Granuloma annulare is a self-limited inflammatory skin lesion occurring in both adults and children. Subtypes with distinct clinical features include localized granuloma annulare, generalized granuloma annulare, perforating granuloma annulare, and subcutaneous granuloma annulare (SGA). SGA occurs exclusively in children and consists of deep dermal or subcutaneous nodules. On histologic evaluation, these nodules are similar to the nodules seen in adults with rheumatoid arthritis and to the lesion recognized in adult diabetic patients as necrobiosis lipoidica diabetorum. Synonyms for SGA include deep granuloma annulare, pseudorheumatoid nodule, subcutaneous palisading granuloma, and the more general term necrobiotic granuloma.

In adults, granuloma annulare and its variants as well as rheumatoid-like nodules have been reported in association with connective tissue disease, diabetes, and other conditions. In contrast, several series in the pathology and dermatology literature have demonstrated that the presence of these lesions in children is not a harbinger of connective tissue disease. However, SGA is not commonly encountered in pathologic practice and so continues to be a source of question in our pathology consultation service. We report our experience with the subcutaneous variant of granuloma annulare and suggest a possible association of SGA with diabetes in children.

METHODS
The pathology files at the Mayo Clinic (Rochester, MN) from 1983 through 1998 were searched for cases in which SGA, deep granuloma annulare, or necrobiotic granuloma was diagnosed in children <10 years old. All cases were reviewed for histologic confirmation of SGA; immunohistochemical methods were used when necessary to rule out infectious (Gomori’s methenamine-silver stain, acid-fast bacillus stain) or neoplastic (cytokeratin AE1/AE3) causes for the granulomatous lesions. Medical records were reviewed for clinical features and postoperative course. For consultation cases (approximately half of the cases), a questionnaire was sent to the referring pathologist requesting information on the patient’s clinical status before biopsy and at last follow-up. The questionnaire specifically inquired about the presence of rheumatologic or other connective tissue disease, diabetes mellitus, and recurrence of the lesion. If the pathologist did not have access to the medical records, the questionnaire was forwarded to the child’s pediatrician.

RESULTS
For the 15 years studied, 34 cases of SGA in children <10 years old were identified for whom clinical information was available. The lesion predominantly occurred in girls (21 girls and 13 boys; ratio of 1.6:1.0). Average age at diagnosis was 4.6 years. In 30 cases, SGA presented as slowly enlarging painless nodules; in 4 cases, as slight tenderness to palpation. In the 34 cases, SGA occurred at the following sites (Table 1): leg or foot, 28 cases (76%); hand or finger, 5 cases (15%); and forehead or scalp, 3 cases (9%). In 9 cases (26.5%), lesions were found in >1 location at initial presentation. The pretibial location was the single most common site, with SGA occurring there in 8 cases (24%). The average time between onset and biopsy for diagnosis was 4 months.

Follow-up information was unavailable in only 3 cases. Average follow-up was 60 months (range: 3
months to 14 years). Local recurrence within 1 month to 7 years of the initial lesion was clinically documented in 13 cases (38.2%). Typically, these consisted of multiple recurrences over several years, with lesion persistence for months to years. Recurrence at other locations was noted in 5 cases (14.7%). In 1 case (2.9%), a syndrome of generalized granuloma annulare developed, waxing and waning for 3 years.

In all cases the results of histologic evaluation were consistent with those previously described for SGA (Fig 1). The lesions consisted of multiple nodules in the deep dermis and subcutaneous tissue with central degenerative collagen and admixed mucin. The sharply demarcated areas of necrobiosis were surrounded by palisading histiocytes and a peripheral zone of mononuclear inflammatory cells. The overlying epidermis was not atrophic.

No child developed rheumatoid arthritis or symptoms of other connective tissue disease. One child had a father who had severe rheumatoid arthritis. Two children had diabetes mellitus. In 1 of these children, diabetes mellitus was diagnosed 2 years before the development of SGA; in the other child diabetes mellitus developed 1 month after the diagnosis of SGA. In both cases, the lesions were located on the lower leg or ankle, and there were multiple local recurrences over months to years. The histologic evaluation of these lesions did not differ from that of the other cases. Recurrences were observed without biopsy.

<table>
<thead>
<tr>
<th>Location</th>
<th>Cases, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leg or foot</td>
<td>26 (76)</td>
</tr>
<tr>
<td>Pretibial area</td>
<td>8 (24)</td>
</tr>
<tr>
<td>Hand or finger</td>
<td>5 (15)</td>
</tr>
<tr>
<td>Forehead or scalp</td>
<td>3 (9)</td>
</tr>
</tbody>
</table>

Fig 1. SGA: the lesion consists of nodules of histiocytic cells arranged around a central necrotic zone (hematoxylin-eosin). A, ×140; B, ×280.
Granuloma annulare was first described by Colcott Fox in 1895. Ziegler9 in 1941 was the first to note the presence of subcutaneous pseudorheumatoid nodules occurring concomitantly in a patient with localized granuloma annulare. These subcutaneous lesions, seen on histologic evaluation to have a central zone of necrotic collagen surrounded by palisading histiocytes and mononuclear inflammatory cells, have since been recognized as a distinct subtype of granuloma annulare, occurring exclusively in children, in isolation or in temporal association with localized granuloma annulare.1

In our pathology files we identified 34 cases of SGA that occurred in a period of 15 years. Although this relatively small number suggests a low prevalence of this entity, this number may underrepresent the actual frequency of the lesion. Lesions that are clinically recognized may be observed without biopsy.

The clinicopathologic features observed in the 34 children in this study are consistent with those previously reported. Children with SGA are usually 2 to 5 years old and otherwise healthy.7,8,10,11 The most common lesion location is the lower extremity, especially the pretibial area, followed by the hands and scalp.7,8,11 Local or distant recurrences over months to years are common, being reported in 30% to 75% of cases.7,8,10

Adults presenting with rheumatoid nodules, histologically identical to SGA, are at significant risk for the development of rheumatoid arthritis or other connective tissue disease. Because of this association, efforts have been made to determine whether children with these lesions are at similar risk. Draheim et al12 collected 54 cases at the Armed Forces Institute of Pathology in 1959; in no case did connective tissue disease develop after 1 to 14 years of follow-up. Subsequent reports with smaller numbers of cases have also concluded that there is no increased risk for systemic rheumatologic disease in these children6,8,13–15; however, scattered reports of necrobiotic granuloma in children with known rheumatoid disease have perpetuated concern about these lesions.11 A recent review of 47 cases by Felner et al7 confirmed the self-limited course of SGA. Our findings corroborate these reports, with no patients developing connective tissue disease after a lengthy follow-up period.

Several investigators have attempted to demonstrate a relationship of granuloma annulare with other systemic diseases, most notably with diabetes mellitus. The association of granuloma annulare with diabetes mellitus is not yet established. Studer et al13 noted diabetes mellitus in 12% of 84 adult patients with granuloma annulare (localized or generalized), as opposed to the 5% prevalence of diabetes mellitus among the regional population. Comparison with an age-matched population was not performed. A large population study by Muhlemann and Williams8 also found an increased coincidence of localized granuloma annulare and diabetes mellitus, and Kidd et al16 reported a reduced glucose tolerance and higher insulin levels in patients with granuloma annulare. However, other studies looking for carbohydrate intolerance by glucose tolerance testing17–20 or hemoglobin A1C values21 failed to find an increased prevalence of altered carbohydrate metabolism in patients with granuloma annulare.

An association of SGA with diabetes mellitus has not been established in the medical literature. Two of 34 patients (5.9%) in our series had concomitant or subsequent diabetes mellitus. Histologically, the lesions in these patients were not distinctly different from those of the other children. In a series of 20 children with SGA, Evans et al18 noted that 1 child also had diabetes mellitus. Given the rarity of childhood diabetes (0.16% of US population <20 years old),22 this finding in these 2 studies may suggest an association between these 2 entities. Other series6–8,11–15 have focused on rheumatologic disease and did not comment on the presence or absence of diabetes. Additional series with larger numbers of patients and prospective study design would be required to confirm an association.

Although their clinical features are distinct, SGA shares histologic features with necrobiosis lipoidica diabeticorum, a well-recognized dermatologic complication of diabetes mellitus. In both conditions, palisading histiocytes surround zones of degenerated collagen. Necrobiosis lipoidica diabeticorum usually involves the entire dermis and subcutis, with the palisading histiocytes arranged in a tiered linear manner combined with dermal sclerosis, thickened subcutaneous septae, thickened blood vessels, and a mixed infiltrate of plasma cells, lymphocytes, and, on occasion, giant cells.2,4 The overlying epidermis is characteristically atrophic.4 SGA is characterized by smaller, rounder, multiple foci of degenerated collagen associated with more abundant mucin and involving only the deeper dermis and subcutis. Extensive chronic inflammatory infiltrate, vascular alterations, and epidermal atrophy are uncommon in SGA.4 Given the histologic similarities between granuloma annulare and necrobiosis lipoidica diabeticorum, these conditions may be 2 points along a continuum representing the same dermal process. Indeed, in 1 study, several of the adult patients with localized granuloma annulare and diabetes mellitus later developed lesions more characteristic of necrobiosis lipoidica diabeticorum.5 Similarly, SGA may represent an early-stage dermatologic manifestation of diabetes in a subset of children.

CONCLUSION

SGA is a lesion that presents as subcutaneous nodules on the lower extremities, hands, or scalp of young children. Recognition of its natural history allows the physician to alleviate anxiety and avoid unnecessary medical investigation when no sign of systemic connective tissue disease is present. Recurrences locally or at other sites are common but usually do not warrant additional biopsy.

REFERENCES

Subcutaneous Granuloma Annulare in Childhood: Clinicopathologic Features in 34 Cases
Karen L. Grogg and Antonio G. Nascimento
Pediatrics 2001;107;e42
DOI: 10.1542/peds.107.3.e42

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