Cutaneous recurrence of long term pulmonary sarcoidosis - literature review and case report

Julia Bargiel¹, Justyna Cabaj¹, Izabela Chmielewska², Marta Adamczyk-Korbel³, Anna Grzywa -Celińska²

¹ Studenckie Koło Naukowe przy Klinice Pneumonologii, Onkologii i Alergologii, Uniwersytet Medyczny w Lublinie
² Klinika Pneumonologii, Onkologii i Alergologii, Uniwersytet Medyczny w Lublinie
³ Samodzielny Publiczny Szpital Kliniczny nr 4 w Lublinie

ABSTRACT

Sarcoidosis is a systemic granulomatous disease, the exact etiology of which is unknown. This paper presents a case of a patient with a long course of pulmonary sarcoidosis with exacerbation of the disease in the form of skin lesions.

A 50-year-old female patient was admitted to the Department of Tuberculosis and Lung Diseases, Medical University of Lublin, because of cervical lymphadenopathy. Based on the histopathological examination, she was diagnosed with sarcoidosis. The patient reported constant fatigue, throat tightness and difficulty swallowing, as well as decreased exercise tolerance. Computed tomography studies revealed small nodular changes in both lungs and mediastinal lymphadenopathy. The patient was actively monitored. The results of
spirometry tests improved spontaneously and remained at a satisfactory level for years. After 15 years of follow-up, the patient reported skin lesions that are constantly progressing. Examination of the cut from the skin lesion confirmed skin sarcoidosis. This case report highlights the varied course of sarcoidosis, which, as a multi-system disease, may show various manifestations. In clinical practice, therefore, one should consider the possibility of disease progression and transmission to multiple organs. It is important that the patient is under constant observation and that new lesions undergo differential diagnosis and histopathological examination.

Key words: sarcoidosis, lymphadenopathy, skin lesions.

INTRODUCTION

Sarcoidosis is a multi-system disease, the main characteristic of which is the formation of non-keratinizing granulomas within altered tissues. The most common locations are the lungs and lymph nodes, however, numerous manifestations of the disease are repeatedly observed in the heart, skin, liver, kidneys, eyes, nervous and osteoarticular systems.

According to data from 2020, the prevalence of sarcoidosis ranges from 64/100,000 in Scandinavia, 20/100,000 in Great Britain to lows in Greece - 7/100,000 and Japan - 1/100,000. In the Polish population, these numbers are approximately 10/100,000 people per year [1]. Among the epidemiological issues, the significant relationship between the incidence of sarcoidosis and ethnicity deserves special attention. African Americans have been reported to develop the disease three times more often than Caucasians. Gender and age are also important - the risk group includes mainly women in the 20-40 age group [1, 2].

For years, researchers have been trying to find the causes of sarcoidosis, but the etiology is still unknown. However, there are several hypotheses that show a high probability of the impact of certain factors on the development of the disease. The most convincing claims include the existence of a specific sarcoid factor that negatively affects the immune system in genetically predisposed individuals, leading to the generation of an inflammatory response with a predominance of Th1 lymphocytes. Staying with the topic of genetics, it should be additionally emphasized that the presence of some alleles, i.e. HLA-DR3, HLA-
DR5, HLA-DR8, HLA-DR9, HLA-DR12, HLA-DR14, HLA-DR15, HLA-DR17, HLA-DPB1, HLA-DQB1 influences the increased susceptibility to the occurrence of sarcoidosis [1].

Among the factors that may be related to the induction of sarcoidosis, infectious factors should also be mentioned. The relationship between HHV-8, HCV, CMV, EBV, retrovirus and Coxsackie B virus infections with the sarcoidosis development has not been proven. However, the influence of bacterial factors such as Propionibacterium, Mycobacterium, Chlamydia pneumoniae, Borrelia burgdorferi, Pneumocystis jirovecii and leprosy bacilli should also be taken into account. Among the mentioned species, Mycobacterium tuberculosis is most likely influential - specific sequences for mycobacterial proteins were detected in tissue samples of patients with sarcoidosis

Exposure to dust and gases may also be important, moreover, there are reports connecting the adverse effects of silica and beryllium with sarcoidosis, hence dental technicians, jewelers, people working in the arms industry and fluorescent lamps factories may be at risk. The release of toxins under the influence of high temperatures accompanying fires and other disasters should also be considered - firefighters and people participating in rescue operations on a large scale are therefore at risk of developing sarcoidosis [1, 2, 3].

The pathogenesis of sarcoidosis is mainly based on the immune reaction in response to specific antigens. Some of them are not degraded by cells of the immune system, which creates a feedback loop, as a result of which antigen presenting cells, such as dendritic cells or alveolar macrophages, secrete high amounts of TNF-alpha, II-12, II-15, II -18, MIP-1 and MPC-1. Presentation of antigens to CD4+ T lymphocytes initiates the formation of granulomas consisting of macrophages, epithelial cells and giant cells, which are a hallmark of sarcoidosis. Activated CD4 + cells can differentiate into two distinct lines of T helper cells - Th1 or Th2, the proportion of which is critical in the degradation or maintenance of granulomas. Alveolar macrophages activated in a Th2-rich environment stimulate the proliferation of fibroblasts and collagen, causing fibrotic changes in tissues and organs. Moreover, regulatory T lymphocytes play an important role, by secreting TNF-beta, they contribute to fibrosis and the organization of granulomas [1, 3-5].

However, due to, on the one hand, often latent course of the disease, and on the other hand, its multi-system nature, the diagnostic process can be full of difficulties, and the final diagnosis is sometimes delayed. In over 50% of cases, patients do not report any symptoms, maintaining a very good quality of life for years. The symptoms of disease at the time of onset are often unspecified, patients report systemic ailments that cannot be assigned to any specific disease entity. The symptoms include fatigue, weakness, apathy, weight loss,
joint pain and fever. With time, a cough and a feeling of dyspnea can appear, which prompts patients and doctors to expand the pulmonary diagnostics.

The diagnostic process involves a physical examination, but chest computed tomography (CT) is an examination that most often leads the initiation of diagnostics in sarcoidosis. Most often, sarcoidosis in the CT image presents as bilateral lymphadenopathy affecting the mediastinal and hilar nodes - 90% of cases [1,5]. In more advanced stages of the disease, interstitial lung disease may develop. A valuable test confirming the final diagnosis is the histopathological evaluation of samples taken from non-cervical granulomas present in the affected organs [1,6].

Apart from the pulmonary sarcoidosis, the second most common is the cutaneous form, accounting for about 25% of all cases. Due to the complexity of dermatological manifestations, there is a high risk of omitting sarcoidosis in the differential diagnosis of lesions. The wide range of symptoms includes erythema nodosum, hypo- and hyperpigmentation areas, subcutaneous nodules and keloids can be seen in sarcoidosis. A special form of cutaneous sarcoidosis is called *pernio lupus*, also known as Besnier-Tenneson syndrome, with blue-red-purple smooth shiny nodules and plaques on the head and neck, especially on the ears, lips and cheeks [5,7]. Much rarer, but associated with serious complications, is the involvement of the heart, that can be conformed by heart muscle magnetic resonance imaging (MRI). The granulomatous infiltration of the heart muscle mainly causes conduction disturbances, an increased risk of atrioventricular block, arrhythmias and cardiomyopathies, are also observed [5, 8-9]. In 5-10% of patients with sarcoidosis, changes in the nervous system are noted, including cranial neuropathy, involvement of the meninges and cranial nerves, in particular nerves II, VII and VIII. Rarely, the disease affects the parenchyma of the brain, spinal cord or peripheral neuropathy. It is worth remembering that the eye may also be at risk - the most common symptoms are anterior uveitis, acute pain, visual disturbances and photophobia [5,10].

Our clinical experience indicates that recurrences of pulmonary sarcoidosis in the form of involvement of another organ are rare. Therefore, this paper presents a case of a patient with a long course of pulmonary sarcoidosis with exacerbation of the disease in the form of skin lesions.
A CASE REPORT

A 50-year-old patient was admitted to a Pulmonology Department due to enlargement of the submandibular and cervical lymph nodes, fatigue and low exercise tolerance. Chest X-ray showed no infiltrative changes in the lung parenchyma. A histopathological examination of the removed cervical lymph nodes showed the typical picture of sarcoidosis such as inflammatory granulomas containing macrophages and lymphocytes. During subsequent (twice a year) visits to the clinic, the patient complained of constant mild fatigue, throat tightness and difficulty swallowing, as well as reduced exercise tolerance. However results of pulmonary function tests improved during that period of observation, and remained at a satisfactory level for years (Table 1, Scheme 1).

<table>
<thead>
<tr>
<th>date</th>
<th>FEV1 l/s (% of normal value)</th>
<th>FVC l/s (% of normal value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2006</td>
<td>57%</td>
<td>65%</td>
</tr>
<tr>
<td>2007</td>
<td>85%</td>
<td>89%</td>
</tr>
<tr>
<td>2011</td>
<td>96%</td>
<td>120%</td>
</tr>
<tr>
<td>2014</td>
<td>102%</td>
<td>123%</td>
</tr>
<tr>
<td>2015</td>
<td>105%</td>
<td>136%</td>
</tr>
<tr>
<td>2017</td>
<td>109%</td>
<td>136%</td>
</tr>
<tr>
<td>2019</td>
<td>100%</td>
<td>115%</td>
</tr>
<tr>
<td>2020</td>
<td>88%</td>
<td>101%</td>
</tr>
</tbody>
</table>

Table 1 Results of spirometry tests, i.e. forced expiratory volume (FEV1) and forced vital capacity (FVC) at 8 checkpoints over a 15-years period
No systemic treatment was implemented. The patient periodically underwent control CT examinations, which showed no changes. In 2006, single, small nodular thickenings of the dorsal pleura and the pleura of the interlobular gaps in both lungs were found. Five years later, the study showed single nodules in both lungs and small nodules resembling a budding tree [Fig. 1, 2].

Fig. 1 Changes in the course of thoracic sarcoidosis
In 2015, there was an intensification of changes in the upper field of the left lung. Another study in the same year showed splenomegaly as well as enlargement of numerous retroperitoneal and mesenteric lymph nodes, partly in bundles. In order to exclude possible neoplastic changes, two lung specimens and bronchial epithelium fragments were collected for histo-pathological examination but no neoplastic cells were found.

After 15 years of follow-up, the patient reported skin lesions that are constantly progressing. Initially, in 2020, there were small subcutaneous nodules up to 1 cm in diameter on the left upper limb and trunk. Examination of the skin sample confirmed cutaneous sarcoidosis. In the following months, an oozing lesion of 1 cm in diameter was observed in the area of the left brow bone and neck [Fig. 3], evidence of the cutaneous form of sarcoidosis. The patient started taking tacrolimus and clobetasol in the form of an ointment. The therapy resulted with significant improvement.
However, a follow-up CT scan of the chest showed unexpected progression of pulmonary sarcoidosis. The CT image showed an enlargement of the atelectasis-infiltrative area at the level of the tracheal bifurcation, with a visible mass effect and "bulging" of the oblique interlobular fissure. At the same time, the concern was caused by the infiltration causing obstruction of segmental bronchi, and there was a suspicion of neoplastic transformation. A histopathological examination ruled out the neoplasm, the lesion has the character of non-keratinizing granulation tissue typical of sarcoidosis. It was decided to start systemic treatment with the use of steroids at a decreasing dose form 0.5mg /kg. The applied treatment resulted in a significant improvement of the patient’s clinical condition. Currently, the patient is under constant observation and control in the pulmonary clinic (Scheme 1).
DISCUSSION

As shown by epidemiological data and observations from daily medical practice, the main localization of sarcoidosis is in the lungs. The above case report highlights the unpredictability of the disease. The patient came to our Department due to enlargement of the lymph nodes, which was the only visible symptom. After the histopathological evaluation and diagnosis in the form of sarcoidosis, the patient remained under the care of the Clinic. The presented case shows many difficulties which can be associated with diagnostics and treatment of sarcoidosis. An individual approach is advisable, taking into account several important diagnostic aspects. Firstly, the results of imaging tests (CT of the lungs, MRI, PET), laboratory tests (blood counts, liver tests) and functional tests (spirometry) should be carefully analyzed. At the same time, one should bear in mind the patient's subjective feelings, which include shortness of breath, increased cough, pain from various organs, fatigue, and lack of appetite. Taking into account all the criteria allows appropriate selection of therapeutic treatment in patients with sarcoidosis. Unfortunately, these aspects often do not correlate with each other, which may make it difficult to make a therapeutic decision. Therefore, it is often required to target three interrelated pathways: treatment of the effects of granulomatous inflammation, control of co-morbidities, and mitigation of immunosuppressive toxicity [11].

Research shows that more than half of sarcoidosis patients do not have any disease manifestations and changes in the lungs spontaneously regress. However, it is significant to treat each patient individually based on psychophysical condition, deterioration of pulmonary function tests or progressing changes in the CT scans. It should be known that patients with high risk of progression also should be treated [1, 12].

Generally, in the case of exacerbation of disease symptoms, there is a three-step path of therapeutic management (Scheme 2).
Treatment of sarcoidosis should begin with the use of corticosteroids. Numerous studies have shown that corticosteroids inhibit the production of cytokines that contribute to the formation of persistent granuloma, including TNF-α and IFN-γ [11,13-14]. Therefore, a reduction in disease manifestations and an improvement in the quality of life of patients treated with corticosteroids were observed. Unfortunately, there is little research into the long-term use of corticosteroids, which makes it difficult to find the perfect dose. Patients are usually treated with the dose of 20-40 mg prednisone daily. Sarcoidosis involving only the lung parenchyma responds well to low-dose treatment. Infiltrative changes regression was observed during the treatment with 15 mg of prednisone daily. In the case of severe symptoms involving nervous, cardiovascular and ocular systems usually higher doses are proposed. However, patients should be carefully monitored, as long-term use of high doses of prednisone is associated with increased toxicity and the risk of life-threatening conditions [11,15].

Second-line drugs such as methotrexate, azathioprine, leflunomide and mycophenolate mofetil (MMF) are used to prevent adverse side effects of corticosteroid use in severe sarcoidosis. Methotrexate is the most frequently chosen therapeutic option - it has a known and favorable safety profile and a proven benefit in the treatment of autoimmune diseases. Due to its anti-inflammatory effect, it reduces the production of cytokines by T lymphocytes, improves respiratory capacity and alleviates the symptoms of the disease. The dosage of methotrexate ranges from 7.5-15 mg per week with a simultaneous reduction in the use of corticosteroids [11, 16-17]. Similar properties, both in terms of action and side effects, are exhibited by leflunomide - a dihydroorotase inhibitor, administered in combination with
methotrexate or as monotherapy. The second line of treatment also includes azathioprine and MMF, which is highly effective in sarcoidosis involving the nervous system. Moreover, MMF has few side effects, thus being the safest and mildest option among other immunosuppressants [11, 18].

Antimalarial drugs as hydroxychloroquine, which, thanks to the ability to interfere with antigen presentation, prevents the activation of lymphocytes T, and also inhibits toll-like receptor signaling, reducing the secretion of pro-inflammatory cytokines. This drug has proved to be very effective in the treatment of cutaneous sarcoidosis [11, 19-20].

Among patients with severe forms of sarcoidosis or lack of response to the above-mentioned drugs, the introduction of third-line therapy, including biological treatment, can be considered. The best known and showing the greatest therapeutic value is infliximab - a chimeric monoclonal antibody directed against TNF-alpha receptors. The drug significantly increases the level of predicted FVC and reduces the amount of pro-inflammatory cytokines, resulting in improved reticular opacity in control chest X-rays. The recommended dosage is 3-5 mg/kg body weight with maintenance therapy every 4-8 weeks after the initial load [11,21]. Numerous randomized studies also confirm the effectiveness of adalimumab, especially in the case of infliximab resistance and in the treatment of ocular and skin sarcoidosis [11, 22-23].

The formation of granulomas in the course of inflammation is not unique to sarcoidosis. There are a number of other diseases with a similar symptom, so proper differential diagnosis remains a key issue (Scheme 3).
Particular similarity in the histopathological picture is shown, among others, by chronic berylliosis, neoplasms and immunodeficiencies with the formation of granulomas. Also noteworthy are tuberculosis, cat scratch disease, toxoplasmosis and fungal infection, which include rare coccidiomycosis and histoplasmosis, as well as genetic disorders such as Blau's syndrome. There have also been suggestions that some drugs, notably recombinant alpha and beta interferons, may also induce granulomatous inflammation [3,24-25].

**CONCLUSIONS**

Sarcoidosis is a disease that presents a major challenge to the medical team. The etiology brings with it many controversial issues, and remains unknown to this day. Due to the non-specific clinical features, it is important to take into account the possible impact of this disease on the patient's malaise during routine diagnostic tests. Moreover, it is important that even the correct diagnosis of sarcoidosis may entail some difficulties in further patient care. This disease can remain asymptomatic for years, thus reducing the vigilance of doctors. The above case confirms the risk and unpredictability of sarcoidosis, which, as a multi-system disease, can spread to virtually any organ. Hence, it is important that patients remain under constant medical observation in order to quickly intervene in the event of worsening disease symptoms.

**REFERENCES**


4. Celada LJ, Kropski JA, Herazo-May JD, et al. PD-1 up-regulation on CD4+ T cells promotes pulmonary fibrosis through STAT3-mediated IL-17A and TGF-β1 production. Sci


**WYKAZ MATERIAŁÓW DODATKOWYCH**

**Table 1:** Results of spirometry tests, i.e. forced expiratory volume (FEV1) and forced vital capacity (FVC) at 8 checkpoints over a 15-years period

**Scheme 1:** Results of spirometric tests conducted in 2006-2020

**Scheme 2:** Therapeutic options

**Scheme 3:** Differential diagnosis of sarcoidosis

**Figure 1:** Changes in the course of thoracic sarcoidosis

**Figure 2:** Small nodular changes in the lung parenchyma in the course of sarcoidosis

**Figure 3:** Skin changes in the course of sarcoidosis - 2020

**Autorskie Wkłady**


Wszyscy autorzy przeczytali i zgodzili się na opublikowaną wersję manuskryptu.

**Finansowanie**

Badania te nie otrzymały żadnego zewnętrznego finansowania.
Oświadczenie instytucjonalnej komisji rewizyjnej

Nie dotyczy.

Oświadczenie o świadomej zgodzie

Nie dotyczy.

Oświadczenie o dostępności danych

W tym badaniu przeanalizowano publicznie dostępne zbiory danych. Dane te można znaleźć tutaj w bazie danych Pubmed, odnośniki do artykułów znajdują się w bibliografii.

Konflikt interesów

Autorzy oświadczają, że badanie zostało przeprowadzone przy braku jakichkolwiek powiązań handlowych lub finansowych, które mogłyby być interpretowane jako potencjalny konflikt interesów.