Abstract

In this review, we use the term epithelioid cell granuloma for granulomas that show focal collections of epithelioid histiocytes in the absence of additional changes such as acute inflammatory cells and altered collagen or foreign material. Giant cells, lymphocytes, and histiocytes are often seen in these granulomas. Various features are useful in recognizing the specific cause of an epithelioid cell granuloma and include coalescence or discreteness of granulomas, presence and type of necrosis, inclusion bodies within giant cells, and identification of organisms, but the arrangement of granulomas within the dermis may be the single most important feature. Leprosy shows well-circumscribed, oval, oblong, and curvilinear epithelioid cell granulomas in a perivascular and peri-appendageal location involving superficial and deep dermis with minimal interstitial spill. Cutaneous tuberculosis is recognized by a lichenoid granulomatous pattern comprising a dense upper dermal infiltrate with granulomas that impinge on the overlying acanthotic epidermis accompanied by more localized, nodular granulomas in the deep dermis. Sarcoidosis has closely huddled yet discrete granulomas that have a paucity of lymphocytes. Other patterns and clues include follicular/perifollicular granulomas in lichen scrofulosorum and granulomatous rosacea, prominent necrosis in lupus miliaris disseminatus faciei, branching granulomas with plasma cells in granulomatous secondary syphilis, granulomatous lobular panniculitis with vasculitis in erythema induratum, messy granulomas in cutaneous leishmaniasis, and granulomas extending to the muscles in granulomatous cheilitis/Melkersson–Rosenthal syndrome. Histopathological findings, in combination with clinical and laboratory information, can lead to a specific diagnosis in the majority of cases.

Keywords: Epithelioid cells, granulomas, histopathology

Introduction

Although some workers use the term granuloma to denote a focal collection of histiocytes, we believe the term is more meaningful if it is restricted to denote a focal collection of epithelioid cells [Figure 1]. By this definition, every granuloma is an epithelioid cell granuloma. However, when the term is used without qualification, epithelioid cell granuloma refers to those granulomas that do not show any additional findings such as acute inflammatory cells in suppurative granulomas, altered collagen in necrobiotic granulomas, and foreign material in foreign body granulomas.

Epithelioid cells are transformed or activated macrophages or histiocytes, formed in response to various inflammatory mediators.[1] Histologically, they appear as cells with abundant eosinophilic cytoplasm with indistinct cell margins and elongated or slipper-shaped vesicular nuclei with prominent nucleoli [Figure 1]. They have increased functional activity but decreased phagocytic activity evidenced by an increase in the number of endoplasmic reticulum and fewer lysosomes.[2]

Apart from epithelioid histiocytes, other cells may be part of a granuloma. Giant cells are formed by the fusion of macrophages and are typically large and multinucleate. Nuclei are arranged in a complete or partial wreath at the periphery in Langhans giant cells and are arranged haphazardly toward the center of the cell in foreign body giant cells.[3]

Lymphocytes are commonly seen in granulomas and may be arranged in a cuff or mantle around a core of epithelioid cells [Figure 2]. This cuff of lymphocytes is typically absent in sarcoidosis [Figure 3]. In addition, other cells such as histiocytes and plasma cells may be noted. Less frequently, small numbers of neutrophils and eosinophils may be seen though they are more prominent in mixed cell or suppurative granulomas.

The presence or absence of necrosis is an important finding that helps to categorize epithelioid cell granulomas. Necrosis

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some cases of lupus vulgaris, while it is usually absent in tuberculoid (TT) leprosy, sarcoidosis, and most cases of cutaneous tuberculosis. The type of necrosis is also used as a clue, for example, caseation necrosis in LMDF and fibrinoid necrosis in sarcoidosis, but this is a more difficult and less reproducible differentiating feature.

Cytoplasmic inclusion bodies, usually within giant cells, are a feature of some granulomas. Asteroid bodies are eosinophilic stellate bodies. They have a red-brown center with blue radiating spikes on staining with phosphotungstic acid hematoxylin and are composed of either cytoplasmic filaments or microtubular elements, though their exact composition is not known. Schaumann bodies are round, laminated, bluish bodies formed of calcium deposits.[4] Rarely, small brown Hamazaki–Wesenberg bodies, periodic acid-Schiff (PAS)-positive large lysosomes containing hemolipofuscin, have been reported. Initially thought to be specific for certain types of epithelioid cell granulomas, it is now recognized that these inclusions are more common in some conditions than others but not diagnostic of any particular disease.[5]

The tendency of epithelioid cell granulomas to coalesce or stay discrete is also a helpful morphological feature in differentiating the causes of this reaction pattern. Granulomas are discrete in sarcoidosis and coalescent in leprosy, tuberculosis, and leishmaniasis.

Apart from the findings in individual granulomas, their arrangement within the dermis provides clue to specific disorders, for example, the branched granulomas of leprosy, the lichenoid granulomatous pattern of lupus vulgaris, and the huddled but discrete granulomas of sarcoidosis.

Epithelioid granulomas may be due to both infectious and noninfectious causes. In general, epithelioid cell granulomas are associated with good host immunity and it is difficult to find organisms in infective granulomas. However, a search for organisms should be undertaken to ensure that an infective cause is not missed. Organisms can be seen within histiocytes and giant cells or in extracellular locations using hematoxylin and eosin or special stains such as Ziehl–Neelsen staining for mycobacteria, Giemsa stain for leishmaniasis, and PAS and Gomori’s silver methenamine for fungi. Immunohistochemical stains are also available for some organisms such as Treponema pallidum. Nucleic acid amplification tests may aid in the identification of some pathogens.

Clinically, granulomatous disorders show some common features. They are usually chronic, long-standing, gradually progressive plaques that are only mildly symptomatic. The plaques tend to be annular or arciform with central healing and peripheral activity [Figure 4]. The central area shows fibrosis and scarring in some diseases such as lupus vulgaris and cutaneous leishmaniasis, while there is only slight flattening and reduced inflammation in other diseases such as leprosy and sarcoidosis [Figure 5]. The active area shows deep-seated, erythematous papules that have a persistent yellow-brown color.
when they are blanched with a glass slide, an appearance referred to as apple jelly nodules. (This finding can be seen in many granulomatous disorders and is not confined to lupus vulgaris.) Papules tend to coalesce into plaques, but in sarcoidosis, they may remain discrete, especially on the upper trunk. The degree of erythema varies and tends to be more prominent in cutaneous leishmaniasis [Figure 6]. The degree of verrucosity is also variable, being most prominent in tuberculosis verrucosa cutis [Figure 7], less prominent in lupus vulgaris and cutaneous leishmaniasis, and absent in leprosy and sarcoidosis.

Other findings that are seen in individual diseases and point to the diagnosis include sensory loss, nerve thickening, and peripheral neuropathy in leprosy; plaques on the skin of exposed areas in cutaneous leishmaniasis; condyloma lata and generalized lymphadenopathy in granulomatous syphilis; hilar lymphadenopathy, pulmonary parenchymal involvement, and ocular lesions in sarcoidosis; pulmonary tuberculosis or tuberculosis elsewhere in cutaneous tuberculosis and tuberculids; multiple papules, papulo-nodules, and some pustules on the face and neck with eyelid involvement in LMDF; background erythema and telangiectasias in granulomatous rosacea; remittent edema of the lip and face with geographic tongue and facial nerve palsy in Melkersson–Rosenthal syndrome (orofacial granulomatosis) [Figure 8]; knife-cut fissures and gastrointestinal involvement in cutaneous Crohn’s disease [Figure 9]; tiny, skin-colored papules on the tips of fingers and penis in lichen nitidus; similar, tiny papules in a blaschkoid distribution in lichen striatus; and crusted and smooth, tiny papules on the trunk in small groups or discretely, in lichen scrofulosorum [Figure 10], among other granulomatous diseases.

A large number of conditions show epithelioid granulomas [Table 1]. A description of those conditions in which the histomorphological appearance of the granulomas is distinctive or diagnostic appears below.

**LEPROSY**

In leprosy, epithelioid cell granulomas are a characteristic feature of TT leprosy (both TT and borderline TT [BT] leprosy). They are also a constant feature of mid-borderline (BB) leprosy, often
associated with foamy histiocytes. Borderline lepromatous (BL) leprosy is dominated by foamy histiocytes and lymphocytes but may occasionally show small epithelioid cell granulomas.

Although the nature and composition of granulomas varies across the leprosy spectrum, the arrangement of infiltrates in a characteristic, “leprosy pattern” is a helpful clue to the diagnosis [Figure 11]. There are superficial and deep, well-circumscribed, oval, oblong, or curvilinear infiltrates in a perivascular and peri-appendageal distribution with minimal extension into the interstitial dermis. The overlying epidermis is normal. This is a distinctive and easily recognizable pattern that can be identified under low power. The oblong appearance of leprosy infiltrates is believed to be due to involvement along the neurovascular bundles.

When present, infiltrates around and within nerve twigs and arrectores pilorum are useful additional clues [Figure 12].

TT leprosy is characterized by compact granulomas with a central core of epithelioid cells and a dense cuff of lymphocytes. Langhans giant cells are often seen. Necrosis is not a feature except in large intraneural granulomas which are seen only rarely. Granulomatous infiltrates in the upper dermis may abut on the overlying epidermis with damage to basal cells. BT leprosy is reported to show fewer lymphocytes and fewer and smaller giant cells, but this is a blurry line and it may be easier to make the distinction between TT and BT on clinical grounds. Rarely, sarcoidal and necrobiotic granulomas may be seen in addition to the typical epithelioid granulomas of TT leprosy.

BB leprosy shows two patterns: the first pattern is a diffuse, loose infiltrate composed almost exclusively of epithelioid cells with a paucity of lymphocytes and other cells. It is difficult to identify the leprosy pattern in these cases. The second, and more common pattern in our experience, shows an about equal admixture of epithelioid cell granulomas and foamy histiocytes in the typical leprosy distribution [Figure 13].

BL leprosy does not usually show epithelioid granulomas and infiltrates are composed of foamy histiocytes and

| Table 1: List of conditions showing granulomatous infiltrate |
|----------------------------------------------------------|
| 1. Leprosy                                               |
| 2. Tuberculosis                                           |
| 3. Sarcoidosis                                           |
| 4. Leishmaniasis                                         |
| 5. Syphilis (secondary and late)                         |
| 6. LMDF                                                  |
| 7. Granulomatous rosacea                                 |
| 8. Peri-oral dermatitis                                  |
| 9. Crohn’s disease                                       |
| 10. Blau’s syndrome                                      |
| 11. Lichen nitidus                                       |
| 12. Lichen striatus                                      |
| 13. Sezary syndrome                                      |
| 14. Herpes zoster scars                                  |
| 15. Systemic lymphomas                                   |
| 16. Common variable immunodeficiency                     |
| 17. Fatal bacterial granuloma                            |
| 18. Protothecosis                                        |
| 19. Idiopathic facial aseptic granuloma                  |

LMDF: Lupus miliaris disseminatus faciei
many lymphocytes are arranged in the leprosy pattern. Occasionally, small collections of epithelioid cells may be noted.\(^6\)

Epithelioid granulomas are absent in lepromatous (LL) and indeterminate leprosy.

A similar histopathological spectrum is seen in nerve biopsies, though they tend to show more advanced disease than skin biopsies from the same patient.\(^7\)

Stains for acid-fast bacilli are usually negative in TT and BT and positive in BB and BL leprosy.

The histopathological appearance of granulomas in leprosy is altered in type 1 reaction. A striking change is the development of edema both within the granuloma and in the adjacent dermis. The circumscription of infiltrates is lost and they spill into the interstitial dermis. This is accompanied by an increase in the number of lymphocytes, epithelioid cells, and giant cells, which may be more difficult to discern unless a baseline biopsy is available for comparison. Rarely, granulomas may erode the overlying epidermis, and caseous necrosis may occur within nerves.

Granulomas resolve following treatment, but resolution may be incomplete even several months after effective treatment. Jain et al. studied 44 biopsies taken immediately following the end of 6 months of paucibacillary-multidrug therapy (PB-MDT) and found disease activity in 27 (61\%) cases. Following treatment, there was a predominance of lymphocytes and loose granulomas.\(^8\) In another study, 33\% (8/24) of cases of BT leprosy showed histological activity after 6 months of multidrug therapy.\(^9\) When biopsies were taken 12 months after single-dose rifampicin-ofloxacin-minocycline therapy for PB leprosy, persistent granulomas were noted in 15\% of cases.\(^10\) Joshi has described several changes in treated leprosy including the presence of noncohesive epithelioid cell granulomas with edema.\(^11\)

In one series, 13\% (4/30) of biopsies showed an increase in disease activity after treatment, including half that had not shown granulomas at baseline. Dermal fibrosis was noted in about half (54.5\%) of biopsies that showed granulomas at baseline.\(^12\)

**Cutaneous Tuberculosis**

Epithelioid granulomas are seen in many biopsies from cutaneous tuberculosis. The granulomas are often accompanied by a dense cuff of lymphocytes along with Langhans giant cells. Eosinophils and neutrophils are not seen in significant numbers, but a few may occasionally be noted. Occasionally, plasma cells may be present. Necrosis within granulomas is not as frequent as in tuberculosis of the lung and other sites, but may be seen. Epidermal hyperplasia is frequent and dermal fibrosis is common. The subtypes of cutaneous tuberculosis are described below. Scrofuloderma typically shows supplicative granulomas and is not discussed in this article.
Biopsies of lupus vulgaris show granulomas in about 70% of cases.\cite{13,14} There is a characteristic distribution of granulomas with a broad, confluent granulomatous infiltrate in the upper dermis abutting on the overlying epidermis with lichenoid basal cell damage. This is referred to as the lichenoid-granulomatous pattern or the lupus vulgaris pattern. The mid-dermis is relatively spared, while the lower dermis shows smaller, discrete, nodular granulomas that may be arranged around sweat glands or hair follicles [Figure 14]. The overlying epidermis is acanthotic with follicular plugs that are often parakeratotic. The degree of epidermal hyperplasia is variable but is often quite significant, noted in 41.2%–77.3%.\cite{13-15} Uncommonly, the epidermis may be atrophic. This prototypical presentation is seen in about 20% of biopsies, while other biopsies show epithelioid granulomas and epidermal and dermal changes but lack any particular distribution.

Necrosis within granulomas is not usual and was seen in 11%–59% of cases in different series.\cite{13-16} Dermal fibrosis is commonly seen and was found in 29.4% and 72.7% of cases in two studies of 165 and 103 cases, respectively.\cite{15,16} In some cases, depending on the type of lesion and site of biopsy, fibrosis may dominate the picture with a few granulomas within the fibrosis. Acid-fast bacilli are hardly ever seen. Other findings that have been reported include transfollicular elimination of granulomas seen as granulomas engulfed by hyperplastic follicular infundibulum in a case of lupus vulgaris.\cite{17}

In a series of 14 cases of lupus vulgaris, Pai \textit{et al.} found epithelioid granulomas in all cases, epidermal hyperplasia in 11 (78.5%), caseous necrosis in 3 (21%), dermal fibrosis in 3 (21%), and foreign body giant cells and calcific nodules in giant cells in 2 (14%). Acid-fast bacilli were not seen in any case.\cite{18}

Tuberculosis verrucosa cutis shows findings similar to lupus vulgaris with prominent epidermal features such as hyperkeratosis, acanthosis, papillomatosis, and pseudoepitheliomatous hyperplasia [Figure 15].\cite{19} Neutrophilic microabscesses are noted in the epidermis and neutrophils may be seen in the upper dermal infiltrate. Deep biopsies are required for a diagnosis as characteristic granulomas may be seen only in the deep dermis. Acid-fast bacilli are usually not seen.

By definition, tuberculids show epithelioid cell granulomas. In lichen scrofulosorum, there are focal granulomas centered on and replacing hair follicles and also around sweat glands [Figure 16]. They may be accompanied by papillary dermal granulomas resembling lichen nitidus.\cite{20} Papulonecrotic tuberculid (PNT) shows focal, wedge-shaped necrosis of the epidermis and dermis with leukocytoclastic vasculitis. In addition, loose epithelioid cell granulomas are seen adjacent to the necrosis.\cite{21} PNTs of the penis show focal, epithelioid cell granulomas with lymphocytes accompanied by fibrosis in long-standing lesions. Erythema induratum is a granulomatous lobular panniculitis with vasculitis. There are nodular, epithelioid cell granulomas within lobules that are...
often, but not invariably, accompanied by vasculitis of small and/or medium vessels [Figure 17]. In a series of 12 cases of erythema induratum, diffuse, lobular granulomatous panniculitis was seen in 75%, focal septolobular in 25%, vasculitis in 75%, caseous necrosis in 83.3%, and eosinophils in 83.3%.[22]

**Cutaneous Leishmaniasis and Post Kala Azar Dermal Leishmaniasis**

Epithelioid granulomas are a feature of chronic cutaneous leishmaniasis and leishmania recidivans though they have also been described in around 30% of cases of acute leishmaniasis.[23] Although most cases of nodular post kala azar dermal leishmaniasis are non-granulomatous, epithelioid granulomas are seen in some cases. Presence of epithelioid cells in leishmaniasis has been found to be associated with a lower requirement of drug for treatment.[24,25] They are also more frequent in diseases caused by *Leishmania braziliensis* and in recurrent cutaneous leishmaniasis.[25,26]

Leishmania–Donovan bodies (LD bodies) are amastigotes appearing as blue-gray bodies of size 2–4 µm with a nucleus and a kinetoplast on higher magnification. Seen within or outside macrophages, these can sometimes be confused with nuclear debris or other fungal elements such as histoplasma. This diagnostic finding is seen only in 15%–30% of biopsies, showing a granulomatous infiltrate.[27,28] However, one group noted that epithelioid cells were as frequent in biopsies with Leishmania amastigotes as in those without them.[28] Plasma cells are frequent in biopsies of cutaneous leishmaniasis but are less common when there are epithelioid cell granulomas [Figure 18].

Epidermal changes ranging from atrophy to ulceration to hyperplasia can be seen depending on the clinical manifestation. Some authors have reported amastigotes within the epidermis representing transepithelial elimination.[23] The granulomas are loose involving the upper and mid-dermis, though compact granulomas can be found. Andrade-Narvaez et al. and Quintella et al. observed granulomas in 6.8% and 39.7% of cases, respectively.[24,30] Necrosis is usually absent, but was noted in about a quarter of biopsies in two different series.[24,31]

Recently, Fernandez-Flores and Rodriguez-Peralto described a “messy granuloma” in cutaneous leishmaniasis. They found granulomas in 82% of biopsies (14/17); out of which, 8 showed discrete and 6 showed confluent granulomas. According to them, messy granulomas are loose epithelioid cell granulomas with low cellularity. Granulomas are composed of elongated histiocytes with glassy cytoplasm arranged haphazardly, with an intervening hyaline dense substance, likely degenerated collagen (as stained green by Masson trichrome stain). There were few lymphocytes, no giant cells, or necrosis.[32]

Epithelioid granulomas are not usually seen in nodular post kala azar dermal leishmaniasis but may be observed in a minority of patients. They were seen in 4 (4.5%) of a large series of 88 cases reported by Singh et al. Biopsies showed nodular aggregates of epithelioid cells and macrophages surrounded by lymphocytes and plasma cells along with epidermal atrophy [Figure 19].[33]

Special stains such as Giemsa stain, immunohistochemistry for leishmanial antigens such as G2D10, culture, and polymerase chain reaction studies may aid in the diagnosis of leishmaniasis.[34]

**Sarcoidosis**

The prototypical sarcoidal granuloma is the so-called naked granuloma, composed almost exclusively of epithelioid cells accompanied by a sprinkling of lymphocytes. The granulomas tend to be round and of small to moderate size. An important histological clue is the lack of confluence of individual granulomas even when they are huddled close to each other [Figure 20]. Giant cells in granulomas may contain Schaumann bodies, lamellar inclusions of calcium or asteroid

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**Figure 17:** Lobular granulomatous panniculitis in erythema induratum (H and E, ×400)

**Figure 18:** Plasma cells (left side), epithelioid cells (center), and Leishmania–Donovani bodies (arrow) in cutaneous leishmaniasis (H and E, ×400)
bodies, star-like structures composed of degenerated collagen or elastin. Necrosis is typically absent and fibrosis is not a feature of sarcoidosis.

However, there are several variations on this theme. While naked granulomas formed the majority, significant lymphocytic infiltrates accompanied the granulomas in 14%–29% of biopsies in three series of 28, 31, and 32 cases.[4,35,36] Coalescent granulomas were seen in most biopsies in one study (29/42, 69%) and was a striking finding in five biopsies.[4] Similarly, Cardoso et al. noted coalescent granulomas in 65% (20/31) of cases.[35]

Giant cells were seen in nearly all biopsies (30 of 31, 97%) in one series, but other cells such as neutrophils and plasma cells were hardly ever noted (1 case each, 3%).[35]

Schaumann and asteroid bodies were found within giant cells in four (9.5%) cases and ten (32%) cases in two series.[4,35] However, we have seen Schaumann bodies in leprosy and cutaneous tuberculosis on rare occasions and asteroid bodies were seen in 33% (8/24) of cases of necrobiotic xanthogranuloma, with paraproteinemia in one series.[5]

Another important finding in cutaneous sarcoidosis is the presence of polarizable foreign bodies. It was initially believed that the demonstration of foreign bodies in a sarcoidal granuloma refuted the diagnosis of sarcoidosis. However, it is now recognized that authentic sarcoidosis often shows these inclusions within giant cells. Mangas et al. found foreign material in 26%, Cardoso et al. in 13%, and Ball et al. in 50% of biopsies.[4,35,36]

Although necrosis and fibrosis are typically absent in sarcoidal granulomas, these findings have been reported in different studies. Focal necrosis was seen in 6%–43% in various studies though it was not seen in any case in one study.[4,35,36] We have frequently noted small foci of fibrinoid necrosis at the center of sarcoidal granulomas and use this finding as a diagnostic clue to differentiate sarcoidosis from other granulomatous disorders [Figure 21].

Fibrosis is a constant finding in scar sarcoidosis where, by definition, sarcoidal granulomas are seen in the context of dermal fibrosis. However, mild fibrosis can be seen in other variants of sarcoidosis and was noted in 10% of cases in one study.[35] Fibrosis or sclerosis is the predominant feature along with epithelioid cell granulomas in morpheaform sarcoidosis which presents with indurated, morphea-like plaques. Fibrosis and obliteration of fat along with granulomas has been reported in this variant.[37] Other rare features noted in sarcoidosis include elastophagocytosis (39%) and increased dermal mucin (18%) in a series by Ball et al.[36]

The density of the infiltrate also varies from mild infiltrates seen in 19% (6/31) to moderate in 45% (14/31) and severe in 36% (11/31). In this series, the infiltrate was oriented horizontally most commonly (61%) followed by vertical (23%) and mixed horizontal and vertical (13%) orientation, while one biopsy showed infiltrates in the adventitial dermis.[35]
In a study on histological features of 53 cases of granulomatous rosacea, epithelioid cell granulomas were seen in 11%, granulomas with caseation in another 11%, histiocytic infiltrates with a few giant cells in 34%, and lympho-histiocytic infiltrates in 40%.[43]

In another study on 24 biopsies of granulomatous rosacea, 4 distinct patterns were noted: nodular (33%), perifollicular (12.5%), diffuse (8.3%), and combined perifollicular and nodular (54%). Other histological features seen were solar elastosis (100%), fibroplasia (100%), telangiectasia (67%), demodex mite (29%), and spongiosis (13%).[44]

Miscellaneous Causes

There are a number of other granulomatous conditions that show some features that may be helpful in diagnosis.

Epithelioid cell granulomas are classically seen in tertiary syphilis (gummas), and occasionally in secondary syphilis. Gummas, rarely encountered now, show necrotizing granulomas.[45] In secondary syphilis, granulomas appear to be more frequent in long-standing disease that presents with a nodular eruption.[46] These granulomas are arranged in a band-like manner around the superficial papillary dermal vasculature with deeper extension into the reticular dermis along the appendages.[47] Rysgaard et al. have described this finding as T-shaped or candelabra-shaped pattern.[48] Besides this, a perivascular and peri-appendageal distribution and perineural distribution resembling the leprosy pattern have also been reported.[49,50] Plasma cells are a clue to the diagnosis of secondary syphilis but their numbers may vary in biopsies from granulomatous lesions. When present, they may be seen around appendages, away from the epithelioid granuloma. Endothelial cell swelling is usually not a feature.[46,51] Sarcoidal granulomas and interstitial granulomas also have been described in secondary syphilis.[49,52]

Figure 22: Epithelioid cell granulomas with prominent central necrosis in lupus miliaris disseminatus faciei (H and E, ×100)

Figure 23: Epithelioid cell granulomas in superficial and deep dermis extending up to muscle in granulomatous cheilitis (H and E, ×40)
T. pallidum can be identified with the help of special stains such as Warthin–Starry stain, direct immunoﬂuorescence, or immunohistochemistry. However, in granulomatous syphilis, the chances of finding Treponema are low.

Orofacial granulomatosis or Melkersson–Rosenthal syndrome presents with granulomatous inflammation. In a study on recurrent facial swelling in 104 cases, granulomatous inflammation was seen in 47% (40/85). Among these, there were 68% (27/40) cases of orofacial granulomatosis and 43% (3/7) cases of solid facial edema.

In an unpublished study conducted in our department, 10 (52.6%) of 19 cases of clinically diagnosed granulomatous...
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cheilitis showed granulomas. In three of them, granulomas were seen between the skeletal muscle bundles at the deep aspect of the lip biopsy, in addition to dermal granulomas [Figure 23]. Granulomas were noted more frequently in those who had more severe lip swelling and for a longer duration.[41]

Granulomatous peri-orificial dermatitis shows a histopathological resemblance to granulomatous rosacea. There are peri-appendageal lympho-plasmacytic infiltrates with non-caseating epithelioid cell granulomas and many multinucleated giant cells.[54]

Peri-oral dermatitis is another condition that resembles granulomatous rosacea on histology. It shows perivascular and perifollicular lymphocytic infiltrates with giant cells and dermal edema.[55]

Facial aseptic granuloma presents as an asymptomatic erythematous nodule over the cheeks in children. Histopathology shows peri-folliculitis, granulomatous follicular inflammation with surrounding lympho-plasmacytic infiltrate. Some consider it to be a variant of granulomatous rosacea.[56] Mixed inflammatory infiltrates can also be seen.[57]

Cutaneous Crohn’s disease, also known as metastatic Crohn’s disease, shows the presence of non-suppurative, sarcoidal, epithelioid cell granulomas in dermis and subcutis with many Langhans and foreign body giant cells and a mild-to-moderate perivascular mixed inflammatory infiltrate. Rarely, granulomatous vasculitis, necrobiosis, and eosinophils in the infiltrate have been reported.[58-59] Emanuel and Phelps found non-caseating epithelioid cell granulomas with a slight cuff of lymphocytes in a nodular or diffuse manner with perivascular mixed inflammatory infiltrate as the predominant finding in 12 cases of metastatic Crohn’s disease. The infiltrate was both superficial and deep in the majority (75%) of cases. Other findings noted were epidermal infiltration (25%), lichenoid infiltrate (16.7%), ulceration (41.7%), presence of eosinophils (66.7%), granulomatous vasculitis (16.7%), and dermal edema (16.7%).[60]

**CONCLUSION**

A large number of conditions present with granulomas on biopsy. The histopathological appearance is quite suggestive of the diagnosis in some diseases such as leprosy, sarcoidosis, and lupus vulgaris. In other conditions, the histopathological appearance is not enough by itself but when taken with the clinical appearance can lead to the diagnosis as in LMDF, penile tuberculid, granulomatous cheilitis, or Crohn’s disease. In all these diseases, additional clinical information and laboratory tests are helpful to provide further evidence for the diagnosis. This may include information about residence in an endemic area for cutaneous leishmaniasis or kala-azar, risky sexual behavior in syphilis, and co-existence of pulmonary sarcoidosis. Although organisms are usually difficult to find or grow from epithelioid granulomas, positive cultures and nucleic acid amplification tests for fungi, mycobacteria, and leishmaniasis may be of help in diagnosis. In some cases, the answer comes from a therapeutic trial and prolonged follow-up, while in some, the diagnosis cannot be established. Histological salient features of various granulomatous conditions are mentioned in Table 2. An approach to biopsies showing epithelioid granulomas is outlined in Figure 24.

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**Conflicts of interest**

There are no conflicts of interest.

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