Chapter 8
Extrapulmonary Sarcoidosis

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Abstract Sarcoidosis is a systemic granulomatous disorder that can involve any organ in the body. Although the lungs are the most commonly affected organs, extrapulmonary involvements are not uncommon and contribute to the morbidity. The decision to treat extrapulmonary sarcoidosis is dependent on specific organs as not all organ involvement requires treatment. This chapter is a comprehensive review of the clinical presentation, diagnostic pathways, and therapeutic interventions in extrapulmonary sarcoidosis.

Keywords Sarcoidosis • Extrapulmonary • Diagnosis • Treatment

Introduction

Sarcoidosis is a systemic granulomatous disorder with unclear etiology that can involve any organ in the body. Although the lungs are the most commonly affected organ, concomitant involvement of extrapulmonary organs is common and can be seen in up to 50 % of cases of sarcoidosis [1]. Conversely, only 2 % of cases in A Case–Control Etiologic Study of Sarcoidosis (ACCESS) were found to have

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extrapulmonary involvement without pulmonary disease [1]. Extrapulmonary sarcoidosis is important to recognize as it adds to the morbidity, mortality, and reduction of quality of life in patients with pulmonary sarcoidosis.

The prevalence and the extent of extrapulmonary sarcoidosis vary on the demographic of the population that is affected from this disease. For example, African Americans are typically more likely to be affected from extrapulmonary sarcoidosis than Caucasians. However, dysfunction of calcium metabolism is found more in Caucasians. A study comparing the manifestations of sarcoidosis in Japanese and Finnish subjects revealed the rates of sarcoidosis in the heart and eyes to be significantly higher in Japanese subjects [2]. Additionally, extrapulmonary sarcoidosis appears to be more common in females, especially with ocular sarcoidosis, erythema nodosum, and neurosarcoidosis [1]. Finally, peripheral lymph nodes were more commonly seen in subjects with ages less than 40 as opposed to dysfunction of calcium metabolism were significantly higher with ages greater than 40 [1].

Extrapulmonary sarcoidosis can develop anytime during the course of the disease. A detailed physical examination in addition to basic laboratory tests (complete blood cell count, complete metabolic panel including serum calcium and urinalysis), electrocardiogram, ophthalmic examination, and imaging studies are essential in detecting extrapulmonary disease. In general, the diagnosis of extrapulmonary sarcoidosis is typically based on the combination of these clinical evaluations and diagnostic studies with histologic evidence of noncaseating granulomas. It is important to note that histological evidence is not necessarily required from the particular organ of interest to make the diagnosis of extrapulmonary sarcoidosis as long as sarcoidosis has been histologically confirmed in another organ. As part of ACCESS, Judson and colleagues have proposed criteria that categorize the likelihood of each potential organ to definite, probable, and possible involvement (Table 8.1) [1, 3].

The decision whether to institute treatment in extrapulmonary sarcoidosis is dependent on specific organs involved and the extent of organ involvement as not all extrapulmonary sarcoidosis requires treatment. In fact, asymptomatic extrapulmonary involvement typically does not require treatment. However, neurologic, cardiac, and ocular involvement typically mandates treatment as the sequelae are significant and potentially life threatening.

Neurosarcoidosis

Epidemiology

Neurosarcoidosis is a less common manifestation of sarcoidosis with a prevalence of 5–13 % of sarcoidosis with symptomatic neurologic involvement, although, other studies have quoted up to 26–45 % [4, 5]. A prospective epidemiologic study of 736 patients in the USA (ACCESS) found that only 4.6 % had definite or probable neurosarcoidosis [1]. In another study, almost 25 % of systemic sarcoidosis patients

Table 8.1 Clinical criteria for extrapulmonary sarcoidosis organ involvement in patients with biopsy-confirmed sarcoidosis in another organ[a]

Organ	Definite	Probable	Possible
Skin	1. Lupus pernio 2. Annular lesion 3. Erythema nodosum	1. Macular/popular 2. New nodules	1. Keloids 2. Hypopigmentation
Eyes	1. Lacrimal gland swelling 2. Uveitis 3. Optic neuritis	1. Blindness	1. Glaucoma 2. Cataract
Liver	1. Liver function tests > three times normal	1. Compatible computed tomography (CT) scan 2. Elevated alkaline phosphate	
Hypercalcemia/ hypercalciuria/ nephrolithiasis	1. Increased serum calcium with no other cause	1. Increased urine calcium 2. Nephrolithiasis analysis showing calcium	1. Nephrolithiasis-no stone analysis 2. Nephrolithiasis with negative family history for stones
Neurological	1. Positive magnetic resonance imaging (MRI) with uptake in meninges or brainstem 2. Cerebrospinal fluid with increased lymphocytes and/or protein 3. Diabetes insipidus 4. Bell's palsy 5. Cranial nerve dysfunction 6. Peripheral nerve biopsy	1. Other abnormalities on magnetic resonance imaging (MRI) 2. Unexplained neuropathy 3. Positive electromyogram	1. Unexplained headaches 2. Peripheral nerve radiculopathy
Renal	1. Treatment responsive renal failure	1. Steroid responsive renal failure in patient with diabetes and/or hypertension	1. Renal failure in absence of other disease
Cardiac	1. Treatment responsive cardiomyopathy 2. Electrocardiogram showing intraventricular conduction defect or nodal block 3. Positive gallium scan of heart	1. No other cardiac problem and either: – Ventricular arrhythmia – Cardiomyopathy	1. In patient with diabetes and/or hypertension: – Cardiomyopathy – Ventricular arrhythmias

(continued)

Table 8.1 (continued)

Organ	Definite	Probable	Possible
Non-thoracic lymph node		1. Palpable node above the waist 2. Lymph node > 2 cm by CT scan	1. New palpable femoral lymph node
Bone marrow	1. Unexplained anemia 2. Leukopenia 3. Thrombocytopenia		1. Anemia with low mean corpuscular volume (MCV)
Spleen		1. Enlargement by: – Exam – CT scan – Radioisotope scan	
Bone/joints	1. Cystic changes on hand or feet phalanges	1. Asymmetric, painful clubbing	1. Arthritis with no other cause
Ear/nose/throat		1. Unexplained hoarseness with exam consistent with granulomatous involvement	1. New onset sinusitis 2. New onset dizziness
Parotids/ salivary glands	1. Symmetric parotitis with syndrome of mumps 2. Positive gallium scan ("Panda Sign")		1. Dry mouth
Muscles	1. Increased creatine phosphokinase (CK)/ aldolase, which decrease with treatment	1. Increase CK/aldolase	1. Myalgias responding to treatment

[a]There can be no other explanation for the clinical finding in this table for these criteria to be valid. In addition, biopsy of each of these organs would constitute "definite" involvement. Adapted from Judson et al. [3]

were found to have CNS involvement on autopsy and 10 % had evidence of CNS involvement by imaging studies with or without neurologic manifestations [6].

Furthermore, less than 1 % of sarcoidosis patients have isolated neurosarcoidosis without any clinical evidence of extraneural sarcoid. The true incidence remains elusive as making a diagnosis poses a challenge to clinicians as procedures to obtain histological confirmation can lead to life-threatening circumstances.

Clinical Presentation

Cranial Neuropathies

The most common manifestation in neurosarcoidosis includes cranial neuropathies, especially with optic and facial nerves which accounts for 23–70 % of neurologic manifestations in neurosarcoidosis [7]. Facial nerve palsy is the most commonly affected cranial nerves and it presents more commonly as a unilateral finding, although a third of the facial nerve palsy may involve both facial nerves [4]. In one series of 24 patients with facial nerve palsy from sarcoidosis, a complete recovery of about 23 out of 24 patients was observed with treatment using corticosteroids and/or in combination of nonsteroidal immunomodulators [8]. Optic neuritis is the second most commonly affected cranial nerves and it usually presents with diplopia or visual defects (Fig. 8.1). Bilateral disease portends a poorer prognosis versus unilateral disease. Involvement of the base of the brain is thought to be the cause of cranial neuropathies; however, infiltration or compression of nerves may also cause dysfunction [4, 9].

Meningeal Involvement

The occurrence of acute or chronic meningitis ranges from 8 to 40 % of neurologic manifestation of sarcoidosis. This is usually due to meningeal infiltration involving the basal leptomeninges (Fig. 8.2). Clinically it can manifest with headaches, neck stiffness, hydrocephalus, or cranial nerve palsies. The course can be monophasic, chronic, or relapsing. Acute meningitis responds well to corticosteroids and has favorable outcomes [9]. Chronic meningitis often requires long-term treatment with a tendency to relapse.

Seizures

Seizures can occur in up to 22 % of patients with neurosarcoidosis and can occur secondary to leptomeningeal involvement, parenchymal masses, encephalopathy, vasculopathy, hydrocephalus, and metabolic disturbances related to hypothalamic dysfunction [1, 7, 9]. Prognosis of seizures remains controversial as older studies described a poor prognosis; however, more recent studies suggest no evidence in support of the unfavorable prognosis [8, 10].

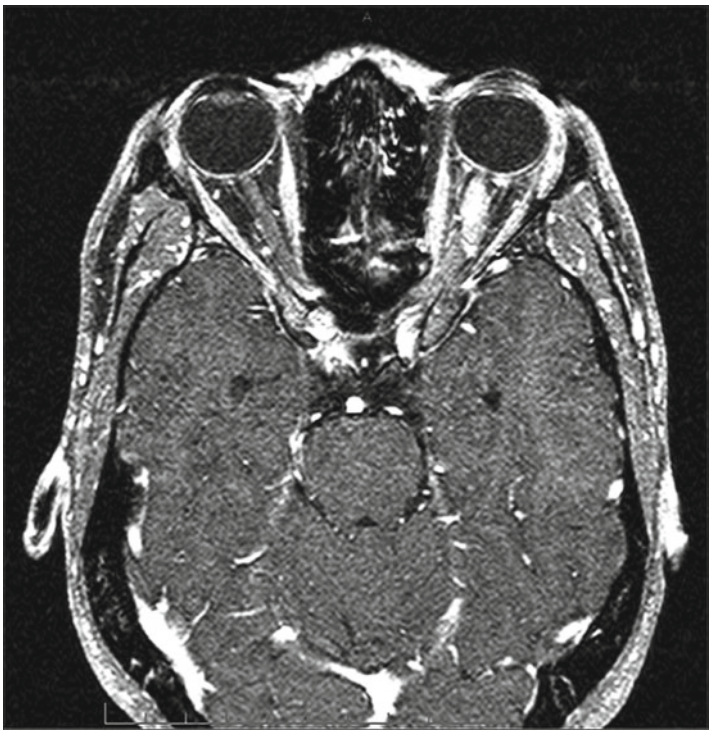

Fig. 8.1 MRI image showing enhancement of optic nerve typical for sarcoid infiltration

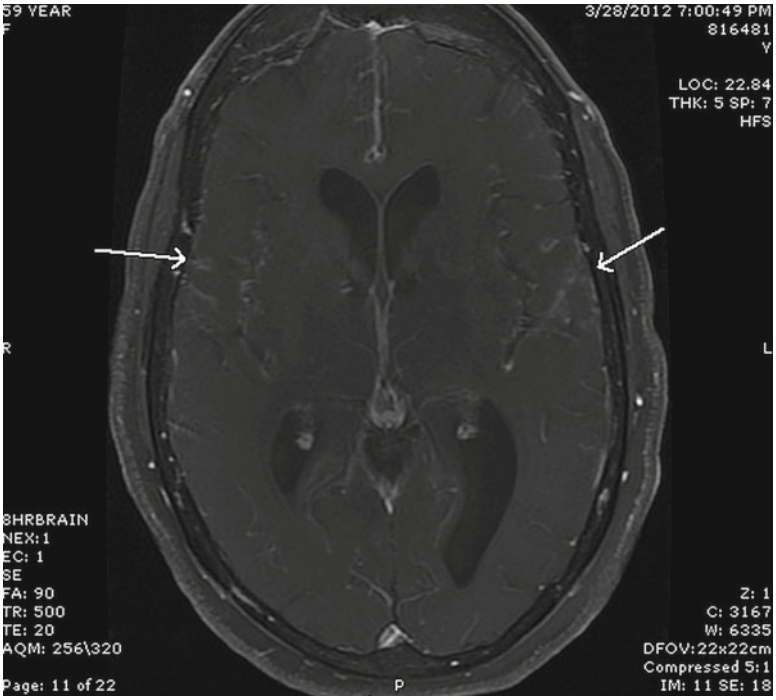

Fig. 8.2 T1-weighted contrast-enhanced MRI image of mild leptomeningeal enhancement and nodules along Sylvian fissures

Hypothalamic/Pituitary Involvement

Endocrinopathies related to neurosarcoidosis are related to granulomatous infiltration of the hypothalamo-hypophyseal region. Hyperprolactinemia (3–32 %) and diabetes insipidus (17–90 %) are the most frequent reported endocrinopathies in neurosarcoidosis. Other clinical features resulting from hypothalamo-pituitary involvement include morbid obesity, dysregulation of body temperature, insomnia, personality changes, syndrome of inappropriate antidiuretic hormone secretion (SIADH), hypothyroidism, hypoadrenalism, growth hormone deficiency, and impaired counter-regulatory response to hypoglycemia [11, 12].

Peripheral Neuropathy

The manifestation of peripheral neuropathy in neurosarcoidosis carries a wide spectrum of symptoms. In a study examining 11 patients with confirmed histologic changes consistent with peripheral nerve involvement from sarcoidosis, Said and colleagues were able to describe Guillain–Barre syndrome like presentation with ascending and progressive muscle weakness with paresthesias, multifocal neuropathies, and sensory polyneuropathies [13].

Small fiber neuropathy is a subtype of peripheral neuropathy or a "paraneuropathy" involving thinly myelinated and unmyelinated nerve fibers causing an aggregate loss of intraepidermal nerve fibers. The typical symptoms consist of pain, dysesthesias (44 %), and abnormal temperature dysfunction (81 %). Additionally, autonomic dysfunction has been described in relation to the small fiber neuropathy [14, 15].

Diagnosis

The process of diagnosing neurosarcoidosis poses a significant challenge to clinicians due to its diverse clinical presentations, nonspecific imaging and laboratory findings, and difficulty in obtaining a neural tissue biopsy. There are two diagnostic criteria that have been summarized by Zajicek et al. [9] (Table 8.2) and Judson et al. [3] (Table 8.1) Both of these criteria have three categories of diagnosis including definite, probable, and possible neurosarcoidosis. For a diagnosis of definite neurosarcoidosis, biopsy of the neural tissue is a prerequisite in the criteria proposed by Zajicek et al., whereas it is not required in the criteria proposed by Judson et al. The latter criteria provide some clinical advantage and practicality in diagnosing patients with a high likelihood of neurosarcoidosis, although there have been no direct comparative studies between these two proposals. As for the diagnosis of probable and possible neurosarcoidosis, various combinations of clinical presentations, imaging studies, and laboratory findings are used to confirm the diagnosis.

Histological confirmation of noncaseating granulomas from neural tissue without any evidence of infectious etiology is the gold standard. However, this option is often impractical due to inherent risks associated with procedures in obtaining neural tissue. If biopsy is considered, it usually involves the meninges or a parenchymal

Table 8.2 Diagnostic criteria for neurosarcoidosis adapted from Zajicek et al. [9]

Definite
Clinical presentation suggestive of neurosarcoidosis with exclusion of other possible diagnoses and the presence of positive nervous system histology
Probable
Clinical syndrome suggestive of neurosarcoidosis with laboratory support for CNS inflammation (elevated levels of CSF protein and/or cells, the presence of oligoclonal bands and/or MRI evidence compatible with neurosarcoidosis) and exclusion of alternative diagnoses together with evidence for systemic sarcoidosis (either through positive histology, including Kveim test, and/or at least two indirect indicators from Gallium scan, chest imaging and serum ACE)
Possible
Clinical presentation suggestive of neurosarcoidosis with exclusion of alternative diagnoses where the above criteria are not met

lesion apparent on the imaging study. Accordingly, sampling of tissue from areas that have evidence of involvement by imaging studies improve the sensitivity of the biopsy [16]. Therefore, tissue biopsy is typically obtained from extraneural areas to secure the diagnosis with sarcoidosis which coupled with clinical manifestations can lead to the diagnosis of probable or possible neurosarcoidosis [4].

There is considerable overlap with neurosarcoidosis and other neurologic diseases that mimic neurosarcoidosis based on clinical manifestations. Therefore, the differential diagnoses one must consider in those suspected with neurosarcoidosis include, lymphoma, infections (tuberculous, fungal), Wegener's granulomatosis, Lyme disease, Behcet's disease, and vasculitis. The differential diagnosis for neurosarcoidosis with ocular involvement includes, multiple sclerosis, which typically has more optic nerve involvement than anterior uveitis [4].

Noninvasive test imaging of the brain and spine by MRI with gadolinium contrast is extremely useful with both aiding in diagnosis and in following treatment effect. Common findings on brain MRI are dural involvement (34 %), leptomeningeal enhancement (31 %), cranial nerve enhancement (34 %), and enhancing parenchymal lesions (22 %) [16]. Other areas involved on MRI, include hypothalamus and pituitary involvement (9 %) seen as thickening and enhancement on T1-weighted images [6, 17]. Hydrocephalus occurs in 5–12 % of cases with neurosarcoidosis which can be due to involvement of the dura or leptomeninges by altering the resorption of cerebrospinal fluid (CSF). Common finding on spine MRI are enhancing intramedullary lesions (13 %), enhancing extramedullary lesions (6 %), and cauda equina enhancement (6 %) [16]. MRI findings, however, are nonspecific for neurosarcoidosis as previous studies have shown that lesions seen on MRI can be related to MS (46 %), metastatic disease (36 %), high grade astrocytomas (9 %), and meningioma (5 %) [18].

Other tests that can be used in combination with histology and imaging include cerebrospinal fluid (CSF) analysis. CSF analysis is quite nonspecific as the typical findings for neurosarcoidosis includes lymphocytosis, elevated protein levels, pleocytosis, hypoglycorrhachia, and positive oligoclonal bands. However all of these findings can be seen in a multitude of diseases such as MS, infections, and

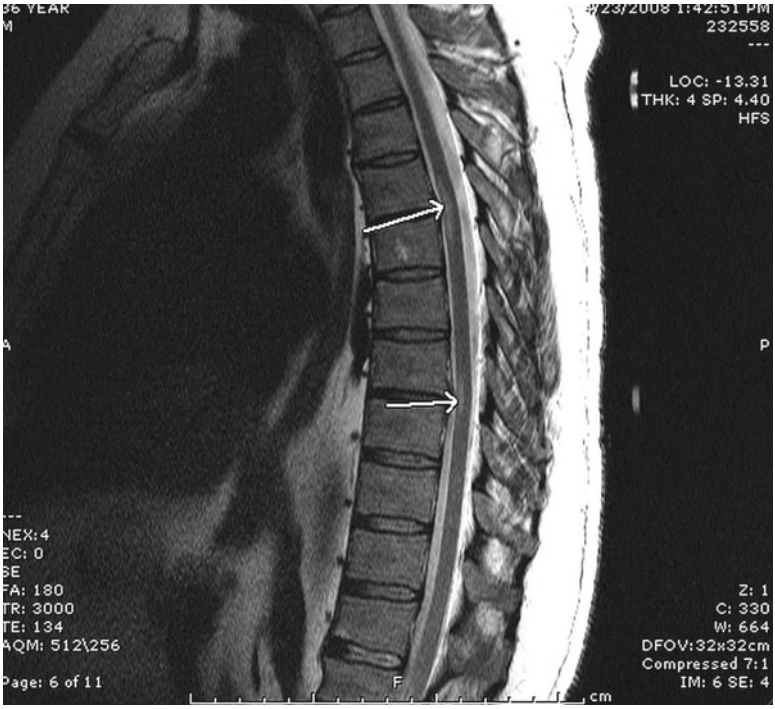

Fig. 8.3 Neurosarcoidosis involving the spine. T2-weighted, contrast-enhanced MRI sagittal images demonstrating two areas of enhancements involving the thoracic spine

vasculitis. CSF analysis may not help with establishing a diagnosis; however, it can exclude possible infectious etiologies such as cryptococcal, tuberculous, and lymphomatous meningitis [4]. The diagnostic utility of CSF angiotensin-converting enzyme (ACE) is uncertain. Elevated CSF ACE levels have a sensitivity and specificity of 55 % and 94 %, respectively [19]. However, other inflammatory diseases such as MS, Bechet's disease, and Guillan–Barre syndrome are also associated with elevated ACE levels [20].

Treatment

Neurosarcoidosis can range from being a self-limiting disease to a chronic and progressive disease. Isolated cranial nerve involvement (i.e., facial nerve palsy) and aseptic meningitis have a good chance of spontaneous recovery or resolution with a short course of corticosteroids [16]. Those with chronic remitting–relapsing course, such as those with parenchymal, leptomeningeal disease, myopathy, or spinal disease will require more intense treatment (Fig. 8.3).

The mainstay of treatment is with the use of corticosteroids. To date, there are no clinical trials to establish initial doses or duration of therapy. However, there is consensus opinion within the field of starting prednisone at doses of 40–80 mg/day [7]. The statement guideline from the American Thoracic Society recommends use of prednisone at 1 mg/kg or its equivalent in severe cases when high dose steroids is necessary [21]. Full recovery with use of corticosteroids or combination of corticosteroids with another immunomodulatory agent varies in range from 29 to 76 % [9, 22–25]. However, Zajicek and colleagues reported that despite treatment with corticosteroids, disease progression or recurring symptoms were observed in about 70 % of patients with neurosarcoidosis during follow-up [9]. Corticosteroid therapy in moderate to severe cases usually mandates prolonged duration of therapy over months to years. As a result, patients become highly susceptible to unwanted side effects from long-term therapy of corticosteroids including osteoporosis, glucose intolerance, weight gain, neuropathy, myopathy, and peptic ulcer disease.

Steroid-sparing immunomodulator therapy may be necessary in patients who are not responding to corticosteroid therapy alone or if they develop intolerance to prolonged corticosteroid therapy. Nonsteroidal immunomodulators include agents such as methotrexate, cyclosporine, azathioprine, cyclophosphamide, chlorambucil, chloroquine, and mycophenolate.

Stern and colleagues were able to lower baseline corticosteroid therapy doses by 30–58 % with the addition of cyclosporine at doses of at 4 mg/kg/day with monitoring of cyclosporine trough levels and for adverse effects of hypertension, renal failure, hypomagnesemia, and neurotoxicity [26].

Methotrexate, another well-known steroid-sparing agent can be started at a dose from 5 to 15 mg/week. The side effects include hepatotoxicity, pulmonary toxicity, and renal toxicity. Hematologic effects such as neutropenia, anemia, and thrombocytopenia can also be seen with methotrexate; however, the side effects can be minimized with the addition of folic acid. Lower and colleagues were able to obtain a beneficial response in 61 % of steroid refractory patients with neurosarcoidosis [8].

Cyclophosphamide is highly toxic with side effects that include bone marrow suppression, teratogenicity, and carcinogenicity. It is usually limited to patients with severe neurosarcoidosis refractory to other agents. One study showed reduction of corticosteroid doses by as much as 58 % with symptomatic and radiologic recovery [27].

Recent case reports using infliximab, a tumor necrosis factor alpha (TNFα) inhibitor, have demonstrated successful treatment of refractory neurosarcoidosis. One case series included seven patients who received infliximab infusion with dramatic improvements in neurologic symptoms after 1–3 infusions; however, symptoms and radiologic abnormalities recurred after cessation of therapy. These patients responded well after reinstitution of infliximab therapy [28].

Prognosis

In general, prognosis in neurosarcoidosis is difficult to predict, although the prognosis to some degree appears to be dependent on the clinical manifestation. Facial

nerve palsy and acute meningeal involvement portend a more favorable prognosis [4]. Heerfordt syndrome, which consists of the triad of facial nerve palsy, parotitis, and anterior uveitis, also predicts a favorable prognosis [29].

Myelopathy is associated with poor prognosis based of a case series of 30 cases [30]. In another study that followed 79 patients with seizures and neurosarcoidosis, these patients had more severe, progressive, or relapsing forms of CNS sarcoidosis [10]. Involvement of bilateral optic nerves is also associated with poor prognosis [31].

Cardiac Sarcoidosis

Epidemiology

In the USA, cardiac involvement that is clinically apparent is seen in only minority of patients with sarcoidosis. However approximately 25 % of patients with systemic sarcoidosis had myocardial involvement observed during autopsy [32]. Cardiac sarcoidosis has a poor prognosis with a median survival of less than 2 years following development of clinical signs and symptoms of myocardial involvement [33]. It accounts for about 13–25 % of deaths and is the second most common cause of death from sarcoidosis [34]. In contrast to the USA, up to 85 % of deaths from sarcoidosis in Japan is reported to be from cardiac sarcoidosis, suggesting a geographic and ethnic predilection [33].

Clinical Presentations

The clinical presentation in cardiac sarcoidosis is protean and may be generally categorized into heart failure, conduction abnormalities, and pericardial disease. Only 5 % of patients with cardiac sarcoidosis manifest signs and symptoms that suggest cardiac involvement [34]. The symptoms may be subtle including dyspnea and fatigue. Other symptoms such as palpitations and syncope suggest involvement of the myocardium and conduction system, whereas angina and pleuritic chest pain may raise the suspicion of myocardial and pericardial involvement. In rare instances, sudden cardiac death may occur.

Heart Failure

Heart failure is a significant morbidity in cardiac sarcoidosis and is seen in 23 % of patients with cardiac sarcoidosis [34]. Both restrictive and dilated cardiomyopathy can occur leading to ventricular dysfunction that causes heart failure. In addition, 14–59 % have diastolic dysfunction on echocardiography findings [35, 36]. Furthermore, cor pulmonale as a sequelae of secondary pulmonary hypertension

due to sarcoidosis can account for about 5–15 % of heart failure due to sarcoidosis. The functional status of the heart failure is closely related with the prognosis as congestive heart failure is the most common cause of death accounting for approximately 73 % of deaths from cardiac sarcoidosis [36]. In a retrospective study of 95 patients, Yazaki and colleagues demonstrated that worsening of NYHA functional class by one functional class, sustained ventricular tachycardia, and left ventricular end-diastolic diameter were independent predictors of mortality. In the same study, the severity of congestive heart failure was the most powerful prognostic predictor in steroid-treated patients with cardiac sarcoidosis [37].

Conduction Abnormalities

Third-degree heart block or complete heart block is the most common presentation (25–30 %) of conduction abnormalities in cardiac sarcoidosis and it usually presents at a younger age [33]. Bundle branch block occurs in 12–61 % of cases with a predominant presentation of right bundle branch block (RBBB) [38]. These occur as a result of granuloma or scar tissue involving the nodal artery causing ischemia or by direct involvement of the conduction system. The incidence of ventricular tachycardia (VT) is 23 %, with approximately 68 % of the time as a result of reentry mechanisms [33]. Atrial fibrillation/flutter occurs in 19 % of patients due to cardiac sarcoidosis [35]. These supraventricular arrhythmias may be due to atrial dilatation or inflammatory processes involving the atrial foci. Based on an antemortem study of 113 patients, sudden cardiac death was usually caused by arrhythmias with an incidence of about 67 %. Consequently, 35 % of sudden cardiac deaths were the initial manifestation of cardiac sarcoidosis [38].

Pericardial Disease

Pericardial involvement has been demonstrated by echocardiography in about 19 % of patients with sarcoidosis [34]. The clinical presentation for pericardial disease includes pericardial effusion and pericarditis [39]. It is rare for constrictive pericarditis and cardiac tamponade to develop in patients with cardiac sarcoidosis [40, 41]. However, there is significant incidence of asymptomatic pericardial effusion. In a Greek study of 81 histologically confirmed sarcoidosis patients who underwent echocardiogram studies, 21 % of them had mild to moderate pericardial effusions with no clinical evidence of heart disease [42].

Diagnosis

There are multiple diagnostic criteria for cardiac sarcoidosis. The American Thoracic Society (ATS) and World Association for Sarcoidosis and Other Granulomatous Disorders (WASOGD) define cardiac sarcoidosis as cardiac

Table 8.3 Adapted from the Japanese Ministry of Health and Welfare criteria for the diagnosis of cardiac sarcoidosis

Histologic diagnosis: Histologic analysis of endomyocardial biopsy demonstrating epithelioid, noncaseating granulomas
Clinical diagnosis: Histologic confirmation of extracardiac sarcoid demonstrating epithelioid, noncaseating granulomas with the presence of ECG abnormalities (complete RBBB, left axis deviation, AV block, VT, premature ventricular contractions, or abnormal Q or ST-T wave changes) with one or more of the following:
(a) Abnormal wall motion, regional wall thinning, or dilation of the ventricle
(b) Perfusion defect by thallium-201 scintigraphy or abnormal accumulation by gallium-67 or technetium-99m scintigraphy
(c) Depressed ejection fraction, low cardiac output
(d) Moderate-grade interstitial fibrosis or cellular infiltration on biopsy

dysfunction, ECG abnormalities, and thallium-201 scan defects with or without endomyocardial biopsy [21]. Other criteria adapted from the ACCESS report describe definite cardiac involvement as treatment-responsive cardiomyopathy, ECGs with conduction defects, and positive cardiac gallium scans.

A more widely used standard is from the Japanese Ministry of Health and Welfare (1993) which includes histologic and clinical diagnosis criteria (Table 8.3). Diagnosis of cardiac sarcoidosis is confirmed either by histologic diagnosis or clinical diagnosis group. Histologic diagnosis requires an endomyocardial biopsy demonstrating epithelioid, noncaseating granuloma. Alternatively, diagnosis of cardiac sarcoidosis by the clinical diagnosis group is confirmed on the basis of histologic diagnosis of extracardiac sarcoidosis and the presence of ECG abnormality (complete RBBB, left axis deviation, AV block, VT, premature ventricular contraction, or abnormal Q or ST changes) with the addition of any one of the following criteria: abnormal wall motion, regional wall thinning, or dilation of ventricle; perfusion defect on thallium-201 scintigraphy; decreased ejection fraction or low cardiac output; or moderate interstitial fibrosis or cellular infiltration on endomyocardial biopsy [34].

Endomyocardial Biopsy

Histologic confirmation of myocardial involvement is the gold standard for the diagnosis of cardiac sarcoidosis. However, lack of biopsy confirmation or negative findings do not exclude diagnosis of cardiac sarcoidosis in patients with suspected involvement. The sensitivity of endomyocardial biopsy is variable and reported to be in the range of 25–75 % as opposed to its high specificity of almost 100 % [29, 43, 44]. The wide range of sensitivity is thought to be related with sampling error that is inherent with endomyocardial biopsies and secondary to the patchy distribution of the disease. The procedure itself is performed transvenously and the biopsy is usually obtained from the apical septum whereas the typical distribution of sarcoid granuloma tends to be in the basal areas. Accordingly, sampling accuracy is dependent on the location, where the likelihood of diagnosing sarcoidosis from the right ventricular endomyocardial biopsy was 71 % versus 57 % from the left ventricle [45].

Electrocardiography

Electrocardiography (ECG) abnormalities occur in about 20–50 % of patients with cardiac sarcoidosis. First, second- and third-degree AV blocks may be seen. In a study of 41 patients with long-term corticosteroid therapy, 75 % of subjects experienced resolution of atrioventricular block [46]. Arrhythmias such as ventricular tachycardia and paroxysmal atrial fibrillation can be better assessed with the use of Holter monitor.

Echocardiography

Echocardiography has been useful in the diagnosis of cardiac sarcoidosis as an indirect assessment of the myocardium. Echocardiography can be used for assessment of systolic function, diastolic function, and regional wall motion abnormalities. In cardiac sarcoidosis, granulomatous infiltration can lead to heart failure with segmental wall motion abnormality, global hypokinesis, asymmetric septal hypertrophy, and apical hypertrophy [46]. Thus, echocardiography can be used as a screening tool to detect these abnormalities that may prompt further evaluation with other noninvasive imaging processes such as thallium scanning, gallium scanning, cardiac MRI, or FDG-PET scan to confirm areas of sarcoid involvement.

Noninvasive Nuclear Radiography

Cardiac sarcoidosis has adopted three different nuclear medicine scans to help in the diagnosis of cardiac sarcoidosis. Thallium-201 scintigraphy for diagnosis of cardiac sarcoidosis has been in practice since the 1970s. Thallium scanning can identify focal myocardial defects in uptake of the radio-labeled thallium. On autopsy of patients that have undergone thallium scans, histologic evidence of noncaseating granulomas indicative of granulomatous infiltration of myocardium was evident in areas that were positive on thallium scans [47].

Gallium scanning may also aid in assessing myocardial infiltration from sarcoidosis as uptake of radio-labeled gallium are seen in areas with active inflammation or where rapid cell division is occurring. The sensitivity of 96 % is quite excellent with active inflammation; however, the specificity is 37.5 % [48]. The use of Gallium scan to monitor disease progression is less optimal for two reasons; the first being the radiation exposure which makes for repetition of more often than twice yearly undesirable. Second, prednisone treatment may inhibit gallium uptake which poses difficulty with the practicality of its use as a monitoring tool [47]. Therefore gallium scan may be used as an adjunct modality to aide in difficult diagnostic problems in cases of suspected sarcoidosis, but not as a single tool to diagnose or monitor disease activity in cardiac sarcoidosis.

Recently, FDG-PET scanning has been shown to be useful in cardiac sarcoidosis. In one Japanese study, Yamagishi and colleagues compared thallium and gallium scan against FDG-PET scanning in patients with cardiac sarcoidosis [49]. The authors found that thallium scan and gallium scan were able to detect myocardial defects in

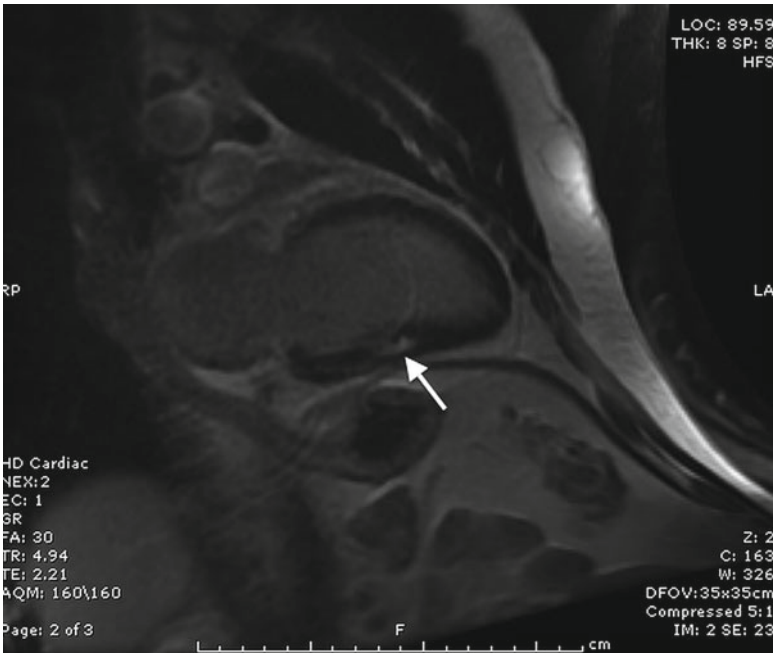

Fig. 8.4 Cardiac sarcoidosis. Focal region of delayed enhancement within the subepicardium and myocardium in the inferior aspect of the left ventricular wall Gadolinium enhanced CMR

35 % and 17 % of the cases, respectively, whereas FDG-PET was able to detect myocardial abnormalities in 82 % of the cases. However, myocardial PET scan abnormalities may represent ischemia and thus a positive finding must be followed with a negative coronary study to confirm the significance of a positive PET scan [50].

Gadolinium-Enhanced Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (CMR) is used to assess myocardium in myocardial infarction, hypertrophic cardiomyopathy, and cardiac hypertrophy. It has been adapted in the utility of cardiac sarcoidosis as a noninvasive diagnostic test and to evaluate treatment efficacy.

A prospective study including 58 patients with histologic confirmation of extracardiac sarcoidosis underwent evaluation of cardiac sarcoidosis [51]. This study investigated the accuracy of the various diagnostic modalities outlined by the Japanese Ministry of Health which included ECG, transthoracic echocardiogram, thallium scintigraphy, and CMR. The sensitivity and specificity for CMR were 100 % and 78 %, respectively. CMR had a positive predictive value (PPV) and negative predictive value (NPV) of 55 % and 100 %, respectively. The significant findings seen on CMR included regional contrast enhancement, segmental enhancement, and decreased LVEF (Fig. 8.4).

CMR has also been studied to follow treatment response of cardiac sarcoidosis [44]. One case series followed 16 sarcoidosis patients who underwent CMR for assessment of cardiac involvement of sarcoidosis. The investigators repeated the scan for assessment of treatment efficacy after 1 month of steroid therapy. All eight patients with positive CMR findings showed resolution of abnormal findings on CMR after 1 month of systemic steroid treatment. CMR may prove to be useful in early diagnosis and assessing treatment efficacy in cardiac sarcoidosis.

Treatment

Corticosteroid

Corticosteroid therapy has been the cornerstone therapy in cardiac sarcoidosis supported by case reports and case series which showed resolution of symptoms, such as dyspnea, arrhythmias, and cardiomyopathy. In a study that followed patients with cardiac sarcoidosis treated with prednisone over an average treatment duration of 43 months (range 6–168 months), Chapelon-Abric and colleagues observed signs of clinical resolution in 31 out of 39 patients [46]. Yazaki and colleagues performed a retrospective study demonstrating a 5-year survival of 75 % for those who received steroid treatments, whereas those not treated with steroids had a 5-year survival of 10 % [37]. Unfortunately, much of steroid therapy in cardiac sarcoidosis is based on clinical judgments without guidelines on dose and duration of therapy.

A recent Delphi study attempted to assess if there a consensus existed on the management of cardiac sarcoidosis [52]. They looked for common practices that over 70 % of experts have adapted to their practice. Based on the questionnaire, immunomodulatory therapy was initiated for the presence of ventricular arrhythmias, hypermetabolic activity on a cardiac FDG-PET scan, and/or LV dysfunction. Although prednisone was the choice for initial immunosuppressive therapy, there was no consensus on either the initial dosage of prednisone or the duration of therapy.

There are weak recommendations to use high dose steroids (60–80 mg/day) during the initial treatment phase; however, there was no difference in outcome in patients that had low dose (<30 mg/day) versus high dose (>40 mg/day) [33]. If severe symptoms exist, treatment is typically initiated with intravenous corticosteroids which is switched to oral corticosteroids as the symptoms improve. Once treatment is instituted, continuing lifelong steroid therapy to prevent relapsing cardiac symptoms is recommended as this disease carries high morbidity and mortality. Specifically 23 % of patients have relapse of cardiac sarcoidosis and importantly there is an increased risk of sudden cardiac death due to abrupt discontinuation of steroids [46].

Nonsteroidal Immunomodulators

Several nonsteroidal immunomodulators are being used instead of corticosteroids or as a steroid-sparing agent. Many experts have treated cardiac sarcoid patients

successfully with methotrexate and azathioprine based on data from treatment of pulmonary and cutaneous sarcoidosis [53]. Infliximab, a TNFα inhibitor, is a relatively new agent used for treatment of various sarcoidosis organ involvements. There have been case reports of using infliximab as a single agent with complete resolution of cardiac symptoms [54, 55].

Automated Implantable Cardiac Defibrillator

Lethal arrhythmias and sudden cardiac death are a significant morbidity in cardiac sarcoidosis with upwards of 60 % of patients developing sudden cardiac death. Interestingly, the correlation between the patient's left ventricular ejection fraction (LVEF) and the likelihood of sudden cardiac death from ventricular arrhythmias in cardiac sarcoidosis is not clear [56]. The goal to treat ventricular arrhythmias that result in sudden cardiac death has been the major indication for automated implantable cardiac defibrillator (AICD) in these patients. Initially AICDs were placed in patients who demonstrated potentially lethal rhythms in cardiac sarcoidosis with success [57], followed by several reports describing the benefits of prophylactic placement of AICD in cardiac sarcoidosis [56, 58]. An AICD can be placed in cardiac sarcoid patients with either sustained or nonsustained VT. Currently, the American College of Cardiology/American Heart Association/Heart Rhythm Society recommends placement of an implantable defibrillator in infiltrative diseases, such as sarcoidosis (Class IIa recommendation) [59].

Ocular Sarcoidosis

Epidemiology

The prevalence of sarcoidosis is 10–20 per 100,000 of which 25–50 % have ocular involvement [60–62]. The geographic distribution, population samples, duration of follow-up, and the extent of ophthalmologic examination in epidemiologic studies are all closely associated with the true prevalence of ocular sarcoidosis. In a study following 121 patients, uveitis occurred in 24 % of patients with systemic sarcoidosis. Furthermore, 58 % of patients with ocular involvement had uveitis which was the most frequent manifestation of ocular involvement [63]. Rothova and colleagues reported 41 % of sarcoidosis patients developed or had ocular involvement which were more commonly seen in the black population (58 %) and in females (56 %) [63]. Birnbaum and colleagues reported similar demographics for ocular sarcoidosis in which about 68 % of patients with biopsy-proven sarcoidosis and clinical signs of ocular involvement were females and 62 % of these patients were African Americans [64]. Furthermore, genetic studies have demonstrated HLA DRB1*0401 polymorphism to be associated with ocular sarcoidosis [65].

Clinical Presentations

Uveitis

Uveitis is the most common ocular manifestation of sarcoidosis with a prevalence of almost 25–50 %. Uveitis can be compartmentalized into anterior, intermediate, posterior, and panuveitis. Rothova and colleagues studied 582 patients with ocular sarcoidosis and reported that 50 % had anterior uveitis, 22 % had posterior uveitis, followed by 18 % who had panuveitis [66]. Anterior uveitis was predominant in black patients in one study from Amsterdam, whereas posterior and panuveitis were observed more in white patients. Posterior and panuveitis had an increased frequency of complications requiring intraocular surgery and laser coagulation treatment for treatment of glaucoma and severe visual loss [63].

Uveitis typically has a subacute onset early in the course of systemic sarcoidosis and can occur at any time in the disease course of sarcoidosis. In fact patients can present with isolated uveitis followed by eventual development of systemic sarcoidosis. Uveitis can also occur with other symptoms to constitute Lofgren's syndrome (hilar adenopathy, erythema nodosum, and polyarthralgias) and Heerfordt's syndrome (parotitis, uveitis, and cranial nerve palsy) [67].

Characteristics of anterior uveitis that are significant in the diagnosis of ocular sarcoidosis include keratic precipitates (KP) (mutton-fat precipitates), iris nodules found at the papillary margins (Koeppe nodules) or on the surface of the iris (Busacca's nodules), and granulomas on trabecular meshwork (occasionally associated with elevated eye pressure) [66, 67]. Typical characteristics of intermediate uveitis include vitritis and snowballing/string of pearls vitreous opacities. Posterior uveitis is a result of retinal perivasculitis which can manifest as retinal hemorrhage, neovascularization, and choroidal infiltrates surrounding retinal veins with a waxy, yellow appearance described as "candle wax dripping"(Fig. 8.5) [67]. These findings are highly suggestive; however, none of them are pathognomonic to ocular sarcoidosis.

Significant unilateral visual impairment is seen in about 10 % of patients and significant bilateral visual impairment in 14 % of patients with uveitis due to sarcoidosis [60]. Posterior uveitis is usually asymptomatic although it is also considered vision threatening [67]. Thus, the American Thoracic Society recommends that all sarcoidosis patients should have routine ophthalmologic examination on initial evaluation regardless of symptoms [68].

Conjunctival and Lid Involvement

Conjunctival and lid involvement are the next most common manifestation after uveitis in ocular sarcoidosis. In patients with sarcoidosis the prevalence is 19 % and 16 %, respectively [63]. Dacryocystitis (lacrimal gland inflammation), keratoconjunctivitis sicca (KC), and periocular soft tissue inflammation have been described (Fig. 8.6). Both dacrocystitis and KC can occur even without lacrimal gland enlargement, but can be detected using gallium scanning and Schirmer's test, respectively [67].

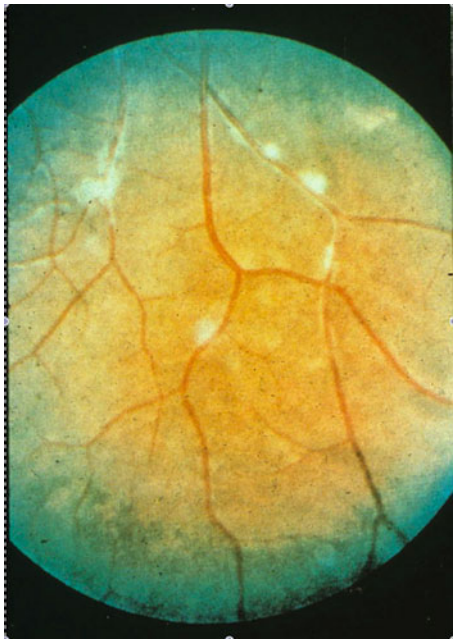

Fig. 8.5 Candle wax drippings appearance secondary to choroidal infiltrates surrounding retinal veins with a *waxy*, *yellow* appearance

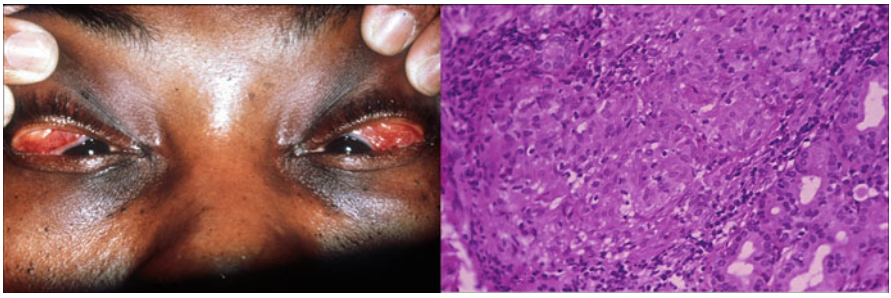

Fig. 8.6 Dacrocystitis presenting as swollen palpebral lobe of the lacrimal glands in both upper eyelids. Biopsy revealed noncaseating granuloma consistent with sarcoidosis

Diagnosis

Diagnosis of ocular sarcoidosis may be challenging as obtaining ocular tissue biopsy can be difficult and the differential diagnosis include entities such as Behcet's disease, ocular tuberculosis, Vogt–Koyanagi–Harada disease, ocular toxoplasmosis, HTLV-1-associated uveitis, leprosy, multiple sclerosis, and syphilis [68].

In 2006, the First International Workshop on Ocular Sarcoidosis (FIWOS) developed criteria for the diagnosis of ocular sarcoidosis [69]. In the guidelines set forth from FIWOS, categories including definite, probable, and possible were incorporated in the diagnosis criteria. These guidelines reflect the difficulty in obtaining

Table 8.4 Clinical signs suggestive of ocular sarcoidosis

1. Mutton-fat/granulomatous KPs and/or iris nodules (Koeppps/Busacca)	
2. Trabecular meshwork (TM) nodules and/or tent-shaped peripheral anterior synechiae (PAS)	
3. Snowballs/string of pearls vitreous opacities	
4. Multiple chorioretinal peripheral lesions (active and/or atrophic)	
5. Nodular and/or segmental periphlebitis (± candlewax drippings) and/or retinal macroaneurysm in an inflamed eye	
6. Optic disc nodule(s)/granuloma(s) and/or solitary choroidal nodule	
7. Bilaterality (assessed by clinical examination or investigational tests showing subclinical inflammation)	
Laboratory investigations in suspected ocular sarcoidosis	
1. Negative tuberculin test in a BCG vaccinated patient or having had a positive PPD (or Mantoux) skin test previously	
2. Elevated serum angiotensin converting enzyme (ACE) and/or elevated serum lysozyme	
3. Chest X-ray: bilateral hilar lymphadenopathy (BHL)	
4. Abnormal liver enzyme tests [any two of alkaline phosphatase (ALKP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), or gamma glutamyl transpeptidase (GGT)]	
5. Chest CT scan in patients with negative chest X-ray	
Diagnostic criteria for ocular sarcoidosis	
All other causes of uveitis, in particular tuberculous uveitis, have to be ruled out	
1. Biopsy supported diagnosis with compatible uveitis	Definite ocular sarcoidosis
2. Biopsy not done; presence of BHL with a compatible uveitis	Presumed ocular sarcoidosis
3. Biopsy not done and BHL negative; presence of three of the suggestive signs and two positive investigational tests	Probable ocular sarcoidosis
4. Biopsy negative, four of the suggestive intraocular signs and two of the investigations are positive	Possible ocular sarcoidosis

ocular tissue biopsy and emphasize the use of seven clinical signs that are characteristic but not pathognomonic for ocular sarcoidosis. It also includes laboratory or radiologic investigations that can be used to support the diagnosis of ocular sarcoidosis. The FIWOS conference utilizes a combination of these factors to establish diagnosis as definite, presumed, probable, and possible ocular sarcoidosis (Table 8.4).

The new guidelines set forth in 2006 were compared to the 1999 criteria to diagnose ocular sarcoidosis [70]. The new guidelines were found to increase the diagnostic specificity from 45.6 to 83 % without sacrificing much on sensitivity which ranged from 80 to 84 %. The newer guidelines were more apt in identifying patients with ocular sarcoidosis versus other etiologies of uveitis.

Treatment

The treatment for ocular sarcoidosis is dependent on the severity of disease. Milder cases of ocular sarcoidosis usually respond well with topical corticosteroids. Most uveitis, especially anterior uveitis, responds well with topical steroids alone or in combination with systemic steroids. However, in one study that followed 75 patients

with sarcoid uveitis, almost 49 % of patients eventually required oral steroids for treatment by 5 years into the diagnosis and almost 74 % required oral steroids by year 10 of the diagnosis [71]. Visual acuity returned to normal in about 54 % of patients after treatment with steroids, whereas only 4.6 % developed severe bilateral visual loss.

Treatment with nonsteroidal immunomodulators such as azathioprine, methotrexate, cyclosporine, tacrolimus, and mycophenolate mofetil have been used for steroid refractory or intolerant patients based on weak evidence from case series and case reports with good outcome [60–62, 72]. There is also a role of TNFα inhibitors, such as infliximab in cases of refractory ocular sarcoidosis. The data in the use of infliximab are anecdotal at best but promising [73, 74].

Prognosis

Ocular manifestations of sarcoidosis can be initially asymptomatic and therefore annual ophthalmologic examination is typically recommended in all sarcoidosis patients as the potential consequences are significant. The prognosis is dependent on the compartment involved; anterior ocular involvement typically portends a better prognosis as opposed to posterior ocular involvement and panuveitis are associated with poorer prognosis.

Skin Sarcoidosis

Epidemiology

Sarcoidosis has been described as one of the greatest mimickers in dermatology due to its wide range of presentation [75]. Cutaneous involvement of systemic sarcoidosis is classified as specific or nonspecific based upon the presence or absence of noncaseating granulomas on histopathologic examination [76–78]. The most common specific lesions include lupus pernio (LP), infiltrated plaques, macular and papular lesions, and subcutaneous nodules. Less common manifestations include hypopigmented patches, ulcers, alopecia, verrucous lesions, and erythroderma [76–80]. The most common nonspecific lesion of sarcoidosis is erythema nodosum (EN) [76, 78, 79].

Recently, the ACCESS trial reported an incidence of cutaneous involvement in the overall sarcoidosis population to be 24.2 % with the African-American population demonstrating an increased incidence of skin involvement other than in cases of erythema nodosum [1]. These findings are consistent with other studies [81], although other reports including the American Thoracic Society's position statement have reported slightly higher incidences with additional evidence that skin sarcoidosis may occur more commonly in females [10, 82]. Cutaneous manifestations of

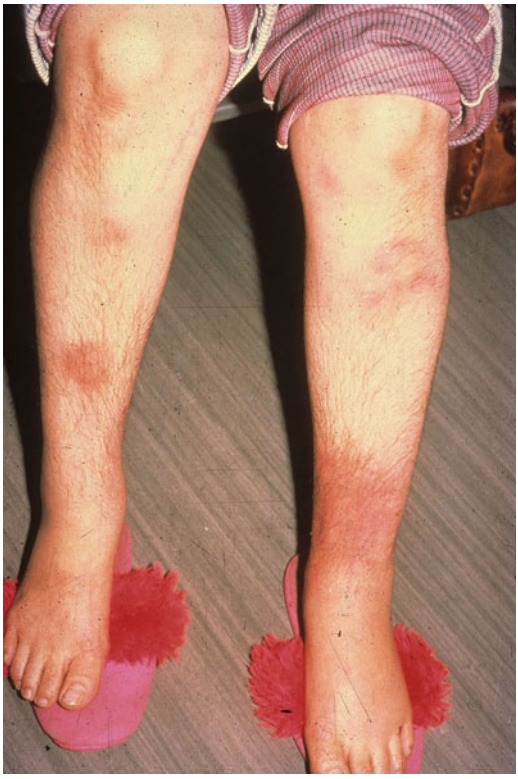

Fig. 8.7 Erythema nodosum presenting as tender erythematous lesion on the pretibial areas of lower extremities

sarcoidosis can be the lone sign of disease and the severity of these lesions can be variable in relation to the degree of systemic disease [83]. Roughly 20 % of patients will have skin lesions prior to the presentation of signs of systemic disease, 50 % will have simultaneous manifestations, and 30 % will experience their first skin involvement several years after their initial diagnosis of systemic sarcoidosis [84].

Erythema Nodosum

EN is found to occur more commonly in European, Puerto Rican, and Mexican patients as well as women of child-bearing age. Furthermore, EN occurs commonly in females with a prevalence between 2 and 20 % [7, 85]. EN is considered a hallmark of acute sarcoidosis. Typical lesions are raised, red, tender, and commonly seen on the anterior aspect of the lower extremities (Fig. 8.7). Additional locations can include the trunk and other limb areas [79, 86]. Adjacent joints are frequently involved with clinically evident swelling or pain. Hallmarks of EN are that granulomas are not seen on skin biopsies, the lesions may resolve with treatment in 6–8 weeks, and that EN serves as a herald of a good overall prognosis [87, 88]. Löfgren's syndrome is a specific syndrome observed in sarcoidosis when EN is combined with fever, hilar

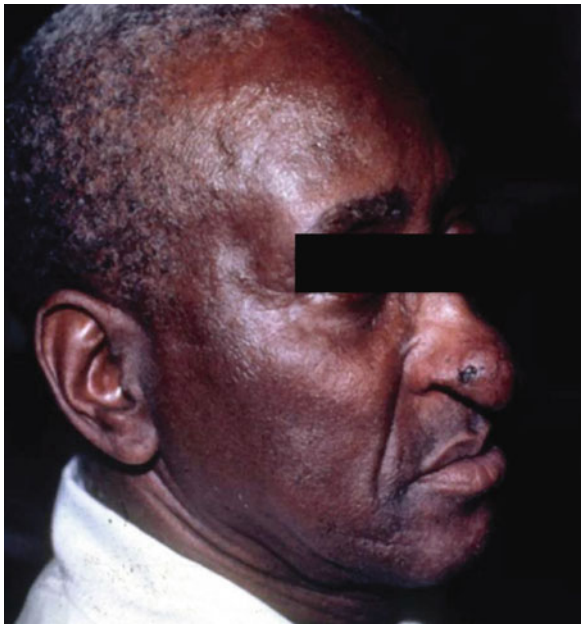

Fig. 8.8 Lupus pernio with indurated plaque involving the forehead, cheeks, and nose

lymphadenopathy, and arthralgia [89]. Löfgren's syndrome's incidence is variable and can be as high as of 20–30 % in Caucasians but less frequent in other races/ethnicities [87, 90]. Löfgren's syndrome typically portends good prognosis. Accordingly, a study that examined the genetic background of Löfgren's syndrome in northern European population found HLA-DRB1*0301 to be associated with higher likelihood of spontaneous remission and good prognosis with this syndrome [91].

Lupus Pernio

In contrast, lupus pernio is an indurated disfiguring plaque with violaceous discoloration typically of the nose, cheeks, lips, ears, and nasal mucosa (Fig. 8.8). Lupus pernio is seen with a higher incidence in African-American females [86, 87] and typically progress to chronic disease without spontaneous remission with worse prognosis. Lupus pernio is often associated with bone cysts, pulmonary fibrosis, and sarcoidosis of upper respiratory tract (SURT) [87, 88].

Macular Skin Lesions, Papules, Nodules, Plaques

Macules can present as hypopigmented, atrophic, or an erythematous variety [92, 93] and lichenoid papules presenting on generalized, localized, or perifollicular areas [94]. Subcutaneous sarcoidosis (Darier–Roussy syndrome), which carries a good prognosis, is a rare condition predominantly affecting middle-aged Caucasian

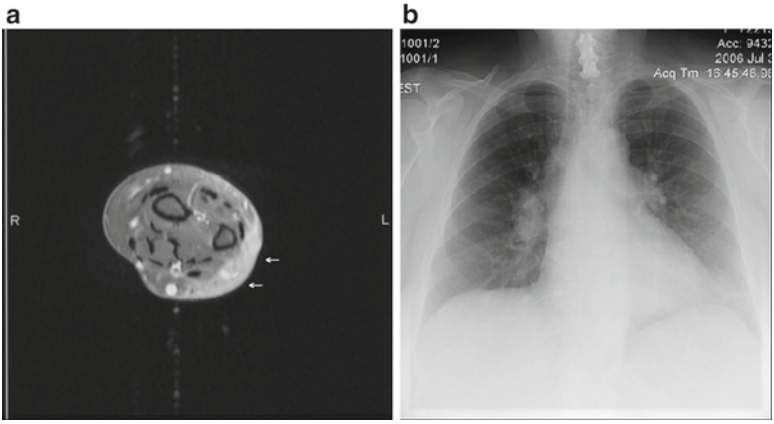

Fig. 8.9 (**a**) Gadolinium-enhanced subcutaneous lesion consistent with Darier–Roussy syndrome. (**b**) Chest radiograph revealed classic bilateral hilar adenopathy consistent with the diagnosis of sarcoidosis

patients. Most cases occur as firm, painless, mobile, round nodules in the upper extremities that demonstrate classic noncaseating epithelioid-cell granulomas on biopsy (Fig. 8.9) [95]. Plaques may present as a morpheaform sarcoidosis that is clinically indistinguishable from true morphea (prominent dermal sclerosis with induration) [96] or erythematous annular lesions with central hypopigmentation [97]. Many of these lesions have been reported to experience high degrees of resolution with various therapies and typically carry a better clinical prognosis than lupus pernio [87].

Other Forms of Skin Sarcoidosis

Additional forms of cutaneous sarcoidosis include ichthyosiform sarcoidosis characterized by noncaseating granulomas in areas of fine scaling on the distal extremities [76], tattoo sarcoid that results as a localized reaction in cosmetic tattoos with systemic spread of tattoo pigment causing reaction in distant systemic sites [98–100], and psoriasiform eruptions that can be indistinguishable from typical forms of psoriasis in the absence of biopsy [101].

Treatment

Treatment of cutaneous sarcoidosis depends on clinical severity and the type of lesion as not all skin lesions require treatment [87]. Topical therapy with corticosteroids in the form of creams, drops, or sprays is a reasonable initial regimen for isolated skin lesions and for lesions of the lip or mucous membranes [87, 102].

Topical regimens may also include the calcineurin inhibitor immunosuppressant tacrolimus. Therapy with 0.1 % tacrolimus ointment twice daily has shown to lead to complete resolution of some skin lesions within a few months and can be used as a single agent or in combination therapy [100, 103–105]. Systemic corticosteroids are the treatment of choice and typically started at a dose between 20 and 40 mg/day. Every effort should be made to taper the corticosteroids to the lowest dose that would provide effect. Alternative treatments including methotrexate, leflunomide, and antimalarial drugs can used as an adjunct to corticosteroid treatment or alone as monotherapy [106, 107]. Thalidomide known for its anti-TNF-α activity has also been used successfully as monotherapy for cutaneous sarcoidosis [108]. Furthermore, other anti-TNF-α medications such as Infliximab or Adalimumab have had success with isolated cases including cases of lupus pernio and other treatment resistant skin lesions, providing hope to patients with lesions that generally carry a relentless clinical course [97, 106, 109–115].

Hepatic Sarcoidosis

Epidemiology

The frequency of hepatic involvement of sarcoidosis is reported with great variability and is dependent on the methods used in these investigations. Autopsy studies have demonstrated liver involvement in up to 44.6 % of patients with sarcoidosis [116] and a case series of needle biopsies in suspected sarcoidosis reported an incidence of granuloma consistent with sarcoidosis in 24–79 % of patients [117, 118]. A number of other studies using a variety of diagnostic modalities have also described hepatic involvement of systemic sarcoidosis with ranges from 50 to 90 % [119–121]. Recently, the ACCESS trial observed an incidence of only 11.5 % for hepatic involvement in sarcoidosis [1] with African Americans being twice as likely to have involvement of the liver than Caucasians ($p < 0.0001$) [1].

Clinical Presentations

Clinical symptoms of hepatic sarcoidosis are often absent and can be highly nonspecific. Manifestations such as fatigue, pruritis, and right upper quadrant pain have only been described in 15.9 % of patients [120]. Weight loss, jaundice, and fever due to hepatic sarcoid are less common and seen in only 5 % of patients [119, 120]. Less than 20 % of patients with hepatic sarcoidosis will have clinically appreciable hepatomegaly [122] and in most cases, liver or spleen involvement is only detected incidentally on radiographic investigations in the absence of clinical or laboratory abnormalities [123].

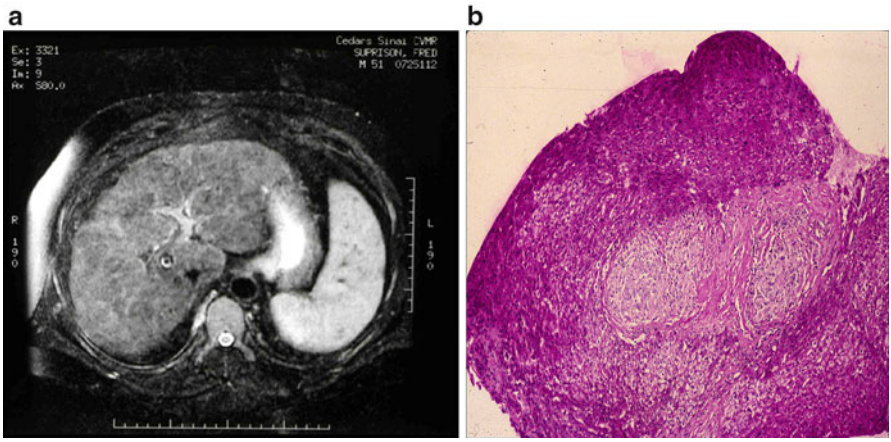

Fig. 8.10 (**a**) Contrast-enhanced axial CT image of multiple low attenuation lesions that appears to be coalescing throughout the liver. (**b**) Biopsy revealing noncaseating granuloma

Cirrhosis is seen in 6 % hepatic sarcoidosis that can further lead to portal hypertension in 3 % of patients [120]. The most common cause is from granulomatous infiltration of the portal areas leading to reduced flow to the hepatic sinusoids. Other known sequelae with portal hypertension such as variceal disease in the esophagus and stomach can be a cause of gastrointestinal bleed [124, 125].

Diagnosis

Laboratory Studies

Reports of abnormal serologic tests in hepatic sarcoidosis range from only 4 to 24.4 % [122, 126]. When abnormal, serum liver tests typically reveal a cholestatic pattern with elevation of serum alkaline phosphatase and only mild elevations in transaminases [119, 127–129]. Laboratory studies may be useful in differentiating hepatic sarcoidosis from other hepatic pathologies like primary biliary cirrhosis (PBC) through evidence of an elevated angiotensin-converting enzyme, hypercalcemia, or a negative anti-mitochondrial antibody titer.

CT Imaging

Radiographically, there are no distinct lesions specific to hepatic sarcoidosis. Most granulomata are less than 2 mm in diameter which cannot be adequately assessed using the resolution of abdominal CT scans [130]. The most common findings on CT imaging are diffuse hepatic heterogeneity with hepatomegaly and splenomegaly seen on CT imaging (Fig. 8.10) [131]. Hepatic nodules representing coalescent

Table 8.5 Differential diagnosis of hepatic granulomas

Differential	Granuloma histology	Extrahepatic manifestations	Serologic findings
Sarcoidosis	Sharply circumscribed, discrete granulomata, predominantly in the portal triad, but occasionally elsewhere in the lobules. Lobular architectures are typically well preserved with absence of necrosis	Pulmonary, neurologic, cardiac, ocular, cutaneous, splenic, or other extrapulmonary sarcoid manifestations	Elevated ACE Hypercalcemia
Primary biliary cirrhosis	May be indistinguishable from sarcoidosis	Delayed-type hypersensitivity reactions (i.e., Sjogren's syndrome, fibrosing alveolitis, ulcerative colitis) [31]	Anti-mitochondrial antibodies Anti-GP210
Drug-induced granulomas	Granulomas in the presence of eosinophilic infiltrates	Specific manifestations with drug	None
Mechanical biliary obstruction	Poorly formed granulomas in close association with necrotic hepatocytes with bile pigment	Disease specific manifestations (i.e., weight loss or B-signs of malignancy, Murphy Sign, or jaundice of acute obstruction)	None
Infectious etiologies	May be indistinguishable from sarcoidosis, but often more irregular or lobulated with more peri-granuloma inflammation	Varies with infectious etiology	Viral hepatitis titers Quantiferon gold + Cultures Gastric washings
Idiopathic	May be indistinguishable from sarcoidosis	Diagnosis of exclusion from above etiologies	

granulomas are less commonly observed and are seen in about 5 % of patients [131]. These lesions are typically well defined with low attenuation on CT imaging.

Histopathology

Klatskin described the characteristic histology of hepatic sarcoid as scattered, sharply circumscribed, discrete granulomata, predominantly in the portal triad, but occasionally elsewhere in the lobules. Lobular architectures are typically well preserved with absence of necrosis. Typically, the diagnosis of hepatic sarcoidosis is pursued after identifying evidence of extrahepatic organ involvement.

The presence of granulomas in the liver can also occur from diseases other than sarcoidosis (Table 8.5). In fact when granulomas are observed on biopsy, the frequency of etiologies has been shown to be more commonly due to PBC (23.8 %) than sarcoidosis (11.1 %) [132]. Both sarcoidosis and PBC can lead to chronic cholestasis and biliary cirrhosis which pose difficulty in distinguishing the two diseases [133]. While hepatic sarcoidosis and PBC may be indistinguishable from one

another histologically, serologic testing can aid in the differentiation. Positive antimitochondrial antibody is commonly detected in PBC but is absent in sarcoidosis [118]. Additionally, anti-GP210 is observed in up to 47 % of patients without antimitochondrial antibodies with PBC, but not in sarcoidosis [118, 134].

Other potential diseases with hepatic granulomas include drug induced granulomas, mechanical biliary obstruction, tuberculosis, brucellosis, and idiopathic hepatic granulomas. The presence of eosinophilic infiltrates in association with culprit medications (glibenclamide, metronidazole, baclofen, nitrofurantoin, and allopurinol) suggests drug-induced granulomas [132]. Granulomas secondary to mechanical biliary obstruction can persist for more than 6 months and are often seen with poorly formed granulomas in close association with necrotic hepatocytes with bile pigment [132]. Infectious etiologies such should be evaluated by additional serologic testing. Finally, in the absence of other supporting elements to conclude the diagnosis of hepatic sarcoidosis or other etiologies, the presence of granulomas can be idiopathic.

Treatment

The vast majority of hepatic sarcoidosis usually do not necessitate treatment as most liver abnormalities spontaneously improve without treatment [135]. Thus asymptomatic patients with abnormal liver function tests can be followed closely with serial tests to document improvement over time.

Corticosteroids is the first-line treatment with hepatic sarcoidosis and may be considered in patients who experience fever, nausea, vomiting, weight loss, or right upper quadrant abdominal pain [12]. In most patients with hepatic sarcoidosis, corticosteroids appear to be effective, although the response to corticosteroids can be variable. Furthermore, systemic corticosteroids have not been shown to definitively prevent progression to portal hypertension [119, 136, 137]. In fact, a retrospective study in patients with hepatic sarcoidosis showed corticosteroids to be associated with higher likelihood to develop recurrent active disease [138].

While corticosteroids may improve hepatomegaly and liver function abnormalities, symptoms associated with cholestasis may not necessarily show improvement. Alternatively, treatment with ursodeoxycholic acid (UDCA), compared to systemic corticosteroids, has been shown to have improvement with Pruritus, fatigue, jaundice, and serologic improvement and may be used in hepatic sarcoidosis [127, 139–141].

Methotrexate (MTX) also has clinical benefit in the treatment of hepatic sarcoidosis. However, given the risk for hepatic toxicity, careful assessment of risks and benefits to the patient must be considered before its use especially with hepatic sarcoidosis. The work-up for patients starting MTX should include clinical and serologic assessment of risk factors for MTX toxicity (including alcohol intake), patient education, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, complete blood cell (CBC), creatinine, and chest X-ray. Additionally, it is important to consider that exacerbation of hepatic disease carries additional risk in obesity, diabetes, and both viral and alcoholic hepatitis. While

liver function test abnormalities may be due to either hepatic sarcoidosis or MTX, lab values 2–4 times the upper limit of normal should lead to a MTX dose reduction, additional folate supplementation, withdrawal of MTX, or a liver biopsy to evaluate for MTX toxicity [142].

Finally, when patients fail to respond to systemic corticosteroids or MTX or develop severe toxicities, alternate therapies should be considered. Azathioprine, leflunomide, or biologicals can be considered [143, 144]. Although end-stage liver disease (significant liver dysfunction, chronic cholestasis, cirrhosis, portal hypertension) from hepatic sarcoidosis is uncommon, transplant may be required in rare instances [120, 137, 145]. In such cases, there are reports of recurrence of hepatic sarcoidosis in the transplanted liver with no increase in hepatic related mortality [146–148].

Splenic Sarcoidosis

Epidemiology

The incidence of splenic involvement from sarcoidosis is highly variable. Older studies have reported incidences to be 38–77 % based on autopsy reports and 24–59 % with fine needle aspiration biopsies [117, 149–151]. Another older study reported the spleen to be the second most common site of organ involvement in sarcoidosis after the lung [152]. However, the rate of splenic involvement in the recent ACCESS study [1] reported splenic involvement to be only 6.7 %, similar to more recent studies among all sarcoidosis patients [153, 154].

Clinical Signs and Symptoms

Splenic sarcoidosis can present in a variety of ways from asymptomatic radiographic findings to abdominal pain, signs of portal hypertension, pancytopenia, and rarely, acute splenic infarct or rupture [87, 155, 156]. Some patients may experience constitutional symptoms including night sweats, fever, and malaise [157]. In patients with systemic sarcoidosis, less than 20 % have any evidence of hepatosplenomegaly [158], 10–15 % have a palpable spleen on examination [149], and only 3 % can be classified as massive splenomegaly [149].

Diagnosis

The diagnosis of splenic sarcoidosis is often made in a patient with known sarcoidosis and radiographic evidence of splenomegaly, which is more common than hepatomegaly [123, 131, 159]. Focal areas of granulomas seen as multiple lesions with

low attenuation on CT imaging may also be seen [160]. However, there may be value in the use of contrast-enhanced ultrasound for the visualization of distinct lesions [154]. Pursuing a potential diagnosis of splenic sarcoidosis is indicated in the setting of abdominal pain, early satiety, leukopenia, anemia, thrombocytopenia, poikilocytosis, or Howell Jolly bodies [161]. Additionally, while not of diagnostic value, spleen size has been shown to be in close correlation with serum markers such as increased angiotensin converting enzyme and relative counts of CD4+ and non-CD4+, non-CD8+ lymphocytes [162, 163].

Treatment

Treatment for splenic involvement of sarcoidosis is not well defined. Case studies have demonstrated spontaneous resolution of the condition with close monitoring and symptom management [164]. Although systemic corticosteroid therapy has been the standard of treatment in regimens for sarcoidosis, its impact on resolution or progression of splenic sarcoidosis has been mixed [155]. Furthermore, splenic involvement has been noted to predict poor efficacy of corticosteroids in treatment of sarcoidosis in other organ systems [157, 165].

Definitive therapy for splenic sarcoidosis is splenectomy and is typically considered when there is concern for, or evidence of, splenic rupture or refractory systemic complications (i.e., thrombocytopenia). Spontaneous rupture of the spleen is extremely rare [166–168] and is not directly associated with the degree of splenomegaly on clinical or radiographic assessment but rather with blood vessel involvement within the spleen with granulomas and fibrinous clots seen on pathologic specimens [169]. Splenectomy has been shown to result in complete resolution of thrombocytopenia in patients with severe disease and repeated episodes of bleeding, but success is limited in patients with only mild disease [170]. Additionally, patient outcomes after splenectomy are impacted by the risk for postoperative death or death from complications of sarcoidosis in additional organs [155]. Therefore, diligent trial of corticosteroid must be pursued and surgical risks must always be weighed with the potential benefits during consideration of splenectomy.

Calcium Dysregulation

The granulomatous disease in sarcoidosis can cause increased 1-α hydroxylase activity leading to increased conversion of 25-hydroxyvitamin D to 1, 25-dihydroxyvitamin D, an active form of vitamin D. As a result, hypercalcemia and hypercalciuria can occur in sarcoidosis [171]. The reported incidence of hypercalcemia can be highly variable ranging from 2 to 63 %, depending on the referenced literature [171]. Hypercalciuria is more commonly seen compared to hypercalcemia and can cause nephrocalcinosis, nephrolithiasis, and renal failure

[172, 173]. Furthermore, hypercalciuria can be the presenting feature of sarcoidosis and occur before hypercalcemia [173]. Therefore serum calcium, creatinine, and urinalysis must be performed as part of the evaluation for sarcoidosis.

Treatment of hypercalcemia must be instituted if serum calcium is greater than 11 mg/dl or there is evidence of renal failure or nephrolithiasis. Milder cases of hypercalcemia may be monitored closely if no other indications for treatment with sarcoidosis exist. Corticosteroids remain the mainstay of treatment and used at a dose between 20 and 40 mg/day. Other treatments such as hydroxychloroquine and ketoconazole have been reported with success [174, 175]. If calcium dysregulation does not improve with treatment, careful evaluation of other disorders that cause hypercalcemia such as parathyroid disease and hematologic and solid organ malignancy must be explored.

Miscellaneous

Sarcoidosis can affect the bones in up to 13 % of patients [176]. African Americans are more commonly affected and it typically involves the bones of the hands and feet, although other bones may be affected. Patients are typically asymptomatic, although some can present as painful lesions with or without adjacent arthritis. Radiographic imaging studies can show cystic or punched-out lesions [177]. Treatment involves using systemic corticosteroids, although alternatives such as methotrexate or azathioprine may be used as an adjunct treatment in addition to corticosteroids [176].

Peripheral lymphadenopathy, with presence of noncaseating granulomas within the affected lymph nodes may be seen in sarcoidosis as part of the involvement of the lymphatic system. However, if noncaseating granulomas are found without other systemic involvement, careful evaluation for infection or malignancy must be undertaken. Findings of granuloma from a lymph node may be seen in the draining lymph nodes of a cancer, as part of "sarcoid-like reaction" [178].

Renal involvement can occur in up to 20 % of patients with sarcoidosis, although clinical manifestations stemming from the granulomas are not common. Interstitial nephritis, membranous glomerulonephritis, mesangioproliferative glomerulonephritis, immunoglobulin A nephropathy, and crescentic glomerulonephritis are rare but have been reported [179].

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