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Practical Issues and Challenges in the Diagnosis and Treatment of Pulmonary Sarcoidosis

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Abstract

Sarcoidosis is a granulomatous disease with multisystem involvement. Diagnosis is generally easy to establish from the characteristic clinical and radiographic features. In India and other developing countries, tuberculosis is the closest clinical mimic and needs to be excluded before therapy for sarcoidosis is instituted. Tuberculin anergy and histopathological demonstration of characteristic compact granulomas help in the diagnosis of sarcoidosis. Corticosteroids constitute

the mainstay of therapy for symptomatic pulmonary and most other forms of extrapulmonary sarcoidosis. Asymptomatic disease does not require any treatment, but milder forms may be treated with topical corticosteroids and symptomatic therapy. Alternative drugs such as cytotoxic agents, hydroxychloroquine and other agents are used either alone or in combination for the treatment of relapses and recurrences and refractoriness or in the presence of complications of corticosteroids. Treatment is usually continued for about a year, but it may need to be prolonged in patients with disease that persists and the response to therapy is delayed.

Sarcoidosis is a systemic disease with primary involvement of the thoracic contents, especially the lungs, and the hilar and mediastinal lymph nodes. The skin and eyes are the other common sites of involvement. Organs of almost all other systems, such as the cardiovascular, central nervous, gastrointestinal and rarely genitourinary systems, may also be affected.

Sarcoidosis, histologically characterised by the presence of noncaseating granulomas, has been confused with tuberculosis (TB) almost since its discovery. The possibility of an aetiological relationship between the two diseases has also been proposed from time to time. Both the epidemiological and the immunological evidence clearly show sarcoidosis as a distinct disease with a distinct aetiopathogenesis, type of treatment and natural history.[1] A recent analysis of surveillance data from Japan on 460 000 employees between 1941 and 1996 and a nationwide survey of the general population (1959–91) has revealed strong epidemiological dissimilarities between sarcoidosis and TB, which do not support a TB aetiology of sarcoidosis.[2] Despite these facts, difficulties prevail for practicing physicians in distinguishing between sarcoidosis and TB in several clinical situations, especially in countries with a high prevalence of TB.[3,4] This is generally attributable to similarities in several clinical features and the histopathological appearance of TB and sarcoidosis. TB is the most important pathological differential diagnosis of sarcoidosis in biopsy and surgical pathology of the lungs, lymph nodes, skin, liver, bone marrow and other biopsy sites.[5]

Added to the difficulty of diagnosis is the fear of activating old lesions with corticosteroids and/or other immunosuppressant agents in patients with healed or latent TB. Therefore, it is all the more important to satisfactorily exclude TB before starting therapy for sarcoidosis. These issues are of great significance not only in countries with a higher prevalence of TB but also in other populations predisposed to TB, including patients with HIV infection and healthcare workers.

1. Diagnosis

There are five important steps in the diagnosis of sarcoidosis: (i) suspecting the diagnosis; (ii) excluding the mimics, i.e. other common causes of similar clinical features (e.g. TB); (iii) establishing the diagnosis; (iv) determination of disease extent and severity; and (v) assessment of activity and treatment responsiveness.

1.1 Suspecting the Diagnosis

The algorithm for the diagnosis of sarcoidosis essentially starts from the symptoms and clinical features with which a patient presents. A patient may report with either general constitutional or respiratory symptoms to a general physician, pulmonologist or other medical practitioner. Often, patients seen in dermatology, ophthalmology, cardiology, neurology or other specialties are suspected of having sarcoidosis on the basis of abnormalities detected on a chest radiograph. Sometimes, a patient may be completely asymptomatic and present with abnormalities on chest radiograph such as hilar and mediastinal adenopathy, or with pulmonary infiltrates detected on a routine examination for medical fitness or insurance purposes.

Isolated pulmonary sarcoidosis is rarely diagnosed from history or physical examination. Most patients with pulmonary sarcoidosis will present with general symptoms of cough; breathlessness on exertion; heaviness, tightness or pain in the chest and/or general constitutional symptoms of malaise, fatigue, joint pains, aches and fever. Other clinical manifestations are non-specific for several aetiological diagnoses.

Physical examination of the chest is mostly normal, since lung involvement generally occurs in the form of isolated hilar and/or mediastinal lymph node involvement. Parenchymal lung involvement, which is characteristically present as diffuse inflammatory infiltration, is generally silent. Very rarely, there is the presence of fine crackles, which may suggest the presence of pulmonary fibrosis. Occasionally, the airways are involved, manifesting as airway obstruction and wheezing on auscultation. Lung cavities, cysts or bullae are rarely seen. Pleural effusion and thickening may also occur. Effusion, if any, is generally serous and exudative. Other rare pleural manifestations include pneumothorax, chylothorax and haemothorax.[6]

There are several published reports on the frequency of involvement of organs in sarcoidosis.[3-8] The lungs are affected in >90% of patients. Involvement of extrapulmonary organs is common, along with that of thoracic structures. Some of the more characteristic features from which the diagnosis of sarcoidosis is suspected are the dermatological manifestations, such as erythema nodosum, lupus pernio and other skin lesions; uveitis, keratoconjunctivitis sicca, dacryocystitis and retinal vasculitis; and bilateral lacrimal, parotid and salivary gland enlargement.[9-11] Several other non-pulmonary organs that may also be involved either in isolation or along with the pulmonary disease include the liver, spleen, gastrointestinal tract, heart, peripheral nerves and kidneys.[12-15]

Thoracic lymph node enlargement, especially bilateral hilar lymphadenopathy, is the most common feature diagnosed on chest radiograph. Enlarged retroperitoneal lymph nodes, rarely palpable, are detected on ultrasound or computerised tomographic (CT) scans. Peripheral supraclavicular, axillary, epitrochlear and inguinal lymph nodes are palpable in about one-third of patients.

Almost similar groups of lymph nodes are also involved in TB. Enlargement in both conditions is painless, but tubercular lymph nodes are generally matted on palpation. On the other hand, sarcoid nodes are discrete, movable and firm in consistency. Differentiation between TB and sarcoid lymph node enlargement is not always possible on the basis of clinical examination. Fluctuations, ulceration and formation of sinuses is rare and almost rules out the diagnosis of sarcoidosis.

1.2 Exclusion of 'Clinical Mimics': Differential Diagnosis from Tuberculosis

Of the many clinical conditions that may simulate a similar overall clinical and/or radiological picture, TB tops the list in developing countries where the general prevalence of TB is high. But lymphomas, fungal infections, vasculitides and other granulomatous disorders are also important. Several clinical features may help in differentiating diagnosis from TB (table I). It is in only the 5–10% of patients who present with overlapping features that the diagnosis may not be easy to make. Demonstration of tuberculin anergy is one of the most important tests to exclude TB. Radiological and other laboratory investigations are generally essential to establish a more definitive diagnosis and to exclude other causes of similar clinical features.

1.2.1 Tuberculin Anergy

Sarcoidosis patients show less reactivity to agents that cause delayed skin reactions.[16] Tuberculin hypersensitivity is also depressed in about two-thirds of patients with sarcoidosis.[17] Anergy to tuberculin in sarcoidosis is best demonstrated with an intradermal skin test. The Mantoux test is one of the most important features to distinguish sarcoidosis from TB. A positive tuberculin test as a marker of tubercular infection has a specificity of >85%. A positive tuberculin test in a patient with hilar lymphadenopathy strongly suggests the aetiological diagnosis of TB. Even in countries with a high prevalence of TB, a positive Mantoux test

Table I. Summary of the differences in clinical features and other parameters between tuberculosis and sarcoidosis

Clinical feature	Tuberculosis	Sarcoidosis
Constitutional symptoms	Fever, chills, malaise, weight loss	Fatigue, myalgias, mild fever
Respiratory symptoms	Cough, sputum, haemoptysis	Dry cough, breathlessness, chest tightness/ heaviness
Thoracic involvement		
Mediastinal and hilar nodes	Less common	Most common
Lung parenchyma	Fibrocavitary, miliary	Nil or interstitial, miliary
Pleural	Common	Rare
Heart and pericardium	Common	Less common
Skin	Lupus vulgaris, sinuses	Erythema nodosum, lupus pernio, plaques
Lymphadenopathy		
Most common	Cervical	Thoracic
Others	Thoracic	Peripheral
Eyes	Choroiditis	Uveitis, chorioretinitis
Other glands	Rare	Parotid, lacrimal, salivary

(irrespective of the size of reaction) in sarcoidosis is very rare, and the incidence of Mantoux negativity in sarcoidosis is not influenced by the high rates of Mantoux positivity in the general population.[18] A negative Mantoux test almost excludes the diagnosis of TB except in seriously ill patients (e.g. those with disseminated miliary disease or TB meningitis) or in heavily immunosuppressed patients such as those with HIV infection.

1.2.2 Radiographic Investigations

Radiological findings on a plain chest radiograph may also be characteristic of sarcoidosis more than any other diagnosis. The most typical findings in sarcoidosis include bilateral hilar lymphadenopathy with or without lung interstitial involvement. Over 95% of 100 consecutive asymptomatic patients with bilateral hilar lymphadenopathy were diagnosed with sarcoidosis.[19] The hilar lymph nodes are characteristically large, symmetrical and sharply outlined and are known as 'potato nodes'. Difficulty arises in patients with atypical features such as unilateral or asymmetrical massive lymph nodes or associated large paratracheal and mediastinal lymph node enlargement, or associated with pulmonary cavitation, pleural effusion or miliary distribution. Miliary lung involvement is also commonly seen in TB, pneumoconioses, hypersensitivity pneumonias and metastases. High-resolution CT (HRCT) images help in characterising the distribution in different groups, e.g. centrilobular, perilymphatic or random in relation to the secondary lobule.[20] The distribution in sarcoidosis is typically perivascular. A 'galaxy sign' indicating large pulmonary nodules composed of coalescent small nodules seen in sarcoidosis has been described in TB as well.

Radiological findings are also useful in diagnosing the involvement of extrapulmonary organs such as the liver, spleen, kidneys, heart and CNS.[21]

1.3 Establishing the Diagnosis

1.3.1 Syndromic Presentation

The clinico-radiological picture is fairly characteristic of sarcoidosis in patients with syndromic presentations such as Lofgren's syndrome (fever, bilateral hilar adenopathy, erythema nodosum and arthralgia) and Heerfordt syndrome of chronic uveoparotid fever (chronic febrile illness, bilateral parotidomegaly and uveitis). Biopsy diagnosis, although useful, may not be considered essential in such patients.

1.3.2 Pulmonary Function Tests

Assessment of pulmonary function tests such as spirometry, carbon monoxide diffusion capacity, cardiopulmonary exercise test and blood gases, although useful in the overall assessment of respiratory involvement and disability, is rarely helpful in the differential diagnosis. The abnormalities depend up-

on the extent of involvement and whether the airways are also affected. The spirometric pattern is generally variable from restrictive to obstructive or mixed functional defect and from mild to severe in degree.

1.3.3 Biochemical Investigations

Hypercalcaemia and hypercalciuria are the only biochemical changes that are fairly characteristic of sarcoidosis. Elevated liver enzymes such as AST, ALT and serum alkaline phosphatase may occur in hepatic sarcoidosis. Hyperuricaemia may occur in about 40% of patients. Elevation of blood urea and creatinine, which indicates renal dysfunction, is more often a result of renal calculi as a result of hypercalcaemia and/or hyperuricaemia than renal sarcoidosis.

Serum ACE is frequently elevated in over half the patients. Serum ACE estimation has been advocated as a measure of granuloma load and, therefore, a marker of disease activity.

1.3.4 Haematological Examination

A number of haematological alterations are described on peripheral blood examination, but none of these is characteristic of sarcoidosis. The commonly reported abnormalities include anaemia in up to 20% of patients and leukopenia in up to 40% of patients. Eosinophilia and thrombocytopenia are relatively rare. Most of the haematological abnormalities are mild and rarely severe. Bone marrow examination is rarely required in patients in whom haematological alterations are severe or pose difficulties in attributing a cause.

1.3.5 Histocytological Diagnosis

Most patients with extrapulmonary sarcoidosis, most with stage II–IV pulmonary sarcoidosis and a few with stage I pulmonary sarcoidosis need histological confirmation of diagnosis. The lung is the most fruitful site for tissue biopsy. Transbronchial lung biopsy provides a diagnostic yield from 40% to >90% when four or five specimens are obtained.[22,23] Endobronchial biopsies were also positive for granulomas in about 35% of patients.[24] Combining endobronchial and transbronchial lung biopsies is shown to improve the yield even more.[25]

Granulomas can also be demonstrated on biopsies of lymph nodes, skin plaques or nodules, enlarged lacrimal or salivary glands, liver, musculoskeletal tissues or other clinically involved organs. Biopsy of the accessory salivary gland was found to be quite useful in elderly patients.[26] Although skin is the most easily available site, it is futile to do a biopsy of the erythema nodosum lesions that occur as a result of a hypersensitivity reaction and do not show any granulomas.

On histological examination, the sarcoid granulomas are typically compact, discrete and do not show any caseation. On the other hand, granulomas seen in TB or other infections are loose, ill formed and often show caseation. Special staining for acid-fast bacilli and fungi may be required for granulomas with atypical features.[5]

1.3.6 Bronchoalveolar Lavage and Induced Sputum Examination

Total and differential cell count in the bronchoalveolar lavage (BAL) fluid and occasionally the induced sputum has been used as an index of disease activity in sarcoidosis, but is rarely helpful in the differential diagnosis. There is a lymphocytic predominance in BAL fluid in sarcoidosis. A log transformation of the ratio of lymphocytes and polymorph neutrophils is rarely found to be useful in differentiating sarcoidosis from idiopathic pulmonary fibrosis. The pattern of differential gene expression on alveolar macrophages obtained from BAL fluid has been examined to distinguish the origin of granulomas, but a large number of granuloma-associated features were found to be common.[27]

1.4 Disease Extent and Severity

The extent of the pulmonary disease is decided based on symptomatology and chest radiograph findings. On the basis of a plain posteroanterior chest radiograph, pulmonary sarcoidosis is classified into five stages: 0, no visible intrathoracic lesions; I, bilateral hilar lymphadenopathy; II, bilateral hilar lymphadenopathy along with pulmonary infiltration; III, pulmonary infiltrations without bilateral hilar lymphadenopathy; and IV, pulmonary fibrosis with honeycombing cysts and bullae forma-

tion.[5] Stage IV disease is generally the most severe and irreversible form of pulmonary sarcoidosis, but not all patients are always symptomatic. Some of the patients with radiological stage IV disease may have mild or even asymptomatic presentation.

The disease extent and severity are also judged from the number of involved organs and the density of granuloma within the organs. These are assessed from symptomatology, number and type of organ involvement, and radiographic investigations. Symptomatic involvement of vital organs such as the eyes (especially the posterior uveal tract), lung parenchyma, liver, kidneys, and cardiovascular or neurological systems is considered to be serious and requires urgent systemic therapy. Lupus pernio, cystic bone lesions, involvement of the upper respiratory tract, e.g. nasal mucosa and larynx, hypercalcaemia and calcinosis, are also forms indicating an adverse prognosis. Isolated skin and lymph node involvement or anterior uveitis alone are considered to be milder forms. Investigations for individual organ dysfunction are helpful in assessing their involvement, but the levels of ACE or other nonspecific markers are rarely useful.

1.5 Disease Activity

Activity implies an active ongoing disease or inflammation. It should not be confused with the disease extent, severity or unfavourable prognosis.[28] Unfortunately, there is no single test to assess disease activity. The presence of systemic constitutional symptoms (e.g. fever, aches and pains, weight loss, nausea, vomiting and headaches), active uveitis, hypercalcaemia and organ inflammation such as serositis, myocarditis, hepatitis and neurosarcoidosis, indicate the presence of active disease. Stage I–III pulmonary disease is generally considered to be active, but stage IV disease on radiography is usually seen as end-stage fibrosis from progressive pulmonary disease.

Laboratory assessments, such as a raised erythrocyte sedimentation rate, leukocytosis, thrombocytopenia or raised serum ACE levels indicate ongoing inflammation. A raised serum ACE level is a good indicator of granuloma load but does not directly correlate with corticosteroid therapy. Analysis of BAL fluid as well as serological markers have been employed for this assessment.[29] There is lymphocytic predominance in BAL fluid but there is no direct correlation with disease activity. Radioisotopic scanning with Gallium-67 localises the site of active inflammation, but does not distinguish between activity due to sarcoidosis, TB, malignancies or other causes.

Scanning procedures such as HRCT have been used to find soft infiltrates suggesting activity in the lungs. Contrast enhancement with gadolinium improves this sensitivity. Positron emission tomography scanning with various markers may also prove to be useful in detecting sarcoidosis activity.[30]

Pulmonary function tests have sometimes been used to decide on the disease progression and to monitor the course and response to therapy.[31] Although a rough correlation was reported between forced vital capacity and overall histological score, there was no direct relationship with radiographic features.[32]

2. Management

Fortunately, the therapeutic response to several anti-inflammatory drugs is good in sarcoidosis. The recommended treatments vary from none to multidrug therapy with a combination of cytotoxic drugs.[5] Corticosteroids, the use of which in sarcoidosis was first reported in 1951, remain the cornerstone of therapy.[33,34] However, more important are the issues about whom to treat and when to start (and stop) treatment. In general, there is a broad consensus on most of these issues.

2.1 Initial Evaluation

As discussed in section 1, before deciding on treatment, each patient requires evaluation for the indication as well as the form of therapy. A detailed history and clinical examination, including eyes, a posteroanterior chest radiograph, electrocardiogram and tuberculin skin test, are important. Routine haematological and biochemical investigations are also carried out for their baseline values. Lung CT scans are required in patients with atypical findings,

normal chest radiograph but strong clinical suspicion, or in the presence of complications.

2.2 Treatment of Asymptomatic Patients

Most investigators agree that asymptomatic pulmonary disease rarely requires any therapy, but patients with persistent pulmonary infiltrates, even if asymptomatic, may require treatment.[5,33-36] Patients with milder forms of disease, such as skin disease (erythema nodosum) alone or anterior uveitis, may need only topical treatments, whereas patients with stage I pulmonary sarcoidosis may be observed without any treatment. Patients manifesting with only cough as a symptom may be treated with inhaled corticosteroid therapy. But all new patients with stage IV radiographic changes, even if asymptomatic, should be given a treatment trial with corticosteroids for 8–12 weeks before being labelled as having end-stage fibrosis.

Treatment is generally started on the basis of symptoms and disease severity. Patients with vital organ involvement (such as the heart, liver or CNS), symptomatic pulmonary disease or hypercalcaemia definitely require oral treatment. Although several laboratory parameters, as discussed in section 1.5, have been used to assess the stage of disease, none has been found to be as useful as clinical features and end organ involvement for making a treatment decision.

There are no clear guidelines for the treatment of patients who are strongly suspected of having sarcoidosis according to various criteria but who exhibit a positive tuberculin test. We generally practice additional anti-tubercular chemoprophylaxis with rifampicin and isoniazid in such patients during treatment for sarcoidosis.

2.3 Standard Treatment for Patients with Symptoms

There are several options of treatment available. Corticosteroids, usually oral, constitute the first choice of treatment for stage II and III disease.[33-37] Alternative or additional drugs are required only in the presence of adverse effects, contraindications or non-responsiveness to corticosteroids. However, each drug is likely to have its own advantages and disadvantages.

2.3.1 Corticosteroids

Efficacy of treatment with corticosteroids was recently evaluated in a meta-analysis of 12 randomised, controlled trials that included 1051 patients.[38] The treatment was shown to improve the chest radiographic findings and a global score of chest radiograph, symptoms and spirometry, but little improvement in lung function. Long-term benefits beyond 2 years were not clearly demonstrable.

Although the earlier studies reported the use of corticotropin (adrenocorticotrophic hormone; ACTH) in the initial treatment, prednisolone or prednisone remain the most commonly used drug. The initial dosage of 20–40 mg/day is continued for 1–3 months depending upon symptomatic response. Higher dosages are required for cardiac- and neurosarcoidosis. Re-evaluation of the condition is required if no response is seen after 3 months of therapy. In patients who show an adequate response, the dosage is tapered to 5–10 mg/day and continued for at least a year as maintenance therapy. Alternate day therapy in equivalent dosages may also be given. Some patients show recurrent relapses and need long-term, low-dose treatment. Inhaled corticosteroids have been used in some studies with a limited benefit.[39]

Adverse effects of corticosteroids are common. Some of the effects, such as fluid retention, mild elevations in blood pressure and glucose intolerance, usually disappear when treatment is tapered and discontinued, but the problems may persist, especially with prolonged corticosteroid use and in patients with pre-existing diseases such as hypertension and diabetes mellitus. Several other important complications include weight gain, cataracts, osteoporosis and bone fractures, which require additional treatment measures. Careful monitoring and control of corticosteroid-induced complications is therefore important in all patients.

2.4 Treatment of Refractory and Recurrent Disease

Cytotoxic agents are required in patients with a recurrence of disease, which is seen in almost one-third of patients within 2 years of the discontinuation of corticosteroid therapy. Cytotoxic agents are also used in the presence of non-responsiveness to corticosteroids or with the development of complications with corticosteroids.

2.4.1 Methotrexate

Methotrexate, the most frequently employed agent, is effective in about two-thirds of patients with cutaneous, pulmonary, joint, ocular or neurological disease.[36,40] Methotrexate is generally used in a 7.5–15mg dose every week for a period of about 6–12 months. Response is usually slow and may not appear up to 6 months after the start of therapy.

2.4.2 Azathioprine

Experience with azathioprine in sarcoidosis is limited. It is generally used in patients with chronic disease at an oral dose of 2–3 mg/kg. Its efficacy is generally similar to that of methotrexate.[41]

2.4.3 Other Cytotoxic Agents

Chlorambucil was used in the past but is no longer favoured.[5] Cyclophosphamide is useful for refractory disease, especially neurosarcoidosis. It is used either orally in a dosage of 50–150mg daily or 500–2000mg intravenously every 2 weeks. In view of an increased risk of malignancy when used on a daily basis for >1 year, it is recommended to use this agent on alternate days.[42] Increased daily fluid intake is recommended with its use to minimise the occurrence of haemorrhagic cystitis. Leflunomide, an analogue of methotrexate, is less toxic but more costly.[43]

2.4.4 Toxicity and Monitoring

Most cytotoxic drugs can cause nausea and vomiting, which are generally dose dependent. With methotrexate, other commonly affected organs are the bone marrow, liver, kidney and the gonads. Azathioprine may cause leukopenia and gastrointestinal effects; however, its hepatic toxicity is less than that of methotrexate. With cyclophosphamide, gastrointestinal symptoms, mucosal ulcers and leukopenia are common adverse effects. Folic acid supplementation at a dosage of 1mg every day is helpful to lessen these adverse effects of cyclophosphamide. Hepatic toxicity may occur with a cumulative dosage of about 1g or more; however, pulmonary toxicity is rare. Cyclophosphamide is commonly associated with haemorrhagic cystitis.

Regular monitoring for hepatic, haematological and renal toxicity is required in patients receiving cytotoxic agents. Complete blood counts and urinalyses are advised every 4–6 weeks in patients receiving azathioprine. Patients receiving cyclophosphamide or methotrexate need similar monitoring with urinalysis, complete blood counts and liver function tests every 3–4 weeks.

Gonadal damage and teratogenicity is an important toxicity observed with the use of cytotoxic drugs. Cyclophosphamide can cause early menopause and aspermia. Recovery from suppression of spermatogenesis as well as from ovarian failure is unpredictable. Azathioprine is relatively less teratogenic.[5] Use of cytotoxic drugs is therefore best avoided for women of childbearing age, but if the indication for the use of cytotoxic drugs is important, pregnancy is better postponed until at least 6 months after the last dose of any of these agents. There is an increased opportunity now to preserve sperm as well as ova before administration of chemotherapy with cytotoxic drugs, so as to enable pregnancy at a later stage. This has been made possible with the advancements in cryopreservation and assisted reproduction techniques such as *in vitro* fertilisation with intracytoplasmic sperm injections.

Readers interested in cryopreservation in patients with non-malignant systemic diseases are referred to Hallak et al.,[44] Ranganathan et al.,[45] Mattle et al.[46] and Sonmezer et al.[47]

2.4.5 Other Agents

Both chloroquine and hydroxychloroquine have been used with some success in patients with sarcoidosis, especially for cutaneous lesions, as well as for hypercalcaemia and neurosarcoidosis. Ocular toxicity, frequently seen with chloroquine, is not seen with hydroxychlorquine, even with prolonged

use.[48] Hydroxychloroquine can also be combined with corticosteroids.

Several other agents that have been used for patients with refractory sarcoidosis include ciclosporin, radiation therapy and immunomodulators such as thalidomide, pentoxifylline and infliximab. Experience with most of these agents is limited and anecdotal.[36,42,49] It is important to screen patients for occult TB and lymphoproliferative disorders before starting therapy with any of these agents.

3. Conclusion

The management of sarcoidosis over the last few decades has seen many new developments. One important aspect that has emerged recently is to avoid treatment for several forms of mild or asymptomatic disease. On the other hand, valuable strategies, alternative drugs and treatment guidelines have now become available for routine decision making in the presence of recurrence, complications or associated medical conditions and co-morbid illness.[5,34-36,50,51]

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