SARCOIDOSIS VASCULITIS AND DIFFUSE LUNG DISEASES 2025; 42 (4): 17211 DOI: 10.36141/svdld.v42i4.17211

What's the connection? Sarcoidosis and combined variable immunodeficiency: A single center retrospective case series

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Abstract. *Background and aim:* Sarcoidosis is a disorder hallmarked by non-caseating granulomas and can involve multi-organ systems but most frequently affects the lungs, eyes, central nervous system, and skin (1). Combined Variable Immunodeficiency (CVID) is a disorder featuring hypogammaglobulinemia, an inadequate response to vaccination, and a history of recurrent bacterial and viral infections, most commonly pneumonia, sinusitis, and ear infections (2). CVID can also present with non-caseating granulomas, including in Granulomatous Lymphocytic Interstitial Lung Disease (GLILD), making distinguishing between these conditions challenging. There is increasing recognition of the diagnostic overlap between sarcoidosis and CVID and it is this uncertainty often complicates decisions related to routine screening for CVID and treatment. This case series seeks to clarify clinical and radiographic features between these two conditions to guide both serologic work-up including screening for quantitative immunoglobulins as well as treatments. *Methods:* This single-center retrospective review was performed at a large midwestern academic center with a large sarcoidosis referral base using available data from the past seventeen years. ICD-9 and ICD-10 codes for CVID and Sarcoidosis were used to identify individuals in billing for outpatient encounters. *Results:* A total of 1920 cases of sarcoidosis and 231 cases of CVID were identified, with eight individuals identified as having both CVID and sarcoidosis diagnoses coded in the same outpatient clinical encounter, which is just 0.042% of the total number of sarcoidosis cases. *Conclusions:* In place of universal quantitative immunoglobulin screening among those with sarcoidosis, which has additional costs and leads to further challenges with other causes of hypogammaglobulinemia other than CVID, this review points out essential patient features where testing should instead be focused. Identified patient features based on this review that should lead to quantitative immunoglobulin testing include a personal history of recurrent sinopulmonary infections, individual or family history of autoimmune conditions, computed tomography (CT) chest with non-traction-related bronchiectasis, and middle to lower lobe pattern of lung involvement on CT.

Key words: sarcoidosis, combined variable immunodeficiency, CVID, granulomatous lymphocytic interstitial lung disease, GLILD

Introduction

Sarcoidosis and CVID (combined variable immunodeficiency) are disorders that can impact multiple organs, including the lungs, eyes, joints, central nervous system, and skin, with non-caseating granulomas present in both conditions (1,2). The pathologic similarities between sarcoidosis and CVID, especially the rare presentation of granulomatous lymphocytic interstitial lung disease (GLILD), is why there continues to be a clinical association between these two conditions. Previous literature has reported an initial diagnosis of sarcoidosis, followed by a more accurate diagnosis of CVID once immunoglobulins were evaluated (1,3). There is ongoing controversy about how best to screen, diagnose, and

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Accepted: 19 August 2025
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treat individuals with presentations that could be related to either sarcoidosis or CVID (3). This single-center retrospective review addresses the overlapping and diagnostic dilemma between these two conditions, which respond to fundamentally different treatments.

Methods

This study obtained ethics approval from the institutional review board (2024H0168). Data was collected from the past 17 years (2024-2007) at a single large Midwestern academic medical center with a large sarcoidosis referral base. ICD-9 and ICD-10 codes for CVID and sarcoidosis based on billing for outpatient encounters were used to identify individual patients and screening accounted for multiple visits for the same individual. Those with each and both conditions based on outpatient billing codes within an outpatient encounter were identified. All those identified as having both conditions based on billing codes were selected for review. A sample of the most recent 45 encounters was also identified for review of clinical features and radiographic findings from each sarcoidosis and CVID group. The CT chest images and radiology reports for each identified subject were reviewed by a board-certified pulmonologist to assess for patterns. The absolute and the percentage of cases were reported. Where median data was used the interquartile range (IQR) was also calculated. Using Prism GraphPad, Fisher's exact tests were used to assess the significance of categorical variables between two groups and was utilized given the small sample size in the CVID misclassified as sarcoidosis group.

Results

1920 cases of sarcoidosis and 231 cases of CVID from 2024-2007 were identified. Eight individuals were identified as having both CVID and sarcoidosis as diagnosis codes in the same outpatient clinical encounter. CT chest images were available for all the individuals reviewed. Due to limited pathology and bronchoscopy data, these were excluded from analysis. Among those with both Sarcoidosis and CVID listed in the same encounter, sarcoidosis was the initial diagnosis in all eight identified individuals. There was an average of 5.4 years between the initial sarcoidosis and later CVID diagnosis. One of the individuals was treated with Rituximab before diagnosis of CVID, and thus, it is unclear if it genuinely represents CVID or a secondary cause of hypogammaglobulinemia. Six of the eight individuals also had a history of recurrent pulmonary or sinus infections before their CVID diagnosis. In all these individuals with recurrent infections, infections improved following immunoglobulin replacement. None of the eight individuals identified had a personal or immediate family history of other autoimmune conditions based on past medical and family history available in chart review. Six of the eight individuals identified had been treated with immunosuppression for the management of sarcoidosis before the eventual diagnosis of CVID. All six of these individuals were treated with varying doses of Prednisone before their CVID diagnosis. Three were also treated with Methotrexate in combination with Prednisone, and one was treated with Imuran in combination with Prednisone. The demographics of those found to have both sarcoidosis and CVID diagnoses are compared to those with either sarcoidosis or CVID in Table 1. Table 2 compares the CT findings of sarcoidosis and CVID alone to those given both sarcoidosis and CVID diagnoses. All of those identified as both sarcoidosis and CVID diagnoses were found to have CT chest abnormalities consistent with lung parenchymal involvement consisting of middle and lower lobe infiltrates when present.

Discussion

Sarcoidosis and Common Variable Immunodeficiency (CVID) are both rare conditions that primarily affect adults and are characterized by the formation of granulomas (4). There are, however, several important clinical, pathologic, and radiographic features to help distinguish these two conditions. From a pathology perspective, CIVD granulomas are often smaller and contain very few to no fibrosis or multinucleated giant cells (5). From a radiographic perspective, CVID often presents with lower lung parenchymal involvement in contrast with the upper lobe predominant parenchymal involvement of sarcoidosis (6). CVID also often presents with a non-perilymphatic nodule distribution again in contrast to the perilymphatic distribution typically seen in sarcoidosis (6). Clinically the most striking clinical difference between these two diagnoses remains a high frequency of recurrent infections which is then linked to bronchiectasis (3,7). While there

are often few differences in the physical exam, velcro crackles on lung auscultation has been seen in 50% of CVID/GLILD patients in one cohort (7). Despite these differences distinguishing between these two pathologies remains a challenge. In this single-center retrospective case series, the overlap diagnosis based on ICD billing codes of sarcoidosis and CVID was rare, occurring in only 0.042% among those with sarcoidosis. Given the clinical difficulties in interpretation and cost-effectiveness, routine screening of immunoglobulins among those with sarcoidosis does not seem practical. If indicated, the timing of the immunoglobulin check is also essential, as steroids (a mainstay in sarcoidosis treatment) can lower immunoglobulins (8,9). All eight individuals identified with both sarcoidosis and CVID diagnoses were first diagnosed with sarcoidosis. This raises consideration for an initial inaccurate sarcoidosis diagnosis. It remains most likely that these two conditions are mistaken for one another rather than representing actual overlapping conditions. Instead of obtaining quantitative immunoglobulins universally as a part of the diagnostic work-up for sarcoidosis, as has been suggested by Pearlman et al. (10), they should instead be checked based on findings during the presentation. A reasonable starting point would be to ask history questions related to any personal or family history of recurrent sinus or pulmonary infections in the initial evaluation of all possible sarcoidosis patients. Additionally, history should include individual or family history of autoimmune conditions (11). CT findings that may indicate Common Variable Immune Deficiency (CVID) include a lower and middle lobe disease pattern and bronchiectasis in the absence of fibrosis, which could also prompt immunoglobulin testing. A multidisciplinary discussion involving

Table 1. Demographics comparing sarcoidosis and CVID diagnosis to those with Sarcoidosis or CVID diagnosis

	Sarcoidosis N=45 (45.9%)	**CVID N=45 (45.9%)**	**CVID misclassified as sarcoidosis N=8 (8.2%)**
Median Age at diagnosis	46.0 years (IQR 21.5)	49 years (IQR 20)	41.5 years (IQR 27)
Gender			
Female	25 (55.5%)	32 (71.1%)	4 (50%)
Male	20 (44.5%)	13 (28.9%)	4 (50%)
Race			
White	32 (71%)	41 (91.2%)	6 (75%)
Black	11 (24%)	1 (2.2%)	1 (12.5%)
Hispanic	0%	1 (2.2%)	1 (12.5%)
Other	2 (5%)	2 (4.4%)	0%

Table 2. CT imaging features of those with lung parenchymal involvement of disease. Thirty individuals were in the sarcoidosis group, twenty were in the CVID group, and all eight were with both diagnoses. **=could not be calculated

	Sarcoidosis N=30	**CVID N=20**	**CVID misclassified as Sarcoidosis N=8**	**p-value**
Bronchiectasis				<0.0001
None	26 (86.3%)	9 (45%)	6 (75%)	
Mild	1 (3.4%)	6 (30%)	1 (12.5%)	
Moderate to Severe	3 (10.3%)	5 (25%)	1 (12.5%)	
Distribution of Lung Parenchymal Involvement				<0.0001
Upper Lobe Predominant	11 (37.9%)	0 (0%)	0 (0%)	
Middle and Lower Lobe Predominant	6 (20.7%)	9 (45%)	6 (75%)	
Diffuse	13 (41.4%)	11 (55%)	2 (25%)	
Lung Nodules				
None	6 (20.7%)	7 (35%)	3 (37.5%)	**
Less than 3cm	24 (79.6%)	13 (65%)	5 (62.5%)	
3cm or larger	0 (0%)	0 (0%)	0 (0%)	

radiology and pathology, similar to what is done for interstitial lung disease, may further enhance the diagnostic accuracy of these challenging clinical presentations. The primary limitation of this review is that identification was based on ICD-based billing. While not able to be evaluated with the available data, it would have also been helpful to assess the population of those with sarcoidosis whose evaluation of serum immunoglobulins changed clinical course or management. A database of sarcoidosis patients and CVID patients with granulomas may also help reveal natural history differences between these conditions (12). Based on the observation that CVID is only rarely misdiagnosed as sarcoidosis, we do not recommend routine screening for CVID in all cases of suspected sarcoidosis. However, there are certain presenting features, such as recurrent sinusitis, bronchitis, and the presence of bronchiectasis, that warrant screening for CVID.

References

1. Allaoui A, Moudatir M, Echchilal K, Alaoui FZ, Elkabli H. A misleading diagnosis of sarcoidosis in an older woman. Eur J Case Rep Intern Med. 2017;4(4):000463. doi:10.12890/2017_000463
2. Friedmann D, Unger S, Keller B, et al. Bronchoalveolar lavage fluid reflects a TH1-CD21low B-cell interaction in CVID-related interstitial lung disease. Front Immunol. 2020;11:616832. doi:10.3389/fimmu.2020.616832
3. Gupta S, Pattanaik D, Krishnaswamy G. Common variable immune deficiency and associated complications. Chest. 2019;156(3):579–93. doi:10.1016/j.chest.2019.05.009
4. Buso H, Discardi C, Bez P, et al. Sarcoidosis versus granulomatous and lymphocytic interstitial lung disease in common variable immunodeficiency: a comparative review. Biomedicines. 2024;12(7):1503. doi:10.3390/biomedicines12071503
5. van Stigt AC, von der Thüsen JH, Mustafa DAM, et al. Granulomas in common variable immunodeficiency display different histopathological features compared to other granulomatous diseases. J Clin Immunol. [INCOMPLETE]
6. Scarpa R, Cinetto F, Milito C, et al. Common and uncommon CT findings in CVID-related GL-ILD: correlations with clinical parameters, therapeutic decisions and potential implications in the differential diagnosis. J Clin Immunol. 2023;43(8):1903–15. doi:10.1007/s10875-023-01552-1
7. Bouvry D, Mouthon L, Brillet PY, et al. Granulomatosis-associated common variable immunodeficiency disorder: a case-control study versus sarcoidosis. Eur Respir J. 2013;41(1):115–22. doi:10.1183/09031936.00189011
8. Prasse A, Kayser G, Warnatz K. Common variable immunodeficiency-associated granulomatous and interstitial lung disease. Curr Opin Pulm Med. 2013;19(5):503–9. doi:10.1097/MCP.0b013e3283642c47
9. Papanikolaou I, Shigemitsu H, Afthinos A. Immune status in sarcoidosis: one size does not fit all. Monaldi Arch Chest Dis. 2020;90(3):1306. doi:10.4081/monaldi.2020.1306
10. Perlman DM, Sudheendra MT, Racilla E, Allen TL, Joshi A, Bhargava M. Granulomatous-lymphocytic interstitial lung disease mimicking sarcoidosis. Sarcoidosis Vasc Diffuse Lung Dis. 2021;38(3):e2021025. doi:10.36141/svdld.v38i3.11114
11. Shanks AM, Alluri R, Herriot R, Dempsey O. Misdiagnosis of common variable immune deficiency. BMJ Case Rep. 2014;2014:bcr2013202806. doi:10.1136/bcr-2013-202806
12. Gerke AK, Judson MA, Cozier YC, Culver DA, Koth LL. Disease burden and variability in sarcoidosis. Ann Am Thorac Soc. 2017;14(Suppl 6):S421. doi:10.1513/AnnalsATS.201707-564OT