DARIER-ROUSSY SUBCUTANEOUS SARCOIDOSIS: A CASE-BASED REVIEW

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Received: February 26, 2024
Accepted: March 23, 2024

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Abstract
Sarcoidosis is a systemic granulomatous inflammatory condition characterized by varied clinical manifestations, with a higher prevalence observed in individuals aged 25 to 40 and women over 50. Typical presentations involve symmetric involvement of hilar and mediastinal lymph nodes, followed by lung involvement. While initial stages are often asymptomatic, the disease can impact various organs. Cutaneous involvement, observed in up to a quarter of patients, includes lupus pernio, papules, plaques, erythema nodosum, and occasionally subcutaneous nodules. Subcutaneous sarcoidosis, once considered rare, is now increasingly recognized. We present a case of Darier-Roussy sarcoidosis in a middle-aged man, demonstrating multiple painless subcutaneous nodules confirmed through biopsy. Our findings suggest that Darier-Roussy sarcoidosis typically manifests early in the disease course, indicating non-severe systemic involvement. Additionally, our patient responded well to hydroxychloroquine treatment, suggesting a positive outcome.

Keywords: sarcoidosis, subcutaneous, nodular.

Introduction

Sarcoidosis is a granulomatous multifocal inflammatory condition of unexplained exact etiology, characterized by non-caseous epithelioid cell granulomas. It has variable clinical presentations and varying prognoses [1]. The disease is observed at a prevalence rate of 10-20 per 100,000 persons, with most cases diagnosed between the ages of 25 and 40 and a second peak in women greater than 50 years old [2].

Sarcoidosis typically demonstrates symmetric involvement of hilar and mediastinal lymph nodes and lung involvement [2]. Patients are usually asymptomatic during the early course, and the diagnosis is usually incidentally made on a chest radiograph. Otherwise, it could involve the heart, liver, nervous system, eyes, skin, or calcium metabolism [3].

Up to one-quarter of patients with sarcoidosis have cutaneous involvement, which includes classic lupus pernio, papules, scars associated with sarcoidosis, plaques, erythema nodosum, and occasionally subcutaneous nodules [4]. Subcutaneous sarcoidosis, also known as Darier-Roussy sarcoidosis, often presents as painless nodules, typically flesh-colored and arranged in linear patterns [5]. It is considered a rare occurrence, observed in approximately 1.4% to 6% of individuals with systemic sarcoidosis [6], but it is thought to be increasing in prevalence [7].

For most sarcoidosis patients, the condition resolves spontaneously and does not necessitate therapeutic intervention [8]; hence, its management requires a multidisciplinary approach, given the wide possible organs involved. For those who require systemic therapy, corticosteroids are often the first line, with immunosuppressants such as methotrexate or biological therapies being alternatives for more severe disease [3].

Our case report features a middle-aged man exhibiting multiple painless subcutaneous nodules, confirmed through biopsy to be Darier-Roussy sarcoidosis. The report adheres to the CARE statement guidelines of the EQUATOR Network (https://www.care-statement.org/checklist). Furthermore, we conducted a comprehensive literature review of published cases of Darier-Roussy sarcoidosis to provide an in-depth discussion of this rare manifestation of sarcoidosis.

Case report

A 55-year-old male presented to the dermatology clinic in July of 2022 with multiple painless subcutaneous slightly pruritic nodules of variable sizes of two months duration. He reported that a single nodule first appeared, followed quickly by the appearance of the remainder of the nodules. Dermatological examination revealed multiple, well-demarcated, hard skin color, non-tender nodules, without secondary changes over the dorsal part of the hands, forearms, abdomen, eye, and legs. The largest one on the arms measured 2-3 cm (Figure 1).

A soft tissue ultrasound was ordered, revealing multiple scattered variable-sized, hypodense subcutaneous nodules with hypervascular appearances. Consequently, the patient was referred to both plastic surgery for excisional biopsy and to the rheumatology clinic for evaluation of a possible systemic disease.

Before developing the lesions, the patient denied a preceding history of fever, weight loss, arthralgia, dyspnea, chest pain, or cough. There were no associated eye symptoms, oral or genital ulcerations, dysphagia, abdominal pain, altered bowel habits, urinary symptoms, headache, seizures, or neurological deficits. He had an unremarkable medical and surgical history and no recent travel or intake of new medications, and he is not a smoker. On physical examination, he looked well, and his vital signs were a temperature of 36.3 °C, blood pressure of 118/73 mmHg, respiratory rate of 18, heart rate of 80 beats per minute, and an oxygen saturation of 98% on room air. The comprehensive physical examination was essentially unremarkable, with no lymphadenopathy or organomegaly.

The patient underwent a series of investigations that included normal blood count with a normal differential of leukocytes, normal creatinine, alanine transaminase, aspartate transaminase and alkaline phosphatase, electrolytes, and serum calcium. The erythrocyte sedimentation rate was modestly elevated at 34 millimeters (mm) per hour, while the C-reactive protein was normal at 4 milligrams / Liter. Urine analysis was unremarkable. Chest radiography showed bilateral hilar adenopathy (Figure 2). The patient underwent an excisional biopsy of one of the forearm nodules, and histopathology demonstrated non-necrotizing granuloma, which is multinucleated giant cells sprinkled with lymphocytes. Special stains for acid-fast bacilli and fungi were negative and negative for malignancy. A subsequent computed tomography scan of the chest with intravenous contrast (Figure 3) confirmed the presence of hilar and mediastinal lymphadenopathy and multiple small nodules 1-2mm, in keeping with sarcoidosis.
Figure 1. Clinical photographs of the patient showing the variable sizes of subcutaneous nodules over the face, arm, and hand.

Figure 2. Imaging findings. A- posterior-anterior chest radiograph showing bilateral hilar enlargement. B-Computed tomography of the chest and mediastinal window showing hilar lymphadenopathy. C: Computed tomography of the chest-lung window showing pulmonary nodules.
Ophthalmologic examination, electrocardiogram, and echocardiogram were normal, with no evidence of ocular or cardiac sarcoidosis.

With these clinical, radiological, and histopathological findings, the Darier-Roussy subtype of sarcoidosis diagnosis was made, which was a big relief for the patient, who was very concerned about possible malignancy. The patient was educated about the diagnosis, and he was offered expectant management, but he opted for treatment. Hydroxychloroquine 400 mg daily was prescribed, and he showed an excellent response. On his last visit, six months after his diagnosis, he was asymptomatic with no respiratory symptoms and with minimal residual subcutaneous lesions.

Search Strategy

Youn P et al. reviewed thirty cases of subcutaneous sarcoidosis published between 2000 and 2020 [9]. Accordingly, we performed a literature review in PubMed and Scopus electronic databases for published case reports between 2020 and February 15, 2024, adhering to comprehensive search recommendations [10]. Only English-language sources were considered, using the search terms «subcutaneous,» «sarcoidosis,» and «Darier-Roussy sarcoidosis.» Articles were initially screened based on their title and abstract, and full texts were reviewed to ensure relevance. The search results can be found in Table 1 and the discussion section.

Discussion

Skin involvement is a prominent feature of sarcoidosis, especially prevalent in Black American females [4], with the neck, upper back, and trunk being the most affected areas [11]. At presentation, sarcoidosis may resemble infectious, drug-induced, or neoplastic processes, potentially causing delays in diagnosis [12, 13]. Accurate diagnosis relies on a comprehensive assessment involving clinical, radiological, biochemical, and pathological findings[14].

Our search results found only three male patients among 14 published cases, and it has been reported in the literature that subcutaneous sarcoidosis is more prevalent in women than men, with a higher incidence observed in the fourth decade of life [15]. The mean age at presentation in the cases we reviewed (Table 1) was 45.6 years ±11.29 years. Subcutaneous sarcoidosis often presents as painless nodules, typically flesh-colored and arranged in linear patterns [5], and is usually asymptomatic and may go unnoticed.

The differential diagnosis encompasses a range of conditions, including lipomas, rheumatoid nodules, subcutaneous granuloma annulare, granulomas attributed to foreign body reactions, and lymphoproliferative malignancies[16].

Darier-Roussy sarcoïdosis was initially thought to affect only the skin, however; advancements in imaging like Computed Tomography (CT) and fludeoxyglucose-18 positron emission tomography (FDG-PET) scan have revealed its potential for widespread involvement [9]. Still, it mostly appears at the start of the sarcoïdosis. This presentation typically signifies sarcoïdosis with non-severe systemic involvement and is not associated with chronic fibrotic disease [7].

There are no established guidelines for the treatment of subcutaneous disease. Instead, treatment is usually based on a case-by-case evaluation and focuses on treating disfiguring lesions involving the skin [17]. Hydroxychloroquine has demonstrated efficacy, particularly in managing cutaneous manifestations, and some considered it the preferred initial treatment for subcutaneous sarcoidosis.[8, 9, 18]. The duration of therapy for subcutaneous sarcoidosis is often unspecified, and the general goal is cure. Despite additional pulmonary involvement, the prognosis of subcutaneous sarcoidosis is generally good.

Youn P et al. reviewed fifteen cases of subcutaneous sarcoidosis published between 2000 and 2020 [9] who had simultaneous lung involvement. Treatment strategies varied, including expectant management, systemic steroids, hydroxychloroquine, and topical steroids, with outcomes of either complete recovery or partial improvement, indicating a positive prognosis associated with the subcutaneous disease. This finding was also observed among the cases published in the last few years (Table 1), with the majority completely resolved either on their own or with hydroxychloroquine, among other therapies.

Lopez-Sundh et al. reported a case series of 19 patients from Spain with subcutaneous sarcoidosis [19]. The lesions were mostly located in the upper extremities. Most patients were female, with a mean age of presentation around 54.6 years old. Presenting symptoms varied, including skin lesions, lung involvement, and extracutaneous manifestations like arthritis and one case with uveitis. Treatment strategies ranged from oral steroids to topical and combination therapies, resulting in remission for most of the patients. However, one patient experienced recurrence, highlighting the importance of long-term follow-up.
Table 1. Published cases of Darier-Roussy sarcoidosis since 2020.

<table>
<thead>
<tr>
<th>Author</th>
<th>Country and Year</th>
<th>Age and gender</th>
<th>Presenting symptoms</th>
<th>Location of subcutaneous lesions</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alnaimat, et al.</td>
<td>Jordan, 2024</td>
<td>55, M</td>
<td>Painless multiple subcutaneous nodules</td>
<td>Dorsum of the hands, forearms, abdomen, face, and legs</td>
<td>Hydroxychloroquine 200 mg</td>
<td>Full resolution at six months</td>
</tr>
<tr>
<td>Gullapalli et al.</td>
<td>USA, 2023</td>
<td>40, F</td>
<td>Multiple soft tissue swellings on the upper extremities</td>
<td>Forearms, bilateral elbows, the extensor aspects of fingers, and the thumb</td>
<td>Systemic steroids, hydroxychloroquine, methotrexate, and adalimumab</td>
<td>Incomplete response to the used therapies until Adalimumab was added, which caused a significant reduction in the nodule size</td>
</tr>
<tr>
<td>Zhang H et al., [22]</td>
<td>India, 2023</td>
<td>49, F</td>
<td>Subcutaneous nodules on extremities with multiple pulmonary nodules and hilar LAP</td>
<td>Rt. hand, Rt. Wrist, Rt. Elbow, and Rt. thigh</td>
<td>Hydroxychloroquine 100 mg bid, thalidomide 50 mg bid,</td>
<td>All subcutaneous nodules disappeared after three months of treatment</td>
</tr>
<tr>
<td>Santos et al. [23]</td>
<td>2022</td>
<td>50, F</td>
<td>Systemic symptoms and subcutaneous nodules on the face and arms in a patient with Porotasis</td>
<td>The frontal and submandibular region, Rt. Side of the face, and Rt. elbow</td>
<td>Prednisone and hydroxychloroquine</td>
<td>Full resolution</td>
</tr>
<tr>
<td>Sharma et al. [5]</td>
<td>Nepal, 2022</td>
<td>35, M</td>
<td>Cough and fever for three months. Initially diagnosed as tubercular lymphadenitis and treated with anti-TB drugs.</td>
<td>Legs, followed by the arms, forearms, thigh, and trunk</td>
<td>Systemic Steroids</td>
<td>Full resolution in two months</td>
</tr>
<tr>
<td>Noritak O et al. [24]</td>
<td>Japan, 2022</td>
<td>64, F</td>
<td>Posterior uveitis, subcutaneous nodules on the extensor aspect of the extremities and buttock, CXR with typical BHL</td>
<td>Rt. forearm, lower leg, and right buttock</td>
<td>Only corticosteroid eye drops</td>
<td>Muco-cutaneous lesions gradually improved after three years</td>
</tr>
<tr>
<td>Lea et al. [26]</td>
<td>Korea, 2022</td>
<td>48, F</td>
<td>Cough, dyspnea, and palpable subcutaneous nodule in Lt. lower leg, chest CT showed mediastinal LAP</td>
<td>Lt. distal lower leg</td>
<td>1 mg/kg/day prednisone</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Deena Patil et al. [27]</td>
<td>India, 2022</td>
<td>40, F</td>
<td>Papules over both forearms, upper back, face, ear lobes, limbs, serosis over both legs, thick ulnar nerve. Coexistent leprosy</td>
<td>Forearm, back, face, ear lobe, and distal legs</td>
<td>0.5 mg/kg/day prednisone</td>
<td>Complete recovery</td>
</tr>
<tr>
<td>Haritha K et al., [28]</td>
<td>India, 2022</td>
<td>40, F</td>
<td>Painful multiple subcutaneous nodules and dactylitis. CXR with BHL. Biopsy from subcutaneous nodules showed sarcoidosis.</td>
<td>Both forearms</td>
<td>Oral prednisolone 40 mg daily with tapering over three months</td>
<td>Complete resolution after eight weeks</td>
</tr>
<tr>
<td>Izadi Firouzabadi L, et al.</td>
<td>Iran, 2021</td>
<td>27, F</td>
<td>Upper and lower extremities, trunk, and abdomen</td>
<td>Lt. arm, upper back, abdomen, and Rt. thigh</td>
<td>Intraleisional triamcinolone (10 mg/mL)</td>
<td>Complete remission after six months</td>
</tr>
<tr>
<td>Noh et al. [14]</td>
<td>Malaysia, 2021</td>
<td>38, M</td>
<td>Acute back pain, skin plaques, subcutaneous nodules, and asymptomatic mediastinal LAP. Confirmed as sarcoidosis by histopathological examination</td>
<td>Throughout the trunk and the limbs</td>
<td>Offered but not given as of the time of the report</td>
<td>Unavailable</td>
</tr>
<tr>
<td>Marcoval J, et al. [30]</td>
<td>Spain, 2021</td>
<td>71, F</td>
<td>Subcutaneous nodular lesion in the Rt. Wrist after pembrolizumab for melanoma, BHL.</td>
<td>Rt. wrist</td>
<td>Observation and Clinical and 18F-FDG PET/CT follow-up to check the evolution of the lesions.</td>
<td>Outcome unavailable</td>
</tr>
<tr>
<td>N. Norikawa, et al. [31]</td>
<td>Japan, 2020</td>
<td>47, F</td>
<td>Subcutaneous nodules on the fingers. Histological examination showed non-caseating epitheliod cell granulomas, chest CT and x-ray showed BHL.</td>
<td>The first to third digits of the Rt. hand</td>
<td>Unavailable</td>
<td>Kobner phenomenon in sarcoidosis due to the nature of his work,“ heavy loads.”</td>
</tr>
</tbody>
</table>

Abbreviations: LAP: lymphadenopathy, CT: computed tomography, CXR: chest radiograph, BHL: bilateral hilar adenopathy, Rt.: right, Lt.: left.
Additionally, a case series from Japan by Toshiyuki Yamamoto [20] reported 13 cases of sarcoidosis. Most patients were female (10 out of 13), with an average age of 58.0 years. Lesions were commonly located in the lower extremities and trunk. Lung involvement was observed in all cases, while eye and heart involvement varied. Treatment outcomes showed one case of spontaneous regression. Comparison with previous studies reveals similar demographics and lesion distributions, with variability in systemic involvement and treatment outcomes.

Conclusion

Darier-Roussy sarcoidosis typically presents early in the disease course, signaling non-severe systemic involvement. Our case demonstrated an excellent response to hydroxychloroquine, suggesting a generally favorable prognosis.

REFERENCES


