Osteomyelitis Caused by Bacille Calmette-Guérin (BCG) Vaccination: 2 Cases

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Seoul, Korea
CASE 1
• M / 11mos
• Pain & LOM, Knee, Rt.
  – Swelling at distal thigh
  – Diagnosed as ‘bacterial osteomyelitis’
  – Antibiotics for 2 weeks

• BCG vaccination (Tokyo strain)
  – 3 weeks after birth
• **Lab. Findings**
  - WBC 12,270/µL
    - Neutrophils 36.5%
    - Lymphocytes 53.5%
  - Hb 13 g/dL
  - Platelet 330,000/µL
  - **ESR** 26 mm/hr
  - CRP 0.19 mg/dL
  - **Tuberculin skin test**
    (2TU of RT23)
    - 17mm induration

• **Immunological Tests**
  - **Normal**
    - T-cell subsets
    - Complement
    - Immunoglobulin
    - Dihydrorhodamine test for CGD
    - HIV virus
Sx. onset

2 weeks after Sx. onset
• Surgical drainage
  – Organized pus
  – No physeal involvement
• “Tuberculosis” (PCR)
• Combination chemotherapy
  – INH
  – RFP
  – PZA
  – SM
CASE 2
• F / 14mos
• Swelling, ankle, Lt.
  – Fever
  – Erythema and tenderness
  – No treatment for 3 weeks

• BCG vaccination (Tokyo strain)
  – 3 weeks after birth
• **Lab. Findings**
  - WBC 12,100/µL
    - Neutrophils 63.3%
    - Lymphocytes 27.8%
  - Hb 12.4 g/dL
  - Platelet 217,000/µL
  - **ESR** 36 mm/hr
  - CRP 0.54 mg/dL
  - **Tuberculin skin test**
    (2TU of RT23)
    - 10mm induration

• **Immunological Tests**
  - **Normal**
    - T-cell subsets
    - Complement
    - Immunoglobulin
    - Dihydrorhodamine test for CGD
    - HIV virus
- **Surgical drainage**
  - Abundant granulation tissue
  - Bone loss, talar body
- **“Tuberculosis” (PCR)**
- **Combination chemotherapy**
  - INH
  - RFP
  - PZA
  - SM

2 months
‘TUBERCULOSIS’?
It was unusual.

- Age at onset: 11 or 14 months old
- Family surveillance: No tuberculosis
- No suspicious history of tuberculosis contact
Mycobacterial Colonies

Real-time PCR (IS6110 region) **POSITIVE**

*M. tuberculosis* complex

Real-time PCR (MIRUs of senX3-regX3 intergenic region) **Only 77-bp**

*M. bovis*

PCR (RD 1) **Deletion (+)**

*M. bovis BCG*
M. bovis BCG

BCG Tokyo strain

PCR (RD 8 & RD 14)  Both POSITIVE

BCG osteomyelitis
Postop. Course

CASE 1

4 months

8 months
(4 M after revision)
10 months
(6 M after revision)

Postop. Course
CASE 1
Postop. Course

CASE 2

3 months
6 months
(3 M after revision)
DISCUSSION
## Bacille Calmette-Guérin (BCG) Vaccine

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
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<tbody>
<tr>
<td>1902</td>
<td>First isolation of <em>Mycobacterium bovis</em></td>
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<tr>
<td>1908–21</td>
<td>BCG developed from serial passage of <em>M. bovis</em> strain (Calmette and Guerin)</td>
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<tr>
<td>1921</td>
<td>First human BCG vaccination (oral form)</td>
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<td>1929–30</td>
<td>Lubeck disaster: 72 children die from oral BCG preparation contaminated with virulent strain</td>
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<tr>
<td>1927</td>
<td>Intradermal technique</td>
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<tr>
<td>1939</td>
<td>Multiple puncture technique</td>
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<tr>
<td>1948–74</td>
<td>WHO and UNICEF campaigns; 1.5 billion vaccinations carried out</td>
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<tr>
<td>1948–97</td>
<td>Yearly increase of BCG vaccination estimated from 50 million to almost 100 million</td>
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(Tuber Lung Dis 73:252-261,1992)
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<thead>
<tr>
<th>Vaccine Strain</th>
<th>Other Names</th>
<th>Year obtained</th>
<th>Culturable particles per Dose</th>
<th>Strength</th>
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<tr>
<td>Russia</td>
<td>Moscow</td>
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<td>Japan</td>
<td>Tokyo 172</td>
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<td>3,000,000</td>
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<td>Prague</td>
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<tr>
<td><strong>Glaxo 1077</strong></td>
<td></td>
<td>1954</td>
<td>200,000-1,000,000</td>
<td>Weak</td>
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<td>Tice</td>
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<td>Phipps</td>
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<td>1938</td>
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<td><strong>Pasteur 1173 p2</strong></td>
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BCG osteomyelitis

- Latent period: ~12 months (5 months to 5 years)
- Resistance to Pyrazinamide
- Milder clinical course without severe sequelae (?)
Incidence of BCG Osteomyelitis

- Reported incidence: wide range
  - 300 / 100,000 (Finland)
  - 0.1 / 100,000 (Japan)

- Korea
  - Vaccination
    - > 95%
    - > 400,000 / year
  - BCG osteomyelitis
    - Only 2 case reports

Underestimated incidence in Korea?
Finland Cases (1960-1988)

- BCG coverage; 90-99% (at birth or 1 mo)
- ①; Gothenburg vaccine; 7.3/100,000
- ②; Copenhagen vaccine (Gothenburg strain using technique identical method); 36.9/100,000
- ③; Glaxo vaccine; 6.4/100,000

**FIG. 1.** Detected cases of BCG osteitis according to the year of birth of the child. In 1978 twelve cases had been vaccinated with the Gothenburg BCG (manufactured in Copenhagen) and four cases with the Glaxo BCG.
CONCLUSIONS
1. **Suspicion** of the disease is important.
   - ‘Tuberculous’ osteomyelitis of young children around 12 months old

2. **Accurate diagnosis** is worthwhile.
   - Proper selection of drug
   - Quality control of vaccines
Thank you.

2008 KPOS case discussion, Daegu