Chapter 184
Sarcoidosis: An Update on Recent Advances

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INTRODUCTION

Sarcoidosis is a multisystem inflammatory disorder of unknown etiology. It commonly affects thoracic organs, but extra-thoracic involvement in the form of ocular, skin, liver, spleen, lymph nodes, etc. may also be seen. The usual presentation is with bilateral hilar lymphadenopathy (BHL) with or without pulmonary infiltration. The diagnosis is established when clinicoradiological findings are supported by histopathological evidence of noncaseating epithelioid cell granulomas and after exclusion of known cause of granuloma and the local sarcoid reaction.

The consensus statement by the American Thoracic Society (ATS) was last published in year 1999 and has become more than a decade old. A lot of new research has been published since then in the field of natural history, epidemiology, immunopathogenesis and treatment of sarcoidosis. The major multicentric study of sarcoidosis “A Case Control Etiologic Study of Sarcoidosis (ACCESS)” has given new insights into epidemiologic exposures associated with increased sarcoidosis risk, including exposure to insecticides, microbial bioaerosols and agricultural employment. The use of newer investigational modalities with MRI and FDG-PET scan has improved the diagnosis and follow-up of active cardiac and neurosarcoidosis. The glucocorticoid remains the mainstream therapy but there is still no consensus on the indication, initiation, doses and duration of its use. In the treatment front, the successful use of anti-tumor necrosis factor-α (anti-TNF-α) in cases of steroid refractory or steroid intolerant patients had given a new hope. The infliximab appears to be the most promising anti-TNF-α biologic and may get approval in near future.

HISTORY AND DEFINITION

The word sarcoidosis is derived from Greek and it means “fleshylike condition.” In 1877, Jonathan Hutchinson described the first case at King’s College Hospital in London. Ernest Besnier, in 1889, described lupus pernio, the cutaneous hallmark of chronic sarcoidosis (Figures 1A to E). Later, Caesar Boeck advanced the description of sarcoidosis by emphasizing the granulomatous inflammation characteristic of this disease. He was first to use the term sarcoid (sarcoid) because he believed the lesions resembled sarcoma but were benign. The first case of sarcoid is published in India was in 1956 by Ghosh PK and Chakravarty AN in journal of school of Tropical medicine, Calcutta.

The Joint statement of American Thoracic Society (ATS)/European Respiratory Society (ERS)/World Association for Sarcoidosis and other Granulomatous Diseases (WASOG) defines sarcoidosis as a multisystem disorder of unknown cause(s). It commonly affects young, middle-aged adults and frequently presents with BHL, pulmonary infiltration, ocular and skin lesions. The liver, spleen, lymph nodes, salivary glands, heart, nervous system, muscles, bones, and other organs may also be involved. The diagnosis is established when clinicoradiological findings are supported by histological evidence of noncaseating epithelioid cell granulomas. Granulomas of known causes and local sarcoid reactions must be excluded.

EPIDEMIOLOGY

As stated in ATS joint statement, the epidemiology of sarcoidosis remains problematic for several reasons including (1) lack of a precise and consistent case definition, (2) variable methods of case establishment, (3) variability in disease presentation, (4) lack of sensitive and specific diagnostic tests resulting in under-recognition and misdiagnosis of the disease, and (5) the paucity of systematic epidemiologic investigations of cause. Sarcoidosis occurs throughout the world affecting both sexes. In most series, it affects females slightly more often than males. People of all ages can be affected, but it particularly occurs in young adults, 20–40 years old (over 70% of cases). Sarcoidosis has been reported in all races and ethnic groups, but with marked variations. The Scandinavian countries (i.e. Sweden) has highest prevalence of 64/100,000 population. In the United States the age-adjusted annual incidence rates are three times higher for African Americans (35.5/100,000) than for whites (10.9/100,000) with a lifetime risk of sarcoidosis for US African Americans of 2.4% and for US whites of 0.85%.

In India, the reported prevalence of sarcoidosis is 10–12 cases/1,000 new registrations annually at a Respiratory Unit in West India and 61.2/100,000 new cases registered in respiratory unit of the Vallabhbhai Patel Chest Institute (VPCI), Delhi. In a recent review by Sharma SK et al. of 210 biopsy proven sarcoidosis and 409 other sarcoidosis patients reported from India, the following salient features were reported in Indian patients: presentation by a decade late (> 40 years), more common in males, spontaneous resolution was less common and more patients required steroid therapy, early and stage-wise progression of stage I lung disease to stage II occurred over 3–5 years compared to western literatures up to 15 years. A more extensive review of Indian sarcoidosis patients was also published in 2009 and in 2011 API medicine update.

ETIOPATHOGENESIS

The etiology of sarcoid is still elusive but interplay of some unknown environmental exposure (organic and inorganic) in a genetically predisposed host has been proposed which leads to activation of immune response, granulomatous inflammation and secondary fibrotic damage to tissue.
Environmental Factors

The cause of sarcoidosis is still unknown. In a multicentric ACCESS trial of 706 newly diagnosed sarcoidosis patients reported an increased risk of sarcoidosis in people with exposure to insecticides, agricultural employment, or moldy environments. Various studies have shown that cigarette smoking decreases the probability of developing sarcoidosis. Possibly as acrolein (breakdown product of cyclophosphamide) in cigarette smoke is cytotoxic to lymphocytes trying to enter the lungs.

Figures 1A to E: Skin manifestations of sarcoidosis: (A and B) Lupus pernio: violaceous plaques on the nose and forehead; (C) Erythema nodosum: tender violaceous subcutaneous swelling over shin (nonspecific for sarcoidosis); (D and E) Waxy interscapular, back of neck and forearm skin plaques.
Mycobacterium tuberculosis has always been at the center for discussion in all sarcoidosis etiology and it’s important to exclude it. The clinical spectrums of both the disease are difficult to separate. The DNA of the M. tuberculosis catalase-peroxidase (mKatG) gene has been identified in archived sarcoidosis biopsy specimens. One group found that nearly 50% of patients with sarcoidosis exhibited anti-mKatG antibodies compared with control subjects. In addition, strongly polarized T helper cell (Th) 1 immune responses to mKatG were more frequently present in patients with sarcoidosis compared with control subjects. In a recent metanalysis, 231 out of the 874 patients were found positive for mycobacteria with a positive signal rate of 26.4 (23.6–29.5%) and the odds of finding mycobacteria in samples of patients with sarcoidosis versus controls was 9.67 (4.56–20.5%). Other infectious agents have also been reported.

Genetic Factors

Genetic factors play a significant role in prevalence, clinical presentations, and severity of sarcoidosis. Documentation of several hundred families with two or more affected members are strong evidence for a genetic involvement to this disease. The ACCESS study showed that first-degree relatives of sarcoidosis patients had over a five times increased relative risk for developing sarcoidosis. In addition, it is reported to be two to four times higher in monozygotic than in dizygotic twins. The intraracial heterogeneity of clinical manifestations and prognosis makes it unlikely that a single gene is responsible for sarcoidosis. Studies have shown that the HLA-A1, B8, DR3 haplotype and HLA-DR17 (a subset of DR3) are associated with an increased risk of developing sarcoidosis in whites, whereas HLA-DR11 confers increased risk in white, African-American, and Japanese patients. Non-HLA candidate genes associated with disease in specific ethnic groups of sarcoidosis patients include certain alleles of cytokine genes (TNF-α, interferon-α) and receptor genes (c-c chemokine receptors). Recently another receptor gene, butyrophilin-like 2 (BTNL2), has been associated with sarcoidosis in whites. This gene on chromosome 6p functions as a negative co-stimulatory molecule.

Immunopathogenesis

Infectious, organic, and inorganic agents are possible antigens in sarcoidosis (Figure 2). Any causative microbe, if present, is probably cleared, leaving behind an undegradable product or initiating a cross-reacting immune response to self-antigen. Antigen-presenting cells (APCs), in addition to producing high levels of TNF-α, secrete interleukin-12, -15, and -18, macrophage inflammatory protein 1 (MIP-1), monocyte chemotactic protein 1 (MCP-1), and granulocyte macrophage colony-stimulating factor (GM-CSF). A cardinal feature of sarcoidosis is the presence of CD4+ T cells that interact with APCs to initiate the formation and maintenance of granulomas. CD4+ T cells release interleukin-2 and interferon-γ. Activated CD4+ cells differentiate into type 1 helper (Th1)-like cells and secrete predominantly interleukin-2 and interferon-γ. The efficiency of antigen processing, antigen presentation and cytokine release is probably under genetic control. Sarcoidal granulomas are organized, structured masses composed of macrophages and their derivatives, epithelioid cells, giant cells, and T cells (Figures 3A and B). Sarcoidal granulomas may persist, resolve, or lead to fibrosis. Alveolar macrophages activated in the context of a predominant type 2 helper (Th2) T cell response appear to stimulate fibroblast proliferation and collagen production, leading to progressive fibrosis.

CLINICAL FEATURES

The clinical spectrum is diverse, ranging from an abnormal chest radiograph in an asymptomatic individual (up to 50% of patients) to severe multiorgan involvement. Other granulomatous diseases caused by mycobacterial infection, fungal infection, berylliosis, drugs, and local reaction to tumors or lymphoma must be excluded. In ACCESS study 95% of patients had thoracic involvement, 50% had extrathoracic involvement and only 2% had isolated extrathoracic sarcoidosis. The acute sarcoid may present as two distinct syndromes. First, the “Löfgren’s syndrome” is characterized by triad of erythema nodosum, BHL on chest radiograph and arthritis. It has good prognosis with more than 90% resolution by 2 years (Table 1). The other acute syndrome is known as “Heerfordt’s syndrome” also called uveoparotid syndrome, it is associated with uveitis, parotid enlargement, fever with or without facial nerve palsy.

Pulmonary Involvement

The entire respiratory tract from sinuses to lungs can be involved in sarcoidosis. Pulmonary involvement is the most common visceral manifestation, the clinical spectrum ranges from asymptomatic hilar adenopathy to an interstitial lung disease with alveolitis. Hilar adenopathy is found in 50–60% in western literature and in 27–45% in Indian sarcoid patients. Pleural effusions are rare (< 5%). Endobronchial involvement is found on biopsy in 50% and may lead to airway stenosis (10%). Symptoms of lung disease include dry cough, dyspnea and chest pain. Wheezing can occur in patients with endobronchial involvement. In pulmonary sarcoidosis, climacteric dissociation is marked with lung crakles are heard in only 20% of patients in spite of significant parenchymal involvement. The Modified Scadding staging system is used for documenting radiologic finding but this does not follow chronology or natural history of disease. Patient of pulmonary sarcoid may present in any stage and progress or improve to any stage: Stage 0: normal; Stage I: BHL; Stage II: adenopathy with pulmonary infiltrates (Figures 3D to F); Stage III: pulmonary infiltrates only; and Stage IV: pulmonary fibrosis. The contrast enhanced computed tomography (CECT) chest is better modality to look for parenchymal involvement as well as non-necrotic hilar lymph nodes.

MANAGEMENT

The classic presentation like Löfgren’s syndrome needs no tissue biopsy. In all other cases, a biopsy specimen should be obtained from one of the involved organ that is most easily accessed, such as the skin, peripheral lymph nodes, lacrimal glands, or conjunctiva. If no peripheral organ is involved then transbronchial lung biopsy (TBLB) is performed with fiberoptic bronchoscopy. A total of 4–6 specimens from the upper and lower lobes or according to radiologic involvement are taken with bronchoscopic lavage which gives a diagnostic yield of 80–90%. In India, where tuberculosis is common, the assessment of lavage and biopsy carries more importance than in developed countries because tuberculosis can be present in tuberculosis and exclusion of it is a must as steroid treatment in TB can lead to disastrous consequences. Bronchoalveolar lavage (BAL), although not diagnostic, but characteristic BAL fluid cell differential shows greater than 30–50% lymphocytosis with a CD4/CD8 T cell ratio more than 3.5 is 94% specific and 52% sensitive.
Sarcoideal granulomas have no unique histologic features to differentiate them from other granulomas. Special stains for acid-fast bacilli and fungi, as well as cultures of such organisms are a must in every case. If TBLB fails to give you adequate tissue (which is not uncommon) the next step of investigation includes tissue biopsy from mediastinal node which can be done either by CT guided percutaneous biopsy, fiberoptic transbronchial fine needle aspiration (TBNA), endobronchial ultrasound (EBUS) guided biopsy or by laparoscopic/open thoracoscopic biopsy. Tremblay and colleagues compared the diagnostic yield of TBNA using a 19-gauge needle.
Miscellaneous

versus EBUS-TBNA in 50 patients with sarcoidosis and hilar or mediastinal adenopathy. The diagnostic yield was 53.8% compared with 83.3% in favor of EBUS-TBNA. 18

Laboratory Findings

Once the diagnosis is confirmed, the following baseline evaluation is recommended (Table 2). Biochemistry may reveal hypercalciuria

Figures 3A to F: (A) Transbronchial biopsy (TBLB) of lung showing noncaseating granuloma with Langhans giant cells (H and E x10); (B) TBLB with reticulin stain showing maintained framework (x10); (C) Endobronchial cobblestone appearance of carina in sarcoidosis on fiberoptic bronchoscopy; (D) Chest radiograph with hilar lymphadenopathy and bilateral parenchymal reticulonodular infiltrate and ground glass opacity (scadding stage II); (E) Contrast enhanced computed tomography (CECT) chest with mediastinal window showing large non-enhancing mediastinal node; (F) CECT lung window showing bilateral parenchymal reticulonodular infiltrate and ground glass opacity
behind scar. The false-positive rate is to the tune of 5%.

period of at least 1 month for observation and repeat biopsy leaves human extract has its own biosafety and legal aspects, long waiting there is no standardized commercially available extract, use of particularly with early disease. The problem with the test is manifold, biopsy of a papule 4–6 weeks after the injection shows characteristic homogenate from a known sarcoid patient into the skin of a patient (0.2 mL) of a 10% saline suspension of lymph node or spleen recommended. It consists of an intradermal injection It is rarely used in current practice and is generally not but is not diagnostic.

Serum Angiotensin Converting Enzyme
Serum angiotensin converting enzyme (ACE) is produced by epithelioid cells and alveolar macrophages at the periphery of granuloma in response to an ACE-inducing factor released by T lymphocytes. ACE levels are found to be elevated in 40–90% of sarcoidosis patients. However, the value of serum ACE levels in diagnosing or managing sarcoidosis remains controversial. The ACE levels may be influenced by ACE gene polymorphisms. As a diagnostic tool, measurement of serum ACE levels lacks sensitivity and specificity. In one series, the positive and negative predictive values were only 84% and 74% respectively. Elevated ACE levels are nonspecific for sarcoidosis and may increase in other diseases like hyperthyroidism, Gaucher’s disease, diabetes mellitus, leprosy, α1-antitrypsin deficiency, Kaposi’s sarcoma in HIV-infected patients, silicosis, hypersensitivity pneumonitis, cirrhosis, histoplasmosis, and asbestosis. Therefore, an elevated ACE level may be supportive, but is not diagnostic.

Kveim-Siltzbach Skin Test
It is rarely used in current practice and is generally not recommended. It consists of an intradermal injection (0.2 mL) of a 10% saline suspension of lymph node or spleen homogenate from a known sarcoid patient into the skin of a patient being evaluated for sarcoidosis. If the patient has sarcoidosis, biopsy of a papule 4–6 weeks after the injection shows characteristic noncaseating granulomas. The test is positive in 50–70% of patients, particularly with early disease. The problem with the test is manifold, there is no standardized commercially available extract, use of human extract has its own biosafety and legal aspects, long waiting period of at least 1 month for observation and repeat biopsy leaves behind scar. The false-positive rate is to the tune of 5%.

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In a review, Reich et al. suggested that patients with recent diagnosis of stage II or III sarcoidosis might experience more long-term harm than benefit from systemic steroids; that the effect on those with disease of intermediate duration is neutral; and that patients with chronic, progressive pulmonary disease respond favorably, at least in the intermediate term. Another study that handled the long-term effects of corticosteroids in a large meta-analysis, investigated the mortality of intrathoracic sarcoidosis patients in referral (2,838 cases) versus population-based settings [e.g. health maintenance organizations and government clinics in Scandinavian countries (812 cases)]. It showed that sarcoidosis mortality was 4.8% in referral settings compared with 0.5% in population-based settings and that this disparity was unlikely to be caused by adverse selection (such as stage or ethnicity) alone. Patients from referral centers received corticosteroids at seven times the frequency of those from population-based settings. It is of note that this provision was shown to be highly correlated with stage-normalized mortality, suggesting that excessive employment of corticosteroids might have an unfavorable influence on long-term outcome in some individuals.

There is no consensus regarding the optimal initial dosage of corticosteroids. The ATS consensus statement suggests a starting dose of 20–40 mg of prednisone or its equivalent, either daily or on alternate days. The ATS statement recommends that for those who respond to steroids, treatment should be continued for at least 1 year. The British Thoracic Society similarly used prednisolone 30 mg/day as a starting dose. After an initial period of treatment lasting approximately 8–18 weeks, those who objectively improve on corticosteroids can start tapering to as low a dose as tolerated without a return of symptoms or organ dysfunction, usually 5–10 mg daily or on alternate days. The use of other immunosuppressive agents in sarcoidosis should be reserved for those patients who experience symptomatic disease progression despite the use of systemic corticosteroids or who require therapy but cannot tolerate steroid side effects.

Methotrexate

Methotrexate (MTX) has been the most studied steroid-sparing drug in sarcoidosis, with more than 30 years of experience in this disease. In one Delphi study, it was considered as the first choice steroid-sparing drug for pulmonary sarcoidosis. One randomized clinical trial of MTX in sarcoidosis indicated steroid-sparing benefits. The largest published experience comes from Lower and Baughman et al. who reported improvement in 33 of 50 patients treated with MTX for a minimum of 2 years. A follow-up report of 209 patients showed that 52% on MTX entered remission and 16% remained stable, with or without low-dose prednisone. Few other reports also confirm the beneficial effects of MTX in cutaneous and musculoskeletal sarcoidosis.

Azathioprine

Azathioprine may be an effective second-line agent in a subset of sarcoidosis patients. It is frequently used in titrated oral doses of 2–3 mg/kg/day; despite a paucity of published studies examining the drug’s efficacy in sarcoidosis. Some data suggest that it may be efficacious for extrapulmonary disease. A retrospective review of 10 patients demonstrated sustained improvement in lung function in only 2 patients, but a prospective evaluation of 11 patients demonstrated symptomatic relief and improvement in lung physiology and radiographic abnormalities in 9 patients after an average of 20 months of therapy. Thus, azathioprine may be an effective second-line agent in a subset of sarcoidosis patients.

Leflunomide

It is an oral cytotoxic agent similar to MTX. Leflunomide has been used to treat sarcoidosis patients. In a series of 32 sarcoidosis patients, the drug was felt to lead to complete response in 16 cases and partial response in nine. The drug was used in 17 patients who were intolerant of MTX due to either nausea or pulmonary symptoms. Another aspect of therapy was the use of leflunomide with MTX. For 15 patients who had progressive sarcoidosis despite at least 6 months of MTX, the addition of leflunomide led to complete response in nine cases and partial response in three cases. The combination of leflunomide with MTX was based on the synergism demonstrated in treating rheumatoid arthritis.

Mycophenolate Mofetil

It acts by inhibiting inosine monophosphate dehydrogenase, which inhibits de novo guanosine nucleotide synthesis, inhibiting T lymphocyte proliferation. Most of the studies reported are on extrapulmonary sarcoidosis. Dosage is 500–3,000 mg/day as a single or divided dose. Frequent side effects include nausea, diarrhea, vomiting, hypertension and infection. Severe side effects include leukopenia, lymphoma, and red cell aplasia. Mycophenolate can cause congenital fetal malformation; hence all patients should have a pregnancy test before starting therapy.

Combination Cytotoxic Therapy

The future for cytotoxic therapy in sarcoidosis appears to be combinations of treatment. In addition to leflunomide, MTX has also been combined with azathioprine. The advantage of this combination is the minimization of toxicity while increasing the immunosuppression by multiple mechanism of action. In addition, the combination of a cytotoxic agent with the biological agent infliximab is considered standard.

Hydroxychloroquine

Chloroquine has proven effectiveness in treating cutaneous manifestations of sarcoidosis, hypercalcaemia and hypercalciuria associated with sarcoidosis, and steroid-refractory neurosarcoidosis. Hydroxychloroquine may be used instead, at a dosage of 200–400 mg/day, because of the lower risk of ophthalmic toxicity.

Infliximab

As discussed in the immunogenesis section regarding the major role TNF-α plays in sarcoidosis granuloma formation and inflammation, it is logical to expect that anti-TNF-α therapies such as etanercept, infliximab and adalimumab and similarly thalidomide/pentoxifylline may have a role in treatment. Therefore few investigators tried to use these agents in chronic refractory cases of sarcoid with some interesting positive drug trials.

Baughman RP et al. conducted a multicentric, placebo controlled randomized double-blind trial consisting of 138 patients with chronic pulmonary sarcoidosis. Patients who received low-dose infliximab therapy (3 mg/kg) demonstrated at 24 weeks a statistically significant 2.5% increase in percent-predicted forced vital capacity (FVC) compared with baseline (P = 0.038). The percent-predicted FVC was unchanged in the placebo group. The proportion of patients who reported adverse drug effects was similar among the treatment groups. Results of post-hoc analyses suggested that patients with...
more severe disease tended to benefit more from infliximab treatment.

Judson et al. evaluated the same cohort of patients in a randomized,
double-blind, placebo controlled trial to determine whether infliximab was effective for the treatment of both extrapulmonary and chronic steroid-dependent pulmonary sarcoidosis.56 The investigators used a novel assessment, extrapulmonary Physician Organ Severity Tool (ePOST), to measure the severity of organ involvement. The ePOST was adjusted for number of organs involved. A modest and transient improvement in ePOST and adjusted ePOST was noted at 24 weeks in the treatment group compared with the placebo group.

Rossman et al. performed a double-blind RCT of infliximab in the
treatment of active pulmonary sarcoidosis.59 After 6 weeks, there was a
trend toward improvement of the vital capacity in the treatment group, but many patients experienced serious adverse effects. Stagaki and colleagues60 retrospectively evaluated the treatment of lupus pernio with infliximab alone or in combination with other anti-
inflammatory agents. Treatment regimens that included infliximab were statistically superior to all other treatment regimens evaluated. More than 75% of all treatment regimens containing infliximab resulted in resolution or near resolution of lupus pernio lesions.

Although infliximab may improve vital capacity in patients with active sarcoidosis, larger scale and longer term studies are needed to assess the safety and efficacy of the drug as there have been reports of a sarcoid-like reaction occurring in patients receiving anti-TNF biologic agents for conditions other than sarcoidosis.61,62 In one series, the incidence of this complication was estimated at 1/2,800 patients treated.62 The mechanism causing this reaction is unclear; however, these observations stress that sarcoidosis is a complex immunologic reaction and modulation of one cytokine is unlikely to resolve all aspects of the disease. There is need for larger RCT before anti-TNF agents become standard of treatment.

Etanercept
It is a soluble TNF receptor antagonist and has been reported to be effective in a few sarcoidosis case reports.63,64 An open label trial of pulmonary sarcoidosis by Utz et al. was abandoned after the majority of 17 patients failed to respond.65 While five patients improved on therapy, eleven patients (65%) deteriorated with either progressive symptoms or worsening chest radiograph.

Adalimumab
Adalimumab, a humanized monoclonal antibody targeted against
TNF is approved for use in Crohn’s disease as well as Rheumatoid arthritis. It is usually given at dose of 40 mg every alternate week. In a retrospective review of sarcoidosis patients from one institution reported benefit with each of the anti-TNF agents.66 These patients, who required treatment for progressive disease despite corticosteroids and cytotoxic treatments, received adalimumab and showed response in approximately 30% of patients, similar to etanercept. Bauschman RP et al. reported up to 50% response with adalimumab with more aggressive and rapid dosing at University of Cincinnati Sarcoidosis and Intersitial Lung Disease Clinic and ILD care center of the Maastricht University Medical Center.67 The study also reported good long-term tolerance.

Other Biologics and Trials
Ustekinumab, a human monoclonal antibody directed against IL-
12 and IL-23 is being evaluated for sarcoidosis. A clinical trial is underway for safety and efficacy of ustekinumab and golimumab (TNF-α antagonist) in the treatment of chronic sarcoidosis.68 In one non-RCT rituximab is being evaluated for progressive sarcoidosis and similarly in another non-randomized open label study, hematopoietic stem cell are being evaluated for refractory sarcoidosis.69

Which Biologic Agent to be Prescribed?
On the bases of the current literature, the best anti-TNF agent for treatment of sarcoidosis appears to be infliximab. However, adalimumab may be an acceptable alternative, with higher doses and more frequent dosing. Certain factors, including toxicity, may influence this decision. Patients developing allergic reactions to infliximab, a chimeric monoclonal antibody, have been successfully treated with another agent. Similarly, infliximab or any other biologics may be more effective and less toxic when given with MTX as seen in rheumatoid arthritis trials. Etanercept having less than 35% response is the least favored biologic. In India adalimumab is still not available commercially.

APPROACH TO A PATIENT WITH PULMONARY SARCOIDOSIS

The Flow chart 1 summarizes a proposed approach to the
management of sarcoidosis, similar approach is already being
employed in some major centers in West.59 Corticosteroids, MTX and infliximab have been the most widely studied drugs for sarcoidosis. In most situations, symptomatic patients should be initially treated with corticosteroid and the use of steroid-sparing agents is reserved for those patients who have significant toxicity at the doses needed to control their disease. The choice of a particular agent is dependent on patient and physician preference.

SUMMARY
The etiology of sarcoidosis still remains unknown; the recent studies suggest that mKatG is a pathogenic antigen in sarcoidosis. Much has been learned about the genetic aspects of the disease. HLA gene loci and polymorphisms in transforming growth factor-β (TGF-β) and TNF-α strongly influence individual susceptibility to sarcoidosis and clinical phenotype.71 Novel genes that determine the immunologic features of sarcoidosis have been identified. Reduced numbers of natural killer (NK) T cells may promote cardinal feature of sarcoidosis: an exaggerated Th1 immune response. The diagnosis of sarcoidosis requires clinicoradiological features with noncaseating granuloma on histopathology. FDG-PET scan of whole body can help to detect the tissue involved in sarcoidosis and may also help in deciding site for tissue sampling. It may be of great help in diagnosis and follow-up of cardiac and neurosarcoid too, as biopsy from these sites remains to be difficult or inaccessible.

Corticosteroids are the most effective treatment of sarcoidosis, but long-standing treatment may result in disabling side effects. The disease modifying drugs like MTX with or without combination may be useful in steroid failure cases. The TNF inhibitors have been investigated for the treatment of sarcoidosis. Although there is a sound pathophyslogic basis for their use in sarcoidosis and few RCTs do support the small to modest benefit in their use. At present infliximab is not approved for sarcoidosis, but considering many positive studies, this drug appears to be the most promising anti-TNF agent in near future, but large RCTs are required before it gets approval. The search for the unknown etiologic agent and effective treatment for sarcoidosis still continues.

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**REFERENCES**


Chapter 184 Sarcoïdosis: An Update on Recent Advances


