medical centers; one of these techniques should be applied periodically to follow the progression of fibrosis among young recipients of PN. In addition, now that soy, medium chain triglyceride, olive, and fish (SMOF) lipid[10] is being utilized in most medical centers, infants and children receiving this emulsion should be carefully studied to understand whether hepatic fibrosis occurs among them.

Gura et al expands our knowledge of how the liver is wounded by PN, it is now incumbent upon us to minimize the scarring. ■

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References

1. Lyman D. The moral sayings of Publilius Syrus, a Roman slave. Cleveland, Ohio: LE Barnard and Company; 1856. p. 13-88.
2. Khalaf RT, Sokol RJ. New insights into intestinal failure-associated liver disease in children. Hepatology 2020;71:1486-98.
3. Matsumoto CS, Kaufman SS, Island ER, Kallakury B, Yazigi NA, Khan KM, et al. Hepatic explant pathology of pediatric intestinal transplant recipients previously treated with omega 3 fatty acid lipid emulsion. J Pediatr 2014;165:59-64.
4. Soden JS, Lovell MA, Brown K, Patrick DA, Sokol RJ. Failure of resolution of portal fibrosis during omega-3 fatty acid lipid emulsion therapy in two patients with irreversible intestinal failure. J Pediatr 2010;156:327-31.
5. Mercer DF, Hobson BD, Fischer RT, Talmon GA, Perry DA, Gerhardt BK, et al. Hepatic fibrosis persists and progresses despite biochemical improvement in children treated with intravenous fish oil emulsion. J Pediatr Gastroenterol Nutr 2013;56:364-9.
6. Mutanen A, Lohi J, Heikkilä P, Koivusalo AI, Rintala RJ, Pakarinen MP. Persistent abnormal liver fibrosis after weaning off parenteral nutrition in pediatric intestinal failure. Hepatology 2013;58:729-38.
7. Gura KM, Premkumar MH, Calkins KL, Pudor M. Fish oil emulsion reduces liver injury and liver transplantation in children with intestinal failure-associated liver disease: a multicenter integrated study. J Pediatr 2021;230:46-54.
8. Pastor-Clerigues A, Marti-Bonmati E, Milara J, Almudevar P, Cortijo J. Anti-inflammatory and anti-fibrotic profiles of fish-oil emulsions used in parenteral nutrition-associated liver disease. PLoS One 2014;9:e115404.
9. Ozturk A, Grajo JR, Dhyani M, Anthony BW, Samir AE. Principals of ultrasound elastography. Abdom Radiol (NY) 2018;43:773-85.
10. Torgalkar R, Dave S, Shah J, Ostad N, Kotsopoulos K, Unger S, et al. Multi-component lipid emulsion vs soy-based lipid emulsion for very low birth weight preterm neonates: a pre-post comparative study. J Perinatol 2019;39:1118-24.

Gastrointestinal Bleeding: Expanding the Shortened Telomere Disorder Phenotype

Telomere biology disorders are a group of disorders characterized by an elevated malignancy risk, mucocutaneous abnormalities, pulmonary and hepatic fibrosis, and bone marrow failure secondary to severely reduced cellular telomere length.[1,2] The presence of vascular alterations in patients with telomere biology disorders, including pulmonary arteriovenous malformations and retinal vessel disease, have been increasingly recognized.[3] In this volume of *The Journal*, Himes et al sought to further elucidate the frequency and etiology of gastrointestinal hemorrhage in patients with an underlying telomere biology disorder. The cause of gastrointestinal bleeding in patients with telomere biology disorder, including those without a diagnosis of Coats plus syndrome with its known elevated intestinal hemorrhage risk resulting from vascular anomalies,[4] is undoubtedly multifactorial. Hepatic fibrosis may be significant, leading to portal hypertension and resultant esophageal varices or gastropathy.[3] Bowel inflammation, including severe colitis and enteropathy, can be present.[5] With an elevated malignancy risk, gastrointestinal bleeding episodes may be the initial presentation of an esophageal or colonic cancer.[1]

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Bleeding risk may further be increased secondary to bone marrow failure/hematologic malignancy associated thrombocytopenia or hepatic dysfunction associated coagulopathy.[2]

Through retrospective analysis, 16 patients with telomere biology disorders with a history of significant gastrointestinal hemorrhage were analyzed, with a median age at time of first bleeding occurrence of 12.5 years. Hematochezia or melena was the most common initial gastrointestinal hemorrhage manifestations, and recurrence was frequent with 15 of 16 patients suffering from subsequent bleeding episodes. Despite a high prevalence of thrombocytopenia among the study subjects, the authors did not believe that their presentation clinically was concerning for a bleeding diathesis. The majority of patients had normal hepatic laboratory studies during their initial hemorrhagic episode, and esophageal varices were only observed in 1 out of 3 of those assessed. Of particular interest, evidence of angiodysplasia was seen in 67% of those undergoing endoscopies. Less than one-third of the patients

HSCT Hematopoietic stem cell transplantation

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included had a Coats plus diagnosis, and 8 patients were noted to have *TINF2* mutations.[6]

Clearly gastrointestinal hemorrhage is not limited to those with Coats plus syndrome but should be considered as a possible clinical manifestation in all patients with telomere biology disorders, including pediatric patients. Although the patients did not clinically present with a bleeding diathesis, future studies in these patients may benefit from more expanded hemostatic testing, such as thromboelastography, as any defects identified could present possible treatment opportunities. The study does suggest more widespread systemic vascular pathology than previously appreciated, particularly in those with *TINF2* genetic alterations. Of note, all included patients with *TINF2* mutations had undergone hematopoietic stem cell transplantation (HSCT). Severe and fatal gastrointestinal hemorrhage in patients with dyskeratosis congenita status post bone marrow transplantation has been previously described.[7,8] It is well known that HSCT causes vascular endothelial pathology[9] even in those without telomere dysfunction and that patients with telomere biology disorders have an elevated risk of veno-occlusive disease without reduced intensity conditioning regimens.[10] Further studies into the effects of transplantation on endothelial cells harboring shortened telomeres is necessary to fully understand the vascular risks to those with telomere biology disorders undergoing HSCT. Although it must be noted that some patients suffered from gastrointestinal hemorrhage outside of the post-transplant setting, signifying additional riskfactors unrelated to HSCT.

Interestingly, colitis or esophageal varices were not believed to be the primary causes of most gastrointestinal bleeding episodes with endoscopy findings predominantly notable for the discovery of angiodysplastic and ectatic vascular lesions. Basic research analyses linking specific genetic alterations impacting telomere length to endothelial pathology are needed to better understand which patients with telomere biology disorders, other than those with Coats plus, are at greatest risk for the formation of such vascular abnormalities. Further study is also warranted to understand the pathophysiology underlying the development of atypical vessels within patients with telomere biology disorders. Altered dyskerin or telomerase reverse transcriptase interactions with vascular epithelial growth factor may play a role, but these biologic signals do not mechanistically appear straightforward.[11-13] Accelerated endothelial cell senescence because of shortened telomeres may also be contributing,[14] especially given the known increased risk of angiodysplasia in the general elderly population.[15] Given this, further analysis of the potential for worsening or progressive vascular lesions overtime in patients with telomere biology disorders is also needed.

Further insight may come by looking to other disorders that present with angiodysplasia, such as hereditary hemorrhagic telangiectasia and von Willebrand disease, given the overall rarity of telomere biology disorders. Recent advancements in technology related to peripherally derived blood outgrowth endothelial cells has substantially progressed the study of endothelial and vascular biology[16] and has been used to study angiodysplasia secondary to von Willebrand disease. This could be exploited in the study of telomere biology disorders with possible collection of blood outgrowth endothelial cells from those with a telomere biology disorder, followed by analysis to better understand their angiogenic characteristics. It is hoped that the identification of biomarkers and less invasive diagnostic studies would soon follow.

Optimal treatment of bleeding secondary to angiodysplasia is not known, and this was reflected in this study as well. Initial hemorrhagic episodes were treated supportively with packed red blood cell and platelet transfusions in addition to proton pump inhibitors (88%), octreotide (44%), and sucralfate (37%). Procedural interventions were used in 37.5% (6 of 16) of cases and most commonly included argon plasma coagulation and radiofrequency ablation. In those with recurrent gastrointestinal hemorrhage, thalidomide usage was believed to be nonbeneficial in the 2 patients the medication was trialed, while bevacizumab resulted in a significant reduction in hemorrhage episodes in 1 of 2 patients who received the drug. No patient deaths were attributed to their first intestinal bleeding event but the median time from index bleeding episode to death was only 2 years.[6]

Although supportive care is necessary, it may not be sufficient. Further work is needed to discover effective therapeutic options with a focus on targeting the underlying mechanism of aberrant vascular formation in patients with abnormal telomeres. Bevacizumab, which has been used successfully in patients with hereditary hemorrhagic telangiectasia,[17] appeared to have promising results in 1 patient, perhaps secondary to its angiogenesis inhibitory effects. More pathophysiologic and clinical data is needed before widespread use of bevacizumab in patients with telomere biology disorders is recommended, and for now it should only be considered in extreme cases of recurrent bleeding. Given the rarity of these disorders, we applaud the authors on their efforts to continue to expand our knowledge on the phenotypes of telomere biology disorders. A prospective study facilitated through a large telomere biology disorder registry is warranted to more fully expand upon their work and help improve the care of these patients. ■

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References

1. Barbaro PM, Ziegler DS, Reddel RR. The wide-ranging clinical implications of the short telomere syndromes. Intern Med J 2016;46:393-403.
2. Dokal I. Dyskeratosis congenita. Hematol Am Soc Hematol Educ Prog 2011;2011:480-6.
3. Higgs C, Crow YJ, Adams DM, Chang E, Hayes D, Herbig U, et al. Understanding the evolving phenotype of vascular complications in telomere biology disorders. Angiogenesis 2019;22:95-102.
4. Simon AJ, Lev A, Zhang Y, Weiss B, Rylova A, Eyal E, et al. Mutations in STN1 cause Coats plus syndrome and are associated with genomic and telomere defects. J Exp Med 2016;213:1429-40.
5. Jonassaint NL, Guo N, Califano JA, Montgomery EA, Armanios M. The gastrointestinal manifestations of telomere-mediated disease. Aging Cell 2013;12:319-23.
6. Himes RW, Chiou EH, Queliza K, Shouval DS, Somech R, Agarwal S, et al. Gastrointestinal hemorrhage: a manifestation of the telomere biology disorders. J Pediatr 2021;230:55-61.
7. Imai J, Suzuki T, Yoshikawa M, Dekiden M, Nakae H, Nakahara F, et al. Fatal hemorrhagic gastrointestinal angioectasia after bone marrow transplantation for dyskeratosis congenita. Intern Med 2016;55:3441-4.
8. Ehlert K, Rossig C, Groll AH, Beyna T, Froehlich B, Juergens H. Diffuse hemorrhagic colitis in a patient with dyskeratosis congenita after non-myeloablative allogeneic hematopoietic stem cell transplantation. J Pediatr Hematol Oncol 2015;37:e41.
9. Carreras E. Vascular endothelial syndromes after HCT: 2020 update. Bone Marrow Transplantation 2020;55:1885-7.
10. Shimamura A, Alter BP. Pathophysiology and management of inherited bone marrow failure syndromes. Blood Rev 2010;24:101-22.
11. Hartwig FP, Nedel F, Collares TV, Tarquinio SBC, Nör JE, Demarco FF. Telomeres and tissue engineering: the potential roles of TERT in VEGF-mediated angiogenesis. Stem Cell Rev Reports 2012;8:1275-81.
12. Liu N, Ding D, Hao W, Yang F, Wu X, Wang M, et al. hTERT promotes tumor angiogenesis by activating VEGF via interactions with the Sp1 transcription factor. Nucleic Acids Res 2016;44:8693-703.
13. Rocchi L, Pacilli A, Sethi R, Penzo M, Schneider RJ, Treré D, et al. Dyskerin depletion increases VEGF mRNA internal ribosome entry site-mediated translation. Nucleic Acids Res 2013;41:8308-18.
14. Erusalimsky JD, Kurz DJ. Endothelial cell senescence. Handbook Exp Pharmacol 2006;176:213-48.
15. Duray PH, Marcal JM, LiVolsi VA, Fisher R, Scholhamer C, Brand MH. Small intestinal angiodysplasia in the elderly. J Clin Gastroenterol 1984;6:311-9.
16. Hebbel RP. Blood endothelial cells: utility from ambiguity. J Clin Invest 2017;127:1613-5.
17. Iyer VN, Apala DR, Pannu BS, Kotecha A, Brinjikji W, Leise MD, et al. Intravenous bevacizumab for refractory hereditary hemorrhagic telangiectasia-related epistaxis and gastrointestinal bleeding. Mayo Clin Proc 2018;93:155-66.