CASE REPORT

Subcutaneous Sarcoidosis (Darier Roussy Sarcoid): A Rare Entity of Cutaneous Sarcoidosis

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Summary
Sarcoidosis is a multisystem disease characterised by granulomatous inflammation possibly due to hyperactivation of the immune system; with unknown etiology. Subcutaneous sarcoidosis (also known as Darier Roussy sarcoid) is a rare type of specific cutaneous lesion of sarcoidosis characterised by multiple firm, asymptomatic to mildly tender, mobile, round to oval, and skin coloured nodules. Herein we report a rare case of subcutaneous sarcoidosis.

Key words: *Subcutaneous sarcoidosis, Darier Roussy sarcoid, Non-caseating granulomas*

Introduction
Sarcoidosis is a multisystem disease characterised by granulomatous inflammation possibly due to hyperactivation of the immune system; with unknown etiology.[1] The clinical features of sarcoidosis can be cutaneous and non-cutaneous. For cutaneous findings, it can be classified into specific and non-specific findings. Subcutaneous nodules (Darier-Roussy sarcoid) is a form of specific cutaneous lesion of sarcoidosis.[1] Subcutaneous sarcoidosis accounts for < 6% of sarcoidosis;[2] with fewer than 100 cases reported so far.[3] Herein we report a rare case of subcutaneous sarcoidosis on both forearms associated with acute polyarthritis in an elderly gentleman.

Case Report
A 69-year-old Indian gentleman with underlying hypertension and type 2 diabetes mellitus for more than 10 years, presented with multiple asymptomatic skin coloured nodules over bilateral forearms for 2 months. Prior to the onset of the nodules, he had an episode of multiple joint pain involving both ankle joints and shoulder girdle of which he was diagnosed with polymyalgia rheumatic (PMR) by a rheumatologist. However, he had no temporal headache or ophthalmic symptoms. This acute episode of polyarthritis was relieved

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drastically with corticosteroid over 24 hours. Subsequently, he noticed multiple soft to firm and painless subcutaneous nodules over both his forearms which gradually increased in size over 2 months. There were no similar nodules on his legs or other parts of his body.

Otherwise he did not experience any cough, shortness of breath, eye symptoms or neurological symptoms. There was no uveitis or peripheral neuropathy. He was diagnosed with gouty arthritis for more than 10 years with history of obstructive uropathy which had resolved. He had been taking allopurinol only when eating seafood which he claimed would precipitate the pain. He had no cardiorespiratory symptoms. Neither had he contact with tuberculosis patient nor contributory family history. He never smoked but drank alcohol on social event. On physical examination, there were multiple non-tender, soft to firm subcutaneous nodules measuring approximately 3cm x 4cm on both forearms with normal overlying and surrounding skin (Figure 1a). It was not attached to the underlying structure.

Respiratory examination was normal and there were no peripheral lymph nodes palpable. There was no organomegaly and examination of other systems were unremarkable. The clinical differential diagnosis included erythema nodosum, nodular vasculitis, rheumatoid nodules, subcutaneous sarcoidosis and subcutaneous granuloma annulare.

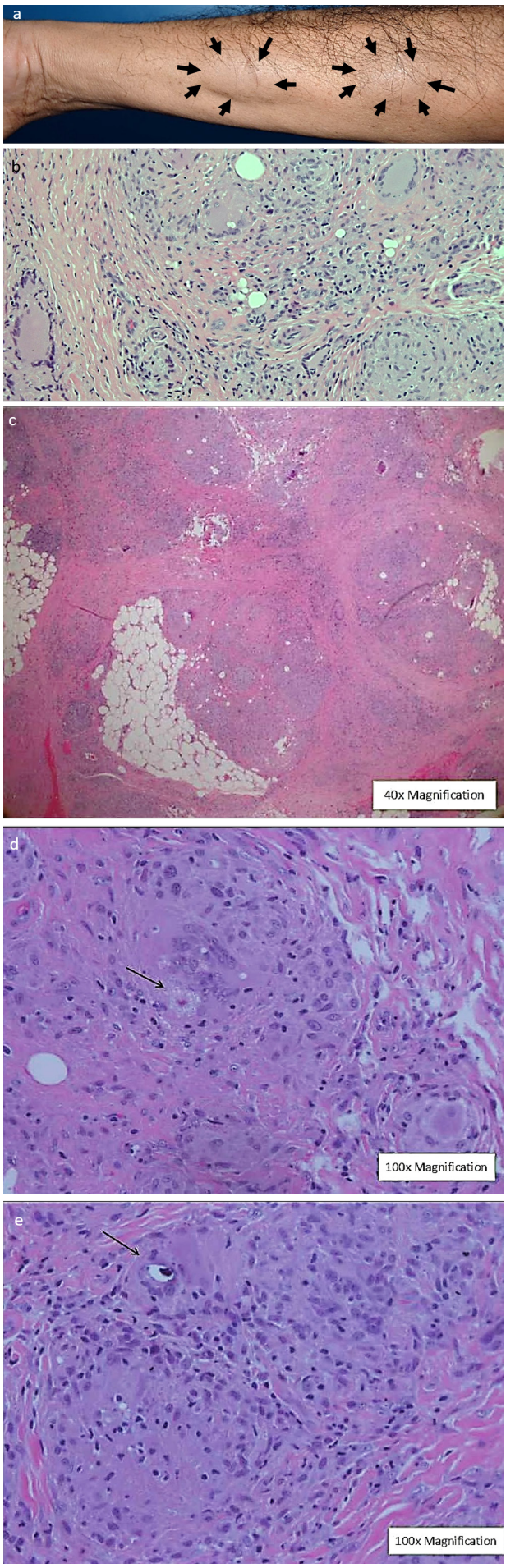

Figure 1(a) Multiple subcutaneous nodules on left forearm (arrows show the outline of the nodules); (b) low power magnification (4x10) of non-caseating granulomas; (c) Non-caseating granulomatous infiltrate in the dermis extends into subcutaneous fat; (d) Non caseating granuloma composed of epithelioid histiocytes, multinucleated giant cells and sparse lymphocytes at the periphery. Asteroid body is seen here (arrow); (d) Non caseating granuloma composed of epithelioid histocytes, multinucleated giant cells and sparse lymphocytes at the periphery. Schaumann body is seen here (arrow).

Laboratory investigations revealed raised ESR 63 mm/hour, C-reactive protein (CRP) 23, negative rheumatoid factor (RF) and anti-citrullinated cyclic peptide (CCP), serum calcium 2.47 mmol/L, normal complete blood count, renal and liver profiles. Skin biopsy was performed which showed multiple noncaseating granulomatous inflammation in the deep dermis and subcutis (Figure 1b&c). The naked granulomas were composed of epithelioid histiocytes with abundant eosinophilic cytoplasm and oval nuclei containing a small central nucleolus, with variable amount of multinucleated giant cells and only sparse lymphocytes at the periphery. Asteroid body and Schaumann body were seen (Figure 1d&e). Ziehl Neelsen stain for acid fast bacilli and Periodic acid-Schiff stain for fungal body were all negative. Tissue culture for tuberculosis was negative.

Further investigation revealed raised serum Angiotensin Converting Enzyme (ACE) levels (123 U/L) (Normal level: 16-85 U/L) or 2.09 mcKat/L (0.27 – 1.45 mcKat/L). His biochemical profiles, serum calcium and phosphate as well as tumour markers were normal.

The quantiferon gold test for tuberculosis was negative. Other blood investigations revealed Anti-nuclear Antibody (ANA) 1:160 (speckled), Erythrocyte Sedimentation Rate (ESR):40 and Rheumatoid Factor:<20. Plain chest radiography was reported as normal. Computed tomography (CT) scan of the thorax revealed multiple hilar, mediastinal and paraaortic lymph node enlargement consistent with stage I sarcoidosis. \

He was diagnosed as subcutaneous sarcoidosis with sarcoid arthritis. He was eventually started on topical clobetasol propionate cream with oral prednisolone 30mg od and tapered off within 1 month. It was combined with oral hydroxychloroquine 200mg od. His skin lesion resolved completely after 1 month of therapy.

Discussion

Cutaneous involvement in sarcoidosis occurs in 20% to 35% of patients and can present as a variety of different morphologies.[4] Cutaneous sarcoidosis can be divided into specific and nonspecific lesions depending on the presence of noncaseating granulomas on histologic studies.[5] Specific sarcoidosis lesions have granulomas on histologic examination and often show the apple-jelly coloration characteristic of granulomatous skin lesions on diascopy.[6] The other differential diagnosis of apple-jelly diascopy include lupus vulgaris, pseudolymphoma and lupoid rosacea.[7] Specific lesions include maculopapules, plaques, subcutaneous nodules, lupus pernio, scar infiltration, annular, verrucous, lichenoid, psoriasiform angiolupoid and ulcerative lesions.[5] Nonspecific skin lesions are lack of granulomas and caused by inflammatory reactions to sarcoidosis.[8] The most common nonspecific lesions are erythema nodosum, erythema multiforme, calcifications, prurigo, nail clubbing, and Sweet syndrome.[2]

Subcutaneous sarcoidosis (also known as Darier -Roussy sarcoidosis) is a rare form of cutaneous sarcoidosis. Clinically it is characterized by multiple firm, asymptomatic to mildly tender, mobile, round to oval, and skin coloured nodules.[5] It commonly involves the extremities, but the trunk and face can also be affected.[2] It is more prevalent in middle aged women, who commonly presents with lymphadenopathy or pulmonary infiltrates on chest imaging; as well as elevated levels of serum ACE.[9]

Systemic involvement was noted in 64% and 60% of patients with specific and nonspecific skin lesions respectively in a review of 120 patients with cutaneous sarcoidosis.[6] Pulmonary sarcoidosis is the most common manifestation of systemic involvement with up to 90% of patients having abnormal chest radiographs.[6] Bilateral hilar adenopathy (stage I disease) is seen in about half of patients with intrathoracic sarcoidosis.[6] Ocular sarcoidosis is seen in one-third of patient with sarcoidosis with at least two-thirds of cases have anterior uveitis while posterior uveitis occurs in up to 28% of sarcoidosis cases.[6]

Other important systemic involvement include cardiac, hepatic and neurological sarcoidosis. Hypercalcemia and hypercalciuria can be seen in patients with sarcoidosis due to activated macrophages in sarcoidal granulomas which promote conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D leading to increase intestinal absorption of calcium, bone resorption, and urinary calcium excretion.[6]

Being a great imitator, diagnosis of cutaneous sarcoidosis requires a high index of clinical suspicion. Cutaneous sarcoidosis is usually an early manifestation of the disease in up to one third of cases.[10] This should prompt the clinician to evaluate for systemic involvement. Moreover, the skin is a convenient source for tissue biopsy and therefore the diagnosis of cutaneous sarcoidosis can be made more rapid than other forms of sarcoidosis. A reasonable diagnosis of cutaneous sarcoidosis can be made in most cases from the appearance of skin lesions supported by confirmatory histology after excluding other noncaseating granulomatous diseases.[6]

The characteristic histologic finding of sarcoidosis is presence of noncaseating epithelioid granulomas, with minimal or absence of lymphocytes or plasma cells (naked granuloma).[11] In subcutaneous sarcoidosis, the non-caseating granulomas is present in the subcutaneous tissue.[12] Within the giant cells, Schaumann bodies and Asteroid bodies may be found but are not specific for sarcoidosis.[6] Schaumann bodies are rounded, laminated basophilic inclusions that represent degenerating lysosomes and observed in 48%-88% of cases in sarcoidosis.[13] Schaumann bodies can also be seen in other inflammatory granulomatous conditions such as tuberculosis, chronic beryllium disease, hypersensitivity pneumonitis and Crohn's disease.[14] Asteroid bodies are star-shaped spiculated structures that represent engulfed collagen seen as eosinophilic stellate inclusions and it is observed in 2%-9% of sarcoidal granulomas.[15] Asteroid bodies are most commonly seen in sarcoidosis, histoplasmosis and foreign body granulomas, but can be seen in any multinucleated giant cells formation.[16]

Angiotensin-converting enzyme (ACE) levels can be increased in up to 60% of cases with sarcoidosis but the value as a diagnostic test and prognostic marker remains limited.[6] It is because serum ACE levels may also be raised in other granulomatous diseases and can be influenced by genetic polymorphisms.[16] In view of lack of a specific diagnostic test, sarcoidosis is a diagnosis of exclusion and diagnosis requires the following 3 criteria: clinicoradiographic findings compatible with the diagnosis, histologic confirmation of noncaseating granuloma and exclusion of other known causes of granulomatous disease.[17]

Differential diagnosis of subcutaneous sarcoidosis include erythema nodosum, subcutaneous granuloma annulare, tuberculosis, rheumatoid nodules, epidermal cyst, lipoma, and deep mycosis.[5] Based on the clinical and histopathological findings in our patient, diagnosis of subcutaneous sarcoidosis was made after excluding all the above differential diagnosis.

Corticosteroid is the mainstay treatment for sarcoidosis as it suppresses inflammation and halt the progress of granuloma formation.[18] Ultrapotent corticosteroid (e.g. Clobetasol) is the drug of choice for limited mild cutaneous lesions.[18] Intralesional corticosteroids are used for small sarcoid plaques and papules, with dose of 3-20mg/ml repeated 4 weekly until the lesions have flattened.[18] Systemic corticosteroid is indicated for severe disfiguring or destructive lesions, widespread involvement, and lesions refractory to localized treatment.[18] Prednisolone dose ranges form 0.3-0.5mg/kg/day; with responses noted within 4-8 weeks after initiation of treatment.[3]

Second line therapy are reserved for steroid-resistant sarcoidosis and for patients who are unable to tolerate steroids.[18] Examples of second-line therapy include antimalarial therapy, cytotoxic agents such as methotrexate, azathioprine, leflunomide, and mycophenolate.[5] Antimalarial agents (e.g. chloroquine and hydroxychloroquine) have anti-inflammatory

properties, but relapse of sarcoidosis following discontinuation of therapy is very common.[18] The recommended dose of hydroxychloroquine is 200-400mg/day for at least 12 weeks to induce clinical improvement. Methotrexate is given at 10-25mg/week for at least 6 months to be effective.[19]

Biologics are reserved as third-line therapy, of which infliximab can be a good choice.[18] Alternative treatment modalities for sarcoidosis include pentoxyfylline, tetracyclines, thalidomide, isotretinoin, allopurinol, cyclosporin and laser therapy.[4,18] Newer treatment that have been proven effective include repository corticotropin injections and rituximab.[4] For our patient he was started on oral prednisolone 30mg od (at 0.5mg/kg/day), hydroxychloroquine 200mg od and topical corticosteroids with complete resolution of lesion following 1 month of therapy.

Conclusion

Subcutaneous sarcoidosis is rare, which requires clinicopathology correlation for diagnosis. It remains a diagnosis of exclusion. Cutaneous sarcoidosis remains one of the great imitators due to its varied clinical presentation. The hallmark of histopathology examination is a naked or sarcoidal non-caseating granuloma. The mainstay of treatment for sarcoidosis include corticosteroid, antimalarials and methotrexate.

Conflict of Interest Declaration

The authors have no conflict of interest to declare.

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