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Letters to *Blood*

TO THE EDITOR:

Age-related diseases of inflammation in myelodysplastic syndrome and chronic myelomonocytic leukemia

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Myelodysplastic syndromes (MDS) and chronic myelomonocytic leukemia (CMML) are myeloid malignancies characterized by clonal expansion of hematopoietic cells, dyspoiesis of 1 or more lineages, and ineffective hematopoiesis. Years before displaying clinical or pathologic manifestations of MDS or CMML, patients may have clonal hematopoiesis of indeterminate potential (CHIP), an age-related nonmalignant clonal expansion of hematopoietic cells with myeloid malignancy–associated somatic driver mutations.[1-3] Increasing evidence associates clonal hematopoiesis with systemic inflammation and polymorphic clinical manifestations, including cardiovascular diseases.[4-6] Similarly, cardiovascular[7,8] and inflammatory diseases[9-11] have been observed in MDS and CMML, and chronic inflammatory stimuli have been implicated in the pathogenesis of myeloid neoplasia.[12,13]

Chronic inflammatory comorbidity and measurable increases in proinflammatory cytokine expression are observed features of "inflammaging," the chronic, low-grade, systemic inflammation that characterizes physiologic aging.[14] Inflammaging has been proposed as a unifying risk factor[15,16] for multiple age-related chronic cardiovascular,[17] pulmonary,[18] metabolic,[19,20] bone and joint,[21] and neurologic diseases.[22] Given the similarity of chronic inflammatory comorbidity noted in CHIP, MDS/CMML, and physiologic aging, we hypothesized that older adults with MDS and CMML, contending with the combined inflammatory stimuli of inflammaging and clonal hematopoiesis, would have an increased prevalence of a breadth of chronic inflammatory conditions in the 5 years antecedent to their MDS/CMML diagnosis.

We performed a case-control study comparing the prevalence of chronic inflammatory conditions previously associated with inflammaging[15] in MDS/CMML cases and controls. Data were acquired from the Surveillance, Epidemiology, and End Results cancer registry linked to Medicare administrative claims (SEER-Medicare), a cohort of patients aged ≥65 years representing 28% of all patients with cancer in the United States. To ensure at least 1 year of antecedent claims, MDS/CMML cases were patients aged ≥66 years diagnosed with MDS or CMML from 2002 through 2015. Two control groups were used. Solid tumor controls were patients aged ≥66 years diagnosed with nonhematologic invasive cancer from 2002 through 2015. Representative Medicare controls were chosen from a 5% sample of randomly selected Medicare beneficiaries who resided in SEER regions during the observation period. A solid-malignancy diagnosis was observed in 22% (n = 8774) of representative Medicare control subjects. Exclusion criteria included lack of continuous Medicare coverage, health maintenance organization (HMO) enrollment, diagnosis from death certificate or at autopsy, and death within 1 year of the diagnosis of the index malignancy. Controls were matched 2:1 to MDS/CMML cases based on the calendar year of diagnosis (±2 years), age (±2 years), sex, and registry location (Table 1; supplemental Figure 1, available on the *Blood* Web site). Medicare controls without a cancer diagnosis were observed starting at their matched case's MDS/CMML diagnosis date (pseudodiagnosis date), and matching was restricted to patients who survived ≥1 year beyond their assigned pseudodiagnosis date. Additional cohort selection details are available in supplemental Methods.

We identified 19 940 MDS/CMML cases, the majority of whom were male (53%), diagnosed with MDS (93%), and having MDS or CMML as their primary malignancy (75%). The median age at diagnosis was 78 years (interquartile range, 72-83). The primary outcome of our study was the prevalence of diseases of inflammaging in the 5 years antecedent to MDS/CMML diagnosis. Time intervals 6 months before diagnosis/pseudodiagnosis date were excluded to limit ascertainment bias. Prevalent conditions were identified from Medicare claims using international classification of disease codes (supplemental Methods), and conditions with 2 or more claims during the 54-month observation period were considered valid.

Diseases of inflammaging were significantly associated with MDS/CMML but not uniformly among all disease groups and diagnoses (Figure 1). Compared with representative Medicare controls, patients with MDS/CMML had a greater prevalence of antecedent cardiovascular (52% vs 36%, odds ratio [OR] 1.42; 95% confidence interval [CI], 1.37-1.48), pulmonary (28% vs 19%; OR, 1.27, 95% CI, 1.22-1.33), metabolic (48% vs 33%, OR, 1.28; 95% CI, 1.23-1.34), and bone and joint diseases (50% vs 38%; OR, 1.45; 95% CI, 1.41-1.51). Our data identify novel associations including greater prevalence of fatty liver disease (2% vs 0.6%; OR, 2.36; 95% CI, 2.03-2.76) and chronic renal disease (2% vs 0.5%; OR, 1.71; 95% CI, 1.62-1.81) in patients with MDS/CMML relative to matched controls. This is consistent with a

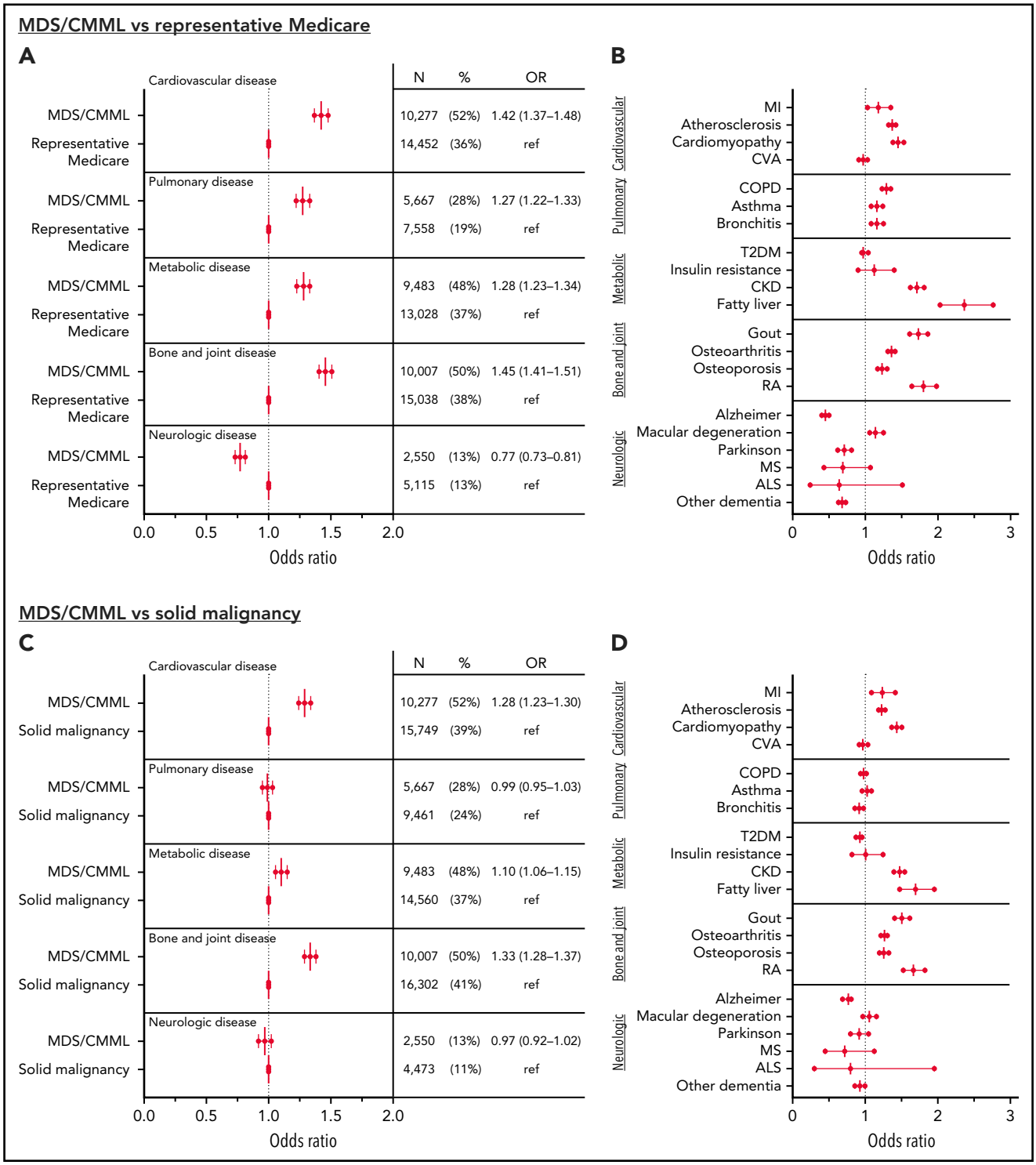

Figure 1. Prevalence of diseases of inflammaging. The prevalence of diseases of inflammaging in months −60 through −6 before diagnosis or at the pseudodiagnosis date was determined for patients with MDS/CMML, invasive solid tumor, or a representative Medicare population. Forest plots show ORs for prevalent diseases of inflammaging. (A) MDS/CMML vs representative Medicare by disease group. (B) MDS/CMML vs representative Medicare by individual diagnosis. (C) MDS/CMML vs solid tumor by disease group. Number of patients, prevalence (%), and OR (95%CI) are presented at the right of the forest plot. (D) MDS/CMML vs solid malignancy by individual diagnosis. Cardiovascular disease includes atherosclerotic heart disease, myocardial infarction (MI), cerebrovascular accident (CVA), and cardiomyopathy (heart failure); pulmonary disease includes chronic obstructive pulmonary disease (COPD), asthma, and chronic bronchitis; bone and joint diseases include a combination of osteopenia, osteoporosis, osteoarthritis, rheumatoid arthritis (RA), and gout; metabolic diseases include type 2 diabetes mellitus (T2DM), insulin resistance, fatty liver, and chronic kidney disease (CKD); and neurologic diseases include Alzheimer disease, Parkinson disease, amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), age-related macular degeneration, and non-Alzheimer dementias (other dementias). Numerical values for the ORs and 95% CIs for individual diagnoses are provided in supplemental Table 1.

Table 1. Baseline characteristics of the SEER-Medicare–matched cohorts

Characteristics*	MDS/CMML n = 19 940	Representative medicare† n = 39 880	Solid malignancy n = 39 880
Age, median (IQR)‡	78 (72-83)	78 (72-83)	77 (72-83)
Sex‡			
Male	10 569 (53)	21 136 (53)	21 136 (53)
Female	9 371 (47)	18 744 (47)	18 744 (47)
Race§			
White	17 348 (87)	33 898 (85)	34 696 (87)
Black	1 197 (6)	2 580 (6)	2 871 (7)
Other	599 (3)	1603 (4)	1 356 (3)
Asian	598 (3)	1 635 (4)	916 (2)
Unknown	198 (1)	164 (0)	41 (0)
Ethnicity			
Non-Hispanic	19 142 (96)	31 106 (78)	37 886 (95)
Hispanic	798 (4)	8 375 (21)	1 994 (5)
Data missing	—	399 (1)	—
Myeloid malignancy subtype			
CMML	1 410 (7)	—	—
MDS	18 530 (93)	—	—
NA	—	39 880 (100)	39 880 (100)
Year of index malignancy diagnosis‡			
2000-2001	—	—	1 994 (5)
2002-2005	5 384 (27)	10 768 (27)	10 369 (26)
2006-2010	7 577 (38)	15 154 (38)	15 155 (38)
2011-2015	6 979 (35)	13 958 (35)	12 362 (31)
Index malignancy is primary			
Yes	14 955 (75)	7 976 (20)	35 892 (90)
No	4 985 (25)	798 (2)	3 988 (10)
No malignancy diagnosis‖	—	31 106 (78)	—
Outpatient visits, median (IQR)¶	4 (1-9)	1 (0-4)	2 (1-6)
NCI comorbidity index¶			
0	16 426 (47)	41 154 (59)	38 585 (55)
1	7 966 (23)	14 636 (21)	16 407 (23)
2	4 667 (13)	7 204 (10)	7 707 (11)
≥3	5 910 (17)	6 944 (10)	7 239 (10)

IQR, interquartile range; NA, not available.

*Baseline characteristics ascertained from claims from months 0 to −12, relative to the index malignancy diagnosis/pseudodiagnosis. All characteristics are presented as n (%), unless otherwise specified.

†Representative Medicare cohort derived from a 5% random sample of Medicare recipients and excludes individuals with a history of hematologic malignancy.

‡Variables used in matching.

§Race derived from Medicare claims.

‖Of the representative Medicare controls subjects, 78% had no diagnosis of a malignancy.

¶Calculated from outpatient visits in months 0 to −12 relative to the index malignancy diagnosis/pseudodiagnosis.

recent report that suggests a causal relationship between CHIP and chronic renal disease.[23] Prior studies also have noted increased incident MDS in patients with rheumatoid arthritis[9] and osteoporosis.[24] The present work reinforces these associations and highlights a previously underrecognized association between prevalent gout and MDS/CMML (supplemental Table 1).

MDS/CMML[7,8] and CHIP[4,5,25] have been associated with increased risk of incident cardiovascular disease–related morbidity and mortality. Importantly, associations were not significantly changed when analysis was restricted to include only cases for which MDS/CMML was the primary malignancy (supplemental Table 2). In the same cohort of patients and controls with MDS/CMML, we observed greater hazards for incident cardiovascular, pulmonary, metabolic, and bone and joint diseases after MDS/CMML diagnosis compared with controls (supplemental Table 3). Five-year survival for our MDS/CMML cohort was 38% and this analysis of incident nonmalignant comorbidity was heavily confounded by competing risk of death. A limitation of these analyses is the lack of ability to measure the presence of CHIP in MDS/CMML and control populations. Future studies of comparably sized cohorts with available exome sequencing and functional studies are necessary to fully define causal relationships between CHIP and inflammaging. Still, our observations that inflammaging conditions are more prevalent in MDS/CMML adds to a growing body of indirect evidence that indicates that cardiovascular disease and a breadth of other diseases of inflammaging actually precede development of overt MDS/CMML occurring during a time period when the myeloid precursor CHIP may be present.

Compared with solid-malignancy controls, disease associations were attenuated, yet cardiovascular, metabolic, and bone and joint diseases remained significantly more prevalent in MDS/CMML. In contrast, pulmonary disease prevalence was not significantly greater in older adults with MDS/CMML compared with solid-malignancy controls. We attribute this observation to unmeasured risk factors for chronic pulmonary disease in patients with a solid malignancy, such as tobacco exposure, which is not reliably acquired from SEER or Medicare claims data. The inability to accurately assess potential confounders such as obesity and smoking status, which are shared predisposing factors for both MDS and many "inflammaging" conditions is a limitation of this analysis.

In contrast to most of the disease groups examined, neurodegenerative disease more prevalent in neither patients with MDS/CMML relative to controls, nor in patients with MDS and CMML examined separately (supplemental Tables 4 and 5). This is consistent with data that indicate similar rates of cognitive impairment in women with or without CHIP.[26] Similarly, the odds of having prevalent type 2 diabetes were not significantly greater in MDS/CMML in adjusted regression models and may be reflective of differences in distribution of unmeasured risk factors or biological differences in the effects of clonal hematopoiesis in different organ systems. For example, the macrophage activation and resistance to apoptosis in clonal hematopoiesis may simultaneously accelerate atherosclerosis[25] and fatty liver disease, attenuating disease phenotype in Alzheimer disease where macrophage apoptosis and phagocytic defects are implicated in pathogenesis.[27]

Overall, these data provide evidence of a broad inflammaging phenotype that precedes MDS/CMML diagnosis. Emerging data suggest that the association between clonal hematopoiesis and nonmalignant comorbidity may be bidirectional. Macrophage and inflammasome activation[5] in clonal hematopoiesis contributes to the etiology of inflammaging conditions, such as atherosclerosis,[4,6,25] and the systemic inflammation caused by age-related inflammatory comorbidity[14] may also drive clonal expansion and selection in the pathogenesis of myeloid neoplasia.[10-13] Functional studies will help determine causal relationships, and prospective evaluations will better elucidate specific factors influencing nonmalignant outcomes in CHIP, MDS, and CMML. The notion of a shared pathophysiology between a constellation of nonmalignant comorbidities and myeloid neoplasia invites consideration of therapeutic interventions that simultaneously address malignant and nonmalignant phenotypes by targeting common inflammatory pathways.

Acknowledgments

The authors thank National Cancer Institute, the Office of Research, Development, and Information, Centers for Medicare and Medicaid Services (CMS), Information Management Services (IMS), Inc, and the SEER Program tumor registries for contributing to the creation of the SEER-Medicare database. This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors.

This work was supported by the National Institutes of Health, National Heart, Lung, and Blood Institute (NHLBI) Grant R01HL082945 and National Cancer Institute (NCI) grants P01CA108631 and P50CA206963; the Howard Hughes Medical Institute; the Edward P. Evans Foundation; the Adelson Medical Research Foundation; and the Leducq Foundation (B.L.E.); and by NIH, NHLBI grant T32HL116324-07 and the American Society of Hematology (ASH)/Robert Wood Johnson Foundation (RWJF) Harold Amos Faculty Development Program (L.D.W); and by the Deutsche Forschungsgemeinschaft (DFG; AG252/1-1). C.R.M. received support from the NIH, NCI Grant K22CA251648. The collection of the cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885, NCI's SEER Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute, and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement U58DP003862-01 awarded to the California Department of Public Health. The ideas and opinions expressed herein are those of the author(s) and endorsement by the State of California Department of Public Health, the NCI, and the Centers for Disease Control and Prevention or their Contractors and Subcontractors is neither intended nor should be inferred.

Authorship

Contribution: L.D.W., C.R.M., D.S., and B.L.E. conceived and designed the study. L.D.W performed manual review of the electronic medical records; L.D.W., C.R.M., and R.R. performed the data analysis and prepared the figure and table; L.D.W wrote the manuscript; and C.M., M.A., A.L., G.A., R.M.S, D.S., and B.L.E. critically reviewed and edited the manuscript.

Conflict-of-interest disclosure: B.L.E. has received research funding from Celgene, Deerfield, Novartis, and Calico and consulting fees from Grail. He serves on the scientific advisory boards and holds equity in Skyhawk Therapeutics, Exo Therapeutics, Neomorph Therapeutics, and TenSixteen Bio. D.S. has received research funding from Grail and from AACR for project GENIE. She has received personal speaker and travel fees from Pfizer and personal fees for editorial services from The *Journal of the American Medical Association* (JAMA). M.A. is cofounder of Iuvando Health and holds equity in the company. R.M.S. reports grants from AbbVie, Agios, Arog, and Novartis. He has received personal fees from AbbVie, Actinium, Agios, Argenx, Astella, AstraZeneca, Biolinerx, Celgene, Daiichi-Sankyo, Elevate, Gemoab, Janssen, Jazz, Macrogenics, Novartis, Otsuka, Pfizer, Hoffman LaRoche, Stemline, Syndax, Syntrix, Syros, Takeda, and Trovagene for projects unrelated to the submitted work. The remaining authors declare no competing financial interests.

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Footnotes

Submitted 13 October 2021; accepted 30 November 2021; prepublished online on *Blood* First Edition 7 December 2021. DOI 10.1182/blood.2021014418.

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The code used for statistical analysis is available upon request by e-mail to the corresponding author (benjamin_ebert@dfci.harvard.edu).

The online version of this article contains a data supplement.

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DOI 10.1182/blood.2021014418