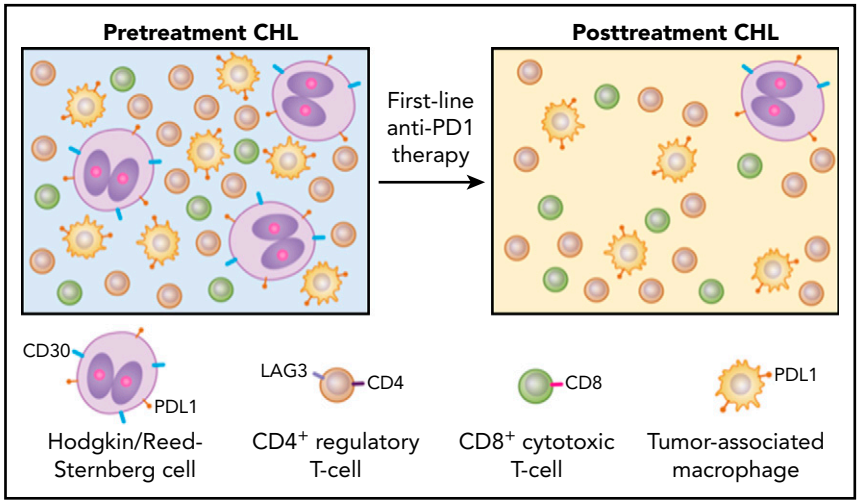

Anti-PD1 blockade as first-line therapy in early-stage unfavorable CHL shows distinct differences in clinical and histologic response. CHL exhibits rare malignant HRS cells in a TME enriched for inflammatory cells, particularly $CD4^+LAG3^+$ Tr1s, $PDL1^+$ TAMs, and fewer $CD8^+$ cytotoxic T cells (left). Biopsies following first-line anti–PD1-based therapy in early-stage unfavorable CHL patients show dramatic decrease in $CD30^+PDL1^+$ HRS cells along with depletion of Tr1 cells and $PDL1^+$ TAMs, especially in the vicinity of HRS cells, with no expansion of $CD8^+$ cytotoxic T cells (right). These findings underscore significant differences in the TME composition of pre- and posttreatment CHL and favor withdrawal of survival factors rather than cytotoxic immune responses as the most likely mechanism of action in first-line immune checkpoint blockade.

the survival of HRS cells and the preservation of its TME. These findings raise the intriguing possibility that a treatment naïve CHL TME is fundamentally different from that of r/r CHL.[1] In the relapse setting, CHL subclones may have emerged that have acquired the capacity to remodel their TME differently and/or are less addicted to an altered TME for survival.

Genetic and epigenetic alterations that generate intratumoral heterogeneity also affect the TME and lead to divergent responses and resistance to immunomodulatory therapy. Neoepitope loss and immunoediting have been proposed as likely mechanisms that regulate intratumoral diversity. These changes are aligned with clinical observations in subsets of patients with r/r CHL, where tissue biopsies show differences in histologic growth patterns, increased numbers and confluence of HRS cells, and changes in immunophenotypic profiles that were not present in the original biopsies. In solid tumors and r/r CHL, the intrinsic ability of the tumor to continuously recruit effector T cells is essential for tumor regression and clinical response after immune checkpoint blockade.[6-8] The lack of an effector T-cell response therefore raises the critical question of why withdrawal of survival factors appear to dominate first-line inhibition of the PD1–PDL1 axis in treatment-naïve CHL patients. Further investigation in larger cohorts receiving first-line immune checkpoint blockade therapy is warranted to explore this important question.

In summary, the findings reported by Reinke et al contribute another notable step forward in the understanding of the CHL TME and highlight essential differences in de novo vs recurrent disease. Although many aspects of the CHL TME remain elusive, the success of first-line immune checkpoint blockade holds promise for durable clinical response coupled with reduced toxicity in patients with CHL and other tumors with an immune infiltrated microenvironment.

Conflict-of-interest disclosure: The authors declare no competing financial interests. ■

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CLINICAL TRIALS AND OBSERVATIONS

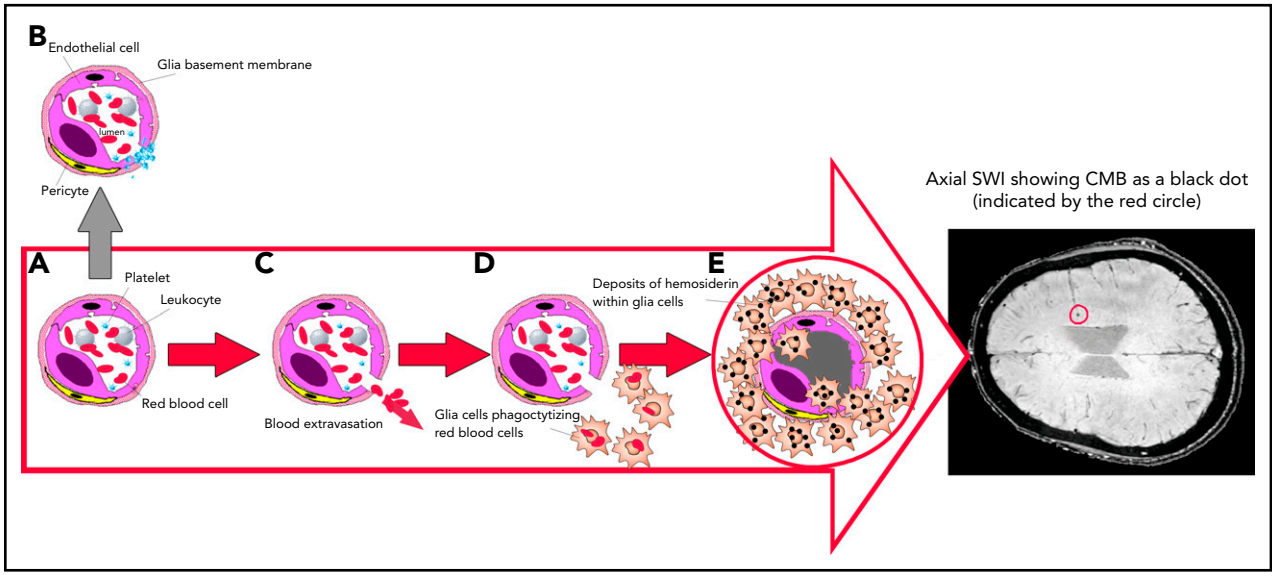
Comment on Cooper et al, page 2875

Cerebral microbleeds in ITP: alarming or innocent?

Francesco Rodeghiero | Hematology Project Foundation

In this issue of *Blood*, Cooper et al show that a substantial proportion of adults with immune thrombocytopenia (ITP) presents asymptomatic cerebral microbleeds (CMBs) as revealed by susceptibility-weighted magnetic resonance imaging (SWI), as illustrated in the figure. This unexpected finding raises critical questions both for the individual patient and for the management strategy of ITP.[1]

ITP is the most frequently acquired isolated thrombocytopenia affecting children and adults, with an annual incidence of 3 to 6 new cases per 100 000. ITP is caused by autoantibodies and autoreactive lymphocytes that recognize megakaryocytes and



Mechanism of SWI of occult CMBs. Breaks in the exceedingly small blood vessels, like capillaries or postcapillary venules, are followed by extravasation of a thin amount of blood. The wall of these microvessels, made by interconnected endothelial cells, covered by a glia basement membrane with embedded pericytes (A), prevents blood from leaking out. If vessel damage occurs in healthy people, a multilayer of platelets is immediately formed to close the break, avoiding blood extravasation (B). However, if platelets are severely reduced, like in ITP, blood cells can escape and invade the cerebral parenchyma (C), inducing glia cells activation into macrophages that phagocytize escaped cells and degrade the hemoglobin into nontoxic hemosiderin deposits (D), preventing the toxicity of free iron. Hemosiderin-laden macrophages (E) may persist indefinitely. Because of their high iron content, SWI allows the detection of CMBs, that appear as small black dots, as shown in the encircled area of the axial brain representation.

platelets, leading to insufficient production of platelets to compensate for their increased destruction. The diagnosis is still by exclusion, requiring a platelet count $<100 \times 10^9$/L without apparent cause.

Bleeding, particularly in skin and mucosae, is limited to patients with a platelet count <50 to 30×10^9/L. In children, most cases resolve spontaneously and are usually untreated due to the lower risk of bleeding. By contrast, in ~70% of adults, the disease is chronic, and treatment is often required to permit a near-normal or normal lifestyle by reducing the risk of major hemorrhage. In most patients, significant bleeding is rare unless the platelet count is $<20 \times 10^9$/L and may be absent or minimal even with a count as low as 5 to 10×10^9/L. In other patients with similar counts, bleeding may be impressive, particularly at diagnosis, with extensive purpura and mucosal hemorrhage. The overall bleeding mortality rate in adults is estimated to be ~1% to 2%. However, the risk is much higher, up to 10% to 15%, in older unresponsive patients. The weak and intriguing relationship between bleeding severity and platelet count has not been fully explored. From 1 side, more young and active platelets may circulate in some phases of the disease, explaining the patient's shorter bleeding time at the same platelet count compared with other thrombocytopenic statuses.[2] On the other side, the endothelium is also a critical component, and its fragility in ITP was implied by older studies showing that corticosteroids improved skin and mucosal bleeding manifestations 1 to 2 days before any platelet count increase was observed.[3,4] Finally, we now know from immunopathology studies that ITP patients have an increased concentration of proinflammatory cytokines.[5] These 3 factors, namely platelet intrinsic activity, endothelium damage, and inflammation, contribute to the unpredictability of the bleeding risk and to the weak correlation with the actual platelet count. These uncertainties cause anxiety in patients (and doctors). Accordingly, the main goal of treatment in adults is to raise platelet count to an ill-defined minimal level, often referred to as a "safe platelet count," thought to be protective. Paradoxically, a slightly increased risk of arterial and venous thrombosis coexists in ITP and may be increased by some treatments.[6] Unfortunately, for most cases, curative approaches are not yet available, and despite the current wide options of treatments, none is without significant adverse effects.

The findings of Cooper et al further underscore the complexity of ITP. Moving from the poor predictability of ITP severity and recognizing that current treatment guidelines, still based on platelet count, are confounded by variable bleeding phenotypes, the authors hypothesized that imaging the brain for CMBs with SWI could provide a sensitive noninvasive biomarker of occult hemorrhage. This could help the identification of patients with more hemorrhagic phenotypes and improve future stratification of treatment.

Forty-nine adult ITP patients who had at least 1 lowest recorded platelet count $<30 \times 10^9$/L (nadir) during the course of their disease and 18 normal controls (both groups with mean age between 40 and 45 years) were investigated using SWI of the brain. In comparison with the less-sensitive widely used gradient echo T2* MRI, Cooper et al adopted an improved technique generating additional tissue contrast. CMBs were identified in 43% of patients (21/49) with prevalence increased with decreasing nadir platelet count. The absence of CMBs in patients with a platelet nadir $>15 \times 10^9$/L and in all 18 healthy controls clearly substantiates ITP as the causative or permissive factor for CMBs. Statistically significant associations of total CMBs per subject were found with longer disease duration, initiated during childhood in some cases, possibly indicating that these microhemorrhages accumulate over time, particularly in refractory cases.

Prevalence of CMBs was also associated with lower platelet counts at the time of SWI and with higher organ bleeding scores, but not with mucosal and skin bleeding scores or with the number of previous treatments, age, and sex. In summarizing their findings, Cooper et al suggest that applying a treatment threshold based on platelet count alone could result in some patients being overtreated and others undertreated, and that SWI could provide a specific noninvasive biomarker of central nervous system hemorrhagic tendency, enabling further stratification of disease phenotypes. The inability to link the occurrence of a CMB to a specific time during the course of the disease is a major limitation of this study. Also, as suggested by the authors, longitudinal prospective studies are needed, in particular, to prove that there are increasing numbers of CMBs over time. In a similar study limited to children and adolescents, only 1 case with a single CMB was found among 27 prospectively investigated subjects, all with a platelet count $\leq 10 \times 10^9$/L at diagnosis or upon symptomatic relapse.[7] Reassuringly, in patients with severe hemophilia, a much more harmful hemorrhagic disease, CMBs were only slightly increased compared with healthy controls.[8]

Appropriately, Cooper et al do not recommend brain SWI outside of a research setting. Minor cognitive symptoms with memory and concentration difficulties have been reported in some patients with ITP, but they were ascribed to emotional distress and often associated with other common subjective symptoms like fatigue[9] Cautiously, the authors avoid making conjectures on the possible ominous long-term neurological consequences of CMBs in ITP.

This excellent study raises more issues than it resolves. It will encourage new areas of investigation to clarify the significance of CMBs in ITP and to better understand the mechanisms underlying different bleeding phenotypes beyond the simplistic parameter of the platelet count.

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

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CLINICAL TRIALS AND OBSERVATIONS

Comment on Vijenthira et al, page 2881

Under COVID of the night

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In this issue of *Blood*, Vijenthira and colleagues report that patients who have 2 life-threatening conditions, a hematologic malignancy and infection with the virulent microbe COVID-19, face a risk of dying that is ~1 in 3.[1]

Severe acute respiratory syndrome coronavirus 2 proved to be the perfect pathogen for a world unprepared. Because it is a novel virus, few people had any immunity, although some may have been spared its nastier consequences from past coronavirus infections. It spread efficiently, with a reproductive number (R0, indicating the contagiousness of the disease) between 2 and 3, meaning 1 infected person transmitted the virus to 2 or 3 others. Compare that to the R0 for the influenza pandemic of 1918, which was 2.0, or of 2009, which was 1.7.[2] It proved deadly in higher numbers of people than did influenza, with a case fatality rate of ~3% in the general populations of the United States. Our global economy and general wanderlust enabled infected hosts to spread the virus to those in immediate filial and social circles, and nearby or far-away states and countries efficiently, whereas geopolitics helped delay recognition of the seriousness of the pandemic and thwart implementation of measures to clamp it down.

Particularly vulnerable populations to COVID-19 proved to be the aged and infirm, who are more likely to have complicated comorbidities and might have an exaggerated inflammatory immune response to the virus[3]; those already at risk for adverse health outcomes based simply, and tragically, on their race[4]; and people with immune systems that were functionally compromised. Patients with hematologic malignancies are potentially ideal viral breeding grounds, with immune systems already corrupted and rendered at least somewhat incompetent by cancer, and by both cytotoxic and immunologic therapies which, by design, further suppress immune function. A recent study of >3000 patients hospitalized with COVID-19, of whom 100 had cancer, showed that patients with hematologic malignancies had higher COVID-19 viral loads, and that this was, in fact, associated with higher mortality rates.[5]

Vijenthria et al conducted a systematic review of studies published in PubMed and EMBASE databases, and reported on patients with hematologic malignancies and COVID-19 to determine risk of death and serious complications, such as intensive care unit admission and ventilation support. A total of 34 adult and 5 pediatric studies were included, comprising 3377 patients, the majority of which were descriptive cohort studies. Types of hematologic malignancies included lymphoid malignancies (~66% of included patients), plasma cell dyscrasias (12%), myeloproliferative neoplasms (8%), acute leukemias (8%), and bone marrow failure syndromes (7%).