Case Presentation

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History

- **Pt:** 53 year-old Asian female

- **CC:** Fatigue, weakness, dizziness, and left knee pain.

- **PMH:** Stage IVB diffuse large B-cell lymphoma (DLBCL), status post 5 cycles of R-CHOP (last regimen: 28 months ago)

- **PE:** Left knee effusion and joint tenderness
Chondrocalcinosis with patellofemoral compartment narrowing, osteophytes and effusion (? r/o malignant effusion).
Tricompartment osteoarthritis, with osteophytes. Loss of patellofemoral cartilage and loose bodies.
Flow Cytometry - Synovial Fluid

(CD45) (SS)

GRANS 11.0%
Blasts 82.7%
Lymphs 1.0%

(CD71) (CD33)
Flow Cytometry - Synovial Fluid

- CD15
- CD13
- CD11b
- CD11c
Flow Cytometry - Results

Synovial Fluid

- **Granulocytic markers:**
  - CD13 dim
  - CD15 subpopulation
  - CD33 moderate/dim

- **Monocytic Markers:**
  - CD11b moderate
  - CD14 bright/moderate
Labs

CBC

- Hb 7.0 g/dL
- Hct 21%
- WBC $5.4 \times 10^3 \, \mu L$
- Plts $107 \times 10^3 \, \mu L$
Flow Cytometry - Marrow

(F1) [Ungated] X0105562_LMD : FL4 LOG/SS

SS

GRANS 9.0%
blast 69.6%
lymphs 1.6%

CD45

(F6) [Blasts4] X0105567_LMD : FL1 LOG/FL2 LOG

CD15

G1 0.8%
G2 3.2%
G3 32.4%
G4 63.7%

CD11b
Flow Cytometry - Marrow

(F7)(Ungated) X0105568.LMD: FL1 LOG/FL2 LOG

CD14 vs. CD13

(F2)(Ungated) X0105581.LMD: FL3 LOG/FL1 LOG

CD4 vs. CD3

F1: 29.1%
F2: 0.4%
F3: 69.4%
F4: 1.1%
Flow Cytometry - Results

<table>
<thead>
<tr>
<th>Synovial Fluid</th>
<th>Bone Marrow</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD15 subpop</td>
<td>CD15 subpop</td>
</tr>
<tr>
<td>CD33 mod/dim</td>
<td>CD33</td>
</tr>
<tr>
<td>CD11b dim</td>
<td>CD14 subpop</td>
</tr>
<tr>
<td>CD117 subpop</td>
<td>CD14 bright/mod</td>
</tr>
<tr>
<td>CD14 subpop</td>
<td>CD117 subpop</td>
</tr>
<tr>
<td>CD14 subpop</td>
<td>CD34 subpop</td>
</tr>
<tr>
<td>CD34 subpop</td>
<td>HLA-DR</td>
</tr>
</tbody>
</table>

**INTERPRETATION:** Myelomonocytic phenotype
Cytogenetics

- 46,XX, del(1)(p13q22), t(8;11)(p11.2;p15), del(12)(p11.2)
  - Deletion 12p:
    - Observed in MDS
    - Intermediate prognostic marker
  - Additional abnormalities suggest evolution of disease.
Diagnosis

- Acute Myelomonocytic Leukemia, Therapy Related
  - Associated with doxorubicin therapy
    (aka, Hydroxydaunorubicin = R-CHOP)

- Leukemic Synovitis
Leukemic Synovitis (LS)

- Well-recognized but rare complication of acute and chronic leukemias
  - 14% of pediatric leukemias
    - Acute lymphoblastic leukemia
  - 4% of adult leukemias
    - Acute & chronic lymphocytic & myeloid leukemia
- Can be the initial manifestation of leukemia or of relapse (even if not present initially).
- The average rheumatic prodrome is 3 months
Leukemic Synovitis (LS)

- Clinical Presentation:
  - Joints warm, swollen, tender
  - Distal and symmetric, or asymmetric, involving large joints
  - Effusions usually small
  - Severe pain is common
  - Osteopenia, lytic lesions on X-rays
  - Seronegative reactive arthritis-like
Leukemic Synovitis - Diagnosis

- Imaging studies often non-specific
- Synovial fluid exam with cytospin morphology
  - Flow cytometry
  - Enzyme cytochemistry
- Synovial biopsy ("Gold Standard")
  - Immunohistochemistry
  - Note: may fail to sample neoplastic infiltrate
Treatment of Leukemic Synovitis

- Leukemic synovitis is a sign of systemic involvement and should prompt immediate and aggressive therapy even in the absence of signs of bone marrow involvement.

- Therapy for the underlying leukemia is the treatment of choice.

- Decreasing joint pain often is the first sign of a clinical response to chemotherapy.
<table>
<thead>
<tr>
<th>Case</th>
<th>Age/Gender</th>
<th>Si/Sx</th>
<th>PMH</th>
<th>Exam</th>
<th>Time course of LS</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case 1</td>
<td>53yo Hispanic Female</td>
<td>L knee effusion</td>
<td>DLBCL</td>
<td>Osteoarthritis</td>
<td>Early</td>
<td>AMML</td>
</tr>
<tr>
<td>Case 2</td>
<td>53yo Asian Female</td>
<td>R knee effusion</td>
<td>Osteoarthritis</td>
<td>Synovial Fluid</td>
<td>Late</td>
<td>AMML</td>
</tr>
<tr>
<td>Case 3</td>
<td>63yo Asian Male</td>
<td>L knee effusion</td>
<td>? OA vs RA</td>
<td>Synovial Fluid</td>
<td>Late</td>
<td>CMML (relapse)</td>
</tr>
</tbody>
</table>
Types of Myeloid Leukemia in Adult Leukemic Synovitis

- **5 Cases:** All FAB types of AML (i.e. AMML, AMoL)\(^1\)
- **58 yo M:** AMML\(^2\)
- **24 yo F:** Acute biphenotypic leukemia\(^3\)
- **60 yo M:** AMML\(^4\)
- **68 yo M:** CMML\(^5\)
- **75 yo F:** MDS → AMML\(^6\)
- **76 yo M:** AMoL\(^7\)
- **27 yo F:** CML → AMML blast phase\(^8\)

\(^3\)Clin Rheumatol 2006:25;380  \(^4\)Lab Med 2003:34;717  
\(^5\)J Rheumatol 2006:33;1709  \(^6\)Rheumatol 2006:45;1143  
Types of Myeloid Leukemia in Adult Leukemic Synovitis

- 5 Cases: All FAB types of AML (i.e. AMML, AMoL)
- 58 yo M: AMML
- 24 yo F: Acute biphenotypic leukemia
- 60 yo M: AMML
- 68 yo M: CMML
- 75 yo F: MDS $\rightarrow$ AMML
- 76 yo M: AMoL
- 27 yo F: CML $\rightarrow$ AMML blast phase
- 53 yo F: MDS $\rightarrow$ AMML
- 53 yo F: AMML
- 63 yo M: CMML
Leukemic Synovitis: Etiology in Myeloid Leukemia

UNANSWERED QUESTIONS

• What is the association with monocytes?
• What role does osteoarthritis play?
Leukemic Synovitis: Etiology in Myeloid Leukemia

OSTEOARTHRITIS

- TNFα is increased by fibroblasts, synoviocytes and damaged chondrocytes

- TNFα increases synovial fibroblast production of:
  - Monocyte chemoattractant protein-1 (MCP-1)
  - IL-8 (CXCL8)
  - Hepatocyte Growth Factor (HGF)
MONOCYTE CHEMOTACTIC PROTEIN-1

- Also known as CCL2
- Part of CC chemokine family
- Found at the site of bone degradation
- Expressed by osteoclasts and osteoblasts
- Recruits monocytes to sites of injury, infection
- Effect is potentiated by other cytokines (ie, HGF)
INTERLEUKIN-8 (CXCL8)

- Also known as Granulocyte Chemotactic Factor
- A member of the CXC chemokine family
- Chemoattractant and potent angiogenic factor
- Target cells: neutrophils, macrophages, mast cells, keratinocytes, and endothelial cells
HEPATO CYTE GROWTH FACTOR (HGF)

- Paracrine cytokine secreted by mesenchymal cells
- Acts on epithelial, endothelial, and hematopoietic cells
- Traditionally thought to play a role in cartilage repair in OA
- Recently shown to facilitate osteophyte development
- Induces secretion of MCP-1 by fibroblast-like synovial cells (FLS) and chondrocytes
Fibroblasts  
Synoviocytes  
Chondrocytes

\[ \text{MCP-1/CCL2} \]
\[ \text{IL-8/CXCL8} \]
\[ \text{HGF} \]

Positive Feedback

TNF\(\alpha\)

Cause monocyte and granulocyte migration to the affected joint

↑↑

↑↑
Leukemic Synovitis: Etiology in Myeloid Leukemia

UNANSWERED QUESTIONS

• Why is leukemic synovitis rare when osteoarthritis is common?
  – Mutated receptors on leukemic cells
  – Other adhesion proteins
Summary

- Leukemic synovitis is a rare complication of leukemia, presenting early or late.
- In adults, it is associated with myeloid leukemia exhibiting a monocytic component.
- May be associated with osteoarthritis:
  - Chemokine-induced adhesion and migration.
References


References

• Tak PT. Chemokine inhibition in inflammatory arthritis. Best Practice & Research Clinical Rheumatology. 2006;20(5):929-939


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