Case Report

Crohn's Disease with Positive Ziehl–Neelsen Stain: Three Case Reports

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Abstract

Because of the similarity of the clinical symptoms, endoscopic, and pathological features, the differential diagnosis between Crohn's disease (CD) and intestinal tuberculosis (ITB) remains difficult, especially in a high-incidence area of tuberculosis (TB). Here we reported three patients with positive Ziehl–Neelsen stain in endoscopic mucosal biopsy specimens. They had a poor response to anti-TB therapy but a good response to immunosuppresses, infliximab, or surgery, and were finally diagnosed as CD. It was not clear that they were CD concomitant with mycobacteria infection or CD induced by mycobacteria infection. Further studies including more clinical cases and related animal models are needed. Our cases highlight the importance of considering the presence of CD in patients with positive Ziehl–Neelsen stain, which were failure to respond to anti-TB treatment.

Keywords: *Crohn's disease, intestinal tuberculosis, Ziehl–Neelsen stain*

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Introduction

Crohn's disease (CD) is a chronic idiopathic inflammatory disorder of the gastrointestinal tract without clear etiology. For lack of gold standard, its diagnosis is usually very difficult. Many diseases need to be excluded, especially intestinal tuberculosis (ITB). Here, we presented three patients with positive Ziehl–Neelsen stain who were initially diagnosed as ITB, but proved to be CD at last.

Case Reports

Case 1

A 25-year-old male was admitted to our hospital with diarrhea (3–4 times per day) for 7 years. He was diagnosed as ITB 7 years ago when lots of acid-fast bacilli on Ziehl–Neelsen stain were found in his colon biopsy sample. He received standard first-line anti-tuberculosis therapy (ATT) for 5 months, then second courses of first-line ATT for 3 months without any improvement. On admission, the physical examination only revealed mild tenderness on peri-umbilicus. Laboratory tests showed mild leukocytosis, anemia, significantly increased C-reactive protein (CRP) levels, and erythrocyte sedimentation rate (ESR). Purified protein derivative (PPD) skin test and TB interferon-gamma release assay (TB-IGRA) were both negative. Chest computed tomography (CT) was normal. CT enterography indicated diffuse thickening of the walls of the colon and rectum, multiple enlarged lymph nodes along the mesenteric vessels. Colonoscopy revealed multiple longitudinal ulcers and polypoid bulge scattered in the colon [Figure 1a]. Mycobacterial culture of biopsy specimens from colon revealed the presence of mycobacterium. Second-line ATT was given. Two months later, he was admitted again with fever and diarrhea. Left psoas abscess were found and drainage was performed. Four months later, he presented with left iliac fossa abscess and colonic fistula, and the following-up colonoscopy did not show any improvement. The Ziehl–Neelsen stain found one acid-fast bacilli in the biopsy samples from the rectum [Figure 1b]. Polymerase chain reaction (PCR) for TB was negative. Subtotal colectomy was performed. Pathology showed crypt abscess and noncaseating granulomas [Figure 1c]. Both PCR and Ziehl–Neelsen stain were negative. CD was diagnosed and azathioprine 33 mg daily (gradually increase the dose to 75 mg daily) was prescribed. Diarrhea slowly

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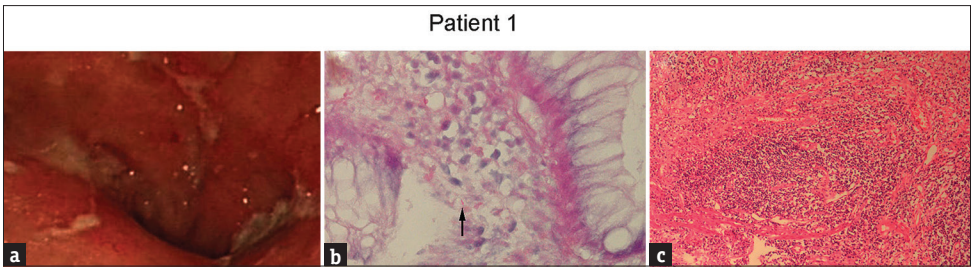

Figure 1: Endoscopic and histologic findings. Patient 1. (a) Colonoscopic finding. It shows multiple longitudinal ulcers in the rectum. (b) Histopathology of a rectum biopsy. It found one acid-fast bacilli (Ziehl–Neelsen stain, ×400). (c) Histopathology of the colon after subtotal colectomy. It showed crypt abscess and noncaseating granulomas (H and E stain, ×100)

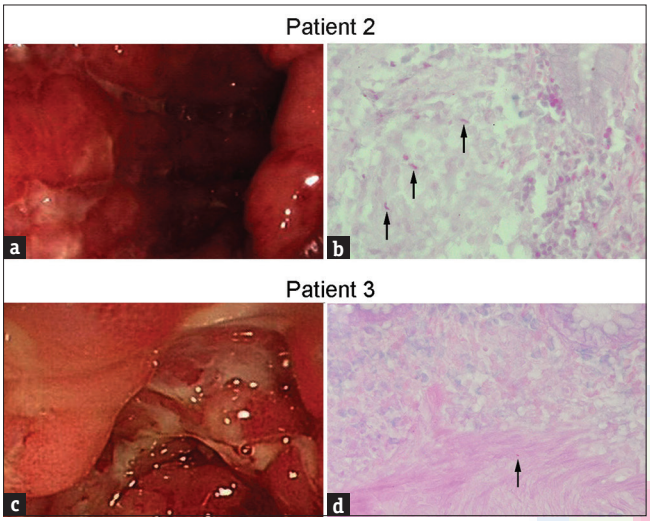

Figure 2: Endoscopic and histologic findings.Patient 2. (a) Colonoscopic finding. It shows multiple longitudinal ulcers in the sigmoid colon. (b) Histopathology of a sigmoid colon biopsy. It found three acid-fast bacilli (Ziehl-Neelsen stain, ×400). Patient 3. (c) Colonoscopic finding. It shows extensive polypoid lesions and irregular ulcers in the hepatic flexure of colon. (d) Histopathology of a hepatic flexure of colon biopsy. It demonstrates acid-fast bacilli (Ziehl-Neelsen stain, ×400)

resolved. A repeat colonoscopy performed 8 months later, demonstrated marked improvement.

Case 2

A 20-year-old male came to our hospital with a history of diarrhea (7–8 times per day) for 5 months and hematochezia (4–5 times per day) for 4 months. The physical examination was unremarkable. Laboratory tests showed increased CRP and ESR. His hemoglobin and white blood cell count were normal. PPD skin test and TB-IGRA were both negative. ASCA and ANCA were also negative. Colonoscopy revealed multiple longitudinal ulcers in the rectum and sigmoid colon [Figure 2a]. Ziehl–Neelsen stain found six acid-fast bacilli in the biopsy from the sigmoid colon [Figure 2b]. PCR was negative. Small-bowel magnetic resonance imaging revealed the walls of sigmoid colon descending colon and splenic flexure of colon were slightly thick with obvious enhancement. The patient was started on first-line ATT for 4 months, but the following-up colonoscopy did not show any improvement. Then second-line ATT was given for 3 months, but the colonoscopy still had no change. He was treated with prednisolone 50 mg daily (tapered off slowly after 3 months) followed by azathioprine 100 mg/day. He noticed a gradual decrease of blood in his feces, then a disappearance of the blood. Weight gain was 25 kg.

Case 3

A 16-year-old male was admitted to our hospital with diarrhea for 2 month, and a 10-day history of fever (37–38°C). The physical examination was normal. The laboratory results were as follow: anemia, increased CRP levels, and ESR. TB-IGRA and chest CT for TB were negative. PPD skin test was 1+ positive. ASCA-IgG and AYMA-IgG were positive. ASCA-IgA was suspicious positive. CT enterography scans showed segmental thickened wall of ileum, ascending colon, and sigmoid colon. Colonoscopy revealed extensive polypoid lesions and irregular ulcers [Figure 2c]. Ziehl–Neelsen stain was positive [Figure 2d] and PCR for TB was negative. He was started on first-line ATT for 4 months, then second-line ATT for 3 months. However, both his symptoms and colonoscopic manifestation had no improvement. Infliximab (5 mg/kg) was given. After 3 doses of infliximab, his symptoms disappeared, CRP and ESR returned to normal. The repeat colonoscopy was performed at another hospital. Colonoscopy revealed remarkable healing of the ulcers.

Discussion

TB continues to be a major health problem in the developing countries like China. TB primarily affects the lung, but any other parts of the body can also be involved. Gut is the sixth most common location of extrapulmonary involvement. Many literatures had reported cases of ITB without lung involvement.[1,2] In a Chinese study, active TB was found only in 33.8% of ITB patient.[1] The causes of ITB can be summarized into four mechanisms: swallowing of infected sputum; hematogenous spread; ingestion of unpasteurized milk

and milk products; or direct spread from adjacent organs.[3] According to a report from China, the ratio of human *Mycobacterium bovis* infection was 4.2%, and in some places reached 10.6%.[4] This seems to be one reason why primary ITB is common.

The Ziehl–Neelsen stain, known as the common acid-fast stain, is an important method for the diagnosis of ITB. The specificity of acid-fast bacilli detection is reported to be as high as 94%.[5] However, the sensitivity is very low and variable, from 5% to 40.5%.[6] Thus, the negative result of acid-fast bacilli does not always rule out ITB, but a positive result usually leads to highly suspicious of ITB. In this study, all the Ziehl–Neelsen stains are performed by our skilled professionals and double checked by the pathologists. Thus, the chance of false positivity is small. In our study, we found evidences of AFB in the patients. Empiric ATT should be considered first. But there is no improvement of endoscopic and clinical symptoms after 3–4 months of therapeutic trial with ATT. On the contrary, they had a good response to immunosuppresses, infliximab, or surgery, and were finally diagnosed as CD. We suggested repeating colonoscopy at 2 months of ATT.[7] Early mucosal responses to ATT can be used to differentiate between ITB and CD. Lacking of ulcer healing may suggest drug resistant ITB or underlying CD.

How to explain CD patients presented with positive Ziehl–Neelsen stain? Could be CD concomitant with ITB infection? In countries with such a high TB prevalence, it is possible that they had both coexisting ITB and CD, but the chance is small. To our knowledge, only one literature reported CD patients with positive Ziehl–Neelsen stain.[8] There is no improvement of endoscopic and clinical symptoms after ATT for at least 1 year. And the patients were finally diagnosed as CD. Could TB act as an infective "trigger" mechanism for the development of CD in persons who are genetically predisposed? Literatures had showed there was an increased risk of some autoimmune diseases after TB infection, such as systemic lupus erythematosus.[9] Molecular mimicry has been suggested as a possible mechanism.[10] Diverse autoantibodies were detected following TB infections.[11,12] Then "mimicking molecules" cause the autoantibodies to react with host antigen, which could contribute to systemic lupus erythematosus development.[9] However, at present there is no conclusive evidence supporting *M. tuberculosis* as a cause of CD. *M. avium* subspecies paratuberculosis (MAP) is suspected of causing CD in humans. Several authors have demonstrated a significant association between CD and detection of MAP-DNA. Sechi *et al.* reported that MAP DNA was detected in intestinal mucosal biopsies of approximately 63% (19/30) of CD patients versus 10.3% (3/29) of controls.[13] Bentley *et al.* found a strong overrepresentation of MAP-DNA in patients with CD compared to control patients (33.8% vs 21.5%, $P = 0.002$).[14] Some reports even suggested that MAP may directly infect endothelial cells and adipocytes, which were involved in the formation of unique pathology to CD.[15]

In our patients, it was not clear that they were CD along with mycobacteria infection or mycobacteria-induced CD. Further studies are needed. Our cases also emphasize the importance of considering the presence of CD in patients with positive Ziehl–Neelsen stain, which were failure to respond to anti-TB treatment.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Yan Zhang and Qin Ouyang conceived the study; Dandan Zhou, Moli Xiong, Li Zhao collected and interpreted the data; Dandan Zhou drafted the manuscript; Yan Zhang critically revised and approved the final manuscript. All authors read and approved the final manuscript. No author has any financial conflict of interest to declare.

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Conflicts of interest

There are no conflicts of interest.

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