SUBCUTANEOUS GRANULOMA ANNULARE OF THE EXTREMITIES IN CHILDREN

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OBJECTIVE: To familiarize surgeons to the natural history and treatment of granuloma annulare of the extremities in children.

DESIGN: Case review and follow-up by appointment and questionnaire.

SETTING: The Children's Hospital of Eastern Ontario, a tertiary referral centre.

PATIENTS: Twenty-seven children (23 girls, 4 boys) seen between 1983 and 1998 with subcutaneous granuloma annulare, proven pathologically. The mean age at initial presentation was 8.3 years (range from 1.8 years to 16.7 years). The mean follow-up was 45 weeks (range from 1 week to 5 years).

INTERVENTION: Biopsy excision of the lesions.

OUTCOME MEASURES: The incidence multiple lesions, the commonest site of occurrence and the incidence of recurrence.

RESULTS: Six children presented with multiple lesions for a total of 46 lesions. The anterior pretibial area was the most frequently affected site (16 lesions), followed by the ankle (6 lesions) and the long finger (4 lesions). Five patients suffered recurrence of the lesion, with a total of 7 lesions recurring.

CONCLUSIONS: Subcutaneous granuloma annulare is a benign inflammatory skin lesion occurring most frequently in the anterior pretibial area in children, predominantly girls. The incidence of recurrence and of multiple lesions is high. Biopsy is required for definitive diagnosis. The lesion resolves spontaneously without treatment.

OBJECTIF : Initier les chirurgiens au déroulement de la maladie et au traitement du granulome annulaire des membres chez les enfants.

CONCEPTION : Étude de cas et suivi assuré par rendez-vous et questionnaire.

CONTEXTE : Hôpital pour enfants de l'est de l'Ontario, centre de référence tertiaire.

Patients : Vingt-sept enfants (23 filles, 4 garçons) traités entre 1983 et 1998 pour un granulome annulaire sous-cutané avec manifestation pathologique. À la première visite, les patients avaient en moyenne 8,3 ans (plage de 1,8 à 16,7 ans). Le suivi moyen s'est établi à 45 semaines (plage d'une semaine à 5 ans).

INTERVENTION : Excision des lésions par biopsie.

MESURES DE RÉSULTATS : L'incidence des lésions multiples, l'endroit atteint le plus souvent et l'incidence de répétition.

RÉSULTATS : Six enfants avaient des lésions multiples, ce qui donnait un total de 46 lésions. La zone prétibiale inférieure était l'endroit atteint le plus souvent (16 lésions), suivie de la cheville (6 lésions) et du majeur (4 lésions). Cinq patients ont été victimes d'une rechute, ce qui a produit au total sept répétitions.

CONCLUSIONS : Le granulome annulaire sous-cutané est une lésion cutanée inflammatoire bénigne qui atteint le plus souvent la zone prétibiale antérieure chez les enfants, surtout de sexe féminin. L'incidence de la répétition et des lésions multiples est élevée. Il faut procéder à une biopsie pour poser un diagnostic définitif. La lésion disparaît spontanément sans traitement.

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Granuloma annulare is a benign inflammatory skin lesion that is seen in children and adults. It was first encountered by Fowler[1] in 1884; however it was not reported again until 1895.[2] There are 4 recognized types of this disease: localized, generalized, perforating and subcutaneous. The subcutaneous form is characterized by its presence on the extremities and scalp and by its exclusive occurrence in children.

Reports of subcutaneous granuloma annulare in the literature have been controversial because of its unknown etiology, pathological findings that may mimic fibrosarcoma,[3] and confusion over the precise name of the lesion, which has been referred to as pseudorheumatoid nodule,[3–6] isolated subcutaneous nodule,[7] subcutaneous palisading granuloma,[8] and subcutaneous granuloma annulare.[9,10]

Clinically, subcutaneous granuloma annulare presents as a firm, non-tender, immobile, soft-tissue mass with a recent history of rapid growth, in a young child. Multiple lesions in may be present. The typical sex predilection is 2-to-1 female-to-male.[6,7,9,11] Radiographs typically demonstrate a soft-tissue mass with no osseous involvement. Magnetic resonance imaging has recently been reported to demonastrate a mass with either decreased or intermediate signal intensity on both T_1- and T_2-weighted images.[12,13] One study has reported poorly defined margins of the lesion on MRI,[12] and the other noted well-defined margins of the lesion.[13] Neither CT nor laboratory tests have been helpful in making the diagnosis.

Owing to the difficulty in establishing the correct diagnosis of subcutaneous granuloma annulare, the disease is rarely diagnosed correctly preoperatively. Biopsy of the lesion has frequently enabled the appropriate diagnosis to be made; however recurrence is frequent.[6–8,10,11] The lesion typically resolves spontaneously without treatment.

Because of the difficulty in diagnosing subcutaneous granuloma annulare of the extremities in the orthopedic literature, we decided to examine the presentation and course of this disease in children in an attempt to increase awareness of the disease. To this end, all pertinent clinical, radiologic, and pathological records of 27 children treated at the Children's Hospital of Eastern Ontario (CHEO) for subcutaneous granuloma annulare of the extremities between 1983 and 1998 were reviewed.

Patients

There were 23 girls and 4 boys, with an mean age at the time of initial presentation of 8.3 years (range from 1.8 years to 16.7 years) (Table I). Six children presented with multiple lesions, 3 with 2 lesions, 1 with 5 lesions, 1 with 6 lesions and 1 with 8 lesions for a total of 46 lesions. The mean follow-up was 45 weeks (range from 1 week to 5 years).

Findings

The most common site of the disease was the anterior pretibial area (16 lesions [35%]), followed by the ankle, (6 lesions [13%]) and the long finger, (4 lesions [9%]) (Table II). The children initially presented to various services, the most predominant being general surgery (9 cases [33%]), followed by orthopedics (8 cases [30%]), dermatology (7 cases [26%]) and plastic surgery (3 cases [11%]). The duration of symptoms averaged 8 months and ranged from 1 month to 60 months (Table I). Twenty-one children (78%) reported a duration of symptoms of 6 months or less. In 24 cases (89%) the cause of the lesion was not known, in 2 cases (7%) there was a history of trauma, and 1 child (4%) reported the lesion subsequent to a recent immunization at the same site as the lesion. Of the 2 children with a history of trauma, 1 (case 15, Table I) suffered a hyperextension injury to the left hallux 5 months before presentation and reported swelling with increasing size immediately after the injury. The second child (case 16) reported a history of a direct trauma to the anterior pretibial area with a lesion that increased in size for 2 years before presentation. No child had a history of rheumatoid disease.

The most common presenting complaint was a mass of increasing size, encountered in 23 children (85%). Four children (15%) complained of discomfort. Of these, 2 had a lesion on the foot, 1 on the ankle, and 1 over the proximal interphalangeal joint of the index finger. In each case the symptoms of pain and discomfort were caused by chronic irritation of the lesion. Clinical findings usually included a soft-tissue mass which was firm, nontender and mobile (Fig. 1). In 5 children (19%), the mass was tender on deep palpation, and 2 children (7%) presented with a soft lesion. One child presented with decreased range of motion; however, this child's lesion overlay the proximal interphalangeal joint of the index finger, and the decreased range of motion was secondary to the site of the lesion.

Radiologic studies were performed in 11 children. In each case, plain radiographs were nonspecific and demonstrated a soft-tissue swelling with no osseous involvement (Fig. 2). Magnetic resonance imaging was performed in 1 child. The results were nonspecific and indicated decreased signal intensity of the lesion on T_1-weighted images and increased signal intensity of the lesion on T_2-weighted images (Fig. 3).

Treatment consisted of a biopsy in each case. Nineteen children (70%) underwent excisional biopsy and 8 children (30%) underwent needle biopsy. Each of the 6 children who presented with multiple lesions underwent biopsy of 1 of the lesions to allow for diagnosis and the remaining

lesions were left untreated. Two children (7%) were treated with an injection of triamcinolone acetonide directly into the lesion, which slightly decreased its size. No child underwent further treatment, although in each case the child and family were reassured about the benign nature and spontaneous resolution of the lesion.

Five children (19%) returned to the clinic with recurrence. In total, 7 lesions recurred, 3 locally and 4 at a distant site (Table I). All of the children who suffered recurrence initially presented with only 1 lesion, and the average age of the children with recurrence at the time of initial presentation was 6.5 years (range 2.4 years to 12 years). The average time that elapsed before recurrence was 2 years (range from 5 months to 5 years).

Table I

Patient Data

Case no.	Age, yr	Sex	No. of lesions	Duration of symptoms, mo	Location of lesion	Recurrence
1	2.4	F	1	2	Left tibia	No
2	10.4	M	1	Unknown	Left hand	No
3	9.8	F	1	13	Right long finger	Local (1) Distant (right index finger) (1)
4	2.5	F	1	4	Left hand	No
5	2.4	F	1	2	Left thigh	No
6	3.3	M	1	6	Left tibia	Local (1) Distant (right tibia) (1)
7	4.7	F	1	6	Left tibia	No
8	16.5	M	6	3	Right thigh, ankle, popliteal fossa Left calf, ankle, forearm	No
9	16.7	F	5	3	Left tibia (3) Right tibia (2)	No
10	11.2	F	1	2	Right 5th metatarsal	No
11	6.1	F	1	1	Right tibia	No
12	16.25	F	1	4	Right index finger	No
13	10.9	F	2	3	Left tibia Right upper arm	No
14	10.4	F	1	3	Left foot	No
15	13.3	F	1	5	Left hallux	No
16	8.6	F	1	24	Left tibia	No
17	1.8	F	1	3	Left thigh	No
18	8.7	F	2	2	Left tibia Right tibia	No
19	9.75	M	8	60	Right index, long fingers, ankle Left all fingers	No
20	10.3	F	1	5	Left long finger	No
21	16.5	F	1	Unknown	Right ankle	No
22	2.4	F	1	2	Left foot	Distant (left ankle) (1)
23	5.0	F	1	1	Left tibia	Local (1)
24	6.25	F	2	36	Left ankle (2)	No
25	3.0	F	1	3	Left tibia	No
26	8.6	F	1	4	Right forearm	No
27	6.75	F	1	4	Left tibia	Distant (left tibia)

PATHOLOGICAL FINDINGS

In each case, the gross appearance was nonspecific and comprised small fragments of firm, yellowish-white soft tissue. The histologic appearance was basically similar in all cases. There was a benign proliferation of histiocytes in a fibrous background with multiple foci of degeneration of the collagen, containing mostly mucinous degeneration but also some degree of fibrinoid degeneration (Fig. 4). The pro-

Table II

Site of Granuloma Annulare of the Extremities

Anatomic site	Right	Left
Pretibial area	4	12
Ankle	5	1
Long finger	2	2
Index finger	2	1
Thigh	1	2
Hand	0	2
Foot	0	2
Forearm	1	1
Calf	0	1
Popliteal fossa	1	0
5th metatarsal	1	0
Upper arm (over humerus)	1	0
Hallux	0	1
Thumb	0	1
Ring finger	0	1
Little finger	0	1

liferating histiocytes were either disposed without organization in the fibrous background or forming well-developed palisades around the foci of mucinous and fibrinoid degeneration. Multinucleated giant cells were not obvious in our material but have been described in the literature. Chronic inflammation was inconspicuous and when present it consisted of sparse lymphocytes surrounding adjacent vessels.

DISCUSSION

Granuloma annulare is a benign inflammatory dermatosis that has been reported in both adults and children. It comprises 4 predominant types: localized, generalized, perforating and subcutaneous. The subcutaneous form is characterized by its presence on the extremities and scalp and by its exclusive involvement in children. Pathological investigation in the literature has classified subcutaneous granuloma annulare as necrobiotic granulomatous dermatoses with a central area containing homogeneous necrotic collagen, an intermediate zone of layered or palisading histiocytes and a periphery of inflammatory cells.[11] Pathologically, subcutaneous granuloma annulare is indistinguishable from pseudorheumatoid nodule, but in children with no history of rheumatoid disease, these lesions are classified as subcutaneous granuloma annulare.

The etiology of granuloma annulare has yet to be clearly elucidated. Proposed theories, yet to be proven, have included the involvement of tuberculosis,[1,2] aberrant cell-mediated immunologic reactions,[14,15] trauma or infection[4,5,16] and a connection to a rheumatoid disease. A possible cause of the lesion was elucidated in only 3 children in this series. Two had a history of trauma and 1had a history of a recent immunization. There were no cases of infection. A connection between subcutaneous granuloma annulare and rheumatoid disease is rare in children and none of the children in this series had a history of rheumatoid disease.

In the literature, patients with subcutaneous granuloma annulare have presented clinically with either single or multiple lesions. These have been firm, nontender, immobile soft-tissue masses on either the extremities or the scalp, associated with a recent history of rapid growth.[6–11] This was the typical clinical presentation in our series, although 5 children presented with lesions that were tender on deep palpation and 2 had soft lesions. Multiple lesions have frequently been reported in the literature.[6,8,10,11] Six children in this series had multiple lesions.

Children as young as 11 days have presented with this lesion[17] and it may occur throughout childhood and adolescence into adulthood;[7] however, the majority of cases have been reported in children between 2 and 5 years of age.[8,10,11] The children in this series were slightly older, having an average age of 8.3 years. Reported cases in the literature have displayed a 2-to-1 female-to-male preponderance,[6,7,9,11] although 1 series of 17 cases consisted of 14 girls and 3 boys.[8] In our series, there was a large female preponderance of 23 girls and only 4 boys. Of all cases of subcutaneous granuloma annulare of the extremities, the majority were located on the tibial area, followed by the ankle or foot and the forearm. The results of this series were similar as the anterior pretibial area was the most frequently affected site, followed by the ankle and the long finger.

Diagnostic tests have frequently been of limited use in establishing the correct diagnosis. Radiographs have typically illustrated a soft-tissue mass with no bony involvement,[6,9–11] while CT and MRI have been noncontributory.[9,11] Recently, a characteristic appearance of these lesions was reported on MRI. The lesion demonstrated de-

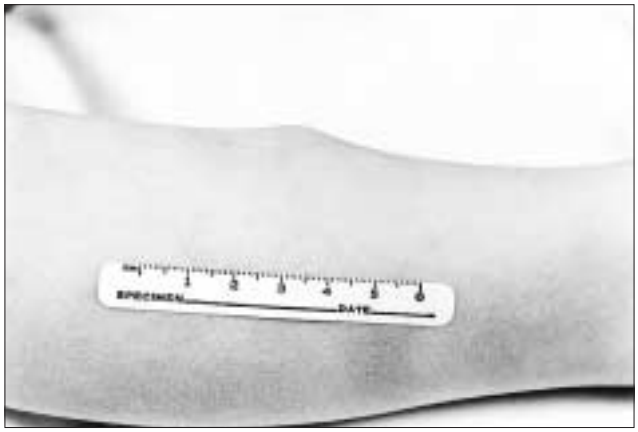

FIG. 1. Typical clinical appearance of subcutaneous granuloma annulare of the anterior tibia in a 4-year-old boy.

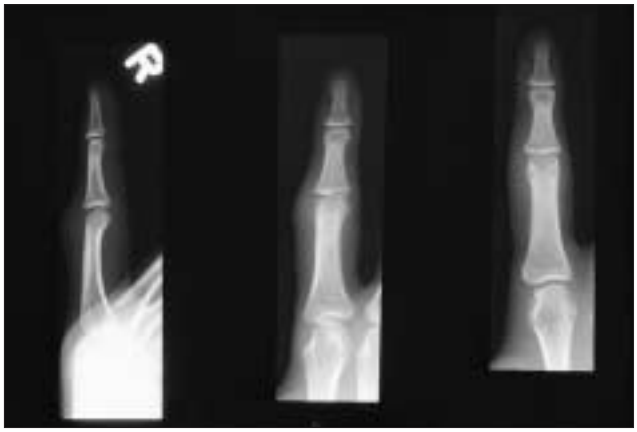

FIG. 2. Characteristic radiographic appearance of subcutaneous granuloma annulare demonstrating soft-tissue swelling with no osseous involvement.

creased or intermediate signal intensity on T_1- and T_2-weighted images.[12,13] The appearance of the margins of the lesion has not been found to be characteristic, because 1 study[12] reported poorly defined margins whereas the other noted well-defined margins.[13] In our series, MRI of lesions demonstrated decreased signal intensity on T_1-weighted images and increased signal intensity on T_2- weighted images, findings that conflict with those reported in the literature. Standard laboratory tests, in particular complete blood count and erythrocyte sedimentation rate, have been normal.[8–11]

Diagnosis of granuloma annulare has been difficult because the history of rapid growth and multiple recurrences can mimic a malignant lesion. These attributes have precipitated the recommendation of amputation.[3,7,11] An inadequate biopsy sample, taken from either the intermediate palisading histiocyte zone or the peripheral area of inflammatory cells, has resulted in the misdiagnosis of fibrosarcoma, precipitating overtreatment and unwarranted morbidity.[3] Biopsy has been reported to be diagnostic in all cases,[6–8,10,11] as was the experience in our series. Despite recent reports of a characteristic appearance of subcutaneous granuloma annulare on MRI,[12,13] these findings are not pathognomonic, so complete excisional biopsy is required for definitive diagnosis.

Recurrence of the lesion has been frequently encountered, with the highest reported rate being 75%.[11] The recurrence rate in our series was significantly lower as only 5 children returned to clinic with a recurrence, representing an incidence of 19%. Recurrence has been reported to predominantly occur locally, although the possibility of distant recurrence has been reported.[8,10,11] This was also our experience: 3 lesions recurred locally and 4 lesions recurred at a distant

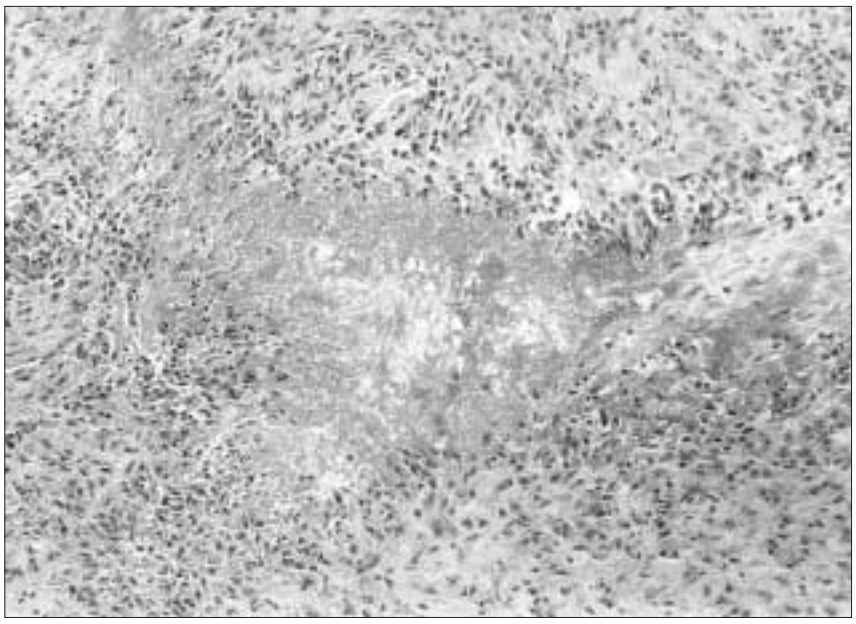

FIG. 4. A granuloma annulare with a central area of mucinous and fibrinoid degeneration surrounded by palisading histiocytes (hematoxylin–phloxine–saffron stain, original magnification × 180).

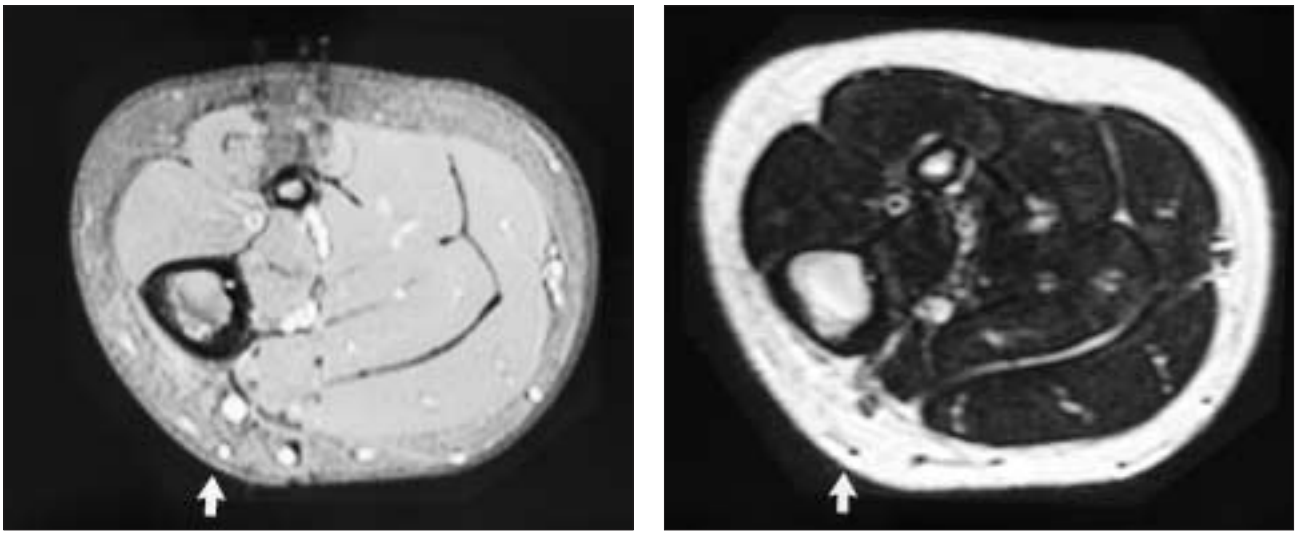

FIG. 3. Left: T_1-weighted magnetic resonance image illustrating decreased signal intensity of the lesion. Right: T_2-weighted magnetic resonance image demonstrating increased signal intensity of the lesion.

site. Regardless of the rapid growth and high rate of recurrence, this lesion resolves spontaneously.[6–11] Recurrence appears to be more prevalent in younger children. The average age of children with recurrence in this series was younger than the average age for the entire series.

Despite the good outcome associated with subcutaneous granuloma annulare without treatment, several studies have described treatment methods. These have included the use of steroids or chemotherapeutic drugs[16] and either simple or wide excision.[3,6–8] None of these treatment methods have been proven to be efficacious. Two children in our series were treated with injection of triamcinolone acetonide, but this treatment did not significantly increase the rate of resolution of the lesion in either child. It is essential that the natural course of spontaneous resolution be emphasized to both the child and family.

CONCLUSIONS

Subcutaneous granuloma annulare of the extremities is a benign, inflammatory skin lesion that occurs frequently on the anterior pretibial area in children, predominantly girls. The lesion typically presents in younger children although adolescents can be affected. There have been rare reports of this lesion in the orthopedic literature, but the large size of this series indicates that the occurrence of subcutaneous granuloma annulare of the extremities may be more prevalent than is reflected by the literature. A compilation of reported cases of subcutaneous granuloma annulare in children in the surgical literature reveals a total of 95 lesions in 66 children, with a high recurrence rate of 45%. Results of our series indicate that recurrence may not be as frequent as previously reported, but the incidence is higher in younger children. Most rapidly growing lesions in children will still mandate excisional biopsy. Recent recommendations of the characteristic findings of this lesion on MRI[12,13] allow for the use of this investigation in aiding the diagnosis; however biopsy is still required for a definitive diagnosis.

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