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Short Communication

Recognition of Non-Myeloma Monoclonal Bands in HIV-Infected Patients to Avoid Overdiagnosis

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Abstract

Human immunodeficiency virus (HIV) is a major global health problem. Infection with this virus leads to humoral immune dysregulation that can span the gamut from benign polyclonal hypergammaglobulinemia to multiple myeloma. Epidemiologic studies have demonstrated that patients with HIV are at increased risk for the development of monoclonal gammopathy of undetermined significance (MGUS) and multiple myeloma, which occur at younger ages compared to the rest of the population. Interpretation of serum protein electrophoresis (SPEP) and immunoelectrophoresis (IEP) results in patients with HIV can be challenging. We present a case of a 66-year-old HIV-positive male with intermittent prior highly active retroviral treatment (HAART) therapy who was found to have an IgG lambda monoclonal band on SPEP and IEP in the background of polyclonal hypergammaglobulinemia. A follow-up bone marrow biopsy demonstrated marked plasmacytosis without evidence of a plasma cell neoplasm. This case highlights the challenges of interpretation of SPEP and IEP results in this setting and highlights the importance of awareness of these potential pitfalls to avoid overdiagnosis and subsequent overtreatment.

INTRODUCTION

Human immunodeficiency virus (HIV) remains a serious global health burden with over 36 million people worldwide and over one million in the United States infected with the virus [1-3]. Approximately 35,000 new HIV-1 infections occur annually in the United States [2]. Only 86% of infected patients know that they are infected, and of these only two-thirds of are on highly active antiretroviral therapy (HAART) [1-3]. Viral infection leads to dysregulation of both the cellular and humoral immune systems [4-6]. It is well known that untreated HIV infection will eventually decrease the CD4+ T-cell counts leading to the clinical signs of acquired immunodeficiency syndrome (AIDS). However, there is increasing research demonstrating that B-cell dysfunction is also a key component of common viral-induced immune dysregulation and ultimate disease pathogenesis [4,6-10]. The spectrum of B-cell dysfunction ranges from benign polyclonal hypergammaglobulinemia to multiple myeloma as well as various B-cell lymphomas [3,9,11,12]. HIV-infected people are at increased risk for the development of plasma cell disorders including monoclonal gammopathy of undetermined significance (MGUS), with an increased incidence ranging from 3-26% [9,11,13]. Epidemiologic studies have shown that HIV-positive patients have an increased risk for the development of multiple myeloma [14-17], which was found to be increased up to 4.5-fold in one study [11]. Monoclonal gammopathies in HIV-positive people typically occur in much younger individuals (mean age 34-43) versus the general population (mean age 70) [3,8,9,18-20]. Multiple myeloma can also be challenging to diagnose clinically in patients with HIV as they can share an overlapping clinical picture of anemia, weight loss, fatigue, renal insufficiency (HIV nephropathy), recurrent infections, and marrow plasmacytosis [20].

Interpretation of serum protein electrophoresis (SPEP) results in patients with HIV can be challenging as a high proportion of HIV-positive patients may demonstrate abnormalities such as polyclonal hypergammaglobulinemia or oligoclonal immunoglobulin bands, which can mask or hinder the detection of low-level monoclonal immunoglobulin bands, specifically in the gamma-region of SPEP electropherograms [8]. In a study of 70 untreated HIV-positive patients, 71% of SPEP gels displayed abnormal results, with 44% containing polyclonal hypergammaglobulinemia and 27% requiring further immunoelectrophoresis (IEP) to exclude a monoclonal immunoglobulin band [7].The incidence of monoclonal immunoglobulin bands in HIV-positive patients is not infrequent occurring in 3-4% of cases [7,8,21,22].

Here we describe a case of a patient with intermittent HAART compliance who was found to have an M-spike on SPEP occurring in the background of polyclonal hypergammaglobulinemia and

IgG lambda monoclonal protein on IEP. A follow up bone marrow biopsy demonstrated a significant plasmacytosis but was negative for evidence of clonality by several additional assays. This case highlights the humoral dysregulation that occurs in HIV-infected people, the complexity of SPEP/IEP evaluation of these patients, the necessity for recognition of the potential pitfalls in this setting, and the importance of expert pathologist evaluation and communication with clinical colleagues to avoid overdiagnosis and overtreatment. Further investigation into the prognostic significance of the monoclonal immunoglobulin bands in these patients and their potential relationship, if any, to subsequent plasma cell neoplasm development is needed.

CASE PRESENTATION

A 66-year-old man with a history of hypertension, hyperlipidemia, prediabetes, hepatitis C status post-treatment, and HIV with intermittent HAART compliance presented to the emergency department with a severe headache. A CT scan ruled out an acute intra-cranial process, but additional workup revealed the patient had pneumonia and was also found to be in renal failure with a creatinine of 19.4 mg/dL and nephrotic-range proteinuria. The patient was admitted to the hospital and started on hemodialysis and antibiotics. CD4 count on presentation was 283/µl. HIV viral load was detectable at 325 copies/ml. Six months previously it had been 55,168 copies/ml. Hepatitis B serology, hepatitis C PCR, and COVID-19 RT-PCR were all negative. Nephrology was consulted and they ordered serum free light chain levels, SPEP, and IEP. The patient was also referred to hematology-oncology where a bone marrow biopsy was performed. He had no lytic bone lesions identified on a CT scan of the chest, abdomen, and pelvis. The patient had never previously received any therapeutic monoclonal antibodies.

MATERIALS AND METHODS

All assays were performed in CLIA certified CAP accredited high-complexity clinical laboratories at UPMC.

SPE and IEP were performed on the Helena SPIFE 3000 analyzer (Helena Laboratories, Beaumont Texas, USA) according to manufacturer protocols with all recommended manufacturer reagents. A Helena Electrophoresis Sample Handler was used to automatically dilute and load serum samples. Serum total protein was established by using a digital refractometer (Index Instruments U.S., Inc., Kissimmee, FL). Antisera to IgG, IgA, IgM, Kappa, and Lambda light chains for IEP were from the SPIFE ImmunoFix Kits. Protein electrophoresis tracings were then reviewed and annotated on Helena's QuickScan 2000 Touch Plus software with a densitometer. Images of SPEP and IEP gels were captured on an Epson Perfection V800 scanner. All proteins used for SPEP were stained with acid blue dye. After immunofixation of immunoglobulins, acid violet was utilized for protein staining, and the gels were visually interpreted by a pathologist.

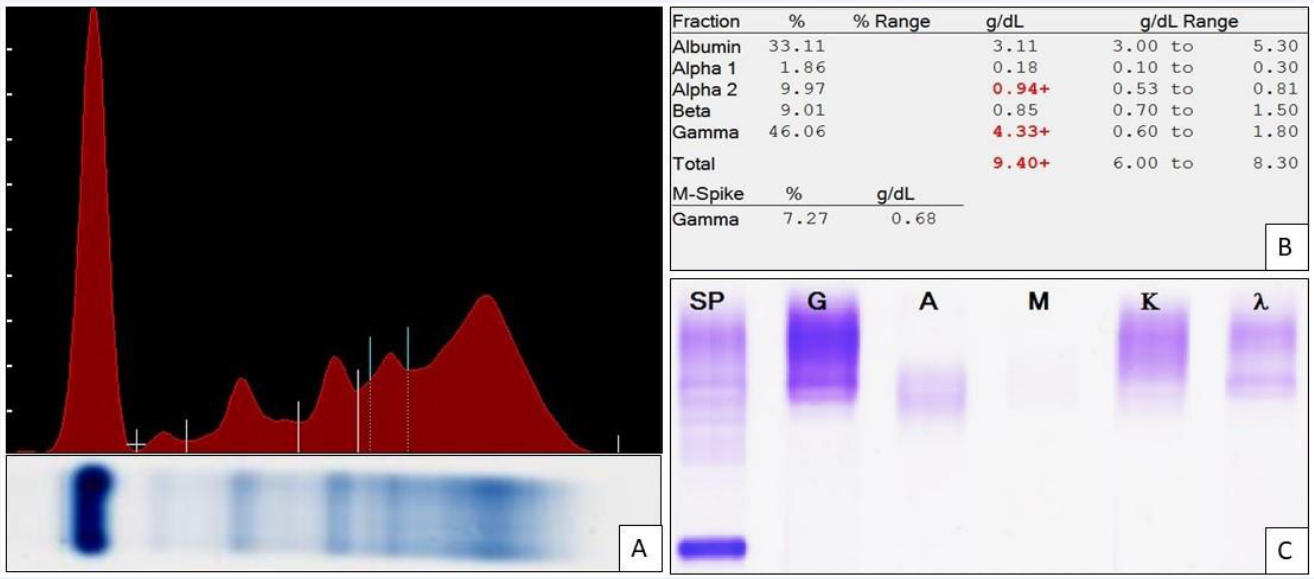
Concentrations of serum free kappa and free lambda light chains (sFLC) were determined by latex-enhanced kappa sFLC and lambda sFLC Freelite assays (The Binding Site Group Ltd, Birmingham, UK) using Optilite turbidimeter (The Binding Site, Birmingham, UK) according to the manufacturer's protocols. Specific protein concentrations in these test samples were automatically determined using a calibration plot established by the instrument. The free light chain concentrations and kappa/lambda ratio were reported abnormal if they were beyond the normal reference range established by the manufacturer (Kappa: 3.3-19.4 mg/L; Lambda: 5.7-26.3 mg/L; kapa/lambda ratio: 0.26-1.65). Quantitative serum IgG, IgM and IgA immunoglobulin analysis was performed on the Optilite (The Binding Site) turbidimeter per the manufacturer's recommendations. Reference ranges: IgA (82-453 mg/dL), IgG (751-1560 mg/dL), and IgM (40-274 mg/dL).

HIV antibody testing was performed on the BioPlex 2200 multiple immunoassay analyzer (Bio-Rad Laboratories, Hercules, CA) in accordance with the manufacturer's recommendations. A BioPlex kit for multiplex detection and differentiation of HIV-1 p24 antigen and antibodies to HIV-1 (Groups M and O) and HIV-2 was utilized. HIV viral load was measured using the Alinity m HIV-1 *in vitro* reverse transcription-polymerase chain reaction (RT-PCR) assay to detect and quantitate HIV-1 RNA (Abbot Laboratories, Abbott Park, IL).

Immunohistochemical staining for CD138, kappa, lambda, Cyclin D1, CD20, PAX-5, and CD56 was performed by Ventana Bond Automated Staining System (Leica Microsystems Inc., Deerfield, IL). Multicolor flow cytometry immunophenotypic analysis to assess plasma cells was performed utilizing the following panel of antibodies: CD138, CD38, CD19, CD20, CD56, CD27, CD81, CD45 (obtained from BD Biosciences, Franklin Lakes, NJ), and cytoplasmic immunoglobulin kappa and lambda light chains (obtained from Dako/Thermo Fisher Scientific Inc., Pittsburgh, PA). Samples were acquired on BD FACSLyric instruments (BD Biosciences), and data analysis was performed using FCS Express Version 7.10 software (De Novo Software). In-depth information regarding institutional methods for cytogenetic evaluation of plasma cells can be found here [23].

RESULTS

The patient was found to be HIV-1 positive via serology on 2/8/2024. A confirmative RT-PCR test revealed that the viral load was 325 copies per mL. Per the electronic medical record, it was 55,168 copies per mL sixth months previously. Subsequent laboratory evaluation revealed an M-spike on SPEP (0.68 g/dL) running in the late beta/early gamma region [Figure 1A] occurring in the background of polyclonal hypergammaglobulinemia. Serum IEP studies revealed the monoclonal protein to be IgG lambda [Figure 1B]. This required a 1:2 dilution due to the presence of strong background polyclonal hypergammaglobulinemia. Serum Free kappa and lambda light chains were both elevated (884 and 1,090 mg/L, respectively) with a normal kappa/lambda ratio (0.82). Quantitative immunoglobulins revealed increased IgG (2,951 mg/dL) and IgM (462 mg/dL), with normal IgA (393 mg/dL) levels. Urine total protein electrophoresis (TPE) revealed a



Fraction	%	% Range	g/dL	g/dL Range
Albumin	33.11		3.11	3.00 to 5.30
Alpha 1	1.86		0.18	0.10 to 0.30
Alpha 2	9.97		0.94+	0.53 to 0.81
Beta	9.01		0.85	0.70 to 1.50
Gamma	46.06		4.33+	0.60 to 1.80
Total			9.40+	6.00 to 8.30

M-Spike	%	g/dL
Gamma	7.27	0.68

Figure 1 Serum total protein electrophoresis gel and densometer tracings demonstrating a monoclonal band (A). Serum total protein fractionation (B). Serum immunoelectrophoresis results identifying the monoclonal band as IgG lambda (C).

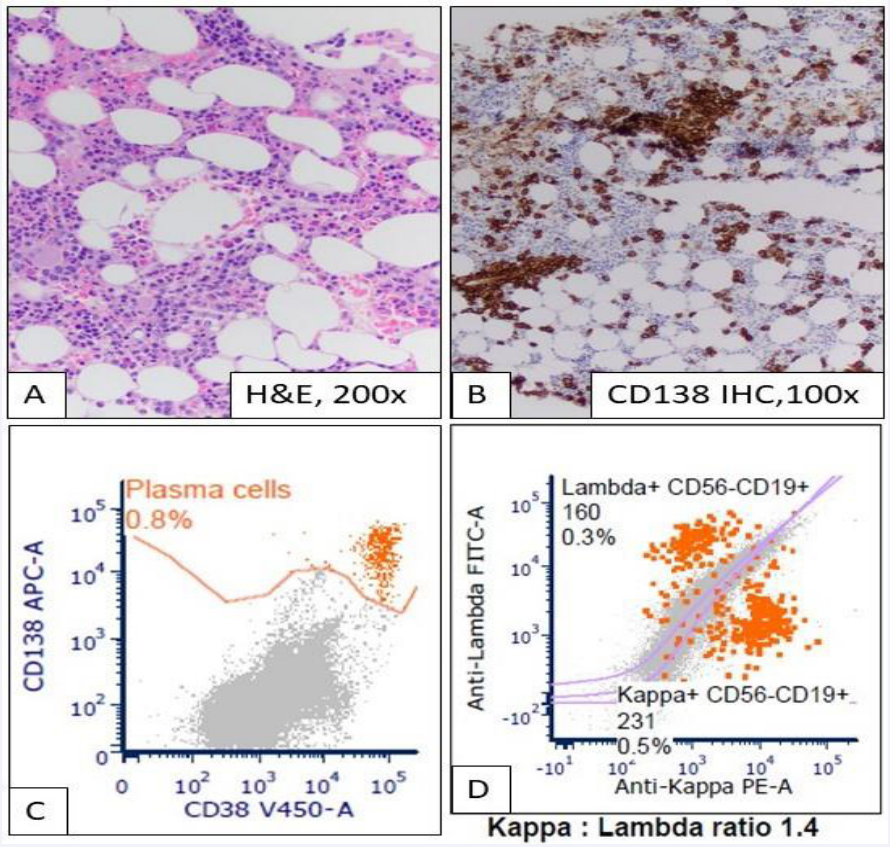


Figure 2 Bone marrow biopsy demonstrating marked plasmacytosis (H&E, 200X) (A), (CD138 IHC) (B). Gating on CD38 bright and CD138 bright positive cells (C) demonstrates polyclonality with a normal kappa/lambda ratio (D).

possible M-spike, which, however, was not confirmed on urine IEP.

The patient's bone marrow biopsy results showed a normocellular marrow with plasmacytosis comprising 15-20% of the cellularity. These plasma cells were polytypic via IHC and flow cytometry [Figure 2]. A Congo red stain was negative for amyloid deposition. Cyclin D1 IHC was negative in plasma cells. Cytogenetic studies revealed a normal 46 XY karyotype. FISH and microarray were performed on CD138-enriched cells. FISH studies were negative for an IgH rearrangement. Whole-genome microarray analysis was normal.

DISCUSSION

While much is widely known and reported regarding the cellular immunodeficiency that occurs in HIV infection, there are many mechanisms in which the virus can modulate the humoral branch of immunity as well. While the hallmark of humoral alterations in HIV-positive patients is polyclonal hypergammaglobulinemia, other modalities include loss of normal T-cell function, increased expression of surface activation markers, subsequent chronic polyclonal B-cell hyperactivation, increased B-cell death, increased plasmablastic differentiation, increased autoantibody formation, and B-cell exhaustion [4,6,10,18,20]. It is postulated that these humoral changes are secondary to a "chronic hyper-stimulated state" induced by viral infection. Whether this state of activation occurs from direct viremia or cytokine dysregulation needs further investigation [10,18]. Regardless, it is thought that this persistent hyper-stimulated state leads to increased immunoglobulin production that can then be detected as either monoclonal or oligoclonal bands on SPEP. Most of these bands appear to be composed of IgG kappa immunoglobulin, with IgG lambda bands occurring less commonly [8,20,22]. Our case is consistent with prior reports in that the immunoglobulin class of the M-spike is IgG.

In addition to changes in the background proteome in HIV infection, interpretation of SPEP gels in patients with HIV infection can be challenging as the M-proteins are often admixed within a polyclonal background [8,18,24]. Identifying a monoclonal immunoglobulin band can be further hindered by low-level monoclonality or comigration with a polyclonal band. These challenges were likely encountered by Zemlin et al., where IEP was needed to rule out a potential monoclonal protein on SPEP in approximately one-quarter of their 70 untreated HIV-positive patients [7]. The presented case is similar, in that SPEP revealed an M-spike within a polyclonal/oligoclonal background [Figure 1], with subsequent IEP revealing the monoclonal protein as IgG lambda. Others have demonstrated that HIV antigenic epitopes can induce the formation of oligoclonal, monoclonal, and even paraproteins in patients with multiple myeloma [8,25,26]. Further investigation into these cases has revealed that bands that appear as an M-spike on SPEP may contain more than 1 light chain type with different avidities against separate HIV antigens [26]. These findings argue that there is a perturbation of the humoral immune response by the virus in HIV infection that leads to B-cell hyper-activation which may manifest in protein electrophoresis as oligoclonal or monoclonal immunoglobulin bands [8]. We recommend performing IEP and ordering free light chains on all equivocal cases of SPE in this setting. The differential diagnosis for polyclonal hypergammaglobulinemia includes liver disease, autoimmune disease, vasculitis, infection, non-hematologic and hematologic malignancy, IgG4-related disease, immunodeficiency syndromes, and iatrogenic/therapeutic antibodies [27].

Previous studies have shown a decreased incidence of monoclonal bands in patients receiving HAART compared to those that were untreated [7,8,13,21,28]. Our patient had a history of intermittent compliance and recently stopped HAART therapy due to leg pain. Upon presentation, the patient's CD4 was 283/ µl with a viral load of 325 copies/ml. The literature on the correlation between CD4 counts and the presence of bands on SPE is inconclusive. Initial reports demonstrated a correlation between higher CD4 count (>350 µl) and the presence of polyclonal hypergammaglobulinemia [8], while others claim that polyclonal hypergammaglobulinemia is associated with lower CD4 counts [7]. The former posits that the banding is due to a more robust immune response while the latter suggests increased antigen burden associated with viremia leads to band formation. Konstantinopoulos et al., also report that younger age, female sex, and viral load were also associated with oligoclonal or monoclonal banding [8]. Zemlin et al., demonstrated that HAART therapy reduced both free kappa and lambda light chain levels, and that the levels of free light chains are inversely correlated with CD4 counts, further offering support to the chronic hyperstimulation hypothesis [4]. Casanova et al., demonstrated an association with the disappearance of monoclonal bands with HAART therapy [18]. These papers suggest that in younger patients with uncontrolled HIV and low pre-test probability for monoclonal gammopathy development equivocal SPE findings or even frank monoclonal bands may be observed and retested after receiving HAART therapy.

The patient's bone marrow biopsy revealed a normocellular marrow with brisk polyclonal plasmacytosis [Figure 2]. Subsequent cytogenetic testing revealed a normal karyotype and was negative for a clonal rearrangement. In a large series of bone marrow morphologic findings in HIV-positive patients, plasmacytosis was observed in 25% of cases. However, O'Brien et al., found this to usually be mild, with an average of 4.6% and only 12.5% of cases having greater than 10% plasma cells [29,30]. The patient demonstrated a significant elevation of IgG levels (2,951 mg/dL), consistent with the appearance of hypergammaglobulinemia on TPE. As mentioned previously, hypergammaglobulinemia can be associated with both HIV infection and multiple myeloma, and can also mask monoclonal bands. We performed a 1:2 dilution to clarify the appearance of the monoclonal band in Figure 2.

The prognostic significance of monoclonal bands and plasmacytosis in HIV-positive patients is unclear. Early reports found them to be of little prognostic significance and a normal

response to HIV antigens [22,26]. Van Vuuren et al., report that many of these monoclonal proteins are of low concentration and IgG isotype [21]. The inverse relationship between these bands and HAART treatment/viral load control supports this hypothesis [8,18,21]. However, as mentioned previously, the incidences of MGUS and multiple myeloma are increased in patients with HIV infection [9,14,15]. It may be possible that prior cases containing a monoclonal protein on serum electrophoresis may have been overcalled as MGUS, rather than a viral immune response. Re-assessing serum protein electrophoresis after HAART treatment may avoid this potential pitfall [18].

Close follow-up is still needed in these patients as HIV-induced chronic stimulation is thought to play a role in lymphoma development [10,13]. Dezube et al., report that HIV-infected people have a 4.5-fold increased risk for myeloma development and Amara et al reported that 28% of HIV-positive patients developed a malignancy (most often B-cell or plasma cell malignancy) with a median follow-up of 21 months [11,13]. HIV-positive patients with multiple myeloma may have a more aggressive clinical course, as they have been shown to have a higher incidence of extramedullary disease, an adverse prognostic factor in multiple myeloma [31]. However, in a small retrospective series, HIV-positive patients with multiple myeloma on HAART had significantly improved progression-free and overall survival compared to the HIV-negative population, highlighting the critical need for early detection of both disease processes [28]. Whether the observed monoclonal band identified on serum electrophoresis and the brisk plasmacytosis in the presented patient represents an exuberant immune response against viral epitopes or early development of a monoclonal gammopathy will need further close observation.

CONCLUSION

We presented a case of a patient with intermittent HAART compliance who was found to have an IgG lambda M-spike within a background of polyclonal hypergammaglobulinemia on SPEP/IEP and brisk polyclonal plasmacytosis on subsequent bone marrow biopsy. This case highlights the complexities of serum protein electrophoresis interpretation in HIV-positive patients. Recognition of the potential for these patients to have monoclonal bands against HIV antigens, even with striking plasmacytosis is important in patients with a low pre-test probability for multiple myeloma development. This is especially important given that patients with a monoclonal gammopathy in HIV have been shown to occur at a younger age. As it has been shown that HAART treatment leads to a reduction in M-spikes on serum electrophoresis, awareness of the patient's treatment history and viral load is important. In untreated or poorly/compliant patients at low risk or lacking other clinical signs and symptoms of a monoclonal gammopathy, it may be reasonable to observe and repeat serum electrophoresis after the patient receives HAART therapy. Pathologist evaluation and communication with hematology-oncology clinical colleagues are essential in challenging cases such as this to avoid misdiagnosis and potential subsequent overtreatment. However, these patients are at high risk of hematolymphoid neoplasm development and should be closely monitored. Further research into the prognostic significance of monoclonal bands and plasmacytosis in HIV-positive patients is needed.

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