CASE REPORT

Recurrent small intestinal perforations during anti-tuberculous treatment

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Summary
Spontaneous intestinal perforation due to tuberculous (TB) enteritis is rare, occurring in 1–15%. Much rarer are TB intestinal perforations among patients receiving their course of anti-TB treatment. This is the so-called paradoxical response phenomenon, e.g., the occurrence of clinical or radiological worsening of pre-existing TB lesions, or the development of new lesions not attributable to the normal course of the disease in a patient who initially improves from the anti-TB treatment. A 52-year-old male patient with three episodes of spontaneous small intestinal perforations in a span of 4.5 months while receiving anti-TB treatment is presented here and the intraperitoneal changes in each operation documented. On each occasion, he recovered uneventfully after resection of the involved segment of intestine. The pathological examination of the resected segments of bowel in the second and third operations failed to show remnant TB granuloma. Seven months after his last operation, he resumed his normal work routine and completed his TB treatment without further medical mishap. The number of spontaneous intestinal perforations in such a paradoxical response phenomenon does not appear to have any bearing on his prognosis for cure of the disease.

1. Introduction

Spontaneous intestinal perforation is a rare complication, occurring in 1–15% among patients with tuberculous (TB) enteritis. Much rarer, are TB intestinal perforations among patients receiving anti-TB treatment. This is the so-called paradoxical response phenomenon, e.g., the occurrence of clinical or radiological worsening of pre-existing TB lesions, or the development of new lesions not attributable to the normal course of the disease in a patient who initially improves from the anti-TB treatment. This may occur once, but recurrent perforations in a single patient is very rare; only a few case reports have so far been published in the English literature describing such perforations.
The purpose of this paper is to present a patient with three episodes of spontaneous intestinal perforation in a 6-month period of anti-TB treatment. We would also like to document intraperitoneal changes in each operation so as to help understand such a phenomenon and guide us in our future dealing with such patients.

2. Case report

A 52-year-old male painter was admitted for the first time on January 25, 2011 because of a sudden severe abdominal pain of 1-day duration. Two to three months prior to admission, he had begun to have severe cough persisting until 1 month prior to the admission when he had a pulmonary consult. A chest X-ray at that time revealed severe lung infiltration with possible abscess formation (Fig. 1A). Culture was positive for mycobacterium. He was started on a four-drug anti-TB regimen (Rifater 5 tabs QD and EMB 2 tabs QD) 20 days prior to admission. Eleven days prior to admission, he had a vague abdominal discomfort and was treated conservatively for an assumed consequence of anti-TB drugs. One day prior to admission, he had severe abdominal pain with inability to take food and, later, manifestations of peritonitis. Laboratory data revealed hemoglobin of 14.4 g and white blood cell (WBC) of 7700 (77% segmented). Renal and liver functions were normal. Abdominal computed tomography (CT) revealed minimal pneumoperitoneum around intestinal walls, and ascites. Emergency laparotomy was done revealing a 0.3 cm perforation with surrounding induration at the mid-jejunum about 3 ft distal to the ligament of Treitz. Suppurative ascites amounting to 500 cc with exudative coating of intestines was noted. Several nodular indurations of the small intestines, interspersed with normal appearing segments, were also seen throughout the whole length of the small bowels. The large intestine, peritoneal surface, and liver were grossly uninvolved. Segmental resection of 1.5 ft of jejunum containing the perforation was done with end-to-end anastomosis. Postoperative recovery was smooth. He was discharged 1 week later with resumption of anti-TB drugs. Pathology of the resected specimen revealed several granulomas with abundant acid-fast bacilli.

Fifty one days after the first operation, another episode of peritonitis was noted. Leucocytosis was found to be 18,920 (90% segmented). He received surgical intervention at another hospital. Operation revealed a 1.0 cm perforation in the terminal ileum, and segmental resection with primary anastomosis was done. Pathologic report of the resected specimen revealed neither granuloma nor TB organism. He was discharged after 10 days of hospital stay. Seventy-five days after the second operation, he had another bout of peritonitis. CT scan revealed frank pneumoperitoneum and a WBC count of 16,220 (85% segmented), and he underwent his third operation. Operative findings consisted of a 0.5 cm perforation at the junction of the terminal ileum and cecum; several flimsy adhesions were noted between the small intestine, pelvis, and peritoneal wall. The entire small intestinal bowel wall was markedly thickened, and purulent ascites of about 300 cc with fecal peritonitis was also noted. Skip lesions were not discernible anymore. Right hemicolectomy was done, including the visible previous anastomosis in the terminal ileum during the second operation, extending to the proximal transverse colon. Postoperative recovery was uneventful, and he was discharged 10 days later. Pathology of the resected specimen revealed thickening of the bowel wall, with a localized thinned out perforation area at the ileocecal junction. No sign of intestinal obstruction was visible. The resected specimen revealed no granuloma or acid-fast bacilli.

Seven months after the third perforation, he is now finishing the 1-year anti-TB regimen. He is currently healthy, has resumed his work routine, and has not suffered further medical mishaps. A chest X-ray showed clearing of the lesions except for the linear fibrosis in the right upper lobe (Fig. 1B).

3. Discussion

The paradoxical response during the course of anti-TB drugs is a known phenomenon. As reported in previous studies, it
may involve a single segment of intestine, usually the terminal ileum, or, occasionally, may be multiple in locations. They usually occur between 2 days and 4 months after the initiation of anti-TB therapy.\(^3\) Of course, caution should be exercised that such perforation be differentiated from uncontrolled TB progression due to nonresponse to treatment or poor immunity of the patient.

When perforation occurs shortly after the institution of anti-TB therapy, it may merely be representing the natural progression of the disease. These should be differentiated from the intestinal perforation despite otherwise good response from the anti-TB treatment, the so-called paradoxical phenomenon. Immunity of such patients is assumed to be recovering, as evidenced by the leucocytosis seen during their succeeding perforations. It has been suggested that a reduced inflammatory response as a result of anti-TB therapy results in impaired ulcer healing and a reduced tendency to adhesions and reinforcement by the mesentery.\(^1\) This was documented by our operative findings of very flimsy adhesions up to the third operation. Normally at this time, in a patient receiving reoperative management, adhesion would be expected to be maximal.

A review of the literature reveals that there is at most a single episode of intestinal perforation during TB treatment, with two episodes occasionally.\(^4,5\) Jayaswal et al\(^6\) from India reported three episodes of recurrent TB perforation of the small intestine associated with miliary TB of the lung in a 33-year-old soldier from India, within a span of 51 days, specifically 7 days, 28 days, and 54 days after anti-TB treatment, respectively. On each occasion, local suture of perforations with biopsy of gut was done. Each time the biopsy of the intestines showed caseating granuloma. Their findings suggested uncontrolled intestinal involvement and probable usual progression of the disease. It is now an accepted fact that segmental resection of the perforation is the norm of treatment rather than its closure because of the higher leakage rate and fistula formation in the latter procedure.\(^7\) Our patient is the second patient reported in the literature to have three successive recurrent perforations. Unlike the previous patient, segmental resection of the involved perforated bowel was performed each time in our patient, adding chances for recovery of immunity. Succeeding pathological examinations of the resected perforated bowels showed neither any remnant granuloma nor any acid-fast bacilli, suggesting the continuing curative response of the intestines to the anti-TB treatment. Likewise, the paucity and flimsy adhesions showed a less hyperplastic response of recuperating intestines as opposed to the usual hypertrophic ileocecal masses.\(^8\) However, as enigmatic as the paradoxical response phenomenon, we are only a passive witness to the development of such a phenomenon: the occurrence of perforation despite the improving pathological condition of the previously infected small intestine. We hope that three perforations will be the maximum number of perforations in a patient experiencing such a phenomenon. More understanding of our immunity response mechanism causing these phenomena is needed.

4. Conclusion

In conclusion, this patient exhibited the classic paradoxical phenomenon effect, suffering three episodes of spontaneous intestinal perforations during anti-TB treatment within a 4.5-month period, despite improving chest X-rays and disappearance of granuloma and acid-fast bacilli in the resected intestinal segment during the last two episodes. The number of spontaneous intestinal perforation in such a paradoxical response phenomenon does not appear to have any bearing on the prognosis for cure of the disease. More understanding of our immunity response mechanism causing this phenomenon is needed to prevent such events in the future.

**References**