Leukemia: Genealogy of Pathology Practice: Old Diseases – New Expectations

Henry Moon Lecture: UCSF Annual Conference
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Disclosure:
• Nothing to disclose

How to get from to and Avoid becoming

Objectives/Outline
1. Appreciate key milestones in the evaluation of leukemias
2. Define optimal strategies for leukemia diagnosis and prognosis prediction
3. Define the changing role of pathologists
Revisions:
1. Check popins on slide 2
2. Move slides 9&10 on pg 2 to page 1 after slide 3
3. delete slide 7 popins
4. add new slide "Who was right", with popins, after slide 10
5. rename slide 22 "Case"
6. Delete titles on images slides 23 &24
7. Add text to legend on slide 24
8. Change title and delete text on slide 25
9. Add slide titled "Diagnosis?"
10. Add slide titled "CML in Stable Phase"
11. Revise original slide 31
12. Add text to legend of original slide 33
13. Add slide titled "Diagnosis?"
14. Add slide titled "Myeloid Neoplasms"
15. Delete original slide #41
16. Update original slide #56
17. Delete original slide #62
18. Change title on original slide #66 (Now last slide)

Check slide numbers, font,pop-ins, and color of all slides
Submit: 2.25.13

3.1.13 Revisions

Slide #9 Remove text
Slide #11 Check popins - good
Slide #26 Remove text and center remaining text
Slide #28 Add "L1" in italics
Slide #36 remove letter "C"

Total number of slides 69

Send electronically to KF 3.1.13

REVISIONS:
UCSF requirements:
add disclosure to 2nd slide
re-checked numbering
rc: 3.8.13
Raquel R. Calderon, 3/8/2013

Slide 2

RC2
Raquel R. Calderon, 3/8/2013
Milestones in CML

- **1845** First description of CML (Virchow, Bennett)
- **1960** Philadelphia chromosome reported by conventional cytogenetics in pt. with CML (Nowell, Hungerford)
- **1973** Exchange of genetic material between chromosomes 9 and 22 in CML (Rowley)
- **1982-85** BCR-ABL1 fusion gene and protein in CML (Baltimore, Witte, others)
- **1987-1998** STI-571 targeted therapy and clinical trials
- **2001** Imatinib FDA-approved

**Autopsy**

Gross Exam:

- Earliest diagnostic tool in leukemia diagnosis

  E.g. Blood thick like gruel; massive enlargement of spleen and liver
Clinico-Pathologic Correlation

Blood: Buffy Coat
CML: WBC > 900,000

Who was right?
A. Bennett - infection
B. Virchow - leukemia
C. Neither
D. Both
Acute myeloid leukemia

Morphology/Cytochemistry

Philadelphia Chromosome

1960

Ph\(^{1}\): first cytogenetic abnormal linked to neoplasm (1960)

Karyotype from 1976

Rowley, 1973

t(9;22) (q34;q11.2)

Nowell and Hungerford

Ph\(^{1}\) first cytogenetic abnormal linked to neoplasm (1960)

1973

Courtesy J. Anastasi
1980's; different groups

David Baltimore, 1980's Courtesy J. Anastasi

Ph^1: reciprocal translocation
BCR-ABL1 fusion gene
1982-1985

Translocation results in constitutive tyrosine kinase activity \(\rightarrow\) CML

Leukemogenic Effects of Constitutive Non-Receptor Tyrosine Kinase Activation


Therapy to Block Tyrosine Kinase Activity (1987-1998)

CML Disease Course: Pre-Imatinib

Chronic phase 3-7 years

Accelerated phase < 2 years

Blast phase < 1 year

- Disease progression inevitable (rare exceptions)
- Linked to additional cytogenetic

CML: Impact of Imatinib

- High rates of complete cytogenetic remission (95% in patients with stable phase CML; estimated > 50% 10-yr survival)
- Improved progression-free survival
- All patients achieving major molecular response alive at 5 years
- Imatinib-resistance more common in patients in accelerated phase at presentation (additional mutations)
- Imatinib not curative

Blast-Phase in CML: 1983-present


Case

55-yr-old female swimmer with new onset fatigue

CBC: WBC 349.000
Cytogenetics

Karyotype:
46,XX,t(9;22)(q34;q11.2)[20]

Diagnosis?

A. CML in stable phase
B. CML in accelerated phase
C. CML in blast phase
CML in Stable Phase

- Complete cytogenetic response to imatinib
- Ongoing therapy with regular quantitative BCR-ABL1 assessment

CML: Accelerated Phase

32-year-old female with splenomegaly and leukocytosis (negative history)

CBC: WBC 24,300, Hgb 8.4, Hct 28%, Plt 701,000

CML:AP 10% blasts, 20% basos, anemia

CML:AP blast, baso, mega fragment, anemia
**CML: Accelerated Phase**

- Increase in blasts (< 20%)
- Cytopenias/dysplasia
- Increase in basophils
- Additional cytogenetic abnormalities
- Imatinib resistance

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**New Approach to Myeloproliferative Neoplasms**

*1st breakthrough:*

Delineation of mechanism of *BCR-ABL1*-related leukemias

1st step: CML vs “non-CML”

Rx: Imatinib for *BCR-ABL1*-related disease
**New Approach to MPN**

*2nd breakthrough:*

Identification of activating (gain of function) mutation of JAK2 resulting in constitutive tyrosine kinase activity in majority of other MPN (PV, ET, PMF)

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**JAK 2 Mutations in MPN**

- **Acquired point mutation** in *JAK2* (9p) results in constitutive cytoplasmic tyrosine kinase activity, conferring to HP precursor cells:
  - growth factor independence
  - other proliferative/survival advantages
- **V617F** (phenylalanine substituted for valine from G→T transversion)
- > 80% PV, > 50% ET, > 50% CIMF (PMF)

Sources: *Nature, Cancer Cell, NEJM, Lancet 2005*

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**Why Does Excess, Unregulated Cell Production Occur?**

**CML**

Ph<sup>1</sup> t(9;22) results in BCR-ABL1 fusion gene with constitutive tyrosine kinase activity

**Other MPN**

Point mutation in regulatory region of JAK2 results in constitutive tyrosine kinase activity
74 yr-old female
Hgb 17
Hct 51%
Plt 950,000

**Erythrocytosis, thrombocytosis, JAK2**

74 yr-old female
Hgb 17
Hct 51%
Plt 950,000

**BM aspirate: ↑ cell, ↑ megakaryocytes**

74 yr-old female
Hgb 17
Hct 51%
Plt 950,000

**BM biopsy: ↑ meg, dilated sinuses, EMH**

**Diagnosis?**

A. Essential thrombocythemia
B. Polycythemia vera
C. Cellular phase of primary myelofibrosis
**Essential Thrombocythemia**

- BM: hyperlobulated megas; Bld: ↑↑ plts

**Myeloid Neoplasms**

- > 50 categories
- Blast percentage
- Many other features
- MDS, MPN, MDS/MPN, AML

**Comparison of blood features**

- MDS
- MPN
- AML

**Comparison of bone marrow features**

- MDS
- CML
- AML
Established Techniques HP Dx

- Morphology (cytochemical stains)
- Immunohistochemistry (>100 antibodies)
- Flow cytometric IP

All are complementary and somewhat overlapping modalities to determine lineage and stage of maturation.

AML: Morphologic and IP Subclassifications

- Pathologists very good at applying criteria
- Morphologic subclassification does not predict outcome (Exception - APL)
AML: Morphologic Classification

AML: Cytogenetic Prognostic Groups

Favorable: t(8;21), t(15;17), inv(16), t(16;16), other

Intermediate: Normal karyotype, +8, -4, +6

Poor: -5/del(5q), -7/del(7q), t(11q23), other, complex karyotype (≥ 3 abnormalities)

AML: Overall Survival by Karyotype

Molecular Genetic Testing

- Highly relevant **prognostic** information
- Determination of clonality
- Progressive integration into **primary** diagnosis
- Potential to replace “established” diagnostic techniques
### AML Classification: Biologic Groups

<table>
<thead>
<tr>
<th></th>
<th>2001</th>
<th>2008</th>
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</thead>
<tbody>
<tr>
<td>AML with recurrent genetic abnormalities</td>
<td>4 types</td>
<td>9 types</td>
</tr>
<tr>
<td></td>
<td>t(1;22), NPM1, CEBPA, inv(3), t(6;9)</td>
<td></td>
</tr>
<tr>
<td>AML with MDS-related changes</td>
<td>AML after MDS</td>
<td>AML after MDS, MDS/MPN</td>
</tr>
<tr>
<td></td>
<td>AML with multi. dysplasia</td>
<td>AML with MDS karyotypes</td>
</tr>
<tr>
<td>Therapy-related AML</td>
<td>Alkylating Agent, Topo II inhibitor</td>
<td>T-AML, MDS, MPN, T-AML with balanced tx</td>
</tr>
</tbody>
</table>

### AML: Overall Survival

![AML: Overall Survival](image)

Source: Grimwade, *Hematology 2009*

### AML: Class I and Class II Mutations

**Class I Mutations** (Proliferation)
- FLT3
- KIT
- RAS
- PTPN11

**Class II Mutations** (Impaired differentiation)
- PML-RARA
- RUNX1-RUNX1T1
- CBFB-MYH11
- MLL fusions

Signal-transduction pathways and classification of mutations in MDS and AML.
Prognostic Relevance of Integrated Genetic Profiling in Acute Myeloid Leukemia

Jay P. Patel, Mithat Gürün, Ph.D., Maria E. Figueroa, M.D., Hugo Fernandez, M.D., Zhusuo Sun, Ph.D., Janis Racuievski, Ph.D., Pieter Van Vlierberge, Ph.D., Igor Dolgalev, B.S., Sabrena Thomas, B.S., Olga Aminova, B.S., Ketty Huberman, B.S., Janice Cheng, B.S., Agnes Viola, Ph.D., Nicholas D. Socci, Ph.D., Adriana Heguy, Ph.D., Athena Chen, Ph.D., Gail Vance, M.D., Rodney R. Higgins, Ph.D., Rhet P. Ketterling, M.D., Robert E. Gallagher, M.D., Mani Lizow, M.D., Marcel R.M. van den Brink, M.D., Ph.D., Hillaard M. Lazarus, M.D., Jacob M. Rowe, M.D., Selina Luger, M.D., Adolfo Ferrari, M.D., Ph.D., Elizabeth Paletta, Ph.D., Martin S. Tallman, M.D., Ari Melnick, M.D., Omar Abdel-Wahab, M.D., and Ross L. Levine, M.D.


400 cases; patients <60 massive parallel sequencing


A Revised Risk Stratification

<table>
<thead>
<tr>
<th>Cytogenetic Classification</th>
<th>Mutations</th>
<th>Overall Risk Profile</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favorable</td>
<td>Any</td>
<td>Favorable</td>
</tr>
<tr>
<td>Normal karyotype</td>
<td>Wild-type ASXL1, MLL-PTD, PHF6, and TET2</td>
<td>Intermediate</td>
</tr>
<tr>
<td>Intermediate-risk cytogeo-</td>
<td>Mutant TET2, MLL-PTD, ASXL1, or trisomy 8-negative</td>
<td>Unfavorable</td>
</tr>
<tr>
<td>Unfavorable</td>
<td>Any</td>
<td></td>
</tr>
</tbody>
</table>
Therapy-Related Leukemia‡:

**Extrinsic events:** Type of therapy, combination therapy (with radiation), total dosage, dosing regimen (genotoxic stress)

**Intrinsic events:** Patient’s genetic makeup; genes involved in DNA repair, genes involved in drug metabolism


Role Change

- Dramatic change in the role of the pathologist
- **Old days:** Confirm diagnosis of advanced disease
- **Current:** Predict development of disease, early detection, identify minimal residual disease, predict response to specific therapy, predict risk of drug toxicity
- **Still:** Maintain Morph/IP skillset

New Focus on Prediction

Profile of polymorphisms of drug-metabolising enzymes and the risk of therapy-related leukaemia


**Practice Changes**

- More rapid implementation of more complex technology into “routine” practice
- Whole new array of diagnostic pitfalls, more rigid specimen requirements, more splitting up (subspecialization) of diagnostic work-up

**New Challenges**

- Stay “state of the art” but be “evidence-based”
- Pathology must take the lead in test selection and development, reporting, and integration
- Pathologist must be leaders in cost-effective testing strategies
- A higher level of expertise will be required for routine practice