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Calcifying aponeurotic fibroma: Radiologic-pathologic analysis of ten cases and review of the literature

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ABSTRACT

Calcifying aponeurotic fibroma (CAF) is a very rare benign entity that principally affects the volar fascia, tendons, and aponeuroses of the hands and feet with a peak incidence of between 5 and 15 years, although there have been cases found for a wide age range and at various anatomical sites. We present ten CAF cases; consisting of eight children and two adults. CAF occurred in the extremities in nine of the cases and in the chest wall in one case. CAF ultrasound and radiological findings are nonspecific but may help orientate diagnosis. Magnetic resonance imaging should be performed when there are doubtful cases, when occurring in nontypical sites, and when there are cases of nontypical clinical presentation. Histologically, all cases showed two components, a fibromatosis-like component and a nodular component. Chondroid areas were present in five cases. Calcifications were observed in nine cases. ERG immunostaining showed the same patterns in all the cases; diffuse positivity in pericalcified areas, and patchy positivity in areas away from calcifications. CAF has distinctive histopathological features which should aid in the differential diagnoses with other entities.

1. Introduction

Calcifying aponeurotic fibroma (CAF) is a very rare entity that was first described in 1953 [1]. It is a benign, solitary, and nonmetastasizing lesion [2,3]. However, malignant transformations have been reported in individual cases [4,5]. The pathogenesis remains uncertain although a fibroblastic/myofibroblastic origin has been suggested [6].

CAF clinical presentations are nonspecific. It is typically a slow-growing solitary lesion and a painless mass [7], although painful cases or multiple tumors have also been reported [8-10]. It is usually poorly circumscribed and may cause limitations to movement or discomfort [11]. CAF typically affects children and adolescents [12] but cases in adult patients have also been reported [8,13]. It is more frequent in males [11]. CAF principally affects the volar fascia, tendons, and aponeuroses of the hands and feet [2,14]. It has also been described in a wide variety of regions such as the neck, lumbosacral region, forearm, wrist, elbow, arm, thigh, popliteal fossa, chest wall, and abdominal wall [2,12,13,15-18]. More than 50 % of cases have been reported to recur locally, being more frequent in patients younger than 5 years old and during the first three postoperative years [7]. The recommended treatment is marginal resection [7].

CAF radiological findings are nonspecific. On radiographs, it appears as a soft tissue mass with or without fine calcification [19], and erosion of the adjacent bone or scalloping of the cortex may be observed [19]. Through ultrasound imaging (US) examination, CAF may be seen as well-defined or irregular masses, being either hypoechoic or isoechoic, and may have hyperechoic foci if there are calcifications [20]. Magnetic resonance imaging (MRI) is the best option for evaluating these lesions [19]. On the MRI, the calcification of CAF does not appear during the early stage and radiologists should be aware of this fact when differentiating CAF from other soft tissue tumors [20,21]. On the MRI at the later stage, fat-like signals can appear at the site of calcification [21]. CAF may mimic malignancy, particularly with synovial sarcoma or undifferentiated pleomorphic sarcomas [2,19], on preoperative MRI due to its ill-defined appearance. Computerized tomography is the best modality for the characterization of the calcifications located in an otherwise nonspecific soft tissue mass [22].

Macroscopically, most CAFs are poorly defined, gray-white, with or

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without calcifications, and measure less than 3 cm [11]. In terms of histology, various evolution phases have been suggested [16]. In the first phase, there is high cellularity composed of spindle mesenchymal cells with round or ovoid nuclei without atypia, which are arranged in loose infiltrative fascicles and small nests. They present scanty mitoses. Nodules with cartilaginous foci and no calcifications or focally calcified nodules may be present [11]. In the second phase, the presence of granular calcifications in the nodular component predominates. These are bordered by epithelioid cells arranged in short radiating columns with occasionally scattered osteoclast-like giant cells [11]. In the final phase, the tumor is predominantly hypocellular with a diffusely fibrotic and calcified stroma [11]. The lesion often extends into the adjacent tissue [11]. The main features seen in fine needle aspiration procedures are benign-appearing spindle cells, chondroid cells, multinucleated giant cells, hyaline, myxoid stroma, and calcified debris [23].

In terms of immunohistochemistry, CAF is positive to vimentin, CD99, CD68, muscle-specific actin (50 % of the cases), smooth muscle actin (50 % of the cases), S100 and WT1; and is negative to CD34 and

Table 1
Summarized patients and tumours characteristics.

Case	Age (years)	Sex	Site	Image test	Clinical presentation	Relapse or metastasis	Size (cm)	Cartilage areas	Calcification areas	Giant cells	Atypia	Mitoses	ERG % and intensity
1	34	M	Third finger of the hand (multiple lesions)	Ultrasound: well-defined nodular lesions, heterogeneous, with calcified areas in the center	Trigger finger	No	1,3	Yes	Marked, central and peripheral chondroid aura	No	No	No	10, moderate
2	9	M	Inner forearm	Not performed	Slow-growing painless mass	No	0,4	No	No	No	No	No	20, moderate
3	9	M	Sole of the foot	Ultrasound: well-demarcated, fibrous soft tissue lesion	Slow-growing painful mass	No	1	Yes	Peripheral, chondroid aura, pericellular	Isolated	No	No	25, moderate
4	14	F	Third finger of the hand	Not performed	Slow-growing painless mass	No	0,8	Yes	Peripheral, chondroid aura, pericellular	Isolated	No	No	30, moderate
5	3 months	M	Palm of the hand	Radiography: solid, heterogeneous mass, cystic areas and calcifications, poorly defined borders	Slow-growing painless mass	No	1	No	Marked, peripheral and central areas	Isolated	No	Yes (one)	15, marked
6	13	M	Fourth finger of the hand	Not performed	Tendinitis	No	0,6	No	Central, chondroid aura, pericellular	Isolated	No	No	50, moderate
7	6	M	Chest wall over 9th intercostal space	Ultrasound: well delimited soft tissue, heterogeneous with medium echogenicity, no significant intratumoral vascularization	Rapid-growing mass	No	2,1	No	Very focal, central	Isolated	Mild	Yes (one)	25, moderate
8	51	F	Back of the left hand	Radiography: radiolucent lesion with well circumscribed margins and peripheral sclerosing halo	Slow-growing painless mass	No	2	Predominant	Peripheral areas	No	No	No	20, moderate
9	11	F	Root of the second toe	Ultrasound: well demarcated, solid lesion of fibrous nature	Growing painful mass	No	1,4	Yes	Central, pericellular	No	No	No	85, marked
10	10	M	Sole of the foot	Ultrasound: hypoechoic, well defined borders, heterogeneous content, no increased flow on Doppler	Growing painful mass	No	1,2	No	Peripheric, chondroid aura	Isolated and grouped	No	No	65, moderate

desmin [11,16,23]. Positivity to EGF is also described [24]. The FN1 – EGF gene fusion appears to be the driver mutation of CAF and has not been observed in any other neoplasm [24].

In this study, we report ten cases of calcifying aponeurotic fibroma diagnosed in the La Paz University Hospital in Madrid with correlations between the clinical, radiological, and pathological features of this unusual mesenchymal neoplasm.

2. Materials and methods

Our retrospective study reviewed thirteen cases with a diagnosis of calcifying aponeurotic fibroma in the Pathology Department at the La Paz University Hospital in Madrid between 1966 and 2021. Clinical information and radiological images were obtained from the patients' medical records. All available material from the pathology records was reviewed, including the hematoxylin-eosin and the immunohistochemical stains. ERG immunostaining was performed. Appropriate positive and negative controls were used for each antibody. The inclusion criterion consisted of patients with a diagnosis of CAF. The exclusion criterion consisted of having an unconfirmed diagnosis after a histopathological review conducted by some of the authors (EP, CGG, JJPK). Three cases were reclassified as deep leiomyoma, myofibroma, and desmoplastic fibroblastoma, respectively. Ten CAF cases were finally obtained. We analyzed the patients' epidemiology characteristics (gender, age), clinical aspects (pain, growth, recurrences), localization, radiologic images, macroscopic images (size, borders, consistency, color), histological findings (growth pattern, fibrous areas, cartilage areas, calcification areas, cellularity, mitoses, vascular pattern, stroma), and immunohistochemical profile.

3. Results

The main characteristics of the patients are summarized in Table 1.

3.1. Clinical findings

The patients were three females and seven males. Eight cases were children with ages between 3 months and 14 years and two cases were adults (34 and 51 years old). In five cases, CAF was located in the hands (third finger, fourth finger, back, and palm of the hand), in three cases in the feet (sole, base of the second toe), in one case in the forearm, and in one case in the chest wall (intrathoracic space).

Nine cases were solitary lesions and one patient showed three lesions in the same hand (first, second and third fingers). CAF as a slow-growing mass was the most frequent clinical presentation, with four cases being painless and the other three being painful. The 3-month-old patient presented symbrachydactyly. The thoracic wall lesion was a rapid-growing mass. One of the patients had tendonitis and another patient presented a trigger finger. None of the cases showed local recurrence or distant metastasis. The intrathoracic mass had affected surgical borders and a second surgery was performed to extirpate the affected rib, this time with free surgical borders.

3.2. Radiological findings

In seven cases a diagnostic imaging test was performed, two radiography and five US tests. One radiography showed a heterogeneous solid mass with cystic and calcificated areas, and the other showed a heterogeneous radiolucent and well-defined mass with a sclerotic peripheric halo (Fig. 1A). All sonography images were similar, showing well-defined heterogeneous fibrous masses (Fig. 1B), some with calcificated areas inside and with no significative vasculature pattern by Doppler study. The pre-operative clinic-radiological differential diagnosis in our cases included bone cysts, ganglion or congenital fibrosarcoma.

3.3. Macroscopical findings

All cases were small masses, between 0.4 and 2.1 cm. Nine cases were soft, nodular, and white lesions and one case presented a hard consistency. None of the cases showed capsule. All cases presented ill-defined borders with focal extension into adjacent soft tissues. Nine cases focally contacted the surgical margins.

3.4. Histological, cytological and immunohistochemical features

All patients underwent an excisional biopsy and one of the patients also underwent a fine needle aspiration procedure. All cases microscopically showed two components, a fascicular growth pattern, and central hypocellular nodules (Fig. 2A). All cases presented ill-defined borders (Fig. 2B). Hyalinized stroma was predominant in all cases (Fig. 2C). Fibrous areas were observed in all cases, especially in the peripheral zone, creating tracts towards the interior and around the more hyalinized zones (Fig. 2D). Only five cases showed a cartilage matrix (Fig. 2E), which was very extensive in one case. Calcifications were present in nine cases with a highly heterogeneous distribution (Fig. 2F). Two of these cases showed widespread areas of calcification and seven cases presented them only focally. Calcifications were both central and peripheral in two cases, exclusively peripheral in four cases, and only with central distribution in two cases. Calcifications in all cases had a granular aspect and were pericellular. In all cases, the cells were radiating from calcification zones (Fig. 2G). In the fascicular areas, cells were ovoid with small nuclei with an inconspicuous nucleolus. Six cases presented multinucleated osteoclast-like giant cells, which were usually

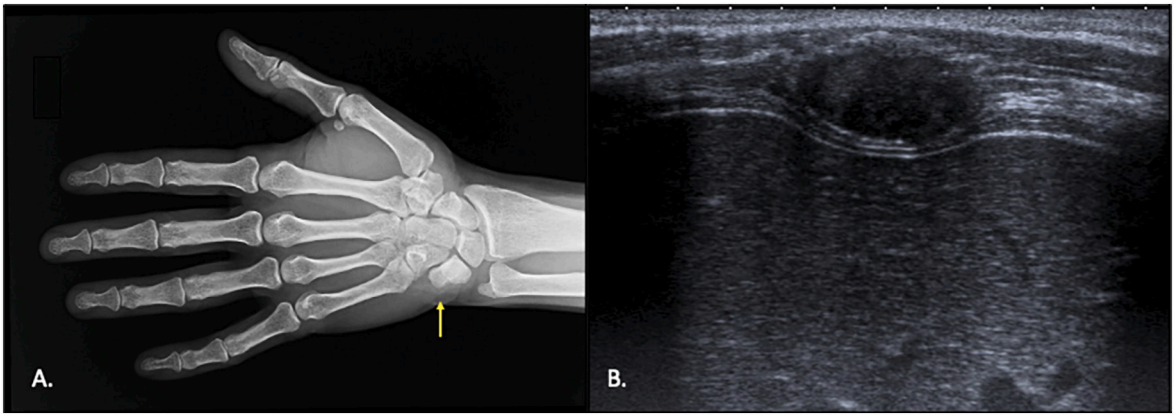

Fig. 1. A. Soft tissue mass with small calcifications that produces erosion of sclerotic edges of the ulnar margin of the piramidal bone. B. Heterogeneous fibrous mass with no significative vasculature pattern.

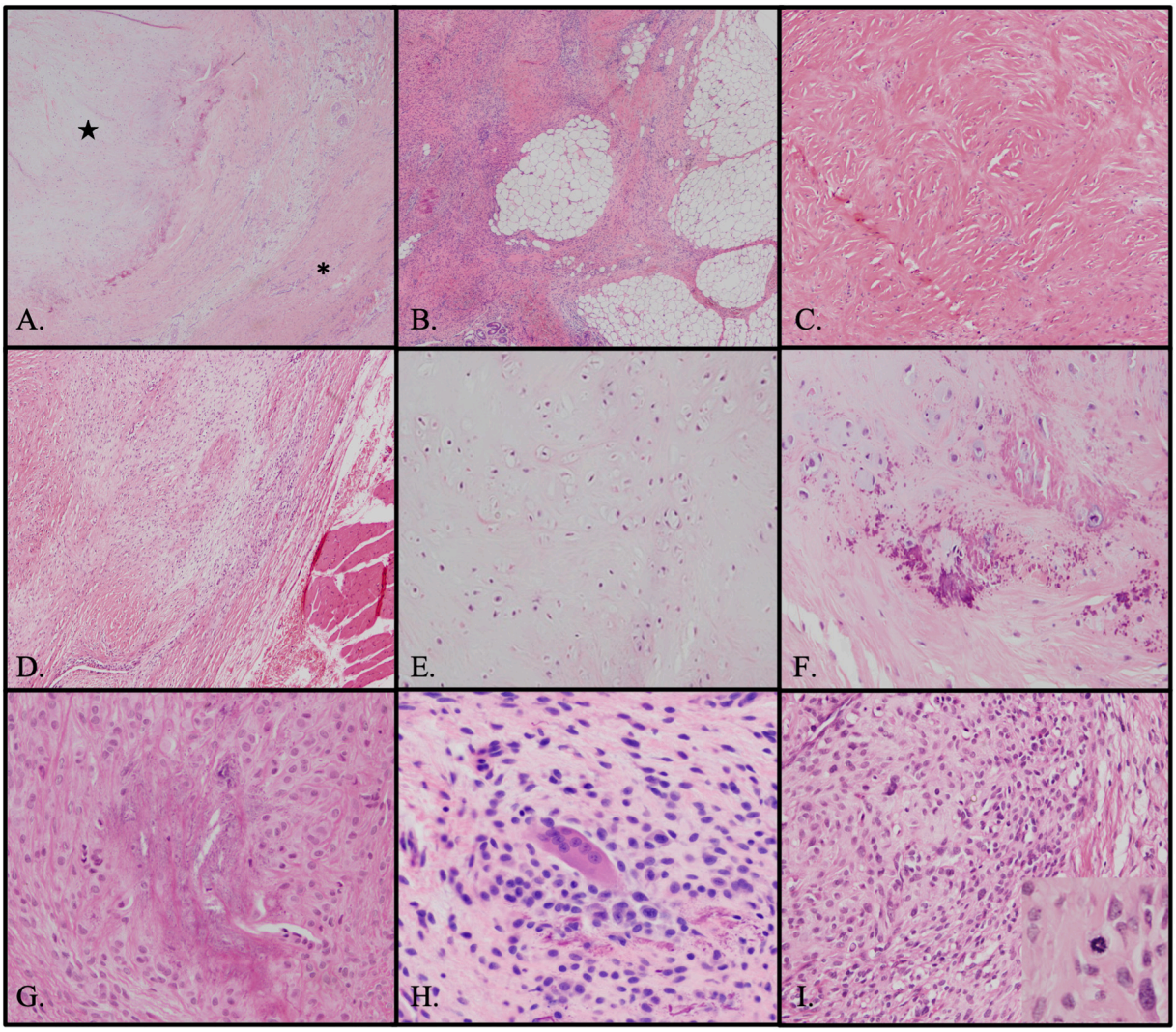

Fig. 2. A. Two components, a fascicular growth pattern (*) and nodular pattern (★) (HEx10). B. Ill-defined borders (HEx10). C. Predominant hyalinized stroma (HEx20). D. Peripheral area with fibrous tracts (HEx10). E. Cartilaginous matrix (HEx10). F. Calcifications (HEx20). G. Cells radiating from calcification zones (HEx20). H. Multinucleated osteoclast-like giant cell (HEx40). I. Mild atypia and mitosis (HEx40).

isolated (Fig. 2H). Single mitoses were identified in two cases, and mild atypia was observed in one case (Fig. 2I). No specific vascular patterns were observed.

In terms of immunohistochemistry, ERG (clone EP111, Ready to Use (RTU), Agilent-Dako) presented the same staining pattern in all cases. Diffuse nuclear positivity was seen in pericalcified areas, while patchy staining was observed in areas away from calcifications and loss of the expression was observed in the most remote areas (Fig. 3A and B). The noncalcified case shows more intense ERG positivity in cellular areas. Positivity was more frequent in high cellular areas. ERG

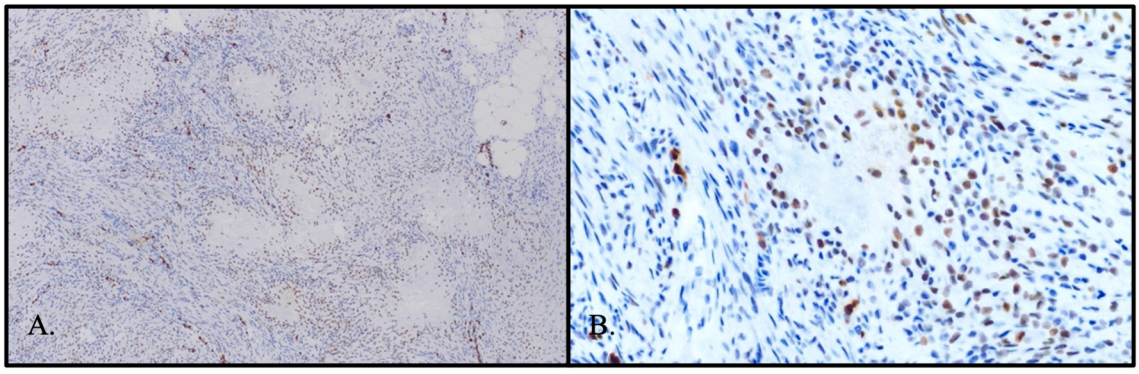

Fig. 3. A. ERG (x10). B. ERG (x40). Diffuse linear nuclear positivity around pericalcified areas, patchy staining away from calcifications and loss of the expression in the most remote areas.

immunostaining ranged from 10 % to 85 % of tumoral cells. Other immunostains were studied in three of the cases, being positive for vimentin (clone V9, RTU, Agilent-Dako); and negative for smooth muscle actin (clone 1A4, RTU, Agilent-Dako), S100 (polyclonal, RTU, Agilent-Dako), desmin (clone D33, RTU, Agilent-Dako), and MYOD1 (clone 5.8A, RTU, Agilent-Dako).

Fine needle aspiration (FNA) was performed in the intrathoracic lesion. The material obtained consisted of spindle-cell and round cells in a hyaline stroma (Fig. 4) with some calcification debris suggestive of a mesenchymal tumor with round and spindle cells.

4. Discussion

CAF is considered to be a member of the benign fibroblastic-myofibroblastic tumor group [6], whose diagnosis is a challenge because of its infrequent occurrence [7] (infrequent in children and even more infrequent in adults). CAF can be difficult to diagnose due to its wide clinical presentation, radiologic image, and morphological spectrum [7].

Nine of the patients presented a solitary nodular lesion and only one patient exhibited multiple CAFs. Only one case of multiple CAFs has been reported in the literature [10]. Seven patients were in the same age range as other previously reported cases in the literature [11]. We report two new CAFs cases in adults (34 and 51 years old) [8,13] and one case of a 3-month-old patient. Only one other case in a patient younger than 6 months has been reported, but with the CAF in a different location [17]. As with the previous cases described in the literature, in this study, males outnumbered females [11].

Regarding clinical features, the most frequent presentation in our series of cases was a slow-growing painless mass [7]. Only three cases reported painful masses, coinciding with García Navas and Khullar [8,9]. Eight of our specimens were located in the feet and the hands [7] and two individuals presented movement limitations, as described in the literature [11]. No previous CAFs had been reported in patients with symbrachydactyly. As in the previous reports [2,17], our series included cases observed in unusual locations such as the forearm and the chest wall.

All cases were treated with marginal resection (excisional biopsy) [7]. None of the patients showed local recurrence. This is not in line with previous literature reports, where local recurrences were described in more than 50 % of the cases [7]. None of the patients developed metastasis [11].

None of the cases showed suspected malignancy after clinical evaluation and US or radiographic studies and, as such, despite MRI being considered the best option to evaluate CAF [19], it was not conducted in any of the cases. All US and radiographic studies showed well-defined masses, and calcification was seen in two patients [19].

On radiographs and ultrasound images, CAF findings are nonspecific. Kang et al. [20] propose that microlithiasis in a soft tissue lesion affecting the tendon and fascia ligamentous structures may be suggestive of CAF in US images, and this was observed in one of our cases. Depending on the evolution phase [16], US images vary from diffuse and infiltrative margins in the initial phase to well-demarcated and nodular aspects in the final phase [20]. All the cases with US studies showed well-demarcated margins, histologically corresponding to a nodular growth pattern with a chondroid and calcified area.

Intralesional calcifications were observed in one of our radiographic studies, and differential diagnoses should be carried out with other benign lesions such as pilomatrixoma or extraskeletal chondroma (EC) [20]. Pilomatrixoma is located in more superficial sites and does not appear in palms and soles [20]. CAFs are usually presented as amorphous calcifications, while ECs are punctuated or granular [20]. Malignant lesions, such as synovial sarcoma, undifferentiated pleomorphic sarcoma, and epithelioid sarcoma are bigger lesions and may present intralesional stippled calcifications [7,21], but they are usually eccentric and focal, while CAF calcifications are evenly distributed [20].

In our series, all cases measured <3 cm and none of them were encapsulated. All cases presented the two above-mentioned components; fascicular and nodular [11]. We have observed that fibrous areas are predominant in peripheral zones creating tracts towards the interior and around more hyalinized zones. Our youngest case did not show higher levels of cellularity, matching with other previous reports [11].

CAF is morphologically variable and could be misdiagnosed as various illnesses such as myofibromatosis [16] which typically presents hemangiopericytoma-like vessels; fibrous hamartoma of infancy which does not present cartilage nor calcification areas and is not usually located in the hands and feet [16]; or superficial (palmar and plantar) and desmoid fibromatosis which do not habitually present calcification or chondroid differentiation and show β-catenin nuclear staining [7]. Some authors report that a small subset of lipofibromatosis may represent early CAF without the characteristic calcified component [3].

Other tumors to consider in the differential diagnosis are those with chondroid differentiation, like extraskeletal chondroma, which is usually well-defined with more well-developed chondroid differentiation, no infiltration of adjacent tissue, and no surrounding epithelioid cells [11]. These are located predominantly in the fingers of adults older than 30 years rather than in the hands of patients younger than 25 years [25]. Other entities that are included in the differential diagnosis are soft tissue tumors with dystrophic calcification, such as soft tissue leiomyoma or calcium pyrophosphate dihydrate deposition disease [2,13]. Tumors with giant cells, such as tenosynovial sheath giant cell tumors, which are lobulated nodules with epithelioid cells that may contain hemosiderin, and which rarely present calcifications in children but may show cartilaginous metaplasia [16,21,26], should be discarded.

CAF are histologically nonaggressive tumors. CAF differs from malignant tumors such as synovial sarcomas [18], clear cell sarcoma [7,21], and epithelioid sarcoma [7,16] based on the cellularity, cytomorphology, and immunohistochemical and molecular profiles,

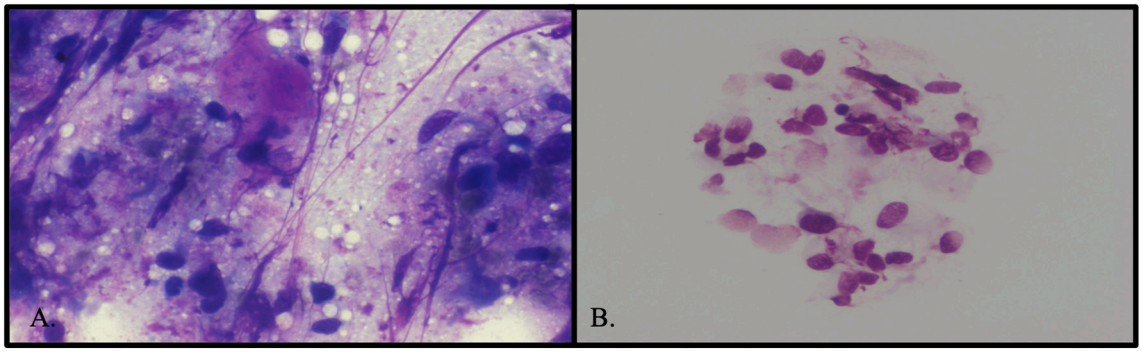

Fig. 4. FNA. A. Fusocelular and round cells in a hyaline stroma. B. Ovoid and round nuclei without atypia.

respectively.

Cytological findings regarding CAFs have been previously reported [23] and one of the cases showed the same characteristics which allowed the case to be oriented as a benign spindle cell or round cell mesenchymal lesion.

ERG immunostaining showed a consistent pattern in all the cases, diffusely positive in pericalcified areas, and patchily positive in areas away from calcifications. ERG positivity has been previously described regarding CAF as a weak to moderate staining in most cells [27]. It could be a helpful tool for differential diagnosis. EWSR1-SMAD3-positive fibroblastic tumors are also localized in acral sites with nodular growth and a zonal pattern with a hyalinized center and peripheral spindle cells arranged in short fascicles. They express diffuse nuclear ERG positivity [27]. In an acral-located case of our series that presented an intense and marked ERG immunostaining, a molecular biology study for the translocation of the EWSR1 gene using the FISH technique on the interphase nuclei (SureFISH EWSR1 5′ and 3′ Chr22 probes, Agilent-Dako) was performed, showing negative results.

5. Conclusions

The diagnosis of CAF may be challenging due to its clinical, radiological, and histologic similarities with other benign entities. The typical presentation is a small solitary painless slow-growing acral nodule in young patients. US and radiographic CAF findings are nonspecific, although they can help to orientate the diagnosis. MRI studies would help to better characterize CAFs, especially when located in nontypical sites and when showing nontypical clinical presentations. Two histological components, the fibroblastic cells in fascicles and central hyalinized nodules, with or without cartilage or calcifications, may be recognized. The characteristic ERG staining pattern could contribute to an accurate diagnosis in some cases.

Compliance with ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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CRediT authorship contribution statement

- Conception and design of the study and acquisition and analysis of data: Pena-Burgos EM, Iglesias-Urraca C, Ortiz-Cruz EJ, Pozo-Kreilinger JJ.
- Drafting the manuscript: Pena-Burgos EM, Iglesias-Urraca C, González-García MC, Rodríguez-García AM, Tapia-Viñe M, Ortiz-Cruz EJ, Pozo-Kreilinger JJ.
- Radiology images: Tapia-Viñe M.
- Pathology figures: Pena-Burgos EM, González-García MC, Rodríguez-García AM, Pozo-Kreilinger JJ.

Declaration of competing interest

The authors declare that they have no conflicts of interest.

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