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Histomorphological Features of Sarcoidosis - 4 Year Study in a Tertiary Care Center, South Kerala

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Abstract

Pathologists are frequently involved in the diagnosis of sarcoidosis on conventional biopsies and cytology specimens. Histology generally does not pose difficult tasks in the correct clinical and imaging scenario, but atypical forms of sarcoidosis exist, and in these cases, the diagnosis may become difficult. The final diagnosis always requires the careful integration of the histology with the clinical, laboratory, and radiologic findings. The differential diagnoses of sarcoidosis includes granulomatous infections, hypersensitivity pneumonitis, pneumoconiosis, autoimmune diseases, drug reactions, chronic aspiration, and even diffuse fibrosing diseases. In this study, we discuss the histomorphological aspects of Sarcoidosis, along with radiological, biochemical and clinical aspects. The most important finding is the presence of non caseating granulomas by histology which needs to be interpreted in the light of appropriate clinico-radiological and laboratory findings. This study emphasises the role of the pathologist and discusses the differential diagnosis.

Keywords: Sarcoidosis; histology; morphology

Introduction

Sarcoidosis is a chronic granulomatous systemic disease of unknown etiology.

Hutchinson recorded the first case of Sarcoidosis in 1865.In India, the first case was reported in 1957. Sarcoidosis is said to be a disease of disordered immune regulation in genetically predisposed individuals. The incidence of Sarcoidosis has been increasing, which is possibly explained by more awareness and recognition of this condition. Most common site involved is intrathoracic region [2]. Radiologically, mediastinal and hilar adenopathy with or without pulmonary infiltrates or fibrosis is seen, and virtually any organ can be affected [4].Biochemical investigations give a clue to the diagnosis as ACE level may be increased with altered Serum Calcium levels. Different diagnostic modalities for confirmation include fibre optic bronchoscope, bronchoalveolar lavage, EBUSTBNA, transbronchial lung biopsy, VAT and mediastinoscopy. The diagnostic yield of EBUS TBNA in Sarcoidosis has been reported to be up to 79% [6]. Histology and cytology shows typical Sarcoid granulomas which is noncaseating along with multinucleate giant cells and various inclusion bodies [3].Histopathological examination should be done initially itself prior to starting treatment. A pathologist's role in the diagnosis of Sarcoidosis is identification of granulomas in tissue specimens and performance of studies to exclude known causes of granulomatous inflammation. This study aimed to describe the histomorphological features of Sarcoidosis in detail along with clinical, radiological and biochemical aspects. We also assessed the diagnostic yield of EBUS biopsy and cytology in Sarcoidosis.

Methods

This was a retrospective four year study in a tertiary care center in South Kerala. All histologically proven granulomatous lesions diagnosed as Sarcoidosis during study period were taken. The clinical, biochemical, radiological data were collected from electronic medical records. Histopathological and cytology slides along with special stains were retrieved and reviewed in detail.

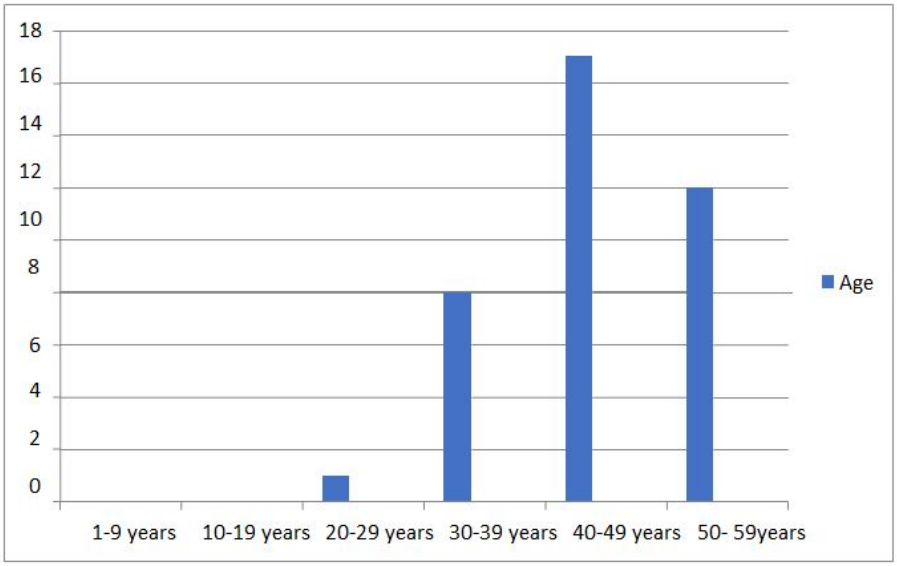
Results

During the study period ,clinical, biochemical, radiological and pathological features of 44 cases of Sarcoidosis were studied, and age and sex distribution was studied of which 52 % (n=23) were females .The age group ranged between 20-80 years with 38% being in 40-49 years (n=17).

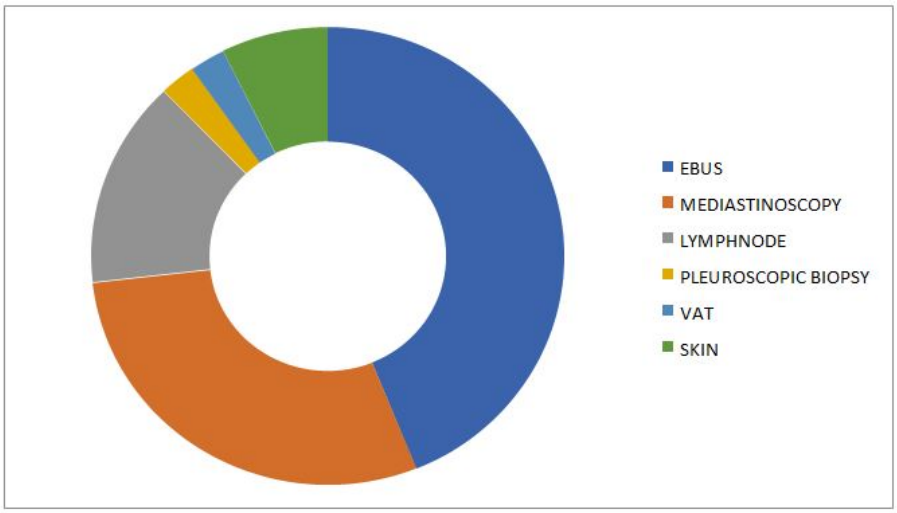
Most common clinical presentation was cough in 47% (n=21) with associated respiratory symptoms followed by fever, weight loss and loss of appetite. Nonspecific rheumatological symptoms including myalgia, ankle swelling and pain were observed in 15% (n=7) cases. Skin involvement was seen in 6.8% (n=3) and liver lesion in 2% (n=1). Primary lung and mediastinal involvement occurred in 75 % cases (n=33).

Biochemical investigations showed subnormal serum calcium level in 1 case with laboratory reference value (8.6-10.2mg/dl). For other patients calcium reports were not available in medical records. ESR was increased in 29% (n=44). Increased ACE (Angiotensin converting enzyme) level was seen in 75% cases (n=27) with a reference range of 8- 52U/L .In 17 cases, no report on ACE levels was available in EMR.

Radiology showed hilar and mediastinal lymphadenopathy with lung parenchyma involvement in 84% cases (n=37) followed by isolated mediastinal and hilar lymphadenopathy; and generalized lymphadenopathy. With clinical, radiological and biochemical investigations the differentials included TB/ Sarcoidosis / lymphoma in 25% (n=11), followed by Sarcoidosis /TB. PCR for MTB detection was done in 35 cases and all were negative.



Our laboratory received specimens of different sampling methods including EBUS TBNA with tissue biopsy, mediastinoscopic and pleuroscopic biopsy, VAT, lymphnode excision biopsy, skin and liver biopsy. EBUS TBNA with tissue biopsy constituted 40% followed by peripheral lymphnode sampling 13% (n=6).



Cytology samples were received for EBUS TBNA sampling, in 18 cases out of which 16 cases were reported as granulomatous inflammation. Two samples were inadequate for an opinion as cellularity was less with scattered lymphocytes only. Histologically we identified characteristic noncaseating granuloma in 40 cases. A few core biopsies (n=4) were showing scant tissue. Both confluent and discrete granulomas were seen in 23 cases, discrete granuloma alone in 8 cases. Granulomas with numerous multinucleate giant cells were seen in 9 cases, and 17 showed only occasional to few giant cells. Lymphocyte rimming was observed in 18 cases. Typical naked granulomas were seen in nine cases. Different inclusion body like asteroid body was seen in 5 cases and chaumann body in 2 cases. Hamazaki wesenberg body was seen in one case which was PAS positive. Fibrinoid necrosis was seen in 7 cases. Reticulin was done in 40 cases, and showed condensation around the granuloma with permeation in 29 cases.

All cases were screened for Acid fast bacilli using Ziehl Neelsen stain and were negative. Fungal stains like PAS also were done in all cases and were found to be negative. In our study the characterization and interpretation of granuloma were limited in biopsies which had scanty tissue.

Table1: Histomorphological aspects of Granuloma

Histomorphological aspects of Granuloma		
Type of granuloma	**Confluent and discrete 52% (23)**	**Naked 20% (9)**
Noncaseating 91% (40)	Discrete 18% (8)	Lymphocyte rimming 40% (18)
Scanty tissue 9% (4)	Confluent granuloma 10% (4)	Lymphoid aggregate 27% (12)
Multinucleate Giant cells	**Inclusion bodies**	**Reticulin stain**
Numerous 20% (9)	Asteroid body 11% (5)	Permeation of fiber 65% (29)
Occasional 38% (17)	Schaumann body 4% (2)	Inconclusive 6% (3)
Absent 42% (18)	H-W body 2% (1)	Not done 9% (1)

Image3: Sarcoid granuloma

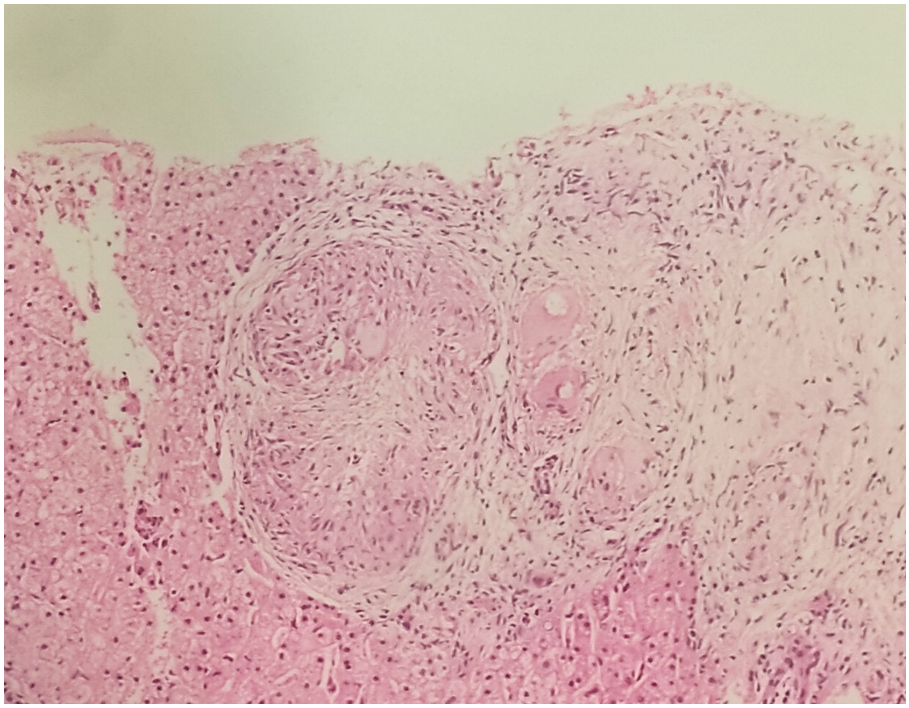
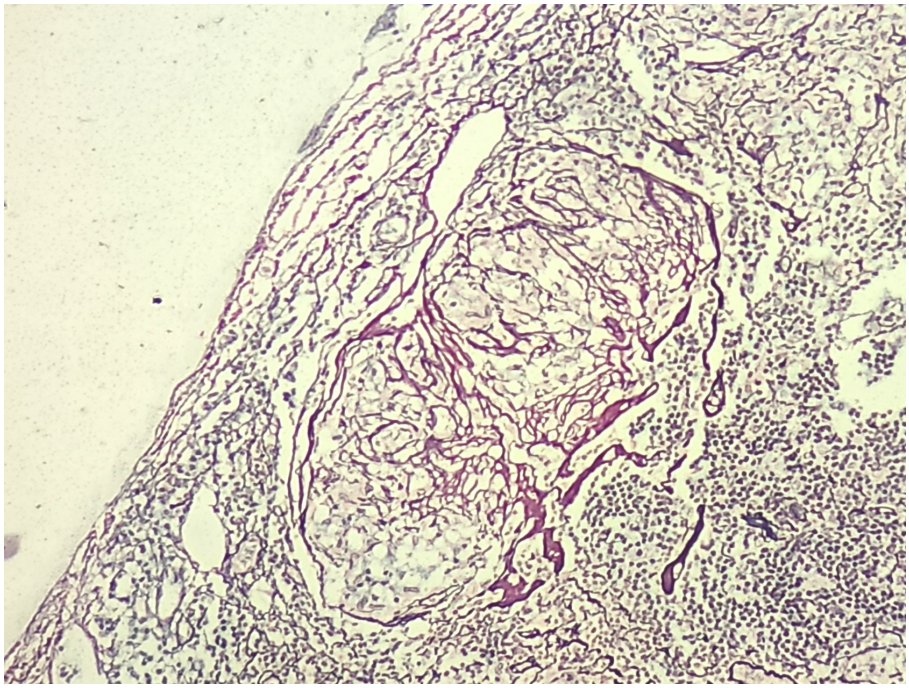


Image4: Reticulin stain



Discussion

Sarcoidosis is multisystem granulomatous disease with varying clinical manifestations. Pathology plays a pivotal role in the diagnosis.

In our study females were affected more than males (F: M=1.09:1) and most common age group affected was in fifth decade. The results were comparable with [8] .They got a male to female ratio of 0.81:1 in a study of 120 cases of Sarcoidosis and mean age distribution was 46 +-10.9 years. [6] study also showed similar results. According to literature, cough was one of the most common clinical presentations with intrathoracic involvement. In [7,8], cough was the most common symptom which was seen in 95% patients. History of dyspnea, chest pain, fever, and fatigue was present in 68.3%, 28.3%, 40.0%, and 29.2% patients respectively. In [16] of 448 cases of Sarcoidosis, 97% intrathoracic involvement was observed with 43% having a respiratory symptom which is comparable with current study (47%). Extrapulmonary sites from where we got biopsy were analysed. Cutaneous involvement was observed in 6.8% cases with skin being the third most common site of involvement after thorax and lymphnodes . In [13] study skin lesions were seen in 10.4%. [8] study showed 23.3% extrapulmonary involvement with GIT being the most common site. We also observed liver nodule with GIT involvement (2%).

Biochemical investigations support the diagnosis of Sarcoidosis. In [14] study ,normal levels of serum calcium was foundin 83% and hypercalcemia in 8% cases, hypocalcemia in 9% cases which is similar to our findings (98%).In [12] study, hypercalcemia was seen in 21.2% patients, hypercalciuria was noted in 56.8% of patients. ACE level are described to be elevated in arcoidosis. In [12] study, high serum ACE levels with >40 U/L were observed in 57.5% patients.

Radiologically hilar and mediastinal lymphadenopathy was seen in 84% cases, with lung parenchyma involvement in our study. In [10] study, the most common radiological finding was well defined mediastinal and hilar lymphadenopathy in estimated 95% cases. With clinical radiological and biochemical investigations, the differentials included TB/ Sarcoidosis / lymphoma in 25% (n=11), followed by Sarcoidosis /TB. Biopsy and cytology sampling by EBUS TBNA were done in 40% of our cases. Among 18 cytology specimens, 88% (n=16) were reported as granulomatous inflammation from cytology. [8] study showed cytopathology diagnosis of granulomas from TBNA in 23.3 %; in a study of 120 cases. Even in a small study population, we got a better yield from cy-

tology.

Histologically we got noncaseating granulomas in all cases. [2] study states that granulomas show relatively well-defined borders with the surrounding tissue. As the disease progressed further, there were manifestations of confluent granulomas. We got confluent and discrete granulomas in 18% cases. [17] study stated that histologically, cases showed the presence of noncaseating granulomas with multiple well defined, "tight", and discrete granulomas which in some instances coalesced. Typical caseating necrotising granuloma was absent in all cases studied. Although necrosis is uncommon, small foci of central, fibrinoid necrosis may be seen occasionally and the presence of focal necrosis should not exclude the diagnosis of sarcoidosis. But extensive confluent necrosis is usually absent. Necrotising Sarcoid Granulomatosis is an entity which can show marked necrosis and sarcoid like granulomas away from the areas of necrosis and can also involve lood vessels. The major differential in such cases is Granulomatous polyangiitis which does not usually produce Sarcoid like granuloma.

According to [18] the granulomas may show scattered multinucleate giant cells, and current study observed 20% cases with numerous multinucleate giant cells. We observed langhans giant cells in one biopsy. According to [19] study Sarcoid granulomas showed Langhans and other giant cells. In typical cutaneous lesions of Sarcoidosis, giant cells are few in number. Those that are present are usually of the [23]. Inclusion bodies are formed in epithelioid or giant cells and may be extruded into the extracellular space. The asteroid bodies present are organic protein structures, mostly complex lipoproteins and appear as 10 to25 μm, reddish pink, spider-like, spiculated, stellate inclusions. Schaumann bodies (conchoidal body) are concentrically laminated, dark blue, oval structures composed of a protein matrix impregnated with calcium phosphate or carbonate and iron. They are strongly basophilic and are also found in Berylliosis and TB. Hamazaki-Wesenberg bodies are giant lysosomes usually present extracellularly at or near the peripheral sinus of involved lymph nodes and almost always outside the granulomas. Stained with Gomori silver stain, they appear as clusters of budding yeast like organisms that can easily be mistaken for fungi. But none of these inclusions are pathognomonic for Sarcoidosis. We observed Asteroid body in 11% cases, Schauman body in 4% and Hamazaki wesenberg bodies in 2.27% of cases. In Sarcoid granuloma asteroid bodies were seen in 2-9% cases according to Iochim HL et al's[18]observation.Schaumann bodies were seen upto 48-88% in different studies [18, 20]. [21] study showed schaumann body in 88% cases out of 17 cases of Sarcoid studied. Discordance may be due to specimens having scanty cellularity and most of them being small biopsy specimens. Various studies showed Hamazaki Wesenberg bodies in 11-68% cases[18].

A special stain which is widely used in the diagnosis of sarcoidosis is Reticulin stain. This is a silver stain which highlights the Reticulin fibres. Reticulin staining demonstrated condensation around granuloma with permeation in 72.5% cases. [22]study also showed that I n Sarcoid, the reticulin fibres are seen surrounding and within the granuloma.

The first and foremost differential diagnosis of granulomatous inflammation is infections including bacterial like mycobacterial, atypical mycobacterial, brucellosis, fungal like histoplasmosis, blastomycosis, coccidioidomycosis, pneumocystis, cryptococcus, and parasites like leishmania, echinococcus, schistosoma, leishmania, toxoplasma. In all our cases, we do special stains like Ziehl Neelsen to look for acid fast bacilli; PAS and GMS are done to look for fungal organisms.

Samples should always be sent for microbiological investigations including culture, serology and molecular studies like PCR to exclude other possibilities. Sarcoid like granulomas have been reported to occur during the course of various neoplasias, particularly lymphomas, and in other unrelated diseases. Histopathology and cytology only give clue to diagnosis and final diagnosis is always by excluding all causes of granulomas by proper investigations.

Conclusion

The typical histology, an intact reticulin pattern and failure to demonstrate infective agents permit an unequivocal statement of compatibility with the diagnosis of Sarcoidosis. But the final diagnosis requires the careful integration of histology with clinical, laboratory and radiological findings. Some cases may deviate from the so called 'typical' pattern and the exclusion of infective

agents is never absolute. In such instances, subsequent surveillance including possible response to treatment may show a clinical course justifying the diagnosis of Sarcoidosis.

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