PET/CT in TB & HIV

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IAEA, Vienna
The Changing Landscape in TB

- Cell Characterization
- Drug Resistance
- Overtreatment/Relapse
- Bacteria Specific Drug Development
- Latent/Active
- Staging/Biopsy
- Reduce Multiple Investigations
- TB Imaging
Changing the Mindset in HIV

Viremia

HIV pathogenesis

CNS

Viral Imaging

Drug Development

Vaccine Development

Reservoirs
Effect of AIDS on Women Who Have Sex-Determined Health Issues

Mike Sathekge, MD, PhD,* Alex Maes, MD, PhD,*,†,‡ Christophe Van de Wiele, MD, PhD,*,§ and Ekaterina Dadachova, PhD*,¶
FDG-PET Imaging in HIV Infection and Tuberculosis

Mike Sathekge, MD, PhD,* Alex Maes, MD, PhD,*,†,‡ and Christophe Van de Wiele, MD, PhD*,§
TB: Insightful and Meaningful Interpretation

1: Characteristics of TB granuloma

2: TB and HIV (IRIS, Extrapulmonary TB)

3: Latent infection vs Active

4: SPN in TB endemic areas

5: Drug Resistance

6: Prospective prediction of relapse

7: Specific tracers-
   TB pathophysiology – unique challenge
TB and immune cell populations

Granuloma: Victor or Villain

Ramakrisnan. Reviews 2012
Characteristics of tuberculosis granulomas

- Macrophages
  - M1 and M2
  - Contain the infection and limit its spread
  - to function as an immune microenvironment
    - limit replication of bacilli
    - serve as a “niche” for persisting organisms
  - Neutrophils – worsening disease
  - M1 macs – worsening disease
  - M2 macs – resolving disease

- Neutrophils
  - CD8+ and CD4+ T-cells

FDG has been successfully used to image TB granulomas, but it is taken up by all metabolically active cells and cannot distinguish immune cell populations

Anderson C et al
TB and immune cell populations

Translating Science into the Clinic – the Role of Nuclear Medicine
Neutrophil Responses to *Mycobacterium tuberculosis* Infection

1: Correlates with cavitary disease

2: Longer duration of sputum smear positivity

3: Poor prognosis

4: Higher mortality

5: Strategy to suppress neutrophil recruitment – Rx ??
Irreversible lesions

- Hallmark of TB
- Permanent loss of function
- Lack of Vascularity
- Luminal surface Devoid CD4 & CD8
- MDR
- Relapse
HIV-FOU
Often - TB

Seroconversion:
Acute retroviral syndrome

CD4⁺ (cells/µL)

Pneumococcal pneumonia
Candida vaginitis
ITP

Oral Candida-infection
Kaposi sarcoma
Lymphoma
Dementia
Oral haircell-leukoplacia

Cachexia
Toxoplasmosis
PJP
HSV
Candida esophagitis
Cryptococcosis

TB

Years after infection
Extrapulmonary TB & Rx
TB Pericarditis

1% to 2% of instances of PTB

Pericadial effusion = common (80%), Constriaction (5-10%)

Pericardial involvement = retrograde lymphatic spread from
  peritracheal
  peribronchial
  mediastinal lymph nodes

Imaging
  Pericardial effusion and thickening (>3 mm) and typical mediastinal and
  tracheobronchial lymphadenopathy (>10 mm, hypodense centers, matting),
  with sparing of hilar lymph nodes.

50% of large effusions – HIV

Mayosi et al. BMC Infect Dis  2006
TB vs Idiopathic Pericarditis

All have nodal uptake:
Pericardial tuberculosis may develop from mediastinal lymphadenopathy

Some have nodal uptake:
Lymphadenopathy in acute idiopathic pericarditis may be secondary to pericarditis.

PET/CT in Pericarditis

Help to understand the pathogenesis

Early diagnosis, especially in negative investigations
  • *Prevention of constriction*

Possible interpretation criterion

Extracardiac staging

Crucial in monitoring of response to antimicrobial treatment
  • *Especially in HIV*
FDG PET best for EPTB

Negative Effusion in TB Spine

Sathekge M, et al. Nuklear Medizin 2010
A 28 yr. old man with a large right-sided pleural effusion and Mycobacterium Tuberculosis on pleural fluid analysis.
PET/CT images demonstrate intense $^{68}$Ga-citrate uptake in this left-sided psoas abscess in a 44 yr old male patient with concomitant HIV infection. SUVmax: 6.89
Active vs Nonactive

Source: Demura Y, et al. EJNMMI 2009
Active Disease

Moderately increased $^{68}$Ga-citrate uptake was noted in the LUL mass SUVmax: 5.24

Limitations of TST & IGRA: Infection vs Disease
57 yr old HIV negative female presented with a mass in the left upper lobe (3.5 cm x 3 cm) on CXR. PCR Confirmed TB

28 yr old man with a large right-sided pleural effusion and Mycobacterium Tuberculosis on pleural fluid analysis.

44 yr. old male with HIV and TB (Absolute CD4 196 x106/l) who presented with quadriparesis.
Comparison FDG vs $^{68}$Ga-citrate

Fibrosis

Annals of Nuclear Medicine
July 2014, Volume 28, Issue 6, pp 523-530

Date: 29 Mar 2014

Evaluating the possible role of $^{68}$Ga-citrate PET/CT in the characterization of indeterminante lung lesions

Mariza Vorster, Alex Maes, Aldrich Jacobs, Sidney Malefahlo, Hans Pottel, Christophe Van de Wiele, Machaba Mike Sathekge
Latent TB with Higher Risk of Active TB

Latent TB infection is not simply a state of bacterial stasis, but rather a state of dynamic bacterial and immunological equilibrium.

Dual time-point FDG PET/CT for differentiating benign from malignant solitary pulmonary nodules in a TB endemic area

“Hence FDG-PET is unable to distinguish malignancy from TB and therefore cannot be reliably used as a tool to reduce futile biopsy/thoracotomy in these patients.”

Sathekge et al. SAMJ. 2010

Ellmann et al. MIBI in TB Nucl Med Com 2008
Triple Phase in TB

60 min p.i

120 min p.i

240 min p.i
What about Ga68-Citrate Dual Time Point Imaging?

60 min

120 min
Drug Susceptibility in TB

Prognosis

Responder vs Nonresponder
Use of $^{18}$F-FDG PET to Predict Response to First-Line Tuberculostatics in HIV-Associated Tuberculosis

Mike Sathekge, Alex Maes, Mpho Kgomo, Anton Stoltz, and Christophe Van de Wiele

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THE JOURNAL OF NUCLEAR MEDICINE • Vol. 52 • No. 6 • June 2011

Responder

Non-Responder
Tuberculous lymphadenitis: FDG PET and CT findings in responsive and nonresponsive disease

Mike Sathekge · Alex Maes · Yves D'Asseler · Mariza Vorster · Harlem Gongxeka · Christophe Van de Wiele

Neutrophils

Fig. 1 ROC curve analysis of SUVmax of involved LN basins for separating responding LN from nonresponding LN to TB treatment (AUC 0.952) A SUVmax cut-off value of 4.5 yields a sensitivity and specificity of 95% and 85%

Fig. 3 PET/CT findings: (a) a responder with basins of homogenous involved LNs and (b) a nonresponder with basins of involved LNs displaying central attenuation and peripheral rim enhancement

a Caseous granuloma
Cavities and MDR and Relapse

- These are formed by liquefaction of caseous necrosis and subsequent fibrosis with lung destruction.
- Multiple cavities have MDR.
- Common in pts with > 1month Hx of Rx.
- Increased risk of relapse.
44 yr old male smoker with RVD and bilateral lung changes. 
Sputum cultures: *Mycobacterium Tuberculosis* 
MRD
Irreversible lesions

- Permanent loss of function
- Lack of Vascularity
- Luminal surface Devoid CD4 & CD8
- Hallmark of TB
- MDR
- Relapse
Apoptosis is a major cause of so-called "caseous necrosis" in mycobacterial granulomas in HIV-infected patients

A S-Y Leong,¹ P Wannakraiot,² T Y-M Leong³
Necrotic Lesions

1: Hypoxia – key distinguishing feature in caseous granulomas (both active & latent)

2: Caseum of necrotic lesions – acidic (early and transient)
   Chronic/Mature lesion – slightly basic

3: Caseum – rich in lipids (cholesterol, cholesterol esters, triglycerides)
Duration of TB Treatment
And Relapse Free Cure
Prospective Prediction of Relapse

- Sputum culture at 2 months = 40% sensitive
- FDG 2 weeks vs 1 month vs 2 months
- Duration of Rx – (benefit MDR toxic injectables)
Left upper Lobe: tree-in-bud pattern, consistent with active infection and SUVmax of 2.14

Monitoring
At 1 month
Monitoring at 2 months

Cervical LNs (Right: 7.78→3.23; Left: 6.98→3.13)
Baseline & Follow-up study: Axillary LNs (Right: 10.79→5.19; Left: 6.98→6.50)

Nodal Responder At 2 months?

Will the liver & spine Relapse?

Heterogeneity of TB lesions
Is one month ideal for TB IPET?

LZD-resistant patient one month (middle) and six month (bottom) showing the initial response and subsequent development of a new lesion.

Coleman MT et al Sci Transl Med. 2014.
FDG PET: associated with long-term outcomes

CT: predictive of outcomes at 6 months but not 2 months (computed abnormal volumes were predictive at both time points)
FDG PET: associated with long-term outcomes at 2 months

Good Therapy Response

Mediastinal tuberculous lymphadenopathy post-chemo-radiotherapy Persistently enlarged mediastinal lymph nodes on CT with metabolic PET response

PET/CT demonstrates that non-human primates and humans have similar beneficial therapeutic responses to linezolid.

Coleman MT et al Sci Transl Med. 2014.
Heterogeneity of TB lesions

TB lesions evolve independently in MDR patient on Linezolid:
  Lt Apical lesion = resolving
  Rt Apical lesion = progressing

Potential role of F18 FDG PET-CT as an imaging biomarker for the noninvasive evaluation in uncomplicated skeletal tuberculosis: a prospective clinical observational study

Sugandha Dureja · Ishita Barat Sen · Shankar Acharya

Eur Spine J (2014) 23:2449–2454

Table 2  Fall in mean SUV during course of antitubercular therapy

<table>
<thead>
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<th></th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Minimum</th>
<th>Maximum</th>
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<td>33</td>
<td>14.8</td>
<td>6.2</td>
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<tr>
<td>SUVmax 6 months</td>
<td>30</td>
<td>6.3</td>
<td>3.2</td>
<td>2.1</td>
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<td>SUVmax 12 months</td>
<td>25</td>
<td>3.0</td>
<td>1.0</td>
<td>1.6</td>
<td>5.3</td>
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<tr>
<td>SUVmax 18 months</td>
<td>18</td>
<td>1.8</td>
<td>0.4</td>
<td>1.1</td>
<td>2.4</td>
</tr>
</tbody>
</table>
Baseline study

Follow-up at 12 weeks
Mixed Response

1: class 1: homogenous response

2: class 2: dominant response

3: class 3: dominant non-response

4: class 4: homogeneous non response (or one progressive lesion)

• Impact of MixR on treatment outcome / prognosis
• Interesting path to explore treatment resistance mechanisms through direct correlation with tissue-based diagnosis
Why many probes not suitable as bacteria-specific infection imaging agents

1: Inability of the compound to discriminate infection from sterile inflammation

2: Different ways of reading the scans

3: Differences in the performance of the labeling procedure leading to formation of different complexes

4: Insufficient quality control

These limitations have been largely overcome by the hybrid PET/CT and SPECT/CT technology
Investigation of $6-[^{18}\text{F}]$-Fluoromaltose as a Novel PET Tracer for Imaging Bacterial Infection

Gayatri Gowrishankar$^1$, Mohammad Namavari$^1$, Erwan Benjamin Jouannot$^2$, Aileen Hoehne$^1$, Robert Reeves$^1$, Jonathan Hardy$^3$, Sanjiv Sam Gambhir$^{1,4\ast}$
Why cationic antimicrobial peptides?

- Positive prognosis (UBI-Fragments such as 29-41 are specific & sensitive towards infection)
- Straightforward radiolabeling expected “shake and shoot”
- Non-toxic with no side effects
- NOTA is more ⁶⁸Gallium specific than DOTA
- ⁶⁸Gallium half life matches most peptide’s pharmacology

Sathekge, Nucl Med Commun 2008, 26:663-65
Preclinical Evaluation of $^{68}$Ga-Labeled 1,4,7-Triazacyclononane-1,4,7-Triacetic Acid-Ubiquicidin as a Radioligand for PET Infection Imaging

Thomas Ebenhan$^{1-3}$, Jan Rijn Zeevaart$^4$, Jacobus D. Venter$^5$, Thavendran Govender$^6$, Gert H. Kruger$^2$, Neil V. Jarvis$^3$, and Mike M. Sathekge$^1$

*J Nucl Med 2014; 55:1–7*

Axial PET/CT images show contra lateral hind legs at
(1) muscular infection site
(2) muscular inflammation site

Coronal PET image of $^{68}$Ga-NOTA-UBI at 60 min p.i.
Targeting M.Tb infections with 68Ga-UBI

Positive control s.c. S.aureus

M. Tuberculosis
Detecting organ TB lesions - 68Ga-UBI

Multiple TB lesions detected

No TB lesions visible

68Ga-UBI  18F-FDG

Multiple TB lesions detected
$^{68}$Ga-UBI-PET/CT in PTB

Ability to differentiate between infection and disease
Synthesis, $^{68}$Ga-Radiolabeling, and Preliminary In Vivo Assessment of a Depsipeptide-Derived Compound as a Potential PET/CT Infection Imaging Agent

Botshelo B. Mokaleng, Thomas Ebenhan, Suhas Ramesh, Thavendran Govender, Hendrik G. Kruger, Raveen Parboosing, Puja P. Hazari, Anil K. Mishra, Biljana Marjanovic-Painter, Jan R. Zeevaart, and Mike M. Sathekge
HIV-associated neurocognitive disorder (HAND)

- HAND consists of 3 subdisorders:
  - Asymptomatic neurocognitive impairment (ANI)
  - Mild neurocognitive disorder (MND)
  - HIV-associated dementia (HAD)

- HAART has dramatically decreased the prevalence of the severest form of HAND (HAD)

BUT

- The overall prevalence of HAND (MND & ANI) and associated morbidity remain high (~50%)

Why Persistent HAND???
HIV-associated neurocognitive disorder (HAND)

$^{11}$C-PiB: Amyloid-β protein 1-42 (Aβ42)
HIV-associated neurocognitive disorder (HAND)

- HAND & AD individuals have increased fibrillar Aβ42 deposition in cortical and subcortical regions.

- HAND and AD may therefore share similar molecular mechanisms that lead to neurodegeneration

- Only the symptomatic AD participants had increased fibrillar amyloid deposition using 11C-PiB

- 11C-PiB may provide a diagnostic biomarker for distinguishing symptomatic AD from HAND in middle-aged HIV+ participants.
Effects of AIDS on Women who have Sex determined health issues

HIV-associated neurocognitive disorder
Dementia
Reservoirs maintain infection/Latency

Cellular
- Long-lived cell populations with HIV in a state capable of surviving for prolonged periods
- Resting CD4+ T cells, monocytes/macrophages, dendritic cells, hematopoietic progenitor cells
- Mechanisms still under investigation

Anatomical
- Low ART drug accessibility
- Key sites: Central Nervous System, Gut-Associated Lymphoid Tissue

Need a combined strategy for eradicating HIV both systemically and in the CNS:
1) block infection of new cells (ART)
2) eliminate existing infected cells

Williams D. et al. PLOS ONE, 2013
Reservoirs maintain infection/Latency

Whole-body immunoPET reveals active SIV dynamics in viremic and antiretroviral therapy–treated macaques

Santajelo PJ. et al. Nature Methods

Need a combined strategy for eradicating HIV both systemically and in the CNS:
1) Reservoir-specific imaging and therapy
2) Imaging to understand Neuro-HIV (HAND)

Williams D. et al. PLOS ONE, 2013
Santajelo PJ. et al. Nature Methods
Advanced Stage of HIV

FDG RELATION TO LYMPH NODES & TO CD4 CELL COUNT
Apoptosis & Homing

Sathekge et al., Nucl Med Commun 2010
HAART with lipodystrophy: FDG uptake in subcutaneous fat

FDG Uptake reflect ongoing apoptosis

Sathekge et al., Nucl Med Commun 2010
HIV and Cancer

Pinzone et al. Seminars in Oncology, 2015
Lymphoma Behaving Differently?

Rapidly progressive disease

Extra-nodal involvement
Lymphoma Behaving Differently?

Extra-nodal involvement
A 31 year old female with RVD & Diffuse Large B-cell Lymphoma.
The Response of HIV-Associated Lymphadenopathic Kaposi Sarcoma to Highly Active Antiretroviral Therapy Evaluated by $^{18}$F-FDG PET/CT

Satveer K. Mankia, MA, MB, BChir, MRCP,* Robert F. Miller, MBBS, FRCP, CBiol, FSB,*† Simon G. Edwards, FRCP,*‡ Alan Ramsay, DM, FRCPPath,§ and Siow Ming Lee, PhD, FRCP¶
HIV-Lung Cancer

- Advanced disease (stage III or IV)
- Younger age group
- Lower CD4 count
- Smoking
- 2 to 4 times that of the general population
Does ICC behave differently?

- Reports more rapidly progressive disease (Mitchel 1998)
- Younger age at presentation:
- More advanced stage wrt CD4 counts
  - Lomalisa et al: CD4 <200 more advanced disease (77% vs 55.8%)
- Recurrence rates: up to 88% (Maiman 1997)
ICC & HIV

Majority HIV (+) poorly diff. tumors

Rapidly progressive disease
Anal Ca

Very aggressive and at younger age
PET/CT in assessment of treatment response of TB

Paradigm shift in our understanding of lesion progression

- Heterogeneity of TB lesions
- Caseous necrotic lesions: Neutrophil-dominated (↑ Mortality)
- Early detection of non-responders
- Prognosis and detection of residual disease in extrapulmonary TB
- Duration of treatment and prediction of relapse

Ehlers S et al, Front. Immunol 2013