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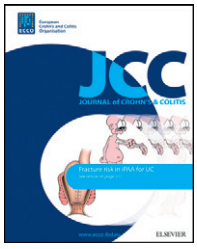

SHORT REPORT

Severe inflammatory bowel disease associated with congenital alteration of transforming growth factor beta signaling

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Abstract

Transforming growth factor beta is a pleiotropic cytokine which plays a central role in the homeostasis of the immune system. A complex dysregulation of its signaling occurs in Loeys–Dietz syndrome, a monogenic disorder caused by mutations of transforming growth factor beta receptors type 1 or type 2, characterized by skeletal involvement, craniofacial abnormalities, and arterial tortuosity with a strong predisposition for aneurysm and dissection. In addition, several immunologic abnormalities have been described in these patients, including an increased risk of allergic disorders as well as eosinophilic gastrointestinal disorders. The occurrence of inflammatory bowel disorders has been also reported, but it is poorly documented. We describe two unrelated children with Loeys–Dietz syndrome affected by severe chronic inflammatory colitis appearing at an early age. The intestinal disease presented similar features in both patients, including a histopathological picture of non-eosinophilic chronic ulcerative colitis, striking elevation of inflammatory markers, and a distinctly severe clinical course leading to failure to thrive, with resistance to multiple immunosuppressive treatments. One of the patients also presented autoimmune thyroiditis. Our report confirms

Abbreviations: TGF-β, transforming growth factor beta; LDS, Loeys–Dietz syndrome; TGFBR-1, transforming growth factor beta receptor type 1; TGFBR-2, transforming growth factor beta receptor type 2; Treg, regulatory T cells; IL, interleukin; Th17, IL-17-producing T helper cells; Th2, Type 2 helper T cell; UC, ulcerative colitis; CD, Crohn's disease; IBD, inflammatory bowel disease

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that chronic ulcerative colitis may be associated with Loeys–Dietz syndrome. This finding suggests that an alteration of transforming growth factor beta signaling may by itself predispose to inflammatory colitis in humans, and represent an invaluable model to understand inflammatory bowel diseases.

1. Introduction

Transforming growth factor beta (TGF-β) is a pleiotropic cytokine which plays a central role in the regulation of the immune response to mucosal antigens.[1] Dysregulated TGF-β signaling occurs in Loeys–Dietz syndrome (LDS), an autosomal dominant disorder caused by heterozygous mutations of the genes encoding transforming growth factor beta receptor type 1 or 2 (TGFBR-1 and TGFBR-2, encoded by *TGFBR1* and *TGFBR2*, respectively). The disease is characterized by skeletal involvement (joint hyperlaxity, arachnodactyly, pectus deformity, scoliosis, vertebral instability) and arterial tortuosity with a strong predisposition for aneurysm and dissection. Craniofacial abnormalities (hyperthelorism, cleft palate or bifid uvula, craniosynostosis) may or may not be present.[2] Recently, an increased risk of immunologic abnormalities, including allergic disorders and eosinophilic gastrointestinal disorders, has been described in these patients.[3,4] The occurrence of inflammatory bowel diseases (IBD) has been also reported,[5] yet it is poorly documented. We report two unrelated children with LDS affected by severe inflammatory colitis appearing at an early age.

2. Case report

2.1. Case 1

Patient 1 is a female child who from the age of 13 months developed chronic bloody diarrhea and intermittent fever, eventually leading to failure to thrive. Laboratory tests showed persistently elevated erythrocyte sedimentation rate (ESR, 80–100 mm/h), hypergammaglobulinemia, and chronic anemia. There was no blood eosinophilia nor a story of allergic disorders. She also presented peculiar phenotypic features (hyperthelorism, proptosis, blue sclerae, joint hyperlaxity, arachnodactyly, mild dilation of the ascending aorta, and cervical spine instability) which had led to a diagnosis of LDS that had been confirmed by demonstration of a mutation of *TGFBR2* already described in LDS (p.R528C).[2] Infectious causes of diarrhea (including bacterial and viral pathogens, tuberculosis, and parasites) were excluded. The evaluation of the immune system was normal except for a moderate deficiency of recent thymic emigrant T cells (defined as CD4+ CD45RA+ CD31+ cells, 23% of all CD4+ cells at 4 years of age; normal values 37–100%),[6] while regulatory T cells (Treg, defined as CD4+ cells highly expressing CD25 and FOXP3) were normal. Testing for chronic granulomatous disease resulted negative. Genetic testing for interleukin (IL)-10 receptor mutations resulted negative. A computed tomography angiography scan did not show alterations of the mesenteric vessels. At colonoscopy, all the colonic mucosa appeared fragile, edematous and diffusely ulcerated (Fig. 1). At esophagogastroduodenoscopy the gastric mucosa appeared hyperemic with some petechiae, while the duodenal mucosa appeared normal. Histopathological examination of the colonic biopsies appeared suggestive of chronic active ulcerative colitis (UC), with a moderate-to-severe inflammatory infiltrate made of lymphocytes, plasma cells, neutrophils and some eosinophils in the lamina propria; architectural distortion of the crypts (Fig. 2A); crypt abscesses (Fig. 2B); basal plasmocytosis (Fig. 2C); goblet cells depletion; and Paneth cell metaplasia. There was no evidence of granulomas. Immunohistochemical study of the colonic mucosa showed CD8+ cells being 25% of all CD3+ cells, GATA3+ cells 85% of all CD3+ (Fig. 3), and FOXP3+ cells being 5% of all CD3+ cells. A moderate lymphoplasmacellular infiltrate was also evident in the lamina propria of stomach and duodenum. Oral mesalazine and prednisone were started with good clinical response, yet the disease relapsed on prednisone tapering. Adding intravenous cyclosporine and oral azathioprine resulted only in limited improvement. Infliximab at 10 mg/kg was therefore added to azathioprine and prednisone, while cyclosporine was discontinued, yet with only modest clinical improvement, while tapering corticosteroids often resulted in clinical relapses that required an increase of prednisone and short courses of antibiotics (ciprofloxacin and metronidazole). After one year (13 infusions) infliximab was discontinued. At 4 years

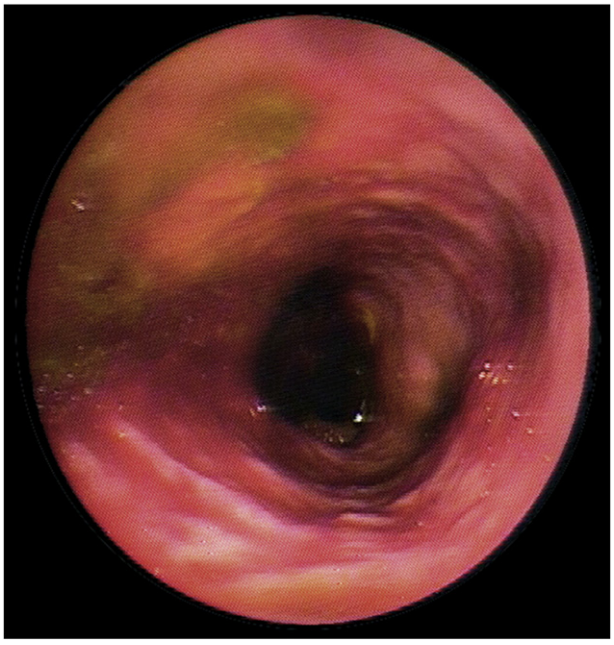

Figure 1 Colonoscopy of patient 1. The colonic mucosa appears diffusely hyperemic and ulcerated.

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