Uncommon Manifestations of Sarcoidosis

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Abstract

Objective: To study the uncommon manifestations in patients of sarcoidosis.

Methods: This is a prospective study of uncommon manifestations observed in 93 of the 210 biopsy proved patients (mean age 43.8 ± 6.4 years; 58 males) of sarcoidosis seen by us over the last 22 years at the All India Institute of Medical Sciences, New Delhi.

Results: Clinical presentation of acute sarcoidosis in the form of Löfgren’s syndrome (n=5) was uncommonly observed. Rare pulmonary manifestations included seasonal dyspnoea with audible wheezing mimicking bronchial asthma (n=30); narrowing of main bronchi, fixed upper airways obstruction (n=1); pleural involvement (n=7); bullous lung disease (n=2); chronic respiratory failure (n=2); and vocal cord involvement (n=4). Other notable features were glaucoma (n=4); digital clubbing (n=3); sarcoid nephritis (n=1); and sicca syndrome (n=1). Uncommon neurological manifestations included bilateral sequential facial nerve palsy (n=2); optic atrophy (n=2); optic neuritis, proximal myopathy, multiple brainstem lesions, pituitary stalk lesion (one patient each). Cardiac involvement occurred in 15 patients. This included complete heart block (n=2); congestive heart failure (n=4); supraventricular ectopics (n=6); ventricular ectopics (n=2); and recurrent ventricular tachycardia requiring radiofrequency ablation (n=1). Contrast-enhanced computerised tomographic scan (CECT scan) of the abdomen revealed intrabdominal lymphadenopathy (n=5); infiltrates in the liver and spleen (n=3). Portal hypertension was observed in four patients with grade IV (n=2) and grade II oesophageal varices (n=2). One of the patients with grade IV oesophageal varices had recurrent haematemesis and successfully underwent endoscopic sclerotherapy while another patient with grade IV varices succumbed to massive haematemesis. CECT scan was found to be useful in localising the lesions in patients with extrapulmonary sarcoidosis.

Conclusion: Awareness regarding uncommon manifestations of sarcoidosis will facilitate early confirmation of diagnosis.

INTRODUCTION

The clinical manifestations of sarcoidosis are protean. Therefore, sarcoidosis figures in the list of differential diagnosis of several conditions. While pulmonary involvement is by far the commonest, any organ system can be affected depending on the site and extent of involvement. Patients with sarcoidosis may often be asymptomatic with incidental findings on the chest radiograph. Due to lack of awareness of the disease, reluctance of patients to undergo invasive diagnostic procedures, and the expense involved in special investigations, many patients with sarcoidosis in India remain undiagnosed or get treated as “tuberculosis”. Furthermore, the remarkable resemblance between tuberculosis and sarcoidosis and the observation that patients with sarcoidosis are known to develop tuberculosis, render the diagnosis even more difficult especially in developing countries like India.

While there is sparse literature on the typical presentation of sarcoidosis, very little has been documented regarding the uncommon manifestations of sarcoidosis from India. Keeping these facts in mind we report the uncommon manifestations observed in biopsy proven patients with sarcoidosis from northern India.

MATERIAL AND METHODS

We studied the uncommon manifestations in 210 biopsy proven patients of sarcoidosis seen by us between January 1980 and August 2003 at the All India Institute of Medical Sciences, New Delhi.
Sciences (AIIMS) Hospital, New Delhi. The diagnosis of sarcoidosis was based on the following criteria.1,2 (i) clinical picture; (ii) radiographic features compatible with sarcoidosis; and (iii) biopsy evidence of non-caseating epithelioid cell granulomas. Patients with evidence of mycobacterial, fungal or parasitic infections and those with a history of exposure to organic or inorganic material known to cause granulomatous lung disease were excluded from the study. While 653 patients seen by us during this period fulfilled criteria (i) and (ii), only 210 of these fulfilled all three criteria and these form the basis for the present communication. The clinical characteristics, pulmonary function abnormalities and outcome of prednisolone treatment in 106 of these patients have been reported earlier.1

In all patients, the clinical characteristics and details of various investigations were recorded. Chest radiographs (postero-anterior projection) were performed in all patients at initial presentation. The disease was staged by the traditional radiographic criteria.1,2 Contrast-enhanced computerised tomographic scan (CECT scan) of the chest, abdomen and head and fibreoptic bronchoscopy (FOB) were done where relevant. Histopathological proof of the diagnosis was frequently obtained from biopsies of relevant body sites. Kveim-Siltzbach test was not done. Pulmonary functions were studied as described previously.1

**Treatment and follow-up**

Twenty-one of the 210 patients were seen for a second opinion and confirmation of the diagnosis only and did not follow-up subsequently. No treatment was given in four patients as they did not have symptoms related to sarcoidosis. The remaining patients were started on oral prednisolone, 30 mg/day. Prednisolone was then tapered at the rate of 2.5 mg/week until a maintenance dose of 0.25 mg/kg/day was reached. Thirteen patients with musculoskeletal symptoms, six of whom had cutaneous involvement as well, received chloroquine/hydroxychloroquine in addition to prednisolone. Prednisolone treatment was usually given for six months.

The patients were followed-up monthly for initial six months and thereafter at three to six months interval or yearly depending on the nature of the treatment and response. The follow-up included clinical, radiographic and physiological evaluation. The potential side effects of prednisolone therapy and occurrence of intercurrent infections were carefully monitored.

**RESULTS**

Uncommon manifestations were observed in 93 of the 210 patients. Their mean age was 43.8 years (SD 6.4; range 36-62 years). There were 58 males. The mean duration of follow-up was 170.3 weeks (SD 166.4; range 4-728). There was no correlation between the duration of disease and the occurrence of uncommon manifestations. Most of these patients were referred from outside as a diagnostic dilemma and remained undiagnosed till they were evaluated at our centre.

In the present series, 82 of the 210 patients (39%) manifested arthralgias/arthritis. Acute sarcoidosis in the form of fever, bilateral hilar adenopathy, erythema nodosum, and arthralgia (Löfgren’s syndrome) was observed in only five patients. The remaining 77 patients manifested arthralgias of chronic nature. We did not encounter chronic sarcoïd arthritis in our patients.

Rare pulmonary manifestations included seasonal dyspnoea with audible wheezing mimicking bronchial asthma (n=30); pleural involvement (n=7); vocal cord involvement (n=4); and chronic respiratory failure (n=2). Two patients presented with bullous lung disease (Figs. 1a, 1b). In one of them CECT scan of the abdomen also revealed hepatosplenomegaly, infiltrative lesions in the liver and spleen (Fig. 2) and intrabdominal lymphadenopathy. Fixed upper airways obstruction (Fig. 3) observed in one patient. In this patient, FOB revealed evidence of narrowing of mainstem bronchi. The patients with chronic respiratory failure are doing well on long term domiciliary oxygen therapy. Other notable features were glaucoma (n=4); digital clubbing (n=3); sarcoid nephritis (n=1); and sicca syndrome (n=1). Uncommon neurological manifestations included bilateral sequential facial nerve palsy (n=2); optic atrophy (n=2); optic neuritis, proximal myopathy, pituitary stalk lesion, multiple brainstem lesions (one patient each). Cardiac involvement occurred in 15 patients. This included complete heart block (n=2), congestive heart failure (n=4). One patient with recurrent ventricular tachycardia required radiofrequency ablation. Other cardiac manifestations included supraventricular ectopics (n=6) and ventricular ectopics (n=2).

CECT scan of the abdomen revealed intrabdominal lymphadenopathy (n=5); and infiltrates in the liver and spleen (n=3) (Fig. 2). One of the patients with infiltrates in liver and spleen and retroperitoneal lymphadenopathy also had bullous
lung disease (detailed above). Portal hypertension was observed in four patients with grade IV (n=2) and grade II oesophageal varices (n=2). One of the patients with grade IV oesophageal varices had recurrent haematemesis and successfully underwent endoscopic sclerotherapy while another patient with grade IV varies succumbed to massive haematemesis.

**Familial sarcoidosis**

Ten families were observed to have familial sarcoidosis. In seven families, brothers had sarcoidosis; in one family cousin brothers had sarcoidosis; in one family a brother and sister had sarcoidosis; and in another family, the patient and uncle had sarcoidosis.

**DISCUSSION**

In the literature reported from the West, sarcoidosis is known to have an acute or a chronic onset. Clinical presentation of acute sarcoidosis in the form of Löfgren’s syndrome and Heerfordt’s syndrome has been commonly reported especially in female patients in Scandinavian countries. Observations from the present study and other published studies from India suggest acute presentation in these forms is rare in Indian patients. We did not encounter patients with chronic “sarcoi[d] arthritis”. A series published from India reported on the rheumatic manifestations in patients with sarcoidosis. Of the 29 patients studied, 14 (49%) had acute and 15 (51%) had chronic arthritis. We believe this could be because of the selection bias as the findings were reported from a clinical immunology unit.

Clinically significant pleural involvement has been observed in 2% to 4% patients with sarcoidosis. Pleural manifestations include pleural effusion, pleural thickening, pneumothorax, chylothorax among others. Pleural effusions are more often encountered in patients with chronic stage II or stage III disease and may be transudative or exudative. CT scan of the thorax is more likely to reveal small pleural effusions or pleural thickening or pleural based noduls compared with the conventional chest radiograph. One of the patients in the present study had hepatosplenomegaly, intraabdominal lymphadenopathy, and bilateral bullous lung disease on CT scan (Figs. 1a and 1b). Pneumothorax may result from the rupture of subpleural blebs or emphysematous bullae. The details of one patient with recurrent bilateral pneumothoraces have been published earlier.

The lung function abnormalities of sarcoidosis are typical for interstitial lung disease. Stenosis or compression of bronchi due to granulomatous inflammation of the bronchial wall, extrinsic compression from the enlarged hilar lymph nodes or distortion of the architecture of the lung parenchyma...
by the end-stage sarcoidosis are other manifestations. Fixed intrathoracic obstruction on flow-volume loops due to compression of main stem bronchi is an extremely rare manifestation and was observed in one patient in the present study (Fig. 3). In this patient, fibroptic bronchoscopy revealed evidence of narrowing of mainstem bronchi. Endoscopic evidence of bronchostenosis has been described in 2% to 26% patients undergoing FOB. Severe endobronchial segmental or lobar stenosis producing airflow limitation, localized wheezing or stridor mimicking asthma has been reported in 10% patients with sarcoidosis. We observed reversible airflow obstruction in 30 of the 210 patients (14%).

Sarcoidosis can affect the larynx either as a manifestation of systemic disease or in isolation. Classically, laryngeal involvement affects the supraglottis, and less commonly the subglottis, and true vocal fold involvement is rare. Vocal cord involvement was observed in four patients in the present series. When associated with vague complaints and constitutional symptoms, the diagnosis of laryngeal sarcoidosis is often delayed. One of the patients who developed end-stage lung disease and chronic respiratory failure is doing well symptomatically on domiciliary oxygen therapy.

In an earlier report, asymptomatic liver involvement in sarcoidosis has been reported to occur in 35.2% of the 44 patients studied and most of these abnormalities have been observed to regress spontaneously. Our experience has been similar. Portal hypertension rarely occurs in sarcoidosis and other causes of chronic liver disease which can result in portal hypertension should be carefully ruled out in these patients by thoroughly investigating them. Our patients with grade IV oesophageal varices had recurrent haematemesis. Endoscopic sclerotherapy helped in controlling the bleeding in one of them and the other patient died due to massive haematemesis. Obliteration of the hepatic venous bed by granulomas, granulomatous phlebitis of portal and hepatic veins and fibrosis seem to be the most plausible mechanisms for the development of portal hypertension. Endoscopic tissue glue injection in the treatment of hepatic sarcoidosis related gastric variceal bleeding has been found to be useful in the control of bleeding. Other well-recognised clinical syndromes observed in patients with sarcoidosis of the liver include chronic intrahepatic cholestasis and the Budd-Chiari syndrome.

Cardiac manifestations of sarcoidosis depend upon the location and extent of myocardial involvement. Complete heart block, congestive heart failure, and sudden death have all been described. Published evidence suggests that sustained or unsustained ventricular arrhythmias are more often encountered than supraventricular arrhythmias. These constitute sudden but potentially reversible cause of death. However, we observed supraventricular ectopies more often than ventricular arrhythmias or complete heart block. Congestive heart failure develops because of massive infiltration of the myocardium by granulomas and is a leading cause of death in adult patients with sarcoidosis. Patients with complete heart block require implantation of permanent pacemaker and those with refractory ventricular arrhythmias may need radiofrequency ablation or automatic implantable cardioverter defibrillator and antiarrhythmic therapy.

Cranial nerve involvement is often encountered in patients with sarcoidosis. In the series reported by Colover et al, 58 of the 118 patients with neurosarcoidosis had facial nerve involvement. It was unilateral in 65% and bilateral in 35% of the patients. In most cases, it is lower motor neuron type and is transient. Two patients in the present study developed bilateral sequential facial nerve palsy. Localised granulomatous lesions in the central nervous system are known to occur in some patients with sarcoidosis. Supratentorial granulomas are more common than infratentorial ones. One patient in the present series had thickening of the pituitary stalk and manifested panhypopituitarism. Trial with systemic corticosteroids along with other supportive measures resulted in substantial improvement in this patient.

Familial sarcoidosis has been described with a rate of at least 19% in affected black families and 5% in while families. The incidence of sarcoidosis in more than one member in a family is so uncommon that it is considered to occur no more than would be expected by chance, while the most commonly observed relationship in familial sarcoidosis is brother-sister, followed by mother-child involvement, we observed familial sarcoidosis more frequently among brothers.

Patients with sarcoidosis can present with intraabdominal lymphadenopathy or with hypoechoic lesions in the liver and spleen. These may sometimes be incidental findings in an otherwise asymptomatic patient. In a study involving 59 patients with sarcoidosis, Warshauer et al reported that extensive intrabdominal lymphadenopathy was seen in 10%; marked hepatic and splenic enlargement was seen in 8% and 6% patients respectively. Nodules were seen in the spleen in eight (15%) patients and in the liver in three (5%). Abdominal CT scan findings were related to clinical status and elevated angiotensin converting enzyme levels but not to chest radiographic stage. Thus CECT of the abdomen (Fig. 2) appears to be a useful modality in detecting lesions in patients with extrapulmonary sarcoidosis. Radiologically guided needle biopsy of the lesion in conjunction with excision biopsy of the accessible peripheral lymph nodes can help in the confirmation of diagnosis. Laparoscopic biopsy also seems to have potential as a minimally invasive diagnostic method. Sarcoidosis can be a rare cause of nephritis. Patients may present with proteinuria and associated nephrocalcinosis may be present. Sicca syndrome is another rare manifestation.

Clinicians should remember that no single histopathological observation or combination of features can distinguish sarcoidosis from tuberculosis. Though sarcoid granulomas seldom manifest necrosis, we have often encountered necrotising granulomas with negative staining for acid-fast bacilli in patients with sarcoidosis especially in
skin and lung biopsy specimens. The observation that these necrotising granulomas are reticulin rich has been useful in distinguishing sarcoidosis from tuberculosis. Awareness of the atypical manifestations of sarcoidosis reported in the present series and other rare manifestations reported in Indian patients such as superior venacaval obstruction, breast lumps, will help in diligent pursuit of invasive methods for the confirmation of the diagnosis. Judicious use of the conventional Ziehl-Neelsen smear and Lowenstein-Jensen culture along with the modern molecular diagnostic methods such as polymerase chain reaction (PCR) may be required to distinguish sarcoidosis from tuberculosis.

REFERENCES


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