## Granulomas

*by Amanda Laska, MD and Danielle Neal, DO*

| Disease | Epidemiology | Pathogenesis | Clinical features | Histopathology | Treatment |
|---|---|---|---|---|---|
| **Sarcoidosis** | Bimodal: ages 25-35 and 45-65; more often in African-Americans, esp. women; children may develop before age 4 or at ages 8-14 | Th1 CD4+ pattern upregulated following antigen stimulation; unknown antigen (perhaps infection due to seasonality); HLA-DRB1, -DQB1 good prognosis | 25% with skin involvement; red-brown papules/plaques on head, neck, upper trunk/arms; hypopigmentation, nodules, alopecia; erythema nodosum a/w good prognosis; may koebnerize with trauma | Superficial and deep collections of epithelioid histiocytes with sparse lymphocytic infiltrate; Langhans giant cells possibly containing asteroid/Schaumann bodies | Corticosteroids (topical, IL, systemic)<br>Antimalarials<br>Tetracyclines<br>PUVA<br>Methotrexate<br>TNF-alpha inhibitors |
| **Granuloma annulare** | 2:1 female to male affected; 2/3 younger than 30 years old; no racial predilection; *Classic:* children, young adults; *Generalized:* middle-aged females; *SubQ:* children (boys>girls) < 6 years old | Unknown: possibly incited by infection, trauma, UV light; Th1-type inflammation; can exhibit Koebner response; possible relationship to HLABw35 | *Classic:* annular plaque on dorsal hands/feet, arms, legs and trunk; *Generalized:* 10-100s small coalescing papules on trunk/symmetric extremities, a/w lipid abnormalities; *Perforating:* papules with umbilication; *SubQ:* deep nodules common on dorsal foot | Two patterns:<br>1. Palisading histiocytes + lymphocytes around central altered collagen in superficial and deep dermis; mucin present<br>2. Interstitial: histiocytes, monocytes + mucin amongst altered collagen | Observation<br>Topical/IL steroids<br>Topical calcineurin inhibitors<br>Cryosurgery<br>PUVA/UVA1<br>IL IFN-gamma<br>*For systemic:*<br>Niacinamide<br>Isotretinoin<br>Triple antibiotics with rifampin, ofloxacin, minocycline |
| **Necrobiosis lipoidica** | >50% of patients have diabetes/glucose intolerance; 3:1 female to male ratio | Unknown: possibly vascular disease resulting from immunoreactants or microangiopathic change seen in glucose intolerance | Red-brown papules that coalesce and become yellowish, atrophic plaques with elevated border usually in pretibial region; rarely a/w squamous cell carcinoma, ulceration | Square punch with palisaded alternating tiers of epithelioid histiocytes and degenerated collagen: superficial and deep perivascular mixed infiltrate with plasma cells; mucin rare | *First-line:*<br>Topical/IL/oral steroids<br><br>*Second-line:*<br>Pentoxyfylline<br>ASA+dipyramidole<br>Niacinamide<br>PUVA/UVA1<br>Thalidomide<br>Surgery for severe lesions |
| **Annular elastolytic giant cell granuloma (Miescher's granuloma, actinic granuloma of O'Brien)** | Uncommon: middle-aged women (>40); however, children can also be affected | Unknown: may be variant of GA; possible cell-mediated response to antigen on actinically-damaged elastic fibers | Sun-exposed sites (head, neck, upper extremities): annular plaques with atrophic center and raised, erythematous border; multiple small papules usually < 10cm and fewer than 10 lesions that coalesce on sun-exposed skin | Upper-mid dermis with histiocytes, giant cells, lymphocytes with occasional palisading and no altered collagen; giant cells engulf elastin (elastophagocytosis) and stain positive with elastin stains; lack of elastin within granulomatous regions characteristic; no mucin | *Difficult to treat; responds poorly to:*<br>Topical/IL steroids<br>PUVA<br>Antimalarials<br>Retinoids<br><br>*Anecdotal reports:*<br>Cyclosporine<br>Chloroquine |
| **Cutaneous Crohn's disease (metastatic Crohn's forms non-caseating granulomas while other cutaneous findings do not necessarily)** | 20-45% of patients with Crohn's will develop cutaneous Crohn's; 2/3 are female | Th-1, Th-17 cytokines elevated; thought to be immunologic response to enteric bacteria | Genital lesions include labial/scrotal swelling, perianal lesions (fistulas, ulcers); non-genital lesions include oral/leg ulcers, non-descript erythematous papules/nodules in other locations | Epithelioid granulomas with surrounding lymphocytes, non-caseating, superficial and deep dermis involved | Severity unrelated to intestinal Crohn's<br><br>Metronidazole<br>Topical steroids<br>Treat underlying Crohn's |
| **Foreign body reaction** | *Non-biologic foreign bodies include:* tattoo, paraffin, silicone, silica, aluminum, beryllium, talc<br><br>*Biologic foreign bodies include:* hair, cactus, sea urchin spines, silk, bovine/hyaluronic acid fillers, corticosteroids | First have infiltrate of neutrophils followed by macrophages that engulf foreign material; then may form multinucleated giant cells | Acute erythema/inflammation initially followed by chronic inflammation manifested most commonly as red-brown papules, nodules or plaques at site of injury | *Several patterns possible:* lichenoid, pseudolymphomatous and granulomatous; in latter, may have predominance of either epithelioid histiocytes or Langhans-type giant cells that may contain inciting particles in cytoplasm | Depends on inciting agent:<br><br>*Tattoo reaction:* IL/topical steroids, surgical excision, lasers<br><br>*Other non-biologic agents:* excision<br><br>*Fillers reaction:* hyaluronidase/IL steroids |
| **Necrobiotic xanthogranuloma** | Rare condition affecting men and women equally; average age is sixth decade | Strongly associated with monoclonal gammopathy (IgG-k) and lymphoproliferative disorders (usually not aggressive); may elicit giant cell granulomatous response | *Cutaneous findings include:* yellow periorbital papules and plaques; trunk may form red-yellow annular plaques with atrophic center | In mid-dermis or subcutis, palisading granulomas composed of histiocytes, foam cells, giant cells surrounding zone of altered collagen; cholesterol clefts present | *Treatment of underlying paraproteinemia:*<br>Chlorambucil, melphalan or cyclophosphamide<br>Systemic corticosteroids<br>Radiation<br>CO2 laser<br>Plasmapheresis |
| **Rheumatoid nodule** | 20% of rheumatoid arthritis patients affected; associated with moderate to high titer RF | Interplay of genetic and environmental factors; link to HLA-DR4; aggregates of immune complexes consisting of RF may contribute | Skin colored, nontender nodules millimeters to centimeters in size over extensor joints, commonly elbows and dorsal hands; rapid appearance of multiple nodules a/w methotrexate/TNF inhibitors | In deep dermis/subcutis are palisaded histiocytes around fibrin; no mucin is present | Excision (often recur)<br>Intralesional steroids can reduce size<br>RA treatment usually has no effect |

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## Granulomas (cont.)

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| **Primary inoculation tuberculosis (cutaneous primary complex)** | Worldwide distribution, but commonly seen in developing and impoverished populations; less than 10% of infection leads to clinical disease | *M. tuberculosis* infection and interaction with T lymphocytes/mycobacterial antigens → increased MHC II antigens and IL-2 → macrophages accumulate and granulomas are formed; (patient with no immunity to bacteria) | Inoculation into skin/mucosa → painless, firm, red-brown papule develops 2-4 weeks after inoculation → erodes into sharply demarcated ulcer → spontaneous healing in 3-12 months with residual atrophic scar | Initial lesions may have a suppurative mixed dermal infiltrate (neutrophils, lymphocytes, plasma cells) and subsequently become granulomatous with necrosis, ulceration and caseation (weeks); AFB may be isolated | *First line:* Rifampin + isoniazid + pyrazinamide + ethambutol, Streptomycin<br>*Second line:* Thiacetazone Streptomycin Amikacin Quinolones |
| **Tuberculids** | Similar geographic distribution as primary inoculation tuberculosis<br>1. Erythema induratum: most common in women, bimodal with peaks in adolescence and menopause<br>2. Lichen scrofulosorum: all ages, most common in children with skeletal tuberculosis<br>3. Papulonecrotic tuberculid: favors children/young adults | Immune reaction in skin due to hematogenous dissemination of M. tuberculosis antigens from an internal focus; (patient with high cell-mediated immunity to bacteria) | 1. Erythema induratum: subcutaneous, erythematous nodules on bilateral calves → involution creating ulcers that heal with scarring<br>2. Lichen scrofulosorum: perifollicular, clustered, pink to yellow-brown, firm papules with scale; spontaneous resolution without scar<br>3. Papulonecrotic tuberculid: symmetric, widely scattered, dusky red papules and papulopustules +/- central necrosis; extensor surfaces and buttocks; spontaneous resolution with scar | 1. Erythema induratum: lobular panniculitis, may see extension of tuberculoid granulomas into lower dermis<br>2. Lichen scrofulosorum: non-caseating tuberculoid granulomas present in the upper dermis around hair follicles and sweat ducts<br>3. Papulonecrotic tuberculid: palisading histiocytes surrounding ulceration and areas of necrosis, leukocytoclastic vasculitis | *First line:* Rifampin + isoniazid + pyrazinamide + ethambutol, Streptomycin<br>*Second line:* Thiacetazone Streptomycin Amikacin Quinolones |
| **Leprosy (tuberculoid leprosy- TT, borderline tuberculoid- BT, borderline- BB)** | Prevalent in tropical environments, including India, Asia, Central Africa, Central and South America<br>Men and women equally affected; bimodal age distribution (10-15 and 30-60 years old) with no racial predilection | Incubation period from months to years; bacilli affects peripheral nerves, skin, mucous membranes, bones and viscera<br>1.TT: TH1 response (IL-2 and IFN), few bacilli<br>2.BT: TH1 > TH2, cell mediated immunity > humoral response (IL-2, INF > IL-4, IL-10)<br>3.BB: TH1 = TH2, cell mediated immunity and humoral response (IL-2, INF = IL-4, IL-10) | Clinical presentation highly dependent on immunologic status of infected patient<br>1.TT: few, localized, well demarcated hyper or hypopigmented plaques with raised border, hyperesthetic or anesthetic<br>2.BT: single infiltrated erythematous plaque with satellite lesions, well-defined, sharp borders, typically anesthetic<br>3.BB: many poorly defined erythematous plaques in asymmetric distribution, diminished sensation, hair absent | 1.TT: well defined, non-caseating granulomas composed of epithelioid cells, Langhans giant cells and lymphocytes scattered throughout dermis; characteristic extension into peripheral nerves/arrector pili<br>2.BT: non-caseating granulomas with significantly fewer lymphocytes and Langhans cells<br>3.BB: poorly formed granulomas with diffuse edema, absence of giant cells, rare neural involvement; if exhibiting more of a lepromatous pattern, may see more Virchow cells | *Paucibacillary (single lesion)*- single dose rifampicin, ofloxacin and minocycline<br>*Paucibacillary (<5 lesions)*- rifampicin monthly and dapsone daily over 6-9 months<br>*Multibacillary (>5 lesions)*- rifampicin monthly, clofazimine monthly, dapsone daily over 12-18 months |
| **Late syphilis (tertiary syphilis)** | Worldwide distribution, higher rate in homosexual men<br>Seen in 1/3 of untreated individuals months to years after initial infection | Small number of organisms and high cellular immune reactivity to treponema → infection of skin, CNS, CVS | 'Benign' tertiary syphilis involves gummas affecting bone and skin equally; nodular skin lesions that can ulcerate and heal with scarring<br>Cardiovascular and neurosyphillis are other manifestations of tertiary syphilis | Granulomatous pattern with visualization of small, non-caseating epithelioid cells, + plasma cells | Penicillin G is the treatment of choice for all stages of syphilis |
| **Cutaneous leishmaniasis** | *'Old World'*: Middle East, Eastern Mediterranean, North Africa, Asia; most common in men/all races<br>*'New World'*: Central and South America; Texas; most common in men/all races | *'Old World'*: *L. major*, *L. tropica* > *L. infantum*; transmission by *Phlebotomus* sandfly<br>*'New World'*: *L. mexicana*, *L. brasiliensis*; transmission by *Lutzomyia* sandfly | *Acute lesions:* papules that become nodular and ulcerated over time, leaving a scar<br>*Chronic lesions:* persistent over 1-2 years, discrete raised, non-ulcerated plaques; may involve mucosa | Tuberculoid granulomas (more common in chronic) present as a deep dermal infiltrate of lymphocytes, parasitized macrophages ('marquee' sign as organisms localize to periphery of macrophages) and plasma cells; pseudoepitheliomatous hyperplasia may be appreciated in long standing lesions | Antimonials (meglumine antimoniate, sodium stibogluconate) |
| **Granulomatous Rosacea** | Fair-skinned individuals, reported in both adults and children; also in association with HIV | *Unknown:* granuloma formation may be in response to *Demodex* | Persistent erythema and telangiectasia of bilateral cheeks, less often chin, nose, forehead; +/- papules, pustules, rhinophyma | Infiltrate of lymphocytes, histiocytes, plasma and giant cells arranged into tuberculoid granulomas; granulomas may be centered around ruptured hair follicles; necrosis only noted in 11% of cases | *Topical*: metronidazole, azelaic acid, tretinoin<br>*Oral:* tetracyclines, TMP/SMX, isotretinoin |
| **Periorificial dermatitis** | Young females; also reported in children | *Unknown:* may be variant of rosacea | Erythematous papules, pustules and occasionally vesicles arranged symmetrically around mouth, chin, and nasolabial folds; characteristic sparing of immediate perioral area | Stark parakeratosis surrounding follicular ostia, spongiosis and acanthosis characterizes the epidermis, associated perivascular lymphohistiocytic infiltrate; occasional tuberculoid granuloma noted in several cases | *Topical:* metronidazole, azelaic acid, tretinoin<br>*Oral:* tetracyclines, TMP/SMX, isotretinoin |
| **Lupus miliaris disseminatus faciei** | Males and females equally affected<br>Adolescents/young adults > elderly | *Unknown:* may be related to rosacea | Discrete red to yellow/brown papules localized over central face and periorbital region; lesions may last for months, then heal with scarring | Demarcated area of dermal caseation necrosis surrounded by multinucleated giant cells, histiocytes and lymphocytes; more often than not associated with ruptured pilosebaceous units, granulomas indicative of established lesions | *Topical:* metronidazole, azelaic acid, tretinoin<br>*Oral:* tetracyclines, TMP/SMX, isotretinoin |

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