Screening for and Assessment of Osteonecrosis in Oncology Patients

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Osteonecrosis (ON)
Avascular necrosis (AVN)
Aseptic necrosis
Ischemic necrosis

Dorland’s Medical Dictionary (28th ed): “death, or necrosis, of bone”

: “death of bone…”

: “…a disease caused by reduced blood flow to bones in the joints. …, the bone starts to die and may break down…”
Osteonecrosis

Not a specific disease entity, but the final common pathway of several conditions, most leading to impaired blood supply

17 y/o girl after ALL
Symptoms of osteonecrosis

- Early stages
  - Often asymptomatic
- Disease progresses
  - Joint pain when weight bearing
  - Joint pain when resting
- Pain usually develops gradually
  - Mild to severe
- Joint Collapse
  - Dramatic increase in pain
Hip ON lesion size correlates with pain score ($p=0.0023$) but…

… pain is an unreliable indicator of presence or severity of ON

Osteonecrosis

Most common anatomic locations

– Femoral head (hips; greatest morbidity)
– Distal femur/proximal tibia (knees)
– Humeral head
– Tarsal bones of the foot
Osteonecrosis

• Etiology multifactorial
• Associated risk factors
  – High-dose steroid therapy
  – Alcohol
  – Dysbaric
  – Radiation
  – Sickle cell disease
  – Gaucher’s disease
  – Trauma
• Idiopathic
Osteonecrosis

- Etiology multifactorial
- Associated risk factors in pediatric oncology
  - High-dose steroid therapy
  - Radiation

  - Direct effect on osteoblasts (inhibits bone formation)
  - Direct effect on osteoclasts (accelerates bone resorption)
  - Premature apoptosis
  - Increase adipocytosis
  - Increase intraosseous pressure
Osteonecrosis – in pediatric oncology...

Typically attributed to glucocorticoid exposure

– Glucocorticoids induce occluding angiopathy
  (Janke et al 2013)

– Association with inherited genomic variations
Multi-joint involvement predominates in pediatric oncology

- 80% bilateral knees leukemia/lymphoma
  - Karimova et al. AJR:186, 2006
- >50% bilateral ankles cancer
  - Chollet et al. Clin Orthop Rel Res:430, 2005
- 79% bilateral hips leukemia/lymphoma
- 5/33 bilateral hips; 29/33 bilateral knees
ON prevalence in pediatric oncology

- Varies between 1%* and 72%**
  - Symptomatic versus asymptomatic cases
  - Radiographic versus MR-determined
  - Treatment era
  - Definitions used
  - Self- versus imaging-reported

“At-risk” oncology cohorts

Acute lymphoblastic leukemia

Allogeneic bone marrow

Brain tumors
Available imaging modalities

- Radiographs (XR)
- Ultrasound (US)
- Computed tomography (CT)
- Magnetic resonance imaging (MR)
  - Diffusion weighted imaging
  - Perfusion weighted imaging
  - Whole body MR
  - Other innovative sequences
- Nuclear medicine imaging
  - 99mTc-MDP bone scan (BS)
  - 18F-FDG PET/PET-CT imaging (PET or PET-CT)
Standard MR sequences

- Coronal non-contrast T1 and STIR
- Sagittal FLASH 2-D
- When needed to answer a specific question:
  - Contrast-enhanced T1 and subtraction may be helpful
What the oncologist and orthopedic surgeon need to know

- Presence or absence of ON
- Lesion location
  - Epiphysis
    - Extending to articular surface or not
    - Extent of articular surface involved
  - Metaphysis
  - Diaphysis
- Lesion size
- Status of skeletal maturity
- Other findings
Osteonecrosis present or absent?
Presence or absence of ON

- Normal
- Abnormal
  - Mimickers of ON
  - ON-associated findings
  - Unexpected findings
ON-associated inflammatory changes

T1

STIR

FS T1 C+

Subtraction
ON-associated bone marrow edema
ON-associated soft tissue edema
Presence or absence of ON

- Normal
- Abnormal
  - Mimickers of ON
  - ON-associated findings
  - Unexpected findings
Acute recurrent mixed phenotypic leukemia - unexpected
What the oncologist and orthopedic surgeon need to know

- Presence or absence of ON
- Lesion location
  - Epiphysis
    - Extending to articular surface or not
    - Extent of articular surface involved
  - Metaphysis
  - Diaphysis
- Lesion size
- Status of skeletal maturity
- Other findings
Lesion location

Epiphyseal and metaphyseal
Talar dome

Diametaphyseal
What the oncologist and orthopedic surgeon need to know

• Presence or absence of ON
• Lesion location
  – Epiphysis
    • Extending to articular surface or not
    • Extent of articular surface involved
  – Metaphysis
  – Diaphysis
• Lesion size
• Status of skeletal maturity
• Other findings
Lesion size: large lesions progress

Size A (<15% of femoral head), 56 hips
Size B (15-30% of femoral head), 24 hips
Size C (>30% of femoral head), 34 hips

Karimova et al J Clin Oncol 2007 (25) 1525-1531
Implications

Early identification of patients at risk for developing large (> 30%) lesions of hips will allow us to target earlier interventions to the correct patient population, optimizing joint integrity and ameliorating progression of ON.

Karimova et al J Clin Oncol 2007 Apr 20;25(12):1525-31
Utility of early screening magnetic resonance imaging for extensive hip osteonecrosis in pediatric patients treated with glucocorticoids

• 462/498 patients newly diagnosed with acute lymphoblastic leukemia underwent screening MR regardless of presence or absence of symptoms
• MR hips and knees performed at:
  – 6.5 and 9 months from diagnosis (early screening)
  – at completion of chemotherapy (final evaluation)
• Lesions coded as < versus ≥ 30% (extensive) involvement articular surface femoral head

Utility of early screening magnetic resonance imaging for extensive hip osteonecrosis in pediatric patients treated with glucocorticoids

- Extensive asymptomatic osteonecrosis found by early screening:
  - 26 patients (41 hips)
  - another 4 patients (7 hips) after the screening period
  - screening sensitivity 84.1%; specificity 99.4%
- Number of joints screened to detect one lesion was 20.1 for all patients
  - 4.4 for patients older than 10 years
  - 198 for younger patients (p<0.001)
- 19/40 extensive lesions in patients older than 10 yrs, required total hip arthroplasty and none improved.
- 0/8 extensive lesions in younger patients, required arthroplasty and four improved.

Lesion size: large lesions progress

5 y/o girl; protocol-driven prospective MR
Lesion size: large lesions progress

2 years later: collapse of both femoral heads
Lesion size: large lesions progress

5m later

4m later (18 years old)
Lesion size: large lesions progress

3 years later (age 21 years)

5 months later
Same patient: virtually all major joints involved
Progression can be rapid – baseline (asymptomatic)
Progression can be rapid – 5 weeks later (now with pain in knees and ankles)
What the oncologist and orthopedic surgeon need to know

• Presence or absence of ON
• Lesion location
  – Epiphysis
    • Extending to articular surface or not
    • Extent of articular surface involved
  – Metaphysis
  – Diaphysis
• Lesion size
• Status of skeletal maturity
• Other findings
Advanced MR sequences – roles as yet to be defined
Summary: What we know …

**Age:** only consistently identified risk factor for extensive vs. mild ON
- Increased risk for development and severity

**Symptoms:** unreliable to detect disease
- Only large lesions reaching articular surface and affecting greater are consistently associated with symptoms
- Symptoms occur late in the progression; limiting options for intervention

**Large lesions tend to progress**

**Many factors contribute to risk of developing ON**
Thank you!