A CHIP off the old (MDS) block

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TITLE	Clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes.
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While clonal hematopoiesis (CH) is now considered a precursor to myeloid neoplasia, this concept is relatively new. Unlike other premalignant hematologic conditions, which have been recognized for decades (e.g., monoclonal gammopathy of undetermined significance [MGUS] was first characterized in the 1960s), Steensma *et al*. established the framework for CH in their landmark 2015 paper.[1]

This work highlights the importance of DNA sequencing to our understanding of myeloid neoplasia. Over the preceding years, researchers found that >85% of MDS harbor somatic mutations in a stereotyped set of genes. Simultaneously, similar changes were identified in healthy individuals as they aged – and although these were associated with an increased risk of blood cancer development (hazard ratio [HR]=11.1), most cases did not progress.[2] Given their partial overlap, it was initially unclear how to parse these phenomena. Furthermore, if the latter group had cytopenias, they would have met the criteria for myelodysplastic syndrome (MDS), leading to overdiagnosis. In this context, Steensma *et al*. codified a definition for CH (Figure 1) and proposed an updated diagnostic schema for MDS. By doing so, they deconvoluted the two conditions and established a myeloid disease spectrum.

Recognition of CH as a distinct entity permitted more extensive investigation and led to the identification of clinical

A

Clonal Hematopoiesis of Indeterminate Potential (CHIP)

Features:

- Absence of morphological evidence of a hematologic neoplasm
- Does not meet diagnostic criteria for PNH, MGUS or MBL
- Presence of a somatic mutation associated with hematologic neoplasia at a variant allele frequency of at least 2% *(e.g., DNMT3A, TET2, JAK2, SF3B1, ASXL1, TP53, CBL, GNB1, BCOR, U2AF1, CREBBP, CUX1, SRSF2, MLL2, SETD2, SETDB1, GNAS, PPM1D, BCORL1)*
- Odds of progression to overt neoplasia are approximately 0.5-1% per year, similar to MGUS

B

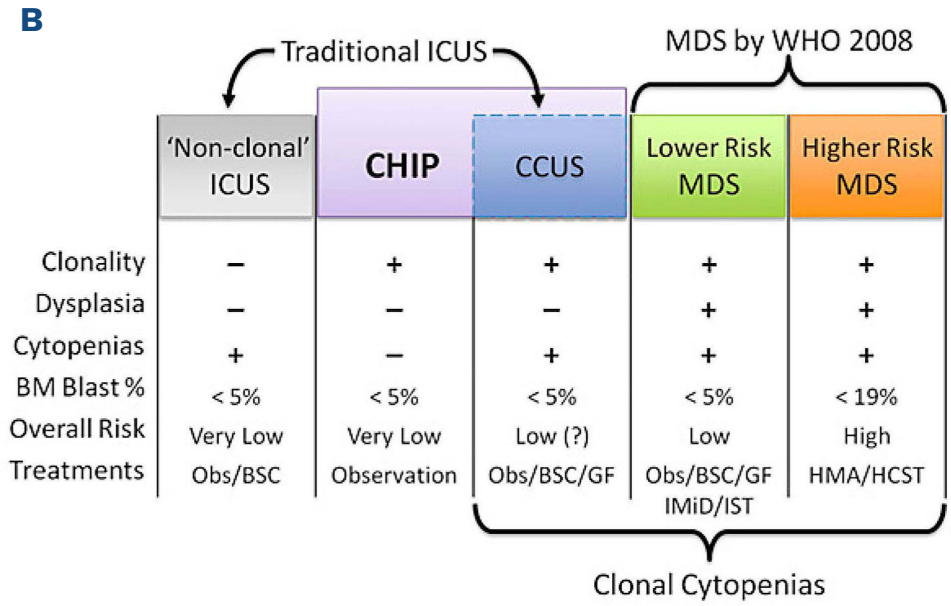

Figure 1. Definition of clonal hematopoiesis of indeterminate potential and its distinction from myelodysplastic syndromes and non-clonal cytopenic states. (A) A proposed definition of clonal hematopoiesis of indeterminate potential (CHIP). A mutation that is commonly associated with clonal expansion of hematopoietic cells in older persons should be present, whereas criteria for other diagnoses should not be met. Evidence of mildly disordered erythropoiesis, such as an elevated red cell distribution width or mean corpuscular volume, can be compatible with CHIP rather than myelodysplastic syndromes (MDS), and occasional dys-

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plastic cells might be seen, as is common in the general population with careful scrutiny of blood and marrow. CHIP is associated with an increased risk of all-cause mortality and subsequent diagnosis of hematologic malignancy. The 19 genes most commonly mutated in healthy older adults in sequencing studies to date are listed. The roster of CHIP-associated mutations will likely change in the future, with some genes being removed and others being added. As a working definition, we propose a variant allele frequency of 2% in order to be considered CHIP (since extremely deep sequencing will detect mutations in almost every person), but this may need to be revised with further population analyses. (B) The spectrum of clonal hematopoiesis, idiopathic cytopenias of undetermined significance (ICUS), and MDS. ICUS is a broad category that includes a heterogeneous group of individuals, some of whom have benign (nonclonal) hematopoiesis. Other patients with ICUS may have CHIP, differing only from lower-risk MDS by their lack of dysplasia and, currently, an undetermined disease risk. CHIP can also include patients with clonal hematopoiesis and non-malignant causes of cytopenias (e.g., immune cytopenias, liver disease, or nutritional deficiencies) who would not be considered to have ICUS because of the presence of a clone, but may have a distinct natural history. PNH: paroxysmal nocturnal hemoglobinuria; MGUS: monoclonal gammopathy of undetermined significance; MBL: monoclonal B-cell lymphocytosis; WHO: World Health Organization; CCUS: clonal cytopenias of undetermined significance; BM: bone marrow; Ob: observation; BSC: best supportive care; GF: hematopoietic growth factor (e.g., epoetin); HMA, hypomethylating agent (e.g., azacitidine); IMiD: immunomodulatory drug (e.g., lenalidomide); IST: immunosuppressive therapy; HSCT: hematopoietic stem cell transplant. Figure adapted, with permission, from Blood.[1]

sequelae. Progression to neoplasia is the most worrisome outcome, and identifying those at risk, prognostication, and management are paramount in cancer prevention. Multiple studies have confirmed that the prevalence of CH (~10% in individuals >65 years old) and average rate of progression (~0.5-1% per year) are on a par with similar precancers (e.g., MGUS). There are now many known risk factors for progression, and these have been integrated into a prognostic schema that can identify the small minority at high risk of developing myeloid neoplasia.[3] CH has also been linked to many non-neoplastic conditions. It was initially associated with an increased risk of developing severe coronary artery disease (HR=4.0) and now appears to affect cardiovascular disease more broadly (e.g., hypertension, thrombosis, stroke) as well. It has since been connected to various inflammatory pathologies (e.g., diabetes, vasculitis, osteoarthritis) and exaggerated immune responses (e.g., improved expansion of chimeric antigen receptor T cells). Importantly, patients with CH have an increased risk of death (HR=1.4) from all-cause mortality.

Like many significant discoveries, this paper enhanced our understanding of CH but raised further questions. Although it was the earliest form of CH identified and is potentially much more common than the better-known single nucleotide variants, the role of mosaic chromosomal abnormalities remains largely unexplored. As we have come to understand that inflammation likely drives CH development, more attention has been paid to circumstances under which it arises, particularly those that are iatrogenic. Recent reports of secondary myeloid malignancies following adoptive cell therapies and radioimmunoconjugates raise the question of whether they contribute to CH expansion and whether evaluation of CH should be considered when making treatment decisions.[4] The most pressing concerns involve management. While we can identify high-risk patients, the optimal timing and means of treatment remain unclear and warrant prospective studies in the future.

Disclosures

No conflicts of interest to disclose.

Contributions

SML and BTC contributed equally to this article.

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