Leukemia

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Short Communication Open Access

# Molecular Twist of an Innocent Leukocytosis: "Dream or Dread" for a Clinician

**Debalina Das**[1], **Elizabeth Arze**[2], **Elnora Spradling**[1], **Chad King**[2], **Devapiran Jaishankar**[1] **and Kanishka Chakraborty**[1*]

[1]*Department of Internal Medicine, Quillen College of Medicine, East Tennessee State University, USA*

[2]*Department of Pathology, Quillen College of Medicine, East Tennessee State University, USA*

[*]**Corresponding author:** Kanishka Chakraborty, Assistant Professor, East Tennessee State University-Quillen, College of Medicine, Internal Medicine, JOHNSON CITY, Tennessee 37604, USA, Tel: 4232326979; E-mail: chakrabk@etsu.edu

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A reactive etiology is the most commonly considered differential diagnosis for mild chronic leukocytosis. With the advancement of molecular techniques in hematology the balance between temptation of finding a 'needle in hay stack' and cost effectiveness of diagnostic tests are becoming a professional challenge. But at the same note presence of pertinent clinical findings may dictate keeping a low threshold to explore an apparent minor abnormality more comprehensively. This judgment call is art of practicing 21st century clinical medicine. Here we discuss unfolding of clinical events leading to diagnosis of sub-clinical presence of two different hematological malignancies in a patient.

A 62 year old female presented with complaints of bone pain and worsening fatigue. Past history of breast cancer, left mastectomy followed by five years of adjuvant tamoxifen, cardiac dysrhythmia requiring ablation, hypertension, obesity, tobacco abuse and recent development of mild leukocytosis and erythrocytosis noted. Family history was negative for malignancy. Patient did not have fever, chill, night sweats, and loss of weight or appetite. Physical examination was unremarkable with normal vitals, no adenopathy or hepato-splenomegaly and absent focal bony tenderness. Labs showed mild leukocytosis of 10.3 k/uL and elevated hemoglobin to 16.5 g/dl. Peripheral blood smear (PBS) was unremarkable except rare immature monocytes and lymphocytes. Erythropoietin level was 8mU/ml. Reactive leukocytosis and erythrocytosis due to smoking was high on the list of differential diagnoses. But considering patient's age, worsening fatigue, bone pain and especially PBS findings, molecular testing for bcr/abl (9:22) translocation and JAK2 mutation were requested to exclude possibility of early myelo-proliferative disorder (MPD). RT-PCR for bcr/abl translocation was positive (0.114%). Bone marrow biopsy confirmed molecular presence of bcr/abl translocation but no morphologic evidence of chronic myeloid leukemia (CML). Interestingly enough FISH was negative too for bcr/abl translocation and in focal areas morphology was consistent with monoclonal B cell lymphocytosis or pre-B-CLL (chronic lymphocytic leukemia). Peripheral blood Flow Cytometry confirmed expression of CD5, CD19, CD20, CD23 but no early myeloid markers. Radiological imaging excluded presence of adenopathy and myeloidsarcoma. There is little in the medical literature reporting the co-presence of CML-CLL in the same patient. Moreover in our patient both these entities were diagnosed in their sub-clinical/molecular stage. Morphological absence of disease precluded the need for treatment. Patient was followed with clinical and laboratory surveillance (Figures 1 and 2).

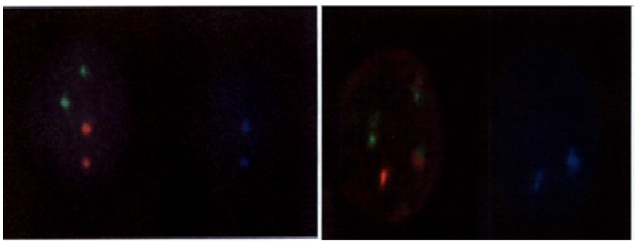

**Figure 1:** Negative FISH for BCR/ABL, Positive FISH for BCR/ABL

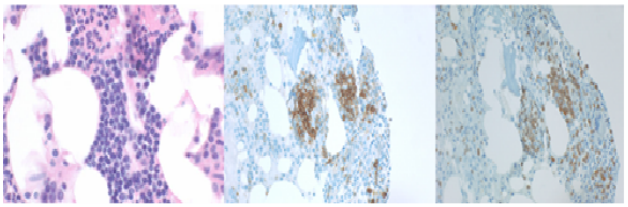

**Figure 2:** Interstitial lymphoid infiltrate with positive CD20 and CD79 stain

CML a myeloproliferative disorder and CLL a lymphoproliferative abnormality are distinctly different in their pathogenesis and prognosis. Case reports documenting co-presence of CML-CLL or development of second neoplasia after initial diagnosis of CML or CLL are available. But molecular/sub-clinical CML and CLL at diagnosis without a past history of hematological malignancy are non-existent in the current medical literature. The presence of a single abnormal pluripotent stem cell leading to leukemic proliferation of both myeloid and lymphoid series is tantalizing possibility. The molecular presence of bcr/abl translocation without morphologic and cytogenetic evidence of CML is not well studied and understood. Literature in this regard is sparse. Biernaux et al reported presence of BCR/ABL transcripts in healthy individuals for the first time [1]. This translocation can be found in blood cells of 30% healthy individuals. Probability of acquiring these non-consequential translocations go up with age as incidence in pediatric population is very rare. Only small group of individuals will develop CML as fusion gene most likely are present in differentiated cell lines not in self-renewing leukemic stem cells. It will require comprehensive population based data collection to analyse the incidence of molecular CML in the population and profile the risk of progression to overt CML.

It also raises question regarding cost-effectiveness of these molecular diagnostic techniques when implication of result cannot be prognostically quantified due to lack of evidence based data. On the other hand these tests could be life saving for many other patients by unveiling a sub clinical fatal disease process. Chromosomal abnormalities are important diagnostic tools to diagnose and monitor both myeloid and lymphoid leukemias. Presence of various disease defining translocations like t(9:22), t(14:18), t(2:5) and MLL duplications in normal individuals have been reported in clinical literatures sparsely [2]. Data is now available to risk stratify chance of progression from monoclonal gammopathy of undetermined significance to myeloma and even monoclonal B-cell lymphocytosis to CLL. But implication of mere molecular presence of bcr/abl translocation without morphological and cytogenetic evidence of CML is not well studied and understood. Literatures on this regard are very not comprehensive at all. Before this becomes 'PSA' (Prostate Specific Antigen) of hematology world likely it needs more comprehensive population based data to conclusively analyze risk of a molecular disease transforming into a true CML.

## References

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