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REVIEW

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Case series of extradigital glomus tumors: imaging findings, differential diagnosis and radiologic–pathologic correlation

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Abstract

Background Glomus tumors are benign mesenchymal tumors of the neuromyoarterial glomus bodies. They are generally localized at the subungual area of the fingers. Extradigital or non-subungual glomus tumors are less common. Their diagnosis can be challenging because of their lower incidence, nonspecific symptoms, and the fact that they can be missed during the physical examination. The aim of this case series is to provide an overview of non-subungual glomus tumors, including the patients' epidemiology characteristics, tumor localization and size, their varied imaging manifestations in ultrasound and magnetic resonance imaging, differential diagnosis and histopathological features.

Main body of the abstract Our report included 64 patients with the diagnosis of non-subungual glomus tumor in the Pathology Department at the La Paz University Hospital in Madrid from January 1966 to September 2022. There were 44 men and 20 women (mean age, 55.8 years; range, 8–85 years). The tumors had a mean size of 1 cm and were located in the lower limbs in most cases (59.3%). In 17 cases (27%) a diagnostic imaging test was performed (US, MRI or both). The radiological appearance of a glomus tumor on ultrasound was in most cases a circumscribed hypoechoic oval nodule located in the subcutaneous layer. Spectral Doppler can demonstrate both venous and arterial intralesional flow and in some cases a "Vascular stalk sign," seen in 4/9 cases. MRI assists in providing a more detailed characterization of these lesions, which present as T2-weighted hyperintense nodules with avid enhancement.

Short conclusion Glomus tumors are considered rare neoplasms, accounting for a small percentage of all tumors. Our report brings together the most up-to-date information available regarding the imaging findings and differential diagnosis of this entity. Although ultrasound images are not specific, they are crucial for early diagnosis, provide precise location information, and serve as a guide for tumor excision. MRI study helps to better characterize these tumors. The diagnosis is mostly clinical, with confirmation in the histopathologic study.

Keywords Glomus tumor, Ultrasound, Magnetic resonance imaging, Neoplasm, Soft tissue, Glomangioma, Glomangiomatosis, Perivascular neoplasm

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Background

Glomus tumors (GT) are benign mesenchymal tumors of the neuromyoarterial glomus bodies. They are generally localized in areas rich in glomus bodies, such as the subungual area of the fingers. Extradigital or non-subungual glomus tumors (NSGT) are less common. Their diagnosis can be challenging because of their lower incidence, nonspecific symptoms, and the fact that they can be missed during the physical examination [1]. These patients may report an asymptomatic or mildly uncomfortable nodule or skin color change [2] rather than the conventional symptom triad of pain, localized soreness, and cold hypersensitivity that is frequently found in digital GT [3].

Main text

The La Paz University Hospital in Madrid is a tertiary hospital and one of the expert hospitals for bone and soft tissue tumor management in Spain. All the NSGT cases diagnosed in the Pathology Department at the La Paz University Hospital in Madrid between 1966 and 2022 were reviewed in the present study. Clinical information and radiological images were obtained from the medical records. All available materials from the pathology files were reviewed, including hematoxylin and eosin-stained slides and immunohistochemical stains. The inclusion criterion consisted of patients with a diagnosis of NSGT. The exclusion criteria consisted of patients with multiple GT because they represent a distinct clinical entity and patients with no clinical information available.

We analyzed the patients' epidemiology characteristics (gender, age), tumor localization and size, radiologic images in the available cases, and histopathological features.

Results

Clinical findings

There was a male predilection, with 20 females and 44 males. In 21 cases the tumor was located in the upper limb (10 cases in the forearm, 5 in the arm, 2 in the elbow, 2 in the hands, 1 in the shoulder, and 1 in the wrist), in 38 cases it was located in the lower limb (16 in the knee, 11 in the leg, 7 in the thigh, 2 in the buttock, 1 in the ankle and 1 in the foot), and in 5 cases in other locations (2 in the back, 1 in the neck, 1 in the vagina labia majora and 1 in the head). 30 tumors were on the right side of the body and 34 on the left side.

The mean age at the time of diagnosis was 55.8 years. Among the male patients, the mean age at diagnosis was 55.7 years (8–83 years), and in the female patients, the mean age at diagnosis was 56.3 years (13–85 years). Two cases were younger than 19. Twenty-one cases had ages between 60 and 69 (the largest group age), and 4 cases were older than 65 years. The main characteristics of the patients and tumors are summarized in Table 1.

Some alternative clinical diagnoses listed were epidermal inclusion cyst, lipoma, angioma, and hemangioma.

Radiological findings

All (magnetic resonance) MR examinations were performed with a 1.5 T MR unit with extremity coils. All MR images (MRI) were retrospectively reviewed by one experienced radiologist. Sequences included were T1-weighted, fat-suppressed T1-weighted, and fluid-sensitive sequences such as fat-suppressed proton–density–weighted and T2-weighted, as well as gadolinium-enhanced sequences. All ultrasound (US) examinations were performed by experienced radiologists using an ultrasound machine equipped with high-frequency transducers (10–17 MHz).

Imaging studies were performed in 18/64 cases (28%), including 17 US and 4 MRI. We had access to the imaging tests of 11 patients. The mean size of the 64 tumors was 1 cm (0.1–9.5 cm). Thirty-seven tumors measured less than 1 cm, 25 measured between 1 and 2.5 cm, 1 measured 3.6 cm, and one reached 9.5 cm.

Of the 10 US examinations most were similar, showing small, well-defined, solid, hypoechoic nodules with mainly homogeneous echotexture (Fig. 1a, b), 9/10 cases showed intralesional arterial flow or arterial and venous

Table 1 Characteristics of the 64 study patients

Male–female ratio	2.1/1
Mean age at time of diagnosis (y)	
All patients	55.7
Men	55.6
Women	56.3
Anatomical site	
Upper limb	21
Lower limb	38
Others	5
Imaging studies	
US	17
MRI	4
Pathological findings	
Glomus tumor	62
Angiomatoid glomus tumor	2
Mean tumor size (cm)	1
Range (cm)	0.1—9.5

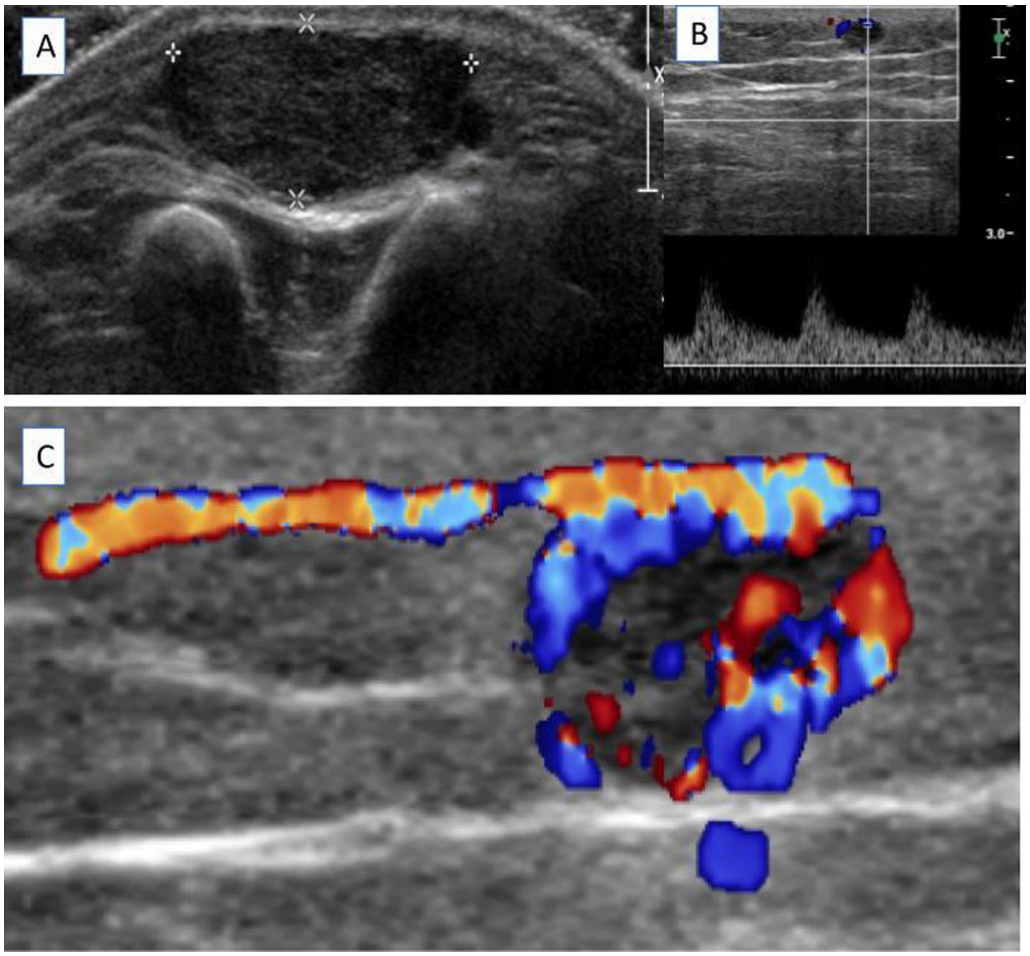

Fig. 1 Sonographic appearance of non-subungual glomus tumors in different patients. **a** B mode ultrasound appearance: small, hypoechoic, well defined, horizontally oriented nodule. **b** Spectral Doppler study shows arterial flow. **c** Doppler study shows the "Vascular stalk sign"

flow in the Doppler study (Fig. 1c, d), and 4/10 cases showed the "Vascular stalk sign" (Fig. 1 e,f). The margins were well-circumscribed in all cases and none of them showed calcifications. MRI was conducted in 4 cases, and ¾ MRI studies showed a well-defined nodular lesion with high-intensity signal in T2 sequences, areas of low or intermediate T1 signal (Fig. 2a, b) and avid enhancement after contrast administration (Fig. 3a, b).

One case of a giant thigh GT was found. A full description of the case has been recently published [4]. The radiological characteristics of the patients with image studies are summarized in Table 2.

Histopathological and immunohistochemical features

All hematoxylin and eosin-stained slides and immunohistochemical stains were retrospectively reviewed by one experienced pathologist. All cases were non-encapsulated and well-defined nodules (Fig. 4a) composed of rounded cells with central nuclei with heterogeneous chromatin (glomus cells) (Fig. 4b). In cases where the immunohistochemical analysis was performed, they showed the same prolife, being positive against smooth muscle actin (SMA) (Fig. 4c), and collagen IV (Fig. 4d). Two cases showed densely cellular zones intermixed with blood-filled cavities (angiomatoid glomus tumor) (Fig. 4e, f). No mitosis, atypia, or necrosis were detected.

Discussion

Due to their rarity, unusual location, and clinical expression, NSGT provide a difficult diagnostic problem [6], which has resulted in long delays in diagnosis or misdiagnosis of these lesions [7]. In our literature revision

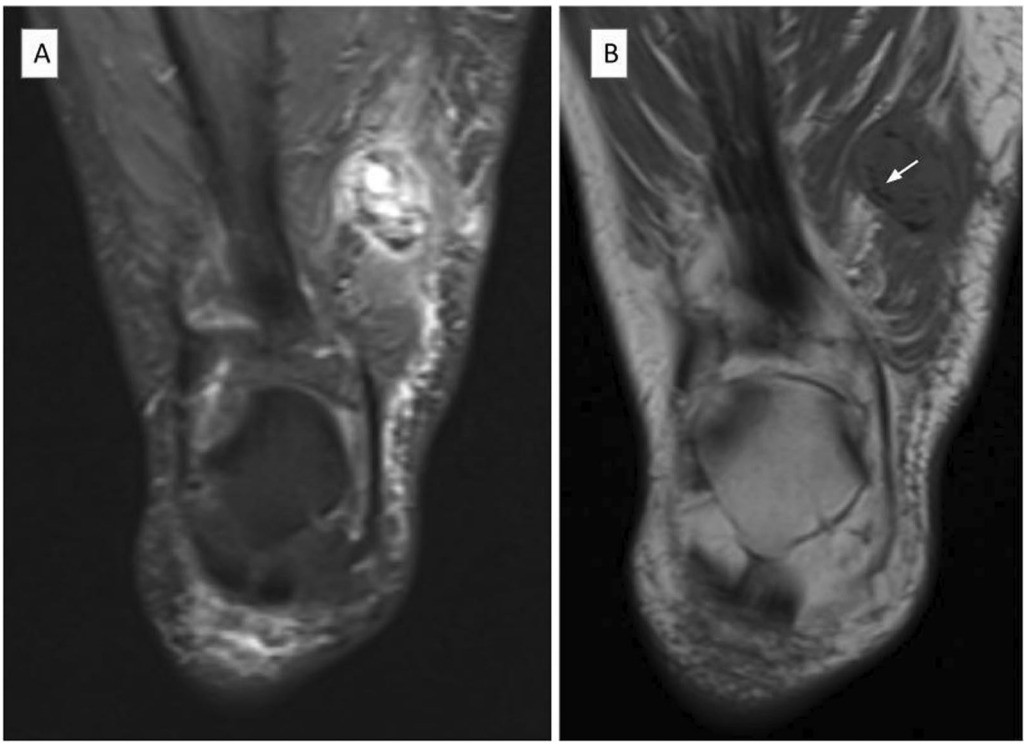

Fig. 2 35-year-old man with NSGT of the thigh. **a** Coronal T2WI shows predominantly high signal (→) and **b** Coronal T1WI shows low to intermediate signal with lower signal areas (→) consistent with hemosiderin deposit

most published articles about this topic are case reports or brief retrospective case series [1, 2, 8, 9]. There is only one other institutional review of NSGT [3].

Some epidemiological findings of NSGT in our study are similar to those reported by Schiefer et al. [3], such as a male prevalence and the age at diagnosis between the fourth and seventh decades of life. There were differences in the average tumor size, which was 1 cm in our study and 0.6 cm in that review [3]. Regarding the anatomical location, NSGT were more common in the lower extremities in our study and in the upper extremity in other studies [1–3].

The use of imaging tests was similar, in our study 27% of the cases had at least one imaging test, compared to 21% in Schiefer et al. [3] review. US was conducted in 10 cases (15.6%), and the results demonstrated that nine of ten patients with accessible imaging tests had well-defined nodules with interior vascularization, which is consistent with the findings reported by Gomez- Sanchez et al. [10].

Nine of ten of the lesions were solid hypoechoic nodules, whereas one lesion was mixed with heterogeneous echogenicity, probably due to its greater size. These findings were similar to most cases published [1–3, 10–12]. Only one case of an NSGT being reported as a hyperechoic nodule was found [13].

Four out of ten cases (40%) exhibited the "Vascular stalk sign," which is associated with the presence of strong vascular flow bridging the lesion and the nearby soft tissue. [11]. This finding was noted in 67% of cases by Park [14].

In our study, nine of ten lesions were located in the hypodermis and only one lesion was located more profoundly in the muscular plane. NSGT can be located in the hypodermis or in deeper tissues such as intramuscular [15] or in the bone [15].

MRI was conducted in 4 of the cases (6.2%). MRI sensitivity approaches 90%, although the specificity is estimated at 50% [12]. False negatives occur especially with smaller lesions, in which cases it is recommendable to follow clinical suspicion and proceed with exploration and excision [8, 16].

Three of four cases showed a round or oval shape, similar to the ten cases revised by Lee. [17].

Table 2 (a) US Characteristics of 10 patients: (b) MRI Characteristics of 4 patients

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7	Case 8	Case 9	Case 10	
a											
B Mode											
Localization	Hypodermis	Hypodermis	Hypodermis	Hypodermis	Hypodermis	Hypodermis	Hypodermis	Hypodermis	Hypodermis	Hypodermis	
Echogenic structure	Solid	Solid	Solid	Solid	Solid	Solid	Solid	Solid	Solid	Mixed	
Borders	Well defined	Well defined	Well defined	Well defined	Well defined	Well defined	Well defined	Well defined	Well defined	Polylobulated well defined	
Echogenicity	Hypoechoic	Hypoechoic	Hypoechoic	Hypoechoic	Hypoechoic	Hypoechoic	Hypoechoic	Hypoechoic	Hypoechoic	Heterogeneous	
"Vascular stalk sign"	(–)	(+)	(+)	(–)	(+)	(–)	(+)	(–)	(–)	(–)	
Doppler color											
Flow (±)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(+)	(–)	(+)	
Flow localization	Intralesional	Both	Both	Both	Intralesional	Intralesional	Intralesional	Intralesional	DA	Intralesional	
Spectral Doppler											
Flow (arterial/venous/both)	Both	NR	Arterial	NR	Both	NR	Both	NR	DA	NR	
		Case 2					Case 7			Case 10	Case 11
b											
T1 signal		Low to intermediate SI					Low to intermediate SI			Heterogeneous	Low to intermediate SI
T2 signal		Intense high SI					Intense high SI			Heterogeneous	Intense high SI
T1 + Contrast: Enhancement		Avid					Avid			Solid component	Avid

NR not referred, *DA* does not apply

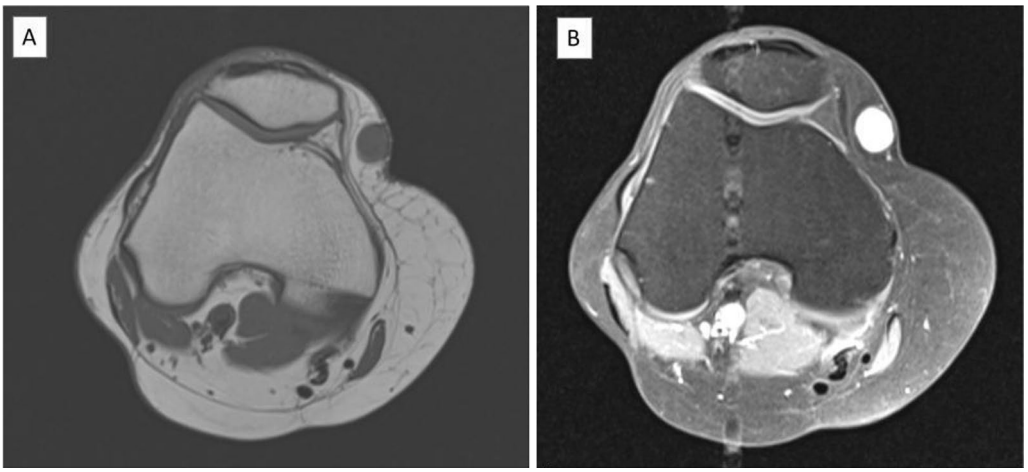

Fig. 3 43 year old man with NSGT of the knee. **A** Axial T1WI shows a hypointense subcutaneous nodule **B** Axial T1WI after contrast administration shows avid enhancement of the nodule

In three of four cases, it showed the classic appearance of a small nodule with a high T2WI signal and low T1WI signal. After gadolinium administration all lesions showed enhancement. MRI findings were consistent with other studies [6, 18–21, 26].

The most frequent radiological differential diagnoses are hemangioma, angiomyoma, arteriovenous malformation, venous malformation, pyogenic granuloma and myopericytoma. Hemangiomas (Fig. 5) are more heterogeneous in echotexture, have less well-defined margins, show less vascular flow as blood pools are present, and do not show the "vascular stalk sign" and calcification is common[22]. Angioleiomyoma or vascular leiomyoma (Fig. 6) usually occurs as a solitary subcutaneous lesion with a preference for the lower extremities of adult females. It has a similar ultrasound appearance to GT, but MRI study shows T1 isointense signal compared with muscle and T2 slightly high signal with mixed areas of hyper- and isointense to skeletal muscle signal and strong enhancement of the hyperintense areas [14]. Arteriovenous malformations are ill-defined lesions and usually show the typical arteriovenous shunt [23]. Venous malformations (Fig. 7a–e) are usually poorly demarcated from surrounding tissues, demonstrate only venous flow on spectral ultrasound, and might show calcifications due to phleboliths (calcified thrombi) [22]. Pyogenic granuloma or lobular capillary hemangioma (Fig. 8) usually presents as a painless superficial vascular lesion that may exhibit fast growth. These lesions are usually presented in cutaneous or mucosal surface [24]. Myopericytoma/myofibroma predominantly appears in the skin and subcutis of the extremities, head, neck and trunk and presents as asymptomatic, slow growing lesions. MRI may show a well-defined small (less than 2 cm), nodular subcutaneous lesion with avid enhancement, and are generally seen connected to a vessel. Many of these characteristics coincide with those of other entities and a biopsy is eventually required for diagnosis [25] (Figs. 5, 6, 7, and 8).

Most of our cases presented the typical histopathological findings of glomus tumors, with a well-defined nodule composed by glomus cells, with no atypia or mitosis. Only two cases were angiomatoid. Folpe et al. proposed a classification for GT with benign cases, uncertain malignant potential cases (GT-UMP), and malignant potential cases (MGT). None of our cases fulfilled the histopathological criteria for GT-UMP nor MGT, although two of the four cases were lesions larger than 2 cm or located in deep tissues, being diagnosed as GT-UMP [5].

The main histopathological differential diagnosis of benign GT is mainly made with myopericytomas and myofibromas. Typical GT are composed of round cells with well-defined membranes, while myofibromas and myopericytomas contain less rounded cells with ill-defined borders. Myofibromas show a distinctive biphasic pattern with a center composed of immature cells

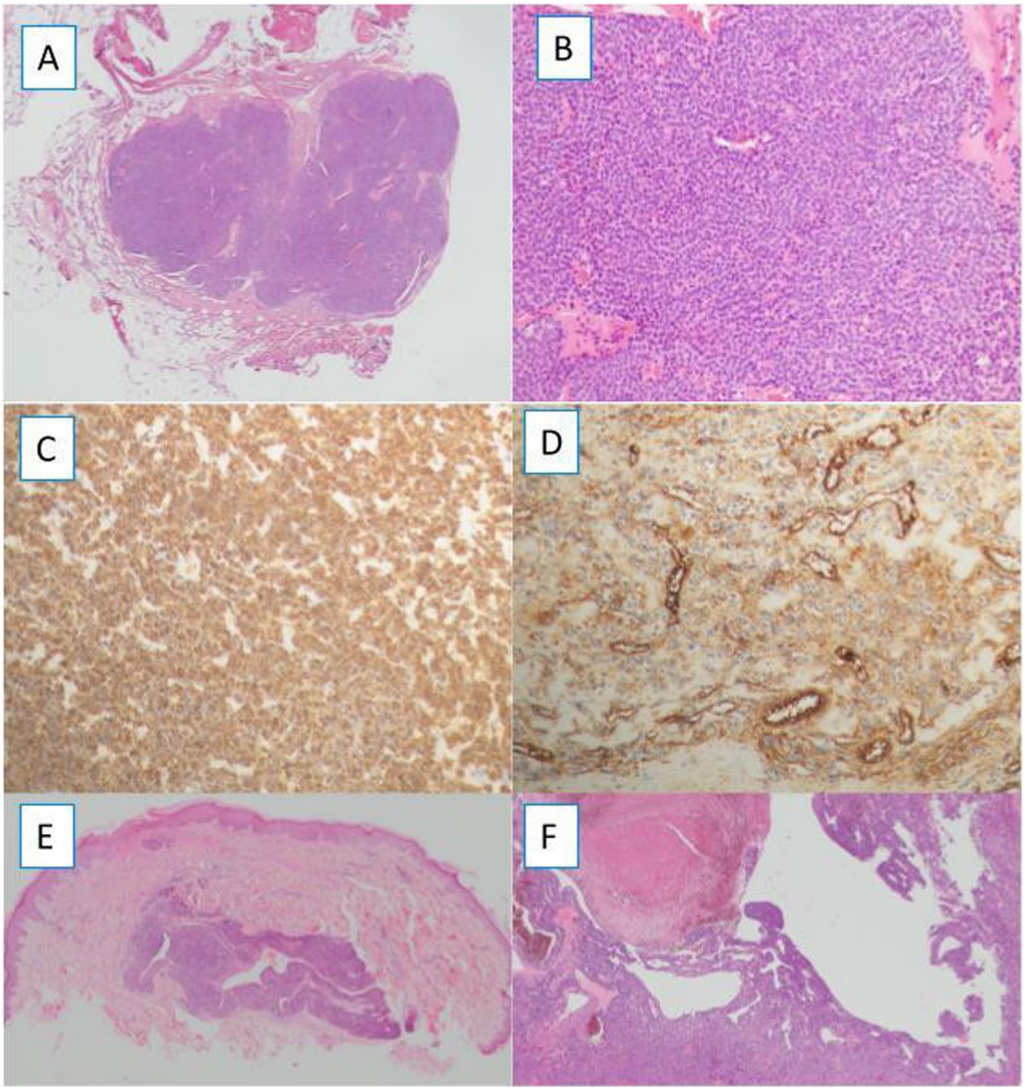

Fig. 4 High-power microscopic view showing **A** The typical cytologic features of a glomus tumor. Nodular, well-defined and densely cellular lesion with small blood vessels. **B** Round cells with well-defined margins, eosinophilic cytoplasm and central oval nuclei with heterogeneous chromatin. **C** Glomus tumor Immunohistochemical analysis. Smooth muscle actin (SMA): Diffuse cytoplasmic positivity. **D** Collagen IV: Diffuse pericellular deposits. **E** Angiomatoid glomus tumor. Well-defined subcutaneous lesion with small blood-filled cavities. **F** Angiomatoid glomus tumor. Densely cellular zones intermixed with blood-filled cavities

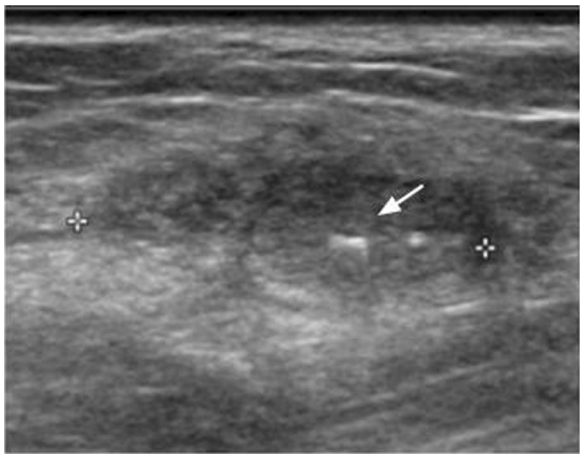

Fig. 5 52-year-old women with an hemangioma on the leg. Ultrasound shows an ill-defined hypoechoic lesion with central punctate calcifications (→)

protruding into slit-like vessels and others more areas hyalinized with myoid cells. Some GT may present spindled morphology and hemangiopericytoma-like vessels overlapping with myofibroma. In these cases, classical GT cells should be carefully searched. Other vascular lesions such as hemangiomas and angioleiomyomas may be confused with GT, but collagen IV pericellular staining is only seen in GT[5].

Conclusions

Some epidemiological findings of NSGT in the study are similar to those previously reported by other authors, such as male prevalence and age at diagnosis. There were differences in tumor size and anatomical location. NSGT ultrasound exhibits well-defined nodules with interior vascularization, and the "Vascular stalk sign" is present in some cases. Despite the fact that ultrasound images

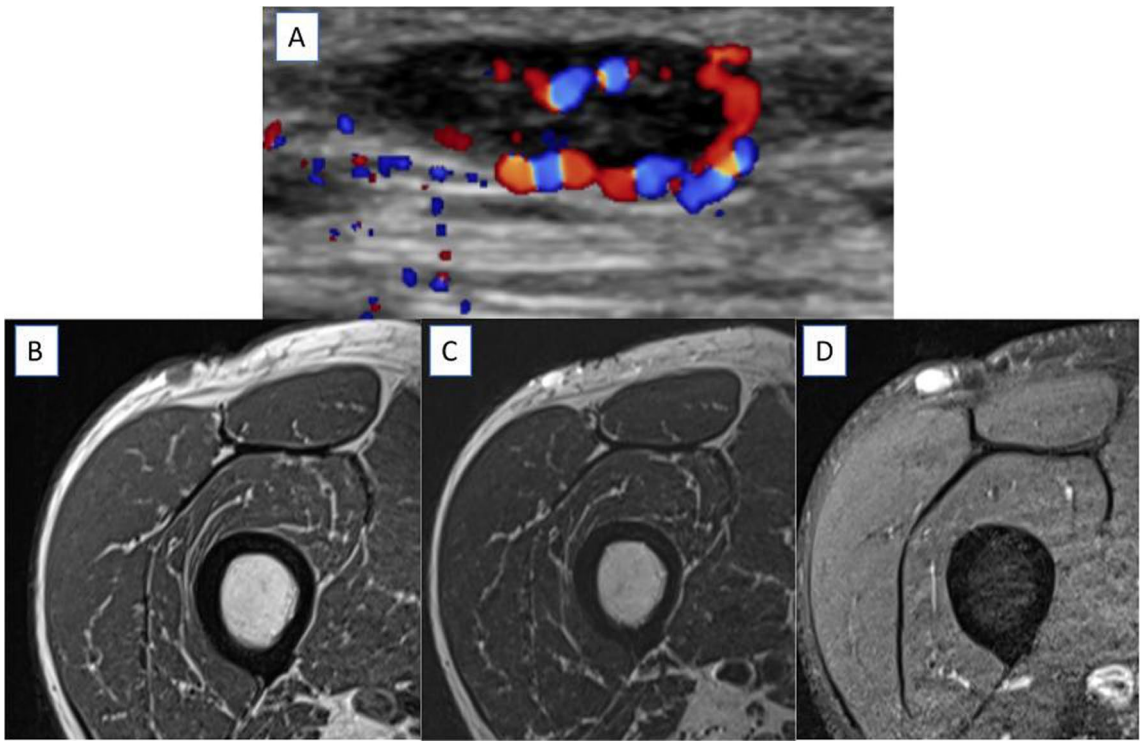

Fig. 6 34-year-old man with angiomyoma or vascular leiomyoma **a** Doppler study shows a vascularized hypoechoic nodule. **b** Axial T1 weighted shows isointense signal compared with muscle and **c** Axial T2 weighted slightly high signal **d** Axial T1 after contrast administration shows strong enhancement

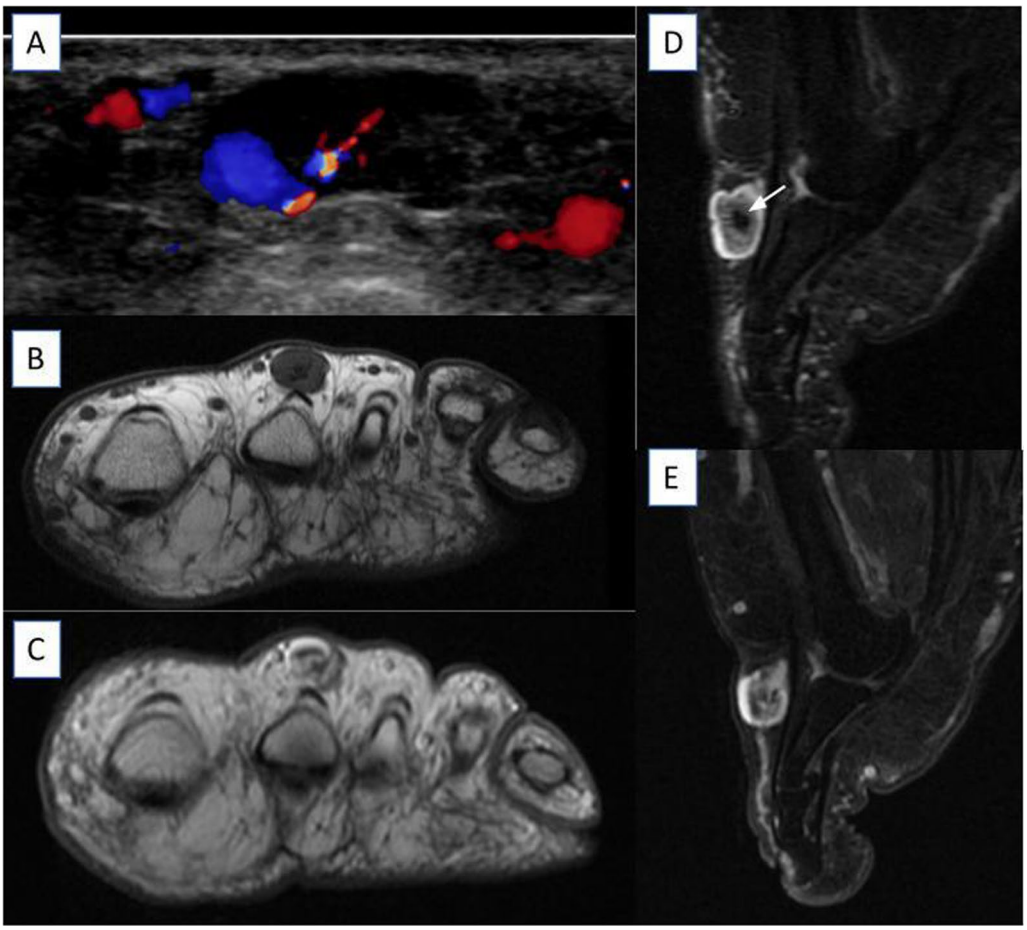

Fig. 7 24-year-old women with venous malformation. **a** Ultrasound shows an ill-defined hypoechoic nodule with some internal vascularization. **b** Axial T1 weighted shows a hypointense nodule. **c** Axial T1 weighted after contrast administration shows avid enhancement. **d** and **e** Sagittal STIR images before and after contrast administration show a high signal lobular lesion with low signal internal areas that do not enhance (→) consistent with fibrina, phlebolith or thrombosis

are not specific, they are crucial for early diagnosis, provide accurate locational information, and serve as a guide for tumor excision. MRI helps to better characterize NSGT, seen as a T2W hyperintense lesion with avid enhancement due to its high vascularity. The majority of diagnoses are clinical, with histopathologic study serving as confirmation; nonetheless, imaging tests are helpful for a precise and rapid diagnosis.

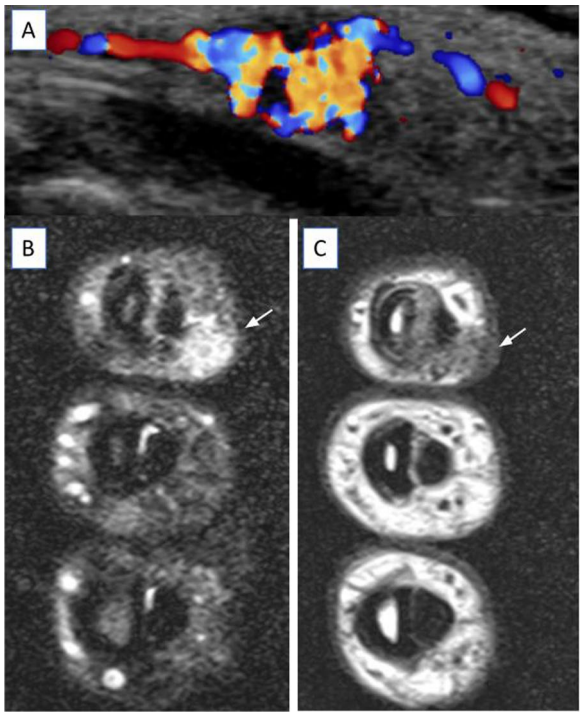

Fig. 8 Pyogenic granuloma. **a** Ultrasound shows a subcutaneous nodular lesion with profuse intralesional vascularity. **b** T2 and **c** T1 axial images show a lesion of high and low signal, respectively, in contact with the dermis

Abbreviations

GT	Glomus tumor
NSGT	Non-subungual glomus tumor
MRI	Magnetic resonance imaging
US	Ultrasound
SMA	Smooth muscle actin

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Author contributions
PB and PK contributed to conception and design of the study and acquisition and analysis of data. PB, SC, TV, PL, PP, and BT contributed to drafting the manuscript. SC, TV, and BT contributed to radiology images. PB and PK contributed to pathology figures. All authors have read and approved the manuscript.

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Competing interests
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