Case Report

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Sarcoidosis with a Necrotizing Sarcoid Granulomatosis Pattern Presenting as Persistent Low-Grade Fever: A Case Report

지속적인 미열을 동반한 괴사성 사르코이드성 육아종증 형태의 사르코이드증 환자의 임상적, 영상의학적 특징: 증례 보고

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Necrotizing sarcoid granulomatosis (NSG), now referred to as "sarcoidosis with NSG pattern," is an uncommon variant of sarcoidosis. NSG is characterized by a trio of features: sarcoid granulomas, vasculitis, and extensive areas of necrosis. Symptoms can include cough, fever, chest pain, and dyspnea, typically presenting as either solitary or multiple lung nodules or masses. In this report, we describe a case of NSG accompanied by a persistent low-grade fever. Unlike the dominant presentation of NSG with single or multiple nodules, our case demonstrated diffuse micronodules with combined perilymphatic and random distribution on CT. Histological examination revealed widespread necrotizing granulomas surrounded by anthracotic pigmentation, alongside necrosis and vasculitis, diverging from the classic presentation of sarcoidosis. The diagnosis of NSG was established through a multidisciplinary discussion. The patient was administered oral prednisolone that led to noticeable clinical and radiological improvement within three months.

Index terms Case Report; Sarcoidosis; Multiple Pulmonary Nodules; Granuloma, Vasculitis

INTRODUCTION

Necrotizing sarcoid granulomatosis (NSG) was first identified in 1973 by Liebow (1) as a distinct yet rare condition, exhibiting characteristics akin to both sarcoidosis

and granulomatosis with polyangiitis (1, 2). NSG shares a number of pathological, radiological, and clinical features with nodular sarcoidosis, which is a form of sarcoidosis characterized by one or more nodular lesions and accounts for 1.6%–4% of pulmonary sarcoidosis cases (3). Unlike classical sarcoidosis, which is marked by dense, non-necrotizing granulomas, occasionally with small areas of necrosis and granulomatous vasculitis, NSG is histologically defined by a triad of sarcoid-like granulomas, vasculitis, and extensive areas of necrosis (3-5). Recent studies have reported that necrosis may also occur in nodular sarcoidosis, prompting the recommendation for the diagnostic term "sarcoidosis with NSG pattern." Common clinical symptoms of NSG include cough, fever, chest pain, and dyspnea (3). Radiologically, NSG is typically identified by solitary or multiple lung nodules or masses, sometimes accompanied by hilar lymphadenopathy (3, 4, 6). Here, we present a case of NSG with a persistent low-grade fever. In contrast to multiple or solitary nodules being the dominant features of NSG, our case showed diffuse micronodules with combined perilymphatic and random distribution on CT, initially misinterpreted as malignancy with hematolymphangitic spread. This report also includes a review of the clinicoradiologic features of NSG as documented in the literature.

CASE REPORT

A 62-year-old male presented at our hospital with a month-long history of cough, sputum production, chest pain, low-grade fever, and a weight loss of 6 kg, without any extrapulmonary symptoms. The patient had a history of smoking 30 pack in a year and was still smoking. Laboratory tests on admission indicated elevated C-reactive protein levels at 85.04 mg/L (normal range 0–5 mg/dL) and a white blood cell count within the normal range at 9640/μL (normal range 4000–10000/μL). Pulmonary function tests showed a mild obstructive lung defect and a slight reduction in diffusing capacity forced expiratory volume in 1 sec/forced vital capacity = 64%, diffusing capacity for carbon monoxide = 69% of predicted). Chest radiography revealed multiple diffuse small nodular opacities across both lungs, predominantly in the right middle zone (Fig. 1A). Contrast-enhanced chest CT images displayed numerous ill-defined and well-defined micronodules in both lungs with both perilymphatic and random distribution. Observations included smooth peribronchovascular interstitial thickening and mild interlobular septal thickening in the right middle and lower lobes (Fig. 1B). Additionally, multiple slightly enlarged lymph nodes with heterogeneous enhancement were present in the bilateral mediastinum, hilum, and subcarinal areas (Fig. 1C). In addition, there was mild bilateral pleural effusion. Initial suspicions pointed towards malignancy with hematolymphangitic spread or lymphoproliferative disease, compounded by the patient's persistent low-grade fever of 38°C. The revelation of a previous chest CT scan from three months prior showing no substantial abnormalities indicated rapid radiographic progression, leading to considerations of non-infectious granulomatous diseases like sarcoidosis in the differential diagnosis. The patient's worsening symptoms, including aggravated cough and persistent fever, along with deteriorating chest radiography findings (Fig. 1A), raised concerns for potential miliary tuberculosis or fungal infection, granulomatosis with polyangiitis, amyloidosis, as well as sarcoidosis.

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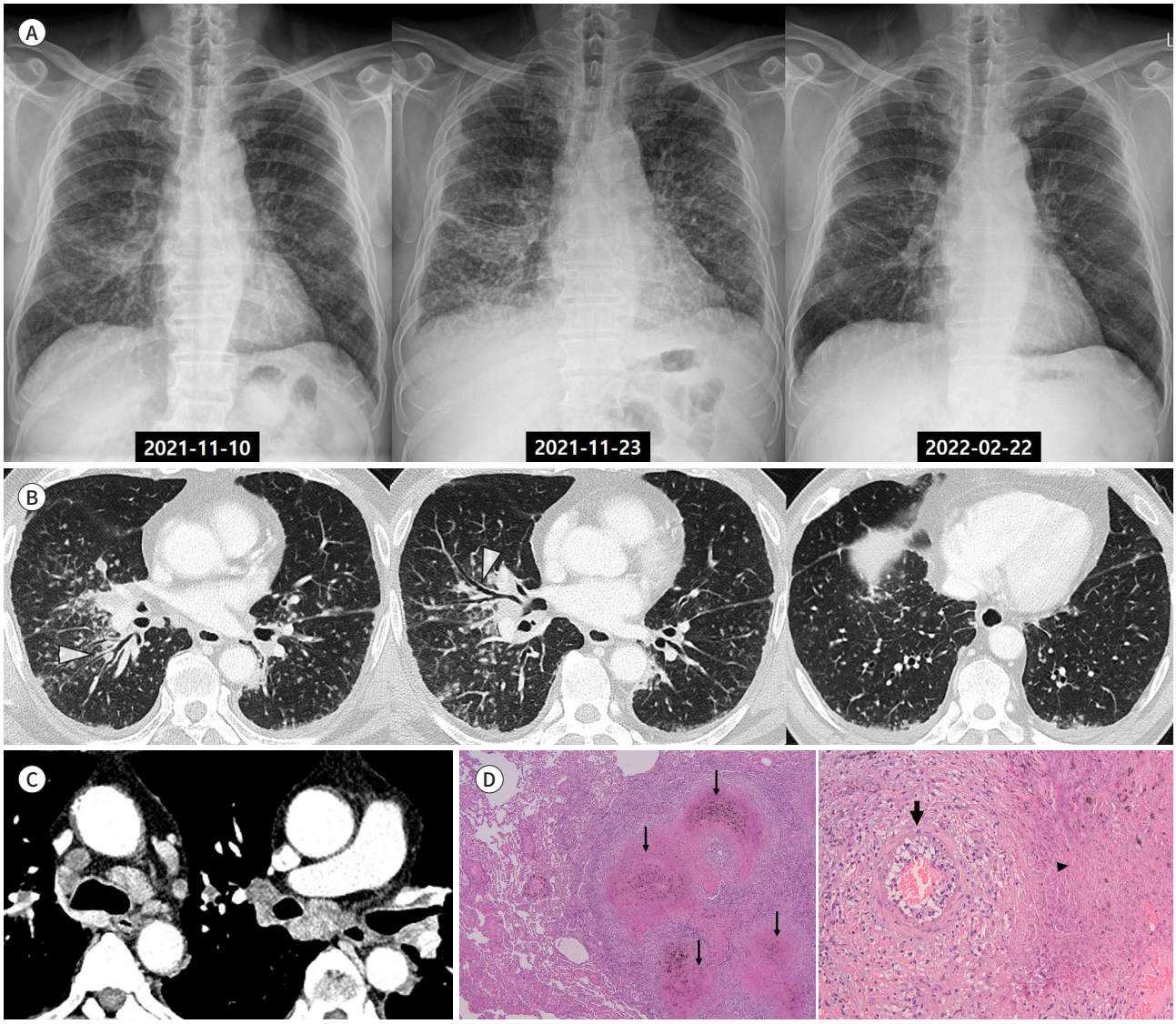
The patient underwent an ^{18}F-fluorodeoxyglucose (FDG) PET/CT scan, which highlighted hypermetabolism in both the lung nodules and the enlarged lymph nodes, with maximum standardized uptake value (SUVmax) of 5.6 and 10.9, respectively. Since malignancy could not be excluded by PET/CT, a wedge resection was conducted on the lateral segment of the

Fig. 1. A 62-year-old male with necrotizing sarcoid granulomatosis.
A. Initial chest PA (left) shows diffuse multiple small nodular opacities in both lungs, predominantly in the right middle zone. Follow-up chest PA at two weeks (middle) shows an increase in the number of diffuse multiple small nodules in both lungs. Chest PA at three months (right) shows a significant improvement of the nodules.
B. Contrast-enhanced chest CT axial images with lung window setting show numerous concurrent ill-defined and well-defined micronodules throughout both lungs with combined perilympahtic and random distribution. Smooth peribronchovascular interstitial thickening is seen in the right middle lobe and right lower lobe (arrowheads). Smooth interlobular septal thickening is also observed in the mediobasal segment of the right lower lobe (right).
C. CT axial images with mediastinal window setting show slightly enlarged lymph nodes with heterogeneous enhancement in bilateral lower paratracheal, subaortic, bilateral interlobar and subcarinal area.
D. Histopathologic examination shows the necrotizing granulomas (long arrows) surrounded by anthracotic pigmentation in low power (H&E stain, ×40, left). Combined necrosis (arrowhead) and vasculitis (short arrow) are also noted in mid power (H&E stain, ×20, right).
H&E = hematoxylin and eosin, PA = posteroanterior



right middle lobe and the superior segment of the right lower lobe. The histopathological analysis revealed diffuse necrotizing granulomas surrounded by anthracotic pigmentation, characterized by combined necrosis and vasculitis (Fig. 1D). This finding deviated from the typical features of classical sarcoidosis, which are marked by non-necrotizing granulomas. Moreover, no evidence of tuberculosis or fungal infection was observed, both of which can lead to granuloma formation. Based on these findings and after thorough multidisciplinary discussions, NSG was diagnosed. The patient was prescribed oral prednisolone (70 mg/day) for two weeks, followed by a gradual taper. Three months later, a follow-up demonstrated resolution of clinical symptoms and substantial improvement in the chest radiography findings, particularly concerning the lung nodules (Fig. 1A).

This study received approval from our institution's Institutional Review Board, which waived the requirement for informed consent (IRB No. WKUH 2022-11-010).

DISCUSSION

NSG, now recognized as "sarcoidosis with NSG pattern," was once considered extremely rare but is currently understood as a distinct variant of sarcoidosis. This form is characterized by a combination of sarcoid granulomas, vasculitis, and extensive areas of necrosis (3-5).

NSG has been identified in individuals ranging from 8 to 68 years old, with a median age of 42 years (3). NSG is more commonly diagnosed in females and nonsmokers. The most frequent clinical signs of NSG include a non-productive cough (50%), fever (45%), chest pain (38%), and dyspnea (34%) (3). Beyond respiratory symptoms, patients may experience systemic effects such as weight loss, night sweats, and extrapulmonary manifestations affecting the eyes, skin, liver, lacrimal glands, and central nervous system (3, 6). While NSG shares many clinical features with classical sarcoidosis, including a predominance in females and similar symptomatology, NSG is less likely to involve extrapulmonary organs (3).

Radiologic characteristics of NSG have been outlined through analyses of a relatively limited number of cases (3, 4, 6). In the most extensive review of 130 cases by Karpathiou et al. (3), the presence of multiple lung nodules (65%) was the predominant finding, with solitary nodules or masses (20%) and diffuse infiltrates (14%). Hilar and mediastinal lymphadenopathy was observed in 36% of cases (3). Pleural effusion and cavitation of nodules have also been reported (2, 3). By contrast, classical sarcoidosis is typically marked by well-defined, round, bilateral, symmetrically distributed micronodules concentrated in the upper and middle lung zones, accompanied by nodular peribronchovascular interstitial thickening and bilateral symmetric enlargement of the hilar lymph nodes (2, 7).

The patient in our case reported a persistent low-grade fever of undetermined origin, accompanied by CT images that showed rapid radiographic progression. Considering the clinical and radiological characteristics, non-infectious granulomatous diseases like sarcoidosis seemed more plausible than malignancy. Unlike the dominant presentation of NSG with single or multiple nodules, our case was characterized by diffuse micronodules with combined perilymphatic and random distribution. Additionally, while mediastinal and hilar lymphadenopathies are generally less common and cavitation is a distinct feature of NSG (2, 3), our patient presented with lymphadenopathy without cavitation. Thus, NSG can display a range of

CT findings, as seen in our case, necessitating histopathological confirmation for diagnosis.

Furthermore, an ^{18}F-FDG PET/CT was conducted to exclude malignancy, revealing hypermetabolism in the nodules and enlarged lymph nodes. Arfi et al. (8) have reported a broad range of SUVmax values (1.6–6.6) for pulmonary nodules in NSG. Although ^{18}F-FDG PET/CT can aid in biopsy guidance and in assessing the extent of disease, its utility in distinguishing malignancy from other conditions is considered limited.

Systemic steroids are the most commonly adopted treatment for NSG, similar to the approach for classical sarcoidosis. NSG shares histopathological, radiological, and clinical similarities with nodular sarcoidosis but also exhibits unique clinical features. While generally responsive to treatment and exhibiting a relatively benign progression, NSG is less likely to show improvement without steroid therapy compared to nodular sarcoidosis (4). Thus, recognizing and understanding the clinical and radiologic manifestations of NSG can facilitate accurate diagnosis and effective management.

Here, we present a case of NSG with atypical radiological findings. This case underscores the importance for clinicians and radiologists to consider NSG in patients who exhibit persistent fever, rapidly evolving diffuse micronodules with combined perilymphatic and random distribution on CT, and diffuse necrotizing granulomas histologically. Being aware of the varied radiological presentations may prompt early diagnosis through histopathological examination.

Author Contributions

Conceptualization, R.J.Y.; data curation, K.S.R.; investigation, K.S.R.; supervision, R.J.Y.; validation, K.S.R.; visualization, C.K.H.; writing—original draft, K.S.R.; and writing—review & editing, R.J.Y.

Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

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지속적인 미열을 동반한 괴사성 사르코이드성 육아종증 형태의 사르코이드증 환자의 임상적, 영상의학적 특징: 증례 보고

강세리[1] · 최금하[2] · 노지영[1]*

괴사성 사르코이드성 육아종증(necrotizing sarcoid granulomatosis)은 현재 '괴사성 사르코이드성 육아종증 형태의 사르코이드증(sacroidosis with necrotizing sarcoid granulomatosis pattern)'으로 불리며, 사르코이드성 육아종, 혈관염, 그리고 대규모 괴사를 특징으로 하는 희귀한 사르코이드증 유형이다. 기침, 열, 흉통, 호흡곤란과 같은 증상이 나타날 수 있으며, 보통 폐결절이나 종괴로 나타난다. 본 증례 보고에서는 지속적인 미열을 동반한 괴사성 사르코이드성 육아종증의 증례를 보고한다. 다른 괴사성 사르코이드성 육아종증에서 다수 또는 단일 결절이 우세한 특징인 것과는 달리, 본 증례에서는 CT에서 림프관 주위 및 임의 분포하는 미만성 미세결절이 있었다. 조직학적으로는 색소 침착으로 둘러싸인 넓게 퍼진 괴사성 육아종들과 동반한 괴사 및 혈관염이 관찰되었으며, 이는 고전적인 사르코이드증과 일치하지 않았다. 다학제적 토론을 기반으로 괴사성 사르코이드 육아종증이 진단되었으며, 환자는 경구 프레드니솔론을 투여받아 3개월 이내에 임상 및 방사선학적 개선을 보였다.

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