

Common Variable Immunodeficiency with Rheumatoid Arthritis.

Gouranga Santra

Department of Medicine, Midnapore Medical College, Vidyasagar Road, Paschim Medinipur, West Bengal, India

Abstract : Common variable immunodeficiency (CVID) presents with hypogammaglobulinaemia of unknown origin with heterogeneous clinical manifestations including recurrent infections, chronic lung disease, lymphadenopathy, hepatosplenomegaly, gastrointestinal disease and lymphoma. Immune dysregulation of B and T cells and antigen presenting cells is responsible for autoimmune, inflammatory and lymphoproliferative disorders in CVID. We report a case of CVID in an 18 years old male. He had recurrent respiratory tract infections and diarrhoea since childhood. He had short stature and pubertal delay. Patient also had rheumatoid arthritis involving both small and large joints but rheumatoid factor and anti-cyclic citrullinated peptide were negative. Despite the name common, CVID is diagnosed rarely because of unawareness in physicians. Diagnosis of rheumatological disorders may be problematic in CVID because of absent or low titre of antibodies and subtle clinical features due to inherent immunosuppression. CVID should be considered in arthritis patients especially in the background of recurrent infections.

INTRODUCTION

Common variable immunodeficiency (CVID) presents with hypogammaglobulinaemia of unknown origin with variable immunological and clinical phenotypes. Patients usually suffer from recurrent infections of respiratory and gastrointestinal tract. A significant proportion of patients develops autoimmune, inflammatory or lymphoproliferative disorders¹. Idiopathic thrombocytopenic purpura and autoimmune haemolytic anaemia are common. Rheumatoid arthritis (RA) has been reported less frequently in association with CVID²⁻⁴. In CVID immune dysregulation of B and T cells and antigen presenting cells leads to autoimmune and inflammatory disorders. Here we report a case of CVID with RA.

CASE REPORT

An eighteen-year-old male presented with recurrent cough and expectoration since childhood. He also had recurrent diarrhoea with frothy stool. He had recurrent abdominal pain, bloating, nausea and vomiting. He had polyarthritis of both small and large joints including hands, feet and knee joints for one year with early morning stiffness of more than one hour. He had stunted growth. His family history was uninformative. He had three siblings, who were in good health. On examination, he had mild pallor, cervical lymphadenopathy and moderate hepatosplenomegaly. Bilateral hand and feet joints and knee tenderness was present but no deformity was found. Tender joints count was 18/28 and swollen joints count was 2/28. His height was 108 cm (3.5 ft). His upper and lower body segment ratio was equal. Secondary sexual characters were not developed including absence of axillary and pubic hair, beard and moustaches, testicular growth. He had testicular size of 2.1 cm longitudinally in both side, and had micropenis. Sexual maturity rating (Tanner stage) was I for both pubic hair stages and male genital stages. Chest auscultation revealed bilateral coarse crackles. Cardiovascular and neurological system examination did not reveal any abnormality.

Investigation revealed haemoglobin 8.5 g/dL, total leucocyte count 8900/cmm including 38% lymphocytes and 58% neutrophil, normal platelet count, and ESR 50 mm/hr. Rheumatoid factor, anti-cyclic citrullinated peptide (anti-CCP) antibody and anti-nuclear factors were negative. Chest x-ray revealed bilateral pneumonic changes. Serum IgG was 210 mg/dL (normal range 540-1600 mg/dL), IgA 40 mg/dL (normal range 80-280 mg/dL), Ig M 80 mg/dL (normal range 50-190 mg/dL), and serum IgE 1.5 IU/ml (normal range 3-150 IU/ml). Stool examination revealed giardial infection. Serological tests of HBsAg, anti-HCV antibody; HIV I and II were negative. Blood sugar, urea and creatinine levels were normal. Liver function test revealed total protein 5 g/dL, albumin 2.4 g/dL and globulin 2.6 g/dL. Aspartate aminotransferase (AST), alanine aminotransferase (ALT) and prothrombin time were normal. FNAC from cervical lymph node revealed reactive hyperplasia. His thyroid function tests were normal. LH (0.3 U/L), FSH (0.2 mIU/ml) and testosterone (18 ng/dL) levels were prepubertal. X-ray of hand joints showed osteopenia.

The case was diagnosed to have CVID complicated with seronegative RA (score 7/10) [according to the 2010 ACR-EULAR classification criteria]. Pain and swelling of arthritis used to improve with non-steroidal anti-inflammatory drugs (NSAIDs). He was also prescribed with hydroxychloroquine and sulfasalazine. No immunosuppressive was prescribed, as patient was already immunosuppressed. Patient could not afford immunoglobulin. He used to take repeated courses of antibiotics.

Correspondence: Dr. Gouranga Santra, Associate Professor of Medicine, Block-P, Flat-306, Binayak Enclave, 59 Kalicharan Ghosh Road, Kolkata-700050, West Bengal, India-e-mail: g.santra@yahoo.com
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DISCUSSION

Primary immunodeficiencies include large number of rare disorders including CVID. CVID is characterized by low levels of serum immunoglobulins. Serum Ig G and Ig A with or without IgM may be decreased. A clear pattern of inheritance of CVID has not been defined, but an association is seen with MHC haplotypes HLA-B8 and HLA-DR3. Currently identified genetic mutations [*ICOS* (inducible costimulator), *TACI* (transmembrane activator and calcium-modulating cyclophilin ligand interactor), *CD19*, *BAFF-R*, *CD81*, *CD20*, *CD21* and *LRBA* (lipopolysaccharide responsive beige-like anchor protein)] account for minority of cases of CVID⁵⁻⁷. Most CVID patients have normal numbers of B-lymphocytes that are clonally diverse. B-lymphocytes are able to recognize antigens and respond with proliferation, but they are unable to become memory B cells and mature plasma cells. Abortive differentiation pattern of B cells lead to nodular B lymphocyte hyperplasia resulting in lymphadenopathy, splenomegaly and intestinal lymphoid hyperplasia. B cells fail to receive proper signals from T cells for a normal antibody response but T cell defects have not been defined well in CVID.

The word “variable” in CVID refers to heterogeneous clinical manifestations of the disease. Both males and females are equally affected. Clinical features vary from severe to mild. Although CVID is commonly diagnosed in adults in third decade, it may develop even during infancy or childhood. Our patient was diagnosed in second decade but symptoms appeared since childhood. Presenting features of CVID include recurrent infections involving the ears, sinuses, nose, bronchi and lungs. Repeated lung infections may lead to bronchiectasis. Some patients have enlarged spleen and lymph nodes in neck, chest or abdomen. Infection, immune dysregulation, or both are responsible for enlarged lymph nodes. Intestinal diseases include chronic giardiasis, intestinal malabsorption, and atrophic gastritis with pernicious anaemia.

Although patients with CVID have hypogammaglobulinaemia, sometimes paradoxical immune-dysregulation leads to autoimmune diseases. Most common autoimmune diseases include idiopathic thrombocytopenic purpura and autoimmune haemolytic anaemia. Autoantibodies may also cause arthritis or thyroid disease. In joint manifestations resembling RA or juvenile rheumatoid arthritis in CVID antinuclear antibodies or a rheumatoid factor are typically absent due to lack of antibody production^{2,3}. Histologic abnormalities include subtle synovial hyperplasia and capillary proliferation without major lymphocytic or polymorphonuclear infiltrate⁸. Diagnosis of RA is difficult because of absent autoantibodies or rheumatoid factor and