INTRODUCTION

A granuloma is a collection of epithelioid histiocytes. In some cases, these cells are abundant and closely opposed, resembling epithelium. They may form palisades around extracellular material. In other cases, the cellular aggregates are smaller and less distinct, showing histologic features that overlap with nongranulomatous histiocytic lesions. Some granulomatous infiltrates are caused by infection, and these are described in Chapters 21-24. Granulomatous conditions may also show histologic resemblance to “histiocytoses”, many of which are likely neoplastic, and these are considered in Chapter 26.

GRANULOMA ANNULARE

Clinical Summary. Granuloma annulare is an idiopathic granulomatous condition. It occurs most commonly in children and young adults but may affect all age groups. Females are affected somewhat more commonly than males. The clinical morphology of granuloma annulare can be variable, with the most common presentation consisting of small, firm, asymptomatic papules that are flesh colored or pale red and are often grouped in an annular fashion (Fig. 14-1). There usually are several lesions, but there may be just one or many. The lesions are found most commonly on the arms, hands, legs, and feet. The trunk may also be involved, and rare sites of involvement include the palms, penis, ear, and periocular regions (1). Although chronic, the lesions usually subside after a number of years. Variants of granuloma annulare include (a) a generalized form, consisting of hundreds of papules that are either discrete or confluent and may not show an annular arrangement (2–4), (b) perforating granuloma annulare, with umbilicated lesions occurring usually in a localized distribution (5,6) and, rarely, in a generalized distribution (7–9), (c) erythematous or patch granuloma annulare, showing large, slightly erythematous patches, with a palpable border, on which scattered papules may subsequently arise (10,11), and (d) subcutaneous/deep granuloma annulare, in which subcutaneous nodules occur, especially in children, either alone or in association with intradermal lesions (12–18). The subcutaneous nodules have a clinical appearance similar to that of rheumatoid nodules, although there is no history of arthritis, and there is a greater tendency to occur on the legs, feet, and, occasionally, the head (14,19,20). In adults, similar lesions may be found near the small joints of the hands (21). A very rare, deep, destructive form of granuloma annulare has also been described (22,23).

A correlation between generalized papular granuloma annulare, diabetes mellitus, and hyperlipidemia has been observed by several authors, with additional rare reports suggesting an association with thyroid disease (2,3,24,25). Granuloma annulare has been reported in at least 60 patients with HIV or AIDS, with a greater incidence of generalized disease in this population (26–30). Granuloma annulare–like lesions have also been reported to develop at sites of resolved herpes zoster (31,32) and, occasionally, in association with tattoos (33), necrobiosis lipoidica (34), and sarcoidosis (35).

Histopathology. Histologically, granuloma annulare shows an infiltrate of histiocytes and a perivascular infiltrate of lymphocytes that is usually sparse. The histiocytes may be present in an interstitial pattern without apparent organization or in palisades surrounding areas with prominent mucin (Figs. 14-2 to 14-5). Patterns between these two
extremes occur, and a single biopsy may show interstitial, slightly palisaded, and well-palisaded histiocytes. Although degenerated collagen or small quantities of fibrin may be present (36), increased mucin is the hallmark of granuloma annulare. Occasionally, sections will not reveal increased mucin, particularly those lacking a palisaded arrangement of histiocytes. In biopsies with well-developed palisades, the central mucinous area is commonly accompanied by a few nuclear fragments or neutrophils. Plasma cells are present rarely. A sparse infiltrate of eosinophils is seen in approximately half of cases, and occasional biopsies show abundant eosinophils (37,38). Multinucleated histiocytes are present more often than not, but they are usually few and often subtle. They can occasionally be seen to have engulfed short, thick, blue-gray elastic fibers (39). The histiocytic infiltrate is usually present throughout the full thickness of the dermis or the middle and upper dermis, but occasionally, just
the superficial or the deep dermis is involved (40). Mitotic figures are usually rare (fewer than 1 per 10 high-power fields), but may be as frequent as 7 per 10 high-power fields in rare examples (41).

Rare examples of granuloma annulare show aggregates of epithelioid histiocytes, usually with some giant cells and a rim of lymphoid cells, which resemble the granulomas of sarcoidosis (35,36,40). These usually differ from sarcoidal granulomas, however, by showing poorer circumscripton and by lacking asteroid bodies. Vascular changes in granuloma annulare are variable but generally inconspicuous (42). Among the variants of granuloma annulare mentioned, the usual histologic picture of palisaded and interstitial pattern is found in the generalized form (4). Occasionally, there is a band of histiocytes and giant cells in the superficial dermis with perivascular lymphocytes (4). An interstitial pattern predominates in the erythematous and patch variants (10,11). In perforating granuloma annulare, at least part of the palisading granulomatous process is located superficially and is associated with disruption of the epidermis (5,7,8).

The subcutaneous nodules of deep granuloma annulare usually show large histiocytic palisades surrounding mucin and degenerated collagen (Fig. 14-5). These central, degenerated foci exhibit a pale appearance (43); however, examples in which mucin was not apparent or in which the central area appeared more fibrinoid have also been reported (19,20). Thus, subcutaneous granuloma annulare may be histologically indistinguishable from rheumatoid nodule, an appearance that has led to the term pseudorheumatoid nodule.

Pathogenesis. The cause of granuloma annulare is unknown. Possible precipitating events in small subsets of patients have included insect bites, warts, erythema multiforme, herpes zoster, exposure to sunlight, hepatitis B vaccine, and tuberculin skin tests (44–47). There is likely an increased incidence and increased disease severity in patients with diabetes mellitus. Thrombi or vasculitic changes have been noted in some examples, and it is possible that what we term granuloma annulare may represent a variety of disease processes.

Electron microscopic examination reveals degeneration of both collagen and elastic fibers in granuloma annulare (36). The macrophages (histiocytes) show a high content of primary lysosomes and considerable cytoplasmic activity with release of lysosomal enzymes into the extracellular space (48). Synthesis of types I and III collagen also occurs, probably as a reparative response (49). A cell-mediated immune response also appears to be involved, marked by prominent activated helper T cells (50–52). One immunoperoxidase study of the histiocytic population showed staining for lysozyme but not for other macrophage markers such as HAM 56 or CD-68 (53). Another demonstrated positivity for these two markers (41).

Blood vessel deposits of immunoglobulin M and the third component of complement (C3) have been observed by some investigators (51), but others have found them only rarely (54) or not at all (55). Thus, the existence of an immune complex vasculitis in granuloma annulare (51) appears unlikely.

Differential Diagnosis. Granuloma annulare and necrobiosis lipoidica may resemble one another histologically. Although much has been written about the difficulty of separating these disorders histologically (42), the distinction can be accomplished clinically in most circumstances (56). Furthermore, although it is true that histologic distinction may be impossible, usually it can be accomplished by using the criteria in Table 14-1. Other palisading granulomas (e.g., to foreign material) can mimic granuloma annulare (see Table 14-1) (57).

The interstitial type of granuloma annulare, in which palisades of histiocytes are not well developed, is less likely to be confused with necrobiosis lipoidica. This pattern is more likely to be mistaken for a process that can also show a superficial and deep lymphocytic infiltrate, such as the inflammatory stage of morphea, but the subtle presence of histiocytes in an interstitial pattern usually allows for a diagnosis of granuloma annulare. Mycosis fungoides can have a granulomatous infiltrate with a granuloma annulare–like pattern (58,59). Such examples of this cutaneous T-cell lymphoma can usually be recognized by a dermal lymphocytic infiltrate that is more dense around the superficial plexus than around the deep one, by a lichenoid component to the infiltrate and, occasionally, by the presence of intraepidermal lymphocytes. The interstitial type of granuloma annulare may also resemble a xanthoma. Distinction is usually possible because in granuloma annulare a foamy appearance to the histiocytes is either completely lacking or very subtle; in xanthoma, at least some of the histiocytes are foamy. In addition, granuloma annulare tends to show an obvious perivascular lymphocytic infiltrate, whereas most xanthomas do not (60). Drug reactions may also mimic granuloma annulare, but these usually show interface changes that allow for their distinction (61). Rarely, infection with Mycobacterium marinum may have few neutrophils and may produce a histologic picture resembling interstitial granuloma annulare (62). Interstitial granulomatous dermatitis (IGD) may represent a variant of granuloma annulare or be a closely related entity. There may be associated arthritis. IGD is more strongly associated with underlying rheumatoid arthritis and inflammatory/systemic autoimmune diseases. A variety of clinical lesions have been reported in IGD and/or similar conditions. These range from linear and “ropelike” on the trunk to erythematous patches, plaques, and papules that are sometimes annular (63–68).

Differentiation of subcutaneous granuloma annulare from a rheumatoid nodule is not always possible on histologic grounds, but subcutaneous granuloma annulare is
more likely than rheumatoid nodule to show prominent mucin and less likely to show foreign-body giant cells or prominent stromal fibrosis or abundant fibrin (43).

Finally, it should be remembered that granuloma annulare and other palisading granulomas may be simulated by epithelioid sarcoma, a lesion that may also contain mucin. Clues to epithelioid sarcoma include ulceration, cytologic atypia, necrotic foci that include necrotic epithelioid cells, and history of recurrence. Although atypia tends not to be striking, the epithelioid cells in epithelioid sarcoma usually show more nuclear hyperchromasia and pleomorphism, more mitotic figures, larger size, and redder cytoplasm than do the histiocytes of granuloma annulare (69). Immunohistochemically, epithelioid sarcoma can be distinguished from granuloma annulare by positivity for epithelial membrane antigen and keratins and loss of INI1 (70). Whereas a variety of keratins may be present in epithelioid sarcoma, the most common is cytokeratin 8/CAM 5.2, present in 94% of cases (71).

**Principles of Management.** Granuloma annulare, especially if asymptomatic, does not need to be treated, particularly since lesions may spontaneously resolve. If a patient desires treatment, first-line medications include topical and intralesional corticosteroids for localized disease, and a variety of treatments ranging from phototherapy to antimalariales, **Table 14-1**

<table>
<thead>
<tr>
<th>Entity</th>
<th>Pattern and Location</th>
<th>Material Within Palisades</th>
<th>Inflammatory Cells</th>
<th>Other Distinguishing Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granuloma annulare</td>
<td>Superficial ± deep dermis</td>
<td>Abundant mucin ± Fragmented neutrophils</td>
<td>Perivascular lymphocytes Few giant cells and plasma cells</td>
<td>Normal collagen outside of palisades</td>
</tr>
<tr>
<td>Annular elastolytic giant-cell granuloma</td>
<td>Upper dermis, usually</td>
<td>Dermis lacking elastic fibers</td>
<td>Giant cells with engulfed elastic fibers</td>
<td></td>
</tr>
<tr>
<td>Necrobiosis lipoidica</td>
<td>Pan-dermal, usually</td>
<td>Necrobiotic/sclerotic collagen</td>
<td>Prominent giant cells and plasma cells</td>
<td>Cholesterol clefs Dermal sclerosis Thickened blood vessel walls Lymphoid follicles</td>
</tr>
<tr>
<td>Rheumatoid nodule</td>
<td>Deep dermis (sometimes subcutis)</td>
<td>Fibrin</td>
<td>Histioocytes and giant cells</td>
<td></td>
</tr>
<tr>
<td>Palisaded neutrophilic and granulomatous dermatitis</td>
<td>Dermal and perivascular</td>
<td>Fibrin and neutrophilic dust</td>
<td>Intact neutrophils Neutrophilic dust</td>
<td>Leukocytoclastic vasculitis–like changes early</td>
</tr>
<tr>
<td>Foreign-body granulomas</td>
<td>Variable</td>
<td>Foreign</td>
<td>Foreign-body giant cells</td>
<td>Often polarizable</td>
</tr>
<tr>
<td>Necrobiotic xanthogranuloma</td>
<td>Pan-dermal Palisading may be subtle</td>
<td>Necrotic dermis</td>
<td>Prominent multinucleated giant cells Foamy histiocytes Touton giant cells Plasma cells</td>
<td>Cholesterol clefs Lymphoid follicles</td>
</tr>
<tr>
<td>Gout</td>
<td>Circular to irregular palisades</td>
<td>Amorphous material with a feathery, crystalline outline</td>
<td>Histioocytes</td>
<td>Crystals rarely evident with polarization</td>
</tr>
</tbody>
</table>
anti-inflammatory antibiotics, retinoids, and systemic immunosuppressive agents for more widespread disease.

**ANNULAR ELASTOLYTIC GIANT-CELL GRANULOMA**

*Clinical Summary.* Annular elastolytic giant-cell granuloma is the name that is currently in vogue for a condition with unclear nosologic status, and it is uncertain whether it is truly distinct from granuloma annulare (72–74). It almost always occurs on sun-exposed skin, such as the face, neck, dorsum of hand, forearm, and arm, hence the previous name *actinic granuloma* (75,76) (Fig. 14-6). The appearance of lesions after prolonged tanning bed use has been reported (77). However, there are a few reports of similar lesions involving sun-protected sites (78–81). The lesions clinically resemble granuloma annulare. They are typically large, somewhat annular plaques. The border may be serpiginous and is slightly raised, and pearly to red-brown. The central zone may show depigmentation and/or atrophy. Smaller papules may also occur, and lesions may be solitary, few, or numerous (75,82,83). Other names under which these lesions have been described include *atypical necrobiosis lipoidica of the face and scalp* (84), *Miescher granuloma of the face* (83), *granuloma multiforme* (82), and *actinic granuloma of O’Brien*. A possibly related process occurs on the conjunctiva (85).

*Histopathology.* The histologic features are best appreciated in a radial biopsy that contains the central zone, the elevated border, and the skin peripheral to the ring (75,82,83). The central zone shows the hallmark of the disease, that is, near or total absence of elastic fibers, best appreciated with an elastic tissue stain (e.g., Verhoeff-van Gieson) (Figs. 14-7 to 14-9). The collagen in this zone may show horizontally oriented fibers, producing a slight...
scar-like appearance (Fig. 14-7). By contrast, the zone peripheral to the annulus shows an increased amount of thick elastic material with the staining properties of elastic tissue. The transitional zone at the raised border shows a granulomatous infiltrate with either of the patterns seen in granuloma annulare, that is, histiocytes arranged interstitially between collagen bundles or, less commonly, in a palisade. Occasionally, there are contiguous epithelioid histiocytes in small clusters. Multinucleated histiocytes are conspicuous, usually being large and containing as many as a dozen nuclei, mostly in haphazard arrangement, but sometimes in ringed array. Elastotic fibers are present adjacent to and within the giant cells (Fig. 14-8). Asteroid bodies that stain like elastic fibers may be found in the giant cells (83). The infiltrate also contains lymphocytes and often some plasma cells. Mucin is inapparent.

**Differential Diagnosis.** The principal differential diagnosis is granuloma annulare, which may in fact be an artificial distinction. Because engulfment of abnormal elastic fibers can also occur in granuloma annulare (39) as well as in other granulomatous processes, it has been argued that the elastophagocytosis of annular elastolytic giant-cell granuloma does not qualify it as a distinct entity (73). Although some elastolysis has also been described in granuloma annulare (82), it is the complete loss of elastic tissue in the central zone that has been used as the primary basis for separating the diseases. Other features that have been evoked for distinguishing them are the presence of larger and more numerous giant cells, the absence of mucin in annular elastolytic giant-cell granuloma (75,86), and sparing of areas that lack elastic tissue, such as scars (81).

Necrobiosis lipoidica differs by the lack of a central zone of elastolysis and the presence of degenerated collagen, sclerosis, and, in some circumstances, lipids and vascular changes. Furthermore, annular elastolytic giant-cell granuloma involves mostly the upper and middle dermis, whereas necrobiosis lipoidica tends to affect the entire dermis and sometimes the subcutis. Foreign-body granulomas generally have more distinct collections of epithelioid histiocytes, lack zonation in density of elastic fibers, and often have identifiable foreign material.

**Principles of Management.** This condition is chronic and generally responds poorly to topical/intralosional corticosteroids and ultraviolet light treatment; there exist individual case reports of success with oral hydroxychloroquine and anti-inflammatory antibiotics, including dapsone (87).

### NECROBIOsis LIPOIDICA

**Clinical Summary.** Necrobiosis lipoidica is an idiopathic disorder typified by indurated plaques of the shins (Fig. 14-10). In 1966, in a large series, Muller and

**Figure 14-10 Necrobiosis lipoidica.** Waxy, red-brown plaque with central fine telangiectasia on the shin.

Winkelman (88) reported that two-thirds of patients with necrobiosis lipoidica had overt diabetes at the time of diagnosis. Of the rest, all but 10% developed diabetes within 5 years, had abnormal glucose tolerance, or had a history of diabetes in at least one parent. In a more recent series, only 11% of patients had diabetes at presentation, with an additional 11% developing diabetes or impaired glucose tolerance over 15 years (89). Of all patients with diabetes, fewer than 1% develop necrobiosis lipoidica (89). Some reports have suggested that necrobiosis lipoidica heralds a more rapid progression of diabetes in patients with that disorder, and may suggest an increased likelihood of end-organ microvascular damage, including retinopathy and earlier renal dysfunction (90).

In well-developed necrobiosis lipoidica, one observes one or several sharply but irregularly demarcated patches or plaques, usually on the shins (91). Usually they are bilateral, and the condition is more often present in women. The lesions appear yellow-brown in the center and more actively inflamed with red, orange, or violaceous erythema at the periphery. Whereas the periphery of the lesions may show slight induration, the center of the lesions gradually becomes atrophic, shows telangiectases, and may ulcerate. When lesions first begin, red-brown papules can be observed. In addition to the shins, lesions may be present elsewhere on the lower extremities, including the ankles, calves, thighs, popliteal areas, and feet. In about 15% of the cases, lesions are present also in areas other than the legs, especially on the dorsa of the hands, fingers, and forearms. Rarely, the head and abdomen are affected. Necrobiosis lipoidica with lesions exclusively outside the legs is extremely rare; it is reported to occur in 1% of patients with necrobiosis lipoidica (88).

Lesions located in areas other than the legs may appear raised and firm and may have a papular, nodular, or plaque-like appearance without atrophy. Clinically, they may resemble granuloma annulare (88). Involvement of...
the scalp by large, atrophic patches occurs occasionally. This is usually seen in association with lesions on the shins and elsewhere (92,93) but also, rarely, in isolation (94–96).

In rare instances, transfollicular elimination of necrotic material takes place in necrobiosis lipoidica, producing small hyperkeratotic plugs within a plaque (97,98). Necrobiosis lipoidica occasionally coexists with sarcoid (99) or granuloma annulare (34). Rare examples of squamous cell carcinoma arising in lesions of necrobiosis lipoidica have been reported (100,101).

**Histopathology.** Usually, the entire thickness of the dermis or its lower two-thirds is affected by a process that exhibits a variable degree of granulomatous inflammation, degeneration of collagen, and sclerosis (Figs. 14-11 and 14-12). Histologic changes of necrobiosis lipoidica may be seen in subcutaneous septae (102,103). Occasionally, only the upper dermis is affected (40,42,56,88). The epidermis may be normal, atrophic, or hyperkeratotic. In some instances, the surface of the biopsy shows ulceration. The granulomatous component is usually conspicuous, and the histiocytes may or may not be arranged in a palisade. Occasionally, there are just a few scattered epithelioid histiocytes and giant cells. The latter picture is more likely to occur in sections in which sclerosis is extensive, and occasionally in such biopsies several sections must be examined before a granulomatous component becomes apparent. Giant cells are usually of the Langhans- or foreign-body type; occasionally, Touton cells or asteroid bodies (104) are seen. If the histiocytes are arranged in a palisade, the palisades tend to be somewhat horizontally oriented and/or vaguely tiered. Occasionally, histiocytes may be seen completely to encircle altered connective tissue, particularly degenerated collagen, but, more commonly, altered connective tissue is incompletely surrounded by histiocytes. This alteration of connective tissue has also been referred to as “necrobiosis.” The altered collagen appears different from normal collagen by having a paler, grayer hue and by appearing more fragmented and haphazardly arranged; it may also appear more compact or smudged (Fig. 14-12). Areas of sclerosis with a diminished number of fibroblasts can be seen. A clue to the presence of sclerosis can be found by looking at the edges of the biopsy specimen, which tend to be straight with less of the inward retraction of the dermis ordinarily associated with punch biopsies (Fig. 14-11). Increased mucin is usually inapparent or subtle in contrast to granuloma annulare. Other findings include a sparse to moderately dense, primarily perivascular lymphocytic infiltrate, plasma cells in the deep dermis in some biopsies (Fig. 14-13), involvement of the upper subcutis with thickened fibrous septa, and lipids which may be present in foamy histiocytes (105) or which may be inferred from the presence of cholesterol clefts (seen in <1% of cases) (106). Deep lymphoid follicles may be present in up to 10% of cases.

![Figure 14-11 Necrobiosis lipoidica. The presence of sclerosis can be identified by the relatively straight edges of the punch biopsy. The infiltrate involves the full thickness of the dermis and is arranged in a tier-like fashion.](image)

![Figure 14-12 Necrobiosis lipoidica. Histiocytes, lymphocytes, and degenerated collagen are present.](image)

![Figure 14-13 Necrobiosis lipoidica. Plasma cells at the dermal–subcutaneous junction are a typical finding.](image)
Older lesions show telangiectases superficially. Blood vessels, particularly in the middle and lower dermis, often exhibit thickened walls. The thickened walls may be infiltrated with periodic acid–Schiff (PAS)–positive, diastase-resistant material (42). Vascular changes of this type are seen particularly near loci containing thickened, hyalinized collagen bundles. Whereas the vascular changes often are conspicuous in lesions of the lower legs, they usually are mild or absent elsewhere (95). Histologic findings that are possibly correlated with the clinical presence of diabetes include florid palisading around degeneration of collagen (88) and cholesterol clefts (106).

Pathogenesis. The cause of necrobiosis lipoidica is unknown, and it is unclear whether the degeneration of collagen is a primary or a secondary event (91). Some authors have postulated that the degeneration of collagen is the result of vascular changes secondary to clinical or latent diabetes (107). However, evidence against a vascular cause includes the absence of vascular pathology in approximately one third of biopsies examined (88) and the fact that vessels that are affected are often situated in the lower dermis and are of a larger caliber than the vessels affected by diabetic microangiopathy. Abnormal glucose transport by fibroblasts has also been implicated (108).

Direct immunofluorescence studies have shown that necrobioitic foci contain fibrinogen. Deposits of immunoglobulin and C3 have been found in the vessel walls (110,111), but this is not a consistent finding (112). Electron microscopic examination shows degenerative changes in collagen and elastin with loss of cross-striation in collagen fibrils. Collagen synthesis by fibroblasts is diminished (109).

Direct immunofluorescence studies have shown that necrobioitic foci contain fibrinogen. Deposits of immunoglobulin and C3 have been found in the vessel walls (110,111), but this is not a consistent finding (112).

Differential Diagnosis. See Table 14-1 for differentiation of necrobiosis lipoidica from granuloma annulare. Differentiation of necrobiosis lipoidica from annular elastolytic granuloma was discussed in the section on annular elastolytic granuloma. Occasionally, necrobiosis lipoidica shows discrete collections of epithelioid cells that may resemble those seen in sarcoidosis (92); however, significant alteration of the collagen is usually present in necrobiosis lipoidica and absent in sarcoidosis (92).

Necrobioitic xanthogranuloma with paraproteinemia can simulate necrobiosis lipoidica but differs by showing a denser, more diffuse infiltrate with a greater number of foamy histiocytes, Touton giant cells, more extensive inflammation of the subcutis, and greater disruption of normal subcutaneous architecture. Lymphoid follicles and cholesterol clefts are more commonly seen in necrobiotic xanthogranuloma than in necrobiosis lipoidica (113).

Principles of Management. No treatment has been proven to be effective in large studies. Potent topical or intraleisional corticosteroids are first-line therapy (114).

RHEUMATOID NODULES

Clinical Summary. Rheumatoid nodules are deeply seated firm masses that occur in patients with rheumatoid arthritis, particularly over extensor prominences, such as the proximal ulna, the olecranon process, and the metacarpophalangeal and proximal interphalangeal joints (115). They may occur elsewhere, such as the back of the hands, over amputation stumps (116), and, rarely, in extracutaneous sites, such as the lung and heart (117,118). The nodules vary in size from a few millimeters to 5 cm and may be solitary or numerous. Rarely, rheumatoid nodules show a central draining perforation (119). Rheumatoid factor is almost always found in high titer. Rarely, nodules may precede apparent joint disease (115). The rapid appearance of many small rheumatoid nodules has been reported in some patients treated with methotrexate and rarely with other disease-modifying antirheumatic drugs. This presentation has been termed accelerated rheumatoid nodulosis (120,121). The term rheumatoid nodulosis has also been proposed for the clinical presentation of multiple nodules on the hands/elbows with intermittent arthralgias/arthritus but no evidence of systemic rheumatoid arthritis (122). Rheumatoid nodules also occur in occasional patients with systemic lupus erythematosus who do not exhibit rheumatoid arthritis (123–125).

Pseudorheumatoid nodule is a term that has been applied to nodules in the subcutis that mimic rheumatoid nodules histologically but that develop in the absence of joint pain, rheumatoid arthritis, or systemic lupus erythematosus (13,20). These occur in children or adults. The subsequent development of rheumatoid arthritis occurs infrequently in adults and rarely, if ever, in children. Because some of these nodules occur in patients with other lesions that are typical of intradermal granuloma annulare (13), the nodules are now generally considered to represent a subcutaneous variant of granuloma annulare.

Histopathology. Rheumatoid nodules occur in the subcutis and deep dermis. They exhibit one or several areas of fibrinoid degeneration of collagen that stain homogeneously red (Fig. 14-14). Nuclear fragments and basophilic material are often present, but mucin is almost always minimal or absent (43). These foci of degenerative change are surrounded by histiocytes in a palisade. Foreign-body giant cells are present in approximately 50% of biopsies (43). In the surrounding stroma, there is a proliferation of blood vessels associated with fibrosis. A sparse infiltrate of other inflammatory cells is associated with the histiocytes and surrounding stroma. Lymphocytes and neutrophils are most common, but mast cells, plasma cells, and eosinophils may be present. Occasionally, lipid is seen (43). Vasculitis has been described (126) but is not usually encountered (43). In perforating rheumatoid nodules, the central fibrinoid material extends through the skin surface (119).
noninfectious granulomas

Pathogenesis. Factors that have been implicated in the formation of rheumatoid nodules include trauma, vasculitis, and a specific T-cell–mediated immune reaction (115,127).

Differential Diagnosis. The principal differential diagnosis is subcutaneous granuloma annulare, which was discussed in the section on granuloma annulare. A distinction should be made from epithelioid sarcoma, also covered in that section. Nonabsorbable sutures or other foreign material may produce periarticular palisaded granulomas like those of rheumatoid nodule (128,129); in such instances, there should be a history of previous surgery or trauma, and birefringent material may be visible under polarized light. Rheumatic fever produces nodules (rheumatoid nodules), especially over the elbows, knees, scalp, knuckles, ankles, and spine (130), which were confused with rheumatoid nodules in the early part of the 20th century. Histologically, a rheumatic fever nodule is less likely to show central, homogeneous fibrinoid necrosis. A palisade of histiocytes is usually not as well developed, and fibrosis is minimal or absent (117,131). Rarely, an infectious process, such as cryptococcosis, can produce a deep, palisaded granuloma. It can be differentiated from rheumatoid nodule because the palisade surrounds primarily necrotic debris and organisms rather than fibrinoid material.

Principles of Management. Treatment of rheumatoid arthritis may improve rheumatoid nodules. For particularly symptomatic rheumatoid nodules, intralesional corticosteroids or surgical excision can be effective.

PALISADED NEUTROPHILIC AND GRANULOMATOUS DERMATITIS

Clinical Summary. The classic clinical presentation is umbilicated papules and nodules on the elbows and extensor surfaces of the digits, often seen in a patient with an associated collagen-vascular disease (132) (Fig. 14-15). Lesions previously termed Churg–Strauss granuloma, cutaneous extravascular necrotizing granuloma, rheumatoid papules (133,134), and superficial ulcerating rheumatoid necrobiosis (135–137) present in a similar fashion and may represent the same condition. Over time, small case reports and case series have expanded the clinical spectrum of PNGD from the classic lesion to include variants presenting with plaques, patches, and other atypical morphologies. There exists considerable overlap with interstitial granulomatous dermatitis.

Histopathology. There are three sometimes overlapping histologic patterns in this rare condition: (a) early lesions resembling leukocytoclastic vasculitis but with broader cuffs of fibrin around vessel walls and abundant dermal basophilic nuclear debris, (b) fully developed lesions with a granuloma annulare–like appearance but associated with prominent neutrophils and neutrophilic dust (Figs. 14-16 and 14-17), and (c) a fibrosing, necrobiosis lipoidica–like final stage, sometimes with a sparse, superficial, and deep...
developed lesions are believed to be a response to the vasculitic changes accompanying ischemia and enzymatic degradation by neutrophils.

**Differential Diagnosis.** See Tables 14-1 and 14-2.

**Principles of Management.** PNGD usually occurs in the setting of a systemic disease, and therapy is generally targeted at the underlying disease. Treatment of localized lesions with topical or intralesional corticosteroids may be helpful. Antimalarials and dapsone have also been used successfully (141).

**SARCOIDOSIS**

**Clinical Summary.** Sarcoidosis is a multisystem granulomatous disease of undetermined cause. A distinction is made between the subacute, transient type of sarcoidosis and the chronic, persistent type.

In subacute transient sarcoidosis, erythema nodosum is associated with hilar adenopathy, fever, and, in some cases, migrating polyarthritis and acute iritis, termed Löfgren syndrome. The disease subsides in almost all patients within a few months without sequelae. Cutaneous manifestations other than erythema nodosum do not occur (142,143). Occasionally, there is enlargement of subcutaneous lymph nodes (143,144).

In systemic sarcoidosis, cutaneous lesions are encountered in approximately one-fourth of patients (35,145–148). In the United States, this disorder is much more common, more severe, and more chronic in African Americans (149,150). It is rare in children (151–153). A rare genetic disorder, Blau syndrome, may present in childhood and...
mimic sarcoidosis. This autosomal dominant disorder, with mutations in the NOD2 gene, is marked by granulomatous inflammation of the skin, uveal tract, and joints, notably sparing the lungs (154,155).

The most common cutaneous lesions of sarcoidosis are brown-red or purple papules and plaques (156) (Fig. 14-18). Sarcoidosis is one of the “great mimickers,” and almost every cutaneous morphologic lesion type is possible. When papules or plaques of sarcoidosis are situated on the nose, cheeks, and ears, the term lupus pernio is applied (157). This presentation has been associated with upper respiratory involvement and greater disease severity (156,158).

Less common manifestations of sarcoidosis include annular, lichenoid, erythrodermic, ichthyosiform, atrophic, ulcerating, verrucous, angiolupoid, hypopigmented, alopecic, and morpheaform variants. Lichenoid sarcoidosis manifests with small, flat violaceous papules (159). In erythrodermic sarcoidosis, the erythroderma may be generalized (160) or may consist of extensive, sharply demarcated, brown-red, slightly scaling patches with little or no palpable infiltration (161). In ichthyosiform sarcoidosis, ichthyotic changes favor the lower extremities (162), but at times they also may be present elsewhere on the skin (163,164). Rarely, there are extensive atrophic lesions (165). They may undergo ulceration (166,167). Multiple ulcers have been described also in plaque-like lesions (168). Angiolupoid sarcoid is characterized by a prominent telangiectatic component (169). Lesions of hypopigmented sarcoid appear as macules with or without an associated papular or nodular component (170). Subcutaneous nodules of sarcoidosis are also rare. Originally described by Darier and Roussy (171), they may occur in association with other cutaneous lesions (161,172) or alone (173). Sarcoidosis has been described in AIDS patients (174), and a transient form of chronic sarcoidosis has been reported in patients with hepatitis C undergoing treatment with interferon alfa and ribavirin (175). Interferon alfa can induce localized and systemic granulomatous inflammation. Other drugs, particularly TNF inhibitors, have also been described to induce localized granulomas and widespread drug-induced sarcoidosis-like syndromes.

Systemic sarcoidosis occasionally coexists with granuloma annulare (35). Cutaneous lesions of sarcoidosis may localize to areas of scarring, as in herpes zoster scars (176,177). Tattoos (178,179), exogenous ochronosis (180), or other exogenous materials in the skin (181) may serve as a nidus for cutaneous lesions in patients with sarcoidosis. Two studies demonstrated polarizable foreign material in approximately 20% of cutaneous sarcoidal lesions from patients with systemic sarcoidosis (182,183).

**Histopathology.** The lesions of erythema nodosum occurring in subacute, transient sarcoidosis have the same histologic appearance as “idiopathic” erythema nodosum (144).

Like lesions in other organs, the cutaneous lesions of chronic, persistent sarcoidosis are characterized by the presence of circumscribed collections of epithelioid histiocytes—so-called epithelioid cell tubercles—which show little or no necrosis (Figs. 14-19 and 14-20). The papules, plaques, and lupus pernio–type lesions show variously sized aggregates of epithelioid histiocytes scattered irregularly through the dermis with occasional extension into the subcutis (184). In the erythrodermic form, the infiltrate shows small granulomas in the upper dermis intermingled with numerous lymphocytes (161,185) and, rarely, also giant cells (186). Typical sarcoidal granulomas

![](image1.png)

**Figure 14-18 Sarcoid.** Pink-brown papules in clusters on the neck.

![](image2.png)

**Figure 14-19 Sarcoid.** There are well-circumscribed, nodular collections of epithelioid histiocytes in the dermis. This example also shows subcutaneous involvement, which is less common than purely dermal involvement.
are found in the ichthyosiform lesions (163), in ulcerated areas (168), and in atrophic lesions (187,188). Verrucous sarcoid exhibits prominent associated acanthosis and hyperkeratosis (189,190). Biopsies of hypopigmented sarcoid may reveal granulomas, which may have a perineural component or fail to reveal granulomas (191). In subcutaneous nodules, larger epithelioid cell tubercles lie in the subcutaneous fat (173).

In typical cutaneous lesions of sarcoidosis, the well-demarcated islands of epithelioid cells contain few, if any, giant cells. Those that are present are usually of the Langhans type. A moderate number of giant cells can be found in old lesions. These giant cells may be large and irregular in shape. In a minority of cases, giant cells contain asteroid bodies or Schaumann bodies (192). Asteroid bodies (Fig. 14-21), which are more common, are star-shaped eosinophilic structures that, when stained with phosphotungstic acid–hematoxylin, produce a center that is brown-red with radiating blue spikes (193). Schaumann bodies are round or oval, laminated, and calcified, especially at their periphery. They stain dark blue because of the presence of calcium. Neither of these two bodies is specific for sarcoidosis: They have been observed in a variety of other granulomas, including those of leprosy, tuberculosis, foreign-body reactions, and necrobiotic xanthogranuloma (193).

Classically, sarcoid has been associated with only a sparse lymphocytic infiltrate, particularly at the margins of the epithelioid cell granulomas (Fig. 14-20). Because of the scarcity of lymphocytes, the granulomas have been referred to as “naked” tubercles. However, lymphocytic infiltrates in sarcoid may occasionally be dense, as in tuberculosis (Fig. 14-22) (194). Occasionally, small foci of fibrin or necrosis showing eosinophilic staining is found in the center of some of the granulomas (Fig. 14-23) (158,184). A reticulum stain of sarcoid reveals a network of reticulum fibers surrounding and permeating the epithelioid cell granulomas. If the granulomas of sarcoidosis involute, fibrosis extends from the periphery toward the center, with gradual disappearance of the epithelioid cells (184). Fibrosis, however, is minimal to absent in most examples of sarcoidosis, with the exception of the morpheaform variant, where it is prominent (195). Other features that may sometimes be seen include elastophagocytosis, increased dermal mucin, and lichenoid inflammation (196).

**Systemic Lesions.** The lungs are the most commonly involved organ in the chronic, persistent type of sarcoidosis, and respiratory symptoms are present in approximately 50% of patients (143). The lesions may be either nodular or diffuse with extensive parenchymal fibrosis.

In about 25% of the patients, ocular manifestations occur, most commonly chronic iridocyclitis. Splenomegaly is present in about 17%. In approximately 12%, osseous...
Figure 14-23 Sarcoid. On the left is fibrinoid material within the granulomatous component.

Granulomas are present, most commonly in the phalanges of the fingers and toes. Involved phalanges appear swollen and deformed, often sausage-shaped (197). The skull may show circumscribed lytic lesions (198). About 8% of the patients have involvement of large salivary glands, usually the parotid. In about 5%, one encounters paresis of a cranial nerve, most commonly of the facial nerve (143). Oral mucosal involvement occurs very rarely (199). Asymptomatic enlargement of the hilar lymph nodes is present in 70%, of peripheral lymph nodes in 30%, and of the liver in 20% of the patients (143,200).

Sarcoidosis, although usually a benign disease, is fatal in approximately 5% of patients (143,200). The most common cause of death from sarcoidosis is right ventricular failure resulting from massive pulmonary involvement. Pulmonary hemorrhage and superimposed tuberculosis are rare causes of death. Another potentially fatal complication is renal insufficiency resulting from hypercalcemia and hypercalciuria (201) or from sarcoidal glomerulonephritis (202). In very rare instances, death results from massive involvement of the myocardium (203) or liver (204). Hypopituitarism from involvement of either the pituitary gland or the hypothalamus is also a rare fatal complication (205).

The diagnosis of sarcoidosis in a patient with systemic disease is based on clinical presentation, biopsy findings, and exclusion of other granulomatous processes. If skin lesions are present, they are an obvious choice for biopsy. In the absence of skin lesions, a Kveim test was frequently used in the past. The Kveim test involves intradermal injection of antigen derived from heat-sterilized suspension of sarcoidal tissue, particularly spleen or lymph node. The site is sampled 6 weeks later, with a positive result being the formation of a sarcoid-like granuloma (206,207). The test has a sensitivity of about 80%, with false-positive reactions occurring in less than 2% of cases (208). However, Kveim antigen is neither widely available nor approved by the U.S. Food and Drug Administration. It is infrequently used (149). The most accepted alternative approach for confirming a presumptive diagnosis of systemic sarcoidosis is fiberoptic bronchoscopy with transbronchial lung biopsy (209). Endobronchial biopsy has also been shown to be useful (210), as has asymptomatic gastrocnemius muscle biopsy (211). Less specific ancillary tests, such as serum angiotensin-converting enzyme levels, can provide supportive data.

Pathogenesis. The cause of sarcoidosis is unknown, and the disease may not have the same pathogenesis in all individuals. Alterations in immunologic status have long been recognized, including hypergammaglobulinemia, impaired delayed-type hypersensitivity reactions to cutaneous antigens (anergy), and a shift of helper T lymphocytes from peripheral blood to sites of disease activity (212). However, these immunologic phenomena may represent a response to an as-yet-unidentified antigen (213). Mycobacteria, especially cell wall-deficient forms, have been postulated to represent the antigen source (213–216). Mycobacterium tuberculosis has been implicated by some studies, whereas others have suggested atypical mycobacteria (216,217). Other infectious causes such as Propionobacterium acnes and Rickettsia (218) have also been suggested. Others suggest the granulomas are a response to an inorganic antigen or misfolded amyloid protein sheets.

Electron microscopic examination of epithelioid cells fails to show any evidence of bacterial fragments, unlike the macrophages seen in granulomas caused by mycobacteria, although the cells contain primary lysosomes, some autophagic vacuoles, and complex, laminated residual bodies (219). The giant cells form through the coalescence of epithelioid cells with partial fusion of their plasma membranes. Schaumann bodies likely arise from laminated residual bodies of lysosomes. Asteroid bodies consist of collagen showing the typical 64- to 70-nm periodicity. It seems likely that this collagen is trapped between epithelioid cells during the stage of giant-cell formation (219).

Differential Diagnosis. The histologic differentiation of sarcoidosis from lupus vulgaris may be very difficult, and it is occasionally impossible. There is no absolute histologic criterion by which the two diseases can be differentiated with certainty. However, as a rule, the infiltrate in sarcoidosis lies scattered throughout the dermis, whereas the infiltrate in lupus vulgaris is located close to the epidermis. Furthermore, sarcoidosis usually shows few lymphoid cells at the periphery of the granulomas, giving them the appearance of “naked” granulomas. By contrast, lupus vulgaris often shows a marked inflammatory reaction around and between the granulomas. The granulomas of sarcoidosis usually show much less central necrosis than the granulomas of lupus vulgaris (220); however, not all biopsies of tuberculosis show necrosis, and some biopsies of sarcoid do. The epidermis in sarcoidosis is usually normal or atrophic. In lupus vulgaris, in addition to atrophy,
Histopathology. A nonallergic foreign-body reaction typically shows a granulomatous response marked by histiocytes and giant cells surrounding foreign material. Often, some of the giant cells are of the foreign-body type, in which the nuclei are in haphazard array. In addition, lymphocytes are usually present, as may be plasma cells and neutrophils. Frequently, some of the foreign material is seen within macrophages and giant cells, a finding that of course is of great diagnostic value. The most common cause of a foreign-body granuloma is rupture of a hair follicle or follicular cyst, and sometimes only the cyst contents, rather than residual cyst wall, is identifiable (Fig. 14-24). Exogenous substances producing nonallergic foreign-body reactions include silk and nylon sutures (Fig. 14-25), wood or other plant material (Fig. 14-26), paraffin and other oily substances, silicone gel, talc,

FOREIGN-BODY REACTIONS

Clinical Summary. Foreign substances, when injected or implanted accidentally into the skin, can produce a nonallergic foreign-body reaction or, in persons specifically sensitized to them, an allergic response (225). In addition, certain substances formed within the body may produce a nonallergic foreign-body reaction when deposited in the dermis or subcutis. Such endogenous foreign-body reactions are produced, for instance, by urates in gout and by keratinous material in pilomatricoma, as well as in ruptured epidermoid and trichilemmal cysts.

Figure 14-24 Ruptured epidermoid cyst. There are neutrophils and histiocytes surrounding cornified cells from the center of the cyst.

Figure 14-25 Foreign-body granuloma caused by nylon suture. The suture is composed of blue-gray, linear material and is surrounded by histiocytes, including many multinucleated foreign-body-type giant cells.
dyes used in tattoos. Some substances that at first act as foreign material may later, after sensitization has occurred, act as allergens, as in the case of sea urchin spines and silica.

A histologic decision as to whether a granuloma is of the foreign-body type or of the allergic type is not always possible. A granuloma of the allergic type is more likely to show rounded, well-circumscribed collections of epithelioid histiocytes and less likely to have multinucleated histiocytes of the foreign-body type.

**Principles of Management for Foreign-Body Reactions (see sections following).** Foreign-body reactions may eventually improve with time. Simple excision of smaller lesions is often curative. Extensive lesions can be treated with intraslesional or oral corticosteroids (226).

**Paraffinoma**

**Clinical Summary.** Foreign-body reactions may occur following injections of oily substances such as mineral oil (paraffin) typically into the breasts (227), genitalia, or scalp (228) for cosmetic purposes. These occur as irregular, plaque-like inductions of the skin and subcutaneous tissue (229,230). Ulcers or abscesses may develop. The interval between the time of injection and the development of induration or ulceration may be many years.

The misleading term *sclerosing lipogranuloma* was given to paraffinoma of the male genitalia because of the disproved assumption that it was a local reactive process following injury to adipose tissue (231,232).

**Histopathology.** Paraffinomas have a “Swiss cheese” appearance because of the presence of numerous ovoid or round cavities that show great variation in size. These cavities represent spaces occupied by the oily substance (233). The spaces between the cavities are taken up in part by fibrotic connective tissue and in part by an infiltrate of macrophages and lymphocytes. Some of the macrophages have the appearance of foam cells. Variable numbers of multinucleated foreign-body giant cells are present.

In frozen sections of paraffinoma, the foreign material stains orange with Sudan IV or oil red O, although less so than neutral fat (233).

**Silicone Granuloma**

**Clinical Summary.** Reactions to medical-grade silicone have occurred after injection of its liquid form for cosmetic purposes or from leakage or rupture of silicone gel from breast implants. Leakage from silicone breast implants can cause development of subcutaneous nodules and plaques (234). Lesions containing silicone at sites adjacent to and, rarely, distant from areas of injection or implantation may occur (235,236). A localized reaction at injection sites by silicone-coated acupuncture or venepuncture needles has also been reported (237,238).

**Histopathology.** As in paraffinoma, numerous ovoid or round cavities of varying sizes are seen, resulting in a “Swiss cheese” appearance (Fig. 14-28). These spaces are
what remain after the silicone has been removed during processing, although occasionally scant residual silicone is seen as colorless, irregularly shaped, refractile, nonpolarizable material within the spaces. Histiocytes may be present between the cavities; they can be foamy or multinucleated and accompanied by lymphocytes and eosinophils (234,239). In addition, varying degrees of fibrosis are present. The identification of silicone within a specimen can be facilitated via thick sectioning, dark-field microscopy, and other techniques (240).

**Talc Granuloma**

*Clinical Summary.* Talc (magnesium silicate) may produce granulomatous inflammation when introduced into open wounds. Historically, talc was used as powder on gloves, but this use has been abandoned for many years, and starch is now used for surgical dusting powder (241). However, talc may still be introduced into wounds either because of accidental contamination by a surgeon who uses talcum powder (242) or because talcum may be incorporated into the rubber glove during manufacturing (242). Talc may also be introduced into the skin through topical application of medications (243).

*Histopathology.* Histologic examination reveals histiocytes and multinucleated giant cells, some of which may contain visible particles of talc. Talc crystals can be needle shaped with a yellow-brown or blue-green hue and appear as white birefringent particles with polarized light (244). Their presence can be confirmed by X-ray diffraction studies (244) or energy-dispersive X-ray analysis (242).

**Starch Granuloma**

*Clinical Summary.* Granulomas may result from the contamination of wounds with surgical gloves powdered with corn starch (245).

*Histopathology.* A foreign-body reaction with multinucleated giant cells is present. Scattered through the infiltrate, one observes starch granules as ill-defined ovoid basophilic structures measuring 10 to 20 μm in diameter. Most of the granules are seen within foreign-body giant cells. They react with PAS and methenamine silver and, on examination in polarized light, are birefringent, showing a Maltese cross configuration (243).

**Cactus Granuloma**

*Clinical Summary.* Cactus granulomas show, within days or weeks after the injury, tender papules from which cactus spines may still protrude. They may be extruded spontaneously within a few months.

*Histopathology.* Early papules—a few days after the injury—show fragments of cactus spicules in the dermis that are associated with an intense, perivascular lymphohistiocytic infiltrate containing many eosinophils. After a few weeks, the infiltrate consists of lymphocytes, macrophages, and giant cells (246,247). Sharply margined spicules are seen within giant cells and lying free in the dermis. The spicules are PAS positive (248).

**Pilonidal Sinus**

*Clinical Summary.* The pilonidal sinus is most often seen in young adult men over the sacrum (249). In barbers, the implantation of human hair in the interdigital web spaces may cause small, asymptomatic or tender sinus tracts (250,251). Similar lesions are even more common within web spaces or in other sites in dog groomers and other animal caretakers (252,253).

*Histopathology.* Histologic examination reveals a sinus tract lined by squamous epithelium containing one or several hairs, thus resembling a hair follicle. Either the sinus tract encases the hair completely, or, if the hair extends deeper than the sinus tract, one finds at the lower end of the hair a foreign-body giant-cell reaction intermingled with inflammatory cells (250,254).

**Sea Urchin Granuloma**

*Clinical Summary.* Injuries from the spines of sea urchins occur most commonly on the hands and feet. Even if the friable spines have been only incompletely removed, the wounds tend to heal after spontaneous extrusion of most of the foreign material (255,256). However, in some persons, violaceous nodules appear at the sites of injury after a latent period of 2 to 12 months (257).

*Histopathology.* The nodules are composed largely of epithelioid histiocytes and giant cells (253,258). Doubly refractile material is present in a minority of the granulomas. If remnants of a spine are still present, they are surrounded by leukocytes and many large foreign-body giant cells (256). A minority of patients show nongranulomatous findings, the most common of which is a neutrophilic infiltrate (259).
Pathogenesis. The appearance of sarcoid-like granulomas after a latent interval of months in only a small proportion of the injured patients suggests a delayed hypersensitivity reaction (257). The spines of sea urchins, in addition to the calcified material, contain remnants of epithelial cells (257). The double refraction that may be found in the granulomas may be due to the presence of a small amount of silica in the calcified spines (256).

Silica Granuloma

Clinical Summary. Silica (silicon dioxide) is present in rocks, soil, sand, and glass. It frequently contaminates accidental wounds, in which it sets up a foreign-body reaction of limited duration followed by fibrosis (260). In the vast majority of cases, silica causes no further sequelae. In exceptional cases, a granulomatous delayed hypersensitivity reaction occurs at the site of the old scar (261). The mean interval for this delayed hypersensitivity reaction is approximately 10 years, but it may be less than 1 year or more than 50 years after the original injury (262). When this reaction occurs, indurated papules or nodules develop at the site of injury.

Histopathology. In silica granuloma, there are groups of epithelioid histiocytes with a lymphocytic infiltrate that tends to be sparse (261–265). Foreign-body giant cells may be abundant or absent, and Langhans giant cells also may be present. If multinucleated histiocytes are not numerous, a picture resembling sarcoid is produced. However, the diagnosis of sarcoidosis may be excluded by clinical information and the presence, especially within giant cells, of crystalline particles varying in size from barely visible to 100 μm in length; they represent silica crystals. When examined with polarized light, these particles are doubly refractile (Fig. 14-29). The presence of silica can be confirmed by X-ray spectrometric or energy-dispersive X-ray analysis (262,263).

Pathogenesis. Evidence suggests that the sarcoid-like granulomatous response to silica that occurs long after initial injury represents a delayed-type hypersensitivity reaction (261,262,264,266).

Zirconium Granuloma

Clinical Summary. Deodorant sticks containing zirconium lactate and creams containing zirconium oxide may cause a persistent eruption composed of soft, red-brown papules in the areas to which they have been applied. Zirconium lactate is no longer present in antiperspirants sold in the United States; however, a granulomatous reaction has also been described in response to roll-on antiperspirant containing aluminum–zirconium complex (267,268).

Histopathology. Histologic examination shows large aggregates of epithelioid cells with a few giant cells and a sparse or moderately dense lymphocytic infiltrate, producing a picture that may be indistinguishable from sarcoidosis (269–271). Because of the small size of the zirconium particles, they cannot be detected on examination with polarized light (269). Their presence, however, can be demonstrated by spectrographic analysis (270) or energy-dispersive X-ray analysis (267).

Pathogenesis. Evidence that zirconium granulomas develop on the basis of an allergic sensitization to zirconium includes the following: (a) They occur only in persons sensitized to zirconium (272), (b) the pattern of granuloma inflammation is like that of other granulomatous dermatitides that have been attributed to delayed-type hypersensitivity reactions, and (c) autoradiographic analysis of experimentally induced lesions in sensitized individuals reveals no zirconium within histiocytes (273).

Reactions to Aluminum

Clinical Summary. Reactions to aluminum occur most often in the setting of surgical scars secondary to the use of aluminum chloride as a hemostatic agent, although these reactions are not clinically apparent. However, single or multiple persistent subcutaneous nodules may appear several months or even years after the subcutaneous injection of a variety of vaccines or allergen desensitization extracts that are aluminum adsorbed (274). The aluminum adjuvant is believed to prolong the period of activity of the vaccine or desensitization agent, thus increasing the immunologic response.

Histopathology. In surgical scars, the hemostatic agent aluminum chloride can be seen as granular violaceous-to-gray stippled deposits within macrophages (Fig. 14-30). In subcutaneous nodules at injection sites, the most striking finding in some biopsy specimens is the presence of nodular aggregates of lymphocytes with lymphoid follicles and germinal centers within the dermis and subcutis. There is fibrosis, which may occur in bands that separate the lymphocytic nodules. Eosinophils may be prominent, and
in the formation of granulomas, internally and in the skin, the latter as a consequence of body piercing (275). Palisading granulomatous reactions have also been reported (278). There may be prominent septal and lobular inflammation of the panniculus (279). In any of the patterns that may occur, a key to making the diagnosis is the identification of histiocytes with abundant violaceous-to-gray granular cytoplasm; these granules contain aluminum and are PAS positive and diastase resistant (275).

Pathogenesis. This condition is believed to represent a delayed hypersensitivity reaction to aluminum. Electron microscopic examination reveals irregular membrane-bound, electron-dense material within macrophages. X-ray microanalysis has shown that the electron-dense material contains aluminum (275).

Titanium Granuloma

Clinical Summary. Titanium has been implicated rarely in the formation of granulomas, internally and in the skin, the latter as a consequence of body piercing (280).

Histopathology. An infiltrate of histiocytes, lymphocytes, and plasma cells is present, and some macrophages contain minute brown-black particles (280).

Zinc-Induced Granuloma

Clinical Summary. Local allergic reactions to insulin are not uncommon. However, the granulomatous response, which may occur with zinc-containing insulin preparations, is rare. It may begin with sterile furunculoid lesions (281,282).

Histopathology. The early furunculoid lesions show a dense neutrophilic infiltrate and many birefringent rhomboidal crystals of zinc insulin. Later, fibrosis and granulomatous inflammation develop (282).

Berylliosis

Clinical Summary. Beryllium granulomas are mostly of historical interest. Up to 1949, beryllium-containing compounds were widely used in the manufacture of fluorescent light tubes. Two diseases resulted from this: systemic berylliosis and local beryllium granulomas. Systemic berylliosis developed in some workers in plants manufacturing fluorescent tubes through inhalation of these compounds. Systemic berylliosis primarily shows pulmonary involvement, which results in death in about one third of the patients (283). Beryllium may reach the skin through blood circulation and cause cutaneous granulomas. However, this is a rare event, having been observed in one series in only 4 of 535 patients with systemic berylliosis (283). The granulomas consist of only a few papular lesions over which the skin remains intact.

Purely local beryllium granulomas occurred in persons who cut themselves on broken fluorescent tubes that were coated with a mixture containing zinc-beryllium silicate (284). The cutaneous granulomas after laceration show, as their first sign, incomplete healing of the laceration, followed by swelling, induration, tenderness, and, finally, central ulceration (285).

Histopathology. The cutaneous granulomas of systemic berylliosis, similar to those of sarcoidosis, show very slight or no caseation (283). The cutaneous granulomas following laceration, in contrast to the cutaneous granulomas of systemic berylliosis, show central necrosis, which may be pronounced (284). A moderately dense infiltrate of lymphocytes may be present, resembling the granulomas of tuberculosis. The epidermis shows acanthosis and possibly ulceration. No particles of beryllium are seen in histologic sections, but its presence in the lesions can be demonstrated by spectrographic analysis (285).

Pathogenesis. Systemic berylliosis develops on the basis of a delayed hypersensitivity reaction (286,287).

Mercury Granuloma

Clinical Summary. Mercury granuloma is generally secondary to injury (i.e., with a broken thermometer) or deliberate self-injection. Rarely, elevated serum and urine mercury can be associated with these granulomas.

Histopathology. Implanted mercury appears as dark gray to black, opaque globules and spheres of varying sizes, often surrounded by dermal necrosis. Granulomatous inflammation is present (287a).

Tattoo Reactions

Clinical Summary. Clinically apparent inflammatory reactions to permanent tattoos, although uncommon, are now seen with greater frequency due to the rise in popularity of tattoos. They have been observed most commonly
with red dyes containing mercuric sulfide, such as cinnabar (Chinese red). More recently, there has been a move away from using mercury-containing dyes toward the use of dyes containing other red pigments, such as ferric hydrate (sienna or red ochre), cadmium selenide (cadmium red), and organic dyes, but such mercury-free red dyes may also produce adverse reactions (288,289). Reactions have also been reported with chrome green (290), cobalt blue (291), purple manganese salts (292), yellow cadmium sulfide (293), and iron oxide (294). In some instances, an allergic response to the pigment has been suggested by a positive patch test. Infection, particularly mycobacterial, should also be considered when seeing a tattoo reaction (295); infection may be secondary to dilution of tattoo pigment with contaminated tap water. Notably, some tattoo reactions have overlying epithelial hyperplasia that can be striking both clinically and histopathologically and mimic squamous cell carcinoma (296).

Reactions to “temporary” tattoos are rare. Usually comprised of black commercial henna, these tattoos are painted onto the skin surface. The most common reaction is allergic contact dermatitis, but a lichenoid dermatitis, a scarring reaction, and hypopigmentation have been reported (297–301).

Tattoos may also occur due to pigmented materials accidentally implanted in the skin, such as graphite or gunpowder, or due to solutions employed for hemostasis (302,303), particularly Monsel’s solution (ferric subsulfate).

**Histopathology.** Permanent tattoos that are not clinically inflamed show irregularly shaped granules of dye that are located within macrophages and extracellularly in the dermis (304).

Inflammatory reactions in clinically inflamed permanent tattoos may or may not be granulomatous. Phototoxic exacerbation has been described with reactions to red pigments (288,289) and yellow pigments (293). Non-granulomatous reactions include a perivascular lymphocytic infiltrate with pigment-containing macrophages (288,304), a lichenoid response, which in some instances may resemble lichen planus or hypertrophic lichen planus (288,289,305,306), and a pseudolymphomatous picture with a dense, nodular or diffuse, predominantly lymphocytic infiltrate that also contains histiocytes and coarse tattoo pigment granules (307,308). Infected tattoo reactions generally may not show detectable organisms (295). If present, overlying epithelial hyperplasia generally shows minimal cytologic atypia (296).

Granulomatous reactions may be either of the sarcoidal type (290,309,310) or the foreign-body type (290,294). A tuberculoid pattern has also been described in response to cobalt blue, but this may have been due to a mycobacterial infection (311). The granulomatous responses show tattoo granules scattered throughout the infiltrate. In the sarcoidal type, the infiltrate contains nodules of epithelioid histiocytes (Figs. 14-31 and 14-32), and in the foreign-body type, there are obvious multinucleated histiocytes of the foreign-body type. A sparse or dense lymphocytic infiltrate may be present. In the sarcoidal type of reaction, regional lymph nodes may also show tattoo granules (312). There are some reports of patients with sarcoidal granulomas in their tattoos who also had pulmonary disease (178,309,310,313), uveitis (291,314), or erythema nodosum (309), suggesting a systemic hypersensitivity response to the tattoo, or true sarcoidosis.

Traumatic graphite tattoos show black granules free in the dermis and sometimes within histiocytes (Fig. 14-33). Monsel’s tattoos, also typically seen in conjunction with scars, show multinucleate histiocytes containing coarse, brown, refractile pigment (Fig. 14-34), which is positive on staining for iron. Larger, brown, extracellular jagged aggregates of pigment are suggestive of Monsel’s tattoo (315). Ferruginization of collagen bundles is typical, and a proliferation of spindled fibrohistiocytic cells may also occur.

Electron microscopic examination of tattoos without an allergic reaction shows that most tattoo granules are
“wrinkles,” such as glabellar creases and prominent nasolabial folds. A small minority of patients develop an allergic granulomatous response at the site of injection. This response usually develops within 1 month of injection, is manifested by induration and erythema, and usually resolves spontaneously in less than 1 year (239,317). Hyaluronic acid has also been used for similar cosmetic purposes. Although it is less immunogenic, reactions to this injected material have been reported in approximately 3% of patients (318,319), including granulomatous reactions. Recent additions to the soft tissue augmentation armamentarium include synthetic substances such as polymethylmethacrylate (ArteFill, ArteColl) and polydimethylsiloxane (Bioplastique). Adverse reactions to these materials have been reported (320–322), with polymethylmethacrylate and silicone probably being the fillers to which reactions are most commonly encountered.

Histopathology. Bovine collagen differs from native collagen by exhibiting a paler, less fibrillar appearance and by its nonbirefringence when examined with polarized light. It may lie within the center of a palisaded granuloma containing many foreign-body giant cells, or it may be associated with a more diffuse granulomatous reaction. There is a variable associated infiltrate of lymphocytes, eosinophils, plasma cells, and neutrophils that tends to spare the implanted collagen (239).

**Bovine Collagen Implant and Other Tissue Augmentation Materials**

**Clinical Summary.** Injectable bovine collagen is used for cosmetic purposes, principally on the face to diminish

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**Figure 14-33** Traumatic tattoo from graphite. A: A circumscribed collection of black material is present in the dermis. B: The black material is darker than melanin, and the clumps have irregular shapes and sizes; some are intracellular and some are extracellular. There are also knife marks from the foreign material.

**Figure 14-34** Monsel's tattoo. Monsel's solution may produce a granulomatous response associated with pigment that is gray-brown, with pigment sometimes in larger clumps.
Biopsies of patients with erythematous raised areas at sites of hyaluronic acid injections have revealed a granulomatous infiltrate with prominent giant cells in most patients. A mild lymphohistiocytic infiltrate without granulomas appears to be less common (318). Polymethylmethacrylate granuloma shows numerous sharply circumscribed, seemingly empty round spaces, uniform in size and shape, mimicking normal adipocytes (320). Epithelioid histiocytes with occasional giant cells surround these spaces. Within them, on lowering the microscope condenser, one notes vaguely visible round, sharply circumscribed, translucent, nonbirefringent foreign bodies. Polydimethylsiloxane granuloma exhibits numerous irregularly shaped spaces distributed diffusely throughout a sclerotic stroma (320). At higher power, nonbirefringent foreign material is apparent within these irregularly shaped spaces, which are outlined by multinucleate giant cells. The histologic findings of other currently used fillers have been described (323–326).

**Corticosteroid Deposits**

*Clinical Summary.* Corticosteroid preparations for intralesional use are suspensions of insoluble crystalline chemicals; soluble corticosteroids are not effective for intralesional use. These suspensions may be identified histologically after injection of triamcinolone or other steroids. Sites where these deposits have been described include the skin (e.g., in keloids), the nasal mucosa, and the Achilles tendon. The material may persist at the site of injection for months or years (239,327).

*Histopathology.* Corticosteroid deposits are recognizable by their acellular, amphophilic, granular appearance in association with clear spaces. The spaces may represent the sites of dissolved crystals. Uncommonly, birefringent crystals can be seen with polarized light. Inflammation tends to be absent or sparse, but a palisaded granuloma may develop (327–330).

**CHEILITIS GRANULOMATOSA (MIESCHER–MELKERSSON–ROSENTHAL SYNDROME)**

*Clinical Summary.* The classic triad of Miescher–Melkersson–Rosenthal syndrome consists of recurrent labial edema, relapsing facial paralysis, and fissured tongue (331). However, not all patients have the classic triad. In a review of 220 patients, labial swelling was seen in 84%, facial palsy in 23%, and fissured tongue in 60% (331). Whereas monosymptomatic labial edema is recognized as part of the syndrome, lingua plicata by itself is not, because this is not uncommon in the general population. One occasionally observes, either in addition to or in place of swelling of the lips, swelling of the forehead, chin, cheeks, eyelids, or tongue (332,333). Submandibular or submental lymph nodes may be enlarged (334). Swelling of the buccal mucosa, gingiva, and palate also can occur (331). Chronic swelling of the vulva or of the foreskin has been described as a genital counterpart of cheilitis granulomatosa (335,336).

*Histopathology.* Granulomatous inflammation is not present in all biopsies of clinically involved lips (337). Sections may show simply edema, lymphangiectasia, and a predominately perivascular lymphoplasmacytic infiltrate. The infiltrate is often sparse but may be dense, producing a nodular appearance. If granulomas are present, they are noncaseating and tend to be small and scattered (Fig. 14-35). Collections of epithelioid histiocytes may be poorly circumscribed and are often associated with lymphocytes, but occasionally larger and/or “naked” tubercles are present, producing an appearance similar to that of sarcoidosis (333,334,337–341). Affected lymph nodes may also show granulomatous inflammation (342).

*Pathogenesis.* The cause of cheilitis granulomatosa is unknown. Idiosyncratic reactions to exogenous factors,
such as food additives, have been postulated to be causal in some cases (343,344). A relationship to sarcoidosis, originally assumed by some authors (342), appears unsubstantiated. Likewise, this syndrome appears to be distinct from Crohn disease, which may also produce granulomatous inflammation of the lip (344,345).

**Principles of Management.** Intralesional and oral corticosteroids as well as other oral anti-inflammatory medications have been reported as having some success in the literature (346).

## CHEILITIS GLANDULARIS

**Clinical Summary.** Cheilitis glandularis is a rare condition marked by persistent enlargement and eversion of the lower lip. Labial salivary ducts appear to be dilated and exude mucoid material or clear fluid that may be accentuated by gentle squeezing (347,348). A papular component may be present (349). Diagnosis is based primarily on clinical features (347). It has been described mostly in adults, but also in children.

**Histopathology.** Various histologic findings have been reported, none consistently, and this condition may not represent a specific disease (see section on pathogenesis). Salivary gland hyperplasia, duct ectasia, fibrosis, and inflammation comprising lymphocytes, plasma cells, and histiocytes have been described (348,349). However, any or all of these features may be absent (347). Hyperkeratosis can also occur (347).

**Pathogenesis.** Cheilitis glandularis is probably caused by several different factors. Marked, chronic sun and wind exposure has been implicated as a common cause, and it has been suggested that this is not truly a disorder of salivary glands because they may appear histologically normal (347). An atopic diathesis, factitious cheilitis, and hereditary factors have also been implicated (347,349). There are reports in the literature that describe an increased incidence of squamous cell carcinoma in association with cheilitis glandularis (350–352). This may be a consequence of actinic damage, which tends to be associated with this condition and may be exacerbated by the eversion of the lip (350).

**Principles of Management.** Vermilionectomy and removal of minor salivary glands may be helpful in severely affected individuals (351).

## GRANULOMA GLUTEALE INFANTUM

**Clinical Summary.** Granuloma gluteale infantum, first described in 1971 (353), shows asymptomatic, round to oval, smooth papules and nodules irregularly distributed over regions covered by diapers (353–356). The lesions are typically reddish blue in color, ranging from a few millimeters to a few centimeters in diameter. Although usually seen in infants, this condition has also been described in incontinent adults (356,357), and a similar process with an erosive component has been reported in adults with extensive use of benzocaine (358). Although clinically this disorder may appear similar to a granulomatous condition, histologically it is not.

**Histopathology.** Acanthosis is usually present. A dense, mixed infiltrate is seen throughout the dermis. Lymphocytes, histiocytes, plasma cells, neutrophils, and eosinophils may all be seen (355). In addition, there may be microabscesses composed of neutrophils and eosinophils, as well as extravasation of erythrocytes together with a proliferation of capillaries (353). Multinucleated histiocytes or well-developed granulomas are not a feature of the infiltrate. In a few instances, staining with the PAS reaction has revealed spores and pseudohyphae consistent with the presence of *Candida albicans* in the stratum corneum (359), but fungi are often not detected.

**Pathogenesis.** In nearly all patients described in the literature, the development of granuloma gluteale infantum has been preceded by a diaper dermatitis, which only in some instances has been associated with a *C. albicans* infection (354,359). Topical applications of fluorinated corticosteroid preparations for a prolonged period of time and prolonged wearing of plastic diapers have been implicated, but a consistent cause has not been identified (360). It appears very likely that exogenous factors including irritants and external trauma contribute to this eruption (353,358).

**Principles of Management.** Avoidance of external irritants/trauma is important; lesions often spontaneously resolve over time (361). *Candida* infection, if present, should be treated appropriately.

## MISCELLANEOUS GRANULOMATOUS LESIONS

### Interstitial Granulomatous Drug Reaction

**Clinical Summary.** A limited number of patients have been described with annular to solid erythematous patches/plaques on the inner arms, proximal thighs, and intertriginous areas, often occurring symmetrically. Implicated agents include antihypertensives (particularly calcium-channel blockers), antihyperlipidemics, antihistamines, anticonvulsants, antidepressants (61), tumor necrosis factor-α inhibitors (362), and herbal medications (363).

**Histopathology.** An interstitial infiltrate of lymphocytes and histiocytes with slight fragmentation of collagen is reported, in conjunction with variable numbers of eosinophils and neutrophils and vacuolar interface change.
Differential Diagnosis. Clinical presentation and the presence of vacuolar interface change may be helpful in distinguishing this condition from granuloma annulare and interstitial granulomatous dermatitis (137).

Principles of Management. Discontinuation of the offending medication results in resolution of the lesions.

Zoster-Related Granulomas

Clinical Summary. Following herpes zoster, patients may present with persistent reddish papules in a zosteriform distribution.

Histopathology. A variety of reaction patterns may be found in zoster-related scars. The most common granulomatous patterns are granuloma annulare-like (364) and sarcoid-like patterns.

Principles of Management. Lesions may self-resolve; topical corticosteroids may hasten resolution (365).

Common Variable Immunodeficiency

Clinical Summary. Patients with common variable immunodeficiency often have multiple cutaneous warts and systemic signs and symptoms, which include diarrhea, chronic/recurrent bacterial infections, hepatosplenomegaly, and lymphadenopathy. Patients may also develop granulomas of the skin and other organs.

Histopathology. Biopsy of the nodules may show granuloma annulare-like (366), tuberculoid leprosy-like (367), sarcoid-like, and/or tuberculosis-like (368,369) granulomas.

Principles of Management. Corticosteroids, localized or systemic, are the treatment of choice, with absent to only partial responses in many cases (370).

Nonspecific Manifestation of Underlying Lymphoma

Clinical Summary. Patients with lymphoma may sometimes present with granulomatous lesions.

Histopathology. A spectrum of histologic findings has been described, including granuloma annulare-like, annular elastolytic-like, sarcoid-like, and tuberculoid patterns (371).

Principles of Management. Treatment of the underlying lymphoma is indicated but does not always lead to resolution of cutaneous lesions (371).

REFERENCES


