Sarcoidosis and Autoimmunity: From Genetic Background to Environmental Factors

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ABSTRACT: Sarcoidosis is a chronic multisystem disease with variable course resulting from the interaction between environmental factors and the immune system of individuals genetically predisposed. The evidence linking sarcoidosis with environmental triggers such as metals is increasing. We describe the case of a 44 year old female with a history of smoking since age 30 and previous mercury dental filling who presented at physical examination with numerous subcutaneous nodules. Laboratory data showed accelerated erythrocyte sedimentation rate and high titer of anti-U1 ribonucleoprotein antibodies (U1 RNP). Skin biopsy and chest X-ray suggested the diagnosis of sarcoidosis. In this report we illustrate the different causes involved in the onset of sarcoidosis.

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Sarcoidosis is a chronic multisystem disorder characterized by the formation of non-caseating granulomas that most commonly affect young and middle-aged individuals of both genders; its overall prevalence is 10–20 per 100,000 people [1]. Whereas Caucasians tend to present with asymptomatic and chronic disease, Afro-Caribbeans and African-Americans, besides being more frequently affected, are at higher risk of developing severe forms of the disease [1]. Although the pathophysiology remains obscure, it is likely that heterogeneous triggers lead to the formation of granulomas involving multiple organ systems in genetically susceptible individuals [1]. Clinical presentation and long-term prognosis vary significantly according to the organ involved. In up to 20% of patients, cutaneous lesions such as macules, papules, plaques, nodules, infiltrated scars, subcutaneous lesions or lupus pernio can occur, often at the onset of systemic illness [1]. Diagnosis is based on the combination of clinical, radiographic and histologic features and the exclusion of other known causes of inflammatory granulomas including local sarcoid-like reactions [2]. Since there is no specific diagnostic test, the diagnosis often remains uncertain. The differential diagnosis may include granulomatosis with polyangiitis, giant cell arteritis, systemic lupus erythematosus (SLE), polyarteritis nodosa, and eosinophilic granulomatosis with polyangiitis [3]. The prognosis of sarcoidosis depends on different organ manifestations: if the central nervous system (CNS) or the cardiac system is affected the prognosis gets worse. Thus, a multidisciplinary approach is necessary for the comprehensive care of the sarcoidosis patient [3].

PATIENT DESCRIPTION

A 44 year old Caucasian woman first presented with subcutaneous nodules, tremor of the hands, diplopia and arthralgia. Apart from smoking and having a dental amalgam filling that contained mercury, her history was unremarkable. She led a sedentary lifestyle and worked as a hairdresser. Her family history for autoimmune diseases included autoimmune hypothyroidism, SLE and rheumatoid arthritis (RA). Clinical examination revealed subcutaneous nodules, predominantly on the arms and upper chest region. Laboratory workup was normal except for the high sedimentation rate and high titers of anti-U1 ribonucleoprotein antibodies (anti-U1-RNP). Despite normal levels of angiotensin-converting enzyme and serum calcium, the skin biopsy demonstrated typical non-caseating granulomas compatible with sarcoidosis. With regard to imaging studies, chest X-ray demonstrated bilateral hilar-mediastinal lymphadenopathy (stage 1), and brain magnetic resonance imaging (MRI) was normal.

Despite high anti-U1RNP antibodies, there was no other clinical evidence to suggest the diagnosis of mixed connective

Table 1. Several autoantigens related to common autoimmune diseases

Autoantigen	Remarks
Myasthenia gravis	
nAChR	Antibodies in most MG patients [32]
MuSK	Antibodies in "seronegative" MG patients [33]
Diabetes mellitus type 1	
Insulin	Antibodies already in pre-diabetics [34]
IA-2	Antibodies in 50% of diabetics [35]
Glutamic acid decarboxylase (GAD 65)	Considered a biomarker for the early diagnosis of DM1 and related inflammations [36]
Rheumatoid arthritis	
Fc-part of immunoglobulins (rheumatoid factor)	Antibodies in › 80% of RA patients
Citrullinated antigens	Antibodies before and during disease course, specific B cells in synovial fluid
Carbamylated antigens	Antibodies in 45% of RA patients [37]
Collagen	Antibodies to post-translationally modified forms [38]
65 kDa heat shock	Antibodies in RA patients
Sjögren's syndrome	
Ro/SSA and/or La/SSB	Primary SS negative for anti-Ro/SSA, and anti-La/SSB antibodies appear to be characterized by a lower risk of lymphoma
Systemic lupus erythematosus	
dsDNA	50–70% of SLE patients [39]
P ribosomal protein	Antibodies associated with psychosis and cognitive impairment (NPSLE)
Phospholipids	Antibodies anti-β2GPI, LA, anti-cardiolipin [40]
Sarcoidosis	
ZNF688 MRP-PL43 NCOA2 ARFGAPA1 Serum amyloid A (SAA) NOD2 (CARD15)	There is a narrow connection between Blau syndrome and early-onset sarcoidosis as they are respectively defined as the familial and sporadic forms of the same non-caseating granulomatous auto-inflammatory disease in children. Blau syndrome and early-onset sarcoidosis are characterized by granulomatous arthritis, dermatitis, uveitis and sometimes systemic involvement
MCTD	
U1RNP	Raynaud's phenomenon, puffy hands, arthritis, myositis, acro-sclerosis

MG = myasthenia gravis, DM1 = diabetes myelitis type 1, SS = Sjogren's syndrome, SLE = systemic lupus erythematosus, LA = Lupus anticoagulant, NPSLE = neuropsychiatric SLE, anti-β2GPI = anti-β2glycoprotein I

tissue disease (MCTD). Based on the high sedimentation rate and progressive involvement of the lung and skin (she later developed skin granulomas in other parts of the body), the diagnosis of sarcoidosis was determined.

DISCUSSION

Sarcoidosis can be considered a multifactorial disorder resulting from exposure of a genetically prone individual to an unidentified (probably environmental) antigen that triggers a Th1-type cellular immune response leading to the formation of granulomas. The clinical variability among different individuals and populations of different ethnicity probably reflects the distinct genetic backgrounds and environmental exposures [4]. Clearly therefore, what is needed is a full understanding of the close link between the distribution of autoimmune diseases across different geographic regions (and ethnic groups) and the corresponding genetic and environmental factors that may trigger the disease [2].

SARCOIDOSIS AND GENETICS

Concerning the association between sarcoidosis and genetic susceptibility, it is well known that the genetic variants in molecules involved in antigen presentation – such as specific haplotypes of the human leukocyte antigen (HLA) – are associated with a greater risk of developing several autoimmune diseases as well as sarcoidosis and that they vary among populations. For instance, in the ACCESS study (A Case Control Etiologic Study of Sarcoidosis) considerable differences were observed in the distribution of HLA class II alleles between black and white populations. Only the HLA-DRB1*1101 was associated with sarcoidosis in both ethnic groups. Additionally, in the same study the HLA-DRB1*1101, DRB1*1201, DRB1*1501 and DRB1*0402 were suggested to be the strongest alleles predisposing to sarcoidosis [5]. Moreover, variants of the HLA-DRB1 locus are associated with disease course [6] and specific organ involvement [7]. Ozylimaz et al. [8] found an intriguing link between the haplotype HLA-DRB1*15 and sarcoidosis in the Turkish Caucasian population and a potential protective effect of HLA-DRB1*11 from extra-pulmonary involvement of disease. Furthermore, Levin et al. [9] showed that carriers of the HLA-DRB1*0301 had a decreased risk of extra-pulmonary manifestations of sarcoidosis in non-thoracic lymph nodes, eyes, skin and liver. On the other hand, the HLA-DR3 seems to be associated with extra-pulmonary manifestations. Other predisposing HLA include HLA-DRB1*0301 (acute sarcoidosis), HLA-DQB1*0201 (remitting disease), and DQB1*602-DRB1*150101 (chronic active disease).

The genetic background of sarcoidosis has not been completely depicted; nonetheless, non-HLA genes seem to be involved in its onset. In this context, a number of studies showed that several polymorphisms in genes encoding for cytokines, chemokines and other molecules involved in the inflammatory pathway, such as tumor necrosis factor-alpha (TNFα), interleukin-1 (IL-1), interferon-alpha (IFNα) and CCR2, may predispose to the development of sarcoidosis. Bordignon et al. [10] suggested that TLR7 gene polymorphisms could be related to disease severity. It is possible that other polymorphisms could serve as protective factors against the disease.

SARCOIDOSIS, AUTOANTIGENS AND AUTOANTIBODIES

Antigen presentation is a pivotal step in host defense against pathogens, or when the immune system is unbalanced, thus

leading to the development of an autoimmune disease [11]. Autoantigens found in the most frequent autoimmune diseases are shown in Table 1. One of the most interesting reports, by Haggmark et al. [12], demonstrated the presence of several sarcoidosis-associated autoantigens in the bronchoalveolar lavage and in serum samples from patients with sarcoidosis. The zinc finger protein 688 (ZNF688) and the mitochondrial ribosomal protein (MRP-PL43) showed a higher frequency in sarcoidosis patients, highlighting that these proteins could act as autoimmune targets. In addition, high levels of antibodies to the adenosine-diphosphate-ribosylation GTPase activating protein-1 (ARFGAPA1) and an increased reactivity toward nuclear receptor coactivator 2 (NCOA2) were found in patients with sarcoidosis. It was proposed that serum amyloid A (SAA) could be another antigen involved in the pathophysiology of sarcoidosis. SAA may have a role in promoting the chronic inflammation in sarcoidosis since it is found in epithelioid granulomas. Moreover, by interacting with a diverse family of receptors such as TLR2, RAGE, CD36 and FPRL1, SAA may enhance the expression of several cytokines (TNF, IL-18, IL-10) that are upregulated in sarcoidosis and enhance the sequestering capability of sarcoid granulomas [13]. Hence, the persistence of granulomatous inflammation in the lung in an experimental model that received the protein supports the fact that SAA can represent a sarcoidosis antigen.

Concerning antibodies, there is one report of two patients who developed sarcoidosis a few years after being diagnosed with mixed connective tissue disease (MCTD). In these patients, the levels of anti-U1RNP antibodies increased as sarcoidosis developed and decreased after appropriate treatment. Although our patient described in the present report did not meet the criteria for the diagnosis of MCTD, the finding of high titers of anti-U1RNP is interesting. Indeed, the mere presence of anti-U1RNP might be a factor associated with sarcoidosis [14].

SARCOIDOSIS AND ENVIRONMENTAL FACTORS

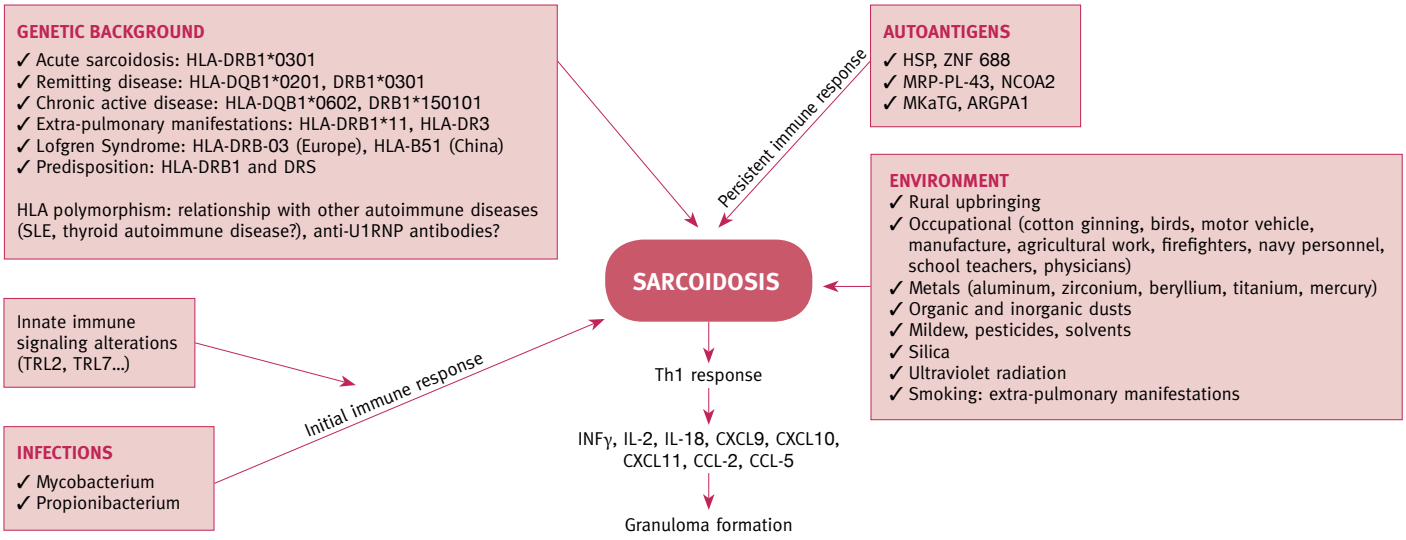
Multiple infectious agents including viruses and fungi have been suggested over the years as the etiologic agents of sarcoidosis. Many reports supported a role of either Mycobacteria or Propioni bacteria in the pathogenesis of sarcoidosis [15]. In a study by Eishi [16], the presence of DNA of *Propionibacterium acnes* was detected in over 70% of tissues samples from Japanese and European patients with sarcoidosis. It should be underlined that *P. acnes* can be commonly found in healthy people as well. Nonetheless, it was suggested that reactivation of a latent form might occur in patients with hypersensitivity to *P. acnes*, favoring sarcoidosis onset. Due to the pathologic similarities that exist between sarcoidosis and tuberculosis (TB), Dubaniewicz et al. [17] suggested that mycobacterial antigens such as heat shock protein Mtb-HSP (especially Mtb-HSP65) may cross-react with the human HSP (chaperone proteins produced in cells during stress and after T cell activation), causing the development of sarcoidosis. In genetically different individuals the same antigens, especially Mtb-HSP65, may produce a different immune response developing into acute (e.g., Löfgren's syndrome) or chronic stages of sarcoidosis, or TB. This suggests that not the entire *M. tuberculosis* but its particular antigens, such as Mtb-HSP70, Mtb-HSP65 and Mtb-HSP16, may take part in sarcoidosis pathogenesis through a mechanism of cross-reaction with human HSP. Another example of *M. tuberculosis* involvement in sarcoidosis was suggested by Song et al. [18]. Those authors showed the presence of *M. tuberculosis* catalase-peroxidase protein (mKatG) in lung tissues of approximately 50% of patients with sarcoidosis, reinforcing the idea that mycobacterial antigens may have a central role in the pathophysiology of the disease [18].

Among other environmental factors, airborne antigens could be other contributing elements to sarcoidosis onset since the lungs, eyes and skin are the most frequently involved organs. Iannuzzi et al. [19] suggested that exposure to inorganic particles and insecticides, and to tree pollen, and in general, living in unhealthy environments may potentiate the risk of developing sarcoidosis. Certainly, an occupational risk exists for metalworkers, agricultural workers, health care professionals, people who handle building supplies, and firefighters as demonstrated by the increased incidence of sarcoidosis and other pulmonary diseases among New York City Fire Department workers involved in the 2001 World Trade Center disaster [20]. In addition, crystalline silica, solvents and ultraviolet radiation can contribute to the generation of autoimmune diseases. In this context, Solà et al. [21] reported the interesting case of a male patient who developed clinical features of the disease after exposure to the anhydrous colloidal silica contained in a drug formulation for hypertension. The mechanism of silica granuloma development remains unclear. Skin granulomas are mainly localized in scars and areas of previous trauma; thus, external agents may serve as a stimulus for the establishment of granulomas. The Swaisgood murine model showed that silica generates granulomas in the lungs, given the predominant role of the respiratory tract in processing external agents [22], possibly explaining why the pulmonary system is usually involved in sarcoidosis.

During the past few years, a link was suspected between metals and autoimmune disease. Pathophysiologically, the exposure to some metals may produce similar symptoms to those found in the autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA) which denotes a complex of signs and symptoms that suggests a possible direct link between adjuvants, including silicone and vaccine-adjuvants, and "autoimmune"-like syndromes [23].

Today, there is insufficient evidence that exposure to metals is associated with the development of any autoimmune disease. Nevertheless, murine models of mercury-induced autoimmunity suggested the possibility that the pathogenesis of an autoim-

Figure 1. Hypothetical pathogenic pathways in sarcoidosis. Infections, autoantigens and other environmental factors may trigger an immune response in a genetically prone individual leading to granuloma formation



mune disease can be triggered by heavy metals. Stejskal [23] suggested that mercury might serve as a potent adjuvant inducing ASIA. Mercury is used for dental filling amalgam and, in the past, was used as a treatment for syphilis and for toothache in children. In people who carry dental amalgam, mercury appears to be constantly released from amalgam surfaces as elemental mercury vapors, and abrasions from mastication may cause further mercury release [24]. Nonetheless, as mentioned above, it is still not clear how mercury induces an autoimmune disorder, although a relationship has been observed between the emission of mercury from dental fillings and the onset of lichen planus, a mucosal inflammatory autoimmune disease. Furthermore, a few case reports of a possible relationship between the presence of local skin granulomas and the local injection of mercury have been published [25]. Mercury and other heavy metals may play a double role, either by creating damage as toxic agents or by producing immunological reactions. The allergic potential of these compounds has also been demonstrated by several patch tests as well as in vitro studies. Thus, it is possible that one of the contributing factors to sarcoidosis developing in our patient could be her previous mercury dental fillings.

Smoking is another crucial and controversial risk factor in the disease. Interestingly, cigarette smoke seems to reduce the incidence of sarcoidosis, as the increased number of alveolar macrophages in smokers may determine a "protective" role. Indeed, previous studies observed that alveolar macrophages could inhibit the formation of sarcoidosis granulomas by hampering T lymphocyte proliferation [26]. More recently, the immunomodulatory potential of nicotine was demonstrated: following nicotine treatment, patients with active pulmonary sarcoidosis exhibited the phenotype of asymptomatic patients. On the other hand, in another study on 518 patients with sarcoidosis followed over 5 years, Krell et al. [27] found that, especially in female patients, smoking was a risk factor for the development of extra-thoracic manifestations. According to this, it is possible that our patient's smoking habit contributed to the development of her extra-pulmonary involvement.

SARCOIDOSIS AND OTHER AUTOIMMUNE DISEASES

Autoimmune diseases can be subdivided into organ-specific, i.e., when the autoimmune damage is focused on a specific organ, and systemic, i.e., when the disease affects a large number of organs and systems. Above all, autoimmune endocrine disorders are often related to sarcoidosis; in particular, the association with autoimmune thyroid disease has long been recognized. Interestingly, the pathogenesis of many organ-specific autoimmune diseases such as type 1 diabetes, SLE, Crohn's disease, Sjögren's syndrome, psoriasis, systemic sclerosis, and even sarcoidosis may be partly explained by a feedback loop mechanism promoted by Th1 lymphocytes in the thyroid gland. In fact, Th1-mediated response enhances IFNγ and TNFα production, which in turn stimulates CXCL10 secretion and consequently the CXCR3 binding, thus starting, amplifying and perpetuating the autoimmune process. In a perspective case control study, Malli et al. [28] found that of 68 patients with sarcoidosis, 29.4% presented thyroid disorders and 16.1% had clinical autoimmune thyroid disease. Hence, the presence of thyroid autoimmunity was significantly more frequent in sarcoidosis patients compared to controls, and increased thyroid peroxidase antibodies (TPO-Ab) were widely associated with

clinical autoimmune disease in sarcoidosis. Likewise, another report described a patient affected by concomitant sarcoidosis, Sjögren's syndrome, Raynaud's phenomenon, waxy skin lesions and previous ulcerative colitis. This complex condition was therefore given the acronym "TOASSUC" (thyroiditis, other autoimmunity, Sjögren's syndrome, sarcoidosis, ulcerative colitis).

Our case is interesting because of the family history of SLE and RA. The concurrence of sarcoidosis and SLE is not common but has been described [29]. Although an overlap between RA and sarcoidosis rarely occurs, a few cases of sarcoidosis onset following treatment with a TNFα inhibitor (etanercept) have been reported. The mechanism could be related to the specific binding pathways of the drug determining the formation of non-caseating granulomas [30]. Thus, sarcoidosis can be considered a consequence of several autoimmune disorders that present a common immunopathogenetic mechanism (autoantibody production including rheumatoid factor and antinuclear antibodies); this mechanism has yet to be elucidated [31].

CONCLUSIONS

In this case report, we focused on the different pathways that cross each other, leading to the onset of sarcoidosis. Firstly, we examined the need for a predisposing genetic background, including individual susceptibility and a family history of autoimmunity. Then, environmental factors, chronic infections and chemical compounds are likely to induce the disorder more frequently in such predisposed individuals. In our case, a positive family history for autoimmunity, smoking habit and possibly external agents may have interacted, causing the formation of skin granulomas as an early feature of sarcoidosis [31]. Lastly, the presence of anti-U1RNP antibodies in sarcoidosis may represent a specific subgroup associated or not with MCTD. The identification of responsible triggering factors as well as the contributing genes will be fundamental to the management of patients with this disorder. Furthermore, avoiding exposure to potentially harmful environmental factors appears to be an important factor to avert perpetuation of the disease.

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References

1. Heinle R, Chang C. Diagnostic criteria for sarcoidosis. *Autoimmun Rev* 2014; 13: 383-7.
2. Shapira Y, Agmon-Levin N, Shoenfeld Y. Geoepidemiology of autoimmune rheumatic diseases. *Nat Rev Rheumatol* 2010; 6: 468-76.
3. Wessendorf TE, Bonella F, Costabel U. Diagnosis of sarcoidosis. *Clin Rev Allergy Immunol* 2015; 49: 54-62.
4. Smith G, Brownell I, Sanchez M, et al. Advances in the genetics of sarcoidosis. *Clin Genet* 2008; 73: 401-12.
5. Rossman MD, Thompson B, Frederick M, et al. HLA-DRB1*1101: a significant risk factor for sarcoidosis in blacks and whites. *Am J Hum Genet* 2003; 73: 720-35.
6. Wennerstrom A, Pietinalho A, Vauhkonen H, et al. HLA-DRB1 allele frequencies and C4 copy number variation in Finnish sarcoidosis patients and associations with disease prognosis. *Hum Immunol* 2012; 3: 93-100.
7. Sato H, Woodhead FA, Ahmad T, et al. Sarcoidosis HLA class II genotyping distinguishes differences of clinical phenotype across ethnic groups. *Hum Mol Genet* 2010; 9: 100-11.
8. Ozyilmaz E, Goruroglu Ozturk O, Yunsel D, et al. Could HLA-DR B1*11 allele be a clue for predicting extra-pulmonary sarcoidosis? *Sarcoid Vasc Diffuse Lung Dis* 2014; 31: 154-62.
9. Levin AM, Adrianto I, Datta I, et al. Association of HLA-DRB1 with sarcoidosis susceptibility and progression in African Americans. *Am J Respir Cell Mol Biol* 2015; 53: 206-16.
10. Bordignon M, Bargagli E, Agostini C, et al. TLR7 Gln11Leu single nucleotide polymorphism in patients with sarcoidosis. *Sarcoid Vasc Diffuse Lung Dis* 2013; 30: 157-61.
11. Riedhammer C, Weissert R. Antigen presentation, autoantigens, and immune regulation in multiple sclerosis and other autoimmune diseases. *Front Immunol* 2015; 6: 322.
12. Haggmark A, Hamsten C, Wiklundh E, et al. Proteomic profiling reveals autoimmune targets in sarcoidosis. *Am J Respir Crit Care Med* 2015; 191: 574-83.
13. Eklund KK, Niemi K, Kovanen PT. Immune functions of serum amyloid A. *Crit Rev Immunol* 2012; 32: 335-48.
14. Szodoray P, Szollosi Z, Gyimesi E, et al. Sarcoidosis in patients with mixed connective tissue disease: clinical, genetic, serological and histological observations. *Rheumatol Int* 2008; 28: 743-7.
15. Oswald-Richter KA, Beachboard DC, Seeley EH, et al. Dual analysis for mycobacteria and propionibacteria in sarcoidosis BAL. *J Clin Immunol* 2012; 32: 1129-40.
16. Eishi Y. Etiologic aspect of sarcoidosis as an allergic endogenous infection caused by Propionibacterium acnes. *Biomed Res Int* 2013; 2013: 935289.
17. Dubaniewicz A, Kampfer S, Singh M. Serum anti-mycobacterial heat shock proteins antibodies in sarcoidosis and tuberculosis. *Tuberculosis* (Edinb) 2006; 86: 60-7.
18. Song Z, Marzilli L, Greenlee BM, et al. Mycobacterial catalase-peroxidase is a tissue antigen and target of the adaptive immune response in systemic sarcoidosis. *J Exp Med* 2005; 201: 755-67.
19. Iannuzzi MC, Rybicki BA, Teirstein AS. Sarcoidosis. *N Engl J Med* 2007; 357: 2153-65.
20. Izbicki G, Chavko R, Banauch GI, et al. World Trade Center "sarcoid-like" granulomatous pulmonary disease in New York City Fire Department rescue workers. *Chest* 2007; 31: 414-23.
21. Sola R, Boj M, Hernandez-Flix S, et al. Silica in oral drugs as a possible sarcoidosis-inducing antigen. *Lancet* 2009; 373: 1943-4.
22. Swaisgood CM, Oswald-Richter K, Moeller SD, et al. Development of a sarcoidosis murine lung granuloma model using Mycobacterium superoxide dismutase A peptide. *Am J Respir Cell Mol Biol* 2011; 44: 166-74.
23. Shoenfeld Y, Agmon-Levin N. 'ASIA' – autoimmune/inflammatory syndrome induced by adjuvants. *J Autoimmun* 2011; 36: 4-8.
24. Pigatto PD, Guzzi G. Linking mercury amalgam to autoimmunity. *Trends Immunol* 2010; 31: 48-9.
25. Bradberry SM, Feldman MA, Braithwaite RA, et al. Elemental mercury-induced skin granuloma: a case report and review of the literature. *J Toxicol Clin Toxicol* 1996; 34: 209-16.
26. Rich EA, Tweardy DJ, Fujiwara H, et al. Spectrum of immunoregulatory functions and properties of human alveolar macrophages. *Am Rev Respir Dis* 1987; 136: 258-65.
27. Krell W, Bourbonnais JM, Kapoor R, et al. Effect of smoking and gender on pulmonary function and clinical features in sarcoidosis. *Lung* 2012; 190: 529-36.
28. Malli F, Bargiota A, Theodoridou K, et al. Increased primary autoimmune thyroid diseases and thyroid antibodies in sarcoidosis: evidence for an under-recognised extrathoracic involvement in sarcoidosis? *Hormones* (Athens) 2012; 11: 436-43.
29. Begum S, Li C, Wedderburn LR, et al. Concurrence of sarcoidosis and systemic lupus erythematosus in three patients. *Clin Exp Rheumatol* 2002; 20: 549-52.
30. Verschueren K, Van Essche E, Verschueren P, et al. Development of sarcoidosis in

etanercept-treated rheumatoid arthritis patients. *Clin Rheumatol* 2007; 26: 1969-71.

31. Jamilloux I, Valeyre D, Lortholary O, et al. The spectrum of opportunistic diseases complicating sarcoidosis. *Autoimmun Rev* 2015; 14: 64-74.
32. Leite MI, Jacob S, Viegas S, et al. IgG1 antibodies to acetylcholine receptors in 'seronegative' myasthenia gravis. *Brain* 2008; 131: 1940-52.
33. Hoch W, McConville J, Helms S, et al. Auto-antibodies to the receptor tyrosine kinase MuSK in patients with myasthenia gravis without acetylcholine receptor antibodies. *Nat Med* 2001; 7: 365-8.
34. Toma A, Haddouk S, Briand JP, et al. Recognition of a subregion of human proinsulin by class I-restricted T cells in type 1 diabetic patients. *Proc Natl Acad Sci USA* 2005; 102: 10581-6.
35. Peakman M, Stevens EJ, Lohmann T, et al. Naturally processed and presented epitopes of the islet cell autoantigen IA-2 eluted from HLA-DR4. *J Clin Invest* 1999; 104: 1449-57.
36. Tilz GP, Wiltgen M, Borkenstein M. On the occurrence of the diabetes-associated antigen GAD 65 in human sera. *Int Arch Allergy Immunol* 2011; 155: 167-79.
37. Alessandri C, Bartosiewicz I, Pendolino M, et al. Anti-carbamylated protein antibodies in unaffected first-degree relatives of rheumatoid arthritis patients: lack of correlation with anti-cyclic citrullinated protein antibodies and rheumatoid factor. *Clin Exp Rheumatol* 2015; 33 (6): 824-30.
38. Strollo R, Ponchel F, Malmstrom V, et al. Autoantibodies to posttranslationally modified type II collagen as potential biomarkers for rheumatoid arthritis. *Arthritis Rheum* 2013; 65: 1702-12.
39. Conti F, Ceccarelli F, Perricone C, et al. Systemic lupus erythematosus with and without Anti-dsDNA antibodies: analysis from a large monocentric cohort. *Mediators Inflamm* 2015; 2015: 328078
40. Conti F, Alessandri C, Perricone C, et al. Neurocognitive dysfunction in systemic lupus erythematosus: association with antiphospholipid antibodies, disease activity and chronic damage. *PLoS One* 2012; 7 (3): e33824.