MAYO CLINIC

REVIEW

Clinical Implications of Clonal Hematopoiesis

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Abstract

Clonal hematopoiesis (CH)—an expansion of blood cells derived from a single hematopoietic stem cell—is a defining feature of hematologic cancers, but recently CH was also found to be a frequent consequence of aging. When aging-associated CH results from acquisition of a somatic mutation in a driver gene associated with leukemia, and this mutation is present at a variant allele frequency of at least 0.02 (2%) yet the patient does not meet World Health Organization diagnostic criteria for a hematologic neoplasm, this state is termed *clonal hematopoiesis of indeterminate potential* (CHIP). CHIP is present in approximately 10% to 15% of people older than 70 years and more than 30% by age 85 years and represents a precursor state for neoplasia akin to monoclonal gammopathy of undetermined significance. Recently, CHIP was unexpectedly found to be an important risk factor for cardiovascular events, with accumulating evidence supporting a mechanism of accelerated atherogenesis as a result of vascular inflammation driven by clonally derived monocytes/macrophages. Risk factors for CHIP include aging, male sex, cigarette smoking, and a common germline variant in the telomere-associated gene *TERT*. Clonal hematopoiesis can also occur after cytotoxic chemotherapy or radiotherapy for a solid tumor, after hematopoietic stem cell transplant, in the context of aplastic anemia, or after induction chemotherapy for acute leukemia; in each setting, CH has distinct clinical implications. This review summarizes recent studies of CH and CHIP and outlines challenges in clinical management of affected patients.

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As we age, a substantial proportion of us will develop an expanded "clone" of blood cells bearing a somatic mutation in a leukemia-associated driver gene such as *DNMT3A* or *TET2* (for expansion of gene symbols, see http://www.genenames.org) yet will not fulfill any of the World Health Organization (WHO) diagnostic criteria for a hematologic malignancy.[1-3] Most people with such blood cell clones have an entirely normal complete blood cell count, or at most a slight elevation in the mean cell volume.

Such mutant marrow–derived clones are common, present at a variant allele frequency (VAF; ie, mutation burden, proportional to the number of abnormal cells) of 2% or greater in more than 10% of the population aged 65 years and older. When defined using a 2% VAF cutoff value (because very small clones with <0.05% VAF are almost universal in middle age and beyond), these clones confer a 0.5% to 1% annual risk of developing a hematologic cancer, mostly myeloid neoplasms, in the same way that the small plasma cell clones defining monoclonal gammopathy of undetermined significance (MGUS) represent a risk factor for overt plasma cell neoplasms such as myeloma or that monoclonal B-cell lymphocytosis can subsequently lead to chronic lymphoid leukemia or non-Hodgkin lymphoma.[4,5]

In addition, and of far greater public health consequence, clonal hematopoiesis (CH) increases an individual's risk of experiencing a myocardial infarction or stroke and of dying from a cardiovascular event.[2,6] Investigators are only just beginning to elucidate the mechanisms by which CH contributes to acute cardiovascular events. Compelling new evidence supports the concept that inflammatory proatherogenic interactions between circulating clonally derived cells and vascular endothelium accelerate vascular disease and increase the risk of atherosclerotic plaque rupture.[6,7]

In addition to aging-associated CH, CH can also occur in several other clinical settings, such as after aplastic anemia, hematopoietic stem cell transplant, or cytotoxic therapy for a nonmyeloid neoplasm (eg, adjuvant therapy for breast cancer). Clonal hematopoiesis is a neoplasia precursor state, similar to a colon polyp or atypical cellular changes in the breast, but it lacks an anatomical form and thus can be detected only by DNA sequencing. This review outlines the distinct states in which CH can be detected

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ARTICLE HIGHLIGHTS

- Clonal hematopoiesis—expansion of genetically identical blood cells derived from a single hematopoietic stem cell—is commonly observed in older persons.
- Clonal hematopoiesis is a risk factor for hematologic neoplasia, cardiovascular events, and overall mortality.
- Clonal hematopoiesis can also be observed in other settings, such as aplastic anemia, after therapy for a nonmyeloid neoplasm, after stem cell transplant, or after therapy for acute myeloid leukemia; clonal hematopoiesis has distinct implications in each of these settings.
- Clonal hematopoiesis cannot be treated directly, but clinical management includes monitoring for disease progression and attention to cardiovascular risk factors.

and the clinical implications in each setting. The PubMed and MEDLINE databases were searched for articles published from January 1, 2012, through March 1, 2018, using the following terms: *clonal hematopoiesis*, *myeloid neoplasia*, *age-related clonal hematopoiesis*, *myelodysplastic syndromes*, *acute myeloid leukemia*, and *somatic mosaicism*. Articles were considered for inclusion if they represented primary data or were review articles published in high-impact journals.

DISCOVERY OF CH IN THE GENERAL POPULATION

Although it has long been recognized that a small proportion of healthy individuals can be found transiently to have low levels of oncogenic genetic alterations in circulating blood cells, such as the *BCR-ABL* fusion that is associated with chronic myeloid leukemia, the discovery that CH is common in the general population is relatively recent. In 2012, Busque et al[8] observed that somatic *TET2* mutations were present in 5% of 182 older women with acquired age-related skewing of hematopoiesis, defined by imbalanced expression of polymorphic X-linked genes, 1 copy of which normally is unexpressed in each cell in females due to lyonization (ie, chromosome condensation) during fetal life.[8] *TET2* mutations are present in 15% to 25% of patients with myeloid neoplasms and were described as leukemia driver events in 2009, and such mutations had not previously been recognized in healthy persons without cancer.[9]

Also in 2012, 2 groups analyzed genomic array data from more than 50,000 people and reported that acquired chromosome mosaicism, including aneuploidy and large segmental deletions, occurs in 2% to 3% of elderly persons, but is rare before age 50 years.[10,11] Somatic mosaicism at the chromosome level in those series was associated with a 10-fold increased risk of developing a hematologic cancer, as well as reduced survival. Finally, in 2014, 3 independent groups of investigators analyzed DNA sequencing results from thousands of patients who had enrolled in large genome-wide association studies that had been conducted to assess genetic risk for nonhematologic diseases, such as schizophrenia or diabetes mellitus.[1-3] The 3 groups of investigators each noted that mutations in genes previously associated with the development of leukemia are common in older persons and that the frequency of these mutations increases with aging.

DEFINITION OF CHIP AND RISK FACTORS FOR DEVELOPMENT OF CHIP

In 2015, several colleagues and I proposed a new term to describe the presence of a clonal blood cell population associated with a leukemia driver mutation at a VAF of 2% or greater but in the absence of severe cytopenias or a WHO-defined disorder: CH of indeterminate potential (CHIP).[12] Although CHIP is not a hematologic disorder by itself, and in many cases this biological state has no detectable clinical consequences, CHIP is important to identify because it represents both a risk factor for evolution to various WHO-defined hematologic malignancies (Figure 1) and a cardiovascular danger. Perhaps due to the intellectually satisfying parallel with the well-described hematologic malignancy precursor states of MGUS (described by Robert Kyle and Jan Waldenström more than 40 years ago[13,14]) and monoclonal B-cell lymphocytosis,[15] as well as the need to have a term to easily communicate with other investigators about a common and clinically consequential state, the hematology community quickly adopted the acronym *CHIP*. CHIP was featured in a front-page story in the *New York Times* in January 2018—the first time the word *hematopoiesis* had appeared in the 167-year history of the *Times*.[16]