Comment on Kolijn et al, page 1557

Premonoclonal B-cell lymphocytosis: the CLL cell of origin

Gerald Marti | National Heart, Lung, and Blood Institute

In this issue of *Blood*, Kolijn et al¹ demonstrate the findings of a longitudinal analysis of chronic lymphocytic leukemia (CLL) buffy coat genomic DNA.

Using next-generation sequencing, Kolijn et al sequenced the B-cell receptor (BCR) immunoglobulin heavy chain (IgH) repertoire for patients with CLL in blood samples collected up to 22 years before the diagnosis of CLL. Their findings include B-cell repertoire skewing and the dynamics of clonotypic evolution regardless of IgH mutational status or stereotypy. Mutational status is defined as unmuted CLL (U-CLL) if the IqHV sequence shows \geq 98% homology (identical) to a reference germ line sequence and as mutated (M-CLL) if the IgH sequence shows <98% homology. Stereotypy is defined by the IqHV CDR3 sequence, and distinct subsets have been defined for CLL. The diagnostic BCR IgHV sequence could be detected in the background or as a dominate clonotype $\geq 2\%$ in most samples tested. IgHV mutational status and stereotypy have clinical significance at the time of diagnosis in terms of indolent or aggressive disease, but there was no difference in the time from first appearance of the clonotype to the time of clinical diagnosis, whether U-CLL or M-CLL. The key finding is that these early clonotypic changes seem to prolong the already indolent preclinical stage of CLL. Also, the poor-prognosis stereotype subset 2 (CDR3 sequence associated with worse prognosis) and U-CLL clonotype were found 16 years before the diagnosis of CLL. These findings represent the earliest detection of a clonotypic precursor cell for CLL.

Some time ago, using routine flow cytometric immunophenotyping, we and others observed a precursor to CLL in healthy individuals without hematologic abnormalities.² It was defined as monoclonal B-cell lymphocytosis (MBL). Absolute B-cell lymphocyte count was used as a cutoff to define CLL as >5000 clonal B cells per μL of blood.³ Low-count MBL was further defined as MBL \leq 500 cells per microliter or clone occupation \geq 85% of the B-cell population and sometimes referred to as population-based MBL. High-count MBL, referred to as clinical MBL, exists when B-cell lymphocytosis is >500 B cells per μL but <5000 cells per microliter. Low-count MBL is usually stable and non-progressive. However, the longitudinal study of MBL in familial CLL by Slager et al⁴ shows that low-count MBL may progress to high-count MBL.

Clinical high-count MBL is associated with increased infections and second primary tumors; Mayo data suggest that the risk of infection, even without hypogammaglobulinemia, is greater than the risk of progression to CLL,⁵ and a similar finding for the relationship between high-count MBL seems to exist for second primary tumors. Salamanca investigators showed that these clinical correlations were also present in patients with low-count MBL, accompanied by a decrease in overall survival.⁶ Given the fact that very few cases of low-count MBL progress to CLL, low-count MBL has been designated an age-related immune senescence.³

Given the recognition of MBL as the precursor state in CLL, a question arises as to what determines which MBL cases progress. A partial answer to this question is that some of the same prognostic markers of early CLL (Rai stage 0, Binet A) are found in high-count MBL and to a lesser extent in low-count MBL. The data would suggest that the pathway to the "evolution from low-count MBL to highcount MBL and subsequently [treatment naïve] CLL occurs in a stepwise fashion, with gradual acquisition of high-risk genetic abnormalities."⁷ In particular, the studies by Kostopoulos et al⁷ have delineated some of these earliest cytogenetic changes in high-count MBL. Clonal evolution can occur in stable low count.

Now that the emergence of the clonotypic cell in CLL can be detected and followed through a pre-MBL stage to both low count and high count, what are the first steps in leukemogenesis and lymphomagenesis that precede the appearance of a clonotypic cell? And what is the anatomic location of this pre-MBL cell? Lymph node? Bone marrow? Peripheral blood? The laboratory of Wiestner in collaboration with the Chiorazzi laboratory studied the proliferation rate of a subpopulation of proliferating lymphocytes in CLL and found that the lymph node has the highest rate of proliferation, followed by cells circulating in blood, with bone marrow showing the lowest rate of proliferation.⁸ The presence of proliferation centers in CLL lymph nodes is also well known, and a nodal MBL correlate has been identified.

In terms of a pregerminal center or postgerminal center cell of origin, both suggest a lymph node as the site of origin but do not rule out either bone marrow or spleen as the initial source of this long-sought-after cell of origin in CLL. B-cell subsets have not been extensively examined, particularly in the setting of vaccination. However, the role of autonomous cell signaling and chronic immune stimulation in low-count MBL needs to be further investigated. Where do we go from here? CLL has a long evolutionary history in which early branching may start as an oligoclonal process (antigen stimulation) and include driver mutations. A long-term analysis of the B-cell repertoire in familial CLL might shed light on this process. Further clarification of the mechanisms of age-related immune senescence is also of interest.

In conclusion, a clonotypic cell or cluster predates the onset of either lowcount or high-count MBL dating back to between 16 and 22 years. The multiclonal dynamics of pre-MBL may equal or surpass this process that has been observed during the course of CLL.⁹ Dissecting or separating this clonotypic cell from a polyclonal background presents a new challenge.

Downloaded from http://ashpublications.net/blood/article-pdf/139/10/1436/1879403/bloodbid2021014339c.pdf by guest on 08 June 2024

Conflict-of-interest disclosure: The author declares no competing financial interests.

REFERENCES

- Kolijn PM, Saberi Hosnijeh F, Späth F, et al. High-risk subtypes of chronic lymphocytic leukemia are detectable as early as 16 years prior to diagnosis. *Blood*. 2022;139(10): 1557-1563.
- Marti GE, Rawstron AC, Ghia P, et al; International Familial CLL Consortium. Diagnostic criteria for monoclonal B-cell lymphocytosis. Br J Haematol. 2005;130(3): 325-332.
- Scarfò L, Ghia P. What does it mean I have a monoclonal B-cell lymphocytosis? Recent insights and new challenges. *Semin Oncol.* 2016;43(2):201-208.
- Slager SL, Lanasa MC, Marti GE, et al. Natural history of monoclonal B-cell lymphocytosis among relatives in CLL families. Blood. 2021;137(15):2046-2056.
- 5. Parikh SA, Kay NE, Shanafelt TD. Monoclonal B-cell lymphocytosis: update on

PLATELETS AND THROMBOPOIESIS

Comment on Lee et al, page 1564

Vaccinations and ITP: keep on track(ing)

Tamam Bakchoul and Anurag Singh | University Hospital of Tuebingen

In this issue of *Blood*, Lee et al report a retrospective analysis of the effects of SARS-CoV-2 vaccination on thrombocytopenia in patients with immune thrombocytopenia (ITP).¹ This study shows that SARS-CoV-2 vaccines are safe in general for patients with preexisting ITP. Although the data presented should encourage the administration of both the doses of 2-dose vaccines to counter the virus, the authors also observed that thrombocytopenia exacerbations may occur, and, hence, careful monitoring is required. The authors emphasize the need for more careful postvaccination tracking of vulnerable patient groups, such as those who have had splenectomy and those who have received 5 or more therapies for ITP because they have a higher risk for worsening thrombocytopenia.

A major breakthrough was achieved in the ongoing COVID-19 pandemic by the rapid development, emergency rollout, and administration of several vaccines against SARSCoV-2 coronavirus.² There has also been a global push to understand potential side effects, especially in patients with comorbidities. Although SARS-CoV-2 vaccines are largely effective and safe, with the increasing number of vaccinated individuals across the world, there have been reports of thrombocytopenia after vaccinations with SARS-CoV-2 vaccines.³

The goal of the study by Lee et al was to track the development of de novo ITP in patients after COVID-19 vaccination and to track postvaccination exacerbation in preexisting patients with ITP. The authors used 4 different data sets to look for thrombocytopenia post-SARS-CoV-2 vaccination. They used Vaccine Adverse Events Reporting System for estimating the cases of a de novo ITP. Furthermore, for patients with preexisting ITP, data from a 10-center retrospective study, and surveys distributed by the Platelet

diagnosis, clinical outcome, and counseling.

Clin Adv Hematol Oncol. 2013;11(11):

6. Criado I, Rodríguez-Caballero A, Gutiérrez

ML, et al; Primary Health Care Group of

monoclonal B-cell lymphocytosis persists

7. Kostopoulos IV, Paterakis G, Pavlidis D,

2018;103(7):1198-1208.

2017;31(6):1340-1347.

DOI 10.1182/blood.2021014339

Salamanca for the Study of MBL. Low-count

after seven years of follow up and is associ-

ated with a poorer outcome. Haematologica.

et al. Clonal evolution is a prognostic factor

B-cell lymphocytosis. Blood Cancer J. 2017;

for the clinical progression of monoclonal

8. Herndon TM, Chen SS, Saba NS, et al. Direct

marrow and peripheral blood. Leukemia.

9. Zhao Z, Goldin L, Liu S, et al. Evolution of

of a CLL patient. Nat Commun. 2016;7:

multiple cell clones over a 29-year period

in vivo evidence for increased proliferation of

CLL cells in lymph nodes compared to bone

720-729

7(8) e 597

13765.

Disorder Support Association (PDSA) and the United Kingdom (UK) ITP Support Association. From the Vaccine Adverse Events Reporting System dataset, 77 cases of de novo ITP were identified at ~1 week postvaccination. Of these, 92.9% (26/28 of available data) responded well to treatment with corticosteroids and/ or intravenous immunoglobulin, and/or platelet transfusions (see figure).

In 109 patients identified with preexisting ITP who received a SARS-CoV-2 vaccine, approximately 20% experienced an ITP exacerbation following the first dose with 14 of 70 patients having an exacerbation after the second dose. Data from the Platelet Disorder Support Association (57 patients) and UK surveys (43 patients) confirmed the absence of severe bleeding but identified splenectomy as a risk factor for an ITP exacerbation. Along with splenectomy, 5 or more prior lines of therapy for ITP was also shown to increase risk of exacerbation. Response to treatment and outcomes were also favorable in the patients with preexisting ITP, and no major bleeds were reported after vaccination. Therefore, the authors concluded that ITP might worsen in some patients with preexisting ITP, or may occur de novo post-SARS-CoV-2 vaccination. However, under both circumstances, patients respond well to treatment regimes. Most importantly, although vaccinations were applied intramuscularly, no local vaccination-related hematomas were reported in this study. Authors recommend, however, a proactive monitoring of platelet counts for patients with known ITP, and especially those in high-risk groups including postsplenectomy and more refractory disease. Cases of de novo ITP were reported previously in healthy recipients following SARS-CoV-2 vaccination followed with a broad global attention.4,5 Although rare but serious adverse events have also been reported with a higher fatality rate after ChAdOx1 nCoV-19 (AstraZeneca) vaccination.^{6,7} These thrombotic events associated with thrombocytopenia after vaccination against SARS-CoV-2 are collectively referred as vaccine-induced immune thrombotic thrombocytopenia or thrombosis with thrombocytopenia syndrome.⁸ Cases of thrombosis, including cerebral venous sinus thrombosis, associated with severe thrombocytopenia have also been reported after administration of Ad26.COV2.S vaccine (Johnson & Johnson/Janssen).⁹ This important study