were similar (CREBBP, TNFRSF14, EZH2), fewer cases harbored mutations in KMT2D (also known as MLL2), and cases with multiple KMT2D mutations as seen in patients with advanced stage disease were notably absent. These results are similar to those reported by Mamessier et al using array comparative genomic hybridization to study both duodenal-type FL and another early lesion of FL, in situ follicular neoplasia (ISFN), formerly referred to as follicular lymphoma in situ.[6] A low level of genetic complexity was seen in all "early lesions" studied, including duodenal-type FL, ISFN, and lymph nodes with partial involvement. Cases of FL with partial nodal involvement have been shown to be associated with low-stage disease.[7] Interestingly, in the current report, cases of FL with limited-stage disease also showed a low mutational load, sharing many features with the duodenal-type lesions.

Are there any positive results that distinguish duodenal-type FL from nodal FL? Using whole genome sequencing, the authors found 2 genes mutated at a higher frequency, HVCN1 and EEF1A1, than previously reported in FL. Unfortunately, the authors were not able to examine these genes in their cohort of advanced-stage or limited-stage FL cases, so the specificity of these findings for duodenal-type FL is unclear.

In a separate aspect of the study, the authors address the question of the microenvironment in duodenal-type FL; namely, do the cells localize in, and remain confined to, the intestinal mucosa, because of the microenvironment, or intrinsic attributes of the neoplastic lymphoid cells. They use gene expression profiling of paraffin embedded sections to examine a panel of cytokines and chemokines. Using hierarchical clustering, they compare a small number of samples of duodenal-type FL and limited-stage FL. They show that the 2 groups of lesions cluster separately, suggesting that the microenvironment might be relevant to the disease pathophysiology. However, it is difficult to sort out whether the microenvironment is simply a reflection of the biopsy site, rather than central to disease biology. Future work might address these points by comparing duodenal-type FL with other inflammatory lesions affecting the intestine, as well as lymphomas with secondary involvement. A single such case was examined in the current study, and that 1 "secondary case" appeared

to cluster with the nodal FL cases. Another recent report found common themes in the gene expression profile of duodenal-type FL and MALT lymphoma, distinguishing both from nodal FL. Again, it is difficult to sort out the role of the biopsy site in the generation of these data points.[8]

In conclusion, this study confirms the importance of recognizing duodenal-type FL as a separate variant of FL, both in terms of disease pathogenesis and in patient management. Duodenal-type FL, ISFN, and FL-like B cells in the peripheral blood comprise a group of early lesions that can help us understand the earliest events in FL pathogenesis (see figure).[9] Future studies, including assessment of relative allele frequencies of key genes, may identify secondary aberrations predictive of clinical progression.[10]

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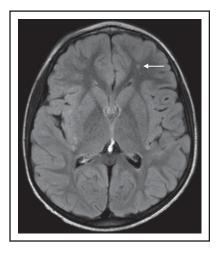

RED CELLS, IRON, AND ERYTHROPOIESIS

Comment on Ford et al, page 1714

Silent cerebral infarction: supply and demand

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In this issue of *Blood*, Ford et al show that silent cerebral infarction (SCI) in sickle cell anemia occurs mainly in brain regions at the highest anatomic and hemodynamic vulnerability to ischemia, indicating that a tenuous and easily disrupted balance between oxygen supply and demand is the predominant cause of SCI.[1]

SCI is the term for a subset of strokes, usually small, that have no localizing signs. However, it should not be reassuring that the physical examination of an individual with SCI is normal, because the brain is composed of more than motor and somatosensory cortex and associated long tracts. These small

strokes (see figure) are morbid, not silent, and can limit academic attainment and impair cognition in children and adults with sickle cell anemia.[2] Moreover, SCI increases the risk for subsequent overt strokes, even in those who have normal transcranial Doppler (TCD) examinations.[2,3]

SCI is a supply-side problem in sickle cell anemia. The arrow shows a small stroke by magnetic resonance imaging (MRI) that has no corresponding deficit on physical examination (ie, SCI) in the left frontal white matter in a 6-year-old child with sickle cell anemia.

Because it is a covert lesion, which even neurologists cannot detect by examination,[4] SCI must be identified by MRI scans of the brain. Like most organ injury in sickle cell anemia, SCI begins in early life. At a mean age of 14 months, 13% of infants who had MRI scans in the BABY HUG trial already had SCI.[5] Thereafter, the prevalence of SCI increases with age, reaching 30% to 40% in adolescents and more than 50% in adults.[2] Given that this progressive form of brain injury begins in early childhood, preventing SCI would be ideal. Primary prevention of SCI has not been established. However, DeBaun and colleagues[3] demonstrated in the Silent Infarct Transfusion Trial (SIT Trial) that chronic transfusions can prevent recurrent cerebral infarction in children with SCI. In that trial, 196 children (age 5-15 years) with sickle cell anemia who had SCI and normal TCD examinations were randomly assigned to chronic transfusions or standard care (no transfusions) for 3 years. The relative risk reduction with chronic transfusions for recurrent infarction was 58% with a number needed to treat of 13.[3]

Why was transfusion therapy beneficial in the SIT Trial? To answer this question, one needs to understand the cause of SCI. Speculation has included vaso-occlusion in the brain, thrombosis, embolism, and small vessel disease (posited to be distinct from the occlusive cerebral vasculopathy that occurs in the large arteries around the circle of Willis). However, the main risk factors for SCI are lower baseline hemoglobin concentration (ie, more severe chronic anemia),[6,7] acute anemic events,[7,8] and higher systolic blood pressure.[6] Together, these risk factors suggest a different cause for most SCI: a mismatch between oxygen supply and demand. To test this hypothesis, Ford and colleagues sought to demonstrate in children with sickle cell anemia that SCI occurs most commonly in regions of brain with the highest risk of ischemia, as defined both by anatomic vulnerability (occurrence in the anterior or posterior vascular border zones) and hemodynamic vulnerability (occurrence in regions with lowest measured resting cerebral blood flow [CBF]).

The investigators first outlined all the SCI lesions that were identified in the SIT Trial screening population (N = 286) and co-registered these to a standard brain atlas to create an SCI density map. They found evidence to support their hypothesis that most SCI lesions occurred in a small, vulnerable region of the brain. Specifically, 90% of SCI lesions were in vascular border zone distributions in deep white matter, which makes up only 5.6% of total brain volume. Resting CBF was then measured using arterial spin labeling in an independent group of children with sickle cell anemia (N = 41) with clinical characteristics similar to those in the SIT Trial screening population. As postulated, measured CBF was lowest in the independently defined regions of highest SCI density. In the ideal study, both of these measurements would be made in the same study population, but the expense and logistics of large-scale MRI studies make this a prohibitive design.

In summary, Ford and colleagues have shown that the majority of SCI occurs in regions of the brain that have the highest vulnerability to ischemia, by both anatomic and functional hemodynamic criteria. This speaks to an ongoing and tenuous balance between oxygen supply and demand in these brain regions in sickle cell anemia. These results explain why SCI occurs even during the overtly well or steady state[9] and at an even higher frequency during acute exacerbations of anemia.[8] The findings also demonstrate the pathophysiologic basis of known risk factors for SCI, including degree of chronic anemia, history of acute anemic events, and higher systolic blood pressure. These factors can dysregulate or decrease the supply of oxygen to the brain. Increased cerebral metabolic rate (increased oxygen demand), especially during acute illnesses, may further disrupt this tenuous balance. Therefore, one main mechanism by which chronic transfusions prevent SCI is alleviation of chronic anemia (and limitation of the degree of acute exacerbations of anemia), that is, improvement in the supply of oxygen to the brain.

These findings should also focus our attention and future studies on what we can do better to prevent SCI, such as disease-modifying therapies to decrease the degree of chronic anemia (as long as these interventions do not also impair oxygen delivery to the tissues). We also need to be aware that SCI can occur in the acute ischemic phase during acute anemic events.[8] Because we cannot assess brain hemodynamics or detect SCI by physical examination,[4] we should give strong consideration to transfusion for acute exacerbations of anemia, even when patients are hemodynamically stable and asymptomatic.

Finally, with the exception of vascular pruning, we should move away from the notion of SCI as a consequence of "small vessel disease" or, necessarily, proximal steno-occlusive cerebral vasculopathy. In the SIT Trial, fewer than 3% of the randomly assigned participants (with SCI and normal or conditional TCD measurements) had vasculopathy by magnetic resonance angiography, and progression of SCI was independent of abnormal TCD.[10] The cause of most SCI seems to be the tenuous and easily disrupted balance between oxygen supply and demand in regions of brain most vulnerable to ischemia.

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