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Sarcoidosis – A Diagnostic Challenge

Chavan RB[1], Belgaumkar VA[2], Gosavi AP[3], Chirame SS[4]

Department of Skin & VD Sassoon General Hospital Pune, Maharashtra, India

Abstract: ***Sarcoidosis is a multisystem granulomatous disease of unknown cause. The lung is the most commonly affected organ, but the skin is frequently involved. Infiltration with noncaseating granulomas is the hallmark of the disease, and it may result in various clinical manifestations thus called as "great imitator" in dermatology so many times clinical as well as histopathological diagnosis is challenging and needs clinicopathological correlation. We present two such cases of sarcoidosis which were a diagnostic challenge.***

Keywords: sarcoidosis, noncaseating granuloma, granulomatus disease, great imitator

1. Introduction

Sarcoidosis is a multi-systemic disorder that can involve any organ system. Infiltration with non-caseating granulomas is the hallmark of the disease, resulting in various clinical manifestations. The underlying cause of sarcoidosis remains unknown. Although it has no predilection for age, gender or race, previous studies suggest that sarcoidosis more frequently affects persons of Scandinavian, Irish, or black descent[1] Amongst few estimates available from India, sarcoidosis constituted 10-12 cases per 1000 new registrations annually at a respiratory unit at Kolkata with Marwari community at a higher risk and 61.2 / 100,000 new cases seen at an institute in Delhi.[2] However, there seems to be paucity of data on cutaneous involvement from Indian sub-continent.

2. Case Reports

Case 1

A 47 years male was referred with erythematous infiltrated plaques over extremities, trunk, nape of neck (Fig1,2,3). He had been diagnosed as borderline tuberculoid leprosy and treated with multidrug therapy (Tab. Rifampicine , Dapsone, Clofazimine) for 12 months without improvement. Peripheral nerves were soft, non-tender. No sensory-motor deficit or trophic ulcers were found. Systemic examination was unremarkable. Biopsy was done considering sarcoidosis as another differential diagnosis.

Case 2

A 44 years old female presented with asymptomatic lesions since one month. Dermatological examination revealed multiple well defined normoaesthetic skin coloured to erythematous firm papules coalescing to form oval plaques over side of neck and extremities (Fig 4,5). Peripheral nerves were soft and non-tender. Her systemic examination was within normal limits. Although skin biopsy was initially reported as borderline tuberculoid leprosy, on meticulous observation diagnosis of sarcoidosis was confirmed by clinicopathological correlation.

In both cases histopathology confirmed diagnosis of sarcoidosis with multiple non-caseating granulomas comprising epitheloid giant cells, scanty lymphocytes and histiocytes. At some places these were periadnexal. Ziehl-Neelsen stain was negative (Fig 6,7). Angiotensin converting enzyme levels were elevated (110 in case1, 125 in case2). Serum calcium level was normal in both cases. Fortunately no systemic involvement was detected in either case despite thorough investigation. Both patients were initiated on Tab hydroxychloroquine 200 mg once a day after opthalmological evauation with significant regression noted over two months.

3. Discussion

Clinical diagnosis of sarcoidosis is baffling, especially when it presents with nonspecific cutaneous lesions or without systemic involvement as seen in both our cases. Although cutaneous manifestations are present in 30 % of patients and may be the first presenting sign [3], they are the sole manifestation of sarcoidosis in approximately 10 percent of patients[4]. Because lesions assume a vast array of morphologies, cutaneous sarcoidosis is known as one of the "great imitators" in dermatology. Involvement may be mild or severe, self-limited or chronic. Although the list is exhaustive diverse presentations and differential diagnoses of cutaneous sarcoidosis are enumerated in Table 1[5].

Cutaneous sarcoidosis is classified as acute, subacute and chronic depending upon stage of disease[6] [Table 2] Cutaneous involvement is classified as "specific" or "nonspecific"[7] Histopathologically, specific lesions manifest as non-caseating granulomas, whereas non-specific lesions do not reveal granulomas on histopathologic examination.[Table 3]

Recommended basic assessment for sarcoidosis includes thorough history and investigations to detect systemic involvement [8] [Table 4]

Histopathological differential diagnosis includes mainly leprosy, granuloma annulare, necrobiosis lipoidica, annular elastolytic giant cell granuloma, Crohn"s disease.[9] [Table 5] Tuberculoid leprosy, which may show granulomas in association with only a sparse lymphocytic infiltrate, is difficult to distinguish from sarcoidosis. Only 7% of tuberculoid leprosy biopsies show occasional acid-fast bacilli which may easily be overlooked . The most likely place to find bacilli is within degenerated dermal nerves. In contrast with sarcoidosis, the granulomas of tuberculoid leprosy form around dermal nerves that are undergoing necrosis and hence often appear elongated. Moreover, these

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granulomas show small areas of central necrosis more often than in sarcoidosis[10] Clinical correlation may be required to distinguish between these two diseases. Schaumann (conchoid) and asteroid (stellate) bodies composed of collagen[11] are inclusion bodies often found in giant cells in sarcoidosis and other sarcoidal granulomas. Though not specific, their identification may provide a vital clue to diagnosis. Their numbers increase as lesions age.

Although cutaneous lesions may show spontaneous resolution, various treatment options available are high-potency topical corticosteroids, intralesional triamcinolone injections, tacrolimus, cryotherapy, radiotherapy, PUVA therapy. Systemic therapy options like systemic corticosteroids, methotrexate, azathioprine, and mycophenolate mofetil, infliximab and etanercept, alefacept are reserved for patients with progressive organ damage.[12] Other drugs like allopurinol, doxycycline and chloroquine [13] Minocycline, levamisole, isotretinoin, thalidomide have also shown efficacy. Newer modalities like laser, ultraviolet radiation and photodynamic therapies are also effective. Antimalarial drugs are useful for skin and joint sarcoidosis, and hypercalcemia. [14] As both the patients had isolated cutaneous involvement they were started on Tab Hydroxychloroquine .

In India, sarcoidosis is probably either underdiagnosed or misdiagnosed as its closest and more common differential i.e. leprosy. Although sarcoidosis is often a diagnosis of exclusion, a thorough histopathological evaluation of every suspicious case is necessary.

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Tables

Table 1: Common presentations and differential diagnoses of Cutaneous Sarcoidosis

Papules	Granulomatous rosacea, Acne, Benign appendageal tumors
Plaques	Psoriasis, Lichen planus, Nummular eczema, Discoid lupus erythematosus, Granuloma annulare, Cutaneous T-cell lymphoma, Kaposi's sarcoma, Secondary syphilis, Lupus pernio, Cellulitis, Other inflammatory panniculitis

Table 2: Classification of cutaneous sarcoidosis

Stage of the disease	Type of cutaneous lesions
Acute („benign“)	Erythema nodosum
Acute and subacute	Erythematous and erythematopapular, Scar sarcoidosis, Papular
Subacute and chronic	Erythrodermic, Nodular,
Chronic	Plaque, Lupus pernio, Miscellaneous(Ulcerative, psoriasiform, palmoplantar, ungual, mucosal Sarcoidosis of black Africans)

Table 3: Specific and nonspecific lesions of sarcoidosis

Specific lesions	Nonspecific lesions
Angiolupoid form Annular Lupus pernio Macular Papular(small nodular) Erythematus Nodular Plaque form Scar Erythroderma	Erythema nodosum Sweet disease Pyoderma gangrenosum Eruptions resembling viral exanthem or drug reaction Prurigo nodularis Erythema multiforme erythroderma

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Table 4: Basic assessment for sarcoidosis in patients

No	Basic assessment for sarcoidosis in patients
1	History (including occupational and environmental exposures)
2	Physical examination
3	Slit lamp and ophthalmoscopic examination
4	Chest radiograph
5	Urine and serum calcium level
6	Liver and renal function tests
7	ACE level
8	Electrocardiogram
9	Pulmonary function tests (including spirometry and diffusion of carbon monoxide)
10	Tuberculin skin test

Table 5: Histopathological differential diagnosis

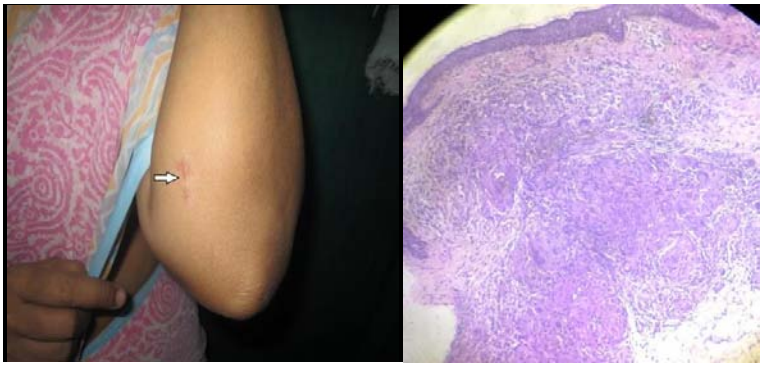
	Cutaneous Sarcoidosis	Granuloma annulare	Necrobiosis lipoidica	Annular elastolytic giant cell granuloma	Crohn"s Disease
Typical location of granuloma	Superficial and deep dermis	Superficial and mid dermis	Entire dermis, subcutis	Superficial and mid dermis	Superficial and deep dermis
Granuloma pattern	Tubercle with few peripheral lymphocytes ("naked")	Palisading or interstitial	Diffuse palisading and interstitial	horizontal "tiers" Palisading	Irregular Tubercle with Surrounding lymphocytes
Necrobiosis (altered collagen)	No	Yes ("blue")	Yes ("red")	No	No
Giant cells	Yes	Variable	Yes	Yes	Yes
Elastolysis	No	Variable	Variable	Yes	No
Elastophagocytosis	No	No	No	Yes	No
Asteroid bodies	Yes	Variable	Variable	Yes	No
Mucin	No	Yes	Minimal	No	No
Extracellular lipid	No	Variable	Yes	No	No
Vascular changes	No	Variable	Yes	No	No

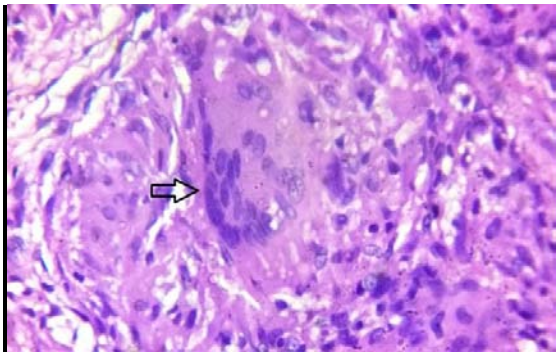
Legends

1) Case 1, Annular normoaesthetic infiltrated plaque on nape of neck.
2) Case 1, Normoaesthetic infiltrated plaques on back.
3) Case 1,Normoaesthetic infiltrated plaques on face , scalp.
4) Case 2, Multiple well defined normoaesthetic skin coloured to erythematous firm papules coalescing to form oval plaques over nape of neck.
5) Case 2, Skin coloured to erythematous firm papules over extremities.
6) H and E(10X), Multiple non-caseating granulomas comprising epitheloid giant cells, scanty lymphocytes and histiocytes. At some places these were periadnexal. ZN stain was negative.
7) H and E (40X), Giant cell in non-caseating granuloma.



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