Extramedullary precursor T-lymphoblastic transformation of CML at presentation

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Clinical History

- 30 year old man presented to the emergency room with groin pain and inguinal lymphadenopathy in October 2006
- Past medical history not significant
**PB**

- **CBC**
  - Hgb: 15.5 g/dl
  - WBC: 300 K/ul
  - Plt: 25 K/ul

- **Differential count**
  - Blasts: 7%
  - Pros: 10%
  - Myelos: 44%
  - Metas/bands: 9%
  - Segs: 20%
  - Monos -: 1%
  - Eos: 4%
  - Basos: 2%
Bone Marrow aspirate

- Hypercellular
- 8.4% blasts
- 75% maturing neutrophils with myelocyte peak
- Eosinophils
- Basophils
Markedly hypercellular bone marrow with large aggregates of blasts and myeloid hyperplasia
Lymph node biopsy
Immunostains on lymph node

- Majority of the cells positive for CD3, CD5, CD7 and CD43
- Focal positivity: Tdt, MPO and Leder’s CAE
- Ki-67 index: >95%
- CD20, Bcl-2, Bcl-6: Negative
Flow cytometry (marrow and lymph node)

- **T-cell antigens**
  - CD7, CD2, CD5, cCD3 positive
  - CD4, CD8 and surface CD3 negative

- **Myeloid antigens**
  - CD13 and CD33 (weak and partial) positive

- **B-cell antigens**
  - cCD79a positive

- **Others**
  - CD34 and Tdt (weak and partial)
Karyotype

- 46,XY,der(9)(9pter-- >9q34.1::13q12→13qter),der(13)(13pter->13q12::22q11.2->22q11.2::9q34.1- >9qter),del(22)(q11.2q11.2)
  - Interpretation: Complex rearrangement between the long arms of chromosomes 9, 22 and 13
FISH

- 21% Ph’ chromosome
- 51% Ph’ chromosome and additional small green signal
- 4% additional copy Ph’ chromosome
- 6% variant signal pattern resulting with Ph’ chromosome
- suggestive of karyotype evolution and an advanced disease state
Differential diagnosis

- CML with extramedullary pre T-lymphoblastic transformation at presentation.
- CML with granulocytic sarcoma and mixed lineage phenotype.
- Philadelphia positive T-lymphoblastic lymphoma/leukemia with early bone marrow involvement.
Final diagnosis

- Extramedullary precursor T-lymphoblastic transformation of CML at presentation
Rationale

- Leukocytosis (306 K/uL)
- Shift to left in the granulocytic series with myelocyte peak
- Eosinophilia, basophilia, monocytosis
- Hypercellular marrow, myeloid hyperplasia (M/E:7/1) with myelocyte peak
- Similar phenotype of the blasts in the lymph node and bone marrow
- Ph +
Genetic / Molecular analysis

- Complex Translocation involving Ph chromosome, with evidence of clonal evolution
  - Karyotype
  - FISH
- Retrospective PCR from lymph node
  - TCR negative
  - IgH negative
Clinical Course

- Leukapheresis and ARA-C initially
- Hyper CVAD, 6 cycles (completed March 2007), simultaneous Imatinib
- Remission
- Follow up study done in Feb 2007
  - Leukocytosis (19 k/uL) with shift to left in the neutrophilic series but no blasts.
  - Mild thrombocytosis
  - Hypercellular marrow with 2% blasts
A month later (March 07)

- Developed skin lesions
  - Likely due to Imatinib
  - Not biopsied
- Switched to Dasatinib; tolerated well
- Unrelated donor allogenic bone marrow transplant, August 2007
- Shortly after transplant found to be in blast crisis
- Unsuccessful re-induction
- Sent home on hospice Sep 15, 2007
CML and Ph positive ALL

- CML: Clonal stem cell disease affecting myeloid, monocytic, erythroid, megakaryocytic, B-cell and occasionally T-cell lineages.
- Ph positive ALL
  - 5% pediatric and 15-30% of adult ALL
  - Ph positive ALL in adults
    - Majority are of B-cell phenotype
      - Typically elderly male patients with high WBC and extensive marrow involvement
    - Only few reported cases of T-ALL
      - Young men with bulky mediastinal disease
      - Although clinical significance of this translocation in T-ALL; not known, it seems to be an indicator of poor prognosis
CML blast crisis

- Lymphoid blast transformation of CML
  - 20-30% of blast crisis of CML
  - majority of these are of B-cell origin
  - bone marrow involvement in half
  - extramedullary involvement very common (lymph node being the commonest)
Review of literature

- 3 cases of T-lymphoid blast crisis of CML
  - Rozman et al, 1991, Med clin (Brac)
- 4 cases of T-cell extramedullary blast crisis
- T-cell blast crisis of CML presenting as mediastinal mass
  - Craig et al, 2002; Hum Pathol
- Ph positive T-lymphoblastic leukemia: 2 cases
  - Ben-Bassat et al, 2005; Acta Hematol
- Biphenotypic extramedullary blast crisis as a presentation of Ph positive CML in a child
  - Bakhshi et al, 2007; Pediatr Hematol Oncol
Of the published 45 cases of T-cell blast crisis of CML

- 7/45 presented in the blast phase
  - 6 out of these 7 cases had extramedullary disease.
- In others median time for development of T-cell blast crisis was shorter than for myeloid or B-cell blast phase
T-cell blast crisis of CML (cont)

- T-lymphoid phenotype may be more aggressive
- In blast crisis additional chromosomal abnormalities are usually detected
- Prognosis grave for both Ph positive T-ALL and T-cell blast crisis of CML.
Ph positive lymphoid malignancies

- Vardiman et al; 1996; Leukemia, 10(5)
  - Used FISH to study lineage involvement in Ph positive lymphoid malignancies
  - FISH distinguished between
    - the two common molecular variants
    - identified multilineage vs lymphoblast restricted disease

- Multilineage disease was associated with morphologic features of CML at diagnosis and reversion to chronic phase after treatment

- Survival of patients with multilineage disease was longer than for lymphoblast restricted disease
Question?

- Both entities have poor prognosis so is the differentiation between T-ALL and T-cell blast crisis of CML of clinical relevance or only of academic interest?
Answer

In the targeted therapy era it may help choose

- best treatment option for ‘the specific” patient
- the optimal dose and timing of Imatinib administration, stem cell transplant and/or combination of therapeutic modalities like monoclonal antibodies