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Highly active antiretroviral therapy alone may be an effective treatment for HIV-associated multicentric Castleman's disease

Multicentric Castleman's disease (MCD) is a rare lymphoproliferative disorder mainly seen in HIV-infected patients and associated with poor prognosis. Pre-HAART mortality was 70-85%.[1] Proliferation of polyclonal but often monotypic plasmablastic cells is thought to be driven by Kaposi sarcoma herpes virus (KSHV) infection, present in all patients with HIV-associated MCD.[2] There is no standard treatment. Interventions include rituximab, lymphoma-type treatment with chemotherapy and splenectomy,[1,3-7] Many are used concomitantly making it difficult to ascertain which is of greatest efficacy.

We describe 4 cases of biopsy-proven HIV-associated MCD who showed a complete clinical and radiological response to MCD, and a reduction in KSHV viral load to HAART alone without additional therapeutic interventions. All patients are alive and relapse free 19-38 months later.

Between February 1st 2007 and October 1st 2008, we identified 4 consecutive patients who received HAART alone for lymph node biopsy-proven HIV associated-MCD (Table 1). Median duration of HIV infection prior to MCD was two years (range 1-14). In all patients, nodes showed a mixture of reactive lymphoid follicles and follicles with irregular, regressed germinal centers. At the periphery of these regressed germinal centers were large plasmablastic cells with prominent nucleoli and basophilic cytoplasm, usually CD20 negative, and showing positive staining for KSHV, IgM and lambda light chains (Figure 1). All patients presented with fever, lymphadenopathy, hepatosplenomegaly and elevated C-reactive protein (CRP). Three patients investigated with FDG PET/CT scan showed FDG avid lymphadenopathy above and below the diaphragm. Three patients had started HAART less than 3-5 weeks before presentation with MCD; HAART had been initiated due to a combination of CD4 decline and constitutional symptoms. HAART was modified in one patient and interrupted in one patient due to renal and liver impairment. In all patients, resolution of constitutional symptoms occurred within three months of starting HAART. Patient 2 had a recrudescence of symptoms (fever, splenomegaly and elevated CRP) eight months after diagnosis of MCD which resolved spontaneously. Serum KSHV was 6,600 copies/mL during this flare. Three months previously KSHV had been 3,600 copies/mL. Three patients who initially demonstrated significant FDG avid lymphadenopathy now showed complete metabolic response on repeat PET/CT scan and the remaining patient CRu on repeat whole body CT scan. At time of MCD diagnosis, all samples from patients were positive for KSHV between 420 and 120,000 copies/mL; 3 patients had sustained undetectable KSHV viral loads following antiretroviral therapy. KSHV was detectable in 2 patients in whom retrospective sampling of stored blood was avail-

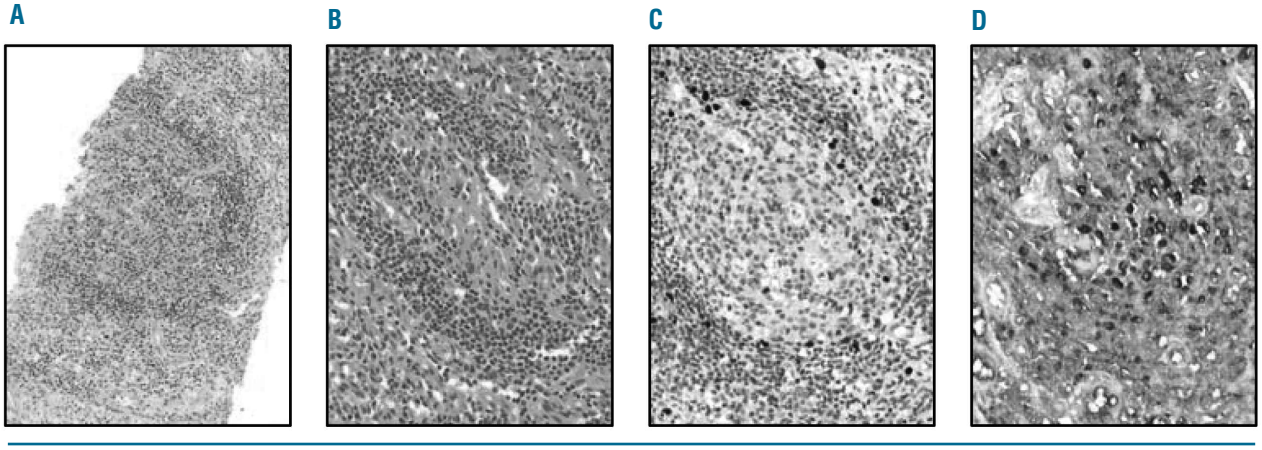

Figure 1. Composite histological figure showing features of MCD in lymph node biopsy. (A) Routine Hematoxylin and Eosin (H&E) section of a needle core biopsy of node showing an abnormal germinal center with irregular outline and scattered large plasmablastic cells (x110 original magnification). (B) High power H&E from a whole node biopsy showing a characteristic regressed germinal center with plasmablastic cells (x220 original magnification). (C) KSHV immunohistochemistry showing a target-like arrangement of KSHV-positive plasmablasts around a germinal center. (D) Lambda light chain immunohistochemistry showing cytoplasmic positivity in the plasmablastic cells in a germinal center.

able (Patient 2: KSHV 2,050 copies/mL seven months before diagnosis; Patient 3: KSHV 180 copies/mL three months before diagnosis).

Previous reports regarding the utility of HAART as treatment of MCD are conflicting. Anecdotal case reports describe clinical and radiological benefit from HAART in patients naïve to antiretroviral therapy.[8-10] In one case, remission of MCD and reduction in KSHV viremia were attributed to rituximab.[4] However, HAART had been initiated prior to improvement in both. Failure of HAART has been reported by De Jong *et al.* who describe the occurrence of MCD despite full suppression of HIV infec-

Table 1. Characteristics of 4 biopsy-confirmed cases of plasma cell variant Castleman's disease and clinical, virological and radiological response to antiretroviral therapy.

Case number	Sex, Ethnicity & Age (years)	Clinical and laboratory parameters at time of clinical presentation				Baseline imaging and histopathology results	HAART (CD4 & HIV VL prior to HAART initiation)	Outcome
		Clinical and significant laboratory abnormalities	CD4 count (cell/mm^3)	HIV viral load (copies/mL)	Plasma KSHV DNA (copies/mL)			
1	Male, white British 31	Fever, night sweats, generalized lymphadenopathy, anemia (Hb=8.0g/dL), thrombocytopenia, renal impairment (urea=16.1mmol/L, creatinine=188mg/dL), CRP=188mg/l	330	600	5300	CT scan showed bilateral lymphadenopathy measuring up to 1.5cm, para-aortic lymphadenopathy (1.7cm), small superior mediastinal nodes and an enlarged spleen measuring 8 x 15 x 21 cm. MCD identified in axillary LN	TRV + LOP started 5 weeks before MCD diagnosis. (TRV stopped due to renal impairment). Didanosine and emtricitabine added after resolution of renal impairment CD4= 160 VL= 128,000	Alive. Follow up =38 months Clinical resolution at 4 weeks after MCD diagnosis HIV VL<50 CD4= 420 KSHV= undetectable Imaging: CRu on repeat CT scan
2	Male, white British 31	Fever, night sweats, productive cough, generalized lymphadenopathy, hepatosplenomegaly, anemia (Hb=8.0g/dL), thrombocytopenia, hypoalbuminemia, CRP=170mg/L	180	1100	150,000	PET/CT scan showed generalised lymphadenopathy, hepatomegaly and an enlarged spleen measuring 10 x 15 x 20 cm. FDG avid lymphadenopathy above and below the diaphragm MCD identified in axillary LN KSHV positive staining in bone marrow trephine	TRV + LOP started 4 weeks before MCD diagnosis. CD4= 160 VL= 250,000	Alive. Follow up = 23 months Clinical resolution at 4 weeks after MCD diagnosis. Transient flare of symptoms 8 months later. HIV VL<50 CD4= 510 KSHV= 2,000 Imaging: complete metabolic response
3	Male, black other 41	Fever, lymphadenopathy and hepatosplenomegaly, anemia (Hb=11.3g/dL), eosinophilia=1.6, bilirubin=44, ALT=1100, ALP=777, CRP=54mg/L	380	360,000	420	PET/CT scan showed widespread lymphadenopathy, hepatomegaly and an enlarged spleen measuring 17 x 7 x14 cm. FDG avid lymphadenopathy above and below the diaphragm MCD identified in axillary LN KS identified in inguinal LN	KVX + Nevirapine started 3 weeks before MCD diagnosis. HAART stopped due to hepatitis. TRV, Atazanavir, Ritonavir restarted. CD4=180 VL=56,700	Alive. Follow up =32 months Clinical resolution at 4 weeks after MCD diagnosis HIV VL<50 CD4= 390 KSHV= undetectable Imaging: complete metabolic and radiological response
4	Male, black other 32	Fever, night sweats, weight loss, cutaneous KS, lymphadenopathy, hepatosplenomegaly, anemia (Hb=8.5g/dL), platelets=129, neutropenia=1.95 CRP=127mg/mL	250	220,000	30,000	PET/CT scan revealed multiple enlarged axillary, mediastinal, mesenteric and inguinal lymph nodes and hepatosplenomegaly. FDG avid lymphadenopathy above and below the diaphragm including FDG avid diffused spleen uptake MCD identified on liver biopsy KS identified in axillary LN and skin biopsy	TRV and Efavirenz started at MCD diagnosis CD4 =250 VL =220,000	Alive. Follow up = 19 months Clinical resolution at 6 weeks after MCD diagnosis. HIV VL<50 CD4= 430 KSHV= undetectable Imaging: complete metabolic response

HIV: human immunodeficiency virus; KSHV: Kaposi sarcoma herpes virus; HAART: highly active antiretroviral therapy; KS: Kaposi sarcoma; LN: lymph node; MCD: Multicentric Castleman's disease; Hb: hemoglobin; ALT: alanine aminotransferase; ALP: alkaline phosphatise; TRV: tenofovir-emtricitabine (Truvada); LOP: lopinavir-ritonavir (Kaletra); KVX: abacavir-lamivudine (Kivexa); CRu: complete remission unconfirmed.

tion with HAART.[11] Clinical deterioration despite HAART alongside promising clinical outcomes of newer therapies such as rituximab,[5] has led many physicians to advocate the use of rituximab or chemotherapy as first-line treatment of MCD. However, benefit ascribed to newer agents may be confounded by the natural history of MCD and the co-prescribing of HAART.

The role of other therapies instead of, or in addition to HAART is not clear. Rituximab, an anti-CD20 monoclonal antibody, is increasingly being adopted for first-line treatment due to good tolerability and reported clinical activity, despite little understanding of its anti-MCD activity, as many of the KSHV infected plasmablastic cells do not express CD20.[3-5,12] In a case series of 21 patients with HIV-associated MCD, rituximab resulted in clinical and radiological response. However, the temporal relationship between clinical response to rituximab and institution of HAART is not described.[5] In one case, remission of MCD and reduction in KSHV viremia were attributed to rituximab.[4] However, HAART had been initiated prior to this improvement. Based on our findings, the benefits of many anti-MCD treatments might be attributable to concurrently administered HAART that suppresses KSHV viremia, probably via restoration of immune function, as evidenced by increased CD4 counts and reduction of HIV viral loads. While optimal treatment for HIV-associated MCD remains undefined, our findings suggest HAART alone may represent an effective treatment for MCD patients, avoiding unnecessary splenectomy or chemotherapy with attendant toxicity and impeding immune reconstition/CD4 recovery.

In 3 of the 4 patients described, MCD was diagnosed 3-5 weeks after starting HAART. They presented with persisting constitutional symptoms with generalized lymphadenopathy and hepatosplenomegaly, resembling an immune reconstitution phenomena, an observation previously suggested by Zeitz.[13] However, we demonstrated that continuation of HAART was associated with clinical improvement of MCD in our patients who remain disease free 23-38 months later, suggesting that the initial deterioration seen following HAART may be transient and not imply treatment failure. The remaining patient was antiretroviral naïve at MCD diagnosis, with CD4 count of 250 cells/mm^3 and no organ failure. By comparison, the patient described by De Jong *et al.* was already taking HAART, initiated at a significantly lower CD4 count (15 cells/mm^3).[11]

KSHV was detected in 2 patients for whom sampling of stored blood was available. This observation raises the possibility that the incidence of HIV-associated MCD may be far higher than reported in the literature, because HAART given to many KSHV co-infected patients, presenting with constitutional symptoms and low CD4 counts but with undiagnosed MCD, may induce clinical remission before diagnosis of MCD. KSHV and FDG-PET/CT testing of HIV-infected HAART-naïve patients presenting with constitutional symptoms and enlarged glands may result in identification of more cases of MCD by performing biopsy for histological diagnosis.

These 4 patients demonstrate that HAART may be an effective treatment for HIV-associated MCD. Currently there is a lack of data to offer clear guidance to clinicians on treatment strategy. Multi-center clinical trials are needed to examine the role of HAART for first-line treatment of MCD.

Siow Ming Lee[1], Simon G. Edwards,[2] Daniella N. Chilton,[2] Alan Ramsay,[3] and Robert F. Miller[4]

[1]Department of Oncology, University College London Hospitals, London; [2]Department of Genitourinary Medicine, Mortimer Market Centre, Camden Provider Services, London; [3]Department of Histopathology, University College London, London; and [4]Centre for Sexual Health and HIV Research, Research Department of Infection and Population Health, University College London, London, UK

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Correspondence: Professor Siow Ming Lee, Department of Oncology, University College London Hospitals, 250 Euston Road, London NW1 2PG, UK. Phone: international +44.207.3809091. Fax: international +44.207.3809055. E-mail: sm.lee@uclh.nhs.uk

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