Clonal Hematopoiesis: Malignant Implications, Extrahematologic Manifestations, and Management

Kelly S. Chien, MD[1]; Courtney D. DiNardo, MD, MSCE[1]; and Guillermo Garcia-Manero, MD[1]

[1]Department of Leukemia, The University of Texas MD Anderson Cancer Center, Houston, Texas

Corresponding author:
Kelly Chien, MD
1515 Holcombe Blvd, Unit 428
Houston, TX 77030
Tel: (713) 745-7584
Email: kchien@mdanderson.org

Keywords
Cardiovascular disease, CCUS, CHIP, clonal hematopoiesis, malignancy, therapy-related myeloid neoplasm

Abstract: As individuals age, their hematopoietic stem cells can sporadically acquire genetic mutations, known as clonal hematopoiesis. Although most of these genomic aberrations are of little consequence, particular changes in certain contexts can lead to the development of hematologic malignancies, such as myelodysplastic syndromes and acute myeloid leukemia. Owing to its pervasive extrahematologic interactions, clonal hematopoiesis is a recognized risk factor for and is causally implicated in the development of several chronic diseases of aging and/or inflammation, such as atherosclerotic cardiovascular disease. Here, we provide a review of the diagnosis and clinical implications of clonal hematopoiesis, as well as evolving management strategies in the absence of formal consensus guidelines.

Introduction

Clonal hematopoiesis is the sporadic acquisition of somatic mutational changes in hematopoietic stem cells with normal aging. These mutations have been detected in healthy individuals, with a rise in frequency with increasing age; by the age of 65 years, more than 10% of healthy people will have clonal hematopoiesis.[1-3] There have also been several population studies linking clonal hematopoiesis with certain environmental factors, such as exposure to smoking and chronic infections.[4,5]

This acquisition of mutations is not unique to the hematopoietic system, as somatic mosaicism can develop in a variety of organs over an individual's lifetime with stressors and/or aging.[6] There have been studies demonstrating somatic mosaicism in different organs, such as the attainment of *TP53* and other mutations in sun-exposed skin,[7] gain of *NOTCH1* in esophageal tissue with aging,[8,9] and higher mutational burdens in cirrhotic liver when compared with normal hepatic tissue.[10] Some key differences between clonal hematopoiesis and other forms of somatic mosaicism involve the accessibility of

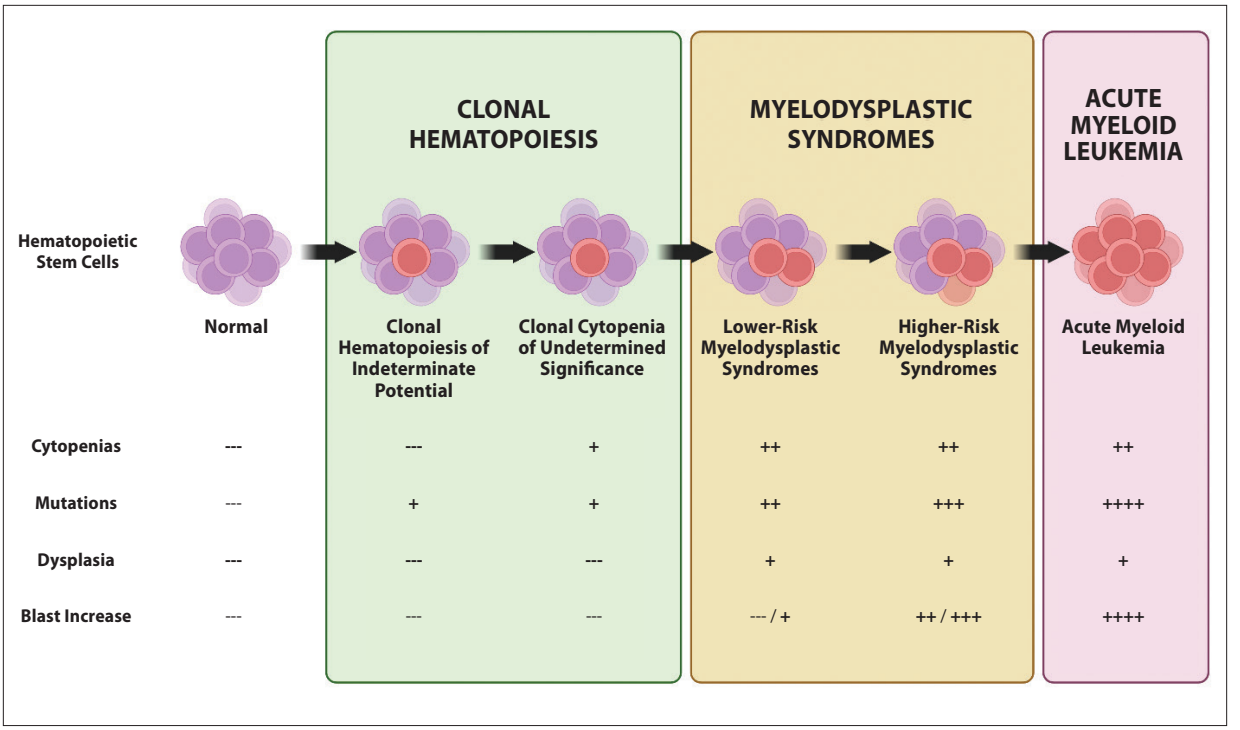

Figure. Spectrum of myeloid conditions from clonal hematopoiesis to acute myeloid leukemia. Created with BioRender.

tissue of hematologic origin for sequencing in the form of peripheral blood and bone marrow, ubiquitous extrahematologic interactions, and immunosenescence, or dysregulation of the immune system.[11] In this review, we aim to describe the diagnosis of clonal hematopoiesis, its oncologic implications and extrahematologic manifestations, and current management considerations.

Diagnostic Criteria

Clonal hematopoiesis encompasses both the terms clonal hematopoiesis of indeterminate potential (CHIP) and clonal cytopenia of undetermined significance (CCUS).[12,13] CHIP is defined as the presence of a somatic mutation with a variant allele frequency (VAF) of at least 0.02 in an individual with normal blood counts, whereas CCUS is CHIP in an individual with otherwise unexplained peripheral blood cytopenia. Both CHIP and CCUS require no morphologic findings of a hematologic malignancy.[14] Recently, both the World Health Organization (WHO) and the International Consensus Classification have added clonal hematopoiesis to their myeloid neoplasm classifications.[15,16] Cytopenias for CCUS are defined by WHO criteria (anemia: hemoglobin <12 g/dL in females or <13 g/dL in males; thrombocytopenia: platelet count <150 × 10^9 cells/L; neutropenia: absolute neutrophil count less than 1.8 × 10^9 cells/L).[15,17] Given that individuals with CH do not have a hematologic malignancy, they lie on one end of the spectrum of myeloid disorders, including myelodysplastic syndromes (MDS) and acute myeloid leukemia (AML), as shown in the Figure.

Malignant Implications

It is now well-established that the presence of CH leads to an increased risk of a hematologic malignancy,[1,2] and this elevated risk has been demonstrated for both myeloid and lymphoid malignancies, leading to the terms myeloid CHIP (M-CHIP) and lymphoid CHIP (L-CHIP).[18] Because L-CHIP is a relatively novel discovery, most current malignant implications refer to the risk of myeloid malignancies from clonal expansion of M-CHIP.

Progression to Myeloid Malignancies

The risk of developing a myeloid malignancy from CH is gene-specific. Studies have shown that healthy individuals with somatic mutations in spliceosome genes (eg, *U2AF1*, *SRSF2*), *IDH1/2*, *JAK2*, and *TP53* have an increased risk of developing AML.[19-21] Various factors, including increased VAF of at least 0.1 to 0.2, 2 or more CH mutations, and adverse mutational profiles, have

also been implicated in the transformation to myeloid malignancies.[22-24]

The Clonal Hematopoiesis Risk Score (CHRS) was recently published as an innovative personalized prediction tool for the risk of progression to myeloid neoplasms in healthy adults with CH based on specific mutations, VAF, age, and several peripheral blood laboratory values, including peripheral blood counts, red cell distribution width, and mean corpuscular volume.[25] It was able to risk stratify 11,337 healthy individuals with CH into high- (CHRS score ≥12.5, n=123 [1.1%]), intermediate- (CHRS score 10-12, n=1196 [10.5%]), and low-risk (CHRS score ≤9.5, n=10,018 [88.4%]) categories, with a cumulative 10-year incidence of myeloid transformation of 52.2%, 7.8%, and 0.7%, respectively.

Therapy-Related CH

The presence of CH in patients with nonmyeloid malignancies who receive antineoplastic therapy is associated with an increased incidence of therapy-related myeloid neoplasms and adverse clinical outcomes.[26,27] Mutations in DNA damage response genes (*TP53*, *PPM1D*, *CHEK2*, and *ATM*) are preferentially selected for in patients with therapy-related CH, especially those who received prior platinum, topoisomerase II inhibitors, and/or radiation.[4] In a group of patients with *TP53*-mutated therapy-related MDS or AML, small hematopoietic clones with *TP53* mutations were detected in baseline blood or bone marrow samples before any exposure to chemotherapy or radiation therapy.[28] Other CH-associated mutations, such as those in *TET2*, *RUNX1*, and *SRSF2*, were discovered to be common in patients with therapy-related myeloid neoplasms at the time of their initial cancer diagnosis and before receiving any antineoplastic therapy.[29,30] Notably, clinical outcomes, including survival and nonrelapse mortality, in patients with CH who have undergone stem cell transplant (SCT) are inferior.[31] Lymphoma patients with CHIP at the time of autologous SCT have an increased incidence of therapy-related MDS or AML, inferior overall survival (OS), and increased risk of death from cardiovascular disease after transplantation.[32] Similar unfavorable survival outcomes were observed in patients with multiple myeloma after autologous SCT,[33] although this was not corroborated by another group.[34]

Extrahematologic Manifestations

Various nononcologic comorbidities have also been linked with CH clones and myeloid disorders. When applying the Adult Comorbidity Evaluation 27 score to patients with MDS,[35,36] OS was found to be inversely proportional to comorbidity burden irrespective of age and risk by the International Prognostic Scoring System.[37] When examining MDS patients with CH-associated mutations, mutations in *DNMT3A* were associated with cardiovascular disease, mutations in *JAK2* were associated with veno-occlusive disease, and mutations in *TP53* were associated with a neoplastic history.[38] The extrahematologic manifestations and comorbid conditions associated with CH are described in further detail below.

Cardiovascular Disease

CH is strongly associated with an increased risk of atherosclerotic cardiovascular disease.[1] In individuals with CHIP (particularly *DNMT3A*, *TET2*, *ASXL1*, and *JAK2* mutations), an increased incidence of coronary artery disease and coronary artery calcification was detected.[39] Moreover, inferior long-term clinical outcomes have been demonstrated in ischemic heart failure patients harboring CHIP mutations, particularly in *DNMT3A* or *TET2*.[40]

Both CH and cardiovascular disease are associated with aging, making it difficult to determine if CH is a cause of heart disease, is merely associated with aging, or promotes vascular endothelial injury leading to cardiovascular conditions. However, a growing body of evidence suggests that CH is an independent risk factor for atherosclerotic cardiovascular disease, similar to hyperlipidemia and smoking.[1,39] The exact pathophysiologic mechanism linking CHIP to cardiovascular risk is unknown, but there are several postulations. First, *JAK2*-mutated neutrophils have been linked with vascular inflammation owing to activation of β1 and β2 integrins with consequent enhancement of atherosclerotic plaque cores,[41] and *JAK2*-mutated macrophages more readily engulf red cells compared with wild-type macrophages.[42] The association of CH with cardiovascular disease may be due to the generation of proinflammatory mediators and endovascular interaction with circulating clonal macrophage progenitor cells. Furthermore, in *Tet2*-knockout mice, atherosclerotic plaque sizes were increased and expression of proinflammatory cytokines, such as interleukin (IL)-1β and IL-6, was amplified when stimulated with low-density lipoprotein.[39,43] Thus, *TET2* mutations appear to potentiate the development of atherosclerotic disease by stimulating inflammation.

The use of anti-inflammatory therapies is a promising approach for reducing clonal hematopoiesis-related cardiovascular risk. The CANTOS study demonstrated that the administration of canakinumab (Ilaris, Novartis), an anti–IL-1β monoclonal antibody, led to a decreased rate of recurrent cardiovascular events when compared with placebo.[44] Overall, patients with baseline CH had a greater risk of major adverse cardiac events, and interestingly, there was a preferential reduction in secondary cardiovascular events in patients with *TET2*-mutated CH treated with canakinumab.[45]

Table 1. USPSTF Guidelines for Cancer Screening in Adults

Cancer type	Recommendation grade (age, y)	Patient age, y	Testing guidelines
Cervical[68]	A	21-29	Pap smear every 3 y
		30-65	HPV screening ± Pap smear every 5 y
Breast[a,69]	B	40-74	Mammogram every 2 y
Colorectal[70]	A (50-75) B (45-49)	45-75	Colonoscopy every 10 y
			Virtual colonoscopy every 5 y
			Stool testing every 1-3 y
Lung[b,71]	B	50-80	Low-dose chest CT every y

CT, computed tomography; HPV, human papillomavirus; USPSTF, United States Preventive Services Task Force; y, year(s).
[a]Undergoing updates with 2023 draft recommendation available.
[b]Those with 20 pack-year smoking history and current smokers or those who have quit within the past 15 y.

Autoimmune Disease

Less has been established about the mechanistic link between CH and other comorbidities, but there is a growing body of evidence implicating certain forms of CH in the development of autoimmune disease. An association between CHIP and antineutrophil cytoplasmic antibody-associated vasculitis was discovered,[46] but no linkage was established between CH and rheumatoid arthritis.[47] It is thought that patients with *TET2*- or *IDH1/2*-mutated CH may be at an increased risk for autoimmune conditions owing to T-cell dysregulation.[48] Additionally, there has been great interest in VEXAS syndrome, a life-threatening autoimmune condition with relapsing polychondritis involving a rare form of CH with mutations in the *UBA1* gene.[49,50]

Other Medical Conditions

An assortment of studies have connected CH with other medical conditions, potentially as a driver of systemic inflammation. Individuals with CH are at increased risk for type 2 diabetes mellitus,[1] chronic obstructive pulmonary disease,[51,52] chronic liver disease,[53] osteoporosis,[54] gout,[55] and a variety of infections,[56] such as HIV and severe COVID-19.[57,58] Furthermore, the presence of CH may be protective against Alzheimer disease.[59] In patients undergoing cellular therapy for hematologic neoplasms, CH is associated with increased toxicities from chimeric antigen receptor T-cell therapy.[60,61] The presence of donor CH may correlate with an increased risk of graft-versus-host disease (GVHD) after allogeneic SCT (allo-SCT) and potentially a decreased risk of relapse, although results from available publications are conflicting.[62-66] However, results from a large cohort of 2572 patients who underwent allo-SCT from unrelated donors showed no statistically significant association between donor CH and GVHD, relapse, and OS, but trends toward increased mortality were observed, in conflict with previously published data.[67] Of note, surveillance of donors for CH before allo-SCT is not routinely performed.

Management of Individuals With Clonal Hematopoiesis

Many academic institutions, especially comprehensive cancer centers, have implemented dedicated clinics for individuals with CH for comorbidity mitigation and potential leukemia prevention. The main referral streams are: (1) individuals with cytopenias with detection of CH-associated mutations but without diagnostic criteria for a hematologic malignancy (ie, CCUS); (2) patients undergoing bone marrow evaluation for an established nonmyeloid hematologic cancer (such as chronic lymphocytic leukemia or multiple myeloma) in which somatic CH-associated mutations are detected; and (3) those with nonhematologic malignancies, such as solid tumors, who undergo sequencing of their neoplasm with presumed CH-associated somatic mutations detected on peripheral blood control. Occasionally, referrals occur for CH detected in prospective donors for allo-SCT and in individuals who underwent sequencing to evaluate for potential inherited cancer predispositions.

There are no consensus guidelines regarding the optimal screening, monitoring, and management of individuals with CH. However, there is a growing need for multidisciplinary guidance and clinical recommendations for these patients. The following details the clinical care and guidance provided by dedicated CH clinics to individuals. Of note, because CH is a consequence of aging, the therapeutic approaches and monitoring strategies provided to younger patients will inevitably differ from those given to older patients.

Health Maintenance

Similar to the general population, individuals with CH should undergo routine cancer screening and vaccinations

Table 2. Clinical Trials Available for CH

Agent	Conditions	Included mutations[a]	Cytopenia definition	Goal enrollment, n	Primary endpoint	NCT number
Enasidenib	CCUS	*IDH2*	Hgb <10 g/dL, ANC <1.8 × 10^9/L, plt <100 × 10^9/L	15	Rate of hematologic improvement	NCT05102370
Ivosidenib	CCUS	*IDH1*	Hgb <10 g/dL, ANC <1.8 × 10^9/L, plt <100 × 10^9/L	15	Rate of hematologic improvement	NCT05030441
Atorvastatin or rosuvastatin	CCUS, LR-MDS	Any CH-associated mutation	Hgb <11.3 g/dL in females or <13 g/dL in males, ANC <1.8 × 10^9/L, plt <150 × 10^9/L	16	Change in high-sensitive C-reactive protein levels	NCT05483010
Canakinumab	CCUS (vs placebo)	Splicing mutation at any VAF, *TP53* at VAF >0.05, DTA and/or other CH-associated mutations in combination or at higher VAF	Hgb <11 g/dL, ANC <1.8 × 10^9/L and >0.5 × 10^9/L, plt <150 × 10^9/L and >50 × 10^9/L	110	Time to myeloid malignancy diagnosis	NCT05641831
	CCUS, LR-MDS	Any CH-associated mutation	WHO criteria[15,17]	70	Rate of hematologic improvement	NCT04239157
Curcumin	CCUS, LR-MDS, MPN (vs placebo)	Any CH-associated mutation	Hgb <11.3 g/dL in females or <12.9 g/dL in males, ANC <1.8 × 10^9/L, plt <150 × 10^9/L	30	Change in inflammatory cytokines and symptom scores	NCT06063486
Ascorbic acid	CCUS, RR lymphoma (IV)	*TET2*	Hgb <10, ANC <1.0 × 10^9/L, plt <100 × 10^9/L	55	Rate of hematologic improvement	NCT03418038
	CCUS, LR-MDS, CMML-0/1 (PO, vs placebo)	Any CH-associated mutation	Hgb <11.3 g/dL in females or <12.9 g/dL in males, ANC <1.8 × 10^9/L, plt <150 × 10^9/L	109[b]	Change in VAF from baseline	NCT03682029
Metformin	CCUS, LR-MDS	Any CH-associated mutation	Hgb <11.3 g/dL in females or <12.9 g/dL in males, ANC <1.8 × 10^9/L, plt <150 × 10^9/L	40	Safety (AEs, MTD) and feasibility (rate of recruitment and study completion)	NCT04741945

AEs, adverse events; ANC, absolute neutrophil count; CCUS, clonal cytopenias of undetermined significance; CH, clonal hematopoiesis; CMML, chronic myelomonocytic leukemia; DTA, *DNMT3A*, *TET2*, and *ASXL1*; Hgb, hemoglobin; IV, intravenous; LR, lower-risk; MDS, myelodysplastic syndromes; MPN, myeloproliferative neoplasms; MTD, maximum tolerated dose; plt, platelets; PO, by mouth; RR, relapsed/refractory; VAF, variant allele frequency, WHO, World Health Organization.

[a]Minimum VAF 0.02 unless otherwise specified.

[b]Actual enrollment, not actively recruiting.

according to the Centers for Disease Control and Prevention recommendations. Table 1 summarizes the current United States Preventive Services Task Force grade A and B guidelines for cancer screening in adults.

Given the increased risk of atherosclerotic cardiovascular disease, all patients with CH should undergo cardiovascular screening. In 2019, a clinical algorithm for the primary prevention of cardiovascular disease in patients with CH was proposed.[72] In general, all individuals should undergo laboratory monitoring, including a lipid panel, hemoglobin A1c test, and thyroid function test, every 6 to 12 months. If the individual has angina symptoms, urgent cardiology clinic referral is warranted for a stress test or left heart catheterization. However, if the patient has no angina symptoms, the risk of cardiovascular disease is calculated by the atherosclerotic cardiovascular disease (ASCVD) 10-year score,[73] a risk stratification tool validated for those older than 40 years. In younger patients, a coronary computed tomography (CT) angiogram should be considered. Recently, the use of coronary CT scans to calculate the coronary artery calcium score has been advocated to add additional risk stratification to the standard ASCVD score.[74] If needed, aspirin and/or an appropriate statin will then be initiated based on American College of Cardiology/American Heart Association guidelines.[75] Although there have been no prospective studies dedicated to CH patients with cardiovascular disease, a randomized, placebo-controlled clinical trial investigating DFV890 (an NLRP3 inhibitor) and MAS825 (a bispecific anti–IL-1β/IL-18 monoclonal antibody) for *DNMT3A*- and/or *TET2*-mutated CHIP patients with coronary artery disease is pending (NCT06097663).

Leukemia Prevention

No consensus guidelines exist regarding the monitoring of individuals with CH. Nevertheless, close hematologic monitoring with complete blood counts and potentially bone marrow evaluation is warranted, although the frequency of testing may vary depending on an individual's risk of developing a myeloid malignancy with prognostication tools such as the CHRS.[25] In general, repeated complete blood counts every 3 to 12 months, depending on the presence of cytopenias and predicted transformation risk, and a bone marrow evaluation with repeated mutational testing at the time of worsening cytopenias or symptoms concerning for progressive hematologic disease, are recommended.[76]

Certain antineoplastic therapies have been implicated in the development of therapy-related myeloid neoplasms. These oncologic agents, including alkylating agents, topoisomerase inhibitors, lenalidomide (particularly in *TP53*-mutated CH), and poly(ADP-ribose) polymerase inhibitors, are associated with the transformation of CH to therapy-related MDS or AML in some patients.[4,77-80] The fitness of specific CH mutations, such as in *TP53* and *PPM1D*, leads to clonal expansion and consequent progression to therapy-related myeloid neoplasms, especially under the selective pressure of antineoplastic therapy.[81-83] For cancer patients with CH, it is increasingly imperative to engage in a risk-benefit discussion regarding their planned oncologic therapies, future leukemic implications, and potential treatment modifications.

There are currently no US Food and Drug Administration–approved strategies for the prevention of hematologic malignancies in the setting of CH. However, several clinical trials are available for CCUS and are summarized in Table 2. The primary endpoints of the trials vary significantly, from safety/feasibility to hematologic response rates to changes in different inflammatory markers. The risk-benefit of treating CCUS remains unknown.

Need for Further Investigation

The identification of individuals with CH has surpassed the evidence base regarding surveillance and management. There is an urgent and unmet need for consensus guidelines on CH, from hematologic monitoring to extrahematologic comorbidity management to leukemia prevention. Future management guidelines will also need to account for the differential risk in CH mutations, such as a small *DNMT3A*-mutated clone vs a large clone harboring *TP53* mutations, as not all CH is the same. Although an inevitable consequence of aging, CH may lead to a better understanding of science and translation to patient care in the field of clonal expansion and cancer risk. Studying CH not only provides the opportunity to develop early-intervention prevention strategies for those at the highest risk of developing hematologic malignancies, but allows for a deeper comprehension of the biologic mechanisms and origins of myeloid neoplasms.

Disclosures

Dr Chien has consulted for AbbVie and Rigel. Dr DiNardo has received research support (to institution) from AbbVie, Astex, BeiGene, BMS, Foghorn Therapeutics, Immune-Onc Therapeutics, Jazz Pharmaceuticals, Rigel, Schrödinger, and Servier; has served as a consultant for or on the advisory board of AbbVie, AstraZeneca, BMS, Genentech, Genmab, GSK, ImmunoGen, Notable Labs, Rigel, Schrödinger, and Servier; and is supported by the LLS Scholar in Clinical Research Award. Dr Garcia-Manero has received research support from AbbVie, Astex, BMS, Chordia, Curis, Genentech, Novartis, Rigel, and Zentalis; and has received honoraria from Astex, Curis, and BMS.

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