Successful treatment of HIV-associated multicentric Castleman’s disease and multiple organ failure with rituximab and supportive care: a case report

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Abstract

Introduction: Multicentric Castleman’s Disease (MCD), a lymphoproliferative disorder associated with Human Herpes Virus-8 (HHV-8) infection, is increasing in incidence amongst HIV patients. This condition is associated with lymphadenopathy, polyclonal gammonopathy, hepato-splenomegaly and systemic symptoms. A number of small studies have demonstrated the efficacy of the anti-CD20 monoclonal antibody, rituximab, in treating this condition.

Case presentation: We report the case of a 46 year old Zambian woman who presented with pyrexia, diarrhoea and vomiting, confusion, lymphadenopathy, and renal failure. She rapidly developed multiple organ failure following the initiation of treatment of MCD with rituximab. Following admission to intensive care (ICU), she received prompt multi-organ support. After 21 days on the ICU she returned to the haematology medical ward, and was discharged in remission from her disease after 149 days in hospital.

Conclusion: Rituximab, the efficacy of which has thus far been examined predominantly in patients outside the ICU, in conjunction with extensive organ support was effective treatment for MCD with associated multiple organ failure. There is, to our knowledge, only one other published report of its successful use in an ICU setting, where it was combined with cyclophosphamide, adriamycin and prednisolone. Reports such as ours support the notion that critically unwell patients with HIV and haematological disease can benefit from intensive care.

Introduction

The spectrum of HIV-associated disease on the ICU has changed markedly since the widespread adoption of combination antiretroviral therapy (Highly Active Anti-retroviral Therapy, HAART) in the late 1990s. Whilst the incidence of opportunistic infections has decreased, that of several neoplasms, including Multi-centric Castleman’s Disease (MCD) and Hodgkin’s lymphoma is increasing. MCD is a lympho-proliferative disorder associated with Human Herpes Virus-8 (HHV-8) infection, characterised by fever, lethargy, anaemia and lymphadenopathy. Lymph node histology typically reveals angio-follicular hyperplasia and plasma cell infiltration. There is as yet no accepted therapeutic gold standard for MCD. Initial treatment approaches involved chemotherapy with agents such as vinblastine, etoposide and doxorubicin plus corticosteroids. More recently the anti-CD20 monoclonal antibody, rituximab, has been used. This targets HHV-8-infected plasmablasts, which co-express the B cell antigen CD20. Small case series of patients with MCD have shown rituximab to be an effective therapy in patients that do not require organ support on the intensive care unit [1-3].

Case Presentation

A 46 year old Zambian woman was referred from another hospital with a 4 week history of fevers, night sweats, vomiting, diarrhoea, and renal impairment. She had been diagnosed HIV positive in 2005, and started on HAART one year later. She had previously been treated for Herpes simplex virus infection, Cytomegalovirus...
confirmed the clinical suspicion of Multi-centric Castle-

pelvis (Figure 1). Inguinal lymph node excision biopsy

lymphadenopathy involving the thorax, abdomen and

paenia, and acute renal and liver dysfunction.

A CT scan showed hepato-splenomegaly and gross

lymphadenopathy involving the thorax, abdomen and

pelvis (Figure 1). Ingual lymph node excision biopsy

confirmed the clinical suspicion of Multi-centric Castle-

man’s disease (MCD) (Figure 2). Rituximab (375 mg/m²)

together with hydrocortisone and rasburicase, was ad-

ministered as specific treatment. She developed rapidly

progressive metabolic acidosis, oliguria, and rising

serum creatinine and was admitted to the ICU for ha-

emofiltration. Antiretroviral therapy was continued on

the ICU with ritonavir-boosted lopinavir and saquinavir.

Abacavir and lamivudine, which the patient was already

taking, were stopped because of their association with

lactic acidosis and hepatic steatosis.

Following admission to ICU she rapidly became hypo-
tensive, hypoglycaemic, coagulopathic and more ana-

emic. A possible basis for this could have been the

systemic manifestations of a "cytokine storm" associated

with MCD; increased expression of IL-6 is typical of

MCD. Vasopressor and inotropic support with noradre-
naline and dobutamine was required to maintain an

adequate mean arterial pressure (MAP). Because of

rapidly escalating requirements for noradrenaline she

received a continuous infusion of hydrocortisone (10

mg/h) as per local departmental protocol, to treat prob-

able relative adrenal insufficiency. Empirical antibiotics

and antifungal agents were given to treat sepsis as a

possible basis for this could have been the systemic

manifestations of a "cytokine storm" associated

with MCD; increased expression of IL-6 is typical of

MCD. From day 10 there was evidence of clinical

improvement. She had a tracheostomy in the second week

of her ICU stay, and she was slowly weaned from inotro-

pic/vasopressor, ventilatory, and finally renal support. At
day 21 of her ICU admission, she was discharged to the

ward to complete her treatment with rituximab, and to

continue rehabilitation from global muscle weakness,

and reduce dependence on her tracheostomy. The

patient was discharged home, in remission from her dis-

ease, after 149 days in hospital. When last seen in clinic

she remained in remission and living independently 14

months from her treatment.

Discussion

Survival of patients with HIV admitted to the ICU has

improved substantially in the last 10 years, with HIV

patients now being able to expect a similar chance of

survival through to hospital discharge as general medical

patients admitted to the ICU. The basis for this

improvement is likely to be multifactorial, reflecting bet-

ter understanding of HIV-associated disease, the avail-

ability of new combination antiretroviral therapy, the

improved care of HIV patients both outside and within

the ICU, and protective ventilation strategies for HIV

patients with respiratory failure and acute lung injury.

Prognostic factors previously shown to be associated

to target early shock reversal and removal of IL-6,

increased expression of which is a hallmark feature of

MCD.

The chest radiograph progressed over four days to

bilateral diffuse patchy consolidation (Figure 3), asso-

iated with greatly increased oxygen requirements (FiO2

0.8), and consistent with a diagnosis of acute respiratory

distress syndrome (ARDS). The patient became drowsy

and hypercapnic. Her trachea was therefore intubated,

and mechanical ventilation was commenced.

Table 1 Laboratory investigations on admission to Royal

Free Hospital Haematology unit

| Parameter                  | Value             |
|----------------------------|-------------------|
| Haemoglobin 8.4 g/dl       | Urea 56 mmol/l    |
| White Cell Count 17 x 10⁹/l| Creatinine 367 μmol/l |
| Neutrophils 13 x 10⁹/l     | Bilirubin 101 μmol/l |
| Platelets 43 x 10⁹/l       | Aspartate transaminase 185 IU/l |
| Prothrombin time 20.5 seconds| Albumin 18 g/l |
| Fibrinogen 5.4 g/l         | Lactate 8.6 mmol/l |
| C-reactive protein 140 mg/l|                  |
physiology score I; or APACHE II: acute physiology & chronic health evaluation II), and the need for, and duration of, mechanical ventilation whilst on the ICU [4]. In addition, a haematological malignancy also independently further confers a poor prognosis. Such patients typically have severely impaired host defences and the undertaking of invasive procedures, such as endotracheal intubation and central venous cannulation, carries a major risk of infection.

Cornet et al [5] reported an ICU mortality rate of 60% for haemato-oncological patients compared with a rate of 27% for general critically ill patients. They also highlighted the poor long-term prognosis, with a 1 year mortality of 88% for haemato-oncological patients. However, such patients may not fare so badly on ICU if organ support facilitates administration of a specific therapy for a treatable condition. Benoit et al [6] have recently described successful outcomes in severely ill patients with haematological malignancies who receive intravenous chemotherapy in intensive care. Hence admission to ICU for specific therapy can be lifesaving.

The gold standard therapy for HIV-associated MCD is yet to be established. Vinblastine, etoposide and doxorubicin plus corticosteroids have all been used previously. Etoposide has been shown to be effective with resolution of systemic symptoms during its administration. However it has not been associated with prolonged remission. Interruption of chemotherapy usually results in clinical recurrence and most patients remain chemotherapy-dependent for life. In addition its use can be associated with cytopenias. The use of etoposide would have been considered as adjuvant therapy in our case had the MCD not responded to rituximab monotherapy. In contrast rituximab is well tolerated and has been shown to be effective in case reports and series [1-3]. The role of rituximab in therapy for critically ill patients is less well established. In previously published reports, those admitted to ICU did not survive. Recently,
however, a successful outcome of rituximab, in conjunction with cyclophosphamide, Adriamycin and prednisolone, in the ICU setting, has been described [7].

In our patient, the clinical presentation was consistent with a systemic illness with a large inflammatory/infective component. The patient was originally from a country with endemic mycobacterial and fungal infection. Investigations therefore were undertaken to exclude a variety of possible causes - including disseminated mycobacterial and fungal disease, as well as lymphoma-like conditions, such as MCD. Prompt diagnosis was made following lymph node biopsy. The decision to biopsy an inguinal lymph node, rather than a cervical node was based on the clinical findings of a large and easily palpable inguinal lymph node mass. Although small volume bilateral cervical lymphadenopathy was present, this was far less clearly abnormal than the groin lymph nodes. A particular issue in HIV patients is the presence of persistent generalised lymphadenopathy, which represents an immune response directed against HIV. This typically results in findings similar to the cervical adenopathy present in this patient; and therefore neck biopsy may have in fact slowed the diagnostic process.

Antiretroviral therapy was continued, but modified on the ICU. Notably the patient had been using antiretroviral therapy (HAART) for two years prior to her presentation to our service. She had had a persistently undetectable plasma HIV load (<50 copies/mL). Her nucleoside reverse transcriptase inhibitors (abacavir and lamivudine) were stopped because of their association with lactic acidosis and hepatic steatosis. Although it would be surprising for this to occur after such a prolonged time on these drugs, it was important to
minimise any possible mitochondrial toxicity that might have resulted from these agents; and which in turn could have contributed to acidosis. Monotherapy with ritonavir-boosted protease inhibitors is a useful treatment option in patients who are intolerant or resistant to other agents [8]. The approach is particularly successful in patients who have already suppressed their plasma HIV load, such as in this case.

Her condition progressed rapidly to one of multiorgan failure requiring a high level of support on the ICU. Supportive strategies included mechanical ventilation for acute respiratory distress syndrome; circulatory support with inotropes/vasopressors and corticosteroids; and high volume haemofiltration for renal failure and severe metabolic acidosis. Corticosteroids were used empirically to treat probable underlying relative adrenal insufficiency. This occurs in up to 25% of critically ill patients with sepsis. Surviving Sepsis guidelines [9] published in 2004 do not suggest mandatory testing (by adrenocorticotropic hormone: ACTH stimulation test) unless there is strong suspicion of undiagnosed primary adrenal insufficiency. The 10 mg/h infusion used in our patient was in line with the recommended 24 hour total dose of 200-300 mg. High volume haemofiltration was undertaken to target early shock reversal and removal of IL-6, increased expression of which is a hallmark feature of MCD. In animal studies, such a strategy is associated with improved haemodynamics and gas exchange, reduced immuno-paresis and increased survival [10]. The length of hospital stay post ICU discharge for our patient largely reflects the need for weaning from respiratory support and rehabilitation. Patients such as ours often experience profound muscle weakness (ICU-acquired weakness) after mechanical ventilation on intensive care, and require intensive physiotherapy, as well as nutritional, psychological and social support.

Conclusion
Our patient’s successful outcome can be attributed to relatively simple treatment for MCD: that is rituximab; and extensive multi-organ care support on the ICU. Rituximab is a newly-established therapy for MCD [1]. Its efficacy has thus far been chiefly demonstrated in limited studies of patients outside of the intensive care setting. Recent literature suggests ICU admission and support can be beneficial for haematology-oncological patients to facilitate specific chemotherapy [6]. Consistent with this notion, our report illustrates the benefit of ICU support during rituximab treatment for HIV-associated MCD.

Consent
Written informed consent was obtained from our patient for publication of this case report. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Abbreviations
ACTH: adrenocorticotropic hormone; AIHA: autoimmune haemolytic anaemia; APACHE II: acute physiology and chronic health evaluation II; APTT: activated partial thromboplastin time; ARDS: acute respiratory distress syndrome; CNS: central nervous system; DIC: disseminated intravascular coagulation; FiO₂: fraction of inspired oxygen; HAART: highly active antiretroviral therapy; HIV-8: human herpes virus-8; HIV: human immunodeficiency virus; ICU: intensive care unit; MAP: mean arterial pressure; MCD: Multicentric Castleman’s Disease; PT: prothrombin time; SAPS I: simplified acute physiology score I.

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Authors’ contributions
All authors were involved in managing this case. RHJ wrote the manuscript with TD, input with MC. All authors read and approved the final manuscript.

Competing interests
The authors declare that they have no competing interests.

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