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CASE REPORT

RARE CASE OF CD19 MUTATION IN CVID (OMIM613493) VARIANT WITH AUTO IMMUNE HAEMOLYTIC ANAEMIA

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ABSTRACT

16-year-old female patient Radhika born of a 2 consanguineous marriage, presented with repeated episodes of cough, cold and fever for 2 years of age, was repeatedly investigated and has been undergoing treatment for the same. In 2016, HRCT was done, which revealed features of bronchiectasis. In December 2019 patient got admitted for LRTI in CPR Hospital. She had anaemia, hepatitis, and hepatosplenomegaly. HRCT was repeated and which was strongly suggestive of Koch's. Patient was given Hepato safe ATT for 6 months. Later pt presented with fever for 15 days on and off, vomiting, and abdominal pain for 4 days and breathlessness on examination pt was icteric after lab report pt was diagnosed as autoimmune haemolytic anaemia. In case of Recurrent respiratory infections, bronchiectasis, autoimmunity one should suspects primary immunodeficiency. Lymphocyte subset analysis and genetic studies aided the diagnosis. Only the early diagnosis and intervention can prevent the complications in these patients

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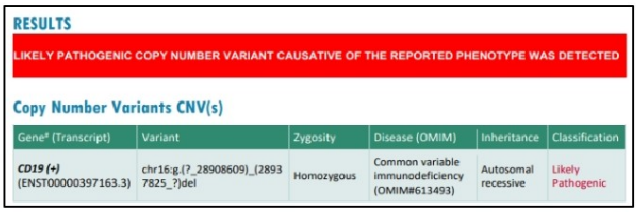
INTRODUCTION

Common variable immunodeficiency (CVID) is a primary antibody deficiency characterised by hypogammaglobulinemia, impaired production of specific antibodies after immunisation and increased susceptibility to infections.Patients with CVID present a broad range of clinical manifestations, including recurrent bacterial infections, autoimmunity, interstitial lung disease, enteropathy, lymphoproliferation, malignancy, and allergic diseases [1]. Common variable immunodeficiency (CVID) is a commonly occurring primary immune deficiency, affecting approximately 1 in every 50,000 individuals. [2] It is caused by homozygous or compound heterozygous mutation in CD19 gene. A reduced serum IgG as well as a lowered serum IgA and/or IgM, two standard deviations or more below the mean, together with proven antibody deficiency, establishes this diagnosis. Patients with CVID may encounter additional complications due to the absence of antibodies and poorly understood immune system dysregulation.

These complications can include autoimmune disorders, malignancies, or the formation of granulomatous infiltrations in various areas such as the lungs, lymph nodes, or other parts of the body. Autoimmune illness was previously discovered in 22% of 248 CVID patients. Recurrent infections are among the first and the most common clinical manifestation of the disease. Acute and chronic infections are a leading cause of morbidity in patients with CVID.Approximately, all CVID patients presented with recurrent upper and/ or lower respiratory tract infections, including otitis media, sinusitis, bronchitis, and pneumonia. Recurrent infections especially respiratory tract infections (20–96%) and gastrointestinal infections (30–88%) are associated with a low subset of B cells, specifically reduced isotype-switched memory B cells and reduced immunoglobin levels [6] Autoimmune manifestations may, at times, be the first and only clinical presentation of CVID, resulting in diagnostic dilemma for the treating physician. Autoimmune cytopenia (autoimmune haemolytic anaemia and/or thrombocytopenia) are the most common autoimmune complications seen in patients with CVID [5].

Test Name	Result	Unit	Normal Range
CBC Count.			
Total WBC Count	8240.00	/cmm	10000 - 26000
Lymphocytes	4.70	%	
Absolute Lymphocytes Count (ALC)	387	counts/mm3	1400 - 3300
Lymphocyte Subpopulation			
B lymphocytes	1.00	%	7.8 - 23.7
Absolute B lymphocytes (CD3-/CD19+)	04	counts/mm3	110 - 570
T lymphocytes (CD3+/CD19-)	60.00	%	
Absolute T lymphocytes (CD3+/CD19-)	232	counts/mm3	1000 - 2200
Th lymphocytes (CD3+/CD4+)	21.00	%	
Absolute Th lymphocytes (CD3+/CD4+)	81	counts/mm3	530 - 1300
Tc lymphocytes (CD3+/ CD8+)	28.00	%	
Absolute Tc lymphocytes (CD3+/ CD8+)	108	counts/mm3	330 - 920
NK cell (CD3-/CD16+/CD56+)	2.00	%	
Absolute NK Cells (CD3-/CD16+/CD56+)	08	counts/mm3	70 - 480

Figure 1. Immunology subset analysis


RESULTS

LIKELY PATHOGENIC COPY NUMBER VARIANT CAUSATIVE OF THE REPORTED PHENOTYPE WAS DETECTED

Copy Number Variants CNV(s)

Gene# (Transcript)	Variant	Zygosity	Disease (OMIM)	Inheritance	Classification
CD19 (+) (ENST00000397163.3)	chr16:g.(?_28908609)_(28937825_?)del	Homozygous	Common variable immunodeficiency (OMIM#613493)	Autosomal recessive	Likely Pathogenic

Figure 2. Gene mutation finding (done at national institute of immune haematology)

Autoimmune diseases occur in up to 30% of CVID cohorts. In a recent study focused on non-infectious CVID complications, among 632 patients followed since 1974, autoimmune thrombocytopenic purpura (AITP) was the most common (16.2%), followed by autoimmune haemolyticanaemia (AIH 7.7%). Other associated autoimmune conditions include rheumatoid arthritis (2.7%) and uveitis (1%)[9]. Different members of the tumour necrosis factor (TNF) receptor superfamily have been reported to be involved in the pathogenesis of CVID. The single gene defects reported in this pathway affect transmembrane activator and calcium modulator and cyclophilin ligand interactor (TACI, encoded by TNFRSF13B), B-cell activating factor belonging to the tumour necrosis factor family BAFF receptor (BAFF-R, encoded by TNFRSF13C), TNF-like weak inducer of apoptosis (TWEAK, encoded by TNFRSF12), and CD27 encoded by TNFRSF7[1]. CD19 is a protein belonging to the immunoglobulin superfamily, and it is found on the outer surface of B lymphocytes. It is believed to have a crucial function in the differentiation and activation of B cells. Four hypogammaglobulinemia patients from two unrelated families were recently found to have defective CD19 due to CD19 gene mutations.Among these, mutations of inducible costimulatory, and CD19, appear to be disease causing by themselves [7]. Present report demonstrates the rare case of CD19 Mutation in CVID (OMIM613493) variant with auto immune haemolytic anaemia**.**Diagnosis was done based on lymphocyte subset analysis and genetic studies.

Case presentation

A 16-year-old female child born through 3rd degree consanguineous marriage presented with feversince 15 days on and off, vomiting and abdominal pain since 4 days and breathlessness. On physical examination, she had pallor+, icterus + clubbing + and features like an increased epicanthal distance, thumb sign, high-arched palate, crowding of teeth, sandal gap (the widened gap between the first and second toes), and near sightedness. She had hepatomegaly+ splenomegaly+. Weight and height On history, she had episodes of cough, cold, and fever, starting as early as the age of 2 years. Over the years, she underwent multiple investigations and treatments to address these symptoms. In 2016, a significant finding emerged from a high-resolution CT scan (HRCT): it revealed the collapse of the medial segment of the right middle lobe and the anterobasal segment of the left lower lobe, as well as the presence of areas of tubular bronchiectasis and a narrowing of the middle lobe bronchus. The scan further showed enlarged lymph nodes in various regions, including the pre-tracheal, para-tracheal, and subcarinal areas, prompting suspicion of active infection, potentially tuberculosis (TB) In December 2019, the patient's health took a concerning turn, leading to her admission to hospital due to a lower respiratory tract infection (LRTI). During this admission, she presented with anemia, hepatitis, and hepatosplenomegaly. Subsequent re-evaluation through HRCT strongly suggested a Koch's (TB) infection. Consequently, she commenced treatment with Hepatosafe ATT (anti-tuberculosis treatment) for a duration of 6 months. During our hospital stay,her blood reports suggestive ofHb 5.1 g/Dl, TLC 6300(P77,L20)Plat count 4.3, MCV 128.6FL,RDW 22.5,PS s/o macro+normo+ polychromasia+, Retic count-60% cRetic count- 26.40%,elevated total bilirubin levels of 6.5 mg/dL with indirect hyperbilirubinemia, and positive direct Coombs test (DCT)and increased LDH which was suggestive of autoimmune haemolytic anaemia. Repeated respiratory tract infection, bronchiectasis, hepatosplenomegaly, failure to thrive along with autoimmune haemolytic anaemia points towards primary immunodeficiency. So, Immunoglobulin tests sent and unveiled a low IgA level of 3.01 g/L and IgG 3.98(2.4-16.2), reduced complement C3 levels at 80.5 mg/dL. LYMPHOCYTE subset analysis shows absolute B lymphocytes,absolute T lymphocytes and Absolute NK lymphocytes . Gene mutation analysis suggestive of common variable immunodeficiency (CVID). In view of AIHA , Injection methyl prednisolone was given for 5 days f/b oral steroid. Her haemoglobin levels increased from 5.1 to 6.7 g/dL, and her bilirubin levels decreased from 6.5 to 1.7 mg/dL.IvIg was advised to patients which should be taken every 1 monthly.

DISCUSSION

CVID also called acquired hypogammaglobulinemia, adult-onset hypogammaglobulinemia, or dysgammaglobulinemia, is the commonest symptomatic primary antibody deficiency syndrome. This case presents a complex clinical picture involving recurrent respiratory symptoms, suspected tuberculosis, bronchiectasis, hepatosplenomegaly, anaemia, hepatitis, and features suggestive of an autoimmunity. Autoimmune manifestations may, at times, be the first and only clinical presentation of CVID, resulting in diagnostic dilemma for the treating physician. Autoimmune cytopenia (autoimmune haemolytic anaemia and/or thrombocytopenia) are the most common autoimmune complications seen in patients with CVID[5]. Autoimmune haemolytic anaemia (AIHA) is characterized by a decreased haemoglobin concentration as a result of a shortened red cell lifespan induced by autoantibodies directed against antigens on the patient's erythrocytes. Mutations in the CD19 gene can lead to functional defects in B cells and contribute to immune system dysregulation. Additionally, this case involves the presence of autoimmune hemolytic anemia, which is a condition where the immune system mistakenly attacks and destroys red blood cells. Autoimmune complications can sometimes occur in individuals with CVID, further complicating their clinical presentation. In the context of CVID, a rare case has been reported where a CD19 mutation (specifically associated with OMIM613493) is present. This particular mutation may result in abnormal B cell function and further compromise the immune system.

CONCLUSION

In case of Recurrent respiratory infections, bronchiectasis, autoimmunity one should suspects primary immunodeficiency. Only

the early diagnosis and intervention can prevent the complications in these patients. Regular follow up and teaching hygienic practices to patient reduces infections rates.

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