Doctoral Thesis

Subcutaneous granuloma annulare versus subcutaneous vascular anomalies: Is there a way to simplify the diagnostic difficulties, increase the diagnostic accuracy, and therefore facilitate the appropriate management.

submitted by

Besiana P. BEQO

for the Academic Degree of

Doctor of Medical Science
(Dr. scient. med.)

at the

Medical University of Graz
Department of Paediatric and Adolescent Surgery

under the Supervision of
Priv.-Doz. Dr. med. univ. Emir Q. HAXHIJA

2023

Declaration

I hereby declare that this thesis is my own original work and that I have fully acknowledged by name all individuals and organisations that have contributed to the research for this thesis.
Due acknowledgment has been made in the text to all other material used. Throughout this thesis and in all related publications I followed the guidelines of "Good Scientific Practice and Ombuds Committee at the Medical University of Graz".

This thesis reproduces parts of the following publications, all authored by the doctoral candidate. All articles are open access articles (copyright lies with the authors) distributed under the terms and conditions of the Creative Commons Attribution (CC.BY 4.0). All four publications are included in this cumulative dissertation and are preceded by a preamble describing the flow of the results which led to the respective publications.

I. **Beqo BP,** Tschauner S, Gasparella P, Brcic I, Singer G, Till H, Haxhija EQ. Granuloma anulare bei Kindern: eine seltene Läsion. Paediatr. Paedolog. 57, 125–130 (2022). doi:10.1007/s00608-022-00985-y.
II. **Beqo BP**, Tschauner S, Gasparella P, Brcic I, Haxhija EQ. The epifascial cap: A typical imaging sign for subcutaneous granuloma annulare in children. Front Pediatr. 2023 Mar 21;11:1069428. doi: 10.3389/fped.2023.1069428. PMID: 37025295; PMCID: PMC10071042
III. **Beqo BP,** Gasparella P, Flucher C, Tschauner S, Brcic I, Haxhija EQ. Subcutaneous Granuloma Annulare vs. Subcutaneous Vascular Malformations in Children: A Diagnostic Challenge. Children. 10, 362 (2023) doi:10.3390/children10020362. PMID:36832491; PMCID: PMC9955411
IV. **Beqo BP**, Haxhija EQ. Subcutaneous Granuloma Annulare in an Atypical Age Group in Immediate Post-Covid-19 Phase. *Dermatol Pract Concept.* 2023;13(2):e2023172. doi: 10.5826/dpc.1302a172. Accepted: March 20, 2023; Published: April 2023

As to the Journals` policies the copyright for the illustrations remains with the authors.
See also the original publications.

During the years 2021 and 2022 this work has been presented by me on several national and international scientific meetings listed below:

1. Beqo B, Haxhija EQ. Localized and Subcutaneous Granuloma Annulare in Childhood: An Institutional Review.
   10. – 13.11.2021; Melbourne, Australia, 13th International Congress of Dermatology
2. Beqo BP, Tschauner S, Haxhija EQ. Subcutaneous "Epifascial Cap" as the Pathognomonic Imaging Sign of Subcutaneous Granuloma Annulare in Childhood – First Description!
   15. - 17.06.2022; Graz, Austria. 63rd Annual Congress of Austrian Surgeons Society
3. Beqo BP, Tschauner S, Haxhija EQ. Imaging signs for granuloma annulare – epifascial mound sign, and subdermal inverse mound sign: first descriptions!
   13. - 17.07.2022; Vienna, Austria. European Congress of Radiology ECR 2022
4. Beqo BP, Tschauner S, Gasparella P, Haxhija EQ. Subcutaneous granuloma annulare can be distinguished from subcutaneous vascular anomalies by the epifascial mound sign in the imaging.
   07. - 11.10.2022; Barcelona, Spain. 9th Congress of the European Academy of Paediatric Societies

I am immensely grateful to the entire vascular anomalies team at the Pediatric Center of the Medical University of Graz for welcoming me into several projects within the field of vascular anomalies. My participation in these ongoing endeavors not only earned me co-authorship in various colleagues' manuscripts, all focusing on the topic of vascular anomalies, but also significantly broadened my understanding of this scientific domain.
In addition, I was fortunate to have the opportunity to explore additional research questions and complete a body of work that culminated in 4 manuscripts accepted for publication.
I sincerely appreciate the support and collaborative spirit of the vascular anomalies team, which has greatly enriched my doctoral journey.

1. Gasparella P, **Beqo BP,** Haxhija EQ, Castellani C, Arneitz C, Sorantin E, Kampelmühler E, Singer G, Till H. Chylous Content Might Determine the Optimal Surgical Approach for Mesenteric Lymphatic Malformations in Childhood. J Vasc Surg Venous Lymphat Disord. 2022 Mar;10(2):430-435. doi: 10.1016/j.jvsv.2021.06.008. Epub 2021 Jun 23. PMID: 34171533

2. Karastaneva A, Gasparella P, Tschauner S, Crazzolara R, Kropshofer G, Modl M, Pfleger A, Burmas A, Pocivalnik M, Ulreich R, Zenz W, Schwinger W, **Beqo BP,** Urban C, Haxhija EQ, Lackner H, Benesch M. Indications and Limitations of Sirolimus in the Treatment of Vascular Anomalies – Insights from a Retrospective Case Series. Front Pediatr. 2022 May 23;10:857436. doi: 10.3389/fped.2022.857436. PMID: 35676905
3. Gasparella P, Flucher C, **Beqo BP,** Schmidt B, Spendel S, Arneitz C, Till H, Haxhija EQ, Singer G. Outcome after Surgical Treatment of Venous Malformations of the Hand in Childhood. J Vasc Surg Venous Lymphat Disord. 2023 Mar 9: S2213-333X(23)00065-3. doi: 10.1016/j.jvsv.2023.02.004. PMID: 36906103
4. **Beqo BP,** Gasparella P, Flucher C, Spendel S, Quehenberger F, Haxhija EQ. Indications for surgical resection of complicated Infantile Hemangiomas in the β-Blocker's era: a Single-Institution Experience from a Retrospective Cohort Study. Int J Surg 2023 Mar 27. doi: 10.1097/JS9.0000000000000324. PMID: 36974689

The following co-authors listed below in alphabetical order, actively contributed to this doctoral thesis through their expertise, and authorize the use of their personal data:

- Dr. med. univ. Christina Flucher, Department of Paediatric and Adolescent Surgery, Medical University of Graz, Graz, Austria
- FOA Priv.-Doz. Dr. Emir Q. Haxhija, Department of Paediatric and Adolescent Surgery, Medical University of Graz, Graz, Austria.
- Assoz. Prof. Priv.-Doz. Dr.med.univ. Georg Singer, Department of Paediatric and Adolescent Surgery, Medical University of Graz, Graz, Austria.
- Univ. Prof. Dr. Holger Till, Department of Paediatric and Adolescent Surgery, Medical University of Graz, Graz, Austria.
- Univ. FÄ Priv.-Doz. DDr. Iva Brcic, Institute of Pathology, Medical University of Graz, Graz, Austria
- Dott. univ. Paolo Gasparella, Department of Paediatric and Adolescent Surgery, Medical University of Graz, Graz, Austria
- Univ. FA Priv.-Doz. DDr. Sebastian Tschauner, Division of Pediatric Radiology, Department of Radiology, Medical University of Graz, Graz, Austria

Disclosure

It is hereby that I confirm that all co-authors listed above, agree to the use of their published data in the present doctoral thesis and grant permission to reproduce text, figures, tables, data and interpretation of their published work.

MSc. Besiana P. Beqo, eh

Graz, 17.04.2023

. Desiana Deqo .

. Graz 2023 .

Table of Contents

Acknowledgments

This dissertation has been carried out in collaboration with the Doctoral School of "Bone, Muscle, and Joint" at the Medical University of Graz, Austria. The study has received approval from the Ethics Committee of the Medical University of Graz (EK-No. 33-126 ex 20/21).
Doctoral student Besiana P. Beqo was funded by the Medical University of Graz through the Doctoral School of "Bone, Muscle, and Joint." The funding body had no influence on the study design, data collection, analysis, interpretation, manuscript composition, or the decision to publish the results.

I would like to express my deepest gratitude to my family for their unwavering support throughout this journey. I also wish to extend my heartfelt thanks to all the co-authors whose invaluable assistance made the completion of this study possible. I am particularly grateful to my mentor, Emir Q. Haxhija, who expertly guided me through the entire process of my doctoral studies, ensuring that the work is coherent and easily comprehensible.

Furthermore, I would like to convey my appreciation to the entire staff of the Department of Pediatric and Adolescent Surgery at the Medical University of Graz for their valuable contributions to this study. Lastly, I am profoundly grateful to the Doctoral Program for Medical Science at the Medical University of Graz and its Doctoral School of "Bone, Muscle, and Joint" for their continuous support during my academic pursuit.

Thank You,

Besiana P. Beqo

Abbreviations and Definitions

AVM	Arterio-Venous Malformation
B	Biopsy
CE	Complete Excision
F	Female
GA	Granuloma Annulare
GGA	Generalized Granuloma Annulare
ISSVA	International Society for the Study of Vascular Anomalies
L	Left
LGA	Localized Granuloma Annulare
LM	Lymphatic Malformation
LVM	Lymphatico-Venous Malformation
M	Male
MRI	Magnetic Resonance Imaging
N	Number of patients
R	Right
SGA	Subcutaneous Granuloma Annulare
SVM	Subcutaneous Vascular Malformation
US	Ultrasound
VA	Vascular Anomaly
VM	Venous Malformation

Preamble

I. Introduction

The occurrence of lumps and bumps in children is common and their causes vary. One of the most frequent reasons is trauma. Some subcutaneous lumps are easily identifiable due to their specific appearance time or anatomical location and should not pose major diagnostic challenges. Examples include dermoid cysts in the eyebrow area and subcutaneous infantile hemangiomas in infants. Parents typically seek medical attention when one or more subcutaneous lumps persist or grow. Physicians make a differential diagnosis by evaluating clinical characteristics such as softness, firmness, mobility, or painfulness, as well as the lesion's history and anatomical location. Additionally, the vast majority of subcutaneous lesions in children can be evaluated accurately with sonographic imaging. This allows physicians to provide appropriate advice regarding the lesion's prospects, the possibility of observation, the need for excision without urgency, or the need for prompt intervention. Unfortunately, surgical intervention is sometimes performed unnecessarily, as in the case of subcutaneous granuloma annulare (SGA), due to diagnostic challenges and the rarity of this diease.

While benign subcutaneous lumps such as low-flow subcutaneous vascular malformations (SVMs) may require surgical resection at some point because of their continuous growth, others, like SGA, can only be observed because they self-resolve over time. However, accurately distinguishing between these two lesions presents a major clinical challenge, especially when evaluating a child with SGA, which is often mistaken for a low-flow SVM [1].

i. SGA

Granuloma annulare (GA) is a self-limiting granulomatous disease of unknown etiology that affects the skin and/or subcutaneous tissue [2]. The subcutaneous variant of GA occurs exclusively in children and presents as one or multiple immobile, painless subcutaneous lumps, primarily located on the extremities or scalp of otherwise healthy children. Due to its rarity and firm consistency, accurately diagnosing SGA poses a significant clinical challenge, as it is often mistaken for a malignancy [3]. Furthermore, SVMs with low-flow characteristics are among the primary differential diagnoses of SGA, typically determined after patient evaluation using ultrasound and magnetic resonance imaging (MRI) [1].

ii. SVM

Subcutaneous vascular malformations are a subset of a larger family of vascular anomalies (VAs) that may persist throughout a person's life and often grow proportionally with the patient's growth [4]. Some VAs grow faster than children, and therefore, require accurate and early diagnosis to ensure appropriate treatment and successful disease management. VAs consist of two major groups of clinical entities: 1) vascular tumors and 2) vascular malformations. These groups are further classified into many specific clinical and histopathological diseases by the International Society for the Study of Vascular Anomalies [5]. The group of vascular malformations includes capillary, venous, lymphatic, arterial, or mixed vascular malformations and represents inborn errors of angiogenesis. Mixed vascular malformations consist of various combinations of any of the mentioned vascular components, and are further divided into two groups: 1) high-flow lesions, which include malformed arteries, and 2) low-flow lesions, which do not contain an arterial component [6]. VAs, like GA, are mostly located in the skin and subcutaneous tissue, but they can also be found intramuscularly and invade various organs and cavities.

iii. Overview of Study Significance

The similarities between SGA and low-flow SVMs constitute significant diagnostic difficulties when evaluating subcutaneous lumps in children. These children with SGA often visit multiple physicians before receiving an accurate diagnosis. There is no specific test to diagnose SGA. A detailed patient history, laboratory findings such as blood count, C-reactive protein, rheumatoid factor, and lipid profile, can help rule out some differential diagnoses of SGA as it is the case with many autoimmune, infectious, traumatic, and tumorous diseases. Imaging is also taken into consideration for an accurate diagnosis of SGA. Magnetic resonance imaging provides useful information about the lesion's extension and its relationship to underlying tissues. However, many subcutaneous lesions, including low-flow SVMs, fibrous tissue, rheumatoid nodules, and fat necrosis, have been reported to have a similar appearance on MRI and are challenging to distinguish from SGA. Currently, a surgical biopsy is necessary for definitive diagnosis and to differentiate SGA from other similar subcutaneous lesions. This doctoral thesis aimed to retrospectively evaluate the charts

and imaging of children diagnosed with SGA and low-flow SVMs at the Department of Pediatric and Adolescent Surgery of the Medical University of Graz to identify clues that would aid in the diagnosis of SGA without invasive diagnostic procedures.

II. Summary of the Publications

The first article provides an overview of GA and its subvariant SGA. Various clinical and histopathological characteristics of the disease are discussed. Apparently, different imaging methods are used to clarify these lesions, and ultimately, surgery is often required to confirm the SGA diagnosis. This is illustrated by a case study of a girl who presented with an SGA lesion after a fall, which was confirmed through a biopsy. The article highlights the importance of clinical suspicion of SGA in locations typical for this disease, which can spare patients unnecessary surgical interventions to confirm the diagnosis [7].

The second article aimed to identify an imaging sign that could aid in the accurate diagnosis of SGA without the need for invasive diagnostic procedures [8]. This study retrospectively analyzed the charts and complete imaging of 28 children diagnosed with SGA at the Department of Pediatric and Adolescent Surgery of the Medical University of Graz. It was found that all SGA lesions had a pure epifascial extension with a well-defined broad-based rounded fascial border and an ill-defined crescent, cap-shaped epifascial border. We named this typical shape of the SGA lesion the "epifascial cap sign". We concluded that this imaging sign in combination with a detailed patient history, physical examination, and laboratory findings can lead to an accurate diagnosis of SGA without the need for a biopsy.

The third publication aimed to investigate the diagnostic challenges between SGA and SVMs in children [9]. Differentiating between SGA and SVM lesions is crucial for appropriate treatment and disease management. This study included a retrospective analysis of 12 children with SGA and 47 with low-flow SVMs who all underwent an MRI imaging. The results of the study showed that SGA and SVMs may have similar clinical appearances, but they differ substantially in imaging characteristic. We found that the presence of a homogenous epifascial cap, was a typical imaging sign for SGA, while SVMs present as irregular lesions with tubular or cystic appearance. These imaging differences should further aid in distinguishing between these two types of lesions.

The fourth article [10] is a letter to the editor concerning the article “Subcutaneous Granuloma Annulare in an Atypical Age Group in Immediate Post-Covid-19 Phase” by Kaur et al [11]. We have suggested that the case presented in the article is more compatible with the diagnosis of generalized granuloma annulare (GGA) rather than SGA. The article explains that the clinical and histopathological images presented in the original article do not reveal typical SGA lesions but rather indicate GGA with a patchy pattern of small granulomatous islands. Our letter to the editor provides the reader with new insights about the novel SGA imaging sign that may help avoid unnecessary examinations and specialist consultations for children with SGA and enable accurate diagnosis through imaging alone.

III. Conclusions

This doctoral thesis highlights the importance of accurate diagnosis of subcutaneous lesions in children and offers a non-invasive diagnostic tool to differentiate SGA from other subcutaneous lesions and especially from SVMs. The epifascial cap is a typical imaging sign of SGA lesions which, to the best of our knowledge, distinguishes this disease from other subcutaneous lesions. Recognition of this sign in an otherwise healthy child presenting with a symptomless subcutaneous lump over bony prominences should enable clinicians to diagnose SGA accurately, schedule the patient for a follow-up visit and prevent the majority of children with this disease from undergoing further invasive diagnostic procedures. A management algorithm for children with SGA has been developed.

IV. Zusammenfassung der Veröffentlichungen

Der erste Artikel gibt einen Überblick über das Granuloma anulare (GA) und seine subkutane Untervariante. Es werden verschiedene klinische und histopathologische Merkmale der Krankheit diskutiert. Zur Diagnose des subkutanen Granuloma anulare (SGA) werden oft erfolglos verschiedene Bildgebungsmethoden angewendet. Letztendlich ist meistens ein operativer Eingriff nötig, um die Diagnose zu bestätigen. Dies wird in diesem Artikel durch eine Fallstudie eines Mädchens veranschaulicht, das sich mit einer prätibialen Läsion nach einem Sturz vorstellte, die durch eine Biopsie als SGA bestätigt wurde. Der Artikel unterstreicht die Bedeutung der krankheitstypischen Lokalisation von SGA und betont, dass bei entsprechendem klinischem Verdacht unnötige chirurgische Eingriffe zur Diagnosesicherung vermieden werden könnten [7].

Der zweite Artikel zielt darauf ab, ein bildgebendes Zeichen zu identifizieren, das bei der genauen Diagnose von SGA helfen könnte, ohne dass invasive diagnostische Verfahren erforderlich sind [8]. Diese retrospektive Studie analysierte die Krankengeschichten und die vollständige Bildgebung von 28 Kindern, bei denen SGA an der Klinik für Kinder- und Jugendchirurgie der Medizinischen Universität Graz diagnostiziert wurde. Es wurde festgestellt, dass alle SGA-Läsionen eine reine epifasziale Ausdehnung mit einem gut definierten breitbasigen abgerundeten Faszienrand und einem schlecht definierten halbmondförmigen, kappenförmigen epifaszialen Rand aufwiesen. Diese typische Form der SGA-Läsionen haben wir das "epifasziale Kappenzeichen" genannt. Wir kamen zu dem Schluss, dass dieses bildgebende Zeichen in Kombination mit einer detaillierten Anamnese, körperlichen Untersuchung und Laborbefunden zu einer genauen Diagnose von SGA führen kann, ohne dass eine Biopsie erforderlich ist.

Die dritte Veröffentlichung zielte darauf ab, die diagnostischen Herausforderungen zwischen SGA und den subkutanen vaskulären Malformationen (SVM) zu untersuchen [9]. Die Unterscheidung zwischen SGA- und SVM-Läsionen ist entscheidend für die Anwendung einer entsprechenden Behandlung und das optimale Krankheitsmanagement. Diese Studie umfasste eine retrospektive Analyse von 12 Kindern mit SGA und 47 Kindern mit Low-Flow-SVM, die alle einer MRT-Bildgebung unterzogen wurden. Die Ergebnisse der Studie zeigten, dass SGA und SVM ein ähnliches klinisches Erscheinungsbild haben können, sich jedoch wesentlich in den Bildgebungseigenschaften unterscheiden. Wir fanden heraus, dass das Vorhandensein einer homogenen epifaszialen Kappe ein typisches bildgebendes Zeichen für SGA war, während SVM als unregelmäßige Läsionen mit tubulärem oder zystischem Aussehen auftraten. Diese Bildgebungsunterschiede sollten bei der Unterscheidung zwischen diesen Läsionen entscheidend helfen.

Der vierte Artikel [10] ist ein Leserbrief zum Artikel „Subkutanes Granuloma Annulare in an Atypical Age Group in Immediate Post-Covid-19 Phase“ von Kaur et al. [11]. Wir haben bemerkt, dass der im Artikel vorgestellte Fall eher mit der Diagnose eines generalisierten Granuloma anulare (GGA) als mit einem SGA vereinbar ist. Der Artikel erklärt, dass die im Originalartikel vorgestellten klinischen und histopathologischen Bilder keine typischen SGA-Läsionen zeigen, sondern eher auf GGA mit einem fleckigen Muster kleiner granulomatöser Inseln hinweisen. Unser Leserbrief bietet dem Leser neue Erkenntnisse über das neuartige SGA-

Bildgebungszeichen, das helfen kann, unnötige Untersuchungen und Fachkonsultationen für Kinder mit SGA zu vermeiden und eine genaue Diagnose allein durch die Bildgebung zu ermöglichen.

V. Schlussfolgerung

Diese Doktorarbeit unterstreicht die Bedeutung einer genauen Diagnose subkutaner Läsionen bei Kindern und bietet ein nicht-invasives diagnostisches Zeichen zur Unterscheidung von SGA von anderen subkutanen Läsionen und insbesondere von SVM. Die epifasziale Kappe ist ein typisches bildgebendes Zeichen von SGA-Läsionen, welches diese Krankheit von anderen subkutanen Läsionen unterscheidet. Die Erkennung dieses Zeichens bei einem ansonsten gesunden Kind mit einer symptomlosen subkutanen Beule über knöchernen Vorsprüngen sollte Ärzte in die Lage versetzen, SGA genau zu diagnostizieren, den Patienten für einen Nachsorgetermin einzuplanen und zu verhindern, dass sich die Mehrheit der Kinder mit dieser Krankheit weiteren invasiven diagnostischen Verfahren unterzieht. Ein Managementalgorithmus für Kinder mit SGA wurde entwickelt.

VI. Bibliography

1. Keimig EL (2015) Granuloma Annulare. Dermatol Clin 33:315–29
2. Requena L, Fernández-Figueras MT (2007) Subcutaneous granuloma annulare. Semin Cutan Med Surg 26:96–9
3. Ran Cai Z, Mamet F, Kokta V, Coulombe J (2020) Subcutaneous nodules in children: Don’t forget deep granuloma annulare: A Case Report. SAGE Open Med Case Rep 8:2050313X20935713
4. Nosher JL, Murillo PG, Liszewski M, Gendel V, Gribbin CE (2014) Vascular anomalies: A pictorial review of nomenclature, diagnosis and treatment. World J Radiol 6:677–92
5. ISSVA Classification for vascular anomalies. https://www.issva.org/UserFiles/file/ISSVA-Classification-2018.pdf. (Accessed on February 7, 2023)
6. Cox J, Bartlett E, Lee E (2014) Vascular Malformations: A Review. Semin Plast Surg 28:058–063
7. Beqo BP, Tschauner S, Gasparella P, Brcic I, Singer G, Till H, Haxhija EQ (2022) Granuloma anulare bei Kindern: eine seltene Läsion. Pädiatrie & Pädologie 57:125–130

8. Beqo BP, Tschauner S, Gasparella P, Brcic I, Haxhija EQ (2023) The epifascial cap: A typical imaging sign for subcutaneous granuloma annulare in children. Front Pediatr. https://doi.org/10.3389/fped.2023.1069428
9. Beqo BP, Gasparella P, Flucher C, Tschauner S, Brcic I, Haxhija EQ (2023) Subcutaneous Granuloma Annulare vs. Subcutaneous Vascular Malformations in Children: A Diagnostic Challenge. Children 10:362
10. Beqo BHE (2023) Letter to the Editor: Granuloma Annulare in an Atypical Age Group in Immediate Post-Covid-19 Phase. Dermatol Pract Concept 13:e2023172
11. Kaur L, Chakraborty D, Dayal S, Singh S, Yadav K (2022) Subcutaneous Granuloma Annulare in an Atypical Age Group in Immediate Post-Covid-19 Phase. Dermatol Pract Concept 12:e2022156

Publications

Paediatr. Paedolog.
https://doi.org/10.1007/s00608-022-00985-y
Angenommen: 7. April 2022

Besiana P. Beqo[1,2] · Sebastian Tschauner[3] · Paolo Gasparella[1] · Iva Brcic[4] · Georg Singer[1] · Holger Till[1] · Emir Q. Haxhija[1]

[1] Universitätsklinik für Kinder- und Jugendchirurgie, Medizinische Universität Graz, Graz, Österreich

[2] Harvard Medical School, Boston, USA

[3] Klinische Abteilung für Kinderradiologie, Universitätsklinik für Radiologie, Medizinische Universität Graz, Graz, Österreich

[4] Diagnostik und Forschungsinstitut für Pathologie, Medizinische Universität Graz, Graz, Österreich

Granuloma anulare bei Kindern: eine seltene Läsion

Das Granuloma anulare (GA) ist eine seltene, nichtinfektiöse, gutartige, granulomatöse Erkrankung des kutanen und subkutanen Gewebes, die in verschiedenen Varianten vorkommt, alle Altersgruppen betrifft und bis zu 3-mal häufiger beim weiblichen Geschlecht auftritt [1].

Die lokalisierte Variante des GA (LGA) ist durch ringförmige, rötliche Pappeln an der Haut mit einer leichten zentralen Einsenkung charakterisiert. Diese können eine unterschiedliche Größe haben und einzeln oder multipel auftreten. Bei mehr als 10 GA-Läsionen spricht man von der generalisierten Variante des GA. Diese ist im Kindesalter jedoch sehr selten anzutreffen. Während die lokalisierten GA-Läsionen weder jucken noch schmerzen und sich in der Regel innerhalb von 2 Jahren zurückbilden, sind generalisierte GA-Läsionen oftmals kosmetisch beeinträchtigend und zwingen folglich zu einem oder mehreren Therapieversuchen. Als außerordentlich seltene Varianten des GA bei Erwachsenen sind vollständigkeitshalber noch die perforierenden und die plaqueförmigen Varianten des GA zu nennen [2].

Die subkutane Variante des GA (SGA) findet sich fast exklusiv im Kindesalter und ist aufgrund ihrer Seltenheit und der relativ plötzlich auftretenden, indolenten subkutanen Schwellungen schwierig zu diagnostizieren. Diese Charakteristika machen diese Variante des GA trotz ihrer Seltenheit zu der am häufigsten biopsierten Läsion an den unteren Extremitäten bei Kindern bis zum 5. Lebensjahr [3].

Inzidenz, Ätiologie und Histopathologie

Eine rezente datenbankbasierte Arbeit zeigte eine Inzidenz des GA von 0,04 % und eine Prävalenz von 0,06 % in der Bevölkerung der USA und damit ein 10-mal selteneres Vorkommen als zuvor aus anderen Veröffentlichungen angenommen [1, 4]. Die Ätiologie des GA ist weder für kutane noch für subkutane Varianten bekannt. Histopathologisch sind diese Läsionen – unabhängig von der klinischen Variante – identisch [5]: Sie bestehen aus granulomatösen Entzündungsherden (**Abb. 1**) mit zentralen Muzinhaltigen Nekrosearealen, umgeben von in typischer Weise palisadenartig angehäuften Gewebsmakrophagen (Histiozyten). Zusätzlich finden sich in den Läsionen auch reichlich weitere Entzündungszellen wie Lymphozyten und eosinophile Granulozyten, die den Eindruck der Gewebsaufräumarbeit hinterlassen. Diese Entzündungszellen haben die Aufgabe, Eindringlinge zu neutralisieren oder Gewebsläsionen abzugrenzen, um sie dann abzubauen. Da diese Granulome auch mehrere Jahre andauern können, bevor sie von selbst wieder verschwinden, muss angenommen werden, dass es sich bei GA um eine Störung im Rahmen dieses Prozesses handelt [4]. Es gibt jedoch bislang keinen Beweis für eine generalisierte Störung solcher Prozesse im Körper von Patienten mit GA und die Patienten sind sonst in der Regel gesund. Daher müsste es sich um eine lokale Störung im betroffenen Gewebe handeln, deren Ursache noch ungeklärt ist. Die aktuelle Hypothese für die Entstehung von GA-Läsionen ist die lokale Aktivierung von spezifischer T-Zell-Immunität über Zytokine wie Tumornekrosefaktor-alpha, Interferon-gamma und andere, ohne den genauen auslösenden Faktor zu kennen [2]. Das Auftreten von GA ist unter anderem nach Traumata, Impfungen, viralen Entzündungen, Tätowierungen und Sonnenexposition beschrieben worden [1, 2].

Diagnostik

Im Kindesalter sind vor allem die lokalisierte und die subkutane Variante des GA von Bedeutung [6]. Aufgrund ihrer Seltenheit können diese Läsionen diagnostische Schwierigkeiten bereiten, insbesondere wenn untersuchende Ärzte dieses seltene Krankheitsbild zuvor noch nicht selbst in der Praxis kennengelernt haben. Die lokalisierte Variante des GA ist aufgrund des typischen ringförmigen Aussehens der Pappeln insbesondere für einen Dermatologen meist leicht zu diagnostizieren (**Abb. 2**). Differenzialdiagnostisch werden am häufigsten unterschiedliche Dermatitisformen oder auch Pilzerkrankungen in Erwägung gezogen. Eine diesbezügliche Diagnostik führt im Bedarfsfall der Dermatologe durch, was bewirkt, dass der Großteil dieser Patienten lediglich eine klinische Untersuchung benötigt und nur ganz selten die Diagnose durch eine invasive Therapie, wie Gewebsuntersuchung, gesichert werden muss.

Published online: 05 May 2022

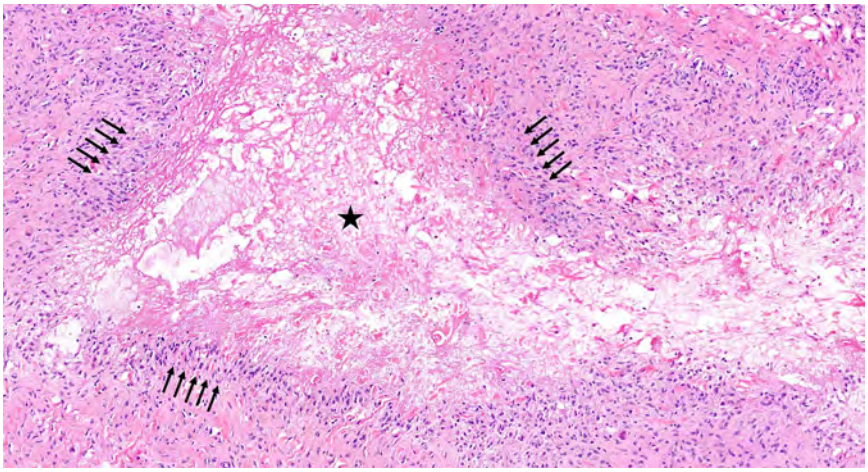

Abb. 1 ▲ Histopathologisches HE-gefärbtes Präparat eines Granuloma anulare. Mit einem *Stern* ist die zentrale Nekrose markiert, die von palisadenartig angeordneten Histiozyten und Lymphozyten umgeben ist (*Pfeile*; © Medizinische Universität Graz)

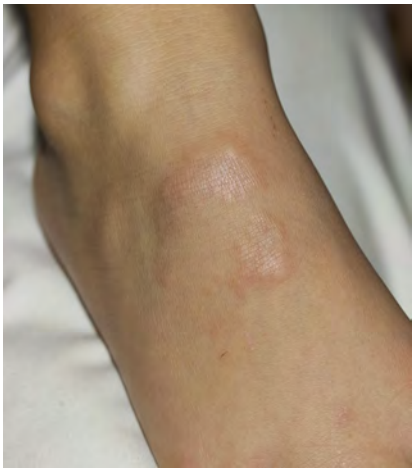

Abb. 2 ▲ Lokalisiertes Granuloma anulare am Fußrücken *rechts*. Es zeigen sich ringförmige, rötliche bis hautfarbene Papeln (© Medizinische Universität Graz)

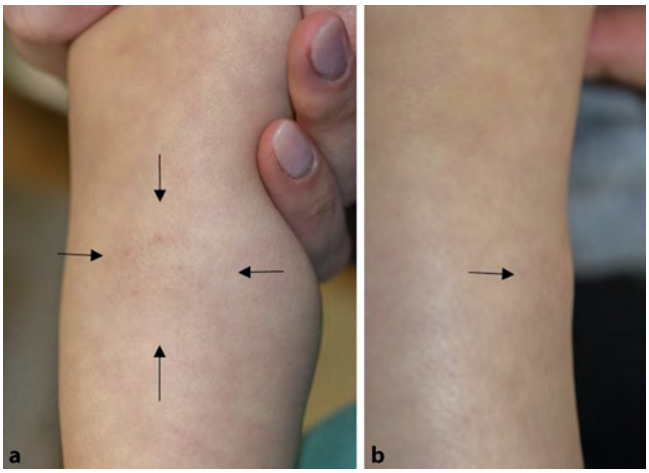

Abb. 3 ◀ Subkutanes Granuloma anulare prätibial *rechts* bei einem 3,5-jährigen Mädchen. In der anterior-posterioren Aufnahme (**a**) sind minimale Hautverfärbungen sichtbar (*Pfeile*), während die subkutane Schwellung in der seitlichen Aufnahme (**b**) sichtbar wird (*Pfeil*; © Medizinische Universität Graz)

Die subkutane Form des GA befindet sich in der Regel auf gut exponierten, dem Trauma leicht zugänglichen Körperstellen, wie Schienbeinvorderseite, ulnare Unterarmseite, Schädel, Hände und Füße [7]. Oft berichten die Eltern, dass die Schwellung aufgetreten sei, nachdem sich ihr Kind angeschlagen hatte. Die subkutanen Läsionen sind mit der Faszie fest verbunden und daher nicht verschieblich. Die Haut darüber ist unversehrt und die Schwellung relativ derb und indolent. Da es sich beim GA um einen inflammatorischen selbstlimitierenden Prozess handelt, ist auch die Derbheit der Schwellung vom Zeitpunkt der Vorstellung des Kindes abhängig. Diese Läsionen können nach einigen Monaten verschwinden oder auch jahrelang verbleiben, wobei sich die Konsistenz der Läsionen mit der Zeit von derb auf weich verändert. Es werden zur Diagnosesicherung unterschiedliche bildgebende Verfahren angewendet und zum Schluss oft auch die Chirurgie benötigt, was durch das folgende Fallbeispiel illustriert werden soll.

Fallbeispiel

Die Erstvorstellung eines Mädchens erfolgte im Alter von 3,5 Jahren aufgrund einer Schwellung im Bereich des rechten Unterschenkels, die schon seit über 2 Monaten bestand und der Erinnerung der Eltern nach aufgrund eines Sturzes im Park aufgetreten sei. Weil die Läsion jedoch nicht wie üblich verschwand und auch nicht kleiner wurde, gingen sie mit ihrem Kind zum Kinderarzt, der sie mit der Diagnose einer unklaren subkutanen Läsion zur weiteren Abklärung zu uns überwies.

Bei der klinischen Untersuchung zeigte sich prätibial rechts proximal eine etwa 3 cm im Durchmesser große schmerzlose Vorwölbung, die eine feste Konsistenz zeigte und nicht verschieblich war (**Abb. 3**). Die Haut des Unterschenkels im Bereich der Schwellung war vollkommen unauffällig, die Läsion konnte nicht kleingedrückt werden und schimmerte auch nicht bläulich. Aus diesem Grund wurde zuerst, um eine ossäre Läsion auszuschließen, ein Röntgen des Unterschenkels durchgeführt (**Abb. 4**). Es zeigten sich keine ossäre Auffälligkeiten, jedoch eine schattengebende subkutane Läsion in der seitlichen Röntgenaufnahme. Zur weiteren Abklärung wurde ein Ultraschalluntersuchung der subkutanen Schwellung angefordert (**Abb. 5**). Diese zeigte eine inhomogene, echoarme und schlecht abgrenzbare Läsion mit einer ungefähren Größe von 3,0 × 2,4 × 0,8 cm, die epifaszial lag und nur gering durchblutet war. Die Verdachtsdiagnose einer low-flow vaskulären Malformation wurde erhoben und eine Magnetresonanztomographie (MRT) indiziert, die aufgrund des Alters des Kindes in Narkose durchgeführt werden musste. Die MRT zeigte eine zur Gänze subkutan gelegene Weichteilläsion mit einem inhomogenen Signalverhalten, unscharfen Grenzen und einer engen topografischen Beziehung zur Faszie des Musculus tibialis anterior (**Abb. 6**). Nach Kontrastmittelapplikation zeigte sich ein deutli-

ches Enhancement in der Läsion. Die Größe der komplett epifaszialen Läsion war genauer zu bestimmen und betrug 2,8 × 1,9 × 0,8 cm. Die Läsion war neuerlich nicht sicher einzuordnen. Zusätzlich zur low-flow vaskulären Malformation wurden die Differenzialdiagnosen einer Fibromatose, einer Fasziitis und einer posttraumatischen Läsion gestellt. Eine potenziell aggressive Erkrankung konnte auch nicht explizit ausgeschlossen werden. Da das Kind beschwerdefrei war und die Läsion, die zuletzt über 2 Monate lang unverändert war, klinisch als gutartig imponierte, wurde zuerst ein abwartendes Prozedere empfohlen, jedoch den Eltern erklärt, dass mittels Biopsie eine Diagnosesicherung möglich ist. Aufgrund des Fortbestands der Läsion, die sich inzwischen wiederum nicht verändert hat, wurde einen Monat später auf Wunsch der Eltern die Biopsie der Läsion durchgeführt. Diese ergab ein subkutanes GA. In weiterer Folge wurden Kontrolluntersuchungen durchgeführt. Ein Jahr nach der bioptischen Abklärung waren zusätzliche subkutane Herde im Bereich des linksseitigen Schienbeins und auch im Bereich des rechten Ellbogens aufgetreten. Zusätzlich zeigte sich auch ein lokalisiertes GA an der Haut des linken Unterschenkels. Es wurden nun in der klinischen Abklärung dieser Läsionen lediglich eine Ultraschalluntersuchung und keine weiteren invasiven diagnostischen Maßnahmen durchgeführt. Da die Patientin immer wieder über Fußschmerzen und Handschmerzen klagte, wurde eine rheumatologische Abklärung eingeleitet, die bis auf eine Positivität für antinukleäre Antikörper (ANA) unauffällig blieb. Auch nach einer 10-jährigen Nachsorgeperiode ist die Patientin bezüglich der rheumatologischen Erkrankung weiterhin unauffällig geblieben. Nachdem sowohl die subkutanen als auch die kutanen Läsionen verschwunden waren, ist 9 Jahre postoperativ ein weiterer Schub des lokalisierten GA – diesmal im Bereich des rechten Mittelfußbereichs – aufgetreten. Auch diese Läsion ist nach einem halben Jahr wieder spontan verschwunden.

Zusammenfassung · Abstract

Paediatr. Paedolog. https://doi.org/10.1007/s00608-022-00985-y

B. P. Beqo · S. Tschauner · P. Gasparella · I. Brcic · G. Singer · H. Till · E. Q. Haxhija

Granuloma anulare bei Kindern: eine seltene Läsion

Zusammenfassung

Das Granuloma anulare (GA) ist eine seltene, gutartige, selbstlimitierende granulomatöse Erkrankung des kutanen und subkutanen Gewebes, die in verschiedenen Varianten vorkommt und alle Altersgruppen betrifft. Die lokalisierte Variante des GA ist durch Pappeln mit typischem ringförmigem Aussehen gekennzeichnet und ist insbesondere für einen Dermatologen leicht zu diagnostizieren. Die subkutane Form des GA tritt fast exklusiv im Kindesalter auf und findet sich auf gut exponierten, dem Trauma leicht zugänglichen Körperstellen, wie Schienbeinvorderseite, ulnare Unterarmseite, Schädel, Hände und Füße. Diese Läsionen können nach einigen Monaten verschwinden oder auch jahrelang verbleiben. Es werden im Rahmen der Abklärung unterschiedliche bildgebende Verfahren angewendet und letztendlich wird zur Diagnosesicherung oft auch die Chirurgie benötigt, wie im folgenden Fallbeispiel illustriert wird. Die Erstvorstellung eines Mädchens erfolgte im Alter von 3,5 Jahren aufgrund einer seit 2 Monaten nach einem Sturz aufgetretenen prätibialen Schwellung rechts. Aufgrund der derben Konsistenz der schmerzlosen Vorwölbung wurden eine Röntgenaufnahme, eine Ultraschalluntersuchung und ein Magnetresonanztomogramm in Narkose durchgeführt, die allesamt eine unspezifische epifasziale subkutane Weichteilläsion zeigten. Eine weiterführende Biopsie in Narkose ergab die Diagnose des subkutanen GA. Im weiteren Verlauf entwickelte das Mädchen in den nächsten 10 Jahren noch mehrere subkutane und kutane GA-Läsionen, die sich allesamt von selbst zurückbildeten. Bei subkutanen Läsionen an den für das subkutane GA typischen Stellen, insbesondere prätibial, sollte es möglich sein, dass diese Diagnose klinisch vermutet wird und den Patienten somit ein chirurgischer Eingriff zur Diagnosesicherung in der Regel erspart bleibt.

Schlüsselwörter

Granulomatöse Läsionen · Dermatose · Subkutane Läsionen · Benigne Läsionen · Selbstlimitierende Erkrankung

Granuloma Annulare in Children: a rare Lesion

Abstract

Granuloma annulare (GA) is a rare, benign, self-limiting granulomatous disease of the cutaneous and subcutaneous tissue that occurs in different variants and affects all age groups. The localized variant of GA is characterized by the typical ring-shaped appearance of the dermal papules and is easy to diagnose, especially for a dermatologist. The subcutaneous variant of GA occurs almost exclusively in childhood and is found on well-exposed parts of the body that are easily accessible to trauma, such as the front of the lower leg, the ulnar side of the forearm, the skull, hands, and feet. These lesions can disappear after a few months or remain for years. Different imaging methods are used to clarify these lesions, and ultimately, surgery is often required to confirm the diagnosis, as illustrated in the following case study. A girl first presented at the age of 3.5 years because of a pretibial swelling on the right that had occurred after a fall 2 months before. Owing to the firm consistency of the painless lump, an X-ray, an ultrasound examination, and magnetic resonance imaging were performed under general anesthesia, all of which showed a nonspecific, epifascial, subcutaneous soft-tissue lesion. A further biopsy under general anesthesia revealed the diagnosis of subcutaneous GA. In the course of the next 10 years, the girl developed several subcutaneous and cutaneous GA lesions, all of which resolved on their own. In the case of subcutaneous lesions in areas typical for subcutaneous GA, especially pretibial, a clinical suspicion of this diagnosis should be possible and thus usually spare patients surgical intervention to confirm the diagnosis.

Keywords

Granulomatous lesions · Dermatosis · Subcutaneous lesions · Benign lesions · Self-limiting disease

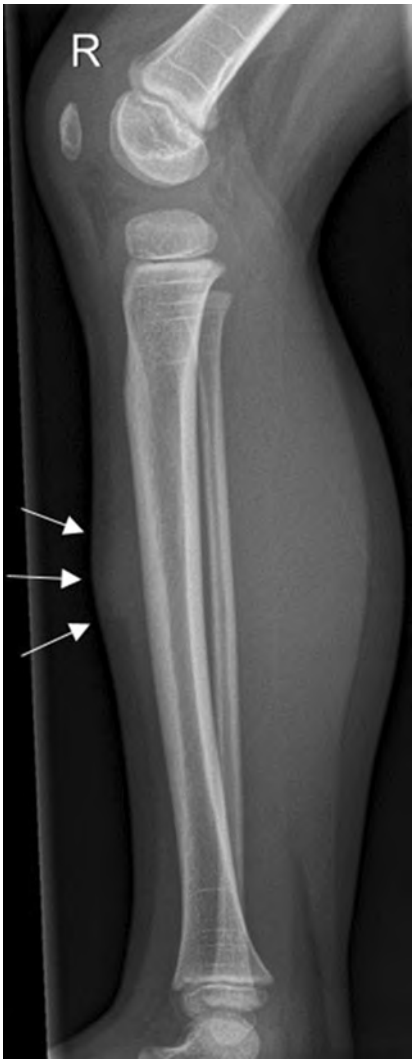

Abb. 4 ▲ Subkutanes Granuloma anulare prätibial *rechts* bei einem 3,5-jährigen Mädchen. Die seitliche Röntgenaufnahme des Unterschenkels wurde zum Ausschluss einer knöchernen Veränderung durchgeführt. Die *Pfeile* zeigen auf eine prätibiale Verschattung, hinweisend auf eine Verdickung des subkutanen Gewebes im Bereich der mittleren bis proximalen Tibiavorderkante (© Medizinische Universität Graz)

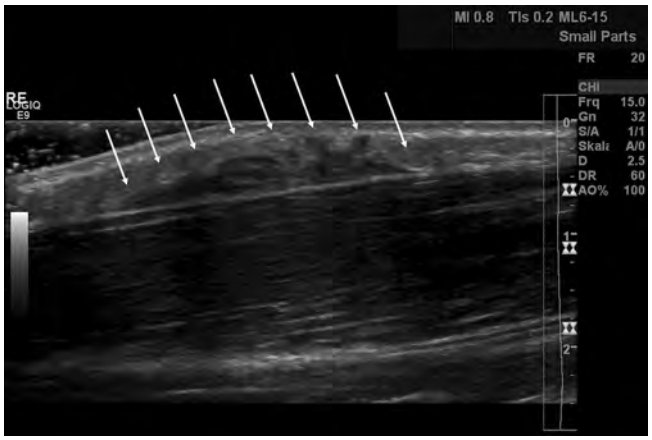

Abb. 5 ▲ Ultraschallbild in Längsausrichtung eines subkutanen Granuloma anulare prätibial *rechts* bei einem 3,5-jährigen Mädchen. Die *Pfeile* weisen auf die inhomogene Verdickung des subkutanen Gewebes im Bereich der mittleren bis proximalen Tibiavorderkante hin. Es zeigen sich unscharf begrenzte echoarme Areale, die epifaszial liegen (© Medizinische Universität Graz)

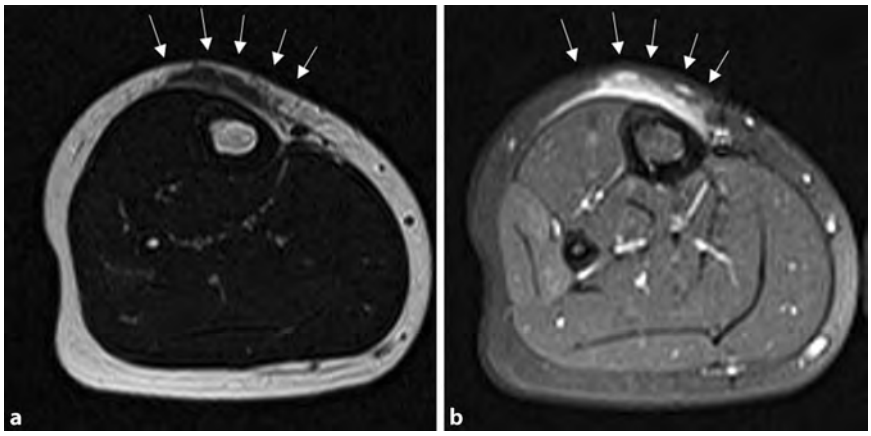

Abb. 6 ▲ Magnetresonanztomografie des *rechten* Beins eines 3,5-jährigen Mädchens mit einem subkutanen Granuloma anulare prätibial (*Pfeile*). In der T1-Wichtung (**a**) zeigt sich die Läsion in Relation zum Muskel iso- bis hypointens. In der fettsupprimierten T2-Wichtung (**b**) zeigt sich die Läsion in Relation zum Muskel hyperintens. Die Läsion liegt epifaszial und ist unscharf begrenzt (© Medizinische Universität Graz)

Diskussion

GA-Läsionen sind im Kindesalter selten und es ist immer ratsam für die Begutachtung von unklaren kutanen Veränderungen den Hautarzt zu konsultieren. Die subkutane Variante des GA stellt häufig eine diagnostische Herausforderung dar und bedarf oft mehrere diagnostische Untersuchungen, bevor am Ende die häufige Entscheidung für eine bioptische Abklärung der unklaren subkutanen Läsion fällt.

Soweit sind bei Patienten mit subkutanem GA im Rahmen der Bildgebung keine spezifischen Zeichen zur Diagnosesicherung beschrieben worden. Diese Läsionen werden sowohl im Ultraschall als auch im MRT als schlecht abgegrenzt und mit unterschiedlicher Homogenität beschrieben [8]. Sowohl Stenzel et al. [9] als auch Riebel und Scheer [10] haben vorgeschlagen, dass die auf subkutanes GA verdächtigen prätibialen Läsionen, trotz fehlenden bildgebenden pathognomonischen Zeichen, lediglich klinisch und sonografisch beobachtet werden sollen [9, 10]. Dies sollte möglich sein, weil die Lokalisation der Läsionen, die Beschwerdefreiheit der Kinder, die typischen klinischen Zeichen einer indolenten, nichtverschieblichen, hautfarbenen, prätibialen Schwellung bei Kindern zwischen dem 2. und 6. Lebensjahr, mit geringer Wachstumstendenz nach der Erstvorstellung beim Arzt ausreichend Information bieten sollte, um die Verdachtsdiagnose eines subkutanen Granuloma anulare zu stellen.

Ebenso zeigten sich bisher auch alle laborchemischen Untersuchungen, die zur Abklärung von Kindern mit subkutanem GA durchgeführt wurden, als unauffällig und unspezifisch. Daher müssen sich Ärzte auf ihre klinische Erfahrung verlassen, wenn sie die Entscheidung treffen, ein Kind mit einer unklaren subkutanen

Läsion lediglich zu beobachten. Ein solches Vorgehen könnte auch stark vom Klagwesen in verschiedenen Staaten abhängig sein und sich dadurch deutlich zwischen Europa und den Vereinigten Staaten unterscheiden.

Weiterhin bleibt es unklar, welcher Mechanismus für das Entstehen von GA verantwortlich ist. Am häufigsten wird in der Literatur die Kombination einer exogenen Noxe in Verbindung mit fehlerhafter Aktivierung der sich lokal ansammelnden T-Helferzellen als mögliche Ursache des GA diskutiert [2, 4]. Bei der lokalisierten Variante des GA befinden sich die Granulome in der oberen und mittleren Dermis, während diese bei der subkutanen Variante des GA in der tiefen Dermis und in der Subkutis vorzufinden sind [5]. Für beide Varianten ist eine Zeitperiode von etwa 2 Jahren für die spontane Auflösung der Läsionen nötig, wobei unserer Erfahrung nach sich die Rezidivläsionen schneller zurückbilden als die primären Läsionen.

Während mehrere Fallberichte die Assoziation zwischen GA und Diabetes mellitus sowie anderen Autoimmunerkrankungen wie rheumatoide Arthritis auch im Kindesalter beschrieben haben, zeigten andere Langzeitstudien, dass Patienten mit GA keine höhere Anfälligkeit für systemische Erkrankungen haben [6]. Rezente Studien über GA bei Erwachsenen zeigen jedoch eine signifikant höhere Inzidenz von Diabetes mellitus, rheumatoider Arthritis, Hypothyreoidismus, Hyperlipidämie und ischämischer Herzkrankheit bei Patienten mit GA verglichen mit der Kontrollgruppe [2, 4].

Fazit für die Praxis

Wenn unklare subkutane Läsionen an den für subkutanes Granuloma anulare typischen Stellen auftreten, insbesondere prätibial, sollte es möglich sein, dass durch engmaschige klinische und Ultraschallkontrollen den Patienten ein chirurgischer Eingriff zur Diagnosesicherung erspart bleibt.

Korrespondenzadresse


© Haxhija

Priv.-Doz. Dr. Emir Q. Haxhija, MD, PhD
Universitätsklinik für Kinder- und Jugendchirurgie, Medizinische Universität Graz
Auenbruggerplatz 34, 8036 Graz, Österreich
emir.haxhija@medunigraz.at

Funding. Open access funding provided by Medical University of Graz.

Einhaltung ethischer Richtlinien

Interessenkonflikt. B.P. Beqo, S. Tschauner, P. Gasparella, I. Brcic, G. Singer, H. Till und E.Q. Haxhija geben an, dass kein Interessenkonflikt besteht.

Für diesen Beitrag wurden von den Autoren keine Studien an Menschen oder Tieren durchgeführt. Für die aufgeführten Studien gelten die jeweils dort angegebenen ethischen Richtlinien. Diese Studie wurde von der Ethikkommission der Medizinischen Universität Graz bewilligt (Nr. 33–126 ex 20/21).

Literatur

1. Barbieri JS, Rodriguez O, Rosenbach M, Margolis D (2021) Incidence and prevalence of granuloma Annulare in the United States. JAMA Dermatol 157:824–830
2. Joshi TP, Duvic M (2021) Granuloma annulare: an updated review of epidemiology, pathogenesis, and treatment options. Am J Clin Dermatol 8:1–14
3. Kransdorf MJ (1995) Benign soft-tissue tumors in a large referral population: distribution of specific diagnoses by age, sex, and location. AJR Am J Roentgenol 164:395–402
4. Piette EW, Rosenbach M (2016) Granuloma annulare: clinical and histologic variants, epidemiology, and genetics. J Am Acad Dermatol 75:457–465
5. Stefanaki M, Tsivitanidou-Kakourou T, Stefanaki C, Valari M, Argyrakos T, Konstantinidou CV, Karentzou O, Katsambas A (2007) Histological and immunohistochemical study of granuloma annulare and subcutaneous granuloma annulare in children. J Cutan Pathol 34:392–396
6. Patrizi A, Gurioli C, Neri I (2014) Childhood granuloma annulare: a review. J Ital Dermatol Venereol 149:663–674
7. Letts M, Carpenter B, Soucy P, Davidson D (2000) Subcutaneous granuloma annulare of the extremities in children. Can J Surg 43:425–430
8. Navarro OM, Laffan EE, Ngan BY (2009) Pediatric soft-tissue tumors and pseudo-tumors: MR imaging features with pathologic correlation: part 1. Imaging approach, pseudotumors, vascular lesions, and adipocytic tumors. Radiographics 29:887–906
9. Stenzel M, Voß U, Mutze S, Hesse V (2010) A pretibial lump in a toddler—sonographic findings in subcutaneous granuloma annulare. Ultraschall Med 31:68–70
10. Riebel T, Scheer I (2011) Subkutanes Granuloma annulare: eine nicht zu vergessende Differenzialdiagnose bei expansiven (Weichteil-)Läsionen an den unteren Extremitäten von jungen Kindern. Ultraschall Med 32:604–607

frontiers | Frontiers in Pediatrics

TYPE Original Research
PUBLISHED 21 March 2023
DOI 10.3389/fped.2023.1069428

OPEN ACCESS

EDITED BY
Oliver Muensterer,
LMU Munich University Hospital, Germany

REVIEWED BY
Anko Antabak,
University of Zagreb, Croatia
Hüseyin Özbey,
I.M. Sechenov First Moscow State Medical University, Russia
Francisco Reyes-Baraona,
Pontifical Catholic University of Chile, Chile

*CORRESPONDENCE
Emir Q. Haxhija
✉ emir.haxhija@medunigraz.at

SPECIALTY SECTION
This article was submitted to Pediatric Surgery, a section of the journal Frontiers in Pediatrics

RECEIVED 13 October 2022
ACCEPTED 20 February 2023
PUBLISHED 21 March 2023

CITATION
Beqo BP, Tschauner S, Gasparella P, Brcic I and Haxhija EQ (2023) The epifascial cap: A typical imaging sign for subcutaneous granuloma annulare in children.
Front. Pediatr. 11:1069428.
doi: 10.3389/fped.2023.1069428

The epifascial cap: A typical imaging sign for subcutaneous granuloma annulare in children

Besiana P. Beqo[1], Sebastian Tschauner[2], Paolo Gasparella[1], Iva Brcic[3] and Emir Q. Haxhija[1]*

[1]Department of Paediatric and Adolescent Surgery, Medical University of Graz, Graz, Austria, [2]Department of Radiology, Division of Paediatric Radiology, Medical University of Graz, Graz, Austria, [3]Institute of Pathology, Medical University of Graz, Graz, Austria

Objectives: Subcutaneous granuloma annulare (SGA) is a rare, self-limiting granulomatous disease in children, commonly diagnosed by histopathology following biopsy or surgical excision. This study aimed to identify imaging clues for SGA that could expedite accurate diagnosis and avoid the need for biopsy in children.
Methods: We retrospectively analyzed complete hospital records of all children diagnosed with SGA at our institution from January 2001 to December 2020. Detailed disease history, imaging findings, management, and outcome were evaluated.
Results: We identified 28 patients (20 girls) at a median age of 3.75 (range 1–12.5 years). Ten patients presented with multiple lesions. Most lesions were located on the lower extremities ($n = 26/41$). Ultrasound examinations were performed on all patients, and 12 (43%) patients also received an MRI. Surgical intervention was conducted in 18 (64%) patients either by incisional biopsy ($n = 6$) or total excision of the lump ($n = 12$). In all patients who did not undergo surgery, SGA resolved spontaneously. A careful review of the MRIs led to the discovery of a characteristic imaging shape of SGA lesions: the epifascial cap with a typical broad circular base laying on the fascia, extending towards the subdermal/dermal tissue. This distinctive shape was evident in every patient in our cohort.
Conclusions: The "Epifascial Cap Sign" is a specific imaging sign for SGA, which to the best of our knowledge, helps distinguish this disease from other subcutaneous lesions. Recognition of this novel diagnostic sign combined with the historical and physical findings should enable clinicians to establish SGA diagnosis easily and diminish the need for further invasive diagnostic procedures.

KEYWORDS

subcutaneous lesion, lumps and bumps, treatment, benign lesion, self limiting disease, children, granuloma annulare, lumps and bumps, treatment

Introduction

Granuloma annulare (GA) is a self-limiting granulomatous disease of unknown etiology with a clear histopathological appearance. The GA lesions consist of typical palisading granulomas, with a central necrotic zone surrounded by radially oriented histiocytes, lymphocytes, and fibroblasts (1, 2). GA can present in a generalized fashion GA (GGA), localized (LGA), subcutaneous (SGA), and more rare variants of patchy and perforating GA.

Abbreviations
GA, granuloma annulare; SGA, subcutaneous granuloma annulare; GGA, generalized granuloma annulare; LGA, localized granuloma annulare; MRI, magnetic resonance imaging; US, ultrasound.

GGA is defined as the presence of more than ten widespread skin lesions (3). A diverse assortment of therapies for GGA has been reported, yet missing an algorithm for treatment choices (4). LGA is characterized by less than ten asymptomatic skin papules with a circular appearance mainly localized on the dorsum of the hands and feet (5, 6). While LGA occurs in adults and children, SGA is a condition postulated to occur mainly during childhood (1, 2, 7). SGA consists of solid, non-tender, non-inflammatory, solitary, or multiple subcutaneous lumps. These lesions are commonly located above bony prominences, such as the anterior side of the lower legs, the dorsum of the hands and feet, and the scalp (5, 8). LGA and SGA lesions spontaneously regress without any treatment within a couple of years (3).

In most cases, diagnosing LGA and GGA as visible ring-shaped skin lesions is straightforward for a dermatologist. Unfortunately, this is rarely the case among pediatric patients with SGA lumps. Regardless of its harmless, self-resolving nature, SGA still is the most frequently biopsied, benign soft tissue mass in the lower extremity of children under the age of 5 (9, 10). The initial clinical impression about the sudden appearance of an unclear subcutaneous lump in a child can be either dubious or misleading, thus, making this disease notoriously difficult to diagnose (11–13). Although various imaging features of SGA lesions have been described in the literature, no specific hallmark is yet recognized to help clinicians distinguish SGA from other differential diagnostic considerations (9, 12–17). As a result, children often undergo several unavailing investigations before a biopsy is performed to rule out malignancy and establish an adequate SGA diagnosis. Incisional or excisional biopsy is the intervention preferred since punch biopsy may yield false negative results as it may miss the necrobiotic mucin-containing areas, characteristic of the SGA lesion (2, 5, 7).

We have performed this institutional review to investigate the current practice of diagnosing children with SGA, intending to find a specific imaging sign of this disease that can quickly and effectively achieve a definite, accurate diagnosis without needing a biopsy.

Patients and methods

We retrospectively analyzed the electronic hospital records (medocs) of all children aged 0–18 years diagnosed with SGA from January 2001 to December 2020. Evaluation of the data according to the patient's disease history, management, and outcome is done. The information identified and analyzed for each patient included: sex, age at first presentation, the duration

TABLE 1 Characteristics of patients treated for subcutaneous granuloma annulare (SGA).

Patient	Age [y]	Sex	Number of Lesions	Lesion Location	Side	Diagnostics	Surgery	Recurrence	Other Diseases
1	2.5	M	1	Knee	R	US + x-ray + MRI	CE	No	–
2	2.5	F	1	Lower leg	R	US + x-ray	CE	Yes	–
3	4	M	1	Forearm	L	US + MRI	CE	No	–
4	4	F	1	Lower leg	L	US + x-ray + MRI	B	No	–
5	4.5	F	3	Head	R	US + MRI	B	No	–
6	3	F	1	Foot	L	US + MRI	CE	No	–
7	2.5	F	1	Lower leg	R	US + x-ray + MRI	CE	No	Atopic diseases
8	2.5	F	2	Hand and Thorax	L & R	US + MRI	CE	No	Juvenile Chronic Arthritis
9	4	F	1	Lower leg	L	US + x-ray + MRI	B	No	–
10	5	F	2	Lower legs	R & L	US + x-ray	–	No	–
11	2	M	2	Lower legs	R & L	US + x-ray	–	No	–
12	3.5	F	3	Lower legs	R & L	US + x-ray + MRI	B	No	–
13	4	F	2	Foot and Elbow	L & R	US	–	No	Atopic diseases
14	2.5	M	1	Foot	L	US	–	No	–
15	6	F	1	Lower leg	R	US + x-ray	–	No	–
16	4	M	1	Foot	L	US	CE	No	–
17	3	M	1	Pelvic crest	L	US	–	No	–
18	1	F	1	Lower leg	R	US + x-ray	–	No	–
19	12.5	F	1	Lower leg	R	US + x-ray	CE	No	Ulcerative Colitis
20	4.5	F	1	Lower leg	L	US + x-ray	–	No	–
21	5	M	2	Lower legs	R & L	US + x-ray	–	No	Urticaria
22	5.5	F	1	Hand	L	US	CE	Yes	
23	1	F	1	Lower leg	R	US + x-ray	–	No	
24	3.5	F	3	Lower legs & Foot	R & L	US + x-ray	B	No	–
25	2	F	2	Head	L	US + MRI	CE	No	–
26	5.5	F	1	Knee	R	US + x-ray	CE	No	–
27	5	F	1	Forearm	L	US + MRI	CE	No	–
28	3	M	2	Head	Frontal	US + MRI	B	No	–

28 patients diagnosed with SGA presented with a total of 41 lesions. Seven patients had two lesions each, and three patients had 3 lesions each. Abbreviations: M, male; F, female; R, right; L, left; MRI, magnetic resonance imaging; US, ultrasound; CE, complete excision; B, biopsy.

of symptoms and signs prior to the first presentation, the location of the lesion(s), the number of the lesions, associated pain, the clinical description of the lesion(s), the report of trauma prior to the appearance of the lesions, the time between the first presentation at our Department and treatment starting, the diagnostic imaging and lab work performed, the histopathologic report provided, the type of conservative or surgical treatment performed, the recurrence after treatment and the follow-up time from the first presentation. Three-dimensional reconstructions of MR images were performed with 3D Slicer (https://www.slicer.org/) version 4. 7.0-2016-11-04 r25501 by manually segmenting the SGA lesions and superimposing them by volume renderings of the respective body regions in all relevant slices (18). After the procedure, volumes could be read out automatically with the "label statistics" module. The MR imaging studies were either performed on a Magnetom Sola or a Magnetom Symphony scanner with 1.5 Tesla magnetic field strength (Siemens Healthineers, Erlangen, Germany). Radiologists were confronted with different body regions, resulting in different examination protocols. Typically, the MRI protocol included two planes of T2-weighted fat-suppressed sequences and one T2-weighted sequence without fat-suppression. A T1-weighted sequence was also performed, typically in a coronal orientation. Diffusion-weighted imaging was invariably performed. Post-contrast T1-weighted sequences with fat-suppression were available in all situations. Descriptive statistical analysis was performed. This study has been approved by the Institutional Ethics Committee (EK-No. 33–126 ex 20/21), and informed consent was waived.

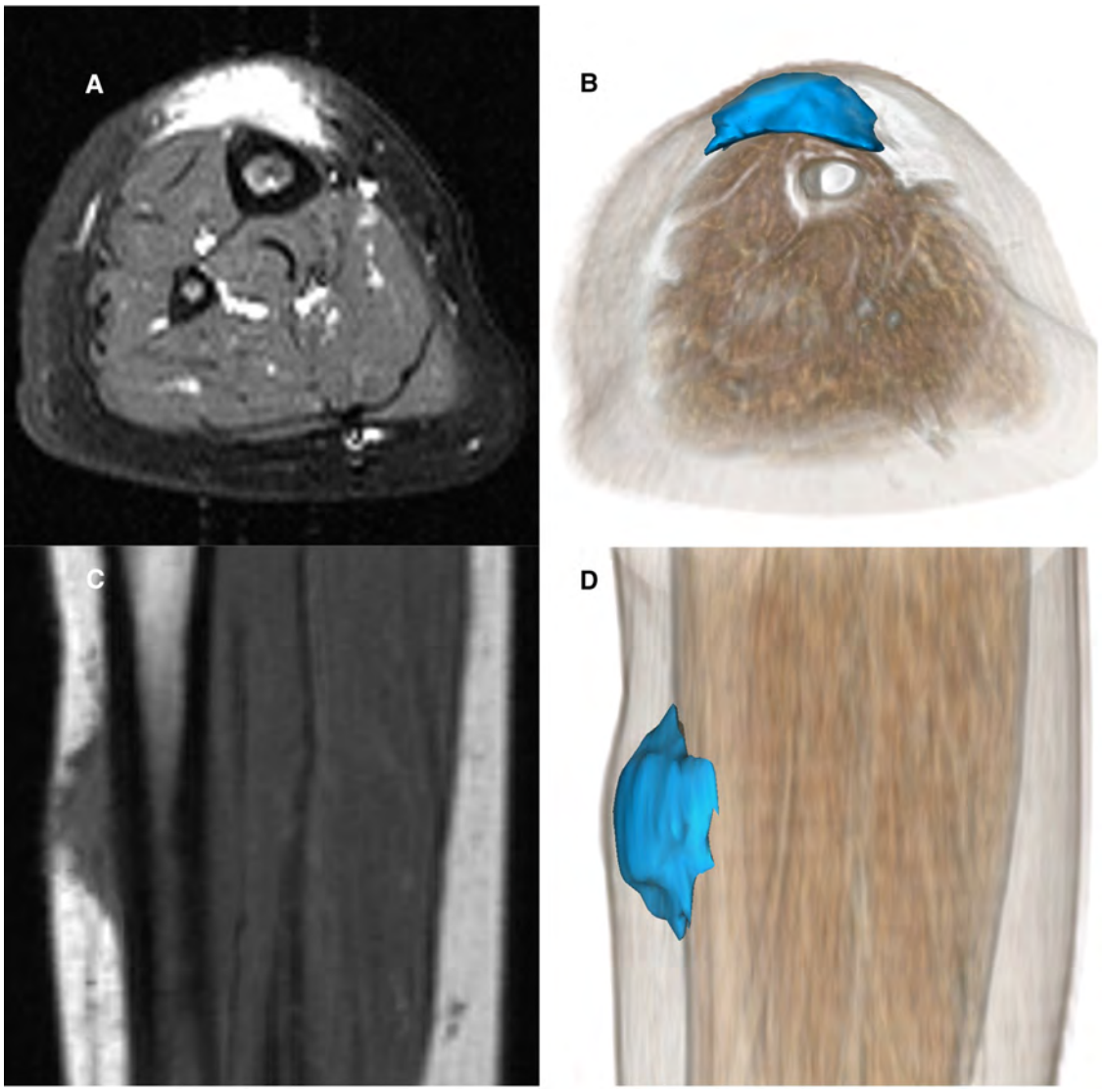

FIGURE 1
Representative MRI sections and 3D-reconstructions of subcutaneous granuloma annulare lesion (colored blue) on the right lower leg of a 2.5-year-old girl (**A–D**). A T2-weighted slice in axial orientation (**A**) shows the cap-shaped epifascial lesion with high signal intensity (bright). The corresponding 3D reconstruction is given in (**B**), visualizing the lesion in blue color and the remaining other tissues by overlaying a volume rendering in a skin-like color. (**C**) shows the lesion in a T1-weighted sagittal slice with low signal intensity (dark). The corresponding 3D rendering (**D**) demonstrates the cap-shaped morphology, extending from the deep fascia to the subcutaneous layer.

Results

We identified 57 patients diagnosed with GA in the last 20 years. Twenty-nine of them were LGA cases and were excluded from the present study. Twenty-eight SGA patients were included for further analysis. Other variants of GA were not reported. The provided **Table 1** illustrates in more detail the characteristics of every SGA patient included in our study.

A strong female predilection of 2.5:1 is noted among our patients. The median age at the first presentation was 3.75 years (range 1–12.5 years). SGA lesions were mainly found on the lower extremities ($n = 26$). In 50% of the patients, the SGA lesions were located on the lower leg area, indicating the high clinical possibility of a typical location for an SGA lump. Ten patients presented with multiple lesions. The SGA lumps were described as solid, nontender, and without signs of inflammation. All children were otherwise healthy, and the SGA lumps were not associated with overlying cutaneous abnormalities.

The median time from the subcutaneous lump(s) appearance until the first presentation at the hospital reported by parents was 2 months (range 0.5–5 months). In 9 SGA patients (33%), parents reported that trauma preceded the appearance of the lump(s), and its persistence made them seek a doctor's opinion.

Every SGA patient included in the study has received an ultrasound examination (US) at the time of the first presentation. An unclear subcutaneous soft tissue mass with poorly defined borders, hypo- and hyperechoic zones, and mild vascularization was regularly described. In 16 SGA patients (57%), x-rays were performed at the time of the first presentation to exclude osseous abnormalities. Because of the several possible pathologies and the difficulty in excluding a potential malignancy, 12 patients (43%) were referred for magnetic resonance imaging (MRI), all of which had to be performed under general anesthesia. Yet, MRI findings did not yield a definitive diagnosis in any of the cases. The lesions were regularly described as subcutaneously located with ill-defined borders. Imaging led to the consideration of several differential diagnoses, most commonly a subcutaneous low-flow vascular anomaly, fibromatosis, fasciitis, and post-traumatic fat necrosis. Only in one case was SGA considered among the potential differential diagnoses.

Surgical intervention was performed in 18 patients (64%), including all who received an MRI. The median time between the first presentation of the child in the hospital and the surgical intervention was one month. Biopsy ($n = 6$) or complete excision ($n = 12$) was performed depending on the size of the lesion(s). Preoperative lab work included a complete blood count and basic metabolic panel, which resulted uneventfully in every case.

All patients who did not undergo surgery (10/28) were diagnosed by an attending specialist who recognized SGA after clinical and imaging examinations. These children experienced a spontaneous resolution of the subcutaneous lesion(s) which lasted from 7 to 29 months. Two of these patients received local corticosteroid treatment for 2 weeks, which led to a mild reduction of the lump

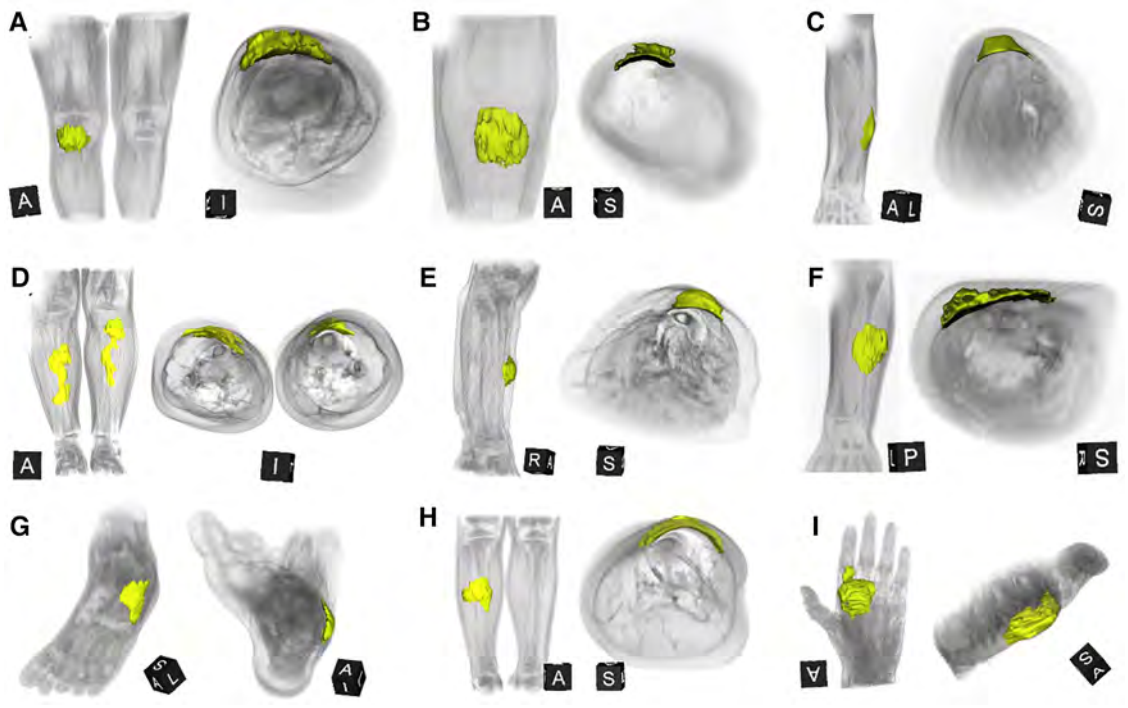

FIGURE 2
This composite figure shows 3D-reconstructions of magnetic resonance imaging (MRI) of all 9 patients with subcutaneous granuloma annulare (SGA) on the extremities who were evaluated by MRI. The 3D reconstructions of SGA (yellow) are overlaid by volume renderings of the respective extremity regions (gray) for reference. Note that all SGA lesions characteristically demonstrate a round or oval area with cap-shaped morphology, extending from the deep fascia into the subcutaneous layer. (**A**) right knee; (**B**) left lower leg; (**C**) left forearm; (**D**) right and left lower legs; (**E**) right lower leg; (**F**) left forearm; (**G**) left foot; (**H**) right lower leg; (**I**) left hand.

(s) size, whereafter the local treatment was discontinued. The pediatric surgeons who clinically suspected these lesions to be SGA lesions decided on the clinical follow-up of these patients.

The median time of the follow-up was 19 months (range 14–48 months). Two patients who underwent complete surgical excision of the lump experienced a local recurrence occurring 4 and 5 months after surgery, respectively. Both recurrent cases resolved spontaneously 6 months later.

All patients were reviewed in November 2021 in the frame of the long-term follow-up. One girl had developed juvenile chronic arthritis 5 years after the biopsy for SGA, and another girl was diagnosed with chronic inflammatory bowel disease 9 years after having a complete excision of SGA.

A careful retrospective review of all imaging led to the recognition of a novel and specific imaging sign for SGA, which we are not aware to be present in other pathologies. The SGA lesions show a well-defined broad-based rounded fascial border and an ill-defined crescent, cap-shaped epifascial border (**Figure 1**). We have named this typical shape of the SGA lesion "the epifascial cap sign". The 3D reconstructions of 9 MR investigations in 9 children with SGA lesions on the extremities are performed to present the SGA lesions in a more illustrative way and are shown in **Figure 2**. They can help better estimate the lesion's location and shape, but regular MRI sequences are sufficient to identify the "epifascial cap sign". The 3D analysis takes about 10 to 15 min for each lesion, mainly depending on the software solution available. SGA lumps mirror raised, rounded masses that project over the surface of the muscle's fascia without invading the underlying tissues. The SGA lesions are isointense relative to the muscles on T1-weighted images (**Figures 1C**, **3**) and hyperintense relative to the muscles on T2-weighted images (**Figures 1A**, **4**). In addition, the lesions are homogeneous in both T1 and T2 weighted MRI sequences and show variable enhancement after contrast material injection (**Figure 4**, small boxes). The MRIs of patients with SGA lesions on the head were performed to exclude intracranial and/or osseous abnormalities. The SGA lesions on the head had a median volume of 0.11 ml (range 0.05–0.14 ml) and were too small for a 3D reconstruction (**Figure 5**). The median volume of the SGA lesions on the extremities in patients receiving MRI was 2.7 ml (range 1.3–6.3 ml). A detailed retrospective review of the archived ultrasound images of our SGA patients confirmed the cap shape of SGA lesions (**Figure 6**).

Discussion

In the present study, we show for the first time that SGA lesions mirror a raised-rounded epifascial cap with a broad circular base and a continuous curved surface shape that extends towards the more superficial tissues. This shape of SGA is characteristic of this disease and, to the best of our knowledge, is not found in any other subcutaneous lesions.

Most SGA cases occurred around the age of 4 years (**Figure 7**) with greater frequency in girls, confirming the female predilection of this disease, as reported in previous studies (14, 19–21). Our

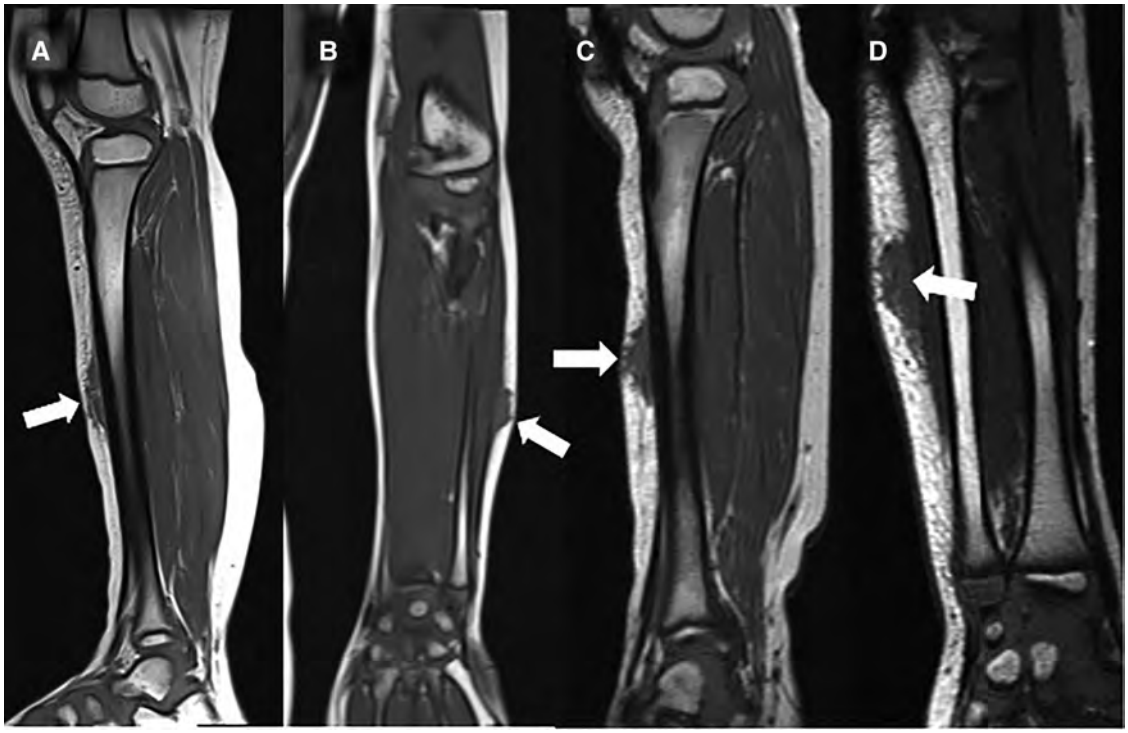

FIGURE 3
This composite figure shows representative T1-weighted magnetic resonance images (MRI) in sagittal or coronal orientation through the extremities of 4 children with subcutaneous granuloma annulare (SGA). Note the cap-shaped appearance of SGA lesions and that in T1-weighted MRIs they present as homogenous lesions (arrows) isointense relative to the muscles. (A) left lower leg, (B) left forearm, (C) right lower leg, (D) left forearm.

investigation highlights that children with SGA present with painless, nonmobile, subcutaneous lumps on their lower extremities, mainly on the pretibial area and other trauma-exposed bony prominences, like the scalp, the ulnar side of the forearms, hands, and feet. Children are otherwise healthy, and the SGA lumps are not associated with overlying cutaneous abnormalities.

Trauma has repeatedly been reported as one of the triggering events in the etiology of SGA (22). However, the pathophysiologic mechanisms behind it are still unknown. Local trauma has also been reported in one-third of our patients. Therefore, it is possible that lesions on the lower extremities, especially areas vulnerable to trauma like the pretibial areas, are related to repetitive, sustained injuries from minor events during physical activities. Minor trauma of the bony prominences in the pediatric age group is a normal and common event, elucidating further the predisposition of the pediatric population to this condition. However, in most cases, a history of injury cannot be obtained, perhaps due to the prolonged interval between trauma and the initial observation of the lesion or other unknown factors. Thus, there must be other overriding factors, the presence or absence of which determines whether or not children develop SGA.

In the absence of a trauma history, the clinical picture usually resembles a manifestation of a neoplastic disorder in the eyes of a physician unfamiliar with the SGA entity. As a matter of fact, despite the harmless nature of the SGA lumps, a large portion of

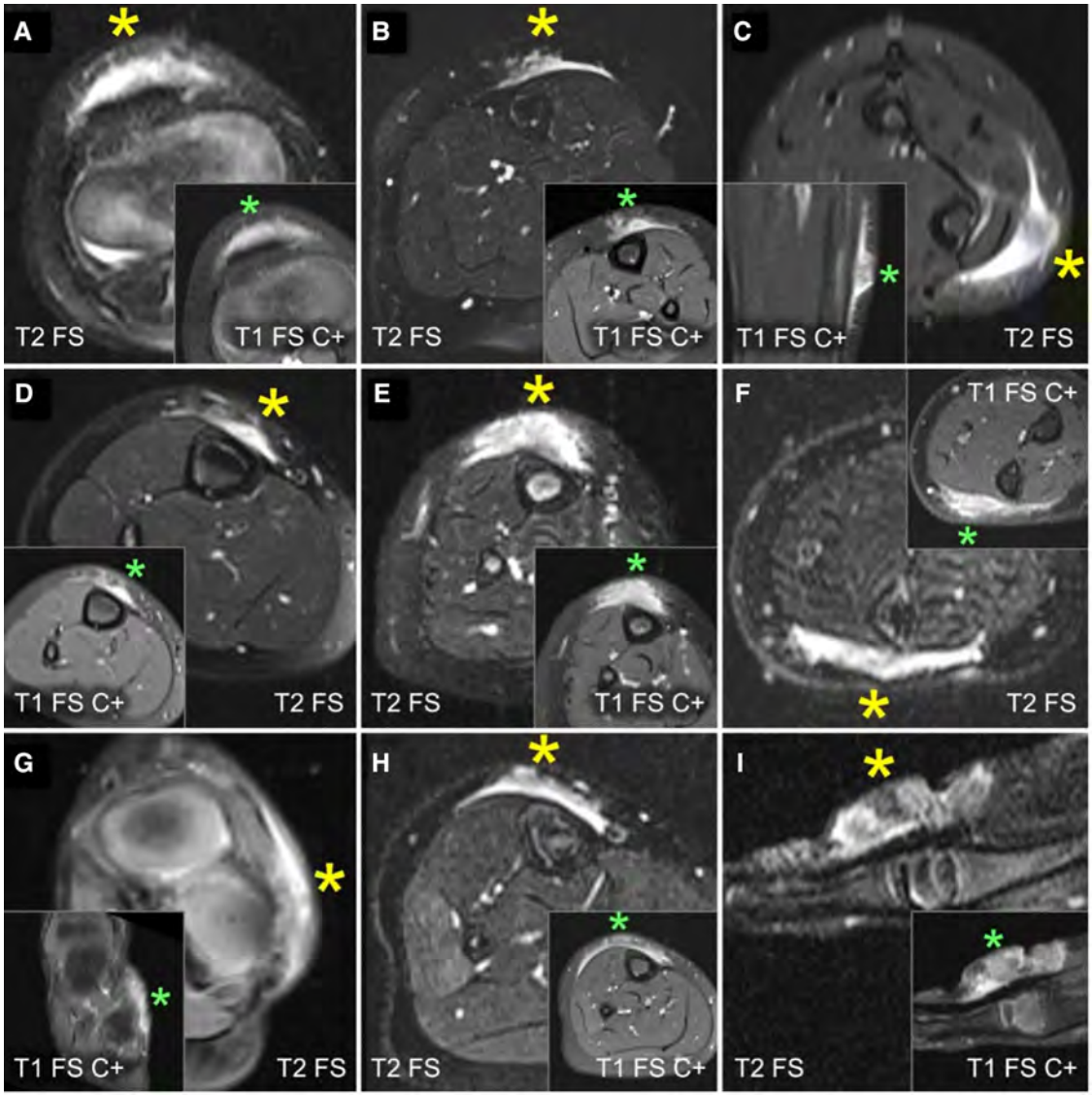

FIGURE 4
This composite figure shows representative slices of magnetic resonance imaging (MRI) through the subcutaneous granuloma annulare (SGA) on the extremities of 9 patients evaluated by MRI. The large boxes depict T2-weighted sequences with fat suppression ("T2 FS"). The small boxes depict T1-weighted sequences with fat suppression and intravenous contrast ("T1 FS C+"). Asterisks mark the locations of the SGA. A common finding in all presented cases is the cap-shaped lesion extending from the deep fascia into the subcutaneous fatty tissue. These lesions show heterogeneously hyperintense signal relative to the muscles in T2 FS images and marked contrast enhancement in T1 FS C+ . (**A**) right knee; (**B**) left lower leg; (**C**) left forearm; (**D**) right lower leg; (**E**) right lower leg; (**F**) left forearm; (**G**) left foot; (**H**) right lower leg; (**I**) left hand.

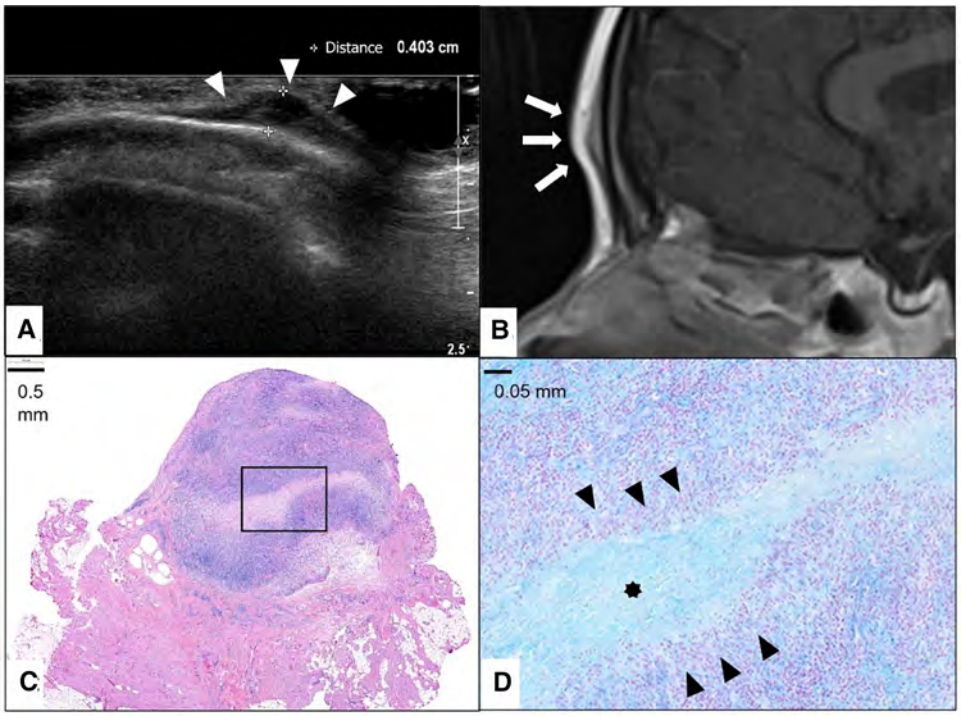

FIGURE 5
This composite figure shows a frontal location of the subcutaneous granuloma annulare (SGA). Note the epifascial cap sign in the ultrasound image marked with white arrowheads (**A**) and in the representative slice of magnetic resonance imaging (MRI) marked with white arrows. (**B**) The completely excised SGA lesion is localized in the subcutis overlying the fascia and is characterized by areas of necrobiotic granulomas shown here in hematoxylin and eosin staining. (**C**) The area marked with a box in (**C**) is enlarged in (**D**), showing alcian blue stain highlighting the mucin within the central zone of necrobiosis (star) surrounded by palisading histiocytes and lymphocytes (black arrowheads).

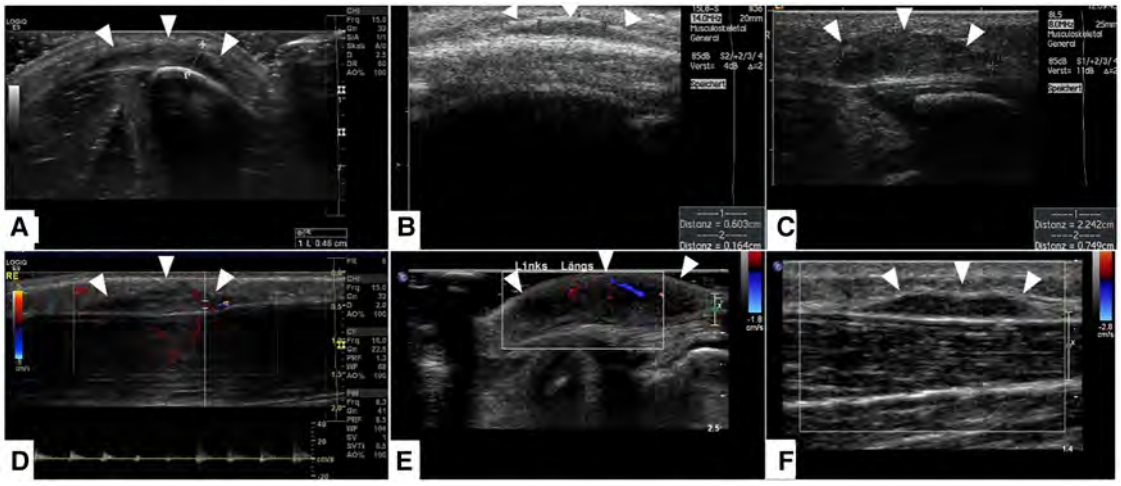

FIGURE 6
This composite figure shows representative slices of ultrasound imaging through the subcutaneous granuloma annulare (SGA) in 6 patients who had their final diagnosis by histopathology after excisional or incisional biopsy. A common finding in all presented cases is the cap-shaped SGA lesion extending from the deep fascia to the subcutaneous fatty tissue. The epifascial border is marked with white arrows. These lesions show heterogeneously hypoechoic signal in B-mode (**A–C**). The lesions stay hypoechoic and show mild perfusion in color mode US (**D–F**). (**A**)—right lower leg, (**B**)—scalp, (**C**)—right lower leg, (**D**)—right lower leg, (**E**)—left foot dorsum, (**F**)—left lower leg.

our patients underwent either incisional or excisional biopsy of the painless lump due to an unclear diagnosis and fear of a possible malignant trait. Indeed, according to a review from Chung et al., SGA is the most frequently biopsied, benign soft tissue mass in children under 5 despite its very low clinical incidence in the United States (9).

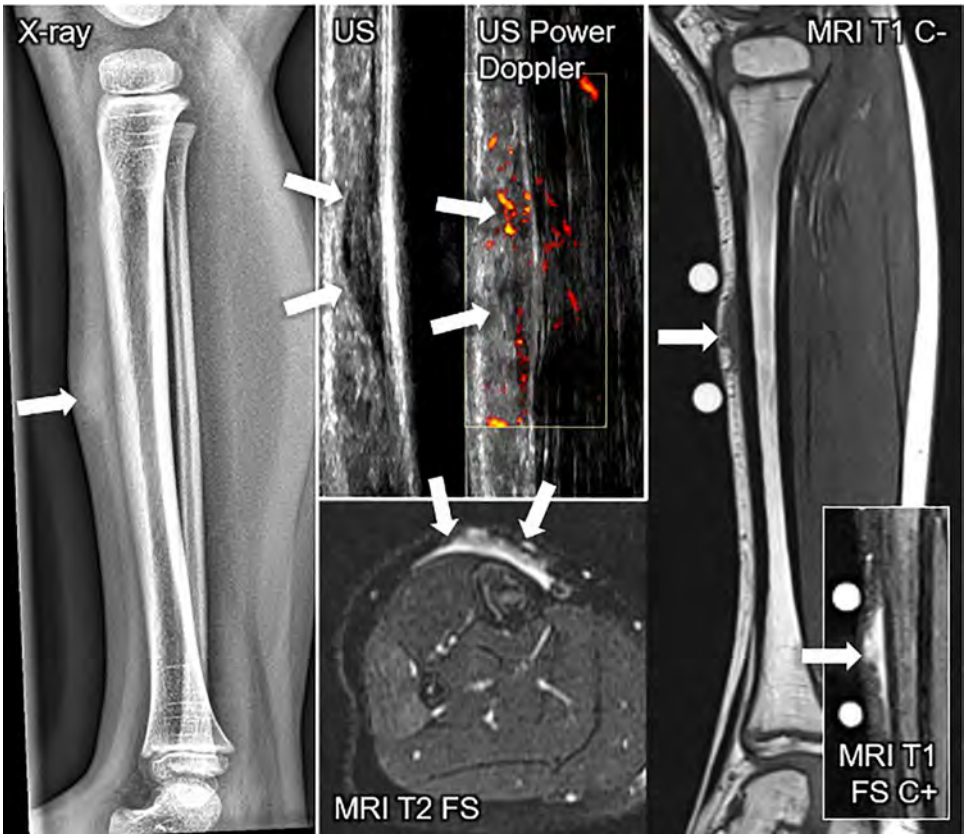

FIGURE 7
This composite figure shows various imaging methods used to evaluate a firm, immobile, indolent subcutaneous lesion in the mid-pretibial region of the right lower leg of a 4-years old girl. The lateral x-ray view of the lower leg depicts a thickened pretibial subcutaneous tissue (arrow), but no osseous abnormalities. The ultrasound image (US) shows a hypoechoic lesion in the typical epifascial cap shape (2 arrows) characteristic of subcutaneous granuloma annulare (SGA), confirmed by histopathological examination. Power Doppler US indicates slight hyperperfusion (2 arrows) in the area of SGA as compared to the surrounding tissue. In T1-weighted magnetic resonance images (MRI T1 C-), SGA presents as a homogenous lesion (1 arrow) isointense relative to the muscles. In T2-weighted images with fat suppression (MRI T2 FS), SGA shows a heterogeneously hyperintense signal relative to the muscles (2 arrows) extending from the muscular fascia into the adjacent subcutaneous tissue in a cap shape. Finally, in T1-weighted images with fat suppression and intravenous contrast (MRI T1 C+) SGA shows a marked contrast enhancement (1 arrow).

Few studies have described the MRI characteristics of the SGA lesions but failed to find a common pathognomonic imaging pattern, enabling clinicians to properly diagnose and differentiate SGA from other possible diseases based solely on imaging characteristics (9, 11, 14, 16, 23). Our present study recognized a reproducible shape of the SGA lesions, consistent in MR imaging of all children with SGA. This typical shape of SGA nodules mirrors a raised-rounded cap projecting on the surface of the muscle's fascia, which can be reliably used as a typical imaging shape for SGA lumps in MRI. Recognition of this sign in an otherwise healthy child presenting with a symptomless subcutaneous swelling should lead clinicians to suspect SGA, recommend a follow-up visit in 4 weeks, and prevent the majority of children with SGA from undergoing further invasive diagnostic procedures. We believe this sign to be the typical sign for SGA as, to the best of our knowledge, we are unaware of another subcutaneous disease that presents in this shape. Because SGA is a self-limiting disease, we speculate that the tissue characteristics of SGA lesions might change over their lifetime. In addition, the number and size of necrobiotic areas might also influence the imaging appearance of these lesions. However, the epifascial cap shape of the lesions seems not to be significantly impacted. Experience with SGA in terms of characteristic imaging findings is limited. Lack of awareness is believed to be the most crucial factor in why differential diagnoses did not include SGA, as in the present study. Learning new patterns or finding more specific signs in rare lesions like SGA is challenging.

The epifascial cap shape of the SGA lesions is also evident in US examinations, even though our retrospective analysis of the US images has limited value and reliability due to inter-examiner differences and the lack of standardized guidelines for image assessment of subcutaneous tissues. The US has three major obstacles which are difficult to standardize: the cooperation of a young patient, the subjectivity of the examiner, and the intensity of pressure applied to the lesions with the US probe, which often alters the shape of the subcutaneous lesions. On the US images of most of our SGA patients, we have detected the same cap-shaped presentation located on the muscle's fascia compatible

with the sign as it is seen on the MRI images of these patients. US findings were otherwise described as solid nodules with ill-defined borders and noted central hypoechoic zone surrounded by a hyperechogenic periphery, agreeing with the sonographic characteristics of SGA reported in a few previously published studies (11, 12, 15, 17, 24–26). MRI is often performed because it is one of the most specific imaging modalities to noninvasively clarify lesions whose entities have remained unclear. However, MRI is expensive, and downside of MRI is that in children under the age of 7, it often requires general anesthesia. It would be an outstanding achievement to diagnose SGA based on US findings alone. However, it must be considered that the incidence of SGA is low, impairing the potential gain knowledge at a high rate.

In addition, we have reviewed all previously published cases of SGA that have provided MR or US imaging of the lumps and confirmed that every reported image in the literature so far consistently presents as an epifascial cap formation (9, 11, 12, 14–16, 19, 20, 24–30). The only reference in the current literature we found to describe different MR characteristics of the SGA lump as compared to what we have just described concerns an unusual infiltrative forearm lesion in a 3-year-old girl with juvenile-onset diabetes (31). According to the authors of this report the lesion disappeared one month after the biopsy and when the glycemic control was achieved.

There are numerous subcutaneous pathologies in children, with both specific and unspecific imaging findings. In some diseases, subcutaneous lesions can be one of several clinical signs in the context of systemic diseases such as rheumatoid arthritis, sarcoidosis, tuberculosis, and others, with imaging findings that are not specific. Most of these lesions present as nodules, which can be singular or multiple, and vary in size. The nodules are mobile, show irregular shape and margins in imaging, and enhance after the application of a contrast agent in MRI, due to inflammation [10, 14, 15]. Therefore, clinical correlation and, if necessary, histological confirmation of diagnosis are crucial for accurate diagnosis and management of subcutaneous pathologies that present in the nodular form. To the best of our knowledge, these lesions have not been reported in the literature as presenting in the "epifascial cap" shape, as observed in completely healthy children with SGA. Given the typical cap shape of each SGA lesion, the initial still illusive stimulus that triggers the recruitment of the inflammatory particles may lie in the subcutaneous tissue. These inflammatory cells migrate along the fascia and accumulate to form a tight aggregate around the inflammatory stimulus. The activated inflammatory cells seem unable to efficiently remove the inflammatory stimulus, leading to a secondary inflammatory response that ultimately gives rise to granuloma formation. SGA granulomas consist of central necrosis surrounded by histiocytes, eosinophils, and lymphocytes in a tier-like fashion. This massive tight aggregate of inflammatory cells around the stimulus probably explains why SGA often presents as a non-vascularized immobile subcutaneous lesion, even though peripheral vascularization has often been described in color Doppler mode (24, 25). Elucidating the pathogenesis of SGA seems challenging, but our understanding is constantly evolving. Recently a study by Min et al. reported the upregulation of Th1 and Th2 pathways in these lesions, and a 2021 study by Wang et al. found activation of the Th1 and JAK-STAT pathways in their cohort (32, 33).

The hypothesis of granuloma formation on an autoimmune basis and its association with diabetes mellitus, rheumatoid disease, and other systemic disorders have been investigated in several studies (34–36). A study by Grogg et al. (21) reported 2 cases of diabetes mellitus in 34 SGA patients. Yet, Felner et al. (34) found no significant correlation between diabetes mellitus and SGA in their cohort of 47. None of the children in our study developed diabetes mellitus during the long-term follow-up. Even though further evidence is needed to support any possible association, we have noted that occasional SGA female patients seem susceptible to developing autoimmune conditions later in life, as one case of juvenile chronic arthritis and one chronic inflammatory bowel disease were also reported in our cohort. However, it is unclear if this occasional association is related to the clear female gender bias of autoimmune disorders in general, as SGA also occurs more frequently in females. The association of SGA lesions with vascular and connective tissue diseases is also often discussed (21, 37), but none of the children in our study presented with vascular changes or connective tissue disorders. While many inconsistencies exist in the published literature, further research is needed to clarify the discrepancies and draw definite causal conclusions about this rare disease.

The epifascial cap is a typical imaging sign of SGA lesions which, to the best of our knowledge, distinguishes this disease from other subcutaneous lesions. Recognition of this sign in an otherwise healthy child presenting with a symptomless subcutaneous lump over bony prominences should enable clinicians to diagnose SGA accurately, schedule the patient for a follow-up visit and prevent the majority of children with this disease from undergoing further invasive diagnostic procedures.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

This study was approved by the Institutional Ethics Committee of the Medical University of Graz (EK-No. 33-126 ex 20/21), and informed consent was waived. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

EQH: supervision and project dministration. This manuscript is a part of the doctoral thesis of BPB. BPB, ST and EQH: contributed to the conception and design of the study. ST:

created and analyzed the 3D reconstruction of each case included in the study. PG and IB: contributed to data collection and data analysis of the outcomes of interest. All listed authors contributed to the acquisition, analysis, or interpretation of the data for the study. BPB: wrote the first draft of the manuscript. All authors contributed to the article and approved the submitted version.

Acknowledgments

The authors thank Candidate of Medicine Dora Haxhija for administrative and technical support. This work has been funded by the Doctoral School "Bone, Muscle and Joint" of the Medical University of Graz, Graz, Austria.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. Keimig EL. Granuloma annulare. *Dermatol Clin*. (2015) 33:315–29. doi: 10.1016/j.det.2015.03.001

2. Piette EW, Rosenbach M. Granuloma annulare: clinical and histologic variants, epidemiology, and genetics. *J Am Acad Dermatol*. (2016) 75:457–65. doi: 10.1016/j.jaad.2015.03.054

3. Thornsberry LA, English JC. Etiology, diagnosis, and therapeutic management of granuloma annulare: an update. *Am J Clin Dermatol*. (2013) 14:279–90. doi: 10.1007/s40257-013-0029-5

4. Joshi TP, Duvic M. Granuloma annulare: an updated review of epidemiology, pathogenesis, and treatment options. *Am J Clin Dermatol*. (2022) 23(1):37–50. doi: 10.1007/s40257-021-00636-1

5. Patrizi A, Gurioli C, Neri I. Childhood granuloma annulare: a review. *G Ital Dermatol Venereol*. (2014) 149:663–74. PMID: 25279495.

6. Butsch F, Weidenthaler-Barth B, von Stebut E. Granuloma anulare. *Der Hautarzt*. (2015) 66:867–77. doi: 10.1007/s00105-015-3704-z

7. Requena L, Fernández-Figueras MT. Subcutaneous granuloma annulare. *Semin Cutan Med Surg*. (2007) 26:96–9. doi: 10.1016/j.sder.2007.02.006

8. Endo Y, Sekiguchi A, Motegi S, Ishikawa O. Subcutaneous granuloma annulare on the heel: a case report and review of the Japanese published work. *J Dermatol*. (2020) 47:677–9. doi: 10.1111/1346-8138.15352

9. Chung S, Frush DP, Prose NS, Shea CR, Laor T, Bisset GS. Subcutaneous granuloma annulare: MR imaging features in six children and literature review. *Radiology*. (1999) 210:845–9. doi: 10.1148/radiology.210.3.r99mr11845

10. Kransdorf MJ. Benign soft-tissue tumors in a large referral population: distribution of specific diagnoses by age, sex, and location. *AJR Am J Roentgenol*. (1995) 164:395–402. doi: 10.2214/ajr.164.2.7839977

11. Pederiva F, Paloni G, Berti I. Subcutaneous granuloma annulare: a diagnostic conundrum-learning from mistakes. *Pediatr Emerg Care*. (2017) 33:e30–1. doi: 10.1097/PEC.0000000000000591

12. Vázquez-Osorio I, Quevedo A, Rodríguez-Vidal A, Rodríguez-Díaz E. Usefulness of ultrasonography in the diagnosis of subcutaneous granuloma annulare. *Pediatr Dermatol*. (2018) 35:e200–1. doi: 10.1111/pde.13470

13. Sabuncuoğlu H, Oge K, Söylemezoğlu F, Sağlam A. Subcutaneous granuloma annulare of the scalp in childhood: a case report and review of the literature. *Turk Neurosurg*. (2007) 17:19–22. PMID: 17918673.

14. Navarro OM, Laffan EE, Ngan B-Y. Pediatric soft-tissue tumors and pseudotumors: MR imaging features with pathologic correlation: part 1. Imaging approach, pseudotumors, vascular lesions, and adipocytic tumors. *Radiographics*. (2009) 29:887–906. doi: 10.1148/rg.293085168

15. Shah SH, Callahan MJ. Ultrasound evaluation of superficial lumps and bumps of the extremities in children: a 5-year retrospective review. *Pediatr Radiol*. (2013) 43:23–40. doi: 10.1007/s00247-012-2590-0

16. Kransdorf MJ, Murphey MD, Temple HT. Subcutaneous granuloma annulare: radiologic appearance. *Skeletal Radiol*. (1998) 27:266–70. doi: 10.1007/s002560050379.

17. Rodríguez-Garijo N, Tomás-Velázquez A, Estenaga A, Antoñanzas J, Segurado-Rodríguez MA, García-Tobar L, et al. Granuloma annulare subtypes: sonographic features and clinicopathological correlation. *J Ultrasound*. (2022) 25(2):289–95. doi: 10.1007/s40477-020-00532-0

18. Fedorov A, Beichel R, Kalpathy-Cramer J, Finet J, Fillion-Robin J-C, Pujol S, et al. 3D Slicer as an image computing platform for the quantitative imaging network. *Magn Reson Imaging*. (2012) 30:1323–41. doi: 10.1016/j.mri.2012.05.001

19. Jankowski PP, Krishna PH, Rutledge JC, Waldhausen J, Avellino AM. Surgical management and outcome of scalp subcutaneous granuloma annulare in children. *Neurosurgery*. (2008) 63:E1002. doi: 10.1227/01.NEU.0000333264.11514.FE

20. Letts M, Carpenter B, Soucy P, Davidson D. Subcutaneous granuloma annulare of the extremities in children. *Can J Surg*. (2000) 43:425–30. PMID: 11129830.

21. Grogg KL, Nascimento AG. Subcutaneous granuloma Annulare in childhood: clinicopathologic features in 34 cases. *Pediatrics*. (2001) 107:e42. doi: 10.1542/peds.107.3.e42

22. Evans MJ, Blessing K, Gray ES. Pseudorheumatoid nodule (deep granuloma annulare) of childhood: clinicopathologic features of twenty patients. *Pediatr Dermatol*. (1994) 11:6–9. doi: 10.1111/j.1525-1470.1994.tb00064.x

23. de Maeseneer M, vande Walle H, Lenchik L, Machiels F, Desprechins B. Subcutaneous granuloma annulare: MR imaging findings. *Skeletal Radiol*. (1998) 27:215–7. doi: 10.1007/s002560050368

24. Stenzel M, Voß U, Mutze S, Hesse V. A pretibial lump in a toddler—sonographic findings in subcutaneous granuloma annulare. *Ultraschall Med*. (2008) 31:68–70. doi: 10.1055/s-2007-963786

25. Riebel T, Scheer I. Subkutanes granuloma annulare: eine nicht zu vergessende differenzialdiagnose bei expansiven (weichteil-) läsionen an den unteren extremitäten von jungen kindern. *UltraschallMed*. (2010) 32:604–7. doi: 10.1055/s-0029-1245498

26. Davids JR, Kolman BH, Billman GF, Krous HF. Subcutaneous granuloma annulare: recognition and treatment. *J Pediatr Orthop*. (1993) 13:582–6. doi: 10.1097/01241398-199309000-00005

27. Vandevenne JE, Colpaert CG, de Schepper AM. Subcutaneous granuloma annulare: MR imaging and literature review. *Eur Radiol*. (1998) 8:1363–5. doi: 10.1007/s003300050553

28. Shehan JM, El-Azhary RA. Magnetic resonance imaging features of subcutaneous granuloma annulare. *Pediatr Dermatol*. (2005) 22:377–8. doi: 10.1111/j.1525-1470.2005.22427.x

29. Lega S, Rabusin M, Pederiva F. Acute-onset pretibial swelling. *Indian Pediatr*. (2014) 51:334. doi: 10.1007/s13312-014-0390-3

30. Vogel MN, Hansmann S, Kümmerle-Deschner J, Schäfer J, Horger M. Das subkutane granuloma annulare. *RöFo—Fortschritte auf dem Gebiet der Röntgenstrahlen und der Bildgebenden Verfahren*. (2007) 179:1215–8. doi: 10.1055/s-2007-992883

31. Agrawal AK, Kammen BF, Guo H, Donthineni R. An unusual presentation of subcutaneous granuloma annulare in association with juvenile-onset diabetes: case report and literature review. *Pediatr Dermatol*. (2012) 29:202–5. doi: 10.1111/j.1525-1470.2011.01638.x

32. Min MS, Wu J, He H, Sanz-Cabanillas JL, del Duca E, Zhang N, et al. Granuloma annulare skin profile shows activation of T-helper cell type 1, T-helper cell type 2, and Janus kinase pathways. *J Am Acad Dermatol*. (2020) 83:63–70. doi: 10.1016/j.jaad.2019.12.028

33. Wang A, Rahman N-T, McGeary MK, Murphy M, McHenry A, Peterson D, et al. Treatment of granuloma annulare and suppression of proinflammatory cytokine activity with tofacitinib. *J Allergy Clin Immunol*. (2021) 147:1795–809. doi: 10.1016/j.jaci.2020.10.012

34. Felner EI, Steinberg JB, Weinberg AG. Subcutaneous granuloma annulare: a review of 47 cases. *Pediatrics*. (1997) 100:965–7. doi: 10.1542/peds.100.6.965

35. Yun JH, Lee JY, Kim MK, Seo YJ, Kim MH, Cho KH, et al. Clinical and pathological features of generalized granuloma annulare with Their correlation: a retrospective multicenter study in Korea. *Ann Dermatol*. (2009) 21:113–9. doi: 10.5021/ad.2009.21.2.113

36. Davison JE, Davies A, Moss C, Kirk JMW, Taibjee SM, Agwu JC. Links between granuloma annulare, necrobiosis lipoidica diabeticorum and childhood diabetes: a matter of time? *Pediatr Dermatol*. (2010) 27:178–81. doi: 10.1111/j.1525-1470.2010.01099.x

37. Dahl Mv, Ullman S, Goltz RW. Vasculitis in granuloma annulare: histopathology and direct immunofluorescence. *Arch Dermatol*. (1977) 113:463–7. doi: 10.1001/archderm.1977.01640040071010

children

IMPACT FACTOR 2.835

Indexed in: PubMed

Article

Subcutaneous Granuloma Annulare vs. Subcutaneous Vascular Malformations in Children: A Diagnostic Challenge

Besiana P. Beqo, Paolo Gasparella, Christina Flucher, Sebastian Tschauner, Iva Brcic and Emir Q. Haxhija

MDPI

https://doi.org/10.3390/children10020362

children

MDPI

Article

Subcutaneous Granuloma Annulare vs. Subcutaneous Vascular Malformations in Children: A Diagnostic Challenge

Besiana P. Beqo [1,2], Paolo Gasparella [1,3], Christina Flucher [1,3], Sebastian Tschauner [4], Iva Brcic [5] and Emir Q. Haxhija [1,5,*]

[1] Department of Paediatric and Adolescent Surgery, Medical University of Graz, A-8036 Graz, Austria
[2] Boston Children's Hospital and Harvard Medical School, Boston, MA 02115, USA
[3] VASCERN VASCA European Reference Centre, Bichat-Claude Bernard Hospital, 75018 Paris, France
[4] Division of Paediatric Radiology, Department of Radiology, Medical University of Graz, A-8036 Graz, Austria
[5] Institute of Pathology, Medical University of Graz, A-8036 Graz, Austria
* Correspondence: emir.haxhija@medunigraz.at; Tel.: +43-(0)316-38513762; Fax: +43-(0)316-38513775

Abstract: Objectives. There are various subcutaneous lesions in children and often there is difficulty in obtaining an accurate diagnosis by non-invasive diagnostic procedures. Subcutaneous granuloma annulare (SGA) is a rare granulomatous disease that, even after imaging, is often mistaken for a low-flow subcutaneous vascular malformation (SVM). This study aimed to accurately identify clinical and imaging clues to distinguish SGA from low-flow SVM. Methods. We retrospectively analyzed complete hospital records of all children with a confirmed diagnosis of SGA and low-flow SVM who underwent MR imaging at our institution from January 2001 to December 2020. Their disease history, clinical and imaging findings, management, and outcome were evaluated. Results. Among 57 patients with granuloma annulare, we identified 12 patients (nine girls) with a confirmed SGA diagnosis who underwent a preoperative MRI. Their median age was 3.25 years (range 2–5 years). Of 455 patients diagnosed with vascular malformations, 90 had malformations limited to the subcutaneous area. Among them only 47 patients with low-flow SVM were included in the study and further analyzed. Our SGA cohort had a female predilection (75%) and a short history of lump appearance of 1.5 months. SGA lesions were immobile and firm. Before MRI, patients underwent initial evaluation by ultrasound (100%) and X-ray (50%). Surgical tissue sampling was performed in all SGA patients to establish a diagnosis. All 47 patients with low-flow SVM were diagnosed correctly by MRI. A total of 45 patients (96%) underwent surgical resection of the SVM. A careful retrospective review of imaging findings of patients with SGA and SVM showed that SGA present as homogenous lesions in the shape of an epifascial cap with a typical broad fascial base extending towards the subdermal tissue in the middle of the lesion. In contrast, SVMs always present with variable-sized multicystic or tubular areas. Conclusions. Our study shows clear clinical and imaging differences between low-flow SVMs and SGA. SGA presents characteristically in the shape of a homogenous "epifascial cap," which distinguishes these lesions from multicystic heterogenous SVMs.

Keywords: granuloma annulare; subcutaneous granuloma annulare; self-limiting; children; low-flow subcutaneous vascular malformations; venous malformations; lymphatic malformations

Citation: Beqo, B.P.; Gasparella, P.; Flucher, C.; Tschauner, S.; Brcic, I.; Haxhija, E.Q. Subcutaneous Granuloma Annulare vs. Subcutaneous Vascular Malformations in Children: A Diagnostic Challenge. *Children* **2023**, *10*, 362. https://doi.org/10.3390/children10020362

Academic Editor: Kyle J. Van Arendonk

Received: 31 December 2022
Revised: 1 February 2023
Accepted: 4 February 2023
Published: 11 February 2023

1. Introduction

Subcutaneous granuloma annulare (SGA) is a benign, subcutaneous disease of an unknown etiology that exclusively affects young children [1]. This uncommon disease is characterized by the sudden appearance of firm, immobile, solitary, or multiple subcutaneous lumps usually located over the bony prominences of the extremities or the scalp [2]. These lesions are painless and seem to spontaneously self-resolve in about two years without requiring any type of treatment [3,4].

Reaching an informed and accurate diagnosis in children with SGA commonly presents a real clinical challenge for a medical examiner [5]. The challenge becomes evident when

one tries to develop a reasonable differential diagnosis for the patient's symptoms. Considering all the possible diverse pathologies and their overlapping clinical behaviors, SGA is most commonly mistaken for subcutaneous low-flow vascular malformations (SVM) [6,7].

Vascular malformations are not neoplasms but inborn errors of angiogenesis that grow proportionally with the child and usually persist lifelong [8,9]. They can be clinically depicted as venous, capillary, lymphatic, arteriovenous, or mixed [10]. In addition, vascular malformations can be classified as low-flow or high-flow, depending on their hemodynamic characteristics. The low-flow vascular malformations are composed of nonarterial components and can either be capillary, venous, lymphatic, or any combination of these components [11]. Depending on their variable clinical appearance and presentation, subcutaneous low-flow vascular malformations can also substantially vary in imaging appearance.

To date, little to nothing has been reported on clinical imaging characteristics that could distinguish SGA from SVM. This knowledge gap gives rise to diagnostic confusion, and reaching a definitive diagnosis in these cases often requires further invasive diagnostic procedures [5,12–14]. As a consequence, regardless of the harmless and self-limiting nature of the SGA, accurate diagnosis is most commonly achieved only by histopathologic analysis after an incisional or excisional biopsy of the child's lump(s) [15–17].

This study aims to analyze the distinctive clinical and imaging characteristics of SGA and SVM and highlight a rational diagnostic-pathway approach to patients suspected of having SGA.

2. Patients and Methods

This is a cross-sectional, explorative, retrospective study of patients 0–18 years old diagnosed with SGA or low-flow SVM who underwent MR imaging to evaluate their subcutaneous lesions between 1 January 2001, and 31 December 2020. All patients with a confirmed diagnosis of SGA and low-flow SVM were eligible to be included in our study. A positive histopathologic analysis report for SGA was accepted as a confirmed SGA case.

The specific vascular malformation category for the SVMs was assigned based on the evaluation of an expert clinical examination, medical history, lab, and imaging diagnostics. Using the classification of the International Society for the Study of Vascular Anomalies (ISSVA), SVM patients were grouped into arterio-venous malformations (AVM), venous malformations (VM), lymphatic malformations (LM), and mixed malformations [10].

Exclusion from the study followed all patients clinically diagnosed by pathognomonic clinical signs, such as lesion pulsation for AVMs or bluish compressible lesions for VMs, and patients who did not undergo an MRI evaluation of their lesion(s).

The electronic hospital records (medocs) of all patients included in the study were retrospectively reviewed regarding the patient's disease history, management, and outcome. The information identified and analyzed for each case included: sex, age at the initial encounter, the location of the lesion(s), the number of the lesion(s), associated pain, the clinical description of the lesion(s), the report of trauma prior to the appearance of the lesion(s), the time between the first presentation at our department and treatment starting, the diagnostic imaging and lab work performed, the histopathologic report provided, the type of treatment, the recurrence after treatment, and the time to follow-up. Descriptive statistical analysis was performed. This study has been approved by the Ethics Committee of the Medical University of Graz (Approval code: EK-No. 33-126 ex 20/21; date: 20 January 2021).

3. Results

A total of 57 patients presented with granuloma annulare at our department during the study period. Twenty-eight of these patients had a confirmed diagnosis of SGA. However, only 12 of them had a preoperative evaluation by magnetic resonance imaging (MRI) and, therefore, qualified to be included in this study.

Among 455 patients diagnosed with various vascular malformations at our department during the study period, 90 patients presented with a vascular malformation located just beneath the skin, in the subcutaneous tissue. Twenty-three of them were diagnosed clinically and therefore were excluded from further analysis; nine presented with pulsatile subcutaneous lesions, making the clinical diagnosis of an arteriovenous malformation obvious (Figure 1); and 14 had a history of bluish compressible subcutaneous lesions that clinically suggested the diagnosis of a venous malformation (Figure 2).

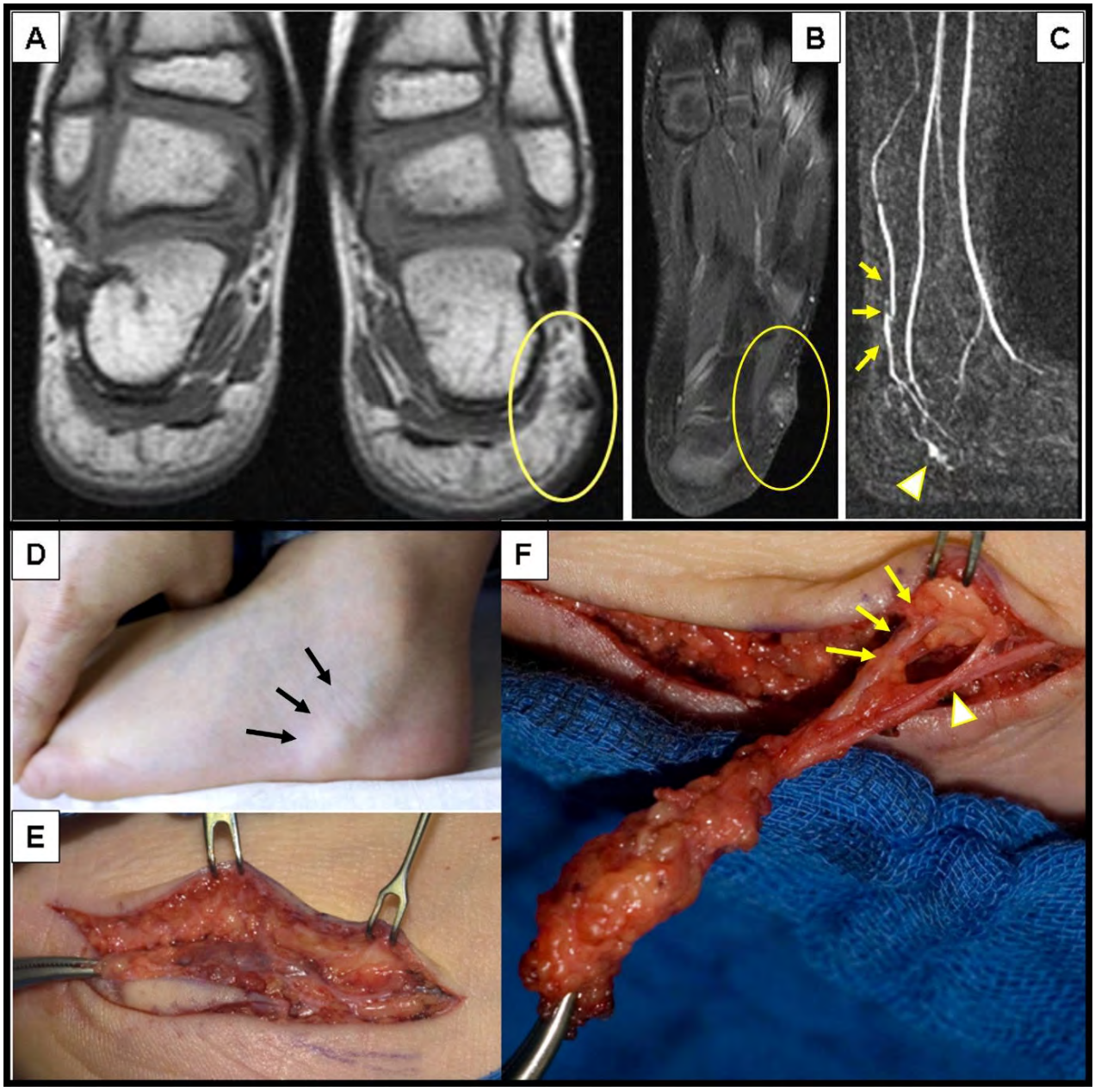

Figure 1. A 3-year-old boy with a pulsatile lesion under the malleolus lateralis of the left foot (**D**)—(black arrows). MRI showed a localized arterio-venous malformation in the subcutaneous tissue (**A**,**B**) with an AV shunt in the MR-angiography (**C**)—(arrowhead) depicted by the early visualization of the vein (**C**)—(yellow arrows). Complete surgical excision was performed (**E**) with ligation of the feeding artery (**F**)—(yellow arrows) and the draining veins (**F**)—(arrowhead).

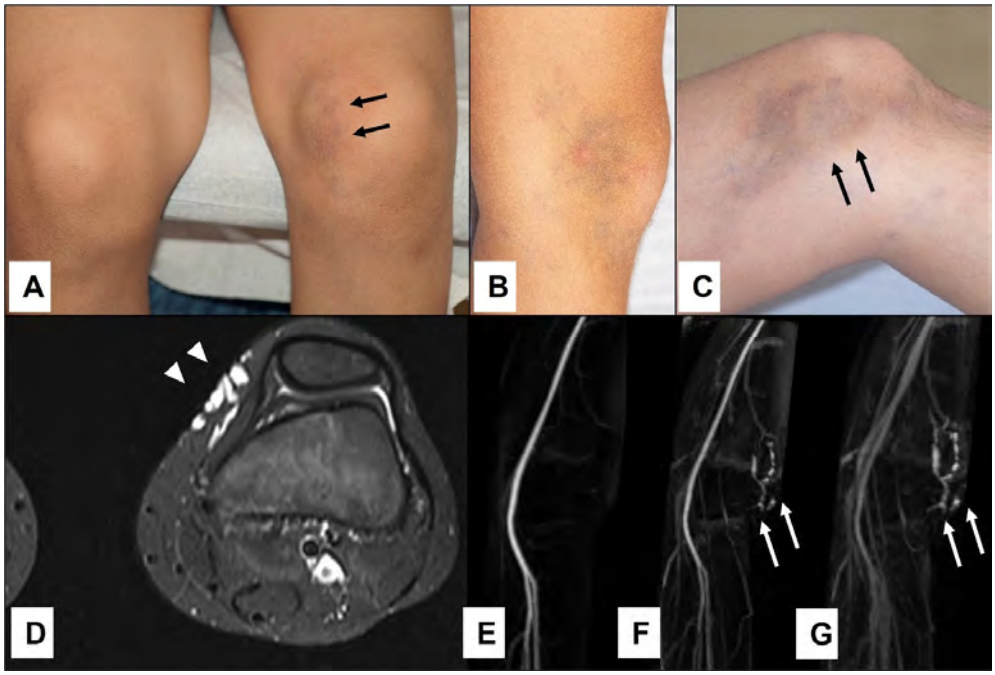

Figure 2. An 11-year-old boy presented with bluish swelling medially on the left knee (**A**): white (arrowheads). The lesion was compressible and would drain and flatten with the elevation of the leg indicating clinically the venous malformation (**B**,**C**)—(white arrowheads). MRI showed the exact location and extension of tubular-cystic venous malformation (**D**)—(white arrowheads), which filled with contrast material in the venous phase of the MR angiography (**E**–**G**)—(white arrows), confirming the clinical diagnosis. The patient was referred to sclerotherapy.

Out of 67 patients with a confirmed diagnosis of an SVM, only 47 had MRI records and were further qualified to be included in this study.

The demographic characteristics of the patients included in this study are presented in Table 1. Table 2 shows the location of the lesions in patients with SGA and low-flow SVM that underwent MR imaging.

Table 1. Characteristics of patients with subcutaneous granuloma annulare (SGA) and low-flow subcutaneous vascular malformations (SVM) who underwent MR imaging.

	N	Age in Years—Median (Range)	Girls N (%)	Surgical Intervention N (%)
SGA	12	3.25 (2–5)	9 (75%)	12 (100%)
SVM	47	5 (0–18)	19 (40%)	45 (96%)

Legend: SGA = subcutaneous granuloma annulare; SVM = subcutaneous vascular malformations; N = number of patients.

Table 2. Location of the lesions in patients with subcutaneous granuloma annulare (SGA) and low-flow subcutaneous vascular malformations (SVM) who underwent MR imaging.

	Total N (%)	Head and Neck N (%)	Upper Extremity N (%)	Lower Extremity N (%)	Trunk N (%)
SGA	12 (100%)	3 (25%)	3 (25%)	6 (50%)	0
SVM	47 (100%)	6 (13%)	23 (51%)	8 (19%)	10 (17%)
LM	27 (57%)	1	16	3	7
LVM	8 (17%)	3	3	1	1
VM	12 (26%)	2	4	4	2

Legend: SGA = subcutaneous granuloma annulare; SVM = subcutaneous vascular malformations; LM = lymphatic malformation; LVM = lymphatico-venous malformation; VM = venous malformation; N = number of patients.

3.1. Patients with Subcutaneous Granuloma Annulare

3.1.1. Clinical Presentation

A strong female predilection of 3:1 is noted in our SGA cohort. All patients with SGA who received an MRI were preschool children from two to five years old, with a median age of 3.25 years at their first presentation. Seven SGA patients presented with singular lesions, three patients had two lesions each, and two patients had three lesions each. All our patients with SGA on the scalp had multiple lesions. The pretibial area was noted to be the most commonly presented location for SGA, as almost half of our patients had at least one pretibial lesion. All SGA lesions were clinically described as firm, nontender, and immobile subcutaneous lumps without any signs of inflammation. No overlying cutaneous abnormalities were reported, and all the children were described as otherwise healthy. The SGA were said to have appeared on an average of one and a half months (range 0.5–3 months) before the time of encounter, and previous trauma at the site of SGA was reported in five cases (42%).

3.1.2. Presentation on X-ray

An X-ray examination was performed in half of our SGA patients (i.e., 6/12 or 50%) because of the firm and immobile nature of the lumps and the trauma history reported by parents. While excluding any types of bony abnormalities, a homogenous subcutaneous soft tissue shadow was regularly reported (Figure 3).

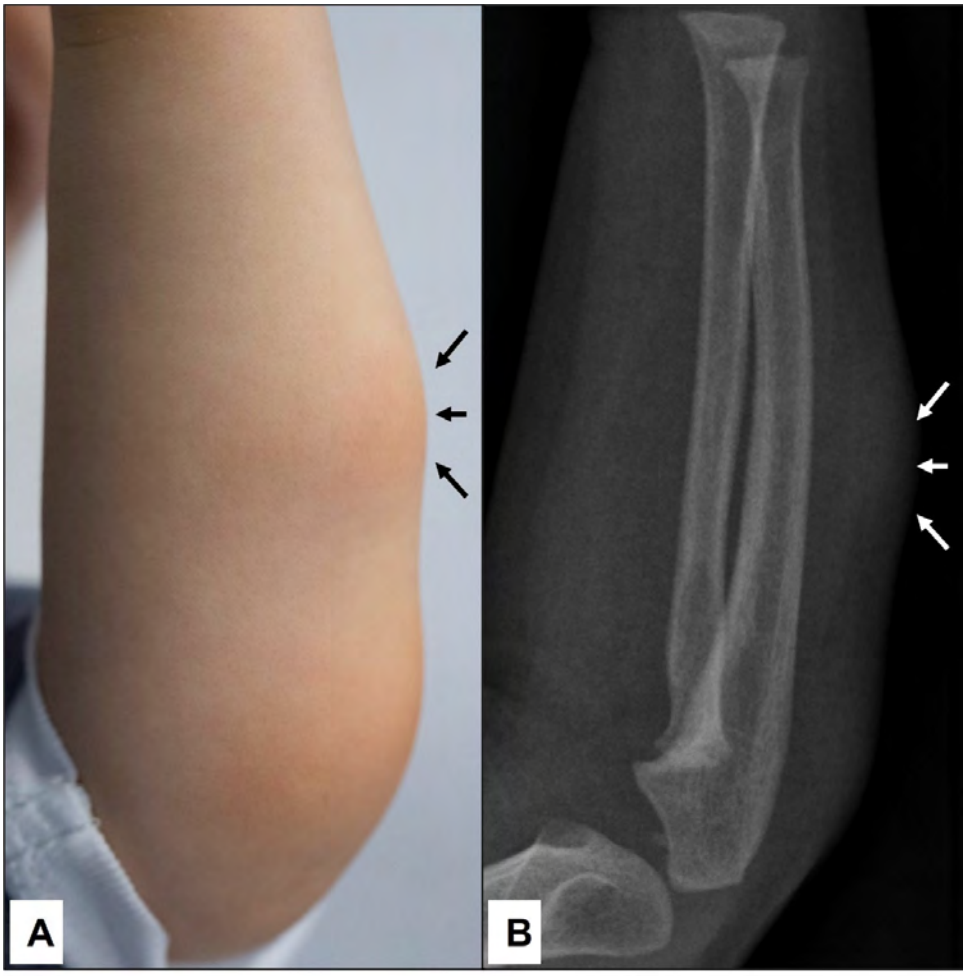

Figure 3. A 2-year-old boy was presented by his parents due to the swelling on the left forearm, which persisted for the last 2 months (**A**)—(black arrows). Because the subcutaneous lump was firm and immobile, an X-ray was conducted to exclude bone abnormalities (**B**). Note the homogenous soft tissue expansion in the subcutaneous area (white arrows) but no osseous involvement.

3.1.3. Presentation on Ultrasound

All SGA patients received an ultrasound examination (US) at their first encounter. On the US, SGA were described as nonspecific mass(es) with interacting hypo- and hyperechoic zones, ill-defined borders, and mild hypervascularization (Figure 4).

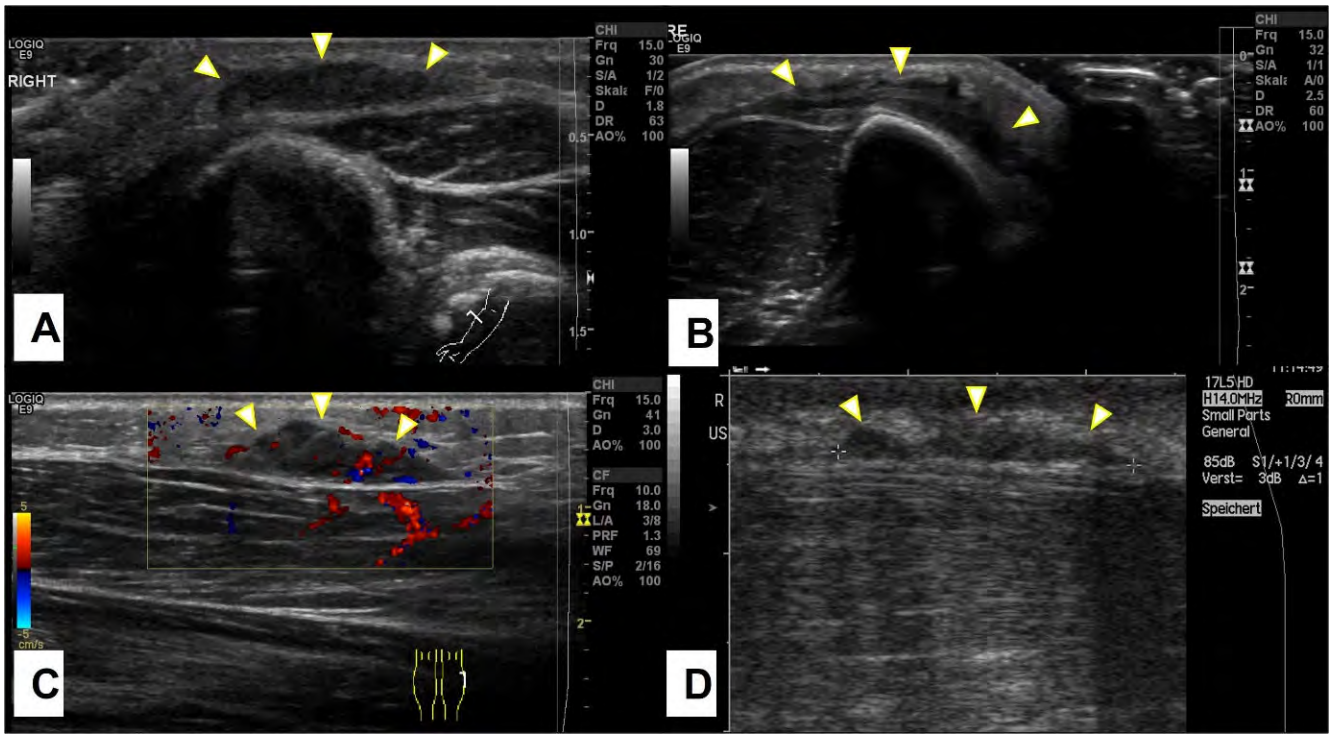

Figure 4. Representative slices of ultrasound imaging of subcutaneous granuloma annulare (SGA). The lesions are strictly epifascial with hypo- and hyper-echogenic zones and mild hypervascularization. A common finding is the cap shape of these lesions, marked with arrowheads. The depicted lesions were located on (**A**) the right forearm; (**B**) the right lower leg; (**C**) the left lower leg; (**D**) the right lower leg.

3.1.4. Presentation on MRI

Because the etiology of the subcutaneous lesions remained unclear, all patients were referred for further evaluation by MRI. However, the reported results of all 12 MRI examinations neither excluded malignancy nor determined the accurate diagnosis. On the MRI, the SGA was consistently described as limited to the subcutaneous tissue without invasion of the muscle's fascia. SGA was reported to be isointense relative to the muscles on T1-weighted images and hyperintense relative to the muscles on T2-weighted images. The lesions enhanced after contrast agent administration. The primary differential diagnosis in all patients was low-flow vascular malformation, followed by fibromatosis, fasciitis, panniculitis, and post-traumatic fat necrosis. SGA was considered as a differential diagnosis in one case only.

3.1.5. Invasive Diagnostic Procedures

Since a possible malignant nature of the lesion(s) could not be excluded, all children were referred for invasive tissue sampling. The preoperative lab work included a complete blood count and a basic metabolic panel, which resulted uneventfully in every case. Seven children underwent an excisional biopsy, and five had an incisional biopsy performed; all resulted in the histopathologic diagnosis of SGA. The median follow-up time after the surgical intervention was 11 months (range 6–17 months), and no further interventions were needed.

3.2. Patients with Low-Flow Subcutaneous Vascular Malformations

3.2.1. Clinical Presentation

In contrast to SGA, patients with SVM were mainly boys (60%) who presented at a median age of 5 years with a wide age range from birth to 18 years. The subcutaneous lesions in patients diagnosed with SVM were often clinically described as indolent, soft, and mobile. The lesions were described as bulging and tender in cases with sudden enlargement of the SVM after intracystic bleeding.

While SGA patients regularly presented with a firm, nontender lump persisting for at least one month, patients with SVM presented with various medical histories and clinical presentations. Twenty-two patients with SVM (47%) presented at their first encounter between birth and the third year of life. Only four (18%) of these patients had a sudden enlargement of the affected area of the body, which was caused by intracystic bleeding (Figure 5). Parents were aware of their child's vascular malformation from birth or the first month of their life in 15 cases (68%). Eight patients (17%) presented between their fourth and 10th year of life. Among them, five (63%) patients had a sudden enlargement of the lesions with intracystic bleeding.

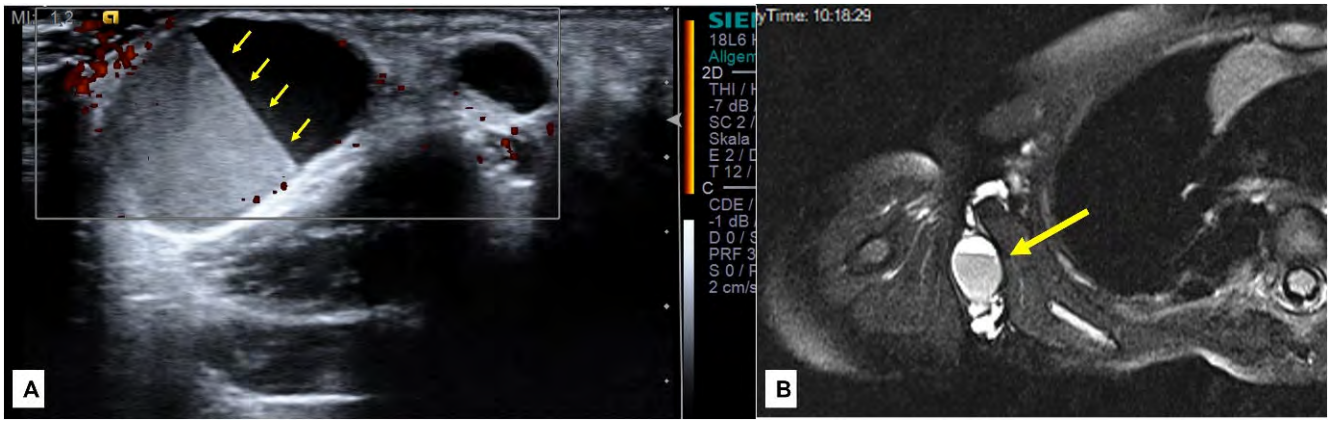

Figure 5. A 2.5-year-old girl with a sudden appearance of a lump in the right axilla. Ultrasound examination showed a multi-cystic mass with intracystic bleeding documented by the fluid-fluid level in the cyst representing the clot retraction (**A**)—(yellow arrows). The MRI (**B**) showed the exact extension of the mass (arrow), which was limited to the subcutaneous tissue and facilitated the indication for surgical resection.

Seventeen patients (36%) presented after their 10th year of life, and nine (53%) of these patients presented after a sudden enlargement of their lesions. Altogether, 18/47 patients (38%) with only subcutaneous extension of their low-flow vascular malformations presented after a sudden enlargement of their SVM due to intracystic bleeding, most of which occurred in patients older than three years. The most common location for the SVM was the upper extremity; in particular, the axillary and upper arm region (Figure 6), where more than half of the SVM of our cohort were located, as shown in Table 2.

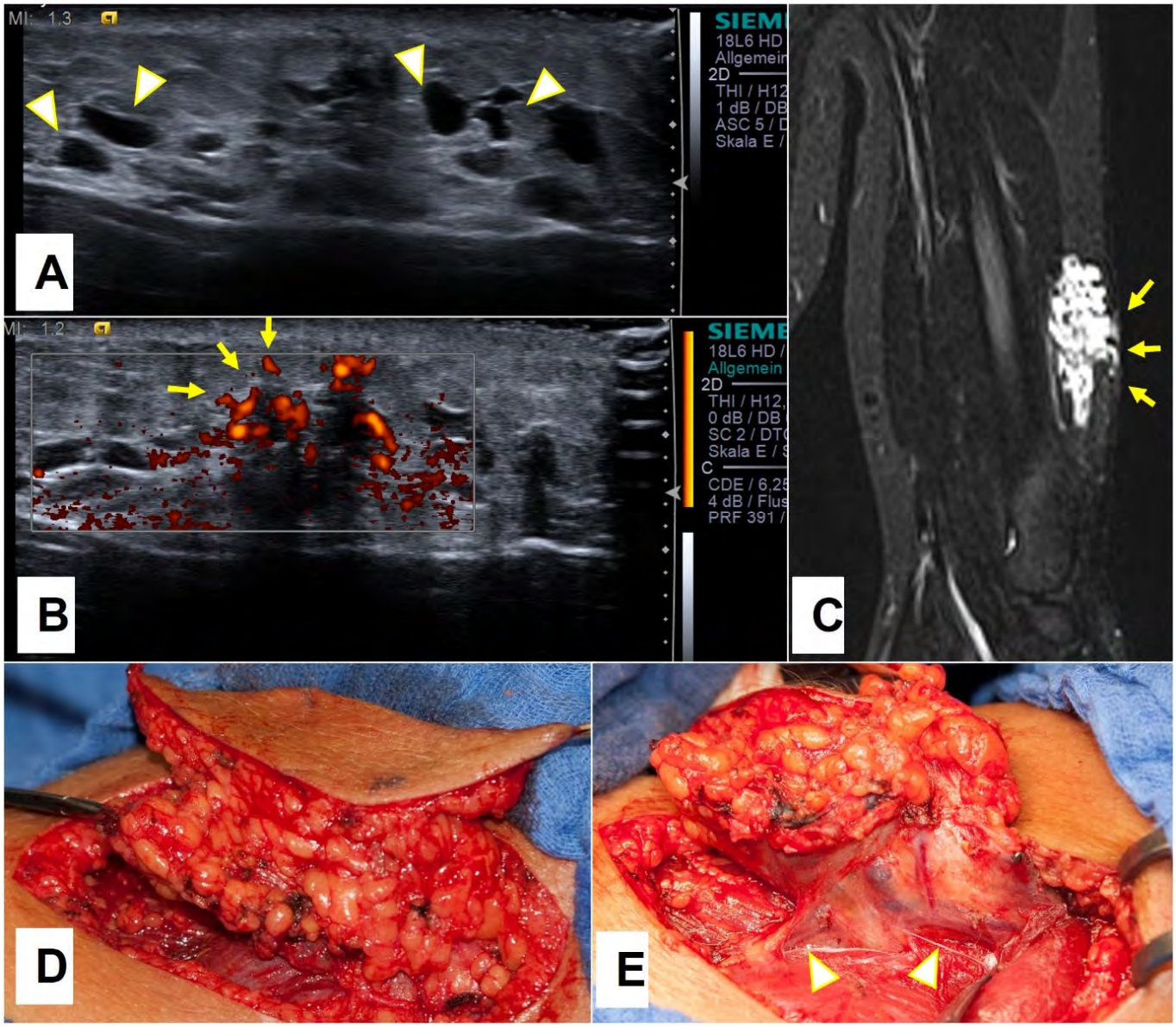

Figure 6. A 14.5-year-old boy was presented because of the minor swelling on his left upper arm, which appeared after he started to go to the gym. Ultrasound imaging showed a tubulo-cystic lesion (arrowheads) on the lateral aspect of his upper arm (**A**) which showed perfusion (arrows) in a power Doppler mode with venous flow characteristics (**B**). MRI depicted a venous malformation (arrows) of the localized extension located in the subcutaneous area (**C**). Complete excision of the VM was performed (**D**). Draining veins are depicted with arrowheads (**E**).

3.2.2. Presentation on Ultrasound

At their initial encounter, each SVM patient underwent an ultrasound examination. The SVMs were mainly described as ill-defined masses of heterogeneous echotexture with visible multiple cystic spaces within. In cases that presented with sudden enlargement and recent or past bleeding into the cysts, a clear-cut sedimentation line was noted through the cyst representing the clot retraction as a pathognomonic sign of intracystic bleeding (see Figure 5). In five patients with SVM, no clear cystic areas were described during the ultrasound examination.

3.2.3. Presentation on MRI

In all 47 cases, the MRI showed that the lesions consisted of multicystic or tubular vascular areas, and the diagnosis of low-flow SVM was considered in all cases. Figures 7 and 8 illustrate the findings in one patient with a confirmed LM who presented with a lesion located over the pretibial area clinically mimicking SGA.

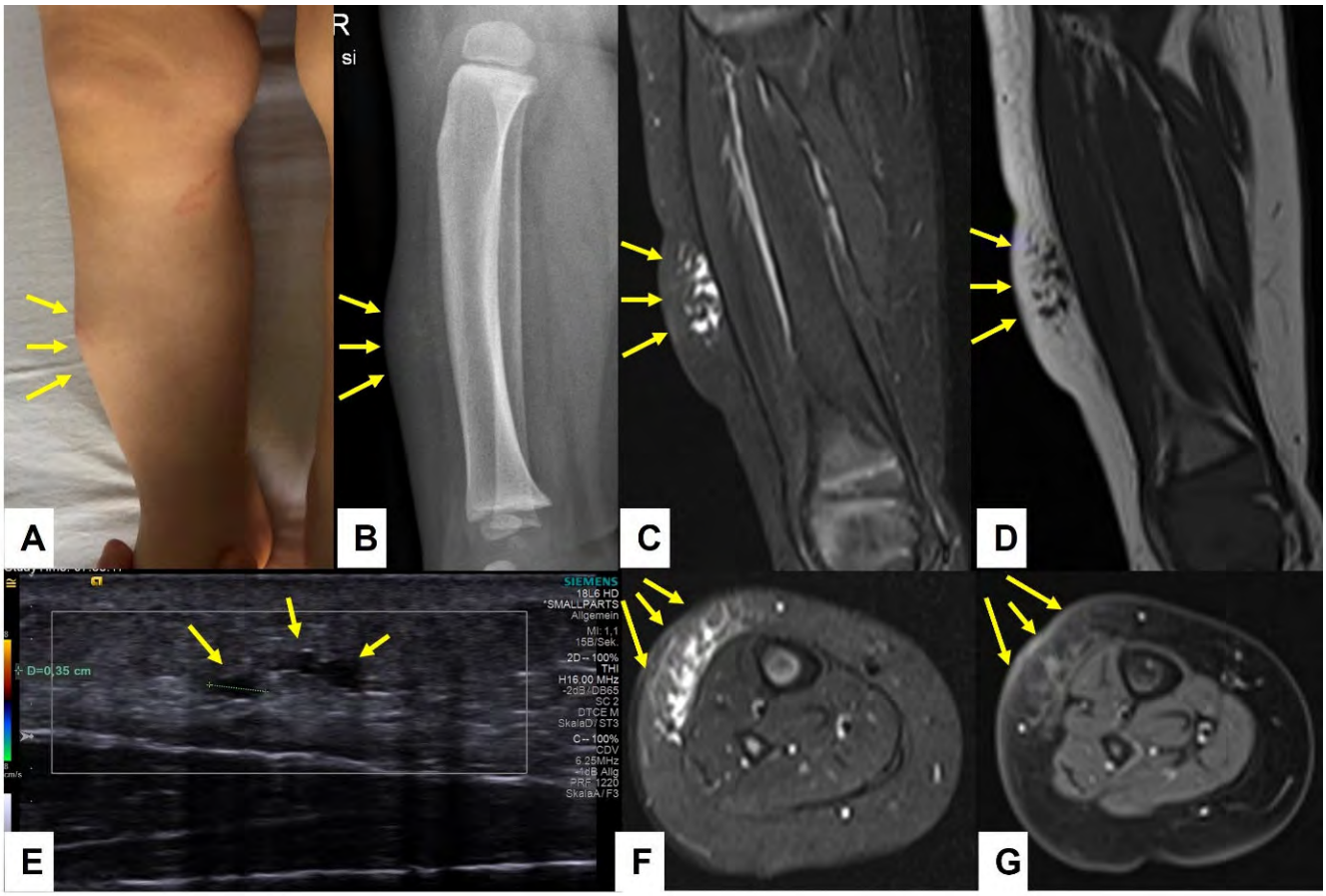

Figure 7. This composite figure illustrates a subcutaneous lump on the right lower leg of a 12-month-old girl (**A**)—(arrows). X-ray at presentation showed a cloudy pretibial soft-tissue lesion with no osseous deformities (**B**)—(arrows). Ultrasound imaging of the lesion was unspecific but showed some small cystic areas in the deep dermis (**E**)—(arrows). MR imaging at the age of 13 months showed a strict epifascial tubulo-cystic lesion in the subcutaneous tissue in the anterolateral area without contrast enhancement (**C**,**D**,**F**,**G**)—(arrows).

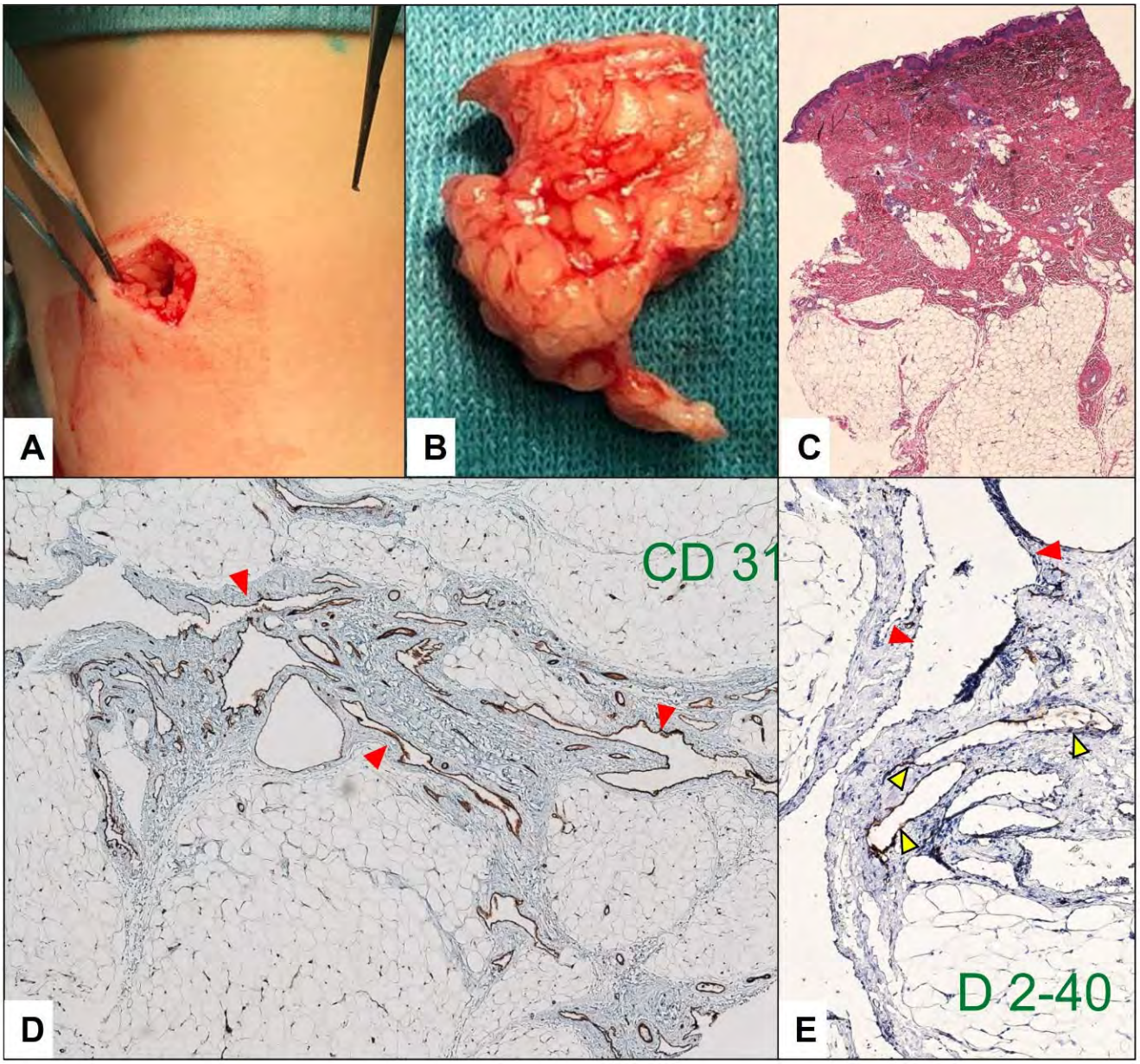

Figure 8. The patient from Figure 7 underwent an incisional biopsy of the pretibial lesion at 15 months of age (**A**,**B**). The H&E staining showed no granulomatous tissue in specimen (**C**). Immunohistochemistry showed irregular, dilated vascular structures surrounded by fat tissue in the deep subcutaneous tissue layer, which strongly expressed the CD31 vascular marker (**D**)—(red arrowheads). D2-40 (**E**) stains positive in the lymphatic component (yellow arrowheads) and is negative in the endothelial cells of the veins (red arrowheads).

3.2.4. Invasive Diagnostic Procedures

All except two patients with low-flow SVM underwent a complete surgical excision. In three of these patients, a recurrence of the SVMs was observed, and a second surgical intervention was needed for the complete removal of the SVM. The median follow-up time after surgical intervention in patients with SVMs was three years (range 2–5 years).

3.3. Retrospective Image Analysis

A retrospective review of all MR images showed that all MRIs of patients with low-flow SVMs showed multicystic and/or tubular lesion appearance, whereas MRIs of patients with SGA never showed any cyst-shaped structures. An SGA presents as a raised-rounded

homogenous mass that projects over the surface of the muscle's fascia without invading the underlying tissue (Figure 9). These lesions have a typical broad circular base laying on the fascia and a raised, continuous, irregular curved surface that extends from the deep fascia towards the more superficial tissues. One can easily describe the shape of an SGA as an island rising from the ocean. We recently named this characteristic shape "the Epifascial Cap," the hallmark shape of an SGA (Figure 10) [18]. The enhancement of contrast material seen in these lesions during the MRI is homogenous and should not be mistaken for a low-flow SVM (Figure 11).

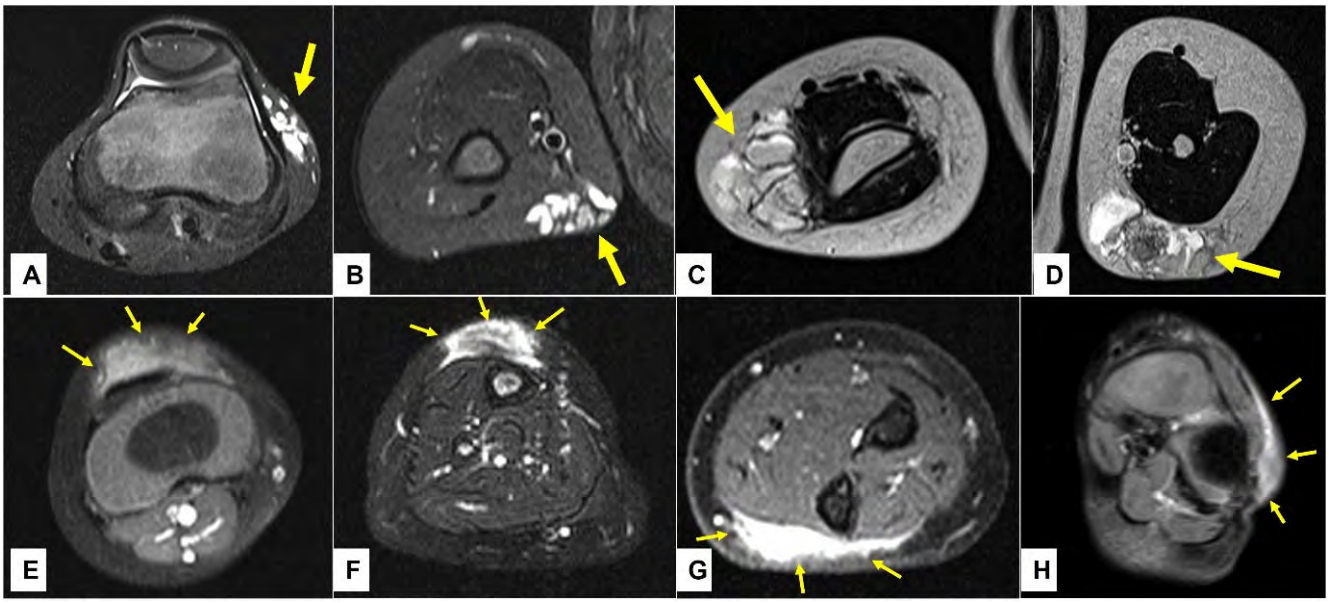

Figure 9. This composite figure illustrates the typical imaging differences between the low-flow subcutaneous vascular malformations (SVM) and subcutaneous granuloma annulare (SGA) as seen on the MR images. In images (**A**–**D**), four patients with multicystic subcutaneous lesions pointed out by yellow arrows are presented. These lesions were accurately diagnosed by MRI and after excision, also confirmed by histopathology as a venous malformation on the left knee in an 11-year-old boy (**A**); venous malformation on the right upper arm in a 4-year-old boy (**B**); lymphatic malformation on the right elbow in a 4-year-old girl (**C**); lymphatic malformation on the left upper arm in an 8-year-old girl (**D**). In images (**E**–**H**), four patients with homogenous subcutaneous lesions marked with 3 yellow arrows each are presented. These lesions remained inconclusive after MRI, with the main differential diagnosis being the low-flow SVM in all cases. Because malignancy could not be excluded, surgical biopsy was needed, and the diagnosis of SGA was confirmed by histopathology in all cases. (**E**) right knee in a 2.5-year-old boy, (**F**) right lower leg in a 3-year-old girl, (**G**) left forearm in a 4-year-old boy, (**H**) left foot in a 3-year-old girl. Note that all SVM have a cystic appearance on the MRI, whereas SGA shows the typical epifascial extension with gradual rise of the lesion towards the more superficial tissues, which we have named the "epifascial cap" sign. These self-limiting lesions show a homogenous appearance in the MRI and do not invade the fascia.

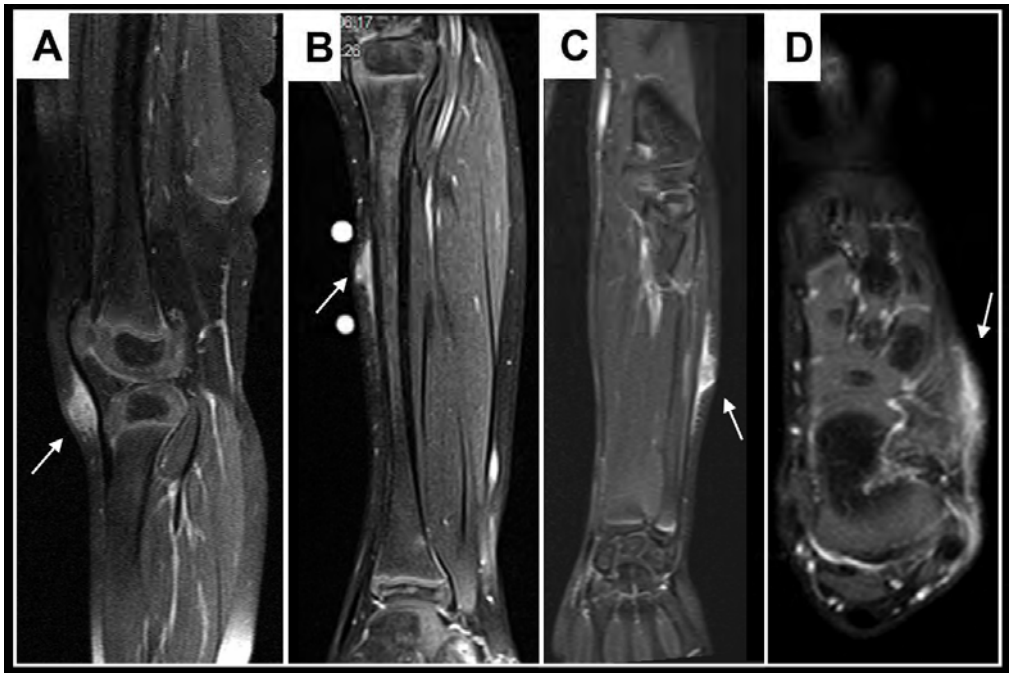

Figure 10. These images show representative MRI slices through SGA (indicated by white arrows) at the knee (**A**); lower leg (**B**); forearm (**C**); and foot (**D**) in four different cases. Note that all SGA lesions show the typical epifascial extension with gradual rise of the lesion towards the more superficial tissues, which we have named the "epifascial cap" sign.

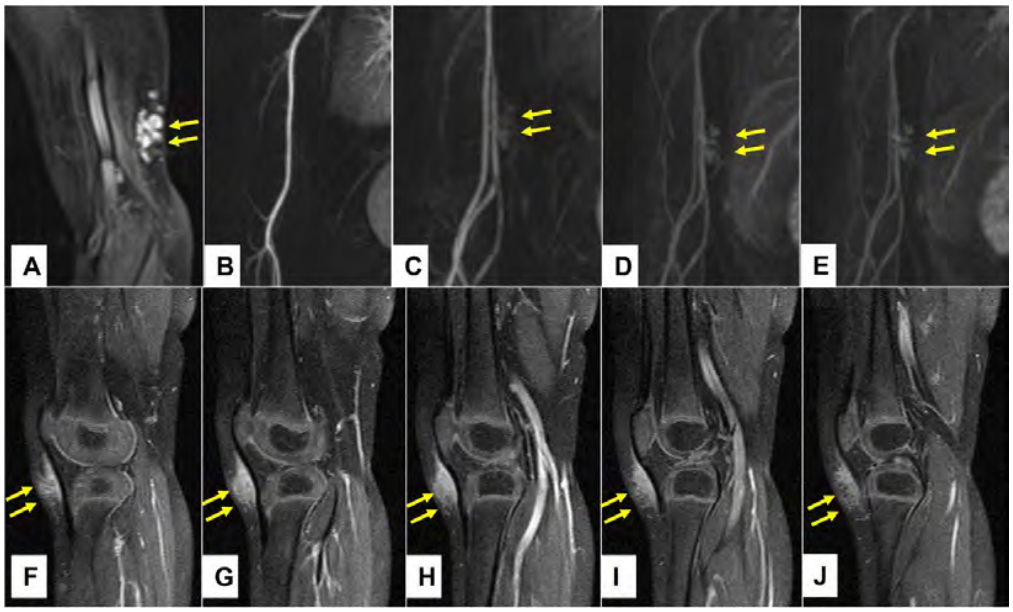

Figure 11. This composite figure illustrates the typical differences in contrast enhancement between the subcutaneous venous malformations (VM) and subcutaneous granuloma annulare (SGA) during MRI. The lesions are pointed out by yellow arrows. Image (**A**) depicts the extension of the VM on the medial side of the right upper arm. The lesion cannot be seen during the arterial phase of MR angiography (**B**). The VM fills slowly at the beginning of the venous phase at 32 s post-contrast application (**C**) and intensifies at 96 (**D**) and 120 s (**E**) post-contrast application. The SGA on the anterior side of the right knee, as depicted in image (**F**), shows a homogenous enhancement after contrast application which slowly fades away at the end of the examination (**G**–**J**).

Based on the patients' medical history, clinical investigations, laboratory, and imaging findings, we have developed an algorithm of care for children with subcutaneous lesions suspected to be SGA, showed in Figure 12.

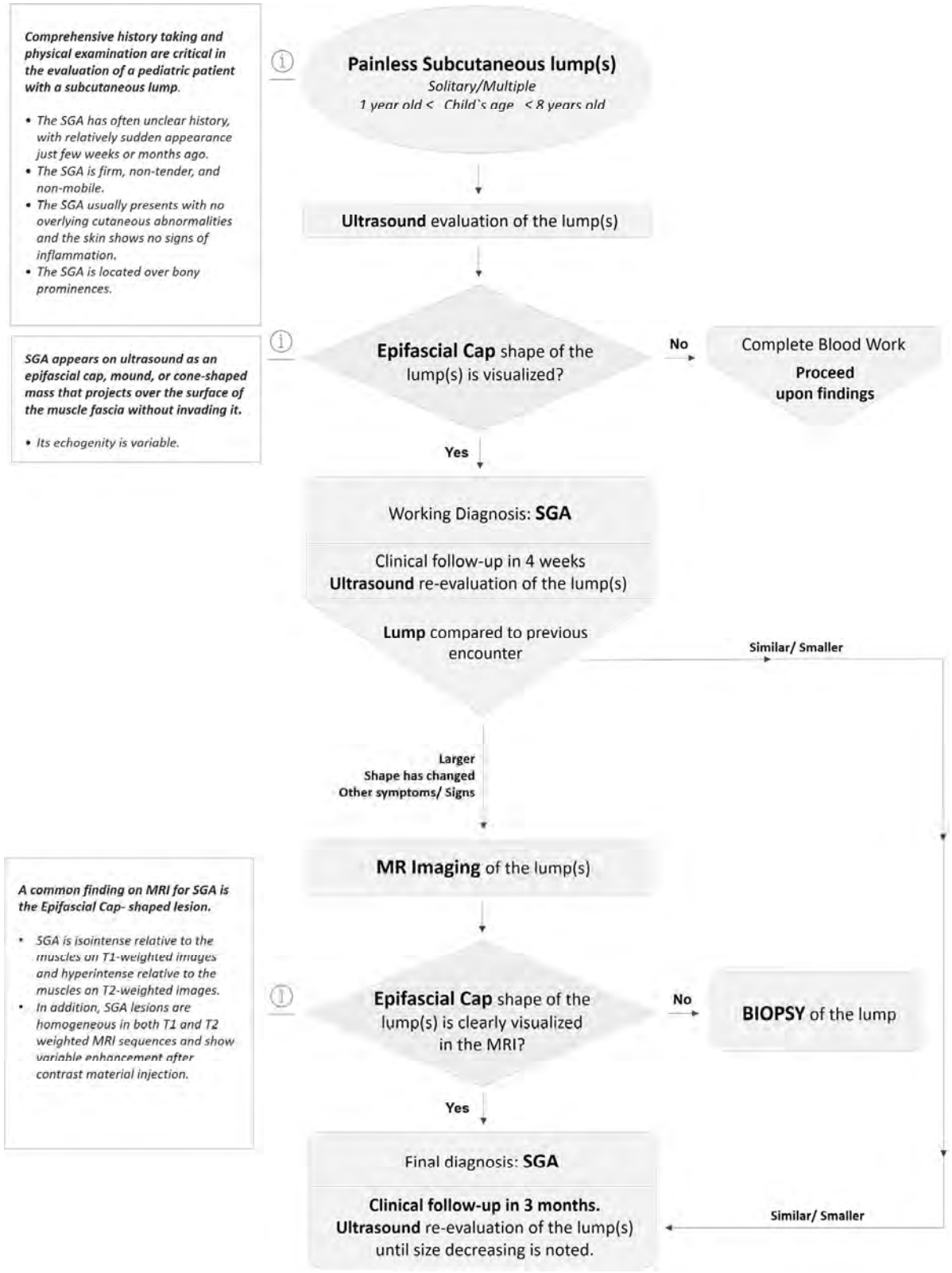

Figure 12. Management algorithm for Subcutaneous Granuloma Annulare in children.

4. Discussion

Up to date, SGA is not easy to diagnose [2,5,19]. The sudden appearance, persistence, and growth of one or more subcutaneous lumps in a child usually incites parents to seek help from a physician [20–22]. These patients often see a number of specialists, such as pediatricians, pediatric surgeons, pediatric orthopedic surgeons, or pediatric dermatologists [23]. Most of the time, thorough diagnostic work-up is completed in order to identify the entity of an unclear subcutaneous lesion. Unfortunately, due to the present ambiguity, surgical intervention is frequently performed in patients with SGA which would not require any intervention [23–25].

Based on our study's results, we propose a management algorithm for SGA in children. To provide appropriate recommendations for further treatment, clinicians must be knowledgeable about the clinical characteristics of the SGA and low-flow SVM, such as the exact history of the lesions, their softness, firmness, mobility, pain, and their predilected anatomic areas, as well as their imaging characteristics [21,26].

The first step towards an accurate diagnosis is taking a comprehensive medical history and a detailed physical examination, which are critical in evaluating a pediatric patient with a painless subcutaneous lump. SGA is usually located on trauma-exposed bony prominences of the lower extremities, scalp, and the ulnar side of the forearms. They often have an unclear history, with a relatively sudden appearance a few weeks to a couple of months ago. The lumps are firm, non-tender, and non-mobile. They present with no overlying skin abnormalities and show no signs of inflammation. Our 20-year cohort supports these findings and that the SGA is usually found in preschool-age children and most commonly in girls, confirming the female predisposition of this disease [14,15,23,27].

Low-flow SVMs are often present at birth but can become apparent also in the first or second decade of life. They grow in proportion with the child's growth until puberty and can expand in response to certain stimuli such as trauma, infection, or pregnancy [11,28–30]. Venous malformations (VMs) are the most common type of vascular malformations, and their clinical presentation is variable. They may appear as a group of ectatic and dysplastic superficial veins or, more frequently, as deeper, real masses in the soft tissue with a soft, bluish, compressible appearance on the superficial skin [31,32]. However, the consistency of these lesions can increase due to the formation of internal clots, and they can appear as firm and immobile lumps, making it challenging to distinguish clinically from an SGA. They are most commonly found on the face, upper extremity, or trunk. LMs are often evident at birth and their most usual locations are the neck, the axillary region, and the mediastinum. LMs are slow-growing lesions that can enlarge significantly, leading to distortion of anatomy, especially of the soft tissues and bones of the face and trunk [28,31–35]. Most cases of SVMs are clinically obvious, and because of the specific time of their appearance and/or anatomic predilected areas, they do not pose diagnostic difficulties when differentiating from a rare SGA. However, when a diagnosis is not clear, we recommend referring the pediatric patient for routine complete blood work and US of the lesion, as the vast majority of subcutaneous lesions in children can be accurately evaluated with sonographic imaging [36,37]. Imaging evaluation allows us to provide appropriate recommendations concerning the prospect of the subcutaneous lesion(s). Should we observe them, we have to decide if the lesion requires observation and follow up, if the lesion needs excision but there is no urgency, or if there is a need for a prompt intervention to clarify the entity of the lesion(s).

On ultrasound, an SGA appears as an epifascial subcutaneous soft tissue mass, hypoechogenic in the center, with a hyperechoic zone in the periphery and mild vascularization. This lesion projects over the surface of the muscle's fascia without invading it. Supposing that during the ultrasound evaluation, it is possible to recognize the epifascial cape shape of the lesion, we recommend using SGA as your primary working diagnosis and referring the child for a clinical follow-up with a repeat US of the lump in 4 weeks (Figure 12).

On ultrasound, VMs appear as well margin masses with a spongiform heterogenous echostructure which is hypoechoic compared to the surrounding tissues. Hypoechoic venous spaces and hyperechoic septa form the heterogenous echostructure of a VM. Some-

times on the US, it is possible to identify anechoic tubular structures that are recognized as vascular channels [32,38,39]. A pathognomonic sign that definitely aids in the diagnosis of VM is the presence of intralesional calcifications. Unfortunately, this sign is not frequent and its occurrence is reported variously from 9% to 16% in previously published series [32,38,39]. LMs appear as lesions that contain scattered, cystic formations of variable dimensions, with liquid content, separated by septa. LM are usually deformable, and the compression with the probe alters the shape of the cysts that never collapse entirely. The cystic spaces can be anechoic or have a variable degree of echogeneity due to intracystic bleeding or infections [32,40,41]. Given the extreme variety of ultrasound presentations of low-flow SVM and the difficulty of obtaining accurate information about the extent of the SVM, further imaging by MR is recommended. MRI is also recommended in case of doubt or if, upon returning for a clinical follow-up, it is noted that the size, consistency, and mobility of the lesion may have changed, or the family is now reporting other symptoms and signs associated with the lesion.

An SGA is isointense relative to the muscles on T1-weighted images and hyperintense relative to the muscles on T2-weighted images. In addition, SGA is homogeneous in both T1- and T2-weighted MRI sequences and shows variable enhancement after contrast material injection. If the epifascial cap shape is visualized on MRI evaluation, consider SGA as the final working diagnosis, and request a clinical follow-up of the lump in 3 months with a repeat ultrasound evaluation to assess the size of the lesion.

VM on MRI will appear as multiple serpentine, tubular structures or amorphous dilated channels containing intermediate signal on T1-weighted images, high signal on T2-weighted images, intermediate signal on gradient echo sequences, and delayed enhancement on dynamic contrast-enhanced MRI [29,38,42–47]. LM appear as micro- or macrocystic spaces (depending on the type of the LM) that may contain fluid levels due to intracystic bleeding. Cysts will often be hyperintense on T2-weighted images and show no contrast enhancement [29,43–47].

If "worrying features" are noted during the follow-up visit, such as a recent increase in the size of the lump, deeper location relative to the fascia, and/or invasive growth patterns, then a prompt verification of the histopathologic diagnosis by biopsy is mandatory. Usually, low-flow SVM will require treatment at some point in life, while SGA spontaneously self-resolves in approximately two years' time and does not need any treatment or surgical excision.

A limitation of our single-center study is the limited number of SGA cases identified during the 20-year study period. This is firmly attributed to the fact that SGA is a rare disease with an unknown etiology and is commonly overlooked by clinicians. Nevertheless, we hope our study results will give rise to other future investigations that can shed light on etiology of SGA and its current occurrence in the general population.

5. Conclusions

To the best of our knowledge, this is the first study that directly compared the clinical and imaging characteristics of rare SGA with low-flow SVM, based on a vast cohort of patients from a 20-year time period. We are showing for the first time that SGA is found in different predilected anatomic areas than SVMs, and their clinical and imaging characteristics are significantly different. Low-flow SVMs present in imaging as cystic lesions, while SGA always presents in a homogenous epifascial cap shape. Recognizing these imaging characteristics should enable clinicians to diagnose SGA without requiring further invasive diagnostic workup.

Author Contributions: Conceptualization, B.P.B. and E.Q.H.; methodology, B.P.B. and E.Q.H.; software, B.P.B., S.T. and I.B.; formal analysis, B.P.B., S.T. and I.B.; investigation, B.P.B., P.G., C.F. and E.Q.H.; data curation, B.P.B. and E.Q.H.; writing—original draft preparation, B.P.B.; writing—review and editing, B.P.B., E.Q.H., P.G., C.F., I.B. and S.T.; visualization, B.P.B., E.Q.H., I.B. and S.T.; supervision, E.Q.H.; project administration, E.Q.H.; This manuscript is prepared from the doctoral thesis of B.P.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: This study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the Medical University of Graz (ethical approval code: EK-No. 33-126 ex 20/21; date: 20 January 2021).

Informed Consent Statement: Informed consent for publication was not necessary since this study was part of in-house research with anonymized retrospective patient datasets.

Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors without undue reservation.

Acknowledgments: The authors thank Candidate of Medicine Dora Haxhija for administrative and technical support. The data from patients with SVM are presented in this manuscript for the first time. The data from patients with SGA presented in this manuscript are part of a larger cohort of patients with SGA presented in a manuscript dealing only with SGA.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Patrizi, A.; Gurioli, C.; Neri, I. Childhood granuloma annulare: A review. *G. Ital. Dermatol. Venereol.* **2014**, *149*, 663–674.
2. Requena, L.; Fernández-Figueras, M.T. Subcutaneous granuloma annulare. *Semin. Cutan. Med. Surg.* **2007**, *26*, 96–99. [CrossRef] [PubMed]
3. Keimig, E.L. Granuloma Annulare. *Dermatol. Clin.* **2015**, *33*, 315–329. [CrossRef] [PubMed]
4. Thornsberry, L.A.; English, J.C. Etiology, Diagnosis, and Therapeutic Management of Granuloma Annulare: An Update. *Am. J. Clin. Dermatol.* **2013**, *14*, 279–290. [CrossRef] [PubMed]
5. Pederiva, F.; Paloni, G.; Berti, I. Subcutaneous Granuloma Annulare: A Diagnostic Conundrum-Learning from Mistakes. *Pediatr. Emerg. Care* **2017**, *33*, e30–e31. [CrossRef] [PubMed]
6. Vogel, M.N.; Hansmann, S.; Kümmerle-Deschner, J.; Schäfer, J.; Horger, M. Das subkutane Granuloma annulare. *RöFo Fortschr. Auf Dem Geb. Röntgenstrahlen Und Bildgeb. Verfahr.* **2007**, *179*, 1215–1218. [CrossRef] [PubMed]
7. Cai, Z.R.; Mamet, F.; Kokta, V.; Coulombe, J. Subcutaneous nodules in children: Don't forget deep granuloma annulare: A Case Report. *SAGE Open Med. Case Rep.* **2020**, *8*, 2050313X20935713.
8. Vogel, S.A.; Hess, C.P.; Dowd, C.F.; Hoffman, W.Y.; Kane, A.J.; Rajaii, R.; Frieden, I.J. Early Versus Later Presentations of Venous Malformations: Where and Why? *Pediatr. Dermatol.* **2013**, *30*, 534–540. [CrossRef]
9. Haxhija, E.Q.; Spendel, S.; Höllwarth, M.E. Chirurgische Therapie vaskulärer Malformationen bei Kindern und Jugendlichen. *Handchir. Mikrochir. Plast. Chir.* **2009**, *41*, 100–106. [CrossRef]
10. ISSVA Classification for Vascular Anomalies©. Homepage of International Society for the Study of Vascular Anomalies. Available online: https://www.issva.org/UserFiles/file/ISSVA-Classification-2018.pdf (accessed on 7 February 2023).
11. White, C.L.; Olivieri, B.; Restrepo, R.; McKeon, B.; Karakas, S.P.; Lee, E.Y. Low-Flow Vascular Malformation Pitfalls: From Clinical Examination to Practical Imaging Evaluation—Part 1, Lymphatic Malformation Mimickers. *Am. J. Roentgenol.* **2016**, *206*, 940–951. [CrossRef]
12. Endo, Y.; Sekiguchi, A.; Motegi, S.; Ishikawa, O. Subcutaneous granuloma annulare on the heel: A case report and review of the Japanese published work. *J. Dermatol.* **2020**, *47*, 677–679. [CrossRef] [PubMed]
13. Sabuncuoğlu, H.; Oge, K.; Söylemezoğlu, F.; Sağlam, A. Subcutaneous granuloma annulare of the scalp in childhood: A case report and review of the literature. *Turk. Neurosurg.* **2007**, *17*, 19–22.
14. Jankowski, P.P.; Krishna, P.H.; Rutledge, J.C.; Waldhausen, J.; Avellino, A.M. Surgical Management and Outcome of Scalp Subcutaneous Granuloma Annulare in Children. *Neurosurgery* **2008**, *63*, E1002. [CrossRef] [PubMed]
15. Grogg, K.L.; Nascimento, A.G. Subcutaneous Granuloma Annulare in Childhood: Clinicopathologic Features in 34 Cases. *Pediatrics* **2001**, *107*, e42. [CrossRef] [PubMed]
16. Evans, M.J.; Blessing, K.; Gray, E.S. Pseudorheumatoid Nodule (Deep Granuloma Annulare) of Childhood: Clinicopathologic Features of Twenty Patients. *Pediatr. Dermatol.* **1994**, *11*, 6–9. [CrossRef]
17. Lega, S.; Rabusin, M.; Pederiva, F. Acute-onset pretibial swelling. *Indian Pediatr.* **2014**, *51*, 334. [CrossRef]
18. Beqo, B.; Tschauner, S.; Haxhija, E.Q. Subcutaneous "Epifascial Cap" as the Pathognomonic Imaging Sign of Subcutaneous Granuloma Annulare in Childhood—First Description! *Eur. Surg.* **2022**, *54* (Suppl. S1), 75.
19. Vázquez-Osorio, I.; Quevedo, A.; Rodríguez-Vidal, A.; Rodríguez-Díaz, E. Usefulness of ultrasonography in the diagnosis of subcutaneous granuloma annulare. *Pediatr. Dermatol.* **2018**, *35*, e200–e201. [CrossRef]
20. Pesce, V.; Notarnicola, A.; Moretti, B. Diagnostic dilemma of a subcutaneous nodule following a trauma in a child: Immunohistochemical examination put the final diagnosis of deep granuloma annulare. *Musculoskelet. Surg.* **2010**, *94*, 49–51. [CrossRef]
21. Li, W.-Y.; Reinisch, J.F. Cysts, pits, and tumors. *Plast. Reconstr. Surg.* **2009**, *124* (Suppl. S1), 106e–116e. [CrossRef]
22. Knight, P.J.; Reiner, C.B. Superficial lumps in children: What, when, and why? *Pediatrics* **1983**, *72*, 147–153. [CrossRef]

23. Letts, M.; Carpenter, B.; Soucy, P.; Davidson, D. Subcutaneous granuloma annulare of the extremities in children. *Can. J. Surg.* **2000**, *43*, 425–430.
24. Riebel, T.; Scheer, I. Subkutanes Granuloma annulare: Eine nicht zu vergessende Differenzialdiagnose bei expansiven (Weichteil-) Läsionen an den unteren Extremitäten von jungen Kindern. *Ultraschall der Med. Eur. J. Ultrasound* **2010**, *32*, 604–607. [CrossRef]
25. Stenzel, M.; Voß, U.; Mutze, S.; Hesse, V. A Pretibial Lump in a Toddler—Sonographic Findings in Subcutaneous Granuloma Annulare. *Ultraschall der Med. Eur. J. Ultrasound* **2008**, *31*, 68–70. [CrossRef]
26. Putnam, T.C. Lumps and bumps in children. *Pediatr. Rev.* **1992**, *13*, 371–378. [CrossRef]
27. Navarro, O.M.; Laffan, E.E.; Ngan, B.-Y. Pediatric soft-tissue tumors and pseudo-tumors: MR imaging features with pathologic correlation: Part 1. Imaging approach, pseudotumors, vascular lesions, and adipocytic tumors. *Radiographics* **2009**, *29*, 887–906. [CrossRef] [PubMed]
28. Cox, J.A.; Bartlett, E.; Lee, E.I. Vascular Malformations: A Review. *Semin. Plast. Surg.* **2014**, *28*, 58–63. [CrossRef] [PubMed]
29. Nosher, J.L.; Murillo, P.G.; Liszewski, M.; Gendel, V.; Gribbin, C.E. Vascular anomalies: A pictorial review of nomenclature, diagnosis and treatment. *World J. Radiol.* **2014**, *6*, 677–692. [CrossRef]
30. Pappas, D.C.; Persky, M.S.; Berenstein, A. Evaluation and treatment of head and neck venous vascular malformations. *Ear Nose Throat J.* **1998**, *77*, 914–916, 918–922. [CrossRef] [PubMed]
31. Johnson, C.M.; Navarro, O.M. Clinical and sonographic features of pediatric soft-tissue vascular anomalies part 2: Vascular malformations. *Pediatr. Radiol.* **2017**, *47*, 1196–1208. [CrossRef] [PubMed]
32. Esposito, F.; Ferrara, D.; di Serafino, M.; Diplomatico, M.; Vezzali, N.; Giugliano, A.M.; Colafati, G.S.; Zeccolini, M.; Tomà, P. Classification and ultrasound findings of vascular anomalies in pediatric age: The essential. *J. Ultrasound* **2019**, *22*, 13–25. [CrossRef]
33. Kollipara, R.; Odhav, A.; Rentas, K.E.; Rivard, D.C.; Lowe, L.H.; Dinneen, L. Vascular anomalies in pediatric patients: Updated classification, imaging, and therapy. *Radiol. Clin. N. Am.* **2013**, *51*, 659–672. [CrossRef]
34. Dubois, J.; Alison, M. Vascular anomalies: What a radiologist needs to know. *Pediatr. Radiol.* **2010**, *40*, 895–905. [CrossRef] [PubMed]
35. Colletti, G.; Valassina, D.; Bertossi, D.; Melchiorre, F.; Vercellio, G.; Brusati, R. Contemporary Management of Vascular Malformations. *J. Oral Maxillofac. Surg.* **2014**, *72*, 510–528. [CrossRef] [PubMed]
36. Shah, S.H.; Callahan, M.J. Ultrasound evaluation of superficial lumps and bumps of the extremities in children: A 5-year retrospective review. *Pediatr. Radiol.* **2013**, *43* (Suppl. S1), 23–40. [CrossRef]
37. Hwang, E.J.; Yoon, H.-S.; Cho, S.; Park, H.S. The diagnostic value of ultrasonography with 5-15-MHz probes in benign subcutaneous lesions. *Int. J. Dermatol.* **2015**, *54*, e469–e475. [CrossRef]
38. Paltiel, H.J.; Burrows, P.E.; Kozakewich, H.P.W.; Zurakowski, D.; Mulliken, J.B. Soft-Tissue Vascular Anomalies: Utility of US for Diagnosis. *Radiology* **2000**, *214*, 747–754. [CrossRef] [PubMed]
39. Trop, I.; Dubois, J.; Guibaud, L.; Grignon, A.; Patriquin, H.; McCuaig, C.; Garel, L.A. Soft-tissue venous malformations in pediatric and young adult patients: Diagnosis with Doppler US. *Radiology* **1999**, *212*, 841–845. [CrossRef]
40. Morrow, M.S.; Oliveira, A.M. Imaging of Lumps and Bumps in Pediatric Patients: An Algorithm for Appropriate Imaging and Pictorial Review. *Semin. Ultrasound CT MRI* **2014**, *35*, 415–429. [CrossRef]
41. Bansal, A.G.; Rosenberg, H.K. Sonography of pediatric superficial lumps and bumps: Illustrative examples from head to toe. *Pediatr. Radiol.* **2017**, *47*, 1171–1183. [CrossRef]
42. Hyodoh, H.; Hori, M.; Akiba, H.; Tamakawa, M.; Hyodoh, K.; Hareyama, M. Peripheral vascular malformations: Imaging, treatment approaches, and therapeutic issues. *Radiographics* **2005**, *25* (Suppl. S1), S159–S171. [CrossRef]
43. Donnelly, L.F.; Adams, D.M.; Bisset, G.S. Vascular malformations and hemangiomas: A practical approach in a multidisciplinary clinic. *AJR Am. J. Roentgenol.* **2000**, *174*, 597–608. [CrossRef]
44. Burrows, P.E.; Laor, T.; Paltiel, H.; Robertson, R.L. Diagnostic Imaging in the Evaluation of Vascular Birthmarks. *Dermatol. Clin.* **1998**, *16*, 455–488. [CrossRef] [PubMed]
45. Rak, K.M.; Yakes, W.F.; Ray, R.L.; Dreisbach, J.N.; Parker, S.H.; Luethke, J.M.; Stavros, A.T.; Slater, D.D.; Burke, B.J. MR imaging of symptomatic peripheral vascular malformations. *AJR Am. J. Roentgenol.* **1992**, *159*, 107–112. [CrossRef] [PubMed]
46. van Rijswijk, C.S.P.; van der Linden, E.; van der Woude, H.-J.; van Baalen, J.M.; Bloem, J.L. Value of dynamic contrast-enhanced MR imaging in diagnosing and classifying peripheral vascular malformations. *AJR Am. J. Roentgenol.* **2002**, *178*, 1181–1187. [CrossRef] [PubMed]
47. Meyer, J.S.; Hoffer, F.A.; Barnes, P.D.; Mulliken, J.B. Biological classification of soft-tissue vascular anomalies: MR correlation. *Am. J. Roentgenol.* **1991**, *157*, 559–564. [CrossRef] [PubMed]

Dermatology Practical & Conceptual

Subcutaneous Granuloma Annulare in an Atypical Age Group in Immediate Post-Covid-19 Phase

Besiana P. Beqo[1], Emir Q. Haxhija[1]

1 Department of Pediatric and Adolescent Surgery, Medical University of Graz, Graz, Austria

Citation: Beqo BP, Haxhija EQ. Subcutaneous Granuloma Annulare in an Atypical Age Group in Immediate Post-Covid-19 Phase. *Dermatol Pract Concept*. 2023;13(2):e2023172. DOI: https://doi.org/10.5826/dpc.1302a172

Accepted: March 20, 2023; **Published:** April 2023

Funding: None.

Competing Interests: None.

Authorship: All authors have contributed significantly to this publication.

Corresponding Author: Emir Haxhija MD PhD FEBPS, Department of Paediatric and Adolescent Surgery, Medical University of Graz, Auenbruggerplatz 34, A-8036 Graz, Austria. Phone: +43-(0)316 – 38513762 Fax: +43-(0)316 – 38513775 Email: emir.haxhija@medunigraz.at

Dear Editor,

We are writing in response to the article "Subcutaneous Granuloma Annulare in an Atypical Age Group in Immediate Post-Covid-19 Phase" (DOI: https://doi.org/10.5826/dpc.1204a156) that was recently published in your esteemed journal [1]. As the topic of subcutaneous granuloma annulare (SGA) is of particular interest to us, we would like to offer our comments regarding the case presented in the article.

Upon review of the clinical and histopathological features described, we respectfully suggest that the case presented in the article appears to be more compatible with the diagnosis of generalized granuloma annulare (GGA), rather than SGA.

GGA is characterized by the presence of 10 or more skin plaques with a circular appearance "affecting at least the trunk and either upper or lower, or both extremities" [2], with smaller or larger subdermal extensions of the granulomas beneath these skin lesions, sometimes seen in a patchy pattern [3]. GGA is more common in adults. Although its etiology is still unknown, various triggering mechanisms, including infectious diseases, have been reported [4], which could have been the case in the report presented by Kaur et al.

In contrast, SGA is almost exclusively seen in children and presents as immobile, solid, non-tender, non-inflammatory subcutaneous lumps that often appear as single or multiple lesions with rare overlying cutaneous abnormalities. These lumps are asymptomatic and attached to the deep fascia with a clear epifascial extension, and they spontaneously regress without any treatment over a period of 1-2 years [5]. The histopathologic images presented in the report by Kaur et al do not appear to reveal typical SGA histopathology as it is classically seen in children but rather suggest GGA with a patchy pattern of small granulomatous islands.

Our recent research has shown that SGA can be recognized by the epifascial cap shape of the subcutaneous lesions on ultrasound and MR imaging, which can aid in the accurate diagnosis of SGA [5]. This new imaging sign may help avoid unnecessary examinations and specialist consultations for children with SGA and enable accurate diagnosis through imaging alone (Figure 1).

Finally, it is worth noting that SGA lumps typically self-resolve in up to 2 years, while lesions described by Kaur

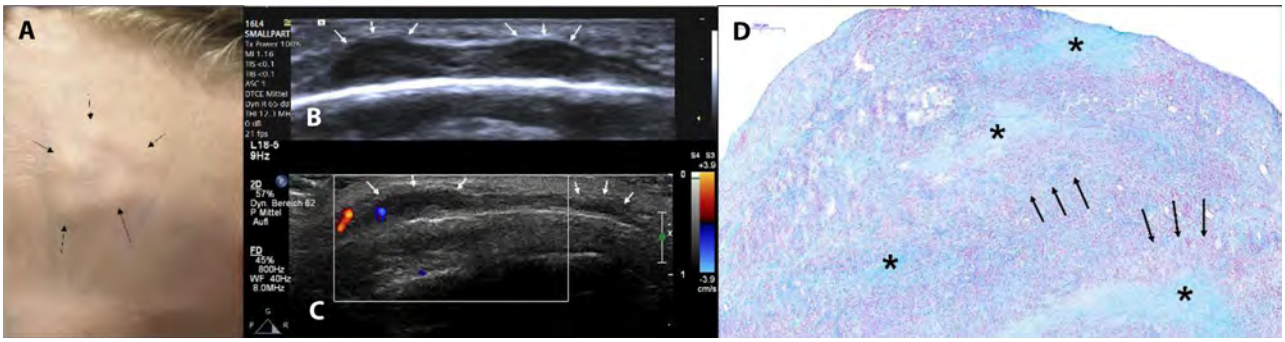

Figure 1. This composite figure shows a clinical picture of the frontal location of multiple subcutaneous granuloma annulare (SGA) lumps (A). Note the epifascial cap sign in the ultrasound image of two SGA lesions marked with multiple white arrows (B), and in another ultrasound image showing mild peripheral hypervascularization (C). The histopathology of the SGA lesions is characterized by pathognomonic mucin positive staining of necrobiotic collagen (stars) which is surrounded by inflammatory histiocytes and lymphocytes, ordered in palisades (black arrows).

et al disappeared within 15 days after intralesional injection of triamcinolone acetonide (10 mg/ml), as commonly observed in patients with localized or generalized variants of granuloma annulare.

References

1. Kaur L, Chakraborty D, Dayal S, Singh S, Yadav K. Subcutaneous Granuloma Annulare in an Atypical Age Group in Immediate Post-Covid-19 Phase. *Dermatol Pract Concept*. 2022;12(4):e2022156. DOI: 10.5826/dpc.1204a156. PMID: 36534560. PMCID: PMC9681236.
2. Piette EW, Rosenbach M. Granuloma annulare: Clinical and histologic variants, epidemiology, and genetics. *J Am Acad Dermato.l* 2016;75(3):457-465. DOI: 10.1016/j.jaad.2015.03.054. PMID: 27543209.
3. Tsuruta D, Sowa J, Hiroyasu S, Ishii M, Kobayashi H. Concomitant occurrence of patch granuloma annulare and classical granuloma annulare. *J Dermatol*. 2011;38:(5):482-485. DOI: 10.1111/j.1346-8138.2010.01070.x. PMID: 21352310.
4. Piette EW, Rosenbach M. Granuloma annulare: Pathogenesis, disease associations and triggers, and therapeutic options. *J Am Acad Dermatol*. 2016;75(3):467-479. DOI: 10.1016/j.jaad .2015.03.055. PMID: 27543210.
5. Beqo BP, Gasparella P, Flucher C, Tschauner S, Brcic I, Haxhija EQ. Subcutaneous Granuloma Annulare vs. Subcutaneous Vascular Malformations in Children: A Diagnostic Challenge. *Children (Basel)*. 2023;10(2):362. DOI: 10.3390/children10020362. PMID: 36832491. PMCID: PMC9955411.