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5-Hydroxymethylcytosine Immunohistochemical Staining Correlates with Overall Survival in Patients with Chronic Myelomonocytic Leukemia

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Introduction

Chronic myelomonocytic leukemia (CMML) is a myelodysplastic/myeloproliferative neoplasm that has been associated with a number of genetic mutations, most commonly TET2 mutations in up to 50-60% of cases. Mutations in epigenetic genes such as TET2 are known to disrupt the conversion of 5-methylcytosine to 5-hydroxymethylcytosine (5hmC), contributing to oncogenesis. We hypothesized that CMML cases would exhibit decreased 5hmC expression, reflecting the propensity for TET2 mutations in CMML. We also sought to determine whether 5hmC IHC status reflected disease severity in terms of progression to AML and overall patient survival.

Methods

Thirty-five cases of CMML from between 1/2006 and 12/2014 were identified from the pathology archives at UMass, under an IRB-approved protocol. IHC was performed on FFPE bone marrow biopsy specimens with an anti-5hmC antibody. Staining was scored based on intensity of nuclear staining: 0 (neg) to 3+ (strong); and proportion of cells staining: 0 (<1%), 1 (1-25%), 2 (26-50%), 3 (51-75%), 4 (>76%). A combined product score was calculated yielding scores of 0-12. Correlation to clinical parameters (age, blast count, progression to AML, and overall patient survival) was investigated.

Results

60% (21/35) of CMML cases showed low expression of 5hmC (combined score ≤ 4). This loss of 5hmC expression correlated significantly with poorer overall survival in Kaplan-Meier curves ($p=0.0287$). There was no significant correlation between 5hmC score and patient age, blast count, or AML progression.

Conclusion

IHC detection of 5hmC in CMML is significantly correlated with patient overall survival and could potentially be utilized as a prognostic biomarker. Loss of 5hmC expression likely reflects mutations to epigenetic pathways and could be useful in guiding treatment with hypomethylating agents.

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