



## A Case Report of two Chronic Myeloid Leukemia Patients in Chronic Phase Exhibiting IgVH Gene Rearrangement

Authors

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### Abstract

*In CML-CP, 90% of patients present with ph chromosome as sole genetic abnormality in neoplastic cells. Among the additional cytogenetic abnormalities, loss of Y chromosome, trisomy 8, trisomy 19, other single chromosome/gene abnormalities and complex abnormalities with double ACAs were found in that order. Abnormalities involving 14q32 has not been found in literature describing CML-CP, and in limited number of studies have been shown to be exclusively found in lymphoid blast crisis. We are presenting two cases of Chronic myeloid leukemia here, who presented to us with IgVH rearrangement along with ph+ chromosome, and are in chronic phase without any haematological or molecular indication of progressive disease.*

Chronic myeloid leukemia (CML) is a myeloproliferative disorder associated with the Philadelphia chromosome, develops as a tri-phasic disease, leading to a fatal, acute leukemia like condition if left untreated. The disease develops in three clinical stages, namely: Chronic phase (CP), accelerated phase (AP), and blast crisis (BC). The evolution of CML-CP to CML-BC is characterized by growth factor-independent proliferation and differentiation arrest<sup>(1,2)</sup>. In most cases the t (9;22) or its variant is the sole chromosomal anomaly in the CP of the disease but in the course of the disease to the BC phase, 60- 80% additional genetic changes are observed (3). Most of the secondary genetic abnormalities are +ph, i(17q), +8,+19,t(3;21)(q26;q22), t(7;11)(p15;p15), and molecular abnormalities

include p53, p16/ARF mutations, deletion of Rb and RAS mutations<sup>(4)</sup>.

The immunoglobulin heavy chain variable locus is located in chr14q32 and encodes for the variable region of immunoglobulin heavy chain in antigen-activated B cells of germinal center. It is subject to somatic hyper mutation (SHM) which creates variants with selective affinity to antigens<sup>(5,6)</sup>. SHM is not restricted to IGHV but has also been found in other GC B cell genes like BCL6, CD79a. Rearrangements of the IGH and TCR delta alleles have been shown to be useful clonal markers in lymph proliferative disorders of B lymphoid and T lymphoid lineages<sup>(7)</sup>, but are not found in myeloproliferative disorders. Ndikung in 2006 showed that extensive and deregulated activity of lymphoid specific gene- rearrangement

and mutation carry the risk of secondary genetic aberrations in MPDs like CML likely contributing to progression of disease. He further showed TCR and IGVH gene rearrangements/deletions in 26% of patients with lymphoid blast crisis. Later on, such mutations were studied on large scale of patients with accelerated and blastic phase of CML. Deletions of Immunoglobulin heavy chain and T cell receptor gene regions were found to be uniquely associated with lymphoid blast transformation of chronic myeloid leukemia<sup>(8)</sup>. Subsequently Galimberti and co. evaluated the role of IgH rearrangement in MRD detection of CML-BC.

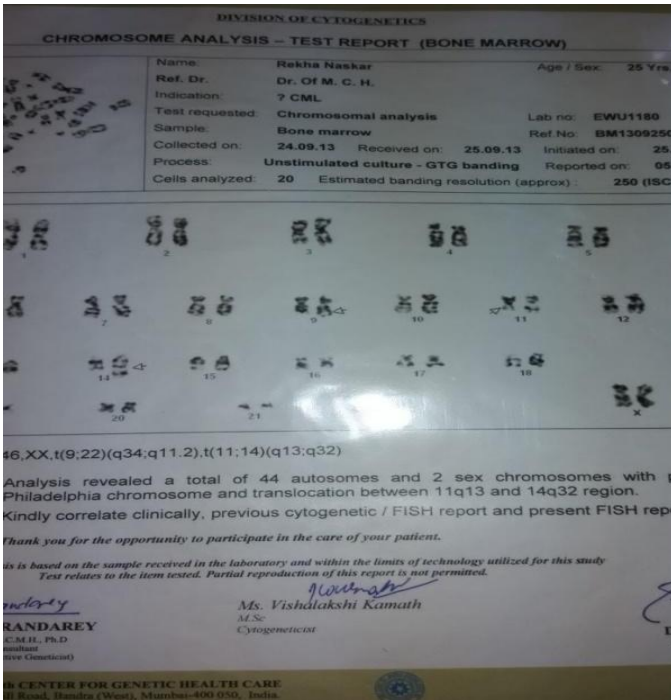
In CML-CP, 90% of patients present with ph chromosome as sole genetic abnormality in neoplastic cells. Among the additional cytogenetic abnormalities, loss of Y chromosome, trisomy 8, trisomy 19, other single chromosome/gene abnormalities and complex abnormalities with double ACAs were found in that order<sup>(9)</sup>. Abnormalities involving 14q32 has not been found in literature describing CML-CP.

We are presenting two cases of Chronic myeloid leukemia here, who presented to us with IgVH rearrangement along with ph+ chromosome, and are in chronic phase without any haematological or molecular indication of progressive disease.

### 1. RN, 25yr/Female

She presented to us in Sept, 2013 with symptoms of moderate anemia and massive hepatosplenomegaly. On evaluation, she had palpable spleen of 16cms, Liver of 6cms. PBS showed granulocytic hyperleukocytosis with left shift, basophilia(14%), normal platelet count (3.25L/cumm) and circulating blasts(2%). She was high risk in EUTOS and Sokal index. Bone marrow aspiration and biopsy showed normoblastic erythropoiesis, adequate number of megakaryocytes with many hypolobated forms, no dysplasia in any lineages, markedly accelerated granulopoiesis, 1/3 myelofibrosis and 5% blasts. Pending Cytogenetics report, she was initially

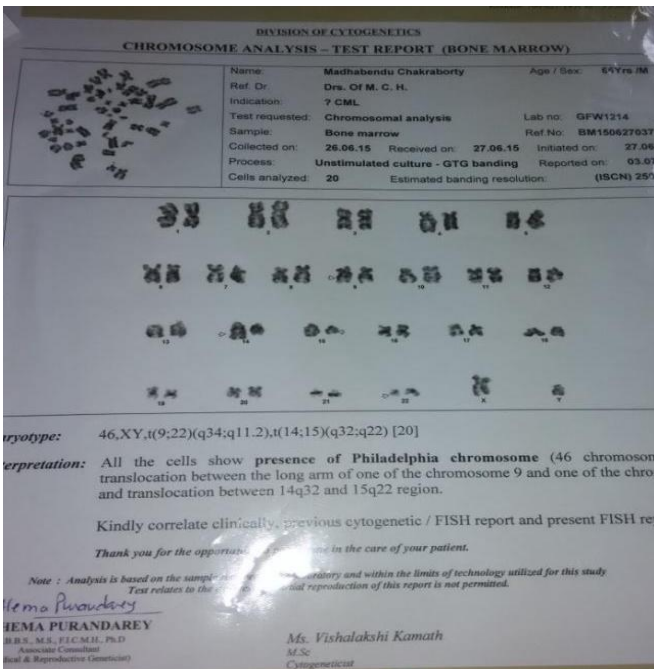
treated with Hydroxyurea for 2 weeks, and then started on Imatinib mesylate at 400mg/day from 14<sup>th</sup> Oct, 2013. Karyotyping from bone marrow aspirate showed **46,XX,t(9;22)(q34;q11.2), t(11;14)(q13;q32)**. Apart from an initial recurrent, grade3 thrombocytopenia, for which therapy was put on hold for 2 weeks in 1<sup>st</sup> 60days, there has not been any significant side effects' warranting treatment discontinuation, change or dose modifications. At 6months, she had a BCR-ABL transcript level of 4.87% indicating warning molecular response. She was continued on Imatinib 400mg/day. She defaulted the response assessment scheduled at 12months. In January, 2015, she developed frequent episodes of diarrhoea, which was relieved temporarily with anti-secretory drugs. Quantitative assessment of BCR-ABL1 was done by PCR at 18months of therapy on 25/03/15, which showed a transcript level of 3.7% indicating treatment failure. At the same time, she also had developed Gr3 bilateral pedal edema, thrombocytopenia (42000/cumm) and severe anemia (Hb-6.4%) for which 2 units of packed cells were transfused. There was however no palpable spleen or liver. TKI was put on hold for 1month and after symptomatic improvement, was cancelled for a repeat bone marrow examination including cytogenetic study and TKI domain mutation analysis. Pending financial ability for above investigations, she was put on Imatinib 600mg/day and planned to increase to 800mg/day if she tolerates. She was last seen on 25/07/15 and she is continuing on Imatinib at 600mg/d. Her last hemogram showed Hb-8.8gm%, TLC-4000/cumm, Platelet-68000/cumm, and DC of N-43%, L-51%. She was afebrile, doesn't have loss of weight, no bleeding manifestations and also have no evidence of organomegaly.



routine blood examination showed moderate anemia with leucocytosis. He was referred to us in June,2015 when he presented to us with a spleen of 8cm, liver-4cm, TLC-21,400/cumm with 5%basophils, 8% eosinophil and no circulating blasts, Hb of 9.4gm% which was normocytic normochromic and platelet of 90,000/cumm. A bone marrow examination was carried out on 23/06/15, and biopsy was suggestive of CML-CP. Qualitative BCR-ABL1 by PCR was positive. He was started on Imatinib 400mg/day from 1/07/15. His cytogenetics by conventional karyotyping of bone marrow aspirate was found to be **46,XY,t(9;22)(q34;q11.2),t(14;15)(q32;q22)** in all the 20 metaphases examined. 1<sup>st</sup> follow up was done 10days after, when his peripheral blood picture was almost normalized. Subsequent follow ups were done fortnightly. Complete hematologic response was recorded on 25/07/15. Apart from a mild imatinib induced facial and pedal edema, there have not been any significant side effects. His glycemic profile and hypertension are under control. He was last seen on 4<sup>th</sup> September, when his hemogram was Hb-9.8gm%, TLC-7700/cumm, Platelet-1.79L/cumm with no basophils and immature granulocytes. Spleen was not palpable and there were no constitutional symptoms attributable to disease.

**Discussion**

Among 450 patients of CML-CP currently under our follow up, we found this unique chromosomal abnormality involving 14q32 in the above two patients. Case1 developed imatinib failure after 18moths of therapy, but she has not shown progression of disease and currently is awaiting 2<sup>nd</sup> generation TKI therapy. It is to be seen whether like some other additional cytogenetic abnormalities, 14q32 rearrangement too behaves in an adverse way with frontline Imatinib therapy<sup>(9)</sup>. For that we will need analysis of some more patients with CML-CP. It is too early to comment on disease response to TKI for Case2 who is yet to undergo 1<sup>st</sup> molecular assessment, but he has



**2. MC, 66Y/M**

This gentleman from Barasat locality in the outskirts of Kolkata has been having type2 Diabetes Mellitus hypertension for more than 15years. He suffered a hypertensive ICH in right parieto occipital region last year, which was managed conservatively. Since March this year, he has been experiencing a growing lump in left upper quadrant, and progressive fatigability. Evaluation revealed a splenomegaly of 8cms. And

indicated good responsiveness by achieving CHR in 1<sup>st</sup> month of therapy. Unlike data showing this abnormality as fore binger of lymphoid blast crisis, our both patients have been in chronic phase.

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