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Case Report

Common Variable Immunodeficiency: A Long Road to Diagnosis?

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ABSTRACT

Common variable immune deficiency (CVID) is recognized as the most prevalent primary immune deficiency (PID) according to the European Society for Immunodeficiencies (ESID). It has an estimated prevalence of approximately 1 in 30,000 individuals. Meanwhile, thalassemias are an aggregate of hemoglobin disorders that involve defects in the structure of alpha or beta chains of this protein, resulting in varying degrees of severity. We present the case of a 30-year-old female patient who exhibited both these conditions, and the extensive journey underwent in order to identify the underlying cause of their hardship. This patient has a significant medical history, characterized by frequent hospital admissions resulting from recurrent respiratory tract infections. The most recent episode of infection served as an opportunity to investigate the patient's underlying immunological condition, ultimately leading to the diagnosis of CVID. The comprehensive examination of the patient's clinical history, diagnostic assessment, and treatment regimen offers valuable insights into the complexities involved in the management of immunodeficiency cases within a secondary care unit.

INTRODUCTION

CVID is a heterogeneous primary immunodeficiency disorder characterized by hypogammaglobulinemia and recurrent infections caused by either bacteria, viruses, parasites, or fungi, in this order of prevalence. CVID has a genetic component, and is the most common among the PIDs [1-5]. The ESID establishes diagnostic criteria, assigning them varying degrees of certainty. The diagnosis of CVID is based on the identification of low serum IgG levels, at least 2 standard deviations below the mean for their age. Additionally, the diagnosis requires the fulfillment of at least one of the following criteria:*1) Onset of immunodeficiency at greater than 2 years of age, 2) Absent isohemagglutinins and/or poor response to vaccines, 3) Defined causes of hypogammaglobulinemia have been excluded*. Meeting all of the aforementioned criteria raises the certainty level of the diagnosis [6]. There are also more extensive indicators that can be met, encompassing the multitude of clinical and paraclinical findings associated with this immune disorder, such as:

- *increased susceptibility to infection*
- *autoimmune manifestations*
- *granulomatous disease*

– *unexplained polyclonal lymphoproliferation*

– *affected family member with antibody deficiency*

- *AND marked decrease in IgG and marked decrease in IgA with or without low IgM*

- *AND at least 1 of the following:*

– *poor antibody response to vaccines (and/or absent isohemagglutinins)*

– *low switched memory B cells (<70% of age-related normal value)*

- *AND secondary causes of hypogammaglobulinemia have been excluded*

- *AND diagnosis is established after the fourth year of life (although symptoms may be present earlier)*

- *AND no evidence of profound T-cell deficiency, defined as 2 of the following:*

▪ *CD4 cells/µL: 2-6 years <300, 6-12 years <250, >12 years <200*

▪ *% naive CD4: 2-6 years <25%, 6-16 years <20%, >16 years <10%*

▪ *T-cell proliferation absent [4]*

The central pathophysiological mechanism thus consists of an impaired production of gammaglobulins, that can be a result of a malfunction in different immunoregulatory pathway, that affect either the B-cell, the T-cell, or the signaling between them [7].

Thalassemia is a hematological disorder in which the body's ability to produce hemoglobin is affected. As the globin genes of the adult are responsible for the synthesis of four polypeptide chains, two alpha and two beta, the situs of the defect divides the two main types of thalassemia into alpha and beta, both with varying degrees of severity [8]. Beta-thalassemia results from the absence of, or underproduction of beta-globin, with three main degrees of severity. The carrier state, also known as beta-thalassemia minor, is the mildest form of the condition, with patients typically not exhibiting any symptoms, but with a complete blood count (CBC) showing mild microcytic hypochromic normosideremic anemia. Thalassemia intermedia and thalassemia major are more debilitating forms on the spectrum, needing treatment in order to ensure a good quality of life. The pathophysiology of thalassemia is based on oxidative and mechanical damage tied to the amount of left over alpha-globin chains. These chains form tetramers, which precipitate inside the erythroid precursors, leading to the inclusion bodies observed at the microscopic exam [9].

CASE REPORT

A thirty-year-old female patient, a light smoker, having been diagnosed with minor beta-thalassemia and allergic rhinitis prior to this infection episode, known with a history of recurrent upper respiratory tract infections, was hospitalised for symptoms suggestive of pneumonia, consisting of malaise, fever (38.5°C), chills, vomiting, dyspnea, persistent cough, and right pleuritic chest pain. Last reported respiratory episode occurred two weeks prior to her current stated hospital presentation, its resolution being managed with a six-day antibiotic cure with Clarithromycin.

On clinical examination, the patient had mild tachypnea and tachycardia, with percussion dullness and crackles on auscultation in the upper right thorax, otherwise being in stable hemodynamic and respiratory condition. They also had cold sores in the right alar region, which were characteristic of an active Herpes Simplex 1 virus infection. No other significant findings.

The radiological imaging results also indicated a lower respiratory tract infection, describing consolidation in the right upper pulmonary lobe, with air bronchogram present.

Upon admission, the laboratory findings showed significant leukocytosis with marked neutrophilia (WBC= 19.45 x10^3/µL, Neutrophils=* 16.54 x10^3/µL), minor microcytic hypochromic anemia (HGB=10.4 g/dl, MCV= 66.5 fL, MCH= 22.0 pg), which is consistent with the patient's known diagnosis of thalassemia minor. Additionally, an inflammatory syndrome was identified (CRP=9.0 mg/dL, FIBRINOGEN= 578 mg/dl, ESR= 20 mm/h), as well as leukocyturia with microhematuria (LEU=500 leuc/ml, ERY=* 10 eritr/ml).

As per the proper protocol implemented to increase the chances of a successful bacterial identification [10], sputum samples were obtained before initiating empiric antibiotic therapy. The primary objective was to efficiently implement treatment by promptly administering extended-spectrum antibiotics. A secondary objective was obtaining the judicious use antibiotics, by determining the pathogen's profile of antibiotic sensitivity and resistance, necessary for a coveted efficient antimicrobial therapy de-escalation. Blood cultures

were analysed when the patient exhibited subfebrility (T=37.5°C), with the caveat that ceftriaxone therapy had already been initiated for less than 48 hours at that time. In both instances, the laboratory was unable to definitively identify the microorganism. The procedure of sputum analysis was possibly flawed by the recent exposure to Clarithromycin [10,11], as well as the challenges associated with obtaining a sputum specimen of high quality. Ideally, the sample should have been collected in the first part of the day, before eating, and after rinsing the mouth with water and expelling saliva, followed by three deep breaths and coughing consequentlyat 2-minute intervals until enough sputum was provided [12]). Another hypothesis could be that the bacteria could not grow on the provided medium.

Being that apical pulmonary infiltrate is more prevalent in Mycobacterium tuberculosis infections [13], lung tuberculosis (TB) was considered for a potential differential diagnosis. However, the Ziehl-Nielson stain failed to identify any acid-fast bacillus (AFB), which could have potentially been the causative agent for the patient's condition. Special media for mycobacterial growth were not used, and nucleic acid amplification test (NAAT) was not available, thereby preventing the definitive exclusion of the AFB etiology [14].

Although one blood sample culture yielded a result, it was deemed inconclusive, as the presence of Coagulase-negative Staphylococcus could have been a result of contamination.

Non-respiratory pathogens were also taken into consideration as potential contributors to the infectious processes following a more in-depth anamnesis. The presence of additional symptoms, such as mild odynophagia and vaginal discharge, necessitated the involvement of both an ENT doctor and a gynecologist. These specialists collaborated to investigate on the initial suspicion, and subsequently identified clinical indicators of chronic tonsillitis, including enlarged palatine tonsils and left submandibular lymphadenopathy, as well as signs of vaginitis, such as leukorrhea. The pharyngeal exudate and vaginal discharge yielded negative results for bacterial presence, however, Candida spp. was identified in both samples.

Given the recurring nature of the upper and lower respiratory infections reported by the patient, as well as other mucosal infections identified through the patient's medical history or clinical examination (such as vaginitis, tonsillitis, recurrent middle ear infections, and asymptomatic urinary tract infection), careful consideration was given to the potential presence of an underlying immunodeficiency disorder. As a result, there was a shift in focus towards immunological tests. HIV (1+2) serology tests were performed, resulting in a negative result. Subsequently, a serum protein electrophoresis was performed (with results presented in Table no. 1) and immunoglobulin (Ig) levels were measured (with results displayed in Table no. 2).

Table 1: Serum protein electrophoresis.

PROTEIN COMPONENT	VALUE	UNIT
ALBUMIN	3.8*	g/dL
ALPHA 1	0.4*	g/dL
ALPHA 2	0.8	g/dL
BETA 1	0.4	g/dL
BETA 2	0.2*	g/dL
GAMMA	0.1*	g/dL
A/G	1.94*	N/A
P.T.	5.8*	g/dL
C_ALBUMIN	66	%
C_ALPHA 1	7.2*	%
C_ALPHA 2	14.6*	%
C_BETA 1	6.7	%
C_BETA 2	3.3	%
C_GAMMA	2.2*	%

Table 2: Immunoglobulin levels.

IMMUNOGLOBULIN	VALUE	UNIT
IgG	*117	mg/dL
IgA	*27.9	mg/dL
IgM	*17.8	mg/dL

Following the consultation on this patient, the Haematology Department determined that additional testing was necessary due to the immunogram indicating significantly decreased levels of immunoglobulin G, A, and M. In consequence, the patient was referred to the National Primary Immunodeficiencies Treatment Programme, where they would receive specialized care for the intensive management of this rare condition.

Complications associated with CVID encompass a diverse array of infectious, post-infectious, as well as non-infectious manifestations. Infections arise as a natural outcome of a weakened umoral immune response, of a quantitative capacity. The most prevalent infections are those affecting the respiratory system, with infections of the upper respiratory tract ranking second to pneumonia. This is followed by infections of the gastrointestinal tract [5]. Depending on the

severity and frequency of these episodes, there are negative consequences that persist even after the resolution of the acute episode. These ramifications primarily pertain to various forms of residual structural damage, such as bronchiectasia, which is a relatively prevalent, with significant consequence that can have an impact on mortality. When discussing other undesired consequences that further expand the broader clinical spectrum of this PID, autoimmunity, systemic polyclonal lymphocytic infiltration, enteropathy, and malignancies have also been linked to it. Each category contributes with a plethora of additional manifestations. According to one study, non-infectious complications are present in more than two-thirds of patients diagnosed with this condition, while in another multi-centric prospective study, it was observed that over 80% of the participants either had only one of the aforementioned non-infection-related complications or did not have any complications at all. The overlap between these immunological findings is relatively infrequent, with a prevalence of slightly over 10% of the cases [15-18]. Another prevalent observation among individuals exhibiting this particular form of immune dysregulation is the manifestation of symptoms resembling allergies, including asthma, conjunctivitis, and allergic rhinitis. One study documented the presence of these symptoms in nearly two-thirds of the participants [19].

Treatment and evolution

The treatment approach for CVID focuses on addressing the immunological deficiency by periodically correcting the diminished levels of circulating antibodies through intravenous or subcutaneous administration of immunoglobulin. Tailored vaccination recommendations are also provided based on the severity of the antibody deficiency. Additionally, targeted measures should be implemented for cases that present associated complications [15,20].

The primary strategy employed at our clinic involved prioritizing the management of active infections through the utilization of available resources: broad spectrum antibiotics, as well as implementing rigorous clinical and paraclinical monitoring.

The antibiotics administered were Ceftriaxone, initiated as empirical treatment (Cefort 1 gram x 2 daily), and continued for the full course. After nearly 2 days, when the patient became subfebrile, a Fluoroquinolone (Levofloxacin 250 milligrams x 2 daily) was added to escalate the treatment. This decision was made after considering the potential exposure of the patient, who reported owning an air conditioning unit, to Legionella or other intracellular pathogens. As the patient presented with symptoms of chronic tonsillitis, the otolaryngologist made a diagnosis and prescribed a treatment plan. The prescribed medications included Benzylpenicillin (8 million IU daily) and Metronidazole (1 gram daily). Furthermore, the gynecologist advised a 14-day course of antifungal medication in the form of vaginal administration of Nystatin.

We acknowledge the apparent misuse of antimicrobial agents, as empirical therapy was the predominantly employed approach to address this particular case. However, it is important to highlight that this decision was made as a result of the inability to clearly identify the bacteria involved in this case, due to the constraints posed by the technical limitations. Nonetheless, despite the challenging nature of this case, the management approach implemented led to the patient's relatively quick recovery.

Blood samples were collected on a quasi-daily basis to closely monitor the patient's condition. This was of utmost importance due to the limited knowledge regarding the characteristics of the pathogens, which increased the risk of administering suboptimal pharmacotherapy to the patient. The levels of inflammatory markers, including C-reactive protein, erythrocyte sedimentation rate, and fibrinogen, as well as the leukocyte count, exhibited a downward trend, despite this potential setback. The clinical and radiological evolution were also favorable, suggesting the resolution of the infectious episode. The subsequent course of action involved the referral of this patient to an Excellence Centre for Immunodeficiencies located in a different hospital.

Following her discharge, she was admitted to the aforementioned Excellence Centre for Immunodeficiencies. The conducted tests have effectively excluded any secondary factors contributing to immunodeficiency and have conclusively diagnosed the patient with common variable immunodeficiency. She was also enrolled in a program for intravenous Immunoglobulin administration, and subsequent to several months, the patient exhibited satisfactory health conditions with

no instances of recurring mucosal infections during this time frame.

Differential diagnosis and further analysis

When encountering patients who have documented records of infections, it is imperative to consider immunodeficiency conditions as a potential underlying cause. The underlying cause can be categorized as either primary or secondary. Primary causes are typically associated with congenital immunodeficiency disorders, which fall under the umbrella of over 200 existing PIDs [21]. On the other hand, secondary causes occur when an external factor influences the immunological system of the organism.

Some of these conditions are more prevalent in certain individuals, whose profiles made up of characteristics such as age, sex, drug usage, exposure to toxic compounds or risky activities, familial history, and others, can be constructed. The limitations of this approach, which relies on profiling, are readily apparent. There exists a significant convergence of potential scenarios when considering the intricacies of an individual's life, which is further compounded by the passage of time, introducing additional variables. Combined with the inherent nature of the invading pathogen as a potential black box and the fact that not all immune deficiencies are overtly manifested, the limitations of a clinical-based approach become evident in this era of great information dissemination. This is particularly true when considering the potential benefits that can be derived from advanced analysis methods, which have the potential to greatly benefit patients.

A notable example of a scenario in which a minor component of a complex system, namely the immune system, can malfunction is observed in the rare cases of caspase-8 deficiency. This protein plays a crucial role in mediating CD-95 signaling, which triggers apoptosis and is regarded as a pivotal component in the pathogenesis of autoimmune lymphoproliferative syndrome (ALPS). When examined through a clinical lens, the case of two adult siblings with ALPS, recurrent complicated pneumonias, and granulomatous lung disease, described in the literature by Niemela, J., Kuehn, H.S., Kelly, C. et al., meets, like several other PIDs, at least partly, the clinical criteria of CVID. If no abnormalities in Ig levels were detected in our case, the possibility of pursuing such a rare pathology would arise, and obtaining results would only be feasible in a tertiary care unit, equipped with the necessary resources for such a task [4,22,23].

As a further step, the literature in the field has described the potential association between acquired thalassemia and CVID as a possible manifestation of clonal hematopoiesis. The genetic status of the patient's parents was not readily available, making it difficult to determine whether the beta thalassemia was hereditary or acquired. Thus, a myelodysplastic syndrome (MDS) was taken into consideration [24-26], prompting the performance of a complete blood count (CBC) along with a peripheral smear analysis. Discrete morphological abnormalities were observed in the erythroid cell line, specifically aniso-poikilocytosis, which is characteristic of the patient's beta-thalassemia. These abnormalities did not provide any further evidence for a hematologic neoplasm.

CONCLUSION

This case report highlights the diagnostic and management challenges encountered in a 30-year-old patient with CVID who presented with recurrent respiratory infections. Early recognition in adult patients with a history of recurrent infections is crucial in order to mitigate the potential complications that this pathology might entail. Hence, the importance of obtaining a comprehensive medical history and the significance of conducting a meticulous diagnostic assessment, with particular emphasis on the diagnostic workup, and the need for appropriate immunological investigations, along with a strong emphasis on interdisciplinary care, are of utmost importance in such instances.

The patient's clinical profile was consistent with a PID, having a relevant history of susceptibility to infections and allergies. Additionally, clinical findings were indicative of simultaneous active infections, including pneumonia, tonsillitis, herpes simplex infection, and vaginitis. Paraclinical investigations results met the necessary diagnostic criteria for CVID, namely significant hypogammaglobulinemia with a normal lymphocyte count, the cornerstone of this particular PID.

Interdisciplinary care was paramount for an efficient approach of this case, achieved through collaboration between the main hospitalization hub, the internal medicine ward, and other specialists, namely ENT doctors, gynecologists, hematologists, and infectious disease specialists. This approach also relied on

the support provided by laboratory medicine and radiology specialists.

The patient was closely monitored during treatment. The levels of immunoglobulin were tested after 11 days of hospitalization, and, after an additional 6 days in the hospital, she was discharged in good clinical condition. The favorable evolution under the antibiotic pleaded for a non-mycobacterial etiology.

Comprehensive immunological evaluations, including the separation of protein fractions through serum electrophoresis and the assessment of immunoglobulin levels, with the additional step of B-cell and T-cell subsets identification, are important for a thorough and accurate diagnosis. Individualized management strategies, such as immunoglobulin replacement therapy, antibiotic prophylaxis, and vaccination protocols, play a pivotal role in reducing the frequency and severity of infections, and improve patient outcomes. Thus, the patient was directed to enroll in the National Primary Immunodeficiencies Treatment Programme, in a tertiary center, in order to access the best available care.

Further research is needed to gain a better understanding of the pathogenesis of CVID and to develop targeted therapies for this complex immunodeficiency disorder.

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