Chapter 12

SARCOIDOSIS

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INTRODUCTION

Sarcoidosis is a chronic granulomatous, multisystem disease of unknown etiology. It is an inflammatory disorder that affects people of all races and ages throughout the world. Since the first documented cases in the 1800s, genetic predisposition and environmental factors like infections are thought to play role in its pathogenesis (1). Despite all advanced efforts, a specific etiological agent has not yet been determined. Growing evidence assumes that sarcoidosis develops due to the complex interaction of environmental exposures or infectious diseases with multiple genes (2).

ACCESS (A Case Control Etiologic Study of Sarcoidosis) conducted in the United States, is an important effort on identifying the possible causative agents and recognizing some occupations like cotton workers, raising birds, radiation or organic dust, pesticide exposure which might be keys in etiology of sarcoidosis. (3) Even though, no relation was found in this study between occupation or environmental exposure and sarcoidosis.

The hypothesized external agent or antigen triggers a type 1 T-lymphocyte response which depends on the host susceptibility results in granuloma formation (4). The granulomas are typically noncaseating; means that not containing focal areas of necrosis, and composed of epithelioid cells, multinucleated giant cells, mononuclear phagocytes with surrounding CD4+ and CD8+ T cells. Macrophage aggregates and multinucleated giant cells are generally located in the central core of the granuloma and layers of immune cells are concentrically grouped. Several dendritic cells often accompany the T lymphocyte organized in an outer layer. Rarely, B lymphocytes surround the granulomas (5). Sarcoidosis granulomas are recognized as nonnecrotic but in nodular form of pulmonary sarcoidosis, necrotic and nonnecrotic granulomas may be found together. The

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most common place for these granulomas is lungs and lymph nodes though they may be seen in any organ system (4). As these granulomas can also occur in some malignant neoplasms, fungal or atypical mycobacterial infections, tuberculosis, hypersensitivity pneumonitis, pneumoconiosis, berylliosis, vasculitis, drug-induced lung diseases, sarcoid-like reactions induced by drugs, and common variable immune deficiency syndrome, it is therefore critically important to keep in mind these granulomatous diseases in differential diagnosis (6). The diagnosis of sarcoidosis is constructed by three criteria; clinical presentation compatible with the disease, the histopathological findings of nonnecrotizing granulomatous inflammation (sometimes tissue sampling is not required), exclusion of alternative causes as mentioned before (4). To date the diagnosis and management is not yet fully established with standardized or objective measures.

EPIDEMIOLOGY

Sarcoidosis is known to be a middle-aged persons' disease, with the average age of diagnosis between 35-50 years, but the clinical features vary depending on races, gender, and sociodemographic status. It is thought to be associated with progressive disease when initial presentation is> 40 years. The prevalence reports reveal African Americans's predominance in the United States. The highest incidence is shown among American black and Scandinavian populations in the comparative epidemiological studies (7). Higher rates of liver, bone marrow, extra thoracic lymph node and skin involvement (other than erythema nodosum) are observed in Black patients. Whites tend to have more asymptomatic disease and erythema nodosum compared to Blacks.

To date, accumulating data suggests that sarcoidosis is much more prevalent than previously evaluated and mortality is much higher among some populations like Afro-American women than the previous reports. Myocardial involvement is the commonest cause of death in Japanese people (8,9). In ACCESS study, while extrapulmonary involvement of sarcoidosis; uveithis, neurosarcoidosis and erythema nodosum are found to be more common in women likewise hypercalcemia is found to be more common among men (3). The annual incidence for sarcoidosis is calculated as 4/100000, with a mean age 38+12 for men and 48+13 for women, in the epidemiological studies for Turkey. The female/male ratio is noted as 2,08 in these Turkish studies (10).

Additionally, specific gene polymorphisms correlated with familial sarcoidosis clusters are pronounced in recent multicenter based studies from the USA. (11)A linkage analysis study in families with a member having sarcoidosis reveal that sarcoidosis-associated genes may be present within the major histocompatibility complex region of chromosome 6. (12) 2,4% of sarcoidosis cases are siblings in Ireland (13).

CLINICAL FINDINGS

Pulmonary Sarcoidosis

Lungs and intrathoracic lymph nodes are affected in >90% of these patients. The clinical presentation is often asymptomatic disease with an incidentally finding of intrathoracic lymphadenopathy on chest X-ray. But the spectrum ranges from mildly symptomatic state to progressive, relapsing disease with pulmonary impairment with fibrotic lungs or cardiac involvement leading to sudden death with arrhythmias or myocarditis. In an asymptomatic patient with a significant right paratracheal and bilateral hilar adenopathy, it is usually accepted as sarcoidosis and no histopathological sample is recommended for a diagnosis regarding the latest consensus. Most of the patients with sarcoidosis have mediastinal adenopathy and/or pulmonary infiltrates, but only <50% of them present with pulmonary symptoms. Cough, dyspnea, and chest pain are the commonest symptoms. In 1961, Scadding noted one of four patterns on plain chest X-rays of most of the sarcoidosis patients, which has then become a standard for staging thoracic involvement all around the world (14). These stages of sarcoidosis are:

Stage 1: Mediastinal and hilar adenopathy (usually bilateral) without pulmonary infiltrates

Stage 2: Mediastinal and hilar adenopathy (usually bilateral) with pulmonary infiltrates

Stage 3: Pulmonary infiltrates without adenopathy (adenopathy already regresses)

Stage 4: Pulmonary fibrosis with volume loss, no adenopathy

The frequency at presentation is 40-50% for Stage 1 disease, 30-40% for Stage 2, 15-20% for Stage 3 and 2-5% for Stage 4.

Although pulmonary sarcoidosis is considered to be a disease with favorable prognosis, the overall prognosis depends on the stages. In Stage 1 disease, most patients are asymptomatic and spontaneous radiographic regression may be seen up to 80% of patients. In <5% of these patients may develop chronic respiratory impairment whereas 5-fold increased risk of respiratory deterioration is stated for the patients in Stage 3 and Stage 4 disease. Spontaneous resolution is also observed in only 30% among those with Stage 2 and Stage 3 disease. Only 15% of patients were found to be in Stage 3 or Stage 4 disease in ACCESS study (3).

Sarcoidosis is differentiated from other interstitial lung diseases with commonly involvement of lymphatics. As the hilar adenopathy gets larger and symmetrical, one can think more likely about the diagnosis of sarcoidosis. EBUS (endobronchial ultrasound) is a low cost and available diagnostic tool which is preferred over mediastinoscopy with lower morbidity rates (15). Bronchovascular involvement is the other feature of sarcoidosis but may also occur in lymphoma, lymphangitic carcinoma, hypersensitivity pneumonitis (16). Parenchymal lung disease is another common feature of sarcoidosis. In more than >50% of patients with Scadding stages 2, 3 and 4 interstitial changes like nodules, ground-glass opacities and fibrosis are seen in high-resolution CT scan (HRCT) (17). Parenchymal infiltrations are commonly reticulonodular and may be in patchy or diffuse pattern, with upper or middle lobe predominancy. Volume loss and traction of hilum frequently contributes to fibrosis. Nodules tend to be symmetrical and locate in upper and middle lobes with a perilymphatic distribution.

Upper lobe bronchiectasis is frequently seen in sarcoidosis fibrotic lung which may lead to infections in these areas (18). Antibiotics and glucocorticoid treatment may be indicated due to worsening symptoms of these patients. If cavities associated with bronchiectasis generate by time, aspergillus or other fungal infections may occur in these cavities which are called as “mycetomas” (19). Massive hemoptysis caused by mycetomas was a significant risk of morbidity and mortality in past years. But nowadays, it has been shown by some studies that widespread treatment with azoles in aspergillus infections lead the mycetomas to be not an independent risk factor for mortality in sarcoidosis (20). These studies also reveal no association between mycetomas and pulmonary fibrosis or pulmonary hypertension which are the hallmark of mortality in pulmonary sarcoidosis.

The severity of the disease is milder than the other interstitial lung diseases. Although sarcoidosis is considered predominantly as a restrictive lung disease, the parenchymal involvement leads to both restriction and obstruction in Pulmonary Function Tests (PFT). In a German study, it has been noted that <20% of patients have a forced vital capacity (FVC) <70% of predicted at time of diagnosis (21). In a USA based study, only 30% of spirometries of patients showed FVC<70% of predicted value at time of diagnosis, who were already in Stage 4 disease (22). Although lungs are affected in 90% of sarcoidosis patients, pulmonary function defects are present in 55% of individuals, because of the heterogenous characteristics of the disease.

In several studies other phenotypic patterns in PFT of sarcoidosis with pulmonary involvement were described as obstructive phenotype, mixed obstructive and restrictive phenotype which is highly associated with mortality and a marker of more severe disease, and an isolated diffusion defect (23). The pulmonary impairment of obstructive phenotype is due to the distribution of granulomas in the airways, restrictive phenotype is due to interstitial granulomas and isolated reduction of diffusing capacity is a result of pulmonary vascular involvement. It is noteworthy that disease progression varies by phenotypes and PFT is essential in the follow-up of the patients even the clinical or radiological findings are not compatible. Kouranos et al. showed in their study that combined obstructive and restrictive pattern is associated with increased risk of mortality especially among White subjects (24). Sharp et al.'s study showed these phenotypic impairments of PFT were effected not only with race and gender but also with disease duration and tobacco use (23). The patients who have normal PFT in this study (44%) were more likely among Whites than Black patients. White patients more likely have obstructive pattern in PFT, whereas Black patients more likely present with restrictive phenotype and isolated diffusion defects. Black patients had worse lung functions, and current or ex- smokers and patients with longer duration of disease more likely have mixed obstructive and restrictive pattern. Men tend to have obstructive pattern, whereas women have restrictive phenotype. But restrictive pattern was the most common PFT abnormality in this study although only 27% of entire cohort present with restrictive phenotype.

FVC is the marker of restrictive lung disease and most of the clinical trials on treatment of sarcoidosis targets the threshold change in FVC as an appropriate clinical endpoint for evaluating the response to therapy. The results of Sharp

et al.'s study is suggestive to change the consideration that even if FVC % predicted is the primary pulmonary outcome measure for judging efficacy of the drugs or interventions, FVC is not enough to represent all subjects with pulmonary sarcoidosis irrespective of radiological features (23). As the efforts for establishing treatment algorithms for sarcoidosis are going on with new clinical trials, FVC should not be the sole criterion to assess success or failure on the basis of outcomes for the new therapeutic options because of the patients' baseline phenotype.

Sarcoidosis is an interstitial lung disease, reduction of lung volumes and DLCO without obstruction is not surprising. But historically defining it as a restrictive disease has led the clinicans mistakenly focus on spirometry alone. Nowadays, mixed ventilatory pattern requires to be evaluated with the integration of reduced FEV1/FVC ratio and total lung capacity (TLC) values. 2/3 of these patients with mixed pattern are in the Stage 4 disease, and they have lower DLCO levels and higher mortality rates than the other patterns. Measurement of spirometric volumes, pletismographic volumes and carbon monoxide diffusing capacity (DLCO) levels should be performed in the presence of chest X-ray abnormalities pointing the parenchymal lung involvement. Decrease in DLCO levels with an obstructive pattern indicates concurrent interstitial lung disease and pulmonary vascular disorders which necessitates further evaluation (25). The mixed obstructive and restrictive ventilatory defect is related with the airway distortion due to fibrosis.

PULMONARY VASCULAR INVOLVEMENT

Sarcoidosis-associated pulmonary hypertension (SAPH) is found in up to 20% of sarcoidosis patients and exhibits significant morbidity and mortality in which identified with recent studies(26). SAPH is defined in half of the sarcoidosis patients with exertional dyspnea(27). Granulomatous involvement of pulmonary vasculature, pulmonary venooclusive disease, hypoxic vasoconstriction, compression of vasculature with lymphadenopathy are the mechanisms of SAPH (28). Chest imaging is an important procedure for evaluating pulmonary artery stenosis and mediastinal compression (29). >50% of patients with SAPH have precapillary form of pulmonary hypertension which may respond to therapeutic agents directed at reducing pulmonary vascular resistance (30). New evidence points out that presence of pulmonary hypertension in sarcoidosis is associated with significant symptomatology and morbidity in advanced

pulmonary disease and is an independent predictor for mortality. The 2014 Heart Rhythm Society statement suggests using echocardiogram to investigate pulmonary hypertension, valve disease or cardiac failure in sarcoidosis (32). Pulmonary hypertension experts recommend transthoracic echocardiography for the sarcoidosis patients who have one or more of these listed clinical features using a Delphi method. If the peak tricuspid regurgitant velocity determined by echocardiogram is >3,4 m/s, pulmonary hypertension (PH) is highly likely; if it is 2,9-3,4 m/s the probability is intermediate; if it is<2,9 m/s PH is unlikely, but some other features may support the probability. Pulmonary artery diameter>25 mm, early diastolic pulmonary regurgitation velocity >2,2 m/s, right ventricle/left ventricle basal diameter ratio>1 are other findings of PH on echocardiography (48). Right heart catheterization is the most important procedure in confirming pulmonary hypertension and allowing to determine postcapillary or precapillary pulmonary hypertension as the prognosis differs regarding the response to therapy (30). In summary, diagnosis, treatment decision and follow-up should be made by a multidisciplinary approach in sarcoidosis associated pulmonary artery hypertension.

EXTRAPULMONARY SARCOIDOSIS

Skin

Skin lesions are more common among women and black population. Up to 1/3 of sarcoidosis patients have skin manifestations and cutaneous sarcoidosis can be classified as sarcoid-specific skin lesions and nonspecific skin lesions which have equally common incidence (33). Papules, macules, pustules, erythroderma, plaques and subcutaneous nodules are the most common sarcoid-specific skin lesions which tend to locate on extremities, and head and neck area with skin-colored, hyperpigmented or hypopigmented colors (34). Sarcoid-specific lesions usually accompanies chronic disease. These nodules form by granulomatous inflammation of adipose tissue just under the skin and are generally found on the extremities. Most of the skin lesions, except diffuse, irresponsive disease, can be treated with topical agents.

Erythema nodosum is the most common nonspecific lesion, 18% of Finnish and 30% of British sarcoidosis present with this symptom (35). It is nongranulomatous panniculitis, which is known with the painful, erythematous nodules, typically appearing on the anterior surface of the lower extremities.

Erythema nodosum usually indicates an acute form of sarcoidosis; and when combined with arthritis and bilateral hilar lymphadenopathy, it is termed as "Löfgren Syndrome" (34). Constitutional symptoms like fever and malaise frequently accompanies Löfgren Syndrome and the prognosis is often favorable with spontaneous resolution (34). Inflammation around scar tissue and tattoos are less common skin lesions.

Lupus pernio is a particular cutaneous manifestation and sign of chronic course of sarcoidosis, which requires systemic treatment. It is characterized by red to purple hard plaques on the nose, cheeks, lips or ears, and commonly seen in African Americans and Caucasians. Nasal bone and cartilage erosion may develop in the nasal lesions. Bone cysts and pulmonary fibrosis may accompany the disease.

Eye

Ocular involvement is seen 20-50% of patients and 5% of patients initially present with ocular symptoms. The prevalence is higher among blacks than whites, and among women than men (33). Anterior uveitis, keratoconjunctivitis and optic neuropathy are the most common disorders. Red, painful eye with photophobia or blurred vision are the symptoms of uveitis (36). Not only anterior but also intermediate, posterior and panuveitis are the subtypes of the uveitis that may ocur in sarcoidosis patients. Posterior and intermediate uveitis present with painless visual loss and mostly common among blacks (36). The prognosis of sarcoid uveitis on the basis of visual outcome is favorable, and serious loss of visual acuity while following up the patients is not common (33). The nonuveitis ocular disorders are conjunctivitis, scleritis, lacrimal gland involvement, optic neuritis and orbital mass in which response to therapy is favorable (36). As ocular inflammation is insidious and patients may stay asymptomatic for a long time, screening examination for ocular sarcoidosis for the newly diagnosed patients is essential.

Heart

Skin and eyes are the commonest region for extrathoracic sarcoidosis but health and nervous system involvement are the most serious ones. Cardiac sarcoidosis may result in life-threatening disease course and even in fatal clinical outcomes (37). Only 5% of patients present with symptoms but postmortem studies reveal up to 25-70% of prevalence in cardiac sarcoidosis

(38). New reports suggest an increase in the incidence of cardiac sarcoidosis due to the improved technological advances in cardiac imaging systems. It may be seen either as an isolated form without other organ involvement. Arrhytmias are the most common manifestation as the granulomas infiltrate the conducting system and myocardium (39). Atrioventricular block, ventricular tachycardia, and supraventricular arrhytmia are the commonest type of arrhytmias(37). Palpitations and syncopes are recommended to be evaluated with electrocardiography. Dilated cardiomyopathy may also develop due to sarcoidosis involvement and as progressive heart failure and sudden death are the most serious complications, any suspicion of these disorders requires ecocardiographic examination and urgent consultation of a cardiologist to improve patients' prognosis (40). Most of the expert guidelines recommend screening the sarcoidosis patients for cardiac involvement with physical examination and 12-lead electrocardiography (31). Heart failure may be the presenting manifestation in 10-20% of patients (41). It may also ocur in another form with preserved ejection fraction from restrictive cardiomyopathy. Cardiac sarcoidosis frequently responds to corticosteroids and immunosupressant therapy but patients with end-stage cardiomyopathy may be referred for heart transplantation (39). Cardiac Magnetic Resonance (CMR) imaging shows detailed cardiac morphology and functions. While native T1 mapping and late gadolinium enhancement (LGE) may be useful in determining focal fibrosis, T2-weighted sequences may show focal edema (42). Patchy LGE uptake with sparing of the endocardium suggests cardiac sarcoidosis as CMR is highly sensitive for the diagnosis. A nuclear medicine technique FDG-PET scan helps to identify the active myocardial inflammation using a radioactive glucose tracer. FDG-PET changed the diagnostic process of cardiac sarcoidosis and is also good at monitoring the response to systemic immunosuppressive therapy (42). But the procedure needs experienced preparation for sarcoidosis workup as the tracer is affected by physiological myocardial uptake. Treatment of cardiac sarcoidosis aims primarily to prevent myocardial fibrosis and managing arrhythmias and heart failure.

Nervous System

Neurosarcoidosis is not so common, the reported prevalence is approximately 3-10% (33,43). Lung and intrathoracic lymph node involvement is already present in over 90% of patients with neurosarcoidosis. Neurologic symptoms

are the first signs of the disease that leads to diagnosis of sarcoidosis in most of the patients (44). Cranial nerves, meninges, brain parenchyma are the most frequent sites for the involvement. Although any cranial nerve can be involved by neurosarcoidosis, cranial nerves 2, 7, 8 are the most common ones. Epineural granulomatous inflammation or the compression of the inflammation of the leptomeninges compressing the nerves are the possible underlying mechanisms (43). Unilateral or bilateral facial palsy are the commonest manifestation which is a result of cranial nerve 7 involvement which has a good prognosis with an over 90% complete resolution (44). The triad of facial nerve palsy, parotitis and anterior uveitis is a particular presentation of sarcoidosis which is called as Heerfordt Syndrome (33). Optic neuritis is another commonest manifestation of neurosarcoidosis, presented with blurry vision and retrobulbar pain, which has not a favorable prognosis and may result in permanent impaired visual acquity(46). Involvement of vestibulocochlear nerve may cause hearing loss and peripheral vertigo. Leptomeningeal abnormalities may result in headache, in which cerebrospinal fluid analysis reveals monocyte pleocytosis and high protein levels (47). The leptomeningeal abnormalities usually responses to glucocorticoid therapy. Less common involvement of neurosarcoidosis include intraparenchymal granulomatous lesions like solitary mass or multiple nodules which may cause focal neurologic deficits and seizures (44). These lesions are hard to diagnose, and seizures usually require long-term treatment. Paresthesia, burning sensation and pain are the clinical presentation of small fiber neuropathy with a prevalence of 10% (44).

Liver

An asymptomatic increase of hepatic enzymes alkaline phosphatase and gammaglutamyltransferase levels are the most common presentation (47). Infections are the alternative causes for differential diagnosis with similar changes in hepatic enzymes. The disease has a silent clinical course and is usually discovered incidentally by this abnormal liver tests, but postmortem autopsy studies reveal that the prevalence is probably higher than expected (49). In liver imaging, hypodense nodules and hepatomegaly are the commonest findings (50). Granulomas can be detected by liver biopsy for definite diagnosis of hepatic sarcoidosis. The prognosis is favorable, in which spontaneous resolution is possible but in minority of patients persisting inflammation may result in cirrhosis.

Gastrointestinal Tract

Gastrointestinal sarcoidosis is rare, although any part of the gastrointestinal tract from oral cavity to colon may be involved (33). As granulomatous infiltration in the mucosa leads to mucositis; ulcers, obstruction and stricture may develop in gastrointestinal tract (51). Stomach is the most frequent organ affected by sarcoidosis in which epigastric pain is the commonest symptom in gastric sarcoidosis (52).

Kidneys

The classic renal pathology of sarcoidosis is granulomatous interstitial nephritis however it is often not clinically evident (53). The important point to keep in mind is that granulomatous interstitial nephritis may be seen also in tuberculosis, fungal infection, autoimmune diseases as the same histopathologic picture. It usually causes impairment of renal functions with or without uryanalysis abnormalities like proteinuria or microscopic hematuria. Interstitial nephritis has a favorable prognosis but the patients who have high burden of fibrosis at the time of diagnosis may have renal impairment (54). Hypercalcemia and hypercalciuria may result in nephrocalcinosis and nephrolithiasis in some patients with sarcoidosis (55).

Joints

Inflammatory arthritis; typically, acute oligoarthritis, presented with joint pain occurs up to 5-15% of the patients (56). Ankle joints are the commonest part of involvement. Other systemic arthritis like rheumatoid arthritis shoul be excluded in these patients. The resolution may take time from 6 weeks to 2 years. On the other hand, chronic arthritis is not common. Erythema nodosum may accompany arthritis.

DIAGNOSIS

In 1999, World Association of Sarcoidosis and Other Granulomatous Disorders (WASOG) committee defined the diagnosis of sarcoidosis as "when clinicoradiological findings are supported by histological evidence of noncaseating epitheloid cell granulomas" (4). This means that a histopathological confirmation is required for diagnosis, but tissue sampling is not easy and sufficient all the time. Moreover, noncaseating granulomas are seen in many alternative conditions other than sarcoidosis. New approach shifts away from

1999 statement with pointing that the indication for a biopsy when diagnosis is not clear (57). In some particular features like, Scadding Stage 1 disease presenting with bilateral mediastinal lymphadenopathy on chest X-ray, Lofgren Syndrome, Heerfordt's Syndrome, which are highly spesific for sarcoidosis, lymph node biopsy is no longer recommended. Some chest tomography especially thin slice high resolution CT scann findings are highly suggestive for sarcoidosis. Combining clinical history, occupational exposures, with long-term lung disease and stable chest tomography findings one may diagnose pulmonary sarcoidosis without any biopsy. American Thoracic Society and British Thoracic Society both suggests endobronchial ultrasound-guided transbronchial node aspiration as a biopsy procedure regarding the new studies. (58,59) The extrapulmonary sites like cervical lymp nodes where accessible primarily should be prefered for sampling. Endobronchial ultrasound-guided transbronchial node aspiration plus transbronchial biopsy is recommended predominantly in parenchymal disease (60). Bronchoalveolar lavage assessing CD4:CD8 ratio is used for supporting the diagnosis rather than confirming (61).

TREATMENT

As sarcoidosis may have an asymptomatic disease course with spontan resolution, not all the patients require systemic treatment. But a chronic and fulminant form of disease is on the other side of the spectrum. To reduce the risk of mortality and disability in life-threatening organ involvement (cardiac sarcoidosis, central nervous system sarcoidosis, pulmonary fibrosis, pulmonary hypertension) or imroving quality of life are the aims of treatment in chronic sarcoidosis. Steroid treatment and immunosupression are the hallmarks of the treatment. However, side effects limit long-term treatment, and decision-making in management of sarcoidosis with risk versus benefit evaluation is a difficult task. As lung is the most frequent target organ, glucocorticosteroids are the initial therapy recommended for patients who have major involvement with pulmonary sarcoidosis in order to improve predicted FVC values and quality of life according to European Respiratory Society 2021 guidelines. In chronic pulmonary sarcoidosis which is defined as an active disease for at least two years, methotrexate, azothioprine, leflunomide and mycophenolate are used as the second-line drugs in terms of steroid-sparing agents. Infliximab and adalimumab are the third-line agents. The treatment of extrapulmonary sarcoidosis targets to reduce organ dysfunction risks and mortality and improve

the parameters of quality of life. Despite new advances, diagnosis and treatment of sarcoidosis remains a challenging clinical issue.

Conclusion

Sarcoidosis necessitates a detailed physical investigation and attention as an accurate diagnosis is not simple. It can mimic many diseases in clinical practice and misdiagnosis may lead to poor prognosis. Despite many advances, the treatment protocols are yet not fully established. Corticosteroids are still in the first line of the theurapeutics, but as they have important side effects, decision making to initiate treatment requires special effort.

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