

# Small Fiber Neuropathy in Pulmonary Sarcoidosis and Tuberculosis: Clinical and Histological Correlates

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## Research

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# Abstract

Sarcoidosis (SC) is the granulomatous disease of an unknown origin, where the differential diagnosis with tuberculosis (TB) is challenging and vital for patients' prognosis. The common neurological complication in SC is a small fiber neuropathy (SFN), that is considered to be the result of the chronic inflammation, and remains significantly understudied. There is no reliable data, whether such complication is observed in TB patients, where the systemic inflammation is also described.

**Aim:** To identify the clinical and histological correlates of the small fiber neuropathy in sarcoidosis and tuberculosis patients.

**Materials and methods.** A study was performed in 2018 – 2019 years and included 71 patients with pulmonary sarcoidosis (n=25), pulmonary tuberculosis (n=21), and healthy subjects (n=25). For the clinical verification of the SFN, the "Small fiber neuropathy screening list" (SFN-SL) was used. A punch biopsy of the skin was performed followed by the enzyme immunoassay analysis with PGP 9.5 antibodies.

**Results of the study:** Up to 60% of sarcoidosis patients and 19% tuberculosis patients report the presence of at least one complaint, which may be associated with SFN. The most frequent complaints included dysfunctions of the cardiovascular, musculoskeletal system and gastrointestinal tract. A negative, statistically significant correlation between the intraepidermal nerve fiber density (IEND) and SFN-SL score was revealed in both groups (Spearman coefficient,  $r = -0.3508$ ,  $p = 0.0102$ , and  $r = -0.7382$ ,  $p = 0.0064$ , respectively). Wherein, the density of small nerve fibers in the patients with pulmonary sarcoidosis was lower, compared to the patients with tuberculosis (Mann-Whitney test,  $p = 0.0047$ ).

**Conclusion:** In patients with pulmonary sarcoidosis, small fiber neuropathy may develop as a result of systemic immune-mediated inflammation. The most common symptoms of this complication were dysautonomia and mild sensory dysfunction. Wherein, in tuberculosis patients clinical and histological symptoms of the small fiber neuropathy were subsequently less prominent, which may represent the difference between the autoimmune and bacterial inflammation. The validated questionnaires and histologic verification of the diagnosis help to establish the severity of neuropathy of small fibers, to determine the prognosis, to plan the treatment strategy, and also may allude the possibility for the additional criteria of differential diagnosis between two diseases.

## Introduction

In patients with sarcoidosis, the development of systemic inflammation and internal organ dysfunction are observed, which significantly reduces the quality of life and worsens the prognosis of the patients. One of the most common complication is considered to be a small fiber neuropathy (SFN), that remains significantly understudied (1-4).

The prevalence of sarcoidosis varies throughout the world. In Japan there is 1 case per 100,000 people, while in Scandinavian countries the prevalence of sarcoidosis is as much as 63 cases per 100,000 people, In Russian Federation sarcoidosis is described with the prevalence from 22 to 47 cases per 100,000 people, depending on the region (12-15). The prevalence of SFN may also vary because it presents not only with neuropathic pains and paresthesias, but also with various symptoms of autonomic dysfunction, which may not be recognized as a neurologic complication (16-20).

The development of SFN is considered to be the result of a cytokine-mediated inflammation, which is typical for various autoimmune diseases, including sarcoidosis (5-8). Small nerve fiber damage is also observed in systemic lupus erythematosus, Sjogren's syndrome, and fibromyalgia (9, 10). Considering the significant role of the genetic predisposition and the possible provocative role of exogenous triggers in the development of this complication, SFN in patients with sarcoidosis can be considered as a part of the autoimmune/inflammatory syndrome induced by adjuvants (ASIA) (11). Several cases of the proven SFN were also observed in patients, suffering from the bacterial inflammation, e.g., Lyme disease and leprosy (1-4). To our best knowledge, there is no studies on the detecting the reduction of the small nerve fibers in patients with tuberculosis, though this data may contribute to the better understanding of the pathogenesis of different types of inflammation and also allude the new marker of the differential diagnosis between tuberculosis and sarcoidosis.

Currently, there are no generally accepted criteria for the diagnosis of SFN. The presence of a small nerve fibers dysfunction in a patient usually is based mainly on clinical criteria, such as neurological examination and validated scales (for example, small fiber neuropathy screening list) (19, 24-26). In addition, electroneuromyography can be performed mainly to exclude damage to large nerve fibers. The "gold standard" for diagnostics is immunofluorescence or immunohistochemistry of skin biopsy with the calculation of the density of intraepidermal nerve fibers. This technique requires special training and equipment, and is significantly time consuming (27-33). Preliminary clinical diagnosis of SFN in patients with sarcoidosis is important due to the low awareness of healthcare practitioners about this complication and the need for a quick assessment of neuropathy signs for the further skin biopsy performance.

## Aim Of The Study

To identify the clinical and histological patterns and correlates of the small fiber neuropathy in lung sarcoidosis and lung tuberculosis patients for differential diagnostic.

## Materials And Methods

A prospective comparative study was performed in 2018 – 2019 years at St. Petersburg Research Institute of Phthisiopulmonology and St. Petersburg City Public Health Institution "City Multi-disciplinary Hospital No. 2". The study was approved by the independent ethics committee of the St. Petersburg Research Institute of Phthisiopulmonology (extract from protocol No. 46.1 of 04/20/2018). All study participants signed an informed consent.

The study entailed 119 patients with lung sarcoidosis and lung tuberculosis, and healthy subjects. Among them were 42 men and 56 women, average age was  $38.4 \pm 7.2$  years. The first group consisted of patients with lung sarcoidosis ( $n = 25$ , average age  $33.4 \pm 8.5$  years), the second group - patients with verified lung tuberculosis before initiating specific therapy ( $n = 21$ , average age  $36.6 \pm 9.3$  years), the third group included healthy subjects ( $n = 25$ , average age  $43.2 \pm 11.7$  years). There were no statistically significant differences in gender and age among the patient groups.

The inclusion criteria were age from 18 to 65 years and signing informed consent to participate in the study. The patients from the group 1 were also diagnosed with sarcoidosis, stage I-II, for group 2 - focal and disseminated lung tuberculosis in the pre-treatment period.

Exclusion criteria were: A hormonal therapy, the presence of Löfgren's syndrome and a chronic course of the disease (for patients with sarcoidosis), the presence of other infectious diseases (HIV, hepatitis C), the history of cancer and their treatment using chemotherapy, the presence of other diseases (diabetes, hypothyroidism, renal failure, vitamin deficiency or overdose), medications (metronidazole, nitrofurantoin, linezolid, flecainide, statins), as well as the medical history of autoimmune diseases.

According to the design of the study, patients with sarcoidosis and pulmonary tuberculosis underwent a standard examination using X-ray, morphological, bacteriological and molecular genetic methods. A neurological examination with an assessment of the superficial and deep pain sensitivity, muscle strength and muscle-tonic reflexes was performed. For clinical verification of the SFN, the validated questionnaire for the detection of small fiber neuropathy was used (Small fiber neuropathy screening list, SFN-SL, (19)). The questionnaire consists of 2 parts and 21 questions, from 0 to 4 points each, evaluating both the frequency of development of symptoms and their intensity. A moderate likelihood of neuropathy is established when the diagnostic threshold is reached at 22 points, high - at 48 points. With scores less than 11, sensitivity is 100%, specificity is 31.0%. With scores of more than 48 - sensitivity - 19.0%, specificity - 100%.

In 13 patients with lung sarcoidosis and 10 patients with lung tuberculosis, a punch biopsy of the skin was performed (10 cm proximal to the external malleolus) followed by the fixation of the specimen in Zamboni solution and the performance of enzyme immunoassay with primary PGP 9.5 antibodies (Abcam) and secondary AlexaFluor goat-anti rabbit antibodies 488 (Abcam). The results were compared with the normal values obtained in the worldwide normative reference study [23].

Statistical analysis was performed using the Statistica 8.0 software package. The distribution of patients into groups was carried out in accordance with the presence of verified diagnoses of lung sarcoidosis, lung tuberculosis or in the absence of verified somatic diseases (for healthy subjects).

All data collected during the study were analyzed using methods of descriptive statistics. The data with the normal distribution are presented in the form of the "mean  $\pm$  standard deviation" formula. Data that were not normally distributed are presented in the form of the "median (interquartile range 25 - 75 quartiles)", where the confidence interval was also calculated. Normality testing was performed using the Shapiro-Wilk test.

All data were analyzed using methods of parametric and nonparametric statistics, Chi-square test and statistical comparison methods for two (Mann-Whitney U-test) and three (Kruskal-Wallis test) groups were performed, correlations were carried out using the Spearman coefficient.

Differences or association rates were considered statistically significant at a  $p < 0.05$ .

## Results Of The Study

The average score of the SFN screening list scale (SFN-SL) in patients with sarcoidosis was 2.0 (0.0; 7.0), with tuberculosis - 0 (0; 0), and in healthy volunteers - 0 (0; 0) points (Table 1).

Statistically significant differences were found in the results of patients with sarcoidosis and tuberculosis ( $p = 0.0012$ , the Mann-Whitney U-test), in patients with sarcoidosis and healthy subjects ( $p < 0.0001$ ), as well as in patients with tuberculosis and healthy subjects ( $p = 0.03$ ). Thus, in the first group, a higher average SFN-SL

score was observed than in the second group, while the results of the 1 and 2 groups exceeded those of healthy individuals.

The main clinical symptoms of the SFN were: pain, changes in body temperature, impaired motility of the gastrointestinal tract and urinary system, heart palpitations (Table 2).

In patients with sarcoidosis, the most frequent clinical symptoms include impaired cardiovascular regulation (arrhythmias, orthostatic hypotension), pain in the chest or in the extremities, and blurred vision. It is important to note that in 76% of patients with sarcoidosis, clinical symptoms had a severity of no more than 1 point on the SFN-SL scale and, in most cases, did not bother patients or lead to a decrease in the quality of life. Among patients with tuberculosis, in general, fewer clinical manifestations were noted, the main of which were dysfunction of the gastrointestinal tract, muscle cramps and chest pain (Table 3).

Twenty three biopsy specimens have been obtained in patients with sarcoidosis and tuberculosis, where the intraepidermal density (IEND) of small nerve fibers was calculated (Fig. 1, 2).

Of the 23 biopsies, 13 were obtained in patients with sarcoidosis, 10 - in patients with tuberculosis (Table 4). The calculations of intraepidermal density of the small fibers was performed in accordance with the values from the worldwide normative reference study [23].

Thus, in all examined patients, the number of small nerve fibers was within normal limits, but below average values. There is a tendency to a higher density of small nerve fibers in patients with tuberculosis compared with sarcoidosis (Mann-Whitney test,  $p = 0.0047$ ). A negative, statistically significant correlation was revealed between IEND results and SFN-SL score in patients with sarcoidosis (Spearman's nonparametric rank correlation coefficient,  $r = -0.3508$ ,  $p = 0.0102$ ).

A negative, statistically significant correlation between IEND results and SFN-SL score was observed in patients with tuberculosis (Spearman's nonparametric rank correlation coefficient,  $r = -0.7382$ ,  $p = 0.0064$ ).

Thus, a decrease in the density of small nerve fibers in patients with sarcoidosis was noted, compared with the results of patients with tuberculosis (Mann-Whitney test,  $p = 0.0047$ ). A negative, statistically significant correlation between the IEND and SFN-SL score was described in both groups (Spearman coefficient,  $r = -0.3508$ ,  $p = 0.0102$ , and  $r = -0.7382$ ,  $p = 0.0064$ ).

Table 1

The results of the "Small Fiber Neuropathy Screening list" (SFN-SL) testing in patients with pulmonary sarcoidosis, pulmonary tuberculosis and healthy volunteers

Group	% (n/N)	SFN-SL scale points, median (IQR)	CI 95%
Sarcoidosis (n=25)	60.0* 15/25	2.0 (0.0;7.0)	1.836-2.748
Tuberculosis (n=21)	19.1, 4/21	0 (0;0)	0.00-0.00
Healthy volunteers (n=25)	8.0 2/25	0 (0;0)	0.00-0.00

Table 2

Clinical symptoms of small fiber neuropathy in patients with pulmonary sarcoidosis, pulmonary tuberculosis and healthy volunteers

	Sarcoidosis, (n=25), n (%)	CI 95%	Tuberculosis, (n=21), n (%)	CI 95%	p <sup>1</sup>	Healthy volunteers, (n=25), n (%)	CI 95%	p <sup>2</sup>
Cardiovascular disorders	9 (36.0)	34.5-38.0	0	0	<b>0.005</b>	0	0	<b>0.005</b>
Gastrointestinal disorders	3 (12.0)	11.8-12.3	2 (9.5%)	8.7-9.9	0.837	1 (0.04)	0.8-1.9	0.084
Urinary disorders	0	0	1 (4.8%)	4.1-5.2	0.930	0	0	-
Musculoskeletal disorders	4 (16.0)	15.5-16.7	2 (9.5%)	9.0-10.1	0.834	1 (0.04)	0.7-1.8	<b>0.020</b>
Skin and mucous membranes disorders	7 (28.0)	27.6-29.0	0	0	0.261	0	0	-
Ophthalmologic disorders	5 (20.0)	19.4-20.9	0	0	0.091	0	0	<b>0.005</b>
<b>Note:</b> p <sup>1</sup> is the difference between the results of groups 1 and 2, the Chi-square test with Yates correction. p <sup>2</sup> - the difference between the results of groups 1 and 3, Chi-square criterion with Yates correction.								

Table 3

Clinical manifestations of small fiber neuropathy in patients with sarcoidosis, tuberculosis and healthy individuals

Clinical manifestation of SFN	Sarcoidosis, (n=25), n (%)				Tuberculosis, (n=21), n (%)				Healthy volunteers, (n=25), n (%)			
	points				Points				points			
	1	2	3	4	1	2	3	4	1	2	3	4
Cardiovascular disorders	4 (16.0)	2 (8.0)	3 (12.0)	0	0	0	0	0	0	0	0	0
Gastrointestinal disorders	2 (8.0)	0	1 (4.0)	0	1 (4.8)	1 (4.8)	0	0	0	1 (0.08)	0	0
Urinary disorders	0	0	0	0	1 (4.8)	0	0	0	0	0	0	0
Muscular spasms	2 (8.0)	2 (8.0)	0	0	2 (9.5)	0	0	0	1 (0.08)	0	0	0
Pain syndrome	3 (12.0)	1 (4.0)	0	2 (8.0)	2 (9.5)	0	0	0	0	0	0	0
Temperature dysfunction	1 (4.0)	0	0	1 (4.0)	0	0	0	0	0	0	0	0
Skin discoloration	3 (12.0)	0	0	1 (4.0)	0	0	0	0	0	0	0	0
Paresthesias	1 (4.0)	0	1 (4.0)	0	0	0	0	0	0	0	0	0
Blurred vision	2 (8.0)	2 (8.0)	0	1 (4.0)	0	0	0	0	0	0	0	0
Dry mucous membranes, change in skin moisture	1 (4.0)	0	0	0	0	0	0	0	0	0	0	0
<b>Results</b>	<b>19 (76.0)</b>	<b>7 (28.0)</b>	<b>5 (20.0)</b>	<b>5 (20.0)</b>	<b>6 (28.6)</b>	<b>1 (4.8)</b>	<b>0</b>	<b>0</b>	<b>1 (1.4)</b>	<b>1 (0.08)</b>	<b>0</b>	<b>0</b>
<b>CI 95%</b>	<b>75.6- 77.4</b>	<b>27.6- 29.0</b>	<b>19.5- 21.1</b>	<b>18.3- 20.8</b>	<b>26.5- 29.3</b>	<b>4.3- 5.2</b>	<b>0</b>	<b>0</b>	<b>0.9- 1.9</b>	<b>0.9- 1.9</b>	<b>0</b>	<b>0</b>

## Discussion

In our study, neurological disorders were described in 60% of patients with sarcoidosis and 19.1% of patients with tuberculosis. Small fiber neuropathy can manifest with a wide range of symptoms, including autonomic and sensory dysfunction. The most common clinical manifestations observed in our study in patients with sarcoidosis were impaired cardiovascular regulation (36% of cases), e.g. the development of cardiac

arrhythmias and orthostatic hypotension. In 32% of cases, patients noted pain in the chest or limbs, which often accompanied with allodynia, a subjective perception of tactile touch as pain. In some cases, this can result in sleep disturbances or restless legs syndrome, arising from the discomfort sensations of bed linen touching the skin. Another symptom that is often noted by patients with sarcoidosis is blurred vision, described in 20% of cases. A physician needs to clarify whether visual impairments are transient or permanent in nature, for the differential diagnosis of ophthalmic pathology. In the neuropathy of small fibers, blurred vision is transient, arising while overworking or physical exertion. It is considered to be associated with the immune-mediated inflammation of the optic tracts. Less typical for patients with sarcoidosis are disorders of the gastrointestinal tract. In 12% of the cases, patients complained of impaired intestinal motility with the development of both diarrhea and constipation, which occurred simultaneously with the onset of sarcoidosis. This also includes subjective complaints of swallowing dysfunction, which is associated both with impaired muscle innervation and with the progression of dryness of the mouth. In the tuberculosis group much less clinical symptoms were observed. The most common symptoms were the dysregulation of the gastrointestinal (9.5%) and urinal tract motility (4.8%) and arthralgia (9.5%). No cardiovascular complaints were observed in this group and the intensity of the symptoms were much less prominent, compared to the sarcoidosis group.

While a negative, statistically significant correlation between the IEND and SFN-SL score was described in both groups (Spearman coefficient,  $r = -0.3508$ ,  $p = 0.0102$ , and  $r = -0.7382$ ,  $p = 0.0064$ ), a decrease in the density of small nerve fibers in patients with pulmonary sarcoidosis was more prominent, compared with the results of patients with pulmonary tuberculosis (Mann-Whitney test,  $p = 0.0047$ ).

Thus, neuropathy of small fibers seems to be a widespread pathology with the development of multiple organ dysfunction. Given the low awareness of both medical specialists and patients about the development of this complication and the difficulties in diagnostic, further study of this issue is required. In patients with pulmonary sarcoidosis, small fiber neuropathy may develop as a result of systemic immune-mediated inflammation. Wherein, in tuberculosis patients clinical and histological symptoms of the small fiber neuropathy were subsequently less prominent, which may represent the difference between the autoimmune and bacterial inflammation and will be useful in differential diagnostic with both diseases. The validated questionnaires and histologic verification of the diagnosis help to establish the severity of neuropathy of small fibers, to determine the prognosis and to plan the strategy for treatment, and also may allude the possibility for the additional criteria of differential diagnosis between two diseases.

## Declarations

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The authors declare that there is no potential conflict of interest regarding the publication of this article.

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Natalia Basantsova, Anna Malkova and Valeria Shapkina. Patient selection and supervision were performed by Yulia Zinchenko, Maria Pavlova, Ekatherina Belyaeva. General supervision was carried out by

Anna Starshinova, Pyotr Yablonskiy. General research concept, guidance and article review was performed by Yehuda Shoenfeld. All authors read and approved the final manuscript.

## Ethics approval

All human studies have been approved by the independent ethics committee of the St. Petersburg Research Institute of Phthysiopulmonology (extract from protocol No. 46.1 of 04/20/2018) and have been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

## Consent to participate

*All study participants signed an informed consent.*

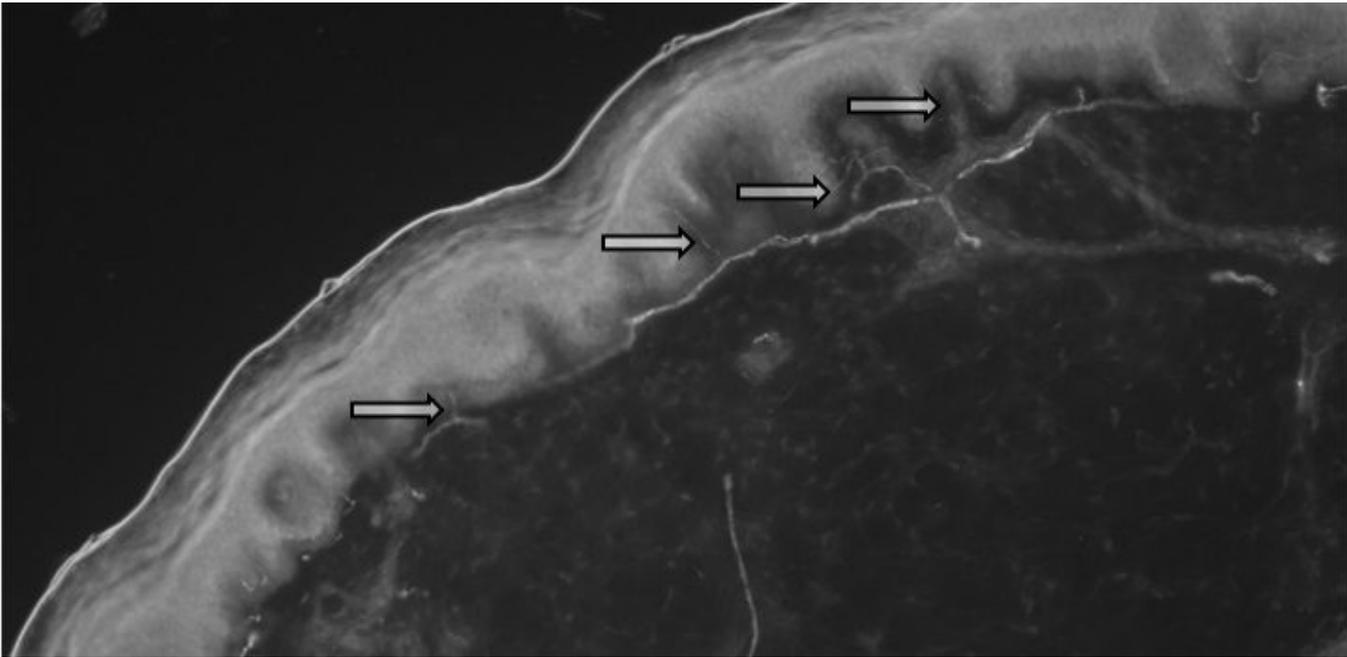
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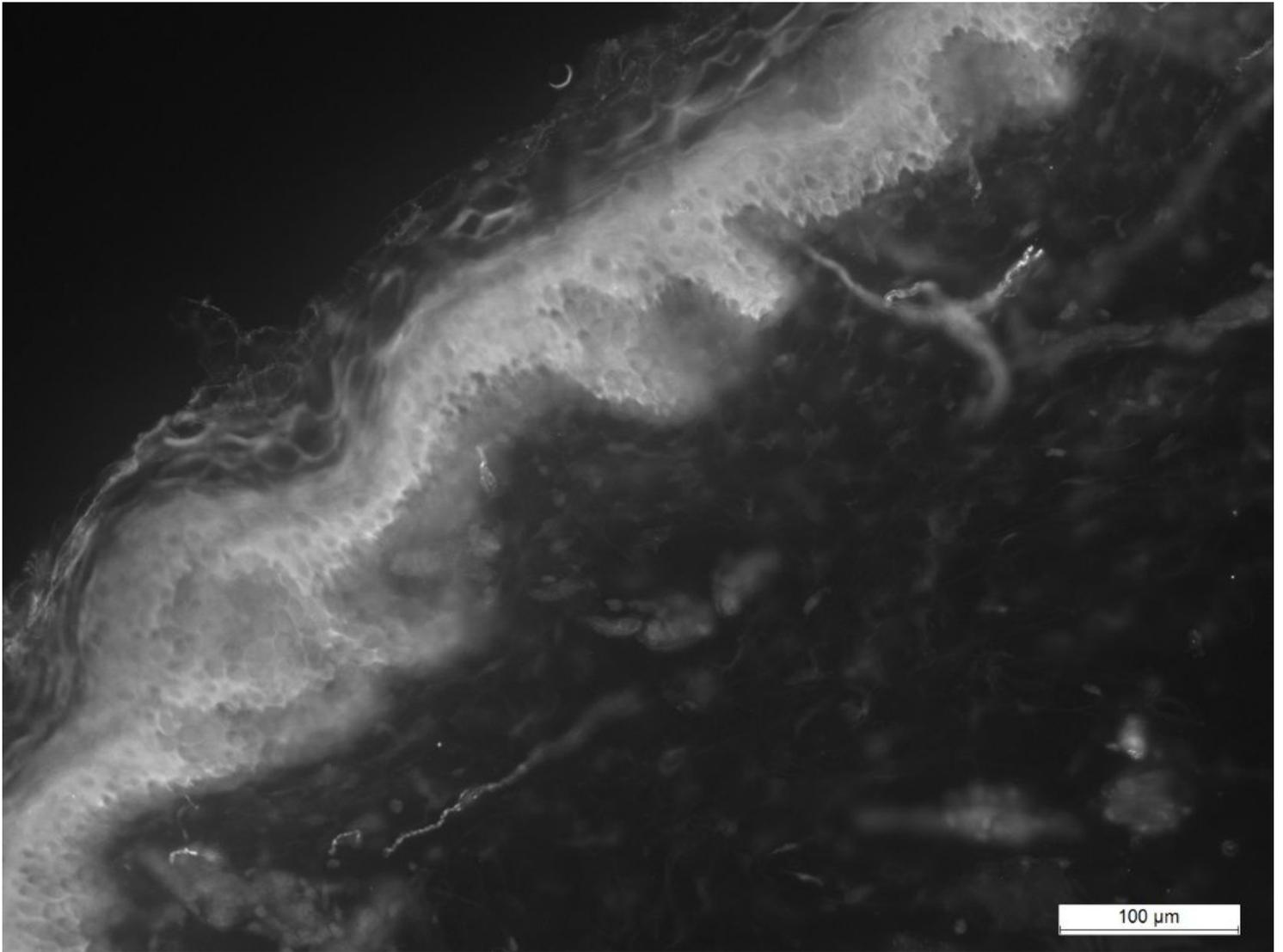
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## Figures



**Figure 1**

Enzyme immunoassay analysis of skin biopsy in a patient with sarcoidosis (male, 34 years old). Small fibers stained with PGP antibody 9.5. Arrows indicate the small nerve fibers, penetrating in the epidermis.



**Figure 2**

Enzyme immunoassay analysis of skin biopsy in a patient with sarcoidosis (male, 45 years old). Small fibers stained with PGP antibody 9.5. The significantly lower density of the intraepidermal small nerve fibers is shown, compared to the Fig.1.