HIV Malignancy – pt 2

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AIDS defining malignancies

Kaposi’s sarcoma
High grade B-cell non-Hodgkin’s lymphoma
Invasive cervical cancer
Kaposi’s sarcoma

Annus Mirabilis by Philip Larkin

Sexual intercourse began in 1963
(which was rather late for me)
Between the end of the Chatterley ban and the Beatles first LP
“RARE CANCER SEEN IN 41 HOMOSEXUALS”

By Lawrence K Altman
1993

AIDS-KS
Clinical features of KS

Multicentric (non metastatic)
Pigmented
Non-blanching (subcutaneous)
Painless

Kaposi’s sarcoma
Conjunctival KS
Classical KS
St. Peregrine (1260-1345)

Born at Forli, Italy. He was cured of cancer of leg, after he received a vision of Christ on the cross reaching out His hand to touch his impaired limb. He was canonized in 1726.
KS histology

Black arrows: Spindle cells
White arrows: Erythrocytes

KS epidemiology

20,000 x commoner in HIV+ than general population

300 x commoner in other immune suppressed (e.g. kidney transplants)
KS by HIV transmission groups

Is KS caused by an infection?

Epidemiology suggests sexual transmission

Risk of KS increased with no. of sexual partners
Searching for the cause

Comparison of DNA in KS lesion and adjacent skin by subtraction

Representation of DNA differences analysis (RDA)

Selective amplification of DNA sequences present in KS lesions but absent from normal skin
HHV8 (KSHV) discovery

1994 Novel herpesvirus sequences from KS lesions

Human herpesvirus 8 (HHV8)

or

Kaposi sarcoma herpesvirus (KSHV)
**HHV8 pathogenesis**

<table>
<thead>
<tr>
<th>Host response to viral infection</th>
<th>Molecular mimicry of HHV8 genes</th>
</tr>
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<tbody>
<tr>
<td>Stimulate proliferation</td>
<td>vIL6</td>
</tr>
<tr>
<td></td>
<td>vGCR</td>
</tr>
<tr>
<td>Avoid cell cycle arrest</td>
<td>LANA inhibits p53</td>
</tr>
<tr>
<td>Evade apoptosis</td>
<td>vBCL2</td>
</tr>
<tr>
<td>Escape cell mediated immunity</td>
<td>vIRF inhibits MHC</td>
</tr>
<tr>
<td></td>
<td>class 1 expression</td>
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</tbody>
</table>

**HHV8 antibody prevalence**

- Up to 50% African population
- 25-35% gay men, greater if HIV co-infected
- 10% Sardinia, Sicily, Greece, Israel
- 1% US blood donors
Out of Africa

The Nobel prize in Physiology or Medicine 1905
Koch's postulates

4 postulates that link a disease with a cause (originally TB and mycobacteria)

1. Present in every case of the disease
   HHV8 infects spindle cells and endothelial cells in KS lesions (all types)
2. Isolated from the host with the disease and grown in pure culture

KSHV in culture from cell line derived from patient

3. Disease must be reproduced when a pure culture of the bacteria is inoculated into a healthy susceptible host

HHV8 infection precedes KS
4. The bacteria must be recoverable from the experimentally infected host

HHV8 infects primary human endothelial cells in culture and causes cellular transformation & encodes several potential oncogenes
HHV8 prevalence & number of partners

No. of Male Intercourse Partners in Previous 2 Years

HHV8 Prevalence in Uganda by age
More than just sex?

Vertical transmission
(10%+ <3yrs)

Non-sexual horizontal transmission
(20%+ at 10yrs)

HHV8 transmission

30% HHV8+ shed virus in saliva

1% detection in anal/genital secretions

No HHV8 in semen of healthy donors
More than just KSHV

The risk of NHL & KS correlate with CD4 cell count

Kaposi's sarcoma
Non-Hodgkin's lymphoma

KS staging

<table>
<thead>
<tr>
<th>TIS Staging</th>
<th>Good risk (all of the following)</th>
<th>Poor risk (any of the following)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(T) Tumour</td>
<td>Confined to skin, lymph nodes or minimal oral disease</td>
<td>Tumour-associated oedema or ulceration Extensive oral KS KS in non-nodal viscera</td>
</tr>
<tr>
<td>(I) Immune Status</td>
<td>CD4 count &gt;150/mm³</td>
<td>CD4 &lt;150/mm³</td>
</tr>
<tr>
<td>(S) Symptoms</td>
<td>No OIs, Karnovsky &gt;70%</td>
<td>Ols or Karnovsky &lt;70%</td>
</tr>
</tbody>
</table>
KS associated oedema (T1)

KS ulceration (T1)
Management of KS

Early stage KS (T0, I0-1)
1. HAART
2. Intralesional vinblastine (lesions <1cm²)
3. Radiotherapy (lesions >1cm²)

HAART healing KS (3m apart)
HAART as treatment for KS

Response rate to HAART alone >65%

Takes 6-12 months (longer than VL & CD4 responses)

10% paradoxical deterioration (Immune reconstitution syndrome IRIS)

HAART alone for KS

80% don’t need any other treatment for KS over 10 years of follow-up
Radiotherapy

Intralesional therapy
Management of KS

Late stage KS (T1, I0-1)
1. HAART and
2. Systemic chemotherapy
   - Liposomal anthracyclines
   - Paclitaxel (second line)

Chemotherapy healing at 6 weeks
KS responding to chemotherapy

Effect of HAART on KS

Incidence

Outcome
Incidence rates for KS 1992-6 versus 1997-9

<table>
<thead>
<tr>
<th>Study</th>
<th>Adjusted incidence rate per 1000 per year (No.)</th>
<th>Rate ratio (RR) for 1997 through 1999 versus 1992 through 1996</th>
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<tbody>
<tr>
<td></td>
<td>1992 through 1996</td>
<td>1997 through 1999</td>
</tr>
<tr>
<td>Amsterdam</td>
<td>22.7 (53)</td>
<td>7.7 (7)</td>
</tr>
<tr>
<td>Aquitaine</td>
<td>18.5 (170)</td>
<td>3.3 (18)</td>
</tr>
<tr>
<td>ASD</td>
<td>15.1 (627)</td>
<td>5.5 (115)</td>
</tr>
<tr>
<td>CASCADE</td>
<td>10.4 (149)</td>
<td>3.1 (8)</td>
</tr>
<tr>
<td>DMI-2</td>
<td>15.3 (156)</td>
<td>0.1 (5)</td>
</tr>
<tr>
<td>HERS</td>
<td>0.4 (1)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>HOPS</td>
<td>21.0 (104)</td>
<td>9.4 (29)</td>
</tr>
<tr>
<td>MACS</td>
<td>29.3 (189)</td>
<td>4.2 (7)</td>
</tr>
<tr>
<td>MHCS</td>
<td>0.7 (2)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>RH/HP</td>
<td>0.3 (1)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>SFCCC</td>
<td>37.3 (37)</td>
<td>8.6 (1)</td>
</tr>
<tr>
<td><strong>ALL STUDIES</strong></td>
<td><strong>15.2 (1489)</strong></td>
<td><strong>4.9 (190)</strong></td>
</tr>
</tbody>
</table>

Falling incidence of KS in EuroSIDA

Test for trend (Poisson regression), 0.01; 95% CI, 0.57-0.65, P < 0.0001
HAART stops you getting KS

NNRTI protects as well as PIs despite “anti-angiogenic” properties of PIs

Patients presenting with KS since 1996 are mostly not on HAART

Patients on HAART who develop KS usually have virological failure
Improving outcomes in KS

Survival Distribution Function

Cum. Survival

n=327

KS diagnosed in era of HAART

Years

0 2 4 6 8 10

0 .2 .4 .6 .8 1.0

0 30 60 90 120 150

Time (months)

pre-HAART era

HAART era

n=327
Castleman’s disease

Benjamin Castleman

Castleman B, Towne VW: Case Records of Massachusetts General Hospital, Case 40001. NEJM, 1954; 26: 250

The first ever case….

Castleman’s disease

<table>
<thead>
<tr>
<th></th>
<th>Hyaline vascular</th>
<th>Plasmablastic</th>
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<tbody>
<tr>
<td>Localised</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multi-centric</td>
<td></td>
<td>HIV-MCD</td>
</tr>
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</table>
Onion skin arrangement of mantle zone cells

IgM $\lambda$ light chain restricted (monotypic polyclonal)
HHV8 in plasmablasts in MCD

Kaposi sarcoma

Almost all spindle cells infected with KSHV

KSHV is latent (LANA)
vIL6 (lytic) staining of MCD

HHV8 genome
HHV8 genome expression (lytic/latent)

ORF K2 (vIL6) a primary lytic gene

Functions of IL6

B-cells
Proliferation & differentiation

CD4 T cells
Differentiation to Th2
(with IL2)

NK cells
Proliferation

IL6

Acute phase reaction

CRP & fibrinogen

Albumin

IL6

Latent

Latent / lytic

Primary lytic genes

Secondary lytic genes

Tertiary lytic genes

Not analyzed
Serum IL6 in MCD

Serum IL6

![Graph showing Serum IL6 levels in MCD with active and remission states.](chart.png)

MW p=0.06

Castleman’s clinical presentation

Fever, night sweats, weight loss

Localised or diffuse lymphadenopathy

Hepatosplenomegally

Anaemia, hypoalbuminaemia, polyclonal hypergammaglobulinaemia
HIV MCD treatment options

- Splenectomy
- HAART
- Vinblastine
- Etoposide
- Interferon $\alpha$
- Anti IL6 receptor blocking antibody
### Treatment algorithm

<table>
<thead>
<tr>
<th>State</th>
<th>Treatment</th>
</tr>
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<tbody>
<tr>
<td>Well</td>
<td>Rituximab</td>
</tr>
<tr>
<td>Ill</td>
<td>Rituximab &amp; Etoposide</td>
</tr>
<tr>
<td>±Hypersplenism</td>
<td>Splenectomy</td>
</tr>
<tr>
<td>Maintenance</td>
<td>Valganciclovir ?</td>
</tr>
<tr>
<td></td>
<td>Rituximab ?</td>
</tr>
</tbody>
</table>

### MCD Conclusions

1. MCD occurs at any CD4/VL
2. HAART does not prevent MCD
3. Usually relapse
4. Plasma HHV8 “tumour marker” in diagnosis and monitoring