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Case report: Co-existing chronic myeloid leukemia and chronic myelomonocytic leukemia–A clinically important but challenging scenario

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ABSTRACT

Chronic myeloid leukemia (CML) and chronic myelomonocytic leukemia (CMML) are two common myeloid neoplasms with overlapping morphologic features. We report a patient initially diagnosed with CML and treated with Tyrosine kinase inhibitor (TKI) but who then developed persistent monocytosis and worsening thrombocytopenia one year later. Repeat bone marrow biopsies only showed CML at the molecular level. However, markedly hypercellular bone marrow, megakaryocytic dysplasia, and *SRSF2, TET2*, and *RUNX1* mutations by NextGen sequencing pointed to a diagnosis of CMML. For CML patients with persistent monocytosis and cytopenia, a mutational profile by NGS is helpful to exclude or identify the coexisting CMML.

1. Introduction

Chronic myeloid leukemia (CML) is a myeloproliferative neoplasm driven by t(9;22) *BCR/ABL1* fusion, and patients typically present with granulocytosis and no evidence of dysplasia. Tyrosine kinase inhibitor (TKI, including first-generation imatinib; second-generation nilotinib, dasatinib, and bosutinib; and third-generation ponatinib) has been the mainstream therapy for the past two decades [1–4]. The 10-year overall survival has exceeded 80% for patients in the chronic phase CML [5,6].

Chronic myelomonocytic leukemia (CMML) is another myeloid neoplasm with both myelodysplastic and myeloproliferative features (persistent monocytosis >3 months with a level above 950/μL and >= 10% of white blood cells, WBC). A subset of CMML (15%) has the potential to progress into acute myeloid leukemia within 3 to 5 years [7]. The diagnosis of CMML requires a FISH or PCR study for BCR/ABL to exclude CML [5] and other myeloid neoplasms based on the World Health Organization (WHO) classification. Of note, some cases of CML, especially those with the *BCR/ABL1* p190 variant, often resemble CMML due to the associated marked monocytosis [8].

Progression from CML to CMML has rarely been reported [9]. Secondary myeloid neoplasm after CML treatment is rare but could also occur. Detection of a second myeloid neoplasm is essential for managing these CML patients because a treatment strategy other than TKI, such as a hypomethylation agent or transplant, might be necessary.

This report presents a CML patient with either coexisting or secondary CMML, which is clinically significant and challenging to identify.

2. Case presentation

We present a 66-year-old male patient with a past medical history of atrial fibrillation, including ablation in 2010 and 2011. He developed leukocytosis (WBC of 43.8 k/uL) and thrombocytopenia (platelet count of 107 k/uL) in April 2020. A bone marrow biopsy showed markedly hypercellular marrow (100% cellularity) with granulocytic hyperplasia and atypical small hypolobated megakaryocytes (Fig. 1). Blasts were not increased. At that time, the monocytes accounted for 6% of the white blood cells and 2628/uL in absolute number. A FISH study performed on the peripheral blood was positive for BCR/ABL1 rearrangement in 91% of the cells. Bone marrow karyotyping also detected the Philadelphia (Ph) chromosome in all 20 metaphases examined: 46,XY,t(9;22)(q34;q11.2)[20]. BCR/ABL major p210 was positive. There was no p190 transcript detected. NextGen sequencing was not performed at that time. He was diagnosed with chronic myeloid leukemia, chronic phase, and was started on imatinib 400 mg daily on 5/13/2020.

Although his WBC count was significantly reduced, he developed worsening thrombocytopenia and persistent monocytosis in June 2021. A repeat bone marrow biopsy in November 2021 showed hypercellular marrow (80%) with maturing trilineage hematopoiesis, monocytosis, and no increase in blasts. Monocytes accounted for 34% of the white blood cells with an absolute count of 1.34 k/uL. A FISH study was negative for the BCR-ABL1 translocation, and cytogenetics revealed a normal male karyotype. *BCR-ABL1* p210 was detected at 0.039% IS, suggesting low-level or residual CML. A next-generation sequencing

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(NGS) study performed on the marrow showed the following mutations: *SRSF2* P95H (VAF 50.6%), *TET2* C1289Y (VAF 44%), and *TET2* Q769 (VAF 49.1). Imatinib treatment was reduced to 300 mg daily due to severe thrombocytopenia on 12/17/2021.

The patient presented at our institution in January 2022 for a second opinion concerning persistent monocytosis. Monocytes accounted for 29% of the white blood cells with an absolute count of 1.47 k/uL. Flow cytometry for the peripheral blood monocyte subset showed increased CD14+/CD16- classical monocytes (99.48%) (Fig. 2A). A repeat bone marrow biopsy in February 2022 showed hypercellular marrow (70%) with left-shifted myelomonocytic hyperplasia, occasional small hypolobated megakaryocytes, and no increase in blasts (Fig. 2B-D). A FISH study for the *BCR/ABL1* translocation and MDS was negative. The karyotype was also normal (46,XY[20]). The P210 form of BCR-ABL1 was detected at 0.0347% IS, suggesting a low level of CML. An NGS myeloid mutational panel showed the following mutations: *SRSF2* P95H (VAF 44.6%), *RUNX1* L161P (VAF 35.7%), *TET2* C1289Y (VAF 40%), and *TET2* Q769 (VAF 41.5%). We diagnosed CMML, in addition to residual CML, due to persistent monocytosis, increased MO1 monocytes by flow cytometry, megakaryocytic dysplasia, and the characteristic NGS molecular profile. The patient received treatment with hypomethylating agents and was referred to the transplant team for a possible allogeneic stem cell transplant.

3. Discussion

CML and CMML are common myeloid neoplasms and can coexist in the same patient. They can both present with agranulocytosis and monocytosis, making it necessary to exclude one or the other during the initial diagnosis. The P190 variant of CML often resembles CMML and has marked monocytosis [8]. CML has no morphologic dysplasia and has BCR/ABL1 rearrangement, while CMML shows morphologic dysplasia and no BCR/ABL rearrangement. In one study, 54% of patients with peripheral blood basophils $>0.40 \times 10^9$ /L were CML, while CMML only accounted for 4.2% of cases with that level of basophilia [5]. Therefore, a high basophil count might hint at CML instead of CMML.

In the new 2022 5th WHO classification [10], the disease phases of CML include chronic phase (CP) and blast phase (BP) only. The accelerated phase (AP) was omitted mainly due to a change in the risk of disease progression with TKI therapy and careful disease monitoring. The new classification emphasizes the high-risk features associated with CP progression to BP, including resistance stemming from ABL1 kinase mutations and/or additional cytogenetic abnormalities. Atypical CML (aCML) is renamed MDS/MPN with neutrophilia. This change underscores the MDS/MPN nature of the disease and avoids potential confusion with CML. The diagnostic criterion for this disease is unchanged. However, there are significant changes made to the CMML diagnostic criteria, which now include prerequisite and supporting criteria. The cutoff for absolute monocytosis is lowered from 1.0 × 109/L to 0.5 × 109/L. Abnormal partitioning of peripheral blood monocyte subsets is also introduced as a new supporting criterion. In addition, the blast-based subgroup of CMML-0 has been eliminated due to evidence that its addition provides limited prognostic significance.

In 2022, experts developed the International Consensus Classification (ICC) of myeloid neoplasms and acute leukemias [11]. CML is still defined as a three-phase disease in this classification: CP, AP, and BP. The ICC dropped BCR-ABL1 negative from aCML's name. In addition, ICC acknowledges that in aCML, eosinophils should account for <10% of the WBC, as hypereosinophilia is incompatible with this diagnosis. Like the WHO, the ICC also eliminated the CMML-0 subgroup due to its

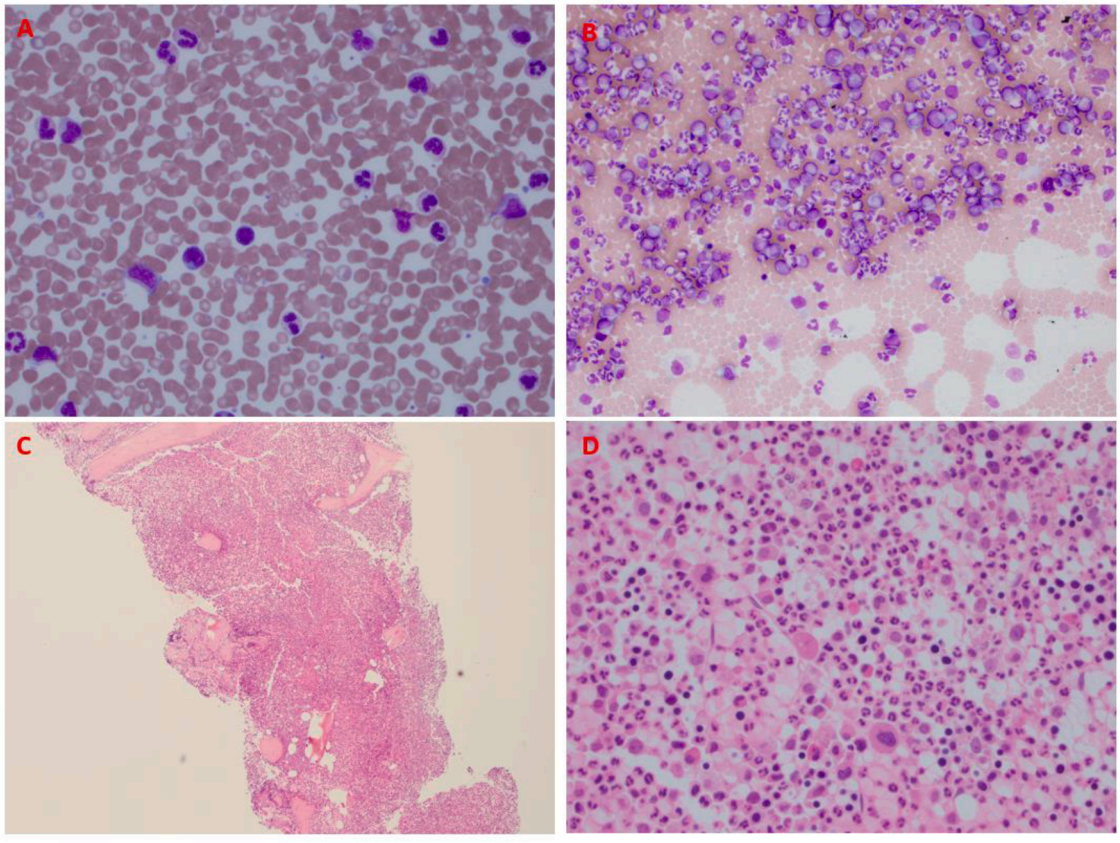

Fig. 1. Bone marrow biopsy from April 2020 and diagnosis of CML. A. The peripheral blood smear with granulocytosis, monocytosis, left-shift, and no obvious myeloid dysplasia. B. The aspirate smears also show myeloid hyperplasia and left-shift, no obvious erythroid dysplasia, and no increase in blasts. C and D. Bone marrow core biopsy with marked hypercellularity, myeloid hyperplasia, small hypolobated megakaryocytes, and no obvious increase in blasts.

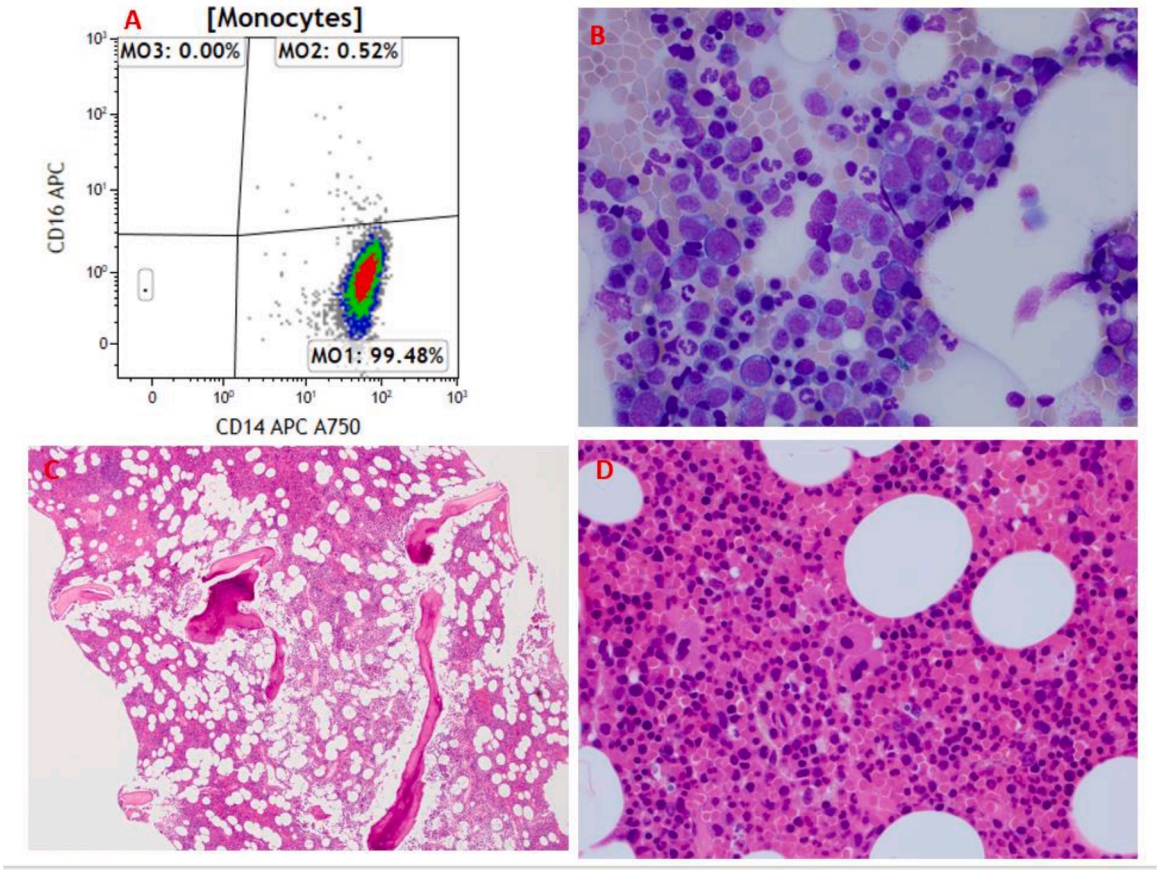

Fig. 2. Bone marrow biopsy from February 2022 and diagnosis of CMML. A. Flow cytometry of the peripheral blood showing increased classic MO1 monocytes (99.48%). B. The aspirate smears show myeloid and monocytic hyperplasia but no obvious erythroid dysplasia or increase in blasts. C and D. The bone marrow core biopsy shows markedly hypercellular bone marrow with myeloid and monocytic hyperplasia, many small hypolobated megakaryocytes, and no obvious increase in blasts.

limited impact on prognosis. The ICC emphasized the need for clonality as one of the necessary CMML diagnostic criteria. Consequently, the modified criteria now require a lower level of absolute monocytosis, $>0.5 \times 109$/L; however, monocytes must still comprise >10% of the WBC.

In this report, we presented a patient with an initial diagnosis of CML, status post-TKI treatment, who later developed or was diagnosed with CMML. The patient was diagnosed with CML in May 2020 with monocytosis below 10% of the threshold for CMML. The next-generation sequencing results were not performed, so CMML could not be diagnosed or ruled out. After treatment of CML with TKI, the granulocytosis and Ph chromosomes nearly disappeared, but the monocytosis persisted or gradually developed. One year later, the second bone marrow biopsy, in November 2021, showed monocytosis meeting the diagnostic criteria for CMML. Additionally, peripheral blood flow cytometry showed increased MO1 monocytes, and NGS revealed features of CMML (*SRF2* and *TET2* mutations), suggesting a concurrent CMML with CML. The in-house biopsy in February 2022 showed similar findings with an additional mutation in *RUNX1*, further confirming the diagnosis of CMML. Thus, the CMML in this patient either coexisted with CML at the beginning or developed later as a second myeloid neoplasm.

It is unknown if the CMML in this patient developed from a different clone from CML cells or as a consequence of CML therapy. Secondary myeloid neoplasms were attributed to cytotoxic chemotherapy before the TKI era [9]. Two possible causes of TKI-associated secondary myeloid neoplasm have been proposed: TKI therapy unmasking the separate myeloid abnormalities by inhibiting the CML process and TKI side effects on non-CML cells [12]. The patient in our case report presented with CMML only one and a half years after the TKI treatment, and presented with monocytosis (even though <10% of the white blood cells) at the initial diagnosis. NextGen sequencing was not performed at the initial diagnosis, so the existence of ASXL1/SRSF2/TET2 could not be excluded. Therefore, we think CMML is more likely a coexisting disease at the initial diagnosis rather than a secondary neoplasm in our patient. The use of TKI might have modified the balance of the clones, and thus the CMML disease came to the surface.

Dr. Zhang etc. [13] have performed whole-exome and RNA sequencing on chronic neutrophilic leukemia (a myeloproliferative neoplasm like CML), atypical CML, and MDS/MPN, including CMML. They found that these diseases show a similar combination of genetic and epigenetic alterations and a similar pattern of multiple pathway mutation co-occurring. Thus, these conditions represent a continuum of related diseases rather than discrete entities. CMML is likely the linear evolution of atypic CML or even CML.

In CML patients, cytogenetic abnormalities associated with other myeloid neoplasms (including MDS and AML), such as trisomy 8, deletion 5 or 7, +21, +17, have been reported in CML or non-CML cells after TKI therapy [1,12]. These abnormalities can appear after TKI suppression of the CML cells. Khorashad et al. reported the case of a CML patient who rapidly converted to fatal CMML after imatinib therapy and found that *TET2* and *ASXL1* were involved in the disease evolution [9]. Genetic mutations independent of *BCR-ABL1* fusion were frequently found in Ph-negative and Ph-positive clones in CML patients [1]. In addition to BCR-ABL, somatic mutations were found in 33% of CML patients, including *ASXL1, DNMT3A, RUNX1*, and *TET2*. At diagnosis, analysis of individual hematopoietic colonies revealed that most mutations were

part of the Ph-positive clone [1]. For CMML, around 20–30% of the patients have clonal cytogenetic abnormalities, commonly trisomy 8 and deletion 7/7q [7,14–16]. More than 90% of CMML patients show somatic gene mutations by NGS, with *ASXL1, TET2*, and *SRSF2* being the most common combinations [7]. The presence of *ASXL1, RUNX1,* and *DNMT3A* and the absence of *TET2* mutations have been associated with poor prognosis [7].

4. Conclusion

In summary, we reported a patient with CML and CMML, two different myeloid neoplasms that could share similar clinical or morphologic findings but need to be mutually excluded due to different prognoses and treatment options. For CML patients with persistent monocytosis and cytopenia after cytogenetic CML remission, an NGS mutational profile is helpful to exclude or identify the coexisting CMML.

Declaration of Competing Interest

The authors have no confliction of interest to declare.

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