Medical Dermatology Society: Sarcoidosis
Systemic symptoms, workup, and management

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Conflicts of Interest

• Investigator: Centocor/J&J
  – Sarcoidosis clinical trial investigating biologics for chronic/refractory sarcoidosis

• Off label uses of medications will be discussed
Goals

• Recognize and diagnose
• Evaluate extent of disease
• Treatment strategies
Med-Derm Society

- Founded in 1994, 1st mtg 1995, mission statement 1996\(^1\)
- Combined internal medicine-dermatology training programs\(^2\) approved 2000
- Now, half-dozen programs, 52 current or past residents
  - Survey data suggests more likely to pursue inpatient dermatology, connective tissue disease, immunobullous disease, infectious diseases of the skin, psoriasis\(^3\)

3. Mostaghimi A., in progress
## MDS: 2005-2013

<table>
<thead>
<tr>
<th>TOPIC</th>
<th># times</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemphigus</td>
<td>18</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>12</td>
</tr>
<tr>
<td>Lupus</td>
<td>7</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>4</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>4</td>
</tr>
<tr>
<td>GvHD</td>
<td>4</td>
</tr>
<tr>
<td>Drugs (incl chemo)</td>
<td>4</td>
</tr>
<tr>
<td>Hidradenitis</td>
<td>3</td>
</tr>
<tr>
<td>Scleroderma / fibrosing</td>
<td>3</td>
</tr>
<tr>
<td>Melanoma</td>
<td>3</td>
</tr>
<tr>
<td>Inpatient</td>
<td>2</td>
</tr>
<tr>
<td>Pyoderma</td>
<td>2</td>
</tr>
<tr>
<td>Psoriasis (incl PsA)</td>
<td>2</td>
</tr>
</tbody>
</table>

Thank you Debbie Kovacs
Sarcoidosis talks at the MDS
Genetically susceptible host
• Familial clustering
• 5-fold sib risk
• 80-fold monozygotic risk

Environmental risk factors
• Microbial-rich environments
• Exposure to insecticides, pesticides, mold/mildew
• (non-smoker)
• Occupation (firefighter, Navy, first responders)

Potential microbial triggers
• Mycobacteria (10-20 fold higher detection in sarcoid tissues than controls)
  Mycobacterial catalase-peroxidase (mKatG) protein
• *Propionibacterium* spp.

Serum amyloid A misfolding

Autoantigens

Host immune response
• \(T_{H1}\) cytokines upregulated
  \(\text{IFN}_\gamma, \text{IL12}, \text{IL18}\)
  \(\text{TNF}_\alpha\) critical
• \(T_{H2}\) cytokines downregulated
• Decreased FoxP3 \(T_{REG}\) cells

Result:
• Overabundant inflammatory response
• Trigger contained or destroyed
• Leftover granulomatous inflammation

\[\text{Sarcoidosis}\]
Diagnosis

• Clinicoradiographic findings + biopsy showing nonceaseating epithelioid cell granulomas, and ruling out other causes of granulomas
<table>
<thead>
<tr>
<th>Affected organ</th>
<th>Frequency of occurrence (%)</th>
<th>Common findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs and thoracic lymph nodes</td>
<td>&gt;90</td>
<td>Dyspnea, cough, chest pain, pulmonary hypertension, mixed pulmonary function test abnormalities (obstruction, restriction, diffusion deficits)</td>
</tr>
<tr>
<td>Skin</td>
<td>20–30</td>
<td>Nodules, plaques, lupus pernio, erythema nodosum (a nongranulomatous panniculitis)</td>
</tr>
<tr>
<td>Eyes</td>
<td>20–25</td>
<td>Uveitis, conjunctivitis, lacrimal gland enlargement, sicca syndrome, optic neuropathy</td>
</tr>
<tr>
<td>Liver and/or spleen</td>
<td>10–20</td>
<td>Hepatosplenomegaly, jaundice, elevated liver function tests, cirrhosis, hypersplenism</td>
</tr>
<tr>
<td>Cardiovascular system</td>
<td>10–20</td>
<td>Ectopy, heart block, arrhythmias, cardiomyopathy, sudden death</td>
</tr>
<tr>
<td>Central nervous system</td>
<td>10–25</td>
<td>Cranial neuropathy, mass lesions, aseptic meningitis and/or encephalitis, myelitis, spinal cord and peripheral neuropathy, small fiber neuropathy, pain, hypothalamic–pituitary involvement</td>
</tr>
<tr>
<td>Sinuses and upper respiratory tract</td>
<td>5–10</td>
<td>Chronic sinusitis, laryngeal involvement, parotid gland involvement</td>
</tr>
<tr>
<td>Bones, joints, muscle</td>
<td>5–15</td>
<td>Chronic arthritis, dactylitis, lytic bone lesions, myopathy</td>
</tr>
<tr>
<td>Hematologic system</td>
<td>&gt;50</td>
<td>Peripheral lymphopenia, hypergammaglobulinemia</td>
</tr>
<tr>
<td>Renal system (including calcium abnormalities)</td>
<td>5–10</td>
<td>Hypercalcemia and/or hypercalciuria, nephrocalcinosis, nephrolithiasis</td>
</tr>
<tr>
<td>Endocrine system</td>
<td>5–10</td>
<td>Hypothalamic–pituitary involvement, pancreatic mass, Heerfordt syndrome (uveoparotid fever)</td>
</tr>
<tr>
<td>Gastrointestinal and reproductive tract</td>
<td>&lt;1</td>
<td>Gastric nodules, ovarian or testicular masses</td>
</tr>
</tbody>
</table>
Initial Evaluation

- History (occupational, environmental exposure, symptoms)
- Physical exam
- Chest X-ray, PA and Lateral
- Pulmonary function tests (including DLCO)
- Routine ophthalmologic examination
- Complete blood count
- Comprehensive serum chemistries (Ca, LFTs, creatinine)
- Urinalysis
  - If history of stones, 24h urine calcium
- EKG
  - If history of palpitations, additional testing
- Tuberculin skin test or IFNγ release assay
- Thyroid testing
- Vitamin D 25, Vitamin D 1,25

Adapted from: Statement on sarcoidosis
Am J Respir Crit Care Med 1999; 160: 736-755
Cardiac sarcoidosis

- Clinically present in 5-10%
  - Postmortem studies suggest 20-25%
- Cardiac sarcoidosis may present as sudden cardiac death
- All patients must be screened
- Screen with history, physical, ECG
- Symptoms or ECG abnormalities should prompt referral
- Echo, Holter, and advanced imaging are indicated
  - Cardiac MRI versus PET scan is controversial

Rosenbach M, JAMA Dermatol 2013
Mantini N et al., Cardiac Sarcoid... Clin Cardiol (In press)
Vitamin D

• Patients with sarcoidosis often have low 25-hydroxyvitamin D, but elevated 1,25-dihydroxyvitamin D₃
  – Inappropriate supplementation can lead to hypercalcemia

• Sarcoidal granulomatous IFNγ mediated inflammation stimulates 1α-hydroxylase, which converts vitD25 to vitD1,25

Sage RJ, et al. JAAD 2011;64:795-796
Table 1: Recommended items for initial and follow-up examinations in patients with cutaneous sarcoidosis

<table>
<thead>
<tr>
<th>Initial Evaluation:</th>
<th>*To be performed annually:</th>
</tr>
</thead>
<tbody>
<tr>
<td>History (occupational/environmental exposure, complete review of systems)</td>
<td>History</td>
</tr>
<tr>
<td>Physical exam</td>
<td>Physical exam</td>
</tr>
<tr>
<td>Chest X-ray (PA and Lateral)</td>
<td>Chest X-ray (PA and Lateral)</td>
</tr>
<tr>
<td>Pulmonary function tests (including DL\textsubscript{co})</td>
<td>Pulmonary function tests (including DL\textsubscript{co})</td>
</tr>
<tr>
<td>Ophthalmologic examination</td>
<td>Ophthalmologic examination</td>
</tr>
<tr>
<td>Complete blood count</td>
<td>Complete blood count</td>
</tr>
<tr>
<td>Comprehensive serum chemistries (includes Ca, LFTs, Cr)</td>
<td>Comprehensive serum chemistries (includes Ca, LFTs, Cr)</td>
</tr>
<tr>
<td>EKG +/- TTE (consider additional testing if symptomatic)</td>
<td>EKG</td>
</tr>
<tr>
<td>Urinalysis (if history of stone, then 24 hour urine calcium)</td>
<td></td>
</tr>
<tr>
<td>Tuberculin skin test or IFN\gamma release assay</td>
<td></td>
</tr>
<tr>
<td>Thyroid testing</td>
<td></td>
</tr>
<tr>
<td>Vitamin D 25, Vitamin D 1,25</td>
<td></td>
</tr>
</tbody>
</table>

*Patients should be evaluated more frequently if they are on systemic medications, if there is a change in clinical signs or symptoms, or if their diseases is not well controlled

** Any abnormalities detected on history, review of systems, laboratory or radiologic workup may warrant further investigation with additional targeted diagnostics and/or expert referral

PA: posteroanterior, DL\textsubscript{co} (diffusion lung capacity, carbon monoxide), Ca: calcium, LFTs: liver function tests, Cr: creatinine, EKG: electrocardiogram, TTE: transthoracic echocardiogram
So...

- After all this diagnosis, biopsying, testing, working-up, evaluating...
- How do you treat it?
Simplified Cutaneous Sarcoidosis Treatment Algorithm

SEVERITY

Topicals
Intralesional

Antimalarials
Minocycline

Methotrexate
Thalidomide

Adalimumab
Infliximab

Wanat KA, Rosenbach M. Am J Clin Derm, In Press
Step-wise approach

Topical steroids, topical tacrolimus, intralesional steroids

Antimalarials, TCN-class antibiotics, pentoxifylline, combination therapy

Methotrexate, prednisone, thalidomide, (mycophenolate, isotretinoin, azathioprine)

Infliximab / Adalimumab, cyclosporine

Less data and experience with: chlorambucil, melatonin, allopurinol, cytoxan, leflunomide

Clinical Trials

Topical steroids, topical tacrolimus, intralesional steroids (laser surgery)
Skin directed therapy

- Topicals
  - Steroids
  - Retinoids
  - Tacrolimus
- Intraleisional steroids
- Laser therapy (pulsed-dye)
- Photodynamic therapy
“Low-risk systemics”

- Antimalarials (hydroxychloroquine +/- quinacrine, chloroquine)
- Tetracycline-class abx (minocycline > other)
- Pentoxifylline
  - Apremilast
“Traditional systemics”

- Prednisone
- Methotrexate

- Combination therapy
  - Antimalarials
  - TCN-class antibiotics
  - Skin directed therapy
  - multiple agents
Alternate systemics

- Thalidomide
- Isotretinoin
- Azathioprine
- Mycophenolate
- Cyclophosphamide
Biologics

• Indication: chronic or refractory (second line therapy)
• Potential mechanism of action:
  – Antibodies target TNFα or TNFα receptor
• Dosing:
  • Infliximab 3mg/kg or 5mg/kg (q8 to q6wk)
  • Adalimumab appears to work better at 40mg every week
• Data:
  • Infliximab has some of the strongest data available with large double blind randomized controlled trials
  • Adalimumab has small series
    • Pariser JAAD 2013: 10 pts vs 6 controls RCT, skin improved
    • Etanercept should not be used; ineffective, may be associated with worsening
• Special: Multiple case reports of TNFα-induced granulomatous disease / sarcoidosis
The Treatment of Lupus Pernio*

Results of 116 Treatment Courses in 54 Patients

Eleni Stagaki, MD; William K. Mountford, PhD; Daniel T. Lackland, DrPH; and Marc A. Judson, MD, FCCP

(CHEST 2009; 135:468–476)

• 54 patients, 116 courses of treatment
• Resolution/near resolution: Infliximab 77%, Steroids + Other 29%, Steroids 20%, Other 11%
• “Infliximab appears superior”
• “Noninfliximab, noncorticosteroid-containing regimens are of little use”
• Paradigm changing?
What’s on the horizon

• **IL 12/23 inhibitors**
  – One trial, poor response

• **Other TNF inhibitors**
  – One trial, Golimumab with trend towards skin improvement

• **CLEAR / combination antibiotic regimen**

• **IL 17 inhibitors?**
# Cutaneous Sarcoidosis Activity and Morphology Index

Select the score in each anatomical area that describes the most severely affected lesion in that site.

<table>
<thead>
<tr>
<th>ANATOMICAL LOCATION</th>
<th>ACTIVITY</th>
<th>DAMAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inflammation</td>
<td>Post-inflammatory result</td>
</tr>
<tr>
<td></td>
<td>Induration or Depression</td>
<td>Scalp</td>
</tr>
<tr>
<td></td>
<td>Surface Change</td>
<td>Periorificial (eyes, mouth)</td>
</tr>
<tr>
<td></td>
<td>Area</td>
<td>Nose (incl. nares)</td>
</tr>
<tr>
<td>Scalp</td>
<td>0 = absent</td>
<td>0 = no residual</td>
</tr>
<tr>
<td>Ears</td>
<td>1 = flesh-colored to brown (active)</td>
<td>1 = hyper-/hypo-pigmentation</td>
</tr>
<tr>
<td>Periorificial (eyes, mouth)</td>
<td>2 = faint erythema (pink)</td>
<td>2 = scarring</td>
</tr>
<tr>
<td>Nose (incl. nares)</td>
<td>3 = bright erythema (red) of violaceous (purple)</td>
<td>3 = Anatomical Location</td>
</tr>
<tr>
<td>Rest of face</td>
<td>0 = flat</td>
<td>0 = no surface change</td>
</tr>
<tr>
<td>Chest</td>
<td>1 = &lt;1mm</td>
<td>1 = scaling</td>
</tr>
<tr>
<td>Abdomen</td>
<td>2 = 1-2mm</td>
<td>2 = thick / extensive scale</td>
</tr>
<tr>
<td>Back (incl. buttocks)</td>
<td>3 = &gt;2mm</td>
<td>(&gt;1mm)</td>
</tr>
<tr>
<td>Arms (incl. hands)</td>
<td>0 = no surface change</td>
<td>1 = single lesion</td>
</tr>
<tr>
<td>Legs (incl. feet)</td>
<td>1 = no surface change</td>
<td>2 = &lt;25% of site</td>
</tr>
<tr>
<td></td>
<td>2 = surface change</td>
<td>4 = 25-50% of site</td>
</tr>
<tr>
<td></td>
<td>3 = ulcerated</td>
<td>6 = &gt;50% of site</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Anatomical Location</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gross lesion score</th>
<th>Gross damage score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Macules</td>
<td>Macules</td>
</tr>
<tr>
<td>Hyperkeratotic</td>
<td>Hyperkeratotic</td>
</tr>
<tr>
<td>Psoriasiform</td>
<td>Psoriasiform</td>
</tr>
<tr>
<td>Plaques</td>
<td>Plaques</td>
</tr>
<tr>
<td>Hypopigmented</td>
<td>Hypopigmented</td>
</tr>
<tr>
<td>Tattoo associated</td>
<td>Tattoo associated</td>
</tr>
<tr>
<td>Subcutaneous</td>
<td>Subcutaneous</td>
</tr>
<tr>
<td>Ulcerative</td>
<td>Ulcerative</td>
</tr>
<tr>
<td>Erythrodermic</td>
<td>Erythrodermic</td>
</tr>
<tr>
<td>Alopecia</td>
<td>Alopecia</td>
</tr>
</tbody>
</table>

Specific lesions:
- Lupus pernio: Present/Absent
- (Infiltrated/raised/nodular violaceous lesions on the central face/nose often with surface change/scaling/scarring)
- Erythema nodosum: Present/Absent

Morphologic type:
- Predominant morphological type (check one)
- Subcutaneous
- Ulcerative
- Erythrodermic
- Alopecia
- Other, please specify: ________________________

Other morphological types present (check all that apply):
- Macules
- Hyperkeratotic
- Psoriasiform
- Plaques
- Hypopigmented
- Tattoo associated

Specific lesions:
- Lupus pernio: Present/Absent
- (Infiltrated/raised/nodular violaceous lesions on the central face/nose often with surface change/scaling/scarring)
- Erythema nodosum: Present/Absent
Conclusion

• Sarcoidosis is a multisystem disorder of unknown cause characterized by granulomatous inflammation
• Etiopathogenesis is unknown
• Diagnosis can be challenging
• Patients require multisystem evaluation
• Multiple therapeutic options

• Treat the patient, not the disease
Thank you

Our sarcoidosis patients
Ellen Kim, MD
Andras Schaffer, MD PhD
Steve Prystowsky, MD
Joe English III, MD
Penn Clinical Studies Unit

Marie Buchanon, RN
Joel Gelfand, MD

Department of Pulmonary and Critical Care Medicine

Milt Rossman, MD
Maryl Kreider, MD
Karen Patterson, MD
The Dermatology Foundation has supported & advanced my career.
http://www.wasog.org


Sarcoidosis - European Respiratory Monograph 2009; 46, 126–154

Sarcoidosis - Clin Chest Med 2008; 29


Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. NEJM 2007; 357: 2153-65


