Non-infectious granulomatous dermatoses

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Non-infectious granulomas

- Sarcoidosis
- Granuloma annulare
- Rheumatoid nodule
- Necrobiosis lipoidica
- Elastolytic granuloma
- Crohn’s disease
- Necrobiotic xanthogranuloma

Sarcoidosis

- Systemic disease of unknown etiology
- Non-caseating granulomas
  Third and fourth decades
  Female predominance
  African americans

Cutaneous lesions in sarcoidosis

- Papules, plaques and nodules
  - Verrucous
  - Hypopigmented
  - Alopeic
- Lupus pernio
- Subcutaneous nodules
- Lichenoid
- Erythodermic
- Vasculitic (rare variant)
  - Atrophic
  - Ulcerative

Courtesy of Dr Linda Wang

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Systemic lesions in sarcoidosis

- Hilar lymph nodes (70-90%)
- Lungs (50-90%)
- Peripheral lymphadenopathy (30%)
- Ocular lesions (25%)
  - Chronic iridocyclitis
- Hepatomegaly (20%)
- Splenomegaly (17%)

Systemic lesions in sarcoidosis

- Bone lesions (15%)
  - Phalanges (sausage-shaped)
- Large salivary glands (8%)
- Neurosarcoidosis (5%)
  - Hypothalamus, pituitary gland, leptomeninges, and cranial nerves particularly facial nerve
- Cardiac involvement, uncommon
  - Granulomas in conduction system

Sarcoidosis

- Usually benign disease
- Fatal in 5% of cases
  - Cardiac involvement
  - Respiratory or renal failure

Pathogenesis

Antigen-driven disorder in which the helper/inducer T cell arm of the immune system reacts in an exaggerated fashion to a yet undetermined antigen (Mycobacteria).
Lupus pernio

- Chronic variant of sarcoidosis
- Nose and central face
- May be locally destructive
Sarcoidosis: Diagnosis of exclusion

- Histology
- Imaging studies
- ACE (angiotensin converting enzyme) levels
- CD4/CD8 in bronchoalveolar lavage
- Negative work up for infectious etiology
- Presence of foreign bodies does not rule out the diagnosis

Differential diagnosis

- Infectious granulomata (use special stains!)
- Foreign body granulomata
- Crohn’s disease (it may be the first manifestation)

Interstitial and Palisading Granulomatous Dermatitis

Group of disorders in which the unifying histiologic feature is histiocytic infiltration with variable alteration of the connective tissue framework

Necrobiosis

Areas of altered dermal connective tissue with loss of definition of collagen bundles and alteration in staining (H&E)

Degeneration and loss of collagen/elastic fibers and connective tissue cells

Replacement by mucin, fibrin, lipids, sclerosis

Interstitial and Palisading Granulomatous Dermatitis

- Granuloma annulare
- Elastolytic granuloma
- Necrobiosis lipoidica
- Rheumatoid nodule
- Necrobiotic xanthogranuloma
- Palisaded neutrophilic and granulomatous dermatitis
- Crohn’s disease

Granuloma annulare

- Frequent palisaded granulomatous condition of unknown etiology
- Benign, self-limited
- Children and young adults
- Females
Distribution of Lesions

- GA: hands, feet and wrists, most commonly
- Also on elbow or trunk

Clinical variants

- Localized
- Generalized
- Perforating
- Subcutaneous
- Papular
- Linear

Histologic considerations: Granuloma annulare

- Three phases in evolution:
  1. Interstitial histiocytic infiltration
  2. Mucin deposition
  3. Areas of necrobiosis with fibrin deposition
- Tissue eosinophilia in up to 2/3 of biopsies
Subcutaneous granuloma annulare
• Disorder of childhood
• Mean age of presentation: 4.3 years
• Sites: extremities and scalp
• No patients have developed systemic disease in 26 years of follow-up

Subcutaneous granuloma annulare
• Associated with large zones of necrobiosis and fibrin resembling rheumatoid nodule
• Eosinophils may be prominent

Granuloma Annulare Tissue Reactions Associated with Systemic Disease
• Granuloma annulare has an atypical presentation(unusual sites like elbow) or multiple lesions
• Interstitial neutrophilia
• Plasma cells
• Thrombosis
• Neutrophils in vessel wall with fibrin
Atypical GA as a manifestation of underlying systemic disease

- Infections: Parvovirus B19, CMV, HIV, and hepatitis C
- Collagen vascular disease: Rheumatoid arthritis
- Diabetes Mellitus
- Thyroid disease
- Low grade B cell malignancy (Paraproteinemia)

Generalized GA in the setting of HIV disease

Atypical GA Tissue Reaction In the setting of IBD

Granulomatous Vasculitis

Hepatitis C associated GA tissue reaction
Clue to the Atypical GA tissue
Reaction: Vasculopathy

Differential diagnosis

- Necrobiosis lipoidica
- Actinic granuloma
- Infectious granulomas
  - Mycobacterium marinum
- Xanthomas
- Rheumatoid nodule
- Epithelioid sarcoma
- Palisaded neutrophilic and granulomatous dermatitis

Annular elastolytic giant-cell granuloma

- Actinic granuloma
- Sun-exposed skin
- Granuloma annulare variant?
- Clinically similar to GA
Necrobiosis lipoidica

- Idiopathic disorder
- Indurated plaques on the shins
- Associated with diabetes mellitus (DM)
  Prevalence in DM 3/1000
- Female preponderance (3:1)

Necrobiosis lipoidica

- Circumscribed plaque
- Bilateral
- Symmetrical
- Pretibial location

Necrobiosis Lipoidica

Patient BH
A 74 year old woman with arterial hypertension on an ACE inhibitor developed a plaque on the ankle
Necrobiosis lipoidica

- Entire dermis usually involved by zones or layers
- Layers include fibrosis alternating with areas of altered collagen, with scattered lymphocytes and histiocytes, and cellular debris, especially around altered collagen
- Multinucleate giant cells and foamy macrophages scattered throughout lesion
- 20% show necrobiosis of the subcutaneous septa, a form of panniculitis
- Foci of mucin not present
- NL diffuse, involving entire dermis; GA focal or multifocal

Histopathological variants

- Diffuse
- Sarcoidal
- Perforating
- Subcutaneous
Necrobiosis Lipoidica Tissue Reactions associated with systemic disease

- Sarcoïdal granulomas seen in sarcoidosis, autoimmune thyroid disease and diabetes
- Thrombosis seen in diabetes, rheumatoid arthritis, and low grade B cell malignancy
- Neutrophilia in rheumatoid arthritis
- Clonal plasma cell infiltrates in the setting of myeloma

5 year history of facial plaques compatible With a sarcoïdal diathesis

Subsequently developed NL like plaques on legs
Subsequent evaluation revealed a monoclonal marrow plasmacytic infiltrate consistent with myeloma.

Differential diagnosis

- Granuloma annulare
- Infectious granulomas
- Necrobiotic xanthogranuloma
- Rheumatoid nodule
- Sarcoïdosis
- Crohn’s disease
- Epithelioid sarcoma

Rheumatoid nodule

- Subcutaneous
- Sites of trauma or at pressure points
- Adults with rheumatoid arthritis (30%)
  - severe disease
  - high titer of rheumatoid factor
  - joint erosions
  - increased incidence of rheumatoid vasculitis

Rheumatoid nodule

- Extensor aspect of forearms and elbows, knuckles, feet, knees, buttocks, scalp, back etc
- Extracutaneous sites (heart, larynx, lungs, pleura, etc)

Rheumatoid nodules

- Lesions appear in subcutaneous tissue and extending into dermis
- Irregular-shaped, broad zones and necrobiosis with hypereosinophilic appearance due to fibrin deposition
- Peripheral palisade of histiocytes
- Vessels show endothelial necrosis and fibrin thrombi in necrobiotic zones
- Peripheral to palisading areas is granulation tissue-like appearance

Necrobiosis lipoidica

Lesions appear in subcutaneous tissue and extending into dermis. Irregular-shaped, broad zones and necrobiotic zones with hypereosinophilic appearance due to fibrin deposition. Peripheral palisade of histiocytes. Vessels show endothelial necrosis and fibrin thrombi in necrobiotic zones. Peripheral to palisading areas is granulation tissue-like appearance.
Pathogenesis:
- Trauma
- Immune complex mediated: IgG and IgM in vessels surrounding nodules
- Rheumatoid factor and complement in nodules
- Cytokine and cell adhesion molecules
- Vasculitis

Differential diagnosis
- Deep granuloma annulare (pseudorheumatoid nodule)
- Foreign body granulomas
- Infectious granulomas
- Epithelioid sarcoma
Necrobiotic xanthogranuloma (NXG) with paraproteinemia

- Described by Kossard + Winkelmann (1980)
- A progressive periorbital dermatosis associated with paraproteinemia or a myeloproliferative disorder
- Rare disorder
- Large, yellow plaques
- Paraproteinemia (IgG kappa type)

Pathogenesis

Both the pathogenesis of NXG and its link to paraproteinemia are unclear

DIF: IgM, C3 and fibrinogen in blood vessel walls

Necrobiotic xanthogranuloma: clinical features

- Asymptomatic, itchy or painful indurated yellow, red-orange or violaceous plaques and nodules involving head and neck, trunk, proximal limbs
- Lead to scarring, atrophy, local infection
- Hepatosplenomegaly, uveitis, iritis, proptosis, periorbital ulceration
- No gender preference

75 y/o male with myeloma developed papules and plaques on abdomen with periorbital xanthomas
NECROBIOTIC XANTHOGRANULOMA: histopathology

- A necrotizing granulomatous dermatitis with cholesterol clefts and lipidized histiocytes including Touton giant cell forms
- Unlike plane xanthoma, foamy histiocytes are not predominant
- Lymphoid follicles, plasma cells, occasional eosinophils may be seen
NECROBIOTIC XANTHOGRAHULOMA: systemic disease associations

- Associated in 80% of cases with myeloma, typically of IgGκ-restricted plasma cells
- Also described in patients with
  - Scleroderma (Russo, Cutis, 2002)
  - Asthma
  - Systemic amyloidosis (Westermann et al. Med Clin 2001)

Differential diagnosis

- Necrobiosis lipoidica
- Granuloma annulare
- Rheumatoid nodule

Massive necrobiosis
Cholesterol clefts
Bizarre multinucleated giant cells
Touton giant cells

Palisaded neutrophilic and granulomatous dermatitis associated with systemic diseases

- Connective tissue disorders
  - Rheumatoid arthritis
  - Sjögren’s syndrome
  - Vasculitis (Churg-Strauss, Wegener’s etc)
- Inflammatory bowel disease
- Infection
- Carcinomas
- Endocrine disorders:
  - Thyroiditis
  - Diabetes
- Drug reactions
  - Immuno regulatory drugs: ACE inh, β-blockers, Ca-channel blockers, Lipid lowering agents, antihistaminics.
  - Sulfonamides, Methotrexate

Clinical features

- Urticarial
- Livedoid
- Papules
- Plaques
- Nodules
- Indurated linear bands
Palisaded neutrophilic and granulomatous dermatitis

**Histological features**

- Urticaria-like lesions
- Leukocytoclastic vasculitis
- Palisaded granulomatous reaction
- Dermal fibrosis/NLD-like lesions

Neutrophils and nuclear dust
Vasculitis
Thrombosis
Atypical clinical presentation
Cutaneous granulomatous Crohn's disease

- Large bowel involvement (80%)
- No correlation with activity of the disease
- Perianal, genitalia, perineum, lips, lower extremities, colostomy sites
- Contiguous or not ('metastatic' Crohn's dx)
- May precede bowel involvement

Cutaneous granulomatous Crohn's disease

- Single or multiple
- Papules, plaques, skin tags, nodules, ulcers, edema, deep fissures, abscesses, fistula formation

Cutaneous granulomatous Crohn's disease

Histological features

- Non-caseating granulomas
- Necrobiosis
- Granulomatous vasculitis
- Granulomas in lymphatics (diagnostic)
- Palisading neutrophilic and granulomatous dermatitis

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