

Simultaneous occurrence of CML and CLL: A Rare Presentation

Abstract:

Chronic lymphocytic leukemia (CLL) and chronic myeloid leukemia (CML) are amongst the commonest forms of leukemia seen in adult population. Both of these chronic leukemias have different lineage of origin and have rarely been reported to be present simultaneously in one patient. Here we report a rare case where both CML and CLL were diagnosed at the same time and discuss management of this rare clinical scenario.

Introduction

AIM:

CLL is an indolent lymphoproliferative condition arising from accumulation of CD5 positive monoclonal B-cells. It is associated with some degree of immune failure and patients are predisposed to second primary malignancies including richter's transformation to high grade lymphoma, solid organ tumors like carcinoma of breast, prostate and secondary haematological malignancies, most commonly therapy related acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS).¹ Whereas, CML is a myeloproliferative neoplasm which develops when a pluripotent hematopoietic stem cell acquires Philadelphia chromosome that carries the *BCR-ABL1* (break cluster region – Abelson gene) fusion gene, allowing Ph+ clone a survival advantage gradually replacing the normal hematopoiesis. The usual clinical course of CML progresses through a chronic phase, an accelerated phase and a blast crisis. Simultaneous occurrence of CLL-a lymphoproliferative disorder and CML-a myeloproliferative disorder in the same patient is a rare case scenario despite both being common individually. This coexistence has only been reported occasionally,²⁻¹¹ with most cases presenting with CML during the evolutionary course of CLL. In the latter cases, the potential leukemogenic effect of the therapy employed and the increased risk of a secondary neoplasms associated with CLL have been thought as possible mechanisms in explaining the sequence of events. However, these explanations do not apply where these two chronic neoplasms occur simultaneously without any prior history of one. It may be coincidental or may be considered to have originated from a unique stem cell capable of differentiating into two different cell lineages. Molecular studies are needed to ascertain the origin of cells.¹⁰ Here we present an interesting case with simultaneous occurrence of both diseases with CLL being quiescent on presentation while the treatment of CML was initiated. Over the period of time as haematological response was achieved for CML, CLL took the front seat and presented with lymphocytosis and thrombocytopenia requiring treatment.

Case Report:

A 68 year old male farmer, with no comorbidities presented in November 2021 with complains of generalised weakness and abdominal discomfort. Physical examination showed gross splenomegaly. CBC showed Hb-10.6 g/dl , WBC-1,60,110 cells/cumm and platelet count of 2,86,000/ul with 2% blast cells, 13% myelocyte , 7% meta myelocyte, 9% Band cells, 28% polymorph, 25% Lymphocytes, 6% monocytes , 3% eosinophils, 7% basophils. LDH-647 U/L. Bone marrow aspiration was done on 25/11/21 which suggested myelo-poly peak (60%) with peripheral eosinophilia and basophilia with 17% lymphocytes with few smudge cells. Diagnosis was given as CML-CP with subclinical CLL. Trepine biopsy was suggestive of proliferation of granulocytic precursors with increase in eosinophils with grade II fibrosis (WHO 2016). FISH t(9;22) showed 64% cells variant positive for BCR-ABL fusion. Cytogenetic analysis showed abnormal chromosomal complements in all metaphases and presence of Philadelphia chromosome. Patient was started on Imatinib Mesylate 400mg OD and kept on follow-up for CLL. Following were his follow up CBCs:

Table 1: Pathological test report

Time	Haemoglobin (gm/dl)	WBC (cells/cumm)	Platelet (/ul)	Polymorph (%)	Lymphocyte (%)	Others (%)
March 2022 (3 months)	12	32890	318000	40	50	2% myelocyte, 2% basophils , 2% eosinophils and 4% monocytes
June 2022 (6 months)	13.9	31660	253000	29	64	4% monocytes and 3% eosinophils.
September 2022 (9 months)	13.4	30580	103000	22	70	8% monocytes
December 2022 (12 months)	12.4	37650	44000	15	80	3% monocytes and 3% eosinophils.
January 2023 (13 months)	12	33800	37000	12	88	none

Bone marrow aspiration was done again which suggested hypercellular marrow with 44 % lymphocytes with abundant smudge cells suggestive of controlled CML activity and persistent CLL. Repeat FISH t(9;22): negative for BCR-ABL fusion. Cytogenetic analysis showed normal chromosome complements in all metaphases. Immunophenotyping of bone marrow done on FACS Canto Eight color flow cytometer suggested CD200-99% moderate positive, CD79b: 45% dim positive, CD-20: 70% moderate positive, CD 43: 98% moderate positive, Kappa-87% moderate positive, CD 23: 76% moderate positive, CD 5 : 99% moderate positive, FMC7 – 0% negative, CD10: 0% negative, Lambda: 0% negative

suggestive of B-cell CLL. RT-PCR for M-BCR-ABL suggested M-BCR-ABL/ C-ABL Ratio : 0.5952. Anemia work up and direct and indirect coomb's test was negative. Diagnosis of RAI stage IV and Binet C B-CLL concurrent with CML with complete cytogenetic response was made. CECT suggested above and below diaphragm lymphadenopathy with spleen-15cm and liver-18cm. Anti-Hb core antibody was tested negative. Taking into consideration of pharmacokinetic interactions, overlapping side effects and finances, patient was started on Chlorambucil with rituximab along with continuation of imatinib with informed consent. He tolerated first cycle well with improving CBC post 1 week of treatment with HB-11.9, TLC-34220/cumm with 89% lymphocytes and 74000/uL platelet count.

Discussion:

A similar case of CLL and CML co-existence was reported from our institute in 2018¹¹ where CLL was diagnosed 48 months after diagnosis of CML. Unlike our present case, that patient was kept on observation for CLL as no indications for treatment were present.

In literature, several cases have been reported where CML was diagnosed after CLL or vice-versa¹⁵⁻²⁰. However, to the best of our knowledge, simultaneous occurrence of CML and CLL has been seen in only 9 cases. Ours is the next in row.

Following are the case reports where CLL and CML were diagnosed simultaneously :

Table 2: Literature resources of different treatments

Authors	Age	Gender	Treatment received
Leoni F, et al (5)	55	Male	-
Browett et al. (6)	69	Male	-
Maher VE, et al (8)	69	Male	Chlorambucil, Hydroxyurea
Crescenzi B, et al (16)	64	Male	Hydroxyurea
Vilpo JA, et al (3)	58	Male	Busulphan
Esteve J et al (10)	71	Female	Hydroxyurea
Mansat-De Mas F et al. (17)	68	Male	Hydroxyurea , interferon-alpha
Katovic et al. (18)	55	Male	-
Rahman K et al. (19)	57	Male	Imatinib
Present Case	68	Male	Imatinib , Chlorambucil, Rituximab

An informative data was published by Bhagavathi et al.¹² who presented a case series of simultaneous CLL and CML occurrence. In most of the cases CLL preceded the diagnosis of CML (10 cases), synchronous presence of the two malignancies was seen in 6 cases, and merely in two cases CLL was diagnosed after initial diagnosis of CML. Overall, male predominance was seen. The time lapse between diagnosis of the secondary neoplasm ranged between 2 and 84 months. Most CML patients were reported from pre-imatinib era and hence, were treated with chemotherapeutic agents (such as interferon, hydroxyurea and

busulphan). Only one case was treated with imatinib ¹². Few of the CLL patients were also treated with chlorambucil, fludarabine, vincristine, or radiotherapy.

Chemotherapeutic drugs might have played the confounding factors that would have contributed to the development of secondary neoplasm. Evaluating the pathogenesis in this group of patients might be misleading then.

Very few cases in literature were seen where simultaneous treatment for both CLL and CML was needed. In most of the cases, either CLL was treated prior to the diagnosis of CML or there was no indication for treating CLL and hence it was kept under observation. However in our case, patient was initially kept on observation for CLL while treatment for CML with Imatinib was begun. Eventually in a year, patient developed thrombocytopenia and increased absolute lymphocyte counts needing treatment for the same. Extensive literature review was done but only one case was found from Imatinib-era, reported by Przespolewski ER et al.²⁰ where patient was treated for both CLL and CML simultaneously with venetoclax with imatinib. Due to resource constraint, venetoclax could not be offered to our patient. Looking into pharmacokinetic interactions and overlapping toxicity profile, patient was started on rituximab with chlorambucil while continuing imatinib . He has received first cycle and has tolerated well. Thrombocytopenia has improved 1 week post therapy and patient is doing well.

Conclusion:

Reporting two cases from same institute, it is an attempt to contribute to the existing scarce data of the two chronic leukemias occurring concurrently. Treatment of both conditions simultaneously is not well studied . We look forward to study the toxicity profile, tolerance and results of the given regimen and establish a treatment of such cases in future.

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