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Durable remission of both multicentric Castleman's disease and Kaposi's sarcoma with valganciclovir, rituximab and liposomal doxorubicin in an HHV8 positive, HIV-negative patient.

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SUMMARY

What is known and objective

Human herpes virus 8 (HHV-8) positive, HIV-negative multicentric Castleman's disease is a rare lymphoproliferative disorder with no standardised treatment. Concurrent Kaposi sarcoma, another HHV-8 related disease, is uncommon in HIV-negative patients. The role of antiviral therapy and rituximab in HIV-negative patients is not well established.

Case Description

We report a case of a five year, durable remission of HHV-8 positive, HIV-negative co-morbid multicentric Castleman's disease and Kaposi sarcoma treated with long-term valganciclovir, following initial rituximab and liposomal doxorubicin.

What is new and conclusion

Currently there is no defined role for anti-viral therapy in the treatment of HIV-negative HHV-8 positive multicentric Castleman's disease and Kaposi sarcoma. Ganciclovir followed by indefinite, continuous valganciclovir is thought to have contributed significantly to the durable response in this case.

WHAT IS KNOWN AND OBJECTIVE

Human herpes virus 8 (HHV-8) is an oncogenic virus involved in the pathogenesis of Kaposi sarcoma, primary effusion lymphoma and multicentric Castleman's disease. Multicentric Castleman's disease is a rare systemic lymphoproliferative disorder that most commonly occurs in patients infected with human immunodeficiency virus (HIV). Almost all cases of HIV-positive multicentric Castleman's disease are co-infected with HHV-8.¹ This is in contrast to HIV-negative multicentric Castleman's disease, where HHV-8 co-infection occurs in only 7 – 50% of cases.² A concurrent diagnosis of Kaposi sarcoma has been reported in less than 13% of HIV negative multicentric Castleman's disease.³ Due to the rarity of this disease, large prospective trial data are lacking. Chemotherapy and, more recently, targeted therapy with anti-CD20 and anti-IL-6 monoclonal antibodies have demonstrated efficacy.⁴⁻⁷ The role of anti-viral drugs in the management of HHV-8-positive, HIV-negative multicentric Castleman's disease and Kaposi sarcoma has not been established. We present a case of HHV-8 positive, HIV-negative multicentric Castleman's disease with concurrent Kaposi sarcoma in whom the combination of antiviral therapy with ganciclovir and valganciclovir and treatment with the anti-CD20 monoclonal antibody rituximab resulted in long-term control of HHV-8 viraemia and consequently long term remission of both diseases.

CASE DESCRIPTION

A previously well 62 year old man of Mediterranean descent presented with fevers, sweats, fatigue and anaemia. Examination and imaging revealed widespread lymphadenopathy, splenomegaly and Kaposi sarcoma involving all four limbs. Intranodal Kaposi sarcoma with associated plasma cell variant multicentric Castleman's disease was confirmed on inguinal node biopsy. HIV serology was negative. Quantitative real-time polymerase chain reaction revealed HHV-8 DNA in pooled plasma and lymphocytes (cycle threshold (C_t) 32.5). The C_t for positive controls included in each HHV-8 PCR assay were all within 2 C_t of their standard values (VIDRL, Australia). Lower C_t values reflect higher viral load. The virus is deemed undetectable at $C_t >45$ (**Figure 1**).

The patient received prednisolone 60mg daily for one week prior to commencing 6 cycles of liposomal doxorubicin (**Table 1**). The prednisolone was weaned over the course of chemotherapy. Treatment resulted in clinical improvement and radiological response.

Less than two months after completing chemotherapy the patient relapsed with biopsy confirmed recurrence of multicentric Castleman's disease. Two cycles of cyclophosphamide, etoposide, prednisolone and vincristine (**Table 1**) were administered with documented partial radiological response. Cycle two was complicated by a life-threatening pneumonia which did not respond to broad spectrum antibiotics and required both inotropic and non-invasive ventilator support. No bacterial pathogen was identified on blood or sputum cultures, however HHV-8 viraemia (C_t 25) was noted. Intravenous ganciclovir was commenced with clinical improvement and reduction in HHV-8 viral levels (C_t 28). Ganciclovir was replaced with valganciclovir 900mg oral twice daily. After three weeks the patient recovered and HHV-8 was undetectable, therefore valganciclovir was ceased.

Within seventeen days of ceasing valganciclovir multicentric Castleman's disease recurred along with re-emergence of HHV-8 viraemia (C_t 35) and a new Kaposi sarcoma lesion. Intravenous ganciclovir was recommenced, resulting in resolution of symptoms and regression of the lesion and lymphadenopathy but ongoing low-level viraemia (C_t 34-38). The patient was discharged on continuous oral valganciclovir 900mg daily.

A confirmed relapse of multicentric Castleman's disease occurred three months after this admission, at which time, notably, HHV8 was still detectable (C_t 38). The multicentric Castleman's disease was successfully controlled with 4 doses of weekly rituximab (**Table 1**). Kaposi sarcoma progressed shortly after completion of rituximab. A rechallenge with 6 cycles of liposomal doxorubicin (**Table 1**) achieved a documented near-complete clinical response.

Another biopsy-confirmed relapse of multicentric Castleman's disease and an associated rise in HHV-8 levels (C_t 30), occurred eleven months after completion of rituximab therapy and six months following cessation of liposomal doxorubicin. One cycle of cyclophosphamide, vincristine and prednisolone (**Table 1**) was administered but due to thrombocytopenia, chemotherapy was replaced with four doses of single-agent weekly rituximab (**Table 1**). Valganciclovir was continued throughout treatment. Near-complete clinical and radiological response in multicentric Castleman's disease were achieved and there was a reduction in HHV-8 levels, although these were still detectable.

Low-level HHV-8 viraemia (C_t 30-38) persisted and another flare of Kaposi sarcoma followed this second course of rituximab. This required retreatment with a further six cycles of liposomal doxorubicin (**Table 1**) and during this time HHV-8 viraemia resolved. Valganciclovir 900mg oral daily has continued and HHV-8 levels have remained undetectable. With more than five years of follow up from completion of chemotherapy no further treatment has been required for either multicentric Castleman's disease or Kaposi sarcoma.

In summary, this man had multiple and frequent relapses of both multicentric Castleman's disease and Kaposi sarcoma early in the disease course, all of which occurred in the presence of detectable HHV-8 viraemia. Introduction of life-long valganciclovir reduced HHV-8 viral load to an undetectable level over a period of almost 18 months. Subsequently, HHV-8 levels remained undetectable and no further relapses have occurred with more than 5 years follow up.

Several chemotherapy regimens have been evaluated in multicentric Castleman's disease and, with few exceptions, yielded poor outcomes.⁸ Liposomal doxorubicin or paclitaxel induce response in Kaposi sarcoma but, in most cases, duration of response is limited.⁹⁻¹¹ In the twenty years since HHV-8 was first identified there have been significant advances in our understanding of its role in the oncogenesis of multicentric Castleman's disease leading to the implementation of new treatment strategies for this disease.¹² The HHV-8 infected cells in multicentric Castleman's disease are large CD20+ plasmablasts.¹³ Depletion of these cells by the anti-CD20 antibody rituximab, and subsequent restoration of anti-viral T-cell immunity may contribute to the efficacy of these agents.² In prospective trials of HIV-positive multicentric Castleman's disease, rituximab improved constitutional symptoms and produced objective responses in up to 70% of patients.^{6, 14} Improvement in overall survival has also been demonstrated, albeit in a retrospective study.¹⁵ As a result rituximab has become a standard component of first-line treatment for HIV-positive multicentric Castleman's disease.⁷ In HIV-negative diseasedata are scarce, with few reports describing remissions following rituximab.^{2, 16, 17}

In HIV-positive patients diagnosed with dual multicentric Castleman's disease and Kaposi sarcoma the use of rituximab to treat multicentric Castleman's disease is associated with disease progression of Kaposi sarcoma in up to 50% of patients.⁷ In this population Kaposi sarcoma progression can be managed with the addition of liposomal doxorubicin to rituximab therapy.⁵ The phenomenon of rituximab-related Kaposi sarcoma flare was noted in this case and has been described in one other case of HIV-negative HHV-8-positive multicentric Castleman's disease.¹⁶ Whilst in our patient the Kaposi sarcoma was successfully controlled with liposomal doxorubicin and anti-viral treatment, the outcome of the Kaposi sarcoma flare in Law *et al*'s case has not been reported.

There is evidence in HIV-positive multicentric Castleman's disease and Kaposi sarcoma that HHV-8 levels can be used to monitor and predict relapse.¹⁸ In this population, cidofovir, foscarnet and ganciclovir have all been associated with a reduction in the development of Kaposi sarcoma¹⁹ and ganciclovir and foscarnet with a decrease in HHV-8 viraemia.²⁰⁻²² In HIV-negative patients the relationship between HHV-8 viral load and these diseases, particularly multicentric Castleman's disease, remains unclear. HHV-8 viraemia is a common finding in multicentric Castleman's disease recurrence,²³ and there is some data suggesting a relationship between reduced HHV-8 viral load and disease response.¹⁷ Broad-spectrum anti-viral agents directed against HHV-8 are not part of the routine management of multicentric Castleman's disease or Kaposi sarcoma due to lack of proven benefit. Only a few reports of this treatment approach exist, mostly in HIV-positive patients, however even responses considered durable are reported as lasting only 3-18 months.²⁴⁻²⁶ In all of these cases anti-viral treatment was ceased upon resolution of multicentric Castleman's disease recurrence, except for one case where continuation was not explicitly stated.

In our case HHV-8 viraemia was associated with severe systemic symptoms and progression of both multicentric Castleman's disease and Kaposi sarcoma followed by clinical and biochemical response to antiviral treatment. Ongoing suppression of HHV-8 altered the disease course of both conditions. Prior to the use of antiviral suppression our patient experienced rapid symptomatic recurrences punctuated by responses to chemotherapy

which were not durable. In contrast the two relapses of multicentric Castleman's disease and Kaposi sarcoma during the first year of antiviral therapy achieved remissions of relatively long duration. Of note, these occurred in the context of an initial interruption to valganciclovir and declining but persistent HHV-8 viraemia. Whilst rituximab induced responses in multicentric Castleman's disease during this period, it was associated with progression of Kaposi sarcoma in both instances necessitating treatment with liposomal doxorubicin. Following complete resolution of HHV-8 viraemia, and with ongoing valganciclovir, there has been no recurrence of either disease observed in more than five years of follow up at our institution. Inarguably rituximab contributed to remission of multicentric Castleman's disease in this case but the disease recurred following the first course of treatment in the setting of persistent HHV-8 viraemia. Rituximab has no activity in Kaposi sarcoma, suggesting the addition of valganciclovir to conventional chemotherapy and anti-CD20 targeted treatment in this patient played a role in the long-term control of these diseases.

WHAT IS NEW AND CONCLUSION

Dual HHV-8 related diseases are rarely seen in HIV-negative patients. To our knowledge this is the first case where a durable remission of both multicentric Castleman's disease and Kaposi sarcoma was achieved with the addition of ongoing antiviral therapy to sequential rituximab and liposomal doxorubicin in an HHV8-positive, HIV-negative patient. Repeated flares of Kaposi sarcoma followed treatment with rituximab, demonstrating this phenomenon is not isolated to HIV-positive patients. We suggest that long-term control of HHV-8 contributed to the treatment of multicentric Castleman's disease and Kaposi sarcoma in this patient with HIV-negative disease and was, in part, responsible for his durable remission.

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Tables & Figures

Table 1. Chemotherapy and targeted therapy regimens

Regimen	Doses	Cycle length
Liposomal doxorubicin	liposomal doxorubicin 20mg/m ²	28 days
CEOP	cyclophosphamide 750mg/ m ² etoposide 100mg/m ² vincristine 1.4mg/m ² D1 (dose capped at 2mg) prednisolone 100mg D1-5	21 days
Rituximab	rituximab 375mg/m ²	7 days
CVP	cyclophosphamide 750mg/m ² D1 vincristine 1.4mg/m ² D1 (dose capped at 2mg) prednisolone 40mg/m ² D1-5	21 days

Figure 1. HHV-8 viraemia ($C_t^{\dagger}$) and disease activity

[†] lower C_t values reflect higher viral load

Figure 1. Abbreviations: CEOP cyclophosphamide etoposide vincristine prednisolone; CVP cyclophosphamide, vincristine, prednisolone; KS Kaposi sarcoma; MCD multicentric Castleman's disease

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