



## CASE REPORT

# A subset of ulcerative colitis with positive proteinase-3 antineutrophil cytoplasmic antibody

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ulcerative colitis with positive PR3-ANCA may belong to a subtype of refractory ulcerative colitis. The particular Chinese medicine compound used in our study is by far the most effective in the management of these patients, with additional advantages of having no noticeable side-effects and less financial burden.

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## Abstract

A small subset of patients with active ulcerative colitis is non-responsive to major known non-biological therapies. We reported 5 patients with positive serum proteinase-3 antineutrophil cytoplasmic antibody (PR3-ANCA) and tried to (1) identify the common clinical features of these patients; (2) investigate the efficacy of a novel therapy using a Chinese medicine compound; and (3) attract more gastroenterologists to be engaged in further study of this subset of patients. The common manifestations of disease in these 5 patients included recurrent bloody diarrhea and inflammatory lesions involving the entire colorectal mucosa. Initial treatment with intravenous methylprednisolone successfully induced remission. Four of these 5 patients were steroid-dependence, and immunosuppressants, such as azathioprine and cyclophosphamide, were ineffective. In 3 patients, only the particular Chinese medicine compound could induce and maintain remission. One patient underwent colectomy. No vascular inflammatory lesions were found by histopathological examination. Although more cases are needed for confirmation, our study indicates that

## INTRODUCTION

Ulcerative colitis (UC) is a disease of chronic inflammation of colon, which is diagnosed by a combination of clinical, colonoscopic, histopathological, radiological findings and therapeutic response. Infectious and non-infectious colorectal diseases such as Crohn's disease, ischemic colitis, collagenous colitis, lymphocytic colitis and colorectal cancers should be excluded. The principle therapy is 5-aminosalicylic acid for mild to moderate disease, and corticosteroids for moderate to severe disease. If both are ineffective, cyclosporin A is considered as a salvage therapy<sup>[1]</sup>. Colectomy has to be used in those who fail on medical treatment. Either 5-aminosalicylic acid or azathioprine is recommended for maintenance of remission<sup>[2]</sup>. In clinical practice, some patients would prefer to die rather than have a colectomy as this can impair quality of life. These patients are the challenge for gastroenterologists who are trying their best to seek promising medicine.

In 2006, a refractory UC patient treated in the Division of Gastroenterology, Shanghai Renji Hospital was unexpectedly found to be serum proteinase-3 antineutrophil cytoplasmic antibody (PR3-ANCA)

positive. Therefore, all UC patients admitted from Jan 2003 to Dec 2007 were screened and the PR3-ANCA positive patients were studied and analyzed.

## CASE REPORT

The clinical data of 180 UC patients admitted from Jan 2003 to Dec 2007 were analyzed, 65 patients were investigated for ANCA and only 5 patients were positive for PR3-ANCA. Their demographic and clinical characteristics are summarized in Table 1. The disease activity of UC was evaluated according to Truelove & Witts criteria. Serum myeloperoxidase (MPO)-ANCA was negative ( $< 1.4$ ) and PR3-ANCA was positive ( $> 1.4$ ) in all 5 patients. The common disease manifestations in these 5 patients included recurrent bloody diarrhea and inflammatory lesions involving the entire colorectal mucosa (Table 2).

Remission was initially and successfully induced in all 5 patients by treatment with iv Methylprednisolone (Table 3). Four of them relapsed when the prednisone dosage was reduced. In accordance with the principle of UC therapy, azathioprine was prescribed in 3 patients. As 75 mg/d or 100 mg/d could not be tolerated, 50 mg/d was adopted for more than 3 mo but remained without effect. Cyclophosphamide 0.6 g iv was also ineffective. Case 1 had tried cyclosporin A, but this was discontinued because of vomiting. Her life was threatened by bloody diarrhea more than twenty times per day, a high temperature of 40°C, and venous thrombosis of the left leg. She was persuaded again and again, and at last reluctantly accepted colectomy. One patient (case 2) had bloody diarrhea more than ten times per day and a high temperature when prednisone was reduced in dosage from 40 mg/d. She visited a traditional Chinese medicine physician and successfully withdrew the prednisone by taking a Chinese medicine compound prescribed by that physician. Remission was successfully maintained for more than 1 year. She discontinued the Chinese medicine compound by herself because she thought the disease was cured but bloody diarrhea recurred within 2 mo. She started to take the Chinese medicine compound again and her bloody diarrhea quickly disappeared. She returned to her work without any side effects caused by the Chinese medicine, but refused to undergo colonoscopy again.

As a result of this outcome, cases 3 and 4 were recommended to visit the same traditional Chinese medicine physician. They were able to reduce the dose of prednisone gradually after taking the Chinese medicine compound and successfully maintain the remission.

Repeat colonoscopies were performed in 4 of these 5 patients because of recurrent bloody diarrhea. Case 1 showed severe inflammatory lesions involving the entire colorectal mucosa with bleeding and many large deep irregular ulcers before therapy. After prednisone treatment, scars in the cecum and ascending colon, pseudopolyps in the transverse colon, and scattered erosions in the rectosigmoid colon were observed. When bloody diarrhea relapsed 20 times per day, colonoscopy revealed severe inflammatory lesions of entire colorectal mucosa. Case

Table 1 Demographic data of the five patients

Case	Gender	Age (yr)	Date of admission <sup>1</sup>	Date of initial diagnosis
1	Female	57	Dec 2006	Nov 2006
2	Female	48	Feb 2007	Jun 2006
3	Male	67	Jun 2007	May 2007
4	Female	33	May 2006	May 2004
5	Male	55	Jul 2007	May 2007

<sup>1</sup>Patients were admitted to Division of Gastroenterology, Shanghai Renji Hospital.

2 initially showed inflammatory lesions involving the entire colorectal mucosa. When bloody diarrhea relapsed during the maintenance therapy with sulphasalazine 1.5 g/d, colonoscopy revealed again inflammatory lesions from the hepatic flexure to the rectum. Case 3 revealed severe inflammatory lesions involving the entire colorectal mucosa initially and limited lesions were found in the rectosigmoid colon with several ulcers after treatment with prednisone. Case 4 initially showed inflammatory lesions involving the entire colorectal mucosa. Once bloody diarrhea was alleviated, ulcers in the rectosigmoid colon were observed. However, colonoscopy showed inflammatory lesions involving the entire colorectal mucosa again when she was taking prednisone 15 mg/d. Case 5 showed mild inflammatory lesions involving the entire colorectal mucosa with scattered erosions but no ulcers. He was the only patient who did not relapse during nearly 1 year follow up.

The colonoscopic biopsies of 4 patients (cases 1, 2, 3 and 5) and the surgical colon resection specimen of case 1 were examined by 2 experienced pathologists. No vascular inflammatory lesions were found.

Constituents of the particular Chinese medicine compound were: Fllase Asiabell Root Tangshen, Garden Burnet Root, Milkvetch Root, Largehead Atractylodes Rhizome, Lignum et Radix Cudrania, White Peony Root, Whiteflower Patrinia Herb, Herba Viola, Common Bletilla Tuber, Japanese Pagodatree Flower-bud, Lalang Grass Rhizome, Whipformed Typhonium Rhizome, Folium Isatidis, Hairyevein Agrimonia Herb and Bud, *etc.*

## DISCUSSION

ANCA is a group of antibodies directed against certain proteins in the cytoplasm of neutrophils. There are 2 major categories of ANCA that can be determined by immunofluorescence staining. Perinuclear ANCA (pANCA) refers to the more localized perinuclear or nuclear staining pattern; cytoplasmic ANCA (cANCA) refers to the diffuse, granular staining pattern. It has been shown that ANCA is associated with small-vessel vasculitis. MPO-ANCA is related to polyangiitis or allergic granulomatous angiitis, and PR3-ANCA is a specific and sensitive marker of Wegener's granulomatosis<sup>[3,4]</sup>. Wegener's granulomatosis is a systemic and necrotizing granulomatous vasculitis. The main manifestations of Wegener's granulomatosis are lung nodular infiltration, upper respiratory tract diseases and proteinuria/

Table 2 Common manifestations of disease in the five patients

Case	Bloody diarrhea	Abdominal pain	Relapse	Activity	Colonoscopy	Histological examination	Other colorectal inflammation
1	20 times/d	Yes	Yes	Severe	Entire colorectum erosion, ulcer	Mucosa inflammatory	No
2	4 times/d	Yes	Yes	Moderate	Entire colorectum erosion, ulcer	Mucosa inflammatory	No
3	6 times/d	Yes	Yes	Severe	Entire colorectum erosion, ulcer	Mucosa inflammatory	No
4	7 times/d	Yes	Yes	Severe	Entire colorectum erosion, ulcer	Mucosa inflammatory	No
5	5 times/d	Yes	No	Moderate	Entire colorectum erosion	Mucosa inflammatory	No

Table 3 Treatment of the five patients

Case	Induction of remission	Immunosuppressant		Maintenance of remission
		Azathioprine	Cyclophosphamide	
1	Methylprednisolone 40 mg/d, iv	50 mg/d, po	0.6 g, iv	Colectomy
2	Methylprednisolone 40 mg/d, iv Chinese medicine compound			Chinese medicine compound
3	Methylprednisolone 40mg/d, iv + prednisone 20 mg/d, po Chinese medicine compound	50 mg/d, po	0.6 g, iv	Chinese medicine compound
4	Methylprednisolone 40 mg/d or 80mg/d, iv	50 mg/d, po	0.6 g, iv	Chinese medicine compound
5	Methylprednisolone 40 mg/d, iv			Sulphasalazine 2 g/d

hematuria. Kidney, nasal mucosa or lung biopsies reveal granulomatous lesions. If the disease involves the colon, the patient may have bloody diarrhea. The principle treatment of vasculitis is to use prednisone or cyclophosphamide to induce remission and then use cyclophosphamide or azathioprine for the maintenance of remission. Three to 6 mo therapy is usually needed for inducing remission, but the relapse rate is high. Long-term morbidity and mortality are high<sup>[5,6]</sup>.

The 5 patients reported here did not meet the criteria of Wegener's granulomatosis (case 2 had a nasal polyp but CT scan showed no lung lesion, and biopsies of the nasal polyp and kidney did not show any granuloma). Also, histopathological studies of the 4 patients examined did not reveal any vascular inflammation in either biopsy or surgical specimen of the colon.

It was reported that UC had a high pANCA positivity, which was further identified as MPO-ANCA, LF-ANCA, and BPI-ANCA, *etc*<sup>[7,8]</sup>. The presence of pANCA combined with anti-Saccharomyces cerevisiae mannan antibodies was recommended as a way to distinguish UC from Crohn's disease<sup>[9]</sup>. PR3-ANCA belongs to cANCA, which is not a deep concern with UC because of its low positivity. Liu et al reported 5 of 58 UC patients had positive PR3-ANCA, but the significance of this finding was not mentioned<sup>[10]</sup>. In Elzouki's report, 17 of 141 UC patients were PR3-ANCA positive, but no relationship was found between PR3-ANCA and the severity of UC<sup>[11]</sup>. In the 5 patients reported here, inflammatory lesions involving the entire colorectum were seen. The probable reason for the difference is that our patients were naïve, while corticosteroids could lessen the extent of the lesion. Although corticosteroids could induce remission

temporarily, maintenance of remission and recurrence are problems that are hard to solve. What is the effective treatment for UC with positive PR3-ANCA?

Azathioprine was employed in 3 steroid-dependent patients. In the 3 patients, 50 mg/d had been used for more than 3 mo, but bloody diarrhea relapsed when the dose of prednisone was reduced to 30 mg/d. Azathioprine has been recommended for maintenance therapy of both UC and ANCA-associated vasculitis<sup>[4,6]</sup>, but was ineffective in our UC patients. Recurrence of bloody diarrhea suggested that azathioprine was ineffective.

Cyclophosphamide has been recommended for the management of active vasculitis, and it was also reported that it could successfully induce remission in Crohn's disease and indeterminate colitis<sup>[12]</sup>. Cyclophosphamide had been given in our 3 steroid dependent patients; however it was ineffective. Anti-tumor necrosis factor- $\alpha$  antibody has been reported to be effective for refractory UC patients<sup>[13]</sup>. However, it is too expensive and could not be afforded by ordinary Chinese patients. In our 3 patients, the Chinese medicine compound successfully induced and maintained remission. (Case 1 had a colectomy and did not have a chance to try the Chinese medicine compound). It is suggested that the Chinese medicine compound might be one of the best treatments for UC with positive PR3-ANCA.

Our preliminary study indicates that UC with positive PR3-ANCA may belong to a subtype of refractory UC. The Chinese medicine compound prescribed is not only more effective than Methylprednisolone but also has the merit of being without noticeable side-effects. However, more evidence is needed. We hope more gastroenterologists can be attracted and more cases will be accumulated. The particular Chinese medicine compound

is worthy of further study and the effective constituents should be identified.

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