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Case Report
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Treatment of Acute Severe Ulcerative Colitis Complicated by Disseminated Intravascular Coagulation Using Dual Biological Therapy: A Case Report and Literature Review

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Abstract

Acute Severe Ulcerative Colitis (ASUC) complicated by Disseminated Intravascular Coagulation (DIC) is extremely rare. The disease progresses rapidly and may be life-threatening. Biological agents are essential to Ulcerative Colitis (UC) treatment, nevertheless, the combination of Infliximab (IFX) and Ustekinumab (UST) for ASUC treatment has been rarely reported. We report a case of ASUC complicated by DIC that was successfully treated with a multidisciplinary approach, including two biological agents. To the best of our knowledge, this case was the first reported case of UST combined with IFX for the treatment of ASUC complicated by DIC in China.

Keywords: Ustekinumab; Infliximab; Combined therapy; Acute severe ulcerative colitis; Disseminated intravascular coagulation

Introduction

Ulcerative Colitis (UC) is a chronic intestinal inflammatory disease, which typically presents with recurrent diarrhea, bloody stools, tenesmus and abdominal pain. Although UC limits to mild symptoms in the majority of patients, it may lead to life-threatening systemic complications that require urgent intervention [1]. Around 25% of patients with UC require admission to hospital at some point during their disease course for severe flares of UC [2]. Acute Severe Ulcerative Colitis (ASUC) is defined by the modified Truelove and Wits criteria that combine presence of bloody stools ≥ 6 times a day with symptoms of systemic toxicity such as temperature ≥ 37.8°C, hemoglobin $<10^5$ g/L, erythrocyte sedimentation rate <30 mm/h and/or a pulse rate of ≥ 90 bpm [3]. The mortality of Acute Severe Ulcerative Colitis (ASUC) is about 1% [4]. Disseminated Intravascular Coagulation (DIC) is a rare complication in ASUC patients. As an acquired systemic thromboembolic syndrome, DIC is characterized by extensive microthrombosis and secondary fibrinolysis based on severe primary disease, including sepsis, major trauma, pathological obstetrics and others. Once DIC occurs, intestinal injury is aggravated by ischemia [5], which will make the condition worse. Clinical investigations have shown that DIC is an independent and controlling prognosticator of organ dysfunction and death [6]. Patients with ASUC are challenging to treat, especially when complicated by DIC, it is even more difficult for doctors to choose the optimal management. Here, we met an ASUC patient complicated by DIC, who was successfully treated and got through the dangerous period after a multidisciplinary approach, including Ustekinumab (UST) and Infliximab (IFX) combination therapy. To the best of our knowledge, this case was the first reported case of UST combined with IFX for the treatment of ASUC complicated by DIC in China.

Case Presentation

The patient is a 27-year-old woman with a 12-year history of UC characterized by recurrent episodes of mucous, bloody stools. She had been treated with mesalazine, glucocorticoids, cyclosporine, azathioprine, leukocyte adsorption, and Chinese medicine (oral and suppositories), nevertheless, her disease relapsed. The patient was admitted to our hospital with a chief complaint of increased bloody stool for 1 week. One week before admission, the patient developed hematochezia attributed to psychological stress. She reported copious hematochezia 6 to 8 times daily, without emesis, abdominal pain, abdominal distension, chest tightness, palpitation, dizziness, sweating, petechiae, or fever. After taking self-prescribed traditional Chinese medicine therapy (treatment unknown), she presented to our emergency department and was diagnosed with UC and

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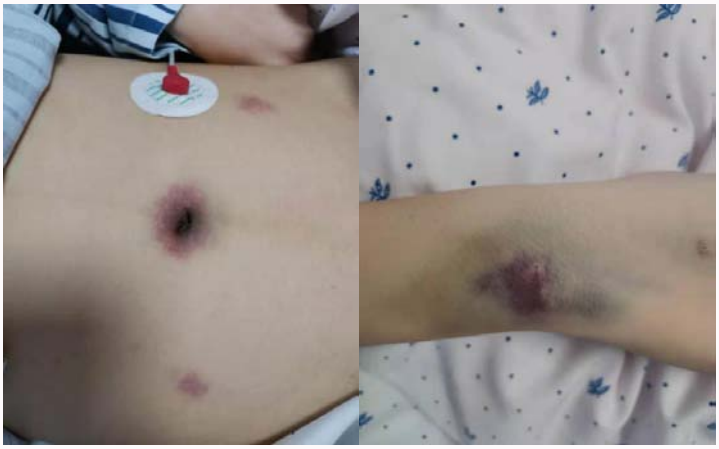

Figure 1: Ecchymoses on the patient's middle and lower abdomen and right wrist.

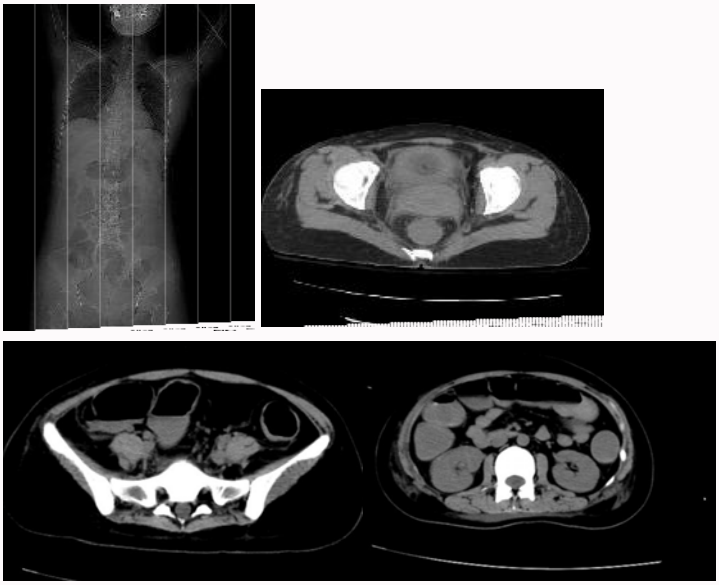

Figure 2: Abdominal computed tomogram.

hemorrhagic anemia. Emergency treatment was provided, including somatostatin injection to reduce gastrointestinal blood flow, levofloxacin for potential infections, 1.5 units of leukocyte-reduced red blood cells and nutritional support. An indwelling catheter was placed due to perineal swelling and dysuria. Within 5 h of admission to the emergency department, the patient experienced more than 10 bloody stools without apparent abdominal pain, abdominal distension, palpitations, or fever. Hematuria was observed in the urinary drainage bag, accompanied by perineal edema, pain, and fever (maximum temperature 38°C) without chills. Physical examination suggested heart rate 112 times/min, respiratory rate 20 times/min, blood pressure 116/80 mmHg and weight 50.5 kg. There were ecchymoses around the navel, bilateral mid-abdomen and right wrist. The admission diagnoses were UC (chronic, relapsing, severe, active), lower gastrointestinal bleeding, hematuria, skin ecchymosis, and perineal edema. Her physical examination on the ward was notable for a temperature of 37.2°C, heart rate 124 times/min, respiratory rate 20 times/min, and blood pressure 134/92 mmHg. She was awake and alert with anemic, non-icteric skin and no scleral icterus. There was no enlargement of superficial lymph nodes, no filling of the jugular vein, clear breath sounds in both lungs, no rales and no pathological murmur. The abdomen was slightly tense, with no tenderness or rebound pain. The liver and spleen were not palpable, and bowel sounds were slightly active. Ecchymosis was observed in the middle and lower abdomen and the right wrist (Figure 1), with perineal swelling and mild edema of the lower limbs. Laboratory examinations from the emergency department were notable for C-Reactive Protein (CRP) 10.08 mg/L, Procalcitonin (PCT) 1.6 ng/ml, White Blood Cell count (WBC) 24.70 × 10^9/L, Hemoglobin (Hb) 65 g/L, Platelets (PLT) 666 × 10^9/L. Subsequent laboratory examinations revealed CRP 127.07 mg/L, WBC 21.14 × 10^9/L, neutrophil ratio 0.837, Hb at 64 g/L, and PLT 85 × 10^9/L. Serum biochemistries were notable for glutamic-pyruvate transaminase 19 IU/L, total protein 52.1 g/L, albumin 23.8 g/L, total bilirubin 21.5 μmol/L, creatinine 58.9 μmol/L, and potassium 4.22 mmol/L. Plasma prothrombin time was 21.70 sec (normal value 12.70 sec), international standardized ratio 1.82, activated partial thrombin was 59.20 sec (normal 36.00 sec), thrombin time was 28.90 sec, fibrinogen was 0.88 g/L, D-dimer was >20, and there was a positive plasma protamine accessory coagulation test. Stool routine analysis revealed 4+ red blood cells and 2+ white blood

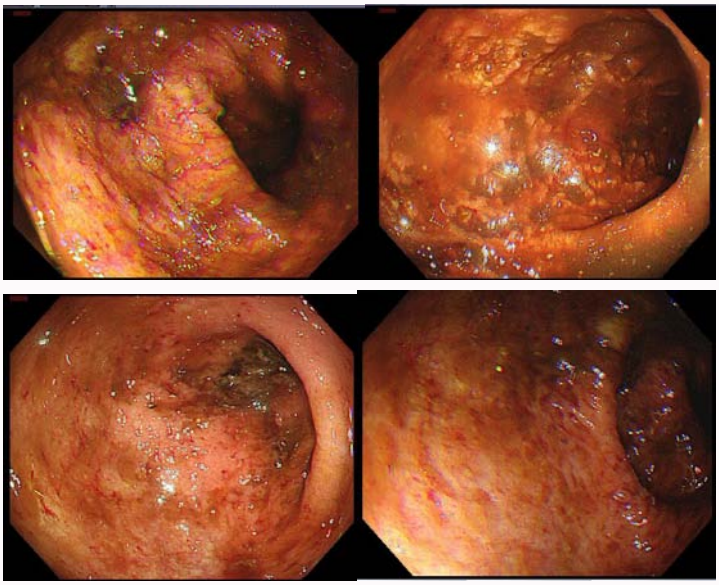

Figure 3: Colonoscopy images.

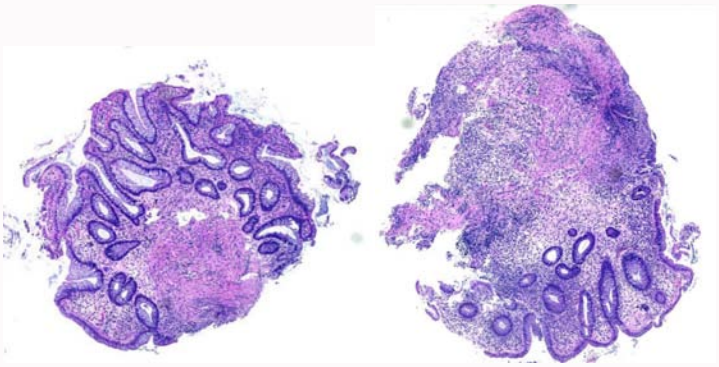

Figure 4: Histopathological findings.
Histopathology: (20 cm from the anal margin) mucosal crypt reduction with structural abnormalities, severe chronic inflammation of the entire mucosa, moderate acute activity, visible crypt abscess, and clinical history consistent with ulcerative colitis.

cells. The day after admission, factor VIII activity was 156%, factor IX activity was 200%, factor XI activity was 84%, factor X activity was 54%, antithrombin was 79%, plasminogen activity was 56.00%, von Willebrand factor was 351.00%, factor XII activity was 58%, factor II activity was 71%, factor V activity was 85%, and VII activity was 46%.

Clinical Course

After transfer to the Department of Gastroenterology, the patient was treated with first-level nursing and electrocardiographic monitoring. Temporary fasting was recommended. She was given meropenem empirically, octreotide to reduce gastrointestinal blood flow, esomeprazole to inhibit acid reflux and protect the gastric mucosa, albumin and fluid supplementation, and other supportive treatments. The departments of hematology, intensive care, nephrology, cardiology, anesthesiology, and others were consulted. DIC was diagnosed based on signs, symptoms, and laboratory examinations, and the patient was transferred to the Intensive Care Unit (ICU). On ICU admission, blood tumor indicators, autoimmune-related antibodies, Epstein-Barr virus, TROCH (Toxoplasma, Other pathogenic microorganisms, Rubella virus, Cytomegalovirus, Herpes virus), HIV (Human Immunodeficiency Virus), HBV (Hepatitis B Virus), HCV (Hepatitis C Virus infection), TPHA (Treponema Pallidum Hemagglutination Assay), T-SPOT (T cell spot detection), *Clostridium difficile*, immunoglobulins, complement series, and other indicators were negative. No pathogens were identified on three blood and stool cultures. A chest Computed Tomogram (CT), echocardiogram, and B-ultrasound of both lower extremities revealed no abnormalities. The patient continued to have bloody dark red stools about 7 to 8 times a day. ICU laboratories were notable for CRP 108 mg/L, PCT 1.87 ng/ml, WBC 23.83×10^9/L, Hb 45 g/L, and PLT 104×10^9/L. A stool examination revealed flood, fluid, 3+ white blood cells, 4+ red blood cells. The provisional diagnosis was ASUC complicated with intestinal infection. Therefore, the patient was treated with fasting, meropenem, suspended red blood cell transfusion, fresh frozen plasma, fibrinogen, dexamethasone, and other symptomatic treatments. Her coagulation functions returned to normal, her Hb increased to 80 g/L, and the frequency of hematochezia decreased to 2 to 3 times a day. Stool quantity diminished, and the color became lighter. One week after admission, she produced bright red bloody stools, accompanied by abdominal pain and distension. Physical examination revealed slight distention of the abdomen and tympany on percussion. Abdominal CT showed dilation of the colon with

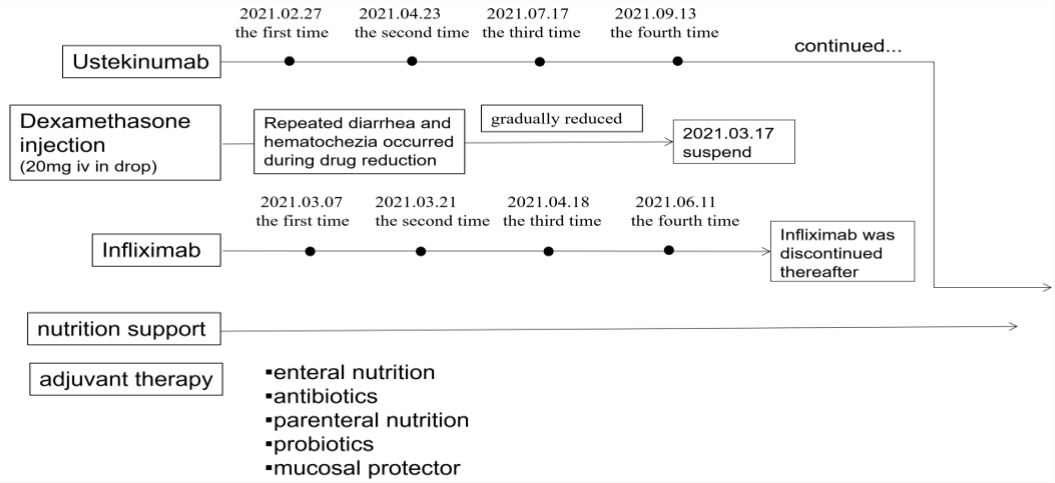

Figure 5: Medication records of ASUC treated with two biologics.

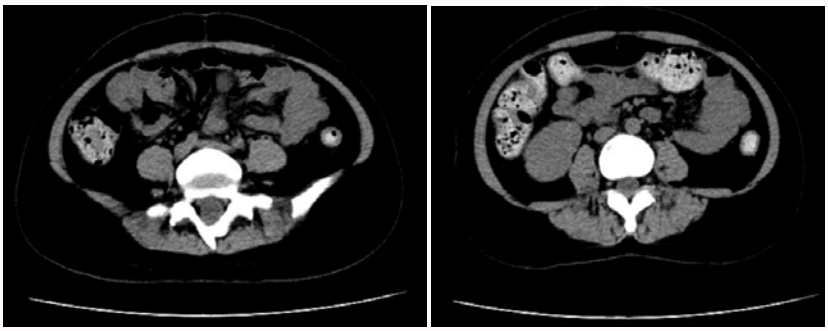

Figure 6: Abdominal computed tomography.

gas and fluid, and the widest dilation was about 5.5 cm, suggesting intestinal obstruction and toxic megacolon (Figure 2). The patient was treated with fasting, somatostatin, blood transfusion, dexamethasone, antibiotics, rehydration support, and other treatments. The ICU attendings convened a multidisciplinary team discussion. The gastrointestinal surgery department recommended total colectomy because of severe UC with a question of toxic megacolon. The gastroenterology department recommended colonoscopy to guide subsequent decision-making. The ICU department recommended aggressive treatment of ASUC and DIC (which was improving at the time of the meeting), as per the hematology department, which suggested continuing plasma and fibrinogen infusions. The urology department recommended medical treatment because the patient had no urinary tract obstruction. The nephrology department suggested that the patient's hematuria was related to a coagulation abnormality. The gynecology department suggested that the vulvar swelling was related to the primary disease and recommended perineal care. The conclusion of the multidisciplinary meeting was to transfer the patient to gastroenterology for colonoscopy, followed by surgery based on the findings. After communicating the meeting's results with the patient's family, the patient's bowel was prepared for endoscopy. Considering the risks of endoscopy and patient tolerance, the endoscope was inserted until reaching 40 cm from the anal margin. The intestinal cavity appeared swollen. Diffuse granular changes were observed in the intestinal mucosa, with hyperemia and erosion on the surface, purulent secretions, and blurred vascular texture (Figure 3). Pathological findings included reduced mucosal crypt and structural abnormalities 20 cm from the anal edge with severe chronic inflammation of the entire mucosa, accompanied by moderate acute activity and visible crypt abscess. Pathological staining was negative for cytomegalovirus, Epstein-Barr virus infection, and acid-fast bacilli. This diagnosis was consistent with UC (active stage, MES: Score of 3) (Figure 4). Following the procedures, the coagulation times returned to normal, hematuria and ecchymoses disappeared, and hematochezia decreased to 4 to 6 times a day. The provisional diagnosis was altered to ASUC complicated by DIC, alimentary canal bleeding, and perineal edema. Stool analysis revealed 4+ blood, 4+ white blood cells, and negative pus cells. Urinalysis revealed turbidity, white blood cell number 2386.00/μl, red blood cell number 44056.00/μl, 3+ occult blood, 2+ ketone bodies, and weakly positive neutrophil esterase. Urine bacterial culture showed *Enterococcus faecium* growth, while showed no *Enterococcus faecium* or L-type bacterial growth, and no fungi were detected. After consultation with the infectious diseases and nephrology departments, the patient was given piperacillin/tazobactam, gentamicin by mouth, and imipenem/cilastatin successively. After oral administration of doxycycline, levofloxacin, oral linezolid, and sulfamethoxazole, the intestinal and urinary tract infections resolved. The patient and her family refused surgical treatment in favor of conservative medical treatment. After dexamethasone injection and other symptomatic treatments, the hematochezia, diarrhea, and abdominal distension diminished significantly. However, due to DIC and urinary tract infection, the patient was given dexamethasone, which was reduced to 10 mg. The patient and her family provided informed consent, and

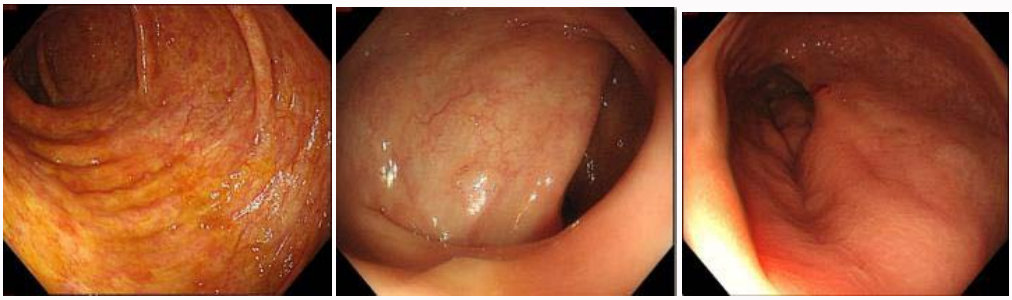

Figure 7: The patient's colonoscopic pictures.

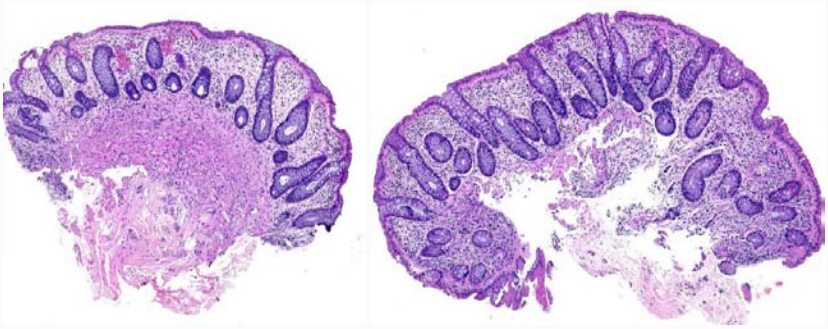

Figure 8: Histopathological findings.
Histopathology: the crypt structure of intestinal mucosa was reduced. There were moderate numbers of lymphocytes, plasma cells, and small numbers of eosinophils infiltrated in the stroma. No crypt abscesses or granulomata were observed.

she received intravenous UST, a biological agent with high safety and low infection-related risk. The dose of dexamethasone was further reduced to 5 mg, and urinary tract infection was further reduced. Due to the recurrence of hematochezia and diarrhea during the steroid wean, she was deemed glucocorticoid-dependent. After the patient and her family members were informed of the related risks, she was treated with IFX and dexamethasone. The patient complained of no diarrhea, hematochezia, abdominal pain, abdominal distension, frequency of urination, the urgency of urination, pain of urination, and was discharged on medications.

After discharge, the patient was treated with IFX and UST (drug records of ASUC treatment with dual biologics are shown in Figure 5). Repeat colonoscopy suggested UC E3, MES at one point (Figure 6). Pathological analysis revealed reduced crypt structures with moderate infiltration of lymphocytes, plasma cells, and a small number of eosinophils in the stroma. No crypt abscesses or granulomatous nodules were observed (Figure 7). The patient had no hematochezia or abdominal pain at this point. After that, she received injections of UST. Her symptoms were well controlled, and there was no hematochezia, abdominal pain, frequency of urination, urgency, or other complaints. ESR, CRP, WBC, stool routine, and coagulation functions were within the normal ranges. An abdominal CT revealed no abnormalities (Figure 8).

Discussion

UC is a group of chronic non-specific intestinal inflammatory diseases caused by genetics, immunity, the environment, and intestinal flora. ASUC is characterized by rapid onset, rapid progression, and poor outcomes [7]. ASUC is often accompanied by a rapid pulse, hypotension, diarrhea, hematochezia, abdominal distension, and other symptoms. ASUC-related inflammation often involves the entire colon. Colonic dilation is a severe complication of ASUC, and toxic megacolon, intestinal perforation, and other emergencies may occur [8]. Our patient's condition was protracted and characterized by a long course. Hematochezia and abdominal distension were accompanied by fever, rapid pulse, and slight abdominal muscle tension. The trigger of mental stress was consistent with the characteristics of the ASUC disease. DIC, intestinal obstruction, and toxic megacolon often occur, and the disease progresses rapidly. DIC is an acquired systemic thrombotic hemorrhage syndrome characterized by extensive microthrombosis and secondary fibrinolysis based on severe primary diseases, including sepsis, major trauma or surgery, pathological obstetrics, and others. Most DIC cases are characterized by acute onset, complex diseases, and rapid progression. The precise etiology is challenging to diagnose, and poor outcomes include death. DIC is rare in UC patients. Currently, a few cases report on ASUC and DIC speculated that colon vascular endothelial injury might be an important cause of DIC in UC patients. Our patient had hematochezia, severe diarrhea, bruises, petechiae, and hematuria. Laboratory examinations suggested DIC, prompting her transfer to the ICU. Following appropriate treatment, her coagulation functions returned to normal. This case highlights the importance of timely coagulation and fibrinolytic tests in patients with active UC.

Patients with ASUC are challenging to treat, and improper treatment may be life-threatening. Guidelines for diagnosis and treatment of Inflammatory Bowel Disease (IBD) recommend glucocorticoids as the first treatment choice for ASUC. However, conversion therapy should be considered when patients fail to respond 72 h after intravenous therapy with adequate doses of intravenous glucocorticoids. Conversion therapy includes medications and surgery. In our patient's case, ASUC was accompanied by colon

dilation and potential toxic megacolon; and the poor response to glucocorticoids prompted treatment with conversion biologic agents [9]. Colonoscopy is not absolutely contraindicated in ASUC and is helpful to evaluate intestinal inflammation after weighing the advantages and disadvantages. In our patient's case, the risk of endoscopy and patient tolerance after bowel preparation led us to perform endoscopy only 40 cm from the anal margin; nevertheless, the procedure was crucial for evaluating the patient's intestinal inflammation. We were able to obtain several mucosal biopsies. The multidisciplinary joint diagnosis and treatment model integrates resources and helps ASUC patients obtain optimal treatment. Although surgery was recommended, the patient and her family refused in favor of medical treatment. The combination of UST and IFX was selected under the premise of sufficient guarantee from the patient and the IBD MDT team. The glucocorticoid was weaned off, and the patient's condition was carefully monitored. The putative urinary tract infection was controlled, and hematochezia, diarrhea, and other symptoms were relieved. Colonoscopy and imaging findings significantly improved after treatment, which successfully preserving the patient's colon and significantly improving her quality of life. In recent years, biologics have played an essential role in the treatment of IBD, among which anti-Tumor Necrosis Factor-α (anti-TNF-α) is the most critical biologic. Anti-TNF-α monoclonal antibodies such as IFX are traditional biological agents for IBD treatment, and they have outstanding efficacy for treating refractory Crohn's Disease (CD) and severe UC [10]. UST is a relatively new biological agent that is an antagonist of Interleukin (IL)-12 and IL-23 P40 subunit. IL-12 and IL-23 are involved in the pathogenesis of UC by activating innate immunity and adaptive immune proliferation. UST acts on the P40 subunit shared by IL-12 and IL-23 to inhibit inflammatory responses [11]. Vedolizumab (VDZ) is a humanized monoclonal antibody that explicitly recognizes α4β7 integrin receptors on lymphocytes and blocks migration from blood to the intestinal mucosa, thereby reducing the inflow of white blood cells into inflammatory tissues. VDZ has a unique intestinal selection effect and few side effects [12]. During ASUC treatment, it is necessary to control intestinal inflammation rapidly. The failure of single-drug therapy is a life-threatening event that constitutes an indication for surgery. Our patient developed glucocorticoid dependence during single-drug therapy with UST, and IFX was subsequently added. Although the safety and efficacy of biologics combined with immunomodulators have been confirmed, there are few reports of the combined use of dual biologics in treatable severe UC in China. There is no high-quality evidence regarding whether biologics can be used in tandem or which patients would benefit the most. Our case highlights the importance of exploring therapeutic strategies to control inflammation rapidly.

To the best of our knowledge, this case was the first reported case of UST combined with IFX for the treatment of ASUC complicated by DIC in China. There are only a few reported cases of dual biological agents combined with IBD in other countries. Clara et al. reported using UST combined with IFX in a 56-year-old patient with total colonic UC with psoriasis, whose intestinal inflammation was relieved after treatment; however, the psoriasis treatment was ineffective, and no significant adverse drug reactions were observed during 21 months of follow-up [13]. Afzali et al. [14] reported VDZ combined with adalimumab to treat severe recurrent CD, which achieved an excellent therapeutic effect, and the patient's intestinal mucosa healed substantially. Olbjørn et al. [15] reported that UST combined with VDZ and IFX combined with UST in children with CD or UC had good clinical efficacy and no evident adverse drug reactions. The authors found that patients with moderate to severe IBD who failed to respond to anti-TNF agents or experienced side effects such as psoriasis may benefit from combining anti-TNF with another biologic agent with a different mode of action without severe adverse events. Studies showed that UST has good efficacy against TNF-induced psoriasis and psoriasis-like alopecia in patients with IBD, and biologic drug combination therapy is well tolerated [16-18]. When treating IBD with UST or VDZ, combination therapy with immunosuppressants is not recommended [19]. Buer et al. [20] found no significant adverse events in IBD patients treated with IFX and VDZ in combination with prospective follow-up for at least 12 months, with good clinical efficacy. Eight of their patients achieved clinical remission, and anti-TNF-α therapy was discontinued. Two of four patients with CD required combination therapy during follow-up to achieve sustained remission. Biscaglia et al. [21] suggested that VDZ combined with UST showed promising efficacy in treating CD with small bowel stenosis, and all patients achieved complete clinical remission, with an effectively reduced risk of surgery. Other studies found that UST combined with VDZ significantly benefited patients with severe ileocolonic CD [22]. These studies suggest that biological agents can inhibit two or more inflammatory cytokines in IBD patients. The treatment of refractory IBD requires synergy, and combination therapy appears to be safe and well tolerated. Short-term double biological therapy may be a reasonable treatment option for resistant UC.

In conclusion, ASUC with DIC is extremely rare and requires a multidisciplinary approach for diagnosis and treatment. Biological agents are essential for conversion therapy. In our case, UST with IFX was used to treat ASUC successfully. Nevertheless, data on the efficacy and safety of dual biologics combined with ASUC treatment remain limited, and specific findings need to be confirmed in future clinical trials.

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