An approach to intracranial mass lesions in HIV-infected patients

Dr David Stead
Division of Infectious Diseases
Frere & Cecilia Makiwane Hospitals
Background:

- Neurological disease: Up to 2/3rds of HIV +
- Heralds onset of AIDS in 10-20%
- Intracranial mass lesions: up to 50% of these
- Presenting symptoms:
  - Seizures
  - Focal signs
  - Headaches
  - Altered mental state
Why are IML’s difficult to manage?

• Significant morbidity and mortality
• Rely on ready access to CT-scan
• Lack of access to brain biopsy in LMICs and risk
  – 1209 diagnostic brain biopsies in HIV-infected patients: overall procedure related morbidity of 5.7% and mortality of 0.9%
• Very little robust or prospective evidence

Lee et al. J Neurol Neurosurg Psychiatry. 2016
Terminology

• Intracranial mass lesions (IML)
• Space occupying lesions
• Ring enhancing lesions
• Focal brain lesions
Aetiologies of IML in HIV infection

➢ **Opportunistic infections:**

- Parasites
  - Toxoplasma gondii
  - Neurocysticercosis
- Fungi
  - Cryptococcus neoformans
  - Candida albicans
  - Aspergillosis
  - Mucormycosis
- Bacteria
  - Mycobacterium tuberculosis
  - Mycobacterium avium-intracellulare
  - Nocardia
  - Listeria monocytogenes
  - Treponema pallidum

➢ **Neoplasms:**

- Primary CNS lymphoma
- Glioma
- Kaposi sarcoma
- Metastatic neoplasm

➢ **Cerebrovascular disease**

- Ischaemic disease
- Intracerebral hemorrhage
Toxoplasma encephalitis (TE)

• Response to therapy
  – 74% by day 7
  – 91% by day 14 (median: 5 days)

• False negative serology?
  – 5 -22%

• SA HIV+ adult Toxo seropositivity rate: 8%

• 2 studies demonstrating higher titres with TE
  – OR 3.3 if >150 IU/ml

• Toxo PCR on CSF: 33-69% sensitive, 100% specific

Luft et al. NEJM 1993
Derouin et al. AIDS. 1996)
## Aetiology of HIV-IML in South Africa

<table>
<thead>
<tr>
<th>Aetiology</th>
<th>Bhigjee et al (n=38) %</th>
<th>Modi et al (n=32) %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis</td>
<td>11</td>
<td>53</td>
</tr>
<tr>
<td>Toxoplasmosis</td>
<td>39</td>
<td>3</td>
</tr>
<tr>
<td>Primary CNS lymphoma</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>Cryptococcomaa</td>
<td>5</td>
<td>14</td>
</tr>
<tr>
<td>Brain abscess</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Neurocysticercosis</td>
<td>0</td>
<td>19</td>
</tr>
</tbody>
</table>


CT scan shows signs of Enhancing Space Occupying Lesion(s) in an HIV-infected Patient

- Any extra-axial collection
- Any lobar lesion with significant mass effect

Refer to Neurosurgery

Refer to Infectious Diseases Registrar: Differential - Toxoplasmosis, Tuberculoma(ta), Lymphoma, Cryptococcoma

Send serum Toxoplasma IgG, serum CLAT, and CSF unless contraindicated

Evaluate for features of TB outside the CNS or features of TBM

ABSENT

Start empiric Rx for Toxoplasmosis
Avoid Steroids

Re-evaluate clinical & CT change at 14 days or before if deterioration

Resolved or Resolving

Complete therapy

No improvement or deterioration before 14 days or Toxoplasma IgG returns negative

Start empiric TB Rx and refer to Neurosurgery to assess for biopsy

Re-assess 3 months after starting TB treatment or sooner if clinically deteriorates on treatment

PRESENT

Toxoplasma IgG known negative

Treat for TB

Toxoplasma IgG unknown or positive, but CT signs of cerebral oedema & midline shift or deteriorating LOC

Dual treatment for Toxoplasmosis & TB with steroid cover

Re-evaluate at 2 months (or sooner if patient deteriorates). Neurosurgical biopsy may be indicated if failure to respond
Methods

• Retrospective folder review 2008-2013

• Intracranial mass lesions in HIV-infected adults

• 90 cases: 4 folders missing - 86 included

• UCT HREC approval 604/2013
Case definitions

• **Confirmed TB:**
  – brain biopsy Ziehl-Neelsen (ZN), culture or PCR-positive for *Mycobacterium tuberculosis* (MTB), or CSF culture or PCR-positive for MTB.

• **Probable TB:**
  – radiological response of lesions in response to TB therapy alone and/or evidence of TB elsewhere

• **Probable cerebral toxoplasmosis:**
  – a positive toxoplasmosis serology, together with a clinical and radiological response to TMX therapy alone.

• **TB/toxoplasmosis or both:**
  – These patients were placed on TMX and anti-TB therapy, had positive toxoplasmosis serology, and were not differentiated due to a rapid early response suggestive of toxoplasmosis.

• **Cryptococcus:**
  – confirmed: positive culture of a brain biopsy,
  – probable: by virtue of a positive CLAT, gram stain, India-ink stain, or culture of CSF, together with a clinical and radiological response to antifungal therapy.

• **Others:** biopsy confirmed diagnoses.
## Baseline characteristics

<table>
<thead>
<tr>
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<th>Total n = 86</th>
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<tbody>
<tr>
<td>Male (%)</td>
<td>59 (69)</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>36 (29-40)</td>
</tr>
<tr>
<td>CD4, median (IQR)</td>
<td>70 (19-139)</td>
</tr>
<tr>
<td>On ART (%)</td>
<td>37 (43)</td>
</tr>
<tr>
<td>On TB therapy (%)</td>
<td>32 (37)</td>
</tr>
<tr>
<td>Toxoplasmosis IgG positive (%)</td>
<td>38/68 (56)</td>
</tr>
</tbody>
</table>
Initial treatment approaches

HIV-related Intracranial Mass lesions

- Toxoplasmosis: Rx only n = 12
- TB Rx only: n = 32
- Toxo and TB Rx: n = 39
- Others: n = 3
Final Aetiology of Intracranial Mass Lesions

- TB probable: 47%
- TB biopsy proven: 13%
- TB/Toxoplasmosis or both: 16%
- Toxoplasmosis (probable): 14%
- Neoplasm (other): 5%
- Lymphoma: 2%
- Cryptococcosis: 2%
- Nocardia: 1%

TB confirmed + probable = 60%
What can help us distinguish TB from Toxoplasmosis at the outset?
Comparative baseline characteristics of TB vs Toxoplasmosis

<table>
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<tr>
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<th>TB total n = 51</th>
<th>Toxo n = 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, %</td>
<td>53</td>
<td>58</td>
</tr>
<tr>
<td>Age, median (IQR)</td>
<td>32 (27-39)</td>
<td>40 (31-41)</td>
</tr>
<tr>
<td>CD4, median (IQR)</td>
<td>102 (30-108)</td>
<td>24 (8-34)</td>
</tr>
<tr>
<td>On ART, %</td>
<td>45</td>
<td>25</td>
</tr>
<tr>
<td>Toxoplasmosis IgG positive (%)</td>
<td>17/42 (42)</td>
<td>12/12 (100)</td>
</tr>
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</table>

CD4 <100 cells/mm3 for cerebral toxoplasmosis demonstrated an odds ratio (OR)=11, p-value=0.027 (95% confidence interval: 1.31-91.72)
Number of CT brain lesions

Percentage of patients

TB confirmed and probable
Toxoplasmosis probable

Number of lesions

0 5 10 15 20 25 30 35 40 45 50

1 2 ≥3
# Brain biopsy findings

17 performed (20%)

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirmed TB</td>
<td>9</td>
</tr>
<tr>
<td>Probable TB</td>
<td>2</td>
</tr>
<tr>
<td>Nocardia</td>
<td>1</td>
</tr>
<tr>
<td>Cryptococcus</td>
<td>1</td>
</tr>
<tr>
<td>inconclusive</td>
<td>4</td>
</tr>
</tbody>
</table>
Mortality by final diagnoses

Percentage

- Total
- TB total
- TB/Toxo or both
- Toxoplasmosis
- Other
Duration of TB therapy for probable & proven TB cases:

Number of patients:

- LTF/deceased/unknown: 24
- 6 to 9: 7
- 10 to 12: 9
- 13 to 18: 7
- 19 to 24: 2
- >24: 2

Duration of TB therapy in months
Complications in TB patients (n=51)

- TB IRIS
- DR TB*
- Subther. Rif/INH^ (Subtherapeutic rif or inh serum levels)
- Deaths

*Drug resistant TB (rif, inh or both)
Drug resistant TB IMLs

- 5/6 died, other LTF
- NB is CSF penetration of drugs
- Low penetration of some new short course drugs:
  - Bedaquiline
  - Clofazimine
Study conclusions

- TB caused 59% of IML in HIV-infected patients at GSH
  - Greater than 1/3 already on TB therapy
  - 16% of TB cases presented as, or developed TB-IRIS

- Toxoplasmosis occurred exclusively at low CD4 counts
  - And was associated with better outcome

- PCNSL is rare in our setting in the ART era

- Brain biopsy is useful for non-responsive lesions
How then to manage a case in 2018?

• Q is whether we shouldn’t just put all on empiric TB & Toxo Rx?
  – Risk is of severe drug reaction (1 fatal SJS)
• Try LP if safe
  – CSF Xpert Ultra, CLAT, Toxoplasmosis PCR?, EBV PCR
• Consider Toxo likelihood into CD4/serology
• Thorough w/u for TB elsewhere
• Close, specialist follow up as available
• Biopsy any non-responders
Acknowledgements

- Marc Mendelson
- Tom Boyles
- John Black
- Sipho Dlamini
- Sean Wasserman
- Andy Parrish