


Occurrence of a Clonal T-Cell Population in a Case of Chronic Myelomonocytic Leukemia

Anupama Patil¹ , Balasaheb Wanve², Pradeep Kar¹ and Shanthy Velusamy¹

¹Department of Pathology, SRL Diagnostics, Fortis Hospital, Bengaluru, Karnataka, India.

²Department of Hemato-Oncology, Fortis Hospital, Bengaluru, Karnataka, India.

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ABSTRACT: Chronic myelo-monocytic leukemia (CMML) is an aggressive myeloid neoplasm with some features of a myelodysplastic syndrome (MDS) and others of a myeloproliferative neoplasm (MPN). Rarely, patients with CMML have a co-existing lympho-proliferative disorder (LPD). In most cases, the lymphoid neoplasm is diagnosed first, and the CMML is considered to be a secondary therapy-induced form of leukemia. We report herein a unique case of de-novo CMML, with an underlying clonal T-cell population and describe its clinical presentation and laboratory findings. A 70-year old male presented with a 3-month history of cough, dyspnea, abdominal distension, and low-grade fever. Physical and radiological examination revealed hepatosplenomegaly but no lymphadenopathy. Peripheral blood had absolute monocytosis with marrow showing CMML with 10% blasts along with dysplasia in myeloid and erythroid lineages. Flow cytometry indicated possibility of chronic myelomonocytic leukemia with 13% monocytic cells along with an additional clonal population of gamma/delta T cells (15%) with aberrant immunophenotype. Polymerase chain reaction (PCR) analysis was positive for clonal T-cell rearrangement. A diagnosis of CMML with an underlying clonal T-CLPD was made. The synchronous occurrence of CMML and T-cell neoplasm may be attributed to a genetic mutation common to both. Currently, there are no treatment guidelines for group of patients; hence individualized therapeutic strategies should be implemented to enable symptomatic improvement and provide optimum care.

KEYWORDS: chronic myelomonocytic leukemia, T-cell leukemia, myelodysplastic syndromes, multiparametric flow cytometry

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CORRESPONDING AUTHOR: Anupama Patil, Department of Pathology, SRL Diagnostics, Fortis Hospital, 154/9, Opp IIM-B, Bannerghatta Road, Bengaluru, Karnataka 560076, India. Email: itsagp@gmail.com

Introduction

Chronic myelo-monocytic leukemia (CMML) is an aggressive myeloid neoplasm with some features of a myelodysplastic syndrome (MDS) and others of a myeloproliferative neoplasm (MPN).^{1,2} According to 2016 iteration of the WHO Classification of hemato-lymphoid neoplasms, a diagnosis of CMML requires the following criteria: (i) the presence of persistent peripheral blood monocytosis (monocyte count $\geq 1 \times 10^9/L$); (ii) Negative for *BCR-ABL1* fusion gene; (iii) No rearrangement of *PDGFRA*, *PDGFRB*, and *FGFR1*; (iv) Blasts constituting $\leq 20\%$ of differential in peripheral blood and bone marrow; (v) Dysplasia involving 1 or more myeloid lineages.^{3,4}

Owing to its heterogeneous clinical presentation and overlapping clinico-pathological features with MDS, diagnosis of CMML can be a challenging process. Very rarely, patients with CMML have a co-existing lympho-proliferative disorder (LPD).⁵⁻¹⁰ In most cases, the lymphoid neoplasm is diagnosed first, and the CMML is considered to be a secondary therapy-induced form of leukemia.¹¹⁻¹⁵ We report herein a unique case of de-novo CMML, with an underlying clonal T-cell population and describe its clinical presentation and laboratory findings.

Case Summary

A 70-year old male presented with a 3-month history of cough, dyspnea, abdominal distension and low-grade fever. There was no history of prior exposure to ionizing radiation or cytotoxic

agents; nor any family history of leukemia. Physical examination revealed abdominal distension with palpable splenomegaly 5 cm below costal margin and mild hepatomegaly, but no palpable lymphadenopathy. On admission, complete blood count showed hemoglobin (Hb) 10.1 g/dL, red blood cell (RBC) 3.36 million/ μL , hematocrit (Hct) 32.2%, platelets (PLT) $35 \times 10^3/\mu L$, white blood cells (WBC) $26.3 \times 10^3/\mu L$ with 65% neutrophils, 11% lymphocytes ($2.89 \times 10^3/\mu L$), and 24% monocytes ($6.3 \times 10^3/\mu L$). Marrow aspirate smear showed medium to large blast cells (10%), having scanty agranular cytoplasm and nuclei showing fine chromatin. In addition, increased number of mature monocytoid cells (12%) was present and 5% lymphoid cells were noted. Myeloid and erythroid series showed dyspoietic changes. Bone marrow trephine biopsy examination revealed normocellular marrow spaces with infiltration of few histiocytic cells having vesicular chromatin and abundant cytoplasm. Immunohistochemistry (IHC) performed on trephine biopsy block with CD68 highlighting monocytic-macrophage lineage cells (25%) and CD56 positivity in around 10% of the cells. CD34 was negative.

Flow cytometry performed on the bone marrow sample indicated possibility of chronic myelo-monocytic leukemia with 13% cells showing phenotypic features of monocytes (positive for CD4, CD16, CD13, CD3, HLADR, CD64, and CD36; 43% of gated monocytes showed CD16 expression). In addition, a population of gamma/delta T cells (15%) was noted with aberrant immunophenotype (CD3+, CD7+, CD5-,



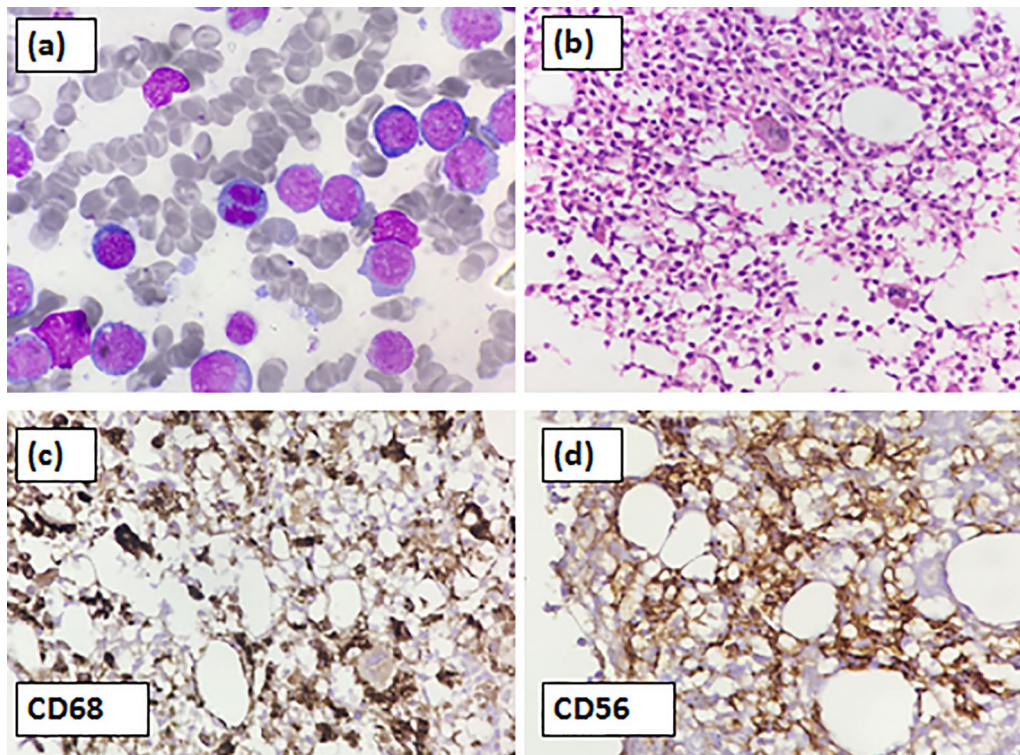


Figure 1. Photomicrographs of the bone marrow aspirate (a) and bone marrow trephine biopsy (b, Haematoxylin and eosin, $\times 400$) showing monocytosis and dyspoietic changes. Immunohistochemistry shows positive staining of marrow monocytes for CD68 (c) and positive staining of T-cells for CD56 (d).

CD4-, CD8-, dim CD16+, and CD56+), positive for TCR-gamma/delta and negative for TCR-alpha/beta. Chromosome analysis revealed an apparently normal male karyotype in all the metaphases analyzed with no structural or numerical abnormalities. Cytogenetic study for deletion of 7q31 locus was negative. Mutation panel for MPNs was negative (*BCR/ABL*, *JAK2V617F*, *JAK2 EXON12*, *CALR*, and *MPL*). Polymerase chain reaction (PCR) analysis was positive for clonal T-cell rearrangement. An extensive work-up including bacterial/fungal cultures, viral serology, and autoimmune panels ruled out secondary causes. Further, the possibility of hepatosplenic T-cell lymphoma (HSTL) was considered as a differential, but the characteristic intrasinusoidal distribution of neoplastic cells seen in HSTL was not evident on the bone marrow trephine biopsy sections. Likewise, T-cell large granular lymphocytic leukemia (T-LGLL) was yet another consideration. But the lymphocytes morphology on peripheral smear was found to be unremarkable. Further work-up for accurate classification of the clonal T-cell population was not possible owing to the deteriorating clinical condition of the patient. Hence, in correlation with clinico-pathological, flow cytometric, and molecular findings, a diagnosis of a diagnosis of CMML with an underlying clonal T-cell lympho-proliferative disorder (T-CLPD) was made. The patient was started on hydroxyurea; however, within 10 days of presentation, patient passed away due to pulmonary complications.

We hereby certify that all appropriate written consent forms were obtained from patient. Case reports or case series do not require ethics approval at our institution.

Discussion

The combination of CMML and lymphoma is rare.¹⁶ However, a polyclonal hypergammaglobulinemia is commonly recorded, possibly indicative of the elevated levels of inflammatory cytokines.^{17,18} Although few studies have reported concurrent MDS and clonal T-cell proliferations, there is a paucity of data on the association of CMML (MDS/MPN) with T-CLPD. To our knowledge, there have been only 4 such cases reported in the literature.^{5,6,8,9} In most patients of CMML with a co-existing LPD, the lymphoid neoplasm is detected first and the CMML is considered to be a secondary therapy-induced form of leukemia; in others, CMML is first diagnosed and later, a lymphoid neoplasm is detected during follow up.^{6,7,12,19,20} But, in some patients, similar to our patient, both malignancies are recognized simultaneously and there is no history of exposure to carcinogenic agents.

The underlying pathogenic mechanism of multiple hemt-lymphoid neoplasms occurring together is not clear. A plausible theory is the instability of a common precursor stem cell or a precursor cells of lymphocytes and monocytes.^{19,21,22} Recent studies have described cases with clonal hematopoiesis-type mutations as factors of common origin of lymphoid and myeloid

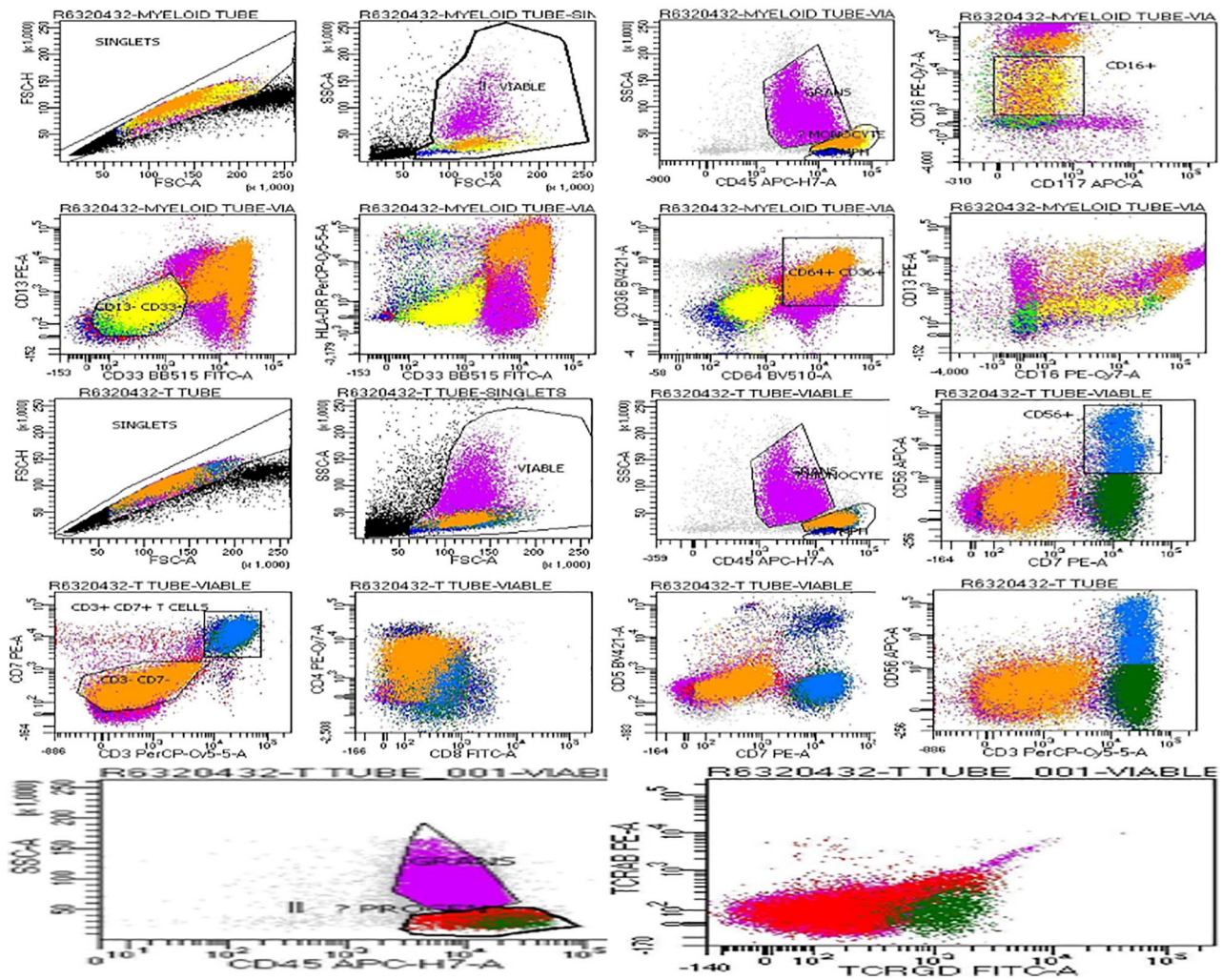


Figure 2. Flow cytometric immunophenotyping showing 2 sub-populations (monocytes which are CD64+, CD36+, and T-cells which are CD3+, CD7+, CD56+, and TCR-gamma/delta+).

neoplasms.^{23,24} Other evidence has suggested that immune dysregulation induced by expanded cytotoxic T-cell clones may result in immune dysregulation, which ultimately manifests as intrinsic stem cell defect causing suppression of normal hematopoiesis, characteristic of MDS/MPN type disorders.²⁵⁻²⁸ Further, it is interesting to note that loss of *TET2* can be detected in both myeloid and lymphoid malignancies²⁹ and *TET2* inactivating mutations are the most frequently detected somatic mutations in CMML,³⁰⁻³² indicative of a mutation occurring in a hematopoietic progenitor cell and the tumor suppressor nature of *TET2* in both these malignancies. Additional genetic studies on this mutation may aid in identifying a potential diagnostic bio-marker or a therapeutic target. Currently, there are no treatment guidelines for this group of patients; hence, individualized therapeutic strategies should be implemented to enable symptomatic improvement and provide optimum care.

Conclusion

This rare case demonstrates the possibility of developing concurrent T-CLPDs and CMML in the same patient and physicians managing patients with MDS/MPN should be

aware of this possibility. A detailed diagnostic workup should be conducted efficiently to initiate supportive therapy expediently. Currently, there are no treatment guidelines and further large scale studies are needed to formulate standard management guidelines for this group of patients. As of now, for these patients, individualized therapeutic strategies should be implemented to enable symptomatic improvement and provide optimum care. (Figure 1 and 2).

ORCID iD

Anupama Patil  <https://orcid.org/0000-0002-9611-1869>

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