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Neutrophilic dermatoses

By Alvaro J. Ramos, MD, FACP, and Marely Santiago-Vázquez, MD

- Heterogeneous groups of inflammatory skin disorders characterized predominantly by sterile neutrophilic infiltrates (epidermal, dermal or subcutaneous) with no evidence of infection or significant fibrinoid necrosis of vessel walls
- Cutaneous findings can vary depending on histological location of neutrophilic infiltrate ranging from:
  - Vesiculo-pustules (epidermal infiltrates)
  - Papules and plaques (dermal infiltrates)
  - Nodules and ulcerations (dermo-hypodermal infiltrates)

Neutrophilic dermatosis	Clinical findings	Important features	Associations	Histology	Treatment
Mainly epidermal neutrophilic infiltrates*					
Subcorneal pustular dermatosis (SPD) (Sneddon-Wilkinson disease)	Chronic, relapsing asymptomatic vesiculo-pustular dermatosis Affects mainly intetriginous areas (axilla, inframammary skin and groin) > flexor extremities and trunk Bilaterally symmetrical Recurrent crops of tiny flaccid vesicles or pustules with visible fluid levels ("hypopyon") →coalescing into annular, polycyclic or serpiginous pattern with central crusts on normal or erythematous skin	F>M; middle aged patients Hypopyon with accumulation of pustular component in dependent portion Mucosal involvement or scarring; may heal with post inflammatory hyperpigmentation Clinical and histologic features indistinguishable from SPD-type of IgA pemphigus	IgA gammopathy IgA multiple myeloma Pyoderma gangrenosum IBD	Intraepidermal (subcorneal) pustule filled with neutrophils +/- eosinophils Acantholysis may be present but not prominent Pustules sit on epidermis with no depression Negative DIF (vs. SPD-type IgA pemphigus)	Preferred: Dapsone Others: Phototherapy Systemic steroids
Amicrobial pustulosis of the folds (APF)	Chronic, relapsing course Sudden onset of follicular and non-follicular pustular eruption, usually symmetrically distributed Crusted, eroded plaques in body folds Onychodystrophy with suppurative paronychia is a common finding Non-scarring alopecia may occur	Young female with underlying autoimmune disease **Obligate dx criteria:*** Pustules involving 1 or more major body folds OR 1 minor body fold + anogenital area. Histology c/w APF Negative microbial culture from unopened pustule **Minor dx criteria:** Association with 1 or more autoimmune disorder (+) ANA (Titers > 1:160) Presence of 1 or more serum autoantibodies (anti-dsDNA)	Autoimmune diseases (SLE > ITP, Sjögren syndrome, autoimmune hepatitis, Hashimoto's thyroiditis, RA, IBD) (Consider screening for autoimmune disorders)	Intraepidermal (subcorneal) spongiform pustules +/- dermal infiltrate Negative DIF (Lupus band test may be (+) if underlying SLE)	Prevention of secondary infections Medium-dose systemic steroids Dapsone Colchicine Cyclosporine TNF-α inhibitors

Alvaro J. Ramos, MD, FACP, is a dermatology resident (PGY-2) at the University of Puerto Rico School of Medicine.

Marely Santiago-Vázquez, MD, is a dermatology resident (PGY-2) at the University of Puerto Rico School of Medicine.

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Mainly dermal +/- hypodermal neutrophilic infiltrates					
Sweet's syndrome (Acute febrile neutrophilic dermatosis)	Abrupt onset of tender, non-pruritic, well-demarcated, erythematous "juicy" papules/plaques (pseudovesiculation appearance) May develop ulcers, pustules, vesicles/bullae Usually heal without scarring Usually involves face and extremities Extracutaneous involvement: Constitutional symptoms +/- joints, ocular, lungs, bones, muscles, kidney, and liver. *Neutrophilic dermatosis of the dorsal hands*: variant with erythematous-to-violaceous plaques +/- bullae involving dorsal hands (features of Sweet's and PG).	F> M (4:1), middle-aged (+) Pathergy **Major dx criteria:**** Acute onset typical lesions Histology c/w Sweet's **Minor dx criteria:** Fever/constitutional symptoms Leukocytosis Presence of associated conditions Rapid response to systemic steroids	Infections: Strep, Yersinia, HIV, Hep B or C, mycobacteria Malignancy: Hematologic (**AML**, myelodysplasia), GU, breast, colon Drugs: G-CSF, ATRA, OCPs, TMP/SMX, minocycline, furosemide, NSAIDS IBD (eg, Crohns) CTDs (eg, SLE) Pregnancy Idiopathic (~50%)	Classic Sweet's: Diffuse/nodular dermal neutrophilic infiltrate with prominent papillary edema +/- mild LCV Neutrophilic dermatosis of the dorsal hands: Same as above, tends to have more LCV Subcutaneous Sweet's: Septal or lobular neutrophilic panniculitis (deep, erythematous, tender nodules clinically) Histiocytoid sweet's: Dermal +/- subcutaneous infiltration of neutrophils and histiocyte-like (immature myeloid) cells that stain (+) for MPO	May spontaneously resolve. Treat underlying cause if found. Systemic steroids Others: Dapsone Potassium iodide Colchicine
Pyoderma gangrenosum (PG)	*Classic (ulcerative) PG*: Papule, pustule or bullae which develops into painful, rapidly enlarging irregular ulcer with purulent base and gray-violet undermined borders that heals with atrophic, cribriform scar. Most commonly affect lower extremities. *Vegetative PG:* Superficial, vegetative lesions usually on trunk; least aggressive. *Pyostomatitis vegetans/peristomal PG*: Ulcerative or vegetative lesions occurring in labial/oral mucosa, or around ostomy site, respectively. *Vesiculobullous PG*: Superficial bullae in erythematous to violaceous background usually in face/upper extremities. *Pustular PG*: Grouped, small, pustular nodules.	F> M, middle-aged (40-60 y/o) (+) Pathergy **Major dx criteria:**** Acute, rapidly progressing painful, necrotic ulcer with irregular, violaceous undermined borders. Other causes excluded: R/o infection, vasculitis, vasculopathy, malignancy (perform sterile skin biopsy) **Minor dx criteria:** (+) Pathergy or cribriform scarring Classic PG histology Presence of associated conditions Rapid response to systemic steroids PAPA syndrome (mutation in *PSTPIP1 encoding* CD2-binding protein), PASH, PAPASH	IBD (UC > CD) Hematologic disorders (IgA monoclonal gammopathy, AML, CML, HCL, MDS, PCV) Inflammatory arthritis Vasculitis Search for associations: CBC /w peripheral smear, CXR, U/A, SPEP/UPEP, +/- BM biopsy, colonoscopy, FOBT/O&P, ANCA	Epidermal ulceration, necrosis and/or pustules + prominent dermal neutrophilic infiltration + dermal edema +/- LCV Frequently histology is non-specific and non-diagnostic, but helpful to exclude other causes.	May spontaneously resolve. Treat underlying cause if found. Wound care Mild cases: Ultrapotent topical or IL steroids Severe cases: Systemic steroids Others: Cyclosporine TNF-α inhibitors (infliximab) Azathioprine Methotrexate Colchicine Dapsone Potassium iodide If concurrent IBD, may benefit the most from: TNF-α inhibitors > cyclosporine > systemic steroids

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Mainly dermal +/- hypodermal neutrophilic infiltrates *(cont.)*					
Necrotizing neutrophilic dermatosis	Variant of necrotizing PG and Sweet's syndrome + systemic inflammation Necrotizing, erythematous or ulcerated edematous plaques with erythematous-violaceous borders +/- satellite lesions May develop rapid progression of purpura and skin necrosis +/- purulence, pustules and edema Lower > upper extremities	Middle aged adults; M >F Fever (>38.3°C) Shock (critically ill patient; resembling sepsis without infection) Leukemoid reaction or leukocytosis Absence of infectious organisms on histopathology, microbiologic stains or tissue culture (+) history of pathergy: surgical procedure, abrasion, venipuncture	Hematologic disorders Malignant neoplasms IBD Connective tissue disease Pregnancy Medications (G-CSF)	Diffuse dermal + subcutaneous neutrophilic infiltrate May have leukocytoclasia and necrosis of fascia and muscles	Systemic steroids Unresponsiveness to antibiotic treatment may be a clue to diagnosis.
Behcet's disease	<u>Aphthosis (oral and genital)</u> Oral cavity/lips: Erythematous papules→ yellowish pseudomembrane → painful nonscarring ulcers with gray base and surrounding erythema. Scrotum/penis and vulva: painful ulcers with irregular margins (may mimic HSV) <u>Other cutaneous lesions:</u> Sterile papules +/- nonfollicular vesiculopustules, purpura, and EN-like deep erythematous, tender nodules <u>Extracutaneous involvement:</u> Arthritis (non-erosive) GI: cramping abdominal pain due to ulcerations within small bowel (ileocecum), colon, esophagus Others: Neurologic, vascular, cardiopulmonary or renal.	Young adult (20-35 y/o) **Major dx criteria:*** Recurrent oral ulcerations at least 3x/yr **Minor dx criteria:** Recurrent genital ulcerations Ocular involvement (leading cause of morbidity) (+) pathergy test *[needle stick→ papulopustule at site of trauma w/in 1-2 days]* EN, papulopustules or pseudofolliculitis; acneiform lesions (in post-adolescent not on steroids)	HLA-B51 allele Middle eastern and Mediterranean ancestry (Prevalence: Turkey > Japan > USA) Vascular thrombosis (SVC, migratory thrombophlebitis) MAGIC syndrome: Behcet's + relapsing polychondritis (antibodies against collagen II)	Neutrophilic angiocentric infiltrate +/- erythrocyte extravasation +/- LCV with or without thrombosis <u>EN-like lesions:</u> Septal or lobular neutrophilic or mixed panniculitis +/- fat necrosis	No preferred treatment Dapsone Colchicine Thalidomide IFN-α-2a Methotrexate TNF-α inhibitors (etanercept) Azathioprine Symptomatic treatment (eg, viscous lidocaine, sucralfate)

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Bowel associated dermatosis-arthritis syndrome (Bowel bypass syndrome)	Prodrome with constitutional symptoms + serum sickness-like symptoms, with: Diarrhea w/ malabsorption + Arthritis + Cutaneous lesions including: Erythematous to purpuric papules, vesiculopustules +/- tender subcutaneous nodules (EN-like)	Lesions favor proximal extremities and trunk Progress within 48 hours May last 2-4 weeks Frequent recurrences	Gastric resection Jejunoileal bypass Blind loops of bowel Biliopancreatic diversion IBD, diverticulitis, PUD	Dermal perivascular nodular neutrophilic infiltrates +nuclear dust + dermal edema EN-like lesions: Septal or lobular neutrophilic panniculitis	Surgical correction of blind loop or bowel bypass revision→ curative Antibiotics (eg, tetracyclines) + systemic immunomodulating agents → symptomatic improvement
Neutrophilic eccrine hidradenitis	Erythematous-to-purpuric painful macules, papules and/ or plaques on face, extremities and trunk. May develop pustules Lesions heal without scarring	Dermatosis usually occur 8-10 days after drug exposure Fever and neutropenia may occur	Chemotherapy (cytarabine, anthracyclines, methotrexate, bleomycin) Other drugs: G-CSF, acetaminophen, carbamazepine Cancer: Leukemia (AML), testicular, breast, bone Infections: HIV, Staph, nocardia, serratia, enterobacter	Neutrophilic infiltrate around eccrine unit +/- necrosis and eccrine squamous syringometaplasia	Treat underlying infection/stop offending agent Usually spontaneous resolution. Systemic steroids Dapsone
Erythema elevatum diutinum (EED)	Violaceous, erythematous or red brown papules, smooth nodules or plaques Extensor extremities (elbows, knees) in a symmetric distribution +/- Arthralgias	Middle-aged adults Lesions may increase in number and size with time	Infections (strep, syphilis, hepatitis, HIV) Hematologic disorders: (Lymphoma, multiple myeloma, IgA monoclonal gammopathy) IBD	Dermal neutrophilic infiltrate +/- eosinophils + LCV Older lesions may have fibrosis	Dapsone Systemic steroids
Neutrophilic panniculitis (NP)	Painful, inflammatory subcutaneous nodules or plaques mainly located on lower extremities. May develop fever, arthralgias, and fatigue	F>M; Middle aged adults	Hematologic malignancies, MDS, monoclonal gammopathies IBD, RA Drugs (eg, BRAF and tyrosine kinase inhibitors, G-CSF)	Lobular neutrophilic panniculitis+/- dermal infiltrate No vasculitis	Systemic steroids

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Rheumatoid neutrophilic dermatitis (RND)	Asymptomatic papules, plaques, nodules, urticarial plaques or palpable purpura Extensor extremities > trunk, shoulder, neck in symmetric distribution	Middle aged female with severe seropositive RA	Rheumatoid arthritis	Dense neutrophilic infiltrate, plasma cells and macrophages +/-microabscess in papillary dermis (similar to dermatitis herpetiformis) DIF: negative	May resolve spontaneously or with treatment of underlying RA High potency topical steroids Dapsone Systemic steroids

*Also includes: pustular psoriasis, acute generalized exanthematous pustulosis, IgA pemphigus, infantile acropustulosis and transient neonatal pustulosis
**Both major and two minor proposed criteria are needed for the diagnosis.
***Diagnosis established if proposed obligate criteria and at least 1 minor criteria present.

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Abbreviations:
F: Female; M: Male; IBD: Inflammatory bowel disease; DIF: Direct immunofluorescence, Dx: Diagnostic ; c/w: Consistent with; ANA: antinuclear antibodies; anti-dsDNA: anti-double stranded DNA; SLE: Systemic lupus erythematosus; PAPA: Pyogenic Arthritis, Pyoderma Gangrenosum, Acne Conglobata; PASH: Pyoderma gangrenosum, Acne, Suppurative Hidradenitis; PAPASH: Pyogenic arthritis, Pyoderma gangrenosum, Acne, Suppurative Hidradenitis; AML: Acute myeloid leukemia; CML: Chronic myeloid leukemia; HCL: Hairy cell leukemia; MDS: Myelodysplastic syndrome; RA: Rheumatoid arthritis; PCV: Polycythemia vera; CBC: Complete blood count; CXR: Chest x-ray; U/A: Urine analysis; SPEP/UPEP: Serum protein electrophoresis/Urine protein electrophoresis; BM: Bone marrow; FOBT/O&P: Fecal occult blood test/Ova and parasites; ANCA: anti-neutrophil cytoplasmic antibodies; G-CSF: Granulocyte-colony stimulating factor; LCV: Leukocytoclastic vasculitis