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INTEGRATIVE RADIOLOGICAL AND CLINICAL ASSESSMENT OF COUGH IN PULMONARY SARCOIDOSIS USING HIGH-RESOLUTION CT IMAGING

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Abstract

Introduction: Sarcoidosis is a systemic inflammatory disease of unknown origin, characterized by the formation of non-caseating granulomas in various organs, most commonly the lungs and lymph nodes. The disease can involve multiple organ systems, leading to a wide range of clinical manifestations. Sarcoidosis is often diagnosed through a combination of clinical presentation, radiological findings, and histopathological evidence of granulomatous inflammation.

The aim of the study is to detect HRCT features of pulmonary sarcoidosis and their correlation with cough.

Material and Methods: In the past two years, fifty patients diagnosed with sarcoidosis were treated at our University Clinic for Pulmonology and Allergology -Skopje. Computed tomography with high resolution was conducted on 128 slice CT scanner PHILIPS INCISIVE, using 1 mm thin-slice thickness and a special reconstruction algorithm.

Results: Cough was present in 80% patients, mostly with low intensity (40%). Micronodular changes (1–3 mm), localized peribronchovascularly in the upper and middle lung zones, were observed significantly less often in patients with cough than in those without cough (10% vs 40%, p=0.041). A statistically significant difference between the cough and no-cough groups was identified in the localization of these changes in the peripheral and subpleural regions (p=0.037). The difference was confirmed between the patients with and without cough in terms of the frequency of hypoattenuation findings in the lower peripheral and subpleural zones.

Conclusion: High-resolution computed tomography (HRCT) is the preferred imaging modality for evaluating pathological changes in pulmonary sarcoidosis. It provides detailed visualization of characteristic findings, such as lymphadenopathy, micronodules, and other lesions, along with their distribution patterns and any atypical changes. Despite its utility, further research is needed to better understand the mechanisms underlying cough in patients with sarcoidosis.

Key words:cough; *HRCT; lungs; sarcoidosis.*

Introduction

Sarcoidosis is a systemic inflammatory disease of unknown etiology that can affect any organ system in the body. The most common manifestations involve the lung parenchyma and mediastinal lymph nodes, which are responsible for the majority of morbidity and mortality associ-

ated with the condition. The diagnosis is based on clinical and radiological findings, along with the demonstration of non-caseating granulomas on histopathological examination.

Imaging plays a crucial role in both the diagnosis and follow-up of patients with sarcoidosis. While chest radiography is frequently used as the initial imaging modality, it has several limitations, including relatively low resolution for detecting parenchymal abnormalities and mediastinal lymphadenopathy. In contrast, computed tomography (CT) is more sensitive in terms of detecting both parenchymal disease and lymphadenopathy (1,2).

High-resolution computed tomography (HRCT) offers superior resolution compared to conventional CT, allowing for the detection and detailed assessment of subtle parenchymal lesions and abnormalities in lung structures (3). HRCT is particularly valuable for distinguishing active inflammation, which represents reversible disease, from irreversible lung damage or fibrosis. This capability aids in prognostication and helps guide therapeutic decisions. Additionally, HRCT is essential for diagnosing sarcoidosis in patients with atypical or unusual radiographic presentations and is considered the gold standard for thoracic imaging (4).

Cough is a prevalent and impactful symptom in sarcoidosis, significantly reducing the patients' quality of life. Objective 24-hour cough monitoring has demonstrated that patients with sarcoidosis experience significantly higher cough frequencies compared to healthy controls, with notable diurnal variation. Cough patterns are gender-specific and show racial differences. Importantly, cough frequency correlates with airway inflammation but is not influenced by the radiographic staging of the disease or the degree of airway obstruction (5).

The aim of the study is to detect HRCT features of pulmonary sarcoidosis and their correlation with cough.

Material and Methods

All patients voluntarily participated in the study after providing written informed consent. The study protocol was approved by the Ethics Committee of the Faculty of Medicine in Skopje and was conducted in accordance with the ethical principles outlined in the Declaration of Helsinki of the World Medical Association for research involving human subjects.

A total of 50 patients with a confirmed diagnosis of sarcoidosis were enrolled over a two-year period at the University Clinic of Pulmonology and Allergology in Skopje. All participants underwent high-resolution computed tomography (HRCT) using a 128-slice PHILIPS INCISIVE CT scanner. Scans were performed with a 1 mm thin-slice protocol and reconstructed using a specialized algorithm optimized for thoracic imaging.

Images were reviewed using standard lung and mediastinal window settings. Lymph nodes were classified anatomically as hilar or mediastinal, with enlargement defined as a maximum short-axis diameter (MSAD) greater than 10 mm.

Pulmonary parenchymal abnormalities were categorized as follows: nodules (micronodules 1–3 mm, macronodules >5 mm), reticular opacities, fibrotic lesions, ground-glass opacities, and confluent consolidations. Nodular distribution was further classified into perilymphatic, centrilobular, and random patterns. The predominant localization of lesions within the upper, middle, or lower lung zones was also recorded.

Results

A total of 50 patients diagnosed with sarcoidosis were included in a statistical analysis. The gender structure of the patients is predominantly made up of female patients – 46 (92%) vs 4 (8%).

The patients were aged between 30 and 73, with an average age of 52.6 ± 12.5 years, and a residing mostly in an urban environment – 42 (84%) vs 8 (16%).

Regarding the smoking status, 8 (16%) patients declared themselves as current smokers, 28(56%) as ex-smokers, with an average smoking experience of 14.9 ± 4.8 years.

In the clinical findings, cough was present in 40 (80%) patients, mostly with low intensity – 20 (40%), while in relation to the character of the cough, dry cough was present in more than 50% of patients – 28(56%).

Correlation of HRCT Features of Sarcoidosis with Cough

The HRCT finding of reticular opacities was not significantly associated with cough (p>0.05).

Patients with cough had a finding of reticular opacities in the upper and middle zones insignificantly less often than patients without cough; and in the lower zones peripherally subpleural (15% vs 40%, p=0.097), and (20% vs 40%, p=0.225), respectively, as well as in the lower zones peribronchovascular (20% vs 40%, p=0.225).

Table 1. Distribution of reticular changes in patients with/without cough

			cough		p-level
			yes n (%)	no n (%)	
Reticular opacities					
Upper and middle zones	Peripheral and subpleural	**yes**	6 (15)	4 (40)	p=0.097
		no	34 (85)	6 (60)	
	Peribronchovascular	**yes**	8 (20)	2 (20)	p=1.0
		no	32 (80)	8 (80)	
Lower lobe zones	Peripheral and subpleural	**yes**	8 (20)	4 (40)	p=0.225
		no	32 (80)	6 (60)	
	Peribronchovascular	**yes**	8 (20)	4 (40)	p=0.225
		no	32 (80)	6 (60)	

p (Fisher's exact test)

Patients with cough had findings of micronodular changes with a size of 1 to 3 mm localized peribronchovascularly in the upper and middle zones (10% vs 40%, p=0.041) significantly less often than patients without cough.

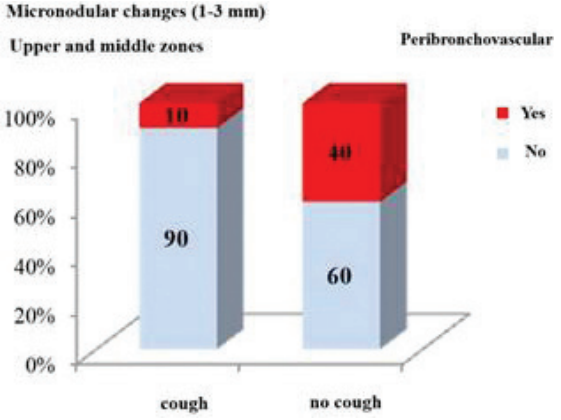
The prevalence of micronodular changes 1 to 3 mm in size in the lower peribronchovascular zones was also less frequent in patients without cough, but without a statistically significant difference (5% vs 20%, p=0.17). In the upper and middle peribronchovascular zones, perilym-

phatic micronodular changes with a size of 1 to 3 mm were seen significantly less often in patients with cough (35% vs 100%, p=0.044). Such changes in the subpleural regions of the lower zones, in the peribronchovascular regions of the upper and middle zones, and in the subpleural regions of the lower zones were seen only in patients with cough, but a statistically significant difference was not manifested between the groups with and without cough (25%, 5%, and 5%, respectively).

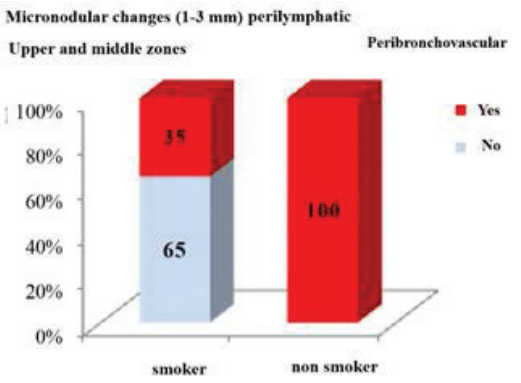
Table 2. Distribution of micron odular changes of 1-3 mm in patients with/without cough

			cough		p-level
			yes n (%)	no n (%)	
Micronodular changes (1-3 мм)					
Upper and middle zones	Centrilobular	**yes**	0	0	
		no	40 (100)	10 (100)	
	Peribronchovascular	**yes**	4 (10)	4 (40)	*p=0.041
		no	36 (90)	6 (60)	
Lower lobe zones	Centrilobular	**yes**	0	0	
		no	40	10	
	Peribronchovascular	**yes**	2 (5)	2 (20)	p=0.17
		no	38 (95)	8 (80)	
Micronodular changes (1-3 мм) perilymphatic					
Upper and middle zones	Peribronchovascular	**yes**	14 (35)	10 (100)	*p=0.044
		no	26 (65)	0	
	Subpleural	**yes**	10 (25)	0	p=0.18
		no	30 (75)	10 (100)	
Lower lobe zones	Peribronchovascular	**yes**	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	
	Subpleural	**yes**	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	

p (Fisher's exact test) *sig p<0.05



Graph-1



Graph-2

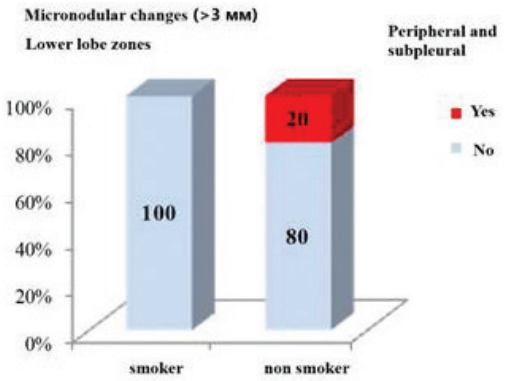
In the groups with and without cough, the representation of patients with findings of micronodular changes greater than 3 mm in the upper and middle lung zones was identical (20%).

In the lower zones, peripheral localization of micronodular shadows larger than 3 mm were detected in 20% of patients without cough, while peribronchovascular localization in 5% of patients with cough. A statistically significant difference between the groups with and without cough was confirmed in the localization of these changes in the peripheral and subpleural regions (p=0.037).

Table 3. Distribution of micronodular changes larger than 1-3 mm in patients with/without cough

			cough		p-level
			yes n (%)	no n (%)	
Micronodular changes (>3 мм)					
Upper and middle zones	Peripheral and subpleural	**yes**	8 (20)	2 (20)	p=1.0
		no	32 (80)	8 (80)	
	Peribronchovascular	**yes**	8 (20)	2 (20)	p=1.0
		no	32 (80)	8 (80)	
Lower lobe zones	Peripheral and subpleural	**yes**	0	2 (20)	*0.037
		no	40 (100)	8 (80)	
	Peribronchovascular	**yes**	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	

p (Fisher's exact test) *sig p<0.05



Graph-3

Localization of opacities seen on HRCT in the central regions of the upper and middle lung zones was significantly less common in patients with cough (5% vs 40%, p=0.011). The remaining localizations of opacities did not differ significantly in patients with and without cough (p>0.055): peripheral and subpleural in the upper and middle zones, and in the lower zones in 5% of patients with cough, central in the lower zones in 25% of patients with cough and 20% of patients without cough. Masses and consolidations in the upper and middle zones with peripheral and subpleural localization were diagnosed in 20% of patients without cough, with a statistically significant difference between the two groups of p=0.037. In 15% of patients with cough and 20% without cough, HRCT showed masses and consolidations in the upper and middle zones centrally, and in the lower zones peripherally and subpleurally, without a statistically significant difference (p=0.65).

Hypoattenuation-type changes were observed in the upper and middle zones only in patients with cough, in the peripheral and subpleural regions in 15%, in the central regions in 20%. For both localizations, the statistical analysis did not confirm a significant difference between the two groups (p>0.05).

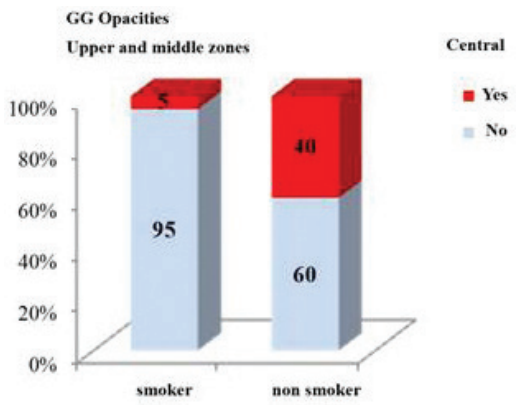
For p=0.041, a statistically significant difference was confirmed between patients with and without cough in terms of the frequency of hypoattenuation findings in the lower peripheral and subpleural zones; such changes were observed significantly less often in patients with cough (10% vs 40%).

Table 4. Distribution of GG opacities, masses and consolidations, and hypoattenuation in patients with/without cough

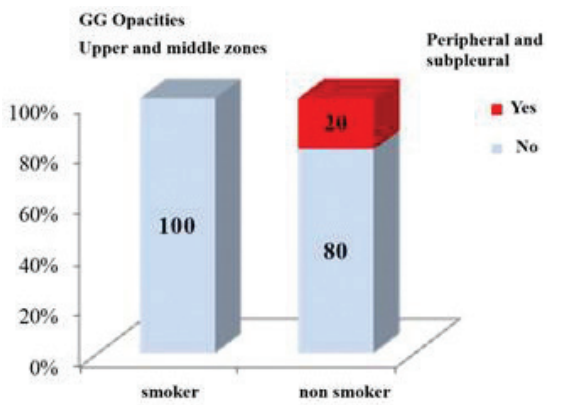
variable			cough		p-level
			yes n (%)	no n (%)	
GG Opacities					
Upper and middle zones	Peripheral and subpleural	**yes**	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	
	Central	**yes**	2 (5)	4 (40)	*p=0.011
		no	38 (95)	6 (60)	
Lower lobe zones	Peripheral and subpleural	**yes**	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	
	Central	**yes**	10 (25)	2 (20)	p=1.0
		no	30 (75)	8 (80)	
Masses and consolidations					
Upper and middle zones	Peripheral and subpleural	**yes**	0	2 (20)	*p=0.037
		no	40 (100)	8 (80)	
	Central	**yes**	6 (15)	2 (20)	p=0.65
		no	34 (85)	8 (80)	
Lower lobe zones	Peripheral and subpleural	**yes**	6 (15)	2 (20)	p=0.65
		no	34 (85)	8 (80)	
	Central	**yes**	0	0	
		no	40 (100)	10 (100)	

Hypoattenuation					
Upper and middle zones	Peripheral and sub-pleural	**yes**	6 (15)	0	p=0.33
		no	34 (85)	10 (100)	
	Central	**yes**	8 (20)	0	p=0.18
		no	32 (80)	10 (100)	
Lower lobe zones	Peripheral and sub-pleural	**yes**	4 (10)	4 (40)	*=0.041
		no	36 (90)	6 (60)	
	Central	**yes**	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	

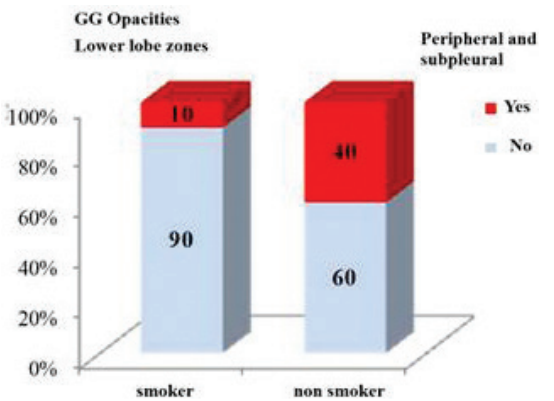
p (Fisher's exact test) *sig p<0.05



Graph-4



Graph-5



Graph-6

The finding of lymphadenopathy was not a significantly different HRCT sign in patients with and without cough. In both groups, bilateral hilar lymphadenopathy was more frequently detected (65% and 80%, patients with and without cough, respectively) and right paratracheal lymphadenopathy (80% of patients in both groups), and conglomerated lymphadenopathy was less frequently seen (20% of patients in both groups).

Calcified nodules were detected only in patients with cough: large focal calcifications in 30%, punctiform in 5%, and scaly in 5%.

Pneumocystis was slightly less common in patients with cough (20% vs 40%, p=0.225) though not significantly, traction bronchiectasis slightly less common in patients with cough (25% vs 40%, p=0.47) though not significantly, fibrosis was slightly less common in patients with cough (30% vs 40%, p=0.71) though not significantly, while honeycomb lung tended to be more common in patients with cough (5% vs 0%, p=1.0), though not significantly.

Table 5. Distribution of lymphadenopathy, calcified lymph nodes, additional findings in patients with/without cough

variable			cough		p-level
			yes n (%)	no n (%)	
Lymphadenopathy	Bilateral Hilar	yes	26 (65)	8 (80)	p=0.47
		no	14 (35)	2 (20)	
	Right paratracheal	yes	32 (80)	8 (80)	p=1.0
		no	8 (20)	2 (20)	
	Others nodal stations	yes	28 (70)	8 (80)	p=0.7
		no	12 (30)	2 (20)	
	Conglomerate lymph nodes	yes	8 (20)	2 (20)	p=1.0
		no	32 (80)	8 (80)	
Calcified Lymph nodes	Focal lymph nodes	yes	12 (30)	0	p=0.09
		no	28 (70)	10 (100)	
	Punctiform lymph nodes	yes	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	
	Egg-shell lymph nodes	yes	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	
Presence of additional finding	Pneumocystis / bullae	yes	8 (20)	4 (40)	p=0.225
		no	32 (80)	6 (60)	
	Traction bronchiectasis	yes	10 (25)	4 (40)	p=0.47
		no	30 (75)	6 (60)	
	Fibrosis	yes	12 (30)	4 (40)	p=0.71
		no	28 (70)	6 (60)	
	Honeycombing	yes	2 (5)	0	p=1.0
		no	38 (95)	10 (100)	

Discussion

Sarcoidosis is a multisystem inflammatory disease of unknown etiology, characterized by the formation of non-caseating granulomas in affected organs. Among its various clinical manifestations, cough is a frequent and significant symptom that can substantially impair the patients' quality of life.

Although the precise mechanisms underlying cough in sarcoidosis remain unclear, current evidence suggests that extensive hilar and mediastinal lymphadenopathy, as well as interstitial lung infiltration, are not solely responsible for its occurrence (6). In our study, neither lymphadenopathy nor reticular opacities were found to be statistically associated with the presence of cough, indicating that other pathological processes may be more relevant.

Recent findings have underscored the predominantly bronchocentric nature of sarcoidosis, wherein granulomatous inflammation targets the airways, potentially contributing to cough. Proposed mechanisms include airway inflammation, mechanical distortion secondary to pulmonary fibrosis, and involvement of the vagus nerve due to compressive effects from enlarged mediastinal lymph nodes (7).

In addition, rare and atypical presentations of sarcoidosis may also provoke cough. These include granulomatous infiltration of the pulmonary veins leading to pulmonary veno-occlusive disease with consequent airway epithelial engorgement, as well as sarcoid involvement of the vagus nerve at the level of the jugular foramen, resulting in vocal cord paralysis and chronic cough (8,9).

In our study, cough was present in 80% of patients, with the majority (40%) reporting symptoms of low intensity. Patients with cough were significantly less likely to exhibit micronodular changes measuring 1–3 mm localized in the peribronchovascular regions of the upper and middle lung zones, compared to those without cough (10% vs. 40%, $p = 0.041$). A statistically significant difference was also observed in the localization of these changes to the peripheral and subpleural regions between the two groups ($p = 0.037$).

Furthermore, a significant difference was identified in the frequency of hypoattenuation findings in the lower peripheral and subpleural zones between patients with and without cough. However, the prevalence of micronodular changes larger than 3 mm in the upper and middle lung zones was identical in both groups (20%). In the lower lung zones, peripheral micronodular shadows larger than 3 mm were detected in 20% of patients without cough, whereas peribronchovascular localization was observed in only 5% of patients with cough.

Lymphadenopathy was not a symptom of a significant statistical difference between patients with and without cough on HRCT. Notably, calcified nodules were detected exclusively in patients with cough. Findings indicative of hypoattenuation, such as pneumoceles, traction bronchiectasis, and honeycombing, were more frequent in patients with cough but did not reach statistical significance.

Hilar and mediastinal lymph node involvement is observed in 50–90% of patients with sarcoidosis (10). Perilymphatic micronodules, a hallmark radiological feature of the disease, are present in over 90% of patients and typically appear symmetrically in the upper and middle lung zones (11–13). These nodules are characteristically well-defined and bilaterally distributed, with predominant involvement of the peribronchovascular interstitium, interlobular septa, and subpleural areas—regions aligned with the pulmonary lymphatic system. Over time, these micronodules may evolve into larger nodular formations. Radiological findings in sarcoidosis can overlap with those of several other diseases, complicating differential diagnosis. Hilar and mediastinal lymphadenopathy, a hallmark feature of sarcoidosis, may also be observed in conditions such as lymphoma, fungal infections, tuberculosis, and certain types of primary lung carcinoma. However, the presence of bilateral hilar and mediastinal lymphadenopathy, particularly in the absence of systemic symptoms typically associated with malignancy or infection—such as unexplained weight loss or persistent fever—strongly favors a diagnosis of sarcoidosis.

The differential diagnosis of perilymphatic nodular distribution on high-resolution computed tomography (HRCT) includes silicosis, coal workers' pneumoconiosis, and lymphangitic carcinomatosis. In sarcoidosis, micronodules are typically well-defined and characteristically distributed along the peribronchovascular interstitium, subpleural regions, and interlobar fissures. In contrast, nodules observed in silicosis and pneumoconiosis are often accompanied by fibrotic changes, and lymph nodes may exhibit coarse or "eggshell" calcification. In such cases, a detailed occupational history is crucial for accurate diagnosis.

In malignant lymphangitic spread, nodules are typically finer and associated with smooth or irregular thickening of the interlobular septa, often lacking the sharply defined and symmetrical distribution seen in sarcoidosis (14).

Conclusion

Pulmonary sarcoidosis demonstrates spontaneous remission in approximately 50% of cases within the first two years, with additional cases resolving over a period of five years. However, in an estimated 20% of patients, the disease follows a progressive and chronic course, often leading to pulmonary fibrosis and significant functional impairment. This progression is associated with a mortality rate of approximately 5%, highlighting the critical need for timely and accurate diagnosis.

High-resolution computed tomography (HRCT) is the imaging modality of choice for assessing pulmonary involvement in sarcoidosis. Given the disease's broad spectrum of radiological manifestations, HRCT plays a vital role in diagnosis and disease monitoring, despite the interpretive challenges it presents. It provides detailed visualization of characteristic features, including lymphadenopathy, perilymphatic micronodules, and other parenchymal abnormalities, along with their distribution patterns and any atypical findings.

HRCT is also essential in guiding treatment strategies by differentiating active granulomatous inflammation from irreversible fibrotic changes. A comprehensive understanding of these imaging features, integrated with clinical symptomatology, enables radiologists to contribute to a more specific and accurate diagnosis of sarcoidosis. Cough is a prevalent and clinically significant symptom in patients with sarcoidosis, often contributing to a substantial reduction in the quality of life. While objective assessments of pulmonary function are essential in evaluating disease severity and treatment response, the subjective burden of cough should also be systematically assessed. The pathophysiology of cough in sarcoidosis is likely multifactorial, with proposed mechanisms including airway hyperresponsiveness, involvement of the upper respiratory tract, cough reflex hypersensitivity, and parenchymal fibrosis. Despite its impact, there are currently no disease-specific guidelines for the management of cough in sarcoidosis. Further clinical and translational research is needed to elucidate the underlying mechanisms and to guide the development of targeted therapeutic strategies.(5)

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