Sarcoidosis is a systemic, chronic, inflammatory disease characterized by noncaseating granuloma formations. The fact that the etiopathogenesis of the disease has not been elucidated yet brings it many theories and assumptions. Being a systemic disease and ability to involve many organs and systems, it attracts the attention of physicians from different branches. In addition to lung involvement, skin, eye, heart, and locomotor system involvement is an important clinical finding. Sarcoidosis may present with very different clinical presentations, and therefore, it is one of the important “imitators” in the medical literature. I like sarcoidosis as a “rainbow,” it is a disease that contains the characteristics of many diseases. Different clinical, radiological, and laboratory prognostic factors (lupus pernio, chronic uveitis, late-onset disease, chronic hypercalcemia, nephrocalcinosis, Afro-American race, progressive pulmonary sarcoidosis, radiologic Stage 4, bone involvement, neurosarcoidosis, cardiac involvement, and chronic respiratory failure) have been defined in this “rainbow.” Early identification of these factors plays an important role in the determination of treatment strategies, morbidity, and mortality of the disease. In this article, clinical, genetic, laboratory, and radiological factors that determine the prognosis of sarcoidosis are discussed in light of the latest data in the literature.

**KEY WORDS:** Factors, prognosis, sarcoidosis

Sarcoidosis is an multisystemic chronic disease characterized by noncaseating granuloma formation.[1] The etiologic of sarcoidosis is unknown. Different microorganisms and/or organic/inorganic substances have been implicated as possible triggers of the granulomatous response in sarcoidosis.[2] Among the best investigated etiologic agents are Propionibacterium acnes, Mycobacterium tuberculosis, and other Mycobacterium strains.[3-5] Using polymerase chain reaction, Eishi et al isolated propionibacterial DNA in most lymph biopsies of patients with sarcoidosis.[6] The relationship between Mycobacterium strains and sarcoidosis has been discussed since the early 1900s. In 1905, Boeck described sarcoidosis as a bacillary infectious disease equal to or closely related to tuberculosis.[7] In a recent study, *M. tuberculosis* catalase-peroxidase (mKatG) antibodies were detected in 50% of serum samples of sarcoidosis patients and this rate was reported as 0% in the control group.[8] Although there is much evidence to support the hypothesis of *Mycobacterium* infection, discussions on this issue are still continuing. Clinical, radiological, histopathological, biochemical, and genetic characteristics are taken into account when defining the disease. Sarcoidosis is usually seen in young and middle-aged adults and is usually characterized by bilateral hilar adenopathy, pulmonary infiltration, and eye and skin lesions.[8] In addition, different organs (liver, heart, nervous...
system, musculoskeletal system, spleen, lymph nodes, and salivary glands) may be involved. Extrapulmonary involvement may develop before, during, or after pulmonary involvement, so there may be reason for a delay in diagnosis. Sarcoidosis may be presented with different clinical symptoms, such a different “colors of rainbow,” and this leads to be recognized this disease as a “great imitator” in the literature. There are many reasons for this. First, the patient’s ethnic origin is a powerful factor. While heart and ocular involvement is common in the Japanese population, this involvement is rare in the White race. Erythema nodosum and joint involvement are more common in White race, whereas skin involvement and chronic disease are more common in African-American race. Second, the prevalence and activity of the granulomatous process may be different in any organs; this is an important factor that determines the heterogeneity and prognosis of the disease. Third, there are serious differences between the initial pattern (acute, insidious, and chronic) of the disease. The diagnosis is based on clinical and radiological findings as well as histopathologically showing the noncaseating epithelioid granuloma. Local sarcoid reactions and known granulomas should be excluded. Immunological features include cutaneous delayed hypersensitivity, suppression of immune response, and increased CD4/CD8 ratio. Circulating immune complexes showing B-cell hyperreactivity have also been reported. The prognosis of the disease is associated with age, gender, and genetic and ethnic factors, as well as its initial form and prevalence. The overall prognosis is good, and in about 60% of all cases, the disease regresses spontaneously. In the remaining patients, sarcoidosis sometimes enters remission or follows as a chronic disease manifested by relapse, following corticosteroid dose reduction. Acute-onset form with erythema nodosum or asymptomatic bilateral hilar adenopathy is a precursor of a generally self-limited disease. However, an insidious onset, especially with multiple extrapulmonary lesions, may cause progressive fibrosis of the lungs and other organs. Sarcoidosis lists a number of clinical prognostic factors; lupus pernio, chronic uveitis, onset age >40 years, chronic hypercalcemia, nephrocalcinosis, Black race, progressive pulmonary sarcoidosis, nasal mucosal involvement, cystic bone lesions, neurosarcoidosis, cardiac involvement, and chronic respiratory failure. In other words, age, sex, race, clinical phenotype, and radiological and laboratory markers are reported among the factors that determine the prognosis of sarcoidosis. These factors have an important role in early identification and early treatment strategies [Table 1].

**FACTORS THAT DETERMINE THE PROGNOSIS OF SARCOIDOSIS**

*Age, gender, and ethnicity*

Sarcoidosis is a disease with different frequencies in different countries around the world, which can involve all race and ethnic groups. The highest incidence was reported in Sweden (65/100,000 cases), whereas in the United States, a higher incidence was reported in Black race compared to White race. Many epidemiological studies have reported that the disease is more common in women. The disease is frequently seen between the ages of 20–50 and makes a second peak over the age of 50 years. Sarcoidosis is rarely seen in the elderly and children. African-American patients are usually older onset. A worse prognosis has been reported in patients with a disease onset >40 years. Gender can also affect clinical symptoms of sarcoidosis. For instance, erythema nodosum is more common in women with acute sarcoidosis and ankle arthritis is more common in men. Women with sarcoidosis experience more symptoms, lower quality of life, and more functional impairment. Women of

**Table 1: Prognostic factor in sarcoidosis according to clinical, radiographic and laboratory findings**

| Prognostic factor according to | Poor prognosis | Good prognosis |
|--------------------------------|---------------|---------------|
| Gender                         | Female        | Male          |
|                                | More symptoms | Ankle arthritis |
|                                | Lower quality of life |
|                                | More functional impairment |
|                                | Higher incidence of coexisting autoimmune disorders |
|                                | More hospitalization |
| Age                            | Elderly-onset | Younger-onset |
| Ethnicity                      | African-American | Caucasian |
|                                | Extrapulmonary involvement |
|                                | Progressive disease |
|                                | High mortality rates |
|                                | HLA-DQB1*1501 | HLA-DQB1*0201 |
|                                | HLA-DQB1*0602 | HLA-DRB1*0301 |
|                                | Annexin A1 gene |
|                                | TNF-308A allele |
|                                | MEFV gene |
| Clinical phenotype             | Chronic sarcoidosis |
| Pulmonary involvement          | Low PFT and DLCO |
|                                | Bronchial obstruction |
|                                | Pulmonary fibrosis |
|                                | PH |
| Heart involvement              | A-V block, ventricular tachycardia, myocarditis |
| Neurosarcoidosis               | Epilepsy |
|                                | Intracranial mass |
|                                | Spinal cord |
|                                | Optic nerve involvement |
| Ocular involvement             | Panuveitis |
| Skin involvement               | Lupus pernio |
| Musculoskeletal involvement    | Chronic arthritis |
|                                | Jaccoud deformity |
|                                | Dactylitis |
|                                | Granulomatous myositis |
|                                | Cystic bone lesions |
| Radiographic Laboratory        | Stage 3 and Stage 4 |
|                                | Neopterin, sIL-2R, KL-6, TNF-alpha, chitinotriosidase, tryptase, chitinotriosidase, hypercalciemia, hypercalciuria, Th17 |
|                                | Stage 1 and Stage 2 |
|                                | Low TNF-alpha |
|                                | CRP |

PFT: Pulmonary function tests, A-V: Atrioventricular, sIL-2R: Soluble interleukine-2-receptor, TNF: Tumor necrosis factor, KL-6: Krebs Von den Lungen-6, Th: T-helper; DLCO: Diffusion lung carbon monoxide, PH: Pulmonary hypertension, CRP: C-reactive protein
African-American background may be at greater risk of comorbidity. Female gender is also associated with a higher incidence of coexisting autoimmune disorders. Women with sarcoidosis are treated at the hospital two times more frequently than men. African-American women have a worse prognosis than male patients. In different ethnic groups, not only different incidence but also phenotype differences have been reported.

For example, Löfgren syndrome is common in Northern European countries, while it is rarely seen in Africans and Japanese. Uveitis and cardiac involvement is more common in patients with sarcoidosis. Again, erythema nodosum, which indicates acute-onset disease and good prognosis, is more common in white race, while lupus pernio and other skin lesions, which are indicative of chronic disease, are more common in Afro-Americans. In African-Americans, extrapulmonary involvement, progressive disease, and mortality rates were reported to be higher compared to other ethnic groups. Gupta et al. reported the clinical characteristics of Indian sarcoidosis patients. Fever, cough, dyspnea, and loss of weight are the most presenting symptoms of Indian patients, while skin lesions and neurologic manifestations are uncommon.

Genetic factors
The role of genetic factors in the pathogenesis of sarcoidosis is well known. Familial cases of sarcoidosis have been reported for years. In different studies, familial sarcoidosis rates have been reported between 1% and 19%. In early twin studies, sarcoidosis was reported more frequently in monozygotic twins than in dizygotic twins. These observations suggest that some genetic variants may affect the development, clinical presentations, and prognosis of sarcoidosis. In some studies, Class 2 MHC alleles were found to be associated with disease susceptibility or phenotype. For example, there was a strong correlation between HLA-DQB1 * 0201 and HLA-DRB1 * 0301 with acute-onset disease, erythema nodosum, and good prognosis, while correlation was found between chronic and severe sarcoidosis with HLA-DQB1 * 1501 and HLA-DQB1 * 0602. While HLA-DRB1 * 01 and HLA-DRB1 * 04 were negatively correlated with sarcoidosis, HLA-DRB1 * 03, HLA-DRB1 * 11, HLA-DRB1 * 12, HLA-DRB1 * 14, and HLA-DRB1 * 15 genes increased the risk for the development of sarcoidosis. In studies investigating the association of non-HLA genes with sarcoidosis, a correlation was found between TNF-308A allele gene polymorphism and Löfgren syndrome. In one study, the association between butyrophilin-like 2 gene (BTNL2) and sarcoidosis was independently detected in HLA-DRB1 variations. BTNL2 nucleotide polymorphism (rs2076530 GRA) results in an incorrect costimulatory molecule that is responsible for T-lymphocyte activation and regulation. The relationship between annexin A11 gene and pulmonary fibrosis in patients with sarcoidosis was also reported. Annexin A11 has regulator functions for apoptosis, calcium-mediated signal transduction, and cell traffic. Annexin A11 dysfunction may affect apoptosis pathways and mechanisms in sarcoidosis. In another study, the frequency of MEFV gene mutation was investigated in Turkish sarcoidosis patients, and lower carrier rates were determined compared to the control group. The MEFV gene was thought to have a protective role in sarcoidosis.

CLINICAL PHENOTYPE
Two main clinical phenotypes have been described in sarcoidosis: acute sarcoidosis and chronic progressive disease. Acute-onset phenotype which had good prognosis is characterized with young age of onset, higher acute-phase reactant, radiologically stage 1/stage 2, and self-limited disease. Chronic sarcoidosis is characterized with insidious-onset, advanced age, radiologically Stage 3/Stage 4, neutrophilic alveolitis, systemic and progressive course, and the need for corticosteroids (CSs). Löfgren syndrome is an acute sarcoidosis characterized by fever, ankle arthralgia/arthritis, erythema nodosum, and bilateral hilar lymphadenopathy. It has good prognosis, 80%–90% of the patients’ symptoms regressed in 2–8 weeks, while lung findings regressed within 2 years. In rare cases, Löfgren syndrome may recur after years. Erythema nodosum is more common in patients with Stage 1 and 2 sarcoidosis and is a good prognostic factor, but in 16% of cases, it was associated with chronic disease.

Pulmonary involvement
Respiratory system symptoms indicating lung involvement are one of the important prognostic factors of sarcoidosis. Although some studies have shown no radiological correlation with pulmonary function tests (PFTs), low PFT and diffusion lung carbon monoxide (DLCO) suggest a progressive lung disease. PFTs can be normal in 80% of Stage 1 sarcoidosis patients and 35% of Stage 2/Stage 3 patients. While 30%–50% of the patients have restrictive patterns, bronchial obstruction is frequently seen. Impaired PFT in the onset of disease indicates poor prognosis in the long term. In a study, the patients with forced expiratory volume in 1 s (FEV1) <50% have increased 4-fold mortality risk compared with patients with FEV1 >80%. Bronchial obstruction (FEV1/FVC <70%) increases the risk of mortality. In addition, patients with total lung capacity <80% of the predicted value are associated with increased mortality risk. In another study, the fact that FVC was <80% of the predicted value was a strong predictor of persistent disease. DLCO, which shows interstitial involvement and fibrosis, is an important and sensitive method that can be used to describe disease progression/regression. In patients with sarcoidosis, DLCO <60% may be a predictor of pulmonary hypertension (PH).

Extrapulmonary involvement
Sarcoidosis is a chronic granulomatous disease, usually involving the lung. It is generally asymptomatic and/or presented with lung symptoms. However, the disease can affect also many systems and organs, not only the lung. According to the organ involvement, patients...
may present with different symptoms and complaints. Skin, eye, heart, and locomotor system are the most commonly involved organs after the lung. In rare cases, liver, spleen, gastrointestinal tract involvement, and/or isolated sarcoidosis cases (prostate, bladder, spine, marrow, and thyroid gland) have also been reported. Although sarcoidosis is primarily associated with lung involvement, extrapulmonary involvement (heart, kidney, and neurosarcoidosis) is important and they may determine the prognosis of the disease. The prevalence of extrapulmonary sarcoidosis has been reported to be 80% depending on geographical location or ethnic origin. Multiorgan involvement is always chronic and more severe, potentially leading to serious disability or potentially fatal consequences. In sarcoidosis patients, cardiac involvement was 13%–25% in the United States, while in Japanese patients, this rate was 58%–85%. Therefore, it is important to evaluate all patients with sarcoidosis in terms of cardiac involvement. Because cardiac involvement is not correlated with the severity of pulmonary involvement, diagnostic difficulties may occur. That is, severe cardiac involvement may be seen without active lung disease. While 5% of the patients had symptoms of cardiac involvement, the frequency of myocardial granuloma was reported as 20%–30% in autopsy series. PH is a poor prognostic marker for sarcoidosis. PH was detected in 73.8% of 363 sarcoidosis patients who were in advanced and lung transplantation list. PH is evolving with different and various mechanisms. Left ventricular dysfunction and/or impaired forward flow are thought to be the result. Eye involvement is one of the most important systemic manifestations of sarcoidosis and is seen in 10%–60% of patients. Ocular disease may be the first clinical manifestation of sarcoidosis and may cause severe visual impairment and blindness. The eye involvement makes two different peaks; the first one is seen between the ages of 20 and 30 years, while the second peak is seen between the ages of 50 and 60 years. Eye involvement has been reported more frequently in women, in the African-American and Japanese population. Granulomatous inflammation affects intraocular and peripheral structures. Uveitis is one of the early findings of sarcoidosis. It occurs in 80% of the patients in the 1st year of disease or without systemic findings. Neurological involvement may be asymptomatic or may be presented with severe neurological findings and can be seen in 5%–20% of patients. Neurosarcoidosis can be seen with central and/or peripheral nervous system findings, and different clinical presentations have different prognosis. While facial nerve palsy, aseptic meningitis, isolated headache, and vertigo generally improve without sequelae, epilepsy, and intracranial mass, spinal cord and optic nerve involvement has a worse prognosis. There is also some extrapulmonary involvement associated with nonlife-threatening, but chronic and progressive course, and thus indicating poor prognosis (e.g., lupus pernio, chronic uveitis, chronic hypercalcemia, nephrocalcinosis, nasal mucosal involvement, and cystic bone lesions). Laboratory prognostic factors

There is no specific laboratory test and/or biological marker in the diagnosis of sarcoidosis. In general, these tests are examined in the serum and bronchoalveolar lavage (BAL) fluid, and they provide information about the activation, progression, and prognosis of the disease. However, these markers are not specific to sarcoidosis and may also be positive in different inflammatory pathologies. High serum hydroxy D3, high calcium, and hypercalciuria are due to the production of abnormal 1,25 hydroxy D3 (calcitriol) from activated macrophages and granulomas. Hypercalciuria is 3–4 times more common than hypercalcemia. Nephrocalcinosis and renal failure may develop. Therefore, serum calcium and 24-h urinary calcium excretion should be measured in all sarcoidosis patients. Hypercalcemia and hypercalciuria are more a manifestation of chronic sarcoidosis than Löfgren syndrome. Serum angiotensin-converting enzyme (ACE) level, which is synthesized from epithelioid cells of sarcoid granuloma and correlates between total granuloma burden, is a useful marker evaluated in sarcoidosis patients. High serum ACE levels are detected in 40%–90% of patients with untreated sarcoidosis. Therefore, although the use of serum ACE for screening purposes is not sensitive enough, it does not seem to be specific enough to confirm the diagnosis of sarcoidosis. It may also increase in pathologies such as tuberculosis, fungal infections, hyperthyroidism, diabetes mellitus, cirrhosis, silicosis, lymphoma, and Gaucher’s disease. Drug use (ACE inhibitor, CS) suppresses serum ACE levels. Serum ACE levels were correlated with the number of organs detected in gallium scintigraphy. The initial high ACE level does not determine disease prognosis and is not an indication for steroid onset. In some selected patients, serum ACE levels can be used to monitor disease activity and respond to steroid therapy. While high levels of serum ACE are detected in the majority of patients with chronic sarcoidosis, it can be detected normally in acute sarcoidosis. In Löfgren syndrome, most patients have C-reactive protein (CRP) elevation but may be in normal range in asymptomatic and chronic sarcoidosis. CRP elevation is observed in patients with extensive and multiorgan involvement. CRP is also used as a marker in response to anti-tumor necrosis factor (TNF) alpha therapy. Serum amyloid A (SAA), another acute-phase reactant, plays an important role in the pathogenesis of sarcoidosis. SAA accumulated in the granuloma cells triggers Toll-like receptor 2-mediated cytokine release and is a precursor of chronic inflammation and disease progression. High levels of immunoglobulin and circulating immune complex were detected in the sarcoidosis patient sera. There was a relationship between serum immunoglobulin and the continuation of activity over time. Among the few biological markers which are not used routinely in clinical practice, but are very important in patients with sarcoidosis, include neopterin, soluble interleukin-2 receptor (sIL-2R), Krebs von den Lungen (KL-6), TNF-alpha, chitotriosidase, and tryptase. Neopterin is a molecule synthesized from macrophages and contributes to chronic inflammation by inducing ICAM-1.
in Type 2 pneumocytes. While serum neopterin level was increased in patients with chronic sarcoidosis, it is normal in Löfgren syndrome, remission, and asymptomatic cases.\(^{47}\) sIL-2R is a marker of T-cell activation and it level increased in patients with chronic sarcoidosis. In another study, serum IL-2R level was found to be high in patients with active sarcoidosis, which need treatment.\(^{48}\) KL-6 is a mucin-like high-molecular weight glycoprotein. It is the only predictor of a progressive parenchymal disease, reflecting the level of lymphocytic alveolitis. In one study, serum KL-6 levels and lung function parameters were found to be inversely correlated with DLCO, and high concentrations of KL-6 were associated with persistence and progression of parenchymal infiltrates.\(^{49}\) TNF-alpha is an important cytokine that is synthesized from alveolar macrophages and T-cells, which plays a key role in granuloma formation. In one study, it was emphasized that low TNF-alpha levels in BAL fluid may be a poor prognostic factor, whereas high TNF-alpha levels were found in Löfgren syndrome with a better prognosis.\(^{50}\) In another study, it was emphasized that low TNF-alpha and Th1-related cytokine levels may be a sign of excellent prognosis. Chitotriosidase, an enzyme secreted by active macrophages and involved in defense against pathogens containing chitin, has also been shown to correlate with the extent of lung changes, as assessed by radiological staging.\(^{51}\) Another example of a biomarker of potential prognostic value is the rising tryptase in the serum of patients with sarcoidosis, and high values were found in patients with progressive disease.\(^{52}\) The typical finding in sarcoidosis is the increase in BAL lymphocyte counts seen in 80%–90% of patients at the time of initial diagnosis. Lymphocyte percentage is an activity marker and an average increase in active disease reaches 30%–60%, but higher percentages are also observed. Approximately 60% of the patients have a CD4/CD8 ratio of more than 3.5, which is very specific for sarcoidosis. High CD4 lymphocyte content or high CD4/CD8 ratio in the BAL are more appropriate activity markers than total lymphocyte BAL percentage.\(^{53}\) Radiologically improved patients were more likely to have a higher number of CD4 cells and a higher CD4/CD8 ratio than patients who worsened or remained unchanged. In addition, higher CD4/CD8 patients in the initial diagnosis respond better to treatment. An increasing number of Th17 cells can be predictive for progressive sarcoidosis and may help in the selection of patients with increased risk of lung fibrosis.\(^{54}\) Some authors report the possible prognostic value of BAL neutrophils. Stage 3 patients had higher BAL neutrophil elastase concentrations than in patients with Grade 1 or 2. Patients with low neutrophil count in the BAL fluid have been shown to have higher chances of spontaneous recovery.\(^{55}\)

**Radiological prognostic factors**

In staging sarcoidosis, the Scadding classification is used even though it is outdated.\(^{56}\) According to the findings in the chest radiography, five different phases have been identified (Stage 0: extrapulmonary, Stage 1: bilateral hilar lymphadenopathy, Stage 2: hilar lymphadenopathy and parenchymal involvement, Stage 3: hilar parenchymal involvement without hilar LAP, and Stage 4: fibrosis). It is important that the Scadding classification has been discussed in recent years; because of the early diagnosis, prevalence, extrapulmonary involvement, and complication of the disease, the chest radiography is insufficient. The prognosis of the disease is closely related to the radiological stage.\(^{57}\) Spontaneous remission is observed in 90% of patients in Stage 1, 40%–70% of patients in Stage 2, and 10%–20% in patients with Stage 3, whereas in patients with Stage 4, spontaneous remission is not observed. Eighty percent of all remissions are seen in the first 2 years. The chest radiograph has an important role in the progression of the disease. In one study, only 9% of Stage 1 patients followed for 5 years progressed to Stage 2 and 1.6% progressed to Stage 3 and Stage 4.\(^{58}\) In another study, dyspnea was found to be associated with conventional chest X-ray findings and no correlation was found with a 6-min walk distance.\(^{59}\)

**THERAPEUTIC APPROACHES IN SARCOIDOSIS-PROGNOSTIC FACTORS ACCORDING TO PATIENTS’ THERAPEUTIC RESPONSE**

Treatment recommendations of sarcoidosis are often based on clinical experience and expert opinion.\(^{60}\) When discussing the treatment of sarcoidosis, organ involvement and disease presentation (acute/chronic), as well as sex, age, race, and additional disease should be considered. As is known, sarcoidosis is a disease that spontaneously regresses and sometimes does not require treatment.\(^{61}\) Spontaneous remission is more frequent in patients with Stage 1 and 2 sarcoidosis (55%–90%), whereas spontaneous remission in Stage 3 sarcoidosis is less common (10%–20%).\(^{60}\) Acute sarcoidosis cases has a better prognosis compared to chronic patients and often does not require treatment and recovery spontaneously.\(^{61}\) However, chronic disease (5 years after the diagnosis) and/or recurrent cases should be treated. All patients with sarcoidosis should be investigated for the presence of additional disease (hypertension, diabetes, and infection) because these patients may be resistant to treatment.\(^{62}\) Sarcoidosis in the African-American race and in some northern countries may be slightly more severe and chronic, so it may require systemic treatment.\(^{63}\) Since the most commonly involved organ is the lung, most studies are related to the treatment of this organ involvement. However, the question of which patients will be treated is controversial.\(^{64}\) The decision-to-treat sarcoidosis is based on existence of danger such as life-threatening or organ-threatening disease and impaired quality of life.\(^{65}\) Several studies have identified factors associated with increased risk for organ failure or death, and in this situation, the disease should be treated [Table 2]. The most commonly used drug in the treatment of sarcoidosis are CS.\(^{66-68}\) In addition to anti-inflammatory and immunomodulatory effects, in patients with sarcoidosis,
Table 2: "Dangers" in sarcoidosis which should be treated

| Heart involvement | Lupus pernio |
|-------------------|--------------|
| Neurosarcoidosis   | Symptomatic lung involvement |
| Progressive lung disease | Extended lung parenchymal infiltrations |
| Eye involvement unresponsive to local treatment | Symptomatic hypercalciemia/hypercalcium |
| Progressive, symptomatic extrapulmonary disease | Chronic skin disease (lupus pernio) |
| Bone involvement | Chronic destructive arthritis/myositis |

CS improves Th1/Th2 cytokines dysregulation. The treatment is not recommended in asymptomatic patients with radiologic Stage 1 and Stage 2; those patients are closely monitored with 3–6 months controls. However, CS should be started in patients with pulmonary symptoms (cough, hemoptysis, shortness of breath, and chest pain) and with impaired PFTs, PH, and progressive radiological progression (interstitial changes). According to the meta-analysis results, steroid treatment in pulmonary sarcoidosis has been shown to cause a significant improvement in radiological improvement and pulmonary function, but it has not been shown to be very effective on vital capacity. There are yet no data on the prognosis of the disease. In another study, patients who were in remission with steroid use and who had spontaneous remission without using steroids were compared, and more recurrence was observed in steroid users. Second-line therapy includes cytotoxic agents such as methotrexate, azathioprine, leflunomide, and mycophenolate. Randomized controlled trials on the efficacy and safety of these drugs in patients with sarcoidosis are limited. Biologics and other agents are third-line therapy. The studies on biologic drugs in sarcoidosis treatment are unsatisfactory, and the data are limited to more open studies, case presentations, and expert experiences. TNF inhibitors (infliximab and adalimumab) have been shown to be particularly effective for advanced disease. Furthermore, improvement in PFTs and quality of life were observed in patients treated with anti-TNF-alpha agents. New treatments modalities, including repository corticotropin injection and rituximab, have been reported as effective in some cases. On the other side, we should never forget that treatment of sarcoidosis may lead to some complications (infections, malignancy), which can determine the outcome and prognosis of disease. Immunosuppressive drugs have been shown to increase the risk of infection in sarcoidosis. The use of combination immunosuppressive agents increases the risk for infections. Pneumonia is the most common infection reported, but extrapulmonary complications such as fungal and mycobacterial infections can also occur. Several of the immunosuppressive agents (methotrexate, azathioprine, and anti-TNF-alpha) used to treat sarcoidosis are associated with increased risk for malignancy. There has been no large prospective study examining the increased risk for any immunosuppressive drug in sarcoidosis. The use of combinations of immunosuppressives should be avoided, because of increased risk for malignancy. There are contradictory data in the literature regarding the relationship between sarcoidosis and malignancy. According to the results of various studies, sarcoidosis has been considered as a risk factor for development of cancer, particularly lymphoproliferative disorders. The sarcoidosis–lymphoma syndrome was described, which is characterized with the uncontrolled lymphocyte proliferation and increased mitotic activity. This process may be triggered by decreased ability of the immune system to eliminate unknown antigens which lead to chronic inflammation. On the other side, there are other studies that have opposites the existence of a close association between the two diseases. The reasons of those controversial results may be explained with biases in patients’ selection and different classification method used. However, the association of sarcoidosis and malignancy is still under debate.

**Morbidity and mortality**

Mortality in sarcoidosis is affected by factors such as age, gender, race, organ involvement, care, and treatment and is estimated to be 1%–8%. The most common causes of mortality are advanced lung fibrosis, cardiac involvement, and neurosarcoidosis. In one study, mortality from sarcoidosis and complications was correlated with impaired lung function and advanced radiological findings. Compared with the general population, patients with sarcoidosis had higher mortality rates but were not statistically significant. While different mortality rates are reported in different ethnic groups, it is stated that skin involvement (lupus pernio) may also be a prognostic factor.

**CONCLUSION**

Sarcoidosis is a chronic granulomatous disease characterized by noncaseating granuloma. There are some clinical, radiological, and laboratory factors that determine the prognosis of the disease. Clinical phenotype of the disease may be presented with acute self-limiting sarcoidosis (Löfgren syndrome) and/or chronic, progressive multiorgan involvement. Radiological staging determines the prognosis of the disease. Laboratory factors are nonspecific and may not always be useful in clinical practice. Good knowledge of all these factors will be useful in determining the treatment algorithms of the disease. In this way, the most frequently asked question “which patients should we treat?” will also be answered. At the same time, the morbidity and mortality rates of the disease will be affected by early treatment. There is a need for new multicenter prospective studies to shed light on this issue.

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