RAEB-2 Transforming to Acute Erythroleukemia

Case # 165

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Clinical History and Presentation

- 82 yo male
- Status 4 months post diagnosis of MDS/RAEB-1
- Treated with Dacogen
- Now presents with:
  - Pancytopenia
  - Worsening fatigue for 2-3 days
Progression with increase of immature erythroids
Myeloblast counts remained stable.
Increased numbers and change in the scatter profile of erythroids

7/5/06

10/9/06
Increase in CD36+, Glycophorin A+ Erythroids

7/5/06

10/9/06
Initial Diagnosis 07/2006

- **BMBx 7/5/06:**
  Markedly hypercellular marrow with multilineage dysplasia, left shift of erythroids and myeloids and excess blasts

**COMMENT:** Overall findings are c/w MDS/RAEB-1

**Differential Count and Flow cytometry:**
- ~7% myeloblasts, dyserythropoiesis and dysgranulopoiesis
Current Diagnosis 10/2006

- **BMBx 10/9/06:**
  Refractory anemia with excess blasts-2 *(RAEB-2)*

**COMMENT:** The erythroid series is markedly increased (~60%) and is predominantly immature. Myeloblasts represent ~5-7% of total, and thus less than 20% of the non-erythroid cells. *Findings are insufficient for the diagnosis of Erythroleukemia*

- **Differential Count and Flow cytometry:**
  - ~5-7% myeloblasts
  - Erythroids account for ~59% of cells

- Iron stores are markedly increased, >15% ringed sideroblasts
**Cytogenetics**

**Karyotype:**
Abnormal highly unstable male karyotype exhibiting multiple aberrations, including deletion of 5q, and trisomies of 1, 6, 11, 14, 15, and 22, consistent with MDS/AML

**FISH studies:** 5q- and 7q-
Is This Case Best Classified as RAEB-2?

- Following WHO strict criteria, the diagnosis is RAEB-2
- Criteria do not take into account:
  - Cytogenetic findings (complex karyotype with or without clonal evolution)
  - The maturation pattern of the erythroid population (i.e. pronormoblast/erythroid ratio)
  - Clinical presentation (acute exacerbation, pancytopenia)
- Bone marrow in RAEB is usually hypocellular, whereas in erythroleukemia it is hypercellular
- Evolution in this case predominantly in the erythroid lineage, while myeloblast percentage relatively stable
RAEB, RAEB-t and AML-M6: Spectrum of Disease?

- RAEB usually follows a progressive course with cytopenias and bone marrow failure
- 25% of RAEB-1 and 33% of RAEB-2 progress to AML
- Erythroleukemia preceded by MDS in 40% of cases
- Multilineage dysplasia is present in 70% of erythroleukemia cases
- Ddx between MDS with excess of erythroblasts and AML-M6 often difficult due to overlapping features (including cytogenetic findings like -5/5q- and -7/7q-)


“Erythrocyte-Predominant MDS”

- 20 yr retrospective study to identify cases with >50% erythrocytic component and <30% blasts (FAB exclusion)
- Multiple variables including myeloblasts and pronormoblast counts were analyzed
- Survival endpoint

RESULTS:
- Considered alone, increasing % myeloblasts and/or % pronormoblasts were significant predictors of decreasing survival.
- Multivariate analysis: Strongest predictor: % Pronormoblasts
  Other: age, IPSS cytopenias, Platelet count, % erythroids

Mazella FM et al Am J of Hematol 2006;81:484-491
Acute Erythroleukemia
Significance of Pronormoblasts

Subdivision of acute erythroleukemia:
- M6a (Myeloblast-predominant)
- M6b (Pronormoblast-predominant)
- M6c (Mixed Myeloblast/Pronormoblast)

Several studies: Survival endpoint
- M6b and M6c decreased survival compared to M6a
  

- M6b worst survival, M6c intermediate, M6a best
  
  Chemotherapeutic remission in M6a and M6c, but not M6b
  M6c in remission significantly shorter than M6a
  Rapid decline with increasing pronormoblasts and decreasing myeloblasts

Hypothesis

- This case illustrates a diagnostic “grey-zone”
- Are the current criteria limiting?
- Do current criteria affect early treatment of some patients?
- This patient should be regarded/managed as AML? (Many centers treat RAEB-2 as evolving AML due to overlap of diagnostic features)
- Can we improve upon current criteria by adding other variables/parameters, especially number of pronormoblasts and/or pronormoblast/erythroid ratio?
- Are new chemotherapeutic regimens necessary for subgroups of patients with increased pronormoblasts?
Giovanni Di Guglielmo

- 1930’s first describes “chronic erythroleukemia”, a “progressive systemic disease of primitive erythrocytic cells, characterized by increasing numbers of cells of all stages of the red cell series and diminishing numbers of the white cell series”
- Disorder was dysplastic in nature and invariably terminated in the death of the patient