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Dermatologic Manifestations of Rheumatic Disease: Cutaneous Manifestations of Sarcoidosis

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Cutaneous Manifestations of Sarcoidosis

Sarah Shapiro, Sindhuja Koppu, Mavra Masood
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A note:

This module uses terminology related to race and ethnicity in order to describe fictional patients and discuss medical conditions. We recognize that “race” (i.e. an individual’s socially-constructed phenotype, which is often misconstrued as biologic) and “ethnicity” (i.e. an individual’s geographic birthplace or cultural/national heritage) are imperfect terms that do not fully encapsulate the breadth of human diversity.

Additionally, we recognize that race, ethnicity, sex, and gender have traditionally been attributed as risk factors for certain health condition, when in reality, many of these risks may be more accurately explained by underlying socioeconomic and sociocultural factors, including racism and prejudice.

In efforts to emphasize patient-centered care and autonomy, this module assumes that all racial-, ethnic-, sex-, and gender-related terms utilized are those specifically preferred by the patient. We are also committed to dissecting potentially biased risk factors in order to promote more equal, just, and comprehensive healthcare for all persons, regardless of their identity, beliefs, or background.

For more information, please visit the Institute for Healing and Justice in Medicine.
Outline

- Objectives
- Pre-test
- Case 1
- Case 2
- Summary
- Post-test
Objectives

By the end of the module, the learner should be able to:

● Define sarcoidosis
● Recall the non-cutaneous manifestations of sarcoidosis
● Recall the basic workup for sarcoidosis
● Identify dermatologic findings in cutaneous sarcoidosis, such as:
  ○ Lupus pernio
  ○ Erythema nodosum
Case #1

TL is a 50-year-old female (she/her/hers) who presents with a chief complaint of reddish-purple plaques on her nose and cheeks. She states that these plaques were barely noticeable a year and a half ago but have now gotten so large that she feels that the shape of her nose has changed. She also reports increased SOB on exertion and a nonproductive cough.

Medications
- Atorvastatin, 80mg
- Levothyroxine 12mcg

Medical Hx
- Hypothyroidism
- Hyperlipidemia
- Interstitial lung disease

Social Hx
- Denies tobacco, alcohol, and illicit drug use

Family Hx
- Mother - Sjogren syndrome

Pertinent ROS
- Dyspnea, cough
Differential Diagnosis and Clinical Pearl

Lupus pernio is a form of cutaneous sarcoidosis that presents as **reddish-purple plaques and nodules over the nose, cheeks, and ears**. It does not present with pain or pruritus; rather, the chief complaint is cosmetic. While lupus pernio can be suspected based on history and physical exam, the diagnosis is confirmed by a skin biopsy showing sarcoidal non-caseating granulomas.

- **Lupus pernio**
  - Most likely: Plaques around nose and cheeks, respiratory symptoms, history of interstitial lung disease

- **Tuberculosis**
  - Red plaques, dyspnea, cough
  - M. tuberculosis on sputum culture

- **Discoid lupus erythematosus**
  - Red plaques around nose and on cheeks
  - Anti-dsDNA antibodies, photosensitivity, arthritis
Lupus Pernio

- Red-violet papules and plaques found on nose, cheeks, and ears; can result in scarring
- **Specific** to sarcoidosis and represents chronic sarcoidosis; associated with more severe systemic problems
- Biopsy shows granulomatous inflammation.
- More commonly found in Black patients
Sarcoidosis

- Systemic immune-mediated disease with an unknown etiology characterized by granulomas, especially in the lung parenchyma and skin
- Common systemic symptoms: fever, night sweats, weight loss
- Patient characteristics:
  - Ages: 25-35 and 45-65 years
  - Sex: Females > Males
- Divided into cutaneous and non-cutaneous sarcoidosis
- Cutaneous sarcoidosis can affect skin, hair, nails, and tattoos.
Health Disparities in Sarcoidosis

Lower SES
- Less likely to be able to afford steroid sparing medications
- More likely to have problems with disability claims

Blacks
- Affected 10 years earlier
- Underrepresented in clinical trials

Females
- Experience more problems with sleep, pain, mobility, self-esteem, and positive feelings
- More likely to be prescribed eye drops, pain killers, and NSAIDs instead of corticosteroids

- Increased job loss
- Worse lung function
- Higher rates of hospitalizations
- Increased psychosocial stress
- Increased perceived discrimination

For more information, please visit Sharp et al. 2020
Factors affecting Patient Outcomes in Sarcoidosis

● Socioeconomic status
  ○ Associated with a more severe phenotype even when controlled for race, sex, education
  ○ Income is a risk factor for increased symptoms and development of new sarcoidosis-associated and steroid associated comorbidities of disability at diagnosis
  ○ Low income individuals are more likely to receive glucocorticosteroid-only regimens (steroid sparing regimens are typically more expensive) and have a higher burden of glucocorticosteroid-related comorbidities

● Race
  ○ Black patients develop more severe comorbidities on avg. 10 years earlier than non-Hispanic whites and present with more advanced disease (could be due to delayed diagnosis from lack of access and other factors)

● Gender
  ○ Females reported to have higher rates of hospitalization and depressive symptoms, and have a lower quality of life in regards to physical and psychological health
  ○ Females more likely to be prescribed eye drops, NSAIDs, and painkillers, while males more likely to receive corticosteroids
# Racial Differences in Sarcoidosis in the U.S.

<table>
<thead>
<tr>
<th></th>
<th>White patients</th>
<th>Black patients</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Disease Incidence</strong></td>
<td>5/100,000</td>
<td>39/100,000</td>
</tr>
<tr>
<td><strong>Lifelong Risk of Developing Sarcoidosis</strong></td>
<td>1% for women; 0.7% for men</td>
<td>2.7% for women; 2.1% for men</td>
</tr>
<tr>
<td><strong>Age of Onset</strong></td>
<td></td>
<td>Peak incidence is 10 years earlier</td>
</tr>
<tr>
<td><strong>Pulmonary Complications</strong></td>
<td></td>
<td>Higher risk of pulmonary hypertension</td>
</tr>
<tr>
<td><strong>Extrapulmonary Complications</strong></td>
<td></td>
<td>More common; can present with eye, skin, and bone marrow involvement</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>Crude rate of 4/1,000,000</td>
<td>Crude rate of 37/1,000,000</td>
</tr>
<tr>
<td><strong>States with Highest Mortality</strong></td>
<td>Vermont, Rhode Island, Maine, Utah, Washington</td>
<td>District of Columbia, Pennsylvania, North Carolina, South Carolina, New Jersey</td>
</tr>
<tr>
<td><strong>States with Lowest Mortality</strong></td>
<td>Arizona, Oklahoma, Nevada</td>
<td>Florida, Texas, Arizona</td>
</tr>
</tbody>
</table>

Mirsaeidi et al. 2015
• Cutaneous sarcoidosis can occur in approximately ⅓ of patients with non-cutaneous sarcoidosis and can occur without non-cutaneous sarcoidosis.
• Nonspecific means that granulomas are not found on biopsy. Specific means that granulomas are found on biopsy.
• Examples of conditions that are categorized under specific cutaneous sarcoidosis are NOT all specific for sarcoidosis. For example, plaques and papules occur in many other conditions.
Diagnostic Criteria and Basic Workup for Sarcoidosis

Goals
1) Identify clinical and radiographic findings supporting sarcoidosis.
2) Find noncaseating granulomas on biopsy.
3) Exclude alternative diseases.

Step #1: Detailed history (including environmental and occupational exposures)

Step #2: Full physical exam

Step #3: Tests

- Chest radiograph and high resolution CT scan
- Pulmonary function tests
- Electrocardiogram
- Eye exam
- Labs

To evaluate non-cutaneous signs and symptoms:

To evaluate cutaneous lesions:

Skin biopsy

*If the patient presents with signs/symptoms of other organ involvement, further focused tests can be conducted.
Workup of Sarcoidosis: Chest X-ray and CT scan

- **Hilar lymphadenopathy**
  - Case courtesy of Asoc Prof Craig Hacking. From the case *Bilateral Hilar Lymphadenopathy from Sarcoidosis*. Modified CC BY-NC-SA license.

- **Interstitial opacification**
  - Case courtesy of Dr. Aneta Kecler-Pietrzyk. From the case *Pulmonary Sarcoidosis*. Modified CC BY-NC-SA license.

- **Normal**
  - Case courtesy of Dr. Henry Knipe. From the case *Normal Chest X-Ray*. Modified CC BY-NC-SA license.

- **Normal**
  - Case courtesy of Dr. Bruno Di Muzio. From the case *Normal Chest CT*. Modified CC BY-NC-SA license.

- **Fibrosis**
  - Case courtesy of Dr. MT Niknejad. From the case *Pulmonary Fibrosis*. Modified CC BY-NC-SA license.

**Symptoms:** Cough, dyspnea
Workup of Sarcoidosis: Pulmonary Function Tests (PFTs)

- ↓ vital capacity (normal: 3-5 L)
- ↓ total capacity (normal: 4-6 L)
- ↓ diffusion capacity (normal >75%)

Symptom: Shortness of breath
Workup of Sarcoidosis: Cardiac

Key clinical manifestations of cardiac sarcoidosis:
- Conduction system disease
- Tachyarrhythmias
- Heart failure
- Cardiomyopathy

Symptoms:
- Palpitations
- Presyncope/syncope

Symptoms:
- Fatigue
- Dyspnea
- Orthopnea

Electrocardiogram
Order an ECG to check for heart block and arrhythmias, some of which can be dangerous.

Echocardiogram
Screen for heart failure with history and physical exam. If screening is positive, order an echo.

PET scan
If signs and symptoms are suspicious for cardiac sarcoidosis, order a PET scan.
Workup of Sarcoidosis: Labs

- **Complete blood count (CBC)**
  - Anemia: uncommon
  - Leukopenia: 5-10% of patients
  - Eosinophilia: 3% of patients
  - Thrombocytopenia: rare

- **Liver function tests (LFTs)**
  - ↑ Serum alkaline phosphatase

- **Renal function tests**
  - ↑ Blood urea nitrogen (BUN)
  - ↑ Creatinine

- **Serum calcium and elevated 24-hour urine calcium**
  - Hypercalciuria is more common than hypercalcemia.
Workup of Sarcoidosis: Eye Exam

Uveitis:

Conjunctival granulomas:

Symptoms: Dry eyes, blurry vision, redness, pain, photophobia


Anterior uveitis by Dr. Jonathan Trobe is distributed under a CC BY 3.0 license.
Workup of Sarcoidosis: Skin Biopsy

The diagnosis of sarcoidosis is confirmed by a skin biopsy showing non-caseating granulomas.

While the photo cited above depicts a bone sample, the non-caseating granulomas (as shown by the yellow arrows) are similar to those that would be seen in skin biopsies from patients with specific cutaneous sarcoidosis.
Cutaneous Sarcoidosis: Papules, Nodules, and Plaques

**Papules**
Red to brown violaceous papules not associated with scarring


**Nodules**
Red to flesh colored nodules that can have overlying telangiectasias (on nose)


**Plaques**
Circular well circumscribed ovoid plaques commonly found on extensor surfaces


**Plaques**
Circular well circumscribed ovoid plaques commonly found on extensor surfaces


**Nails** (may manifest as dactylitis and dystrophy):

*Sausage digits and nail dystrophy in sarcoidosis.*

**Scalp** (may manifest as alopecia):

*Scarring alopecia on scalp.*
Case #2

AM is a 24 year old female (she/her/hers) who complains of tender red “bumps” on her bilateral distal extremities for the past week. She first noticed one or two of the bumps on her right leg while she was shaving in the shower, but now they have gradually appeared all over both shins. She’s tried taking ibuprofen for the pain, but it’s only mildly helpful. She denies any recent trauma to the area. However a few days before she noticed the bumps, she reports having some arthralgias and feeling febrile and fatigued.


Medications
- Ibuprofen PRN, for pain
- Cetirizine (2nd gen antihistamine) daily, for seasonal allergies

Medical Hx
- Chickenpox (age 5)
- Seasonal allergies

Social Hx
- Diet: Variety of meats, vegetables/fruit, grains, and dairy
- EtOH: Two 12 oz glasses of wine/day on weekends
- Drugs/Tobacco: Denies

Family Hx
- Mother: Grave’s Disease
Rest of Physical Exam & ROS:

- **Pulmonary**: Mild dyspnea; No cough, sputum or hemoptysis, wheezing, or sore throat
- **Cardiac**: No chest pain, palpitations, or rubs/murmurs
- **GI**: No constipation, diarrhea, N/V, hematochezia, or hepatosplenomegaly
- **MSK**: Ankles swollen and sore bilaterally with full ROM
- **Neuro**: No focal deficits
- **Ophthalmology**: Mildly injected conjunctiva bilaterally
- **Skin**: No other rashes/skin findings or mucosal ulcers

### (Some) Possible Etiologies of EN

- **Sarcoidosis**
  - Likely: Dyspnea, Uveitis, Prodrome of fever/fatigue/arthralgia
  - No cardiac involvement or lupus pernio
- **Inflammatory Bowel Disease**
  - Likely: Fever, Fatigue, Uveitis, Arthralgia
  - No diarrhea, abdominal pain, other rashes, or weight loss
- **Behcet Syndrome**:
  - Likely: Uveitis, Arthralgia, Family hx of autoimmunity
  - No aphthous/genital ulcers, acneiform rash
- **Sweet Syndrome**
  - Likely: Uveitis, Arthralgia
  - No hx of systemic disease, inciting medications, or recent infections
- **Streptococcus Infection**
  - Likely: Fever, Most common infectious cause
  - No sore throat or lymphadenopathy
- **Disseminated Tuberculosis**
  - Likely: Dyspnea, Fever
  - No sputum/hemoptysis, constitutional sx
- **Histoplasmosis/Coccidioidomycosis**
  - Likely: Dyspnea, Arthralgia, Fever
  - No hepatosplenomegaly or sputum
Erythema Nodosum (EN) Overview

- **Form of septal panniculitis**
  - May be a **Type IV (cell-mediated/delayed) hypersensitivity reaction** (immune complexes in venules of subcutaneous fat → inflammation, neutrophil recruitment → non-caseating granuloma formation)
  - **Infectious, systemic, autoimmune, hormonal, and drug/medication-related etiologies**
  - More common in **white patients** than **Black patients** with **sarcoidosis**
  - Females > Males (3-6:1)
  - Age: 20-30’s

- Typically a **clinical** diagnosis; Suspicion supported by:
  - **Acute** onset
  - **Tender, erythematous/violaceous nodules** or plaques 3-20 cm in diameter
  - Classically on the **shins**, but may also occur on ankles, thighs, arms, buttocks, or face
  - May follow **prodrome** of fever, fatigue, and arthralgia
  - Ulcerations, pustules/vesicles, and/or crusting should be **absent**
Erythema Nodosum (EN) Overview

- Usually **spontaneously resolves** within 8 weeks
  - Turns from red → yellow-brown or blue-green (resembles bruises) = “Erythema Contusiformis,”
  - then heals without scarring or with hypo-/hyper-pigmentation

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Example Images of EN:

[Dermatologic Features: Often pretibial nodules or plaques; Erythematous/violaceous (red/purple); Poorly demarcated (no clear margin); Irregular borders; Tender; Non-pruritic (not itchy); Warm to touch]
Nodules = raised, solid lesions >0.5 cm

Plaques = raised, flat-topped lesion with distinct borders up to 0.5 cm


Additional Examples of EN:


Less Common Sites for EN:

**Forearms:**
- Violaceous plaques on the arms.

**Wrists:**
- Nodules on the distal forearm.

**Hands:**
- Nodules on the hand.

**Cubital Region:**
- Erythematous nodules on the elbow.
Examples of hyperpigmentation caused by resolved EN

Clinical Pearl:
Erythema Nodosum is a form of acute panniculitis (inflammation of subcutaneous fat) that presents as warm, red/purple, tender nodules typically on the pretibial surface. It can be a symptom of various systemic infections, autoimmune and inflammatory conditions, hormonal changes, or drug reactions.
Note: This flowchart is not meant to be memorized! Rather, it is to help get you thinking about the diagnostic framework for EN. Some of the most common etiologies are included (however, keep in mind that there are still other, rarer causes)!
Initial Work-Up
(Should depend on medical history & clinical findings)
- Labs
  - CBC
  - ESR & CRP
  - Pregnancy test for individuals of child-bearing capacity
- Chest X-Ray (CXR)
- Skin Biopsy

Cough, Dyspnea, Fatigue, Fever, Arthralgia, Uveitis, Rash
Diarrhea, Abdominal Pain, Uveitis, Malabsorption
Recurrent oral & genital ulcers, Ocular lesions, Rash
Upper Respiratory Symptoms, Exudative Pharyngitis, Fever
Cough, Dyspnea, Arthralgias, Fever, Night Sweats
Cough, Dyspnea, Hepatosplenomegaly, Fever, Oral ulcers
Cough, Dyspnea, Fevers, Night Sweats, Weight Loss

Suspected EN

Comprehensive Medical History
- HPI, PMHx, & ROS
- Medications (esp. OCP’s, Sulfonamides, Halides, & Sulfonylureas)
- Recent travel/exposures

- Labs
  - CBC
  - ESR & CRP
  - Pregnancy test for individuals of child-bearing capacity
- Chest X-Ray (CXR)
- Skin Biopsy

CXR: Lymphadenopathy & Nodular Opacities
CXR: Lymphadenopathy & Consolidations, IgM
CXR: Lymphadenopathy & Cavities, TST Skin Test, IFN-γ Blood Test

ASCA, p-ANCA, Abdominal X-Ray, Colonoscopy
Demonstrates Pathergy
Antistreptococcal O Titers, Throat Swab Culture

CXR: Lymphadenopathy & Nodular Opacities

Drug-Induced

Sarcoidosis
Inflammatory Bowel Disease
Behcet’s Disease
Streptococcal Infection
Coccidiomycosis
Histoplasmosis
Tuberculosis
Summary

- Sarcoidosis a multisystemic inflammatory disorder characterized by granulomas, most commonly in skin and lungs.
- A basic workup of sarcoidosis involves a chest x-ray, ECG, CBC, CMP, and eye exam.
- The diagnostic test for sarcoidosis is a biopsy showing non-caseating granulomas.
- Cutaneous manifestations of sarcoidosis include: papules, plaques, nodules, lupus pernio, and erythema nodosum.
- Lupus pernio is specific to sarcoidosis and involves reddish-purple papules and plaques on nose, cheeks, and ears.
Summary

- Erythema nodosum (EN) is a form of septal panniculitis, characterized by multiple tender, warm, red to purple nodules.
- The most common site is the shins.
- It is thought to be due to a Type IV HS reaction.
- It is a manifestation of an underlying condition; the most common etiologies are drug-induced, infection, or autoimmune/inflammatory conditions.
- While the diagnosis of EN itself is clinical, the workup of the underlying cause should include a thorough history, review of systems, and medication profile.


