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Diagnosis and treatment of recurrent spontaneous colon perforations and bleeding caused by Vascular Ehlers-Danlos syndromes: challenges and experiences

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Abstract

Background: Ehlers–Danlos syndromes (EDS) is a rare genetic disease, of which vascular Ehlers-Danlos syndromes (vEDS) is the type with more serious clinical symptoms and life-threatening bleeding and intestinal perforation which needs emergent surgical intervention. However, due to a lack of awareness about these rare syndromes, clinicians may develop inadequate treatment plans for patients who are at risk of severe complications and poor prognoses due to multiple surgeries.

Case presentation: Here, we present a case of multiple spontaneous colon perforations and recurrent bleeding in a 7-year-old girl. She has undergone 11 abdominal surgeries due to severe symptoms and postoperative complications, including recurrent wound dehiscence and abdominal abscesses.

She was transferred to our advanced medical center for ano-rectal reconstruction and ileostomy reverse after underdone ten operations performed at the local hospitals. During the 11th laparotomy, surgeons observed that her skin was prone to ecchymosis. They found that her intestinal wall was thin and easily torn or perforated, along with fragile mesenteric tissue and ruptured vessels, despite their efforts to preserve all tissue. Combined with her previous unplanned surgeries due to short-term postoperative adverse events presented with intestinal perforation and bleeding, the surgeons highly suspected her diagnosis of EDS. Therefore, the medical team decided to provide more minimal invasive procedure with permanent ileostomy for her instead of pull-through ileo-ano anastomosis to avoid high-risk anostomotic bleeding and leak.

Her post-operative whole exon sequencing (WES) showed Heterozygous variants were located on the *COL3A1* gene: NM_000090.3: c.2816G>A (chr2: p.Gly939Asp), which is a sensitive gene to missense variants and a single dose deficiency (Haploinsufficiency Score: 3), autosomal dominant inheritance and de novo mutation. This gene is classified as likely pathogenic and associated with vEDS. The patient eventually recovered and discharged from hospital 40 days post-operativelly. She is now in stable without any invasive procedure on 3-year telephone call follow-up with permanent ileostomy.

Conclusions: Recurrent perforations and spontaneous bleeding, along with fragile skin and tissue, should raise suspicion for a possible diagnosis of EDS. Gene testing is the gold method to confirm the diagnosis of EDS, which could help clinicians optimize the surgical strategy for patients.

Introduction

Patients with intestinal perforation caused by inflammation, strangulated intestinal obstructions or autoimmune ulcers need emergent open or laproscotic laprotomy to repair the perforation or resect the involved bowels based on the common reasons in pediatric populations like incarcerated hernias, Neonatal Necrotizing Enterocolitis (NEC), digestive mechanical obstruction or Hirsprung's disease. After primary or staged procedures aimed to original disease, the patients usually heal well. However, in some rare cases, though receiving standard surgical treatments, patients may still present with repeated and confusing bowel perforation and bleeding after anastomosis. Shall we still continue improving our

surgical technical skills or opening our mind to consider more possibilities of specific systemic disease caused by genetic mutation?

Here, we introduce a case of a child with recurrent colon perforation and bleeding caused by genetic mutation disease --vascular Ehlers-Danlos syndromes (vEDS). We hope pediatric surgeons can recognize and be alert to such disease from the diagnosis and treatment process, and provide better diagnosis and treatment plans for patients with the disease in the future.

Case description

This 7-year-old girl who was transferred from another hospital presented with intermittent anal bleeding, despite having undergone a double-lumen ileostomy two years prior. Her appearance is not special. Her facial skin is normal; her height is 121 cm; her weight is 26.5 kg, and her intelligence is normal. She has no special facial appearance.

The child experienced recurrent constipation starting at 8 months old. No standardized treatment was provided during this time. When she was 3 years old, she developed fever, abdominal distension and abdominal pain. She was sent to a local hospital and received CT scan which showed the possibility of rectal perforation. She received her first laparotomy while the perforated anterior rectal wall was repaired and sigmoidostomy was done. On postoperative day-8, the surgeons had to perform the second laparotomy because the abdominal incision cracked and the intestinal tube was exposed. Unfortunately, the night after the second procedure, the child experienced life-threatening hemorrhage. The local surgeon performed a third exploratory laparotomy, during which a splenectomy was necessary due to an unexpected splenic rupture.

Four months later, her surgeon found her rectal stricture and then performed stoma and rectal biopsy which showed the presence of submucosal ganglion cells. The diagnosis of megacolon has been ruled out. However, the cause of the recurred bowel perforation is still unknown. Two months after her fourth procedure, with her intestinal incision tore, she had to have the fifth operation which included pull-through end-to-end sigmoid-recal anastomosis (Soave procedure), continuous stoma closure and incisional hernia repair at the same time.

After the 5th operation, the nightmare did not end. In the following six months, the girl had to undergo four more operations due to recurrent bleeding, incision and stoma poor healing.

The family came to our hospital to ask for anal reconstruction and stoma closure. During this operation, pediatric surgeons felt very confusing that the patient's intestinal wall was thin, easy to tear and perforate; mesenteric tissue and vessels are fragile and prone to bleeding and arresting bleeding seems very difficult. The skin is prone to bruising and tearing (Fig. 1). Considering the relevant literature and her history of unplanned surgeries due to short-term postoperative complications, including repeated intestinal perforations and bleeding, the surgeons strongly suspected that she had Ehlers-Danlos syndrome (EDS). As a result, the medical team chose to improve the surgical strategy, which included

repairing the intestinal perforation, performing a total colectomy with a permanent ileostomy, to reduce the risks of spontaneous colonic perforation, anastomotic leaks, and future bleeding. Considering the patient's medical history, we believe this case is unique and not merely a straightforward surgical issue. We reviewed the relevant literature during the surgery, considered the possibility of EDS in this child, and evaluated the high risks of spontaneous colonic perforation and future bleeding; therefore, we refined the surgical strategy to include intestinal adhesiolysis, intestinal perforation repair, and total colectomy with a permanent ileostomy. Additionally, to identify the disease's etiology, we conducted biochemical, immunological, and genetic tests on the child. After the surgery, the patient experienced a steady recovery and remained on parenteral nutrition for 40 days before being discharged from the hospital according to the reference standard[1].

Supplementary Examination

During the routine blood test, only white blood cells are slightly higher. Other indicators are normal. Blood tests for coagulation, vasculitis, autoantibodies, allergen ingestion, cytokines, neutrophil function, and lymphocyte count are all negative. Blood tests exclude coagulation dysfunction and immune system diseases.

Whole-Exome Sequencing (WES)

Genomic DNA was extracted using a QIAamp® DNA Blood Mini Kit (Qiagen, Germany). WES was performed on an Illumina HiSeq 2,500 sequencer (Illumina, San Diego, CA, United States). After quality control, sequencing reads were aligned to the human reference genome by BWA (hg19). Nucleotide changes of aligned reads were reviewed using NextGENe software (Version 2.4.1.2) (SofGenetics, State College, PA, United States). Novel variants were filtered against the 1,000 Genomes database (http://www.1000genomes.org/), the dbSNP database (http://www.ncbi.nlm.nih.gov/projects/SNP/snp_summary.cgi), and the Genome Aggregation Database (gnomad.broadinstitute.org). Databases were used, including ClinVar, OMIM, ClinGen, and the Human Gene Mutation Database[2]. The genetic variants were annotated and interpreted according to the ACMG (American College of Medical Genetics and Genomics) guidelines[3]. Finally, Sanger sequencing of the targeted gene mutation was performed to verify.

A de novo heterozygous missense variant, NM_000090.3: c.2816G > A (p.Gly939Asp), was identified in proband in the *COL3A1* gene. The variant was not recorded in gnomAD database. Bioinformatic software predicted it was disease-causing / damaging (REVEL: 0.99). It has been reported in previous cases with vascular Ehlers–Danlos syndromes (vEDS)[4], and recorded in HGMD database (ID:CM950300). According to the ACMG guideline, this variant was classified as likely pathogenic (PM2_Supporting+PP3_Strong+ PS2_Strong). The variant was validated by Sanger sequencing (Figure. 3). The *COL3A1* gene is associated with autosomal dominant vascrlar Ehlers–Danlos syndromes (vEDS).

Treatment and follow-up

Based on the clinical symptoms and the results of the children, a vascrlar Ehlers–Danlos syndrome (vEDS) was confirmed. According to the characteristics of this disease, conservative treatment should be given priority to children; surgery may be necessary in emergency situations, and deep wound repair is required after surgery; and can participate in supervised low to moderate exercise. Although the mother hopes to reconstruct the anus through pull-through anorectal replasty and ileostomy reversal, for children with vEDS, a permanent ileostomy is the best option. We explained the reason for the adjustment of the treatment plan and obtained an understanding of the mother. Up to date, after the operation, the patient is in stable condition.

Discussion

The Ehlers–Danlos syndromes (EDS) is an inherited heterogeneous group of connective tissue disorders, of which the main features are skin hyperextensibility, joint hypermobility, and tissue fragility demonstrated by easy bruising and delayed wound healing with atrophic scarring. The prevalence is estimated to be 1 in 5000, without any ethnic predilection [5]. Initially, EDS was proposed to have nine subcategories. Later, it was divided into six major types. With recent developments and increased medical expertise, the latest EDS nosology distinguished fourteen subtypes instead of six[6]. The previous EDS type IV is vascular EDS (vEDS) now.

Vascular EDS comprises 5%–10% of all patients with EDS and is the most serious type due to its association with severe and often fatal rupture of the bowel, other organs, and large arteries[7]. The clinical diagnosis of vascular Ehlers–Danlos syndromes (vEDS) is based on four clinical criteria: easy bruising, thin skin with visible veins, characteristic facial features(thin vermilion of the lips, micrognathia, narrow nose, prominent eyes), and rupture of the arteries, uterus, or intestines. vEDS is an autosomal dominant disorder caused by a type III collagen gene mutation, *COL3A1*. This gene encodes the pro-alpha1 chains of type III collagen, fibrillar collagen found in extensible connective tissues such as the skin, lung, uterus, intestine, and vascular system[8]. Therefore, when the *COL3A1* gene mutation occurs, it can affect collagen formation in these tissues, resulting in increased fragility, easy bruising, and even rupture of these tissues. The prevalence of vEDS has been estimated to be approximately 1 in 90,000, but this estimate is likely low[9]. However, in most individuals, the diagnosis is not suspected (in the absence of a family history of the disorder) until an arterial aneurysm and/or dissection, intestinal perforation, or organ rupture occurs.

In our case, because there was no family history and the patient had no other obvious phenotype, rectal perforation was initially misdiagnosed as a common acute abdomen. However, local doctors are still not alert to the wound rupture, bleeding, and perforation that occurred one after another. It may be that vEDS is a rare disease, and most doctors have no experience with it. Research reports that the age of onset was rare in childhood; 25% of index patients had a first major complication at 20 years, and more than

80% had at least one complication by 40[9]. In another study of 174 children with a positive family history of vEDS tested before age 18, 87% had not experienced a major complication[10].

Kodikara et al. presented a case of spontaneous sigmoid perforation in a 14-year-old boy[11]. He was initially treated with a laparotomy of the sigmoid perforation and a diverting ileostomy. Exudation and wound rupture began on postoperative day 3. Although the wound was repaired, it did not improve. Instead, his wound was completely dehiscent on postoperative day 9. Later, genetic tests showed a *COL3A1* mutation, confirming the diagnosis of vEDS. The doctors changed the treatment with a combination of negative pressure wound therapy and changes in the Eakin pouch. It took a total of 4 months to recover and leave the hospital. Elhattabi et al. also reported the case of a 27-year-old man with colon perforation after an appendectomy for peritonitis secondary to appendicitis[12]. The operation included bowel resection with end-to-end anastomosis and a 10-cm colonic resection. But three months after the operation, the patient presented with an occlusive syndrome complicated by a stoma and necrosis of the small intestine. A genetic test for the mutation of the *COL3A1* gene was shown to have been carried out, which was positive in favor of vascular Ehlers-Danlos disease. Then, a totalization of the colectomy with ileorectal anastomosis was performed, associated with incisional hernia treatment by the Paletot technique. The postoperative and long-term follow-ups were uneventful. These two cases suggest that vEDS is very common in misdiagnosing this disease. And the identified diagnosis is very important for clinical treatment. If it is treated as a general surgical disease, complications such as bruising, perforation, and bleeding will occur again.

Recently, Wilinson NR et al. summarized cases of pediatric vEDS syndrome at the EDS service center in London[13]. There are a total of 63 cases in this article, including 33 males and 30 females. The median age at first event were 11 years, and 4 cases occurring in the neonatal period. Events were most frequently gastrointestinal (47.1%), mainly manifested as intestinal perforation, especially in the sigmoid colon, caecum, and stomach. Next is spontaneous pneumothorax, accounting for 35.3%. On average, each case experiences 1.38 events, with the maximum number of events for a single individual was three. Because this is the regulatory center for EDS syndrome, many cases have undergone molecular diagnosis before the onset of the disease due to a family history. The median age of diagnosis is 7 years(IQR 2–13, range 0–17), which allows for more appropriate treatment at the time of onset. Currently, there are no deaths.

Bowen JM et al. reported a total of 180 vEDS patients aged 13 and above from the Sheffield Centre in the UK over the past 12 years, and analyzed their clinical features[14]. There are 94.6% patients had prominent/hollow eyes, 75.3% delicate midface, 85.2%attached earlobes/lobeless ears. Acrogeria was observed in 41.8% and thinning hair in 29.7%. Easy bruising and thin skin were seen in the majority (83% and 74% respectively) but not all patients. There are 64.1% patients had small joint hypermobility of their fingers, and fewer (32.8%) had generalised hypermobility. 72 patients (40%) had a total of 165 vascular events. 25 patients (13.88%) had bowel perforation. And the prime ages for bowel perforations are late teens and early 20s. They pointed out that surgical risks are higher for those with vEDS and conservative

management options should be considered before surgery. Only when surgery is necessary should it be performed.

If an early diagnosis is made, the appropriate treatment can be selected. For our case, the mother of the child has been asking for an anal reconstruction because she hoped the child could defecate and live like a normal person. However, each surgical operation increases the probability of complications in children, making the condition more serious. The colectomy and permanent ileostomies are maybe the best options for the patient. In addition, prophylactic measures are also of special importance for the vascular type of EDS, including avoiding contact sports or isometric exercises. Refraining from drugs that interfere with platelet function is also advised[15].

In conclusion, vascular Ehlers-Danlos syndromes should be considered in all patients with spontaneous and recurrent visceral perforation (especially sigmoid) regardless of age. Furthermore, the clinical findings of the condition, such as characteristic facial features, translucent skin, and easy bruising, should be sought in patients with spontaneous colonic perforation without a clear cause. Gene testing helps clarify the diagnosis of EDS, helps clinicians understand the characteristics of the disease, and improves the treatment plan.

Conclusion

Recurrent perforations and spontaneous bleeding, along with fragile skin and tissue, should raise suspicion for a possible diagnosis of EDS. Gene testing is the gold method to confirm the diagnosis of EDS, which could help clinicians optimize the surgical strategy for patients.

Declarations

Ethics Statement

The studies involving human participants were reviewed and approved by the ethics committee of Guangzhou Medical University Affiliated Women and Children's Medical Center [GZFEZX Scientific Ethics Approval (2021) No.356B01]. Written informed consent to participate in this study was provided by the participants' legal guardian, including the images or data in this article.

Conflicts of interest:

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Consent to publish

declaration: All authors agree to publish this manuscript on the Journal of BMC Surgery.

Consent to Participate

declaration: All authors agree to participate and submit this manuscript to the Journal of BMC Surgery.

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Author Contribution

Min Pan: wrote the main manuscript text; Wei Zhong, Longlong Hou and Qiuming He: provide cases and prepared figures 1, Guilan Chen:experimental detection and analysis data, prepared figures 2; Dongzhi Li and Wei Zhong:overall supervision; All authors reviewed the manuscript and approved the final version.

Data Availability Statement

All data generated during and/or analyzed during the current study are available upon request from the corresponding author.

Clinical trial number

not applicable

Author contribution statement

Min Pan: wrote the main manuscript text; Wei Zhong, Longlong Hou and Qiuming He: provide cases and prepared Figs. 1, Guilan Chen:experimental detection and analysis data, prepared Figs. 2; Dongzhi Li and Wei Zhong:overall supervision; All authors reviewed the manuscript and approved the final version.

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Figures

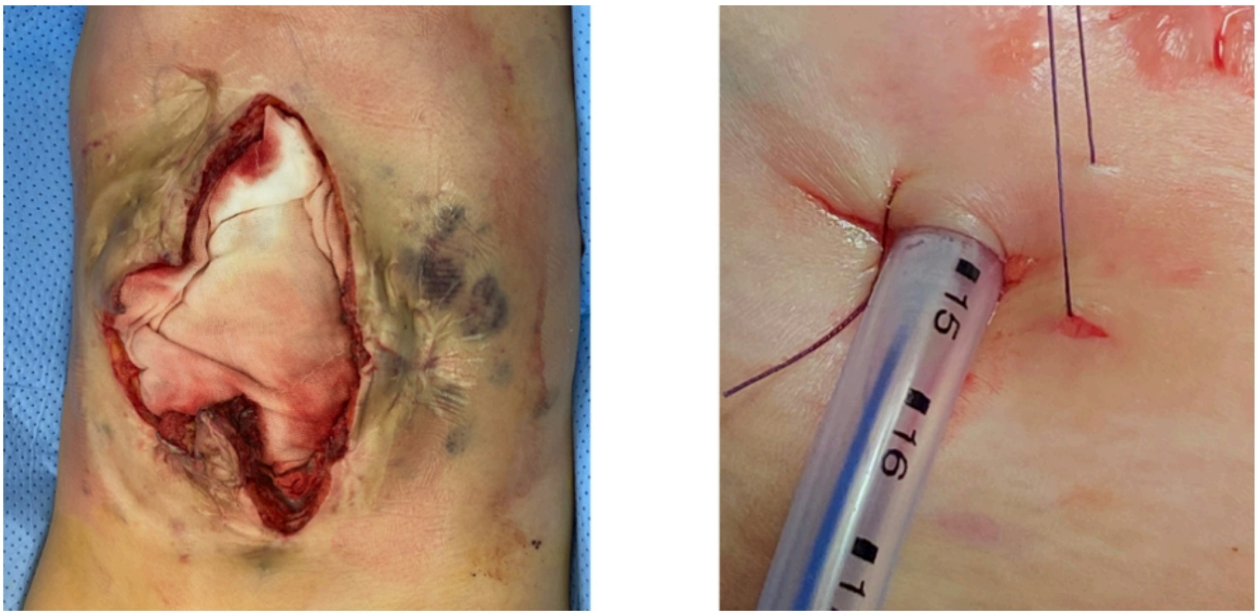


Figure 1

Abdominal wound, the skin is easy to appear ecchymosis and tears.

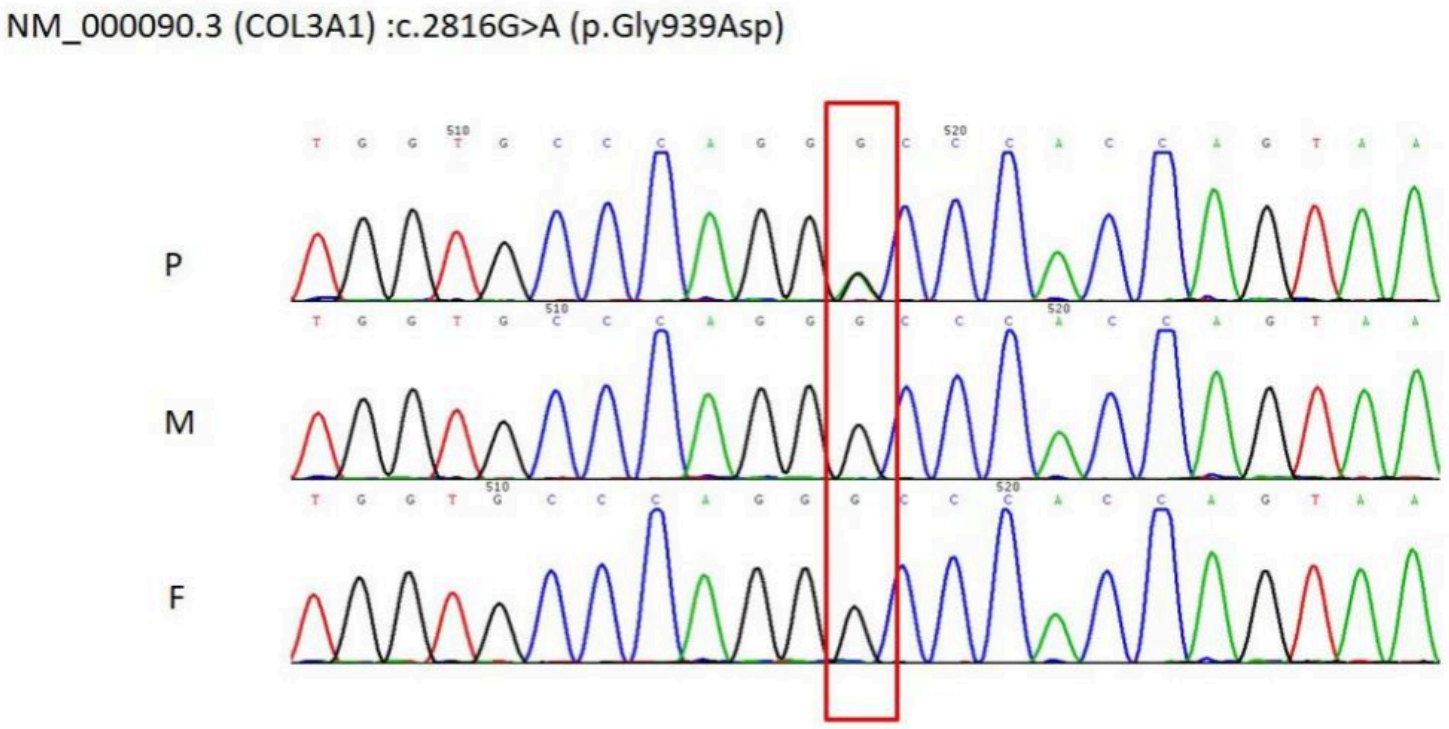


Figure 2

Map of COL3A1 gene mutation sites