“Stable as a table”

MIDG 4/8/2015

Jillian Lau
Monash Health
55 year old male

- IgA nephropathy
- Cadaveric renal transplant
  - 1/1/2015 cx delayed graft function and ATN
- Left nephrectomy 2014
  - Complex cyst → papillary RCC
- Diabetes
- IHD
  - Prev CABGx3
Medications (1)

Tacrolimus       4mg bd
Mycophenolate    1000mg bd
Prendisolone     7.5mg d
TMP/SMX          160/800mg twice per week
Valaciclovir     500mg daily
Medications (2)

Atorvastatin 20mg d
Carvedilol 6.25mg bd
Aspirin 100mg d
Tamsulosin 0.4mg d
Pantoprazole 40mg d
Aranesp 60mcg weekly
Calcitriol
Frusemide 40mg d
Cholecalciferol 50mcg daily
Gliclazide 80mg d
May 2015

1/52 abdominal pain, nausea, lethargy, anorexia

4/52 headache

No

- Fevers, rigors, diarrhoea, dysuria,
- Rash, myalgias, arthralgias
- Photophobia, neck stiffness
- Recent travel, unwell contacts
Investigations Day 1

FBE 110/3.8/169  neut 2.10  lymph 0.46
Creat 124  Ur 7.1  eGFR 56
LFTs normal
CRP 20
Investigations

CXR, AXR  NAD

U/S abdo
  Echogenic hepatic lesion consistent with haemangioma
  Atrophic right kidney with numerous cysts

CT brain and C-spine – NAD

Gastroscopy: chemical gastropathy
CT abdo/pelvis Day 3
CT chest D5
Further Ix

HIV serology               Neg

CMV, EBV serology          Neg

Quantiferon Gold           Neg

Strongyloides/amoebic/hydatid serology – neg

CT guided Liver biopsy
  – Normal liver parenchyma, normal skeletal muscle
  – No evidence of malignancy
Day 12

Neutropaenic 1.64 - MMF decreased

Febrile

Neuro exam – no motor or sensory deficits

? cognitive impairment

Low mood

CL psych review – hypoactive delirium
Further Ix

MRI brain - NAD

EEG – severe diffuse encephalopathy
ID referral
Eskd 2. IgA nephropathy.
Cadaveric renal transplant 01/01/2015
Prior to Reel HTx (per failed PD)
+ forearm AVF
+ CRF - MBD
(Pre @ exploiting for papillary RCC March '14)
No hypertension since 73 (usually 110-120).

In HD
per citbsh in England

TTE Sept '13: Severely dilated globular LV
Severely LVEF (25-30%), predominant
2' LEA territory scar
No sig valvular pathology
Severely dilated LA

Prev study in Tunisia.
Lumbar Puncture

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
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</thead>
<tbody>
<tr>
<td>PMN</td>
<td>6</td>
</tr>
<tr>
<td>Lymph</td>
<td>34</td>
</tr>
<tr>
<td>Gram stain</td>
<td>NOS</td>
</tr>
<tr>
<td>Culture</td>
<td>No growth</td>
</tr>
<tr>
<td>Protein</td>
<td>2.5</td>
</tr>
<tr>
<td>Glucose</td>
<td>1.4</td>
</tr>
<tr>
<td>Lactate</td>
<td>6.2</td>
</tr>
</tbody>
</table>
Lumbar Puncture

- HSV1/2 PCR: -ve
- VZV PCR:  -ve
- CMV PCR:  -ve
- Enterovirus PCR:  -ve
- Crypto Ag:    -ve

Flow cytometry: no monoclonal populations
What other tests?
Encephalitis causes

Flaviviruses PCR
HSV 1+2

Adenoviruses

West Nile

Nipah virus

VZV

CMV

EBV

Hepatitis

Polio

Measles

Mumps

Arbor viruses

Rubella

Varicella

Tick borne

Bunyaviruses

Novirus

Arenaviruses (LCM)

Arboviruses

AKBO

JE

MVE

Dengue

Kunjin

+ immunocompromised

HHV6

Ischaemic

Metabolic

Nutritional deficiency

Toxic

Critical illness

Malignant HT

MEZAS

Herpes

Poncetanispheric

NMS

Traumatic Brain injury

Epileptic

- Joseph B. St Louis, West Nile,

- tick borne encephalitis viruses

- La Crosse strain of California virus

- Colorado tick fever virus

Kunjin Virus
HHV6 PCR  -ve
Influenza PCR  -ve
Adenovirus PCR  -ve
Flavivirus PCR  -ve
TB PCR  insufficient specimen
TB culture  no growth at 6 weeks
EBV PCR +ve

EBV Viral load
- Serum 10946 copies/mL (log 4.04)
- CSF

EBV Serology
- Jan  VCA IgG/IgM ND, EBNA ND
- April VCA IgG/IgM ND, EBNA ND
- June VCA IgG/IgM ND, EBNA ND

Donor EBV IgG +ve
Progress

Currently in rehab back on valaciclovir

VL <400 copies/mL

EBV serology  27/7
  – IgG detected
  – IgM not detected
Summary

EBV encephalitis 6 months post renal transplant
EBV D+/R-

Primary infection likely donor derived

Treated with IV ganciclovir and reduction of immunosuppression
EBV Encephalitis
A SARCOMA INVOLVING THE JAWS IN AFRICAN CHILDREN

THE LANCET

Volume 283, Issue 7335, 28 March 1964, Pages 702–703
Originally published as Volume 1, Issue 7335

Preliminary Communications

VIRUS PARTICLES IN CULTURED LYMPHOBLASTS FROM BURKITT'S LYMPHOMA


RELATION OF BURKITT'S TUMOR-ASSOCIATED HERPES-YTPE VIRUS TO INFECTION MONONUCLEOSIS*

By Gertrude Henle, Werner Henle,† and Volker Diehl

VIRUS LABORATORIES, CHILDREN'S HOSPITAL OF PHILADELPHIA, AND SCHOOL OF MEDICINE, UNIVERSITY OF PENNSYLVANIA

Communicated by John R. Paul, November 21, 1967
BURKITT'S LYMPHOMA


RELATION OF BURKITT'S TUMOR-ASSOCIATED HERPES-YTYPE VIRUS TO INFECTIOUS MONONUCLEOSIS

By Gertrude Henle, Werner Henle,† and Volker Diehl

Virus Laboratories, Children's Hospital of Philadelphia, and School of Medicine, University of Pennsylvania

Communicated by John R. Paul, November 21, 1967
EBV and PTLD

- EBV contributes to the pathogenesis of PTLD in >70% of cases
- 1-16% of solid organ transplant recipients
- Heart > liver > kidney
- RF: serodiscordance, use of anti-lymphocyte antibodies, immunosuppression
- Rx: reduce immunosuppression, mTOR inhibitors, antivirals, rituximab, T cell therapy
Neurological manifestations

Meningitis
Encephalitis
Cerebritis
Transverse myelitis
ADEM
Neuropsychiatric syndromes
Neuropathies/nerve palsies

CNS lymphoma

(MS)
<table>
<thead>
<tr>
<th>Case</th>
<th>Immunosuppression</th>
<th>Timing post transplant</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garamendi et al</td>
<td>Renal transplant</td>
<td>8 years</td>
<td>Ganviclovir</td>
<td>Good</td>
</tr>
<tr>
<td>55 yo</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>MacGinley et al</td>
<td>Renal transplant</td>
<td>11 days</td>
<td>Ganciclovir</td>
<td>Good</td>
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<tr>
<td>43 yo</td>
<td>OKT3 (acute rejection)</td>
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<tr>
<td>Shafiq et al</td>
<td>Liver transplant</td>
<td>1 year</td>
<td>Aciclovir</td>
<td>Good</td>
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<tr>
<td>58 yo</td>
<td></td>
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<td></td>
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<tr>
<td>Kanamori et al</td>
<td>CML</td>
<td>65 days</td>
<td>Aciclovir, IVIg</td>
<td>Good</td>
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<tr>
<td>33 yo</td>
<td>BM transplant</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Barberi et al</td>
<td>ALL</td>
<td>2 months</td>
<td>Foscarnet, Aciclovir, IVIg</td>
<td>Death</td>
</tr>
<tr>
<td>7 yo</td>
<td>HSCT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kremer et al</td>
<td>Aplastic anaemia</td>
<td>6 weeks</td>
<td>Cidofovir, Ganciclovir, Foscarnet, Rituximab</td>
<td>Partial recovery</td>
</tr>
</tbody>
</table>
Clinical characteristics of patients with Epstein Barr virus in cerebrospinal fluid

32/322 EBV PCR +ve
81% immunosuppressed
25% another pathogen identified
13 encephalitis (7 HSCT, 4 normal MRI)
CSF VL ranged from 186 to 76,800 copies/mL
Plasma VL ranged from 530 to 1,040,000 copies/mL
2 primary infection
EBV T cell therapy

• Donor-derived EBV-specific cytotoxic T cells have been used for the management of PTLD in HSCT recipients
• Autologous EBV-CTLs from SOT recipients may restore short-term EBV-specific immunity
• Experimental
• Few side-effects or toxicities
• Role in EBV encephalitis?
Thanks for your message. I'd gladly call you to discuss this case but I have had to close the SAS part of our programme through lack of resources to keep it open. Our original NHMRC funded trial was really only for BMT patients but on request we did treat some off trial patients. However that has proved to be impossible to sustain from a financial and personnel resources point of view.

We have submitted an NHMRC application this year to extend the current trial to include solid organ transplant patients and if that is successful we will be able to offer this therapy to renal/liver etc transplants from 2016 on. If it isn't, we won't be able to continue. I apologise that I can't help at present.

Best wishes,
David

David Gottlieb

Professor of Haematology University of Sydney
Program Director BMT, Head Cell Therapies,
Westmead Hospital Sydney
Monitoring EBV

Screen all donors and recipients pre-transplant.

Monitor D+/R- for EBV by NAT:
- first week after transplantation
- monthly for the first 3–6 months
- every 3 months until the end of the first year
- additionally after treatment for acute rejection
EBV DNAemia as a marker of immune dysfunction

Epstein-Barr Virus DNAemia Is an Early Surrogate Marker of the Net State of Immunosuppression in Solid Organ Transplant Recipients

Rafael San-Juan, Begoña De Dios, David Navarro, Ana García-Reyne, Carlos Lumbreras, Dayana Bravo, Elisa Costa, Jose Maria Morales, Amado Andres, Carlos Jiménez-Romero, Juan Delgado, Mario Fernández-Ruiz, Francisco López-Medrano, and Jose M. Aguado

P0263
Paper Poster Session I
Infections in organ transplant recipients
Epstein-Barr DNAemia as a surrogate marker of immunosuppression and risk of infection in lung transplant recipients


1 Hospital Universitario 12 de Octubre, Madrid, Spain
Conclusion

EBV is a cause of encephalitis in immunocompromised patients

Management includes stopping/reducing immunosuppression

Routine screening for EBV pre-transplant and monitoring of EBV D+/R-
References

• Trigger, pathogen, or bystander: the complex nexus linking Epstein-Barr virus and multiple sclerosis. **Gregory P Owens, Jeffrey L Bennett** *Multiple Sclerosis Journal* 18(9) 1204–1208


• http://cmr.asm.org/content/24/1/193/F1.expansion.html

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• Infusion of autologous Epstein-Barr virus (EBV)-specific cytotoxic T cells for prevention of EBV-related lymphoproliferative disorder in solid organ transplant recipients with evidence of active virus replication. **Comoli, P, Labirio, M, Basso, S et al.** Blood. 2002; 99: 2592–2598

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References (3)

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• American Society of Transplantation Recommendations for Screening, Monitoring and Reporting of Infectious Complications in Immunosuppression Trials in Recipients of Organ Transplantation American Journal of Transplantation. A. Humar Et al. 2006; 6: 262–274

• Epstein-Barr Virus DNAemia Is an Early Surrogate Marker of the Net State of Immunosuppression in Solid Organ Transplant Recipients San-Juan et al. Transplantation 2013; 95: 688-693