An approach to intracranial mass lesions in HIV-infected patients

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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

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 aviumintracellulare
 - Nocardia
 - Listeria monocytogenes
 - Treponema pallidum

Neoplasms:

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

Cerebrovascular disease

- Ischaemic disease
- Intracerebral hemorrhage

EVALUATION AND MANAGEMENT OF INTRACRANIAL MASS LESIONS IN AIDS

Report of the Quality Standards Subcommittee of the American Academy of Neurology



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

Aetiology	Bhigjee et al (n=38) %	Modi et al (n=32) %
Tuberculosis	11	53
Toxoplasmosis	39	3
Primary CNS lymphoma	0	3
Cryptococcoma	5	14
Brain abscess	16	0
Neurocysticercosis	0	19

(Bhigjee et al. SAMJ. 1999; Modi M, et al. Q J Med. 2004)

Groote Schuur HIV-IML clinical algorithm (2008)

CT scan shows signs of Enhancing Space Occupying Lesion(s) in an HIV-infected Patient¹ Any extra-axial collection Refer to Neurosurgery Any lobar lesion with significant mass effect Refer to Infectious Diseases Registrar. Differential² - Toxoplasmosis, Tuberculoma(ta), Lymphoma, Cryptococcoma Send serum Toxoplasma IgG³, serum CLAT⁴, and CSF⁵ unless contraindicated⁶ Evaluate for features of TB outside the CNS7 or features of TBM8 ABSENT PRESENT Start empiric Rx for Toxoplasmosis9 Avoid Steroids¹⁰ Re-evaluate clinical & CT change at 14 days Toxoplasma IgG Toxoplasma IgG unknown or positive, but CT signs of cerebral oedema & or before if deterioration known negative midline shift or deteriorating LOC Treat for TB Resolved or No improvement or deterioration before 14 Dual treatment for Toxoplasmosis¹¹ Resolving days or Toxoplasma IgG returns negative & TB with steroid cover Complete Start empiric TB Rx and refer to Re-evaluate at 2 months (or sooner if patient deteriorates)12. therapy Neurosurgery to assess for biopsy Neurosurgical biopsy may be indicated if failure to respond Re-assess 3 months after starting TB treatment or sooner if clinically deteriorates on treatment

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

	Total n = 86
Male (%)	59 (69)
Age, median (IQR)	36 (29-40)
CD4, median (IQR)	70 (19-139)
On ART (%)	37 (43)
On TB therapy (%)	32 (37)
Toxoplasmosis IgG positive (%)	38/68 (56)

Initial treatment approaches



Final Aetiology of Intracranial Mass Lesions



What can help us distinguish TB from Toxoplasmosis at the outset?

Comparative baseline characteristics of TB vs Toxoplasmosis

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

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



Brain biopsy findings 17 performed (20%)

	Number
Confirmed TB	9
Probable TB	2
Nocardia	1
Cryptococcus	1
inconclusive	4

Mortality by final diagnoses



Duration of TB therapy for probable & proven TB cases:



Complications in TB patients (n=51)



*Drug resistant TB (rif, inh or both)

^Subtherapeutic rif or inh serum levels

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 ito CD4/serology
- Thorough w/u for TB elsewhere
- Close, specialist follow up as available
- Biopsy any non-responders

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