CLINICAL IMAGE

HYPERPIGMENTED NODULAR RASH IN A 61-YEAR-OLD AFRICAN AMERICAN FEMALE

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KEYWORDS:

Cutaneous sarcoidosis

Hyperpigmented rash

Sarcoidosis

A 61-year-old African American female presents to an outpatient family health center with a hyperpigmented nodular rash of 2 months' duration. The rash first appeared on her abdomen before spreading across her upper arms, lower leg, back, face and scalp. She has a history of controlled type 2 diabetes mellitus, cerebral aneurysm rupture, Sjögren's syndrome, asthma and a left below-the-knee amputation due to osteomyelitis. She smokes cigarettes but does not use alcohol or illicit substances. She has also noticed a dry cough with mild dyspnea on exertion over the past 6 months. On physical exam, hyperpigmented nodules are palpable in both the intradermal and subcutaneous layers of the skin. Nodules are firm, mobile and nontender. Alopecia is noted where scalp nodules are present. Her lungs exhibit diminished air movement throughout, with scattered, end-expiratory wheezing.

A 6 mm punch biopsy performed of a skin nodule demonstrates non-necrotizing granulomatous dermatitis.

QUESTIONS:

1. What is the most likely diagnosis?

A. Granuloma annulare

B. Sarcoidosis

C. Tuberculosis

D. Foreign body reaction

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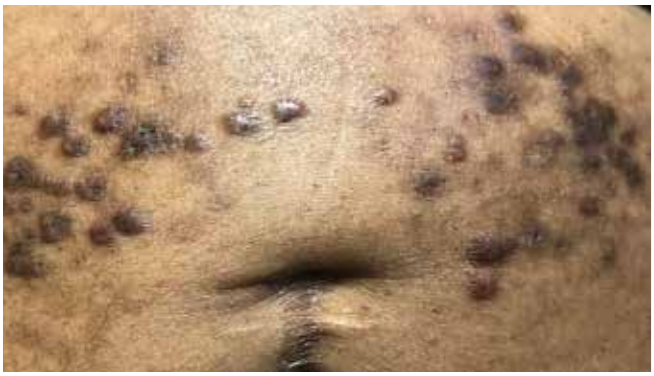

2. What initial imaging study should be performed to help confirm this diagnosis?

A. Ultrasound of skin lesion

B. Brain magnetic resonance imaging (MRI)

C. Chest radiograph

D. Positron emission tomography/computed tomography (PET/CT) scan

ANSWERS:

1. What is the most likely diagnosis?

Correct Answer:
B. Sarcoidosis

Cutaneous lesions are found in 20%–35% of patients with sarcoidosis.[1] Skin manifestations of sarcoidosis come in many different forms, including papules, plaques, nodules (including subcutaneous), alopecia, scar lesions and hyperpigmented patches.[1] Given the variable presentation of sarcoidosis, the diagnosis is often difficult to reach. It is important to consider any suspicious cutaneous lesion as part of a systemic process, as lesions can be utilized to easily obtain a tissue diagnosis. No single test is confirmatory for the diagnosis of sarcoidosis, but histologic evidence of noncaseating granulomas is important supporting evidence.

This patient is exhibiting nodular sarcoid lesions on her abdomen, which is a common cutaneous manifestation.[1] She also had deeper subcutaneous nodules present on the upper arms and posterior lower legs that are far less common. The differential for nodular granulomatous skin lesions includes granuloma annulare, tuberculosis, rheumatoid nodules, primary neoplastic or metastatic lesions, and foreign body reactions. Granuloma annulare is a

relatively common and self-limited primary skin disorder that traditionally involves annular plaques on extremities but can also present as subcutaneous nodules.[2] Tuberculosis skin lesions have subtle histologic differences compared to sarcoidosis.[3] Whereas tuberculoid granulomas exhibit a dense lymphocytic infiltrate, this is notably absent in granulomas in sarcoidosis.[3] A negative acid-fast stain does not rule out tuberculosis; therefore, further workup should determine whether there is a high index of suspicion for mycobacterium infection.[3] Granulomas can form as a reaction to foreign bodies in the skin, and a thorough history should help guide this diagnosis.[3]

2. What initial imaging study should be performed to help confirm this diagnosis?

Correct Answer:
C. Chest radiograph

Although there is no definitive imaging for diagnosis of sarcoidosis, chest radiographs should be obtained to assess for the classic bilateral hilar lymphadenopathy seen in pulmonary sarcoidosis.[4] At least 90% of patients with sarcoidosis have evidence of lung involvement.[5] Findings on radiography should be followed up with high-resolution chest computed tomography and pulmonary function testing to further assess lung structure and function.[5] Ultrasound can be helpful in assessment of a skin lesion but is not helpful as a diagnostic tool in this case. Brain MRI is the imaging modality of choice in patients with suspected sarcoidosis and neurologic symptoms. There is growing literature on the utility of PET/CT in diagnosis and management of sarcoidosis. PET/CT with fluorine 18 fluorodeoxyglucose (FDG) can assess the inflammatory activity of sarcoid lesions throughout the body and is being studied as a means to identify occult lesions that would otherwise be difficult to obtain tissue diagnosis.[6] The clinical usefulness of PET/CT in sarcoidosis is still unclear and is not currently recommended for routine use.

DISCUSSION:

Sarcoidosis is a multisystem inflammatory disorder characterized by tissue infiltration of noncaseating granulomas. Although the exact cause is unknown, research suggests a genetic predisposition to formation of an exaggerated immune response to environmental exposures.[7] A twin cohort study out of Denmark and Finland estimated the heritability to be around 66%.[7] In this study, at least one twin with sarcoidosis was identified in 210 twin pairs.[7] Interestingly, the statistical analysis revealed an 80-fold increased risk of developing sarcoidosis in the co-twin of monozygotic twins compared with a mere 7-fold increase in dizygotic twins.[7]

The prevalence of sarcoidosis is estimated to be 10–20 per 100,000 and is more common in those of middle age, female gender and Black race.[8] Geographical patterns have also identified increased incidence in the United States and Scandinavia.[8] Epidemiologic factors also appear to influence disease presentation. Clinical presentation is highly variable, and up to one-half of all cases are incidentally discovered.[5] Asymptomatic disease is more common in whites, whereas severe musculoskeletal or constitutional symptoms arise more frequently in African Americans.[8] In symptomatic disease, intrathoracic structures are most frequently affected and generally present as persistent cough, dyspnea or chest pain.[5] Cutaneous involvement is the next most common and can take many forms.[5] Fever, fatigue, anorexia, weight loss and weakness are commonly associated symptoms.[9] Additional manifestations can arise from involvement of other organ systems, such as neurologic impairment (central and peripheral), uveitis, vision loss, cardiomyopathy, cardiac dysrhythmia, biliary disease or renal failure.

The diagnosis of sarcoidosis is made through a combination of findings through laboratory testing, imaging and histologic examination. Other possible etiologies for presenting symptoms must be excluded, namely tuberculosis, which can present in a similar manner. The most helpful supporting evidence is histologic evidence of noncaseating granulomas in affected tissue.[5] Although nonspecific, elevated angiotensin-converting enzyme (ACE) is found in 75% of patients.[10] Other associated lab abnormalities include hypercalcemia, hypercalciuria, hypergammaglobulinemia and elevated inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein.[8] Imaging of the chest can reveal the classic bilateral hilar lymphadenopathy, additional adenopathy and/or interstitial lung disease.[4] The diagnosis can be made without histology in two distinct clinical presentations. Löfgren syndrome presents with the triad of hilar lymphadenopathy, erythema nodosum and polyarthralgia, and can have associated fevers and lung parenchymal involvement. Heerfordt-Waldenström syndrome presents with acute parotitis, fever, uveitis and facial nerve palsy. At time of diagnosis, patients should be evaluated for additional organ involvement with electrocardiography (EKG), pulmonary function testing, ophthalmologic evaluation and baseline renal and hepatic function tests.

There is no cure for sarcoidosis, but treatment with immunosuppressive therapy can slow the granulomatous process. First-line treatment is corticosteroids, with methotrexate as second-line.[11] Cutaneous sarcoid has demonstrated a positive response to intralesional corticosteroids, tetracyclines and hydroxychloroquine.[11] A growing body of evidence supports monoclonal antibody therapies (specifically infliximab and adalimumab) as potential third-line treatments for resistant cases.[11] Interestingly, spontaneous remission can occur in up to half of all cases. Sarcoidosis can affect any organ system to incite dysregulation and lead to a host of complications. Although most cases of sarcoidosis are mild or asymptomatic, chronic disease persists in 10%–30% and mortality has been estimated at up to 6%.[12] Keeping sarcoidosis in our differential diagnosis is important for timely identification and treatment to prevent the associated morbidity and potentially deadly complications.

CASE SUMMARY:

In this case, skin biopsy of a suspicious rash led to the diagnosis of sarcoidosis. The patient's associated symptoms of dry cough and dyspnea on exertion were concerning for pulmonary involvement, and a chest radiograph confirmed bilateral hilar adenopathy. Subsequent computed tomography demonstrated peripheral fibrotic changes and ground glass opacities with bilateral axillary,

mediastinal, and hilar lymphadenopathy. Lab studies were significant for an elevated ACE level and hypergammaglobulinemia, and the EKG demonstrated a right bundle branch block. The patient was started on prednisone 20 mg by mouth daily. At 3 months, her rash had completely resolved, and respiratory symptoms had significantly improved. Her chest CT was repeated 6 months after initiation of treatment and showed regression of ground glass opacities and near-resolution of lymphadenopathy.

AUTHOR DISCLOSURE(S)

No relevant financial affiliations or conflicts of interest. If the authors used any personal details or images of patients or research subjects, written permission or consent from the patient has been obtained. This work was not supported by any outside funding.

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