Session 1
Chronic Myelogenous Leukemia, Ph¹⁺, BCR-ABL1 +

J Vardiman, Moderator
CML, a history of “firsts”:

1845  David Craigie:

“Two cases of disease and enlargement of the spleen in which death took place by purulent material in the blood”

1852  Bennett’s series of 37 cases published as a book in 1852

“Leucocythemia”
CML – a model

Disease -> chromosome-> genes-> pathways-> designed Rx

BCR/ABL1 fusion gene

imatinib inhibitor

tyrosine kinase constitutive act.
Issues in CML

1. **Unusual presentations of CML:**
   Atypical morphology of CP, Blast phase, ?BCR-ABL+ AML, Extramedullary presentations

2. **Evolution of disease:**
   Early transformation, drug resistance due to expansion of clones with tyrosine kinase domain (TD) mutations or BCR-ABL amplification, concurrent/subsequent 2nd myeloproliferative disease associated with JAK2 mutations

3. **Fundamental origin of CML:**
   Emergence of clonal cytogenetic abnormalities in BCR-ABL negative cells during remission,

3. **Molecular variants that resemble CML**
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<tr>
<th>Case</th>
<th>Presenter</th>
<th>Institution/Location</th>
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</thead>
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<tr>
<td>750052</td>
<td>Cordelia E. Sever</td>
<td>Univ NM, Albuquerque</td>
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<tr>
<td>750137</td>
<td>Neerja Vajpayee</td>
<td>SUNY, Syracuse</td>
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<tr>
<td>750149</td>
<td>Lawrence Tsao</td>
<td>Univ NM, Albuquerque</td>
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<tr>
<td>750160</td>
<td>Nitin J. Karandikar</td>
<td>UT SWestern, Dallas</td>
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<tr>
<td>750175</td>
<td>David Viswanatha</td>
<td>Mayo, Rochester</td>
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<tr>
<td>750186</td>
<td>Karl Thiele</td>
<td>Cleveland Clinic, Cleveland</td>
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<tr>
<td>Case</td>
<td>Panel Diagnosis</td>
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<tr>
<td>750052</td>
<td>Concurrent CML and PMF in initial specimen</td>
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<tr>
<td>750137</td>
<td>Extramedullary BP, T/myeloid</td>
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<tr>
<td>750149</td>
<td>CML, Chronic Phase</td>
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<tr>
<td>750160</td>
<td>Ph(^1) negative “blast transformation” in Ph(^1) positive CML</td>
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<td>750175</td>
<td>Evolving blast phase</td>
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<tr>
<td>750186</td>
<td>CML, Chronic Phase</td>
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Case 750041 : Scott Dufresne, Univ. of Pittsburgh
9 mo old child with history osteomyelitis, presented with fever, decreased leg mobility. Biopsy of bone showed necrosis, suspicious for primary bone neoplasm. WBC=30.5K/uL with immature granulocytes, Platelets=581K/uL
Findings in 40 children with CML, BCR-ABL+

- Median Age: 12.5 yrs. (range 1-18)
- Median WBC: 242 K/uL (range 10-720)

CML, CP: 95%
CML, AP: 5%

Case 750049: Jonathan Said, UCLA

60-yr old man referred with dx of “acute leukemia”. BM biopsy was dry tap; PB showed nl WBC, but ~5% immature granulocytes

IHC: CD45+, wk/variable CD7+, CD30+, CD117+, Granzyme B+/- CD2-, ALK-, CD20-, CD99-, CD10-, CD34-, HbA-, MPO-, von Willebrands-

Flow: “blast gate” (3% of all cells): CD3+, CD13+, CD33+
Case 750049: Jonathan Said, UCLA

Contributor Diagnosis: Philadelphia chromosome positive ALCL, possibly derived from CML

Cytogenetics: near-triploid karyotype, with t(9;22)(q34;q11.2), +der (22) t(9;22)

FISH: BCR-ABL with ~40% of cells with three fusion signals and ~42% with additional BCR. No rearrangement of 2p23 locus, but trisomy 2 ~40% of cells
Case 750049: Jonathan Said, UCLA

Contributor Diagnosis: Ph¹ chromosome positive ALCL, possibly derived from CML

Some T cells may carry the BCR-ABL fusion gene in CML, CP

Reports of ALCL in CML (Leukemia 1993;7:1896, Leukemia 2003;14:169

Panel Diagnosis: CML, Blast phase, most likely myeloid (CD117, CD33, CD13, CD7)
Case 750080: Beverly P. Nelson, Northwestern University


Contributor diagnosis: CML, BP, precursor B-cell phenotype

Panel Diagnosis: CML, BP, precursor B-cell phenotype

45, XX, dic (7;16)(p13.p11.2), add(8)(q24.1), del (9p13), t(9;22)(q34;q11.2)
Case 750092: Sherif Rezk, City of Hope National Medical Center

66-yr old man presenting with multiple bone lesions, elevated serum calcium, mimicking multiple myeloma

Contributor Diagnosis: CML, BP, with megakaryoblastic component

Panel Diagnosis: CML, BP, with megakaryoblastic component

In CML, lytic lesions often represent extramedullary disease; most reported cases were blast proliferations, or predicted imminent blast transformation. *Euro J Int Med 2005;16:288-209*
Case 750095: Dahua Zhang, University of Wisconsin

40-yr old with one year history of fatigue, dyspnea found to be anemic, with splenomegaly. WBC=4.6K/uL with 19% blasts, Plt=292K/uL. Bone marrow dry tap.

Contributors Diagnosis: CML with myelofibrosis in myeloid blast phase

Panel Diagnosis: CML with myelofibrosis in myeloid blast phase

CD61

MPO
Case 750216: Richard L McMasters, US Labs

26-yr old man with 4-yr hx of CML, treated with imatinib who was in complete hematologic and morphologic remission, cytogenetic remission by FISH, who presented with neurologic symptoms

Contributor’s diagnosis: CML, extramedullary blast phase (myeloid)

Panel Diagnosis: CML, extramedullary blast phase (myeloid)

Leis, et al. Leuk Lymphoma 2004;45:695:

-5/24 pts with CML, BP (2 LBP, 2 MBP, 2 MxBP) had isolated CNS relapse

-Relapse occurred in spite of PB/BM remission

-Imatinib levels in CSF were two logs lower than in blood, suggesting imatinib does not penetrate blood brain barrier
Case 750157: John Frater, Washington University
Case 750120: Sergey Popov, Wayne State University

750157: 58-yr old woman presented with splenomegaly and WBC=205K/uL with predominantly myeloid phenotype with CD19 expression; relapse in 9 mos with predominantly B lymphoid phenotype with partial CD13.

Contributors Dx: Acute leukemia, consistent with CML, BP

750120: 16-yr old young man presented with WBC=206K/uL. Two populations of blasts, one with myeloid phenotype (MPO+, CD13, CD33, CD117, TDT) and one with lymphoid (CD19+, CD79a+, CD10+, CD22+/-, but with weak CD13, CD33).

Contributor’s Dx: Bilineal acute leukemia, myeloid and B lymphoid, arising from Ph+ CML, not previously detected
Acute myeloid Leukemia, BCR-ABL+

- Less than 1% of all cases of AML
- Difficult to distinguish from CML, BP
  
  Higher WBC/blast count, less maturation in granulocytes
  
  Lack of CML, CP or AP after therapy
  
  Lack of clinical and lab features of CML, such as splenomegaly, basophilia
  
  Lack of additional cytogenetic abnormalities that characterize CML, BP
  
  Return to normal cytogenetics after therapy

- In one recent study (Soupir et al, Am J Clin Pathol 2007;127;642)
  
  Less commonly manifests splenomegaly
  
  Lacks significant blood or basophilia

  Major cytogenetic abnormalities of CML, BC (+Ph, +8, etc) less common

- Mixed phenotype (true biphenotypic/bilineal) acute leukemia with BCR-ABL1 should be considered as a possibly unique entity
Case 750157: John Frater, Washington University

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Contributor’s Dx: Bilineal acute leukemia, myeloid and B lymphoid, arising from Ph+ CML, not previously detected

Panel Diagnosis: Mixed lineage leukemia
Case 75022: Karl S. Thiel, Cleveland Clinic

63-year old man evaluated for leukocytosis (69K/uL) and leukoerythroblastosis, occ teardrop RBCs. No hepatosplenomegaly. Cytogenetics: 46,XY, t(9;22)(q34;q11.2){4}/46, idem, add(20)(p13){16}

Contributors Diagnosis: CML, AP with myelofibrosis

Panel Diagnosis: CML, AP with myelofibrosis
70-yr old woman with CML, CP dx 6/97, treated with IFN and ara-C with cytogenetic remission through 1/00. Switched to imatinib 7/04 for evidence of clonal evolution/AP, then, after BP, to dasatinib, then BP, then nilotinib.

### Correlation of Molecular and Genetic Changes with Therapy Shifts.

<table>
<thead>
<tr>
<th>#</th>
<th>Date</th>
<th>Therapy</th>
<th>BM blasts (%)</th>
<th>qPCR % bcr-abl/abl</th>
<th>ABL KD mutation (codons 200-500)</th>
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<tr>
<td>(1)</td>
<td>9/00</td>
<td>IFN for 38m</td>
<td>0</td>
<td>91%</td>
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<tr>
<td>(2)</td>
<td>7/04</td>
<td>imatinib 43m</td>
<td>3</td>
<td>&gt;100%</td>
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<tr>
<td>(3)</td>
<td>2/05</td>
<td>dasatinib 3m</td>
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<tr>
<td>(4)</td>
<td>12/05</td>
<td>nilotinib 8m</td>
<td>4</td>
<td>75.1%</td>
<td>T315I - 3%</td>
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<tr>
<td>(5)</td>
<td>2/06</td>
<td>nilotinib 11m</td>
<td>15</td>
<td>94.3%</td>
<td>T315I - 100%</td>
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<tr>
<td>(6)</td>
<td>6/06</td>
<td>MK-0457 4m</td>
<td>12</td>
<td>6.4%</td>
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</table>
1. At diagnosis of CML, CP: BM cytogenetics, circulating Bcr-Abl transcript numbers (RQ-PCR). If BM cannot be obtained, FISH is a secondary method that can be used.

2. After treatment, if responding, RQ-PCR q3mos, BM cytogenetics q6 mos

3. After complete cytogenetic remission, RQ-PCR q3mos, if stable, BM cytogenetics may be reduced to q12 mos

4. Mutation analysis should be done when there is rising levels of Bcr-Abl transcripts, failure to achieve MMR, inadequate / loss of response, those presenting in advance phase. 

Case 750211: Dennis P O’Malley

60-yr old with weakness, fatigue, splenomegaly. Blood showed leukocytosis with “left shift”, increased basophils. Marrow aspirate showed increased granulocytes, eosinophils, dwarf megakaryocytes.

Cytogenetics: t(9;17;22)(p24;p11.1;q11.2)

Contributor’s postulated dx: variant of the t(9;22)(p24;q11.2)
Case 750211: Dennis P O’Malley

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Contributor’s postulated dx: variant of the t(9;22)(p24;q11.2)


- A BCR-JAK2 fusion gene as the result of (9;22)(p24;q11.2) translocation in a patient with clinically typical chronic myeloid leukemia
- Decr LAP, eosinophilia, basophilia, dwarf megakaryocytes
- Not responsive to imatinib
Case 750211: Shi Ping Jiang, US Labs

57 year old man with CML which initially showed a variant translocation, t(5;9;22)(q35;q34;q11.2). After imatinib, re-evaluation showed two cell lines: one with the initial abnormality, plus one with t(11;22) involving the q arms of both chromosomes, resulting in an apparent Ph chromosome.

After FISH analysis, in the cell line with the 5;9;22, the BCR-ABL fusion signal appeared on chromosome 11. In the t(11;22) cell line, the BCR probe was on chr 11, not 22.

It is likely that the patient has a consitutional t(11;22), and the BCR/ABL occurred between chromosome 9 and the derivative 11.
WHO Classification of Myeloid Neoplasms (2008)

1. Myeloproliferative Neoplasms
2. Myeloid Neoplasms with Eosinophilia and rearrangements of PDGFRα, PDGFRβ and FGFR1
3. Myelodysplastic/Myeloproliferative Neoplasms
4. Myelodysplastic Syndromes
5. Acute myeloid leukemia
Case 750166: Richard McMasters, US Labs

79 yr old with SOB, mild splenomegaly. WBC=105K/uL, with mature/immature neutrophils, 4% eos.

Karyotype: 46, XY, t(4;22)(q12;q11.2), Presumptive BCR-PDGFRA

Contributor’s Diagnosis: CMPD with t(4;22)(q12;a11.2)

Panel Diagnosis: Myeloid neoplasm with eosinophilia and presumed PDGFRA rearrangement.
Case 750134: Rebecca McClure, Mayo Clinic

69-yr old with 13 year hx of platelets >1000K/uL, nl WBC, controlled with anagrelide. More recently during follow-up, a leukoerythroblastic blood smear noted. WBC=12.8K/uL, Plts= 250K/uL.

Molecular analysis: JAK2 V617F positive, 98% mutated alleles

FISH: BCR/ABL fusion signals (0.8% in 500 nuclei)

Contributors Dx: CMPD, not otherwise specified, JAK2 V617+, BCR-ABL+

Panel Ds: Agree, ?BCR-ABL+
Issues in CML

1. Unusual presentations of CML:
   Atypical morphology of CP, Blast phase, ?BCR-ABL+ AML, Extramedullary presentations

2. Evolution of disease:
   Early transformation, drug resistance due to expansion of clones with tyrosine kinase domain (TD) mutations or BCR-ABL amplification, concurrent/subsequent 2nd myeloproliferative disease associated with JAK2 mutations

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