



## Case Report

# Atypical Chronic Myeloid Leukemia: Case Report and Review of Literature

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### Abstract

Atypical chronic myeloid leukemia (aCML) is a BCR-ABL1 negative myelodysplastic/myeloproliferative (MDS/MPN) neoplasm. Patients typically present with elevated neutrophil counts and hypercellular bone marrow, but there are no specific genetic or molecular markers available to diagnose aCML and it is therefore a diagnosis of exclusion. Atypical CML is rare and carries a poor prognosis, and there is currently no standard of care for treatment. In the absence of an available clinical trial, current consensus is for patients with a suitable donor to undergo allogeneic stem cell transplantation, and a comprehensive evaluation for driver mutations should be performed to screen for the potential use of targeted agents. Without an actionable driver mutation, hypomethylating agents are an emerging treatment option based on four reports showing complete hematologic remission in 7 of 8 patients treated with decitabine.

**Keywords:** Atypical chronic myeloid leukemia, atypical CML, mds/mpn

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Atypical chronic myeloid leukemia (aCML) is a BCR-ABL1 negative myelodysplastic/myeloproliferative (MDS/MPN) neoplasm.<sup>[1]</sup> There are no known molecular markers specific for aCML, as it is a diagnosis of exclusion. The 2008 WHO classification provides diagnosis primarily through leukocyte counts and morphology, but it is necessary to utilize classic cytogenetic analysis, polymerase chain reaction (PCR), or fluorescence in situ hybridization (FISH) to exclude the presence of BCR-ABL1.<sup>[2,3]</sup> aCML typically presents in the seventh to eighth decade of life, although a few cases of pediatric aCML have been reported with one child as young as 5 months old.<sup>[4]</sup> Overall, it has a poor prognosis, and the mainstay of treatment is hematopoietic stem cell transplant (HSCT).<sup>[5-9]</sup> One study showed a median overall survival of 10 months, with survival not affected by wheth-

er patients transformed to acute myeloid leukemia (AML).<sup>[10]</sup> Another study showed that patients who were treated with allogeneic stem cell transplants had an overall one-year survival of 76.2%.<sup>[11]</sup>

### Mutations that Activate Signaling in aCML

Most somatic mutations activate growth factor genes either directly or indirectly. RAS proteins are membrane-associated GTPases that control the mitogen-activated protein (MAP) kinase cascade. Mutations in *KRAS* and *NRAS* genes frequently occur at codons 12, 31 and 61, and provide a competitive advantage to hematopoietic stem cells.<sup>[12-14]</sup> The frequency of RAS mutations in aCML is around 10-15%, but the presence of a *JAK2V617F* mutation is much less common.<sup>[15-18]</sup> *CBL* mutations have been reported in

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approximately 10% of cases of aCML.<sup>[13,17,18]</sup> *KIT* mutations are found in only 1-4% of aCML cases.<sup>[21]</sup> Activating mutations or internal tandem duplications in *FLT3* (*fms-like tyrosine kinase III*) gene occur in roughly 5% of aCML cases, with some of those patients showing favorable responsiveness to *FLT3* inhibitors.<sup>[22-24]</sup> The frequency of a *CSF3R* mutation is unclear, with one study reporting a prevalence of 50% and another reporting zero.<sup>[25,26]</sup> Mutations of *SETBP1* gene were reported in almost 25% of aCML patients according to one study.<sup>[27]</sup> *TET2* mutations are somewhat common and reported to occur in around 30% of aCML.<sup>[28-31]</sup>

## Case Report

An 80-year-old woman presented with a 25-pound weight loss over 2 years and with several months of fatigue and night sweats. Complete Blood Count (CBC) evaluation showed white blood cells (WBC) of 16,700 and an absolute neutrophil count (ANC) of 14,000. Hemoglobin and platelet were unremarkable. She did not have any signs of infection or steroid exposure, and peripheral blood testing for BCR/ABL and Janus Kinase 2 (JAK2) mutations were negative. Over the following 8 months, the neutrophilia persisted, and extensive additional testing did not show an underlying cause. A bone marrow biopsy was then performed and showed mild hypercellularity (30%) with trilineage hematopoiesis, no increase in blasts, and no evidence of myelodysplasia. Cytogenetics were completely normal, and BCR/ABL testing was again negative. Six months after initial bone marrow biopsy, her WBC level increased to 68,000 (ANC 34,400), hemoglobin decreased from 11.8 g/dL to 8.1 g/dL, and platelets had fallen from 299,000 to 70,000. Repeat bone marrow biopsy showed greater than 95% cellularity with left-shifted myeloid maturation, marked myeloid hyperplasia, erythroid and megakaryocytic hypoplasia, and 2% blasts. Cytogenetics were again normal, including *CSF3R*. This is consistent with a diagnosis of atypical CML, and the patient was started on treatment with decitabine.

## Discussion

The differential diagnosis for aCML includes chronic neutrophilic leukemia (CNL), but CNL is a purely myeloproliferative disorder which lacks dysplastic features and is strongly associated with *CSF3R* mutations such that the World Health Organization included that mutation in its diagnostic criteria.<sup>[32,33]</sup> Atypical CML is rare, and there is currently no standard of care for treatment. Obstacles to the creation of treatment guidelines include rarity, heterogeneous clinical findings and genetics, high transformation rate to acute myeloid leukemia, and poor overall survival. Absent the availability of a clinical trial, current consensus

is for patients with a suitable donor to undergo allogeneic stem cell transplantation, and a comprehensive evaluation for driver mutations should be performed to evaluate for the potential use of targeted agents.<sup>[34]</sup> Without the presence of an actionable driver mutation, hypomethylating agents are an emerging treatment option based on 4 reports showing complete hematologic remission in 7 of 8 patients treated with decitabine.<sup>[35-38]</sup>

## Disclosures

**Informed Consent:** Written informed consent was obtained from the patient for the publication of the case report and the accompanying images.

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

**Authorship Contributions:** Concept – B.M.; Design – B.M.; Supervision – J.D.M.; Materials – K.A.; Data collection &/or processing – N.M.; Analysis and/or interpretation – B.M.; Literature search – N.M.; Writing – B.M.; Critical review – J.D.M.

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