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Targeting inflammation with infliximab in vascular Ehlers-Danlos syndrome: a possible paradigm shift for a newly recognized inflammatory component

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Abstract

Vascular Ehlers-Danlos syndrome (vEDS) is a rare connective tissue disorder with high risk of spontaneous bowel perforation. The association between vEDS and inflammatory bowel disease is not clearly established.

This article reviews isolated cases described in the literature associated or overlapping inflammatory bowel diseases (IBD) with EDS. CAse-BAsed REview sTandards were use and a case description of vEDS with confirmed bowel inflammation was presented as a basis of this analysis.

None of the articles found were directly related to the vEDS, therefore the case presented uniquely demonstrates the problem as well as showed successful use of biological therapy of patient with vEDS. This suggests an inflammatory component in vEDS pathophysiology.

The potential for bowel intestinal inflammation to occur in a condition previously considered non-inflammatory offers a valuable basis for further discussion. The article highlights the need to consider inflammation and select appropriate diagnostic methods, while also paving the way for treating the inflammatory process including biologics in vEDS.

Key words: inflammatory bowel disease, Ehlers-Danlos syndrome, inflammation, infliximab.

Introduction

Vascular Ehlers-Danlos syndrome (vEDS) is an ultra-rare, autosomal-dominant hereditary connective tissue disorder resulting from deleterious mutations in the *COL3A1* gene, which encodes the pro-α1 chain of type III collagen. This molecular defect culminates in profound structural fragility of the vasculature and hollow viscera, frequently leading to catastrophic arterial or organ rupture. This type of EDS predispose to tissues fragility and carries high risk for severe bleeding and internal injuries.

Beyond the well-characterised mechanical and vascular morbidity, current clinical discourse increasingly explores a potential pathogenic intersection between aberrant collagen synthesis and dysregulated systemic inflammatory pathways [1].

The condition is traditionally classified as a non-inflammatory connective tissue disorder; however, recent studies have demonstrated that EDS could be regarded as a systemic disease with a major inflammatory component and that EDS-related connective tissue dysfunction may contribute to autoimmune susceptibility [1–3]. Whereas inflammatory bowel diseases (IBD) such as colitis ulcerosa and Crohn's disease (CD) are defined as a chronic intestinal inflammation and results of interaction between gut immunological system, host-microbial interactions and genetic predisposition [4]. The context of IBD overlapping with other autoimmune diseases is well known; however, its association with genetic collagen defect syndromes, such as EDS, is not particularly emphasized or described. In presented article the current medical literature linking vEDS with IBD are analyzed [5]. The impuls for seeking such a connection was a unique case, which is also presented in the article.

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Material and methods

A comprehensive search was conducted across PubMed/MEDLINE. The search strategy following the CAse-BAsed REview sTandards (CABARET) utilised the terms "colitis" and "Ehlers-Danlos syndrome". In PubMed, the search was optimised using the Medical Subject Headings hierarchy and "automatic term mapping" to ensure the inclusion of all relevant sub-terms.

The literature search included peer-reviewed articles published in English, specifically focusing on case reports, case series, and literature reviews that addressed the co-occurrence of IBD or colitis in patients with any subtype of EDS. Articles were excluded if gastrointestinal symptoms were solely attributed to structural or mechanical defects – such as diverticulosis, rectal prolapse, or hiatal hernia – without a documented inflammatory component. While the search emphasised publications from the last 10 years to reflect current diagnostic and therapeutic standards, no strict initial date limit was established due to the ultra-rare nature of the vEDS subtype.

Results

The summary of the literature review concerning colitis and EDS is presented in Table I [6–12].

The clinical course suggests that these two conditions may share an underlying pathophysiological mechanism. To our knowledge, no patient with vEDS and IBD has been reported or treated with drugs as presented below.

Case description

A 12-year-old male, with no known chronic illnesses, presented with an acute abdomen. An emergent laparotomy revealed faecal peritonitis and a 2-cm perforation of the sigmoid colon. The abdominal cavity was irrigated, the perforation was repaired, and a descending colostomy was formed. The postoperative course was complicated by clinical deterioration and wound dehiscence with evisceration, necessitating a second laparotomy. During this procedure, an approximately 70-cm segment of small intestine was found to be ischaemic and disintegrating, and another perforation was identified approximately 60 cm distal to the Treitz ligament.

The perforations were sutured, and the ischaemic segment was resected. Despite initial improvement, the patient's condition worsened, and he was transferred to a tertiary care paediatric surgery centre, with symptoms of another gastrointestinal perforation. Multiple further surgical procedures were performed in

Table I. Summary of literature review: colitis and Ehlers-Danlos syndrome (EDS)

Authors	Key findings
Defuentes et al. [6]	Reported that right-sided diverticular colitis in a young patient can be the primary indicator for an EDS diagnosis, suggesting that early-onset diverticular disease warrants connective tissue evaluation
Kakinuma et al. [7]	Described a fatal case of vascular vEDS in which ischaemic colitis led to colon perforation and arterial rupture, highlighting the high vascular risk in this specific subtype
Fikree et al. [8]	Identified a significant prevalence of JHS in patients with organic gastrointestinal diseases, specifically finding it in 32.0% of those with CD and 21.0% of those with ulcerative colitis. Their findings suggest that while JHS is most strongly associated with functional disorders, its substantial overlap with IBD indicates that connective tissue dysfunction may be a relevant factor across diverse gastrointestinal pathologies
Iguidbashian et al. [9]	Reported a case of a 66-year-old patient with EDS and well-controlled ulcerative colitis whose severe symptoms, initially appearing as an IBD flare, were identified as infectious colitis due to *Campylobacter jejuni* and *Pseudomonas aeruginosa* co-infection
Ono et al. [10]	Demonstrated in a mouse model that dermatan sulphate deficiency leads to abnormally arranged collagen fibrils and accelerated colonic contractions, suggesting that these structural and functional changes underlie gastrointestinal symptoms in musculocontractural EDS
Lindberg et al. [11]	Highlighted the diagnostic challenge of "irritable bowel syndrome-like" symptoms in connective tissue disorders, noting that patients with EDS often suffer from unrecognised gastrointestinal motility issues and structural fragility that mimic functional disorders
Vounotrypidis et al. [12]	Identified a significant correlation between JH – a core clinical feature of EDSs – and IBD, with JH detected in 70.7% of patients with CD and 35.7% of those with ulcerative colitis. This high prevalence suggests that underlying structural defects in collagen and the extracellular matrix play a functional role in the pathogenesis of colitis. Such findings imply a potential shared link between connective tissue integrity and susceptibility to chronic intestinal inflammation. While previous studies have reported the co-occurrence of IBD with EDS syndrome, these cases were limited only to the hypermobile type

CD – Crohn's disease, IBD – inflammatory bowel disease, JH – joint hypermobility, JHS – joint hypermobility syndrome, vEDS – vascular Ehlers-Danlos syndrome.

response to the patient's worsening clinical status, resulting in the formation of jejunostomy and colostomy, complicated by the development of an enterocutaneous fistula. The postoperative period was complicated by intra-abdominal haemorrhage requiring fluid resuscitation and administration of blood-derived products. Subsequently, the patient underwent prolonged wound care management over several months using vacuum-assisted closure dressings. The inability to re-establish intestinal continuity ultimately led to short bowel syndrome, with the patient experiencing high-output losses of ~2,000 ml/day from the stomas. Despite multiple dressing changes and prolonged hospital management, the high-output losses (approximately 2,000 ml/day) continued. A Broviac catheter was implanted for parenteral nutrition. Based on molecular testing, the patient was diagnosed with the vascular type of Ehlers-Danlos syndrome (EDS; variant c.547G>A p.[Gly183Ser] of *COL3A1* gene). Following discharge from the hospital, the patient experienced recurrent episodes of gastrointestinal bleeding with chronic abdominal pain and anaemia.

A colostomy site examination revealed friable, ulcerated mucosa with significant spontaneous bleeding. Faecal calprotectin (FC) from the colostomy fluid was elevated at 5,360 µg/g. Infections of the gastrointestinal tract were ruled out; nevertheless, the patient was treated with metronidazole. The patient required blood transfusions, tranexamic acid, and recombinant coagulation factor VIIa, with partial improvement. Local 5-aminosalicylic acid (5-ASA) – mesalazine treatment was carried out, despite this gastrointestinal bleeding persisted, and increasing levels of FC (9,140 µg/g) and inflammatory parameters (C-reactive protein 3 mg/dl, erythrocyte sedimentation rate 45 mm/h) were noted. Colonoscopy showed a "rigid tube" appearance with effaced vascular patterns and spontaneous bleeding, leading to early termination of the procedure due to a high risk of perforation (Fig. 1). Patient was diagnosed with colitis and subsequently qualified for biologic therapy with infliximab (IFX). Gastrointestinal bleeding was significantly limited, losses from the stomas were markedly limited, and FC and inflammatory parameters were decreasing. Colonoscopy was performed after induction therapy with IFX, revealing a significant macroscopic response (small erosions within mucosa with normal vascular pattern, but no ulcers or spontaneous bleeding were found).

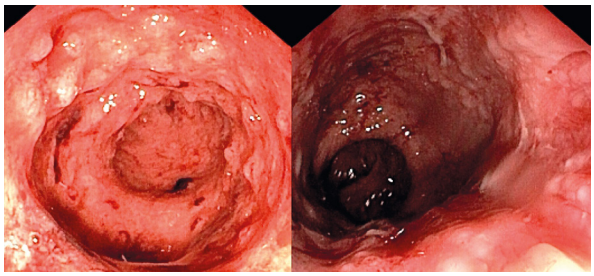

Fig. 1. Colonoscopy image of the sigmoid colon prior to infliximab treatment.

Discussion

To date, the medical literature contains no other reports of vEDS manifesting with severe colitis, making the current case a singular contribution to the field. Although, to our knowledge, this is a unique description of these overlapping conditions, however, We assume that the absence of descriptions does not mean such connections did not exist. Considering the vascular changes associated with vEDS and the potential risk of inflammation, as well as the course of IBD we want to emphasize that in every vEDS patient with gastrointestinal symptoms, repeated FC and serum inflammatory marker testing may be crucial for accurate diagnosis and optimal management. In cases of confirmed inflammation, biological agents may offer an effective treatment path. Cessation of clinical symptoms in addition to the resolution of intestinal inflammation may enable a planned surgery to restore the continuity of the alimentary tract. This is particularly important considering the disability and serious consequences, including life-threatening complications, in the course of enteritis and gastrointestinal bleeding in often very young patients.

Morissette et al. [2] found that acute-phase reactants and many of the established biomarkers of vascular inflammation, including markers of endothelial dysfunction, such as VCAM-1, ICAM-1, and MCP-1, are increased in patients with vEDS, suggesting that chronic microvascular damage leads to systemic inflammation. Among the proposed factors contributing to inflammation in individuals with EDS is the elevated intestinal permeability, commonly known as "leaky gut", a phenomenon consistently linked with autoimmune conditions [13, 14]. Researchers, including Paray's team, posit that structural flaws in the gut's protective lining permit foreign antigens from the intestinal lumen to infiltrate the systemic circulation [13]. This, in turn, triggers an immune response and can promote disease pathology. Consequently, it stands to reason that compromised connective tissue integrity may destabilise this barrier, thereby intensifying immune reactivity. The similar pathophysiological factors are considered to be very important factors triggering and maintaining chronic inflammation in ulcerative colitis [15, 16].

The discussed patient had suffered numerous spontaneous gastrointestinal perforations and numerous surgical procedures, which could have weakened the

intestinal barrier. Additionally, short bowel syndrome and chronic diarrhoea could have caused disruptions in the intestinal microbiota, and intestinal microbiota transfer is also considered a factor in the pathophysiology of ulcerative colitis [14].

Faecal calprotectin has emerged as a well-established, non-invasive, and straightforward biomarker for assessing inflammation within the gut. This readily usable marker is effective in differentiating between inflammatory and non-inflammatory bowel conditions and is valuable for charting the progression of IBD [17, 18].

Gastrointestinal symptoms are common in patients with EDS; nausea, abdominal pain, constipation, and diarrhoea are the most common [19]. They are usually related to structural and functional problems (hiatus hernias, visceroptosis, rectoceles, rectal prolapse, disordered gut motility) as well as functional gastrointestinal disorders.

Patients presenting with gastrointestinal symptoms suggestive of bowel inflammation require a thorough differential diagnosis to rule out infectious causes (such as *Clostridioides difficile*, cytomegalovirus, tuberculosis, or parasitic infections) before confirming a diagnosis of IBD. This process must also exclude other forms of colitis, including ischaemic, microscopic, and drug-induced colitis. Such a meticulous approach is essential to ensure that the clinical management aligns with the specific underlying aetiology.

Bioethical standards

Written permission was obtained from the patient's guardians to publish this case and the corresponding photos or imaging studies.

Conclusions

Presented discussion and observation further suggests that routine screening for colitis should be considered in the vEDS population, and it initiates a discourse on the potential efficacy of anti-inflammatory therapeutic strategies for subclinical disease within this patient population, in order to avoid full-blown symptoms – an area that necessitates robust validation through extensive future investigation.

Disclosures

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