

# Common variable immunodeficiency for the internist – a case report

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European Journal of Medical Case Reports

Volume XX(XX):01–05

DOI: XXXX



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## ABSTRACT

**Background:** Common variable immunodeficiency (CVID) is recognized as the most common form of primary immunodeficiency. Despite its prevalence, CVID often remains underdiagnosed due to its heterogenous clinical manifestations and a lack of awareness among healthcare providers. Early and accurate diagnosis is crucial, as it significantly impacts patient management and outcomes. This case report aims to highlight notable features of CVID, emphasizing the importance of enhanced detection and awareness.

**Case Presentation:** A 39-year-old male, with no significant medical history, presented with recurrent sinopulmonary infections characterized by intermittent fevers and respiratory symptoms over several months. Initial examinations during his first hospital admission revealed patchy lung consolidations and positive tests for human rhinovirus and influenza A. Despite treatment, follow-up was missed, leading to a subsequent hospital admission. Further investigations, including computed tomography scans and biopsies, were negative for infections and malignancies but revealed deficiencies in immunoglobulins IgA, IgM, and IgG. The patient's inadequate response to pneumococcal vaccination confirmed the diagnosis of CVID. He was initiated on intravenous immunoglobulin therapy, aimed at reducing the frequency and severity of infections.

**Conclusion:** This case underscores the challenge of diagnosing CVID amidst recurrent infections and the pivotal role of immunoglobulin testing in suspected cases. Heightened clinical awareness and consideration of CVID in patients with recurrent sinopulmonary infections are essential. Early intervention with appropriate therapy can significantly improve patient outcomes and quality of life. Further research and education are necessary to address gaps in knowledge and management, especially in regions with limited data on CVID prevalence.

**Keywords:** Common variable immunodeficiency, recurrent infections, sinopulmonary infections, immunoglobulins, clinician education, case report.

**Type of Article:** CASE REPORT      **Specialty:** Internal Medicine

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**Received:** 11 October 2025

**Revised (1):** 20 November 2025

**Accepted:** 24 November 2025

## Introduction

Common variable immunodeficiency (CVID) is a primary humoral immunodeficiency disorder characterized by diminished serum levels of immunoglobulins, recurrent infections, enteropathy, autoimmunity, and an elevated risk of malignancy. While patients may present in childhood, the majority of them are diagnosed in their second to fourth decades of life [1]. Clinical manifestations of CVID include infections (such as pneumonia, bronchitis, gastroenteritis, otitis), autoimmune issues (such as immune thrombocytopenia, autoimmune hemolytic anemia), gastrointestinal issues (such as chronic diarrhea, malabsorption), lymphadenopathy, and splenomegaly [1,2]. The International Consensus Document (ICON) diagnostic criteria for CVID are shown in Table 1 [2]. Despite being the most prevalent form of primary

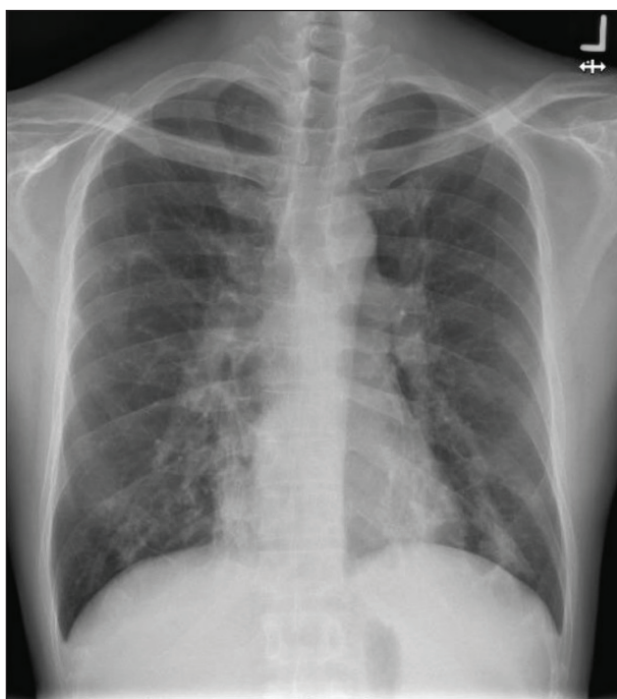
immunodeficiency [1], it is underdiagnosed due to a combination of factors such as a lack of physician awareness, low index of suspicion, and heterogenous clinical manifestations. We present this case report to highlight some of the features of this disease entity, to raise knowledge, and to improve the detection of the disease.

**Table 1.** ICON diagnostic criteria.

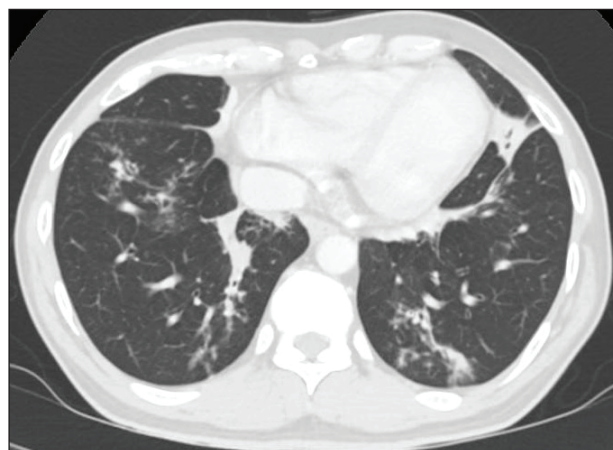
1.	IgG level less than 2 standard deviations below age-appropriate references for 2 measurements more than 3 weeks apart unless the level is very low
2.	Either a low IgA or IgM
3.	Poor antibody responses to vaccination
4.	Greater than 4 years of age
5.	No secondary causes of hypogammaglobulinemia

## Case Presentation

A 39-year-old male, a non-smoker, with no known medical history, was admitted twice in the span of 7 months for intermittent fevers with respiratory symptoms. During his first admission in February 2024, he reported a recent history of COVID-19 infection in December 2023, followed by an intermittent fever occurring once or twice a week associated with rhinorrhea and cough, lasting for 2 months. Prior to this admission, he had never been admitted for sinopulmonary infections. Sexual history was unremarkable for high-risk behaviors. There was no significant animal exposure or travel history. He was febrile with a pulse rate of 110, blood pressure 115/80 mmHg, and oxygen saturation of 96% on room air, with bilateral crepitations on lung auscultation, no enlarged lymph nodes, and no peripheral oedema on physical examination. A chest radiograph (Figure 1) showed patchy consolidation in the bilateral lower zones and right middle zone of the lungs. A respiratory multiplex polymerase chain reaction taken from the nose and throat was positive for both Human Rhinovirus and Influenza A. He was treated with a course of Levofloxacin and Oseltamivir, and further evaluated for other causes of the prolonged fever. Blood cultures, HIV testing, and mycobacterial smears were all negative. A contrasted CT scan of the chest, abdomen, and pelvis was significant for scattered areas of bronchial wall thickening and peribronchial nodularity (Figure 2); mild hepatosplenomegaly (Figure 3), and lymphadenopathy above and below the diaphragm. However, the lymph nodes were only borderline enlarged (up to 1.2 cm) with no optimal sites for biopsy. It was thought that the lymph



**Figure 1.** Chest radiograph on first presentation, showing patchy opacification in bilateral lower zones and right mid zone.



**Figure 2.** CT of the thorax, showing scattered areas of bronchial wall thickening and peribronchial opacification, scattered areas of centrilobular and tree-in-bud nodularity.



**Figure 3.** CT of the abdomen showing mild hepatosplenomegaly.

nodes may be reactive to current infection, and he was discharged with a scheduled follow-up to repeat the CT scan after treatment of the pneumonia.

He failed to attend his follow-up appointments and presented again in September 2024, having seen his general practitioner 3 times for separate episodes of flu-like illnesses since the previous admission. A repeat chest radiograph showed worsening of the right perihilar air-space opacities. He was reviewed by an infectious disease specialist for his recurrent sinopulmonary infections, who arranged additional investigations. Levels of immunoglobulins IgA, IgM, and IgG were tested and were all deficient. A repeat CT scan again showed splenomegaly, borderline enlarged lymph nodes, with worsening of lung parenchymal changes. There were intervening areas of lung consolidation in the right lower lobe, middle lobe, and lingula segment, and new clusters of centrilobular and tree-in-bud nodules in both lungs (Figure 4). Chronic respiratory infections, particularly mycobacterial infection, were considered since tuberculosis is endemic in Singapore. Bronchoscopy with transbronchial lung and lymph node biopsy was performed. The samples were negative on bacterial and fungal cultures and on PCR. Histopathology of the lymph node was negative for malignancy and granulomas, while the lung biopsy histology showed acute and chronic inflammatory cells, negative for epithelial dysplasia or carcinoma (Figure 5). A summary of his investigation results is shown in Table 2.

Following discharge, his vaccine response was assessed. IgG antibodies to 23 serotypes of *Streptococcus pneumoniae* were tested and were all low at baseline. He received a dose of PCV13 pneumococcal vaccine but repeat streptococcal IgG antibodies tested 5 weeks later remained low at <0.1–0.1 mcg/ml, where the cut-off of >1.0 mcg/ml reflects an immune response to the vaccine. He was diagnosed with CVID, initiated on IV immunoglobulin and has since avoided readmission for infections.

## Discussion

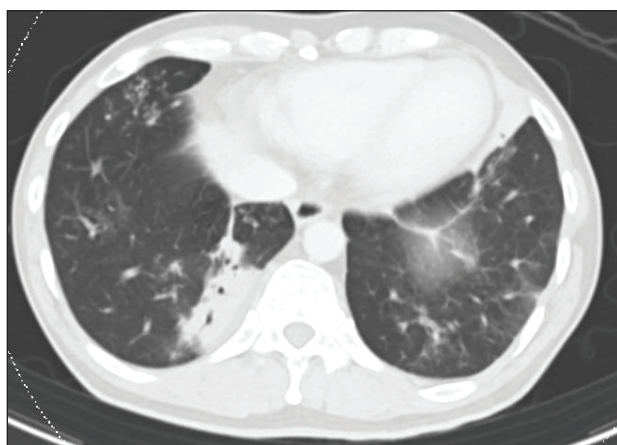
Given the low IgG, IgA, and IgM, poor vaccination response, and his age, the patient meets the ICON diagnostic criteria in Table 1. Since CVID is a primary

immunodeficiency disorder, secondary causes of hypogammaglobulinemia had to be excluded. Extensive microbiological testing excluded HIV, tuberculosis, and fungal infections. Histopathological testing excluded lymphoma and granulomatous diseases like sarcoidosis. There was no evidence of underlying liver disease, nephrotic syndrome, or protein-losing enteropathy on clinical examination, laboratory tests, and imaging. Finally, he was not on immunosuppressive medications.

While radiologic findings are not part of the diagnostic criteria, they are valuable in reaching the diagnosis. Airway abnormalities such as bronchiectasis, mucus impaction, and airway thickening are the most common lung findings seen on lung CT [3,4]. Distal mucoid impaction appears as centrilobular and tree-in-bud nodularity [3,4], which was described in this case. Other significant lung changes seen in CVID include interstitial lung disease, pulmonary lymphoma, and granulomatous lymphocytic interstitial lung disease (GLILD) - a rare entity unique to CVID [3,4]. GLILD is characterized by lower lung-predominant nodularity, consolidation, and interlobular septal thickening on CT imaging. If performed, lung function testing may demonstrate a mixed obstructive-restrictive pattern.

This case illustrates that CVID is often diagnosed only after repeated presentations before the diagnosis is made. The process of confirming the diagnosis also requires extensive investigations and is often invasive, such as endoscopy and biopsies, to exclude other causes. When facing a patient with recurrent infections, clinical suspicion of an underlying disorder is essential, and screening immunoglobulin levels is a useful tool that can reveal a diagnosis of CVID. CVID is treatable with intravenous immunoglobulin, which has been shown to be cost-effective [5].

Being a rare disorder, physicians' familiarity with the condition is limited. Data on CVID is mostly from Western countries, while information from Africa and Asia is lacking. Despite Singapore being a well-resourced, economically developed country, there is little information on CVID prevalence [6]. This contributes to poor physician awareness and delays in diagnosis, leading to greater patient morbidity and mortality. Locally, apart from HIV, the field of immunodeficiency is generally managed by pediatricians rather than internists. Internist training rarely includes any teaching on immunodeficiency, and it is common for an internist to complete training without encountering a patient with primary immunodeficiency. This leads to a low index of suspicion for CVID among physicians managing adult patients. Given the frequency with which internists encounter patients with recurrent infections, it is conceivable that many opportunities to diagnose immunodeficiencies are missed. This observation stands in notable contrast to the pediatric setting, where increased knowledge and vigilance among specialists have led to greater

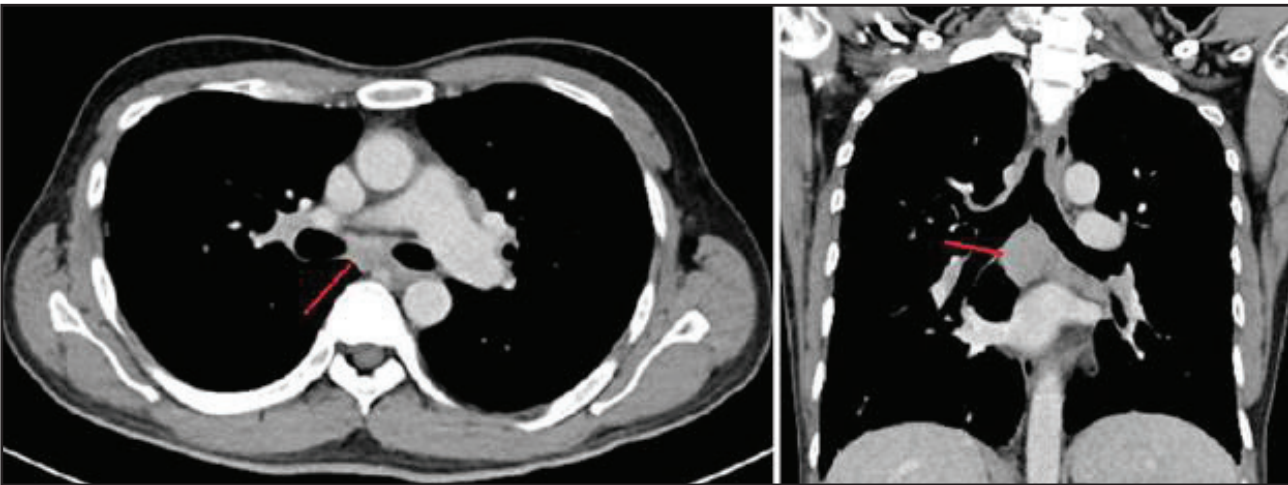


**Figure 4.** CT of the thorax during the second admission, showing worsening lung consolidation.



**Table 2.** Results of key investigations performed.

	RESULT	REFERENCE RANGE
IgG, serum	2.25 G/l	5.49-17.11 G/l
IgA, serum	<0.05 G/l	0.47-3.59 G/l
IgM, serum	0.08 G/l	0.15-2.59 G/l
HIV Ag/Ab	Negative	
Melioidosis serology	Negative	
Vaccination status		
Tetanus IgG Ab	Positive	
Mumps IgG	Positive	
Measles IgG	Negative	
<i>Streptococcus pneumoniae</i> IgG Ab	Low for all 23 serotypes	
Microbiology (bronchoalveolar lavage)		
Gram stain and culture	No growth	
Fungal microscopy and culture	No growth	
Galactomannan antigen	0.28 (negative)	Negative: <0.5 Positive: ≥0.5
<i>Mycoplasma pneumoniae</i> PCR	Negative	
<i>Chlamydia pneumoniae</i> PCR	Negative	
<i>Legionella pneumophila</i> PCR	Negative	
<i>Bordetella pertussis</i> PCR	Negative	
<i>Bordetella parapertussis</i> PCR	Negative	
<i>Legionella</i> culture	Negative	
AFB smear and culture	Negative	
TB DNA amplification	Negative	
<i>Pneumocystis jirovecii</i>	Negative	
Galactomannan	Negative	
HSV antigen	Negative	
CMV antigen	Negative	
Histopathology		
Transbronchial lymph node biopsy	Lymphoid sample, negative for granulomas and metastatic carcinoma	
Transbronchial lung biopsy	Bronchial mucosa with acute and chronic inflammatory cells, negative for epithelial dysplasia and carcinoma	



**Figure 5.** Subcarinal lymph node that was biopsied. Red arrow denoting the 1.6 cm enlarged subcarinal lymph node that was biopsied, which was negative for granulomas and metastatic carcinoma.

diagnostic recognition of primary immunodeficiencies in younger patients. This emphasizes the need for targeted education for internal medicine trainees to improve clinical outcomes.

## Conclusion

Given the prevalence of sinopulmonary infections, there is a real possibility of underdiagnosis of CVID. Clinicians need to be aware of the important clinical features of CVID and consider testing for immunoglobulin deficiencies in the appropriate group of patients.

### What is new

This case highlights the diagnostic challenge in an adult patient cohort in Singapore, where adult primary immunodeficiency is rarely suspected by internists, and physician training often does not include primary immunodeficiencies. Given the frequency that internists encounter patients with recurrent infections, it is conceivable that many opportunities to diagnose immunodeficiencies are missed. It is important for clinicians to be aware of the important clinical features of and consider testing for immunoglobulin deficiencies in the appropriate group of patients.

### List of Abbreviations

CVID Common variable immunodeficiency  
 IVIG Intravenous immunoglobulin

### Conflict of interest

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

### Funding

None.

### Consent for publication

Written informed consent was obtained from the patient.

### Ethical approval

Ethical approval is not required at our institution to publish an anonymous case report.

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## Summary of the case

1	Patient (gender, age)	39 years, male
2	Final diagnosis	CVID
3	Symptoms	Recurrent sinopulmonary infections
4	Medications	Intravenous immunoglobulins
5	Clinical procedure	Bronchoscopy with transbronchial lung and lymph node biopsy
6	Specialty	Internal medicine