Case Report

Idiopathic CD4 Lymphocytopenia Presenting as Cryptococcal Meningitis

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Abstract

A 54-year-old male presented to our center with a 3-month history of headache, giddiness, and blurring of vision. Cerebrospinal fluid examination revealed him to be having cryptococcal meningitis. He was worked up for probable causes of immunosuppression including HIV and other infections and had an autoimmune profile as well as a bone marrow examination, none of which revealed any abnormality. Lymphocyte flow cytometry revealed low counts of CD4 T lymphocytes, likely secondary to idiopathic CD4 lymphocytopenia. He was treated for cryptococcal meningitis. Due to marked immunosuppression, the disease progressed rapidly with deterioration in neurological and hemodynamic status, leading to his demise.

Keywords: Case report, CD4 T-cell, cryptococcal meningitis, flow cytometry, idiopathic lymphocytopenia

Introduction

Idiopathic CD4 T-cell lymphocytopenia (ICL) is a rare entity. Its pathognomonic feature is an unexplained paucity of CD4 T-cells, leading to various clinical manifestations. Low levels of CD4 lymphocytes are not explained by other causes of immunodeficiency, including HIV. The mean age of presentation varies between 17 and 78 years. A wide range of presentations may occur caused by a blunted immune response such as infections, autoimmune disorders, and certain cancers.

Case Report

A 54-year-old male presented to us with a history of headache for the past 3 months, which had gradually increased in severity over this period. It was associated with giddiness and blurring of vision. At the time of onset of the symptoms, he had visited his general practitioner, who had then done a full blood count, which had shown a low white cell count of 3.0/mm^3 (normal range being 4–11/mm^3) with a low lymphocyte count of 0.6/mm^3 (normal range being 1–4/mm^3). No further testing was done. This was diagnosed as a viral prodrome, and he was prescribed symptomatic therapy, but the symptoms still persisted for the next 2 and a half months. Fifteen days before presentation to our center, he was admitted to another hospital with severe headache, which lasted for 1 hour, which he described as an "unbearable headache." Magnetic resonance imaging (MRI) brain was done at that hospital, which was normal. Unable to find a cause at that hospital, and with no improvement in his symptoms, he was transferred to our hospital for further evaluation.

He did not have a history of fever, vomiting, weight loss, rash, or a loss of appetite. There was no episode of loss of consciousness, seizure activity, motor weakness, or bowel or bladder involvement. He did not reveal any history of trauma or of any high-risk sexual behavior, drug abuse, or blood transfusion. He gave a history of pulmonary tuberculosis 25 years back, for which received treatment for 9 months. He was a known hypertensive for 3 years, which was well controlled with medications. His pulse rate, blood pressure, and temperature were normal. Neurological examination did not reveal any focal

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deficit. The rest of the systemic examination was unremarkable. MRI brain showed meningeal enhancement in bilateral cerebellar regions [Figure 1] with leptomeningeal enhancement in the right temporal [Figure 2] and right temporo-occipital [Figure 3] regions. Full blood count revealed a low white cell count of 2.5/mm^3 (normal range being 4–11/mm^3) with a low lymphocyte count of 0.5/mm^3 (normal range being 1–4/mm^3). Lumbar puncture was done, and the cerebrospinal fluid (CSF) analysis revealed 980 cells (normally < 5 cells/mm^3), with a predominance of lymphocytes (60%), glucose was 32 mg/dL (normal is 25–35 mg/dL), and protein was 27 mg/dL (normal is 18–45 mg/dL). CSF polymerase chain reaction (PCR) for tuberculosis was negative. CSF examination for cyptococcal antigen was positive. CSF for viral PCR (herpes simplex virus, varicella-zoster virus [VZV], cytomegalovirus [CMV], and John Cunningham [JC] virus was negative. Lymphocyte flow cytometry was done, and the subset estimation showed low levels of CD4 T-cells, which were at 16% (normal range is above 25%), absolute CD4 count was 200/mm^3 (normally between 500 and 1500/mm^3), whereas CD8 cell count was normal (29%). We further investigated to look for any cause for his immunocompromised state. ELISA for HIV-1 and HIV-2 and PCR for HIV-1 and HIV-2 were negative. Serum PCR for CMV, Epstein–Barr virus, VZV, and parvovirus B19 were negative. Serum PCR for human T-cell lymphotropic virus 1 and 2 was negative. Immunoglobulin levels were normal. Autoimmune workup including antinuclear antibody, anti-dsDNA, extractable nuclear antigens, and antiphospholipid antibodies was negative. Complement levels were normal. The bone marrow examination was normal. There was no evidence of aplasia or myelodysplasia. Once the diagnosis of cryptococcal meningitis was made, the first and foremost differential was HIV infection, but that was ruled out. Severe combined immunodeficiency was another possibility. However, in this condition, immunodeficiency-related infections often start manifesting in childhood and early adulthood. In our patient, cryptococcal meningitis occurred at the age of 54 years. The detailed workup ruled out any autoimmune conditions that could have caused such a clinical picture. He was treated with liposomal amphotericin-B. Flucytosine could not be given in view of its unavailability. He had an episode of generalized tonic–clonic seizures during his hospitalization with the compromise of his airways, and hence he was put on mechanical ventilatory support. His neurological condition progressively deteriorated during the course of his hospitalization, along with hemodynamic instability. He was thus put on inotropic support. Unfortunately, there was no improvement, and he passed away with worsening shock.

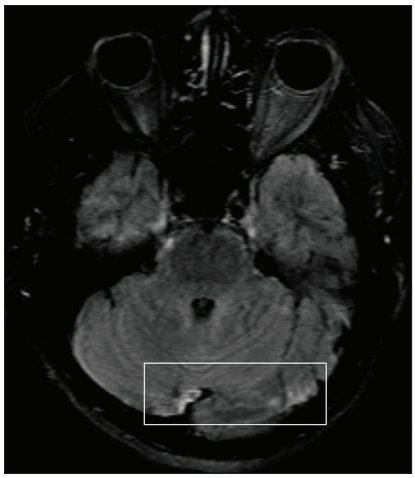

Figure 1: Magnetic resonance imaging brain showing meningeal enhancement in bilateral cerebellar regions

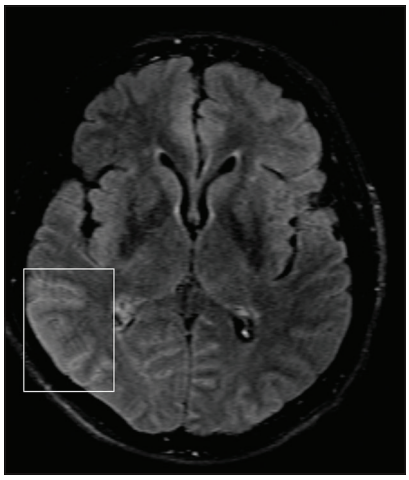

Figure 2: Magnetic resonance imaging showing leptomeningeal enhancement in the right temporal region

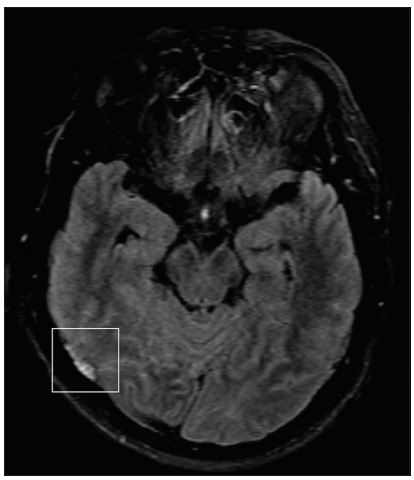

Figure 3: Magnetic resonance imaging showing leptomeningeal enhancement in the right temporo-occipital region

Discussion

The function of T-cells in our body is to attack bacteriae and viruses. CD4 is a protein on the surface of T-cells. Low levels of CD4 T-cells in ICL can result from either decrease in production, increased destruction, or tissue sequestration.[1] The etiology of this condition is unknown. Family history is not significant.[2]

Few individuals carry specific gene mutations in genes coding for lymphocyte-specific kinase; others may have inducible T-cell

kinase deficiency.[3-6] Its association has also been found with high interleukin-17 levels.[7] Affected individuals show signs and symptoms of either opportunistic infections (most common) or autoimmune disease or of a malignancy. Infections include cryptococcosis, candidiasis, tuberculosis, toxoplasmosis, human papillomavirus, herpes virus, and *Pneumocystis jiroveci*.[8] Autoimmune conditions manifesting in ICL include systemic lupus erythematosus, sarcoidosis, autoimmune hemolytic anemia, Sjögren's syndrome, and psoriasis. Malignancies that may occur are usually lymphomas and squamous cell carcinoma. No specific diagnostic criteria have been proposed. A high level of suspicion is needed for diagnosis. It should be suspected in patients with CD4 T-cell counts below 300/mm^3 or counts <20% of the total lymphocyte count, in the absence of other immunodeficiency-causing conditions such as HIV, tested on at least two occasions, 2–3 months apart. It is a diagnosis of exclusion. Our patient had a full blood count when his symptoms first started, which revealed a low lymphocyte count (with no further subset analysis then). It may have been possible that his CD4 cell count might have been low then. When he presented to our center, around 3 months from the onset of his symptoms, the lymphocyte flow cytometry revealed a low CD4 cell count, fulfilling the criteria for ICL. Treatment is usually symptomatic along with treatment of the specific condition. Asymptomatic individuals should be serially assessed with CD4 count estimation, and prophylactic antibiotics are recommended. Other treatment modalities include interleukin-2 administration, since it enhances the function of the immune system.[9] Furthermore, the use of intravenous immunoglobulin has been tried. Bone marrow transplantation has also been tried, but success rates have been variable.[10] In most of the cases, the counts of CD4 T-cells stabilize after some years, rather than reducing. Long-term prognosis depends on the extent of immunosuppression and its associated symptoms.

Take home message

ICL is a rare entity and is a diagnosis of exclusion. An extensive workup is required to determine the cause of the lymphopenia before arriving on this diagnosis. Affected individuals present with features secondary to immunosuppression. The immunosuppression may be profound and can even be fatal.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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