Case Report

Journal Of Clinical & Medical Images Case Reports

Open Access, Volume - 1

Polyclonal hypergammaglobulinemia in HIV infected patient case report and review of the literature

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Received Date : Nov 04, 2021
Accepted Date : Dec 01, 2021
Published Date : Dec 09, 2021
Archived : www.jcmimagescasereports.org

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Abstract

HIV infection and AIDS rarely are associated with plasma cell disorders, since the beginning, in the last 90´s, of the highly active antiretroviral therapy (HAART) the prognosis has improved dramatically and the concentration of monoclonal protein was reduced, with subsequent fewer prevalence of these disorders. Here we present a case report of hypergammaglobulinemia in HIV infected patient, who presented with other infections like Hepatitis B, SARS COV-2 and syphilis. Treatment with HAART generates remission in most cases in the follow-up.

Keywords: HIV; plasma cell disorders; hypergammaglobulinemia; HAART; case report

Introduction

The most common plasma cell disorders reported in patients with HIV infection or AIDS are polyclonal hypergammaglobulinemia, monoclonal gammopathy and symptomatic multiple myeloma [1]. Since the adoption in 1997 of the highly active antiretroviral therapy (HAART) the prognosis for HIV patients has improved dramatically and among the benefits described is a reduced monoclonal protein concentration in these patients. However, there are also case reports that after prolonged antiretroviral therapy, patients develop malignant plasma cell pathologies, for which constant monitoring must be carried out to know the response of patients to treatment [1,2].

Polyclonal hyper gammaglobulinemia is characterized by an increased production of several different immunoglobulins and diffusely increased proteins in the gamma region on serum protein electrophoresis, there is a study where it is reported that 1.9% of patients with HIV presented polyclonal hypergammaglobulinemia [1]. being a rare finding with risk of transformation to malignant pathology of plasma cells this will be the main focus in this review since it is also the condition present in the patient [2].

Case Presentation (case report)

A 56-year-old man presented to the Internal Medicine Department of our hospital complaining of abdominal pain for four months located in the epigastrium, stabbing type, intensity 8/10 on the pain measurement scale, without irradiation, exacerbation or medications and activities that mitigate the pain.

The patient also presented intermittent abdominal distention, occasional nausea, and hematemesis once, without specifying quantity, bloody stools on three occasions, and unintentionally lost weight of about 12 kilograms in three months, therefore, he was admitted starting a study protocol for upper gastrointestinal bleeding.

Upon admission an endoscopy was performed, the diagnostic impression was small Baveno's esophageal varices and McCormack's mild portal gastropathy, as part of the approach and in view of the endoscopy findings, a viral panel was requested, which is reactive for hepatitis B and Human Immunodeficiency Virus; Also within the findings in the laboratory tests, an elevation of total proteins was found at the expense of immunoglobulins, for which an approach was initiated to rule out the presence of multiple myeloma.

As part of the approach to human immunodeficiency virus infection, the protocol to start an antiretroviral regimen for a treatment-naive patient a viral load was requested, the result of which was 682,000 copies and a CD4 count of 20.26% and 33 cells u / l; we rule out opportunistic infections (tuberculosis, cytomegalovirus, toxoplasmosis, cryptosporidium with a negative result and syphilis with a positive result) and given to the current health context, COVID-19 pandemic, anti SARS

Citation: Gonzalez-Villarroel, Lucy, Romero-Bermudez, Javier. Polyclonal hypergammaglobulinemia in HIV infected patient case report and review of the literature. J Clin Med Img Case Rep. 2021; 1(1): 1037.

COV-2 positive with a quantitative value of 0-86 U/mL, patient presented with asymptomatic infection. Nutrition and psychology performed screening tools and initial assessment.

Regarding the approach to the probable multiple myeloma, immunoglobulins were requested, the result of which was immunoglobulin A 686 mg / dL; immunoglobulin G 4700 mg / dL; immunoglobulin M 184 mg / L; Bence Jones Kappa protein 35.40 g / L; and Lambda of 23.20 g / L; a blood smear whose diagnostic impression is pancytopenia and moderate anisocytosis; one erythroblast in 100 leukocytes, with the presence of rouleaux and polychromatophilia (diffuse basophilia); platelets large, decreased in number and bone marrow biopsy was also performed with a moderate increase in plasma cells (20%), in flame with erythroid, granulocytic and lymphocytic conservation with a diagnostic impression of probable multiple myeloma (**Figure 1**).

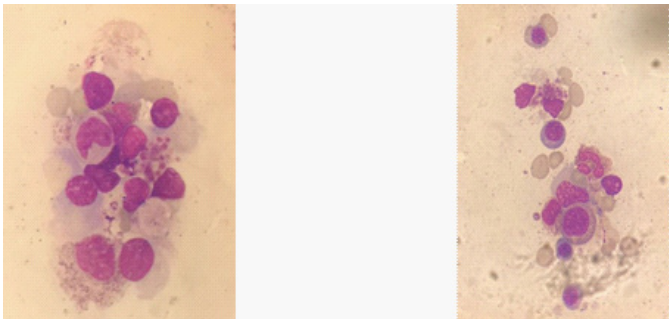

Figure 1: *Bone marrow with infiltration by atypical plasma cells (flame cells), with frayed cytoplasm, blurred archoplasm, with nucleolus and inclusions that correspond to immunoglobulins; with erythroid, granulocytic and lymphocytic conservation.*

To rule out the diagnosis of multiple myeloma 24-hour urine immunofixation was performed where no monoclonal immunoglobulin chains were detected; immunofixation in serum where a polyclonal increase in heavy chains of IgG, IgE, IgA and light chains kappa and lambda was detected; and serum protein electrophoresis where 23.84% albumin was found; alpha 1 2.52%; alpha 2 6.20%; beta 9.15%; gamma 58.27%; total globulins 6.7 g/dL; total proteins 8.8 g/dL; albumin 2.09 g/dL; alpha 1 0.22 g/dL; alpha 2 0.55 g/dL; beta 0.81 g/dL; gamma 5.13 g/dL, so the diagnosis of polyclonal hypergammaglobulinemia secondary to HIV infection was made.

The treatment chosen was Tenofovir, Emtricitabine, and Raltegravir because the patient also had acute hepatitis B infection.

Discussion

IHypergammaglobulinemia is defined as elevated serum levels of immunoglobulin and pronounced antibody responses, it may be seen with infection and inflammation; it is divided into monoclonal and polyclonal subtypes, monoclonal paraproteins are typically associated with plasma cell neoplasms and B cell lymphomas, while polyclonal hypergammaglobulinemia has historically been associated with a variety of conditions including liver diseases, the most common associated condition on 61%, infections such as human immunodeficiency virus, hematologic disorders, non-hematologic malignancies and autoimmune conditions [3].

Polyclonal hypergammaglobulinemia is characterized by an increased production of several different immunoglobulins and diffusely increased proteins in the gamma region on serum protein electrophoresis; Monoclonal gammopathy of undetermined significance is defined by the presence of a serum monoclonal protein (M-protein) at a level < 3 g/dl, clonal bone marrow plasma cells <10%, and the absence of end-organ damage (lytic bone lesion, anemia, hypercalcemia or renal failure) related to the proliferative process; multiple myeloma is a plasma cell malignancy and is characterized by the presence of M-protein, the infiltration of clonal plasma cells in the bone marrow (≥10%) and the evidence of end-organ damage [2].

In HIV infection, immunological functions are gradually lost as the CD4 T cells present a decrease in quantity; however, the patients with HIV infection present hypergammaglobulinemia and spontaneous immunoglobulin (Ig) secretion which indicates abnormal B cell activation; since the B cell population is not a target in HIV infection, the dysfunction of this cells may be caused by a defect in functional CD4 T cells [2,4].

Experimental studies showed polyclonal B cell activation in HIV infection, after being exposed to HIV the proliferate or become activated and begin secreting immunoglobulin; HIV infected T cells can induce contact dependent but antigen independent polyclonal activation of B cells [4].

B cells have a CD27 molecule, type I transmembrane glycoprotein that belongs to de nerve growth factor receptor/tumor necrosis factor family that covers all memory B cells, the expression of this molecule increases with age, high levels of Ig productivity and mutations in Ig variable region genes; the CD27 ligand known as CD70 interaction enhances the differentiation from CD27 memory B cells into plasma cells in the presence of some stimuli [4,5].

In the article of Nagase H, et al., demonstrate that the population of CD70 T cells freshly isolated from HIV patients were increased and CD70 expression greatly enhanced by the stimuli and plasmacytosis was observed in the bone marrow of patients. These findings suggest that the CD27/CD70 interaction in the patients plays a role in plasmacytosis, hypergammaglobulinemia, and the absence of memory B cells. The authors demonstrate an increase in the population of CD70 T cells freshly isolated from HIV patients and, CD70 expression and plasmacytosis greatly enhanced by the stimuli, observed in the bone marrow. Those findings suggest that CD27/CD70 interaction may play a role in plasmacytosis, hypergammaglobulinemia, and the absence of memory B cells [5].

It was also described that the expression of CD154 and CD134, which are the important costimulatory molecules for the development of functional B cells, was not observed on T cells of HIV patients, these molecules promote the generation of memory B cells, so its absence leads to the impaired development of functional memory B cells, which contributes to the reduction of circulating memory B cells, resulting in elevated levels of Igs, probably not containing antigen specific antibodies [5].

IL-6 plays an important role in the differentiation in activated B cells to Ig secreting cells, and is present in the immunopathology of various diseases, it works as and autocrine growth factor since it induces an unregulated production of gammaglobulines and antibodies production mainly in plasma cell disorders, and it has been demonstrated that plasma IL-6 levels are elevated in HIV infected patients, especially in two groups; with an early diagnosis and subjects with an opportunistic infection, as tuberculosis, candidiasis, syphilis confirmed diagnosis and pneumocystis pneumonia, probable diagnosis in our patient [6].Also, infection by COVID 19 is associated with massive release of IL-6, this infection plus the HIV infection causes a lymphocyte depletion that results in a loss of regulatory T cell mediated suppression of aberrant B cell clones, with the consequent dysregulated antibody production resulting in hypergammaglobulinemia which usually reverses once proper treatment is given [7].

Another risk factor associated with hypergammaglobulinemia is syphilis, with especially higher γ-globulin levels as the patient described here with gamma protein of 58.7% (normal limit 19,2) [8].

Commonly patients with HIV and polyclonal hypergammaglobulinemia presented with elevated levels of immunoglobulins and diffusely increased proteins in the gamma regimen of serum protein electrophoresis. A bone marrow biopsy was usually not required, but if performed, these patients show plasmacytosis without light chain restriction, as shown in our patient [2].

Conclusion

As shown here plasma cell disorders in HIV patients are not common. It divides into polyclonal hypergammaglobulinemia, monoclonal gammopathy and symptomatic multiple myeloma. Risk factors associated with those conditions are other infections like hepatitis B, SARS COV and/or syphilis like our patient. The management of plasma cell disorders in HIV-infected patients is quite similar to that in the general population, for HIV-infected patients with polyclonal hypergammaglobulinemia the current standard of care is close follow-up and HAART if indicated, in this case, because the patient also had hepatitis B infection, a regimen with Tenofovir, Emtricitabine, and Raltegravir [2].

Acknowledgement

We thank Dr. Juan Collazo, Department of Hematology, Mexico´s General Hospital, for the help and knowledge in the interpretation of the bone marrow biopsy.

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