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Editorial

EDITORIAL

CHIPing Away at Breast Cancer

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In this issue of the Journal, Comen et al. examine the relationship between clonal tumor infiltrating leukocytes (TILeuks) and the development of myelodysplastic syndrome (MDS) or acute myeloid leukemia (AML) in individuals with early-stage breast cancer (1). One of the most feared consequences of cytotoxic chemotherapy or radiation used in the treatment of solid tumors is the development of subsequent MDS or AML, known as a therapy-related myeloid neoplasms (2). Because these leukemic clones evolve in the presence of chemotherapy, they tend to be driven by a spectrum of mutations shaped by the selection pressure of cytotoxic therapy and are thereby intrinsically resistant to most conventional antileukemic therapies and curable only with allogeneic hematopoietic stem cell transplantation. Understanding which patients with solid tumors are at highest risk of developing MDS or AML has the potential to inform strategies to improve early detection or even prevention of therapy-related myeloid neoplasms.

The presence of a clonal population of cells in the peripheral blood of otherwise normal individuals has been termed clonal hematopoiesis. When a clone contains a leukemia-associated mutation present at a variant allele fraction of at least 2% and the individual does not have morphologic evidence of a blood cancer, the state has been termed clonal hematopoiesis of indeterminate potential (CHIP) (3–5). These mutations are believed to occur within the hematopoietic stem cell and provide the mutant clone with a competitive advantage. Not surprisingly, patients with CHIP have an increased risk of developing hematologic malignancies such as MDS and AML. Multiple studies have identified features that might predict which patients with CHIP will go on to develop MDS or AML. These risk factors include the specific gene mutation, the size of the mutant clone as measured by the variant allele fraction, and the presence of more than one mutation (6,7).

Recent findings indicate that patients with cancer treated with chemotherapy who have CHIP are at an increased risk of developing a therapy-related myeloid neoplasm (8,9). In patients with relapsed non-Hodgkin lymphoma receiving high-dose chemotherapy followed by autologous stem cell transplant, those with preexisting CHIP were at an almost fourfold increased risk of developing MDS or AML compared with those without CHIP (10). All these patients had received chemotherapy before the identification of CHIP; thus it remains unclear whether cytotoxic therapies induce DNA damage and thus generate de novo mutations or just select for small preexisting mutant hematopoietic clones. Understanding how these premalignant clones grow, evolve, and interact within normal tissues is an open question.

The presence of mutant hematopoietic cells has effects beyond increasing the risk for development of MDS and AML. Patients with CHIP have increased levels of coronary artery disease, myocardial infarction, and stroke (4). The most commonly mutated genes in CHIP, *DNMT3A* and *TET2*, encode epigenetic regulators that when lost lead not only to a hematopoietic stem cell advantage but also to alterations in the function of terminally differentiated hematopoietic cells (11). The increased cardiovascular disease risk seen in patients with CHIP is thought to be at least partially due to hyperactive inflammatory signaling in mutant macrophages mediated by increased expression of cytokines such as interleukin-1β (12). Whether this hyperinflammatory phenotype might also play a role in promoting the growth of solid tumors is unknown, but many solid tumors are supported by tumor-associated macrophages and an inflammatory tumor microenvironment has been shown to be important for the growth of some solid tumors (13). This raises the possibility that mutant hematopoietic cells might alter the tumor microenvironment in some way that promotes tumor growth or decreases the efficacy of conventional cytotoxic therapies. In support of this hypothesis, patients with advanced solid tumors have increased rates of CHIP compared with the general population and the presence of CHIP in these patients is associated with worse clinical outcomes (14). Although no increased risk for solid tumors was identified in the large retrospective CHIP studies in healthy individuals reported to date, it is possible that not all CHIP

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mutations lead to a protumor microenvironment or that only some subtypes of cancer would be affected by the presence of an inflammatory tumor microenvironment and thus a connection between CHIP and solid tumor development could have been missed in these analyses.

In an effort to better understand the tumor microenvironment and risk factors associated with the future development of a therapy-related myeloid neoplasm in patients with early-stage breast cancer who received adjuvant chemotherapy and/or radiation, Comen et al. assessed the presence of mutations within TILeuks in seven breast cancer patients who went on to develop AML (1). To identify mutations, the AML samples were analyzed by deep sequencing of a panel of genes recurrently mutated in myeloid neoplasms. Then, TILeuks were microdissected away from breast cancer cells, and both cell populations were examined by amplicon-based sequencing targeting the previously identified mutations. In four of the seven patients, the mutations found in the AML were enriched within the TILeuk sample, demonstrating that these mutations were present in the hematopoietic compartment before the development of the therapy-related myeloid neoplasm. Cells from the mutant hematopoietic clone therefore infiltrate and become part of the tumor microenvironment. The authors were unable to exclude the possibility that previous chemotherapy can induce the generation of these mutations because two of the patients had received therapy before tumor resection (radioiodine for thyroid cancer and neoadjuvant therapy for the breast cancer).

The results from this study and other recently published work suggest that the presence of mutations typically restricted to hematologic malignancies found within solid tumors is likely due to contamination by infiltrating clonal hematopoietic cells (1,15). Although laser-capture microdissection of TILeuks is a research technique that would be difficult to implement in a clinical setting, these mutations are likely to be captured by bulk sequencing of tumor samples, which contain tumor, stromal, and hematopoietic cells. Future work will be needed to determine whether these mutant TILeuks alter the tumor microenvironment in a meaningful way, whether their presence is affected by cytotoxic therapies, and if their detection could represent a biomarker for increased risk of therapy-related myeloid neoplasms.

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References

1. Comen EA, Bowman RL, Selenica P, et al. Evaluating clonal hematopoiesis in tumor infiltrating leukocytes in breast cancer and secondary hematologic malignancies. *J Natl Cancer Inst*. 2020;112(1):djz157.
2. McNerney ME, Godley LA, Le Beau MM. Therapy-related myeloid neoplasms: when genetics and environment collide. *Nat Rev Cancer*. 2017;17(9):513–527.
3. Xie M, Lu C, Wang J, et al. Age-related mutations associated with clonal hematopoietic expansion and malignancies. *Nat Med*. 2014;20(12):1472–1478.
4. Jaiswal S, Fontanillas P, Flannick J, et al. Age-related clonal hematopoiesis associated with adverse outcomes. *N Engl J Med*. 2014;371(26):2488–2498.
5. Genovese G, Kahler AK, Handsaker RE, et al. Clonal hematopoiesis and blood-cancer risk inferred from blood DNA sequence. *N Engl J Med*. 2014;371(26):2477–2487.
6. Abelson S, Collord G, Ng SWK, et al. Prediction of acute myeloid leukaemia risk in healthy individuals. *Nature*. 2018;559(7714):400–404.
7. Desai P, Mencia-Trinchant N, Savenkov O, et al. Somatic mutations precede acute myeloid leukemia years before diagnosis. *Nat Med*. 2018;24(7):1015–1023.
8. Gillis NK, Ball M, Zhang Q, et al. Clonal haemopoiesis and therapy-related myeloid malignancies in elderly patients: a proof-of-concept, case-control study. *Lancet Oncol*. 2017;18(1):112–121.
9. Takahashi K, Wang F, Kantarjian H, et al. Preleukaemic clonal haemopoiesis and risk of therapy-related myeloid neoplasms: a case-control study. *Lancet Oncol*. 2017;18(1):100–111.
10. Gibson CJ, Lindsley RC, Tchekmedyian V, et al. Clonal hematopoiesis associated with adverse outcomes after autologous stem-cell transplantation for lymphoma. *J Clin Oncol*. 2017;35(14):1598–1605.
11. Sperling AS, Gibson CJ, Ebert BL. The genetics of myelodysplastic syndrome: from clonal haematopoiesis to secondary leukaemia. *Nat Rev Cancer*. 2017;17(1):5–19.
12. Jaiswal S, Natarajan P, Silver AJ, et al. Clonal hematopoiesis and risk of atherosclerotic cardiovascular disease. *N Engl J Med*. 2017;377(2):111–121.
13. Greten FR, Grivennikov SI. Inflammation and cancer: triggers, mechanisms, and consequences. *Immunity*. 2019;51(1):27–41.
14. Coombs CC, Zehir A, Devlin SM, et al. Therapy-related clonal hematopoiesis in patients with non-hematologic cancers is common and associated with adverse clinical outcomes. *Cell Stem Cell*. 2017;21(3):374–382.e4.
15. Ptashkin RN, Mandelker DL, Coombs CC, et al. Prevalence of clonal hematopoiesis mutations in tumor-only clinical genomic profiling of solid tumors. *JAMA Oncol*. 2018;4(11):1589–1593.