Case 036

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An 85-year-old female presented, in October 2001, with joint pains and was found to have positive ANA test and absolute lymphocytosis.

**October 2001**

- Absolute lymphocyte count (ALC): 6300/µL
- Hemoglobin: 13.6 G/DL
- Hematocrit: 39.1%
- Platelet count: 300,000/µL
Peripheral Blood Film (2001)
FLOW CYTOMETRIC ANALYSIS OF PERIPHERAL BLOOD (2001)

Absolute CD4 count = 792/µL (Reference range: 430-1760/µL)

CD19+, CD5+, CD20+, CD22+(mod), CD23+, Surface λ+

CD22+ PE, CD19 PE, CD19 PE, CD19 PE, CD19 PE, CD19 PE
Diagnosis

B-Chronic Lymphocytic Leukemia (B-CLL)
Clinical History

June 2003

- Coombs’ negative, mild, normocytic-normochromic anemia
- Managed with Erythropoietin (EPO) and blood transfusions

January 2004

- Normocytic-normochromic anemia worsened.
- Absolute lymphocyte count (ALC) started decreasing.
- Bone marrow aspiration and biopsy were done.
Bone Marrow Aspirate (2004)

CD19+, CD5+, CD20+, CD22+(mod), CD23+, Surface λ+, CD38+(50%)

Absolute CD4 count = 366/µL (Reference range: 430-1760/µL)
Normal 5

Deleted 5

del(5)(q13;q33)
Diagnosis

B-CLL, atypical morphology
5q- Syndrome
Clinical History and Second Marrow

January 2004-January 2007

- EPO and increased frequency of PRBC transfusions till March ’06.
- Worsening of anemia in March 2006
- Higher degree of dysplasia, CLL, and reticulin fibrosis in marrow.

5-azacytidine started in March ’06 and failed in July ’06.
Thalidomide given from August ’06 thru January ’07
Flow Cytometric Analysis of the Bone Marrow (2006)

Absolute CD4 count = 960/µL (Reference range: 430-1760/µL)

CD19+, CD5+, CD20+, CD22+(mod), CD23+, Surface λ+, CD38+(80%), FMC7+

Absolute CD4 count = 960/µL (Reference range: 430-1760/µL)
FISH (October 2006) of interphase cell nuclei with a CLL-specific comprehensive probe set

Arrow indicates cells with trisomy 12

30/200 cells with round nuclei

12cent (D12Z3), 12q15 (MDM2)
FISH (November 2006 )
of interphase cell nuclei with a MDS-specific comprehensive probe set

5p15.2 (D5S630), 5q31 (EGR1)

66/200 cells with reniform nuclei

Cell indicates deletion of EGR1
What are These Cells with Reniform Nuclei?

Reactive lymphocytes, a few monocytes and a few metamyelocytes

100 cells with reniform nuclei

Ratio of reactive lymphocytes : monocytes: metamyelocytes = 92:6:2
Diagnosis

B-CLL, atypical with Trisomy 12
5q- Syndrome
Clinical Course

- OCT '01
- JUN '03
- AUG '04
- MAR '06
- JUN '07
- SEP '07

**ALC drops; Dx of 5q- made**

- JAN '04
- JUN '04

**5-Azacytidine started**

- NO Chemo

- Thalidomide started

- Thalidomide stopped

- Revlimid started

- No Chemo

- JAN '07
- APR '07
Minimally Deleted Regions in Chromosome 5q Deletions

- IL-4
- IL-9 (5q31.1)
- EGR-1 *(5q31.2)
- D5S413 (5q32)
- GLRA1 *(5q33.1)

MDS, t-MDS, AML, and t-AML involving 5q deletions

5q- Syndrome

* EARLY GROWTH RESPONSE FACTOR 1
* GLYCINE RECEPTOR, ALPHA-1 SUBUNIT
Three Important Events

- Diagnosis of B-CLL (October 2001)
- Diagnosis of 5q- syndrome (January 2004)
- Diagnosis of trisomy 12 (November 2006)
What Happened Before October 2001?

? Genetic event in a hematopoietic stem cell

HSC → Mutated HSC → B-CLL clone
What Happened in January 2004?

Acquired mutation in a lympho-myeloid hematopoietic stem cell

LMHSC

LMHSC with 5q-

B-lymphoid Line

T-lymphoid Line

Erythroid Line

Myeloid Line

Megakaryocytic Line

Loss of IL-4 gene
What Happened Between Jan’04 & Nov ‘06?

CLL cell

Trisomy 12

CLL cell with Trisomy 12

B-CLL clone with trisomy 12
What did del(5q) do to the CLL?

- Del(5q) in T-cells
  - Loss of IL4 gene in T-cells
    - Increased apoptosis CLL cells
      - B-CLL disease regression

What did trisomy 12 do to the CLL?

- Acquisition of Trisomy 12
  - Increased HDM2 expression
    - Increased proteasome-mediated p53 destruction
      - Decreased apoptosis of CLL lymphocytes
        - No progression of CLL
          - CLL disease progression

IL-4 producing and secreting cells in B-CLL
1. CLL cells
2. Th2 cells
3. Th2-like cells
Myelodysplastic Syndrome due to isolated del(5q)

Cytokine imbalance

Increased apoptosis of progenitors & their progeny

Myelodysplastic Syndrome
Summary

Hypothesis

Does the acquisition of 5q minus abnormality, with its resultant loss of IL-4 gene in Th2 cells and Th2-like suppressor cells, prevent progressive disease in a B-CLL patient even in the presence of trisomy 12?
5q- Syndrome and B-CLL (Two Diseases in One Patient)

“This town ain’t big enough for the two of us.”


References


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