Neutrophilic and Eosinophilic Dermatoses

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Rapid Fire Dermatologic Updates
Orange County Convention Center – Orlando, FL
Sunday October 18, 2015
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Neutrophilic Dermatoses
Neutrophils

- Originate in the bone marrow from pluripotent stem cells
- Take 7-10 days to differentiate
  - Stages: myeloblast, promyelocyte, myelocyte, metamyelocyte, band, segmented neutrophil
- During maturation, they acquire intracellular granules
  - 1° - i.e. myeloperoxidase, lysozyme, neutrophil elastase
  - 2° - i.e. lactoferrin, neutrophil collagenase
  - 3° - i.e. neutrophil gelatinase
- Produced at a rate of 5-10 x 10^{10} daily
- Generally circulate in peripheral blood for 3-12 hours, then migrate to tissues and stay there for 2-3 days
- 1st cell to arrive during infection
- Fastest moving cell in body- 30 microns/min
Sweet’s Syndrome
Sweet’s Syndrome

Epidemiology

- Occurs in all age groups
- Average age of onset is 30-60
- Female predominance (4:1)
  - Especially in drug-induced variant

Variants

- Classic presentation:
  - URI or GI infection
  - IBD
  - Pregnancy
  - Autoimmune disorder
- Malignancy-associated:
  - AML or MDS
- Drug-induced presentation:
  - G-CSF
Clinical Presentation

- Tender papules or nodules coalescing into plaques favoring the head & neck
  - Often with vesicular, bullous or pustular appearance
  - May have a mammilated surface
- Constitutional symptoms
- Elevated CRP/ESR
- Leukocytosis
- Oral ulcers
- Extracutaneous manifestations
- Exhibit pathergy
Diagnostic Criteria

- Major criteria
  - Abrupt onset of cutaneous lesions consistent with Sweet’s syndrome
  - Histopathology compatible/consistent with Sweet’s syndrome
- Minor criteria
  - Preceded by associated systemic findings, such as infection, pregnancy, drugs, malignancy, or other inflammatory conditions
  - Fever and constitutional signs and symptoms
  - Excellent response to corticosteroids
  - Laboratory abnormalities:
    - Elevated white blood cell count (of which 70% are neutrophils)
    - Elevated erythrocyte sedimentation rate or C-reactive protein levels
Clinical Image and Pathology
Treatment

- **1st line therapy:**
  - *Systemic corticosteroids*
  - Intralesional or topical corticosteroids
  - Potassium iodide
  - Colchicine
- **2nd line therapy:**
  - Dapsone
  - Indomethacin
  - Clofazimine
  - Cyclosporine

- **Alternate therapy:**
  - Interferon-α
  - Immunoglobulin
  - Thalidomide
  - TNF-α inhibitors
  - Anakinra
Pyoderma Gangrenosum
Pyoderma Gangrenosum

- Rare, recurring, chronic and painful disease of unknown etiology
- Commonly affects women 20-50 years of age
- 4% of cases occur in infants and children
- 50% of cases are associated with an underlying systemic disease
- All variants of the disease exhibit pathergy
Clinical Presentation - Variants

- **Classic PG**
  - Tender papulopustule that evolves into ulcer with purulent base and violaceous borders
  - Pretibial areas
  - Frequently occur with IBD and RA

- **Peristomal PG**
  - Occurs around ileostomy/colostomy sites
  - Associated with intestinal cancers or IBD

- **Pustular PG**
  - Multiple, discrete pustules surrounded by erythematous halo
  - Extensor extremities and trunk
  - Frequently occurs with IBD
Clinical Presentation- Variants

- **Bullous PG**
  - Vesicles → Bullae → Superficial ulcers/erosions
  - Face and upper extremities, especially dorsal hands
  - Frequently occurs with AML, MDS, IgA gammopathy

- **Vegetative PG**
  - Sterile pyoderma; possible sinus tracts
  - Labial and buccal mucosa
  - Frequently occurs with IBD

- **Drug-induced PG**
  - EGFRI, G-CSF, PTU
Clinical Presentation
Clinical Presentation

Histology

- **Early Findings**
  - Perivascular lymphocytic infiltrate with endothelial swelling (biopsy taken from the edge of lesion)

- **Late findings**
  - Dense neutrophilic infiltrate, leukocytoclasia without evidence of vasculitis (area of ulceration)
  - Fibrosing inflammation at edge of ulcer with thrombosis of vessels and extravasated RBCs
Histology

Treatment

- Corticosteroids:
  - Systemic, topical or intralesional corticosteroids
- TNF-α inhibitors:
  - Infliximab, Adalimumab, Etanercept
  - Thalidomide
- Calcineurin inhibitors
  - Cyclosporine
  - Oral or Topical Tacrolimus
  - Topical Pimecrolimus
- Antimetabolites/Cytotoxic Chemotherapies
  - Azathioprine
  - Cyclophosphamide
  - Mycophenolate mofetil
Treatment

- Other systemic agents:
  - Clofazimine
  - Colchicine
  - Dapsone
  - Chlorambucil
  - Tetracyclines
  - Alefacept
  - IVIG

- Wound care agents:
  - Avoid debriding tissue
  - Hyperbaric oxygen
  - Biologic dressings
  - Skin grafts
  - Topical corticosteroids
  - Topical calcineurin inhibitors
Behcet’s Disease
Overview

- A rare, multisystem, polysymptomatic inflammatory disorder of unknown etiology
- Classic triad of oral ulcers, genital ulcers, and ocular inflammation
- Peak age of onset 20-35 years, with a relapsing remitting nature
- Diagnostic Criterion:
  - At least 3 episodes of oral ulcerations within 12 months
  - 2 of the following: genital ulcers, eye lesions, skin lesions, positive pathergy test
Clinical Features

- Recurrent aphthous stomatitis and genital aphthae
- Anterior and posterior uveitis, hypopyon, retinal vasculitis
- Erythema nodosum-like lesions, pseudofolliculitis, sterile papulopustular lesions, palpable purpura
- Superficial thrombophlebitis, pulmonary arterial aneurysms
- Arthritis, arthralgias
- Neurologic: memory, behavioral changes, brainstem lesions
Histopathology

- Cutaneous lesions: angiocentric neutrophilic infiltrates with leukocytoclasia and erythrocyte extravasation
- May see a leukocytoclastic vasculitis
- Thrombi and necrosis
- Acneiform lesions: sterile neutrophilic vasculopathy
Clinical Image and Pathology

Treatment

- Difficult secondary to variable nature and multi-organ involvement
- Cutaneous lesions:
  - Topical and intralesional corticosteroids
  - Methotrexate
- Systemic Disease:
  - Cyclophosphamide
  - Prednisone
  - Mycophenolate mofetil
SAPHO
Synovitis-Acne-Pustulosis-HyperOsteitis
Overview

• A clinicoradiologic entity that involves skin, bone, and joints

• Rare in the US; more prevalent in Japan, Scandinavian countries, Germany, and France

• Affects children and young to middle aged adults

• Characterized by osteoarticular lesions and pustular dermatosis
Clinical Presentation

- Osteoarticular lesions: axial skeleton and chest wall
  - Osteitis, hyperostosis, synovitis, aseptic osteomyelitis
    - Pain, tenderness, swelling over affected areas

- Dermatoses:
  - Palmoplantar pustulosis, pustular psoriasis, severe acne
Clinical Photos

Coelho C, Souza M. The Dark Side of SAPHO syndrome. BMJ Case Report. 2011 Dec; bcr1120115197
Pathogenesis

- Some classify SAPHO under seronegative spondyloarthropathies due to its association with HLA-B27
- Other hypotheses include infectious causes:
  - S. aureus, H. parainfluenza, P. acnes isolated from bone lesions
- Bone Scintigraphy shows increased uptake, supporting increased osteoblast activity causing hyperostosis and osteitis
Treatment

- NSAIDS
- Antimicrobial therapies in those with positive biopsy cultures: azithromycin, doxycycline
- Immunomodulators: methotrexate
- Bisphosphonates for bone lesions
- Oral corticosteroids for skin and bone lesions
Overview

- Occurs 3 months to 5 years post-surgery in 20% of individuals
- Most commonly associated with:
  - Gastric resection
  - Jejunoileal bypass
  - Blind loops of bowel
  - Biliopancreatic diversion
- MOA- microbial overgrowth in blind loops of bowel which result in immune complex deposition in skin and synovium containing bacterial antigens
Clinical Presentation

- Flu-like symptoms
- Macules → Papules → Purpuric Vesiculopustules
  - Favor the proximal extremities and trunk
- Erythema nodosum-like lesions
- Tenosynovitis
- Non-erosive, migratory, episodic polyarthritis
- Diarrhea and malabsorption
- Other systemic complications: renal stones, gallstones, hepatic dysfunction, vitamin deficiency
Treatment

• **Mild Disease**
  • Antibiotics:
    • Tetracyclines
    • Clindamycin
    • Metronidazole
  • Anti-neutrophilic agents:
    • Colchicine
    • Dapsone
    • Thalidomide

• **Severe Disease**
  • Immunomodulators:
    • Prednisone
    • Cyclosporine
    • Azathioprine
    • Mycophenolate mofetil
  • TNF-α inhibitors:
    • Infliximab
    • Etanercept
    • Adalimumab
  • Surgical restoration
Eosinophilic Dermatoses
Eosinophils

- Granulocytes that have a major function in allergic reactions and parasitic infections
- Migration and Chemotaxis
  - Through vascular endothelium: VLA-4 binds to VCAM-1
  - Through peripheral tissues: CCR3 binds eotaxin 1-3 and RANTES
- Cytokines
  - Activity from Th2 subset of T cells
    - IL-5, IL-3, GM-CSF
- Autocrine Effects: eosinophils produce IL-3, IL-5, GM-CSF
- Eosinophil Granules
  - Major Basic Protein – stimulates histamine release and activates neutrophils
  - Eosinophilic Cationic Protein, Eosinophil Peroxidase, Eosinophil-Derived Neurotoxin
Granuloma Faciale
Overview

- Benign condition with unknown etiology
- Classic presentation: long-standing asymptomatic red-brown to violaceous solitary smooth plaque with prominent follicular openings on the face
- Most commonly seen in middle-aged Caucasian males
- No associations with systemic diseases
- Histopathology:
  - Prominent Grenz Zone
  - Dense, dermal infiltrate consisting of lymphocytes, neutrophils and characteristic eosinophils
Treatment

- Often resistant to therapy
- Intralional triamcinolone 2.5-5.0 mg/mL
- Dapsone 50-150 mg by mouth daily
- Clofazimine 300 mg by mouth daily
- Topical PUVA
- Topical Calcineurin Inhibitors
- Pulsed Dye Laser
- Physical modalities: dermabrasion, surgical excision, cryotherapy
Wells’ Syndrome
Overview

- Also known as eosinophilic cellulitis
- No predilection for age, sex or race
- Exact etiology unknown
  - Debated as its own entity verses a local hypersensitivity reaction that activates eosinophils
- Recurrent Episodes:
  - Prodrome of itching and burning → multiple areas of large, well-circumscribed edematous erythema in an annular or arcuate pattern → indurated red-brown to violaceous plaques and nodules
  - Pathology: dense dermal infiltrate with lymphocytes, eosinophils and histiocytes, superficial dermal edema, flame figures
Clinical Image and Pathology

Treatment

- Prednisone 20-30 mg by mouth daily until clear
  - Frequently recurring lesions controlled with maintenance 5mg every other day
- Oral antihistamines
- Topical or intralesional corticosteroids
- Resistant cases or for those intolerant to oral Corticosteroids
  - Dapsone, tacrolimus, cyclosporine
- Case report with successful response to adalimumab
- If present, treat underlying disease
Hypereosinophilic Syndrome
Overview

- Disorder characterized by peripheral blood eosinophilia with evidence of organ damage due to eosinophil infiltration and degranulation
  - Skin involvement in 50% of cases
- Three diagnostic criterion
  - Peripheral blood eosinophilia (>1,500 cells/µL) for > 6 months
    - >1,500 cells/µL on 2 separate occasions separated by 1 month
    - Can be expanded to include tissue hypereosinophilia
  - Evidence of eosinophil-related end organ damage
  - Exclusion of all other etiologies (allergic, parasitic, etc.)
Subtypes of HES

There are two subtypes of Hypereosinophilic Syndrome

- Myeloproliferative (Primary): molecular defect leading to abnormal eosinophil proliferation and activation
  - Due to FIP1L1-PDGFRA fusion gene which leads to unregulated tyrosine kinase activity
- Lymphocytic (Secondary): secondary disease process releases cytokines (IL-5) that in turn expands and activates eosinophils
  - Associations: solid tumors, B-cell and T-cell lymphoproliferative diseases
Myeloproliferative HES

- Male predominance (9:1 ratio of males:females)
- Typical presentation: Fever, weight loss, fatigue, malaise
  - Skin lesions: range from pruritic erythematous maculopapules to urticarial lesions to angioedema to mucosal ulcerations (poor prognostic sign)
- Labs: elevated serum B12 and serum tryptase
- Associated with endocardial fibrosis/restrictive cardiomyopathy → monitor with echocardiogram
  - Concern for progression to leukemia
- Treatment: imatinib mesylate (Gleevec)
Lymphocytic HES

- Approximately 25% of HES cases
- Equal incidence in males and females
- Typical presentation: fever, weight loss, fatigue, malaise
  - Skin lesions (more prominent than myeloproliferative HES): severe pruritus, eczematous lesions, erythroderma, urticarial, angioedema
- Labs: elevated serum IgE levels
- Concern for transformation to lymphoma
- Treatment: prednisone 1 mg/kg/day in combination with steroid sparing agent
  - Hydroxyurea
  - IFNα2b: 12-50 x 10^6 U/week
HES Investigational Therapies

- Monoclonal Antibodies against IL-5
  - Mepolizumab
  - Reslizumab
Eosinophilic Fasciitis
Overview

- A rare fibrosing disorder of unclear etiology, often classified as a scleroderma-like syndrome
- Characterized by fibrosis of the skin and subcutaneous tissues, thickening of fascia, peripheral eosinophilia
- May have history of strenuous physical activity preceding onset
- Also seen in chronic GVHD.
- Reported in one case of Mycoplasma arginini infection
Presentation

- Severe pain and edema of extremities, which can quickly progress to fibrosis, causing a woody induration to the skin.

- “Groove sign” – linear depressions where veins appear sunken in within indurated skin.
Clinical Photo

Eosinophilic Fasciitis

- Diagnosis: biopsy of fascia or thickening seen on MRI

- Laboratory values: eosinophilia, hypergammaglobulinemia, elevated ESR, pancytopenia. Normal ANA and complement levels

- Histology: Deep fascia 10-50 times normal width, with a patchy lymphocytic infiltrate and plasma cells
Eosinophilic Fasciitis

- Differential diagnosis: systemic sclerosis, nephrogenic systemic fibrosis, eosinophilia-myalgia syndrome, scleromyxedema, Churg-Strauss syndrome

- Treatment: immediate treatment necessary to preserve function
  - Prolonged course of prednisone for 6-12 months
  - Hydroxychloroquine, cyclosporine or dapsone may also be used
References

- Coelho C, Souza M. The Dark Side of SAPHO syndrome. BMJ Case Report. 2011 Dec; bcr1120115197