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# Occupational or Environmental Sarcoidosis: Enigmatic Diagnosis with many Parents to the Same Syndrome

*Sarcoidosis ocupacional o ambiental: diagnóstico enigmático con muchos progenitores para un mismo síndrome*

Rey, Darío R.[1]

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**Correspondence**
Darío R. Rey. E-mail: dario-raul.rey@gmail.com

## ABSTRACT

The possibility that drugs or monoclonal antibodies used in the treatment of different diseases can cause a sarcoidosis-like syndrome has been known for more than 20 years. Certain lines of evidence have suggested that certain workplaces are associated with the risk of sarcoidosis.

In sarcoidosis, different exposures may be related to visceral involvement. The condition has more than one cause and brings about phenomena that are different from the disease or phenotype.

The one condition that most closely resembles it out of all occupational lung diseases is berylliosis.

When the cause is of occupational origin, its recognition is essential to allow effective treatment by removing the affected worker from the exposure and to establish an intervention aimed at primary prevention through sections specialized in industrial hygiene and security.

Therefore, in view of the aforesaid, sarcoidosis should be considered a syndrome with numerous probable etiological factors, to which both the phenotype and individual susceptibility to a specific noxious agent must be associated.

Based on all that has been stated, cases are periodically published in which the clinical and histological picture of epithelioid non-caseating granuloma found in biopsies is linked to a particular environmental and/or occupational risk.

**Key words:** Sarcoidosis; Environmental Hazards; Occupational Risks

## RESUMEN

Es conocida desde hace más de 20 años, la posibilidad que fármacos o anticuerpos monoclonales utilizados en el tratamiento de diferentes enfermedades, pueden ocasionar la aparición de un síndrome símil Sarcoidosis.

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[1] Director of the Pulmonology Specialization Career, Faculty of Medicine, UBA (University of Buenos Aires)

Ciertas líneas de evidencia han sugerido que determinados lugares de trabajo están asociados con el riesgo de Sarcoidosis

En Sarcoidosis, diferentes exposiciones pueden estar relacionadas con otros compromisos viscerales. La afección presenta más de una causa y provocar fenómenos disímiles de la enfermedad o fenotipo

De las enfermedades ocupacionales de pulmón, la que más se asemeja es la Beriliosis.

Cuando la causa es de origen laboral, su reconocimiento es primordial para admitir un tratamiento eficaz mediante el retiro del trabajador afectado de la exposición y para establecer una intervención dirigida a la prevención primaria mediante las secciones especializadas en seguridad e higiene industrial.

Por lo tanto y por lo expuesto, hay que considerar que la Sarcoidosis es un síndrome con cuantiosos factores etiológicos probables, a lo que hay que asociar tanto el fenotipo como la susceptibilidad individual ante una noxa determinada.

En razón de lo manifestado, ello hace que en forma periódica se publiquen casos en los que la clínica y el cuadro histológico de granuloma epitelioide no caseoso hallado en biopsias, se vincule a un determinado riesgo ambiental y/o laboral.

**Palabras clave:** Sarcoidosis; Riesgos ambientales; Riesgos laborales

Sarcoidosis is a condition of unknown etiology that could be defined as *"characterized by the presence in all affected organs and tissues of non-caseating epithelioid granulomas that evolve either to resolution or conversion into hyaline cartilage."* In general, it presents various non-specific symptoms, and is often confined to the skin, lungs, or lymph nodes, being able to affect any organ in the body.[1]

For more than 20 years now, it has been known that drugs or monoclonal antibodies used in the treatment of different diseases can cause the appearance of a sarcoidosis-like syndrome. Although its presence is exceptional, it should be considered when prescribing said agents, and the literature is being constantly updated with these examples.[2-5]

In the last 10 years, the fact that there is no single cause for this syndrome has been unquestionably accepted. Possibly any antigen in a susceptible individual can trigger the characteristic granulomatous inflammation, to which individual genetics and exposure in the work environment add as risks.

While in many cases it is impossible to find a causal factor, more and more examples are being published that sarcoidosis can occur in work environments where there is exposure to both unusual antigens and inorganic triggering factors, thus eliciting an exaggerated immune reaction. It is likely that this syndrome has more than one originating cause.

The correct pathogenesis of sarcoidosis is unknown. Sharing the concepts from Judson:[6]

A. It is unknown whether these environmental and/or occupational exposures are actually causing sarcoidosis, making the immune system more prone to its development.
B. Producing exacerbation of sub-clinical cases of sarcoidosis.
C. Causing a granulomatous condition other than sarcoidosis.

This includes possible exposure to infectious agents such as mycobacteria, Cutibacterium acnes (a Gram-positive skin commensal bacterium), as well as non-infectious environmental exposures, including inhalation of bioaerosols, combustion products, and metallic particles.

## SARCOIDOSIS-LIKE DISEASE AND CHRONIC BERYLLIOSIS: THE PARADIGM

Beryllium (Be) is a mineral subjected to a processing procedure into alloys, oxides, metal, and composite materials. Its main applications are found in telecommunications, computers, aerospace industry, automotive electronics, and defense atomic equipment or weapons.[7]

The inhalation of large amounts of Be causes a chemical pneumonia known as acute berylliosis. Quoting Middleton, in 1943, the first observations of this entity were reported in the United States in workers extracting Be oxide. In their report, the physicians who reported these cases were not convinced about the role of the mineral, but by 1945, they had identified 170 cases of acute Be poisoning, which they associated with skin ulcers and pneumonitis, including 5 deaths.

Advances in safety and hygiene led to this clinical form of berylliosis declining in the United States, with 53 cases reported in 1947, 28 the following year, and only 1 case found in 1949.

In 1950, a committee of American experts recommended safe levels of Be in the workplace, ceasing to be a problem in this nation.[8]

The chronic form of berylliosis is possibly the one that most closely mimics sarcoidosis of unknown cause. Thus, on clinical suspicion of this condition, data of exposure to Be are collected in order to rule out or confirm the occupational etiology.

To gather possible observations of **chronic berylliosis**, a case registry was developed, establishing 6 criteria for its recognition and inclusion: four regarding the existence of a chronic pulmonary process and two concerning exposures to the material, in addition to obtaining high levels of Be in biopsied tissues.

Evidence of chronic lung disease was based on clinical symptoms, chest X-rays, lung function tests, or pathology. In contrast to sarcoidosis, it occasionally presents with joint symptoms. It has a long latency period: an average of 5-15 years (1-30 years). The medical record is variable; some cases remain stable, others experience recurrence and remission, and in some cases, the disease has a progressive nature.

*Workers at risk of exposure to Be* were those involved in its extraction, production, and maintenance; in facilities producing metallic Be and alloys or powder from the mineral; in smelting factories; and in plants processing Be powder. Hazardous tasks included grinding or rubbing materials containing Be, welding or melting such materials; laser cutting, dental laboratory operations, heat treatment of alloys, and chemical grinding of Be.[9]

The first description of chronic berylliosis as an occupational disease was provided by Hardy and Tabershaw, who published a series of 16 cases occurring in a fluorescent tube factory. Henneberger et al estimate that around 134,000 workers in the United States are currently exposed to Be. The number of individuals exposed at some point is presumably much higher.

As the immunological mechanisms of chronic berylliosis have become clearer, tests of hypersensitivity to Be have played an important role in the diagnosis of the occupational disease. In the 1970s, lymphocyte proliferation tests (LPTs) sensitized in vitro to beryllium sulfate were developed. These tests were used to confirm exposure to the mineral. In the 1980s, studies with LPTs were extended to cells obtained by bronchoalveolar lavage (BAL).[10-14]

Newman et al screened the personnel at a Be machining facility twice a year, and also the new employees who were evaluated within 3 months of their date of employment.

Among 235 employees examined between 1995 and 1997, 6.4% had shown abnormal LPT results, indicating sensitization to Be, and 9 individuals had chronic berylliosis. Within 3 months of initial exposure, 4 out of 15 new hires were similarly diagnosed.

Among the 187 individuals who participated in biannual evaluations, 7 had developed sensitization or chronic beryllium disease, increasing the overall rate to 9.4% (22 out of 235).

The LPTs should be used in monitoring beryllium disease to detect new cases or individuals sensitized and affected by the condition, which can occur within 50 days following initial exposure in the workplace.[15]

In an excellent review of the topic, this author considers the test to have undergone sufficient field experience and practice, providing the following conclusions:

1. The LPT identifies *sensitization to Be and chronic berylliosis* before any other clinical test.
2. Chronic cases identified by the test are clinically significant.
3. Individuals identified by the LPT without clinical evidence will continue evolving and require steroid treatment to prevent disease progression.
4. The test can be used to correct misdiagnoses and optimize clinical diagnostic accuracy.
5. It can be used to detect exposed workers because it is specific, sensitive, and has high posi-

tive and negative predictive values for chronic berylliosis.
6. In the investigated workforce, the LPT has identified beryllium sensitization and chronic berylliosis not manifested by conventional screening measures.
7. Worker populations delineated by the test can help clarify the role of the inflammation in the genesis of occupational lung disease and the genetics of exposure.[16]

These experiments confirmed not only the capacity of the Be to stimulate a cell-mediated hypersensitivity reaction but also the deposit of Be-sensitive CD4+ T lymphocytes in the area of disease activity.

As discussed in the work of Oliver and Zarnke, using in vitro LPTs to detect sensitization to inorganic antigens, which can be Be, metals, or silica, can be highly useful in revealing differences in immunoreactivity in cases of occupational sarcoidosis compared to controls, suggesting that LPTs may be useful in diagnosing work-related diseases.[17]

The chest computed tomography (CT) allows for substantial findings in the mediastinum and lung parenchyma, playing an important role in the diagnosis, evaluation, and monitoring of patients with chronic berylliosis. Its importance lies in accurately locating and assessing the extent of lesions.[18,19]

Despite its prevalence, the health effects related to the mineral may be unknown, either because workers are unaware of the danger posed by the exposure or because doctors do not recognize the occupational disease. Cases of berylliosis have been published and reported worldwide in many nations.[20-23]

To summarize:
1. Chronic berylliosis is the occupational condition most similar to sarcoidosis.
2. When sarcoidosis is suspected, the differential diagnosis should always include occupational disease, which can be then excluded through targeted questioning and the LPT.

## SARCOIDOSIS-LIKE DISEASE RELATED TO THE WORLD TRADE CENTER (WTC) (09.11.2001)

Some time after the massive exposure to dust and construction debris related to the tragic attack of September 11, 2001, annual radiological check-ups in New York City Firefighters (FDNY) showed an increase in intrathoracic adenopathies, with subsequent histological samples confirming a higher incidence of sarcoidosis. This increase was greater than that observed in cohorts of individuals that did not belong to the WTC (with similar sex, age, and race). The average annual incidence rose from 15/100,000 in the 15 years prior to the tragic event to 85/100,000 in 2002, stabilizing at 25/100,000 after that year.[24,25]

Unlike cases of sarcoidosis prior to September 11 within the FDNY cohort, those with newly diagnosed syndrome after that event were more likely to have new symptoms of asthma and bronchial hyperreactivity. Hena et al extensively determined the clinical course of sarcoidosis following September 11 in the FDNY cohort both at the time of diagnosis and in 2015. All had pulmonary involvement at the time of diagnosis, with most having disease-related radiological findings in stages I and II. Nearly 50% experienced resolution of intrathoracic involvement in the 8 to 10 years following. Lung function values were within normal limits for most, with few changes over time and not corresponding to radiographic disease patterns. Extrapulmonary involvement periodically increased from diagnosis to follow-up, with cardiac and osteoarticular involvement being the most prevalent. It is unclear whether the increased prevalence of cardiac injury was solely due to WTC exposure or if it was due to improved monitoring. An argument in favor of surveillance standards is that all individuals in the cohort underwent screening tests for cardiac sarcoidosis, including magnetic resonance imaging (MRI). This study was much more sensitive than ECG and/or echocardiograms, which failed to detect half of the patients with cardiovascular involvement. Considering the clinical severity of this localization and the fact that it can be fatal, their findings need complex cardiac tests that can save lives in asymptomatic patients, especially those with public safety responsibilities.

In a case-control publication based on the degree of exposure at the WTC, considering age, sex, and race, Cleven et al identified 17 unique HLA (human leukocyte antigen) and non-HLA genetic variants associated with chromosomes 1 and 6 in FDNY individuals with sarcoidosis following September 11. Although the prototype used was small for the sarcoidosis cohort of the FDNY to as-

sociate with extrathoracic sarcoidosis phenotypes, they found several biological variations related to extrapulmonary localization. More extensive genetic studies of other WTC cohorts are required to better understand these genetic relationships.[26-28)]

## SARCOIDOSIS-LIKE DISEASE RELATED TO NANOPARTICLES (NPS)

Nanomaterials represent a new field of research and measure 1-100 nanometers (one-billionth of a meter). In medicine, they are used for the diagnosis and treatment of diseases, as well as to fight antibiotic-resistant infections and to transport other substances to certain parts of the body so that drugs reach target cells in greater quantities and reduce the drug's side effects on other organs.

Sometimes it is not easy to differentiate the toxicity of the drug from that caused by NPs. They are used to improve the treatments and comfort of patients suffering from breast cancer, ovarian cancer, multiple sclerosis, hypercholesterolemia, asthma, and kidney diseases.

They are not harmless. They have exposed their ability to cause illness to workers in factories that use this technology. Known risks include severe lung damage, while cytological studies show genetic damage to DNA, release of free radicals, granulomas, pulmonary fibrosis, and increased macrophage function.

The work of Song et al urges that as NPs become widespread in industrial production, attention should be paid to pulmonary and/or pleural diseases of occupational suspicion. In accordance with prevention, measures should be taken to protect workers and provide medical surveillance to their possible health consequences, given that, until now, it is known that NPs remain indestructible in the pleuropulmonary parenchyma.[29, 30]

## SARCOIDOSIS-LIKE DISEASE MISCELLANEOUS

The inhalation of metallic dust or fumes can cause a disease that mimics sarcoidosis. Metals that have antigenic properties and cause the formation of granulomas include barium, aluminum, Be, gold, cobalt, copper, zirconium, titanium, and rare earths.

Rare earths are minerals composed of certain elements characterized by their electrical and magnetic properties.

They are widely used in the industry (manufacture of turbines, electric and hybrid cars, etc.) and in the production of computers, laser devices, televisions, etc.

Occupational anamnesis and environmental exposure are essential for linking these metals to a supposedly idiopathic disease.

In 2006, Laney et al investigated sarcoidosis among office workers in a water damaged building. During the investigation, they found a high index of asthma and bronchial hyperreactivity. The search for sarcoidosis and asthma was conducted through clinical examination, functional tests, and a health questionnaire. Prevalence rates were compared with the Building Assessment and Survey Evaluation (BASE) study and the National Health and Nutrition Examination Survey (NHANES), and 6 cases of sarcoidosis were identified. The prevalence of sarcoidosis in construction is high (2,206 cases per 100,000 inhabitants) compared to the estimated prevalence in the US (40 cases/100,000).[31]

Gorham et al investigated the tendency of the incidence of sarcoidosis in a cohort of Navy personnel and assessed its potential relationship with the work.

They determined incidence rates in hospital admissions for Caucasian and African American male personnel on active duty between 1975-2001. This included potential exposure to several substances, including non-skid coatings used on ship decks that can be aerosolized upon removal. Particles with silicates, titanium, and aluminum were identified in non-skid samples. Improvements were made in personal protective equipment and other instructions were given to prevent or limit respiratory exposures.

The results revealed overall annual incidence rates of hospitalized sarcoidosis of 24.9 per 100,000 for African Americans and 3.5 for Caucasians ($p < 0.0001$). Occupational associations were present in both races. The 23 cases among African Americans on ships and the 12 aviation mechanics had twice the expected incidence compared to all African Americans, while the 15 cases among Caucasians had a similar incidence rate.

Their conclusions were:

1. A significant decrease in the incidence of sarcoidosis among African Americans in the Navy.

2. Possibly, occupational relationships suggest that a dust- or moisture-related lung disease was misclassified as sarcoidosis, or that sarcoidosis had an unrecorded occupational component.[32]

There is a very interesting article published by Schouten et al about the incidence of sarcoidosis in rural areas, determining whether in such an environment, the consumption of unpasteurized milk or untreated water increased the risk of developing it. For this purpose, they investigated individuals aged 18 to 60 years diagnosed with pulmonary sarcoidosis between 1999 and 2005, alongside controls with another chronic respiratory disease. Evaluated by a specialist, they completed a questionnaire about rural life, the use of untreated water, and unpasteurized milk from birth until diagnosis, calculating exposures at birth, at 5 years old, and until diagnosis.

Statistical analysis on 615 cases and 1334 controls revealed that consuming unpasteurized milk seemed closely associated with sarcoidosis. It was considered to be strongly related to raw milk at birth, and that risk persists for those who drank unpasteurized milk until the age of 5 and for those who continued for more than 16 years until diagnosis. When the reference integrated the asthma subgroup, the association with sarcoidosis was stronger, but there was also an association with other chronic respiratory diseases. Those whose family used unpasteurized milk at birth and until the age of 5 increased the risk of sarcoidosis.[33]

Epidemiological studies have suggested the etiology of silica and metals in the pathogenesis of sarcoidosis, so Beijer et al investigated the exposure to these elements through an occupational history related to the type of work exposure in 256 patients with sarcoidosis and 73 controls. Using the LPT, they determined the immunoreactivity to aluminum, zirconium, silica, and Be in both groups.

In sarcoidosis, 32.4% had occupational exposure to metals or silica, and in the control group, it was 24.7% ($p = 0.21$). A higher percentage of sarcoidosis showed immunoreactivity to metals or silica compared to the control group (21.2% and 0%, respectively).

Immunoreactivity to silica and metals was only found in patients with sarcoidosis ($p = 0.039$). When searching for causal agents in patients with sarcoidosis, not only Be but also zirconium, aluminum, and silica deserve to be investigated.[34]

The relationship between aluminum (Al) dust and pulmonary fibrosis/emphysema in workers of manufacturing and processing industries is well established. This publication presents the first case similar to sarcoidosis that is associated with metal inhalation, identifying it through microanalysis of the biopsy, a comprehensive occupational history, and experimental research. Due to the unusual nature of the case, individual idiosyncrasy may play a role in the development of non-caseous granulomas after exposure to Al.[35]

Similar cases are periodically reported. De Vuyst et al reported the case of a chemical professional who worked without protection for 8 years in an atmosphere containing Al dust. Lung biopsies showed epithelioid granulomas similar to sarcoidosis, identifying Al particles by mineralogical analysis. The Kveim reaction was negative for sarcoidosis, but the LPT was positive for Al. Ceasing exposure resulted in the remission of alveolitis, but radiology and lung function remained unchanged.[36]

The publication by Redline refers to a sarcoidosis-like case in a worker who, over the last 13 years, had been involved in supplying aluminum for furnaces for a casting company and exposed to dust and metal vapors released in the production of aluminum and zinc alloys.[37]

Also, the case of Kawano-Dourado et al with symptoms similar to those of sarcoidosis in a 22-year-old non-smoker, with normal radiology one year ago, who worked in tunnel excavation and whose lymph node biopsy revealed the typical pattern of non-caseous granulomas.[38, 39]

Work in dentistry is not harmless, either. Dentists' and dental technicians' activities are exposed to aerosols of inorganic substances and biological material. The instruments used in surgical procedures produce intense heat and generate fumes with biological material (even partially calcined). The splashes and aerosols include microparticles, handpieces operated at high speed, ultrasonic brushes, polishing of restorations, and the use of drills in metal prostheses. During the polishing and whitening of natural teeth, sodium bicarbonate and tricalcium phosphate compounds are sprayed onto the dental surface, releasing part of the enamel and disseminating into the environment, thus exposing patients and operators to the risk of aspiration.

In 2010, Checchi published an observation of sarcoidosis-like disease in a dentist who manipulated dental cleaning material without protection for 25 years, with identification of tricalcium phosphate particles inside granulomas obtained by biopsy.[39]

The halogen lamp is an incandescent bulb with a tungsten filament in an inert gas and a small amount of halogen, which consists of chlorine, iodine, bromine, or fluorine bonded to a metal, improving its performance and lifespan.

Ronsmans et al published two cases of sarcoidosis-like disease in workers at a halogen lamp manufacturing facility who had worked for 14 years in that place. The workplace was dusty, due to the heating and cutting of lamps (which produce dust with silica fused with cristobalite), and also due to the cleaning of machinery. Birefringent particles were observed in pulmonary or mediastinal lymph node biopsies. By isolating the workers from aggressive work, both improved clinically, functionally, and radiologically.[40]

Therefore, in view of the aforesaid, sarcoidosis should be considered a syndrome with numerous probable etiological factors, to which both phenotype and individual susceptibility to a specific noxious agent must be associated. Based on all that has been stated, cases are periodically published in which the clinical and histological picture of epithelioid non-caseating granuloma found in biopsies is linked to a particular environmental and/or occupational risk.

## TREATMENT

There is extensive literature on the subject, with the role of steroids in the favorable evolution of the syndrome being known for many decades. The most significant general guidelines have been summarized by the Task Force of the European Respiratory Society (ERS) in their 2021 document. They provide recommendations regarding therapeutic behaviors, namely:

1. *Patients who are not treated but have significant pulmonary sarcoidosis*, who are at a higher risk of future mortality or permanent disability due to the condition, are strongly recommended (*with low-quality evidence*) to receive treatment based on glucocorticoids to improve and/or preserve FVC (forced vital capacity) and quality of life (QoL).
2. *For patients with manifest pulmonary sarcoidosis who are considered to be at higher risk of mortality or permanent disability due to the condition, or who have been treated with steroids and have either stable or progressive disease and/or unacceptable side effects from glucocorticoids*, the ERS Task Force recommends adding methotrexate to improve and/or preserve both FVC and QoL *(potentially, with very limited evidence quality)*.
3. A similar potential recommendation is made, *upon equal sarcoidosis evolution, regardless of whether the sarcoidosis is occupational or not, and if steroids have not responded to other immunosuppressive agents*, to use infliximab. This is a chimeric murine-human IgG1 monoclonal antibody produced in murine hybridoma cells using recombinant DNA technology, with the purpose of preserving the QoL and FVC.

## CONCLUSION

Although the etiology remains unknown, significant progress has been made since Jonathan Hutchinson's description in 1877 of "papillary psoriasis" as a dermatological disease, to its current recognition as a multiorgan and complex condition. The prevailing conjecture is that various unknown, imperceptibly degradable antigens, possibly of environmental, occupational, or infectious origin, could trigger an exaggerated immune reaction in genetically predisposed hosts. It is suggested that when faced with a clinical presentation suggestive of sarcoidosis, a thorough inquiry should be made regarding occupational exposure to any of the agents described in this manuscript to establish a connection.

Therefore, despite numerous investigations using most current diagnostic methods, no unquestionable cause of sarcoidosis has been demonstrated. Various reasons could explain the difficulty in determining an etiology in such a context. In the first place, it is unlikely to constitute a single syndrome with a single cause. Additionally, the causative agent could be an unidentified bacterium, and the pathogenesis of sarcoidosis may be due not only to unknown antigens but also to possibly genetic idiosyncrasy. [40,41]

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