Multiple remissions of extracavitary primary effusion lymphoma treated with a single cycle of liposomal doxorubicin in a patient infected with HIV

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ABSTRACT

Primary effusion lymphoma (PEL) is a rare human herpesvirus 8 (HHV8)–related large B cell lymphoma with plasmablastic, immunoblastic, or anaplastic features that often carries a poor prognosis. This lymphoma occurs mainly in patients with HIV infection, most often with Epstein–Barr virus (EBV) co-infection, and usually presents as body cavity effusions or, less commonly, as extracavitary lesions without effusion (EC-PEL). Chemotherapeutic treatment options are limited and require concurrent antiretroviral therapy (ART).

Here, we report the case of an adult patient with HIV infection and chronic hepatitis E virus (HEV) co-infection who had low CD4 T cell recovery after years of ART. The patient then developed a cutaneous EC-PEL which rapidly regressed after 1 cycle of liposomal doxorubicin (LD) for his Kaposi sarcoma (KS) before treatment with CHOP chemotherapy. He had previously received numerous cycles of LD for cutaneous KS over 2 years.

Because of the patient's low CD4 T cell count, HEV co-infection, and earlier unexpected remission of EC-PEL before CHOP, the patient opted for a single trial of LD before other options. Surprisingly, he experienced a complete remission lasting 18 months. Subsequently, his EC-PEL relapsed twice at 31 and at 41 months after the initial diagnosis. Upon recurrence, a similar single cycle of LD was given, which again induced remission. The patient today is in complete remission after a total of 4 LD infusions over 54 months.

This patient represents a unique case of HIV-with-HHV8–related, EBV-negative EC-PEL with chronic HEV co-infection, in which rapid remission was achieved after a single cycle of LD, suggesting an antiviral response in addition to the chemotherapeutic effect.

Key Words HIV, HHV8, primary effusion lymphoma, liposomal doxorubicin, chronic hepatitis E virus infection, Epstein–Barr virus

Curr Oncol. 2018 Dec;25(6):e592-e596

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INTRODUCTION

Primary effusion lymphoma (PEL), a rare mature B cell non-Hodgkin lymphoma, is a distinct entity that presents as lymphomatous body cavity effusions, generally in the absence of solid tumour masses^{1,2}. The diagnosis is based on the presence in the neoplastic cells of human herpesvirus 8 (HHV8), with or without Epstein–Barr virus (EBV), by polymerase chain reaction or immunohistochemistry. Extracavitary PEL (EC-PEL—a solid variant without effusion) has a morphology, immunophenotype, and molecular character similar to those of classical PEL³ and shares PEL's

median overall survival of less than 1 year⁴. The disease occurs predominantly in individuals who are immunosuppressed, most often because of HIV infection, and constitutes 5% of AIDS-related non-Hodgkin lymphomas⁵. Most patients with HIV infection who are receiving antiretroviral therapy (ART) and who develop EC-PEL are treated with CHOP (cyclophosphamide–doxorubicin–vincristine–prednisone) or CHOP-derived regimens⁴.

Here, we report the case of a patient with HIV infection who developed an EBV-negative EC-PEL that was treated with 4 single cycles of liposomal doxorubicin (LD) resulting in 4 complete remissions with a mean relapse time of 13.7

months, in the context of chronic hepatitis E virus (HEV) infection. To date, our patient remains in complete remission 54 months after the initial diagnosis.

CASE DESCRIPTION

In February 2012, a 51-year-old white man having sex with men was admitted to the Chronic Viral Illness Service at McGill University Health Centre, Montreal, Quebec, with fever, night sweats, weight loss, and elevated transaminases. He had previously been diagnosed with HIV infection in December 2010 (CD4 T cell count 60/mm³, plasma HIV load 151,000/mL) and was being treated with emtricitabine, tenofovir, and raltegravir.

Upon admission in 2012, the patient had bilateral inguinal lymphadenopathy with multiple cutaneous Kaposi sarcoma (KS) lesions on his thighs, lower legs, and chest, confirmed by biopsies (Table 1). After the diagnosis of KS, the patient was treated with LD (20 mg/m² every 2–3 weeks as determined by response to treatment). The elevation of transaminases was a consequence of HEV infection acquired in Southern France and was treated with oral daily ribavirin (10 mg/kg), which normalized his transaminases without clearing the infection. The KS lesions waxed and waned, and 31 cycles of LD were given in total. The patient's plasma HIV load remained below the limit of detection, with a modest increase in CD4 T cells.

In May 2014, the patient developed growing grey subcutaneous nodular lesions on his back, neck, and chest, which on biopsy showed diffuse proliferation of large plasmablastic cells (Figure 1). By immunohistochemistry, the cells were positive for HHV8, Bcl2, EMA, MUM1, and lambda light chain, with 100% Ki-67 staining of lymphoid cellular nuclei. The cells were negative for CD138, CD3, CD10, CD20, CD30, CD45, CD79a, Bcl6, PD-L1, and kappa light chain. *In situ* hybridization for EBV-related RNA was negative (Figure 2). Those findings were consistent with an EBV-negative EC-PEL.

During this time, the patient experienced new onset of KS lesions and received 1 cycle of LD, which led to rapid regression of the PEL-related lesions on his back and of the KS lesions. The patient then received the planned 4 cycles of CHOP for his stage 1E PEL while already in remission after the single cycle of LD.

In November 2015, a left axillary lymph node mass appeared and was biopsied, confirming a recurrence of the EC-PEL. Because of the chronic HEV and the modest CD4 T cell recovery, chemotherapy options were discussed with the patient, including second-line non-Hodgkin lymphoma or LD therapy (based on his unexpected remission before CHOP). After consideration, the patient opted for a single cycle of LD before the other options. All cutaneous and lymph node lesions disappeared within 2 weeks after that treatment. Complete clinical remission was confirmed 6 months later by a negative positron-emission tomography scan. During his second remission, the patient was treated for his HEV with sofosbuvir (400 mg daily) and ribavirin for 24 weeks, achieving a cure, confirmed by successive negative polymerase chain reaction results.

Thirteen months later, the patient developed a right temporal mass that, on biopsy, was found to be relapsed

EC-PEL. Another complete remission was observed with a cycle of LD. Ten months later, bilateral tonsillar masses appeared, were confirmed to be EC-PEL, and again regressed with a single cycle of LD. To date, the patient remains in complete remission with an increase in his CD4 T cell count to 150/mm³.

DISCUSSION

An aggressive mature B cell neoplasm, PEL constitutes approximately 5% of HIV-related lymphomas^{1,2,4}. On microscopy, the malignant cells appear immunoblastic, plasmablastic, or anaplastic³. By immunohistochemistry, the cells often reveal prominent features of terminally differentiated plasma cells. Most express CD45, but lack other B cell markers; aberrant T cell-associated antigens are rarely expressed^{1,2}. The presence of HHV8 (which is also the causative agent for KS, HHV8-associated diffuse large B-cell lymphoma, and multicentric Castleman disease^{6–9}) in the cells is essential to confirm the diagnosis of PEL. Co-infection with EBV is observed in more than 80% of cases¹⁰. Primary effusion lymphoma that is EBV-negative is most frequently reported in elderly non-immunocompromised individuals living in the Mediterranean region¹¹. Our patient, although EBV-negative by *in situ* hybridization, showed EBV positivity in blood by polymerase chain reaction.

Given the rarity of EC-PEL, guidelines for optimal treatment are limited. Therapy based on CHOP chemotherapy is associated with a 40%–50% response rate⁴. The modest improvement in survival for patients receiving ART compared with untreated individuals was attributed to virus control and immune recovery¹². Historically, median overall survival in EC-PEL is less than 1 year. Surprisingly, our patient achieved several remissions totalling 54 months after the initial diagnosis of EC-PEL. The patient rapidly responded to a single cycle of infusion LD, with remissions ranging from 10 months to 18 months. During the first cycle of LD, when the patient received CHOP, the duration of the remission was not different from the durations achieved after cycles of LD without CHOP. To our knowledge, this patient is the first with EC-PEL to have achieved remission after a single infusion of LD. Two HIV-negative elderly patients with PEL receiving LD with bortezomib and rituximab have been reported, with variable outcomes^{13,14}. Treatment with LD was proposed to our patient because of his chronic HEV infection and because treatment for relapsed non-Hodgkin lymphoma with chemotherapy can lead to HEV reactivation and possibly fulminant hepatitis. In a patient with a CD4 T cell count less than 100/mm³, chemotherapy would also worsen immunosuppression¹⁵.

Hepatitis E is an RNA virus, endemic in certain countries, including Southern France¹⁶. Hepatitis resulting from HEV is usually self-limiting, but can evolve into a chronic infection in immunosuppressed patients and could be fatal in some cases of lymphoma¹⁷. In our patient, HEV might have triggered the development of PEL; chronic viral hepatitis has been reported to be associated with lymphoproliferative disorders^{18,19}. However, because the cure of HEV in our patient did not prevent recurrence of EC-PEL, we do not consider that HEV contributed directly to the development of the lymphoma.

TABLE 1 Patient's clinical course

Clinical variable	2012		2013		2014		2015		2016		2017		2018	
	February	June	August	February	May	May	November	April	October	October	October	October	October	October
Biopsy	Right inguinal lymph node, KS		Left thigh, leg, KS		Back trunk skin lesions, EC-PEL		Skin left axilla, EC-PEL		Right temporal subcutaneous tissue EC-PEL		Tonsils EC-PEL		Clinical remission	
PET	Inguinal regions SUV 4						Left back skin lesion SUV 5		Complete remission					
Chemotherapy cycles		31×liposomal doxorubicin (LD)			1×LD 4×CHOP		1×LD		1×LD		1×LD			
Antiretroviral therapy														
Hepatitis E therapy														
PCR														
HHV8	Positive	Negative	Not done	Not done	Not done	Not done	Positive	Positive	Not done	Not done	Negative		Positive	
EBV (copies/mL)	Not done	Negative	Not done	Not done	Not done	Not done	3910	Not done	6310	5888			4365	
HIV viral load (copies/mL)	<40	<40	<40	<40	<40	<40	<40	<40	<40	<20	<20		<20	
CD4 (cells/ μ L)	11	23	49	75	77	77	110	89	125	169			150	
LDH (U/L)	Not done	Not done	Not done	247	226	226	330	217	343	144			122	
β_2 -Microglobulin (mg/L)	6.7	4.7	4.7	Not done	Not done	Not done	Not done	Not done	4.4	3.5			3.2	
AST (U/L)	101	37	20	61	21	21	25	18	23	21			25	

KS = Kaposi sarcoma; EC-PEL = extracavitary primary effusion lymphoma; PET = positron-emission tomography; SUV = standardized uptake value; CHOP = cyclophosphamide-doxorubicin-vincristine-prednisone; PCR = polymerase chain reaction; HHV8 = human herpesvirus 8; EBV = Epstein-Barr virus; LDH = lactate dehydrogenase; AST = aspartate aminotransferase.

FIGURE 1 Skin biopsy performed in 2014 shows (A) a prominent mid-dermal and deep dermal infiltrate of blue cells, that (B) at high power have a distinctly plasmablastic appearance, characteristic of primary effusion lymphoma.

FIGURE 2 Representative immunohistochemical stains show (A) prominent granular nuclear positivity of the extravascular primary effusion lymphoma for HHV8 (antibody to LANA1), (B) nuclear positivity for MUM1, and (C) cytoplasmic positivity for lambda light chain. (D) *In situ* hybridization for Epstein-Barr virus (EBER) was negative.

The remission associated with LD might be explained by an increase in the doxorubicin concentration caused by the pegylated liposomal formulation in the target organ, enriching the lymphatic system and preventing it from being engulfed by macrophages and monocytes, thus prolonging the drug's half-life²⁰. Another consideration might be that the liposome itself could have interacted with the lipid structure of the envelope of the contributing viruses^{21,22}. Because only a single cycle of LD was given, we propose that the chemotherapy might work by interrupting the interaction between HIV and HHV8 rather than by inducing its cytotoxic effects, an action that would therefore not be associated with development of resistance to chemotherapy.

In addition to ART and chemotherapy, herpes antiviral therapy remains an unconfirmed option for treating PEL²³. Ribavirin and sofosbuvir were used simultaneously to treat

the HEV infection in our patient. Interestingly, ribavirin has shown potential anti-lymphoma activity *in vivo*²⁴. Nevertheless, recurrence has been seen both with and without ribavirin. In addition, 50% of patients with PEL have been shown to be PD-L1 positive, which makes the use of anti-PD-1 and anti-PD-L1 antibodies a promising therapeutic option in patients with HIV infection²⁵. That immune checkpoint blocking approach might control HIV progression without causing further immunosuppression²⁵. Immunotherapy was not an option in our case, however, because our patient's biopsy was negative for PD-L1.

To date, our patient remains in complete remission after having received a total of 4 cycles of infusional LD over 54 months, making this case unique, given that median survival for patients with EC-PEL is less than 12 months.

SUMMARY

We report a case of a patient with HIV infection and chronic HEV infection who developed HHV8-related EC-PEL and who achieved significant remissions after low-toxicity, low-immunosuppressive single cycles of LD, suggesting an antiviral response in addition to a chemotherapeutic effect.

ACKNOWLEDGMENTS

We thank the patient for his consent and help in reconstituting his complex medical history. We thank Angie Massicotte and Kathleen Nasr for coordination and critical reading of this case report. We are supported by Fonds de recherche Québec-Santé [FRQ-S (Le réseau SIDA/maladies infectieuses du Québec and ThéCell)]; the Canadian Institutes of Health Research [CIHR (grants MOP 103230 and 154051)]; the Vaccines and Immunotherapies Core of the CIHR Canadian HIV Trials Network (grant CTN 257); the Canadian Foundation for AIDS Research [CANFAR (grant 02-512)]; and the Canadian HIV Cure Enterprise Team Grant (HIG-133050) awarded by CIHR in partnership with CANFAR. JC was supported by a CTN postdoctoral fellowship award. VM was supported by an FRQ-S Postdoctoral Fellowship Award. JPR is the holder of the Louis Lowenstein Chair in Hematology and Oncology, McGill University.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology's* policy on disclosing conflicts of interest, and we declare that we have none.

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