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Hodgkin Lymphoma With Sarcoid-Like Reaction: Importance of Clinicopathological Correlation in Granulomatous Lymphadenopathy

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Male, 63-year-old
Final Diagnosis: Malignant lymphoma
Symptoms: Fever
Clinical Procedure: —
Specialty: Laboratory Diagnostics

Objective: Mistake in diagnosis

Background: Sarcoid-like reaction, characterized by noncaseating epithelioid granulomas, occurs in 13.8% of Hodgkin lymphoma cases. When the granulomatous component is prominent and neoplastic cells are scarce, the initial biopsy may lead to a misdiagnosis of sarcoidosis. Reliance on pathological findings alone, without integration of the clinical context, can result in considerable diagnostic delay.

Case Report: A 63-year-old man with systemic lymphadenopathy underwent cervical lymph node biopsy, which showed epithelioid granulomas without identifiable neoplastic cells. Sarcoidosis was initially suspected based on the pathological findings. However, comprehensive evaluation revealed no typical manifestations of sarcoidosis, including bilateral hilar lymphadenopathy, uveitis, or elevated serum angiotensin-converting enzyme levels. The discordance between the pathological diagnosis and clinical findings led us to retain malignant lymphoma in the differential diagnosis. During follow-up, the patient developed B symptoms with substantially elevated soluble interleukin-2 receptor levels. Repeat biopsy of the left supraclavicular lymph node, performed 7 months after the initial presentation, revealed Reed-Sternberg-like multinucleated cells surrounded by a sarcoid-like reaction, confirming classical Hodgkin lymphoma.

Conclusions: This case illustrates that pathological findings alone may be insufficient for a definitive diagnosis of granulomatous lymphadenopathy. Malignant lymphoma should remain in the differential diagnosis, even when the initial biopsy suggests sarcoidosis. When clinical features are inconsistent with the pathological diagnosis, clinicians should reconsider the differential diagnosis, and repeat biopsy may be warranted. Integration of clinical findings, imaging, and histopathology is important to avoid diagnostic delay.

Keywords: Sarcoidosis • Hodgkin Disease • Granuloma • Lymphadenopathy • Biopsy • Diagnosis, Differential

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/954572

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Introduction

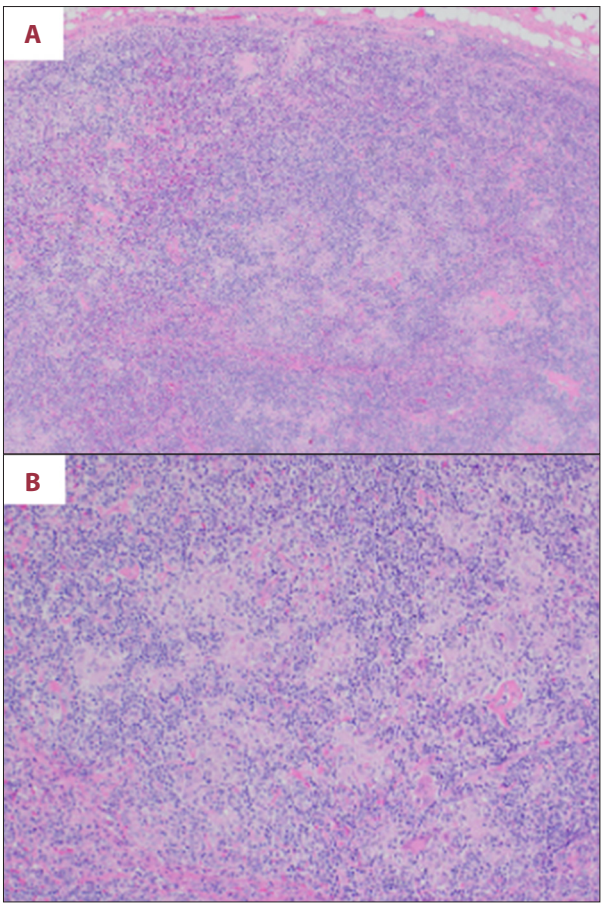
Epithelioid granulomas in lymph nodes can be caused by various conditions, including sarcoidosis, tuberculosis, other infections, and malignancy [1]. Among these, sarcoidosis is the most common cause and is therefore often initially suspected. However, noncaseating epithelioid granulomas can also occur in malignant lymphoma, a phenomenon known as a "sarcoid-like reaction" [2]. Sarcoid-like reactions have been reported in 13.8% of Hodgkin lymphoma and 7.3% of non-Hodgkin lymphoma cases [3]. When the granulomatous component is prominent and neoplastic cells are scarce, lymphoma can be difficult to diagnose and may initially be missed [4].

We report a case of classical Hodgkin lymphoma with a marked sarcoid-like reaction. The patient was initially suspected to have sarcoidosis based on lymph node histology. However, comprehensive evaluation failed to identify any findings suggestive of sarcoidosis. Recognizing this discordance between the pathological diagnosis and clinical presentation, we retained malignant lymphoma in the differential diagnosis rather than relying solely on the initial pathological interpretation. Hodgkin lymphoma was diagnosed after repeat biopsy prompted by subsequent clinical deterioration. This case illustrates the importance of clinicopathological correlation in granulomatous lymphadenopathy and demonstrates how integration of the clinical context with histopathological findings can help avoid diagnostic delay.

Case Report

A 63-year-old Japanese man was admitted to a local hospital for acute cerebral infarction. He had no significant medical history except for colonic polyps and was not taking any medications. During the admission workup, ultrasonography and computed tomography (CT) incidentally revealed multiple enlarged lymph nodes in the cervical, superior mediastinal, left supraclavicular, para-aortic, and bilateral common iliac regions. He had no fever or other signs of inflammatory disease. The clinical course of the cerebral infarction was uneventful, and he was discharged.

Approximately 6 weeks after the initial admission, he was referred to the hematology department of our hospital for further evaluation of the lymphadenopathy. A cervical lymph node biopsy revealed epithelioid granulomas without neoplastic cells (Figure 1); the results of special stains (periodic



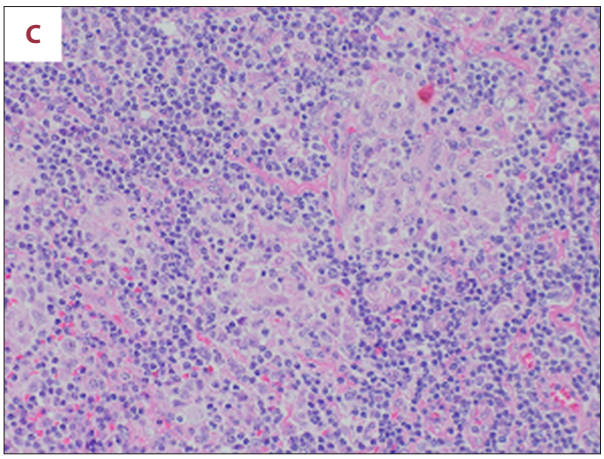


Figure 1. Histopathological findings of the initial lymph node biopsy (cervical lymph node). (A) Low-power view showing numerous small epithelioid granulomas throughout the lymph node, with obscured lymphoid follicular architecture and hyaline fibrosis. (B) Medium-power view demonstrating well-formed noncaseating epithelioid granulomas with intermingled plasma cells and lymphocytes. (C) High-power view showing epithelioid histiocytes with a few multinucleated giant cells. No necrosis or abscess formation was observed. The results of special stains (periodic acid-Schiff, Ziehl-Neelsen, and Grocott) were negative for microorganisms. The findings were suggestive of sarcoidosis or a sarcoid-like reaction, but no definitive diagnosis of malignancy could be made. Original magnification: × 40 (A), × 100 (B), and × 200 (C).

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Table 1. Laboratory findings at the first visit to our department.

Hematology		Chemistry		Serology	
WBCs (/μL)	8000	CRP (mg/dL)	2.37	sIL-2R (U/mL)	3551
RBCs (× 10^4/μL)	325	TP (g/dL)	8.4	IgG (mg/dL)	2835
Hb (g/dL)	10.8	Alb (g/dL)	3.2	IgA (mg/dL)	1222
MCV (fL)	98.5	AST (U/L)	39	IgM (mg/dL)	46
Plt (× 10^4/μL)	35.7	ALT (U/L)	14	ACE (U/L)	13.8
		LDH (U/L)	161	HIV antibody	Negative
Coagulation		BUN (mg/dL)	14	HTLV-1 antibody	Negative
PT (s)	13.9	Cr (mg/dL)	0.77		
PT-INR	1.09	Na (mEq/L)	135		
APTT (s)	37.2	K (mEq/L)	4.2		
Fibrinogen (mg/dL)	429	Cl (mEq/L)	99		
D-dimer (μg/mL)	1.7	Ca (mg/dL)	9.8		

Abbreviations: ACE, angiotensin-converting enzyme; Alb, albumin; ALT, alanine aminotransferase; APTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BUN, blood urea nitrogen; Cl, chloride; Cr, creatinine; CRP, C-reactive protein; Hb, hemoglobin; HIV, human immunodeficiency virus; HTLV-1, human T-lymphotropic virus type 1; IgA, immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M; K, potassium; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; Na, sodium; Plt, platelets; PT, prothrombin time; PT-INR, prothrombin time-international normalized ratio; RBCs, red blood cells; sIL-2R, soluble interleukin-2 receptor; TP, total protein; WBCs, white blood cells.

acid-Schiff, Ziehl-Neelsen, and Grocott) were negative for microorganisms. Based on these findings, sarcoidosis was suspected, and he was referred to our general medicine department for further evaluation 2 months after the initial biopsy.

Physical examination indicated no conjunctival injection. Cardiac examination showed a regular rhythm without murmurs, and lung auscultation was clear. Palpable lymphadenopathy was noted in the bilateral cervical and left supraclavicular regions. Scaly skin lesions were observed on both lower extremities; they were subsequently diagnosed as asteatotic eczema by a dermatologist.

Laboratory findings showed a mildly elevated C-reactive protein level of 2.37 mg/dL. The serum calcium level was within normal limits at 9.8 mg/dL. The soluble interleukin-2 receptor (sIL-2R) level was elevated at 3551 U/mL (reference range, 122-496 U/mL). The angiotensin-converting enzyme level was not elevated. Other laboratory findings are shown in **Table 1**.

Contrast-enhanced CT showed multiple enlarged lymph nodes consistent with the findings at the previous hospital. Additionally, multiple small pulmonary nodules were identified bilaterally.

A comprehensive evaluation for sarcoidosis was performed. Electrocardiography and echocardiography showed no abnormalities suggestive of cardiac sarcoidosis. Ophthalmologic examination showed no findings consistent with ocular sarcoidosis. Pulmonary consultation concluded that the clinical and radiological findings were atypical for pulmonary sarcoidosis; bronchoscopy was deferred in favor of imaging follow-up.

During the subsequent months of outpatient follow-up, the patient developed persistent nocturnal fever, night sweats, and progressive weight loss (B symptoms). C-reactive protein levels progressively increased, and the sIL-2R level rose to 10 135 U/mL. He also developed a generalized erythematous rash, which was diagnosed as a drug eruption secondary to celecoxib prescribed for fever control.

Given the clinical deterioration, ^{18}F-fluorodeoxyglucose positron emission tomography/CT (FDG-PET/CT) was performed. PET/CT showed diffuse lymph node enlargement with intense FDG uptake (maximum standardized uptake value [SUV_{max}], 10.0), as well as multiple hepatic and bone lesions suggestive of advanced-stage lymphoma (Lugano stage IV; **Figure 2**).

Repeat biopsy of the left supraclavicular lymph node was performed. Histopathological examination showed

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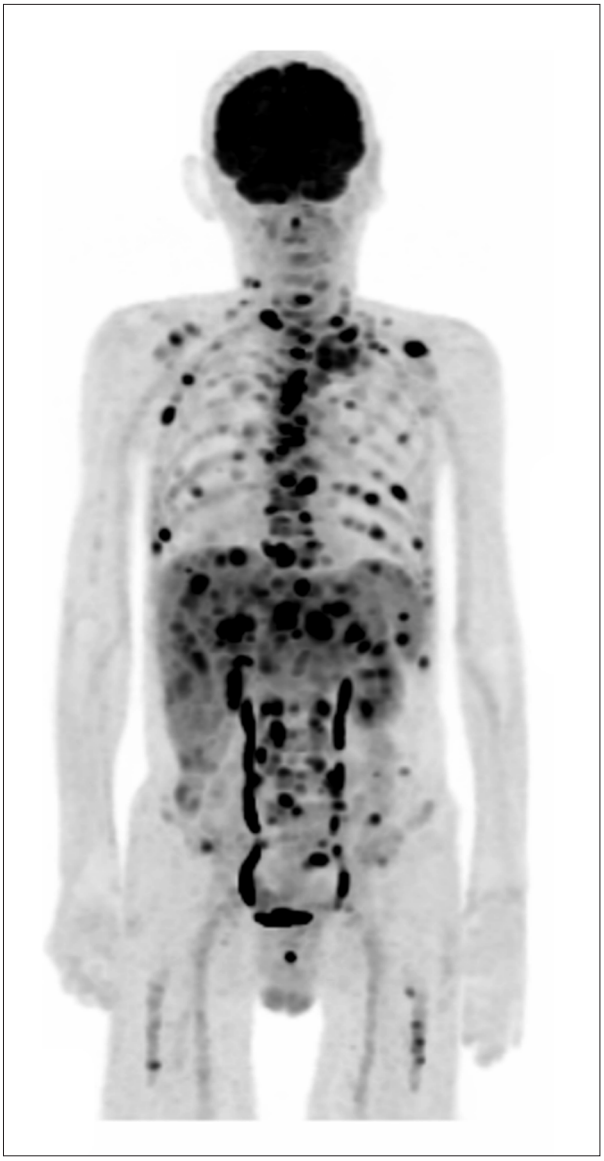

Figure 2. ^{18}**F-fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT) maximum-intensity projection image.** Diffuse FDG uptake is observed in multiple lymph node regions, including the left supraclavicular, mediastinal, and abdominal regions. Additionally, abnormal FDG uptake is noted at multiple sites in the axial skeleton, bilateral femora, liver, and pulmonary nodules (maximum standardized uptake value [SUV_{max}], 10.0), consistent with advanced-stage lymphoma with extranodal involvement (Lugano stage IV).

Reed-Sternberg-like multinucleated cells surrounded by epithelioid granulomas (**Figure 3**). Immunohistochemistry showed that these atypical cells demonstrated cluster of differentiation (CD)30 and CD15 positivity; weak paired box 5 (PAX5) positivity; and CD3, CD5, and CD7 negativity. Based on these findings, classical Hodgkin lymphoma with a sarcoid-like reaction was diagnosed approximately 7 months after the initial presentation. The patient was transferred to the hematology department and received 6 cycles of brentuximab vedotin plus doxorubicin, vinblastine, and dacarbazine (A+AVD) chemotherapy. He achieved a complete response and has remained in remission for 1 year since completion of treatment.

Discussion

This case illustrates how reliance on pathological findings alone, without integration of the clinical context, can lead to diagnostic delay in malignant lymphoma with a prominent sarcoid-like reaction. Although the initial lymph node biopsy showed epithelioid granulomas without identifiable neoplastic cells, we did not accept the presumptive diagnosis of sarcoidosis because typical manifestations of sarcoidosis in other organs were absent. By retaining malignant lymphoma in the differential diagnosis, we were able to promptly recognize the significance of subsequent clinical deterioration and proceed with repeat biopsy, which confirmed Hodgkin lymphoma.

Sarcoid-like reaction refers to noncaseating epithelioid granulomas in patients with malignancy who do not meet the diagnostic criteria for systemic sarcoidosis [2,5]. This phenomenon is thought to represent a T-cell-mediated immune response against tumor antigens, resulting in macrophage activation and granuloma formation [3,6]. Sarcoid-like reactions have been reported in 13.8% of Hodgkin lymphoma and 7.3% of non-Hodgkin lymphoma cases [3]. Patients with sarcoid-like reactions may have a more favorable prognosis, possibly reflecting an effective antitumor immune response [7,8].

When epithelioid granulomas are found in lymph node biopsies, the differential diagnosis includes sarcoidosis, tuberculosis, other infections, and malignancy. Granulomatous reactions are not unique to Hodgkin lymphoma; they may occur in various malignant and nonmalignant conditions, including non-Hodgkin lymphoma, carcinomas, and drug reactions. In a study of 220 cases of granulomatous lymphadenopathy, sarcoidosis comprised 50%, tuberculosis represented 39%, and malignancy, including lymphoma, constituted approximately 1% of cases [9]. Another study showed that among 123 patients diagnosed with granulomatous lymphadenitis by endobronchial ultrasound-guided fine-needle aspiration, 5.6% exhibited malignancy during follow-up [10]. These data suggest that although sarcoidosis is the most common cause of granulomatous lymphadenopathy, malignancy should not be excluded based on histology alone.

In Hodgkin lymphoma with a sarcoid-like reaction, neoplastic Reed-Sternberg cells may be scarce and obscured by the prominent granulomatous infiltrate [4]. Pathologists should carefully

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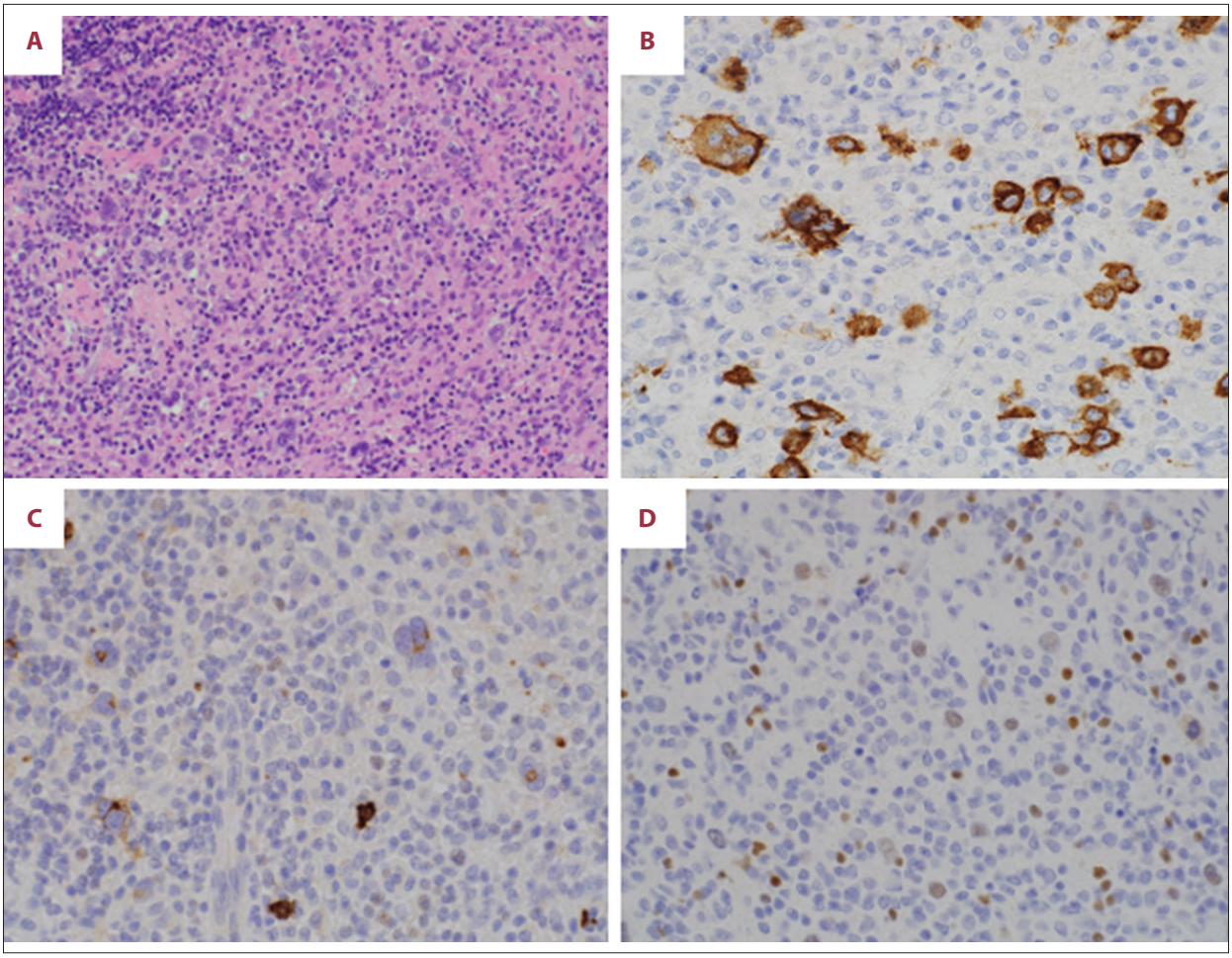

Figure 3. Histopathological findings of the repeat lymph node biopsy (left supraclavicular lymph node). (**A**) Hematoxylin and eosin staining shows large atypical cells with prominent nucleoli resembling Reed-Sternberg cells against a background of mixed inflammatory infiltrates. (**B**) Cluster of differentiation (CD) 30 immunostaining demonstrates strong membranous and Golgi-pattern positivity in large atypical cells. (**C**) CD15 immunostaining shows positive staining in large atypical cells. (**D**) Paired box 5 (PAX5) immunostaining reveals weak nuclear positivity in large atypical cells, characteristic of classical Hodgkin lymphoma. Original magnification: × 400 (**A-D**).

examine the periphery of granulomas because atypical cells tend to be found in these areas [11]. Immunohistochemistry is important for diagnosis; Reed-Sternberg cells typically express CD30 and CD15, with weak or absent expression of B-cell markers such as CD20 and weak PAX5 positivity [12,13]. Among Hodgkin lymphoma subtypes, sarcoid-like reactions are most commonly observed in mixed cellularity Hodgkin lymphoma and grade 2 nodular sclerosis classical Hodgkin lymphoma [11]. These subtypes have a prominent reactive inflammatory infiltrate, which may contribute to granuloma formation. T-cell lymphomas, particularly the lymphoepithelioid variant of peripheral T-cell lymphoma (Lennert lymphoma), can also present with abundant epithelioid histiocytes mimicking sarcoidosis [14]. In such cases, demonstration of clonal T-cell receptor gene rearrangement is necessary for diagnosis [14,15].

Several clinical features in this case were atypical for sarcoidosis and raised suspicion for alternative diagnoses. First, comprehensive evaluation failed to identify sarcoidosis-related organ involvement beyond lymphadenopathy. Second, the pronounced and progressive elevation in sIL-2R levels, although nonspecific, is more commonly associated with lymphoproliferative disorders than with sarcoidosis. Third, the development of prominent B symptoms (fever, night sweats, and weight loss) is characteristic of lymphoma. Although FDG-PET/CT cannot reliably distinguish sarcoidosis from lymphoma due to overlapping FDG uptake patterns, the presence of metabolically active lymphadenopathy with bone and hepatic involvement in the absence of typical sarcoidosis findings suggested a malignant process. These findings supported the decision to pursue repeat biopsy. When an initial biopsy does not identify malignancy, clinicians may be reluctant to perform a repeat biopsy

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because of its invasive nature. However, as this case demonstrates, the initial biopsy may miss the diagnosis if a granulomatous reaction obscures neoplastic cells. When the clinical course is inconsistent with the initial pathological diagnosis, repeat biopsy should be strongly considered.

Conclusions

We report a case of classical Hodgkin lymphoma with a prominent sarcoid-like reaction in which an initial pathological diagnosis of granulomatous lymphadenitis led to a presumptive diagnosis of sarcoidosis. This case illustrates that pathological findings alone may be insufficient for a definitive diagnosis. When clinical features are inconsistent with the pathological diagnosis, such as the absence of typical sarcoidosis manifestations despite granulomatous histology, clinicians should reconsider the differential diagnosis, and repeat biopsy may be warranted. Integration of clinical findings, imaging, and histopathology is important to avoid diagnostic delay.

Department and Institution Where Work Was Done

Nara Medical University, Kashihara, Nara, Japan.

Patient Consent

Written informed consent was obtained from the patient for publication of this case report.

Declaration of Figures' Authenticity

All figures submitted have been created by the authors who confirm that the images are original with no duplication and have not been previously published in whole or in part.

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