Gastrointestinal Hemorrhage: A Manifestation of the Telomere Biology Disorders

Ryan W. Himes, MD[1,2], Eric H. Chiou, MD[1], Karen Queliza, MD[1,3], Dror S. Shouval, MD[4,5], Raz Somech, MD[4], Suneet Agarwal, MD, PhD[6], Kunal Jajoo, MD[7], David S. Ziegler, MBBS, MD[8], Christian P. Kratz, MD[9], James Huang, MD[10], Tiffany L. Lucas, MD[10], Kasiani C. Myers, MD[11], Adam S. Nelson, MBBS, FRACP[11], Courtney D. DiNardo, MD[12], Blanche P. Alter, MD, MPH[13], Neelam Giri, MD[13], Payal P. Khincha, MD[13], Lisa J. McReynolds, MD, PhD[13], Carlo Dufour, MD[14], Filomena Pierri, MD[14], Frederick D. Goldman, MD[15], Youmna Sherif, MD[16], Sharon A. Savage, MD[13], Tamir Miloh, MD[1,17], and Alison A. Bertuch, MD, PhD[18]

Objective To describe the clinical features, therapeutic interventions, and patient outcomes of gastrointestinal (GI) hemorrhage in individuals with a telomere biology disorder, including dyskeratosis congenita, Hoyeraal–Hreidarsson syndrome, Revesz syndrome, and Coats plus.

Study design Clinical Care Consortium for Telomere Associated Ailments members were invited to contribute data on individuals with telomere biology disorders at their institutions who experienced GI bleeding. Patient demographic, laboratory, imaging, procedural, and treatment information and outcomes were extracted from the medical record.

Results Sixteen patients who experienced GI hemorrhage were identified at 11 centers. Among 14 patients who underwent genetic testing, 8 had mutations in *TINF2*, 4 had mutations in *CTC1* or *STN1*, and 1 patient each had a mutation in *TERC* and *RTEL1*. Ten patients had a history of hematopoietic cell transplantation. The patients with Coats plus and those without Coats plus had similar clinical features and courses. Angiodysplasia of the stomach and/or small bowel was described in 8 of the 12 patients who underwent endoscopy; only 4 had esophageal varices. Various medical interventions were trialed. No single intervention was uniformly associated with cessation of bleeding, although 1 patient had a sustained response to treatment with bevacizumab. Recurrence was common, and the overall long-term outcome for affected patients was poor.

Conclusions GI bleeding in patients with telomere biology disorders is associated with significant morbidity and with vascular ectasias rather than varices. *(J Pediatr 2021;230:55-61)*.

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Telomere biology disorders are rare genetic syndromes associated with life-threatening bone marrow failure, pulmonary fibrosis, and cancer predisposition. Dyskeratosis congenita, Hoyeraal–Hreidarsson syndrome, Revesz syndrome, and Coats plus are diagnostic categories on the telomere biology disorder spectrum, based on specific clinical features.[1,2] For example, bilateral exudative retinopathy (ie, Coats disease) is associated with Revesz syndrome and Coats plus. Traditionally, Coats plus also has been differentiated from other telomere biology disorders, in part by recurrent gastrointestinal (GI) hemorrhage owing to vascular ectasias in the stomach, small intestine, and liver.[3-6]

Unifying the telomere biology disorders is the presence of very short lengths of the specialized DNA-protein complexes at chromosome ends, the telomeres.[7,8] Fifteen genes, all of which encode factors that impact telomere biology, are

APC	Argon plasma coagulation
CCCTAA	Clinical Care Consortium for Telomere-Associated Ailments
GI	Gastrointestinal
HCT	Hematopoietic cell transplantation
PRBC	Packed red blood cells
RFA	Radiofrequency ablation

From the [1]Department of Pediatric Gastroenterology, Hepatology and Nutrition, Baylor College of Medicine and Texas Children's Hospital, Houston, TX; [2]Section of Gastroenterology and Hepatology, Department of Pediatrics, Ochsner Health, New Orleans, LA; [3]Gastroenterology, Hepatology and Nutrition Service, Memorial Sloan Kettering Cancer Center, New York, NY; [4]Pediatric Gastroenterology Unit, Edmond and Lily Safra Children's Hospital, Sheba Medical Center, Ramat Gan, Israel; [5]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [6]Boston Children's Hospital, Dana-Farber Cancer Institute, and Harvard Medical School, Boston, MA; [7]Brigham and Women's Hospital and Harvard Medical School, Boston, MA; [8]Kids Cancer Centre, Sydney Children's Hospital, Randwick, NSW, Australia; [9]Department of Pediatric Hematology and Oncology, Hannover Medical School, Hannover, Germany; [10]Division of Hematology/Oncology, Department of Pediatrics, UCSF Benioff Children's Hospital, University of California, San Francisco, CA; [11]Division of Bone Marrow Transplantation and Immune Deficiency, Cincinnati Children's Hospital Medical Center, Cincinnati, OH; [12]MD Anderson Cancer Center, Houston, TX; [13]Clinical Genetics Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD; [14]Hemato-Oncology-Stem Cell Transplant Pole, IRCCS Giannina Gaslini, Genoa, Italy; [15]Department of Pediatrics, University of Alabama-Birmingham, Birmingham, AL; [16]Department of Surgery, Baylor College of Medicine and Texas Children's Hospital, Houston, TX; [17]Miami Transplant Institute, University of Miami, Miami, FL; and [18]Section of Hematology/Oncology, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, TX

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implicated in the telomere biology disorders; *DKC1*, *TINF2*, *TERT*, and *RTEL1* are the genes most commonly mutated in those who present in childhood.[9] Coats plus is unique in that it has been attributed in >90% of cases to mutations in *CTC1* and, less commonly, to mutations in in *STN1* or *POT1*.[5,6,10,11] Similarly, in all but a single case,[12] only mutations in the *TINF2* gene have been reported in individuals diagnosed with Revesz syndrome.[13,14]

Along with advances in the genetics of telomere biology disorders has come an increasing awareness of GI features not previously appreciated beyond single case reports. Whereas oral leukoplakia and esophageal webs or strictures, cirrhosis, and GI cancers have been long associated across the telomere biology disorder spectrum,[15-17] additional GI manifestations have been more recently described in case series. Life-threatening enterocolitis or enteropathy in association with B cell deficiency may be the presenting feature, particularly in early childhood.[18] Hepatopulmonary syndrome with noncirrhotic portal hypertension also has been described in children and adults and may be the ultimate cause of death.[19]

GI bleeding is being increasingly appreciated by providers in the Clinical Care Consortium of Telomere-Associated Ailments (CCCTAA) as a cause of significant morbidity in patients with telomere biology disorder beyond those with Coats plus. The CCCTAA is an international consortium that aims to improve research and clinical care for individuals with telomere biology disorders. The present study was prompted by discussions at a 2017 workshop sponsored by the CCCTAA and the patient advocacy group Dyskeratosis Congenita Outreach (now known as Team Telomere), focused on vascular complications of telomere biology disorders.[20]

Methods

This was an international multicenter retrospective review of patients with telomere biology disorders cared for at CCCTAA member centers who experienced any form of GI bleeding (eg, hematemesis, hematochezia, or melena). A call for cases was sent to 39 members representing 25 institutions, including 12 non-US sites. Twenty-five of the 39 members queried were pediatric hematologists or bone marrow transplantation physicians, and 4 were from other pediatric subspecialties. Eight cared for adult patients, and 2 were clinical geneticists. Baylor College of Medicine was the data coordinating center and facilitated data use agreements with respondents. Institutional review board approval was obtained from Baylor College of Medicine, and institutional review board approval or a waiver of requirement for approval was also obtained from other participating centers. Data abstracted from the medical record included demographics, clinical and genetic diagnoses, laboratory testing, imaging, and medical and procedural management. Data are presented as frequency or median with range. The denominators vary based on the number of responses for a specific data element.

Results

Demographics and Clinical Characteristics

Sixteen patients were identified at 11 centers as having experienced 1 or more episodes of GI hemorrhage. Ten of these patients came from 7 centers that treated a total of 74 patients with telomere biology disorders. Nonetheless, the prevalence of this complication would be best determined by a prospective study via an international telomere biology disorder registry. Summaries of the clinical course for each patient are provided in **Table I** (available at www.jpeds.com). Patients experienced their initial telomere biology disorder clinical feature at a median of 3.5 years of age but did not receive a formal telomere biology disorder diagnosis until a median of 9.5 years of age (**Table II**). Elements of the classic mucocutaneous triad were not uniformly present, with as few as 5 of 16 patients (31%) demonstrating oral leukoplakia and 9 or 10 of 16 (~60%) exhibiting skin pigmentation or nail dysplasia. Although 5 patients had a diagnosis of Coats plus, which is known to predispose to GI hemorrhage,[5,6] 8 were categorized with dyskeratosis congenita, in which GI hemorrhage is less well characterized. Heterozygous *TINF2* sequence variants were present in one-half of the cohort (8 of 16). Biallelic *CTC1* and *STN1* sequence variants were present in 2 patients each.

Thirteen patients (81%) had a history of bone marrow failure (**Table II**); however, none received androgen therapy, which may be used to treat telomere biology disorder–associated marrow failure[21,22] before their first GI bleed. Ten patients (62%) underwent hematopoietic cell transplantation (HCT) at a median of 5.5 years (range, 0-13 years) before the initial GI bleed. Reduced-intensity conditioning was used in all but 1 case, in which the patient received high-dose cyclophosphamide. Regimens were highly variable but commonly included cyclophosphamide, alemtuzumab, and fludarabine.

Clinical Features and Treatment of the Initial GI Hemorrhage

The initial GI bleed occurred at a median of age 12.5 years (range, 0.8-36 years). When analyzed separately, the patients without Coats plus (n = 11) experienced their first GI bleed at an earlier median age (14 years; range, 0.83-36 years) compared with those with Coats plus (n = 5) (median age, 25 years; range, 14-31 years). The 2 groups were not distinguishable by any other features relating to their GI bleed (**Table I**), and thus they were evaluated together for the remaining analyses.

Bleeds most commonly presented as melena or hematochezia (**Table III**). All patients presented with anemia characterized by a hemoglobin concentration of <10 mg/dL, representing a median decline in baseline hemoglobin of 3.7 mg/dL. Although nearly all patients had thrombocytopenia, and 3 had a mildly prolonged international normalized ratio (maximum, 1.43 seconds),

none presented with features concerning for a bleeding diathesis.

GI endoscopy was performed during most of the initial bleeds (12 of 16; 75%; Table III). Six capsule endoscopy procedures and 3 push enteroscopies were performed to visualize the small bowel beyond the reach of regular endoscopes, suggesting that these patients might have had obscure GI bleeding not explainable after standard endoscopy. Figure 1 shows representative endoscopic findings in the esophagus and stomach. Esophageal findings ranged from normal to mild mucosal irregularities, such as linear furrowing. Four patients had esophageal varices, none actively bleeding at the time of endoscopy. A single varix in 1 patient underwent band ligation during endoscopy. The stomach was affected in 6 patients, 3 of whom had Coats plus, typically with patchy, often antral-predominant erythema (Figure 1, D-F). Endoscopists described the findings with such terms as "telangiectasia," "gastritis," "gastric antral variceal ectasia" (GAVE), "ectatic," "vascular dysplasia," and "fragile vessels." Figure 2 shows representative endoscopic findings in the small bowel. Small bowel findings mimicked gastric findings with vascular-appearing erythematous lesions (Figure 2, A-F). Lesions in the colon, which was less commonly affected than the stomach and small bowel, were described as having the appearance of "vascular ectasia" and "friability."

Most patients were managed supportively outside the intensive care unit, with packed red blood cells (PRBCs) and/or platelet transfusions during a median hospital stay of 7 days (maximum, 45 days; Table III). Proton pump inhibitors were the most commonly used medication (in 14

Table II. Demographic and clinical characteristics of the study cohort (N = 16)

Characteristics	Value
Female sex, n (%)	8 (50)
Age at first major telomere biology disorder complication, y, median (range)	3.5 (0.8-16)
Age at telomere biology disorder diagnosis, y, median (range)	9.5 (1-36)
Age at last follow up or death, y, median (range)	16 (2-37)
Deceased, n (%)	12 (75)
History of other telomere biology disorder clinical manifestations, n (%)	
Mucocutaneous triad	5 (31)
Oral leukoplakia	10 (62)
Skin pigmentation abnormalities	9 (56)
Nail dysplasia	13 (81)
Bone marrow failure	7 (54)
Retinopathy	3 (20)
Pulmonary AVM	
Clinical telomere biology disorder diagnosis, n (%)	
Dyskeratosis congenita	8 (50)
Coats plus syndrome	5 (31)
Revesz syndrome	2 (12)
Hoyeraal–Hreidarsson syndrome	1 (6)
Telomere biology disorder gene mutation, n (%)	
TINF2 (monoallelic)*	8 (50)
CTC1 (biallelic)	2 (12)
STN1 (biallelic)	2 (12)
TERC (monoallelic)†	1 (6)
RTEL1 (biallelic)	1 (6)
Not tested	2 (12)
History of PRBC transfusion before first GI bleed (n = 15), n (%)	14 (93)
History of platelet transfusion before first GI bleed (n = 15), n (%)	12 (80)
History of androgen treatment before first GI bleed, n (%)	0 (0)
History of HCT, n (%)	10 (62)
Age at HCT, y, median (range)	3 (1-36)
Source of donor bone marrow (n = 10), n (%)	
Matched related	5 (50)
Matched unrelated	5 (50)
Conditioning regimens, n (%)	
Cyclophosphamide	7 (70)
Alemtuzumab	6 (60)
Fludarabine	5 (50)
Antilymphocyte or antithymocyte globulin	4 (40)

AVM, arteriovenous malformation.
*One patient with a novel synonymous variant.
†Variant of unknown significance.

Table III. Clinical features of the initial GI bleed (N = 16)

Features	Values
Age at first GI bleed, y, median (range)	12.5 (0.8-36)
Presenting signs/symptoms, n (%)	
Melena	8 (50)
Hematochezia	7 (44)
Hematemesis	4 (25)
Hemoglobin at presentation, mg/dL, median (range)	6.7 (4.8-9.9)
Hemoglobin decline at presentation from previous baseline, mg/dL, median (range)	3.7 (0.2-11)
Diagnostic studies	
Upper and/or lower endoscopy performed, n (%)	12 (75)
Time to endoscopy, d, median (range)	2 (1-24)
Additional evaluations, n (%)	
Capsule endoscopy	6 (37)
Push enteroscopy	3 (19)
Endoscopic findings (N = 12), n (%)	
Angiodysplasia	8 (67)
Esophageal varices	4 (33)
Portal hypertensive gastropathy	1 (8)
Supportive interventions	
Intensive care unit admission (N = 16), n (%)	4 (25)
Hospital length of stay, d, median (range)	7 (2-45)
PRBC transfusion (N = 15), n (%)	14 (93)
Platelet transfusion (N = 15), n (%)	9 (60)
Therapeutic interventions, medical, n (%)	
Proton pump inhibitors	14 (88)
Octreotide	7 (44)
Sucralfate	6 (37)
Beta blockers	3 (19)
Androgen	3 (19)
Estrogen	2 (12)
Bowel rest	2 (14)
Sirolimus	1 (6)
Therapeutic interventions, endoscopic and surgical, n (%)	
Radiofrequency ablation	2 (12)
Argon plasma coagulation	2 (12)
Transjugular intrahepatic portosystemic shunt	1 (6)
Bipolar electrocautery	1 (6)
Outcomes, n (%)	
Additional GI bleeds, n (%)	15 (94)
Additional hospitalizations related to GI bleeding, median (range)	5 (0-16)
Additional endoscopic procedures, median (range)	2 (1-11)
Surgery related to GI bleeding, n (%)	2 (12)

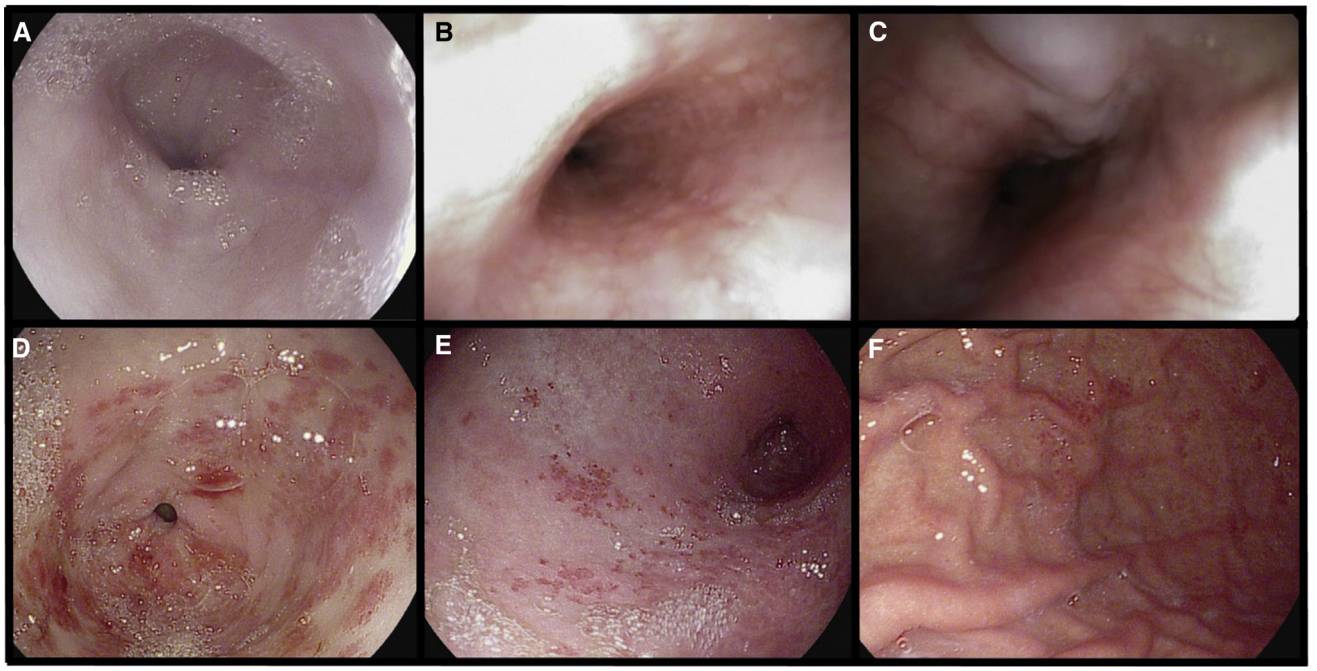

Figure 1. Representative endoscopic photographs from the esophagus and stomach. Findings in the esophagus were variable, ranging from **A,** normal, to **B,** linear furrowing, to **C,** presence of nonbleeding varices. **D-F,** The stomach was commonly affected, typically with a patchy, antral predominant erythema. Frequently, the lesions appear as discrete "pinpoints" occurring closely together in clusters.

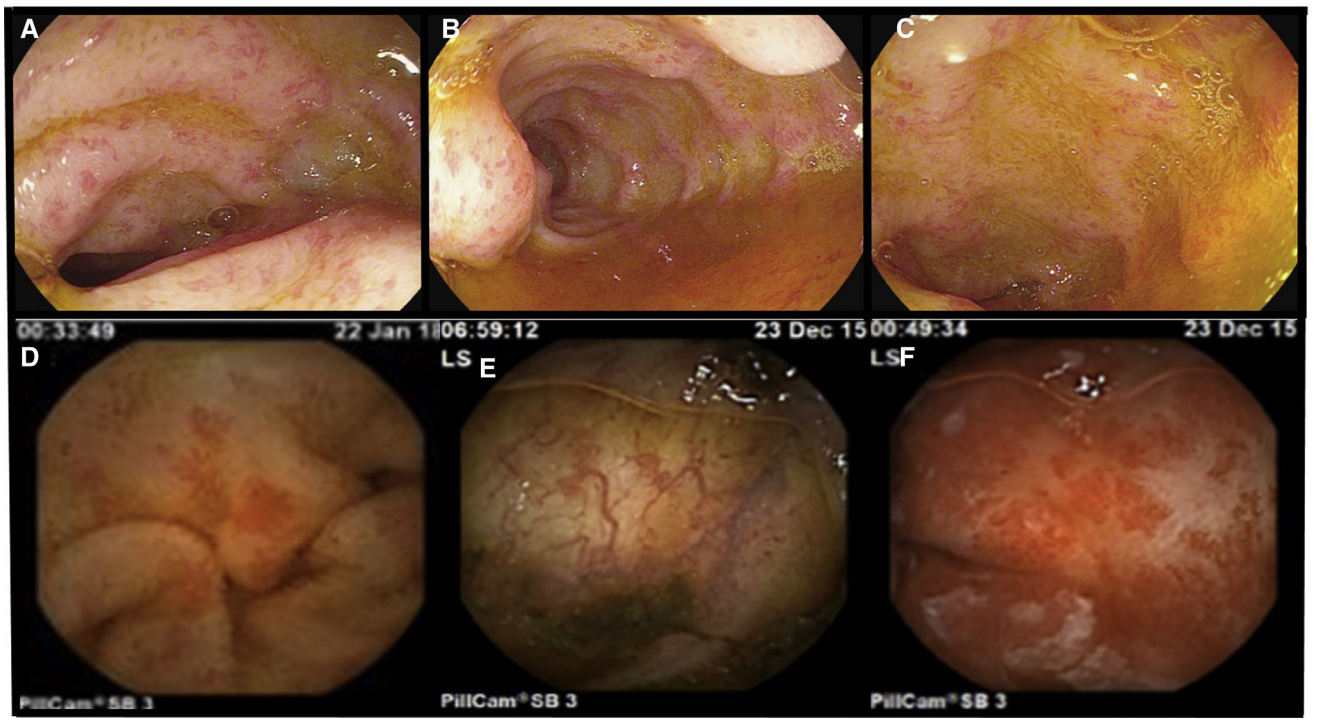

Figure 2. Representative endoscopic photographs from the small intestine. **A-C,** Endoscopic findings in the proximal small bowel were common and similar in appearance to the gastric lesions. **D-F,** Findings in more distal aspects of the small bowel, imaged with capsule endoscopy in 6 patients. Shown are areas of **D,** patchy erythema, **E,** ectatic superficial vessels, and **F,** and confluent areas of erythema.

in 16 patients; 88%), followed by octreotide, sucralfate, beta-blockers, and androgens. Although the investigators felt that no single medical therapy resulted in resolution of bleeding, 4 patients were considered to have had complete resolution of bleeding while being treated with multiple medical and supportive interventions. In the remaining patients, the initial bleeding episode eventually ceased, but this was not considered to be due to any particular intervention(s). There were no patient deaths directly attributed to the initial GI bleed.

Endoscopic and surgical therapies were infrequently used for initial GI bleeds (**Table III**). Argon plasma coagulation (APC) was used twice on gastric antral variceal ectasia–type lesions, and 1 patient showed a partial response. Radiofrequency ablation (RFA) of vascular gastric lesions was performed twice in patients who previously underwent APC, with 1 patient exhibiting a partial response. A transjugular intrahepatic portosystemic shunt was implanted in 1 patient in whom portal hypertension was felt to have a possible role; however, it appeared to have only a minimal impact on bleeding.

Features of Liver Disease

Most patients did not have biochemical evidence of clinically significant concurrent liver disease in the 6 months before or at the time of the initial GI bleed (**Table IV**; available at www.jpeds.com). At the time of the initial bleed, serum aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyl transferase levels were within the normal range in 93%, 73%, and 62%, respectively, of patients for whom data were available. Excretory liver function was maintained, with a normal total bilirubin level in 75% (9 of 12). Although serum albumin level was normal in only 15% (2 of 13), the international normalized ratio was normal in 62% (5 of 8); thus, the extent to which liver synthetic function was impaired is not clear. Features of portal hypertension were present in fewer than one-half of patients at the time of the initial GI bleed, including esophageal varices in 33% (4 of 12), splenomegaly in 38% (6 of 16), and ascites in 31% (5 of 16). Five patients underwent liver biopsy analysis, of whom 4 showed varying degrees of fibrosis. At the most recent follow-up, fewer patients had normal aspartate aminotransferase (43%), alanine aminotransferase (46%), total bilirubin (31%), and albumin (38%) than before the initial GI bleed, and more patients had splenomegaly (50%) than before the initial GI bleed, suggesting the possibility of evolving liver disease (**Table IV**). Four patients (25%) were formally evaluated for liver transplantation; however, none had undergone transplantation at the time of this report.

Recurrence of GI Hemorrhage

Recurrence of GI hemorrhage occurred in 15 of 16 patients (94%), resulting in a median of 5 additional hospitalizations, with 1 patient hospitalized for GI bleeding 16 additional times (**Table III**). One or 2 additional endoscopic procedures were performed in one-half the patients, with the other one-half undergoing up to 11 procedures.

Thalidomide was used in 2 patients, without a clear response. Bevacizumab was trialed in 2 patients. One did not respond; however, the other appeared to have benefited. Although the response became apparent after the initial data collection and analysis, given its remarkable nature, further information was collected and provided here. The patient had multiple GI telangiectasia and recurrent GI bleeding, requiring up to 10 PRBC transfusions per month (**Figure 3**; available at www.jpeds.com). Treatment with octreotide (short- and long-acting), proton pump inhibitors, and thalidomide did not lead to any sustained impact on bleeding or reduce the need for transfusions. At 9 months after the first episode of bleeding, and following the administration of 50 separate PRBC transfusions, intravenous bevacizumab, 5 mg/kg/dose once every 4 weeks, was started. There was a profound and sustained response, with no transfusions required for the subsequent 7 months. Treatment was withheld to allow for the surgical insertion of a feeding tube, with some increase in bleeding following the procedure, followed by a further reduction in bleeding after restarting treatment with bevacizumab.

Long-Term Outcomes

Twelve patients (75%) were deceased at the time of data collection, with a median age at death of 16.5 years (range, 2-37 years) (**Table II**). The median time between the index GI bleed and death was 2 years (range, <1-7 years). Whether a subsequent episode of GI bleeding was the proximate cause of death was not captured; however, the patients had a variety of comorbidities that may have been contributory, such as pulmonary fibrosis, hepatopulmonary syndrome, stage 4 chronic kidney disease, and small bowel obstruction.

Discussion

This series reveals recurrent GI hemorrhage in patients with an underlying telomere biology disorder as a major cause of morbidity for which empiric management strategies have proven ineffective. Although the pathophysiology underlying the GI bleeding remains to be elucidated, certain conclusions can be drawn. First, GI hemorrhage is not exclusive to patients with Coats plus, but also may be observed in patients with dyskeratosis congenita, Hoyeraal–Hreidarsson syndrome, and Revesz syndrome. However, it may be more prevalent in patients with *TINF2*, *CTC1*, or *STN1* mutations, as these genes accounted for 12 of 14 patients in our series who had genetic testing. Given the association of *CTC1* and *STN1* mutation with Coats plus, which has been reported to be associated with GI hemorrhage,[5,6] disease due to these 2 mutations is expected, even in the absence of overt Coats plus. However, the enrichment of *TINF2* cases in particular, with an absence of *DKC1* and *TERT* cases, is notable. *TINF2*-associated disease is known to be more

severe, with early presentation and association with both Hoyeraal–Hreidarsson syndrome and Revesz syndrome phenotypes.[13,14] There may be a specific vascular pathology that derives from mutations in *TINF2*, like *CTC1* and *STN1*, which also may be reflected by the nearly exclusive occurrence of Coats disease in telomere biology disorders owing to mutation in these genes.[5,6,10,13,14]

In addition, we found the median age of the first GI hemorrhage for the entire cohort was 12.5 years. This could reflect the natural history of cases that are severe in many respects, such as early age of telomere biology disorder presentation, need for HCT, multisystem involvement, and premature death. Alternatively, but less likely, it could represent the population from which the cases were drawn, given that the majority of CCCTAA member institutions at the time of the call for cases were pediatric centers. Interestingly, the median age at the first GI bleed was higher for the patients with Coats plus than for those without Coats plus alone, although a patient as young as 3 years with Coats plus and GI hemorrhage has been reported.[3]

Most patients experienced their first GI bleeding event after HCT. Therefore, patients and families should be counseled about this potential disease manifestation even after successful HCT. There were also patients who had not undergone HCT at the time of their GI hemorrhage. Thus, hemorrhage appears to be attributable not to HCT, but rather to the natural history of disease in some patients.

The presence of telangiectatic superficial vessels in the stomach and small intestine in many patients suggests that vasculopathy may underlie GI bleeding. Although features of portal hypertension, including esophageal varices, were present in 4 patients at the time of the initial bleed, these did not appear to be the proximate cause of the GI bleeding, and GI bleeding was not ameliorated in 1 patient who underwent transjugular intrahepatic portosystemic shunt for treatment of portal hypertension.

The management of GI hemorrhage proved challenging across the institutions caring for these patients. The wide variety of medical interventions used during these events highlights the lack of consensus regarding the pathophysiology of the GI bleeding in patients with telomere biology disorders. Although some measures were general in nature, other therapies were aimed at reducing portal hypertension or ulcer-related bleeding. Hormones, both androgens and estrogen, were used, as was sirolimus, for its purported antiangiogenic properties. No single medical therapy emerged in our series as highly efficacious, with the exception of potential response to bevacizumab in 1 of 2 patients who received it. RFA was used in 2 patients who had previously been treated with APC and was felt to be more helpful than the initial APC. The diffuse nature of the GI lesions in patients with GI bleeding may limit the utility of site-directed interventions like these, however.

GI hemorrhage in patients with a telomere biology disorder is associated with significant morbidity. A unifying mechanism of telomere biology disorder–related GI bleeding remains elusive; however, vascular ectasias appear to be common. Treatment modalities that lead to rapid cessation of bleeding and prevention of recurrence are needed. The development of a prospective international registry focused on GI vascular manifestations of telomere biology disorders would be an important first step in improving patient outcomes. Based on the apparent response in 1 patient in this series, bevacizumab warrants further investigation as a potential treatment for telomere biology disorder–associated GI bleeding. ■

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Reprint requests: Ryan W. Himes, MD, Ochsner Health, 1315 Jefferson Hwy, New Orleans, LA 70121. E-mail: ryan.himes@ochsner.org

Data Statement

Data sharing statement available at www.jpeds.com.

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Understanding the Molecular Basis of 11p13 Deletion

Haicken BN, Miller DR. Simultaneous occurrence of congenital aniridia, hamartoma and Wilms' tumor. J Pediatr 1971;78:497-502

Haicken and Miller reported a 17-month-old female infant with aniridia, Wilms' tumor, microcephaly, spina bifida with meningocele, and lipoma. This child had features associated with Wilms' tumor–aniridia syndrome and represented the first occurrence of sacral lipoma and meningocele with this condition. This case represented the 25th case reported in which aniridia occurred in association with Wilms' tumor and the third reported case in which a hamartoma occurred in association with Wilms' tumor–aniridia, suggesting a link between this disorder and disorders of growth control. It had been proposed by Miller et al that a mutagenic agent could be responsible for both aniridia and Wilms' tumor.[1]

Subsequent studies demonstrated a de novo 11p13 deletion resulting in a contiguous gene deletion syndrome in patients with Wilms' tumor–aniridia genitourinary anomalies and mental retardation syndrome (WAGR). Although the size of the 11p13 deletion may vary among different patients, *PAX6* and *WT1* are critical genes in this genomic region.[2] *PAX6* encodes a transcriptional factor that is responsible for lens placode development. *WT1* encodes a zinc finger binding protein acting as a transcriptional activator or repressor and is responsible for normal genitourinary development.

The phenotypic spectrum of WAGR syndrome includes 50% risk for Wilms' tumor in addition to elevated risk for movement disorders, scoliosis, obesity, obstructive sleep apnea, polydactyly, diaphragmatic hernia, behavior, auditory processing deficits, and psychiatric problems. End-stage renal disease is associated with WAGR and includes focal segmental glomerulosclerosis. Early diagnosis of WAGR is extremely important, as WAGR-associated Wilms' tumor is associated with a more favorable histology prognosis as compared with isolated Wilms' tumor.

Philip F. Giampietro, MD, PhD
Division of Medical Genetics
Rutgers-Robert Wood Johnson Medical School
New Brunswick, New Jersey

References

1. Miller RW, Fraumeni JF, Manning MD. Association of Wilms' tumor with aniridia, hemihypertrophy, and other congenital malformations. N Engl J Med 1964;270:922-7.
2. Riccardi VM, Sunansky E, Smith AC, Francke U. Chromosomal imbalance in the aniridia-Wilms tumor association: 11p interstitial deletion. Pediatrics 1978;61:604-10.

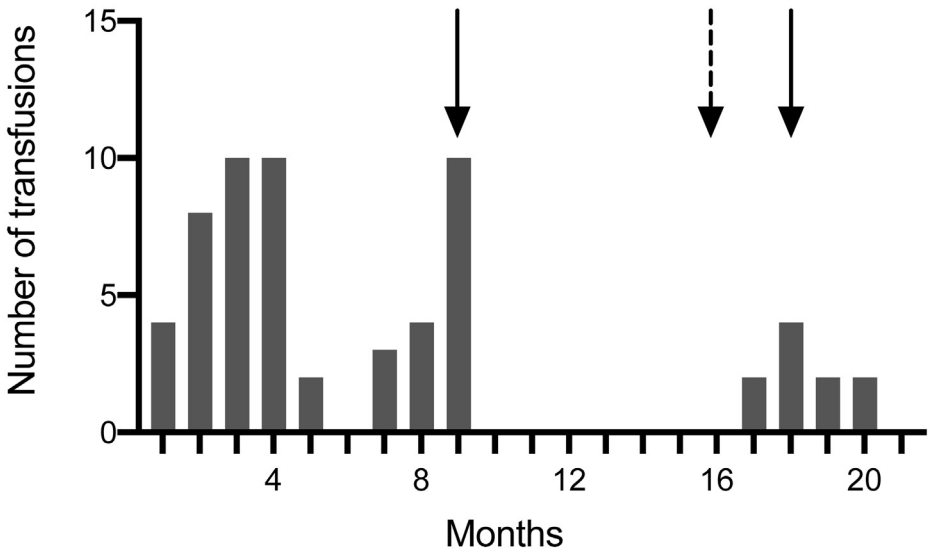

Figure 3. Red blood cell transfusion requirement for a patient treated with bevacizumab. Dark arrows indicate the start of bevacizumab treatment. The dashed arrow indicates the period during which bevacizumab was withheld for performance of a surgical gastrostomy.

Table I. Key clinical features of individual patients in the cohort

Subject number	Telomere biology disorder category	Gene mutated	Age at diagnosis of first major complication of telomere biology disorder, y	Age at HSCT, y, if applicable	Age at first GI bleed, y	Current age or age of death, y	Duration of first hospitalization, d	Number of additional GI bleeds requiring hospitalization	Number of endoscopies	Comorbidities at time of study entry or death
1	Coats plus	*CTC1*	Childhood	24	25	26 at death	7	5	11	Liver disease with ascites and hyperammonemia, portal vein thrombosis, small bowel obstruction with perforation, surgical asplenia, avascular necrosis of the femoral heads
2	Coats plus	*CTC1*	4	N/A	28	28	4	2	1	Moderate pancytopenia, pulmonary fibrosis with clubbing, liver fibrosis/cirrhosis, and dysplasia with portal hypertension and ascites, recurrent spontaneous fractures, h/o retinal hemorrhages
3	Coats plus	*STN1*	13	N/A	14	16 at death	NR	5	6	No entry
4	Coats plus	*STN1*	16	N/A	19	23 at death	45	Many	5	No entry
5	Coats plus	unknown	6	31	31	31 at death	2	0	1	Pancytopenia, liver disease with ascites, renal insufficiency, viral and fungal infections
6	Dyskeratosis congenita	*TERC*	NR	N/A	36	37 at death	25	2	2	Moderate restrictive lung defect, diffuse alveolar hemorrhage, transaminitis, traumatic right subdural hemorrhage, neutropenic sepsis, *Burkholderia* pneumonia
7	Dyskeratosis congenita	*TINF2*	0.83	1	7	9 at death	17	NR	NR	Buphthalmos right, persistent hyperplastic primary vitreous body left, distinct psychomotor developmental delay, perforated stenosis in the area of the upper esophageal sphincter, hyperthyroidism, hypoxia
8	Dyskeratosis congenita	*TINF2*	1	3	11	12 at death	6	6	3	Nasolacrimal duct obstruction, pulmonary fibrosis, dysphagia due to esophageal web, Budd-Chiari syndrome, portal hypertension, leg edema, adjustment disorder with mixed anxiety and depressed mood, malnutrition
9	Dyskeratosis congenita	*TINF2*	2	3	7	9 at death	NR	14	1	Aplastic anemia
10	Dyskeratosis congenita	*TINF2*	4	4	9	12 at death	14	15	5	Nasolacrimal duct stenosis, pulmonary nodule, pulmonary fibrosis, aortic root dilatation, portal hypertension, genu valgum
11	Dyskeratosis congenita	*TINF2*	5	N/A	5	7 at death	30	16	2	Pulmonary restrictive dysfunction, spontaneous tibia and fibula fractures

(*continued*)

Table I. Continued

Subject number	Telomere biology disorder category	Gene mutated	Age at diagnosis of first major complication of telomere biology disorder, y	Age at HSCT, y, if applicable	Age at first GI bleed, y	Current age or age of death, y	Duration of first hospitalization, d	Number of additional GI bleeds requiring hospitalization	Number of endoscopies	Comorbidities at time of study entry or death
12	Dyskeratosis congenita	*TINF2*	5	5	18	25 at death	7	4	4	Pulmonary fibrosis, hypoxemia, portal venous hypertension, hyperammonemia, generalized abdominal pain, small bowel obstruction s/p adhesiolysis, chronic kidney disease, stage 4, erythropoietin deficiency anemia, genu valgum, adjustment disorder with mixed anxiety and depressed mood
13	Dyskeratosis congenita	unknown	2	3	15	17 at death	8	2	Multiple	Pulmonary fibrosis, hepatic fibrosis, history of multiple fractures with minimal trauma
14	Hoyeraal–Hreidarsson syndrome	*RTEL1*	1	N/A	0.83	2	NR	NR	1	Colitis
15	Revesz syndrome	*TINF2*	2	2	4	5	2	5	2	Mild hemophilia A, developmental delay, expressive language delay
16	Revesz syndrome	*TINF2*	3	3	10	10	4	6	2	Persistent thrombocytopenia, iron deficiency anemia, lacrimal duct occlusion, constipation, vesicoureteral reflux, urethral stenosis, phimosis, multiple fractures

N/A, not applicable; *NR*, not recorded.

Table IV. Liver-related findings

Parameters	6 mo before first GI bleed (N = 16)	At time of first GI bleed (N = 16)*	At most recent follow- up (N = 14)
Clinical features, n (%)			
Splenomegaly	6 (38)	6 (38)	7 (50)
Ascites	6 (38)	5 (31)	4 (29)
Varices	2 (12)	4 (33)	NA
Pruritus	1 (6)	NA	NA
Jaundice	1 (6)	NA	NA
Hepatic encephalopathy	0 (0)	NA	NA
Laboratory tests, median (range); normal results, n (%)			
AST, U/L	14 (29-105); 9 (64)	14 (17-91); 13 (93)	14 (19-507); 6 (43)
ALT, U/L	14 (6-62); 8 (57)	15 (8-161); 11 (73)	13 (9-136); 6 (46)
GGT, U/L	8 (13-199); 3 (37)	18 (12-172); 5 (62)	8 (7-281); 4 (50)
Total bilirubin, mg/dL	0.64 (0.13-4.3); 9 (75)	0.82 (0.1-3); 9 (75)	1.42 (0.2-19.7); 5 (31)
Albumin, g/dL	3.5 (2.3-4.2); 8 (61)	2.7 (1.7-3.2); 2 (15)	2.7 (<1.5-6); 5 (38)
Platelets, $\times 10^9$/L	74 (6-269); 2 (16)	72 (2-374); 1 (7)	NA
INR	NA	1.2 (0.9-1.43); 5 (62)	1.1 (0.9-2.2); 7 (64)
Liver transplantation (N = 16), n (%)			
Formally evaluated		4 (25)	
Underwent liver transplantation		0 (0)	

AST, aspartate aminotransferase; *ALT*, alanine aminotransferase; *GGT*, gamma-glutamyl transferase; *INR*, international normalized ratio; *NA*, not asked.
*Except for varices, for which only 12 patients underwent endoscopy.

Laboratory test	Normal cutoff
AST, U/L	<60
ALT, U/L	<35
GGT, U/L	<50
Total bilirubin, mg/dL	<1
Albumin, g/dL	>3
Platelets, $\times 10^9$/L	>150
INR	<1.2