Clinical features and outcome in 61 patients with HIV associated Multicentric Castleman’s disease

Shairoz Merchant, Anne-Marie Young, Tom Newsom-Davis, Kikkeri Naresh, Brian Gazzard, Mark Nelson, Mark Bower
Castleman’s disease

HIV Castleman’s disease

<table>
<thead>
<tr>
<th>Hyaline vascular</th>
<th>Plasmablastic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Localised</td>
<td></td>
</tr>
<tr>
<td>Multicentric</td>
<td>HIV-MCD</td>
</tr>
</tbody>
</table>
Mantle zone with large lymphoid cells with prominent nucleoli (plasmablasts)

Plasmablasts infected by HHV8

HHV8 LANA staining
Plamablasts CD20+

Castleman’s Clinical Presentation

- Fever, night sweats, weight loss
- Localised or diffuse lymphadenopathy
- Hepatosplenomegaly
- Anaemia, hypoalbuminaemia, polyclonal hypergammaglobulinaemia
What’s an attack of MCD?

1. Fever
2. At least 3 of the following:
   - Lymphadenopathy
   - Splenomegaly
   - Oedema
   - Pleural effusion
   - Ascites
   - Cough
   - Nasal obstruction
   - Xerostomia
   - Rash
   - Central neurologic symptoms
   - Jaundice
   - Autoimmune haemolytic anaemia
3. Serum C-reactive protein level > 20 mg/L
   (in the absence of any other cause)

Single institution cohort study

Cohort study to examine:
1. Clinical features of MCD
2. Treatment outcomes
### Features at diagnosis

**MCD at CWH (n=61)**

<table>
<thead>
<tr>
<th>Feature</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age</td>
<td>42 years</td>
</tr>
<tr>
<td>Male</td>
<td>87%</td>
</tr>
<tr>
<td>Prior AIDS</td>
<td>38%</td>
</tr>
<tr>
<td>Median CD4 count (range)</td>
<td>234/mm$^3$ (41-1400)</td>
</tr>
<tr>
<td>On HAART &gt;3m</td>
<td>25/59 (42%)</td>
</tr>
<tr>
<td>On HAART &amp; VL&lt;50 copies</td>
<td>11/25 (44%)</td>
</tr>
<tr>
<td>Median duration symptoms (range)</td>
<td>3 months (0.5-24)</td>
</tr>
</tbody>
</table>

### Frequency of clinical criteria

**in 61 MCD patients**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
<td>98%</td>
</tr>
<tr>
<td>C-reactive protein &gt;20mg/L in the absence of any other aetiology</td>
<td>92%</td>
</tr>
<tr>
<td>Peripheral lymphadenopathy</td>
<td>100%</td>
</tr>
<tr>
<td>Enlarged spleen</td>
<td>95%</td>
</tr>
<tr>
<td>Oedema</td>
<td>18%</td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>18%</td>
</tr>
<tr>
<td>Ascites</td>
<td>8%</td>
</tr>
<tr>
<td>Cough</td>
<td>61%</td>
</tr>
<tr>
<td>Nasal obstruction</td>
<td>40%</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>40%</td>
</tr>
<tr>
<td>Rash (including KS=33)</td>
<td>62%</td>
</tr>
<tr>
<td>Central neurologic symptoms</td>
<td>66%</td>
</tr>
<tr>
<td>Jaundice</td>
<td>14%</td>
</tr>
<tr>
<td>Autoimmune haemolytic anaemia</td>
<td>43%</td>
</tr>
<tr>
<td>Fewer than 3 criteria met*</td>
<td>10%</td>
</tr>
</tbody>
</table>

*But nasal obstruction and xerostomia only prospectively collected on 20 patients*
Other MCD features

Clinical features not seen in the classification

<table>
<thead>
<tr>
<th>Condition</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatomegaly</td>
<td>40/61 (66%)</td>
</tr>
<tr>
<td>Kaposi's sarcoma</td>
<td>33/61 (54%)</td>
</tr>
<tr>
<td>Pulmonary involvement</td>
<td>28/60 (47%)</td>
</tr>
</tbody>
</table>

Plasma KSHV levels measured at MCD diagnosis for 45 patients:
Detectable KSHV DNA:
Median $\log_{10}$ plasma HHV8 DNA load copies/mm$^3$ was 5.3 (range 2.3-8.7)

HIV MCD treatment options

- Splenectomy
- HAART
- Vinblastine
- Etoposide
- Interferon $\alpha$
- Ganciclovir
- Anti IL6 receptor blocking antibody
Survival pre 2002

Median survival 4m

2 year overall survival 42% (95% CI 14-70%)
5 year overall survival 33% (95% CI 6-60%)

Algorithm of care for MCD (2002-2006)

MCD diagnosed in LN
MCD diagnosed following splenectomy

Rituximab 375mg/m² x4

cf: (Oksenhendler et al 1996)
Largest published series
n=20
Median survival 14m
New risk-stratified algorithm 2006-

- PS 0-1, No end organ damage: Rituximab
- PS ≥2, end organ damage: Etoposide & Rituximab

Rituximab-based therapy

49 patients since 2003
   - 35 rituximab monotherapy
   - 14 rituximab & etoposide

2 year OS (95% CI)
- All 49: 94% (87-100%)
- Rituximab monotherapy: 97% (87-100%)
- Rituximab & etoposide: 86% (68-100%)
Overall survival of 49 patients treated with rituximab-based therapy

2 year overall survival 94% (CI 87-100%)
5 year overall survival 90% (CI 81-100%)

Overall survival pre/post Rituximab

n=8
n=49
Response rates

46 patients: achieved resolution of systemic symptoms and fevers

45 patients: radiological response
   1 Complete Response (2%)
   34 Partial Response (76%)
   10 Stable Disease (22%)

Incidence of developing lymphoma: 28/1000 patient years

Post-treatment analysis

4/49 patients died:
   3 pts within 10 days of starting treatment (were on ITU)

   1 patient developed plasmablastic lymphoma 2 years after treatment for MCD – died of progressive lymphoma despite systemic chemotherapy
Post-treatment analysis

Median KSHV DNA load fell from 126,000 copies/mm³ at diagnosis to undetectable at 3 months post treatment in 28/37 (76%)

8/46 patients relapsed
  Median time to relapse 2 years
  All successfully retreated and alive in remission
  Re-treatment with Rituximab monotherapy – 6
  Re-treatment with Rituximab & chemotherapy - 2

Disease-free survival of 49 patients treated with rituximab-based therapy

2 year relapse-free survival: 85% (CI 74-95%)
5 year relapse-free survival: 61% (CI 40-82%)
Factors not influencing overall or relapse free survival (p>0.1)

Using Prognostic modelling

Age
Gender
CD4 cell count
ECOG PS>2
Plasma KSHV load
On HAART therapy
Addition of etoposide

Factors influencing OS and RFS

Low plasma viral load – associated with longer OS (p=0.031), but no difference in relapse-free survival

MOF score>3: associated with worse OS (p=0.0007) and worse RFS (0.0066)
MCD and KS

24 patients had KS at time of MCD diagnosis

Received rituximab based treatment

9 (38%) experienced progression of KS within 3 months of rituximab

8 required systemic anthracycline chemotherapy

No difference between rituximab only and rituximab and etoposide treatments

Conclusion

Largest series of HIV MCD

Dramatic improvement in survival since introduction of Rituximab based therapy, 5 year survival 90% compared to 33% prior to Rituximab use, log rank p<0.0001

Survival has tripled since 2002