histological pattern of nodules with central punctuate calcification surrounded by fibroblasts with plump nuclei within a hyaline cartilage-like stroma or a cartilaginous stroma should indicate the potential diagnosis of calcifying aponeurotic fibroma, particularly if the tumor is localized in the distal extremity of a child or young adult. Some authors suggested the existence of different histological phases of tumor growth. These biphasic features may explain the heterogenous appearance on radiological imaging, which is variable according to the patient's age, presence of calcifications and osseous involvement [25, 66].

In the initial (early) phase, which is more common in infants, the tumor has an infiltrative growth and often lacks calcification. In the late phase, the lesion shows a more prominent degree of calcification and cartilage formation, associated with a more compact and nodular aspect with well defined borders. The tumor maturation is indicated by the histological decrease in cellularity and an increase in collagen stroma [1, 13, 19]. Occasionally, a lesion may have characteristics of both the initial and late phase [64].

The use of immunohistochemistry has demonstrated that the tumor cells usually express immunoreactivity for vimentin, CD99, CD68, S100, muscle-specific actin and smooth muscle actin, but they are negative for desmin [32, 60, 68].

Although the diagnosis of CAF may be rendered on core needle biopsy, the final diagnosis should be rendered on the excisional biopsy [66, 67]. Complete excision or a more conservative surgical approach that may be accomplished without functional compromise is indicated for patients of all ages. The tendons and neurovascular bundles should be preserved even if they are invaded by the tumor [54, 69]. Functional deficits are usually iatrogenic rather than the result of tumor growth [70].

Considering the site and infiltrative features of the lesion, typically into the surrounding fascia and muscle, surgical removal is generally intralesional and incomplete [25, 32, 71, 72]. Recurrence is very frequent, about half of the patients experience a recurrence, particularly during childhood, which is not destructive [73]. The incidence of recurrence decreases in older children and adults [36]. The neoplasm's highly cellular architecture, locally aggressive growth pattern, and tendency to recur may lead to a misdiagnosis of fibrosarcoma and subsequent amputation [29].

If the recurrence is not aggressive and does not interfere with function, a prolonged observation may be permitted. Otherwise, a more radical extirpation may be needed [69, 74, 75]. An unusual aggressive, recurrent calcifying aponeurotic fibroma of the thumb in an adult man with invasion into the distal and proximal phalanges, the skin, the radial and ulnar neurovascular bundles, and the tendons, which necessitated amputation and an immediate toe-to-thumb transfer has been reported [20]. The lesion does not metastasize.

However, malignant transformation to metastatic fibrosarcoma of the lungs and bones has been reported in the literature [59, 76, 77]. In addition, an infantile fibrosarcoma of the elbow successfully treated with chemotherapy alone,

who developed a calcifying aponeurotic fibroma and a spindle cell/pleomorphic lipoma at the tumor site, 12 years later, has also been reported [78]. A report presenting three patients with CAF, treated at our institution, has been previously published [28]. In our 8-year-old patient a firm, mobile subcutaneous solid mass developed on the volar aspect of his left wrist 18 months previously. Radiographs were normal. Under general anesthesia a transverse incision was made across the volar aspect of the wrist between flexor creases

The tumor was located within the substance of the palmaris longus, so the tendon was excised to macroscopically healthy borders. The microscopic picture indicated an 11x6x5 mm lobulated mass with irregular borders demonstrating diffuse fibroblastic growth with a linear arrangement of the rounded fibroblasts and areas of spotty calcification surrounded by chondrocytes.

Fat infiltration as well as remnants of tendon fibers was also found. There was no sign of nuclear atypia and mitotic activity (Fig. 1).

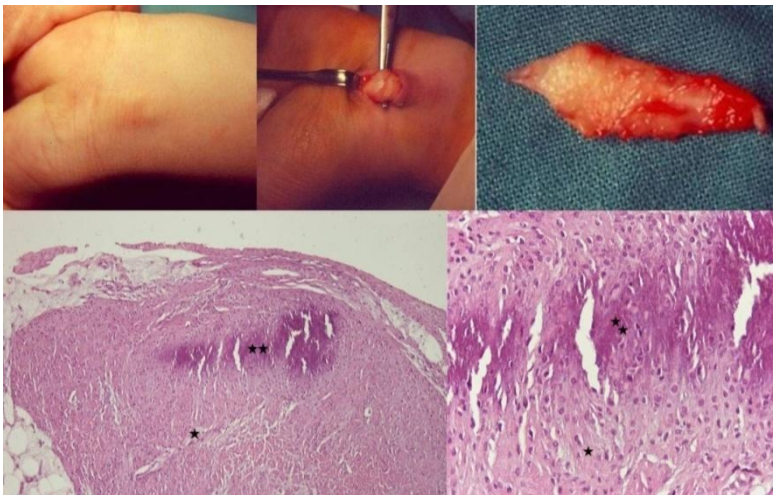

Figure1. *Clinical appearance of the lesion, intra-operative picture and the gross specimen of the resected palmaris longus including the tumor in an 8-year-old boy. Histological examination indicated a diffuse fibrous stroma with small rounded chondrocyte-like cells (one star) and nodules of spotty calcification (two stars).*

In our adult patients the lesions were localized to the foot. They appeared as a firm, well-circumscribed mass causing discomfort with shoe wear.

Radiographs showed a calcified lesion close but with no destruction of the underlying metatarsal (Fig.) or phalanx (Fig. 3), respectively. Both lesions were removed under local anesthesia. The histological findings were almost identical showing extensive degenerative changes i.e. fibrosis and calcification. Microscopically, the mass consisted of dense fibrous stroma exhibiting extensive calcification. The cellularity was low with foci of myofibroblast-like cells. There was no sign of chondroid differentiation. Nuclear atypia, mitotic activity and local tissue destruction were not encountered.

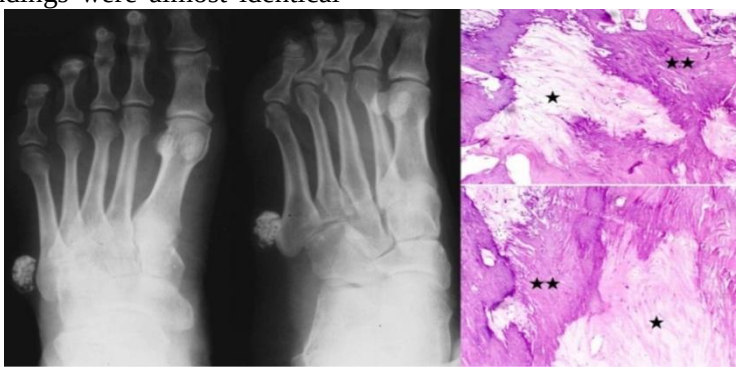

Figure2. *A 43-year-old woman was referred for a 2-cm, nontender tumor in the lateral aspect of the foot at the base of the fifth metatarsal. Since first noted, about 15 years previously, it had grown slowly and caused some discomfort with shoes. Radiographs showed a calcified lesion close to the fifth metatarsal. It was removed under local anesthesia. The lesion was a well-defined mass adjacent to the peroneal tendon. The histological picture was characterized by a heavily collagenized component (one star) exhibiting extensive calcification (two stars). The cellularity was low. There was no sign of chondroid differentiation. Nuclear atypia, mitotic activity and local tissue destruction were not encountered.*

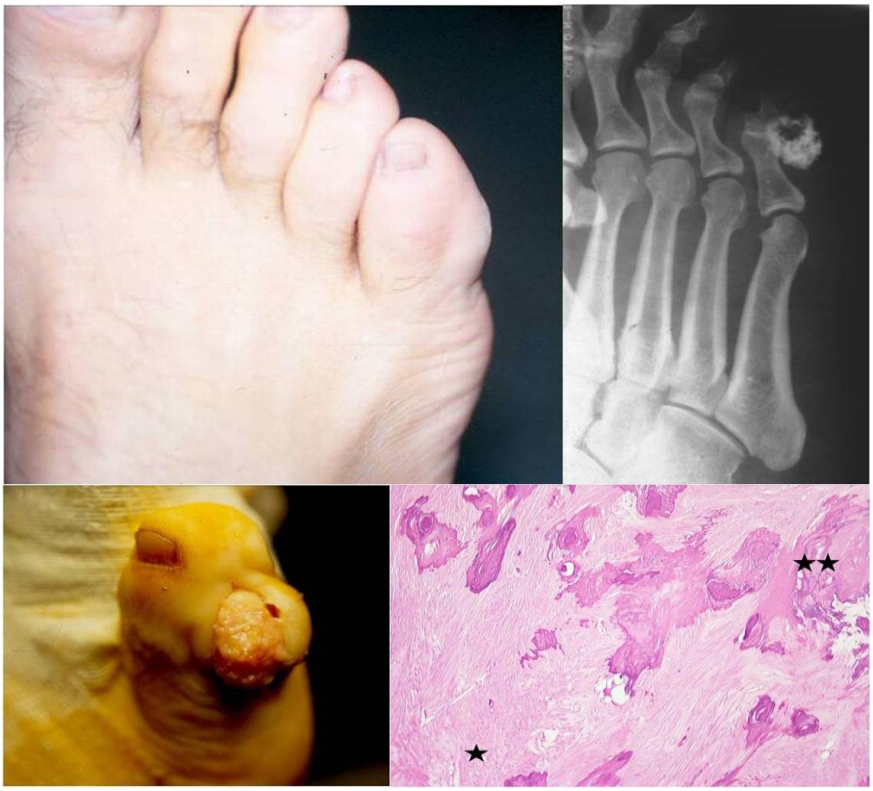

Figure3. *A 48-year-old man came for evaluation of a 2-cm mass of the fifth digit of the right foot. It had appeared about 12 years previously, had grown slowly, and caused some pain and tenderness recently. Radiographs showed a calcified lesion on the plantar and lateral aspect of the proximal interphalangeal joint of the fifth toe but with no bone destruction. A computed tomography indicated a heavily calcified mass entirely separated from bone. The lesion was removed under local anesthesia. The surgical specimen was a firm, well-circumscribed mass adjacent to the flexor tendons. Microscopically, the mass consisted of dense fibrous stroma (one star) with extensive foci of calcification (two stars). There was no evidence of cartilaginous metaplasia.*

Differential diagnosis from hemangioma, parosteal osteochondroma, soft tissue extraskeletal/extrasynovial chondroma, giant cell tumor of the tendon sheath with cartilaginous metaplasia, fibroma, fibrous hamartoma of infancy (FHI), rheumatoid nodules, fibromatosis such as infantile or juvenile, extraabdominal and aggressive forms [65], panniculitis ossificans, calcified soft tissue leiomyoma and malignant soft tissue tumors with intratumoral calcifications may be required in both children and adults [32, 50, 59, 79, 80].

Differential diagnosis from FHI is based on the lack of cartilage and calcification, and FHI does not occur in the hands and feet. In addition, FHI contains immature mesenchyme not found in CAF and fibroblasts arranged in trabeculae rather than in parallel rows around calcified nodules. Infantile desmoid fibromatosis does not occur in the hands and feet, it is not calcified or nodular, it does not have cartilaginous features and it contains large amounts of fat within the center of the tumors. Palmar fibromatosis is rare under the age of 20, it does not infiltrate muscle and nerves it is not associated with calcification and it rarely demonstrates cartilage or chondroid.

Differentiation from bizarre parosteal osteochondroma and extraskeletal/extrasynovial soft tissue chondroma is based on absolute lack of hyaline cartilage in CAF. Chondromas are also lobulated but have a less infiltrating pattern. They may also calcify but they are not associated with nodules of cellular fibrous tissue and are mostly found in adults. In rare cases distinction may be problematic, but this is not critical, since nondestructive recurrence could be the worst complication of both of them.

The most important histological finding distinguishing soft tissue chondroma from CAF is the presence of infiltrating fascicles of fibroblasts at the periphery of CAF [18]. The cells in the differentiated areas of chondroma are almost always S-100 protein positive.

Myositis ossificans and related lesions, including panniculitis ossificans and fibro-osseous pseudotumor of the digits with scant bone and osteoid may contain cells that resemble those in CAF, but do not display cellular nodules and exhibit a distinct mineralization pattern with a

fibroblastic proliferation showing varying degrees of atypia. Nodular fasciitis can be readily distinguished by the presence of plump fibroblasts within a myxoid background, while it is uncommon in infants and children and rare on the hands and feet [32, 81, 82]. Differential diagnosis from a calcified soft tissue leiomyoma is more complicated. In deep soft tissue leiomyomas regressive changes are quite common, and calcium may also be laid down in distinct spherules reminiscent of psammoma bodies. However, the main histological characteristics of leiomyoma i.e. cells with elongated, oblong, fusiform, blunt-ended nuclei as well as proliferation of smooth muscle fibers are not found in CAF [83].

It is important not to confuse it with a soft tissue sarcoma, such as synovial or clear cell sarcoma, [55, 63, 64]. Cases localized to the hand and wrist should be differentiated from common malignant soft tissue tumors particularly in the presence of intratumoral calcifications, such as epithelioid sarcoma, synovial sarcoma and undifferentiated pleomorphic sarcoma [36].

In conclusion, it has been documented that CAF is mainly a lesion of childhood. In infants and young children it may contain little or no calcium, while it may infiltrate fat in a way that it may cause a dilemma whether the fat is part of the lesion, although fat cells are usually present only at the periphery. CAF has a dense fibrous stroma that surrounds nodules, which are formed by circular, parallel rows of cells and may have a center composed of cartilage.

The appearance of cells closely resembling myofibroblasts surrounding the calcified areas is compatible with CAF [14, 84]. CAF in the late phase may appear histologically as a well-demarcated and less cellular lesion with increased collagen deposition between the fibroblasts and with a more prominent degree of calcification suggesting maturation of the process. Finally, chondroid foci, which are typically present adjacent to scattered calcified zones, are not absolute prerequisites for the diagnosis of CAF [32, 53, 59].

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