

Chapter 16

Vascular Complications

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Introduction

The development of gastrointestinal (GI), pulmonary, and retinal vascular telangiectasias have recently been recognized as important complications associated with dyskeratosis congenita (DC) [1-3]. How vascular malformations are related to defective telomere biology is still not clear and further studies are warranted. Several biological mechanisms are currently discussed such as a connection between short telomeres and impaired wound healing, possibly leading to vascular dysfunction [2, 4, 5]. It is prudent to note that there may be other organs whose vascular involvement in DC and related telomere biology disorders (TBDs) have not yet been characterized.

Definitions	
Vascular	Refers to blood vessels, both arteries and veins.
Artery	Carries oxygenated blood from the heart to the rest of the body.
Vein	Carries oxygen-depleted blood toward the heart to then go to the lungs.
Capillary	Small blood vessels that connect arteries and veins.
Telangiectasia	A condition characterized by dilation of the capillaries, which causes them to appear as small red or purple clusters, often spidery in appearance, on the skin or the surface of an organ. Telangiectasias can be very delicate and bleed when disturbed.
Arteriovenous malformation	An abnormal tangle of blood vessels connecting arteries and veins, which disrupts normal blood flow and oxygen circulation.
Retinopathy	Damage to the retina of the eyes, which may cause vision impairment.

Retinal Telangiectasias

Coats plus is a rare phenotypically complex disorder that encompasses bilateral exudative retinopathy, retinal telangiectasias (Figure 1), intrauterine growth retardation (IUGR), intracranial calcifications, bone abnormalities with poor healing, and gastrointestinal vascular telangiectasias [6, 7] (see Chapter 3, Diagnosing Telomere Biology Disorders). The majority of Coats plus patients have biallelic variants in *CTC1*, a telomere capping gene. Coats plus was recognized as a DC-related telomere biology disorder when *CTC1* variants were discovered to also cause DC. Notably, some features of Coats plus, such as bilateral exudative retinopathy and intracranial calcifications, overlap with those of Revesz syndrome, another variant of DC (see Chapter 3, Diagnosing Telomere Biology Disorders) [6-8]. Therefore, individuals with DC should be regularly screened by a trained ophthalmologist for presence of retinal pathology such as retinal telangiectasias.

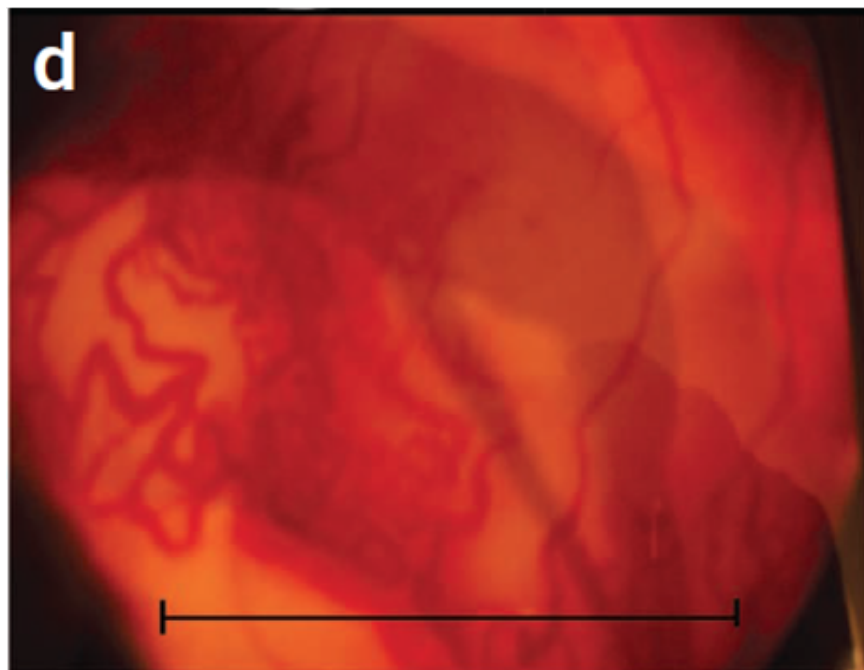


Figure 1. Retinal microangiopathy in Coats plus syndrome. Figure from Anderson BH, Kasher PR, Mayer J, et al. Mutations in *CTC1*, encoding conserved telomere maintenance component 1, cause Coats plus. *Nature genetics*. 2012;44(3):338-342.

Gastrointestinal Telangiectasias

GI telangiectasias (Figure 2) in DC may present as life-threatening GI bleeding and are thus a potentially severe complication of DC [2, 9]. Of note, in some cases of severe GI bleeding in DC patients no origin can be identified [2]. Vascular complications and severe GI bleeding from hemorrhagic colitis have been reported in post-HCT DC patients, suggesting that these patients are particularly vulnerable to GI-related morbidity and mortality [10-12]. In a recent review of the NCI DC cohort study participants, approximately 8% of transplanted patients were diagnosed with GI telangiectasias [13]. DC patients can also develop portal hypertension either from noncirrhotic liver disease or hepatic fibrosis, leading to development of porto-systemic varices [14].

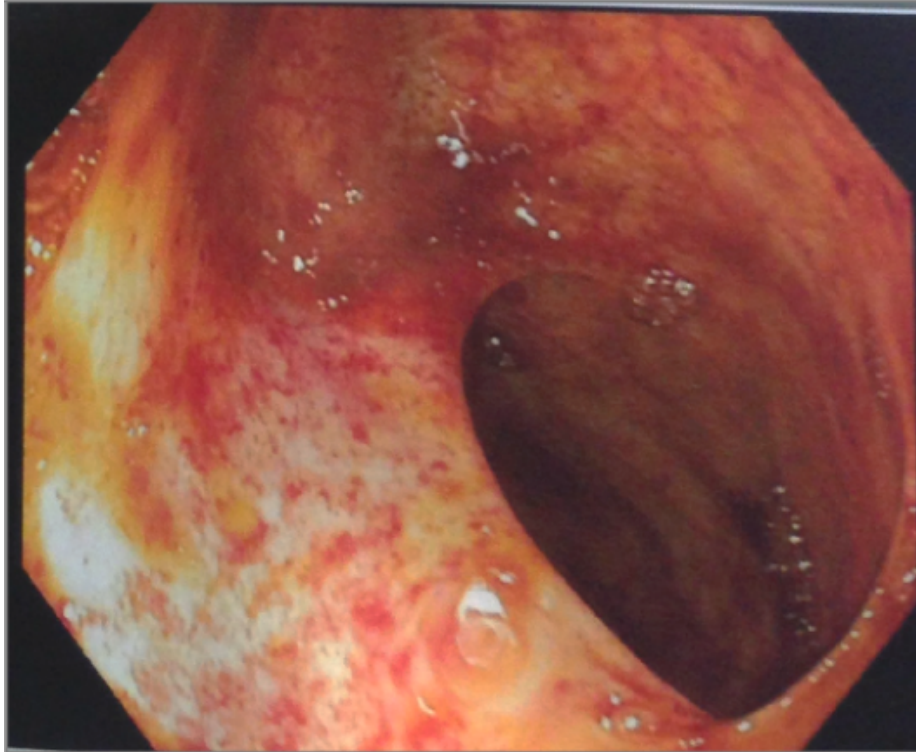


Figure 2. Telangiectasias of the small bowel lumen. Figure from Niewisch MR and Savage SA. An update on the biology and management of dyskeratosis congenita and related telomere biology disorders. *Expert Rev Hematol.* 2019 Dec;12(12):1037-1052.

Recent data indicate that bleeding GI telangiectasias may affect a broader group of individuals with TBDs than previously recognized [9]. In addition to individuals with Coats plus, which was expected, patients with dyskeratosis congenita, Revesz, and Hoyeraal-Hreidarsson syndrome were represented in the case series. The median age at the time of initial bleed was 12.5 years, but the range was wide, encompassing patients <1 to 36 years of age. Initial GI bleeding episodes were recognized both before and after HCT, suggesting that this complication represents the natural history of the disease in certain individuals, rather than an outcome of treatment. Most GI telangiectasias were located in the stomach and small bowel, with a minority of patients exhibiting these lesions in the large bowel (colon). No individuals in this series died as a result of an initial GI bleed, but recurrence of GI bleeding was almost universal (15/16 patients), and thus repeated hospitalizations and multiple diagnostic and therapeutic procedures highlight substantial morbidity associated with this manifestation of TBDs.

Diagnostic modalities for GI telangiectasia include upper GI endoscopy, capsule endoscopy, or colonoscopy. Liver ultrasound and computed tomography (CT) scans may indicate the presence of liver disease or fibrosis that can potentially cause portal hypertension, and clinicians must be particularly vigilant about development of varices in these patients.

Management

The optimal treatment strategy for bleeding related to GI telangiectasias remains unsettled. Most individuals are treated with supportive therapies in-hospital including transfusions of blood products, gastric acid-reducing medications, agents which coat/protect the GI tract, and drugs to modulate blood pressure. Use of endoscopic therapies has been described in a small number of patients. Esophageal varices may be amenable to band ligation. Argon plasma coagulation (APC) and radio-frequency ablation (RFA) have been associated with a partial response in a few patients; however, extensive GI tract involvement, including sites beyond the reach of an endoscope, may limit the broad application of these techniques. Finally, bevacizumab, an intravenous medication indicated for treatment of some forms of cancer, appeared to have a dramatic effect on GI bleeding in one of two individuals who were treated with it in a recent report [9]. More data are required to help clarify the role of this agent as a therapy for bleeding from GI telangiectasia.

Pulmonary Vascular Malformations

Hepatopulmonary syndrome is described as pulmonary vascular dilation due to liver disease of any form that leads to a deficit in arterial oxygenation [15]. It can occur in patients with or without portal hypertension. Individuals with DC are at risk of hepatopulmonary syndrome due to the increased frequency of underlying liver disease in this population [14]. However, pulmonary arteriovenous malformations (PAVMs) in the context of DC have been reported with and without underlying hepatopulmonary

syndrome [1, 16-18]. In DC, PAVMs may be microscopic and multiple, making diagnosis and treatment challenging [1, 16]. Macroscopic pulmonary AVMs have been noted in at least one patient with DC [1]. In general, PAVMs lead to right-to-left shunting of blood, which causes a deficit in arterial oxygenation and progressive respiratory insufficiency if undetected and untreated. Both of these manifestations can present with non-specific symptoms such as dyspnea on exertion, clubbing of the digits, cyanosis, or abnormal pulmonary function tests (PFT). The diagnosis of PAVMs may be missed or delayed as it may present with symptoms similar to those of pulmonary fibrosis, a well described complication of DC (see Chapter 14, Pulmonary Fibrosis) [19]. However, unexplained clubbing and lung diffusion capacity (DLCO) abnormality out of proportion to the degree of pulmonary fibrosis must alert clinicians to the possibility of PAVMs or hepatopulmonary syndrome (in the presence of liver disease).

Bubble echocardiography is a diagnostic modality that detects presence of right-to-left shunting and pulmonary vascular malformations. Further invasive testing such as angiography or cardiac catheterization may be necessary to confirm the presence of these abnormalities, along with a workup to rule out cardiac causes of these symptoms.

Management

At present, there are no specific recommendations for treatment of DC-associated vascular malformations. Testing for other genetic syndromes, such as hereditary hemorrhagic telangiectasia, should be considered in the differential diagnosis for multi-organ vascular telangiectasias. Management guidelines follow medical and surgical recommendations appropriate for each entity, for example, photocoagulation for retinal telangiectasias, and coiling or nifedipine for PAVMs. Currently, the only known successful treatment for hepatopulmonary syndrome is liver transplantation (Chapter 18, Hepatic Complications and Chapter 19, Liver Transplantation) [15].

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