



Link between mutations in *ACVRL1* and *PLA2G4A* genes and chronic intestinal ulcers: A case report and review of literature

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Abstract

BACKGROUND

Genetic factors of chronic intestinal ulcers are increasingly garnering attention. We present a case of chronic intestinal ulcers and bleeding associated with mutations of the activin A receptor type II-like 1 (*ACVRL1*) and phospholipase A2 group IVA (*PLA2G4A*) genes and review the available relevant literature.

CASE SUMMARY

A 20-year-old man was admitted to our center with a 6-year history of recurrent abdominal pain, diarrhea, and dark stools. At the onset 6 years ago, the patient had received treatment at a local hospital for abdominal pain persisting for 7 d, under the diagnosis of diffuse peritonitis, acute gangrenous appendicitis with perforation, adhesive intestinal obstruction, and pelvic abscess. The surgical treatment included exploratory laparotomy, appendectomy, intestinal adhesiolysis, and pelvic abscess removal. The patient's condition improved and he was discharged. However, the recurrent episodes of abdominal pain and passage of black stools started again one year after discharge. On the basis of these features and results of subsequent colonoscopy, the clinical diagnosis was established as in-

inflammatory bowel disease (IBD). Accordingly, aminosalicic acid, immunotherapy, and related symptomatic treatment were administered, but the symptoms of the patient did not improve significantly. Further investigations revealed mutations in the *ACVRL1* and *PLA2G4A* genes. *ACVRL1* and *PLA2G4A* are involved in angiogenesis and coagulation, respectively. This suggests that the chronic intestinal ulcers and bleeding in this case may be linked to mutations in the *ACVRL1* and *PLA2G4A* genes. Oral Kangfuxin liquid was administered to promote healing of the intestinal mucosa and effectively manage clinical symptoms.

CONCLUSION

Mutations in the *ACVRL1* and *PLA2G4A* genes may be one of the causes of chronic intestinal ulcers and bleeding in IBD. Orally administered Kangfuxin liquid may have therapeutic potential.

Key Words: Intestinal ulcers; Crohn's disease; Ulcerative colitis; Activin A receptor type II-like 1; Phospholipase A2 group 4A; Case report

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Core Tip: We present a case of chronic intestinal ulcers and bleeding associated with mutations of the activin A receptor type II-like 1 (*ACVRL1*) and phospholipase A2 group IVA (*PLA2G4A*) genes. The patient's symptoms started at an early age, with the first manifestation being acute gangrenous appendicitis with perforation. However, the patient experienced recurrent abdominal pain and bloody stools one year after surgery. After colonoscopy and intestinal mucosal pathological examination, the diagnosis was established as inflammatory bowel disease without the characteristic features of Crohn's disease or ulcerative colitis. Aminosalicic acid and immunotherapy were not sufficiently effective. Further investigations revealed mutations in the *ACVRL1* and *PLA2G4A* genes. From these observations, we inferred that these mutations may be linked to chronic intestinal ulcers and bleeding. Kangfuxin liquid appears to be promising in terms of therapeutic potential in this type of chronic intestinal ulcers.

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INTRODUCTION

Chronic intestinal ulcers are caused by multiple factors and have a complex etiopathogenesis. On the basis of causation, chronic gastrointestinal ulcers are classified as those due to infectious causes such as bacteria, fungi, viruses, and intestinal tuberculosis; those due to immune causes like inflammatory bowel disease (IBD), Behcet's syndrome, and Sjogren's syndrome; those due to tumor-related causes such as colon cancer and lymphoma; those due to abnormalities of blood supply such as ischemia, portal hypertension, and diverticulum; due to genetic causes involving certain gene mutations; and those due to drug causes such as non-steroidal anti-inflammatory drugs (NSAIDs) are a major cause of gastrointestinal ulcers[1]. Infectious gastrointestinal ulcers are commonly caused by *Helicobacter pylori* and *Mycobacterium tuberculosis*[2,3]. IBD, which encompasses Crohn's disease (CD) and ulcerative colitis (UC), occurs due to an imbalance between the proinflammatory and anti-inflammatory factors in the intestinal mucosa[4]. However, research has shown that genetic factors are responsible for decreased ability of the intestinal mucosa to resist damage and to repair, which leads to the formation of intestinal ulcers; these factors have not garnered much attention in actual clinical practice.

We present a case of chronic intestinal ulcer and bleeding in IBD, which were probably associated with mutations in the active A receptor type II-like 1 (*ACVRL1*) and phospholipase A2 group IVA (*PLA2G4A*) genes. In addition, we review the relevant literature and summarize the diagnosis and treatment in such cases.

CASE PRESENTATION

Chief complaints

A 20-year-old male patient was admitted to our hospital on July 9, 2021, for evaluation of recurring abdominal pain, diarrhea, and black stools, which had been persisting for 6 years.

History of present illness

The patient received treatment at a local hospital 6 years back for seven days of unexplained abdominal pain. On examination, the peritoneal stimulation sign was positive. Abdominal X-ray at the time revealed a gas shadow located below the diaphragm. On diagnostic abdominal puncture, 5 mL of purulent fluid was withdrawn, thereby raising the suspicion of perforation in the digestive tract. Laparotomy performed for exploration revealed diffuse peritonitis, acute gangrenous appendicitis with perforation, adhesive intestinal obstruction, and pelvic abscess. Appendectomy, intestinal adhesiolysis, and pelvic abscess removal surgery were performed during the procedure (July 2, 2015). Following surgery, the patient's condition improved and he was discharged. However, one year after discharge, the patient started experiencing recurrent abdominal pain and dark red loose stools, with positive test results for fecal occult blood and mild to moderate anemia. Colonoscopy had been performed several times before and showed the presence of intestinal ulcers and bleeding at other hospitals. In light of the colonoscopy findings, a clinical diagnosis of IBD was made. Oral treatment with mesalazine was administered at a local hospital, at a dose of 2 tablets four times a day for a total of 6 weeks. However, there was no improvement in the symptoms of rectal bleeding. Subsequently, oral treatment with azathioprine was added, at a dose of 50 mg once a day for a total of 2 months. Even with this treatment, the symptoms of rectal bleeding did not improve. The Mayo score was 8 points both before and after medication (with an increase of 2-3 times per day compared to the normal bowel movements, mixed blood in the stool within less than half of the time, ulcer formation detected by endoscopy, and moderate condition). Considering its ineffectiveness, mesalazine and azathioprine treatment was discontinued.

On July 9, 2021, the patient presented with persistence and worsening of the abovementioned symptoms. The frequency of episodes of abdominal pain and black stool had increased, with approximately 30 mL of dark red loose stools about 3-4 times a day, without mucus, or pus. In addition, he reported dizziness, but did not report any nausea, vomiting, abdominal distension, or constipation. The patient did not experience any loss of consciousness. Moreover, the patient did not show any signs of fever, chills, or night sweats. Subsequently, the patient sought medical attention and was hospitalized for further evaluation, diagnosis, and treatment.

History of past illness

The patient's medical history was the same as before, with no other surgical or traumatic history. He also denied having any history of long-term use of NSAIDs or glucocorticoids. Due to gastrointestinal bleeding, the patient received red blood cell infusion twice, without any negative reactions during the process. There was no evidence of infectious diseases, such as typhoid fever and tuberculosis, or any sexually transmitted diseases.

Personal and family history

The individual reported a history of alcohol consumption for three years, although the amount consumed was unknown. He denied having any history of smoking or exposure to toxins; he also denied any family history of genetic diseases.

Physical examination

On examination, the patient had stable vital signs, a clear mind, an anemic face, and pallor of the palpebral conjunctiva, lips, and nail beds. Superficial lymph nodes were not palpable, and cardiopulmonary examination revealed no apparent positive signs; only an old longitudinal surgical scar measuring approximately 20 cm in length was noted on the abdomen. Tenderness was noted beneath the xiphoid process, but there was no rebound pain or muscle tension. No shifting dullness was detected, and bowel sounds were heard at a rate of 6 per minute. No edema was observed in either lower limb.

Laboratory examinations

Routine blood tests revealed moderate anemia and a decrease in the average red blood cell volume (Table 1). Other tests conducted after admission showed no abnormalities in coagulation function and blood biochemistry. No abnormal findings were obtained in laboratory tests for antineutrophil cytoplasmic antibody, antinuclear antibodies, immunoglobulin, lymphocyte immunochip, C-reactive protein (CRP), blood sedimentation rate, and detection of common viruses such as human immunodeficiency virus, hepatitis B virus, and cytomegalovirus. Analysis of the stool sample collected revealed the presence of occult blood. Fecal bacterial culture and fecal fungal culture did not show positive findings. Additionally, the ¹³C-urea breath test yielded a negative result. Whole-exome sequencing performed for the detection of genetic diseases led to the identification of autosomal ACVRL1 and PLA2G4A gene mutations (July 21, 2021; Figure 1).

Imaging examinations

On gastroscopy performed on July 12, 2021, the esophagus appeared to have normal morphology and color, with no evident abnormalities (Figure 2). The distance from the cardia to the incisor was approximately 40 cm, and the dentate line was clearly visible. No abnormalities were visible in the mucosa and structure of the gastric fundus and gastric body. The gastric fundus showed a moderate amount of mucus and yellow turbidity, with a smoothly curved gastric angle. In addition, congestion and edema of the gastric antrum mucosa were noted, with no signs of ulcers or masses. The pylorus appeared to be circular and functioning properly, with smooth opening and closure. Similarly, no abnormalities were detected in the duodenal bulb and mucosa of the descending duodenum. The above findings led to the conclusion of chronic non-atrophic gastritis with bile reflux.

Colonoscopy performed on July 16, 2021 revealed that the surgical repair site between the ascending colon and the ileum was visible 55 cm from the anus (usually 60-70 cm away from the anus); the ileocecal valve and cecum were indistinguishable (Figure 3). There were scattered nodular protrusions, lamellar vesicle, and shallow ulcers at the site of surgical repair, as well as in the ileum. Additionally, local mucosal protrusions, ulcers, and nodular protrusions were

Table 1 Changes of blood cell counts and hemoglobin level in the patient

Date	WBCs, × 10 ⁹ /L	RBCs, × 10 ¹² /L	HB, g/L	PLTs, × 10 ⁹ /L	MCV, fl
	Ref: 3.5-9.5	Ref: 4.3-5.8	Ref: 130-175	Ref: 125-350	Ref: 80-100
2021-07-09	5.13	3.7↓	75↓	312	68.3↓
2021-07-11	4.83	3.3↓	66↓	249	68.7↓
2021-07-18	6.25	3.8↓	76↓	429↑	67.4↓

WBCs: White blood cells; RBCs: Red blood cells; HB: Hemoglobin; PLTs: Platelets; MCV: Mean corpuscular volume.

Gene	Chromosomal position	Base variant information	Zygotic type	Genetic type	Variant level	Source of variation
ACVRL1	chr12:52308249	NM_000020.3:c.652C>T	het	AD	The clinical significance is unknown	/
PLA2G4A	chr1:186916087	NM_024420.3:c.1258G>C	het	AR	The clinical significance is unknown	/

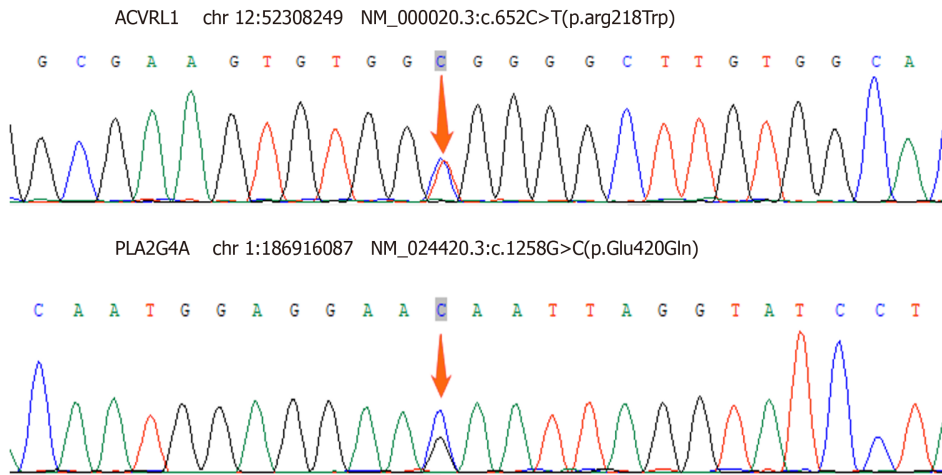


Figure 1 Sanger sequencing of the activin A receptor type II-like 1 and phospholipase A2 group IVA genes in patients. Het: Heterozygote; AD: Autosomal dominance inheritance; AR: Autosomal recessive inheritance.

observed near the hepatic flexure of the transverse colon. The morphology of the remaining part of the descending colon and sigmoid colon appeared normal, with regular folds, a smooth mucosal surface, and rich and clear vascular network; no abnormal secretions, erosion, ulcers, or masses were detected in these segments of the colon. Similarly, the rectal mucosa exhibited no obvious abnormalities, But a fistula in the perianal area was suspected. The colonoscopy findings raised a suspicion of CD.

Histopathologic examination

Pathological examination of the appendix removed on July 2, 2015, showed acute gangrenous appendicitis, peritonitis, appendix perforation, and fecal stone incarceration within the cavity.

Histopathologic examination of a sample of intestinal mucosa obtained on July 19, 2021 revealed superficial mucosa ulceration in the ileum with abundant inflammatory exudates, formation of granulomas, infiltration of lymphocytes and plasma cells, and no caseous necrosis (Figure 4). Additionally, the superficial mucosa of the colon showed signs of acute and chronic inflammation.

Further diagnostic work-up

Multiple routine investigations during hospitalization revealed a decrease in the levels of red blood cells, hemoglobin, and average red blood cell volume; slightly higher fibrinogen levels; and a positive fecal occult blood. Given the patient’s history of appendiceal perforation, special care was taken to remain vigilant for signs of gastrointestinal ulcers, and a careful gastroenteroscopy and pathological examination was performed, which validated the atypical intestinal lesions of CD or UC. Additionally, the patient did not exhibit symptoms such as low fever or night sweats, and did not have abnormalities in chest CT and erythrocyte sedimentation rate. Moreover, enteroscopy did not show any transverse ulcers, and pathological findings did not suggest caseous necrosis. Absence of the typical symptoms and the investigative findings together rule out the possibility of tuberculosis infection[5]. The 13C-urea breath test result was negative, which

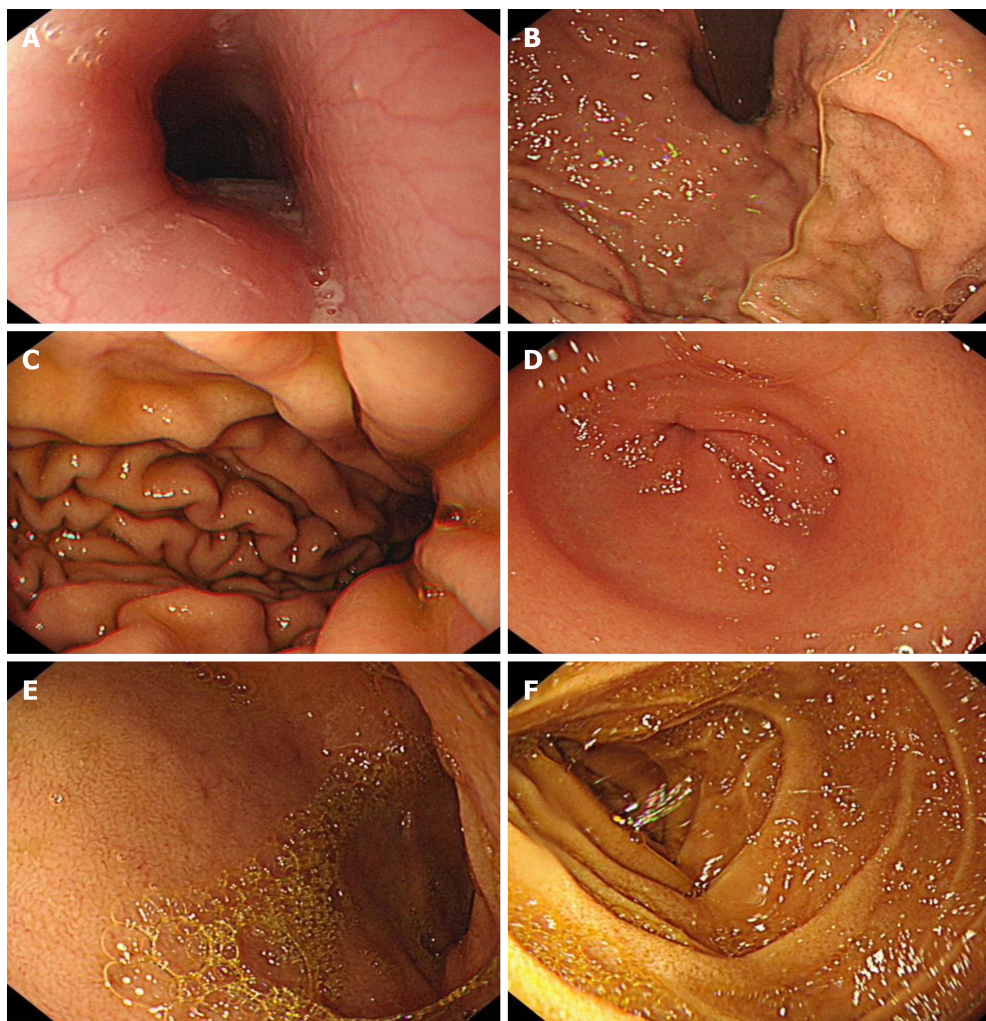


Figure 2 Gastroscopy results. A: Esophagus; B: Gastric fundus; C: Gastric body; D: Gastric antrum; E: Duodenal bulb; F: Descending duodenum. No obvious abnormalities are seen in the morphology and color of the esophagus. The distance between the cardia and the incisor is about 40 cm, and the dentate line is clear. The gastric fundus does not show any obvious abnormalities in the mucosa and morphology, and there is a moderate amount of mucus and yellow turbidity. The gastric body's mucosa and morphology are also normal; the gastric angle is curved and smooth. The gastric antrum's mucosa is congested and edematous, but no ulcers or masses are present. The pylorus is circular in shape and can open and close smoothly. There are no obvious abnormalities in the duodenal bulb and descending mucosa.

ruled out *Helicobacter pylori* infection. Since the patient did not have any history of taking NSAIDs or corticosteroids, drug-induced ulcers were also ruled out. Moreover, no abnormalities were detected in tests for urine cytomegalovirus deoxyribonucleic acid, fecal bacterial culture, fecal fungal culture, and common virological tests; therefore, viral, bacterial, and fungal infections were ruled out. Upon retrospective analysis of the clinical manifestations, enteroscopic and pathological findings, the diagnosis was established as IBD without typical features of CD or UC. The patient did not have extraintestinal manifestations, and tests for CRP, antineutrophil cytoplasmic antibody, antinuclear antibodies, immunoglobulin levels, lymphocyte immunochip showed no abnormalities. Furthermore, despite undergoing mesalazine and immune-modulating therapy with azathioprine, there was no improvement in the patient's symptoms. Thus, the early age of onset; recurrence of symptoms; atypical features of CD and UC; and lack of response to aminosalicic acid, immunotherapy, and related symptomatic treatment raised suspicion of the potential etiopathogenetic role of genetic factors in this case.

Subsequently, whole-exome sequencing for genetic diseases was performed, which revealed mutations in the *ACVRL1* and *PLA2G4A* genes. Mutations of both these genes are known to cause a decrease in the ability of the intestinal mucosa to resist injury and sustain repair. Kangfuxin liquid is known to have an effect of accelerating the repair of pathological tissue, shedding of necrotic tissue, and healing of ulcers and wounds. Accordingly, we modified the treatment plan and administered oral Kangfuxin liquid of 10 mL three times daily to promote the repair of the intestinal repair. The patient was discharged once his symptoms improved on initiating this treatment, and treatment was continued for 4 wk after discharge. If the patient occasionally experiences symptoms such as abdominal pain, diarrhea, and black stool, oral administration of Kangfuxin liquid can alleviate the symptoms.

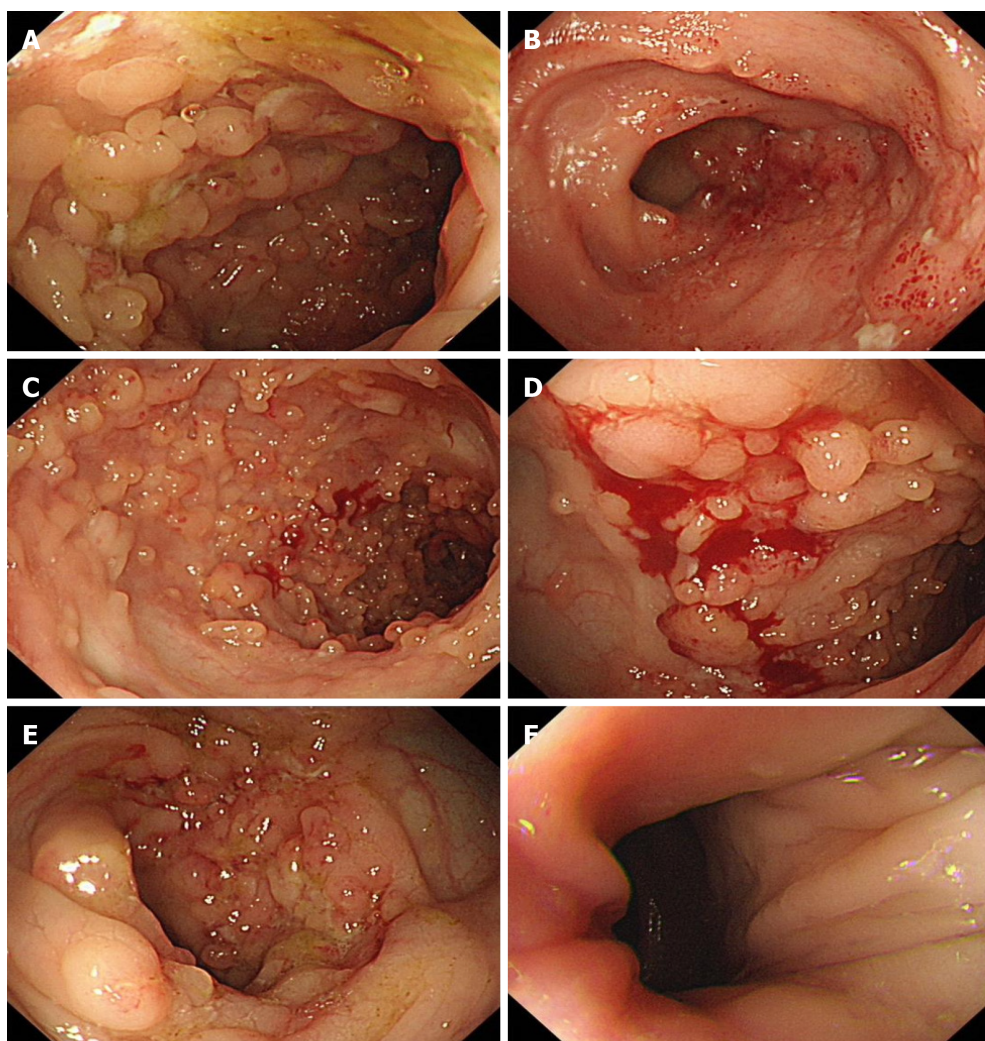


Figure 3 Colonoscopy results. A: Distal ileum; B: Distal ileum; C: Distal ileum; D: Surgical repair site; E: Hepatic flexure; F: Anus. The distal ileal mucosa is congested and edematous, with visible erosion and scattered patchy ulcers, covered with white fur and distributed in segments. The surrounding mucosa is accompanied by pseudopolypoid hyperplasia, presenting as cobblestone-like changes. Local mucosal protrusions, ulcers, and nodular protrusions can be seen near the hepatic flexure of the transverse colon. Suspected formation of a sinus in the anus.

FINAL DIAGNOSIS

Taking into consideration the patient's medical history and the results of investigations, the diagnosis was determined to be IBD, and the patient's chronic intestinal ulcer and bleeding may be related to mutations in the *ACVRL1* and *PLA2G4A* genes.

TREATMENT

The treatment plan comprised the following: Yunnan Baiyao for hemostasis, blood transfusion to correct anemia, and omeprazole to inhibit gastric acid secretion. However, this treatment plan was not sufficiently effective. The patient refused to accept biologic therapy, such as rituximab. Therefore, Kangfuxin liquid was added to the treatment, as explained above. This change was found to be effective in reducing the patient's symptoms. However, there is a possibility of the recurrence of symptoms such as abdominal pain and bloody stools on discontinuation of Kangfuxin liquid.

OUTCOME AND FOLLOW-UP

Modification of the treatment plan to include Kangfuxin liquid was found to have a satisfactory therapeutic effect. The patient's symptoms of bloody stools and abdominal pain improved. However, without treatment, there still remains the possibility of these symptoms resurfacing. The patient opted to continue receiving Kangfuxin liquid for symptom relief.

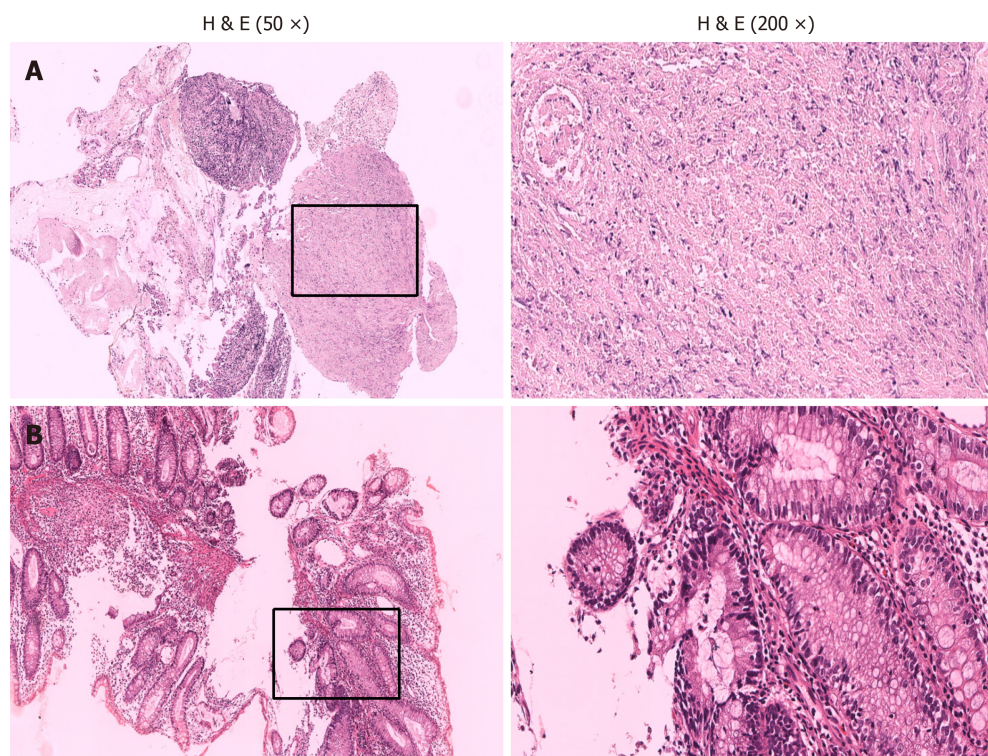


Figure 4 Pathology of intestinal mucosal tissue. A: Colon (a small amount of mucosal tissue and inflammatory exudative necrosis); B: Distal ileum (ulcer formation, large numbers of inflammatory exudates and granuloma formation, and large numbers of lymphocytic plasma cell infiltration).

DISCUSSION

In this paper, we present the case of a 20-year-old man with IBD, whose chronic intestinal ulcer and bleeding may be associated with mutations in the *ACVRL1* and *PLA2G4A* genes. At the age of 14 years, the patient had developed acute gangrenous appendicitis with perforation for which he received surgical treatment. Subsequently, the patient had recurrent intestinal ulcers or bleeding and IBD was diagnosed on the basis of the colonoscopy and histopathologic findings, although the findings were not consistent with those typically seen in CD, or UC. Treatment with aminosalicic acid preparations and immunomodulators was not effective. Subsequent whole-exome sequencing test for genetic diseases revealed mutations in the genes *ACVRL1* and *PLA2G4A*. The *ACVRL1* and *PLA2G4A* genes have been reported to be associated with the repair of the digestive tract mucosa and local hemostasis function[6,7]. Considering the patient's clinical symptoms and findings of imaging studies, histopathologic examination, and genetic testing, we speculate that the patient's chronic intestinal ulcers and bleeding were caused by mutations in the *ACVRL1* and *PLA2G4A* genes. Treatment with orally administered Kangfuxin liquid led to improvement in the patient's condition, probably by promoting the repair of the intestinal mucosa and regulating the local immune balance.

Our patient first developed acute gangrenous appendicitis with perforation at the age of 14 years, and one year after surgical treatment, experienced recurrent abdominal pain and bloody stools. During follow-up, colonoscopy revealed scattered nodular protrusions, lamellar vesicles, and shallow ulcers at the site of surgical repair and in the ileum. Additionally, local mucosal protrusions, ulcers, and nodular protrusions were observed near the hepatic flexure of the transverse colon and presence of perianal fistula was suspected. The histopathological examination of the intestinal mucosal sample showed a superficial mucosal ulcer in the ileum, with a large amount of inflammatory exudate, formation of granulomas, and infiltration of lymphocytes and plasma cells. In addition, the superficial mucosa of the colon shows signs of acute and chronic inflammation. These features are consistent with IBD, which was considered as the initial diagnosis in this case.

IBD is a chronic inflammatory disease of the gastrointestinal mucosa that occurs due to various genetic and environmental factors. IBD encompasses two chronic conditions: CD and UC[8,9]. The clinical symptoms of IBD primarily include abdominal pain, bloody stools, and diarrhea.

In IBD, aminosalicic acid and immunomodulators are frequently employed to control the imbalance between pro-inflammatory and anti-inflammatory factors[10]. The patient had been treated with mesalazine and azathioprine, but his main symptoms such as abdominal pain and bloody stools did not improve satisfactorily and the pathological characteristics of the intestinal mucosa in this case were lacking in the typical manifestations of CD and UC.

CD is more prevalent among adolescents and causes transmural inflammation that may affect any section of the gastrointestinal tract, although it most commonly affects the end of the ileum or adjacent portion of the colon sporadically [11]. The clinical symptoms of CD include abdominal pain, diarrhea, weight loss, anemia, fever, and bloody stools. The histological features of CD are submucosal thickening, transmural inflammation, fissure ulcers, and non-caseating granulomas. CD typically occurs in association with complications such as stenosis, abscesses, and fistulas and extra-

intestinal symptoms such as arthritis and skin nodular erythema. Colonoscopy findings include longitudinal ulcers that are distributed across the ileocecal region, lending the typical cobblestone-like appearance of the intestinal mucosa in CD. In terms of complications, intestinal stenosis and anal fistula are commonly observed in patients with CD.

Similar to CD, UC is more prevalent among young individuals and often presents with diarrhea, abdominal pain, mucopurulent and bloody stools, anemia, and fever[12]. UC is characterized by inflammatory changes of the mucosal lining, which begin in the rectum and continuously spread proximally. It primarily affects the mucosal layer and submucosa of the large intestine. The histological features of UC include superficial inflammatory changes confined to the mucosa and submucosa, along with cryptic inflammation and abscess formation. UC may also result in peripheral arthritis, nodular erythema of the skin, and other extraintestinal manifestations[13], with serious complications such as toxic megacolon and intestinal perforation. Colonoscopy findings in UC frequently include ulcers occurring as continuous diffuse lesions that begin in the rectum. In case of excessive swelling of the mucosa, the “colonic pouch” disappears. The ulcers discharge purulent secretions and exhibit a map-like pattern.

In the present case, the histopathologic examination revealed ulceration of the superficial mucosa of the ileum, with substantial inflammatory exudate and granuloma formation. Significant infiltration of lymphocytes and plasma cells was noted. The superficial mucosa of the colon exhibited signs of both acute and chronic inflammation. The colonoscopy revealed that the surgical repair site between the ascending colon and the ileum was visible 55 cm from the anus, with an indistinguishable ileocecal valve and cecum (usually 60-70 cm away from the anus), which suggests that the length of the colon may have been shortened and the shape of the ileocecal region may have changed. There were ulcers in the ileum and transverse colon. The ileal mucosa exhibited scattered nodular protrusions; flaky erosions; and shallow ulcers, with nodular protrusions on the mucosa; as well as substantial inflammatory exudate and granuloma formation. The histopathologic features of these lesions are similar to those seen in CD in terms of the involvement of the intestinal wall, but their morphologic features, including the presence of nodular protrusions, perianal fistulas, and granulomas, are consistent with those seen in UC. On the other hand, the early age of onset, absence of weight loss, and no related extraintestinal manifestations. Moreover, the patient had previously undergone treatment with mesalazine and azathioprine, which was ineffective. Thus, the clinical features in this case do not align with the typical manifestations of CD or UC.

The underlying pathogenesis of IBD is the disruption of proinflammatory and anti-inflammatory responses, following injury to the intestinal mucosa. Intestinal inflammation in IBD is maintained by lymphocyte subpopulations, especially Th12 Lymphocytes, which are derived from immature Th23 Lymphocytes. The activity of Th12 Lymphocytes is mediated by interleukin-17 (IL-17) and IL-10. IL-23, IL-12, IL-25, and other molecules produced by activated antigen-presenting cells (APCs) bind to IL-12Rb1, thus initiating the intracellular activation pathway of the effector cells. Subsequent cytokine-mediated signaling through the JAK-STAT pathway leads to the activation of Th17 cells, which, in turn, produce several proinflammatory cytokines, such as IL-17A, IL-17F, IL-22, IL-26, and the chemokine CCL20. These cytokines are expressed at high levels during the course of IBD[14]. IL-10 is regulated by the level of phosphorylation achieved through the action of JAK1. This occurs by the binding of IL-10 to the IL-10R1 receptor on white blood cells and is mediated by the STAT 3 signaling pathway. IL-10 can inhibit APC by decreasing the expression of the major histocompatibility complex (MHC). Therefore, increased MHC expression is advantageous in delaying the progression of IBD. Additionally, IL-10 is known to facilitate the proper functioning of the intestinal epithelial barrier by stimulating the regeneration of intestinal stem cells and regulating gut microbiota during fucosylation. Studies have shown that the lack of IL-10 contributes to the onset of IBD[15]. Therefore, the patient was previously administered aminosalicic acid and immunomodulatory therapy, but this did not yield any satisfactory outcome.

Considering the patient's early age of onset, recurring condition, lack of typical CD and UC colonoscopy features, and poor response to aminosalicic acid and immunomodulatory therapy, we sought to investigate the potential involvement of genetic factors in this case. Thus far, genome-wide association studies to determine the contributory role of genetic factors in IBD have revealed more than 200 single nucleotide polymorphisms (SNPs) that are linked to the disease [16,17]. However, gene testing to establish the diagnosis in this case did not reveal mutations in any of the genes typically associated with IBD[16]. Instead, mutations were detected in the *ACVRL1* and *PLA2G4A* genes. Then, we searched the mutations on the ClinVar database (<https://www.ncbi.nlm.nih.gov/clinvar/>), which is a public archive of human genetic variants and interpretations of their significance to the disease. According to the database, pathogenicity of *ACVRL1* c.652C>T (p.Arg218Trp) is benign or likely benign; whereas that of *PLA2G4A* is indicated as clinical uncertainty, benign, and pathogenicity. However, the database does not include the *PLA2G4A* (c.1258G>C) mutation.

The *ACVRL1* gene is responsible for encoding the protein activin receptor-like kinase 1 (ALK1)—a type I receptor of the transforming growth factor- β (TGF- β) family[18] primarily expressed in vascular endothelial cells and other tissues with rich vasculature. Additionally, ALK1 is a homodimeric transmembrane glycoprotein, which implies that it is integrated into the cell membrane[19]. Studies have shown that TGF- β has a biphasic effect on endothelial cells: it promotes angiogenesis at low concentrations, but inhibits angiogenesis at high concentrations[20]. ALK1 plays a crucial role in angiogenesis by mediating TGF- β signal transmission in endothelial cells. ALK1 is responsible for the events involved in the activation of angiogenesis, including the activation of metalloproteinases, proliferation of endothelial cells, and inhibition of differentiation. It phosphorylates the SMAD1/5/8 protein in the cytoplasm of endothelial cells, activating SMAD4 to form the SMAD1/5/8-SMAD4 complex, and transferring it to the nucleus. This process regulates the transcription of target genes, promotes the proliferation and migration of endothelial cells and lumen formation, and increases vascular endothelial growth factor expression[20]. *ACVRL1* has been shown to primarily participate in the formation of blood vessels, and mutations of this gene can cause various hemorrhagic disorders[21-23]. Furthermore, the heightened expression of *ACVRL1* through transcriptional activity exhibits anti-tumor properties in lung adenocarcinoma cells[24].

Our patient had a mutation in the *ACVRL1* gene inherited in an autosomal dominant manner. Specifically, the mutation involves a heterozygous transition from uracil to thymine (c.652C>T) that results in missense mutations and leads to a partial loss of *ACVRL1* function. As explained above, this mutation is responsible for coding the ALK1 disorder and affects the TGF- β expression in the endothelium. The abnormal signal transduction of the bone morphogenetic protein leads to developmental vascular anomalies, such as arteriovenous fistula and disorders of vascular constriction that lead to vasodilation[22]. *ACVRL1* mutations cause autosomal vascular dysplasia, which is commonly referred to as hereditary hemorrhagic telangiectasia type 2 (HHT2)[25,26]. HHT2 is acquired *via* autosomal dominant inheritance, and its homozygous mutation is fatal. The condition is characterized by mucosal and skin telangiectasia, recurrent bleeding from the small blood vessels of the gastrointestinal tract, and lesions in the internal organs[27]. Considering the role of *ACVRL1* in angiogenesis in light of the patient's chronic intestinal ulcer and bleeding manifestations, we speculate that this mutation may be an important factor contributing to the patient's recurrent illness, poor treatment response, and delayed recovery.

Phospholipase A2 (PLA2) refers to an important group of enzymes that can break down the Sn-2 ester bond structure in phospholipids. Cytoplasmic PLA2 (cPLA2) catalyzes the hydrolysis of membrane phospholipids, resulting in the release of arachidonic acid (AA) and lysophospholipids. cPLA2 also plays crucial roles in phospholipid reconstruction, pulmonary surfactant metabolism, cell signaling, host response, the promotion of blood coagulation, *etc.*[28,29]. PL-A2G4A is the most prevalent subtype of cPLA2[30,31], and it has two catalytic regions and a regulatory C2 region at the N-terminal. The C2 region is involved in binding phospholipids to calcium-dependent lipid binding motifs. It participates in many physiological and pathological processes, such as inflammation, cell growth, invasion, and metastasis. AA is the most abundant substance in the human body. Omega-6 polyunsaturated fatty acids are mainly found in platelets and are present in most human cells, predominantly as phospholipids in cell membranes. These fatty acids play a significant role in various physiological and pathological processes, including the regulation of cell proliferation, apoptosis, differentiation, and other functions[32,33]. AA is a direct precursor for the synthesis of eicosanoids, including prostaglandins (which have vasodilating effects and promote angiogenesis and ulcer healing), thromboxane A2 (TXA2) (which promotes platelet production), leukotrienes (which regulate the immune system), and other eicosanoids that are very important for the cardiovascular and immune systems of the human body. Once released, AA peripheral epoxidase (cyclooxygenase, COX) 1 and 2 promote TXA2 and prostacyclin (PGI2), and the production of several types of prostaglandins (PGs). TXA2 and PGs are metabolites of the COX pathway that activate or inhibit adenylate cyclase, which can control normal hemostatic function. It can also alter the vascular tone and is associated with immune regulation. Mutations in *PLA2G4A* can result in the occurrence of gastrointestinal ulceration with platelet dysfunction (GURDP), which is characterized by severe gastrointestinal mucosal ulcers in early childhood, as well as impaired platelet aggregation due to the reduced production of thromboxane A2. Patients may experience gastrointestinal bleeding, gingival bleeding, epistaxis, secondary iron-deficiency anemia, and malnutrition[34]. Several studies have examined the role of *PLA2G4A*. Sarkar *et al*[35] discovered that the activation of *PLA2G4A* could potentially result in the direct disruption of lysosomal membrane integrity, increase its susceptibility to oxidation, and consequently, further exacerbate the damage caused by traumatic brain injury. Similarly, Hudson *et al*[36] found that the impact of *PLA2G4A* on brain phospholipid metabolism is closely related to the occurrence of schizophrenia. *PLA2G4A* has also been shown to have a clear preference for membrane phospholipids to catalyze AA, thus playing an important role in the occurrence and progression of various types of cancer[7,29,31,37]. *PLA2G4A* is increasingly being implicated in the onset and progression of diabetes, blood disorders, and other diseases. Upregulated *PLA2G4A* can hinder insulin resistance, decelerate the advancement of diabetes, and also enhance the inflammatory changes in multiple myeloma and thereby exacerbate the disease progression[38]. Moreover, the proinflammatory impact of *PLA2G4A* is strongly interconnected with cardiovascular disease[39].

Our patient had the *PLA2G4A* gene mutation acquired *via* autosomal recessive inheritance. A heterozygous transition from guanine to uracil (c.1258G>C) occurs in this mutation, resulting in a missense mutation and consequent partial loss of *PLA2G4A* function and expression. Increased levels of *PLA2G4A* contribute to the development of an immunosuppressive microenvironment[7]. Additionally, recessive mutations in the *PLA2G4A* gene can result in the formation of multiple small intestinal ulcers, which aligns with the findings in our case. There are no reports of mutations at this site, but briefly, we speculate that mutations in the *PLA2G4A* (c.1258G>C) gene result in a partial loss of function, decreased expression, and hindered conversion of AA to mediators such as PGs and TXA2. As a result, there is a dilatation of blood vessels, weakened endothelial cell growth, increased inflammatory response and weakened platelet aggregation ability. This could at least partly explain why the patient encountered recurrent episodes of severe intestinal ulcers, and bleeding during adolescence.

Intestinal injury triggers an inflammatory response as part of the host's defense mechanism. This response is responsible for clearing damaged cells and pathogens, as well as for the restoration of tissue structure and physiological function. However, if the inflammatory response is sustained for a long period and is intense, it can cause harm to cells of healthy tissue during the response against pathogens, resulting in the occurrence of inflammatory diseases and negative effects on human health[40].

Therefore, the body also has an anti-inflammatory system to counterbalance excessive inflammatory responses. Typically, these systems remain in a state of dynamic equilibrium. The intestinal epithelial cells continuously undergo rapid proliferation and differentiation to repair the intestine in case of damage, under the influence of genes like *ACVRL1*, thus maintaining the integrity of the mucosal lining and blood vessels in the intestines. Mutations of this gene can disrupt this process, leading to damage in the intestinal mucosa and blood vessels and consequently triggering the inflammatory response and anti-inflammatory system. This is further compounded if mutations of the *PLA2G4A* gene are concurrently present, it can cause a partial loss of function and reduced expression of the gene, which hinders the conversion of AA into mediators like PGs and TXA2, attenuating the vasodilatory effect and exacerbating vascular ischemic necrosis; Reduced platelet production function leads to coagulation disorders; in addition, the ability to upregulate vascular endothelial growth factor is weakened, further exacerbating intestinal injury and worsens the occurrence of ulcers and

bleeding in the intestinal mucosa.

Our patient was found to have mutations of the *ACVRL1* and *PLA2G4A* genes. Currently, no specific treatment is available for patients presenting with these mutations. Therefore, we decided to try Kangfuxin liquid as a treatment option. Kangfuxin liquid is a patented traditional Chinese medicine prepared using the extract from *Periplaneta americana*. It has been approved for use by the China Food and Drug Administration (Z51021834)[41]. The Kangfuxin liquid, which has a wound repair effect, has been extensively used in clinical practice in China for over 20 years. A substantial amount of clinical research data has been accumulated regarding the use of this medication, providing solid evidence of its effectiveness[41-43]. It has also been reported in the literature that the use of Kangfuxin liquid plus proton-pump inhibitor in the treatment of peptic ulcers significantly enhanced the healing rate and overall response rate of ulcers, alleviated the clinical symptoms of PU, and reduced the recurrence of PU[44]. Kangfuxin liquid has been shown to have numerous beneficial effects, including promoting the proliferation of immune cells like neutrophils; increasing the levels of CD34 expression to promote neovascularization; improving microcirculation; reducing inflammation by decreasing the expression levels of IL-1 β , MPO, TNF- α , ICAM-1, and IL-8; regulating the expression of the growth factors EGFR and HGF; and accelerating the repair of pathological tissue, shedding of necrotic tissue, and healing of ulcers and wounds. In clinical practice, it is widely used in the treatment of burns, scalds, various wounds, and ulcers[45,46]. The patient's symptoms of abdominal pain and bloody stools improved while he was taking orally administered Kangfuxin liquid. However, when the preparation was discontinued, the symptoms may resurface. From this, we concluded that such patients probably have chronic intestinal ulcers and bleeding that are caused by mutations in the *ACVRL1* and *PLA2G4A* genes. The ulcer formation in such patients is not caused by increased proinflammatory or weakened anti-inflammatory effects. Instead, they are driven by certain changes induced by mutations in the *ACVRL1* and *PLA2G4A* genes, which cause a specific type of chronic inflammation in the intestinal lining, along with vascular damage and a reduced ability to repair. Therefore, standard immunomodulatory therapy fails to be effective. However, we found that Kangfuxin liquid may have a beneficial effect in the symptomatic management of these patients. We believe that in clinical practice, it is challenging to identify intestinal ulcer diseases that respond poorly to conventional treatment. Clinicians should remain vigilant regarding the role of genetic mutations in patients with chronic intestinal ulcers, and the use of Kangfu Xin liquid for symptomatic management should be considered as an alternative option when response to traditional treatment is poor.

However, this case report has some limitations. First, the link between mutations in the *ACVRL1* and *PLA2G4A* genes and chronic intestinal ulcers needs to be further verified in pathological studies and in vivo animal experiments. Second, the patient's parents did not undergo whole-exome sequencing and colonoscopy examinations. Finally, the therapeutic effect of Kangfuxin liquid in chronic intensive ulcers and bleeding needs further observation or more case support.

CONCLUSION

Mutations in the *ACVRL1* and *PLA2G4A* genes may be one of the underlying causes of chronic intestinal ulcers and bleeding in IBD. These mutations may compromise the ability of the intestinal mucosa to resist injury and to repair. Oral administration of Kangfuxin liquid appears to be promising in terms of therapeutic potential in chronic gastrointestinal ulcers.

FOOTNOTES

Author contributions: Tang YJ and Zhang J contributed equally to this work; He YH, Tang YJ, Wang J, and Chen YH contributed to the conceptualization; Zhang J, Tian RD, Hou BY, Zhong WW, and Chen YH contributed to the data curation; Yao BS, Wang J, He W, and Zhong WW contributed to the investigation; Tang YJ, Zhang J, and Wang J contributed to the writing - original draft; He YH contributed to the writing - review & editing; all authors read and approved the final version of the manuscript.

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