Case Report

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From recurrent infections to ulcerative colitis: a case report on the diagnostic challenge of CVID

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Introduction and importance: Common Variable Immunodeficiency (CVID) is a rare primary immunodeficiency with complex presentations, including recurrent infections and autoimmune diseases. Given its rarity and overlapping symptoms with other gastrointestinal and infectious conditions, it is often overlooked. This case underscores the importance of considering CVID as a differential diagnosis when evaluating patients with recurrent infections and persistent gastrointestinal manifestations. It highlights the complexities of diagnosing and managing multifaceted, multisystemic disorders and reinforces the need for a personalized approach to treatment.

We present a 68-year-old male with recurrent infections, gastrointestinal symptoms, and a family history of autoimmune disease and consanguinity. Initially diagnosed with malabsorption syndrome, the patient was later found to have ulcerative colitis (UC) and CVID.

Case presentation: A 68-year-old Asian male with a history of recurrent pulmonary infections, chronic diarrhea, and fatigue presented with a family history of autoimmune diseases. Investigations revealed a marked reduction in immunoglobulin levels, leading to the diagnosis of CVID. Further investigations, including a colonoscopy, confirmed the presence of UC.

The patient was treated with intravenous immunoglobulin (IVIG), corticosteroids, and azathioprine. The patient's condition stabilized, and his infection frequency reduced significantly.

Discussion: This case illustrates the complexity of diagnosing CVID, particularly when accompanied by autoimmune disorders like UC. The patient's overlapping symptoms of chronic infection, gastrointestinal distress and lack of proper follow through led to delayed diagnosis and treatment.

Conclusion: This case underscores the importance of considering CVID in patients with recurrent infections and unexplained gastrointestinal symptoms, particularly when there is a family history of autoimmune diseases.

Keywords: autoimmune disorder, case report, CVID, immunodeficiency, ulcerative colitis

Method

This case report has been prepared in line with the SCARE 2023 criteria[1].

Introduction

Common Variable Immunodeficiency (CVID) is a primary immunodeficiency characterized by impaired B cell differentiation and defective immunoglobulin production. The term "variable" describes the disorder's varied clinical symptoms, which include gastrointestinal illnesses, autoimmune diseases, chronic lung disease, recurrent infections, and an increased risk of cancer[2]. CVID is likely in male or female patients who exhibit a marked decrease in IgG (at least 2 SD below the mean for age) and a marked decrease in at least one of the isotypes IgM or IgA, and who fulfill all of the following criteria:

1. Onset of immunodeficiency at greater than 2 years of age.
2. Absence of isohemagglutinins and/or poor response to vaccines.
3. Defined causes of hypogammaglobulinemia have been excluded.[3]

CVID affects both adults and children[2]. It was first recognized in 1953[4]. About 1/25,000 Caucasians are affected by CVID; patients have a significant decrease in blood levels of IgG (typically <300 mg/dL) and IgA (~ 5 mg/dl). Approximately half of the

HIGHLIGHT FOR CVID

- Common Variable Immunodeficiency and related presentations of the disease.
- CVID and its challenges for the diagnosis and treatment.
- Importance of family history and lineage in the contribution to the disease.
- Determining quality of life with CVID.
- Immuno deficiency in middle age population.

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patients also have a decrease in IgM (< 30 mg/dl)[5]. Africa and Asia are typically the regions where we know the least about CVID. On the other hand, observed prevalence is comparatively high (from West to East) in North America, Europe, and Australia, where CVID has been more extensively reported in a number of nations. The prevalence of CVID in India was found to be 0.001[6].

Despite decades of investigations, the main cause of CVID is not known; however, environmental and genetic factors are known to be involved. Since most primary immunodeficiencies are inherited in an autosomal recessive manner, regions with high rates of consanguineous marriage tend to have a higher prevalence of them[7].

In this paper, we present a 68-year-old Asian male with a history of recurrent pulmonary infections, gastrointestinal symptoms, and a family history of autoimmune diseases, including vitiligo and Hashimoto's thyroiditis who was diagnosed with and is currently under treatment for CVID, UC, and celiac disease.

Patient information

Patient history

A 68-year-old male, Asian (origin: India), initially presented on 11 September 2001 with recurrent pulmonary infections and unexplained gastrointestinal symptoms, including chronic diarrhea, severe fatigue, and weakness. The patient has a strong family history of autoimmune diseases, including a sister with Hashimoto's thyroiditis and three brothers with vitiligo. His parents were married in a consanguineous union.

Clinical course, laboratory findings, and diagnosis

a. **Initial Presentation and Suspected Conditions**: The patient's initial presentation led to the suspicion of an underlying gastrointestinal disorder. His initial stool examinations were negative for ova and parasites. Immunoglobulin assays revealed an IgM level of 80.7 mg/dL, which was normal. However, the patient did not follow through leading to prolongation in diagnosis and treatment. In the following years, the patient had multiple infections and symptoms, underwent numerous investigations and evaluations but due to a lapse in follow-up, a definite diagnosis was not reached. Various diagnostic tests, including those for intestinal tuberculosis, celiac disease, and inflammatory bowel disease, were ordered to investigate potential causes (Table 1).

Table 1

Patient's lab results through the clinical course of 2001–2009.

Investigations	Patient's Value	Normal range
Alpha 2 globulin	1.28 g% (H)	0.35–1.03 gm%
Gamma globulin	0.57 g% (L)	0.6–1.82 gm%
ELISA done for TB-IgG	<100 U/mL (L)	<125 U/mL
ELISA done for TB-IgM (Normalized value)	0.6 (L)	<0.8
Gliadin anti IgA	1.8 (N)	<20 units/mL
Gliadin anti IgG	1.2 (N)	<30 units/mL
Immunoglobulins		
IgG	385 mg/dL (L)	650–1600 mg/dL
IgM	34.9 mg/dL (L)	54–300 mg/dL
IgA	29.6 mg/dL (L)	40–350 mg/dL

b. **Serum Protein Electrophoresis (10 November 2001):** A significant finding of an elevated alpha-2 globulin level of 1.28 g% and a low gamma globulin level of 0.57 g%, suggesting an underlying immunodeficiency and prompting further investigation. However, the patient was lost to follow-up. The patient continued to experience minor infections and gastrointestinal symptoms. As the patient himself is a medical professional, he continued to self-treat.

c. **ELISA Testing for Koch's Disease and Brucellosis (7 August 2006)**: Given the patient's prolonged gastrointestinal symptoms, an ELISA test was performed to rule out tuberculosis (Koch's disease). The test was negative (Table 1) shifting the focus away from intestinal tuberculosis. Standard tests for Brucella, brucella-abortus, and brucella-melitensis were conducted, all of which were negative, hence, pointing towards other potential causes like tropical sprue or celiac disease.

d. **Diagnosis of Tropical Sprue (8 March 2007)**: A biopsy of the ileum revealed malabsorption syndrome possibly tropical sprue with partial response. Initially treated with antibiotics, the patient's symptoms improved temporarily for some years. However, the recurrence of symptoms raised concerns about an underlying or concurrent condition, leading to further testing.

e. **Serology for Celiac Disease (6 January 2009)**: Serological tests for celiac disease showed Gliadin anti-IgA at 1.8 and Gliadin anti-IgG at 1.2, which were not markedly elevated for the diagnosis. However, the trial of a gluten-free diet improved his symptoms, raising suspicion of possible celiac disease. Despite the unremarkable results of the immunoglobulin tests, this raised the suspicion of underlying immunodeficiency.

f. **Immunoglobulin Levels (3 March 2009)**: As the patient's symptoms relapsed frequently and he had previously been diagnosed with hypogammaglobulinemia, immunoglobulin levels were assessed. The immunological evaluation revealed significant decreases in IgG, IgM, and IgA (Table 1) consistent with a diagnosis of CVID.

g. **Laboratory Evaluation for Ulcerative Colitis (UC) and Anemia (23 March 2010):** Later in 2010, the patient presented with bloody diarrhea, severe fatigue, and weakness. A Complete Blood Count (CBC) and iron profile were conducted, which revealed the findings as shown in Table 2.

These findings indicated microcytic hypochromic anemia caused by severe iron deficiency, possibly due to chronic gastrointestinal blood loss, malabsorption, or chronic conditions like CVID or UC. Suspecting UC, a colonoscopy and biopsy were performed later, which confirmed the diagnosis.

Treatment

The patient had multiple respiratory and intestinal infections, which he self-treated. After the diagnosis of CVID, he was started on intravenous immunoglobulin (IVIG) therapy alongside treatments for UC, celiac disease, and recurrent mucosal infections. His treatment regimen included:

IVIG: 500 mg/kg every 3–4 weeks to manage CVID and prevent infections.

Table 2

Table showing CBC and Iron studies done in 2010.

Investigations	Patient's Value	Normal value
Hemoglobin	10 g/dL (L)	13.5–18 g/dL
Packed Cell Volume	39.4% (L)	42–52%
Mean Corpuscular Volume	75.5 cubic/ micron (L)	Adult: 80–95 cubic/micron Child: 96–108 cubic/micron
Mean Corpuscular Hemoglobin	24.8 pg (L)	Adult: 27–31pg Child: 32–38 pg
Total Iron	25 mg/dL (L)	Male: 50–150 mg/dL Female: 35–145 mg/dL
TIBC	501 mcg/dL (H)	250–450 mcg/dL
Unbound IBC	476 mcg/dL (L)	111–343 mcg/dL
S.Transferrin	351 mcg/dL (N)	215–380 mcg/dL
Transferrin Saturation	4.99% (L)	Male: 15–50% Females: 20–50%
S.Ferritin	3.93 mcg/L (L)	Male: 24–336 mcg/L Female: 11–307 mcg/L

Mesalamine (5-ASA): 800 mg thrice daily to reduce inflammation in the colon associated with UC.

Corticosteroid (Prednisone): 50 mg daily during UC flare-ups, with gradual tapering.

Azathioprine: 2 mg/kg daily to maintain UC remission and reduce steroid dependency.

Gluten-Free Diet: Strict adherence for celiac disease management.

Iron Supplementation: Intravenous iron sucrose at 200 mg every 1–2 weeks to correct severe iron deficiency anemia due to chronic gastrointestinal blood loss.

The patient was advised to continue the medication, and he was compliant with it. No flare-ups occurred during this period.

Follow-up and current condition: The patient was stable without any symptoms until July 2024, when he developed Streptococcal right upper lobe pneumonia (Fig. 1), which was treated with a single course of antibiotics (linezolid). He is currently being followed up every 2–3 months; however, he is reluctant to undergo any further tests as he is in stable condition without any symptoms.

Discussion

This case illustrates the complexity of diagnosing and managing overlapping pulmonary, gastrointestinal, and immunological disorders, especially with a strong family history of autoimmune diseases and consanguinity. The combination of malabsorption syndrome due to tropical sprue, a celiac-like clinical presentation, iron deficiency anemia, and an eventual UC diagnosis posed significant diagnostic and management challenges. The addition of CVID further complicated the clinical picture, necessitating a personalized and multidisciplinary treatment approach. Early recognition, treatment, and patient education in such cases are crucial to prevent long-term complications.

When CVID is diagnosed, patients have typically undergone evaluations by numerous specialists due to the multiple organ systems affected by the disease's clinical symptoms. CVID can present with infections (acute or chronic), hematologic or organ-specific autoimmunity, chronic lung disease, bronchiectasis, gastrointestinal inflammatory disease, malabsorption, granulomatous disease, liver disease/hepatitis, lymphoma, and other cancers[4]. In our case the patient had recurrent lung infections and chronic diarrhea.

Usually, the diagnosis is made when the patient is between the ages of 20 and 40. Due to the heterogeneous nature of the disease, a delay in diagnosis of 6 to 7 years is commonly noticed[4]. In this case, the patient had initially presented in his mid 40s and was diagnosed with CVID 8 years later, owing to the inconsistent follow-up of the patient.

Like the majority of the patients, our patient also initially experienced recurrent respiratory tract infections. There is a considerable delay in diagnosis due to its rarity and substantial clinical variability. Obtaining a low-cost, quantitative measurement of serum immunoglobulins is the initial and crucial stage in diagnosing CVID[8]. The initial investigation revealed a low gamma globulin level of 0.57 gm%, which prompted further investigations toward immunodeficiency. However, the patient was lost to follow-up.

Given the lack of patient adherence to follow-up and the rarity of reported immunodeficiency in the region, initial serologic testing for celiac disease was done. The unremarkable results for CD, temporary improvement of symptoms following a gluten-free diet, and subsequent recurrence of symptoms led to the suspicion of immunodeficiency. Haplotype analysis, homozygosity mapping, and linkage disequilibrium suggest HLA DQ/DR as the major locus for IgA. This strongly indicates the overlap in immune pathogenesis between CVID and CD[9].

The reduction of two isotypes (IgG and IgA or IgM) is necessary for the diagnosis of CVID. IgA (normal 40-350 mg/dL) is usually significantly decreased or undetectable in the majority of patients, while IgG is usually below 500 mg/dL (normal range is

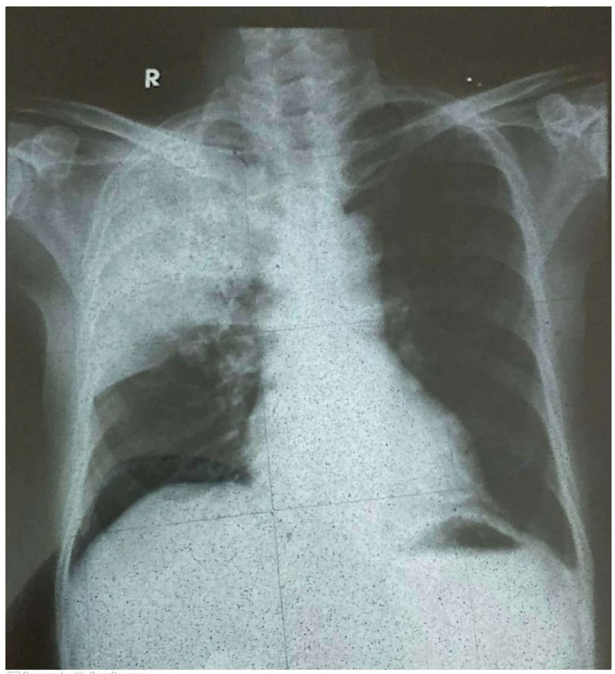

Figure 1. Lobar consolidation involving the right upper lobe of lungs.

650–1600 mg/dL)[8]. The decrease in IgG, IgA, and IgM in this patient, as shown in Table 1, led to the diagnosis of CVID.

For individuals with significant deficiencies in immunoglobulin production, immunoglobulin replacement via intravenous or subcutaneous routes is the cornerstone of treatment. Preventing infections is the main aim of immunoglobulin therapy[10]. Based on this approach to treatment, the patient was started on IVIG. Routine antibiotic prophylaxis to mitigate infections is not recommended in CVID[11]. Adhering to this recommendation, the patient was prescribed antibiotics only during infection flare-ups.

Conclusion

This case emphasizes the need for a multidisciplinary approach in diagnosing and managing complex conditions, particularly in patients with a genetic predisposition to autoimmune disorders due to family history and consanguinity. Continuous monitoring and personalized treatment strategies are essential for optimizing outcomes and improving quality of life. This case also highlights the importance of the patient's adherence to following through with the investigations to reach the diagnosis and treatment.

Ethical approval

Not applicable.

Consent

Written informed consent was obtained from the patient for the publication of this case and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal upon request.

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Author's contribution

All authors contributed in the manuscript writing, and all the reviews were formed during the process. SP – concept; SK – literature review, writing, and reviewing the manuscript; RS – literature review, supervision, writing, and editing the manuscript; MU – writing the draft.

Conflicts of interest disclosure

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