VKS Leung 梁景燊
W Chu 朱　華
VHM Lee 李霞旻
TN Chau 周泰年
ST Law 羅兆棠
SH Lam 林少豪

Tuberculous intestinal perforation during anti-tuberculous treatment

治療結核病時導致結核性腸道穿孔

Intestinal perforation is an uncommon but potentially fatal complication of intestinal tuberculosis. We report on a 63-year-old HIV-negative man who developed terminal ileal perforation approximately 3.5 months following initiation of anti-tuberculous treatment for pulmonary tuberculosis and a concomitant tuberculous perianal abscess. Clinical and radiological improvements were initially evident following commencement of anti-tuberculous treatment, and the paradoxical response phenomenon was suspected. The patient subsequently underwent surgical resection of the affected bowel segment with primary anastomosis, and made an uneventful recovery. Anti-tuberculous medication was continued for another 12 months, and after a further 12 months there was no evidence of recurrent tuberculosis. This case illustrates that tuberculous intestinal perforation can develop during chemotherapy for tuberculosis. Prompt diagnosis and appropriate surgical treatment are essential to avoid morbidity and mortality.

腸道性結核病併發腸道穿孔並不常見但有可能致命。本文報告一名63歲人類免疫缺乏病毒呈陰性的男子，因肺結核及併發的肛門周邊癰疽而接受治療，但進行三個半月後發生末期回腸穿孔。臨床及放射徵狀都顯示病人病情在治療後好轉，醫療人員因此懷疑病人出現逆向病情反應。病人其後接受手術切除受影響的腸道部分，並進行大腸縫合術，隨後順利復原。病人繼續服食抗結核藥物12個月，再過12個月後結核病並無復發。這病例顯示以藥物治療結核病可能引致結核性腸道穿孔，要避免此情況發生或導致死亡，便須及早診斷及進行適當手術治療。

Introduction

The incidence of intestinal tuberculosis (TB) in western countries has increased along with an overall resurgence of TB.[1] This resurgence is related to an increasing incidence of human immunodeficiency virus (HIV) infection, an ageing population, increased use of immunosuppressive drugs, and the emergence of multi-resistant strains of *Mycobacterium tuberculosis*.[1] One of the most feared complications of intestinal TB is intestinal perforation: it occurs in 1 to 15% of patients.[2-4] We describe a patient who developed acute tuberculous intestinal perforation while receiving anti-tuberculous treatment. The patient experienced an initial clinical improvement with anti-tuberculous therapy so the phenomenon known as the paradoxical response was suspected. Paradoxical deterioration during anti-tuberculous therapy refers to the clinical or radiological worsening of pre-existing tuberculous lesions or the development of new lesions not attributable to the normal course of disease in a patient who initially improves with anti-tuberculous therapy.[5]

Case report

A 63-year-old Chinese man was admitted to United Christian Hospital in July 2003 with a history of fever, night sweats, weight loss, malaise, a productive cough, and a perianal discharge. He had no other gastrointestinal symptoms and physical examination of the abdomen was unremarkable. The patient had a history of a perforated peptic ulcer treated by patch repair 7 years ago, but no history of TB. Routine blood tests revealed mild anaemia (haemoglobin 121 g/L), lymphopenia (lymphocyte count, 0.4 x 10^9 /L; reference range, 1.0-3.8 x 10^9 /L), and hypoalbuminaemia (albumin, 20 g/L; reference range,

Key words:
Intestinal perforation;
Tuberculosis, gastrointestinal;
Tuberculosis, pulmonary

關鍵詞：
腸道穿孔；
結核病，胃腸的；
結核病，肺部的

Hong Kong Med J 2006;12:313-5

United Christian Hospital, Kwun Tong, Hong Kong:
Department of Medicine and Geriatrics
VKS Leung, FRCP, FHKAM (Medicine)
TN Chau, MRCP, FHKAM (Medicine)
ST Law, MRCP
Department of Surgery
W Chu, FRCS (Edin), FHKAM (Surgery)
VHM Lee, MRCS
SH Lam, FRCS (Glasg), FHKAM (Surgery)

Correspondence to: Dr VKS Leung
(e-mail: vinju@netvigator.com)

36-48 g/L). A chest radiograph (CXR) upon admission showed diffuse infiltrates over both lung fields. The diagnosis of pulmonary TB with a concomitant tuberculous perianal abscess was made promptly on identification of acid-fast bacilli (AFB) in sputum and in pus aspirated from the perianal abscess. Treatment with once daily isoniazid 300 mg, rifampicin 450 mg, ethambutol 800 mg, and pyrazinamide 1.25 g was commenced 2 days following admission. Cultures of the sputum and pus subsequently yielded a positive growth of *M tuberculosis* that was sensitive to isoniazid, rifampicin, ethambutol, and streptomycin. The anti-tuberculous drug regimen was interrupted for 10 days in August 2003 because of elevated liver enzymes and creatinine. Anti-tuberculous treatment with isoniazid, ethambutol, streptomycin, and levofloxacin was restarted upon normalisation of the liver and renal function tests. The previously abnormal function tests were thought to be due to rifampicin. Liver and renal function tests remained normal, and the regimen was switched to isoniazid 300 mg once daily, ethambutol 700 mg once daily, pyrazinamide 1.5 g once daily, and levofloxacin 400 mg once daily. The patient's condition improved with resolution of his fever and pulmonary symptoms and healing of the perianal abscess. He was discharged from hospital in early October 2003. His lymphocyte count was 1.3 x 10^9 /L, and the albumin level was 36 g/L. Three weeks following discharge (108 days after anti-tuberculous treatment had been started), he presented again with acute-onset abdominal pain and signs of peritonitis on physical examination. The patient reported strict compliance with his anti-tuberculous medication. On admission, a CXR revealed sub-diaphragmatic free gas, and resolution of the previous pulmonary infiltrates. An exploratory laparotomy was carried out approximately 2 hours after admission with a preoperative diagnosis of perforated peptic ulcer. The only positive findings at laparotomy were extensive fibrosis in the region of the terminal ileum, and a 2-cm perforation in the terminal ileum approximately 20 cm from the ileocaecal valve. A limited right hemicolectomy with primary ileocolonic anastomosis was performed. The postoperative period was uneventful, and the previous anti-tuberculous regimen was restarted. Histological examination of the resected segment of small bowel revealed the presence of non-caseating granulomas, and AFB were identified on Ziehl-Neelsen staining. A culture for mycobacteria was not done. Testing for HIV antibodies was negative. Pyrazinamide was continued for another 2 months and the other three anti-tuberculous drugs were continued for a total of 12 months. The patient remained well with no evidence of recurrent TB 1 year after discontinuation of anti-tuberculous treatment.

Discussion

Free intestinal perforation is an uncommon but serious complication of intestinal TB: the reported incidence ranging from 1 to 15%.[2-4] Perforations may be solitary or multiple, and usually occur in the distal ileum. As reported in previous studies, intestinal perforation may occur after anti-tuberculous treatment has been commenced,[6-10] and has been reported as occurring between 2 days and 4 months after the initiation of anti-tuberculous therapy.[6-8,10] When perforation occurs shortly after the institution of anti-tuberculous therapy, it may merely be representing the natural progression of the disease. Alternatively, it has been suggested that a reduced inflammatory response as a result of anti-tuberculous treatment results in impaired ulcer healing and a reduced tendency to reinforcement by the mesentery.[3] Some patients have had clear documentation of initial improvement with anti-tuberculous treatment before the occurrence of intestinal perforation, and such deterioration could be attributed to the paradoxical response phenomenon.[7]

The pathogenesis of paradoxical deterioration during effective anti-tuberculous therapy is not fully understood. Possible mechanisms include a strengthening of the host's delayed hypersensitivity response, and an increased exposure to mycobacterial antigens released as bacilli are killed by effective chemotherapy.[11] This phenomenon has been increasingly reported in HIV-positive patients being treated for TB, especially among those prescribed highly active anti-retroviral therapy.[11] Paradoxical deterioration has also been reported to occur in up to 11.1% of HIV-negative patients during treatment for TB, and it is seen more frequently in patients with extra-pulmonary TB, and among those with low baseline lymphocyte counts.[12] Nevertheless, an inadequate response to anti-tuberculous therapy as a result of drug resistance or poor drug compliance should be excluded before accepting such a diagnosis.

In a review of 122 episodes of paradoxical responses, the median time from commencement of anti-tuberculous treatment to development of the paradoxical response was 60 days (range, 14-270 days).[5] Our patient developed paradoxical deterioration with intestinal perforation approximately 3.5 months after initiation of anti-tuberculous therapy. Although anti-tuberculous therapy was interrupted for a short period, clinical and radiological improvement had been documented before the occurrence of intestinal perforation. Hence, a paradoxical response rather than treatment failure was suspected. Improvement in general health and nutritional status following effective treatment of TB may have contributed to recovery of the immune system in our patient. The rise in albumin levels and recovery of lymphocyte counts after anti-tuberculous therapy support this observation. An upsurge in lymphocyte counts is also common in patients during a paradoxical response.[5,12] In addition, an exaggerated tuberculin skin reaction may be observed: the tuberculin test was not performed in our patient.[5] The strain of *M tuberculosis* identified in our patient was sensitive to standard anti-tuberculous agents. Determination of resistance to pyrazinamide is not routinely performed as this is technically problematic. Nonetheless, resistance to

pyrazinamide is uncommon in the absence of resistance to other first-line drugs.[13] Acid-fast bacilli were identified in the resected surgical specimen but these were probably non-viable organisms: a stain for AFB can remain positive in the affected tissues for up to 5 months despite effective anti-tuberculous treatment.[14]

The treatment of choice for perforation in intestinal TB is resection of the affected bowel segment followed by an end-to-end anastomosis.[9,10] Simple closure of the lesion is not recommended as it is associated with a high incidence of leakage and fistula formation.[9,10] The mortality associated with tuberculous intestinal perforation is high with reported figures ranging from 25 to 100%.[3,9,10] Factors linked to increased morbidity and mortality include delayed operation, presence of multiple perforations, primary closure of perforations, leakage from the operated area, and steroid treatment.[9,10] Anti-tuberculous therapy should be started as soon as possible. A duration of 6 to 9 months is sufficient for immunocompetent patients treated with a regimen of four first-line drugs, namely isoniazid, rifampicin, ethambutol, and pyrazinamide.[13,15] A longer period of therapy is necessary if one or more of these first-line drugs cannot be used because of intolerance or drug resistance.[13] In situations when rifampicin cannot be used, as in the present case, isoniazid, ethambutol, and a fluoroquinolone should be given for a minimum of 12 to 18 months, supplemented by pyrazinamide for at least the initial 2 months.[13]

This case highlights the need to maintain a high index of suspicion when treating patients who present with acute abdominal pain while receiving treatment for TB. Early recognition and timely surgical intervention are essential if excessive morbidity and mortality are to be avoided.

References

1. Horvath KD, Whelan RL. Intestinal tuberculosis: return of an old disease. Am J Gastroenterol 1998;93:692-6.
2. Bhansali SK, Desai AN, Dhaboowala CB. Tuberculous perforation of the small intestine. A clinical analysis of 19 cases. J Assoc Physicians India 1968;16:351-5.
3. Gilinsky NH, Voigt MD, Bass DH, Marks IN. Tuberculous perforation of the bowel. A report of 8 cases. S Afr Med J 1986;70: 44-6.
4. Nagi B, Lal A, Kochhar R, Bhasin DK, Thapa BR, Singh K. Perforations and fistulae in gastrointestinal tuberculosis. Acta Radiol 2002;43:501-6.
5. Cheng VC, Ho PL, Lee RA, et al. Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. Eur J Clin Microbiol Infect Dis 2002;21:803-9.
6. Dore P, Meurice JC, Rouffineau J, et al. Intestinal perforation occurring at the beginning of treatment: a severe complication of bacillary tuberculosis [in French]. Rev Pneumol Clin 1990;46: 49-54.
7. Seabra J, Coelho H, Barros H, Alves JO, Goncalves V, Rocha-Marques A. Acute tuberculous perforation of the small bowel during antituberculosis therapy. J Clin Gastroenterol 1993;16: 320-2.
8. Scriven JM, Berry D. Multiple small bowel perforations in a patient on treatment of tuberculosis. J R Coll Surg Edinb 1996; 41:353.
9. Talwar S, Talwar R, Prasad P. Tuberculous perforations of the small intestine. Int J Clin Pract 1999;53:514-8.
10. Ara C, Sogutlu G, Yildiz R, et al. Spontaneous small bowel perforations due to intestinal tuberculosis should not be repaired by simple closure. J Gastrointest Surg 2005;9:514-7.
11. Aaron L, Saadoun D, Calatroni I, et al. Tuberculosis in HIV-infected patients: a comprehensive review. Clin Microbiol Infect 2004;10: 388-98.
12. Cheng VC, Yam WC, Woo PC, et al. Risk factors for development of paradoxical response during antituberculosis therapy in HIV-negative patients. Eur J Clin Microbiol Infect Dis 2003;22:597-602.
13. Blumberg HM, Burman WJ, Chaisson RE, et al. American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: treatment of tuberculosis. Am J Respir Crit Care Med 2003;167:603-62.
14. Raviglione MC, O'Brien RJ. Tuberculosis. In: Kasper DL, Braunwald E, Fauci AS, Hauser SL, Longo DL, Jameson JL, editors. Harrison's principles of internal medicine. 16th ed. New York: McGraw-Hill; 2005:953-66.
15. Kim SG, Kim JS, Jung HC, Song IS. Is a 9-month treatment sufficient in tuberculous enterocolitis? A prospective, randomized, single-centre study. Aliment Pharmacol Ther 2003;18:85-91.