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Understanding Clonal Hematopoiesis

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Abstract

Clonal hematopoiesis (CH) describes a state in which hematopoietic stem cells (HSCs) with somatic mutations have competitive growth or survival advantage relative to other blood cells derived from wild-type HSCs, in the marrow milieu, resulting in expansion of a clonal population of blood cells in the absence of unexplained cytopenias , hematological cancers, or other clonal disorders. The strongest risk factor for developing CH is advancing age. CH is common in apparently healthy persons (age-related clonal hematopoiesis) especially in middle-aged and elderly populations with 10% to 15% prevalence in people aged 60 to 70 years old. CH is associated with an ever-increasing list of diseases and health comorbidities. Most individuals with CH do not experience severe sequelae. Worse overall survival in CH is largely driven by death resulting from cardiovascular disease and transformation to hematologic malignancy.

Keywords: Clonal Hematopoiesis; Hematopoietic Stem Cells; Anti-Inflammatory; Hematologic Malignancy; Chromosomal Alterations

Abbreviations: CH: Clonal Hematopoiesis; HSCs: Hematopoietic Stem Cells; DDR: DNA Damage Response; MNs: Myeloid Neoplasms; CVD: Cardiovascular Disease; VAF: Variable Allele Fraction; CVD: Cardiovascular Disease

Introduction

Clonal hematopoiesis (CH) describes a state in which hematopoietic stem cells (HSCs) with somatic mutations in leukemogenic genes have a competitive growth or survival advantage relative to other blood cells derived from wild-type HSCs, in the marrow milieu, resulting in expansion of a clonal population of blood cells in the absence of unexplained cytopenias , hematological cancers, or other clonal disorders [1].

CH mutations have been acquired early in life, even during infancy or in utero with some mutations undergoing a gradual expansion throughout life [2]. CH is quite common in apparently healthy persons (age-related clonal hematopoiesis, ARCH) [3] especially in middle-aged and elderly populations with 10% to 15% prevalence in people aged 60 to 70 years old [1]. CH is associated with an ever-increasing list of diseases through diverse mechanisms [2]. A few examples of the expanding list of CH associated disease includes cardiovascular disease (CVD), chronic obstructive pulmonary disease, risk of severe COVID-19, HIV, autoimmune diseases [4], adult onset autoinflammatory disease, hemophagocytic lymphohistiocytosis, anti-neutrophil antibody-associated vasculitis, and solid tumors [3]. A correlation between CH and insulin resistance is postulated [2]. A minority (0.5 -2%) of patients with CH may progress to a malignant process [5].

Risk factors of CH

The strongest risk factor for developing CH is advancing age [1]. Prior therapy with radiation and cytotoxic chemotherapy but not immune checkpoint blockade increases the risk of CH especially that associated with TP53 or PPM1D mutations [3].

Categories of CH

CH is divided into multiple categories according to blood count [5]. These categories are clonal hematopoiesis of indeterminate significance (CHIP), clonal monocytosis of undetermined significance (CMUS), clonal cytopenia and monocytosis of undetermined significance (CCMUS) and clonal cytopenia of undetermined significance (CCUS) [5]. All these subgroups are determined to have a clonal mutation when the variable allele fraction (VAF) is more than 2% [5].

Clonal cytopenia of undetermined significance (CCUS)

The presence of clonal somatic mutation in the myeloid neoplasm related gene in the peripheral blood or bone marrow

sample associated with idiopathic persistent cytopenias (more than 4 months) without other features of malignancy. Cytopenia is defined as platelets less than 150 $x10^9$/L , absolute neutrophils less than 1.8 $x10^9$/L and hemoglobin less than 13 g/dL in males and less than 12 g/dL in females [5].

Clonal monocytosis of undetermined significance (CMUS)

The presence of persistent monocytosis (monocytes ≥10% and ≥0.5 $x10^9$/L of the WBC) associated with somatic mutation in the myeloid neoplasm related gene (5).

Clonal cytopenia and monocytosis of undetermined significance (CCMUS)

Clonal monocytosis of undetermined significance as defined previously associated with cytopenia (5).

Clonal hematopoiesis of indeterminate potential (CHIP)

CHIP is defined as the presence of somatic mutations in myeloid malignancy-associated genes in the peripheral blood or bone marrow sample of healthy individuals at a VAF of ≥ 2% (2) (≥4% for X-linked gene mutations in males) [6] without a known hematologic disorder, unexplained cytopenia or clonal disorder [2]. A related but not entirely overlapping term with CHIP is age-related clonal hematopoiesis (ARCH) [2].

Age-related clonal hematopoiesis (ARCH)

The term ARCH describes the occurrence of somatic mutations in healthy persons without hematologic abnormalities (3). The cutoffs and definitions of ARCH varied between authors and still need to be refined. ARCH is defined as a gradual, clonal expansion of HSPCs carrying specific, disruptive, recurrent genetic variants in individuals without hematologic malignancy. However, some authors defined ARCH as any type of detectable, acquired clonal event in the hematopoietic system without detectable malignancy (2).

Understanding the molecular mechanisms of CH

Clonality of CH can result from a change in genetic profile e.g., cytogenetic changes, copy number abnormalities or a mutation in the gene itself [5]. CH with chromosomal alterations is more likely to develop lymphoid malignancies. There is a strong association between +12, 13q−, and 14q− CH and the development of chronic lymphocytic leukemia (CLL). CH with point mutations or small insertions/deletions is strongly associated with cardiovascular disease (CVD). Chromosomal alterations frequently co-occur with point mutations or small insertions/deletions in the same individuals with CH. This co-occurrence increased the risk of development of hematologic malignancies as well as adverse cardiovascular outcomes in the same iindividuals [2].

The initial acquisition of CH mutations is thought to occur through several mechanisms. One of the most common events in point mutations is spontaneous deamination of 5-methylcytosine to thymine. Less commonly, mutations are acquired by errors arising during repair of double-stranded DNA breaks creating small insertions/deletions or through replication errors by DNA polymerase [2]. The identified mutated genes in CH are largely aligned with those found in myeloid malignancies, with DNMT3A and TET2 variants comprising the vast majority, followed by ASXL1, splicing factors (SF3B1 and SRSF2), JAK2, and TP53. Cases of CH without any known driver mutation can also be identified and these cases are still associated with increased mortality [2].

Clinical and laboratory detection of CH

There are no specific symptoms or clinical picture associated with CH. CH is usually an incidental finding during evaluation of a patient for another disease [5]. Patients with CH may present with sequelae of clinical manifestations and health comorbidities of CH associated disease [2].

Mutations causing CH must be of somatic origin not a germline mutation [2]. Mutations can be detected by different sequencing methods, the most used ones are next generation sequencing which can be whole exome, whole genome sequencing or a panel for certain genes [5]. The source of blood cells, whether from peripheral blood mononuclear cells or bone marrow aspirate samples does not markedly affect the detection of mutation or VAF clone size in CH [1].

No additional diagnostic evaluation is recommended for detection of CH in the absence of concerning findings such as erythromelalgia or splenomegaly or cytopenias [1].

Depending on age and risk profile, blood counts are monitored every 3 to 6 months in these patients. More careful observation is indicated in larger clone size (VAF >0.2), high-risk mutations such as TP53 or multiple mutations, borderline blood counts, or highly abnormal RBC indices [1].

Bone marrow aspiration and biopsy with histochemistry, flow cytometry, and metaphase cytogenetics are reasonable, in some patients with cytopenias.

Additional evaluation by genetic counselors or cardiologists may also be indicated [1].

CH and health Outcome

Most individuals with CH do not experience severe sequelae [2]. Worse overall survival in CH is largely driven by death resulting from cardiovascular disease and increased risk of transformation to hematologic malignancy [1].

Cardiovascular disease (CVD)

Some clonal-hematopoiesis-related mutations have emerged as a major independent risk factor that contributes to the development and clinical progression of atherosclerotic cardiovascular disease, heart failure and thrombosis [4]. TET2-mutant mature myeloid cells have been involved in

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proinflammatory signaling associated with acceleration of atherosclerosis [2]. CH with mutations in JAK2 has been associated with an increased risk of thrombotic and cardiovascular events. Strands of DNA—termed neutrophil extracellular traps released by dying granulocytes—are likely to promote thrombosis [2]. The adverse cardiovascular outcomes associated with CH in DNMT3A and TET2 mutations appear to depend on VAF, with most events occurring in patients with a VAF > 10% [1]. There is some evidence that increased mortality of patients with chronic ischemic heart failure correlates with much lower VAF cutoffs levels (VAF ≥1.15% for DNMT3A and ≥0.73% for TET2) [2].

Myeloid neoplasms

The most commonly encountered hematologic malignancies in patients with CH are myeloid neoplasms (MNs) including acute myeloid leukemia, myelodysplastic syndrome, and myeloproliferative neoplasm (MPN) [7]. Most individuals with CH will never develop MN [7]. The risk of progression to myeloid malignancies is drastically increased in CH with VAFs ≥10% [2]. The clone size appears to be particularly important for certain genes, notably DNMT3A and TET2 [1]. The risk of AML development with a mutation in DNMT3A or TET2 was 4.8- for VAF >10% compared with 3.6-fold for a VAF <10%. It is unclear whether these same associations are true in genes like TP53 and IDH1/2 [1]. Other high-risk features for transition to malignancy include the acquisition of additional genetic aberrations, mutations in TP53, the spliceosome pathway, and IDH1/2. However, mutational features alone or even when combined with other clinical data and blood count parameters provide only modest predictive ability for risk of MN development. Environmental factors, clonal composition, or epigenetic changes, among others are likely play a major modifying role in the risk of developing MN [7]. Recently researchers identified several measures that were highly predictive of an individual's future risk of developing blood cancer in CH patients with CHIP and CCUS who are not actively receiving chemotherapy for other cancers. These measures are patient's age; the type and number of genetic mutations present in blood cells; the fraction of cells in the blood with CH mutation ; low blood counts; and factors related to red blood cell volume. These measures were combined into a computational algorithm, that calculates a clonal hematopoiesis risk score (CHRS). CHRS values define three groups of patients— low risk (a score less than or equal to 9.5); intermediate risk (a score ranging from 10 to 12); and high risk (a score of 12.5 or greater). The 10-year risk of blood cancer is less than 1% in the low-risk group and is over 50% in the high-risk group [8].

Outlook

There is a latency period between detection of CH in the peripheral blood and clinical manifestations of sequelae of CH associated disease suggesting a therapeutic window which opens the prospect of early intervention [2]. Minimizing exposure to certain stressors—including inflammatory or cytotoxic stress—might be a successful strategy to mitigate some of the CH–associated adverse health outcomes. These stressors contribute to the expansion of certain CH clones and to the manifestations of the sequelae of the CH associated disease in high-risk individuals [2].

Anti-inflammatory treatment targeting specific inflammasomes, common downstream mediators such as IL-1β and IL-6, or mutations linked to CH may be directed to individuals with CH. This is based on the recent demonstration of emerging link between CH and the heightened inflammatory responses mediated by tissue-infiltrating mutant immune cells in cardiovascular disease as well as by the benefit of use of anti-inflammatory treatments in cardiovascular disease [6].

Conclusion

Minimizing exposure to certain stressors and the use of anti-inflammatory treatment in individuals with CH might be a successful strategy to alleviate some of the CH–associated adverse health outcomes.

References

1. Miller PG, Steensma DP (2020) Implications of clonal hematopoiesis for precision oncology. JCO Precis Oncol 4: 639-646.
2. Köhnke T, Majeti R (2021) Clonal hematopoiesis: from mechanisms to clinical intervention. Cancer Discov 11: 2987-2997.
3. Von Bonin M, Jambor HK, Teipel R, Stölzel F, Thiede C, et al. (2021) Clonal hematopoiesis and its emerging effects on cellular therapies. Leukemia 35: 2752-2758.
4. Younes IE, Syler L, Hamed A (2023) Review of clonal hematopoiesis, subtypes and its role in neoplasia and different morbidities. Leuk Res 130: 107307.
5. Khoury JD, Solary E, Abla O, Akkari Y, Alaggio R, et al. (2022) The 5th edition of the World Health Organization classification of hematolymphoid tumors: myeloid and histiocytic/ dendritic neoplasms. Leukemia 36(7): 1703-1719.
6. Tall AR, Fuster JJ (2022) Clonal hematopoiesis in cardiovascular disease and therapeutic implications. Nat Cardiovasc Research 1(2): 116-124.
7. Chan ICC, Wiley BJ, Bolton KL (2022) What clonal hematopoiesis can teach us about MDS. Front Oncol 12: 794021.
8. Weeks LD, Niroula A, Neuberg D, Wong W, Lindsley RC, et al. (2023) Predicting of risk for myeloid malignancy of clonal hematopoiesis. NEJM Evid 2(5).

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