FO92 – Granulomatous Disorders of the Adult Skin
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Disclaimer:

• Conflict of Interest
  – None

• Financial Associations
  – None

• Off-label drug usage may be discussed
Practice Gap:

Granulomatous disorders represent a unique group of diseases, both noninfectious and infectious, that require the utmost clinical pathologic correlation combined with a keen sense of inquiry for underlying systemic disease and immunosuppression.

Dermatologists need to be able to differentiate these entities, evaluate patients for specific underlying systemic disease (i.e. from diabetes to cancer), and treat them with a wide range of immunosuppressant to anti-infectious medications.

By being aware of the skin manifestations of these abnormal physiologic responses dermatologists can improve patient safety, outcome and health care costs.
Objectives:

- Differentiate the Non-infectious granulomatous diseases (NIGD) and Infectious granulomatous diseases (IGD) of adult skin.
- Recognize the cutaneous clinical, histological and systemic manifestations of NIGD and IGD.
- Determine the best evidence based therapeutic modalities for the treatment of NIGD and IGD.
Granulomatous Disorders of the Skin

Non-infectious GD

Palisading Granulomas:
- GA
- EGCG
- NL
- RN
- Reactive GD

Epithelioid Granulomas:
- Sarcoidosis
- Cutaneous Crohns
- Orofacial Gran
- Gr. Rosacea/POD

Xanthomatous Granulomas
- Adult onset XG
- Adult onset APXG
- NXG
- MC Reticulohistiocytosis
- Rosai-Dorfman
- Xanthoma Disseminatum

Other:
- Gr. Vasculitis
- Gr. Lymphoproliferative
- Foreign Body Reactions
- Gr. Drug Reactions

Infectious GD

Caseating Granulomas
- Tuberculosis
- Leprosy
- Atyp. Mycobacterium
- Leishmaniasis

Suppurative Granulomas
- Deep Fungal
- Pyodermas
- Gr. STD
Granuloma Annulare

- **Pathogenesis:**
  - Th1 lymphocytes activate macrophage expression of TNF-alpha and matrix metalloproteinases 2,9 and macrophage mucin-1 peptide activating IL-6/10/12 leading to granuloma formation to unknown antigen.
  - Drug reaction

- **Clinical:**
  - Localized, Generalized, Atypical

- **Histological:**
  - Palisaded or Interstitial histiocytic infiltrate.
  - MUCIN!!!!!!

- **Systemic:**
  - Generalized or Atypical forms and >60
  - DM/Autoimmune thyroiditis/HIV, Hep B +C/Elevated Lipids/Lymphoproliferative and visceral malignancy

- **Treatment:**
  - Topical/IL/oral steroids/cryotherapy/phototherapy/laser
  - Oral agents: Hydroxychloroquine, MTX, Mycopenolate mofetil, Acitretin, TNF inhibitors, Antibiotics
Elastolytic Giant Cell Granuloma

Pathogenesis:
- Presumed severe actinic degeneration of skin elastic tissue modifying it to an antigenic form

Clinical:
- Annular plaque with central clearing to polymorphic (50% cases isolated lesion)

Histological:
- Granuloma formation (superficial to mid dermis) distributed peripherally to a central zone of dermal atrophy and loss of elastic tissue. Elastophagocytosis. No necrobiosis of collagen, NO MUCIN!!!!!!
- Elastophagocytosis is not specific

Systemic Manifestations:
- DM, Sarcoidosis
- Malignancy: Lymphoproliferative (AML, Peripheral T cell lymphoma, MGUS) Solid (prostate)

Treatment:
- Steroids, Calcineurin inhibitors, Retinoids
- Hydroxychloroquine, Minocycline, Dapsone, Cyclosporine, Adalimumab
- Laser (Pulse dye, CO2)

Palisading Granulomas:
Necrobiosis Lipoidica

Pathogenesis:
- T-cell mediated hypersensitivity reaction to altered collagen production with immunologically mediated vascular disease and trauma

Clinical:
- Early/Middle/Late Stages (85% on the lower legs)

Histological:
- Multiple layers of hyalinized and necrotic collagen, surrounded by histiocytes and lymphocytes.
- NO MUCIN

Systemic:
- DM/Retinopathy and nephropathy/Ocular inflammation (Retinal vasculitis in Non-DM) / Joint immobility

Treatment:
- Steroids, Calcineurin inhibitors, Retinoids
- Hydroxychloroquine, Pentoxifylline, ASA, Cyclosporine, Mycophenolate mofetil, Thalidomide, Biologics (IL-infliximab), Retinoids, JAK inhibitor
- Pulse Dye, PDT, Hyperbaric oxygen, topical PUVA , UVA-1

Palisading Granulomas:
Rheumatoid Nodules

- Pathogenesis:
  - Presumed complement-mediated process following RF immune complex deposition in small vessels that leads to immunologically-mediated vessel injury with fibrin deposition and subsequent monocyte induced granuloma formation.
  - Drug reaction

- Clinical:
  - Classical RN/ Rheumatoid nodulosis/Accelerated rheumatoid nodulosis

- Histological:
  - Granuloma formation with evidence of necrotic collagen rimmed by eosinophilic fibrin and palisading mononuclear cell infiltrate. NO MUCIN

- Systemic:
  - Rheumatoid arthritis (high titer RF, anti-CCP) with internal nodules can develop in the lung, liver, and heart
  - The presence of RN at baseline is a marker of extra-articular involvement and severe disease, and a predictor of subsequent joint damage

- Treatment:
  - Asymptomatic
    - Leave alone
  - Symptomatic
    - Intralesional injections, surgical excision
Accelerated Rheumatoid Nodulosis:

-Medications:
  MTX/Azathioprine/Biologics
  Aromatase Inhibitors – Letrozole and Anastrozole
    - Joint Bone Spine 2011 Jan;78(1):62-4

- Pathogenesis
  1. HLA DRB-1 or polymorphism of the methionine synthetase reductase gene
  May also occur in lungs - J Clin Rheumatol 2009 (Feb) 15(1):29-30

-Treatment:
  D/C offending agent
  Trial of Plaquinil, Colchicine, Penicillamine, Sulfasalazine, Biologics
Reactive Granulomatous Dermatitis

- **Pathogenesis:**
  - Unknown: ?immune complex deposition reaction
  - Drug reaction

- **Clinical:**
  - IGD-like (Rope sign)/GA-like (Polycyclic) /PNGD-like (Papulo-Nodular)
  - Drug induced RGD or IGDR (interstitial granulomatous drug reaction)

- **Histological:**
  - IGD/GA-Like
    - Sparse palisaded and interstitial histocytic inflammation, degenerated collagen and variable PMNs
  - PNGD
    - Palisading granuloma with degenerated collagen, intense neutrophilic inflammation +/- LCV
  - IGDR
    - Similar to IGD/GA-like but with vacuolar interface change and atypical lymphocytes
    - [*All with no increase mucin]*

- **Systemic:**
  - RA, SLE, Other autoimmune: Sjogren’s, Scleroderma, Autoimmune thyroiditis/hepatitis. IBD
  - MDS/ Lymphoproliferative disorders

- **Treatment:**
  - Steroids
  - Hydroxychloroquine, Dapsone, MTX, Mycophenolate mofetil, Biologics
Reactive Granulomatous Dermatitis

- Interstitial Granulomatous Dermatitis
  “type or like”
- Granuloma Annulare
  “type or like”
- Palisaded Neutrophilic Granulomatous Dermatitis
  “type or like”
- Drug induced RGD GA-type
- Interstitial Granulomatous Drug Reaction
Sarcoidosis

- **Pathogenesis:**
  - Presumed over exuberant Th-1/Th-17 mediated T cell inflammation to unknown agent
  - Genetic, environmental, immunologic and drug induced
- **Clinical:**
  - Specific (+underlying granuloma) or Non-specific (No underlying granuloma)
- **Histological:**
  - Non-caseating granulomas
- **Systemic:**
  - Fatigue, cognitive failure and depressive symptoms, hypothyroidism
  - Internal organ involvement: Ocular/Pulmonary/Cardiac/Neurologic
  - Associations: Testicular cancer/Lymphoma
- **Treatment:**
  - Steroids
  - Minocycline, Hydroxychloroquine, Methotrexate, Azathioprine, Biologics, Apremilast
Cutaneous Crohn’s

• Pathogenesis:
  • Presumed a Th-1 driven delayed-type hypersensitivity reaction

• Clinical:
  – Metastatic/Perigenital + Peristomal/Oral
  – Erythematous edema

• Histological:
  – Non-caseating granulomas with MNGC’s and granulomatous perivascular inflammation

• Systemic:
  – Inflammatory Bowel Disease
  – MCD is in temporal discordance with gastrointestinal involvement and removal of affected bowel doesn’t modify MCD course
  – Overlap with HS, OFG, Anogential granulomatosis

• Treatment:
  – Steroids
  – Metronidazole, Azathioprine, Biologics (Adalimumab)
Orofacial Granulomatosis

- **Pathogenesis:**
  - Presumed reactive inflammation to an unknown allergen.
  - Common sensitivities: Cinnamon-related compounds/Benzoic Acids

- **Clinical:**
  - Cheilitis granulomatosis/Angular cheilitis/Labial swelling + fissuring/Gingival enlargement/Facial erythema + edema/
    Mucosal ulceration + tags or cobblestoning
  - Anogential granulomatosis

- **Histological:**
  - Non-caseating epithelioid granulomas that are paralymphatic and
    intralymphatic +/- Dermal edema and Dilated lymphatics

- **Systemic:**
  - Melkerson-Rosenthal Syndrome (facial paralysis)
  - Gustatory defects and Regional adenopathy
  - Assoc: Psoriasis
    - Crohn's - in children that have OFG check + anti-saccharomyces cerevisiae antibody A levels
      (J Ped Gastro Nutr 2017;65:388)

- **Treatment:**
  - Steroids, Diet modification
  - Doxycycline, Azithromycin
  - HCQ, MTX, AZA, Biologics (Infliximab/Adalimumab)
### Granulomatous Rosacea and POD

#### Gr. Rosacea
- **Pathogenesis:**
  - Cathelicidin antimicrobial peptides, Demodex
- **Clinical:**
  - Red brown papules/rhinophyma/LMDF
- **Histological:**
  - Lymphohistiocytic inflammation and non-caseating epitheliod granulomas that are folliculocentric
  - Necrosis in Lupus Miliariais Disseminata Facei variant
- **Systemic:**
  - Ocular involvement, metabolic syndrome, migraines, RA UC, dementia (JAAD 2017 Oct 26 ePub)
- **Treatment:**
  - Metronidazole
  - Tetracyclines
  - Dapsone
  - Isotretinoin
  - Ivermectin
  - Azelaic acid

#### Gr. Periorificial Dermatitis
- **Pathogenesis:**
  - Presumed granulomatous inflammation due to a non-specific reaction to unknown allergen with focal disruption of the follicular epithelium
- **Clinical:**
  - Yellow-brown monomorphic papules in a periorificial distribution
- **Histological:**
  - Granulomatous perifollicular inflammation
- **Systemic:**
  - None
- **Treatment:**
  - Tetracyclines or macrolides
  - Calcineurin inhibitors, Azelaic Acid
  - Topical antibiotics
    - Erythromycin
    - Metronidazole
    - Sulfacetamide
    - Clindamycin
Adult Onset XG

- **Pathogenesis:**
  - Reaction to trauma, infection, malignancy

- **Clinical:**
  - Isolated/Multiple

- **Histological:**
  - Non-LCH histiocytosis [CD68 (+), S100 and CD1a (-)]

- **Systemic:**
  - Isolated: None
  - Multiple:
    - Cervical spine and Intracardiac infiltration
    - Lymphoproliferative malignancy (Essential thrombocytosis/CLL/Large B cell Lymphoma/MGUS to MM)

- **Treatment:**
  - Isolated: excision
  - Multiple: Spontaneous resolution / Treat underlying malignancy
Adult Onset Asthma with Periocular XG

- **Pathogenesis:**
  - Systemic immunologic derangement with concurrent bronchiolar and ocular adnexal dysfunction.

- **Clinical:**
  - Periorbital yellow-orange plaques, nodules to masses (bilateral)
  - Extends to anterior orbital fat, extraocular muscles and/or the lacrimal gland(s)
  - No optic nerve damage may cause obstruction

- **Histological:**
  - Non-LCH histiocytosis [CD68 (+) S100 and CD1a (-)]

- **Systemic:**
  - Adult onset asthma /Lymphadenopathy
  - Hematologic malignancies reported : CLL/SLL, multiple myeloma, non-Hodgkin’s lymphoma.
  - Associations: Diabetes /Lymphoplasmacytic sclerosing pancreatitis/Rosai- Dorfman

- **Treatment:**
  - Surgery
  - Corticosteroids and radiotherapy
Necrobiotic xanthogranuloma

**Pathogenesis**
- Paraprotein triggering an immune complex formation and inflammation with subsequent granuloma formation
- Reactive inflammation. No presence of monoclonal plasma cells
- TCR-PCR clonality can distinguish reactive NXG from malignant granulomatous MF

**Clinical**
- Erythematous yellow-orange plaques that develop telangiectasia and may ulcerate
- Periorbital location common with secondary eye inflammation (episcleritis, uveitis)

**Histologic**
- Non-LCH histiocytosis [CD68 (+), S100 and CD1a (-)]
- Prominent palisading granulomas with bizarre-appearing foreign body giant cells around cholesterol cleft

**Systemic**
- MGUS to Multiple myeloma IgG kappa > IgG lambda > IgA (25% - Clin Lymphoma Myeloma Leuk 2016;16:447.)
- CTCL, Lymphoma, Leukemia
- Infiltration of internal organs {heart, lungs, eyes}

**Treatment Options:**
- No curative therapy – consider treating paraprotein
- Topical / intralesional corticosteroids, IFN, nitrogen mustard
- Chlorambucil, Melphalan, Fludarabine, Cladribine, Steroids, Interferon alpha 2b, Azathioprine, Cyclophosphamide, Methotrexate therapy, Plasmapheresis, EC photophoresis, IVIG, Rituximab, Thalidomide/Lenalidomide, Hydroxychloroquine
- Surgical excision, radiation
Multicentric Reticulohistiocytosis

- **Pathogenesis:**
  - Unknown

- **Clinical:**
  - Solitary/Multicentric (Periungal coral beading)

- **Histological:**
  - Non-LCH histiocytosis [CD68 (+) S100 and CD1a (-)]
  - Histiocytes demonstrate a “ground glass appearance” - i.e. copious eosinophilic, granular cytoplasm.

- **Systemic:**
  - Solitary: None
  - Multicentric (organ infiltration):
    - Weight loss/anorexia / dysphagia/ pruritus/weakness /myalgia /fever/malaise
    - Systemic erosive arthritis and lymphadenopathy
  - Associations:
    - Autoimmunity (PBC, SS, SLE, DMM, Sjorgens)
    - Malignancy (solid/lymphoproliferative)
    - Pregnancy (solitary and multicentric)

- **Treatment:**
  - Steroids, hydroxychloroquine, methotrexate, leflunomide, mycophenolate mofetil, azathioprine, cyclophosphamide, cyclosporine, chlorambucil, dapsone, TNF-alpha inhibitors (etanercept, infliximab, adalimumab, golimumab), Anakinra, Tocilizumab (anti-IL6) bisphosphonates
**Xanthomatous Granulomas**

**Rosai Dorfman**

* Pathogenesis:
  - Unknown reactive process
  - Mutations in SLC29A3 and RAS-MAP2K1 pathway (Mod Pathol 2017;10:1367)

  - Clinical:
    - Painless bilateral cervical adenopathy and red to red-brown papules or nodules in skin
    - Nodular inflammatory infiltrate by large foamy histiocytes (dermis and lymphatics)
    - Emperipolesis

  - Histological:
    - S100 (+) no beirbeck granules with nodular inflammatory infiltrate by large foamy histiocytes (dermis and lymphatics) + Emperipolesis [CD68 (+) S100 (+) and CD1a (-)]

  - Systemic:
    - Lymphadenopathy, fever, elevated ESR, leukocytosis, anemia, MGUS, organ infiltration
    - Associations: Crohns/Bloodline malignancies

  - Treatment:
    - Surgery or Radiation for vital organ involvement/ Corticosteroids/ MTX/Chemotherapy
    - Interferon, PDT, Cobimetinib (MAPK kinase (MEK) inhibitor – NEJM 2017;377:2398.)
Xanthoma Disseminatum

• Pathogenesis:
  – Remains elusive

• Clinical:
  – Orange-red papulo-nodules to plaques (inverse location)

• Histological:
  – Non-LCH, xanthoma cells, Touton GC, mild inflammatory infiltrate [CD68 (+) S100 and CD1a (-)]

• Systemic:
  – Diabetes insipidus, other hypopituitarism, dysphagia, dysphonea, ocular (corneal/conjunctiva), lipid abnl

• Treatment:
  – Cyclophosphamide, Azathioprine, Vinblastine, 2-chlorodeoxyadenosine, Cladribine, (Skin only C02 laser)
Other Granulomas

• Granulomatous Vasculitis
  – ANCA - associated
ANCA-associated vasculitis

• ANCA-associated vasculitides were renamed (2012 Chapel Hill consensus)
  – Granulomatosis with polyangiitis (GPA), formerly Wegeners
  – Eosinophilic granulomatosis with polyangiitis (EGPA), formerly Churg-Strauss
  – Microscopic polyangiitis

• ANCA testing is 85% sensitive, 98% specific, but can be confusing
  – ANCA: Pt serum + human neutrophils +IIF, staining pattern described (c=cytoplasm, p=perinuclear)
    • C-ANCA = GPA, MPA
    • P-ANCA = EGPA, MPA, plus rheumatologic disease, IBD, other
    • Mixed patterns, atypical = drug, IBD, rheumatologic disease
  – ELISA confirmatory testing: C-ANCA = PR3 antibodies, P-ANCA=MPO antibodies
Granulomatous vasculitis

- **Granulomatosis with polyangiitis**
  - 90% rhinorrhea, sinusitis, nasal ulcerations, epistaxis, fever, weight loss, malaise; failure to respond to sinusitis rx
  - Cough, dyspnea, pulm infiltrates (70%)
  - Glomerulonephritis (85%)
  - Ophthalmic (60%)
  - Cutaneous findings (50%)
    - Palpable purpura, ulcers, SQ nodules
  - C-ANCA/PR3 (90%), P-ANCA/MPO (10%)
  - Treat with Rituximab (or steroids + cyclophosphamide), maintenance w/ MTX or AZA

- **EGPA**
  - Churg strauss granulomatous papules on elbow

- **Giant cell arteritis**
  - Age over 50 (most >70), ESR >50, hard tender pulsating nodule, scalp necrosis, blindness
  - May have granulomatous vasculitis on biopsy
  - Treat w/ steroids
Other Granulomas

• Granulomatous Lymphoproliferative Disorders
  – Gr. T cell Lymphoma
    • Gr MF
    • Gr Slack Skin
  – Lymphomatoid Granulomatosis
Granulomatous MF/Slack Skin

- **Pathogenesis:**
  - Rare subtype of MF with granulomatous inflammation or granulomatous inflammation causing slack skin changes
- **Clinical:**
  - Pendulous lax skin
  - Prefers axilla/groin
- **Histological:**
  - Granulomatous infiltrate with small atypical T-cells, macrophages, MNGC, elastic fiber destruction & elastophagocytosis
  - Immunophenotype: CD3+, CD4+, CD8 –
- **Systemic:**
  - Indolent course
  - Associated with Hodgkin’s Lymphoma
- **Treatment**
  - As for CTCL-MF type
Lymphomatoid Granulomatosis

- **Pathogenesis:**
  - EBV driven lymphoproliferative disorder
  - Seen in medication induced immunosuppression (MTX, AZO) as well as HIV & T-cell defects

- **Clinical:**
  - Lung >>>>skin, nervous system, kidneys
  - Skin: Non-specific papulo-nodules to ulcerations

- **Histological:**
  - Angiocentric/destructive granulomatous polymorphous inflammation with atypical EBV + B-cells and is also T-cell rich
    - Grade I (Low grade) - spontaneous resolution
    - Grade II-III (High grade) - risk for transformation to T-cell rich Large B-cell Lymphoma
  * DDx in atypical vasculitis presentations

- **Systemic:**
  - Cough, dyspnea, pulmonary failure, fever, malaise, weight loss, neurologic abnormalities (mental status change, ataxia, seizures)

- **Treatment:**
  - Rituximab, Interferon
  - Chemotherapy (Etoposide, Doxorubicin)
  - Stem cell Transplant.
Other Granulomas

• Foreign body reactions
  – Tattoo pigment
  – Cosmetic fillers
  – Other:
    • Drugs
    • Minerals
    • Glass, Plants etc.
Other Granulomas

• Granulomatous Drug Reactions
  – Drug-induced GA
  – Drug-induced Accelerated Rheumatoid Nodulosis
  – Reactive Granulomatous Dermatitis to Drugs & Interstitial Granulomatous Drug Reaction
  – Drug-induced Sarcoidosis
<table>
<thead>
<tr>
<th>Drugs that cause Granuloma annulare:</th>
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<tbody>
<tr>
<td>Allopurinol</td>
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<tr>
<td>Amlodipine</td>
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<td>Anti- TNF α agents</td>
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<td>BRAF Inhibitors (Vemurafenib)</td>
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<td>Immune Checkpoint Inhib.</td>
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<td>Immunizations</td>
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<td>PEG interferon α</td>
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<td>Secukinumab</td>
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<td>Topiramate</td>
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Drugs that cause Accelerated Rheumatoid Nodulosis:
- Anti-TNF α agents
- Aromatase inhibitors
- Azathioprine
- Leflunomide
- Methotrexate*
Drugs that cause Drug Induced RGD and IGDR:
ACE inhibitors
Anti-TNF α agents
Calcium channel blockers
Lipid Lowering
Anti-seizure
Topiramate
Drugs that cause Sarcodiosis:

Anti-TNF α agents
BRAF Inhib. – Vemurafenib
Chemotherapy
Immune Checkpoint Inhib.
  - Pembrolizumab
  - Ipilimumab
  - Nivolumab
Interferon α
IL-Ra -Anakinra
Rituximab
Infectious granulomatous diseases:
Caseating granulomas

Tuberculosis

- Pathogenesis:
  - *Mycobacterium tuberculosis*

- Epidemiology:
  - TB is the 2nd leading cause of death worldwide – 8.6 million people diagnosed, 1.3 million died in 2012
  - Skin involvement is rare: 1-2% of all cases

- Clinical:
  - Tuberculosis verrucosa cutis – warty plaques on the extremities from direct inoculation (“prosector’s wart” or walking barefoot where pulmonary-TB infected patients have expectorated contaminated sputum)
  - Lupus vulgaris – red-brown papules coalesce to plaques with gelatinous quality
  - Scrofuloderma – suppurating nodule over affected lymph nodes with ulcerating fistulae
  - Miliary tuberculosis – discrete minute red-to-violaceous papulopustules
  - Rare forms: tuberculosis cutis orificialis, tuberculous gumma, tuberculous chancre
  - Tuberculid reactions:
    - Lichen scrofulosorum: grouped lichenoid papules
    - Papulonecrotic tuberculid: dusky papules with central necrosis
    - Erythema induratum: painful ulcerated nodules on posterior legs
    - Nodular tuberculid: bluish-red nodules on legs
    - Nodular granulomatous phlebitis: subcutaneous nodules along leg veins

- Histological:
  - Tuberculoid granuloma with central histiocytes, giant cells, and rim of lymphocytes; usually with caseation necrosis (plus calcification and fibrosis)
  - Caseation necrosis should make one consider infectious causes of granulomatous inflammation

Treatment:
- Multiple drug treatment: refer to CDC – 8wks daily INH, rifampin, pyrazinamide, and ethambutol or streptomycin, then 16 weeks of INH and Rifampin
Leprosy

- **Pathogenesis:**
  - *Mycobacterium leprae*

- **Epidemiology:**
  - WHO estimate: 220,000 new cases per year, likely underreported. 200/year in the US (Travel, Gulf coast – armadillo)

- **Clinical:**
  - Manifestations vary by immune response
    - Polar tuberculoid (TT) – few macules/patch, sharp margin, usually reduced sensation
    - Borderline tuberculoid (BT) – many macules/patches, sharp margin, reduced sensation
    - Mid-borderline (BB) – macules plaques, both sharp margins and diffuse, reduced sensation
    - Borderline lepromatous (BL) – multiple plaques and nodules, widespread, sensory loss in some
    - Lepromatous leprosy (LL) – plaques, papules, nodules, thickening, widespread, sensory loss in some

- **Histological:**
  - Varies by immunologic response from well-organized epithelioid granulomas involving nerves with rare necrosis, to disorganized aggregates of lymphocytes and histiocytes or sheets of histiocytes; neurotropism is a key feature in all

- **Treatment:**
  - Varies by disease type – dapsone, rifampin, and clofazimine are mainstays; often 1-2 years of treatment

Caseating Granulomas:
Atypical mycobacteria

**Pathogenesis:**
- Nontuberculous mycobacteria (NTM) include over 170 species, can often cause skin and soft tissue infections (SSTI)
- Divided into rapidly growing and slow growing mycobacteria
- RGM: *M. fortuitum, M. chelonae/abscessus, M. mucogenicum, M. smegmatis*, and early pigmenting RGM
- SGM: *M. marinum, M. ulcerans, M. kansasii, M. haemophilum, M. avium complex* and more

**Epidemiology:**
- NTM are ubiquitous – water, soil, plants, animals; tap water is a major reservoir, can contaminate hospital equipment – pedicure/nail salon outbreaks

**Clinical:**
- Varies by species – generally for dermatologists can be disseminated disease (skin seeding in severely immunocompromised patients) or primary skin and soft tissue infection (in suppressed or normal hosts)
- Disseminated disease (HIV, organ transplant, iatrogenic suppression, leukemia): red, draining nodules, ulcerations, abscesses
- SSTI: sporotrichoid nodules, “fish-tank” granuloma, Buruli ulcer, abscesses, cellulitis, sinus tracts, panniculitis, etc

**Histologic:**
- May vary somewhat by organism and clinical morphology; generally intense granulomatous inflammation with neutrophils and necrosis; organisms may be seen on special stains, but cultures and sometimes PCR is necessary to ID

**Treatment:**
- Varies by organism type; most require multidrug therapy and can develop resistance rapidly to single agents.
- Cultures may be slow to grow but should be performed for antibiotic sensitivities (although educated guesses can be made once speciation is available)
- Most cases should be co-managed with an infectious disease doctor
- Local surgical treatment is indicated in some cases
Leishmaniasis

- **Pathogenesis:**
  - Leishmania infection – multiple species, divided into “New World” (Western) and “Old World” (Eastern Hemisphere)
  - Transmitted through bite of female sandfly
  - 4 types: cutaneous leish, diffuse cutaneous leish, mucocutaneous leish, and visceral leish
- **Epidemiology:**
  - 12 million infected, 2 million new cases per year, 20-30,000 deaths annually
- **Clinical:**
  - Subclinical, self-healing disease is common
  - Cutaneous lesions: solitary papules at bite site, enlarge into nodules/plaques, often ulcerate (painless); may have satellite lesions, multiple primary lesions, or sporotrichoid spread
  - Patients can have persistent leish in healed scars and lymph nodes, and can get delayed mucocutaneous disease depending on the organism and immune response
- **Histological:**
  - Ulceration, intense dermal inflammation with variable granulomas and histiocytes; histiocytes with small organisms
  - Confirmatory PCR testing is available through the CDC and speciation can impact follow-up and treatment
- **Treatment:**
  - High cost, toxicity, drug resistance, access issues, paucity of high quality data all complicate treatment
  - Drugs are available through the CDC and patients should be treated in conjunction with an ID doctor
  - Stibogluconate, amphotericin, liposomal ampho, or miltefosine
  - Pentamodine, other agents pending intolerance/response
  - Need long-term follow up of all patients
Deep fungal infections

• Pathogenesis:
  – Generally due to Blastomycosis, Coccidioidomycosis, Cryptococcus, Histoplasmosis, and Sporotrichosis

• Epidemiology:
  – Most are acquired through inhalation and secondary spread to the skin; direct inoculation can occur
  – Blastomyosis: Ohio/Mississippi river valleys
  – Coccidioidomycosis: San Joaquin Valley, SW US (incidence and area increasing due to climate change)
  – Cryptococcus: Pigeon droppings/soil, widespread, seen usually in immunocompromised hosts
  – Histoplasmosis: Contaminated soil/bat-bird droppings, caves, often seen in immunocompromised hosts
  – Sporotrichosis: Rose thorns, moss, other contaminants, causes infection from direct inoculation

• Clinical:
  – Varies by infectious agent; many can cause nodules, papules, ulcerated, and/or verrucous/crusted lesions
  – Characteristic lymphocutaneous spread seen in sporotrichosis

• Histologic:
  – Often a dense mixed infiltrate with neutrophils, histiocytes, giant cells and acute granulomas with overlying pseudoepitheliomatous hyperplasia
    – Blastomycosis – large yeast with broad based, single bud
    – Coccidioidomycosis – thick-walled spherule with endospores
    – Cryptococcus – small narrow-based budding yeast forms
    – Histoplasmosis – very small narrow-based budding, intracellular
    – Sporotrichosis – round/cigar-shaped yeast, rarely visualized (may need EM)
Deep fungal infections

- Treatment:
  - Varies by organism
  - All patients should be evaluated for potential immunosuppression, and in most cases skin findings represent likely secondary seeding from a systemic process (particularly for cryptococcus)
  - Treatment should be conducted in consultation with an infectious disease physician and tailored towards the individual infection
  - Itraconazole, amphotericin, voriconazole, posaconazole, debridement all have a role
Suppurative Granulomas

Blastomycoses like-pyoderma

• Pathogenesis: Abnormal rxn to bacteria, often Staph, in immunosuppressed pts
  *Must exclude: SCC, Deep fungal, Atypical Myco bromoderma, iododerma, PG
• Clinical: Verrucous to vegetative plaques with pustules and elevated border
• Histological: PEH and abscesses
• Systemic: Assoc: Alcoholism, Malnutrition
• Treatment:
  1. Cultures to determine cause & guide antibiotic Tx
  2. Other: acitretin, potassium iodide
     CO2 laser, cryotherapy, curettage,

Bacterial causes:
  S. aureus/Beta-hemolytic streptococci
  E.coli/Proteus/Pseudomonas
  Clostridium perfringens/Prevotella
Granuloma inguinale

- Pathogenesis: STI from *Klebsiella granulomatis*
- Epidemiology: Rare in US, more Tropical/Subtropical areas
- Clinical: Painless beefy to velvety red papules/plaques
- Histological: Dense infiltrate of lymphocytes, neutrophils, plasma cells and histiocytes (with Donovan bodies)
- Treatment:
  - Doxycycline
  - Azithromycin
  - Erythromycin
  - Ciprofloxacin
  - Sulfa
Lymphogranuloma venereum

- **Pathogenesis**: STI from *Chlamydia trachomatis* (*serovars L1,2,3*)
- **Epidemiology**: Tropical areas, Increase in Europe (Sweden, Spain)
  - 85% HIV +, MSM, Co-infection with GC/Syphilis
- **Clinical**: Rarely seen painless ulceration, f/b painful inquinal adenopathy
- **Histological**: Lymph node – stellate central necrosis with neuts and palisading granulomatous rxn + MNGC
- **Treatment**:
  - Doxycycline
  - Azithromycin
  - Erythromycin
Selected References:

- **GA**

- **EGCG**

- **NL**

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• TB & Leprosy
• Atypical Mycobacteria
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