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Pneumococcal meningitis in a young adult female with common variable immunodeficiency

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Patient: Female, 22
Final Diagnosis: Pneumococcal meningitis
Symptoms: Fever • headache • neck stiffness • nuchal rigidity • photophobia
Medication: Ceftriaxone
Clinical Procedure: —
Specialty: Neurology

Objective: Rare disease

Background: Common variable immunodeficiency (CVID) is a primary immunodeficiency associated with hypogammaglobulinemia and other various clinical manifestations. It is a rare disease with a prevalence of CVID is approximately 1: 50,000–200,000. Clinical manifestations of CVID include recurrent bacterial infections, autoimmune, gastrointestinal, lymphoproliferative, granulomatous, and malignancy.

Case Report: Twenty-two year-old Hispanic female presented with a throbbing headache, nuchal rigidity, photophobia and a high grade fever. Lumbar puncture with CSF assessment revealed a turbid fluid with WBC of 6937 per uL, polymorphnuclear cells of 81%, protein 248 mg/dL, glucose <3 mg/Dl. CSF antigens were positive for *Streptococcus pneumonia* and CSF culture grew pansensitive *Strepococcus pneumonia*. Immunoglobin (Ig) levels of IgA, IgE, IgG and IgM were all decreased. Absolute cell counts of CD3, CD4 and CD8 were all low. Bone marrow biopsy was normocellular. Excisional lymph node biopsy revealed lymph nodes with reactive follicular hyperplasia. Common variable immunodeficiency disease (CVID) was diagnosed based on exclusion. IVIG therapy was given and patient received a two-week course of ceftriaxone.

Conclusions: The diagnosis of CVID is made based on the following criteria: 1) Marked decrease of IgG and at least one of the IgM or IgA isotypes. 2) The onset of immunodeficiency at greater than 2 years old. 3) Absence of isohemagglutinins and/or poor response to vaccines 4) Exclusion of other defined causes of hypogammaglobulinemia. A definite diagnosis is often late because it is wrongly assumed that primary immunodeficiencies are extremely rare, hence many patients are already seriously ill at the time of presentation.

Key words: common variable immunodeficiency • immunoproliferative • immunodeficiency disorder • *Streptococcus pneumoniae* • bacterial meningitis

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Background

Common variable immunodeficiency (CVID) is a primary immunodeficiency associated with hypogammaglobulinemia and other various clinical manifestations. CVID is considered the most common cause of clinically expressed primary immunodeficiency but it is still a very rare disease. The prevalence of CVID is approximately 1:50,000–200,000, with a reported incidence of 1 per 75,000 live births [1]. The diagnosis is most commonly made in adults between the ages of 20 and 40 years, but even children or elder adults have been diagnosed to have this immune defect. CVID is not associated with gender predominance and does not show a predilection for any specific race. The definition of CVID includes three key features: the presence of hypogammaglobulinemia of two or more immunoglobulin classes (low IgG, IgA, or IgM), recurrent sinopulmonary infections, and impaired functional antibody responses [2].

Clinical manifestations of CVID mainly include recurrent bacterial infections, however autoimmune, gastrointestinal, lymphoproliferative, granulomatous, and malignant disorders have also been frequently reported [3]. Chronic lung disease is a common problem in patients with CVID and can lead to recurrent hospitalizations and significant morbidity and/or mortality. Encapsulated bacteria such as *Haemophylus influenza* or *Streptococcus pneumoniae* or atypical bacteria such as Mycoplasma species are the major causative agents for recurrent infections of both the upper and the lower respiratory tract. This is due to the failure of antigen-specific IgG production, which increases susceptibility to encapsulated bacteria [3]. Chronic pulmonary complications, including recurrent pneumonia, are the primary causes of significant morbidity and mortality in patients with CVID. Pulmonary fibrosis and bronchiectasis can occur frequently due to the recurrent infectious insults. Approximately 10–20% of CVID patients develop granulomatous interstitial lung disease [4].

The most common autoimmune manifestation is cytopenia: idiopathic autoimmune thrombocytopenia (ITP) is found in up to 14% of patients followed by autoimmune hemolytic anemia (AHA), which is found in up to 7% [4]. The cytopenia in CVID patients has been associated with an increased frequency of splenomegaly. However, it is very important to avoid a splenectomy, in order to minimize the risk of severe infections. The Gastrointestinal (GI) tract is the second organ that is involved in infections in 10–40% of the CVID cases [5]. Various pathogens can cause GI infections in CVID patients including: *Giardia lamblia*, *Campylobacter jejuni*, *Salmonella* spp., *Cryptosporidium parvum* CMV, *Clostridium difficile*, *Helicobacter pylori*, HBV and HCV. Giardiasis is the most prevalent GI infection noted, especially in those with undetectable serum IgA levels.

One-third of these patients develop diffuse or localized lymphadenopathy, intestinal nodular hyperplasia, or lymphoid infiltrates in the lung. Histologically, these infiltrates resemble the reactive lymphoid hyperplasia. Benign lymphoproliferation is found in 40–50% of CVID patients, often as splenomegaly, and in approximately 10–20% as local or diffuse lymphadenopathy [6]. CVID patients carry an increased risk of developing lymphoma. Most lymphomas are of the B-cell non-Hodgkin lymphoma type.

We hereby present a patient with undiagnosed common variable immunodeficiency (CVID) that presented to our care with meningeal signs.

Case Report

A twenty-two year-old Hispanic female presented to our care with a severe, diffusely located, throbbing headache with radiation to her neck, associated with nuchal rigidity and photophobia of the morning on the day of admission. On that day, she had four bouts of nausea and vomiting of food particles with no blood. Other complaints included a fever of 40.1°C, chills and fatigue. She denied any confusion, dizziness, tinnitus, hearing loss, blurry vision, seizures, weakness, numbness, rash, cough, chest pain, shortness of breath, abdominal pain, diarrhea, or dysuria. She also denied any recent drug use, sick contacts at home or work and has not traveled abroad. Past medical history included autoimmune hemolytic anemia (AIHA) with a coombs positive, dysfunctional uterine bleeding and a miscarriage in February 2011. Patient was noted to have received all the usual childhood vaccinations. Her mother was diagnosed with idiopathic thrombocytopenic purpura (ITP). She denied smoking and alcohol use but admitted to occasional use of cocaine, smoking crack, methamphetamine and marijuana. She also had follow up with the hematology and oncology service for the last year for pancytopenia, splenomegaly.

Initial vital signs on admission were within normal limits except for a temperature of 39.7°C and tachycardia (HR of 93–130). Physical examination revealed an alert Hispanic female with adequate cognition with a GCS of 15 but in acute distress due to a severe headache. Her pupils were 3 mm bilaterally, equal round and reactive to light with intact extraocular movements and no nystagmus. Tympanic membrane examination was normal. Nuchal rigidity was present. Skin examination did not reveal any rashes but she had a tattoo on her right forearm. No peripheral lymphadenopathy palpated. Abdominal examination was pertinent for a prominent splenomegaly. All cranial nerve were assessed and normal on examination. No motor or sensory deficits to light touch, pain, position sense or vibration noted. All reflexes such as biceps, knee tendon and babinski sign were normal. No deficits in muscle strength (5/5 all four extremities), fasciculations or tremors. Positive kernig and brudzinski sign.

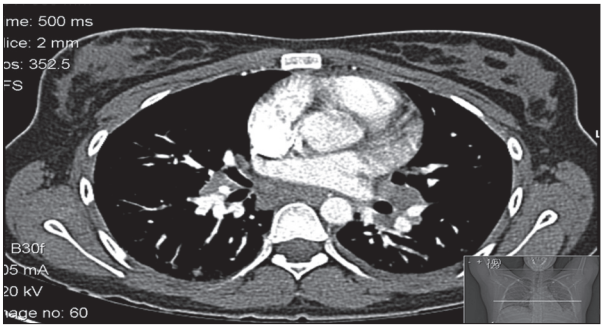

Figure 1. CTA chest.

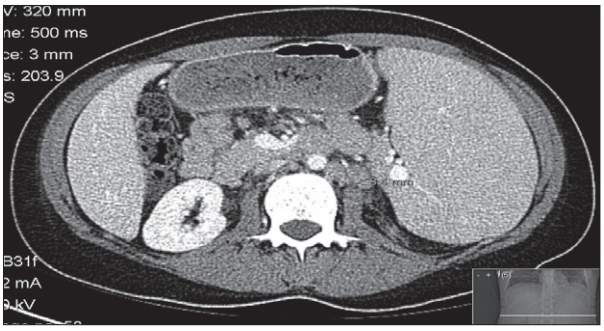

Figure 2. CT abdomen/pelvis with contrast.

She was previously hospitalized four months ago for community-acquired pneumonia. Imaging was obtained during that admission, which included computer tomographic angiogram of the chest that revealed a left lower lobe consolidation, small bilateral hilar, mediastinal, axillary and supraclavicular matted lymph nodes (Figure 1). The computer tomography of the abdomen and pelvis revealed massive splenomegaly, and enlarged retroperitoneal, mesenteric and pelvic lymph nodes that were highly suspicious for a lymphoproliferatve disorder (Figure 2). During this previous hospitalization, bone marrow and lymph node biopsy were performed to rule out lymphoproliferative disorder. Pathology report revealed a normocellular bone marrow demonstrating trilineage hematopoiesis and adequate stainable storage iron. No morphologic abnormalities identified. Flow cytometry analysis showed no evidence of monoclonal B-cells or aberrant T-cells. Excisional lymph node biopsy was done on two left axillary lymph nodes. The lymph node pathology report showed lymph nodes with reactive follicular hyperplasia. The PCR test was negative for monoclonal pattern of gene rearrangement.

Chest x-ray on admission was normal. Computer tomography of the brain was negative for an acute intracranial pathology. Initial laboratory work-up demonstrated white blood cell count of 7.08×10^3/uL, hemoglobin of 12.7 g/dL, and platelet count of 111×10^3/uL. Metabolic panel and liver function tests were not significant. Urinalysis and urine toxicology were negative. Lumbar puncture was performed while patient was in emergency department. CSF assessment revealed a turbid fluid with

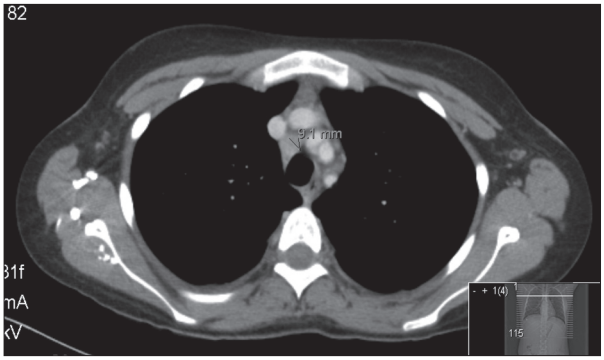

Figure 3. CTA chest.

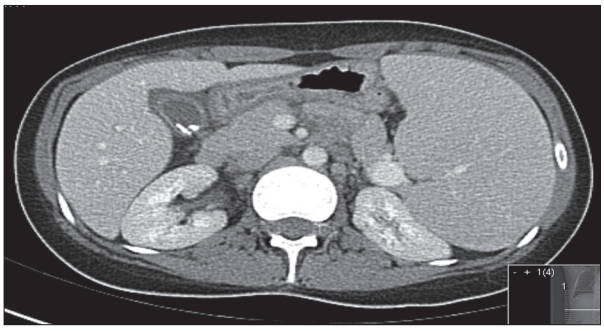

Figure 4. CT abdomen/pelvis with contrast.

WBC of 6937 per uL, polymorphnuclear cells of 81% and lymphocytes of 16%, RBC of 750 per uL, protein 248 mg/dL, glucose <3 mg/dL, sodium 147 mmol/L, and LDH 372 per uL. The serum glucose at the time of lumbar puncture was 166 mg/dL. Within one hour of the lumbar puncture, the patient had an acute deterioration of mental status to a GCS of 8. She was intubated and subsequently transferred to the medical intensive care unit (MICU). CSF antigens were positive for *Streptococcus pneumonia* and negative for group B streptococcus, haemophilus, and Neiserria meningitidis. CSF culture grew pansensitive *Strepococcus pneumonia*.

Empiric therapy was initiated in MICU with vancomycin 1 g IV BID, ceftriaxone 2 g IV daily, dexamethasone 10 mg IV every 6 hours. Our clinical impression included acute bacterial meningitis, pancytopenia and an immunoproliferative or immunodeficiency disorder. Further laboratory workup included C3 level of 80 mg/dL (low), C4 level of 12.4 mg/dL (low), CH50 level of 41 U/mL, Anti-nuclear antibody-test and Human-Immunodeficiency-Virus were negative. On the second hospital day the patient was extubated, and supportive management continued. Both the infectious disease and hematology/oncology services were consulted for further recommendations. The infectious disease service advised to discontinue dexamethasone and vancomycin and continue ceftriaxone 2 g IV daily for total duration of two weeks. By the fourth hospital day a Peripherally-Inserted-Central-Catheter was placed for intravenous antibiotic therapy once discharged.

The hematology/oncology service advised to obtain further imaging studies, laboratory tests and possibly a repeat of the excisional lymph node biopsy. The patient was pancytopenic during the entire hospitalization and was started on filgrastim 480mcg SQ daily for the neutropenia. On the fourth hospital day, the CT chest with contrast showed small nonspecific mediastinal lymph nodes and a borderline enlarged left medius axillary lymph node (Figure 3). CT of the abdomen and pelvis with contrast showed massive splenomegaly and borderline enlarged pelvis lymph nodes (Figure 4). An excisional lymph node biopsy would be technically difficult and therefore, this plan was abandon due to already having a previous normal lymph node biopsy pathology result. Immunoglobin (Ig) levels were all decreased. The specific levels included: IgA was not detectable which is <5 mg/dL (81–463 mg/dL), IgE <2 kU/L (<114 kU/L), IgG 182 mg/dL (694–1618 mg/dL), IgM 18 mg/dL (48–271 mg/dL). IgG subclasses levels were IgG1 of 153 mg/dL, IgG2 of <2 mg/dL, IgG 3 of 21 mg/dL and IgG4 of <0.3 mg/dL. Absolute cell counts of CD3, CD4 and CD8 were all low. CD3 absolute cell count was 364 cells/mcL, CD4 absolute cell count was 284 cells/mcL and CD8 absolute cell count was 77 cells/mcL. The CD4/CD8 ratio was 3.7 (0.86–5.0). Interleukin 10 (IL-10) was 13 pg/mL (0–18 pg/mL). Immunoelectrophoresis revealed low beta gloubin and gamma globulin.

Common variable immunodeficiency disease was diagnosed based on exclusion of other immunoproliferative and immunodeficiency disorders. Intravenous immunoglobulin (IVIG) therapy was given once a day on hospital day four and five. The patient was discharged on hospital day fourteen after receiving two weeks of ceftriaxone, with the appropriate follow up with hematology/oncology and infectious disease services. She was counseled about her diagnosis of CVID, treatment plans and follow up care.

Discussion

Diagnosis of CVID is based on the 1999-criteria issued by the American and European societies for immunodeficiency. The diagnosis of CVID can be made on the following criteria: 1) A marked decrease of IgG (at least 2 SD below the mean for age) and of at least one of the IgM or IgA isotypes. 2) The onset of immunodeficiency at greater than 2 years of age. 3) Absence of isohemagglutinins and/or poor response to vaccines 4) Exclusion of other defined causes of hypogammaglobulinemia [7]. Quantitative determination of serum immunoglobulins is the first and most important step in the diagnosis of CVID. IgG is typically below 5 g/L (normal range 7 to 16 g/L) and IgA is markedly reduced or not detectable in most patients. IgM is also below the normal range in up to 80% of patients. The total number of peripheral B cells is slightly reduced in about 40 to 50% of CVID patients [8]. Patients with CVID may have normal or decreased numbers of B cells. In contrast to X-linked agammaglobulinemia the immunoglobulin levels are low rather than absent.

Most patients with CVID have normal numbers of circulating T and B lymphocytes. However, most patients have somewhat reduced levels of circulating memory B cells and some have impaired T cell function. The basic pathophysiologic process in CVID is a simple failure in the differentiation of B lymphocytes. However, the T-cell receptors show no evidence of abnormality. Of all patients with CVID, 25–30% often have increased numbers of $CD8^+$ T cells and a reduced CD4/CD8 ratio (<1) [9]. In addition, 60% of patients with CVID have a diminished response to T-cell receptor stimulation and expression of receptors for IL-2, IL-4, interleukin 5 (IL-5), and interferon gamma [10].

Studies have noted that the clinical presentation on CVID included recurrent or chronic respiratory tract infections (88%), sinusitis (78%), otitis media (78%), intestinal tract infections (34%), meningitis (25%), sepsis (16%) and pyelonephritis (16%) of patients [11]. Although meningitis does occur in patients with CVID it is not common. Meningitis is usually acquired by the spread of blood-borne bacteria into the cerebrospinal fluid (CSF). The usual hematogenous spread may be facilitated by an immunological deficiency, which makes the host defenses inadequate barriers against potential bacterial pathogens. There is only one other case report in the current literature regarding CVID presenting with acute bacterial meningitis in an adult patient.

Current therapy of CVID can be categorized as follows: regular and sufficient substitution with immunoglobulins (IgG trough levels >7.0 g/L); targeted antibiotic treatment of (breakthrough) infections; adequate treatment of complications; and in selected patients with severe hematological changes (chronic transfusion need, leukopenia, thrombocytopenia), secondary malignancies and suspected combined immunodeficiency, allogeneic peripheral stem cell transplantation is being considered in experienced centers [12]. The immunoglobulin replacement therapy is the mainstay of therapy. Intravenous immunoglobulins (IVIG) have been show to lower the incidence of pneumonic and recurrent bacterial infections, thus preventing chronic pulmonary disease [13]. Early diagnosis and therapy are essential in improving the outcome in patients with CVID. As symptoms of CVID are usually heterogeneous and nonspecific, diagnosis and follow-up of CVID can be challenging.

Conclusions

The heterogeneity in the clinical presentation of CVID presents a unique challenge to physicians. A definite diagnosis is often

late because it is wrongly assumed that primary immunodeficiencies are extremely rare, hence many patients are already seriously ill at the time of presentation. The clinical presentation of meningitis in CVID has not been well documented in the current literature. Special consideration should take place in a patient that presents with meningitis due to encapsulated bacteria despite being previously vaccinated. Another unique finding in his patient was the low absolute value of CD3, CD4 and CD8 considering that in the literature these levels are reported to be within normal range.

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Disclosures

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