OPEN

Trust Your Instinct—Lower Intestinal Bleeding Caused by Ehlers-Danlos-Syndrome

*Dr. Ralph Melchior, †Dr. Rudolf Funke, †Prof. Dr. Bernd Wilken, *Prof. Dr. Andreas Jenke

Abstract: We report a 2.5-year-old boy who was presented with acute lower gastrointestinal bleeding. Emergency endoscopy showed two active mucosal bleeding sites that were successfully clipped. Initially, multiple intestinal angiodysplasias were considered, ruled out by a second control endoscopy. Here, multiple superficial lesions were observed that bled upon contact by the endoscope, suggestive of connective tissue disorder. However, the patient showed no clinical dysmorphias, only hypermobility of the toes but no other symptoms typical for such disorders. Gene testing for Ehlers-Danlos-syndrome (EDS) revealed a pathogenic mutation in the COL3A1 causing loss-of-function of type 3-collagen. Thus, diagnosis of EDS type IV was established. Overall, EDS is a rare cause for intestinal bleeding in children, even in children with no other clinical symptoms. This case is the earliest presentation of EDS type IV with intestinal complications.

INTRODUCTION

Whereas gastrointestinal bleeding (GIB) in general is a common phenomenon in pediatric health care, significant acute GIB with a substantial drop in hemoglobin or even cardiocirculatory impairment is rare, and only 5% to 10% of the cases warrants hospital admission. About one-third of the children have lower GIB, and the remainder has either an upper GIB or the source of bleeding is unspecified (1). Even though the most common reason for lower GIB is benign lesions in the anal region related to constipation, life-threatening conditions such as Meckel's diverticulum, severe ulcerative colitis, or intestinal obstruction need to be always taken into consideration.

CASE REPORT

A 2.5-year-old boy, whose parents immigrated from Afghanistan, presented to our emergency unit with 2 to 3 weeks of daily recurrent intestinal bleeding, increasing, and ongoing in the last hours before admission. Other symptoms, such as weakness, abdominal pain, diarrhea, vomiting, and fever, were not present. He did not take any medication, particularly no antibiotics in the last 3 months. The family history was unremarkable for intestinal disorders including inflammatory bowel disease.

On physical examination, he appeared healthy (weight 15 kg, height 94 cm), with no cardiovascular or other abnormalities apart from profuse bright red rectal bleeding. No dysmorphic features were noted, and psychomotor development was normal.

Laboratory values on admission were only remarkable for microcytic anemia with a hemoglobin of 7.8 g/dL. No signs of inflammation or disturbances of coagulation were noted (Table 1). Because of ongoing rectal bleeding on admission, emergency upper, and lower endoscopy revealed normal upper gastrointestinal tract but multiple lesions that suggested angiodysplasia throughout the entire colon. Two sites of active bleeding were found in the cecum, which were successfully clipped (Fig. 1: Cecal erosion and 2 Clips). With these findings, Meckel scan was not performed. Following the procedure, no further rectal bleeding occurred.

Since we had no satisfactory explanation for the bleeding sites, we performed a follow-up endoscopy 6 weeks later to check for bleeding residuals at the clipped sites and possible new lesions. The endoscopy was performed carefully by the same experienced endoscopist using the same type of endoscopes used previously. Desquamation of the mucosal surfaces with consecutive superficial bleeding simply by touching with the endoscope was observed. During colonoscopy, the formerly described "angiodysplasia"-like lesions were no longer detectable, whereas the clips were still in place (Fig. 1). Importantly, upon retraction of the endoscope multiple lesions of mucosal desquamation with superficial bleeding were noted (Figs. 2 and 3), even though the procedure was assessed as easy and uncomplicated. A connective tissue disorder was suspected. Extensive re-examination performed by an experienced neuropediatrician and syndromologist did not reveal any clinical abnormalities suggestive for a connective tissue disorder apart from hypermobility of the toes but not of the other joints. However, because of the impressive findings during endoscopy a molecular genetic investigation for Ehlers-Danlos-syndrome (EDS) was performed and revealed a pathogenic

TABLE 1. Laboratory result at primary admission

INR leucocytes	0.85–1.15	1.04
(*1000/µL)	5.0–12.0	10.10
Hemoglobine (g/dL)	10.1–13.1	7.60
MCV (fl)	73–101	51.00
Platelets (*1000/µL)	150–400	456.00
AST (U/L)		43.00
CRP (mg/L)	– <5	<3
ALT (U/L)	–<55	22.00
GGT (U/L)	<64	9.00
Ferritin (µg/l)	15–120	6.00

ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; CRP, C-reactive protein; GGT, gamma-glutamyl transferase.

Received March 4, 2022;accepted April 28, 2022.
From the *General Pediatrics and Neonatology, Childrens Hospital, Klinikum Kassel, Kassel, Germany; and †Department of Pediatric Neurology, Childrens Hospital, Klinikum Kassel, Kassel, Germany.The authors report no funding and conflicts of interest.
The study was performed in accordance with the Declaration of Helsinki.
Consent from legal parents was obtained to publish the individual data.
All data generated or analyzed during this study are included in this published article.

JPGN Reports (2022) 3:3(e233)
ISSN: 2691-171X
DOI: 10.1097/PG9.0000000000000233

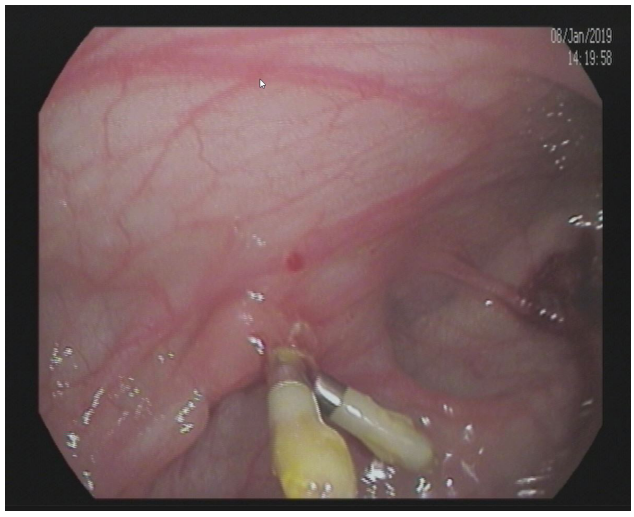

FIGURE 1. Cecal erosion and 2 clips.

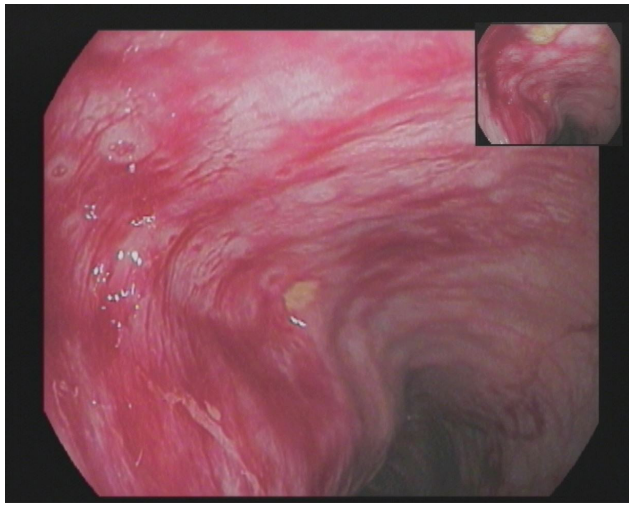

FIGURE 2. Diffuse bleeding in colon seen during retraction the endoscope.

loss-of-function mutation of the COL3A1 gene (c.1662+1G<A; p.?) associated with EDS type IV. Interestingly, further investigations of the large vessels, heart, and eyes did not show any abnormalities typical for EDS type IV.

DISCUSSION

Even though lower GIB is a common phenomenon in children, significant bleeding is rare, and emergency interventional endoscopy is rarely needed. In most cases underlying disorders, such as solitary sigmoid polyps, are benign, but less common conditions need to be considered. Awareness of the endoscopist for the clinical picture needs to be high to be able to detect more complex disorders, even in the absence of other clinical symptoms, such as Ehlers-Danlos syndrome in our patient (2).

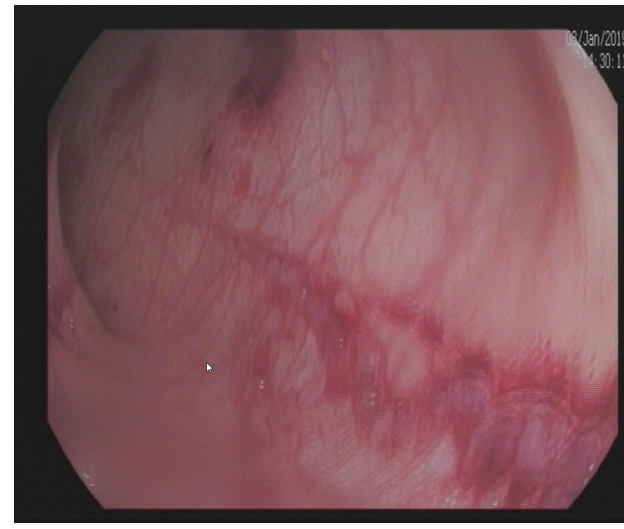

FIGURE 3. Linear desquamation of the mucosa by the endoscope.

EDS represents a group of connective tissue disorders presenting with varying symptoms of musculoskeletal, dermal, or vascular abnormalities. Vascular EDS (vEDS) or EDS type IV, as in this case, is a rare form of this group and is characterized by aneurysms, dissection and rupture of arterial vessels, or bowel rupture. It is associated with pathogenic variants of the COL3A1 gene, which encodes for type III procollagen (3). Primary features of the disease are mitral valve prolapse and joint hypermobility, whereas gastrointestinal complications typically only occur later in life (4,5). Early detection, such in this patient, is crucial to allow regular screening for and thus prevention of significant complications like rupture of large arterial vessels. Ours is one of the earliest presentations of mucosal intestinal abnormalities in a patient with confirmed EDS type IV.

ACKNOWLEDGMENTS

R.M. and R.F. were responsible for the patient during the hospital course. S.B. and her team interpreted the molecular findings. The authors were responsible for clinical decision making. R.M. and R.F. wrote the article. A.J. critically reviewed the article. I.B. and her team performed the histopathological analysis. All authors read and approved the final article.

REFERENCES

1. Pant C, Olyaee M, Sferra TJ, et al. Emergency department visits for gastrointestinal bleeding in children: results from the Nationwide Emergency Department Sample 2006-2011. *Curr Med Res Opin*. 2015;31:347–351.
2. Romano C, Oliva S, Martellossi S, et al. Pediatric gastrointestinal bleeding: perspectives from the Italian society of pediatric gastroenterology. *World J Gastroenterol*. 2017;23:1328–1337.
3. Byers PH, Belmont J, Black J, et al. Diagnosis, natural history, and management in vascular Ehlers-Danlos syndrome. *Am J Med Genet C Semin Med Genet*. 2017;175:40–47.
4. Byers PH. Vascular Ehlers-Danlos Syndrome. In: Adam MP, Mirzaa GM, Pagon RA, Wallace SE, Bean LJH, Gripp KW, Amemiya A, eds. Seattle (WA): University of Washington, Seattle; 1993–2022.
5. Ritelli M, Venturini M, Cinquina V, et al. Multisystemic manifestations in a cohort of 75 classical Ehlers-Danlos syndrome patients: natural history and nosological perspectives. *Orphanet J Rare Dis*. 2020;15:197.