ACTA FACULTATIS MEDICAE NAISSENSIS

UDC: 616.24-002.7

Scientific Journal of the Faculty of Medicine in Niš 2011;28(3):155-159

Review article ■

Disease Activity Markers in Sarcoidosis

Tatjana Rađenović Petković[2], Tatjana Pejčić[1,2,], Desa Nastasijević Borovac[2], Danijela Radojković[1,3], Sonja Cekić[4]

[1]*University of Niš, Faculty of Medicine, Serbia*
[2]*Clinic of Lung Diseases and TBC "Knez Selo", Knez Selo, Clinical Center Niš, Serbia*
[3]*Clinic of Endocrinology and Metabolic Diseases, Clinical Center Niš, Serbia*
[4]*Clinic of Ophthalmology, Clinical Center Niš, Serbia*

SUMMARY

Sarcoidosis is characterized by granulomatous inflammation developing in the affected organs. The ethiopathogenesis of the disease is still unknown. The lungs are most commonly affected, and uncontrolled, long-lasting inflammation can result in pulmonary fibrosis. Many different mediators, such as cytokines, chemokines, and other proteins with various functions that participate in its complex pathogenesis have been studied as markers of the disease. This article is a review of the available literature on the different markers. Although a considerable number of markers are elevated in the active stage of the disease, the studies conducted so far have shown that the values of serum ACE, IL-2R and chitotriosidase decrease with a good treatment response. KL-6 can be useful as a predictive marker for the development of pulmonary fibrosis in sarcoidosis.

In conclusion, prospective studies with a larger number of patients will offer a much better insight considering the importance of these parameters when dealing with sarcoidosis.

Key words: **sarcoidosis, marker, ACE**

Corresponding author:

Tatjana Rađenović Petković•
tel. 062/ 223 101•
e-mail: tatjanarp@gmail.com •

INTRODUCTION

Sarcoidosis is a multisystemic disease of unknown origin. It usually occurs in younger and middle-aged people, and it is clinically manifested by enlarged chilar lymph nodes, pulmonary infiltrates, ocular and skin lesions. The liver, spleen, lymph nodes, salivary glands, heart, kidney, nervous system and bones can also be affected by the disease. The course and the prognosis of the disease depend on particular organs affected, as well as the general spread of the disease (1, 2). The basic pathogen substrates of the disease are sarcoid granuloma, which occur as the immune response to the unknown antigen by gathering of macrophages and CD4+ T lymphocytes (3). In the majority of patients, the disease occurs in its mild form with a spontaneous remission. In one third of the patients, the chronic form of the disease develops with an unforeseeable course. Mortality rate in sarcoidosis is less than 5%. The most common cause of mortality is progressive pulmonary fibrosis, sarcoidosis of the heart or sarcoidosis of the nervous system (4).

Sarcoidosis is a disease with an unforeseeable course and outcome; possible progression and exacerbations can occur. The estimation of the disease activity is based on the clinical estimation, radiological findings and the measurement of certain markers' value in the serum. A large number of biochemical and cellular parameters have been researched in order to monitor the development and the activity of the disease. However, so far, none of them have clinical application except the serum angiotensin-converting enzyme (sACE). Recent results unveil the possible role of new markers that could have diagnostic or prognostic importance.

Angiotensin-converting enzyme (ACE)

ACE belongs to the group of exopeptidases responsible for the transformation of angiotensin I into angiotensin II and the deactivation of bradikinine. It has a significant role in the regulation and maintenance of the liquid volume, as well as in the immune and inflammatory response. Angiotensin II plays the role as chemoatracant for T-lymphocytes (5). ACE also performs the hydrolysis of bradikinine and substance P, the proteins which have an essential role in inflammation, the activation of macrophages, the proliferation of lymphocytes and phagocytosis (6). In granuloma, there is a significant increase in the production of ACE by the activated macrophages, epithelioid and giant cells, which points to the important role of this enzyme in the pathogenesis of the disease. The enzyme is ubiquitous, largely distributed in the body, mostly produced by the endothelial cells of pulmonary capillaries and proximal renal tubules. Increased values of this enzyme in sarcoidosis were first described by Lieberman in 1975. It has remained the most commonly used biochemical marker in sarcoidosis ever since. Still, the majority of studies consider this marker to be insensitive and nonspecific in the diagnostics of sarcoidosis (7, 8).

According to the data available in literature, serum ACE is increased in 40-90% of patients with sarcoidosis. The highest values of this marker have been detected in patients with bichilan lymphadenopathy and parenchymal changes (II radiological stage according to Scadding's scale) (9), but its values have been elevated in the extrapulmonary sarcoidosis as well.

Apart from sarcoidosis, other diseases and physiological conditions can be associated with elevated values of ACE in the serum (Table 1). Importantly, in patients with Hodgkin's disease, which is often a considerable differential diagnosis when compared to pulmonary sarcoidosis, the values of ACE are lower than normal (10).

Table 1. *Diseases other than sarcoidosis with elevated sACE values*

Mildly elevated values
Diabetes mellitus
Chronic renal failure
Age less than 19 years
DD polymorphism
Asbestosis
Silicosis
Moderate to high values
Hypertyreodism
Tuberculosis
Histoplasmosis
Coccidiomycosis
Berylliosis
Constantly elevated values
Gauchiers disease
Leprosy

The reason for the insufficient sensitivity of increased values of ACE in sarcoidosis has been discovered a couple of years ago by the study of genetic polymorphisms connected to ACE. The polymorphism of genes for ACE is based on the presence (insertion I) or absence (deletion D) of the sequence of 287 bp in intron 16. It has been proven that the carriers of the genotype II (25% of the population) have considerably lower values of ACE when compared to the carriers of ID or DD phenotype (11). Consequently, those differences account for the differences in ACE values in patients with sarcoidosis.

Despite the fact that this marker has minor diagnostic importance, most of the authors agree that sACE can be used to observe the course of the disease. The reactivation of the disease in patients who would have higher values in previous exacerbation is almost always followed by the increase in sACE (12). The application of corticosteroids in treatment leads to the decrease in values of ACE in the serum, whereas the reduction of the corticosteroid dosage in treatment can be followed by the increase in sACE. In other words, its values correlate with the therapeutic dosage of corticosteroids, and not with the clinical status of the disease (13, 14). Increased ACE values in tears have been detected in patients with ocular sarcoidosis (15), while increased values in the cerebrospinal fluid have been noted in patients suffering from sarcoidosis of the central nervous system (16).

Lysozyme

Lysozyme is a bacteriolytic enzyme produced by the activated macrophages and it is present in various cells and tissues. In sarcoidosis, it is produced by the macrophages and epithelioid cells of the active granuloma, while its activity is not detected in old lesions (17). Increased values of this enzyme have been detected in patients suffering from tuberculosis (18), certain malignant disease (19), berylliosis, silicosis an asbestosis. Although some authors consider it to be more sensitive than sACE, given the fact that its values are increased in a large number of patients, lysozyme has less specificity than the aforementioned enzyme. Hence, its clinical application in diagnostics and monitoring of the disease is not very relevant (17).

Soluble IL-2 receptor (sIL-2R)

Interleukin 2 (IL-2) is Th1 cytokine which induces T cellular proliferation and activation by the interaction with IL2 receptor. The values of IL-2R are increased in the bronchoalveolar lavage of patients suffering from sarcoidosis, whereas in the serum, the values of IL-2R are higher in patients with extrapulmonary sarcoidosis when compared to patients with the isolated pulmonary form of the disease (20). Soluble IL-2R is a T lymphocyte activity marker that can be used, according to the research data, as an activity marker for the disease (21). Elevated levels of IL-2R would fall during therapy or with spontaneous remission. Increased values of IL-2R in the serum in patients with minimal pulmonary changes can point to extrapulmonary sarcoidosis (22). When examining large numbers of serum markers in sarcoidosis, IL-2R was the only one which proved to be a significant factor of disease progression (20).

Neopterin

Neopterin is a metabolitite of guanosine triphosphate, which is produced in vitro by macrophages under the effect of inteferon gamma (IFNγ). Neopterin is a macrophage activity marker whose increased values have been detected in the serum and urine of patients with an active form of sarcoidosis. On the other hand, its values tend to decrease as the disease resolves (23). Neopterin is considered to be, together with IL-2R, the independent factor of the disease progression (20).

β2 microglobulin

β2 microglobulin is a low molecular protein which comprises the HLA molecule. Activated lymphocytes produce large amounts of this protein, which makes it as an important marker of malign chematological diseases. Increased values of β2 microglobuline in sarcoidosis have been detected in patients with the acute stage of the disease, and they decrease with the good therapeutic response (24). Due to low specificity, this marker is not very important in the monitoring of the disease activity.

Chitotriosidase

Chitotriosidase belongs to the group of chitinases and is produced by activated macrophages. Chitinases have the ability to catalyze hidrolysis of chitine and similar substrates. Chitotriosidase has an essential role in the immune response concerning microorganisms which contain chitine in their layer, such as parasites and insects. A multiple increase in values of this enzyme are detected in patients with sarcoidosis, while the values are normal in patients with tuberculosis (25). Research has confirmed that the values of this enzyme correlate with radiological stage, and that it can be considered a disease progression marker (26). A significat increase in values of chitotriosidase can point to extrapulmonary sarcoidosis (27), whereas a good therapeutic response is followed by the normalization of values of this parameter in serum.

Krebs von den lungen-6 (KL-6)

KL-6 is a mucin which is produced by pneumocytes type II and cells of the bronchial epithelium. KL-6 is a fibroblast chemoattracant, which signifies that it has an important role in the fibrosis process. This is the exact reason why this marker has been investigated in various interstitial pulmonary conditions. Increased values of KL-6 in the serum and the bronchoalveolar lavage have been detected in patients with interstitial pulmonary fibrosis, fibrous form of scleroderma as well as in the fibrous form of the pulmonary sarcoidosis (28). KL-6 is suitable parametar for monitoring disease progression, especially progression to fibrous form of sarcoidosis (17).

YKL-40

YKL-40 (human cartilage glycoprotein 39) is a glucoprotein which is produced by inflammatory cells and which has lately been mentioned as the marker for a large number of cancers, including lung cancer. The

study by Johansen et al. (29) describes this marker as the marker for sarcoidosis which negatively correlates with the value of DLCO (diffusion lung capacity for carbon monoxide), so it can be considered as the fibrosis marker in sarcoidosis. Low specificity of this marker limits its clinical application.

CONCLUSION

The examination of serum markers when diagnosing and monitoring the course of the disease often leads to different, contradictory results. Although a considerable number of markers are elevated in the active stage of the disease, the studies conducted so far have shown that the values of ACE, IL-2R and chitotriosidase decrease with a good treatment response. KL-6 can be useful as a predictive marker for the development of pulmonary fibrosis in sarcoidosis. In conclusion, prospective studies with a larger number of patients will offer a much better insight considering the importance of these parameters when dealing with sarcoidosis.

References

1. Hunninghake GW, Costabel U, AndoM, et al. American Thoracic Society/European Respiratory Society/-World Association of Sarcoidosis and Other Granulomatous Disorders:statement onsarcoidosis. Sarc Vasc Dif Lung Dis 1999; 16: 149–73.
2. Pejčić T, Stanković I, Rančić M, Djordjević I, Isaković Lj, Ristić L. Klinički i radiološki oblici sarkoidoze pluća. Acta Fac Med Naiss 2004; 21: 23-6.
3. Filipović M, Djordjevic Z. Imunoloski aspekt sarkoidoze. Acta Fac Med Naiss 2001; 18: 229-34.
4. Mihailović Vucinić V, Sharma O. Atlas of sarcoidosis-Pathogenesis, Diagnosis, and Clinical Features. Springer; 2005.
5. Weinstock JV, Blum AM, Kassab JT. Angiotensin II is chemotactic for a T-cell subset which can express migration inhibition factor activity in murine schistosomiasis mansoni. Cell Immunol 1987; 107(1): 180–7.
6. Payan DG. Neuropeptides and inflammation: the role of substance P. Annu Rev Med 1989; 40: 341–52.
7. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. N Engl J Med 2007; 357:2153–65.
8. Grutters JC, Drent M, Bosch JM. Sarcoidosis. Eur Respir Mon 2009; 46: 126–54.
9. Loddenkemper R, Kloppenborg A, Schoenfeld N, Grosser H, Costabel U. Clinical findings in 715 patients with newly detected pulmonary sarcoidosis-result of a cooperative study in former West Germany and Switzerland. WATL Study Group. Wissenschaftliche Arbeitsgemeinschaft fur die Therapie von Lungenkrankheitan. Sarcoidosis Vasc Diffuse Lung Dis 1998; 15 (2): 178-82.
10. Bosi A, Borsotti M, Ghelli P, Tozzi P, Bellesi G, Rossi FP. Serum angiotensin-I-converting enzyme and lysozyme levels in untreated and unsplenectomized patients with Hodgkin's disease. Acta Haematol 1984; 71(5): 329–33.
11. Tomita H, Ina Y, Sugiura Y, Sato S, Kawaguchi H, Morishita M, et al. Polymorphism in the angiotensin-converting enzyme (ACE) gene and sarcoidosis. Am J Respir Crit Care Med 1997; 156(1): 255–9.
12. DeRemee RA, Rohrbach MS. Serum angiotensin-converting enzyme activity in evaluating the clinical course of sarcoidosis.Ann InternMed 1980; 92(3): 361–5.
13. Baughman RP, FernandezM, Bosken CH,Mantil J, Hurtubise P. Comparison of gallium-67 scanning, bronchoalveolar lavage, and serum angiotensin-converting enzyme levels in pulmonary sarcoidosis. Predicting response to therapy. Am Rev Respir Dis 1984; 129: 676-81.
14. Gronhagen-Riska C, Selroos O, Niemisto M. Angiotensin converting enzyme. V. Serum levels as monitors of disease activity in corticosteroid-treated sarcoidosis. Eur J Respir Dis 1980; 61(2): 113–22.
15. Sharma OP, Vita JB. Determination of angiotensin-converting enzyme activity in tears. A noninvasive test for evaluation of ocular sarcoidosis. Arch Ophthalmol 1983; 101(4): 559-61.
16. Tahmoush AJ, Amir MS, Connor WW, Farry JK, Didato S, Ulhoa-Cintra A, et al. CSF-ACE activity in probable CNS neurosarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis 2002; 19(3): 191-7.
17. Miyoshi S, Hamada H, Kadowaki T, Hamaguchi N, Ito R, Irifune K, Higaki J. Comparative Evaluation of Serum Markers in Pulmonary Sarcoidosis. Chest 2010; 137; 1391-97.
18. Myrvik QN. Serum and tissue lysozyme levels associated Mwith granulomatous reaction. Tuberculol Thorac Dis 1960; 18: 91-4.
19. Perillie PE, Finch SC. Lysozyme in leukemia. Med Clin North Am 1973; 57(2):395-407.
20. Ziegenhagen MW, Rothe ME, Schlaak M, Muller-Quernheim J. Bronchoalveolar and serological parameters reflecting the severity of sarcoidosis. Eur Respir J 2003; 21(3): 407-13.
21. Rothkrantz-Kos S, van Dieijen-Visser MP, Mulder PG, et al. Potential usefulness of inflammatory markers to monitor respiratory functional impairment in sarcoidosis. Clin Chem 2003;49:1510–17.
22. Grutters JC, Fellrath JM, Mulder L, et al. Serum soluble interleukin-2 receptor measurement in patients with sarcoidosis: a clinical evaluation. Chest 2003; 124: 186-95.
23. Eklund A, Blaschke E. Elevated serum neopterin levels in sarcoidosis. Lung 1986; 164(6): 325-32.
24. Selroos O, Klockars M. Relation between clinical stage of sarcoidosis and serum values of angiotensin conver-

ting enzyme and beta2-microglobulin. Sarcoidosis 1987; 4(1): 13–17.
25. Bargagli E, Maggiorelli C, Rottoli P. Human chitotriosidase: a potential new marker of sarcoidosis severity. Respiration 2008; 76(2): 234-8.
26. Brunner J, Scholl-Burgi S, Zimmerhackl LB. Chitotriosidase as a marker of disease activity in sarcoidosis. Rheumatol Int 2007; 27: 1171-2.
27. Boot RG, Hollak CE, Verhoek M, Alberts C, Jonkers RE, Aerts JM. Plasma chitotriosidase and CCL18 as surrogate markers for granulomatous macrophages in sarcoidosis. Clin Chim Acta 2010; 411(1-2): 31-6.
28. Kobayashi J and Kitamura S. 1996. Serum KL-6 for the evaluation of active pneumonitis in pulmonary sarcoidosis. Chest 109(5): 1276-82.
29. Johansen, JS, Milman N, Hansen M, Garbarsch C, Price PA, and Graudal N. 2005. Increased serum YKL-40 in patients with pulmonary sarcoidosis-a potential marker of disease activity? Respir Med 99(4): 396-402.

MARKERI AKTIVNOSTI BOLESTI U SARKOIDOZI

Tatjana Rađenović Petković[2], Tatjana Pejčić[1,2], Desa Nastasijević Borovac[2], Danijela Radojković[1,3], Sonja Cekić[4]

[1]Univerzitet u Nišu, Medicinski fakultet, Srbija
[2]Klinika za plućne bolesti i TBC, Knez Selo, Klinički centar Niš, Srbija
[3]Klinika za endokrinologiju i bolesti metabolizma, Klinički centar Niš, Srbija
[4]Klinika za očne bolesti, Klinički centar Niš, Srbija

Sažetak

Sarkoidoza je bolest koja se karakteriše inflamacijom sa formiranjem granuloma u zahvaćenim organima. Etiopatogeneza bolesti je nepoznata. Bolest najčešće zahvata pluća i hronična, nekontrolisana inflamacija može rezultirati plućnom fibrozom. Mnogi medijatori zapaljenja, citokini, hemokini, ali i drugi proteini sa različitim biološkim funkcijama koji učestvuju u patogenezi ispitivani su kao markeri bolesti. U ovom radu sagledani su postojeći podaci u literaturi o markerima aktivnosti i progresije u sarkoidozi. Iako je koncentracija različitih proteina povećana u aktivnoj fazi bolesti, studije su pokazale da vrednosti ACE, IL-2 receptora i hitotriozidaze opadaju sa dobrim terapijskim odgovorom. KL-6 može biti značajan prediktivni marker plućne fibroze u sarkoidozi. U svakom slučaju, dalje, prospektivne studije, na većem broju bolesnika, daće bolji uvid u značaj ovih markera u praćenju aktivnosti i prognozi bolesti.

Ključne reči: **sarkoidoza, marker, ACE**