Low-Grade Myofibroblastic Sarcoma (LGMS) of the Extremities – A Systematic Review and Case Report

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Research article

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Abstract

Background: Low-grade myofibroblastic sarcoma (LGMS) is a rare subtype of soft tissue sarcoma of intermediate grade often representing fibromatosis-like features with a rare metastasing behavior. This type of tumor has a predilection for the head and neck region, but also occurs in the extremities. Confirming the diagnosis is difficult and treatment strategies have to be chosen individually.

Methods: The objective of this study was to conduct a systematic review for LGMS of the extremities. The electronic databases PubMed and the Cochrane Library were searched for eligible studies. 141 abstracts were screened on PubMed, while 10 studies were identified as eligible. Cases were summarized in terms of clinical aspects, therapeutic regimen with the primary endpoint of follow-up controls regarding local recurrence or distant metastasis. In addition, we present the rare case and surgical management of a 28-year-old male patient with residual LGMS of the thumb after initial incomplete resection.

Results: 33 cases of LGMS in the extremities were identified on PubMed. Cochrane library didn't show any results. All of them were surgically resected. Only two cases of LGMS in the hand were described in literature so far. Treatment options varied from local excision to wide resection without exact definition of the safety distance. 26 cases provided follow-up information with local recurrence in 6 cases (23 %), while 4 cases (15 %) showed distant metastasis.

Conclusions: Wide resection should be the surgical aim to avoid local recurrence and distant metastases. While the excision of tumors of the thumb and hand often require closer resection margins, due to the close proximity of anatomical structures, tumor-free margins are elementary even if tissue transfer from a donor site is needed for reconstruction.

Background

Low-grade myofibroblastic sarcoma (LGMS) is a rare malignant tumor entity, which was first described as a distinct neoplasm in 1998 by Mentzel et al. [1]. While Vasudev and Harris already described a sarcoma type with ultrastructural features of myofibroblasts in 1978, it was not fully characterized until 1998 and subsequently included in the *International Classification of Diseases for Oncology (ICD-O)* by the World Health organization [2]. LGMS shows a wide anatomic distribution; however, the extremities and the head and neck region seem to be preferred locations without distinct age preference (7–85 years) [1, 3–5]. The tumor incidence is unknown, but LGMS is believed to be more common than previously expected, since an exact diagnosis of the tumor can be challenging. Chan et al. (2016) proposed in his population-based study a 5-year overall survival of 71,6% of patients with LGMS in the United States [3].

Its highly heterogeneous histological aspects make it difficult to diagnose and to differentiate LGMS from other benign or malignant lesions [6, 7]. Histologically, the tumor is composed of spindle-shaped tumor cells, which are embedded in a collagenous matrix and are characterized by a diffuse infiltration of skeletal muscle, a storiform growth pattern and similarities to fibroblasts and smooth muscle cells [8–10]. The characteristic biological behavior of most soft tissue and bone sarcomas is clinically used for the development of treatment protocols [11, 12]. For LGMS definitive treatment criteria remain to be enhanced.

The present study systematically reviews relevant cases of LGMS of the extremities to provide further insights in this rare tumor entity. Furthermore, it concentrates on a rare case and the surgical management of a 28-year old patient with residues of a low-grade myofibroblastic sarcoma (LGMS) of the thumb.

Methods

A systematic review of case series and case reports was conducted for LGMS in the extremities. Data is reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) [13].

Search strategy and study selection

Studies were carried out on the following electronic databases: PubMed and the Cochrane Central Register of Controlled Trials. The search strategy contained the subject heading: low-grade myofibroblastic sarcoma. All abstracts and full articles were reviewed according to the eligibility criteria shown in Table 1. A PRISMA flow diagram outlines each stage of the review (Fig. 1).

Table 1
Eligibility criteria.

Patients	**Patients with reported LGMS in extremities**
Interesting data	Gender, size, therapy regimen, follow-up, outcome
Study design	Clinical trials, observational studies, clinicopathological studies, case reports, case series
Language	Published in English
Publication Year	All

Data extraction and analysis

Data were summarized in an Excel (Microsoft) extraction template by a single reviewer. Extraction data included patient characteristics (mean age, sex distribution, tumor size), treatment regimen (surgery, neoadjuvant/adjuvant therapy), and efficacy endpoints (local recurrence, metastases, lack of recurrence, LGMS-associated mortality and survival) if available in the publication.

Case presentation

A 28-year-old male patient presented to our clinic with a residual tumor of the thumb. Initially he noticed a slowly growing mass of the thumb in September 2019 and introduced himself to another medical center with a tumor mass in the distal phalanx of the thumb in October 2019. There was no history of previous skin lesion or trauma. X-ray of the thumb showed no bone infiltration. MRI wasn't performed initially. The tumor was resected without prior biopsy. Two months later in December 2019 the patient for the first time applied to our hospital with recurrent swelling at the surgical site. A systematic examination revealed the patient was otherwise healthy and reported no tobacco or alcohol use. The thumb showed an elastic nodular tumor mass on the distal ulnar side of the phalanx (Fig. 2). Physical examination revealed no palpable lymph nodes in the axillary region, supraclavicular or head and neck. X-ray indicated no bony changes (Fig. 3). The MRI showed two small adjacent soft tissue nodules with a diameter of 1,8 × 0,9 cm and homogeneous enhancement of the proximal nodule, highly suspicious of a recurrent or residual tumor (Fig. 4). Malignancy could not be excluded with

certainty. A computed tomography of the chest showed no evidence of metastatic disease. Blood count and biochemistry were all within normal range. Histologically, the tumor mass consisted of spindle cells with a central tumor necrosis. The diagnosis of dermatofibrosarcoma protuberans was ruled out via FISH analyses and a positive immunostaining of 10% of tumor cells only, using the antibody against CD34. Due to the expression of TTF1, alveolar soft tissue sarcoma was considered as a differential diagnosis. Despite of a low polymorphism of the tumor cell nuclei, several mitotic figures (5 mitosis/ high-power fields) were emphasized additionally to the infiltrative tumor growth in the periphery. The surgical margins were not tumor-free. The tumor was mainly localized in the dermis and subcutis. Immunohistochemistry revealed a weak expression of actin, a positive immunoreaction against ERG and negativity of tumor cells against Sox-10. In addition, p53 showed a wild type expression. The proliferation activity (Ki-67-index) was in hot spot areas up to 20%. Furthermore, the spindle cells were immunohistochemically negative for CD31, but predominantly positive for D2-40. Most of the nucleoli expressed TFE3. Tumor cells expressed INI-1 but no H3K27me3, and did not show translocations of ALK-1, ROS1 or pan-TRK. No expression of FosB or HHV8. For a further diagnostic specification, RNA sequencing was needed. RNA Sequencing showed a fusion transcript COL1A2-GSN (Exon 6/Exon 4), which was not yet described in literature so far [14, 15]. These findings favored the diagnosis of a malignant mesenchymal soft tissue sarcoma: low-grade myofibroblastic sarcoma.

Results

This is the first systematically review focusing on LGMS in the extremities. We identified 34 cases. Eligible publications included 5 single case-reports, 4 retrospective case series and 1 epidemiological study. Table 2 shows the patient and tumor characteristics of published cases. Age range of the patients was 28–77 years (mean: 48 years). There was a male/female ratio of 1:1,2 (13 men and 11 women) as far as the information was given. A painless, enlarging mass was the most common clinical presentation. 12 tumors arose in the upper extremities, 22 cases in the lower extremities. 19 cases were localized in the soft tissue, 15 cases in the bones with predilection of the distal femur. We identified only 2 case of LGMS in the hand, one of them in the distal phalanx of the finger and another one in the soft tissue of the palm [16, 17]. All patients were treated surgically, either with wide resection or local excision, and 8 of them received an additional adjunctive therapy. The tumor size ranged from 1,5 to 20 cm with multiple nodules in some cases. A follow-up information was available in 26 patients (range 4-172 months). In total, 6 of them (23%) suffered from local recurrence, while one had 2 recurrences and one patient even had 8 recurrences in 8 years (case 32). 4 (15%) cases showed distant metastases in the follow-up time from 8–56 months, while one case with metastasis was identified at time of diagnosis. Watanabe et al. reported one case of a 70-year old woman, who died of the tumor disease and pulmonary metastasis one year after surgical resection of the tumor, localized in the iliac bone. Exact data concerning the surgical procedure to comprehend recurrence is missing. The population-based study of Chan et al. (2016) did not provide any clear information concerning recurrence or metastatic behavior but showed an association of age and survival. Data concerning long-term follow up more than 5 years are missing.

Table 2
Cases of myofibroblastic sarcoma of the extremities

Authors	Year	Case no.	Age/Gender	Tumor location	Size (cm)	Therapy	Follow-up
Mentzel et al. [1]	1998	1	42/F	Ankle (ST)	NA	NA	NA
		2	29/F	Right supraclavicular (ST)	8	LE	NSR at 20 months
		3	31/M	Left thigh (ST)	4	LE	NSR at 22 months
		4	36/M	Pelvis (B)	11	LE	LR at 20 months, NSR 9 months later
		5	52/M	Left shoulder (ST)	4	LE	NA
		6	50/M	Right arm (ST)	3	LE + RT	NA
		7	33/F	Left inner thigh (ST)	3,2	LE + RT	NSR at 12 months
		8	46/F	Pelvis (B)	5–12	Partial/incomplete excision	NA
Watanabe et al. [2]	2001	9	60/M	Distal Femur (B)	5	WR + CT	NSR
		10	63/F	Distal Femur (B)	9	ILR	NSR
		11	66/F	Ilium (B)	9,5	WR + CT	NSR
		12	71/F	Ilium (B)	7	WR + CT	DOD, lung metastasis
Montgomery et al. [3]	2001	13	42/M	Axilla subcutis (ST)	5	LE	NSR at 36 months
		14	33/M	Arm (ST)	NA	NA	NA
		15	69/M	Leg (ST)	NA	WR + CT	LR at 8 months, then RT, further LR at 70 months, then amp

M, male; F, female; LE, Local excision; B, bone; ST, soft tissue; WR, wide resection; ILR, intralesional resection; NA, not applicable; CT, chemotherapy; LR, local recurrence; Amp, amputation; RT, radiotherapy; NSR, no sign of recurrence; DOD, dead of disease; AED, alive with evidence of disease; IMT, inflammatory

Authors	Year	Case no.	Age/Gender	Tumor location	Size (cm)	Therapy	Follow-up
		16	65/M	Tibia (B)	11	LE	LR at 24 months, then amp, then NSR 172 at months
		17	57/M	Anterior thigh (ST)	4	WR + RT	NSR at 144 months
		18	64/M	Arm (ST)	1,5	LE	NSR at 48 months
San Miguel et al. [4]	2004	19	51/F	Distal Phalanx (B)	1,8	Amp dist. phalanx	NSR at 28 months
Nagata et al. [5]	2008	20	36/M	Palm (ST)	2,5 × 1,5	LE	NSR at 25 months
Arora et al. [6]	2010	21	38/F	Femur (B)	20 × 10	WR + prosthesis	AED
Nakashima et al. [7]	2012	22	43/F	Parapatellar tendon (ST)	3	RT + WR	NSR at 36 months
Saito et al. [8]	2013	23	50/F	Distal femur (B)	NA	WR + prosthesis	NSR at 15 months
Wang et al. [9]	2019	24	NA	Right scapula (B)	13 × 13,5	SP	Pulmonary metastasis before operation
		25	NA	Left distal femur (B)	NA	SP	Pulmonary metastasis after 8 months of operation
		26	NA	Right shoulder (ST)	8,9 × 6,8	SP	LR at 48 months
		27	NA	Left armpit (ST)	4,3 × 4	SP	NA
		28	NA	Right distal femur (B)	NA	SP	Pulmonary metastasis after 56 months of operation
		29	NA	Right partesiliaca (ST)	NA	SP	NA

M, male; F, female; LE, Local excision; B, bone; ST, soft tissue; WR, wide resection; ILR, intralesional resection; NA, not applicable; CT, chemotherapy; LR, local recurrence; Amp, amputation; RT, radiotherapy; NSR, no sign of recurrence; DOD, dead of disease; AED, alive with evidence of disease; IMT, inflammatory

Authors	Year	Case no.	Age/Gender	Tumor location	Size (cm)	Therapy	Follow-up
		30	NA	Left distal femur (B)	NA	SP	LR and bone metastasis at 17 months
		31	NA	Right remi inferior ossis pubis (B)	NA	SP	NA
		32	NA	Right thigh (ST)	5,6 × 7,4	SP	IMT translate into LGMS after LR for 3 times, 8 LR within 8 years
		33	NA	Left thigh (ST)	6,6 × 4,4	SP	NA
Present case	2020	34	28/M	Thumb	2 × 1,5	WR + PS	NSR at 4 months

M, male; F, female; LE, Local excision; B, bone; ST, soft tissue; WR, wide resection; ILR, intralesional resection; NA, not applicable; CT, chemotherapy; LR, local recurrence; Amp, amputation; RT, radiotherapy; NSR, no sign of recurrence; DOD, dead of disease; AED, alive with evidence of disease; IMT, inflammatory

Case presentation

Considering the intermediate-grade of the tumor with an early residual growth after initial incomplete resection, the young age of the patient and the importance of the thumb for the hand function a two-stage surgical intervention was indicated. In the first step, a wide excision was performed to obtain clear resection margins. Soft tissue was resected including the ulnar half of the bony distal phalanx (Fig. 4A). Temporarily the tissue was covered by a synthetic skin replacement. Histopathology confirmed the diagnosis of low-grade myofibroblastic sarcoma as a malignant mesenchymal soft tissue sarcoma. Soft tissue resection margins were tumor-free, without tumor infiltration of the bone. Thus, we performed a reconstruction of the defect with a neuro vascular Holevich's flap (Fig. 4B-D) [18]. The island flap was prepared from the dorsum of the index finger, with a proximally based skin pedicle [19, 20]. The flap included the first dorsal metacarpal artery (DMCA) with concomitant veins and the terminal branches of the superficial radial nerve, which provided a stable soft tissue cover to the bone as well as the preservation of fingertip sensation. The donor area was covered by an antecubital full-thickness skin graft. The wound showed primary wound healing. The flap survival was total with good flap sensibility and donor site sensibility. The thumb had a good function, with slightly reduced flexion of the IP joint, opposition to the other four fingers was possible (Fig. 7). The patient showed good grip strength and a stable precision grip. MSTS-Score, which measures pain, function, emotional acceptance, hand positioning, manual dexterity and lifting ability showed a good result of 87%. Tumor control after 4 months with local MRI and chest X-ray showed no local recurrence, not ignoring the limitation of our work in form of the short follow-up period after surgery so far.

Discussion

The purpose of this study was to systematically review all published cases of LGMS in the extremities to provide more demographics as well as clinic-pathologic information on this rare tumor entity. Additionally, we presented the surgical management of a 28y/o patient with the rare case of LGMS of the thumb. Due to the rarity of this tumor, the knowledge is mainly based on case reports or case series resulting in limited statistical significance concerning epidemiology, demographics, clinical characteristics and treatment efficacy [1, 3, 9]. Nevertheless, case report meta-analyses might help improving the clinical practice in the context of rare diseases and provide more information to guide clinicians and surgeons to appropriate treatment [21]. Here we summarized case series and case reports concerning LGMS of the extremities in a quantitative manner.

We have identified and summarized 34 cases. Similar to other locations being published before, there is no distinct age preference, even though the majority of patients was < 60 years old (75%) with a roughly equal gender incidence. Minimal gender differences seen in other publications most likely reflect the limited sample size for examination of this rare tumor. In this systematical review, 23% of LGMS in the extremities presented with a local recurrence. Initially, the painless tumor is often misdiagnosed as a benign lesion and incomplete resection with residual tumor cells leads to local recurrence, just as in the case presented. Many cases do not give any information on the resection margins or the initially suspected diagnosis. Like in our case report and case no. 22 (Tabl. 2) the tumor initially was excised under local anesthesia because a benign lesion was suspected. The tumor recurred after 2 months. The fact that local recurrence was seen only a few months after resection suggests an incomplete initial resection. Literature proposed that recurrent tumor can easily lead to distant metastases and theoretically can dedifferentiate (case 32) [22]. Unfortunately, most published literature mainly focused on reporting pathological studies. That is why information concerning exact surgical procedure is missing. In our opinion, the type of surgical resection (local resection without a margin, marginal resection, wide resection) seems to be important to prevent local recurrence. Another limitation of this review is the different or missing follow-up times in the cases ranging from 4 months up to five years (Tabl. 2). Chan et al. (2017) noticed a significantly different tumor size comparing head and neck LGMS and non-head and neck LGMS having a significantly greater number of cases with tumor size > 4 cm [3]. Non-head and neck tumors were present in the abdomen and pelvis or extremities allowing the tumor to grow silently before symptoms presented. Tumors in the head and neck region are easier visible leading to early diagnose and therapy. LGMS presenting in the extremities also often showed a local recurrence in cases of the tumor size > 4 cm (Tabl. 2). However, we think that not only tumor size and time until therapy, but also surgical procedure is a limiting factor for local recurrence.

LGMS of the hand, especially of the thumb, needs to be distinguished from other tumorous lesions of the extremities because of the proximity of anatomical structures and thus narrow resection margins with the need of a consecutive tissue reconstruction.

Only two case reports describe the incidence of LGMS in the hand (Tabl. 2). We performed a two-stage surgical intervention to secure tumor-free margins. The presented Holevich's neuro vascular flap is a common and a reliable choice at this anatomical region in order to simultaneously provide the defect coverage and the preserving local sensibility without compromising surgical oncologic principles. The most important aspect for flap survival is a careful pedicle preparation, elevation and prevention of the pedicle strangulation. As presented in the study of San Miguel et al. an amputation also is also a feasible surgical option, leading to a functional

loss and an aesthetic impairment [16]. Whenever possible in younger patients, limb salvage should be the first option. Unfortunately, data are sparse concerning the clinical outcome and the patient satisfaction. In the year of 2011 Puhaindran et al. investigated 23 patients in a retrospective study indicating that clinical outcome (regarding surgical management for malignant tumors of the thumb) lead to similar results comparing patients with a thumb amputation at the interphalangeal joint and a thumb-sparing wide excision with reconstruction [23]. Nevertheless, especially younger patients decline amputation. Sarcoma surgery and consecutive flap reconstruction can achieve a high survival rate and a low recurrence rate at any tumor site [24].

Uniform diagnostic criteria using MRI and histopathological evaluation for this rare tumor entity have not yet been well-established. Nevertheless, preoperative MRI is important to avoid an unnecessarily aggressive surgery and to differentiate from a benign lesion even if MR features are nonspecific [25]. A definitive diagnosis is challenging and requires both histopathological and immunohistochemical analyses. The determination of the grade of anaplasia in each tumor is difficult because of wide ranges of histologic features [7, 26]. Incision biopsy is therefore needed to obtain proper diagnosis and justify invasiveness of the surgical management. In cases of a small tumor size, excision biopsy should only be performed if a complete resection with tumor-free margins seems possible, to lower the risk of local recurrence [7, 27]. This suggestion is based on the experiences with other tumor entities and presented case reports without adequate sample size to accurately assess this. Concerning an LGMS we recommend a follow-up care with a regular screening. In the first year there should be a check-up every 4 months, followed by a 6-months interval until the fourth year and finally once a year until 10 years after surgery with local MRI and X-ray of the chest. There is no evidence for pre- or postoperative radiotherapy or chemotherapy [22, 27, 28]. Individual adjuvant or neoadjuvant options should only be evaluated interdisciplinary with a board votum when complete resection of tumor mass is not possible. The prognosis of the tumor may depend upon many factors like the tumor size, staging, site as well as health status of the patient, even if any evidence of this recommendation in studies is missing.

Conclusions

LGMS is a rare malignant neoplasm seldomly located in the extremities. Imaging and clinical appearance frequently leads to misdiagnoses as a benign lesion with a consecutive insufficient resection. An initial complete resection with tumor-free margins should be the primary oncological goal. Concerning tumors of the hand and limb, a function preserving surgery is desirable. Neurovascular flap reconstruction can be used to sufficiently cover the defect and preserve sensibility.

Abbreviations

LGMS
Low-grade myofibroblastic sarcoma; ICD-O:International Classification of Diseases for Oncology; PRISMA:Preferred Reporting Items for Systematic Reviews and Meta-Analysis; MRI:Magnetic Resonance Imaging; FISH:Fluorescence in situ Hybridization; TTF1:Thyroidale Transkriptionsfaktor 1; TFE3:Transcription factor E3; INI-1:Integrase interactor 1; ALK1:activin receptor-like kinase 1; ROS1:ROS Proto-Oncogene 1; RNA:ribonucleic acid; DMCA:dorsal metacarpal artery; IP joint:interphalangeal joint; MSTS score:Musculoskeletal tumor society score.

Declarations

Ethics approval and consent to participate

Ethical approval was not necessary because of the study design. Written consent was obtained for using pictures by the patient included in this study.

Consent for publication

Consent from the patient is available for publication.

Availability of data and materials

Additional datasets from the current study will be provided by the corresponding author BP on request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

AS developed the study design, collected, analyzed, and interpreted the data and wrote the manuscript. GM and GE interpreted histological analyses. LH and BL participated with interpretation of the findings and drafting. BP participated with the study design, analyses, interpretation of the findings and drafting. All authors read and approved the final manuscript.

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Figures

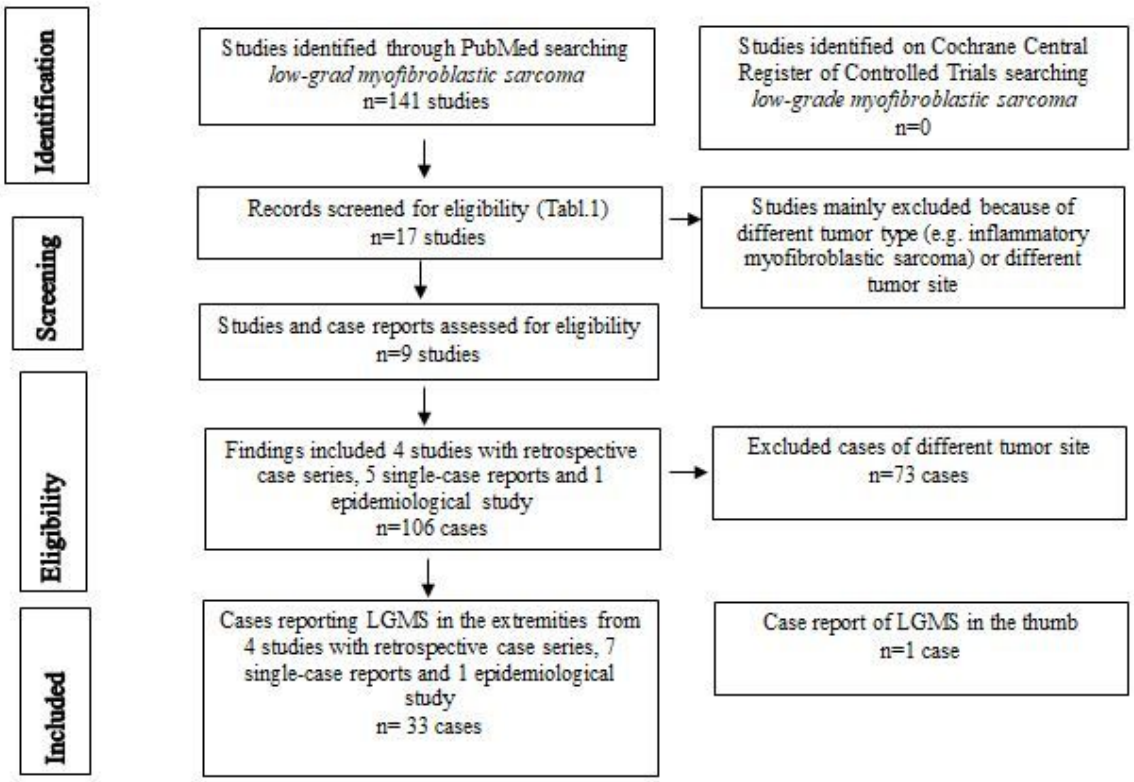

Figure 1

Flow diagram of cases with LGMS in the extremities (PRISMA diagram).

Figure 2

A photograph showing the soft tissue mass, approximately 2 x 1,5 cm in diameter and located on the ulnar side of the distal phalanx of the right thumb.

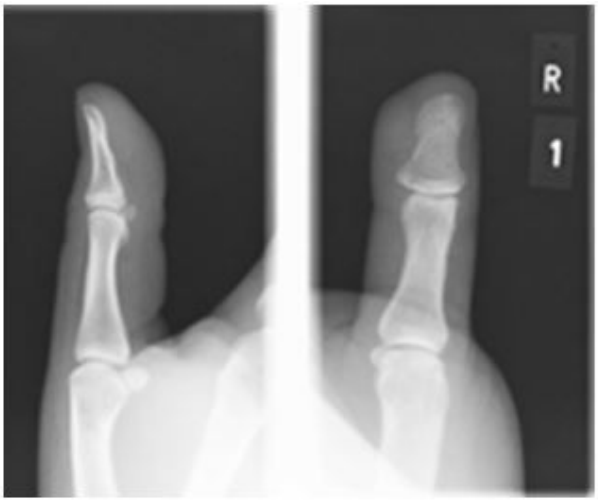

Figure 3

Lateral and anteroposterior plain radiographs reveal no bone erosion close to the soft tissue mass.

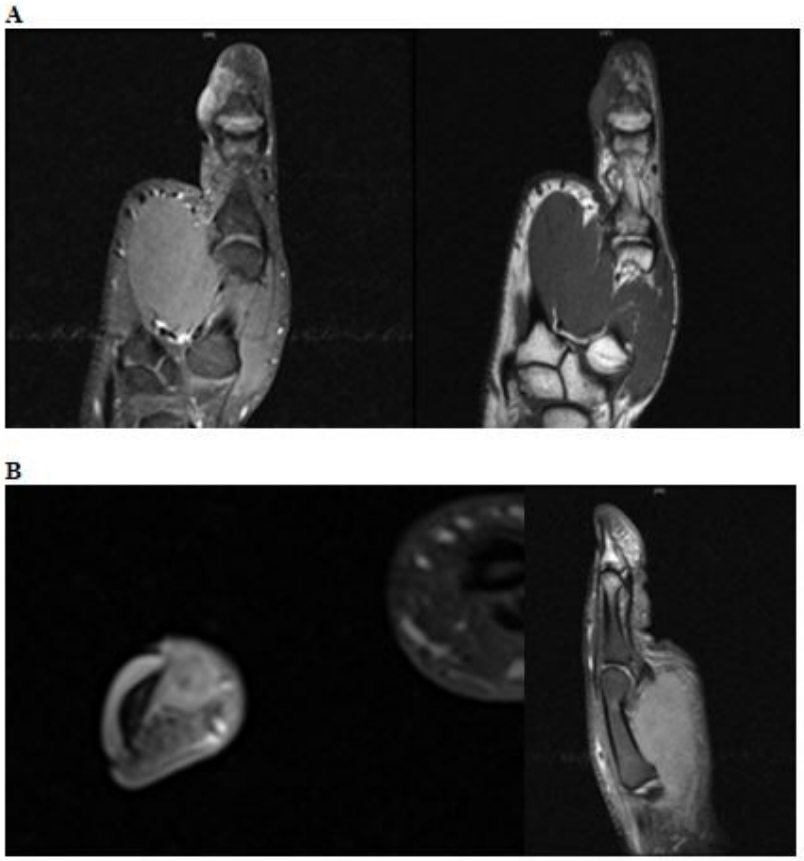

Figure 4

Magnetic resonance imaging (MRI) with contrast material revealed an irregular mass. A. Coronal B. sagittal/transversal view of the predominantly hypointense mass on T1-weighted images, and hyperintense on T2-weighted images. Images show hyperintense bone reaction without direct infiltration of the bone.

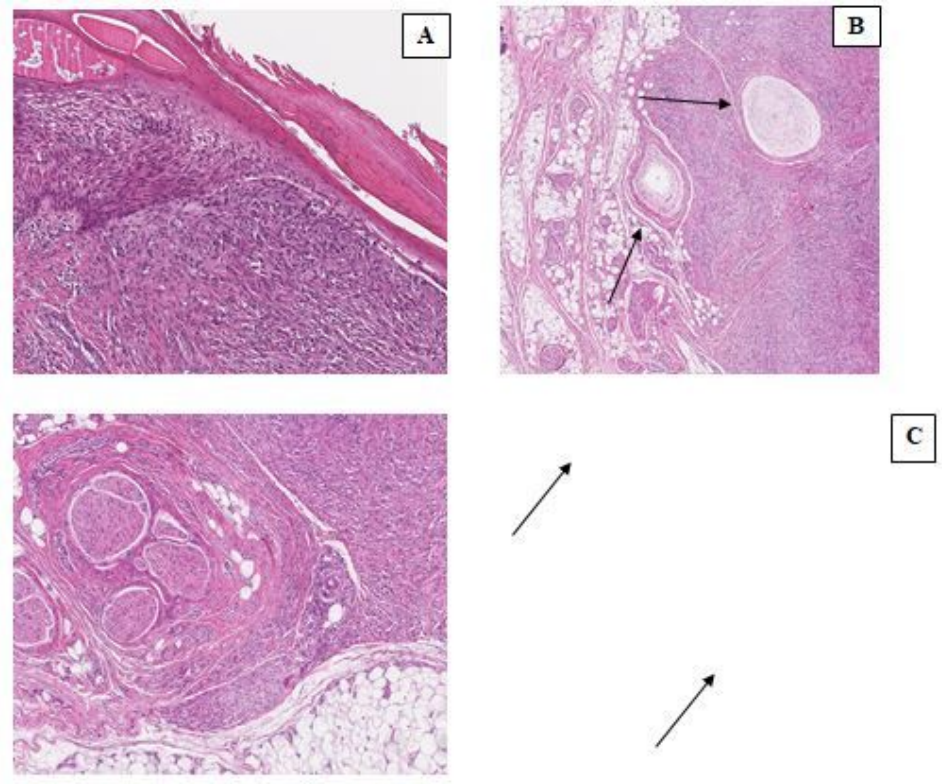

Figure 5

Histological aspects of low-grade myofibroblastic sarcoma. A: LGMS, being characterized by a high cell density in this case, is composed of fusiform tumor cells with spindle-shaped, monomorph, vesicular nuclei with small nucleoli and ill-defined, pale eosinophilic cytoplasm. B: Showing a diffusely infiltrative growth in subcutaneous fatty tissue, this spindle cell tumor with a fascicular arrangement of neoplastic cells includes several Vater Pacini bodies and immures peripheral nerves without a perineural tumorous invasion (C).

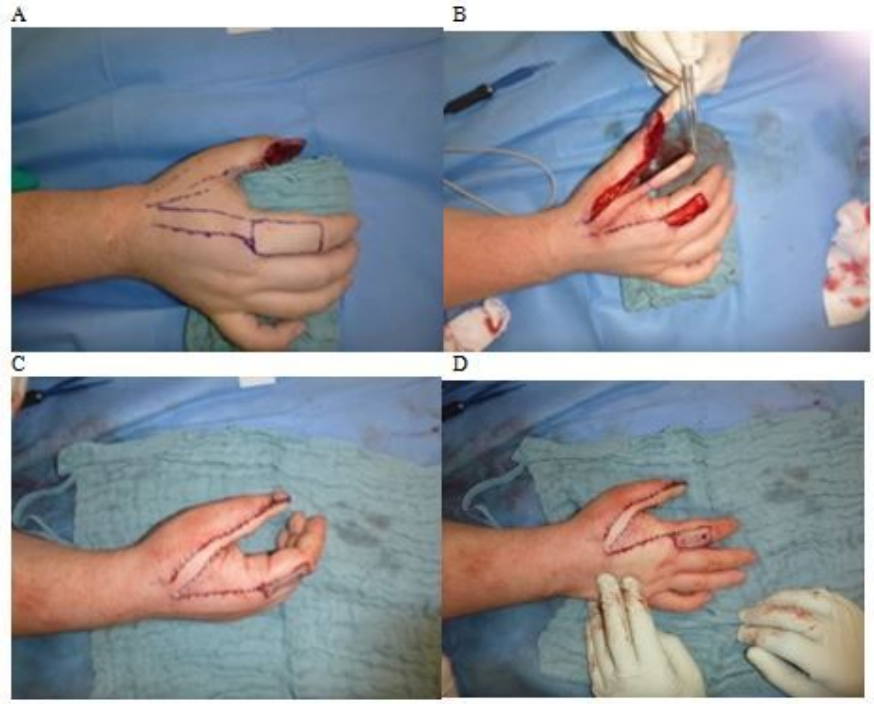

Figure 6

Holevich’s flap. Foucher’s neuro vascular flap: A Defect after tumor resection. B Flap elevation. C Reconstruction with the flap. D The donor area is covered by an antecubital full-thickness skin graft.

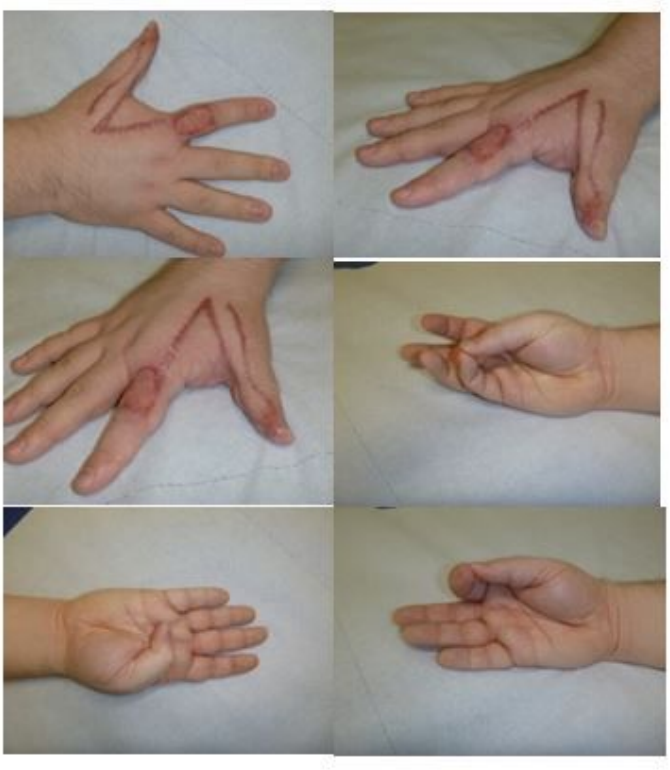

Figure 7

Wound healing and thumb function 12 weeks after operation.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PRISMAchecklistLGMS.doc
- CAREchecklistLGMS.docx