

## SARCOIDOSIS IN IRON-STEEL INDUSTRY: MINI CASE SERIES

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**ABSTRACT.** Sarcoidosis is a disease of unknown etiology. Despite the proposed connection between the development of sarcoidosis and exposure to environmental and toxic substances, no definitive associations could be established. Also, the role of silica and silicates in the etiology of this condition is currently unknown. Heat-treatment of silica results in the generation of tridymite and cristobalite forms and iron-steel industry represents one branch of industry in which silicone element is exposed to temperatures around 2000°C. Studies reporting on the incidence of sarcoidosis in the workers of iron-steel industry are scarce in number, and workers of this industrial branch are known to be exposed to silica in the form of cristobalite, nano-particulate silicone, metal oxides, and silicates. These substances, which have respiratory toxic properties and have been reported to be associated with autoimmune conditions, may also play a role in the pathogenesis of sarcoidosis. In our clinic, sarcoidosis was diagnosed in a total of 4 individuals, who works in the iron-steel industry. Through this report involving a series of patients with sarcoidosis, we also wanted to discuss the role of crystalline silica forms and silicates in the etiology of sarcoidosis, which is also considered to be an auto-immune condition. (*Sarcoidosis Vasc Diffuse Lung Dis* 2017; 34: 365-372)

**KEY WORDS:** cristobalite, iron-steel industry, nano-particulate, sarcoidosis, silicates

### INTRODUCTION

Sarcoidosis is a presumably auto-immune disease of unknown etiology that may lead to multi-system involvement and granulomatous inflammation (1). Recent studies have focused on a multitude of triggering factors that may be associated with the development of sarcoidosis. In line with this argument, there is strong evidence suggesting that the granuloma formation results from the activation of the inflammatory cascade via the triggering effect of

environmental and occupational exposure. Also, the association between genetic propensity and certain occupational agents has been a subject of research (2).

Sarcoidosis's prevalence reported varies considerably across different countries and studies. Usually, it is estimated that 1-40 per 100,000 inhabitants are affected by sarcoidosis (3). There are no reliable data on the annual incidence of the disease. Different epidemiological studies have investigated environmental risk factors for the development of sarcoidosis. But there are no data on incidence and prevalence of this disease in the industry. A study reported that the mean annual incidence of sarcoidosis was 7 per 100,000 in Switzerland. The regional workforce in the metal industry, water supply, air transport factories and the area of potato production, artificial meadows (grassland) and bread grains were positively associated with the frequency of sarcoidosis (4).

Received: 10 February 2017

Accepted after revision: 31 July 2017

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The role of inorganic particles and foreign antigens in the development of granulomatous diseases has been a focus of interest, particularly with respect to the individual response. The 86% increase in the incidence of sarcoidosis in New York City after the terrorist attacks to the World Trade Center has been connected with the triggering role of nanoparticles in initiating inflammation (3). Furthermore, although potential role of indoors pollution due to microbiological agents has also cited, more focus has been given to the role of inorganic particles, and particularly silica, in many recent publications.

Heat-treatment of silicone is known to result in the generation of trydimite and cristobalite forms. Also, the flame-synthesis method is used for the production of silica nano-particles (4). Iron-steel industry also involves processes that results in the conversion of alpha-quartz, the most common form of silicone found in the earth, into other crystalline forms of silicone.

The association between the development of pneumoconiosis and exposure to crystalline silicone in the form of alpha-quartz has been known for centuries.

In this report, we wanted to discuss the role of crystalline forms of silicon and silicates in the etiology of sarcoidosis based on four cases of sarcoidosis who are workers in the iron-steel industry.

## METHOD

A total of 4 male patients, 2 employed in the same iron and steel factory, were referred to our occupational diseases clinic for further assessments at different time-points.

### *Case 1*

29-year old male patient working in mold construction and basket sampling unit in an iron and steel factory for the past 8 years presented to occupational physician at his workplace with complaints of back pain and sweating. A comparison between the most recent and previous radiological findings revealed abnormal findings, prompting a referral to our occupational medicine unit for further investigation and management. Physical examination was unremarkable. A high resolution computed to-

mography (HRCT) performed due to detection of bilaterally increased nodular densities in the chest x-ray showed enlarged mediastinal lymph nodes in the mediastinal window and sub-pleural nodular lesions, the greatest being 11 mm in diameter, in the parenchymal window. A mediastinoscopy was performed, since a differential diagnosis between malignancy and interstitial lung disease could not be made. The histopathological examination of the biopsy sample revealed granulomatous inflammation. Purified protein derivative (PPD) skin test was performed for potential tuberculosis and the diameter of the induration was 14 mm. Induced sputum sample were stained with Erlich-Ziehl-Neelsen method to detect acid-resistant bacilli (ARB) in direct microscopy and ARB was negative and no growth occurred in tuberculosis culture. Blood level of angiotensin-converting enzyme (ACE) was 50.4 U/L (50 U/L as the cut-off point). No calciuria was present in the urinalysis. Markers for collagen tissue disorders were negative. Fundoscopic examination of the eye did not reveal findings suggestive of uveitis or other potential eye involvement of sarcoidosis. Since a definitive association between sarcoidosis and the occupation could not be established, an "occupational disease report" could not be issued by the board of health. However, a report was issued notifying the requirement for work conditions involving no dust, smoke, metal-oxide, and silica exposure.

### *Case 2*

A 47-year old patient was referred to our unit for further investigation due to detection of increased reticulo-nodular density in his periodic chest x-ray examination. He has been working in the steel plant unit of an iron and steel factory for the past 22 years. The initial work involved mold and core model for 10 years, followed by 12 years of work in the melting unit. His main complaint was chronic cough. Physical examination was normal. However, the patient reported occasional occurrence of erythema nodosum like lesions on anterior tibial skin that resolved spontaneously. HRCT showed mediastinal and hilar lymphadenopathy in the mediastinal window, and increased acinar nodular density in the parenchymal window. PPD was performed with an induration diameter of 17 mm. Sputum ARB was negative on 3 consecutive sputum samples. The mi-

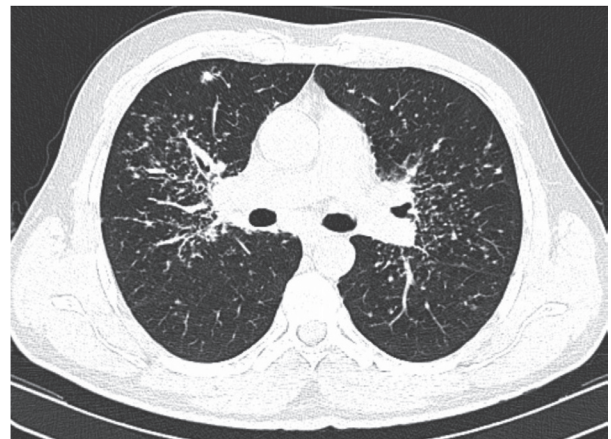
crossoscopic examination of the lavage obtained during bronchoscopy showed no bacterial or fungal growth. No findings suggestive of tuberculosis could be identified. An endobronchial ultrasound (EBUS) guided trans-bronchial nodal aspiration (TBNA) biopsy was performed. Histopathology showed granulomatous inflammation, in addition to anthracotic lymph nodes as well as granulomas consisting of epithelioid histiocytes. Serum ACE level was 13.4 U/L. No hypercalciuria was detected. Markers for collagen tissue disorders were negative. No loss of respiratory functions were present. Since bronchoalveolar lavage (BAL) sampling could not be performed prior to EBUS TBNA, a flow-cytometric examination could not be performed. A diagnosis of sarcoidosis was made based on clinical, radiological, and pathological findings. A report was issued to notify the need for work-place environment devoid of dust and smoke. Currently, the patient is under our follow-up.

### Case 3

This 31-year old male patient presented to the occupational physician at the workplace due to complaints of cough and shortness of breath. He was referred to our unit after detection of abnormalities in his radiological examination. For the past 6 years, he has been working in the rolling plant in the hot rolling mill and cold rolling mill units. He reported that the symptoms had started nearly 1 year ago, with worsening of symptoms at the workplace. He had no co-existing medical conditions. Physical examination showed burn scars on hands, face, and neck and bilateral rhonchus on auscultation. Chest x-ray revealed bilateral diffusely increased nodular densities, patchy areas of consolidation, and a prominent appearance of the hilar areas. Since HRCT findings were suggestive of interstitial lung disease, a diagnostic bronchoscopy was carried out. ARB was negative in BAL samples. No growth occurred in aerobic cultures. Blood calcium level was normal. No hypercalciuria was detected in the urine. The patient diagnosed with sarcoidosis. Because of symptomatic findings we initiated 1 mg/kg steroid to him. A marked improvement in clinical and radiological signs was obtained with steroid therapy. A health report notifying the requirement to work in dust- and smoke-free workplace was issued. Currently, the patient is being followed-up in our unit.

### Case 4

This 44-year old male patient was referred to our outpatient unit due to the detection of bilateral reticulo-nodular appearance and mediastinal widening in periodic x-ray examination. He has been working in an iron and steel factory for the past 17 years. After 3 years of work in the mold and core model construction, he spent 15 years as the master control officer of the billet and slab cutting unit of the same factory. Except for cough and shortness of breath, he had no other complaints. He reported worsening of symptoms in the work environment. Family history revealed a diagnosis of sarcoidosis in the mother and sister. Physical examination was unremarkable. Respiratory function tests were normal. HRCT showed diffusely increased acinar nodular densities in the middle lobe and lingula as well as in the peri-hilar area (Figure 1). Also, he had hilar lymphadenopathies in the mediastinal window. PPD was 0 mm. Serum ACE was 56.3 U/L. He had no calciuria. Examination of the BAL sample obtained during diagnostic bronchoscopy showed abundance of lymphocytes and a CD4/CD8 ratio of 5. An EBUS guided TBNA biopsy was performed. Histopathological examination showed hyalinized fibrous adipose tissue, anthracotic lymph nodes, silicotic nodule, and granulomatous inflammation. A diagnosis of sarcoidosis was made based on radiological, laboratory, and pathology findings. Prednisolone at a dose of 60 mg/day was started. Patient with respiratory symptoms, so we initiated steroid 60 mg/day. The patient also had silicosis. Therefore, we had to start treatment in



**Fig. 1.** Case 4: HRCT findings showed acinar dens nodular density in the middle lobe and lingula as well as in the peri-hilar area

order for the sarcoid-like radiological findings to be rapidly regressed with treatment and to be able to perform the ILO stage of findings consistent with silicosis. Steroid dose was subsequently reduced. A health report was issued notifying the need for dust-free, smoke-free working environment with the use of respiratory protective equipment. Currently the patient is under our follow-up.

Table 1 summarizes the demographic and workplace characteristics as well as the duration of exposure and symptoms. Table 2 shows the result of

tuberculin skin test, blood ACE levels, respiratory functions, and HRCT findings. BAL and pathology results are summarized in Table 3.

## DISCUSSION

Geographical clustering of sarcoidosis patients has been proposed as an indication of the role of environmental factors in addition to genetic predisposition (2, 5). The most comprehensive study ever con-

**Table 1.** The demographic characteristics, workplace history, duration of exposure, presenting symptoms, and physical examination findings of the cases

	Age, year	Work history	Most recent work unit	Exposure, years	Smoking pack/years	Complaint	Family history of sarcoidosis	Physical examination findings
<b>Case 1</b>	29	Chamber, ladle sampling, Clinker removal	Clinker removal	8	10	Back pain, sweating	None	Unremarkable
<b>Case 2</b>	47	Chamber, core, stoker in the melting unit	Stoker in the melting unit	22	15	Cough	None	Unremarkable
<b>Case 3</b>	31	Sand sieving worker in construction sector, hot/cold cutting foreman in the rolling plant	Hot/cold cutting foreman	6	15	Cough, shortness of breath	None	Burn scars in the face, hands, and feet
<b>Case 4</b>	44	Chamber, core construction, billet and slap molding, control system supervisor	Billet and slap mold	17	None	Cough, shortness of breath	Mother and sister	Unremarkable

**Table 2.** TCT, blood ACE levels, respiratory function tests, and HRCT findings results of the patients

	TCT, mm	Serum ACE level, U/L	FEV1 % predicted	FVC % predicted	DLCO % predicted	HRCT results
<b>Case 1</b>	13	50,4	78	73	Not performed	Mediastinal and hilar LAP; bronchovascular infiltrative densities, more marked in the upper lobes of both lungs; scattered areas of increased subpleural nodular density the largest being 11 mm; patchy areas of ground glass appearance
<b>Case 2</b>	17	13,5	99	104	Not performed	Mediastinal and hilar LAPs, scattered areas of increased acinar densities that cannot be distinguished from pleural retractions and vascular structures in both lungs, interstitial thickening
<b>Case 3</b>	7	Not studied	71	68	87	Mediastinal hilar LAPs, bilateral extensive acinar nodular infiltrations more marked in the anterior upper lobe of the right lung, patchy areas of densities isodense with patchy ground glass appearance, subpleural nodules
<b>Case 4</b>	0	56.3	106	104	105	Mediastinal and hilar LAPs, diffuse acinar nodular infiltrations more marked in the middle zones and peri-hilar area in both lungs peribronchovascular thickening, subpleural nodules

TCT: tuberculin skin test; ACE: angiotensin converting enzyme; U/L: units/liter; FEV1: forced expired volume in the first second; FVC: forced volume capacity; DLCO: Diffusion capacity for carbon monoxide; HRCT: high-resolution computed tomography; LAP: lymphadenopathy

**Table 3.** BAL and pathology results in four patients diagnosed with sarcoidosis

	Total cell count 10 <sup>6</sup> cells/ml	Lymphocyte, %	CD4/CD8 Ratio	Diagnostic methods	Pathological findings
<b>Case 1</b>	None	None	None	Mediastinoscopy	Granulomatous inflammatory reaction
<b>Case 2</b>	None	None	None	EBUS TBNA	Anthracotic lymph nodes, granulomas composed of epithelioid histiocytes
<b>Case 3</b>	8.8	76	8.8	BAL, TBB	Granulomatous inflammation without necrosis
<b>Case 4</b>	5	66	5	BAL, EBUS TBNA	Hyalinized fibrous connective tissue, anthracotic lymph nodes, silicotic nodules

BAL: bronchoalveolar lavage; EBUS: endobronchial ultrasound; TBB: transbronchial biopsy; TBNA: transbronchial needle aspiration; LAP; lymphadenopathy

ducted in this area, i.e. the A Case Control Etiologic Study of Sarcoidosis (ACCESS) has demonstrated a 1.5 fold increase risk of sarcoidosis in individuals involved with farming and in those exposed to fungus or pesticides, although a specific agent responsible for the disease could not be demonstrated (6).

Similarly, an association between increased sarcoidosis occurrence and occupations involving contact with lawn and garden tools, home furniture, hardware, and industrial organic dust has been reported, although no reference to the structure or content of the occupational exposure, or to specific exposures has been made. On the other hand silicates such as crystalline silica, beryllium, aluminum, and zirconium are known to trigger the formation of sarcoidosis-like granulomatous inflammation (6-10). Exposure to such agents may occur in many lines of industry including mining, casting, construction, plastic production, ceramic production, space industry, electronic industry, sandblasting, and iron casting.

The four presented cases were employed in the iron-steel industry, and to our knowledge, there are no previous reports of a series of sarcoidosis patients with such an occupational history.

During the production of steel, clinker consisting of Silicon dioxide (SiO<sub>2</sub>) is produced at oxygen oven and desulfurization phases (11, 12). Calcium oxide represents the main residue that is formed after these procedures, followed by SiO<sub>2</sub> (12). Alpha-quartz is known to be converted to tridymite at 740°C and to cristobalite at 1400°C, and during iron-steel production temperatures as high as 2000°C may be reached (4, 13, 14).

All of our cases had prior exposure to crystalline silicone, silicates, and metal oxides. During their

work at the chamber and core units, they had been exposed to alpha-quartz. The onset of symptoms coincides with the time period of employment in units involving high temperature treatments in the rolling and steel plants. This suggests that exposure to tridymite, cristobalite, and crystalline silicone nanoparticles might have played a triggering role in the development of sarcoidosis.

In experimental animal studies, silicone nanoparticles and cristobalite have shown to induce autoimmune diseases, trigger allergic reactions, and lead to the development of systemic inflammation (15, 16). Furthermore, demonstration of silica accumulation in the liver, intestines, kidneys, bone marrow, and even in the brain is also supportive of its role in systemic inflammatory conditions (17-20). Currently, there is strong evidence suggesting a connection between silicones induced pulmonary alveolar proteinosis (PAP) and autoimmune processes (3, 21-23). Sarcoidosis is also considered an auto-immune condition. Thus we may assume that exposure to silica may trigger a systemic inflammation depending on the host response (1, 23). Also there have been previous reports in which inorganic dusts have been implicated in the development of sarcoidosis in individuals with genetic propensity (24-27). One of our patients had a family history of sarcoidosis, i.e. in the mother and sister. However, these case series is the first describing the occurrence of sarcoidosis in a group of individuals with a history of exposure to different forms of crystalline silicone during iron-steel production.

ACCESS study found a negative association between sarcoidosis and metal industry. On the other hand, a study examining specific toxic exposures in the metal industry could probably have allowed iden-

tification of sarcoidosis patients due to silica and silicate exposure, such as in our patients.

A case of sarcoidosis in relation to exposure to cat litter has also been previously reported (27). Cat litter consists of bentonite silicates formed by volcanic ash. It is the most commonly utilized industrial silicate in Turkey (28, 29). Although it has a higher content of montmorillonite silicate, also it is made up of cristobalite (30), which is also used in the iron-steel industry (28). Therefore, detailed examination of the exposure to a specific agent may suggest a role for cristobalite and other silicates.

Cristobalite and quartz comprises approximately 70% and 1-2% of the diatomite earth, respectively. In a previous study, workers exposed to diatomite earth have been found to have a 7.1 to 28-fold increased risk of sarcoidosis as compared to zero risk in individuals without such exposure (31), again supportive of our observation that cristobalite may have a role in the pathogenesis of sarcoidosis.

Examination of a sarcoidosis patient with a history of working in the tire production has revealed exposure to talc, i.e. magnesium silicate (32). Procedures involving heat treatment are also utilized during tire production. In this case, rather than magnesium, the toxic effect after heat treatment induced by  $\text{SiO}_2$  in its structure may be analyzed.

Identification of sarcoidosis in a patient with an occupational history of jeans sanding as well as the observed increase in the incidence of sarcoidosis among firefighters and emergency medical personnel after September 11 World Trade Center attacks suggest that silica may have a significant etiological role in this disease (33-35).

Our literature search has revealed lower report rates of silicosis in workers of iron-steel industry, as compared to other industrial fields such as mining, quartz mill, construction, or road construction. This may be due to the excessive exposure to non-alpha-quartz forms, silica nanoparticles, and other silicates, and their higher pathogenicity and toxicity and lower fibrinogenic potential in the steel production (36, 37).

One of our patients had silicotic nodules, with a final diagnosis of silico-sarcoidosis. Similar to this case, another patient who had worked in casting industry was found to have silicotic nodules (38). Co-occurrence of silicosis and sarcoidosis in these patients is probably due to the excessive alpha-quartz

exposure during chamber and core production. The remaining patients in our study did not have silicotic nodules, although this may be due to inadequate sampling or site of biopsy.

The diagnosis of silicosis is based on the history of occupational history as well as radiological findings, and its classification is based on the duration of exposure, rather than the pathological findings (39). Since biopsy is associated with augmented fibrosis, its use for diagnostic purposes is discouraged, although it may be recommended for the differential diagnosis of conditions other than pneumoconiosis (3, 40, 41). In contrast, the diagnosis of sarcoidosis is based on pathological findings. There may be coincidental and undiagnosed cases of sarcoidosis among those diagnosed with pneumoconiosis, who showed spontaneous remission. Presence of patients with silicosarcoidosis is supportive of our hypothesis. Moreover, common pathogenesis of silicosis and sarcoidosis are mentioned at the present time.

Our case series is suggestive of a potential role in the development of sarcoidosis of different forms of silicates and crystalline silica released in workplaces involving heat treatment of metals or minerals.

The major limitation of our case series is the absence of mineralogical analysis in the tissue and workplace environment. Despite these limitations, this case report involving a discussion on the potential health effects of different forms of silica represents the first of its kind in terms of identification of patients with silicosis and sarcoidosis who were workers in the iron-steel industry.

## CONCLUSION

Rather than emphasizing the obscurity surrounding the causes of sarcoidosis, it may be more appropriate to state that adequate occupational history is generally not obtained from these patients. In the etiology of sarcoidosis occurring in workers of iron-steel industry, the potential role of cristobalite, silicone nanoparticles, and other mineral silicones should be taken into consideration.

In patients with an established diagnosis, a detailed history on the exposure to silicone and silicates should be obtained and if causality is suspected, it should certainly be reported to the relevant authorities in accordance with medical-legal responsibilities

ties. If a connection with occupational exposure is determined, it should be borne in mind that the real treatment and prevention are based on the implementation of strict personal and workplace hygiene regulations, and on the isolation of the patients from the triggering environment.

## RECOMMENDATIONS

In order to better delineate this connection, further studies involving mineralogical analysis of different forms of crystalline silicone released during heat treatment and exploring the role of crystalline silicone forms and silicates in animal models and case-control studies would be appropriate.

## ACKNOWLEDGEMENT

The authors thanks to Prof. Recep Akdur for editing manuscript.

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