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TITRE

Caractéristiques et prises en charge de l'hémangiome intramusculaire de type capillaire: une revue systématique de la littérature et une cohorte rétrospective française multicentrique

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

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TABLE DES MATIÈRES

I. INTRODUCTION GÉNÉRALE

L'hémangiome intramusculaire (HIM), également appelé hémangiome du muscle squelettique, est une affection rare et mal connue qui comprend des entités hétérogènes. En 1972, Allen et Enzinger ont classé les HIMs parmi les tumeurs vasculaires (les opposant ainsi aux malformations vasculaires), et en ont identifié 3 sous-groupes selon les caractéristiques histopathologiques des lésions, notamment la prédominance de la taille des vaisseaux intratumoraux : le groupe des HIM des « petits vaisseaux », des « gros vaisseaux » et des « moyens vaisseaux ou mixtes ». Le groupe à petits vaisseaux a ensuite été mieux identifié grâce à l'apport de l'imagerie, en particulier de l'IRM, pour aboutir à une entité mieux définie appelée hémangiomes intramusculaires de type capillaire (HITC), avec des caractéristiques cliniques, histologiques et d'imageries spécifiques.

Les caractéristiques communes aux HITC sont que ce sont des anomalies vasculaires intramusculaires qui peuvent survenir à tout âge mais plus fréquemment chez les jeunes adultes, d'augmentation progressive sans extension au tissu sous-cutané ou à l'os sous-jacent. La notion de débit rapide à l'imagerie est devenue un critère diagnostique primordial.

La nomenclature diverse et évolutive et les difficultés diagnostiques ont conduit les HITC à être rapportés dans la littérature sous différents noms et à être facilement confondus avec d'autres entités vasculaires intramusculaires.

L'ISSVA (*International Society for the Study of Vascular Anomalies*) classe toutes les anomalies vasculaires en « tumeurs vasculaires » d'une part, et en « malformations vasculaires » d'autre part. Cependant, l'HITC a été inclus dans le groupe des « anomalies vasculaires provisoirement non classées », soulignant bien le manque de connaissances qui subsiste sur cette entité.

L'amélioration des techniques de biologie moléculaire a également conduit à mieux

comprendre et classer les anomalies vasculaires. Dans certains cas d'HITC, des mutations somatiques dans les gènes *MAP2K1* et *KRAS* ont été identifiées, similaires à celles détectées dans plusieurs cas de malformations artérioveineuses extracrâniennes. Ceci mérite d'être confirmé sur un échantillon plus important, mais soulève l'hypothèse d'un chevauchement entre ces 2 groupes d'entités, renforçant le critère principal de débit rapide intramusculaire dans la lésion.

L'objectif de ma thèse a été de me mieux comprendre les caractéristiques cliniques, radiologiques, histopathologiques et moléculaires de l'HITC ainsi que la prise en charge thérapeutique optimale. Pour y parvenir, nous avons réalisé dans un premier temps une revue systématique de la littérature en prenant en compte, dans l'équation de recherche, les différentes dénominations possibles de l'HITC. Dans un second temps, nous avons fait appel aux différents centres français prenant en charge des anomalies vasculaires pour recueillir tous les cas de lésions vasculaires intramusculaires de haut débit afin de les analyser. Un comité d'experts a été constitué et a analysé les cas de cette cohorte pour mieux en préciser les critères diagnostiques.

Ce travail de thèse regroupe ces deux travaux, présentés sous la forme de deux articles ci-après. Nous envisageons de soumettre le premier article dans *Acta Dermato-Venereologica* et le deuxième dans *Journal of the American Academy of Dermatology* (JAAD).

II. RÉSUMÉ DU PREMIER ARTICLE EN FRANÇAIS

Caractéristiques et prises en charge de l'hémangiome intramusculaire de type capillaire : Une revue systématique de la littérature

Introduction

Les hémangiomes intramusculaires sont des anomalies vasculaires rares qui peuvent facilement être diagnostiquées à tort comme d'autres entités. La définition a évolué au fil des années, ce qui a conduit à une entité mieux définie appelée hémangiome intramusculaire de type capillaire (HITC). Nous avons cherché à étudier les caractéristiques cliniques, radiologiques, pathologiques et moléculaires de l'HITC, ainsi que les traitements et les résultats.

Méthodes

Nous avons effectué une revue systématique de tous les cas rapportés comme hémangiome intramusculaire dans la littérature depuis sa première description en 1972. Un comité d'adjudication a examiné tous les cas pour n'inclure que les cas d'HITC.

Résultats

Parmi les 1 143 rapports examinés, 43 articles ont été inclus pour l'analyse, impliquant 75 patients. Le diagnostic différentiel le plus fréquent était les malformations veineuses intramusculaires. L'âge moyen des patients au moment du diagnostic était de 21,2 ans. L'HITC a été principalement décrit comme une masse augmentant progressivement (n=36/44, 81,8%), le plus souvent indolore (n=34/46, 73,9%), qui pouvait se produire n'importe où dans le corps mais le plus souvent dans la région tête et cou (n=33/75, 44,0%). L'IRM a été principalement utilisée pour le diagnostic (n=47/68, 69,1%), et les caractéristiques IRM les plus courantes étaient : une masse bien délimitée avec des signaux hétérogènes, isointense sur les images pondérées en T1, présentant toujours des hypersignaux sur les images pondérées en T2 et prenant le contraste après injection. Le traitement le plus fréquent était l'ablation chirurgicale complète (n=34, 73,9%), qui pouvait être précédée d'une embolisation (n=5), et a conduit à une rémission complète sans récidive dans tous les cas sauf un.

Conclusion

Les relations pathogéniques entre les HITCs et les malformations artérioveineuses (MAVs) ne sont pas encore claires, cependant, la nature peu agressive et le faible taux de récidive après chirurgie des HITCs les distinguent cliniquement des MAVs habituelles.

Mots-clés : Hémangiome intramusculaire ; hémangiome intramusculaire de type capillaire ; débit rapide ; malformation vasculaire intramusculaire ; malformation artério-veineuse extracrânienne ; anomalie vasculaire intramusculaire à débit rapide.

III. RÉSUMÉ DU PREMIER ARTICLE EN ANGLAIS

Characteristics and outcomes of intramuscular capillary-type hemangioma: A systematic literature review

Background

Intramuscular hemangiomas are rare vascular anomalies that might easily be misdiagnosed as other entities. The definition has evolved over the years, which has led to a better delineated entity called intramuscular capillary-type hemangioma (ICTH). Here, we aimed to investigate the clinical, radiological, pathological and molecular features of ICTH as well as treatments and outcomes.

Methods

We performed a systematic review of all cases reported as intramuscular hemangioma in the literature since its first description in 1972. An adjudication committee reviewed all cases to include only ICTH cases.

Results

Among 1 143 reports screened, 43 were included for analysis, involving 75 patients. The most frequent differential diagnosis was intramuscular venous malformations. The mean age of patients at diagnosis was 21.2 years. ICTH was mainly described as a gradually increasing mass (n=36/44, 81.8%), mostly painless (n=34/46, 73.9%), that could occur anywhere in body but most frequently on the head and neck (n=33/75, 44.0%). MRI was mainly used for diagnosis (n=47/68, 69.1%), and the most common MRI features were: a well-delineated mass with heterogeneous signals, isointense on T1-weighted images, always displaying hypersignals on T2-weighted images and after contrast enhancement. The most frequent treatment was complete surgical removal (n=34, 73.9%), which could be preceded by embolization (n=5), and led to complete remission without recurrence in all cases but one.

Conclusion

The pathogenic relationships between ICTHs and AVMs are still not clear, however, the low aggressive nature and low recurrence rate after surgery of ICTHs distinguishes them clinically from the usual AVMs.

Keywords: Intra-muscular hemangioma; Intramuscular capillary-type hemangioma; Fast-flow; Intramuscular vascular malformation; Extracranial arteriovenous malformation; Intramuscular fast-flow vascular anomaly.

IV. PREMIER ARTICLE EN ANGLAIS

Title: Characteristics and outcomes of intramuscular capillary-type hemangioma: A systematic literature review

Running title: Intramuscular hemangiomas

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Abstract (150 words)

Intramuscular capillary-type hemangioma (ICTH) are rare vascular anomalies that might easily be misdiagnosed as other entities. We performed a systematic review of all cases in the literature since its first description in 1972. An adjudication committee reviewed cases to include only ICTHs. Among 1 143 reports screened, 43 were included, involving 75 patients. The most frequent differential diagnosis was intramuscular venous malformations. The mean age of patients at diagnosis was 21.2 years. ICTH was mainly described as a gradually increasing mass (81.8%), painless (73.9%), that could occur anywhere in body but most frequently on the head and neck (44.0%). MRI was mainly used for diagnosis (69.1%) and displayed specific features. The most frequent treatment was complete surgical removal (73.9%), which could be preceded by embolization, and led to complete remission without recurrence in all cases but one. The low recurrence rate after surgery of ICTHs distinguishes them from arteriovenous malformations.

Significance (89 words)

Intramuscular capillary-type hemangiomas (ICTH) are rare and poorly understood vascular anomalies that might easily be misdiagnosed as other entities. We reviewed all cases of ICTH published in the literature to allow for better understanding and management of this entity. The review found that ICTHs most frequently occur in young adults, anywhere in body but mainly on the head and neck, usually gradually increase and are painless. MRI (+/- microscopy observation from a biopsy) is required for diagnosis and surgery (preceded or not by embolization) seems the best therapeutic option.

Keywords: Intra-muscular hemangioma; Intramuscular capillary-type hemangioma; Fast-flow; Intramuscular vascular malformation; Extracranial arteriovenous malformation; Intramuscular fast-flow vascular anomaly.

Introduction

Intramuscular hemangiomas (IMHs), also called hemangiomas of the skeletal muscle, are a rare and poorly known condition that includes heterogeneous entities. In 1972, IMHs were classified into 3 subgroups by Allen and Enzinger [1] by considering histopathological features of the lesions, especially the size of intratumoral vessels (vessels < 140 μm in diameter defined as the "small-vessel group", vessels > 140 μm the "large-vessel group", and both types of vessels in nearly equal proportions the "mixed group") [1]. The definition of IMHs was discussed and evolved over years, leading to a better-defined entity called intramuscular capillary-type hemangiomas (ICTHs), with specific clinical, histology and imaging features [2,3]. Because the nomenclature has been changing, ICTHs might be reported in the literature under various names such as "intramuscular hemangioma small vessel type" [1] "intramuscular angioma-capillary type" [4], or "infiltrating angiolipoma" [5]. The features common to ICTHs are firm intramuscular lesions that might occur at any age but more frequently in young adults, appearing on imaging as intramuscular fast-flow lesions, without extension to the subcutaneous tissue or the underlying bone [2]. They can easily be misdiagnosed as 4 main conditions: 1) intramuscular venous malformations (IVMs), characterized by slow-flow imaging signals, phleboliths, large vessels on microscopy, and the possibility of underlying bone involvement [6]; 2) extra-renal angiomyolipomas (now called angiomyolipomas), which are tumours of uncertain differentiation whose diagnosis is based on microscopy observation of smooth muscles, thick-walled blood vessels and mature fat in varying proportions [7,8]; 3) phosphatase and TENsin homolog (PTEN)-related hamartomatous tumour syndrome, which involves clinically heterogeneous disorders that share a germline mutation in PTEN and damage to the derivatives of the three embryonic laminae, leading to hamartomas, overgrowth and neoplasia [9]; and 4) other high-flow anomalies of various prognosis with extension to the skeletal muscle, such as extracranial arteriovenous malformations (AVMs) [10] or rhabdomyosarcomas [11].

According to the International Society for the Study of Vascular Anomalies, vascular anomalies are classified as vascular tumours and vascular malformations [12]. However, ICTH was included in the group of "provisionally unclassified vascular anomalies", which highlights the remaining lack of knowledge on this entity. In several cases of ICTH, recent molecular analyses identified somatic mutations in *MAP2K1* and *KRAS* genes, similar to those detected in several cases of extracranial AVMs [13,14], which suggests the hypothesis of overlap between those 2 groups of entities [15]. We need a better understanding of ICTH to homogenize its diagnostic and therapeutic management.

The objective of this study was to investigate the clinical, radiological, pathological and molecular features of ICTH as well as treatments and outcome by a systematic review of the literature.

Methods

This systematic review followed the 2020 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and was registered on the PROSPERO database (CRD42021237224).

Search strategy and information sources

We searched the electronic databases MEDLINE via PubMed, CENTRAL and EMBASE on March 1, 2021. The search equations are in **Supplemental file 1**. There were no restrictions on language, and the search included articles from 1972 (year of the first description by Allen and Enzinger [1]) to march 1, 2021.

Eligibility criteria

We included all original reports describing ICTH cases. Criteria for diagnosis were based on clinical, radiological and pathological features when required. Clinically, the mass would be strictly in the muscle without extension to the skin. If performed, ultrasonography had to show an intramuscular lesion and color and spectral Doppler traces to show fast-flow waveforms or arterial supply. For diagnosis, we required at least one set of images from CT scan, MRI or angiogram showing features of intramuscular well-delineated lesions without

cutaneous involvement. MRI imaging had to show characteristic signals (hyperintense on T2-weighted images with hypointense flow voids, with homogeneous contrast enhancement) [2]. The presence of fat might be observed. Angiogram (not mandatory) could show enlarged arterial feeders and inhomogeneous parenchymal but non-tortuous arterial afferences, with a tissular blush without early venous phase drainage in the tumour. Pathologic features (required in case of doubtful imaging) had to be consistent with the diagnosis of ICTH [1,2,15], showing proliferation/hyperplasia of endothelial cells (positive for CD31 immunohistochemistry when performed) [16], capillaries with plum endothelium separating skeletal muscle fibres. Immunohistochemistry for lesional endothelial cells for GLUT-1 and podoplanin (D2-40) should be negative if performed [17].

Exclusion criteria were cases with too much missing data, differential diagnoses and doubtful cases. In particular, we excluded reports describing: slow-flow vascular malformations, especially IVMs that contained phleboliths; intramuscular typical AVMs (with a nidus or arteriovenous shunting); all intramuscular vascular anomalies that extended to the subcutaneous/cutaneous tissue; other tumors (infantile hemangiomas, congenital hemangiomas, malignant tumours etc.), and angiomatosis of soft-tissue (PTEN-hamartomas of soft tissue and fibro-adipose vascular anomaly) [15,18].

We excluded articles that did not report original observations, such as editorials, general reviews, and expert opinions.

Study selection strategy and data extraction

Two authors (JO and AM) independently selected studies on the basis of the title and abstract and then examined the full text. Then, 2 authors (JO and AE) independently extracted the following data: first author, publication year, characteristics of the study and study participants, triggering factors, location of the ICTH, histology and molecular features, imaging and follow-up data, including outcomes and treatment. In doubtful cases, especially for retaining a diagnosis of ICTH, the paper was reviewed by an adjudication committee of experts (AB, DH, MW and AM).

Statistical analyses

Descriptive data are expressed as mean ± SD or median and interquartile range [IQR] for quantitative data and number (%) for categorical data. Quantitative variables were compared by Wilcoxon test and categorical variables by chi-squared test or Fisher exact test. $P<0.05$ was considered statistically significant. We used R v3.6.2 for analysis. No methods were used to handle missing data.

Results

Among 1 143 reports initially screened, 43 were included for analysis (**Fig. 1**), involving a total of 75 patients from 29 clinical cases and 14 case series. The most frequent differential diagnosis that explained the exclusion of reports was description of typical IVMs under the name IMH (90 cases). Nine cases of AVM were excluded (description of a nidus/arteriovenous shunt in 7 cases, extension to skin in 2 cases).

Table 1 summarizes the characteristics of reports and patients. The mean age of patients at diagnosis was 21.2 ± 17.1 years and the median age was 17.0 years (IQR 7.0–31.0), range 1 day to 67 years. Among the 75 patients, 33 (44.0%) were < 16 years old. The ratio of males to females was 1/2. The median time to diagnosis was 12 months (IQR 4.9–36).

ICTH was most commonly a gradually increasing mass (n=36/44, 81.8%), not warm (n=0/29) and not pulsatile (n=3/46), with a firm consistency (n=23/36, 63.9%) and mostly painless (n=34/46, 73.9%) (**Table 2**). A triggering factor was suspected in 7 (14.3%) cases, especially local trauma (n=5). ICTH could occur all over the body, but the most affected body region was the head and neck area (n=33/75, 44.0%). Overall, 29 muscles or muscle groups with ICTH were reported among the 61 cases that included description of the affected muscle(s) (**Fig. 2A**, **2B**), the most commonly affected being the triceps surae (n=7), sternocleidomastoid (n=5), temporalis and quadriceps femoris (n=4), gluteus maximus (n=3), paraspinal (n=3), extraocular muscles (n=3) and lip muscles (n=3), masseter (n=2).

Diagnosis required MRI in 69.1% of cases (n=47/68); the most common features were a well-delineated mass (n=10/13, 76.9%), with heterogeneous signals (23/26, 88.5%), isointense on T1-weighted images (n=27/32, 84.4%), always displaying hypersignals on T2-weighted images and after contrast enhancement (**Table 2**). Flow voids were reported in 21 cases. Angiogram was performed in 40.9% of cases (n=27/66), mostly describing highly vascularized lesions with no nidus, inhomogeneous parenchymal staining and emerged arterial feeders.

Pathology data on biopsy or surgical excision were provided for 90.7% of cases (n=68/75) (**Table 2**). Descriptions mainly included endothelial cell proliferation, with small-size vessels alone in 67.7% of cases (n=42/62) or concomitant with other-sized vessels, and presence of adipose tissue in 93.9% cases (n=31/33). When described, all cases were negative for GLUT-1 and the lymphatic marker D2-40. One article reported mutations in the genes *KRAS* (n=4) and *MAP2K1* (n=2) in a series of 8 cases [15].

Therapeutic management was reported in 46 cases (**Table 3**). The most frequent treatment consisted of complete surgical removal (n=34, 73.9%), often described as a bleeding surgery, which led to complete remission without recurrence in all cases except one (n=1/22), with a median post-treatment follow-up of 14.0 months [IQR 6.0–24.0]. Most ICTH that underwent complete surgery were located on the head and neck (n=22, 64.7%). No treatment with embolization alone was described, but 5 cases of embolization were followed by surgery, with complete remission in 2 (3 missing data). The “wait and see” attitude was reported in 3 cases and showed stabilization of the lesion.

ICTH occurred earlier for trunk than head and neck lesions (median 19.7 vs 31.0 years, p=0.002), were larger (median 36.0 vs 13.0 cm^2, p=0.014), and were the most frequent (**Supplemental file 2**). Pain did not differ by topography, and patients ≤ 16 years and > 16 years old did not differ in characteristics of ICTH.

Discussion

Since its first description by Allen and Enzinger, in 1972 [1], ICTH (i.e., IMH) remains poorly defined and understood. This review of the literature allows for a better characterization: ICTH can occur at every age but mostly in young adults and is often a firm, painless, progressively increasing mass located in a muscle on the head and neck (temporalis or masseter), the trunk (sternocleidomastoideus) or limb (triceps surae, quadriceps femoris, gluteus maximus). MRI is the most widely used imaging technique for diagnosis, showing features of a well delineated hypervascular heterogeneous lesion, isointense on T1-weighted images, hyperintense on T2-weighted images, enhanced after injection of contrast medium and showing flow voids. Pathology examination of samples is also useful for diagnosis and shows a proliferation of capillaries, with GLUT-1 negative endothelial cells, sometimes associated with larger arteries and veins, and with adipose tissue.

The most common differential diagnosis of ICTH is another type of vascular anomaly, IVMs. Among the 1 143 articles screened, 90 cases were excluded after reinterpretation by an adjudication committee because they were considered a misdiagnosis of venous malformations instead of ICTH. Indeed, venous malformations might also be located in a muscle, commonly the lower limbs and head and neck, but are often painful due to localized intravascular coagulopathy within the malformation and lead to thrombosis and phleboliths [19]. In venous malformations, vessels appear much more dilated on microscopy (cavernous vessels) [20] and are not associated with a capillary component. ICTH must be distinguished from IVMs because the management differs [21–23].

The pathogenesis of ICTH remains unknown. Local triggering factors were identified in a few cases, which raised the hypothesis of post-traumatic induced vascular lesions [24,25]. The types of affected muscles would allow for drawing hypotheses: among the 639 muscles of the human body, some are more frequently concerned (the triceps surae was the most frequent in our review), with a predominance of lesions in the head and neck area. These locations are not the most prone to trauma, which does not support the post-trauma hypothesis. The head and neck area is characterized by a thinner thickness between the

muscle and the superficial part of the epidermis, so ICTH is more clinically obvious than it could be in deeper muscles. However, no cases in our review corresponded to incidental diagnosis on imaging.

Regarding treatment, surgical removal, when possible, seems the best therapy, and might be preceded by embolization to control bleeding. Contrary to extracranial AVMs, no exacerbation of lesions was described after embolization alone or partial excision [26]. Except for corticosteroids, which were not found efficient for reducing the mass, no drugs were reported as a treatment for ICTH. In a recent study of ICTHs (named intramuscular fast-flow vascular anomalies) somatic mutations in *KRAS* and *MA2PK1* genes, similar to extracranial AVMs were identified by Goss et al. [15]. This suggests a common pathogenesis or a spectrum of lesions for ICTHs and AVMs. However, ICTHs seems clinically different from usual extracranial AVM, with a very limited local aggressive potential, low recurrence rate, and frequent cure after surgery. Beyond this, ICTH and its analogy to extracranial AVMs questions the dichotomy between tumoral and malformative vascular anomalies. However, future molecular analyses of ICTH are needed to confirm the findings by Gross et al. Future targeted therapies could be useful for non-operable huge lesions if post-zygotic mutations are confirmed, as is increasingly described for AVM treatment [27].

Limitations

The main limitations of the review were first that numerous articles reporting IMHs involved other conditions, mostly IVMs, so we excluded a large number of reports. We cannot definitely rule out that some cases included do not correspond to the definition of ICTH because of limited imaging or pathological descriptions. Second, the included reports had a lot of missing data regarding treatments and follow-up, with very little long-term follow-up information.

Conclusions

This review highlights that ICTH is still often misdiagnosed, and allows for better understanding ICTH and its management. However, molecular data are required to better delineate this entity and allow for studies of personalized targeted therapy.

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Sharing statement: Data will be made available, in addition to study protocols, the statistical analysis plan, and the informed consent form upon publication to researchers who provide a methodologically sound proposal for use in achieving the goals of the approved proposal. A written agreement must be signed with the University Hospital of Tours and the coordinator of the study. Proposals should be submitted to dpo@chu-tours.fr

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Abbreviations

IMH: Intramuscular hemangioma

ICTH: Intramuscular capillary-type hemangioma

IVM: Intramuscular venous malformation

PTEN: Phosphatase and TENsin homolog

AVM: Arteriovenous malformation

Tables

Table 1. Characteristics of reports and patients

Variable	Description	Missing data
Country, n (%)		0
North America	37 (75.5)	
South America	3 (4.0)	
Europe	14 (18.7)	
Asia	18 (24.0)	
Africa	2 (2.7)	
Oceania	1 (1.3)	
Year of publication, median [IQR]	2013 [1996–2014]	0
Sex, n (%)		0
Females	34 (45.3)	
Males	41 (54.7)	
Age at first signs, years, median [IQR], mean ± SD	24.8 [15.8–37.9], 26.6 ± 18.0	36
Age at diagnosis, years, median [IQR], mean ± SD	17.0 [7.0–31.0], 21.2 ± 17.1	0
Diagnostic delay, months, median [IQR]	12 [4.9–36.0]	36
Patients < 16 years old, n (%)	33 (44.0)	
Median post-treatment follow-up, months, median [IQR]	14.0 [6.0–24.0]	45
Comorbidities, n (%)	5 (9.8)	24
Alcoholism	1	
High blood pressure	1	
Recurrent urinary tract infections	1	
Persistent nasal obstruction	1	
Palatal rhabdomyosarcoma	1	
Sports activities, n (%)	2 (4.3)	28
Football	1	
Rugby	1	

IQR: interquartile range

Table 2. Clinical, imaging, pathological and molecular data of intramuscular hemangiomas

Variable	Description	Missing data
CLINICAL DATA		
Size (cm^2), median [IQR]	19.5 [9.0–48.8]	21
Pain, n (%)	12 (26.1)	29
Location		0
Head and neck	33 (44.0)	
Trunk	15 (20.0)	
Lower limb	15 (20.0)	
Upper limb	12 (16.0)	
Progressive increase	36 (81.8)	31
Rapid increase	4 (9.1)	
Warmth, n (%)	0	29
Pulsatility (on palpation), n (%)	3 (6.5)	29
Firm consistency, n (%)	23 (63.9)	36
Soft consistency, n (%)	13 (36.1)	
Identified triggering factor, n (%)	7 (14.3)	26
Trauma	5	
Pregnancy	1	
Air travel	1	
IMAGING DATA		
MRI, n (%)	47 (69.1)	7
Description of the mass		
Well-delineated mass	10 (76.9)	62
Heterogeneous mass	23 (88.5)	49
Homogeneous mass	3 (11.5)	49
T1-weighted sequence description		43
Hyperintense signals	3 (9.4)	
Hypointense signals	2 (6.2)	
Isointense signal	27 (84.4)	
T2-weighted sequence description		44
Hyperintense signals	31 (100)	
Contrast enhancement	34 (100)	41
Flow voids	21 (100)	54
Signal modifications of the underlying bone	2 (4.1)	26
CT scan, n (%)	22 (30,6)	3
Well-delineated mass	4 (66.7)	69
Heterogeneous mass	4 (100)	71
Contrast enhancement	9 (100)	66
Angiogram, n (%)	27 (40.9)	9
PATHOLOGY AND MOLECULAR DATA		
Biopsy/excision performed, n (%)	68 (90.7)	0
Presence of adipose tissue, n (%)	31 (93.9)	42
Description of the vessel size, n (%)		13
Small vessels only	42 (67.7)	
Small and other vessels	20 (32.3)	
Search of somatic mutations, n (%)	6 (8.0)	
MAP2K1 gene	4	
KRAS gene	2	

Table 3. Management and outcome (n=46 patients)

Therapeutic care, n (%)	Outcome, n (%)				
	Total regression	**Partial regression**	**Stabilisation**	**Recurrence**	**Missing data**
Complete surgical removal, 34 (73.9)	21 (95.5)	0	0	1 (4.5)	12
Embolization followed by surgery, 5 (10.9)	2 (100)	0	0	0	3
Incisional biopsy followed by corticosteroid therapy, 2 (4.3)	0	0	2 (100)	0	0
Incisional biopsy, 1 (2.2)	0	0	0	0	1
Partial surgical removal, 1 (2.2)	0	1 (100)	0	0	0
Therapeutic abstention and follow-up, 3 (6.5)	0	0	3 (100)	0	0

Figure legends

Fig. 1. Flow of included reports in the review

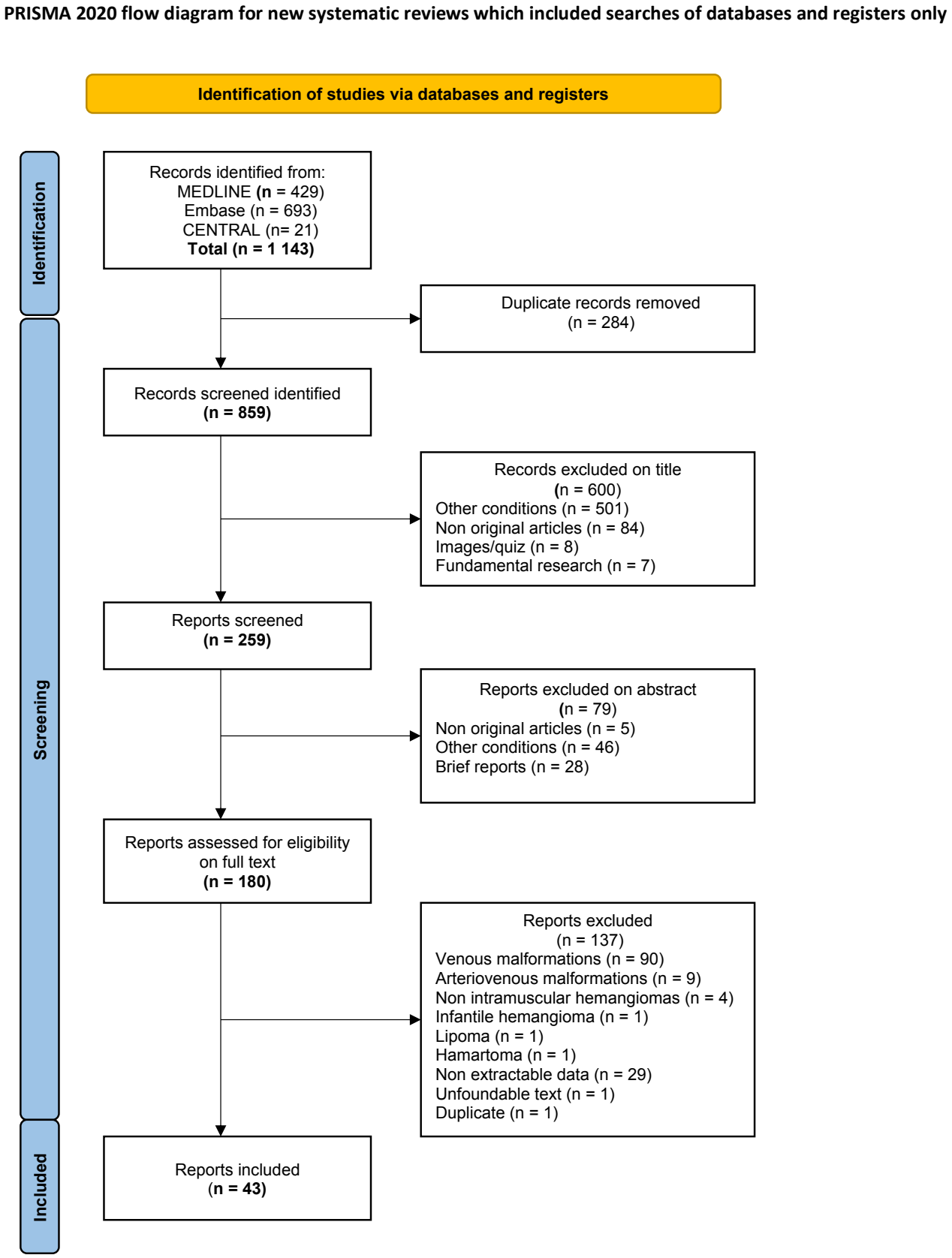


Fig. 2 (A). Muscles affected by the intramuscular hemangioma (Barplot)

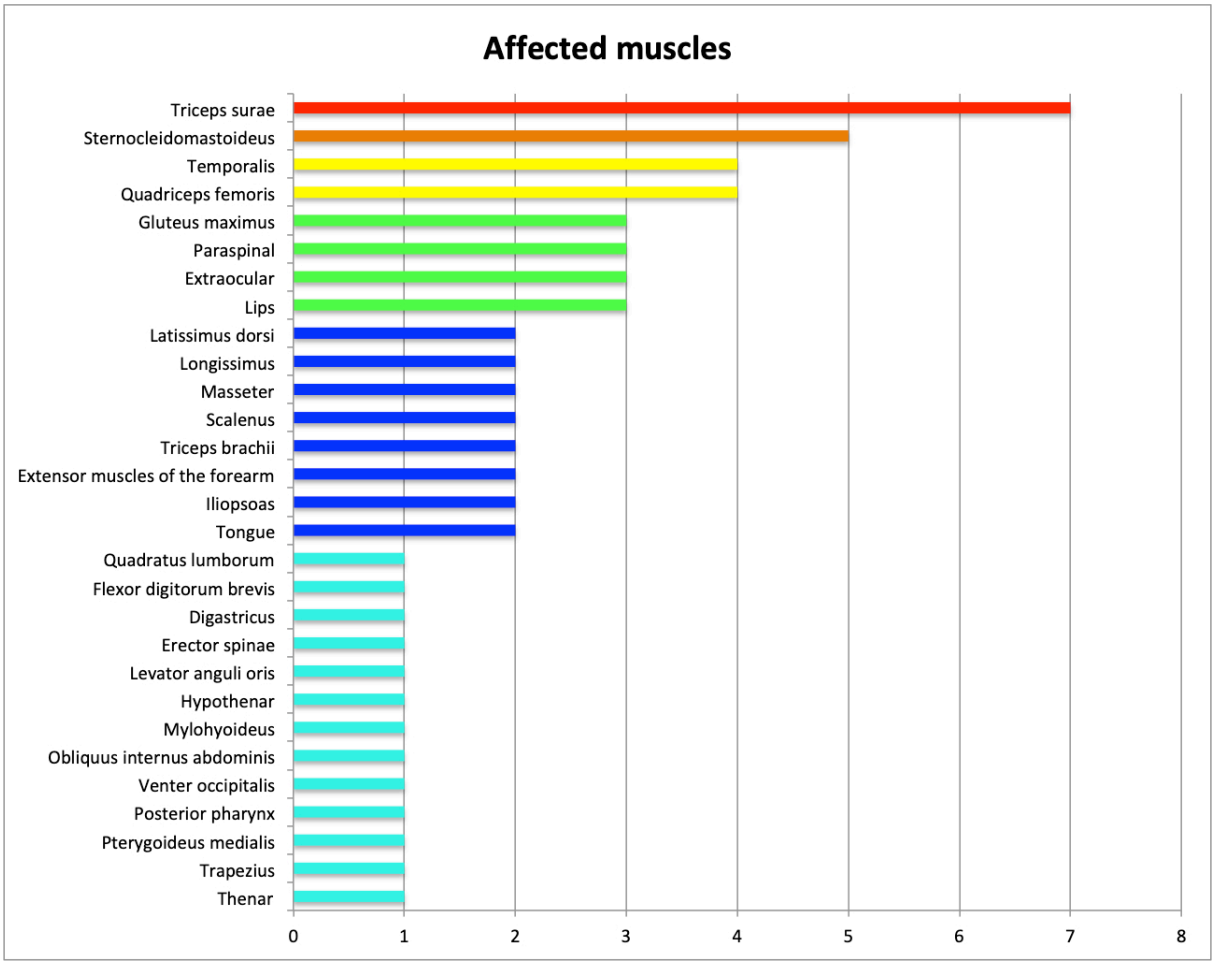
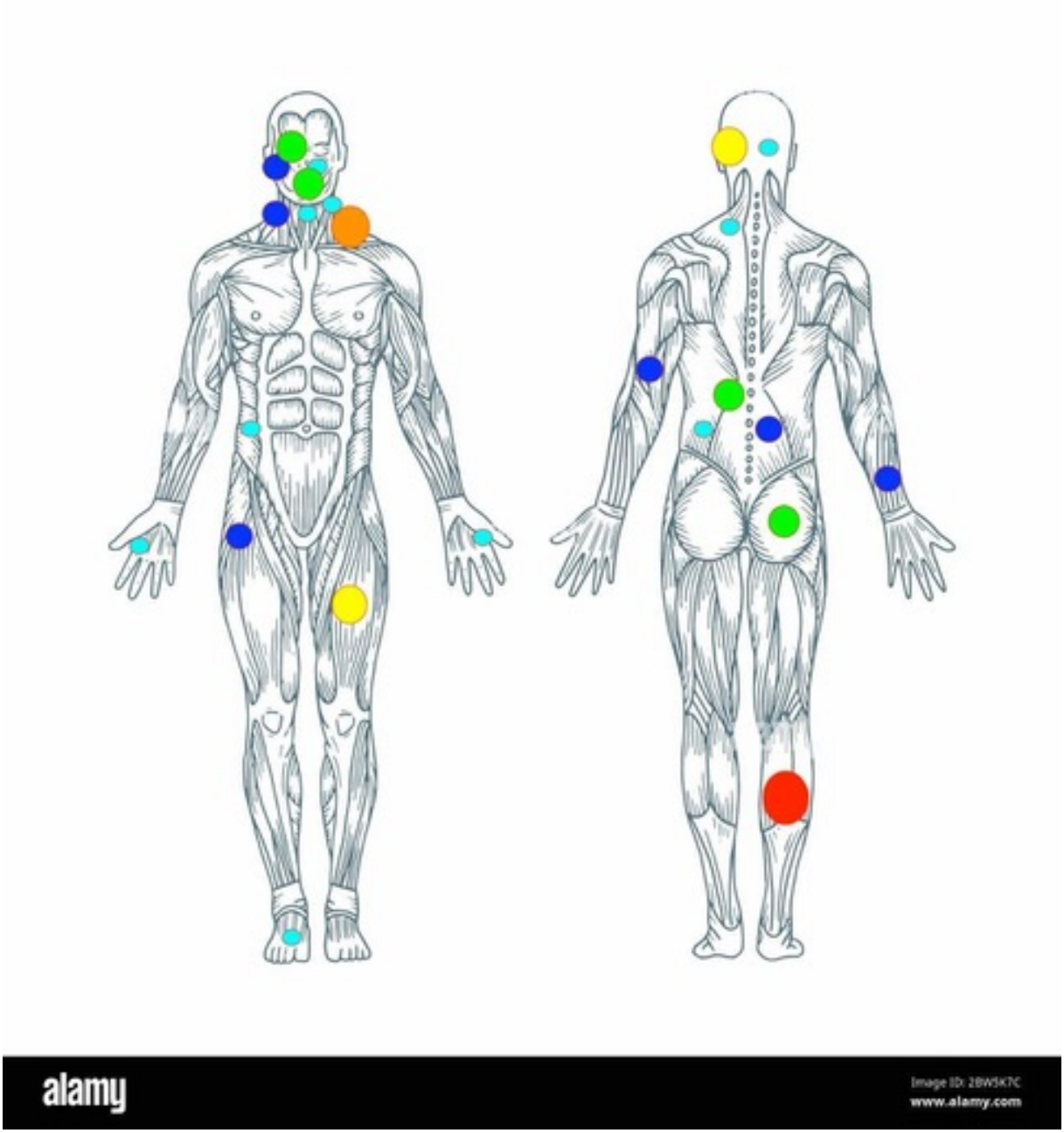


Fig. 2 (B). Muscles affected by the intramuscular hemangioma (schematic of the human body)



Supplemental files

Supplemental file 1. Search equations for the systematic review

(Total: 1143 results)

- **MEDLINE (PubMed)**

(intramuscular AND hemangioma) OR (intramuscular AND arteriovenous) OR (intramuscular AND high flow vascular) OR (intramuscular AND fast flow vascular) OR (skeletal muscle AND angiolipoma) OR (intramuscular AND angiolipoma)

Filters: 1972-28/03/21; Humans

→ 429 results

- **EMBASE**

(intramuscular AND hemangioma OR (intramuscular AND arteriovenous) OR (intramuscular AND high AND flow AND vascular) OR (intramuscular AND fast AND flow AND vascular) OR (skeletal AND muscle AND angiolipoma) OR (intramuscular AND angiolipoma)) AND [humans]/lim AND [embase]/lim AND [1972-2021]/py

→ 693 results

- **CENTRAL**

In Title Abstract Keyword: (intramuscular AND hemangioma) OR (intramuscular AND arteriovenous) OR (intramuscular AND high flow vascular) OR (intramuscular AND fast flow vascular) OR (skeletal muscle AND angiolipoma) OR (intramuscular AND angiolipoma)

1972-2021

→ 21 results

Supplemental file 2. Comparisons among subgroups of patients with ICTH

Table S1. Comparisons according to the trunk/head and neck topography

Variables	Trunk	Head and neck	P	Missing data
Number of patients	N=15	N=33		
Age at first signs (years)	19.7 [8.8–25.0]	31.0 [20.1–46.5]	0.029	36
Age at diagnostic (years)	11.0 [4.8–25.0]	31.0 [20.0–42.0]	0.002	0
Size in diameter (cm^2)	36.0 [22.4–69.5]	13.0 [7.5–19.3]	0.014	21
Pain, n (%) Yes No	 2 (20.0) 8 (80.0)	 5 (17.2) 24 (82.8)	1.000	29
Post-treatment follow-up (months)	24.0 [24.0–24.0]	14.0 [6.0–21.0]	0.258	45

Table S2. Comparisons according to the limb topography

Variables	Lower limb	Upper limb	P	Missing data
Number of patients	N=15	N=12		
Age at first signs (years)	9.0 [8.0–15.0]	16.0 [9.0–23.0]	0.699	28
Age at diagnostic (years)	9.0 [5.3–14.0]	15.2 [7.9–22.6]	0.643	36
Size in diameter (cm^2)	51.8 [34.4–81.1]	18.4 [14.2–22.3]	0.037	21
Pain, n (%) Yes No	 4 (80.0) 1 (20.0)	 1 (50.0) 1 (50.0)	1.000	29
Post-treatment follow-up (months)	3.0 [2.0–13.5]	9.0 [7.5–10.5]	0.564	45

Table S3. Comparisons according to the age of patients

Variables	≤ 16 years	> 16 years	P	Missing data
Number of patients	N=33	N=42		
Age at first signs (years)	2.8 [0.9–5.9]	30.0 [20.2–41.8]	<0.001	36
Age at diagnostic (years)	7.0 [4.0–11.0]	29.5 [21.0–39.8]	<0.001	0
Size in diameter (cm^2)	19.8 [8.5–55.2]	18.6 [12.0–46.5]	0.726	21
Pain, n (%)			0.329	29
Yes	4 (44.4)	8 (21.6)		
No	5 (55.6)	29 (78.4)		
Location, n (%)			0.048	27
Trunk	7 (58.3)	8 (22.2)		
Head & neck	5 (41.7)	28 (77.8)		
Post-treatment follow-up (months)	17.0 [13.0–22.5]	12.0 [6.0–24.0]	0.714	45

V. RÉSUMÉ DU DEUXIÈME ARTICLE EN FRANÇAIS

Diagnostics, traitements et données des hémangiomes intramusculaires de type capillaire : Une cohorte rétrospective multicentrique française

Introduction
L'hémangiome capillaire intramusculaire est passé d'une définition histologique initiale à une définition plus précise dans laquelle la radiologie occupe une place prépondérante.
Des études récentes sur la recherche en biologie moléculaire soutiennent le chevauchement possible entre l'ICTH et les MAV intramusculaires, les deux appartenant à un " spectre de lésions intramusculaires à écoulement rapide " (SPEFIL).

Méthodes
Nous avons réalisé une étude rétrospective pour recueillir tous les cas de SPEFIL, suivis dans des centres tertiaires d'anomalies vasculaires en France pour évaluer les critères de diagnostic, les traitements et les résultats. Un comité de sélection a examiné tous les cas pour n'inclure que les cas de SPEFIL.

Résultats
Le diagnostic différentiel le plus fréquent était les malformations veineuses intramusculaires. L'âge médian des patients au moment du diagnostic était de 29,7 ans. La lésion était principalement décrite comme une masse augmentant progressivement (83,9 %), indolore (88,9 %), qui pouvait se produire n'importe où dans le corps mais le plus souvent sur la tête et le cou (42,4 %). L'IRM a été réalisée dans tous les cas et a permis de distinguer un sous-groupe de 7 cas proches d'une malformation artério-veineuse, nommé "pseudo-malformation artério-veineuse" (pseudoMAV). Le traitement le plus fréquent a été l'ablation chirurgicale complète (36,2%), qui pouvait être précédée d'une embolisation, et a conduit à une rémission complète sans récidive. Il s'agit d'une différence essentielle par rapport aux malformations artério-veineuses qui récidivent souvent après la chirurgie.

Conclusion
Les SPEFILs comprennent 2 sous-types différents d'ICTH, celui typique et celui de type pseudo-MAV. L'IRM est l'examen le plus utile pour le diagnostic, et la biopsie est nécessaire en cas de doute persistant. La chirurgie, précédée ou non d'une embolisation, semble être le meilleur traitement, bien que des complications hémorragiques puissent survenir.

Mots-clés : Hémangiome intramusculaire ; Hémangiome du muscle squelettique ; Hémangiome intramusculaire de type capillaire ; Anomalies vasculaires à flux rapide ; Malformation vasculaire intramusculaire ; Malformation artério-veineuse extracrânienne.

VI. RÉSUMÉ DU DEUXIÈME ARTICLE EN ANGLAIS

Diagnostic, treatment and outcomes of intramuscular capillary-type hemangioma: A French multicentric retrospective cohort

Introduction
Intramuscular capillary hemangioma has moved from an initial histological definition to a more precise definition in which radiology has a prominent place.
Recent studies on molecular biology research support the possible overlap between ICTH and intramuscular AVMs, both belonging to a "spectrum of fast-flow intramuscular lesions" (SPEFIL).

Methods
We performed a retrospective study to collect all cases of SPEFIL, followed-up in tertiary centers for vascular anomalies in France and to assess diagnosis criteria, treatments and outcomes. An adjudication committee reviewed all cases to include only SPEFIL cases.

Results
The most frequent differential diagnosis was intramuscular venous malformations. The median age of patients at diagnosis was 29.7 years. It was mainly described as a gradually increasing mass (83.9%), painless (88.9%), that could occur anywhere in body but most frequently on the head and neck (42.4%). MRI was performed in all cases and allowed to distinguish a subgroup of 7 cases close to an arteriovenous malformation, named "pseudoarteriovenous malformation" (pseudoAVM). The most frequent treatment was complete surgical removal (36.2%), which could be preceded by embolization, and led to complete remission without recurrence. This is an essential difference compared to arteriovenous malformations which often recur after surgery.

Conclusion
SPEFIL include 2 different subtypes of ICTH, the typical one and the pseudo-AVM type.
MRI is the most useful exam for diagnosis, and biopsy is required in case of persistent doubt.
Surgery, preceded or not by embolization, seems the best treatment, although hemorragic complications might occur.

Keywords: Intramuscular hemangioma; Hémangioma of the skeletal muscle; Intramuscular capillary-type hemangioma; Fast-flow vascular anomalies; Intramuscular vascular malformation; Extracranial arteriovenous malformation

VII. DEUXIEME ARTICLE EN ANGLAIS

Article type: Original article

TITLE: Diagnostic, treatment and outcomes of intramuscular capillary-type hemangioma: A French multicentric retrospective cohort

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Keywords: Intramuscular hemangioma; Hemangioma of the skeletal muscle; Intramuscular capillary-type hemangioma; Fast-flow vascular anomalies; Intramuscular vascular malformation; Extracranial arteriovenous malformation

ABSTRACT

Background: Intramuscular capillary hemangioma (ICTH) has moved from an initial histological definition to a more precise definition, with radiology having a prominent place. Recent studies of molecular biology support the possible overlap between ICTH and intramuscular arteriovenous malformations, both belonging to a "spectrum of fast-flow intramuscular lesions" (SPEFIL).

Objective: Collect all cases of SPEFIL and assessed the diagnostic criteria, treatments and outcomes.

Methods: Retrospective study in tertiary care centers for vascular anomalies following SPEFILs in France.

Results: The median age of patients at diagnosis was 29.7 years. The lesion was mainly described as a gradually increasing mass (83.9%) that was painless (88.9%) and could occur anywhere in the body but most frequently on the head and neck (42.4%). MRI was performed in all cases and allowed to distinguish a subgroup of 7 cases close to an arteriovenous malformation, named "pseudoarteriovenous malformation". The most frequent treatment was complete surgical removal (36.2%), which could be preceded by embolization, and led to complete remission without recurrence.

Limitations: Retrospective analysis.

Conclusions: SPEFIL includes 2 different subtypes of ICTH: the typical and the pseudo-AVM type. MRI is essential for diagnosis, and surgery, preceded or not by embolization, seems the best treatment.

CAPSULE SUMMARY

- Our study confirms that ICTH is a vascular lesion for which the notion of rapid flow on imaging is essential.
- All the clinical, radiological and pathological features of this study will help to better recognize ICTH and to distinguish it from other fast flow entities.

INTRODUCTION

Intramuscular capillary-type hemangioma (ICTH) is a poorly understood and often misdiagnosed entity that has been described with several names. Its first description in 1972 by Allen and Enzinger was based on pathology: ICTH was involved in the wide spectrum of "hemangiomas of skeletal muscle"[1], divided into 3 subgroups according to the predominance of vessel size in the lesion, that is, the large, medium and small types. The small vessel size type, or ICTH, was then better identified with a description of specific MRI features, but the diagnosis remains challenging[2].

ICTHs are benign vascular anomalies of the skeletal muscle that most often grow gradually, without pain, mostly affecting young people. Its evolution is poorly understood, but it does not regress spontaneously as in infantile hemangioma[3]. The main differential diagnosis is intramuscular venous malformation[4], very often called "cavernous hemangioma"[5], corresponding to the subclass of large vessels in the Allen and Enzinger classification. These are indeed slow-flow malformations, sometimes triggered by trauma, with phleboliths, and can be painful[6]. More recently, another predominantly slow-flow entity, called fibro-vascular anomaly (FAVA)[7], was described and is another differential diagnosis of ICTH, particularly in the gastrocnemius muscle. FAVA is a rare vascular anomaly characterized by an infiltrating solid lesion that usually invades muscular and neurovascular structures and results in severe pain such as joint contractures.

ICTH is a fast-flow entity, and this is a key feature in the diagnosis. Somatic mutations of the *MAP2K1* and *KRAS* genes, usually found in a subgroup of extracranial arteriovenous malformations (AVMs), were identified in several ICTH cases, which raises the question of the distinction between ITCH and intramuscular AVMs[8]. These molecular results still need to be confirmed in larger cohorts. The possible overlap between ICTH and intramuscular AVMs, both belonging to a "spectrum of fast-flow intramuscular lesions" (SPEFIL), was further highlighted by the International Society for the Study of Vascular Anomalies, which classified ICTHs as "provisionally unclassified vascular anomalies"[9] without specifying whether they

belonged to vascular tumours or vascular malformations.

In this study, we aimed to collect all cases of SPEFIL followed up in tertiary care centers for vascular anomalies in France and assess the diagnostic criteria for better classification, treatments and outcomes.

METHODS

Design and setting

This was a multicenter retrospective observational study of all SPEFIL cases followed up from January 1, 2000, to March 1, 2021, in France. The study was approved by the ethical committee of Tours (#2021 014) (supplementary file 1).

Participants and samples

We included all patients, whatever the age, with a fast-flow vascular lesion into the skeletal muscle and not extending to other tissue, with sufficient data to be able to perform a diagnosis (MRI was mandatory). One or several muscles could be involved.

We excluded lesions belonging to syndromes (e.g., phosphatase and tensin homolog [PTEN])[10], low-flow vascular anomalies, and lesions into non-skeletal muscles or not limited within the muscle. We excluded patients with insufficient data or poor-quality imaging not allowing for a diagnosis.

Outcomes

History, clinical, radiological, pathological and molecular data were collected. An adjudication group of experts consisting of a pathologist (MW), 2 radiologists (AB, GB), 1 surgeon (AJ) and 2 dermatologists (OB, AM) reviewed the cases to classify the lesions. All doubtful cases were excluded.

Diagnostic criteria

The experts pre-defined diagnostic criteria. Clinical characteristics that fit the diagnosis of ICTH were the occurrence of a mass underlying normal skin. ICTH was excluded in the presence of skin necrosis, a port-wine stain, a skin blue color, a segmental overgrowth or any kind of hamartoma.

MRI data with good-quality imaging was mandatory. Lesions should be well defined and/or with a fatty border, hyperintense on T2-weighted images, with hypointense flow voids, isodense to skeletal muscle on T1-weighted images, with a hypervascularization and homogeneous contrast enhancement. Fat may be present.

Exclusion criteria included signs of venous malformations (well-lobulated T2-weighted hyperintense lesion with phleboliths), signs of FAVA (hypersignal "spot") or phosphatase and PTEN-related hamartomatous tumour syndrome (muscle hypertrophy in the whole muscle segment). When ultrasonography was performed, criteria were a non-compressible mass within the skeletal muscle and color and spectral Doppler ultrasonography showing arterial-type vascularization.

Angiography could show enlarged feeder arteries and non-homogeneous but non-tortuous parenchymal arterial afferents, with tissue reddening without early drainage of the venous phase of the tumour.

Pathological features were required if imaging was questionable and had to be compatible if a biopsy had been performed. The core diagnostic criteria were endothelial cell hyperplasia (staining for CD31+), capillaries with bulky endothelium separating skeletal muscle fibres, without clusters of large ectatic vessels, and lesioned endothelial cells staining negative for GLUT-1 and without overexpression of D2-40. Presence of calcifications (phleboliths), bundles of smooth muscle fibres not in the walls or clusters of ectatic vessels were exclusion criteria. Molecular data were not mandatory.

Statistical analyses

Statistical analyses were mainly descriptive. Categorical variables are expressed with number (percentages) and quantitative variables with median (interquartile range [IQR]). We used R v3.6.2 for analysis.

RESULTS

Among 133 patients assessed for eligibility, with history obtained from 9 centers, 66 were included (**Figure 1**). The main reasons for exclusion were not enough data to allow for diagnosis (n=23), intramuscular venous malformations (n=19), non-intramuscular lesions (n=10) or lesions suggesting FAVA (n=6). Extracranial AVM was diagnosed in 2 cases.

Table 1 summarizes patients' characteristics. The median age at the first signs was 28.0 years (IQR 21.0–36.0; range birth to 58 years). The ratio of males/females was 1.28. The median time to diagnosis was 12 months (IQR 5.0–22.0).

ICTH was most commonly a progressive increasing mass (n=52/62, 83.9%), very rarely warm (n=2/64, 3.1%), and with a firm consistency (n=5/6, 83.3%); it was mostly painless (n=56/63, 88.9%) (**Table 1**). A triggering factor was suggested in 8 (12.1%) cases, in particular pregnancy (n=4) and local trauma (n=3). ICTH could occur all over the body, but the most affected body region was the head and neck area (n=28/66, 42.4%). Overall, 31 muscles or muscle groups with ICTH were reported among the 61 cases that included description of the affected muscle(s) (**Fig. 2A**, **2B**). The most commonly affected muscle was the masseter (n=12).

On MRI, the most common features were a well-delineated mass (n=43/49, 87.8%) that was homogeneous (26/43, 60.5%), isointense on T1-weighted images (n=14/22, 63.6%), always displaying hypersignals on T2-weighted images and after contrast enhancement, showing high and homogenous contrast enhancement (n=13/39, 33.3%). Most (83.3%; n=45/54) cases showed flow voids. Angiography was performed in 21.3% of cases (n=13/61), mostly describing highly vascularized lesions with no nidus, inhomogeneous parenchymal staining and emerged arterial feeders. Ultrasonography was performed in 46 (69.7%) cases describing mainly a hyperechogenic lesion (n=14, 87.5%) with a high resistance index (n=5, 55.6%).

We had pathology data from biopsy or surgical excision for 81% of cases (n=51/63) (**Table 1**). Descriptions mainly included capillary proliferation (n=14/30, 46.7%), with small-

size and concomitant other-sized vessels in 86.1% of cases (n=31/36) and presence of adipose tissue in 75.7% (n=28/37). A lobulated architecture was reported in 35.5% of cases (n=11) and endothelial cells between muscle fibres in 17.9% (n=5). On immunostaining, when described, all cases were negative for GLUT-1 and positive for ERG, AML, CD31 and CD34. The Ki67 proliferation index was < 10% in all cases.

Surgery was the most frequent intervention: 11/47 (23.4%) cases had complete surgery alone, 6 (12.8%) preceded by embolization, and allowed for total regression in all cases **(Table 2).** Embolization alone (n=6, 12.8%) resulted in complete regression in one case (16.7%). The 13 cases with therapeutic abstention and follow-up showed no spontaneous regression, and 3 (23.1%) even continued to increase in size. Sirolimus, prescribed at 0.1 mg/day for 6 months in one patient was inefficient. The median post-treatment follow-up was 17.0 months (IQR 8.5-31.0). Three serious adverse events occurred after treatment: major bleeding that required transfusion during partial surgical removal alone, bilateral cerebellar ischemia after embolization alone and haemorrhagic shock during surgery the day after an embolization. No patient died.

DISCUSSION

This retrospective French cohort is the largest reported in the literature and aimed to include all ICTH cases observed in tertiary centers for vascular anomalies and, more globally, all cases of SPEFIL for better understanding these lesions.

The 66 cases included mostly young adults, and lesions presented as a progressively enlarging, firm and painless mass, mostly affecting the head and neck region, especially the masseter muscle. Intramuscular hemangioma is misnamed in the literature to actually describe different lesions; in this cohort, about half of the eligible cases were excluded because they were venous malformations, FAVAs or soft-tissue angiomatosis under this denomination. Intramuscular venous malformations are cavernous vascular anomalies that appear as heterogeneous masses on MRI, are not fast-flowing, and can have phleboliths because of localized intravascular coagulopathy[10,11] . Usually they appear as round hypointense areas on

T1- and T2-weighted MRI images, arguing for in fact a venous malformation[5,13]. In FAVAs, MRI features show a heterogeneous lesion containing rounded areas of low signal within the lesion corresponding to large dysplastic veins, typical of this disease. Histology is mandatory for the diagnosis and reveals mixed fibrous and adipose tissue, specific to this diagnosis, with abnormal veins that are often thin-walled and dysplastic[7]. Also, soft-tissue angiomatosis (Rao and Weiss type) is a fairly common vascular malformation in children and young adults, well defined histologically, but often unrecognized. It is characterized by the presence of a constellation of vascular elements of varied appearance, often with a lymphoid and/or lymphatic component[14]. Many of these lesions could be linked to a mutation in the PTEN gene[15], thus expanding the phenotype of PTEN hamartoma–tumour syndrome[10].

In most cases, MRI images interpreted by expert radiologists are sufficient for the diagnosis of SPEFIL. The most important characteristics of these lesions are that they are well-defined masses, with the presence of flow voids, and with avid homogeneous enhancement. The mass is globally homogeneous, but with the presence of fatty foci or flow voids, it is discreetly heterogeneous. One difficulty might be to distinguish SPEFIL from soft-tissue sarcoma on MRI; then biopsy is necessary[16].

Among the 66 cases, the expert group identified 59 typical cases of ICTH (**Figure 3**) and 7 atypical cases that showed features overlapping AVM and ICTH, which we called the pseudo-AVM type (**Figure 4**). Lesions in the pseudo-AVM type have the same pathological description but are larger than in typical cases, are more often painful and have moderate enhancement on MRI. The description of both types such as identified by the expert group is in Table 3. Extracranial AVMs have similar features as the pseudo-type ICTH and might be present at birth or be revealed at a later age. They increase in size progressively and tend to recur after surgery[17], although surgery is the recommended treatment for ICTH, when possible. The presence of rapid arteriovenous shunting, enlarged arterial and multiple collateral supply are the main discriminating data for a positive diagnosis of extracranial AVM[18]. The findings of Goss et al., identifying *KRAS* and *MAPK* somatic mutations usually found in extracranial AVMs in certain ICTHs, need to be confirmed because they would have

potential impact, beyond the nosological aspect, on the future use of targeted therapies for non-operable mutated ICTH[19]. Further molecular investigations are needed in typical and pseudo-AVM ICTHs.

A traumatic factor and pregnancy were reported as potential triggering factors in 8 of our cases. Four additional cases after pregnancy were reported in the literature[20]. This observation might be fortuitous but needs to be kept in mind because trauma and hormonal changes are also potential triggering factors for extracranial AVMs [21,22].

The study has some limitations, such as biases linked to its retrospective nature, which inevitably induces missing data. Also, the choice to exclude lesions with cutaneous extension may not have taken into account lesions corresponding to the same spectrum.

In conclusion, SPEFIL includes 2 different subtypes of ICTH: the typical and the pseudo-AVM type. MRI is the most useful examination for diagnosis, and biopsy is required in case of persistent doubt. Surgery, preceded or not by embolization, seems the best treatment, although hemorrhagic complications might occur.

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Abbreviations

IMH: Intramuscular hemangioma

ICTH: Intramuscular capillary-type hemangioma

IVM: Intramuscular venous malformation

PTEN: Phosphatase and TENsin homolog

AVM: Arteriovenous malformation

FAVA: Fibro-adipose vascular anomaly

PHOST: Phosphatase and tensin homolog (PTEN) hamartoma of the soft tissue

TABLES

Table 1. Clinical, imaging, pathological and molecular data of intramuscular capillary hemangioma (ICTH) (n=66 patients)

Variable	Description	Missing data
PATIENT CHARACTERISTICS		
City, n (%)		0
Nantes	1 (1.5)	
Reims	1 (1.5)	
Rennes	1 (1.5)	
Bordeaux	2 (3)	
Marseille	3 (4.5)	
Tours	6 (9)	
Lyon	14 (21.2)	
Paris	38 (54.5)	
Sex, n (%)		0
Females	29 (43.9)	
Males	37 (56.1)	
Age at first signs, years, median [IQR]	28.0 [21.0-36.0]	13
Age at diagnosis, years, median [IQR]	29.7 [23.0-37.9]	0
Diagnostic delay, months, median [IQR]	12.0 [5.0-22.0]	13
CLINICAL DATA		
Lesion size		37
Area (mm^2), median [IQR]	1950.0 [1125.0, 4225.0]	
Largest diameter (mm), median [IQR]	60.0 [40.0, 74.0]	
Pain, n (%)	7 (11.1)	3
Reported discomfort, n (%)	9 (14.3)	3
Topography, n (%)		0
Head and neck	28 (42.4)	
Trunk	10 (15.2)	
Lower limb	15 (22.7)	
Upper limb	13 (19.7)	
Progressive increase, n (%)	52 (83.9)	4
Rapid increase, n (%)	8 (12.9)	
No increase, n (%)	2 (3.2)	
Warmth, n (%)	2 (3.1)	2
Firm consistency, n (%)	5 (83.3)	60
Soft consistency, n (%)	1 (16.7)	
Identified triggering factor, n (%)	8 (12.1)	26
Pregnancy	4	
Trauma	3	
Erythema migrans on tick bite	1	
IMAGING DATA		
MRI, n (%)	66 (100)	0
Description of the mass		
Well-delineated mass	43 (87.8)	17
Heterogeneous mass	17 (39.5)	23
Homogeneous mass	26 (60.5)	23
T1-weighted sequence description		44
Hyperintense signals	3 (13.6)	
Hypointense signals	5 (22.7)	
Isointense signal	14 (63.6)	
T2-weighted sequence description		8
Hyperintense signals	58 (100)	
Contrast enhancement	39 (100)	27

High contrast	8 (20.5)	
High contrast and homogeneous	13 (33.3)	
Moderate	3 (7.7)	
Flow voids	45 (83.3)	12
CT scan, n (%)	15 (22.7)	0
Angiography, n (%)	13 (21.3)	5
Echo Doppler ultrasonography, n (%)	46 (69.7)	0
Hyperechogenic	14 (87.5)	50
Isoechogenic	1 (6.2)	50
Hypoechogenic	1 (6.2)	50
Heterogeneity of signals	3 (75.0)	62
High resistance index	5 (55.6)	57
Intermediate resistance index	3 (33.3)	57
Low resistance index	1 (11.1)	57
PATHOLOGY AND MOLECULAR DATA		
Biopsy or excision performed, n (%)	51 (81.0)	3
Biopsy only performed, n (%)	34 (54.0)	3
Compatible ICTH diagnosis	10 (28.6)	
Evoke ICTH diagnosis	24 (68.5)	
Confirmation of diagnosis if excision, n (%)	22 (100.0)	44
Presence of adipose tissue, n (%)	28 (75.7)	29
Description of the vessel size, n (%)	36 (54.5)	30
Small vessels only	5 (13.9)	
Small and larger vessels	31 (86.1)	
Lobulated architecture, n (%)	11 (35.5)	35
Enlarged capillaries, n (%)	3 (10.7)	38
Endothelial cells between muscle fibres, n (%)	5 (17.9)	38
Capillary proliferation, n (%)	14 (46.7)	
Immunostaining, n (%)		36
GLUT-1–negative	9 (100.0)	
ERG-positive	3 (100.0)	57
CD31-positive	8 (100.0)	63
CD34-positive	9 (100.0)	58
D240-negative	3 (37.5)	57
D240-slightly positive	5 (62.5)	58
AML-positive	2 (100.0)	58
KI67 <10%	3 (100.0)	64
Search for somatic mutations, n		63
MAP2K1 and *KRAS* negative	1	
PTEN and *PIK3CA* negative	1	

Table 2. Management and outcomes of ICTH (n=47 patients)

Therapy, n (%)		Outcome, n (%)				
	Total regression	**Partial regression**	**Stabilisation**	**Increase**	**Missing data**	**Serious adverse event**
Complete surgical removal alone, 11 (23.4)	4	0	0	0	7	0
Partial surgical removal alone, 7 (14.9)	0	2	1	2	2	1 major bleeding requiring transfusion
Embolization alone, 6 (12.8)	1	3	2	0	0	1 bilateral cerebellar ischemia
Embolization followed by complete surgery, 6 (12.8)	5	0	0	0	1	1 haemorrhagic shock
Sclerotherapy, 1 (2.1)	0	0	1	0	0	0
Cryosurgery followed by embolisation, 1 (2.1)	0	0	1	0	0	0
Medical care, 2 (4.3) Propanolol Sirolimus	0	1		1	0	0
Therapeutic abstention and follow-up, 13 (27.7)	0	0	10 (76.9)	3 (23.1)	0	0

ICTH, intramuscular capillary hemangioma

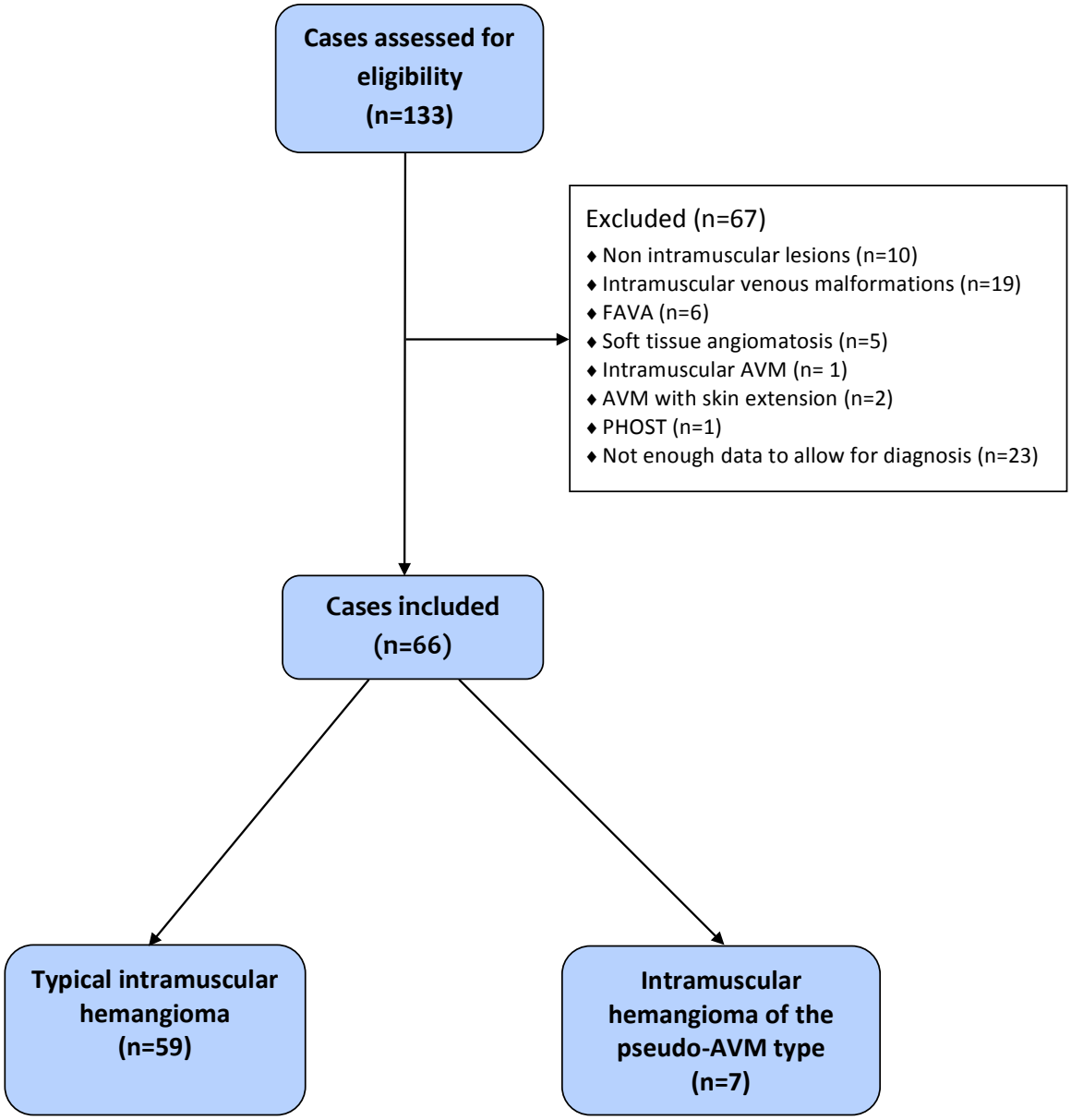
Table 3. Clinical, imaging, radiological, pathological criteria to for diagnosis of "spectrum of fast-flow intramuscular lesions" (SPEFIL)

	Typical ICTH type	Pseudo-AVM type	Extracranial AVM
Clinical	-Ubiquitous, prefentially head and neck - Progressive increase, painless	- Ubiquitous without reaching limb extremities. - Progressive or rapid increase, painful	- Head and neck and limb extremities - Rapid and painful increase
MRI	- Intense and homogeneous contrast enhancement - Well-limited lesion in the muscles -Isointense to muscle on T1/hyperintense on T2-weighted images - Flow voids	- Moderate contrast enhancement - More or less well-limited lesion - Flow voids	- Involvement of surrounding soft tissue - Poorly limited lesion - Flow voids
Angiography	- Highly vascularized lesions without nidus - Inhomogeneous parenchymal staining - Emerged arterial feeders	-High vascularisation with early venous return - Feeding by an artery that may be displastic - Arteriovenous shunt possible	- Rapid arteriovenous shunt - Expanded arterial supply - Multiple collaterals - Ectatic draining veins
Pathology	- Proliferation of small capillaries with lobulated architecture without mitotic activity. - Endothelial cells between muscle fibres - Presence of adipose tissue - Possible lymphatic component - GLUT-1–negative, vascular markers positive	- Lack of mitotic activity - Little or no adipose tissue - Possible lymphatic component - GLUT-1–negative, vascular markers positive	-Large vessels with features of arteries and veins often in the same section - Extensive intimal cell hyperplasia - Small aggregates of compact masses of endothelial-appearing cells scattered in vessels and subcutaneous tissue

ICTH, intramuscular capillary hemangioma; AVM, arteriovenous malformation

FIGURE LEGENDS

Figure 1. Flow of participants in the study



FAVA: Fibro-adipose vascular anomaly

AVM: Arteriovenous malformation

PHOST: Phosphatase and tensin homolog (PTEN) hamartoma of the soft tissue

Figure 2. (A) (B). Muscles affected by intramuscular capillary hemangioma (barplot)

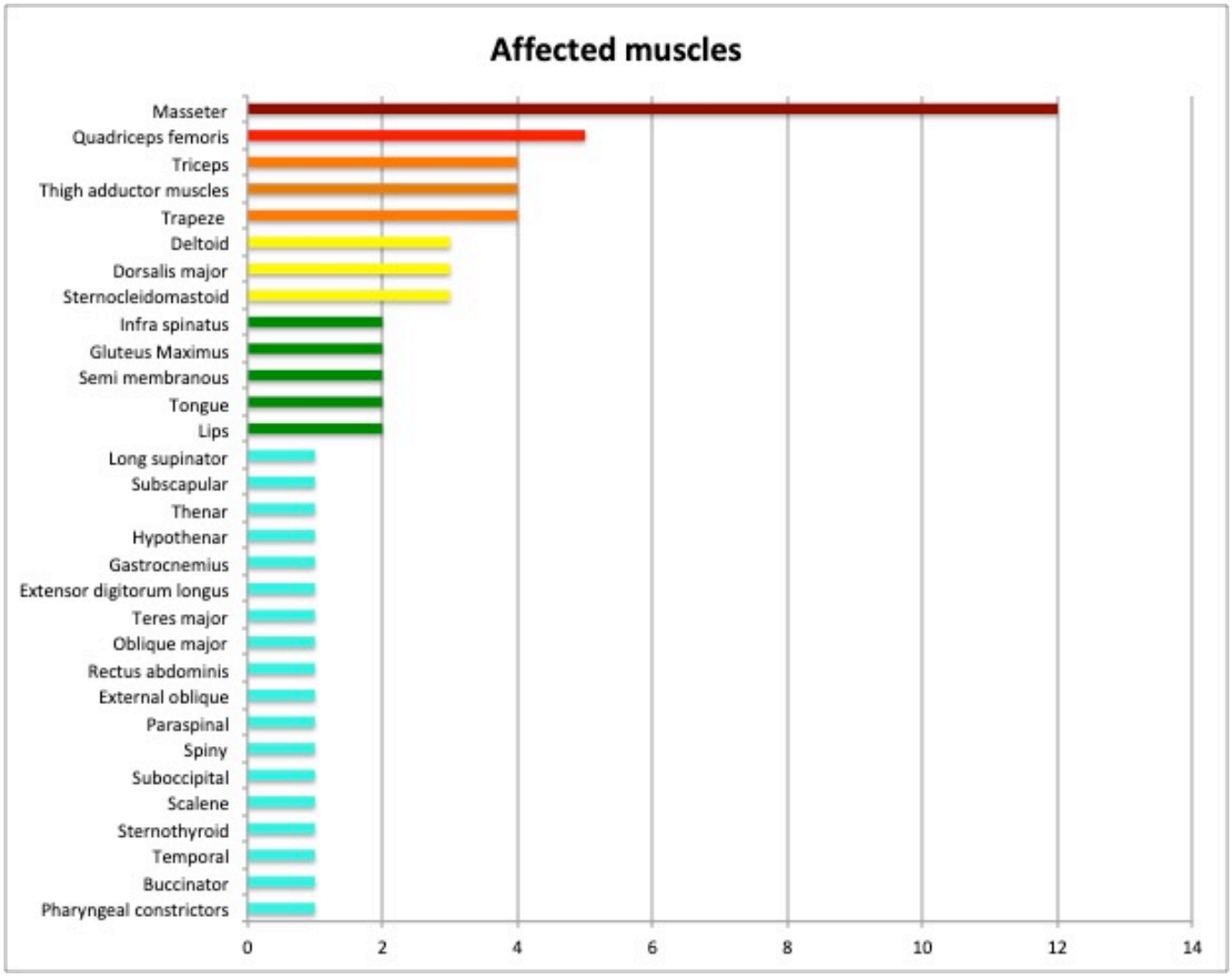


Figure 2 (B). Muscles affected by intramuscular capillary hemangioma (schematic of the human body)

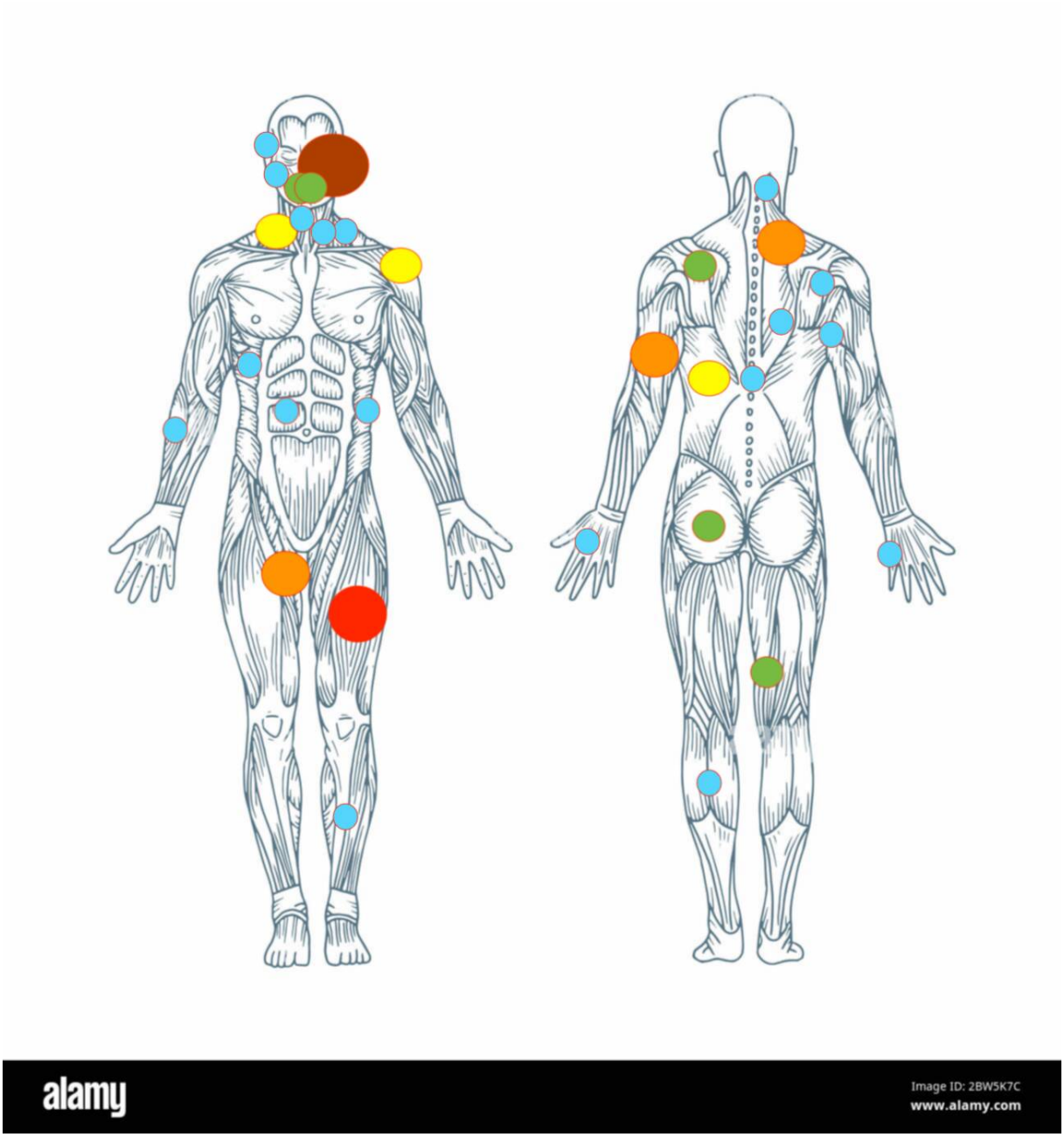


Figure 3. MRI of a typical intramuscular capillary hemangioma, showing a well-limited T2-weighted lesion with a central rounded “pinhead” hyposignal corresponding to a flow void (a), T1 isosignal (b), strongly and homogeneously contrast-enhanced after injection. **(A)** T2-weighted image; **(B)** T1-weighted image; **(C)** T1-weighted image after contrast enhancement

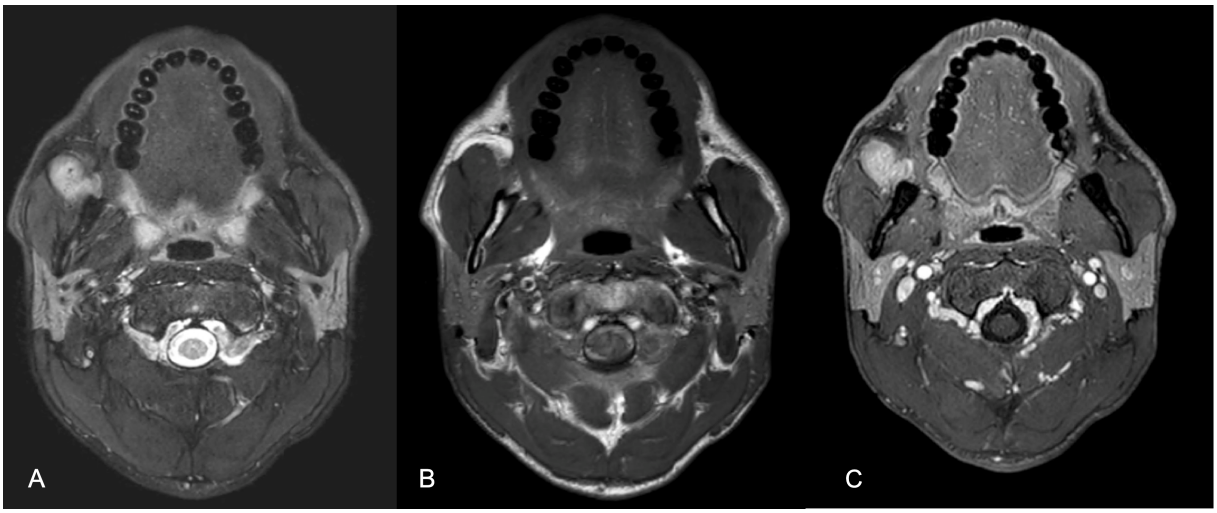
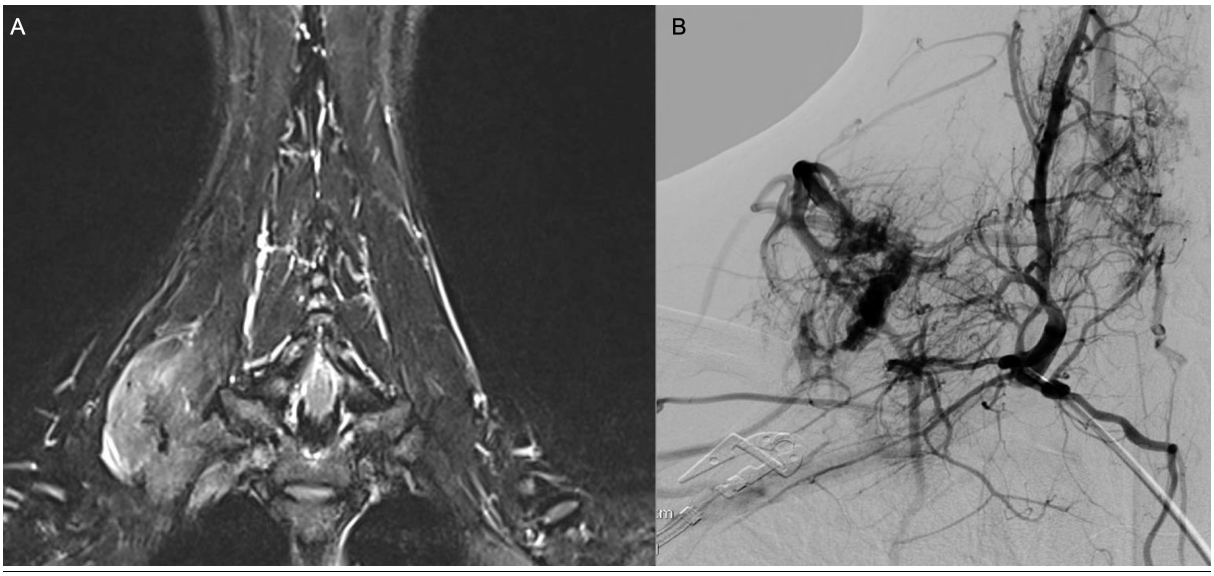


Figure 4. MRI imaging of a pseudo-arteriovenous malformation intramuscular capillary hemangioma showing a rather well-limited lesion in T2-weighted hypersignal to the trapezius muscle (a), with pathological hypervascularisation on angiography from scapular and cervical branches with a fistulous area (b). **(A)** T2-weighted image on MRI; **(B)** Angiography



Supplemental file 1. Opinion of the ethics group

CHRU HÔPITAUX DE TOURS

FACULTÉ DE MÉDECINE TOURS

GROUPE ETHIQUE D'AIDE A LA RECHERCHE CLINIQUE POUR LES PROTOCOLES DE RECHERCHE NON SOUMIS AU COMITE DE PROTECTION DES PERSONNES
ETHICS COMMITTEE IN HUMAN RESEARCH

AVIS

Responsable de la recherche : Pr Annabel MARUANI / Jordan ORLY
Titre du projet de recherche : Spectre des lésions intramusculaires à débit rapide : étude multicentrique rétrospective française (étude SPID)

N° du projet : 2021 014

Le groupe éthique d'aide à la recherche clinique donne un avis

X FAVORABLE

☐ **DÉFAVORABLE**

☐ **SURSIS A STATUER**

☐ **DÉCLARATION D'INCOMPÉTENCE**

au projet de recherche n° 2021 014

A Tours, le 29/04/2021

Dr Béatrice Birmelé
Présidente du Groupe Ethique Clinique

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VIII. CONCLUSION GÉNÉRALE

Depuis sa première description par Allen et Enzinger, en 1972, l'HITC reste mal défini et mal compris. Ces deux études en ont permis une meilleure caractérisation : l'HITC peut survenir à tout âge mais surtout chez les jeunes adultes et se présente cliniquement souvent sous la forme d'une masse ferme, indolore, augmentant progressivement, située principalement dans un muscle de la région tête et cou (en particulier le muscle masseter). L'IRM est l'imagerie indispensable pour le diagnostic, montrant les caractéristiques d'une lésion hypervasculaire bien délimitée, isointense sur les images pondérées en T1, hyperintense sur les images pondérées en T2, rehaussée de manière intense et homogène après injection de produit de contraste et montrant des flow voids. L'analyse histopathologique est également utile pour le diagnostic, comprenant principalement une prolifération de cellules des vaisseaux capillaires, avec présence concomitante possible, dans une moindre mesure, de vaisseaux de plus grosses tailles. L'identification d'une architecture lobulée avec des cellules endothéliales entre les fibres musculaires est un critère de différenciation important.

Dans la littérature comme dans notre cohorte, l'HITC est souvent diagnostiqué à tort. Son principal diagnostic différentiel est la malformation veineuse intramusculaire, également appelé ''hémangiome caverneux''. La présence d'un flux plus lent et de phlébolites permet de s'orienter vers ce diagnostic.

En ce qui concerne le traitement, l'exérèse chirurgicale, lorsqu'elle est possible, semble être la meilleure thérapie, et peut être précédée d'une embolisation pour contrôler l'hémorragie. Contrairement aux malformations artérioveineuses extracrâniennes, aucune exacerbation des lésions n'a été décrite après embolisation seule ou excision partielle.

Dans 6 cas d'HITC, des mutations somatiques dans les gènes *KRAS* et *MA2PK1*, similaires aux malformations artérioveineuses extracrâniennes, ont été identifiées, suggérant une pathogenèse commune ou un spectre de lésions commun intégrant les HITC et les malformations artérioveineuses, et remettant ainsi en question la dichotomie entre anomalies

vasculaires tumorales et malformatives. Dans notre cohorte recensant des cas entrant dans le spectre des lésions à débit rapide purement intramusculaires, un sous-groupe « HITC typique » s'est démarqué d'un autre que nous avons appelés « HITC de type pseudo-MAV ». Ce dernier correspond à des HITC, avec certaines caractéristiques proches d'une MAV. Il est important, dans le futur, d'obtenir une meilleure caractérisation moléculaire de ces deux groupes.

IX ANNEXES

Fichier supplémentaire : Avis du groupe d'éthique

GROUPE ETHIQUE D'AIDE A LA RECHERCHE CLINIQUE POUR LES PROTOCOLES DE RECHERCHE NON SOUMIS AU COMITE DE PROTECTION DES PERSONNES
ETHICS COMMITTEE IN HUMAN RESEARCH

AVIS

Responsable de la recherche : Pr Annabel MARUANI / Jordan ORLY
Titre du projet de recherche : Spectre des lésions intramusculaires à débit rapide : étude multicentrique rétrospective française (étude SPID)

N° du projet : 2021 014

Le groupe éthique d'aide à la recherche clinique donne un avis

X FAVORABLE

☐ **DÉFAVORABLE**

☐ **SURSIS A STATUER**

☐ **DÉCLARATION D'INCOMPÉTENCE**

au projet de recherche n° 2021 014

A Tours, le 29/04/2021

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Atlas

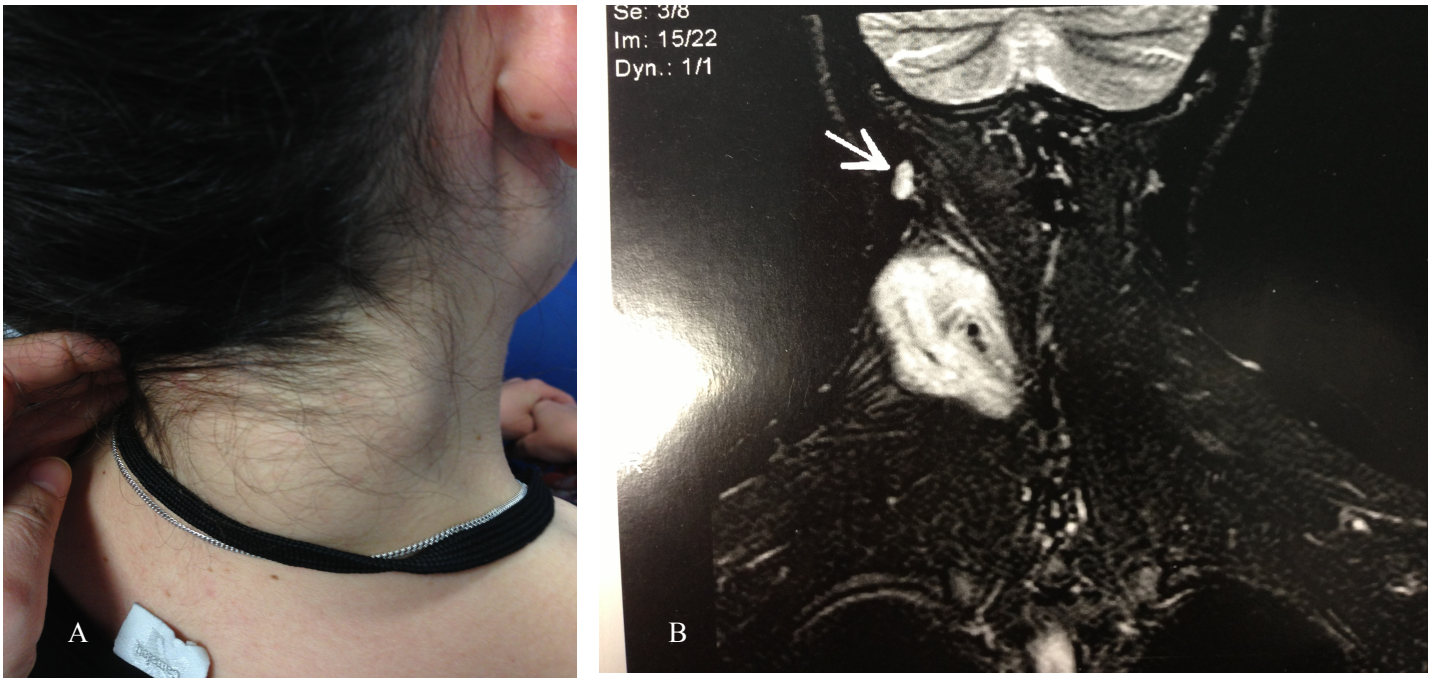

Figure 1 : Hémangiome intramusculaire de type capillaire du muscle trapèze droit chez une femme de 28 ans. Cliniquement (A), il existait une augmentation progressive et indolore dans la région cervicale droite depuis un an. Sur l'IRM en séquence T1 Fat Sat (B), la lésion forme une masse bien délimitée, avec précence de flow voids en son centre.

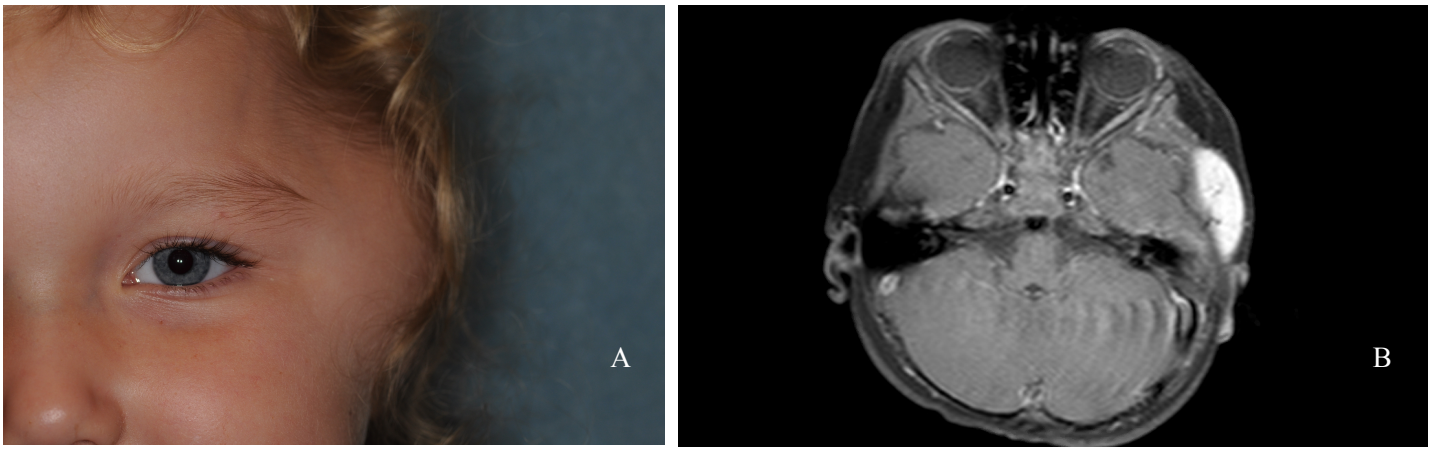

Figure 2 : Hémangiome intramusculaire de type capillaire du muscle temporal gauche chez une fillette de 2 ans. Cliniquement (A), il existait une augmentation progressive et indolore depuis l'âge de 2 mois. Sur l'IRM en séquence T1 après injection de produit de contraste (B), on identifie une masse bien limitée, prenant le contraste de façon intense et homogène, sans atteinte cutanée.

DÉFINITIONS

Anomalie vasculaire fibro-adipeuse (FAVA) est une entité caractérisée par des masses fibro-graisseuses anormales et une infiltration dans le plan intramusculaire et sous-cutané. Des canaux veineux anormaux sont présents, sous la forme de phlébectasies à l'intérieur des masses. Le processus fibrotique conduit à la contraction des muscles concernés, ce qui entraîne une restriction des mouvements. Comme le mollet et le gastrocnémien sont les régions les plus fréquemment touchées, le processus fibrotique entraîne souvent une déformation équine et une marche sur les orteils. La lésion est également associée à une douleur continue qui est multifactorielle (phlébolithes, contracture musculaire…).

Le syndrome tumoral hamartomateux lié à PTEN (STHP) est le terme regroupant des troubles cliniquement hétérogènes ayant en commun une mutation germinale du gène *PTEN* et une atteinte des dérivés des trois feuillets embryonnaires qui se manifeste par des hamartomes, une croissance excessive et potentiellement une néoplasie. Actuellement, les syndromes de Cowden, de Bannayan-Riley-Ruvalcaba, de Protée, de Proteus-like et de SOLAMEN sont classés dans le STHP.

L'angiomatose des tissus mous (ATM) est une malformation vasculaire qui se manifeste cliniquement chez l'enfant ou l'adulte jeune. Elle forme une masse, d'apparition parfois rapide, dans un muscle ou dans le tissu sous cutané, atteignant plus rarement la peau. Elle est révélée par sa taille ou par des douleurs, majorées par l'exercice. Sur les images IRM, elle évoque essentiellement une malformation veineuse, d'aspect cependant un peu atypique (plus hétérogène). Le diagnostic est histologique, basé sur la présence concomitante de plusieurs éléments comme une lésion multinodulaire, des structures veineuses anormales d'épaisseur irrégulière, un aspect en nid d'abeilles de vaisseaux à paroi épaisse, une involution adipeuse et de la fibrose.

Le termes « flow voids », signifiant littéralement « vide de flux », est un terme IRM, généralement synonyme de perméabilité vasculaire, représentant une perte normale de signal en IRM liée au sang des vaisseaux s'écoulant rapidement.

Vu, le Directeur de Thèse

Vu, le Doyen
De la Faculté de Médecine de
Tours Tours, le

ORLY Jordan

76 pages – 6 tableaux – 6 figures – 3 fichiers supplémentaires – 2 illustrations

Caractéristiques et prises en charge de l'hémangiome intramusculaire de type capillaire: une revue systématique de la littérature et une cohorte rétrospective française multicentrique.

Introduction. Les hémangiomes intramusculaires sont des anomalies vasculaires rares qui peuvent facilement être diagnostiquées à tort comme d'autres entités. La définition a évolué au fil des années, ce qui a conduit à une entité mieux définie appelée hémangiome intramusculaire de type capillaire (HITC). Nous avons cherché à étudier les caractéristiques cliniques, radiologiques, pathologiques et moléculaires de l'HITC, ainsi que les traitements et les résultats.

Méthodes. Nous avons effectué une revue systématique de tous les cas rapportés comme hémangiome intramusculaire dans la littérature depuis sa première description en 1972. Un comité d'adjudication a examiné tous les cas pour n'inclure que les cas d'HITC.

Résultats. Parmi les 1 143 rapports examinés, 43 articles ont été inclus pour l'analyse, impliquant 75 patients. Le diagnostic différentiel le plus fréquent était les malformations veineuses intramusculaires. L'âge moyen des patients au moment du diagnostic était de 21,2 ans. L'HITC a été principalement décrit comme une masse augmentant progressivement (n=36/44, 81,8%), le plus souvent indolore (n=34/46, 73,9%), qui pouvait se produire n'importe où dans le corps mais le plus souvent dans la région tête et cou (n=33/75, 44,0%). L'IRM a été principalement utilisée pour le diagnostic (n=47/68, 69,1%), et les caractéristiques IRM les plus courantes étaient : une masse bien délimitée avec des signaux hétérogènes, isointense sur les images pondérées en T1, présentant toujours des hypersignaux sur les images pondérées en T2 et prenant le contraste après injection. Le traitement le plus fréquent était l'ablation chirurgicale complète (n=34, 73,9%), qui pouvait être précédée d'une embolisation (n=5), et a conduit à une rémission complète sans récidive dans tous les cas sauf un.

Conclusion. Les relations pathogéniques entre les HITCs et les malformations artérioveineuses (MAVs) ne sont pas encore claires, cependant, la nature peu agressive et le faible taux de récidive après chirurgie des HITCs les distinguent cliniquement des MAVs habituelles.

Mots clés : Hémangiome intramusculaire ; hémangiome intramusculaire de type capillaire ; débit rapide ; malformation vasculaire intramusculaire ; malformation artério-veineuse extracrânienne ; anomalie vasculaire intramusculaire à débit rapide.

Jury :

Président du Jury :	Professeur Gérard LORETTE
Directeur de thèse :	Professeur Annabel MARUANI
Membres du Jury :	Docteur Patrick MICHENET
	Docteur Aline JOLY
	Docteur Sophie LEDUCQ

Date de soutenance : le 20 septembre 2022