

Chapter 17

Gastrointestinal Disease

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Introduction

Telomere biology disorders (TBD) affect rapidly dividing tissues including the skin and bone marrow. The luminal gastrointestinal (GI) tract refers to the tubular structures from one's mouth to the rectum (e.g. esophagus, stomach, and intestines). The epithelium (lining) of these structures is another high turnover compartment and may also be a site of disease in TBD.

The penetrance of GI disease in TBD is incomplete, and its prevalence varies. In a cohort of predominantly children, GI disease was estimated to affect approximately 16% of individuals. There are three well-described GI luminal manifestations of telomere-mediated disease: esophageal stenosis, enteropathy primarily affecting the small bowel, and enterocolitis which primarily affects the colon [1]. The latter predominantly affects infants and young children.

Gastrointestinal bleeding related to vascular lesions in the GI tract are discussed separately in Chapter 16, Vascular Complications.

Esophageal Stenosis

Presentation

Esophageal stenosis is a narrowing of the esophagus that may interfere with swallowing. It is one of several examples of luminal stenotic lesions that appear in classic dyskeratosis congenita (DC). Lacrimal duct and urethral stenosis may also occur (see Chapter 7, Ophthalmic Manifestations and Chapter 20, Genitourinary Complications). The prevalence of esophageal stenosis in DC is not known, but many of the reported patients are children with classic mucocutaneous features. In cases where the esophageal stenosis is severe and congenital, esophageal stenosis may manifest soon after birth as poor feeding, regurgitation and failure to thrive. In older children and adults, individuals may develop adaptive mechanisms such as thorough chewing and selective food avoidance. This may be because the narrowing develops over time. Regardless, a high index of suspicion in young children and an explicit and detailed swallowing history in older children and adults is often necessary to elicit the symptoms in chronic cases. In addition to stenoses, esophageal webs (a thin membrane that grows inside the esophagus) and Schatzki rings (a circular band of mucosal tissue that can form at the end of the food pipe closest to the stomach) have been described in DC and other TBD.

Diagnostic Workup and Treatment

The ideal initial evaluation for esophageal stenosis is a cine esophagram (video contrast swallow study). It is typically done under the supervision of a speech therapist. This study is preferred to a static barium swallow evaluation which may miss subtle swallowing difficulties because it is not supervised by a speech therapist. Interpretation of these diagnostic studies should include a thorough and focused evaluation of the cricopharynx and proximal esophagus as these regions are frequent sites of stenosis in DC.

Once the location of the stenosis is identified, endoscopic evaluation is necessary to confirm the diagnosis and proceed with therapeutic dilatation. Other causes of obstruction may also be ruled out at this time, including head and neck squamous cell cancers. In cases where the obstruction is proximal, it may be important to have input from an interventional gastroenterologist specializing in the esophagus (i.e. esophagologist) or an otolaryngologist (ears, nose, & throat specialist). Stenoses may at times be severe and, in these cases, pediatric endoscopy equipment may be required for dilatation in symptomatic adults.

Once completed, esophageal dilatation can significantly relieve symptoms. Multiple dilatations may however be required if symptoms recur and have been performed successfully in several cases.

Enteropathy

Presentation

Enteropathies often present with subtle and chronic complaints. Symptoms may include nausea, early satiety, non-specific abdominal pain, food intolerance, difficulty with weight gain, diarrhea, and food allergies. In extreme cases, it may present with failure to thrive. TBD-associated enteropathy can cause significant morbidity even though it is, in most cases, not life-threatening. Its precise prevalence is unknown since the symptoms often overlap with symptoms of irritable bowel syndrome and as outlined below the pathologic findings are patchy and may be missed by localized biopsies.

Diagnostic Evaluation and Treatment

In cases where the onset of symptoms is relatively recent, a diagnostic work-up that excludes other pathology, such as infection or malignancy, should be performed. This may include laboratory evaluation, upper endoscopy with biopsies of the proximal small bowel, and colonoscopy with biopsies, even in the absence of gross pathology. A

specialized pathologist may need to review these specimens to evaluate for subtle findings. The histopathology may reveal intraepithelial lymphocytosis, villous atrophy, and increased apoptosis. These findings are non-specific and are also seen in celiac disease among other enteropathies.

In some cases, affected patients adjust their diet spontaneously in response to their symptoms, thus self-treating their symptoms. There is anecdotal clinical experience that a gluten-free diet may improve symptoms even in patients who do not fulfill typical diagnostic criteria for celiac disease. In severe cases, weight loss and malabsorption may occur and require aggressive nutritional support. Parenteral (intravenous) nutrition has been prescribed with variable degrees of success in achieving nutritional rehabilitation.

Individuals with TBDs may develop enteropathy after solid organ or hematopoietic cell transplantation. This may be related to transplant preparative regimens, immunosuppressive medications, or graft-versus-host disease. In cases where the enteropathy is exacerbated by medications (e.g., mycophenolate mofetil), discontinuing the offending agent may be necessary [2]. A multi-disciplinary evaluation and familiarity with the telomere-associated histopathology is ideal to formulate a treatment plan.

Enterocolitis

Presentation

Enterocolitis is a serious and life-threatening GI complication of TBDs and is generally limited to infants and young children. It is particularly prevalent in Hoyeraal-Hreidarsson (HH) syndrome and may be one of its initial presentations and defining features.

Enterocolitis is marked by abdominal pain, failure to thrive, and bloody diarrhea. In some cases, bacteremia, sepsis, and bowel perforation may occur. The features of TBD-related enterocolitis overlap with those of inflammatory bowel disease (IBD), especially ulcerative colitis. In fact, some of the same genes associated with TBD have

also been implicated in development of very early onset IBD [3], a rare subset of IBD which has monogenic underpinnings, unlike the complex genetic pattern observed in most individuals with IBD. The pathophysiology of this condition likely reflects epithelial-intrinsic defects as well as severe immune system abnormalities including those involving B cells.

Diagnostic Workup and Treatment

The diagnosis of enterocolitis is a clinical one and based on the patient's age and symptoms. Colonoscopy often reveals friable mucosa, gland drop-out, and inflammation. Treatment is supportive including bowel rest, antibiotics, and nutritional support. Often parenteral nutrition is prescribed. In cases of bowel perforation, surgical intervention is required. It is unclear whether immunosuppressive therapies that are used for IBD are helpful in these settings and there may be potential risks of giving immunosuppressive medications (e.g., TNF-alpha inhibitors) to patients with HH since they have an underlying intrinsic immune disorder. Immune reconstitution with hematopoietic cell transplantation has been performed in children with HH or DC who have enterocolitis, but it is unclear from the authors' experience to date, whether it is possible to completely reverse this GI complication. Overall, this condition, when it is severe, may be associated with poor prognosis.

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