Peeling back the onion layers: HIV associated Multicentric Castleman’s Disease

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Infectious Diseases
Registrar
The Alfred Hospital

Disclosures

- Nothing to disclose
Background: Mr YU, 66 yo M

- HIV
  - Diagnosed 1988; CD4 nadir 40 per/uL
  - Virologically suppressed for 10 years
  - VL < 20 copies/mL, CD4 700 per/uL
  - Abacavir/lamivudine (Kivexa) and nevirapine XR commenced 2007

- Syphilis
  - treated, 20 years ago

- Born in Japan, lives in Melbourne
- Retired graphic designer
- MSM

Case: Mr YU, 66 yo M

- Headache – aspirin
- Rash developed 2 weeks later, then high fevers
Case: Mr YU, 66 yo M

- Biopsy confirmed Stevens Johnson Syndrome/ Toxic Epidermal Necrolysis
- Required management on Burns Unit – inpatient for 3 weeks
- 8 weeks post discharge – new rash
- Fevers, lethargy, loss of weight, tender widespread lymphadenopathy
## Case: Investigations

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>FBE</td>
<td>Hb 100 g/L / Platelets 23 x 10⁹/L / WCC 3.7 x 10⁹/L / Neutrophils 0.06 x 10⁹/L</td>
</tr>
<tr>
<td>ESR CRP</td>
<td>91 / 36</td>
</tr>
<tr>
<td>UEC Renal function</td>
<td>Na⁺ 137 / K⁺ 3.2 / Cl⁻ 106 / Bicarbonate 24 Normal</td>
</tr>
<tr>
<td>LFT</td>
<td>Bili 9 / ALT 15 / GGT 47 / ALP 62 / <strong>Albumin 24 g/L / total protein 104 g/L</strong></td>
</tr>
<tr>
<td>HIV Viral load</td>
<td>&lt;20 copies/mL</td>
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## Further Investigations

### Infectious diseases

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Result</th>
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<tbody>
<tr>
<td>Syphilis EIA +, RPR non-reactive</td>
<td></td>
</tr>
<tr>
<td>Parvo IgM neg, IgG neg</td>
<td></td>
</tr>
<tr>
<td>Toxoplasma IgM neg, IgG neg</td>
<td></td>
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<tr>
<td>Mycoplasma neg</td>
<td></td>
</tr>
<tr>
<td>CMV IgM neg, IgG pos</td>
<td></td>
</tr>
<tr>
<td>EBV IgM neg, IgG pos</td>
<td></td>
</tr>
<tr>
<td>Quantiferon TB Gold : unlikely</td>
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</table>

### Autoimmune

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Result</th>
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<tbody>
<tr>
<td>ACE normal / ANCA neg / ANA neg</td>
<td></td>
</tr>
<tr>
<td>C3 / C4 normal</td>
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</table>

### Malignancy

<table>
<thead>
<tr>
<th>Investigation</th>
<th>Result</th>
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<tbody>
<tr>
<td>Ferritin 292</td>
<td></td>
</tr>
<tr>
<td>LDH 165</td>
<td></td>
</tr>
<tr>
<td>B2microglobulin 3.8 mg/L</td>
<td></td>
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<tr>
<td>Serum protein electrophoresis: Oligoclonal bands present - polyclonal immunoglobulins in background. No paraprotein.</td>
<td></td>
</tr>
<tr>
<td>Urine protein electrophoresis: No Bence-Jones protein detected.</td>
<td></td>
</tr>
<tr>
<td>Free light chains: κ FLC 127 / λ FLC 111; κ/λ ratio 1.14</td>
<td></td>
</tr>
<tr>
<td>Hypercellular aspirate with increased plasma cells. Likely reactive in nature, no evidence of marrow involvement with a lymphoproliferative disorder.</td>
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</tbody>
</table>
Summary: Mr YU, 66 yo M

Fever, sweats, weight loss, reactive BMAT, diffuse PET avid LN and rash on a background of recent SJS/TENS and virologically suppressed HIV

Differentials:
- T cell lymphoma
- Haemophagocytic lymphohistiocytosis
- Castleman’s Disease
Lymph node biopsy – H & E stain

HHV-8 immunoperoxidase stain
Pathologist Diagnostic Opinion

Left axilla lymph node core biopsy—Castleman's disease

Clinical Information Provided


Macroscopic Description

Labelled "Left axilla LN core bx". Four cores of tissue, 2mm, 4mm, 5mm and 6mm.

Block Notation: A1 all in. (ft)

D:M:T

Microscopic Description

The core biopsies are fragmented showing lymph node within which there is prominence of endothelial cells reactivity with intervening small lymphocytes and scattered plasma cells. Scattered eosinophils are also seen. Focally, there is an ill-defined angiocentric pattern of lymphocytes circling a central focus with prominent endothelial cells. There is no morphologic monomorphic malignancy. Immunoperoxidase studies show clustered B cell zones with intervening T cells, scattered plasma cells, and focal areas within which the cells are immunoreactive with HHV8.

HIV associated Multicentric Castleman’s Disease (MCD)

1. What is Castleman’s Disease?
2. What is the current epidemiology?
3. What are the major pathologic mediators?
4. What is the expected prognosis?
5. What are the treatment options?
What is Castleman’s Disease?

- Rare lymphoproliferative disorder
- Unicentric and multicentric forms
- Natural history
  - Indolent
  - Episodic, relapsing
  - Rapidly progressive

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**original article**

The role of immune suppression and HHV-8 in the increasing incidence of HIV-associated multicentric Castleman’s disease

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¹Department of Medical oncology, Bart's and the London Medical School; ²Department of Oncology, Imperial College School of Medicine, London, UK

Received 24 September 1998, accepted 3 October 1998

![Graph showing incidence of KS and MCD](image)

**Figure 1.** The incidence of KS and MCD according to the calendar period.

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What are the clinical manifestations?

- Symptoms:
  - Fever, night sweats, weight loss
  - Lymphadenopathy, hepatosplenomegaly

- Laboratory findings:
  - Pancytopenia
  - Hypoalbuminemia
  - Raised ESR/CRP
  - Raised LDH
  - Polyclonal hypergammaglobulinaemia

Diagnosis - confirmed on lymph node biopsy

What is the underlying pathogenesis?

- Interleukin-6
  - Pro-inflammatory cytokine overexpressed in MCD

A. vIL-6 (K2) locus on the HHV-8 genome

Hongyu Deng et al. J. Virol. 2002;76:8252-8264
What is the underlying pathogenesis?

- Human Herpes Virus-8
  - Gammaherpes virus
  - Higher viral load in MCD patients compared to asymptomatic
  - Lytic and latent phases
  - Hyperproliferative state – can evolve to B cell lymphoma
  - Similar to EBV-related lymphoproliferative disorders

What is the expected prognosis?

- Prognosis in untreated is poor
- Death - infection, progressive disease or malignancy
- HIV-associated MCD
  - pre-cART median survival 14 months, overall mortality 70 – 85%
  - Post-cART 2 year overall survival probability of more than 80%
What are the treatment options?

- Multicentre, open-label, prospective study
- Results at 60 weeks, received 16 weeks of Tocilizumab
- 28 patients with iMCD (HIV negative)
- Improvement in LN size, biochemical and inflammatory markers, symptoms
- Sustained effect for 1 year
• Aim: Assess the efficacy of weekly rituximab for 4 weeks
• Results: Open label study in 24 virologically suppressed patients on cART, previously chemotherapy dependent
  – Primary outcome: 92% (n=22) in remission at 60 days
  – Secondary outcome: 71% (n=17) in remission at 1 year
  – Exacerbation of KS in 8 patients

• Pilot study of high dose AZT and valganciclovir (14 patients) – target lytic HHV8 replication
• Results:
  – 86% (n=12) achieved a clinical response
  – Median progression-free survival was 6 months
• Major toxicities:
  – 36% (n=5) developed Grade 4 anaemia
  – 29% (n=4) developed Grade 4 neutropenia
Outcome: Case – Mr YU

- Managed with 4 x weekly rituximab infusions
- Valganciclovir 900mg BD (treatment dose)

- Recovery of energy levels, constitutional symptoms
- Cytopenias improved
- Still requires GCSF 2/weekly
- HHV8 DNA in blood – detected (6 months)

Unanswered questions...

- HIV infection
- HHV-8 infection
- Immune dysfunction
- Active malignancy
Key learning points

- Incidence of HIV associated MCD appears to be increasing
- Cardinal presentation: fevers, weight loss, lymphadenopathy, raised inflammatory markers
- IL-6 and HHV-8 important pathologic mediators
- Without treatment, expected prognosis is poor
- Evidence for different therapies is limited – biologic and anti-viral most promising

Acknowledgements

- Dr Katie Cronin, ID registrar
- Prof Jennifer Hoy, ID physician
- Prof Catriona Mclean, Pathologist
- Dr Rhonda Cameron, Pathologist
- Dr Anish Puliayil, Haematologist
Aim: Outcomes of rituximab-based therapy in post ART era

Methods: Retrospective study

Results:

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<thead>
<tr>
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<th>2 years</th>
<th>5 years</th>
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<tbody>
<tr>
<td><strong>Rituximab (n=49)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Overall survival</td>
<td>94%</td>
<td>90%</td>
</tr>
<tr>
<td>Relapse free survival</td>
<td>85%</td>
<td>61%</td>
</tr>
<tr>
<td><strong>No Rituximab (n=12)</strong></td>
<td></td>
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</tr>
<tr>
<td>Overall survival</td>
<td>42%</td>
<td>33%</td>
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- Median time to relapse = 2 years
- Etoposide did not influence disease free or overall survival