Rare Atypical Subtrochanteric Fractures

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Rare atypical subtrochanteric fractures

• Recent reports of atypical femoral shaft fractures
  • 2 case series (1 in Singapore and 1 in New York) (uncontrolled)
  • Unusual fracture type (cross-femur clean cut), cortical thickening, minor trauma. Upper 2/3 femur
  • Seems to be associated with long term bisphosphonates (>7 years)..more later

Typical subtrochanteric fracture case: Impressions from anecdotes*

- Pain in femur 1-2 months
  - May be evidence of stress fracture

- Then, fracture with little trauma
  - "turned to close door and heard crack"
  - "no fall, just a crack"

- Long term bisphosphonates (>7 years)

- This patient also on HRT

* Email box, D. Black
Efficacy of Bisphosphonates for Reducing Clinical Fracture

<table>
<thead>
<tr>
<th>Drug</th>
<th>Trial</th>
<th>Active</th>
<th>Placebo</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALN*</td>
<td>FIT II(T&lt;-2.5)</td>
<td>15.3%</td>
<td>9.9%</td>
<td>18</td>
</tr>
<tr>
<td>ZOL**</td>
<td>HOR PFT</td>
<td>13.3%</td>
<td>8.3%</td>
<td>20</td>
</tr>
</tbody>
</table>

Characteristics of “atypical femur fractures”

• No generally accepted definition so cases have quite different characteristics

• “I know it when I see it”

• Location of fracture (below lesser troch and in top 2/3 femur)
• Transverse morphology
• Cortical thickening
• Prodromal pain
• Evidence of stress fracture

• Not all case reports have all these characteristics..what is a case?
FIGURE 1. Representative radiographs of femoral shaft fractures sustained from minimal trauma in patients taking alendronate. Although each radiograph demonstrates the pattern in its entirety, we have highlighted the following features. A, Fracture pattern pictured with an arch measuring 30 degrees to highlight transverse nature. B, The arrow pointing out the unicortical beak C, Hypertrophied cortices outlined.
Other Characteristics
(from initial and follow-up cases)

• Some cases with bilateral involvement
  – Prior fracture in other femur
  – Simultaneous fracture in other femur
  – Evidence of cortical thickening and/or stress fracture in other femur

• Prodromal pain

• May be associated with corticosteroids or PPI’s
Characteristics of “atypical femur fractures”: Cortical thickening

• Cortical thickening sometimes described as either
  – Focal (around fracture)—due to stress fracture?
  – Generalized thickening of cortices
  – Thickening of lateral cortex compared to medial

  – Problems with “cortical thickness” as criteria
    ▪ We don’t know what normal cortical thickness and what is variation
    ▪ Focal thickness might be caused by stress fracture
Generalized thickening

Focal thickening

minimal trauma in patients taking alendronate
Characteristics of “atypical femur fractures”:
Fracture Morphology

- Morphology of fracture
  - Transverse, not spiral
  - How oblique?
Characteristics of “atypical femur fractures”

• Need for case definition
  – ASBMR and IOF committees in progress
Types of publications in this area

• Individual case reports
• Case series
• Review of registry cases
• No published reports from randomized trials
  – But will show unpublished data
• Others? What is optimal?
Case reports and case series..

- Limited inference since no controls
- Need epidemiologic studies and RCT’s
Danish population registry study*

- All fractures in Denmark
- Look at fractures based on *reported* location
  1. Subtrochanteric femur
  2. Femoral shaft (diaphyseal)
  3. Hip (control)

- Two components
  1. Cross sectional study of fracture reports
  2. Longitudinal cases and matched controls to look at med use, etc. (1997-2005, >100,000 fractures in analysis)

* ref: Abrahamson, JBMR 2009
Cross-sectional data: Incidence of subtroch and d. femur fractures by age in women

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<th>Age</th>
<th>Incidence Per 1000</th>
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<td>60-64</td>
<td></td>
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<td>75-84</td>
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<td>85+</td>
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- Subtrochanteric femur
- Diaphyseal femur
Cross-sectional data: Incidence of hip fractures by age in women

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The incidence of hip fractures increases significantly with age in women.
Incidence of femur and hip fractures by age in women: Femur/subtroch uncommon

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<tr>
<td>60-64</td>
<td>5</td>
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</tr>
<tr>
<td>75-84</td>
<td>10</td>
</tr>
<tr>
<td>85+</td>
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Hip 10 times higher
Danish registry cross sectional study: Conclusion

- Epidemiology of femur/subtroch fractures are similar to hip fracture
- Risk of femur/subtroch about 20% of hip
- Other finding: Past use of corticosteroid more common than past use ALN
Danish registry longitudinal study: Hip fractures by treatment

Explanation?
Subtroch or diaphyseal fractures by treatment in Danish Registry

![Graph showing cumulative incidence of subtroch or diaphyseal fractures with treatment groups ALN and Not ALN.](imageURL)
From Danish registry studies: Conclusions

• The risks of all 3 types of fracture are higher in alendronate users

• Why? People on alendronate have osteoporosis and are at higher risk of fracture (hip, subtroch, femur)
  – Lower than if not treated

• No evidence that alendronate increases risk of femur fractures

• Limitations
  – Population data
  – Fractures based on location/radiologist..no specific info on trauma, morphology
RCTS???: Subtrochanteric and femoral shaft fractures in randomized trials of bisphosphonates

- Radiologist (HKG) examined occurrence in several trials coordinated by UCSF (2008-09)

- Reviewed all hip (except fem neck) and femur fractures

- X-ray reports from fractures in these trials but radiographs not available (can’t evaluate atypia)

- Focus on location of fracture..fracture appeared to be in upper 2/3 of femoral shaft
  - Overestimates prevalence of true “atypical fractures”

Subtrochanteric and femoral shaft fractures in RCT’s of bisphosphonates

Fracture Intervention Trial
Alendronate (5 mg for 2 years, then 10 mg) vs. pbo
3 to 4.5 years
6459 women, about 20,000 person years
n=84 fractures reviewed

HORIZON PFT
Zoledronic Acid (5 mg annually) vs. pbo
3 years
7736 women (international), about 22,000 person years
n=164 fractures reviewed
### Results from FIT and Zoledronic acid studies (unpublished)

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<th>RR (CI)</th>
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<tr>
<td>FIT (ALN) (n=6459)</td>
<td>1</td>
<td>0.9</td>
<td>0.7 (.04, 11)</td>
</tr>
<tr>
<td>HORIZON (ZOL) (n=7736)</td>
<td>3</td>
<td>2.8</td>
<td>1.9</td>
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?NNH > 11,000?

FIT Long term Extension (FLEX)

- Women ALL of whom had been randomized to alendronate in FIT
- N=1099
- Baseline:
  - 5 years of previous alendronate, 80% still taking daily alendronate
  - Randomized to 5 more years of alendronate or placebo
    - 30% alendronate 10 mg/day (10 years ALN)
    - 30% alendronate 5 mg/day (10 years ALN)
    - 40% placebo (5 years ALN, then placebo)

Black et al, JAMA, 2006
## Results from FLEX study

<table>
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<tr>
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<th>ALN/P BO n=437</th>
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<tr>
<td>N</td>
<td>Per 10,000 years</td>
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| FLEX (n=1099) | 2 | 6             | 1             | 4             | ?NNH > 4,000? (3 years)???

Bauer et al ASBMR 2008
Clinical considerations

- A patient with pain in thigh on bisphosphonates?
- Stop treatment after 5 years?
- More cautious about treating a patient with osteopenia?
- Which bisphosphonate?
Optimal studies..

- Randomized trials can’t really answer question (rare event)
- Population databases with access to radiographs
  - Kaiser is ideal (studies in progress)
- Need more information
  - Co-factors such as glucocorticoid and PPI use
  - Other risk factors (osteopenia? Activity? ?)
Comparison of NNT/NNH

- NNT for 1 clinical fracture (3 years)

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- Consider worst case: NNH for one femur fracture (3 years). Very rough estimate
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Comparison of NNT/NNH

- NNT for 1 clinical fracture (3 years)
- Worst case NNH for one femur fracture (3 years)

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4000 women with ALN: Prevent 200 clinical fractures and cause 1 femur fracture
Summary/conclusions

• “Atypical” femur shaft fractures rare, even among long term bisphosphonate users (less then 1/5000 patient years)

• Not clear how much/if bisphosphonate use increases risk in absence of co-factors (e.g. steroids, ppi’s, HRT)
  – If risk increased, probably still VERY low
  – Not clear if/how strongly related to duration

• Benefits of bisphosphonates, in patients at high risk, outweigh potential risks

• MORE RESEARCH NEEDED!

• More caution toward starting bisphosphonates in low risk patients and continuing very long term