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Viral co-infections and paraproteins in HIV: effect on development of hematological malignancies

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Abstract

The role of viral co-infections and paraproteins in the development of hematological malignancies (HMs) in HIV remains unclear. Using our large database of HIV+ patients, we investigated whether co-infection and paraproteinemia increase the risk of HM. Data on demographics, hepatitis B (HBV) and hepatitis C virus (HCV) co-infections, paraproteinemia, HIV characteristics, and biopsy proven malignant hematological disorders for HIV+ patients were collected over a 10-year period in a large urban hospital setting. We identified 10,293 HIV+ patients who were followed for a median duration of 53 months. Of the 10,293 patients with HIV, 229 (2.2 %) were diagnosed with a HM. Over 85% of patients in both groups were tested; no significant difference in the prevalence of chronic HBV or HCV was noted between the HM positive (n = 229) and HM negative (n = 9992) patients. The serum protein electrophoresis test was performed for 1371 of the 10,221 patients. HM positive patients, compared to HM negative, were more likely to be tested for paraproteins (OR 3.3, 95 % CI 2.5–4.4) and more likely to have a discrete paraprotein band (OR 3.3, 95 % CI 1.2–8.9). Discrete paraproteins exclusively correlated with the development of plasma cell malignancies. Faint or oligoclonal protein bands were seen in high grade B cell lymphomas but did not show a significant correlation with HM development.

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Compliance with ethical standards

Montefiore Medical Center institutional review board approved the study.

Conflict of interest

The authors of the manuscript have no conflict of interest to declare.

Chronic hepatitis B or C infections did not correlate with the development of HM in HIV; however, viral influence on host gene transformation may have been impacted by anti-viral therapy limiting the duration of high viremic states.

Keywords

HIV; Hematological malignancy; Paraproteinemia; Hepatitis B; Hepatitis C

Background

HIV-infected patients are at higher risk of developing several hematological malignancies (HMs) [1, 2]. AIDS-related lymphomas (ARLs) are predominantly aggressive B cell lymphomas, typically presenting at an advanced stage and more often with extranodal involvement and plasmablastic differentiation. ARLs are classified by the WHO into three categories: (i) lymphomas that also occur in immunocompetent patients, such as Burkitt lymphoma (BL) and diffuse large B cell lymphoma (DLBCL); (ii) lymphomas occurring more specifically in HIV-positive patients, such as large B cell lymphoma arising in the HHV8-associated multicentric Castleman disease (HHV8-MCD), primary effusion lymphoma (PEL), and plasmablastic lymphoma; and (iii) lymphomas also occurring in other immunodeficiency states, including polymorphic or post-transplant lymphoproliferative disorder-like B cell lymphoma. In addition to these AIDS-defining HMs, patients infected with HIVare also at increased risk of developing certain non-AIDS-defining HMs including Hodgkin's lymphoma (HL), multiple myeloma (MM), and acute leukemias [1, 3].

The pathogenesis of HIV-related HM is poorly understood, and the role of concurrent viral illnesses and paraproteinemias in their development remains to be further investigated. A better understanding of the risk factors for the development of HIV-related HM will be crucial in formulating appropriate strategies for risk factor modulation and close follow up of at risk HIV positive individuals. We explored our database of HIV-positive patients in Montefiore Medical Center to assess the incidence and distribution of different HMs and to study the role of viral co-infections and paraproteinemia in their development.

Methods

Adult patients over 18 years of age in Montefiore Medical Center with a positive HIV test (defined as either a positive Western blot or detectable HIV viral load) between January 1, 2001 and December 31, 2011 were included. Montefiore Medical Center institutional review board approved the study. Demographic and laboratory data of these patients were retrieved using data mining software called Clinical Looking Glass (CLG). Retrieved laboratory data were then studied and analyzed by the research team.

All CD4 and HIV viral load results available in the database were reviewed. Nadir CD4 was identified from these results. For patients with HM, CD4 and VL results within 6 months before diagnosis were also identified.

Those with concurrent hepatitis B (HBV) or hepatitis C (HCV) infections were identified by the review of serology and viral load results. Patients with a positive HBV viral load (HBV VL) were classified into high viremic (>20,000 IU/ml viral load on at least one occasion) and low viremic (no viral load result ≥20,000 IU/ml) individuals per AASLD guidelines 2009. Outpatient and inpatient prescriptions were reviewed for anti-retroviral therapy prescribed. Emtricitabine, tenofovir, and lamivudine were considered agents active against HBV.

Serum protein electrophoresis (SPEP) tests done after the HIV diagnosis were reviewed and classified as positive or negative. Positive results were confirmed by the review of immunofixation (IFE). The paraproteins were classified by an independent laboratory technician into discrete (D-SPEP) or faint, multiple or oligoclonal paraprotein bands (F-SPEP) based on the gel electrophoresis.

All biopsies performed for these patients were reviewed to identify diagnoses of HM. ICD-9 codes and cancer registry documented HM without biopsy confirmation that underwent chart review. Date of last follow-up was identified using records of the last inpatient, outpatient or emergency room visit, or date of last blood sample draw. Date of death was identified by using the social security death index and the medical records.

Statistical analysis

Statistical analysis was performed by SPSS version 20 (IBM, USA). Continuous variables were expressed as mean with standard error or median with interquartile range. Baseline continuous variables were compared by the *t* test or Kruskal Wallis test as appropriate. Categorical variables were expressed as number and percentages and compared by the chi-squared test or Fisher's exact test as appropriate. A two-sided *p* value of <0.05 was considered significant.

Results

Study population

In the 10 year timeframe, 10,293 patients over the age of 18 with a positive HIV test were identified. Follow-up was 53, 294 person-years with a median duration follow-up of 53 months (0–149 months) after the first positive HIV test in our system. Mean age at the time of the first HIV test in our system was 42 years. Male gender, black race, and Hispanic ethnicity were predominant. Fifty-five percent of patients were prescribed with anti-retroviral therapy on at least one occasion (Table 1).

The research team reviewed the results of all biopsies done for the 10,293 patients. A total of 18,233 biopsy results were reviewed. Of the 10,293 patients, 747 patients had a total of 948 biopsies performed of a lymphatic structure or the bone marrow. Forty-seven biopsies were insufficient for diagnosis, and these cases were excluded. In 254 of 10,293 patients, a premalignant or malignant hematological disorder was diagnosed. Biopsy review identified 241 patients with HM; 13 patients were identified by ICD9 codes or cancer registry data confirmed by chart review. Of the 254 patients with premalignant or malignant

hematological disorders, 10 were excluded from further analysis since their diagnosis was made before known HIV positivity. Premalignant disorders were identified in 15 patients which did not progress to a HM for the median duration of follow-up of 40 months (IQ range 6–48 months). These premalignant disorders included monoclonal B cell proliferation of unknown significance (7), atypical lymphoid proliferation (3), and multicentric Castleman's disease (5). These patients with premalignant disorders were also excluded from further analysis. A total of 10,221 patients of which 229 patients carried a diagnosis of HM and 9992 patients who did not (control) were, therefore, identified and confirmed for further analysis.

Malignant hematological disorders observed in the cohort

The distribution of different malignant hematological disorders and the HIV-related characteristics of the patients including nadir CD4, CD4, and HIV VL within 6 months of diagnosis is detailed in Table 2. The predominant type of HM was high grade B and T cell lymphomas, accounting for about 86.9 % of the cases. In this subgroup, DLBCL (including primary CNS lymphomas) was the most common diagnosis. One case of DLBCL arose from preexisting MCD as noted on the diagnostic biopsy sample.

Role of hepatitis B or hepatitis C co-infections in the development of HM

The HM positive patients (n = 229) were compared to the HM negative controls (n = 9992). A significantly larger number of HM positive patients were prescribed highly active antiretroviral therapy (HAART) compared to the HM negative (61.6 vs 54.9 %, p 0.046). 88.2 % of HM positive patients and 86.6 % of HM negative patients underwent testing for concurrent hepatitis B infection. No significant difference was noted in the prevalence of HBsAg positivity between the two groups (9 vs 6.7 %, p 0.201). Of those positive for HBsAg, there was no difference noted in the proportion of patients receiving anti-retroviral therapy with anti-HBV activity (61 vs 47 %, p 0.34). A greater number of HM positive patients compared to HM negative were tested for HBV VL (83.3 vs 57.9 %; p 0.048). However, of those tested, no significant difference was noted in the proportion of patients with high viremia between the HM positive and negative groups (50 vs 40 %, p 0. 466). About 89 % of patients in both groups were tested for hepatitis C seropositivity or viremia, and no significant difference was found in the prevalence of concurrent HCV between the two groups (Table 3).

Paraproteinemia and its association with HM

Prevalence of monoclonal gammopathy was also evaluated in the cohort. Of the 10,221 patients, 1371 (13.4 %) were tested for SPEP. Paraproteins were detected in 261 of 1371 tested patients (19 %). Paraproteins were of IgG subtype in 79 %, 1.1 % IgA, 1.5 % IgM, 8.8 % light chain, and the remaining 9.6 % comprised biclonal, oligoclonal, multiple bands, and isolated heavy chains. Thirty-two of 1371 patients (2.3 %) had a discrete band (D-SPEP), and 229 (16.7 %) had faint or oligoclonal bands (F-SPEP). SPEP– (n = 1110), F-SPEP (n = 229), and D-SPEP (n = 32) patients were compared. Median nadir CD4 count as compared by the Kruskal Wallis test was significantly different between the three groups with SPEP– patients having the lowest nadir CD4 [SPEP–, 78 (IQ range 15–196), F-SPEP, 100 (IQ range 30–264), D-SPEP, 123 (IQ range 61–216), p 0.003].

All patients were followed for a median duration of 24 months after the SPEP test (IQ range 6–48 months). There was no significant difference in the median duration of follow-up between SPEP–, F-SPEP, and D-SPEP groups. 5.3 % of SPEP–, 5.2 % of F-SPEP, and 15.6 % of D-SPEP patients developed a HM. Of the 5 D-SPEP patients with HM, all patients developed a plasma cell malignancy; 4 patients were diagnosed with multiple myeloma and 1 with an immature plasma cell tumor. Of the 12 patients with F-SPEP who developed a HM, the diagnoses included Burkitts (1), DLBCL (8), and Hodgkin's lymphomas (3). HM positive patients when compared to HM negative were three times more likely to be tested for paraproteins (OR 3.3, 95 % CI 2.5–4.4) and also three times more likely to have a discrete paraprotein band (OR 3.3, 95 % CI 1.2–8.9). D-SPEP in these HIV patients exclusively correlated with the development of plasma cell malignancies (Table 3).

Discussion

This study, to our knowledge, is the largest retrospective single institution study of the role of HBVand HCV co-infections and paraproteinemia in the development of HM in HIV. Our study population encompassed a large group of 10,293 HIV positive patients with 53,294 person-years of follow-up in the post HAART era (>1997). The overall incidence of malignant hematological disorders of 2.2 % (or 4.2 cases per 1000 patient-years of follow-up) is comparable to other studies reported in the post HAART era [4].

HIV-positive patients are at increased risk of co-infection with other oncogenic viruses such as HBV, HCV, Epstein-Barr virus (EBV), and human herpesvirus-8 (HHV-8) [5]. In HIV-negative patients, infection with either HBV or HCV increases the risk of NHL [6–8]. Several cohort studies looking at the co-infection of HIV and HCV did not demonstrate an increased risk of NHL compared to just HIV alone [5, 8–10]. However, most of the studies had quite a small number of NHL cases in the co-infected group. There are limited studies about HBV co-infection; one from a Swiss HIV Cohort Study did not show an association of HBV seropositivity with non-Hodgkin's lymphoma, but in a different retrospective cohort, an increased frequency of malignancies was seen in patients who are co-infected with HBV [10–12]. Over 85 % of patients in our cohort were tested for HBV and HCV co-infections. No significant difference in prevalence of chronic hepatitis B or positive hepatitis C serology was seen between patients with and without malignant disorders. More than 60 % of patients in both groups were highly viremic for HBV on at least one occasion. However, this high viremia was typically unsustained, perhaps due to treatment patterns, and therefore may have mitigated the effects of HBV on the transformation of cellular genes and HM development. A significant proportion of patients in both groups were on anti-retroviral therapy active against HBV virus. These treatment data only capture prescriptions issued in Montefiore and not from outside institutions. Details of compliance with therapy are not available. As for hepatitis C, data regarding interferon based or newer therapies were documented in different outpatient settings and could not be systematically retrieved for all the patients, which remains a limitation of the study.

HIV is associated with abnormal and dysregulated B cell proliferation which results in polyclonal and monoclonal paraproteins; however, their significance in terms of association with the development of HM in HIV remains uncertain [13–25]. In our study, the presence

of a D-SPEP in HIV was strongly associated with the development of plasma cell malignancies. However, F-SPEP positivity, while noted in 12 % of the high grade B cell lymphomas, did not appear to correlate with the development of HM. Whether the immunoglobulin skewing in F-SPEP cases was related to HIV or the lymphoma diagnosis remains unclear. Our study, being retrospective, was limited by the fact that only 13.4 % of patients were tested for SPEP, and a large number of patients with aggressive B cell lymphomas were not tested. Therefore, a stronger association between F-SPEP and HM may have been missed. Prior studies have shown elevated serum free light chains to precede the development of high grade lymphoma in HIV [15]. Limited data of free light chain results was available for patients, especially prior to 2009, in our cohort, and such analysis could not be performed. M spike levels were not consistently available for quantitative correlation.

In conclusion, our study showed that di screte paraproteinemia in HIV was associated with an increased risk of hematological malignancies, specifically with development of plasma cell neoplasms. Concurrent hepatitis B or C infections did not appear to confer additional risk. However, the observation on the role of HBV and HCV may be limited by patients receiving anti-viral agents active against these concurrent infections which may limit the duration of viremia and effect on the transformation of cellular genes.

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Key Points

1. Discrete paraproteinemia is a risk factor for the development of hematological malignancies in HIV and exclusively correlates with the development of plasma cell neoplasms.
2. Co-infection with hepatitis B or hepatitis C does not appear to confer additional risk of hematological malignancies.

Table 1

Patient characteristics

Characteristic	Subcategory	Number of patients *n*=10,293 (%)
Gender	Male	5956 (57.9)
	Female	4337 (42.1)
Ethnicity	Hispanic	4368 (42.4)
	Non-Hispanic	3331 (32.4)
	Missing, not identified	2594 (25.2)
Race	Black	4239 (41.2)
	White	897 (8.7)
	Asian	38 (0.4)
	Mixed	1968 (19.1)
	Other	81 (0.8)
	Missing, not identified	3070 (29.8)
Patients who were prescribed anti-retroviral therapy		5666 (55)
Patients who underwent a lymphatic structure or bone marrow biopsy		747 (7.3)
Patients with hematological malignancy		229 (2.2)

Table 2

Types of hematological malignancies identified

Hematologic neoplasm	Cases *n* (%)	D-SPEP *n* (%)	F-SPEP *n* (%)	Subtypes *(n)*	Median nadir CD4: cells/ul (IQ range)[a]	Median CD4 within 6 months of diagnosis (IQ range)[a]	Median HIV VL within 6 months of diagnosis copies/ml (IQ range)[a]
Plasma cell neoplasms	6 (2.6)	5 (83.3)	0	Multiple myeloma (4) Immature plasma cell tumor (2)	224 (60–486)	282 (146–720)	245 (47–2947)
High grade lymphomas	199 (86.9)	0	12 (6)	DLBCL including primary CNS lymphoma (106)	80 (23–174)	124 (50–216)	28,521 (545–221,881)
				Hodgkin's lymphoma (32)	126 (50–276)	282 (81–391)	1013 (75–115,562)
				Burkitts lymphoma (29)	178 (66–230)	256 (163–401)	18,230 (2015–97,220)
				High grade B cell non–Hodgkin’s lymphoma (15)	155 (71–253)	219 (166–429)	25,400 (1944–59,871)
				Plasmablastic lymphoma (8)	143 (63–247)	136 (100–221)	54,076 (28,690–144,823)
				DLBCL/Burkitts overlap (3)			
				Primary effusion lymphoma (2)			
				Aggressive T cell non–Hodgkin’s lymphoma (2)			
				Extranodal NK/T cell lymphoma (1)			
				Anaplastic large cell B cell lymphoma (1)			
Low grade lymphomas	11 (4.8)	0	0	Marginal zone lymphoma (6)	255 (144–302)	332 (263–500)	16,611 (460–18,263)
				Follicular lymphoma (2)			
				Mycosis fungoides (2)			
				Chronic lymphocytic leukemia (1)			
Acute leukemias and myelodysplasia	8 (3.5)	0	0	Acute myeloid leukemia (5)	85 (32–798)	469 (83–2752)	75 (75–346,315)
				Acute lymphoblastic leukemia (2)			
				Myelodysplasia (1)			
Myeloproliferative neoplasms	3 (1.3)	0	0	Chronic myelomonocytic leukemia (2)			
				Chronic myeloid leukemia (1)			
Dendritic cell neoplasms	2 (0.9)	0	0	Blastic plasmacytoid dendritic cell neoplasm (1)			
				Follicular dendritic cell neoplasm (1)			

[a]Data on median and IQ range for CD4 and VL results provided in categories of neoplasms where more than three patients were identified

Table 3

Risk factors for hematological malignancies in HIV patients (n = 10,221)

Characteristic	HM positive (n = 229)	HM negative (n = 9992)	p value
Male, %	160 (70)	5760 (57.6)	0.0001
Prescribed HAART, %	141 (61.6)	5489 (54.9)	0.046
Hepatitis C			
Number of patients tested for HCV co–infection	204 (89.1 %)	8879 (88.9 %)	0.916
Serology positive or viral load detectable HCV/total number tested	70/204 (34.3 %)	3299/ 8879 (37.2 %)	0.420
Hepatitis B			
Number of patients tested for HBV co–infection	202 (88.2 %)	8652 (86.6 %)	0.476
HBsAg positive / total number tested	18/202 (9 %)	580/8652 (6.7 %)	0.201
SPEP			
Number tested	76 (33.2 %)	1295 (13 %)	0.0001
SPEP positive of those tested	17 /76 (22.4 %)	244/ 1295 (18.8 %)	0.453
Faint paraprotein of those tested	12/76 (15.8 %)	217/1295 (16.8 %)	1.000
Discrete paraprotein of those tested	5/76 (6.6 %)	27/ 1295 (2.1 %)	0.028