Key location: generalized **CASE 3**

Presented by Dorothy Rodenbeck MD, MHS, and Warren Piette MD

History of Present Illness

A 63-year-old woman was admitted for work-up of acute altered mental status. The dermatology service was consulted for a diffuse asymptomatic rash that had been present for 2½ weeks.

The patient denied any preceding illness or medication changes prior to rash onset. She presented to the emergency department due to a 4-day-history of mood instability, behavioral changes, and confusion noted by her family.

Prior to our consult, psychiatry consult in the ED revealed memory and cognition impairment. She was disoriented to location (name of hospital) and time (date and year). She was diagnosed with fluctuating mentation consistent with delirium of unknown cause.

Past Medical History

Melanoma, unknown stage

Medications

None

Travel History

Positive for blackberry picking and camping in Indiana 3 weeks prior to presentation.

Review of Systems

Positive for decreased appetite with a 20-lb weight loss over the prior month. Negative for fever, chills, malaise, headache, nuchal rigidity, paresthesias, weakness, chest pain, palpitations, joint pains, or myalgias.

Physical Exam

Vitals were normal. Skin exam revealed scattered light pink patches, some of which were annular, of various sizes (ranging from 2 to 8 cm in diameter), on her upper extremities, trunk, thighs, and buttocks. Lesions were nonmigratory on 24-hour re-examination.

Laboratory Data

The following labs were remarkable or abnormal:

HGB	11.3	[11.7 – 14.9 g/dL]
ESR	93	[0 – 8 mm/hr]
CRP	4.15	<0.5 mg/dL
Urine tox screen	negative	
ANA	negative	

Radiology

CT, head: unremarkable
MRI, brain: no parenchymal disease/inflammation

Histopathology

Right flank, skin biopsy: Slight ectasia of superficial capillaries with very minimal perivascular mononuclear infiltrate. No evidence of vasculitis. Silver stain negative.

Microbiology
Lyme IgG western blot, serum: +7/10 borrelial proteins
Lyme IgM western blot, serum: +3/3 borrelial proteins
Lyme IgG western blot, CSF: +1 borrelial protein
Lyme IgM western blot, CSF: no bands detected

Diagnosis
Early disseminated Lyme disease

Treatment and Course
We recommended an ID consult to support empiric treatment of Lyme disease. She was started on ceftriaxone and underwent a lumbar puncture. When brain MRI showed no parenchymal disease, a 4-week course of oral doxycycline was initiated.

At 1-month follow-up, patient and family revealed her rash and mood instability had resolved 2½ weeks into her doxycycline course. At 5-month follow-up, she remained asymptomatic.

Discussion
Lyme disease is the most common tick-borne disease in the US. It is a bacterial infection caused by six species in the spirochete family *Borreliaceae*. In North America, infection is caused primarily by *Borrelia burgdorferi* and, less commonly, in a region of the upper mid-West, by *Borrelia mayonii. Borrelia mayonii* has been distinguished from *burgdorferi* by its ability to achieve higher concentrations in the blood in some patients. Both species are transmitted by *the Ixodes scapularis* tick in the eastern and midwestern US.

Clinical signs and symptoms are sufficient for presumptive treatment of disease. According to the CDC, the majority of Lyme cases in the US manifest as early localized disease, characterized by the appearance of the pathognomonic erythema migrans (EM) skin lesion, with or without constitutional symptoms, usually occurring within one month following the tick bite.

Though the EM lesion is classically described as a bull's-eye pattern, it more commonly manifests as circular, homogeneous erythema. Multiple EM lesions represent early disseminated disease, when the spirochete undergoes hematogenous spread days to weeks after infection. Morphology becomes more incongruous and has been described as erythematous rings with central clearing, erythematous plaques or purpura.

With hematogenous spread of spirochetes, early disseminated Lyme may lead to neuroborreliosis with manifestations such as cranial nerve palsies, radiculopathies, meningitis and rarely encephalitis. Many patients with active *Borrelia* infection describe fatigue, cognitive slowing, and memory difficulty, as in our patient. However, these symptoms are nonspecific and are frequent concomitants of many inflammatory disorders so cannot be diagnostic of neuroborreliosis. True brain infection is rare, and diagnosis must be confirmed by CSF abnormalities. CSF *B. burgdorferi* antibody measurement is highly specific for neurologic disease with cross-reactions occurring primarily in neurosyphilis, where clinical distinction can be easily made. When present, encephalomyelitis is evident on MRI as areas of increased signal on T2 and FLAIR sequences. In the absence of such objective evidence of brain infection, these types of symptoms should otherwise not be considered evidence of nervous system infection with *Borrelia* or any other organism.

In addition to neurologic complications, providers should also screen for cardiac complications, such as myopericarditis, in early disseminated disease. Late disseminated disease is characterized by the additional manifestation of large joint arthritis.

Serologic testing for antibodies to *B. burgdorferi* is considered only an adjunct to clinical diagnosis. A two-tiered approach is recommended to support the diagnosis of Lyme disease, with a preliminary sensitive enzyme immunoassay followed by a more specific Western blot test. Following the onset of erythema migrans, IgM antibodies typically appear within one to two weeks; IgG antibodies usually appear within two to six weeks. By the time the patient has findings of early disseminated disease, serologic tests are usually positive for both IgM and IgG antibodies to *B. burgdorferi*.

Guidelines for treatment depend on the symptoms present and the stage of illness. Although the 2006 IDSA guidelines and the 2007 AAN practice parameter recommend parenteral therapy for patients with acute neurologic manifestations other than isolated facial nerve palsy, many experts prefer oral doxycycline based upon several European studies. However, comparison of outcomes of oral vs parenteral therapy has not yet been systematically assessed in the US. Routine follow-up serologic testing is not recommended in assessing the patient who is clinically improving.

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Key location(s): trunk and arms **CASE 4**

Presented by Charles Vainder MD, and Vidya Shivakumar MD

History of Present Illness

A 70-year-old man presented to the Emergency Department due to acute worsening of a chronic skin rash. He first noticed "bumps" on his arms and chest four years ago, which had stabilized after a year. Four weeks prior to presentation, he noted new lesions on his neck and chest. The lesions started small and enlarged over time. There was associated severe pruritus and occasional pain. He had tried an "allergy pill" with no improvement. He had no previous history of skin disease. He denied recent travel. No close contacts had similar complaints.

Past Medical History

Diabetes mellitus

Medications

Glipizide, metformin

Review of Systems

Negative for fever, chills, weight loss, lymphadenopathy, headache, change in vision, chest pain, shortness of breath, cough, abdominal pain, change in bowel habits, bone, and joint pain. Positive for pruritus.

Physical Exam

Skin:	Upper extremities, trunk, neck: hundreds of yellow to red-brown clustered, indurated papules coalescing into plaques

Laboratory Data

CBC	Unremarkable
CMP	Unremarkable
HIV screen	Negative
Serum protein electrophoresis	Unremarkable

Histopathology

Punch biopsy, right superior chest:
Skin with superficial and deep dense histiocytic-like and lymphocytic cell proliferation with a background of rare eosinophils and neutrophils. The histiocytoid cells show relatively abundant cytoplasm (some with foamy appearance), intermediate sized nuclei with round, indented to kidney bean shapes and inconspiuous nucleolus. Mitoses are uncommon.

Immunohistochemistry positive for CD68, CD163, CD1a and S-100, and negative for CD21, CD23, CD30, AE1/3 and EMA. Langerin immunohistochemical study performed was negative.

Radiology

CT chest/abdomen:
No axillary, mediastinal or hilar lymphadenopathy. Visualized abdominal organs appear unremarkable. Right upper and lower lobe nodules stable in size and morphology.

Diagnosis

Indeterminate cell histiocytosis (Indeterminate dendritic cell tumor)

Treatment and Course

The patient was treated with narrow band UVB (NBVUB) light. After five sessions, he noticed improvement in pruritus then self-discontinued therapy. At follow up, he noted new lesions on his neck and restarted NBUVB therapy. We currently are awaiting follow up.

Discussion

Indeterminate cell histiocytosis (ICH) was first described as unique from other histiocytic proliferations by Wood et al in 1985. Since its description, less than one hundred cases have been reported. Unlike Langerhans Cell Histiocytosis (LCH), which can be a multisystemic disease, ICH is characterized by an indolent clinical course with primarily cutaneous involvement. It is distinguished from LCH by immunohistochemical stains. Since its original description, ICH has synonymously been named indeterminate dendritic cell neoplasm and indeterminate dendritic cell tumor- with these terms being used interchangeably in published cases. Given its rarity, it has been prone to misdiagnosis, misclassification, and confusion with other histiocytic neoplasms.

Clinical presentation of ICH is divided into singular lesions or disseminated cutaneous disease. The presentation often mimics non-Langerhans cell histiocytoses like xanthogranuloma, multicentric reticulohistiocytosis, or generalized eruptive histiocytosis. Based on reviews, the vast majority of cases present with skin-limited disease with papules on the head, chest, trunk, and extremities. More rare presentations include plaques, patches, or leonine facies. In contrast to Langerhans cell histiocytosis, a disease that predominantly affects younger age groups, the median age at presentation is 45 years.

Immunohistochemistry is necessary to diagnose and distinguish ICH from other histiocytic diseases. ICH is a neoplasm characterized by a dendritic cell proliferation, which stains positively for CD1a, CD68, and S-100; however, it lacks Birbeck granules that are typical for Langerhans cells. This distinguishing feature can be appreciated by a langerin-specific stain, CD207, which is a marker for Birbeck granules. In contrast to LCH, there is no epidermotropism and a scarcity of eosinophils

Given its rarity and similarity to other histiocytic diseases, there is debate whether it is a unique entity and whether it is truly neoplastic or a reactive process. The origin of the neoplastic cells is unknown. Primary theories are that the indeterminate cell is a precursor Langerhan cell that has not yet developed Birbeck granules or, conversely, that the indeterminate cell is a previously matured Langerhan cell that lost its Birbeck granules. Exclusive to ICH, a translocation of nuclear receptor coactivator 2 (NCOA2) and ETV3 has been reported. This has been used as possible evidence that ICH is a unique neoplastic process.

Characteristically, ICH follows a benign clinical course. Some cases have resolved spontaneously. Despite the benign nature of ICH, a review of 79 cases found that seventeen (22%) cases were associated with a second hematopoietic neoplasm. Six additional cases were associated with chronic myelomonocytic lymphoma and eight more cases had a concurrent lymphoma. While this could represent a bias given the relatively late onset of most cases of ICH, a review of systems and basic bloodwork is recommended.

Owing to the rarity of ICH, there is no consensus protocol or standardized treatment regimen. Solitary lesions have successfully been treated with excision; however, management strategies for disseminated presentations are more difficult. A wide array of therapies have been used including methotrexate, thalidomide, cyclophosphamide, and pravastatin. Recently, case reports have touted the efficacy of narrow band ultraviolet therapy as an effective and safe treatment.

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Key locations: Skin, lymph nodes **CASE 6**

Presented by Susan Hwang MD and Joerg Albrecht MD

History of Present Illness

A 36-year-old man with history of allergic rhinitis and recently diagnosed chronic kidney disease, leukopenia and normocytic anemia presented with a 6-month history of asymptomatic skin lesions which began around the mouth then generalized to involve the neck, torso and extremities.

Past Medical History

Allergic rhinitis, chronic kidney disease, leukopenia, normocytic anemia

Medications

None

Social History

Marijuana several times daily, never tobacco smoker
Stockist at Home Depot
Sexually active with 1 female partner

Review of Systems

Positive for unintentional weight loss, fatigue, night sweats, dyspnea on exertion

Physical Exam

Non-skin:	Vitals stable, cachectic, cervical, axillary, inguinal lymphadenopathy (6cm right groin node, 4cm left groin node)
Skin:	Forehead, upper and lower eyelids, medial canthi, neck, torso, upper and lower extremities with erythematous round to oval plaques with surrounding hyperpigmentation; no mucosal involvement

Laboratory Data

The following labs were remarkable/abnormal:

BUN	37	[8-20 mg/dL]
Creatinine	2.1	[0.6-1.4 mg/dL]
WBC	4.0	[4.4-10.6 k/uL]
Lymphocytes (absolute)	0.6	[1.2-3.4 k/uL]
Hemoglobin	10.6	[12.9-16.8 g/dL]
LDH	501.0	[85-210 U/L]
CRP	3.5	[0.0-0.5 mg/dL]
Calcium (corrected)	12.0	[8.5-10.5 mg/dL]
SPEP	IgG, IgA (polyclonal)	
ACE	>120.0	[8 to 52 U/L]
ANA	>1:160, speckled	
Urinalysis	Protein, blood	

Histopathology

LEFT MEDIAL THIGH, SKIN, PUNCH BIOPSY:
Large, geographic basophilic infiltrate concentrated in the dermis. Necrobiotic granulomata seen on higher power. Trichrome and elastic stains showed destruction of collagen and elastic fibers within the center of these granulomata. AFB, GMS and PAS stains were negative for microorganisms.

RIGHT GROIN, LYMPH NODE BIOPSY:
Right groin node biopsy: Non-caseating granulomatous lymphadenitis. AFB, FITE, GMS statins were negative for microorganisms.

Microbiology
LEFT MEDIAL THIGH TISSUE; URINE, SPUTUM CULTURES:
Negative for organisms.

Radiology
Radiograph, chest: bilateral hilar adenopathy
PET/CT, chest, abdomen, pelvis: splenomegaly, hypermetabolic activity of spleen; lymphadenopathy of chest, abdomen, pelvis; increased metabolic activity in marrow spaces of spine, bony pelvis, proximal femora

Diagnosis
Sarcoidosis, mimicking lymphoma

Treatment and Course
Tests for HIV, HSV, VSV, hepatitis, syphilis and tuberculosis were negative. Skin biopsy demonstrated granulomas. The patient was referred to Hematology and had a lymph node biopsy performed to exclude lymphoma. Follow up and treatment with prednisone was initiated by rheumatology.

The patient had EKG abnormalities, which were judged to be clinically insignificant by cardiology. Pulmonary function test showed obstructive ventilatory defect with normal FEV-1. Renal biopsy was initially planned but abandoned when the renal failure was judged to be secondary to kidney stones on CT scan. Repeat scans and ophthalmologic exam is pending but the patient did not report symptoms. The patient was treated with prednisone 20 mg with improvement in skin lesions and constitutional symptoms.

Discussion
Sarcoidosis is a systemic inflammatory disorder most commonly involving the lungs, skin, lymph nodes, eyes and liver. The disease is characterized by non-caseating granulomas in affected organs; epithelioid macrophages and CD4 T-helper cells are implicated in the pathogenesis. It is a diagnosis of exclusion and all other causes of non-caseating granulomas must be ruled out. Our patient's presentation was unusual and points to a number of idiosyncrasies that can confuse the practitioner; some of them we address in this write up.

Lymphoma
Our patient's presentation with diffuse lymphadenopathy and unintentional weight loss, fatigue, night sweats, dyspnea on exertion made exclusion of a lymphoma mandatory. Since the 1960s a relationship between sarcoidosis and lymphoma has been suggested, and a higher risk of lymphoma and lung cancer has been confirmed in prospective studies. The term sarcoidosis-lymphoma syndrome was devised along with several observations: lymphoma followed sarcoid, the median age of a sarcoid diagnosis in lymphoma patients was 10 years older than those with sarcoid diagnosed first, and Hodgkin lymphoma was the most common lymphoma linked to sarcoid. However, other studies have not been able to replicate these findings. Romer et al found that the incidence of malignancy was higher for all groups with autoimmune and inflammatory disorders than expected; sarcoid patients alone did not have a higher rate. Currently, there are no recommendations to screen sarcoid patients for cancer.

Histology

The patient's skin histology demonstrated prominent necrobiosis, but no non-caseating granulomas and was most consistent with necrobiotic granuloma. This hindered assessment and evaluation because a diagnosis of sarcoidosis could not be readily made. Only the later lymph node biopsy was classic for sarcoid. Parallel histology consisting of necrobiotic granuloma and sarcoidosis in several non-diabetic patients have been reported in the literature.

Cardiac involvement

Our patient had EKG changes, which, on further evaluation by cardiology, were thought to be insignificant. Five percent of sarcoidosis patients have clinically symptomatic disease, but up to 25% of patients with sarcoidosis have heart involvement. Most of the symptomatic patients seem to have little extracardiac involvement. Since the primary problem in sarcoidosis is conduction defects, a baseline EKG can evaluate them easily, especially if the patient has no clinical symptoms. Any cardiac symptoms need to be worked up by a cardiologist. In its extreme form, conduction defects cause the majority of symptoms, ventricular arrhythmias and sudden death. Significant cardiomyopathy may also occur, but is hard to diagnose.

Nephrolithiasis and renal impairment

Our patient had nephrolithiasis possibly secondary to sarcoidosis – though a relationship was never conclusively demonstrated. Nephrolithiasis and nephrocalcinosis can be secondary to calcinuria in patients with sarcoidosis. Renal impairment and failure in sarcoidosis can also be due to hypercalcemia, but our patient did not have this. Renal sarcoidosis can directly lead to granulomatous interstitial nephritis due to immune complex deposition, but usually the renal involvement in sarcoidosis is silent, except when huge granulomas impair function of the lower urinary tract.

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