

Pneumologia

Bronchiectasis: The hidden side of common variable immunodeficiency – Case report

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Abstract

English:

This case report describes a 38-year-old female with a history of recurrent respiratory infections, leading to a diagnosis of common variable immunodeficiency (CVID). CVID, a primary immunodeficiency, is characterized by hypogammaglobulinemia and an increased susceptibility to infections, particularly in the respiratory tract. The patient exhibited bilateral cylindrical bronchiectasis, which was repeatedly superinfected, alongside persistent low levels of IgA, IgG, and IgM. The diagnosis was confirmed through laboratory immunogram analysis. Treatment with subcutaneous human immunoglobulin resulted in significant clinical improvement, including the resolution of respiratory infections and radiological changes, although bronchiectasis remained. This case emphasizes the importance of early diagnosis of CVID in patients with recurrent infections and bronchiectasis, highlighting the role of immunoglobulin therapy in improving patient outcomes. It also underscores the need for ongoing monitoring and treatment adjustments in managing this condition.

Keywords

bronchiectasis • immunodeficiency • immunoglobulin G • immunogram

Bronşiectaziile: Faţa ascunsă a imunodeficienţei comune variabile – Studiu de caz

Rezumat

Acest caz clinic descrie evoluţia unei paciente de 38 de ani, al cărei tablou clinic, marcat de infecţii respiratorii frecvente, a condus la identificarea imunodeficienţei comune variabile (CVID). CVID este o imunodeficienţă primară, caracterizată prin hipogamaglobulinemie şi o susceptibilitate crescută la infecţii, în special ale tractului respirator. Pacienta prezenta bronşiectazii cilindrice bilaterale, frecvent suprainfectate, asociate cu valori scăzute persistente ale imunoglobulinelor IgA, IgG şi IgM. Diagnosticul a fost confirmat prin analiza imunogramei de laborator. Tratamentul cu imunoglobulină umană administrată subcutanat a condus la o ameliorare clinică semnificativă, incluzând remiterea infecţiilor respiratorii şi a modificărilor radiologice, deşi bronşiectaziile au persistat. Acest caz subliniază importanţa diagnosticării precoce a CVID la pacienţii cu infecţii recurente şi bronşiectazii, evidenţiind rolul crucial al terapiei cu imunoglobuline în îmbunătăţirea evoluţiei clinice. De asemenea, evidenţiază necesitatea monitorizării continue şi a ajustării terapiei în managementul acestei afecţiuni.

Cuvinte-cheie

bronşiectazii • imunodeficienţă • imunoglobulină G • imunogramă

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Introduction

Bilateral cylindrical bronchiectasis, which develops in the context of recurrent respiratory infections, is often highly symptomatic and prone to frequent exacerbations (1). One common cause of bronchiectasis, particularly in the younger population, is common variable immunodeficiency (CVID). CVID is a heterogeneous group of immune system disorders characterized by hypogammaglobulinemia and a heightened susceptibility to recurrent infections, especially in the respiratory tract (2, 3). CVID occurs in about 1 in 25,000 individuals, making it the most common condition in the primary immunodeficiency (PID) group (4, 5).

In adults with non-cystic fibrosis (CF) bronchiectasis, the incidence of immunodeficiencies is also notably high, reaching up to 16.7%. As a result, the ERS guidelines for managing bronchiectasis recommend at least a complete blood count (CBC) and immunogram for immunodeficiency screening in these patients. In some cases, further investigations, such as determining IgG subclasses and lymphocyte subpopulations, are advised (6–8).

The diagnosis of bronchiectasis due to immunodeficiencies is based on the International Consensus Document (ICON) or The European Society for Immunodeficiencies (ESID) criteria (see Table 1). Other causes of bilateral bronchiectasis in young patients with multiple pulmonary infections include cystic fibrosis, immunoglobulin deficiencies, complement deficiencies, severe combined immunodeficiencies, Wiskott–Aldrich syndrome, HIV infection, tuberculosis, primary ciliary dyskinesia, chronic bacterial infections, autoimmune diseases, and Hyper IgM syndrome. These conditions present distinct clinical features that require further investigation for accurate differentiation (9).

In addition to bronchiectasis and other respiratory infections, patients with CVID are at risk of developing lymphoproliferative disorders, autoimmune diseases, or vasculitis. Prognosis for patients with CVID varies depending on the complications or diseases that may arise over time (10). Substitution therapy with immunoglobulins, either intravenously or

subcutaneously, is critical for preventing recurrent infections. Depending on the complications, immunomodulators, such as anti-CD20 monoclonal antibodies or cyclosporine A, may also be used, with antibiotics recommended only when infections occur (11).

Case presentation (fara clinical problems and differential diagnosis)

We report the case of a 38-year-old female patient, a nonsmoker with no occupational exposure to vapours, gases, dust, or fumes and without chronic medication. She has worked as a high school teacher for 15 years. The patient is known to experience multiple recurrent respiratory infections (>6 episodes/year), including during warmer months, not associated with periods of seasonal respiratory viruses, despite receiving annual influenza vaccination. These episodes were primarily manifested as acute bacterial bronchitis, pneumonia, otitis, or tonsillitis, each time treated with broad-spectrum antibiotics. The high frequency of infections began in early childhood and persisted into young adulthood.

The St. George Respiratory Questionnaire (SGRQ) was completed, yielding a total score of 40.37 points (symptoms – 44.45 points, activity – 37.18 points, and impact – 41.09 points).

At the initial laboratory examination (complete blood count, routine biochemical analyses, and ionogram), no significant changes were revealed. Pulmonary function tests showed normal respiratory volumes and flows, with a 32% decrease in diffusing capacity of the lungs for carbon monoxide (DLCO). Imaging examination (HRCT) revealed bronchiectasis and bilateral cylindrical bronchiectasis in small and medium-sized bronchi, some with mucoid impaction, associated with ‘ground-glass’ areas and a suggestive appearance of ‘middle lobe syndrome’ (Figure 2A).

As a screening tool for hypogammaglobulinemia in a young patient with recurrent lower respiratory tract infections throughout life, we decided to perform an immunogram

Table 1. Similarities and differences in ICON and ESID criteria for CVID diagnosis (adaptation from Lee, Theodore K et al. “State-of-the-art diagnostic evaluation of common variable immunodeficiency.” *Annals of allergy, asthma & immunology* : official publication of the American College of Allergy, Asthma, & Immunology vol. 127,1 (2021): 19-27. doi:10.1016/j.anai.2021.03.005)

CVID ICON criteria	CVID ESID criteria
5 criteria for CVID diagnosis:	ICON criteria 1 - 4 plus
(1) immunoglobulin (Ig) G level less than SD below age-appropriate references for 2 measurements more than 3weeks apart unless the level is very low (<100-300 mg/dL depending on age);	(1) decrease of IgA is required;
(2) no secondary causes of hypogammaglobulinemia.	(2) low switched memory B cells (less than 70% of age-related normal value) can be used instead of measurement of antibody response to vaccine;
(3) poor antibody responses to vaccination;	(3) no evidence of profound T cell deficiency;
(4) greater than 4 years of age;	(4) a clinical manifestation of disease such as an increased susceptibility to infection, autoimmune manifestations, granulomatous disease, or unexplained polyclonal lymphoproliferation, or an affected family member with antibody deficiency
(5) either a low IgA or IgM;	

(according to ERS 2017 recommendations), which showed the following results: IgA < 0.05 g/L (normal range: 0.65–4.21 g/L), IgG < 1.08 g/L (normal range: 5.52–16.31 g/L), IgM < 0.05 g/L (normal range: 0.33–3.93 g/L), and plasmatic protein electrophoresis was impossible to be done due to low globulins values (12).

Considering the clinical context (recurrent pneumonia and bronchiectasis with multiple complications due to secondary infections, despite routine vaccinations), low levels of IgG (<1 g/L), and low levels of IgA and IgM, we suspected primary humoral immunodeficiency.

A peripheral blood smear was performed (with a negative result), a urine analysis was conducted (to exclude loss of serum proteins), and an HIV test was conducted (with a negative result). The patient was subsequently referred to an immunologist, where the immunogram was repeated (with similar results to the initial investigation) and the panel of immunological tests was extended to exclude other immunodeficiency (lymphocyte subset panel and IgG

subclasses – with negative results) autoimmune diseases (anti-nuclear antibodies [ANA], anti-cyclic citrullinated peptide antibodies [anti-CCP], anti-neutrophil cytoplasmic antibodies [ANCA], rheumatoid factor, C3 complement, and all with negative results).

Considering the IgG values <100–300 mg/dL, significantly low IgA and IgM levels, age over 4 years, and the absence of secondary hypogammaglobulinemia suspicion during the initial evaluation, the diagnosis of CVID was established based on the ICON criteria.

It is important to mention that, considering the extremely low IgG values, the lack of clinical response to previous vaccinations, limitations in interpreting vaccine challenge responses, as well as the additional cost for the pneumococcal vaccine and two laboratory measurements of antibody titres, the criterion regarding ‘poor antibody responses to vaccination’ was considered fulfilled.

Treatment was initiated with human immunoglobulin (2.5 g/24 mL, once-weekly subcutaneous administration, or

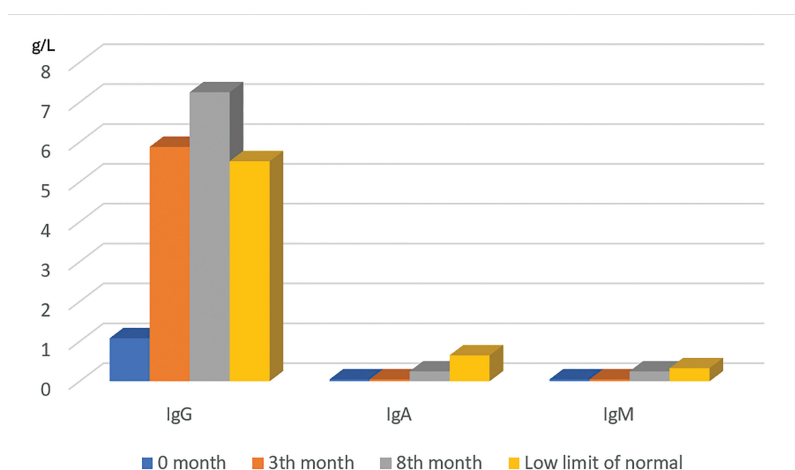


Figure 1. The patient's immunograms (mg/L) at 0, 3, and 8 months.

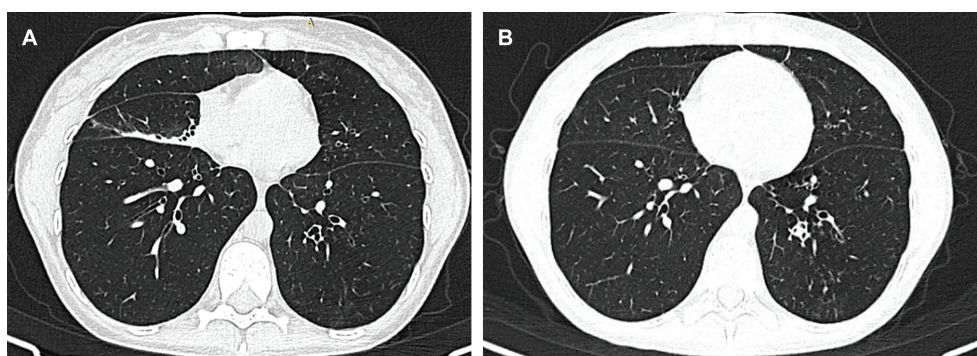


Figure 2. Chest CT image (A) at the first presentation: the appearance of ‘middle lobe syndrome’. (B) After 8 months of treatment: re-expansion of the partial atelectasis of the middle lobe.

10 g of immunoglobulin per month), with the recommendation to repeat the immunogram every 3 months.

At the 3-month laboratory follow-up, the immunogram showed normalization of the IgG values (IgG < 5.88 g/L, ref. value: 5.52–16.31 g/L), but IgA and IgM remained at low levels (<0.05 g/L). During the first 8 months of treatment, the patient did not experience any episodes of respiratory infection and despite an insignificant decreased level of DLCO (66%), was highlighted the improvement of respiratory symptoms (SGRQ, yielding a total score of 14.84 points [symptoms – 14.84 points, activity – 15.73 points, and impact – 9.17 points]). The immunogram revealed the elevation of all immunoglobulin antibodies (IgG 7.25 g/dL, IgA < 0.25 g/L, IgM < 0.25 g/L) (Figure 1). Additionally, chest CT evaluation showed the disappearance of mucoid impaction, 'ground-glass' areas, and 'middle lobe syndrome' images, but with multiple outstanding bilateral bronchiectasis (Figure 2B).

Discussion

The screening criteria for PID for a respiratory physician would include: the presence of cylindrical bronchiectasis, occurring in a recurrent infectious context (>2 episodes/year), without traction or fibrosis phenomena, in young patients (<40 years), inefficacy of active immunization, infections with opportunistic pathogens (e.g., nontuberculous mycobacteriosis), and the association of autoimmune, malignant, or hematological conditions (e.g., hemolytic anemia, thrombocytopenic purpura, autoimmune eczema, etc.). For the diagnosis of CVID, the ICON or ESID criteria are commonly used in clinical practice. The particularity of this case consists of the late diagnosis of a PID in a 38-year-old patient with multiple annual infections of the lower and upper respiratory tract throughout her life, suggesting an ongoing immunological vulnerability.

Although the patient was consulted multiple times by pulmonology and infectious disease specialists, no immunogram or other tests to assess immunity, including vaccine challenge responses, were ever performed. Thus, this case highlights the importance of using the immunogram as a screening tool for treatable immunodeficiencies, and of course, the importance of immunoglobulin replacement therapy, which in our patient resulted in a very good outcome, with immediate improvement in symptoms and quality of life (assessed by the SGRQ), as well as imaging improvements shown by HRCT evaluation. Specifically, this included the disappearance of multiple peribronchial changes, mucoid impactions, and the appearance of 'middle lobe syndrome'.

Considering the absence of associated pathology or complications, the patient's prognosis is considered

favourable. Along with the immunogram (performed at 3 months) and routine follow-up consultations with the immunologist, the patient will undergo biannual pulmonology consultations as part of the bronchiectasis status assessment, including spirometry every 6–12 months and sputum testing to investigate colonization by pathogens such as *Pseudomonas aeruginosa* and *Aspergillus spp.* A thoracic CT will also be performed initially on an annual basis and subsequently as needed. The patient's clinical status should be systematically evaluated to exclude the development of any complications or associated diseases.

Vaccination with inactivated vaccines is not recommended for this patient, considering the limited efficacy in patients with CVID undergoing IgG therapy, particularly in our patient with severe hypogammaglobulinemia G (IgG < 1.08 g/L) before starting replacement therapy, suggesting inefficient residual immunity.

Thus, this case emphasizes the diagnostic approach to CVID, the use of immunoglobulin replacement therapy, and the significant clinical and radiological improvements that can be achieved through timely intervention. However, the residual bronchiectasis underscores the long-term consequences of untreated or poorly managed primary immunodeficiencies.

Conclusions

Although considered a rare disease, PID, especially CVID, should be ruled out in cases of distinct phenotypes of bronchiectasis. We presented this clinical case to highlight the importance of recognizing this entity, active screening among target groups, and the accessibility and efficiency of treatment in CVID.

Funding

None.

Informed consent statement

Informed consent was obtained from all subjects involved in this study.

Data availability statement

Data used to support the findings of this study are available from the corresponding author upon request.

Conflicts of interest

The authors declare no conflict of interest.

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