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EDITORIAL ARTICLE

Clonal Hematopoiesis and Plasma Cell Disorders: Coincidence or not?

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Over the last 10 years, technological progress has refined our understanding and detection of preclinical stages of hematologic cancers. Indeed, monoclonal gammopathy of undetermined significance and clonal hematopoiesis are now recognized as two distinct clonal conditions, both associated with aging with prevalence rates at 70 years of approximately 5-10% and 10-20%, respectively.[1,2] Monoclonal gammopathy of undetermined significance arises from the clonal expansion of plasma cells and is characterized by the production of a monoclonal immunoglobulin, which can lead to plasma cell disorders—also typically diagnosed at a median age of 70 years—such as multiple myeloma or lymphoid neoplasms (notably Waldenström Macroglobulinemia).[3] Clonal Hematopoiesis refers to the age-related expansion of hematopoietic stem and progenitor cells carrying somatic mutations affecting predominantly the genes *DNMT3A*, *TET2*, and *ASXL1*, commonly referred to as DTA mutations and encoding epigenetic regulators. Clonal hematopoiesis is considered a premalignant state that may progress to myeloid neoplasms, and it has also been associated with increased cardiovascular mortality.[2] Although monoclonal gammopathy of undetermined significance and clonal hematopoiesis generally arise independently, recent studies have suggested potential interferences between both entities. The purpose of this letter is to discuss the connection between clonal hematopoiesis and monoclonal gammopathy of undetermined significance and its impact on plasma cell disorders.

As both clonal hematopoiesis and monoclonal gammopathy of undetermined significance prevalence increases with age, co-occurrence analyses were performed. However, in two independent cohorts—one involving elderly dementia patients (median age 91 years) and another from a large US population-based registry—no association was found between both or its progression to myeloma, supporting the hypothesis that these entities reflect parallel but unrelated clonal processes within elderly hematopoiesis.[4,5] Indeed, in myeloma, clonal hematopoiesis mutations have been associated with poorer outcomes following autologous stem cell transplantation and higher rates of therapy-related myeloid neoplasms[6], although lenalidomide maintenance appears to preserve survival regardless of clonal hematopoiesis status. Moreover in Waldenström Macroglobulinemia, DTA mutations have been linked to an increased risk of progression from monoclonal gammopathy of undetermined significance or asymptomatic form to symptomatic one, supporting a possible connection between these 2 conditions.[7]

Another potential link between clonal hematopoiesis, aging and chronic inflammation has progressively emerged, especially for DTA mutations.[8–11] In healthy individuals, DTA mutation-driven clonal hematopoiesis has been associated with elevated C-reactive protein (CRP, one protein produced during inflammation)[9] and pro-inflammatory cytokines such as interleukin-6 or interleukin-1β.[12] Interleukin-6, a key mediator of inflammatory responses, is also implicated in the progression of plasma cell disorders.[13,14] By performing next-generation sequencing on Waldenström Macroglobulinemia patient samples, we recently identified a strong association between clonal hematopoiesis—particularly involving DTA mutations—and an inflammatory subtype of Waldenström Macroglobulinemia, characterized by unexplained CRP elevation above 20 mg/L and frequently associated with chromosome 6q deletion (del6q).[15] Patients presenting this inflammatory phenotype were found to respond less well to immuno-chemotherapy but unexpectedly showed improved outcomes with BTK inhibitor compared to patients with low CRP.[16] Progression from non-inflammatory asymptomatic Waldenström Macroglobulinemia with clonal hematopoiesis to symptomatic inflammatory form was also observed, suggesting a potential link between clonal mutations and inflammatory signaling. The co-occurrence of clonal hematopoiesis and del6q—associated with higher CRP levels compared to either alteration alone—may reflect a synergistic

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mechanism, as both are independently linked to the inflammatory Waldenström Macroglobulinemia phenotype and an increased risk of progression to symptomatic disease.[17,18] However, one limitation of our study was the lack of evidence for clonal independence between clonal hematopoiesis mutation and the malignant B cells, as hematopoietic stem cells harboring clonal hematopoiesis mutations can differentiate into B cells.[19] Finally, a recent study has provided new insights into the relationship between clonal hematopoiesis and Multiple Myeloma.[20] While validating the clonal independence between clonal hematopoiesis and the myeloma cell clone, the study showed that clonal hematopoiesis may significantly reshape the bone marrow microenvironment including altered immune cell composition (increase in inflammatory monocytes and exhausted CD8+ T cells) and enrichment of pro-inflammatory and cytokine-related pathways—such as IFN-α/γ, TNF-α, IL-6/JAK/STAT3, and TGF-β signaling, that together may contribute to immune evasion of clonal plasma cells.

Altogether, these works suggest the coexistence of plasma cell disorders and clonal hematopoiesis that may potentially reflect a functional connection beyond a simple co-occurrence with aging. Clonal hematopoiesis and plasma cell disorders appear to converge on shared inflammatory pathways that drive immune dysregulation and promote clonal plasma cell expansion and/or maintenance—highlighting a potential therapeutic vulnerability that warrants further investigation.

Conflicts of Interest:

PED: Beigene. None for the others.

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