Disclosures

None
Question 1

The characteristic appearance of acute interstitial nephritis on gallium-67 imaging is renal activity that is more intense than activity in the

A. Colon
B. Liver
C. Lumbar spine
D. Spleen
Question 2

Labeled leukocyte imaging is MOST sensitive for detecting inflammations and infections in which the cellular response is primarily

A. Basophilic
B. Eosinophilic
C. Lymphocytic
D. Neutrophilic
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What are the effects of osteomyelitis on the uptake of leukocytes and sulfur colloid by the bone marrow?

A. Osteomyelitis stimulates bone marrow uptake of leukocytes and sulfur colloid
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\(^{18}\text{F-FDG}\) is useful in the evaluation of patients with fever of unknown origin because this radiopharmaceutical is

A. Sensitive and has a high negative predictive value
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What is an advantage of $^{18}$F-FDG compared to $^{99m}$Tc-MDP for diagnosing osteomyelitis?

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B. $^{18}$F-FDG uptake is high in degenerative changes
C. $^{18}$F-FDG uptake is high in bone tumors
D. $^{18}$F-FDG uptake is low in trauma
Radiopharmaceuticals
Single Photon Emitters

$^{67}\text{Ga}$-citrate
Labeled leukocytes
  In-vitro labeled leukocytes
  In-vivo labeled leukocytes
Infection specific agents
  Radiolabeled antibiotics
  Radiolabeled antimicrobial peptides
Radiopharmaceuticals
Positron Emitters

$^{18}$F-FDG
$^{18}$F-FDG-WBC
$^{64}$Cu-WBC
$^{64}$Cu-cFLFLF-PEG
$^{68}$Ga-68
$^{124}$I-fialuridine
Gallium-67
Uptake Mechanisms

Transferrin delivery to inflammation
Lactoferrin binding at inflammation
Siderophore binding at inflammation
Direct bacterial uptake \((S. \text{Aureus}, E.\text{coli})\)
Macrophage uptake (via gallium receptors)

\textit{Leukocyte delivery to inflammation}
Normal Gallium Scans
Indications for $^{67}$Ga Imaging

Interstitial nephritis
Opportunistic infections
Severe leukopenia
Pulmonary Inflammation
Spinal osteomyelitis
FUO
Granulomatosus diseases
  Sarcoidosis
  Mycobacterial infections
  Chronic granulomatous disease
67Ga & Interstitial Nephritis

1. Differentiates acute interstitial nephritis from acute tubular necrosis (ATN)
2. Reliable only in acute renal failure
3. Image $\geq 48$ hrs. post injection
4. Renal uptake $> \text{lumbar spine uptake}$
Spinal Osteomyelitis

MRI: imaging procedure of choice

Nuclear medicine

Useful adjunct when MRI

- Is equivocal
- Differs from clinical impression
- Cannot be performed

Procedures

- $^{18}$F-FDG
- $^{67}$Ga-citrate
Spinal Osteomyelitis

Gallium
Enhances bone scan specificity
Detects adjacent soft tissue infection
May be more sensitive than bone scan
(especially in elderly)
Gallium useful for:
- Extent of disease
- Monitor response to Rx
- Detect recurrent disease
- Scarring vs. active disease

Pre Rx

Post Rx
Active Disease vs. Scarring
In-Vitro Labeled Leukocytes

$^{111}\text{In-oxine}$

$^{99m}\text{Tc-exametazime}$
In-vitro Labeled Leukocytes Uptake Mechanisms

Intact chemotaxis
Number of cells labeled
Type of cells labeled
  Predominantly neutrophils
Inflammatory response
  Most sensitive for neutrophil mediated inflammation/infection
Acute Gouty Arthritis
Sarcoidosis

$^{111}\text{In-WBC}$  $^{67}\text{Ga}$
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<td>SPECT/CT</td>
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Normal $^{111}$In-Labeled Leukocyte Study (24 hrs)
Normal $^{99m}$Tc-Labeled Leukocyte Study*

*10 mCi $^{99m}$Tc-WBC, 15 cm/min 4hrs, 8 cm/min 24 hrs
Pulmonary Uptake of Labeled Leukocytes
Labeled Leukocytes

• Do *not* accumulate in normally-healing surgical wounds

• **Exceptions**
  – Wounds healing by secondary intention
  – Ostomies
  – Skin grafts
  – Bleeding wounds
Gastrointestinal Activity

- Infection
- Inflammation
- Ischemia
- GI bleeding
- Swallowed WBC’s
- Following enemas

$^{111}$In-WBC
Indications for Labeled Leukocyte Imaging

Inflammatory bowel disease (IBD)
Occult infection
Postoperative infection
Infection versus tumor
Vascular graft infection
Complicating osteomyelitis
  Orthopedic hardware
  Joint prosthesis
  Diabetic pedal osteomyelitis
  Charcot joint
Fever of unknown origin
Cardiovascular System

Bacterial Endocarditis  No (SPECT/CT)

Mycotic Aneurysms  Yes

Infected Prosthetic Grafts  Yes
Vascular Graft Infection

Sensitivity: 90%
Specificity: 53%-90%
False positives
  Thrombosis
  Hematoma
  Bleeding
  Recent placement (< 2 weeks)
Central Nervous System

Meningitis: No

Encephalitis: No

Abscess: Yes
Musculoskeletal Infection
Marrow Expansion

Produces
Altered uptake of leukocytes

Creates
Difficulties in labeled leukocyte image interpretation

Solution
$^{99m}$Tc sulfur colloid marrow imaging
Leukocytes and sulfur colloid both accumulate in marrow
Leukocytes accumulate in osteomyelitis; sulfur colloid does not
Image interpretation: Activity on labeled leukocyte image without corresponding activity on bone marrow image = osteomyelitis
Leukocyte/Marrow Imaging

Osteomyelitis Lt. Humerus

Hypercellular Marrow Lt. Humerus (SSD)
Scrutinize the Joint!!

Infected Rt. TKR

Infected Rt. THR
Nodal Activity (Hips)
Nodal Activity (Knees)

Posterior

111In-WBC  

99mTc-SC

Right lateral
$^{99m}\text{Tc-Sulfur Colloid Breakdown}$

$^{111}\text{In-WBC}$  $^{99m}\text{Tc-SC}$  $^{99m}\text{Tc-SC}$
Spinal Osteomyelitis

50%: nonspecific photopenic defects on WBC images

WBC/marrow imaging generally is not useful
# SPECT/CT

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Soft Tissue Infection
($^{111}$In-WBC)

Anterior
Posterior
Lt. Mandibular Osteomyelitis

$^{111}$In-WBC

$^{111}$In-WBC  $^{99m}$Tc-SC
In-vitro Labeled WBC’s

$^{99m}$Tc vs. $^{111}$In

$^{99m}$Tc-WBC

$^{111}$In-WBC
Dual Isotope Planar Images
Infected Lt. THR

Anterior

111In-WBC

99mTc-SC

Posterior
Dual Isotope SPECT/CT
Infected Lt. THR

$^{111}$In-WBC

$^{99m}$Tc-SC
SPECT/CT & Prosthetic Joints

Think out of the Box!
Extent of Infection
Other causes of pain
Loosening
Fracture
Particle disease
Etc.
CT guided joint aspiration
Unanswered Questions About WBC Imaging

- Effect of antibiotics on sensitivity
- Effect of steroids on sensitivity
- Monitoring response to treatment
In-vitro Labeled Leukocytes: Disadvantages

Not infection specific
Labeling procedure
  Labor intensive
  Blood handling
Availability
Dual isotope imaging for MSK infection
Suboptimal resolution
Interval between injection & imaging
In-vivo Labeled Leukocytes
Antigranulocyte Antibodies

$^{99m}$Tc-Besilesomab
Murine monoclonal G1 immunoglobulin
Binds to NCA-95 on leukocytes
Disadvantages
  - High bone marrow uptake
  - High HAMA incidence
  - HAMA prescreening
  - Single use
Antigranulocyte Antibodies

$^{99m}$Tc-Fanolesomab
Murine monoclonal M immunoglobulin
Binds to CD-15 receptors on leukocytes

Disadvantages

Safety issues (No longer available)
Antigranulocyte Antibodies

$^{99m}$Tc-Sulesomab

Murine monoclonal G1 immunoglobulin fragment

Binds to NCA-90 on leukocytes

No HAMA

Disadvantages

Uptake mechanism issues
$^{99m}$Tc-Interleukinin-8 (IL-8)

CXC subfamily of chemokines
Binds to CXC1 and CXC2 receptors on neutrophils
Radiolabeled Antibiotics

$^{99m}$Tc-Ciprofloxacin

Rapidly inhibits bacterial DNA synthesis → rapid bacterial cell death

Inhibits enzymatic activities of the enzymes DNA gyrase and topoisomerase IV, promotes cleavage of DNA in these enzyme–DNA complexes

- Gram (+) bacteria: DNA gyrase
- Gram (-) bacteria: topoisomerase IV
99mTc-Ciprofloxacin

Aseptically Loosened Right TKR

Infected Right TKR

2 hrs.                4 hrs.              24 hrs.
Radiolabeled Antimicrobials

Critical role in biological defense system of multicellular organisms
Bind to bacterial cell membrane
Expression constant or induced on microbial contact
May be transported to infection by leukocytes
Radiolabeled Antimicrobials

Ubiquicidin

Human antimicrobial peptide
Targets bacteria
Radiolabeled synthetic fragments (\(^{99m}\text{Tc-UBI 18-35 and UBI 29-41}\))
  Rapidly detect gram-positive and gram-negative infections
  No accumulation in sterile inflammation
Initial human investigations encouraging

Human Beta-Defensin-3 (HBD-3)
$^{18}$F-FDG
$^{18}$F-FDG

Cellular uptake related to cellular metabolic rate & number of glucose transporters

Transported into cells via glucose transporters

$\uparrow$ glucose transporters in activated inflammatory cells

$\uparrow$ affinity of glucose transporters for FDG

2° to cytokines & growth factors
$^{18}$F-FDG

Small molecule
  Enters poorly perfused regions rapidly
High resolution images
High sensitivity (> 90%)
Minimal uptake in normal bone marrow
Uptake in uninfected fractures normalizes quickly (3-4 months)
Low uptake in degenerative bone disease
Accurate in chronic osteomyelitis
No blood handling
Fever of Unknown Origin

Radionuclide studies typically performed after all other tests are negative

Majority yield negative results

Traditional approach: $^{111}$In-WBC and/or $^{67}$Ga (up to 5 days to complete)

21st Century: $^{18}$F-FDG

High sensitivity & negative predictive value

Negative result: unlikely that focal source of FUO will be identified.
Vasculitis

Very sensitive (77-92%) for detecting large vessel vasculitis (giant cell arteritis)

Useful for
  - Determining extent of disease
  - Monitoring response to therapy

Less useful in
  - Immunosuppressed patients
  - Medium & small vessel disease
    - Temporal arteritis
    - Polyarteritis nodosa
Sarcoid
# FDG & Inflammatory Bowel Disease

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Ulcerative Colitis
Diabetic on Metformin
Vascular Graft Infection

Wasselius et al. (J Nucl Med 2008;49:1601-5) (n=16)

16 vascular grafts demonstrated FDG uptake.
1 was infected.

Spacek et al. (EJNMMI 2009;36:850-8) (n=96)

Focal FDG uptake + irregular lesion boundary on CT had PPV = 97%
No focal uptake + smooth boundaries on CT had NPV of 95%
FDG PET/CT provided definitive diagnosis in about 75% of cases
16 Uninfected Vascular Grafts*

14 (87.5%) grafts demonstrated FDG uptake
  3: focal
  4: diffuse heterogeneous
  7: diffuse homogeneous

SUV’s
  Graft: 3-8.7
  Graft/Blood pool: 1.25-3.62
Values similar to infected grafts

5 grafts: little change over 2 yrs.

*Tomas SNM 2012
Asymptomatic Aortic Graft

Sept 2006

July 2007
Musculoskeletal Infection

High sensitivity
> 90%

Minimal uptake in normal bone marrow

Uptake in uninfected fractures rapidly normalizes
(3-4 months)

Accurate in chronic osteomyelitis
<table>
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FDG & Spinal Osteomyelitis

(+)

(-)
The Diabetic Foot
FDG & Joint Replacements*

Infected Rt. TKR

Aseptically Loosened Lt. TKR

* Courtesy F. Gemmel, MD
Summary

Gallium

Opportunistic infections, interstitial nephritis, pulmonary inflammation, severe leukopenia

*In-vitro* labeled leukocytes

Most infections in immunocompetent patients

FDG

FUO, vasculitis, spinal osteomyelitis, granulomatous diseases (mycobacterial, sarcoid, etc)
The Future

What do we need?
A radiopharmaceutical that is
Safe
Specific for infection
Ubiquitously available
Rapidly completed and
Yields high resolution images
SAM Questions
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Infected Rt. THR
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