

## Cyclosporine A improves ulcerative colitis complicated with deep vein thrombosis with coagulation abnormalities

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### Abstract

Ulcerative colitis (UC) is a chronic inflammatory disease of the colon and rectum. UC patients are at increased risk of deep vein thrombosis. Cyclosporine A (CyA) is an immunosuppressant drug that is used to treat severe UC. A 49-year-old man with UC complicated by DVT was treated with CyA. The patient presented with severe bloody diarrhea, lower extremity edema, and a clinical activity index of 16. The patient's coagulation test results were also abnormal. After CyA administration, the patient's leg pain and swelling improved. In addition, the extrinsic coagulation abnormalities improved first after CyA administration, followed by a gradual improvement in the intrinsic coagulation abnormalities. CyA may be effective in correcting coagulation abnormalities that contribute to DVT in UC patients.

**Keywords:** Cyclosporine A; Ulcerative Colitis; Venous Thrombosis; Coagulation Disorder

### 1. Introduction

Ulcerative colitis (UC) is a type of inflammatory bowel disease (IBD) that causes inflammation of the lining of the colon and rectum [1]. UC patients are known to be at an increased risk for venous thromboembolism (VTE) [2].

Cyclosporine A (CyA) is an immunosuppressant drug that is also used to prevent organ rejection [3]. It is also widely used as an effective drug for the treatment of severe UC [4]. UC is thought to be caused by the activation of T lymphocytes. By suppressing T lymphocyte activation, inflammation can be reduced, and UC symptoms can be improved. T lymphocytes are cells that play a central role in the immune response and are thought to be a key factor in the pathogenesis of IBD [5].

In addition to suppressing the activation of T lymphocytes, CyA is also known to have the ability to suppress the activation of platelets and the coagulation system [6]. Platelets are cells that form blood clots at sites of vascular damage. When platelet activation is suppressed, blood clot formation is suppressed. The coagulation system is a system that is responsible for the process of blood clotting. CyA has the ability to suppress the activation of platelets and the coagulation system, which could increase the risk of coagulation abnormalities [7]. The risk of coagulation abnormalities caused by CyA may be proportional to the dose and duration of administration. However, CyA may suppress the activation of platelets and the coagulation system, which could potentially regulate excessive coagulation abnormalities. In this paper, we report a case in which venous thromboembolism in UC was improved because of adjusting coagulation abnormalities with CyA.

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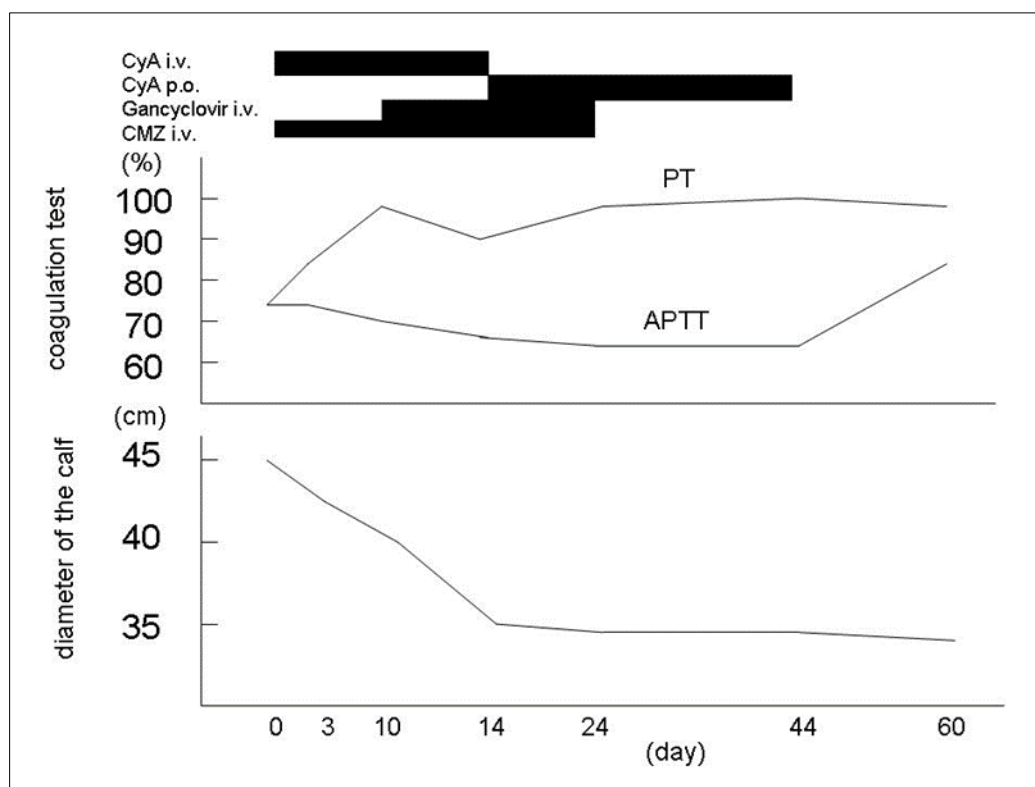
## 2. Case presentation

The patient was a 49-year-old man who presented to the hospital with severe bloody diarrhea and swelling of both legs. He had been diagnosed with UC for 5 years and had been receiving steroid therapy. He had experienced pain and swelling in both legs 3 months before admission. However, the swelling did not improve despite the increase in steroid dosage. On physical examination, the patient had abdominal tenderness and pain in both legs. The circumference of the calf was 45 cm. Pulsed Doppler ultrasound showed decreased blood flow and thrombosis in both legs. The clinical activity index was 16. The blood tests showed severe anemia (Hb 7.8 g/dL), thrombocytopenia (platelet count of  $53 \times 10^4/\mu\text{L}$ ), and elevated inflammation markers (CRP 13.7 mg/dL). Coagulation tests also showed abnormal values: PT 73%, APTT 75%, fibrinogen 370 mg/dL, AT III 120%, plasminogen 125%, protein C 120%, TAT 8.8 ng/mL, PIC 2.9  $\mu\text{g}/\text{mL}$ , protein S 72%, and FDP 25  $\mu\text{g}/\text{mL}$ . A colonoscopy revealed active UC with ulceration, erosion, and pseudopolyps. The Matts endoscopic score was 4 (Figure 1). Colon biopsy confirmed endoscopic findings of IBD, with no evidence of cytomegalovirus (CMV) infection. CyA was administered at a dose of 5 mg/kg/day for 2 weeks intravenously. At 3 days after administration, the frequency of bloody diarrhea and pain in both legs decreased. However, at 10 days, a low-grade fever appeared, and the frequency of bloody diarrhea increased. However, the swelling in both legs had disappeared. Re-examination of the colon biopsy and the presence of CMV antigen in the blood suggested CMV colitis infection. The combination therapy with ganciclovir improved the intestinal symptoms in 14 days, and CMV was no longer detected in the blood. However, the patient was diagnosed with pathogenic *Escherichia coli* O18 infection based on stool culture. Cefotaxime (2 g/day) was administered intravenously for 7 days to clear the infection.



**Figure 1** Endoscopic findings revealed giant ulcer in colon

After 14 days of intravenous CyA, the circumference of the calf was reduced to 35 cm. However, the coagulation test results remained abnormal: PT 90%, APTT 62.8%, fibrinogen 332 mg/dL, AT III 112%, plasminogen 85.2%, protein C 120%, TAT 3.2 ng/mL, PIC 1.27  $\mu\text{g}/\text{mL}$ , protein S 60%, FDP 5  $\mu\text{g}/\text{mL}$ , factor VIII 126.1%, and factor IX 75.5%. The lupus anticoagulant coagulation factor values were negative. Cross-mixing tests showed a deficiency of coagulation factors. No bleeding tendency (such as petechiae on the skin) was observed. Vitamin K (50 mg/day) was administered intravenously because antibiotic-induced vitamin K deficiency was suspected. The coagulation test results did not improve even after ganciclovir and cefotaxime administration was discontinued. The route of administration of CyA was changed from intravenous to oral. The patient's symptoms did not change, but the coagulation abnormality gradually improved. Because the swelling in the legs also improved, oral CyA administration was discontinued after 1 month. The coagulation test values continued to improve after the discontinuation of oral CyA, and no recurrence of swelling or pain in both lower extremities was observed.



**Figure 2** Clinical course after admission

### 3. Discussion

We describe an improvement in VTE in a patient with UC after treatment with CyA. CyA is a widely used drug for the treatment of severe UC, but it is also known to be associated with an increased risk of VTE. The risk of VTE in UC patients is reported to be about three times higher than in the general population [8]. The cause of VTE in UC patients is thought to be due to vascular endothelial damage caused by the production of mediators such as inflammatory cytokines, and abnormal activation of platelets and the coagulation system [9]. CyA is a drug that suppresses inflammation by suppressing the activation of T lymphocytes [10]. It is also known that CyA has an inhibitory effect on the activation of platelets and the coagulation system [11][12]. In this case report, UC symptoms improved with CyA treatment, but intravascular coagulation abnormalities persisted during the course of treatment. In other words, PT, which is a measure of the extrinsic coagulation system, improved quickly with CyA treatment, but APTT, which is a measure of the intrinsic coagulation system, took longer to improve. Based on these results, it is thought that CyA improved the extrinsic coagulation function, resulting in the improvement of venous thromboembolism. Extrinsic coagulation is a part of the coagulation system that plays an important role in the formation of a blood clot at the site of a blood vessel injury [13]. Therefore, this is also theoretically consistent with the case report. This case report suggests that CyA may improve venous thromboembolism in UC. The clinical symptom of severe swelling in the lower extremities was correlated with the improvement of PT. In addition, TAT and PIC were high in the early stages of the disease, suggesting that both coagulation and fibrinolysis were activated, and FDP was also high, suggesting that DIC was also a possible diagnosis. In this case, CyA may have improved thrombotic phlebitis, which was suspected to be DIC. However, we have not been able to confirm any similar case reports to date. The mechanism of action of T lymphocytes in coagulation abnormalities is thought to be that excessive release of inflammatory cytokines by lymphocytes activates the expression of tissue factor in monocytes and vascular endothelial cells, resulting in the production of large amounts of thrombin [14]. As a result, coagulation abnormalities are thought to occur. CyA is not only an effective drug for the treatment of UC, but also has the potential to improve coagulation abnormalities, as suggested in this case report. Our report is only one case, and further research is needed. The usefulness and safety of CyA for venous thromboembolism in UC are expected to be clarified through the accumulation of these studies.

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#### 4. Conclusion

This study reported a case of UC venous thromboembolism that improved with CyA. In addition to evaluating the risk of coagulation abnormalities with CyA, further research is strongly desired to clarify the mechanism by which CyA improves UC venous thromboembolism.

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#### Compliance with ethical standards

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##### *Disclosure of conflict of interest*

All authors declare no conflict of interest of regarding the publication of this paper.

##### *Statement of informed consent*

Informed consent was obtained from individual participant included in this study.

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