Chapter 7
Nodular and Diffuse Dermatitis

Keywords Lymphoid hyperplasia • Sweet's syndrome • Granuloma faciale • Sarcoidosis

There is a significant overlap with the nodular and diffuse pattern and the superficial and deep perivascular pattern; indeed, some entities discussed in Chap. 5 could arguably be included in this chapter as well (e.g., arthropod bite reaction). Other entities discussed in this chapter could also conceivably be discussed in the chapter on perivascular dermatitis (e.g., Sweet's syndrome). The primary difference in the nodular and diffuse patterns from the perivascular pattern is that the inflammation is not just centered on vessels. On scanning magnification, nodular dermatitis is characterized by discrete areas of inflammation, separated by uninvolved areas (Fig. 7.1). In contrast, the diffuse pattern demonstrates dense dermal inflammation without intervening areas of sparing (Fig.7.2). Distinction in individual cases is admittedly arbitrary and subject to individual interpretation. As with automobiles, your mileage may vary.

Reactive Lymphoid Hyperplasia

Clinical Features

Reactive lymphoid hyperplasia (also known as lymphocytoma cutis, pseudolymphoma, and lymphadenosis benigna cutis) refers to a group of conditions in which both the clinical and histologic appearance of lymphocytic infiltrates in the skin closely mimic cutaneous lymphomas. Lymphoid hyperplasia may be provoked by chronic antigenic stimulation (arthropod bite, infections, and contactants) or certain medications (especially anticonvulsant and antidepressant drugs). The clinical presentation is variable, but typically the lesions present as persistent erythematous papules or nodules.

S.D. Billings and J. Cotton, *Inflammatory Dermatopathology: A Pathologist's Survival Guide*, 119
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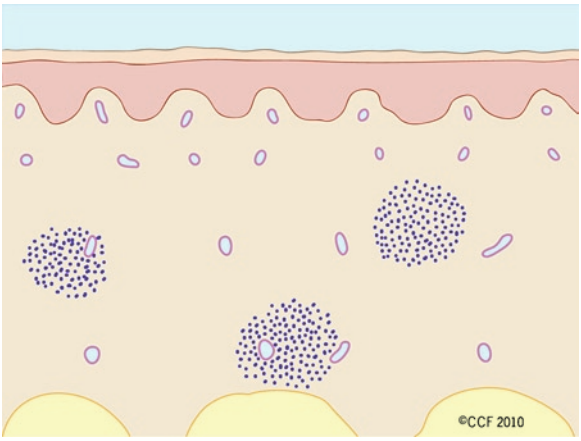

Fig. 7.1 *Schematic representation of nodular pattern.* Inflammatory diseases with a nodular pattern demonstrate nodular collections of inflammatory cells that are not vasculocentric. There are areas of uninvolved dermis

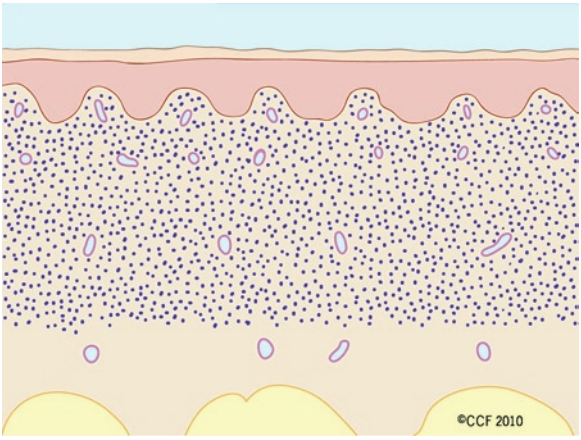

Fig. 7.2 *Schematic representation of diffuse pattern.* In the diffuse pattern, the entire dermis is involved by the inflammatory process

Microscopic Features

Classically, in reactive lymphoid hyperplasia, there are well-demarcated germinal centers with a peripheral cuff of small lymphocytes (zonation) (Figs. 7.3 and 7.4), tingible body microphages, and high mitotic activity (Fig. 7.5). The germinal centers may have a polarized appearance, appearing paler on one side versus the other due to the distribution of centroblasts and centrocytes. The surrounding lymphocytes outside of the germinal center are predominantly T-cells with a minor B-cell component. Some plasma cells are often present, but they lack light chain restriction. In some cases, germinal center formation is absent and the infiltrate is predominantly composed of T-cells with only scattered B-cells (see Table 7.1 for summary of key microscopic features).

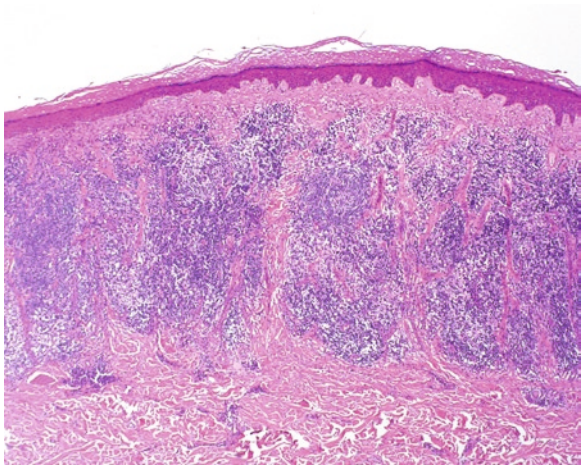

Fig. 7.3 *Reactive lymphoid hyperplasia*. At scanning magnification there is a nodular and diffuse lymphocytic infiltrate with formation of prominent germinal centers

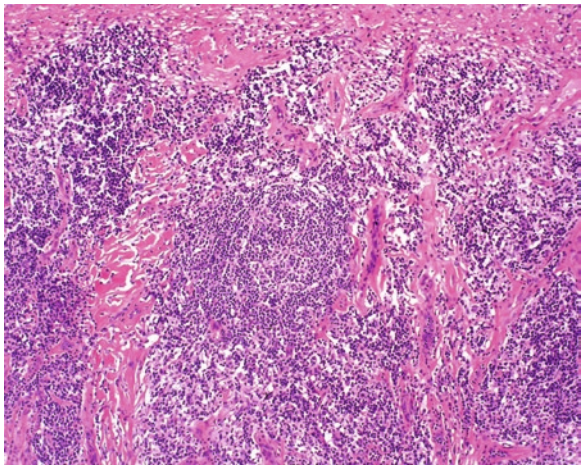

Fig. 7.4 *Reactive lymphoid hyperplasia*. Well-demarcated pale germinal centers accompanied by peripheral cuff of small lymphocytes

Differential Diagnosis

As alluded to above, the main differential diagnosis includes cutaneous B-cell lymphoma; primarily, follicular center and marginal zone subtypes. A detailed discussion of these entities is beyond the scope of this book; however, a few comments will be provided. In general, the architecture of the germinal center is very helpful in distinguishing lymphoid hyperplasia from follicle center cell lymphoma. In follicle center cell lymphoma, the germinal centers are not polarized, but more uniform in appearance. They tend to lack tingible body macrophages. Low-grade follicle center lymphomas also have a low mitotic rate and low Ki-67 proliferative index. They may also have more numerous B-cells outside the follicles. Marginal zone B-cell lymphomas may have a component of reactive germinal centers that can cause confusion

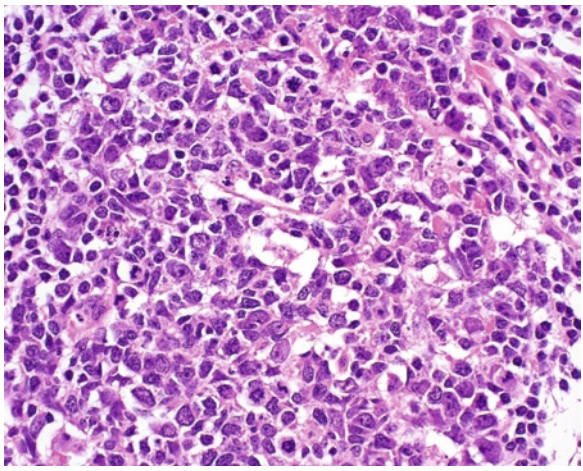

Fig. 7.5 *Reactive lymphoid hyperplasia*. Reactive germinal center demonstrating a mixture of small and large lymphocytes, tingible body macrophages and high mitotic activity

Table 7.1 Key microscopic features: cutaneous lymphoid hyperplasia

- Polarized reactive germinal centers with tingible body macrophages
- Predominantly T-cells surrounding the germinal centers
- B-cells are largely restricted to germinal centers
- Plasma cells and eosinophils may be present
- No light chain restriction

with reactive lymphoid infiltrates. The germinal centers are often disrupted by migration of the neoplastic cells into the germinal center. This can be demonstrated with an immunostain for CD21 to highlight the disrupted follicular dendritic cell network. In marginal zone lymphoma, there may be numerous plasma cells. The plasma cells may show atypical features and are light-chain restricted. Molecular studies for detection of clonal re-arrangements of the immunoglobulin heavy chain may be helpful. While no means entirely sensitive or specific, the presence of a monoclonal population of B-cells is uncommon in reactive lymphoid infiltrates. In general, one must be very cautious in dealing with cases of suspected reactive lymphoid hyperplasia. Table 7.2 highlights histologic features that favor reactive lymphoid infiltrates over low-grade lymphoma. Please refer to select references for a more complete discussion of these lymphomas.

In the cases where the population is predominantly composed of T-cells with very few B-cells, the true nature of the process is somewhat elusive. This may represent the end stages of a resolving inflammatory process. It is important to consider the possibilities of T-cell lymphomas such as folliculocentric mycosis fungoides. Reactive T-cell proliferations have a mixture of CD4 and CD8 positive lymphocytes. In general, the ratio of CD4 to CD8 positive cells can range from 1:1 up to 6:1, and still be consistent with a reactive process. As a practical matter, it is important to remember that histiocytes are immunoreactive for CD4 also. Therefore, when interpreting ratios, one must take this into account and correlate CD4 stains with a CD3 stain.

The diagnosis of reactive lymphoid hyperplasia is tricky. Even in relatively straight forward cases, we often employ a descriptive diagnosis (see sample reports at the end of the chapter). This also reflects the fact that some patients with reactive lymphoid hyperplasia can progress to development of cutaneous lymphoma.

Table 7.2 Practical tips: cutaneous lymphoid hyperplasia

- Differentiation of reactive lymphoid infiltrates from low-grade B-cell lymphoma (follicular center, marginal zone) may be quite difficult
- Features that favor lymphoid hyperplasia include the following:
  - Polarized germinal centers with tingible body macrophages
  - Clinical correlation is paramount to the diagnosis
  - "Top-heavy" (superficial and mid-dermal) infiltrate with preservation of adnexal structures,
  - Mixed cell infiltrate, B-cells generally limited to germinal centers
  - Lack of light chain restriction
  - However, be aware that these are not hard and fast rules
- Immunophenotypic studies are almost always required
- Molecular studies may be helpful in border-line cases

Sweet Syndrome (Acute Febrile Neutrophilic Dermatosis)

Clinical Features

Sweet syndrome, also known as acute febrile neutrophilic dermatosis, is characterized by the acute onset of fever and leukocytosis associated with arthralgias and erythematous plaques. Lesions are most often found on the extremities and face. This entity most often occurs in middle-aged women after a nonspecific respiratory or gastrointestinal infection. An association with an underlying malignancy such as leukemia is seen in about 10% of cases. It is often seen in patients with inflammatory bowel disease, connective tissue disease, and underlying infection. The pathogenesis is not known. The clinical course is usually short-lived, and lesions respond to systemic corticosteroids.

Microscopic Features

Sweet syndrome is a classic manifestation of neutrophilic dermatosis, a histologic pattern characterized by the presence of a heavy dermal infiltrate of neutrophils and variable leukocytoclasis (Fig. 7.6). Despite the latter finding, vascular damage is not a characteristic feature of this syndrome (Fig. 7.7 and Table 7.3). Although a recent report described the presence of some vascular damage in Sweet syndrome, this tends to be seen in older lesions and is presumed to represent secondary vascular damage due to the release of neutrophilic enzymes. Interestingly, recent studies have demonstrated that some cutaneous lesions of Sweet syndrome are histopathologically characterized by an inflammatory infiltrate composed of histiocyte-like immature myeloid cells, not polymorphonuclear leukocytes as is the norm. Deemed "histiocytoid Sweet syndrome" by the authors, this variant may be confused with histiocytic interstitial processes such as granuloma annulare.

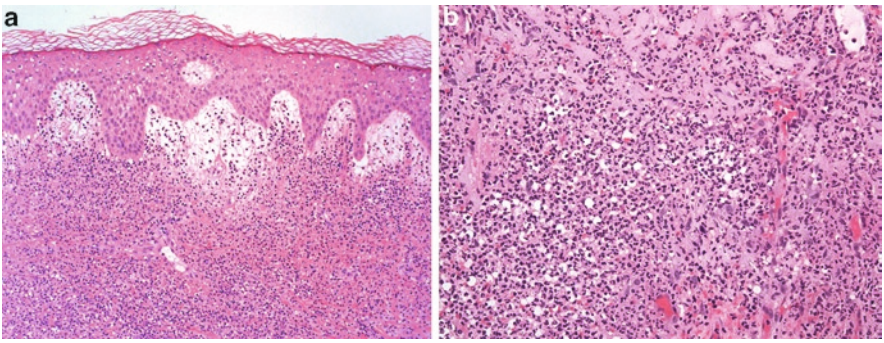

Fig. 7.6 *Sweet syndrome*. (**a**) There is a dense, diffuse infiltrate involving the upper and mid dermis. Papillary dermal edema is also observed. (**b**) The higher power image demonstrates a diffuse infiltrate of neutrophils with associated leukocytoclasis

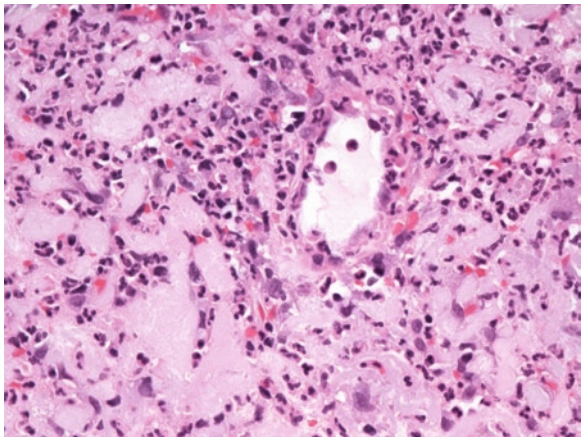

Fig. 7.7 *Sweet syndrome*. There is leukocytoclasis of the neutrophils. Blood vessels may show endothelial swelling with some extravasation of erythrocytes but a true vasculitis is typically absent

Table 7.3 Key microscopic features: Sweet syndrome

- Diffuse infiltrate of neutrophils
- Leukocytoclasis but no vasculitis

Differential Diagnosis

Other neutrophilic dermatoses to be considered in the differential diagnosis include bowel bypass syndrome, which presents as pustular lesions and arthritis in patients who have undergone bowel bypass surgery for obesity. Rheumatoid neutrophilic dermatosis represents a rare manifestation of rheumatoid arthritis characterized clinically by symmetric nodules on extensor surfaces of joints and histologically by neutrophilic infiltrates indistinguishable from Sweet syndrome. Pyoderma gangrenosum, characterized by ulcers with a raised undermined border and diffuse dermal neutrophilic infiltrate, is a diagnosis of exclusion. Leukocytoclastic vasculitis refers to a histologic combination of intramural neutrophils, leukocytoclasis, and

Table 7.4 Practical tips: Sweet syndrome

- No true vasculitis
- Ulceration uncommon in Sweet syndrome
- If an infectious process is a clinical consideration, tissue culture should be pursued
- If Sweet syndrome is considered clinically, but infiltrate looks histiocytic, consider immunostains for myeloperoxidase to exclude histiocytoid Sweet syndrome

fibrinoid necrosis of vessel walls with extravasated erythrocytes (Chap. 6). Granuloma faciale, considered a chronic form of leukocytoclastic vasculitis, is discussed below. Finally, it is of upmost importance to exclude an infectious etiology by liberal use of special stains and tissue culture before rendering an unequivocal diagnosis of Sweet Syndrome (Table 7.4).

Granuloma Faciale

Clinical Features

Granuloma faciale is an uncommon condition characterized by single or multiple asymptomatic nodules that typically involve the face. Lesions are reddish-brown to violaceous in color and may darken with sun exposure. The clinical differential diagnosis includes sarcoidosis, discoid lupus erythematosus, or fixed drug eruption.

Microscopic Features

Granuloma faciale has a fairly distinctive microscopic appearance. On low power examination, there is usually a dense, diffuse infiltrate in the dermis (Fig. 7.8). In well-developed lesions, the infiltrate is polymorphous, composed of neutrophils, eosinophils, plasma cells, and lymphocytes (Fig. 7.9). Often, there is characteristic sparing of the papillary and periadnexal (adventitial) dermis forming a Grenz zone (Fig. 7.10). Granuloma faciale is considered a form of chronic vasculitis, and biopsies of early lesions may show foci of leukocytoclasis accompanied by fibrin in the vessel walls. However, vasculitic changes are often not apparent by the time the lesion is biopsied. In general, the polymorphous nature of the infiltrate combined with the lack of overt vasculitis are features diagnostic of granuloma faciale (Table 7.5).

Table 7.5 Key microscopic features: granuloma faciale

- Polymorphous infiltrate with neutrophils, eosinophils, and plasma cells, and sparing of adventitial dermis is diagnostic
- Evidence of leukocytoclastic vasculitis may be seen in early cases
- Extravasated erythrocytes and hemosiderin may be observed and contribute to the reddish-brown color of the lesions clinically

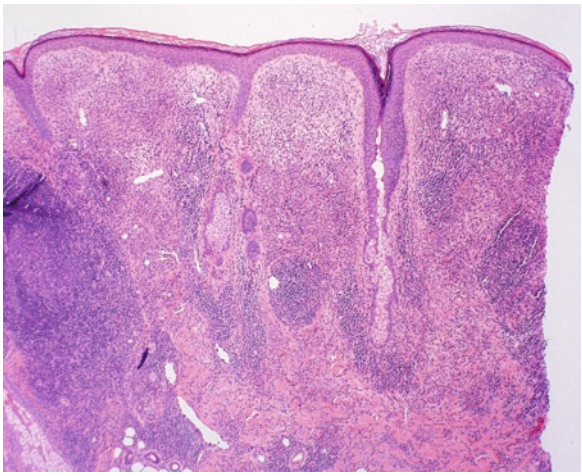

Fig. 7.8 *Granuloma faciale* is characterized by dense, diffuse infiltrate of the dermis. The epidermis is typically unremarkable

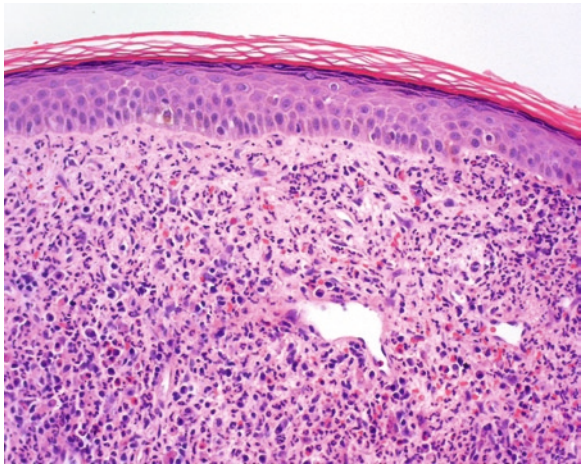

Fig. 7.9 *Granuloma faciale*. In granuloma faciale, the infiltrate is polymorphous, composed of lymphocytes, neutrophils and eosinophils

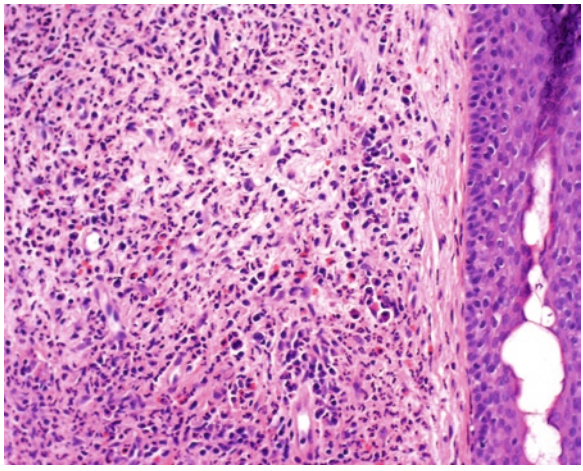

Fig. 7.10 *Granuloma faciale*. The infiltrate typically spares the adventitial and papillary dermis forming a Grenz zone. Note the polymorphous nature of the infiltrate

Differential Diagnosis

The microscopic features together with the clinical information are generally diagnostic. The histologic differential diagnosis includes Sweet's syndrome, arthropod bite reaction, or other hypersensitivity reaction; however, the mixed nature of the infiltrate in GF is fairly distinctive (Table 7.6).

Table 7.6 Practical tips: granuloma faciale

- Polymorphous infiltrate is key to the diagnosis
- Polymorphous infiltrate helps distinguish granuloma faciale from Sweet's syndrome
- May see vasculitis in early lesions; remember, it is rare to see other forms of vasculitis on face

Sarcoidosis

Clinical Features

Sarcoidosis is a common systemic disease of unknown etiology, defined by the presence of non-caseating granulomata usually affecting multiple organ systems. It is more common in women, and in USA, it is relatively common in African–American patients. Although it may present at any age, it most commonly presents in young to middle-aged adults. Between 10 and 35% of patients with systemic sarcoidosis have cutaneous lesions. A diversity of clinical forms of cutaneous sarcoidosis has been described. Violaceous plaques and nodules on the nose, ears, and cheeks are a classic clinical presentation of cutaneous sarcoidosis. The clinical term "lupus pernio" has been used to describe this presentation. It is important to remember that the term lupus pernio has absolutely nothing to do with lupus erythematosus. Cutaneous sarcoidosis is characterized by clinical heterogeneity; indeed, lesions can present on any anatomic location. Moreover, sarcoidosis or sarcoid-like lesions can also present at sites of trauma as a reaction to exogenous substances (e.g., tattoo ink). A subset of this patient group will have underlying systemic sarcoidosis, and patients with sarcoidosis have an increased likelihood of having sarcoidal reactions at sites of trauma. Cutaneous and pulmonary sarcoidosis can also be triggered by interferon treatment that typically resolves with cessation of therapy.

Microscopic Features

Sarcoidosis typically has a superficial and deep nodular pattern (Fig. 7.11), but may have only superficial dermal involvement. The nodules usually have an interstitial pattern without associated dermal appendages. A perivascular pattern can sometimes be seen. The *sine qua non* of sarcoidosis is the non-caseating "naked" granuloma (Fig. 7.12). These granulomas are characterized by relatively tight clusters of

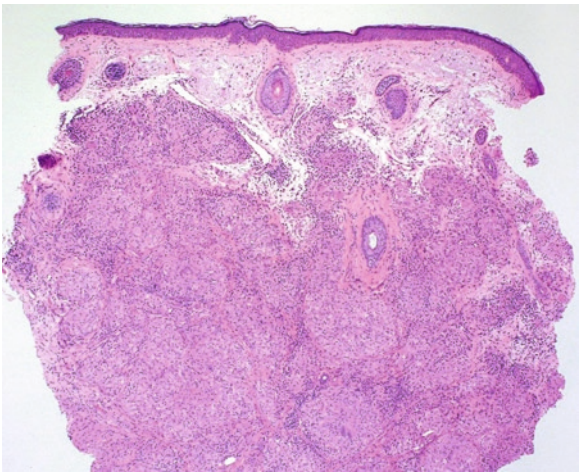

Fig. 7.11 *Sarcoidosis*. The pattern of the infiltrate of sarcoidosis is variable. This case demonstrates diffuse involvement of the dermis

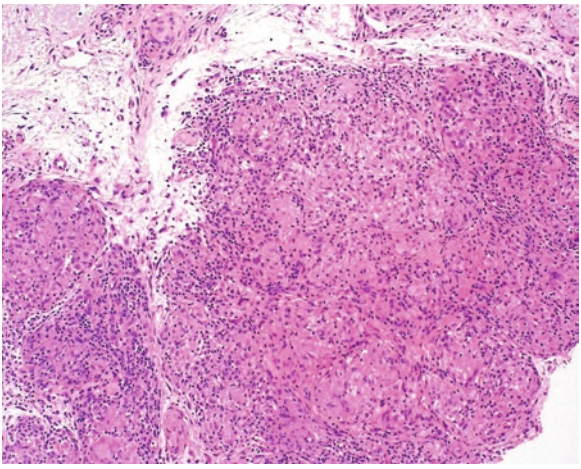

Fig. 7.12 *Sarcoidosis*. Epithelioid granulomas with poorly developed lymphocytic cuffs, so-called naked epithelioid granulomas are characteristic of sarcoidosis

Table 7.7 Key microscopic features: sarcoidosis

- Epithelioid granulomas
- Poorly developed lymphocytic cuff

epithelioid histiocytes with a poorly developed or absent lymphocytic cuff (Table 7.7). Small amounts of centrally located fibrinous or granular material are occasionally seen in some granulomas. Occasional inclusion bodies (Schaumann body and asteroid body) may be evident (Fig 7.13). In some cases, there may be evident or polarizable foreign material (Fig. 7.14). This has been termed scar sarcoidosis. Lesions of sarcoidosis often arise at sites of trauma. In a patient without a history of underlying sarcoidosis, this finding should prompt the pathologist to suggest further evaluation for possible systemic disease.

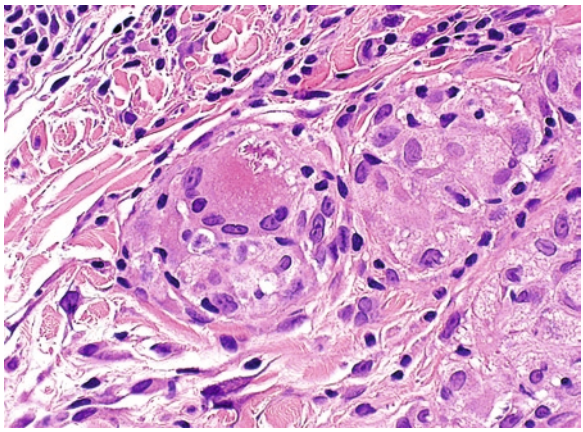

Fig. 7.13 *Sarcoidosis*. Within the multinucleated histiocyte there is a Schaumann, or asteroid body. These are stellate eosinophilic inclusions

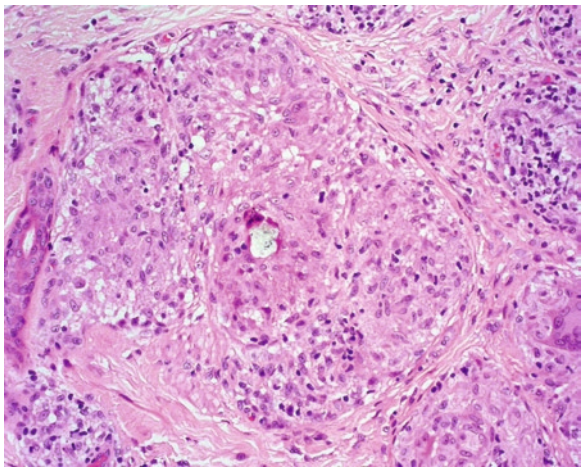

Fig. 7.14 *Scar sarcoidosis*. Within the sarcoidal granuloma, foreign material is evident. Lesions of sarcoidosis often develop at sites of trauma

Differential Diagnosis

Sarcoidosis is a diagnosis of exclusion. In the absence of a well-established underlying diagnosis of systemic disease, it is imperative to exclude infection with appropriate special stains (e.g., GMS and Fite stains) to exclude fungal or mycobacterial infections. Non-infectious entities in the differential diagnosis include cutaneous Crohn's disease. Cutaneous Crohn's disease also has epithelioid granulomas, but usually presents in a perianal location. The cutaneous manifestations of Crohn's disease may precede gastrointestinal involvement. Therefore, the possibility of cutaneous Crohn's disease should always be considered before making the diagnosis of sarcoidosis in a perianal location. Necrobiosis lipoidica may have sarcoidal granulomas, but the altered collagen, lymphoid aggregates, and lymphoplasmacytic infiltrate usually allow discrimination (see Chap. 9). Reactions to

foreign material can also have the appearance of sarcoidosis. When this is seen, the possibility of potential underlying systemic disease should be mentioned. Table 7.8 highlights key points regarding the diagnosis of sarcoidosis.

Table 7.8 Practical tips: sarcoidosis

- Sarcoidosis is a diagnosis of exclusion
- Special stains and tissue culture should be liberally used, especially if there is no history of sarcoidosis
- Polarizable foreign material has been described in patients with sarcoidosis

Sample Report: Reactive Lymphoid Hyperplasia

Clinical history: Erythematous nodule on the left temple of a 25-year-old male.
Diagnosis: Nodular and diffuse lymphoid infiltrate with prominent germinal center formation, see comment.
Comment: There is a nodular and diffuse lymphoid infiltrate that focally extends into the subcutaneous fat. Lymphoid follicles with germinal centers, clear-cut mantle zones, and tingible body macrophages are observed. The interfollicular population includes lymphocytes, plasma cells, histiocytes, and occasional eosinophils. The germinal centers are highlighted with immunostains for CD20, and the germinal center has a high Ki-67 proliferative index. The dominant, surrounding population of cells is CD3+. The histologic and immunophenotypic features together with the clinical findings are most compatible with a reactive lymphoid process, such as to persistent arthropod bite. Recommend clinical follow-up; if lesions persist or progress, re-biopsy is suggested.

Sample Report: Sweet Syndrome

Clinical history: A 32-year-old woman presents with erythematosus nodules and plaques on the face.
Diagnosis: Neutrophilic dermatosis, see comment.
Comment: There is a dense, diffuse dermal infiltrate of neutrophils accompanied by foci of leukocytoclasis. No vasculitis is identified. The epidermis demonstrates slight spongiosis. The histologic findings are consistent with Sweet syndrome. If there is a clinical suspicion of an infectious etiology, tissue culture is recommended.

Sample Report: Granuloma Faciale

Clinical history: A 30-year-old man with erythematous plaque on the nose.
Diagnosis: Diffuse mixed infiltrate with neutrophils, eosinophils, and plasma cells consistent with granuloma faciale, see comment.
Comment: There is a diffuse dermal infiltrate and telangiectatic vessels with sparing of the adventitial dermis. The infiltrate is composed of neutrophils, eosinophils, and plasma cells. Foci of leukocytoclasis are identified. Ectatic vessels with prominent endothelial cells are also observed. These findings are consistent with granuloma faciale. Clinical correlation is recommended.

Sample Report: Sarcoidosis

Remember that sarcoidosis is a diagnosis of exclusion. A descriptive diagnosis of "granulomatous dermatitis" is usually the best approach.

Example 1: (In the setting of an established diagnosis of sarcoidosis)
Diagnosis: Granulomatous dermatitis consistent with sarcoidosis, see comment.
Comment: The biopsy demonstrates numerous epithelioid granulomas. Given the history of underlying sarcoidosis, these findings are consistent with cutaneous sarcoidosis. If there is a suspicion for a potential infectious process, special stains for microorganisms can be performed upon request.

Example 2: (In the setting without an established diagnosis of sarcoidosis)
Diagnosis: Granulomatous dermatitis, see comment.
Comment: The biopsy demonstrates numerous epithelioid granulomas without lymphocytic cuffs. GMS and Fite stains are negative for fungi and mycobacteria. Polariscopy reveals no polarizable foreign material. The histologic features are consistent with sarcoidosis in the appropriate clinical context, but an infectious process cannot entirely be excluded. Clinicopathologic correlation is recommended.

Example 3: (In the setting of sarcoid-like granulomas and foreign material)
Diagnosis: Granulomatous dermatitis and foreign material, see comment.
Comment: There are numerous sarcoidal granulomas in association with polarizable foreign material. Special stains for fungi (GMS) and mycobacteria (Fite stain) are negative. This could represent an idiopathic sarcoidal reaction to a foreign material. The possibility of underlying sarcoidosis should also be considered. Clinicopathologic correlation is recommended.

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