JAMA Dermatology Clinicopathological Challenge

Coalescing Subcutaneous Nodules

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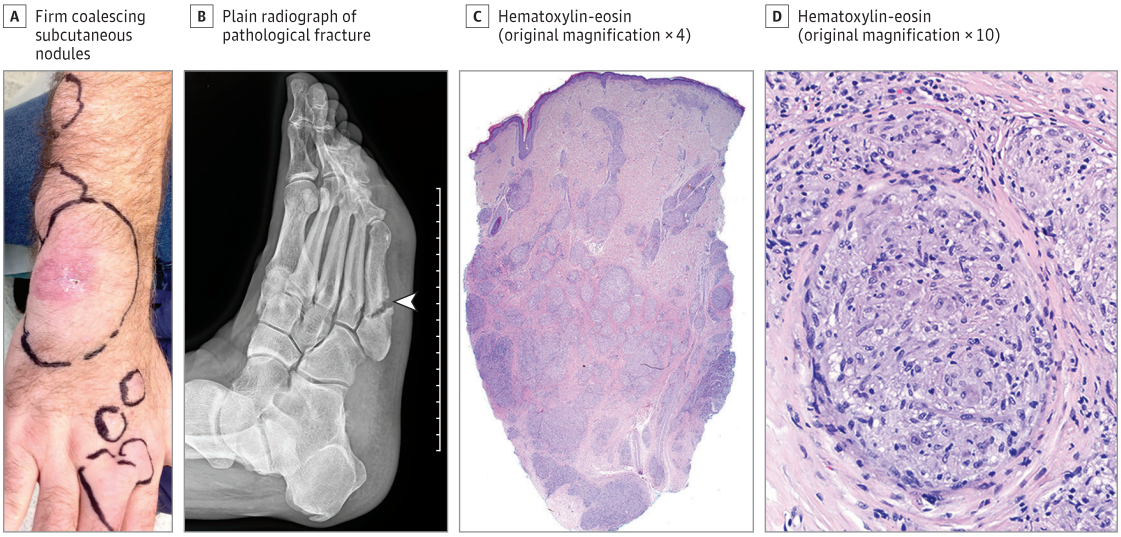

Figure. A, Nodules are 4 to 6 cm in diameter on the right upper extremity. B, A pathological fracture on the fifth metatarsal on the right foot is indicated by the white arrowhead. C, Histopathology shows pale, nodular aggregations of inflammatory cells in the deep dermis, extending into the fibrotic subcutis, as well as (D) aggregations composed of epitheliod histiocytes with few other inflammatory cells, so called "naked granulomas."

A 40-year-old man of Scandinavian descent presented with enlarging, nonpainful upper extremity nodules developing over the preceding 9 months (**Figure**, A). He was renovating a commercial cannabis grow-house in California at time of onset. He described the construction site as being filled with intoxicating mold. He reported shortness of breath and a 20-pound weight loss. He denied recent travel or aquarium exposure. Most concerning was the inability to use his right upper extremity. Also, he developed a pathological fracture of his right foot (Figure, B). Clinical examination of his forearms revealed several yam-size (4-6 cm), nontender, nonulcerated, boggy subcutaneous nodules in a sporotrichoid pattern and large nodules scattered on his trunk and abdomen. There was no palpable lymphadenopathy or lower extremity lesions. His medical history is significant for diabetes mellitus type 2 and hypothyroidism. Medications included glipizide, metformin, and levothyroxine.

The patient's laboratory tests showed fasting glucose of 122.0 mg/dL (reference range, 65.0-115.0 mg/dL); total calcium, 10.2 mg/dL (reference range, 8.5-10.5 mg/dL); blood urea nitrogen, 16.0 mg/dL (reference range, 10.0-24.0 mg/dL); creatinine, 1.30 mg/dL (reference range, 0.6-1.3 mg/dL); hemoglobin A_{1c}, 6.7 (reference range, 4.0-6.0); 1,25-OH vitamin D 70, ng/mL (reference range, 15.9-55.6).

Liver enzymes were within normal limits along with a negative purified protein derivative and quantiferon test results. A culture from a cutaneous nodule with microbial stains for bacteria, fungal culture, and acid-fast bacilli was negative. Computed tomography of the chest revealed hilar lymphadenopathy. An incisional biopsy of a nodule on the right wrist was obtained, which showed nodular aggregations of epithelioid histiocytes with sparse peripheral lymphocytes, extending from the deep dermis into the subcutis (Figure C and D). Periodic acid–Schiff diastase and Fite stains were negative for fungal and mycobacterial organisms, respectively.

WHAT IS YOUR DIAGNOSIS?

A. Sporotrichosis

B. Subcutaneous sarcoidosis

C. Tumoral calcinosis

D. Erythema nodosum

Diagnosis

B. Subcutaneous sarcoidosis

Microscopic Findings and Clinical Course

Analysis of the biopsy specimen showed deep dermal sarcoidal granulomas extending into the subcutis and no evidence of infection, which in combination with his clinical presentation, is consistent with sarcoidosis with cutaneous, pulmonary, metabolic, and bone involvement. He was started on 40 mg of prednisone daily, methotrexate 15mg/week, and hydroxychloroquine 200 mg twice daily. After 12 weeks of therapy, the lesions resolved and he was able to return back to work with full mobility. His pulmonary function improved throughout the course of therapy.

Discussion

Darier-Roussy sarcoidosis is a rare subcutaneous manifestation of sarcoidosis, affecting approximately 1% to 4% of patients with sarcoidosis. It was originally described in 1904 by the French dermatologist Ferdinand-Jean Darier and the Swiss-French pathologist Gustave Roussy.[1] They believed mycobacteria was the inciting microbe. Darier-Roussy sarcoidosis has been associated with systemic and subcutaneous involvement.[2] Clinically, it is characterized by multiple asymptomatic to slightly tender flesh colored nodules commonly located on the extremities. In contrast with erythema nodosum, which is typically seen on the anterior lower extremities, the lesions of subcutaneous sarcoidosis are flesh colored, not tender, and are generally free of lymphocytic infiltrate.[2,3]

Tumoral calcinosis is generally characterized by hypercalcemia with calcium salt deposits occurring in the hip and shoulder joints. Histologically, these masses are comprised of calcium phosphate and calcium hydroxyapatite.[4] Sporotrichosis, an agricultural pathogen caused by the fungus *Sporothrix schenckii*, can manifest as linear subcutaneous nodules that may also show granulomatous inflammation; however, the organism can usually be identified through stains and by culture.[5]

Sarcoidosis is often referred to as the "great imitator" and can have multiple presentations. Although it can involve multiple organ systems, cutaneous lesions are present in about 25% of patients. Common locations affected include the skin, lungs, lymph nodes, eyes, and heart.[6] Skin lesions are heterogeneous and may be specific including facial granulomatous plaques, or present with nonspecific reactive findings, such as erythema nodosum. Biopsy can be beneficial by demonstrating epithelioid granulomatous inflammation.[5]

Dysregulation of calcium metabolism is a complication of sarcoidosis. This results in hypercalcemia, hypercalciuria, and reduced bone density. The most common bones affected in sarcoidosis are the small bones of the hands and feet.[7] Pathological fractures can occur and are attributed to abnormal calcium metabolism, often seen in patients with extensive cutaneous disease.[7] Extra renal synthesis of calcitriol is central to the pathogenesis of abnormal calcium homeostasis. Calcitriol also has known immunosuppressive properties which may be an adaptive response allowing the inciting antigen or microbe to go unnoticed by the immune system.[8]

Environmental, occupational exposure, and Scandinavian descent may have been multifactorial in this patient's development of this rare variant of sarcoidosis. Positive associations of sarcoidal granulomatous development have been demonstrated in patients exposed to mold, mildew, musty odors, and pesticides.[9] Worldwide, the highest incidence of sarcoidosis is in individuals of Nordic heritage.[5]

The majority of microorganisms associated with marijuana are plant pathogens and may affect immunocompetent humans. There is a subgroup of opportunistic plant pathogens associated with postharvest and/or storage decay of marijuana, which may have been the case here. These include several Aspergillus species (including *Aspergillus Mucor*), *Pseudomonas aeruginosa*, *Clostridium botulinum*, and toxigenic *Escherichia coli*.[10] Additionally, opportunistic organisms on cannabis plants can produce dangerous toxins or can elicit allergic reactions when inhaled.[10] Perhaps bronchioalveolar lavage may be another way to further elucidate etiological factors in systemic sarcoidosis.

Despite significant advances in characterizing features of sarcoidosis, the underlying pathophysiological cause remains unclear. As marijuana is becoming a more accepted form of medical therapy for patients, education in its procurement and dissemination is vital for the public's health.

ARTICLE INFORMATION

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