Sarcoidosis- A Rare Disease Diagnosis by Cutaneous Manifestation, Clinical and Histopathological Correlation

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ABSTRACT

BACKGROUND

Sarcoidosis is a multisystem disease the aetiology of which is still undetermined even after extensive search. Caesar Boeck, the pioneering Norwegian dermatologist used the term "multiple benign sarcoid of the skin" for sarcoidosis. Many articles have been published and research is still going on. We wanted to evaluate the diagnosis of sarcoidosis with cutaneous lesions of various morphology along with the clinical profile and relevant investigations including histopathological examination of those patients who attended outpatient department at School of Tropical Medicine for last 5 yrs.

METHODS

We conducted combined prospective and retrospective observational study of skin biopsy cases of 39 patients having clinically suspected cutaneous lesions from January 2014 to December 2018 (sample size taken as per convenience). This study was conducted at the Department of Pathology in correlation with the Department of Dermatology in School of Tropical Medicine, Kolkata.

RESULTS

A total of 39 clinically suspected cases of sarcoidosis in 36-40 years age group were included in the study. 11 showed non-caseating granulomas and diagnosis of sarcoidosis had been considered after clinical correlation along with other relevant investigations. The patients presented with brown red or purple popular lesions over skin of face, chest wall, back, upper extremities for a period of 6 months to 1 year. 4 cases presented with dry cough, occasional fever, weight loss and arthralgia and 2 cases had dyspnoea and palpitation. Poly-arthralgia involving knee, ankle, elbow with skin lesions was present in 2 patients. One patient had recurrent fever, arthralgia, erythema nodosum over ankle, feet and shin bone. Two patients had only skin lesions without any systemic illness.

CONCLUSIONS

Diagnosis of sarcoidosis is tricky and often confused with other diseases. Its diagnosis is by method of exclusion. In most cases, definite diagnosis requires a biopsy of skin, lymph node or lung.

KEY WORDS

Cutaneous Sarcoidosis, Histopathological Examination, Noncaseating Granulomas

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BACKGROUND

Sarcoidosis is a rare multisystem disease of undetermined cause.¹ Although Jonathan Hutchinson described the first case in 1869, the etiology of the disease is still unknown. It may involve any organ system and can occur at any age. Patients are usually presented with various clinical manifestations.² Systemic sarcoidosis may present with cutaneous manifestation up to one third of patients (25-35%). Recognition of skin lesions is very important as because these are visible clues to diagnosis and easily accessible tissue material for histopathological diagnosis.³ Patients can present with various morphologies and for the reason cutaneous sarcoidosis is known as great imitators for dermatologists.⁴ Involvement may be mild or severe; may lead to spontaneous resolution or may lead to chronic disease; may persist as localized lesion or may lead to organ damage.

Different type of skin lesions stating from macules, papules, single plaques or plaques in crops, lupus pernio, scar sarcoidosis to the rarest one like alopecia, ulcers, hypo pigmented patches, ichthyosis can occur. Skin lesions usually appear over nape of the neck, over upper back extremities and trunk. Studies of patients with systemic sarcoidosis along with skin lesions usually have poorer prognosis.⁵

Sarcoidosis commonly involves lungs, but it can involve almost any organ and non-caseating granulomas is the hallmark of the disease. Diagnosis of sarcoidosis is tricky and often confused with other diseases. There is no single confirmatory test for diagnosis of sarcoidosis as all clinical features and laboratory results can be found in other diseases also. Its diagnosis is only by method of exclusion. Patients may be asymptomatic or in very few cases it can be life threatening (Example: severe heart or lung diseases).^{2,6}

The treatment of skin lesions in sarcoidosis is often not satisfactory due to recurrence following successful treatment or skin lesions may not respond to available treatment. Topical steroids are commonly used for localized lesions, but sometimes this may fail improve the condition due to non-penetration. Intralesional use of steroid is found to be more effective. Systemic use of steroid is considered in case of organ dysfunction or functional impairment or in case of progressive disease. It is found that those patients who respond to treatment, often experience disease flare up after completion of treatment.

We wanted to evaluate the diagnosis of sarcoidosis with cutaneous lesion of various morphology along with the clinical profile and relevant investigations including histopathological examination of those patients who attended outpatient department at School of Tropical Medicine for last 5 yrs.

METHODS

We conducted a combined prospective and retrospective observational study of skin biopsy cases of 39 patients having clinically suspected cutaneous lesion from January 2014 to December 2018 (sample size taken as per convenience). Total

skin biopsy received for histopathological examination was 1051 during 5 years out of which 39 were from clinically suspected case of sarcoidosis. This study was conducted at the Department of Pathology in correlation with Department of Dermatology in School of Tropical Medicine, Kolkata.

Statistical Analysis

The data was entered in Microsoft excel 2013. Mean and standard deviation as per necessity were calculated using statistical software STATA version 12.

RESULTS

Out of 39 clinically suspected case of sarcoidosis, we found non caseating granulomas in 11 cases on skin biopsy and diagnosis of sarcoidosis had been considered after clinical correlation along with other relevant investigations of these 11 patients. All the 11 cases had disease duration of 6 months to 1 year; they had more than three skin lesions. The average age of the cases is 38 years in our study. Out of 11 cases, eight were female and 3 were male. (Table I)

Female	8
Male	3
Age	36 years to 40 years, mean=37.72 years (SD= 1.61)
Disease duration	6 months to 12 months, mean=8.9 months (SD=2.16)
Total number of skin lesions	3 to multiple

Table 1. Summary of Age/Sex Distribution, Duration of Illness and Cutaneous Lesions

Clinical Features

The patients presented with brown red or purple papular lesions over skin of face, chest wall, back, upper extremities for a period of 6 months – 1 year. There was no significant past history of major illness in all cases. Four cases presented to us with dry cough, occasional fever, weight loss and arthralgia. We had two cases with complaint of dyspnoea and palpitation. Poly arthralgia involving knee, ankle and elbow with skin lesions was present in two patients. One patient had recurrent fever arthralgia, erythema nodosum over ankle, feet and shin bone. Two patients had only skin lesions without any systemic illness.

Figure 1. A Female Patient with Papular Skin Lesions Over the Back

Biochemical and Haematological Investigations

Complete haemogram, Serum urea, creatinine, liver function test, ASO titre and ECG were within normal limits in all patients. Troponin T and Mantoux test were also negative in all patients. Angiotensin converting enzyme (ACE) was elevated in three patients.

Radiological Examination

Bilateral hilar lymphadenopathy detected in chest radiography in five patients.(figure 2). We found no abnormal chest x-ray in other six patients.

Figure 2. X-Ray Chest with Hilar Lymph Adenopathy

Ophthalmological Examination

One patient had macular and parafoveal hypopigmentation in left eye and dull macular reflex in right eye.

Histopathological Examination

Skin biopsy of all 11 cases showed non-caseating granulomas in H&E stain. Langhan's types of giant cell were seen in 4 cases. All the sections were negative for *M. tuberculosis* and *M. leprae* (Modified ZN stain) and fungal bodies in PAS stain. Reticulin stain was also done in all cases. Overall features were suggestive of sarcoidosis. (Figure 3, 4, 5)

Figure 3. Well Circumscribed Granulomas of Epithelioid Histiocytes, Some Multinucleated & Few Lymphocytes. [H&E (40X)]

Figure 4. PAS Stain- Negative for Fungal Body (100x)

Figure 5. Z-N Stain- Negative for AFB

DISCUSSION

No racial or ethnic correlation found in sarcoidosis. All age group are at risk. Usual age at presentation is below 50 years. Average age of presentation in our study is 38 years (Mean 37.7 years). Sarcoidosis occurs through the world with widely varied incidence. Highest annual incidence observed in Northern Europe and it is 5-40 cases per one lakh population.

As per earlier reports sarcoidosis was thought to be a rare disease for developing countries, rather it was considered to be a common disease in western countries. In 1976 there was a study in eight countries from Asia and Africa and less than 30 cases were reported in this study including India. The recent studies are showing that there are increasing case reports from India as well as other developing countries like Malaysia, Thailand etc. We have no reliable data in India till now from which we can estimate the actual burden of sarcoidosis in this country. As per report published in 2002, sarcoidosis constituted 61.2 per 100,000 new cases at a centre (Vallabhbhai Patel Chest Institute) in New Delhi and 10 to 12 cases per 1,000 new registrations annually at a Respiratory Unit at Kolkata. There is no reliable data regarding the ethnic or regional distribution in the reported cases. In the recent years, we also found the reported cases of ocular sarcoidosis in India too. It should be considered that presence of tuberculosis is masking the disease like sarcoidosis too often in our country.

So, we think that actual incidence and burden of sarcoidosis in our country are likely to be underestimated because most cases remained undiagnosed or unreported. In our institution we received 1051 patients for skin biopsy in last 5 years, out of which 39 was suspected to have sarcoidosis and we confirmed 11 cases as sarcoidosis by histopathological examination with clinical & laboratory correlation. More studies are needed to evaluate the actual incidence of the disease in our country.

Studies for environmental causes like exposure to airborne antigens, free pollen, organic particles, metal working, firefighting, wood burning, mining etc. has been done. Recently Izbicki et al. reported increased incidence of sarcoidosis in fire rescue workers in the city of New York. Mycobacterial and Propionibacterial DNA and RNA has been isolated from isolated sarcoid tissue by PCR technique.^{1,2}

Jordan and colleagues in 2001 evaluated World Trade Center health registry. They found 43 patients having sarcoidosis and their diagnosis were confirmed by histopathological and clinical correlation. They observed that intense rescue and recovery activities in this cohort are associated with excessive dust exposure and this may lead to greater risk of the disease. In our study we had 2 male patients out of 11 who were farmer by profession and free pollen exposure may be the etiological factor. We also found that 2 female patients were professional cook working in remote village and they had continuous exposure to wood burn, and it may be the causative factor for sarcoidosis. As the cohort is small in our study (only 11 cases), a strong relationship between sarcoidosis with free pollen & wood burn is difficult to establish in this study.

Development of sarcoidosis is probably the end result of immune response to various ubiquitous environmental triggers. In histopathological sections noncaseating

granulomas are the fundamental abnormality in sarcoidosis. Macrophages stimulated by the influence of chronic cytokines- TNF α , IL 12, 15, 18, MIP 1, MCP 1, GM-CSF converted into epithelioid cells and fuse to form giant cells. Presence of CD4+ T cells is the cardinal feature of sarcoidosis and CD4+ cells interact with APC to initiate and maintenance of the granulomas. These CD4+ cells release IL4 & IF γ which augment macrophages to TNF α production and amplify local cellular immune response.^{2,5} Granulomas may resolve without much consequences. Pulmonary fibrosis occurs in 20-25% of cases due to action of Th2 cells, IL-4, 10, 13 for fibrosis. Patients of sarcoidosis often come to attention when x-ray chest show some abnormalities during routine screening. Systemic symptoms like cough, loss of appetite, weight loss, fatigue, night sweats are common. Lofgren's syndrome with arthritis, erythema nodosum, bilateral hilar lymphadenopathy may be the presenting symptoms in 09-34% of cases.⁶ Patients having sarcoidosis may present with Heerfordt's syndrome which consists of fever with facial palsy, enlargement of parotid glands and eye involvement. But in India, acute presentation with these two syndromes is not common. We also did not find any case with these acute presentations.

Lung and lymph nodes are the first organ to be involved in sarcoidosis. Skin (25-30%), liver (30-40%), heart (5-25%), eye (20-30%), nervous system, musculoskeletal systems are other organs which are commonly affected by the disease. Skin lesions may be in the form of erythema nodosum, nummular eczema, erythema multiforme, calcinosis cutis, lupus pernio, skin plaques, maculopapular eruptions, Darier-Roussy disease or scar sarcoidosis. Eye involvement may be in the form of granulomatous uveitis, iris nodules, retinochoroiditis, conjunctiva inflammation, lacrimal gland involvement, optic nerve involvement, proptosis. In our study all the 11 patients presented with skin lesion. We had only one patient with macular and parafoveal hypopigmentation in left eye and dull macular reflex in right eye. We could not find any other system involvement clinically or by laboratory findings. Two third of the patients generally have a remission within a decade and one third of the patients having diagnosis of sarcoidosis leading to organ impairment which can develop at any age or in any organ. As a result of that <5% of patients die either due to pulmonary fibrosis and respiratory failure or cardiac or neurological involvement.^{2,3}

Establishment of diagnosis of sarcoidosis is based on presence of non-caseating epithelioid cell granulomas (in tuberculosis, caseating granuloma is found, which is distinguishing feature from sarcoidosis), absence of organism or particle on histopathological examination. Biopsy must be taken from the easily accessible organ like skin, peripheral lymph node, lacrimal gland, conjunctiva etc. We found non-caseating granuloma on skin biopsy in all the 11 cases. The Kveim Siltzbach test (KST) has been used for many years for diagnosis of sarcoidosis by intradermal injection. Sensitivity regarding positive reaction of KST is only 50-80%. There is also 1-5% false positive reaction noted in studies.

Though KST was considered as an important tool for diagnosis of sarcoidosis once upon a time, now a days it is no longer used. There are several drawbacks of this test. First of all, this Kveim reagent is difficult to prepare (Prepared from granulomatous tissue of spleen from patient affected by sarcoidosis); secondly there is possibility of transmission of

disease when injected in suspected person; thirdly there are several modern techniques like trans-bronchial biopsy to diagnose lung involvement and lastly this reagent is not available commercially for routine use. So, in our study we did not perform this test over our cases.

Sarcoid granuloma produces angiotensin converting enzyme (ACE) which can be used to monitor patients.² ACE is found to be raised in serum in case of lung involvement as well as in cerebrospinal fluid in case of nervous system involvement or in tears in case of eye involvement. But it has low sensitivity level (only around 60%) though it is the most commonly used biochemical marker for monitoring the disease activity in sarcoidosis. In our study we had three patients with elevated ACE level.

There are five classifications considered on chest x-ray regarding lung involvement in sarcoidosis-

- Stage 0: Normal chest radiograph.
- Stage I: Hilar or mediastinal nodal enlargement only.
- Stage II: Nodal enlargement and parenchymal disease.
- Stage III: Parenchymal disease only.
- Stage IV: End-stage lung.

Though this staging system may indicate the severity of lung involvement, but actually the disease severity does not correlate with the stages. So, by chest radiograph, when patients progress from one stage to another, clinical correlation is must to consider. In our study we found five patients with stage 2 lung involvement (i.e. bilateral hilar lymphadenopathy) in chest x-ray.

No treatment is required in most cases of sarcoidosis as symptoms usually do not lead to disablement. Only three months observation is enough in mild to moderate cases as spontaneous disappearance of symptoms usually occurs. Treatment is necessary when there is need to relieve the symptoms or there is chance of organ dysfunction. The drug of choice is corticosteroid and it should be continued for several years due to chance of relapse after stoppage of treatment. In case of failure to improve the symptoms with systemic corticosteroids, several immune modifying agents like methotrexate, azathioprine, hydroxychloroquine or tetracyclines are considered for further management. Topical corticosteroids (Eye drops, local injections or creams) are considered for skin or eye lesions. To treat disfigurement of skin plaques or lupus pernio, laser surgery are being used now a days. So, the judgment is very important for treating sarcoidosis. Monitoring of disease activity is also a very important part of sarcoidosis management.

In our study all of the patients responded well with systemic corticosteroids. Routine follow-up is going on as relapse rate is very high in sarcoidosis.^{7,8,9} Depending on the available data, the relapse rate of sarcoidosis varies from 13%-75%. In our study, no relapse case reported till date in fortunately. Mortality rate from complications of sarcoidosis is approximately 1-5% as per available data, may be due to increasing incidence, increasing severity & complications of disease, late detection of the disease etc.

Increasing use of healthcare resources, increasing rate of hospitalisation due to complications are main reflector of morbidity of sarcoidosis. Complications arising from long term use of steroid or other drugs itself increases the rate of morbidity. Organ damage, functional impairment, psychological and social impairment are another form of

morbidity. Though mortality is not frequent, but morbidity is much more common. In our study, no hospitalisation was required for the 11 patients as well as no treatment complications seen till date fortunately.

CONCLUSIONS

No single test can diagnose sarcoidosis with confirmation as all clinical features and laboratory results can be found in other diseases too. Patients may be asymptomatic or may present with variety of symptoms & skin lesions or in many cases it can be life threatening, especially in cases of severe heart or lung disease. Sarcoidosis is diagnosed by method of exclusion. In most cases, definite diagnosis requires a biopsy of skin, lymph node or lung. Non caseating granuloma on histopathological examination is the hallmark of disease and this should be correlated clinically & with laboratory results for confirmation of diagnosis. Skin lesions are very important clues to diagnose sarcoidosis for physicians and it is also an easily accessible tissue for histopathological examination.

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