Granulomatous dermatitis

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Granulomatous dermatitis refers to inflammatory skin diseases in which histiocytes predominate, at least in some foci. In sarcoidal granulomatous dermatitis, histiocytes are present in compact collections, with some lymphocytes, but with only a few lymphocytes around them. In tuberculoid granulomatous dermatitis, infiltrates of lymphocytes are present around the aggregates of histiocytes. In palisaded granulomatous dermatitis, histiocytes surround less cellular areas. In suppurative and granulomatous dermatitis, histiocytes surround neutrophils, both intact and degenerating. The differential diagnosis of that pattern is large, and contains many infections. In diffuse histiocytic infiltrates, histiocytes are present throughout the reticular dermis; some of these cases are examples of “histiocytoses”, poorly understood proliferations of histiocytes or histiocyte-like cells, and others are infections, with parasitized histiocytes.

The key features in distinguishing among the palisaded granulomatous dermatitides are:
- the location of the infiltrates within the dermis/subcutis
- the material that the histiocytes are surrounding
- the presence of other types of inflammatory cells

Sarcoidal granulomatous dermatitis

Some important sarcoidal granulomatous dermatides are:

- Lichen nitidus
- Lichen striatus
- Sarcoidosis
- Crohn’s disease
- Tuberculoid leprosy
- Rosacea

Lichen striatus

Lichen striatus is a condition that presents as papules along Blaschko’s lines in children and in adolescents, being rare in adults. It does not become widespread, and the importance of recognizing it is largely to avoid the diagnosis of the many conditions it can mimic.

Histopathologic features:

- Sarcoidal granulomas can occur, but usually do so in the company of a patchy lymphocytic infiltrate in the papillary dermis and psoriasiform epidermal hyperplasia
- Spongiosis can also be present
- One can see many lymphocytes within the epidermis, simulating mycosis fungoides
- The finding of lymphocytes around eccrine coils can be very helpful in confirming the diagnosis


Lichen nitidus

Lichen nitidus is a condition that is relatively common in dark skinned peoples, resulting in tiny shiny flat topped papules, often on the dorsal hands or genitalia. Its small papules can be confused with those of lichen planus, but are unrelated.

Histopathologic findings:

- Small compact collections of histiocytes with variable numbers of lymphocytes in widened dermal papillae
- Slight epidermal hyperplasia
- Vacuolar change, but not necrotic keratinocytes or colloid bodies in number

Be alert to this pattern, with lymphocytes and plasma cells in sun exposed skin- there is a variant of polymorphous light eruption sometimes termed lichen nitidus actinicus or “pinpoint papular” polymorphous light eruption that can cause these changes.


Sarcoidosis

Sarcoidosis often presents in the skin before internal involvement is noted, and sometimes remains confined to the skin. Its lesions are usually papules, nodules or plaques. A variant with small papules is called “micropapular sarcoidosis”. Annular lesions are more common in dark skinned patients. Subcutaneous lesions without dermal involvement can occur. Lesions on the nose are termed lupus pernio, a confusing state of affairs, as perniosis (chilblains) can occur in
lupus erythematosus. A critical fact to be aware of is that foreign material can form the nidus for the formation of granulomata in patients who are developing systemic sarcoidosis, and that the finding of foreign material in a sarcoidal granulomatous dermatitis does not rule out sarcoidosis.

Histopathologic features:

- “Naked” granulomas, in which histiocytes abut the collagen bundles of the reticular dermis are typical, but are not always present
- Lymphocytes are present in number in some cases, resulting in a tuberculoid pattern
- Necrosis, neutrophils, plasma cells, granulomas along nerves are variable features
- Ichthyosiform sarcoidosis features lamellar hyperkeratosis above the epidermal surface
- Granulomas can be present around follicles, eliciting a differential diagnosis of granulomatous rosacea
- There are endogenous refractile crystals in the granulomata of sarcoidosis, but the finding of authentic foreign material does not rule out sarcoidosis!!!!
- Subcutaneous sarcoidosis is often accompanied by fibrosis in between the granulomatous foci, to a greater extent than its mimic, erythema nodosum


**Tuberculoid leprosy**

Tuberculoid leprosy occurs in patients with a high degree of immunity to M. Leprae. There are usually only a few lesion, often asymmetrically distributed. Sharply bordered plaques are characteristic, often with atrophic centers. Pigmentation may be lost in long standing lesions. There is often hypoesthesia in affected skin.

Histopathologic features:

- Sarcoidal granulomas
- Some granulomas can abut the undersurface of the epidermis (loss of the Grenz zone)
- Either histiocytes or lymphocytes around nerves, with destruction of nerves
- Few bacilli or none on special stains

**TUBERCULOID GRANULOMATOUS DERMATITIS**

**Tuberculosis**

The lesions of cutaneous tuberculosis pose much less of a problem for clinicians and histopathologists than they did in past years. The main clinical challenge in the developed world is recognizing that a patient might have cutaneous TB.

The clinical manifestations range from tuberculous chancre in children, to warty lesions of tuberculosis verrucosa cutis in immunocompetent adults, to lesions caused by direct extension from lymph nodes (scrofuloderma) to a lesion of hematogenous origin, lupus vulgaris.

The histopathologic findings in cutaneous TB vary depending on the type of lesion biopsied.

- Irregular hyperplasia and hyperkeratosis of the dermis overlying granulomata in tuberculosis verrucosa
- Epidermal hyperplasia or atrophy overlying granulomata in lupus vulgaris
- Atrophy or ulceration in scrofuloderma
- Acid fast organisms are often not demonstrable in tissue sections, and may be impossible to find, esp. in lupus vulgaris

The role of polymerase chain reaction (PCR) is debatable, with some labs reporting good and others bad results.


Comprehensive findings on clinical, bacteriological, histopathological and therapeutic aspects of cutaneous tuberculosis

Tropical Medicine & International Health 2006 11 (10), 1521-1528.
Lichen nitidus was discussed in the section on sarcoidal granulomatous dermatitis. Sometimes it presents with a tuberculoid pattern.

Lichen striatus was also discussed in the section on sarcoidal granulomatous dermatitis. Sometimes it too presents with a tuberculoid pattern.

Rosacea

Rosacea is a common condition usually involving the central face, with papules, telangiectases or both. The papular form is the one that is usually biopsied, often to rule out other conditions. Extrafacial rosacea can affect the hair bearing skin at other sites.

Histopathologic features:

- Perifollicular lymphocytes, histiocytes, histiocytic giant cells and plasma cells
- Slight spongiosis of follicular infundibula
- Neutrophils can be present in early lesions (pustules)

Rosacea and the perifollicular variant of sarcoidosis can be difficult to distinguish. The presence of plasma cells is more common in rosacea, but they are present in a small number of lesions of sarcoidosis. Histiocytes palisade around small foci containing degenerated collagen and fibrin in both conditions, and this finding is a consistent one in the form of rosacea-like dermatitis termed lupus miliaris disseminatus faciei.


Deep fungal infections can result in a pattern of tuberculoid granulomatous dermatitis. As they more often are suppurrative and granulomatous, they will be considered later.

PALISADED GRANULOMATOUS DERMATITIS

Granuloma annulare (GA)

GA is one of the protean diseases in dermatology- a condition with many clinical variants. Because it is one of the most common inflammatory skin diseases, and one of the most commonly biopsied ones, it is particularly important that pathologists be able to recognize it microscopically.

Clinical features-

- Patients are usually well (rarely, GA is associated with systemic diseases)
- Localized disease is the most common form
  - annular plaques made up of white, tan or pink papules
-resolution in most cases after a few years, even without treatment
- Generalized papules (often umbilicated), associated in some cases with diabetes
- Deep GA
  - subcutaneous nodules, often in children
  - misdiagnosis as rheumatoid nodule common
- Macular GA
  - dusky, erythematous patches
  - misdiagnosis as morphea, mycosis fungoides, erythema multiforme
- Actinic GA (actinic granuloma of O’Brien, annular elastolytic granuloma)
  - Annular lesions in sun damaged skin
  - Controversy: entity sui generis, or variant of GA

Histopathologic features
- “Interstitial GA”
  - May be early changes in other types of GA
  - Lymphocytes around small vessels, histiocytes between collagen bundles
  - Interstitial mucin (Alcian blue, colloidal iron positive, pH 2.5) in areas of histiocytes
- Differential diagnoses: Morphea, reticular erythematous mucinosis (REM), interstitial pattern of mycosis fungoides

- Palisaded GA
  - Superficial and deep perivascular lymphocytic infiltrates
  - Interstitial histiocytes
  - Rings of histiocytes surrounding degenerating (and regenerating collagen) and mucin
  - A few neutrophils and some dust around necrotic venules in the centers of granulomas (rare)
- Differential diagnosis: Necrobiosis lipoidica, rheumatoid nodule, palisaded neutrophilic and granulomatous dermatitis, others

- Deep GA
  - Large oval mass of histiocytes surrounding less cellular area
  - Degenerating collagen and mucin in the center, but more brightly eosinophlic than in conventional palisaded granuloma annulare
- Differential diagnosis: Rheumatoid nodule, phaeohyphomycotic cyst

- Actinic GA
  - Palisaded histiocytes around fibrosis
  - Giant cells commonly present
  - Elastotic material in cytoplasm of giant cells
  - Elastic tissue absent from centers of granulomatous foci


Patterson JW.
Necrobiosis lipoidica

Necrobiosis lipoidica, formerly or more fully called necrobiosis lipoidica diabeticorum is mostly but not exclusively found in patients with diabetes mellitus.

Clinical features-
- Most lesions bilaterally on shins
- Early lesions are red papules with sharp borders
- Later, yellow, hard atrophic plaques
- 60% have frank diabetes, another 20% abnormal glucose tolerance or +FH

Histopathologic features (fully developed lesions)
- Palisaded granulomatous inflammation involving whole dermis (top to bottom and side to side, with layered appearance)
- Degenerated collagen early, fibrosis in established lesions
- Superficial and deep infiltrates of lymphocytes and plasma cells around vessels
- Secondary necrosis of follicles (rupture leads to suppurative foci in rare cases)
- Neutrophilic dust in centers of some lesions, no mucin
- Extension of process into septa of subcutis if biopsy is deep enough
Differential diagnosis: GA, necrobiotic xanthogranuloma

Histopathologic features (late lesions)
- Rings of histiocytes become less cellular
- Fibrosis=degenerated collagen, with thick collagen bundles
- Lymphocytes and plasma cells less notable
- Elastic tissue lost (unlike morphea)
Differential diagnosis: Morphea, late stage of palisaded neutrophilic and granulomatous dermatitis

Comment: I did not list the features of early lesions of NLD as they are seldom biopsied. NLD may begin as a small vessel leukocytoclastic vasculitis, and even older lesions can have neutrophils or histiocytes in the walls of damaged vessels.

Peyri J, Moreno A, Marcoval J.
Necrobiosis lipoidica.
Rheumatoid nodule

Rheumatoid nodule (RN) is a condition usually found in patients with rheumatoid arthritis or other collagen vascular diseases. They are particularly common among patients with rheumatoid arthritis (20-30%) and lupus (up to 7%). They usually occur in patients with established disease, so the diagnosis of RN should be made with caution if there is no known collagen vascular disease.

Clinical features
- Symmetrical papules and nodules
- Usually subcutaneous, sometimes fixed to tendons
- Skin color unchanged, sometimes yellow (simulating xanthomas)
- Extensive disease with joint destruction (rheumatoid nodulosis)

Histopathologic features
- Large oval mass in deep dermis/subcutis
- Palisaded histiocytes surrounding degenerated collagen, large amounts of fibrin, neutrophils and nuclear dust
- Mucin scant or absent
- Vasculitis in adjacent vessels rarely

Comment: As noted above, RN is seldom a surprise. Most rheumatologists taking care of patients with rheumatoid arthritis or lupus make this diagnosis clinically. The vast majority of diagnoses of RN in well children are misdiagnoses of deep GA!

García-Patos V.
Rheumatoid nodule.
**Palisaded neutrophilic and granulomatous dermatitis**

Palisaded neutrophilic and granulomatous dermatitis (PNGD) is my attempt to define a disease spectrum described in patients with systemic diseases of various kinds. Terms such as rheumatoid papules, Churg-Strauss granuloma, extravascular necrotizing granuloma and Winkelmann granuloma also refer to this condition.

The range of systemic diseases in patients with PNGD includes patients with:

- Systemic lupus erythematosus
- Rheumatoid arthritis (incl. seronegative cases)
- Wegener’s granulomatosis
- Lymphoma/leukemia
- Inflammatory bowel disease
- Systemic vaculitis (incl. Takayasu arteritis, Churg Strauss disease)

In one study, 21/22 patients with the condition on biopsy had evidence of a systemic disease.

The main clinical presentation is of small, umbilicated papules on the dorsal aspects of joints, esp. those of the fingers, elbows and knees.

The salient histopathologic features differ for each stage of PNGD:

_ Early:_
- Fibrin around vessel walls
- Neutrophils and abundant nuclear debris around vessels around fibrin

_ Fully developed:_
- Palisaded histiocytes around neutrophils and their debris
- Thick, but discolored collagen bundles
- Evidence of vasculitis, sometimes

_ Late:_
- Palisaded histiocytes around zones of fibrosis with few neutrophils
- No vasculitis

Comment: There are several other unusual clinical and histopathologic patterns that may overlap with the stereotypic picture noted herein.

“Interstitial granulomatous dermatitis with arthritis” (IGDA) was described by Bernard Ackerman, with several detailed report by Long et al.. and Verneuil and colleagues. The clinical presentations included subcutaneous cords and erythematous plaques, in contrast to those noted.
above. There are interstitially distributed histiocytes, with or without a palisaded pattern, but in the reported cases, no evidence of vasculitis. Interstitial neutrophils and eosinophils are also present. However, the diseases associated with this pattern overlap considerably with those seen in PNGD.

“Interstitial granulomatous drug eruption” has large interstitial histiocytes, and a more subtle palisaded pattern than does PNGD. It presents with dusky erythema in flexural areas. There are small foci in which degenerated neutrophils and/or eosinophils are present. The reported causes include non-steroidal anti-inflammatory medications. An unusual drug eruption manifesting as papules in patients receiving methotrexate also has many interstitial histiocytes, but presents with erythematous papules. Palisaded foci surrounding degenerated neutrophils and eosinophils are not yet reported, but histiocytes form rosettes that surround and adhere to thick collagen bundles, demarcated from the rest of the dermis by clefts. A similar arrangement can occur in PNGD and in IGDA.

Finan MC, Winkelmann RK. The cutaneous extravascular necrotizing granuloma (Churg-Strauss granuloma) and systemic disease: a review of 27 cases. Medicine (Baltimore) 1983 May;62(3):142-58


**Necrobiotic xanthogranuloma with paraproteinemia**

Necrobiotic xanthogranuloma with paraproteinemia (NXG) is a rare condition, but one that is important to recognize as it can maim patients, and some patients have died of its complications. Its name refers to its infiltrates of foamy histiocytes, zones of necrobiosis (degenerating and regenerating collagen) and frequent paraproteinemia. Despite the paraprotein, and the rare eventuation of myeloma in patients with NXG, it seems to be an inflammatory and not a neoplastic condition.
Clinical features:
- Yellow plaques on limbs, with periocular/periorbital lesions in most patients
- Progression of lesions in some patients
- Hyperlipidemia/hypercholesterolemia
- Many patients diabetic
- Serum paraprotein (usually IgG κ)
- Loss of limbs or eye possible

Histopathologic features
- Infiltrate mid- and deep dermis, and both subcutaneous lobules and septa
- Superficial and deep perivascular infiltrates of lymphocytes and plasma cells, sometimes very dense
- Lymphoid follicles
- Palisaded foamy histiocytes surrounding homogeneous eosinophilic material
- Foamy histiocytes and Touton giant cells in subcutis (“Touton cell panniculitis”)
- Giant cells with scalloped margins
- Cholesterol clefts surrounded by rings of foamy histiocytes (cholesterol granulomas)

Comment: NXG is often mistaken for NLD, as both can present as yellow plaques on the limbs of diabetic patients. Cholesterol clefts surrounded by foamy histiocytes are practically pathognomonic of the condition. Cholesterol clefts were present in 3/331 specimens of NLD in one study, but not surrounded by foamy macrophages and Touton giant cells. While there are no magically effective treatments for NXG, the potential loss of an eye, and rare compromised of vasculature of a limb make a misdiagnosis of NLD a poor show.

Chave, T. A. & Hutchinson, P. E. Necrobiotic xanthogranuloma with two monoclonal paraproteins and no periorbital involvement at presentation. Clinical & Experimental Dermatology 26 (6), 493-496.

Gout

Clinical features
- White to yellow papules or nodules above joints, rims of helices
- Extrusion of chalky material in some cases

Histopathologic features
- Palisaded histiocytes, foreign body giant cells at periphery
- Needle like crystals in center, some nuclear dust as well
- While alcohol fixation preserves crystals the best, formalin adequate in most cases
Differential diagnosis: Eruptive xanthoma, oxalosis


**Palisaded granulomatous reactions to foreign material**

Histiocytes can be radially arranged around a variety of foreign substances, including suture material, beryllium, and injectable (bovine) collagen. The mechanism by which the dermis is altered in some of these reactions is unclear.


**SUPPURATIVE AND GRANULOMATOUS DERMATITIS**

Suppurative and granulomatous dermatitis is the most common pattern seen in cutaneous infections, and the specific diagnosis rests on identification of the infectious agent. Conventional bacteria, mycobacteria, filamentous bacteria, fungi, algae and protozoans can all cause this pattern, and I will show only a few examples, as a comprehensive exposition would cover most of infectious skin disease.

This pattern can also be seen in reactions to foreign material (e.g. splinters, cactus spines, etc.) and to material perceived as foreign (extruded corneocytes from ruptured cysts).

**DIFFUSE HISTIOCYTIC INFILTRATES**

As noted above, diffuse infiltrates of histiocytes are present in the diverse conditions known as the “histiocytoses”. Some of these represent proliferations of conventional monocyte-derived melanophages, while others are proliferations of more specialized but related cells, such as sinus histiocytes in Rosai-Dorfman disease.

Parasitized histiocytes can cause nodular or diffuse infiltrates of the skin, especially in *lepromatous leprosy* and in *leishmaniasis*. 