CASE REPORT

SARCOIDOSIS: A CASE REPORT & LITERATURE REVIEW

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INTRODUCTION

Sarcoidosis is a systemic granulomatous disease that primarily affects the lung and lymphatic systems of the body. It was first described in 1877 by English physician, Jonathon Hutchinson. The cause of Sarcoidosis remains a mystery though several hypotheses have been tried and tested. It is, however, generally agreed that Sarcoidosis results from exposure of genetically susceptible hosts to specific environmental agents. The pathological hallmark of Sarcoidosis is a "non-caseating Granuloma". Its presenting features are protean, ranging from asymptomatic but abnormal findings on chest radiography in many patients to progressive multi-organ failure in an unfortunate minority. The illness can be self-limited or chronic, with episodic recrudescence and remissions. Prognosis correlates with mode of onset, host characteristics, initial clinical course, and extent of disease. The diagnosis is established when clinicoradiological findings are supported by histological evidence of non-caseating epithelioid cell granulomas. Granulomas of known causes and local sarcoid reactions must be excluded. The optimal management of Sarcoidosis has not been well defined. Although corticosteroids remain the mainstay of treatment, there is little evidence for the optimal initiation, dosage, or duration of therapy. Cytotoxic agents and immunomodulators usually are reserved for treatment of complex or refractory disease. Of these agents, methotrexate is used more frequently because of its safety profile and possible steroid-sparing effects. It is not known if current therapy alters disease progression.

We present a case of Sarcoidosis that presented with respiratory, cutaneous and glandular involvement.

CASE REPORT

A 32 year old lady was referred to medical unit from E.N.T (Ear Nose Throat) Unit with the chief complaints of bilateral parotid gland swelling and fever of 1 month duration.

The parotid swelling was painless, bilateral and asymmetrical. It was prominent on patients' right side. The swelling developed gradually over days without any obvious precipitating factor. Patient did not report any history of trauma or alcohol intake. She did report, however, dryness of mouth and increased grittiness of her eyes. She also claimed to have mild difficulty in swallowing that was only for solids and improved with increasing fluid intake. She denied any history of nasal obstruction, mouth breathing and snoring but did admit having increased frequency of urination (polyuria) that was more so in day time as compared to night.

The patient also had a low grade fever that was predominantly continuous with occasional spikes. There were no associated night sweats and there was no history of weight loss. The patient did not report any headache, photophobia, discharging nose/ears/eyes, sore throat, cough, palpitations, loose motions, burning micturition, vaginal discharge, abdominal pain, arthralgias or skin rash. The fever poorly responded to ordinary anti-pyretics that she took.

Her past medical history was insignificant except for mild depression for which she took no treatment. She strongly denied any history of allergic disorder. Her drug history was unremarkable except for recently started anti-tuberculosis treatment that was started at ENT unit based on presumptive diagnosis of tuberculosis.

Her family history was unremarkable except for her father who was hypertensive. There was no family history of tuberculosis, diabetes mellitus or coronary artery disease.

Patient was a house-wife with two kids. Her husband was a teacher and sole bread winner for the family. She was living in a pakka house with 2 rooms since her marriage 6 years ago. She denied any change in her health status after she moved from her parent's home to this one. Furthermore, she did not admit to have had any contact with a case of tuberculosis. She was satisfied with her living conditions and denied any history of over-crowding. She reported consuming well balanced diet with no predilections.

On systems review, patient stated that she has noticed a change in the pitch of her voice and she finds her voice hoarser than before. She reports that her observation is shared by her spouse as well. On inquiry, she explained that it was predominantly the dry throat that makes it difficult for her to speak and she improves with fluid intake.

On examination, patient was hemodynamically stable. Her pulse was 94/minute, regular and of normal volume and character. Her blood pressure was 120/80 mm of Hg with no postural drop. Her respiratory rate was 19/minute and her SpO_2 was 98 % while breathing ambient room air. Positive clinical findings included:

- Bilateral parotid gland swelling; more so on right side.
- Bilateral lacrimal gland swelling
- Left Facial nerve palsy; Lower motor neuron type. No vesicles on ear and/or palate.
- Dry oral mucosa and dry tongue.
- Bilateral red, indurated tender lesions on anterior surface of leg consistent with erythema nodosum.

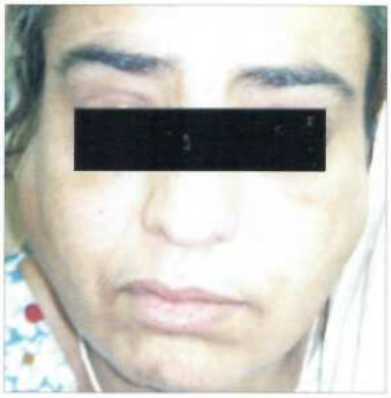

Fig. 1: Bilateral Parotid and lacrimal gland swelling

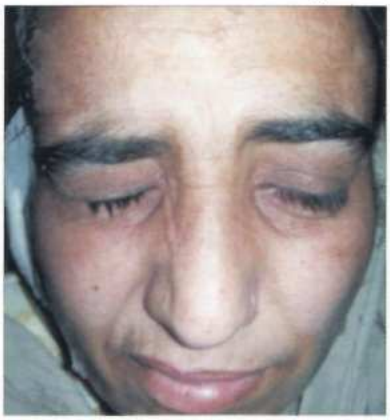

Fig. 2: Left facial nerve palsy

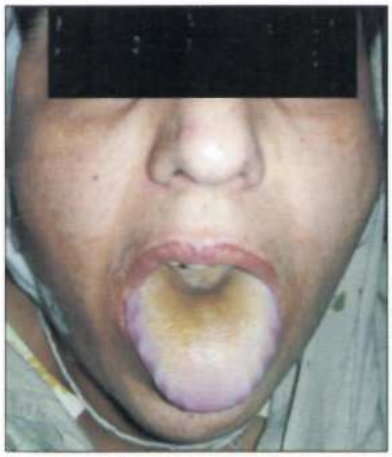

Fig. 3: Dry mouth

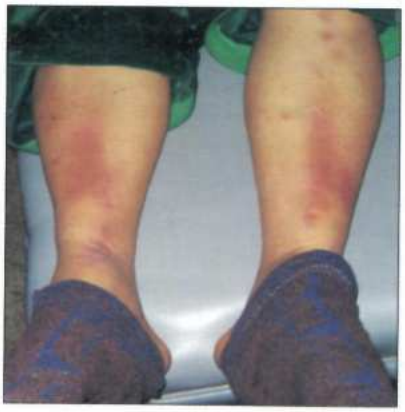

Fig. 4: Erythema Nodosum

Considering the history and clinical features, a provisional list of diagnosis was made to include Sarcoidosis, tuberculosis and connective tissue disorders (including Sjogren syndrome).

Initial laboratory work up, including full blood count, peripheral smear, ESR (erythrocyte sedimentation rate), Blood urea, Random blood sugar, liver function tests and Serum Creatinine were all normal. Her chest radiograph was remarkable for the presence of symmetrical bilateral hilar lymphadenopathy. The finding was confirmed by CT thorax.

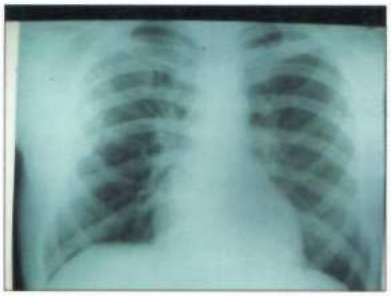

Fig. 5: Chest X ray showing bilateral hilar lymphadenopathy.

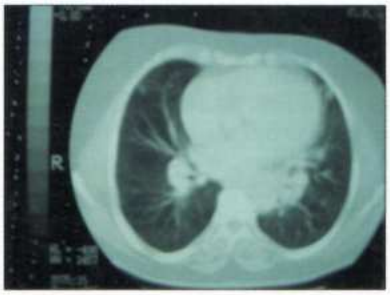

Fig. 6: CT thorax showing bilateral hilar lymphadenopathy.

Since the argument in favor of Sarcoidosis grew strong, it was decided to obtain a tissue diagnosis by taking biopsy from parotid gland. At the same time, complementary evidence was sought by sending serum ACE (Angiotensin converting enzyme) levels, Se-

rum Calcium levels and Full blood count. A shirmer test was also done.

The histopathological result of right parotid gland biopsy revealed typical non-caseating granulomas consistent with the diagnosis of Sarcoidosis. Serum ACE levels turned out to be normal. Serum calcium levels (corrected for serum albumin) were, however, found to be high on numerous occasions. Full blood count failed to reveal characteristic lymphopenia. Shirmer test was found to be positive.

Auto-antibodies including anti nuclear antibody, anti smooth muscle antibody and anti mitochondrial antibody were checked and found to be negative. Similarly an upper gastrointestinal endoscopy, ultra sound abdomen and CT brain failed to reveal any disease process.

Considering the history, examination findings and histological picture, a diagnosis of Sarcoidosis was made.

Patient was started on corticosteroids besides supportive treatment. She started improving gradually. Her swelling subsided, facial palsy improved and her sense of well being improved. She was put on a periodic surveillance and follow-up program and sent home. Till date, she is regularly coming for follow up and is asymptomatic despite her steroids being tapered off.

DISCUSSION

Sarcoidosis is a systemic granulomatous disease of unknown cause affecting young and middle aged adults. Patients commonly present with bilateral hilar lymphadenopathy, pulmonary infiltrates, and ocular and skin lesions. The heart, liver, spleen, salivary glands, muscles, bones, kidneys, and central nervous system also may be involved.

EPIDEMIOLOGY

Sarcoidosis affects men and women of all races and ages worldwide. The disease shows a consistent predilection for adults less than 40 yr of age, peaking in those 20 to 29 yr old. It is slightly more predominant in women than in men, with an incidence of 6.3 and 5.9 cases per 100,000 person-years, respectively[1].

Mortality from Sarcoidosis approaches 1 to 5 percent. Mortality is due most commonly to respiratory failure[2,3] except in Japan where most frequent cause of death for sarcoid patients is from myocardial involvement[4,5,6].

ETIOLOGY

Multiple causes of sarcoidosis have been proposed. Evidence exists to support genetic inheritance, infectious transmission, and shared exposure to environmental agents[7]. Current theory suggests that disease develops in genetically predetermined hosts who are exposed to certain environmental agents that trigger an exaggerated inflammatory immune response leading to granuloma formation[8,9].

Various etiological agents implicated in etiopathogenesis of Sarcoidosis are listed in table 1 given below.

Table 1: Examples of Agents suggested to be involved in etiology of sarcoidosis

Type of agent		
Infectious	**Inorganic***	**Organic**
• Virsuses	• Aluminum	• Pine Tree Pollen
• Borrelia burgdorferi	• Zirconium	• Clay
• Propioni-bacterium Acnes	• Talc	
• Mycobac-terium tuber-culosis and other myco-bacteria		
• Mycoplasma		

* Beryllium which causes berylliosis and not Sarcoidosis is not included.

PATHOLOGY

The characteristic lesion of sarcoidosis is a discrete, noncaseating, epithelioid granuloma. The early sarcoid reaction occurs when activated T cells and macrophages accumulate at sites of ongoing inflammation. These activated cells release chemoattractants and growth factors that result in cellular proliferation and granuloma formation. Sarcoid granulomas resolve or leave behind fibrotic changes. The factors leading to fibrosis are poorly understood[8].

While interpreting noncaseating granulomas, two important entities namely, Sarcoid reaction and GLUS (granulomatous lesions of unknown significance) must be kept in mind.

Noncaseating epithelioid cell granulomas may be found in primary tumors (e.g. Seminoma), liver and Spleen (e.g. in cases of Hodgkin and Non-hodgkin lymphoma) and regional draining lymph nodes (e.g. carcinomas) [10]. Such lesions are termed "*sarcoid reactions*". In such cases, it is important not to be swayed into the diagnosis of Sarcoidosis and a search for primary malignancy, if not already diagnosed, may be appropriate.

Fifteen to 20% of biopsy samples with granulomatous lesions have an undetermined etiology. These patients have a disease process that has been named as *GLUS* (granulomatous lesions of unknown significance) syndrome.

Both of these entities can be differentiated from granulomas of sarcoidosis via immuno-histological staining. GLUS syndrome granulomas and tumor-related sarcoid reactions are B cell positive while granulomas in sarcoidosis and mycobacterial infection are B cell negative[11].

CLINICAL FEATURES

Sarcoidosis can affect any age group though peak incidence is in the age bracket of 20 to 40 years. Children with sarcoidosis have the same organ involvement as adults but a more favorable prognosis. New diagnoses of sarcoidosis in the elderly are rare and should be distinguished from a local sarcoid reaction that occurs with malignancies[8]. Sarcoidosis rarely interferes with pregnancy, but the disease can worsen at six months' postpartum

The clinical presentation of sarcoidosis depends on ethnicity, duration of illness, site and extent of organ involvement, and activity of the granulomatous process. The usual modes of presentation include nonspecific constitutional symptoms or symptoms related to organ-specific involvement[9]. Thirty to 50 percent of patients are asymptomatic and are diagnosed on routine chest radiographs. One third of patients have nonspecific symptoms of fever, fatigue, weight loss, and malaise. This presentation is more common in blacks and Asian Indians.

Acute sarcoidosis is more common in whites than in blacks and usually is associated with spontaneous remission within two years. Spontaneous remission also occurs in patients with Löfgren's syndrome, which consists of bilateral hilar lymphadenopathy, ankle arthritis, erythema nodosum, fever, myalgia, and weight loss[8]. Chronic sarcoidosis presents insidiously with symptoms related to the organ involved, such as cough and dyspnea from pulmonary infiltration. Chronic sarcoidosis commonly follows a relapsing and protracted time course[9]. Chronic progressive disease affects 10 to 30 percent of patients. Spontaneous remission occurs in approximately two thirds of these patients. Blacks have increased rates of pulmonary involvement, a worse long-term prognosis, and more frequent relapses[8].

a. *Lung Involvement:*

The lungs are involved in more than 90 percent of patients, with sarcoidosis usually presenting as interstitial disease. Symptoms are dry cough, dyspnea, and chest discomfort. Pulmonary Sarcoidosis has an unpredictable course that may result in spontaneous remission or lead to progressive loss of lung function with fibrosis. There are four stages of pulmonary Sarcoidosis given below[8].

Table 2: Chest Radiograph Staging of Pulmonary Sarcoidosis

STAGE*	FINDING
Stage 0	Normal chest radiograph
Stage 1	Bilateral hilar lymphadenopathy
Stage 2	Bilateral hilar lymphadenopathy plus pulmonary infiltrations
Stage 3	Pulmonary infiltrations without bilateral hilar lymphadenopathy
Stage 4	Pulmonary fibrosis

* Classification is based on the postero-anterior chest radiograph only.

Patients with stage I or II disease may have no symptoms, whereas stages III and IV can be characterized by progressive dyspnea, loss of lung function, and fibrosis. Airway involvement can occur and may result in airflow limitation, persistent cough and, in severe cases, bronchiectasis. Spontaneous remission can be expected in 55 to 90 percent of patients with stage I disease, 40 to 70 percent with stage II disease, 10 to 20 percent with stage III disease, and zero to 5 percent with stage IV disease[8,9].

b. *Lymphatic Involvement:*

About 90 % of patients with Sarcoidosis demonstrate lymphatic involvement. Hilar or mediastinal involvement incidentally detected by chest x-ray in most patients. Others display non-tender peripheral or cervical lymphadenopathy.

c. *Gastro-intestinal involvement:*

Sarcoidosis predominantly affects liver and spleen as part of its gastro-intestinal involvement. Hepatic involvement is seen in 40–75% of cases. It is usually asymptomatic and manifests as mild elevations in liver function test results or as hypolucencies on CT scans with radiopaque dye. It only rarely causes clinically significant cholestasis, cirrhosis. There is unclear distinction between sarcoidosis and granulomatous hepatitis when sarcoidosis affects liver only.

Splenic involvement is seen in about 10% cases. It is usually asymptomatic but sometimes manifest as left upper quadrant pain, thrombocytopenia or as an incidental finding on x-ray or CT.

Other rare involvements include gastric granulomas, intestinal involvement; and mesenteric lymphadenopathy all of which may cause abdominal pain.

d. *Ocular involvement:*

This is observed in 25% of cases. Uveitis is most common, causing blurred vision, photophobia, and tearing. It can lead on to cause blindness, but spontaneously resolves in most.

Other manifestations include Conjunctivitis, iridocyclitis, chorioretinitis, dacryocystitis, lacrimal gland infiltration (causing dry eyes), optic neuritis, glaucoma, and cataracts.

Ocular involvement more common in black Americans and Japanese Annual or biannual screening indicated for early disease detection.

e. *Musculoskeletal involvement:*

Muscles are involved in 50–80% of cases. This is usually in the form of asymptomatic disease with or without enzyme elevations in most. However, sometimes insidious or acute myopathy with muscle weakness may be observed.

Joint involvement is seen in 25–50% of patients. Ankle, knee, wrist, elbow arthritis are most commonly involved. Sarcoidosis may cause chronic arthritis with Jaccoud's deformities or dactylitis. Löfgren's syndrome is triad of acute polyarthritis, erythema nodosum, and hilar adenopathy. It is often responsive to NSAIDs (Nonsteroidal anti-inflammatory drugs) and is often self limited with low rate of relapse.

Bones are affected in a minority of patients (5%). These present as Osteolytic or cystic lesions apparent on imaging. Osteopenia may also be present.

f. *Dermatological involvement:*

Skin involvement is present in 25% of patients. Two most important manifestations are erythema nodosum and lupus pernio.

Erythema nodosum, red indurated tender nodules on anterior surface of legs, is most commonly seen as part of acute Sarcoidosis (usually as a component of Lofgren syndrome). It usually remits in 1–2 months and is usually considered as a good prognostic sign.

Lupus pernio, Violaceous plaques on nose, cheeks, lips, and ears, is mostly seen as a part of chronic Sarcoidosis. It is more common in black Americans and Puerto Ricans and is often associated with lung fibrosis. It is usually considered as a poor prognostic sign

Nonspecific skin lesions; plaques, macules and papules, subcutaneous nodules, and hypopigmentation and hyperpigmentation are also common.

g. *Neurological involvement:*

Neurologic involvement is rare (< 10%). Cranial nerve involvement, particularly facial palsies and hypothalamic and pituitary lesions, are common. These lesions tend to occur early and respond favorably to treatment (). Space-occupying masses, peripheral neuropathy, and neuromuscular involvement occur later and portend a chronic course. Gadolinium-enhanced MRI is the preferred test for evaluating brain parenchyma, meninges, and spinal cord. MRI manifestations are, however, nonspecific. They should be complemented, where possible, by CSF analysis and histological diagnosis.

h. *Renal involvement:*

It is seen in 10% of cases. Asymptomatic hypercalciuria is by far the most common abnormality. Nephrolithiasis and nephrocalcinosis causing interstitial nephritis and chronic renal failure is another feature observed in chronic Sarcoidosis. Once it develops, it usually requires renal replacement therapy (dialysis or transplantation).

i. *Cardiac Involvement:*

It occurs in 5% of cases. Conduction blocks and arrhythmias are most common manifestations and may cause sudden death. Heart failure from restrictive cardiomyopathy (primary) or pulmonary hypertension (secondary) also occurs. Other rare forms of involvement include transient papillary muscle dysfunction and pericarditis.

Cardiac involvement is more common in Japanese, in whom cardiomyopathy is most frequent cause of sarcoidosis-related death.

j. *Genitourinary involvement:*

Rare Case reports of endometrial, ovarian, epididymal, and testicular involvement have been described. No effects on fertility were observed. Evidence suggests that Sarcoidosis may subside during pregnancy and relapse postpartum.

k. *Oral involvement:*

Oral involvement is fortuitously rare (< 5%). Asymptomatic parotid swelling is most common. It also causes parotitis with xerostomia; may be a component of keratoconjunctivitis sicca. Heerfordt's syndrome (also called uveoparotid fever): uveitis, bilateral parotid swelling, facial palsy, and chronic fever is another form of presentation.

Oral lupus pernio may disfigure hard palate and may involve cheek, tongue, and gums.

l. *Nasal Sinus involvement:*

Involvement is seen in < 10% of cases. Acute and chronic granulomatous inflammation of sinus mucosa produces symptoms indistinguishable from common allergic and infectious sinusitis. Biopsy is the only means to confirm diagnosis. Nasal sinus involvement is more commonly seen in patients with lupus pernio.

m. *Endocrine involvement:*

This is rare. Hypothalamic and pituitary stalk infiltration may cause panhypopituitarism. Sarcoidosis

may cause thyroid infiltration but it is usually without thyroid dysfunction. Secondary hypoparathyroidism due to hypercalcemia is frequent.

n. Psychiatric involvement:

Depression is common in patients with Sarcoidosis. (10%). It is, however, uncertain if is a primary manifestation of sarcoidosis or a response to prolonged course of disease and frequent recurrences.

o. Hematological involvement:

5-30 % of patients with Sarcoidosis have some sort of hematological involvement. This is usually in the form of one of the following: Leucopenia, Lymphopenia; anemia of chronic disease; anemia due to granulomatous infiltration of bone marrow sometimes producing pancytopenia; splenic sequestration producing thrombocytopenia.

DIAGNOSIS

The essential factors for diagnosis include compatible clinicoradiologic features, histologic proof of noncaseating Epithelioid granulomas, and exclusion of similar diseases[8,9].

The gold standard diagnostic procedure is that of biopsy of affected organ. Since more than 90 % cases have respiratory involvement, lungs are usually affected. Hence, transbronchial lung biopsy is recommended in most cases. In case of difficulty, mediastinoscopy with biopsy, Video assisted thoracoscopic lung biopsy and open lung biopsy are other options.

It is important to note that easily accessible skin lesions or peripheral lymph nodes also may be sampled instead of lung biopsy, where applicable[8].

When biopsy is refused or is negative, certain biologic markers may assist in making a diagnosis. Bronchoalveolar lavage fluid with a CD4 to CD8 ratio greater than 3.5, panda and lambda patterns on gallium scan, or an angiotensin-converting enzyme (ACE) level double the normal value may provide additional diagnostic information, although each factor lacks specificity[8,9]. ACE levels usually are followed as a marker of disease activity rather than for diagnostic purposes.

The immunologic imbalance in sarcoidosis may clinically manifest as impaired immunologic function. Cell-mediated immunity is enhanced at sites of disease activity, but it is depressed systemically. Patients may exhibit hypergammaglobulinemia caused by T-cell lymphokine stimulation of B-lymphocytes.

The Kveim–Siltzbach skin test[12] involves an intradermal injection of a sodium chloride suspension of human sarcoid spleen or lymph nodes. Although the Kveim test is specific, it is limited by the unavailability of the antigen, a 4- to 6-week reaction time, and variability in the interpretation of results. The Kveim test is rarely used because the US Food and Drug Administration (FDA) has approved no antigen. However, a few hospitals and clinics may have some standardized test that has been privately prepared for their own use.

The initial evaluation of patients with sarcoidosis aims to confirm the diagnosis, assess the extent and severity of involvement, identify stable versus progressive disease, and judge whether therapy will benefit the patient. Follow-up at recommended intervals and consultation with subspecialists likely will be necessary, depending on disease manifestation. This is summarized in table number 3[8].

Table 3: Initial evaluation and follow up in Sarcoidosis

• Thorough history taking, with emphasis on occupational and environmental exposure
• Physical examination, with emphasis on lung, skin, eye, liver, heart
• Biopsy to obtain histologic confirmation of noncaseating granulomas; special stains; cultures
• Chest radiography
• Pulmonary-function testing — spirometry plus measurement of gas exchange (e.g., diffusing capacity of carbon monoxide or arterial-blood gases) at a minimum
• Electrocardiography
• Ophthalmologic evaluation with slit-lamp examination
• Biochemical panel to evaluate hepatic and renal function; measurement of serum calcium
• Other tests depending on clinical presentation and suspicion of extrathoracic disease; assessment of extent and severity of organ involvement
Follow Up
• Monitoring for resolution or progression of disease and for new organ involvement, since all patients are at risk for clinical deterioration in their condition
• Referral to subspecialists if there is evidence of disease progression or new organ involvement; coordination of care by primary physician or Sarcoidosis specialist (or both)

TREATMENT:

The heterogeneity of the manifestations of sarcoidosis, its uncertain clinical course, and the potential side effects of treatment compound the challenge of clinical management.

Because sarcoidosis often spontaneously resolves, asymptomatic patients and those with mild symptoms do not require treatment, although they should be monitored for signs of deterioration. These patients can be followed with serial x-rays, pulmonary function tests (including diffusing capacity), and markers of extrathoracic involvement (eg, routine renal and liver function testing). Patients who require treatment regardless of stage include those with worsening symptoms; limitation of activity; markedly abnormal or deteriorating lung function; worrisome x-ray changes (cavitation, fibrosis, conglomerate masses, signs of pulmonary hypertension); heart, nervous system, or eye involvement; renal or hepatic insufficiency or failure; or disfiguring skin and joint disease.

Corticosteroids remain the mainstay of therapy, despite the lack of well-controlled clinical trials to show that these agents improve patients' long-term outcome[13].

A. PULMONARY SARCOIDOSIS:

Oral corticosteroids are the mainstay of treatment for pulmonary sarcoidosis. In a Cochrane review[14] of corticosteroids for pulmonary sarcoidosis, treatment with oral steroids for six to 24 months improved chest radiograph findings compared with placebo. Patients with interstitial lung disease (stages II and III) had benefits in global scores and chest radiographs[14]. Data show that no treatment is necessary for patients with stage I disease (bilateral hilar lymphadenopathy alone)[14,15].

A recent joint statement of the American Thoracic Society, the European Respiratory Society, and the World Association of Sarcoidosis and Other Granulomatous Disorders[8] included the following guidelines: an initiation dose of prednisone of 20 to 40 mg per day or its equivalent is recommended. Every-other-day dosing may be considered. Patients should be evaluated after one to three months for response. Patients who fail treatment after three months usually will not respond to a more protracted course of treatment. In responders, the prednisone dosage should be tapered to 5 to 10 mg per day or to an every-other-day regimen, and therapy should continue for a minimum of 12 months. There is no consensus guidance on treatment beyond two years[9]. Patients must be monitored after cessation of treatment for possible relapse; some patients will require long-term low-dose therapy to prevent recurrent disease.

The risk of osteoporosis must be addressed in patients taking prolonged systemic corticosteroids. Although few studies have addressed this issue, the bisphosphonate alendronate and nasal calcitonin have been shown to prevent osteoporosis in patients with sarcoidosis[16,17]. Although not available in the United States, deflazacort, a prednisolone derivative with bone-sparing effects, was favored in one study over prednisone in the treatment of chronic sarcoidosis[18]. Calcium and vitamin D supplementation should be used with caution because of the risk of hypercalcemia and hypercalciuria in patients with sarcoidosis[8].

There is little evidence for the efficacy of ***inhaled steroids*** in the treatment of pulmonary sarcoidosis[14]. Various trials on inhaled budesonide[19,20] as well as a randomized controlled trial on fluticasone[21] failed to show statistically significant improvement in lung function parameters over long term, though there was a slight but negligible tendency towards symptomatic relief.

Cytotoxic agents are reserved for refractory cases. They are mainly used as adjuncts to steroids rather than monotherapy. Various agents tried include Methotrexate, Azathioprine and Chlorambucil. Of these, methotrexate and Azathioprine are preferred agents due to their better safety profile[8,9]. Monitoring for symptoms of drug toxicity is essential and adequate contraception must be ensured to avoid the teratogenic potential of many cytotoxic drugs.

Immunomodulators have been used successfully in select patients with pulmonary sarcoidosis. The action of these drugs stems from immunosuppressive characteristics. Many of them modulate the activity of tumor necrosis factor alpha (TNF-alpha). TNF-alpha secreted by macrophages has been implicated in granuloma formation[22]. These agents include chloroquine, hydroxychloroquine, pentoxyfylline, infliximab and thalidomide.

A recent Cochrane review of immunosuppressive and cytotoxic therapy for pulmonary sarcoidosis was unable to recommend the use of these agents[23].

Surgical intervention may be required in selected patients. This may be in the form of surgical resection and embolization of bronchial arteries in patients of advanced fibrotic sarcoidosis presenting with life threatening hemoptysis that fails to respond to other measures. Similarly, Lung transplantation has been performed successfully in patients with end-stage sarcoidosis. Granuloma formation has been described in lung allografts, although it usually is not clinically relevant.

B. EXTRA-PULMONARY SARCOIDOSIS:

Despite the lack of Randomized Controlled Trials demonstrating therapeutic efficacy, corticosteroids are still the mainstay of treatment for extrapulmonary sarcoidosis. Combination or adjuvant therapy has been investigated in many small studies.

Appropriate referral to specialized centers may be indicated as and when required on patient to patient basis.

PROGNOSIS

Adverse prognostic factors in patients with Sarcoidosis include[8]:

- Age of onset > 40 years
- Black race
- Progressive pulmonary fibrosis
- Chronic Uveitis
- Nasal mucosa involvement
- Lupus Pernio
- Cardiac involvement
- Neurosarcoidosis
- Chronic hypercalcemia
- Nephrocalcinosis
- Cystic bone lesions

CONCLUSION

Despite the protean clinical manifestations of Sarcoidosis, it is worthwhile to note that more than 90 % of patients have pulmonary involvement, usually in the form of bilateral symmetrical hilar lymphadenopathy (visible on chest radiograph). This should always alert the physician to consider the diagnosis of Sarcoidosis in his or her differentials irrespective of the initial presentation. This would enable appropriate diagnostic work up including biopsy and early diagnosis and treatment. Early screening of the diagnosed patients for extent of disease, especially the respiratory and cardiac involvement, may help avert the development of life-threatening complications and thus aid in decreasing the mortality associated with the disease in a subset of patients.

Because most patients with Sarcoidosis do not die of the disease, the medical challenge is to help them live well with their symptoms. This usually means an extended careful and periodic monitoring and surveillance plan that would enable not only the titration of drug therapy but also help pick up patients who would relapse after responding initially. Since treatment is usually required for protracted periods, it is equally important to address the side effects of the drugs being administered on prophylactic basis.

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