

Cecal perforation secondary to a paradoxical reaction in a patient with disseminated tuberculosis: case report and review of the literature

Summary

Paradoxical reactions (PR) in HIV-negative patients with anti-tuberculosis treatment are infrequent, presenting more often in cases of extra pulmonary or disseminated tuberculosis (TB). Patients with central nervous system and lymph node TB are the ones who present this reaction more frequently. Paradoxical reactions in the gastrointestinal system are rare. Intestinal perforation is the most severe complication in this respect. However, an early diagnosis and timely treatment are key to improve prognosis in patients with intestinal perforation.

Volume 9 Issue 6 - 2018

Álvaro Bellido Caparó,¹ Luis Pampa-Espinoza,² Jorge Espinoza-Ríos,^{1,3} Jorge Alave,² Jaime Cok Garcia,⁴ José Luis Pinto,^{1,3} Martín Tagle-Arróspide^{3,5}

¹Gastroenterology Service Cayetano Heredia Hospital, Peru

²Institute of Tropical Medicine "Alexander von Humboldt" Hospital Cayetano Heredia, Peru

³Professor Faculty of Medicine "Alberto Hurtado" – Universidad Peruana Cayetano Heredia, Peru

⁴Department of Pathology, Cayetano Heredia Hospital, Peru

⁵Gastroenterology Service Clinica Angloamericana, Peru

Correspondence: Álvaro Bellido Caparó, Gastroenterology Service Cayetano Heredia Hospital, Avenida Honorio Delgado 262, Lima 15102, Perú, Tel (+51)984 284 899, Email abelledo86@gmail.com, alvero.bellido.c@upch.pe

Received: June 30, 2018 | **Published:** December 12, 2018

Introduction

Gastrointestinal TB represents 3 to 19% of extra pulmonary TB, being the sixth more frequent form of presentation.¹ Abdominal TB includes involvement of the gastrointestinal tract, peritoneum, lymph nodes, liver, pancreas and spleen.² Complications of gastrointestinal TB include intestinal obstruction, bleeding, perforation and fistula.² The incidence of intestinal perforation is 7.6%, with a mortality rate of 30%,² this complication can be single or multiple, and the most frequent location is in the distal ileum.³ The average time from the initial symptoms to perforation is 9 months,⁴ and it can occur either before or at the beginning of TB treatment. Intestinal perforation occurring during or after treatment is suspected to be a paradoxical reaction (PR).⁴

We present the case of an immunocompetent patient developing an intestinal perforation during anti TB treatment, after clinical and radiological improvement, with negative sputum for acid fast bacilli (AFB).

Case presentation

This is a 22-year old peruvian female with an eight month history of intermittent colicky abdominal pain episodes located in the periumbilical area, fever sensation and night sweats. Four months prior to diagnosis she started complaining of 2-5 watery diarrhea episodes per day. One month prior to her first visit she had a persistent and productive cough, and by that time she had lost 22 kg. Pulmonary TB was diagnosed with a chest X ray showing a left upper lobe infiltrate (Figure 1) and presence of acid fast bacilli (AFB) in the Zien Neelsen stain from sputum. Treatment with isoniazid, rifampin, ethambutol and pyrazinamide was initiated. During the next two months she had marked improvement of all the above mentioned

symptoms and she gained 6 kg. Her chest X ray also improved (Figure 2) and the Zien Nielelsen stain from sputum became negative for AFB. However, one month prior to her visit to the Emergency Room she had recurrent episodes of colicky right lower quadrant pain associated with abdominal distension, requiring frequent visits to the hospital where she was treated with intravenous anti-spasmodics. An abdominal CAT scan showed thickening of the ileo-cecal valve and small amounts of ascites. A colonoscopy was performed revealing an exudative and hypertrophic aspect of the ileo-cecal valve, precluding the passage of the colonoscope more proximally (Figure 1) and round, 10 mm ulcers with white exudates in the ascending colon. After ten days of the procedure, four hours prior to her admission to the hospital she had sudden onset of very intense right lower quadrant pain. On physical examination she had diffuse tenderness and guarding, more noticeable in the right lower quadrant. Her laboratory results are shown in Table 1. A chest X ray showed free air under the right hemidiaphragm, and an abdominal CT scan confirmed the diagnosis of perforation, additionally showing ascites, thickening of the ileo-cecal valve and ascending colon (Figure 2). The patient was taken to the operating room and on exploratory laparotomy free purulent fluid (approximately 800cc), thickened ileo-cecal valve with a cecal 1 x 1 cm perforation and thin-walled ascending colon walls were found. A right hemicolectomy and ileostomy were performed. The pathology findings of the resected specimen revealed multiple granulomas, with AFB stains negative for TB. The sputum culture obtained prior to her TB treatment showed *Mycobacterium tuberculosis* sensitive to isoniazid, rifampin, pyrazinamide and ethambutol. An alternative parenteral anti TB treatment was started including Ampicillin, Meropenem, Linezolid, Amikacin and Ciprofloxacin. Her hospital course was favorable, being able to eat one week after surgery, and three weeks later Isoniazid, Rifampin, Pyrazinamide and Ethambutol were restarted at her discharge from the hospital.



Figure 1 (A) Chest X-Ray: Left apical infiltrate. Arrow. (B) Abdomen and pelvis CT SCAN: Show thickening in cecal and in ileocecal valve, with mild ascites. Arrow. (C) In colonoscopy: Hypertrophic lesion in ileocecal valve with whitish exudates. Arrow.

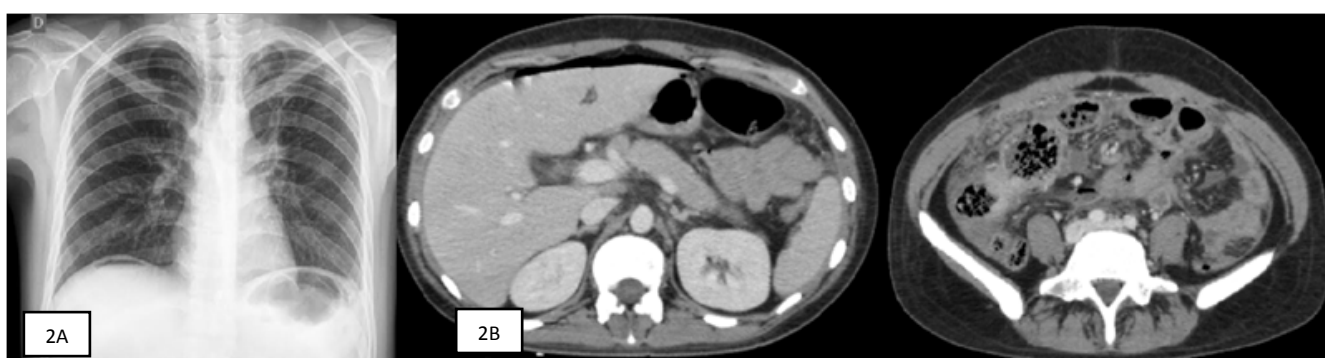


Figure 2 (A) Chest X-ray: Shows pneumoperitoneum (thin arrow) and improvement of lungs infiltrates. (Thick arrow). (B) Abdomen and Pelvis CT SCAN: Shows pneumoperitoneum (thin arrow), moderate ascites and cecal thickening (Thick arrow).

Table 1 Laboratory data.

Laboratory data	
Hemoglobin: (g/dl)	9,3
MCV: (fl)	73
MCH: (pg)	23,3
WBC: ($\times 10^3$)	4800
Neutrophils	4200
Lymphocytes	430
Platelets: ($\times 10^3$)	666
Urea: (mg/dl)	19,2
Cr: (mg/dl)	0,4
Total proteins (g/dl)	6,5
Albumin (g/dl)	3,6
ESR	26
C-Reactive Protein	1/32 (92)
VIH:	Negative

Discussion

Paradoxical reaction (PR) is defined as a clinical or radiological worsening of pre-existing tuberculous lesions, or the onset of new lesions in patients who are improving while receiving anti-TB treatment.^{3,4} It is generally a mild, transient and self-limited phenomenon, except when the central nervous system is involved, where increased morbidity and mortality are reported.^{5,6} The first cases were described in 1950, at the beginning of the initial anti TB regimes.⁴

Paradoxical reaction is associated to a direct effect of the host over bacterial products, being considered a late hypersensitivity reaction to bacterial antigens.⁵ Apparently Tumor Necrosis Factor alpha (TNF- α) plays a key role, since PR cases have been reported associated to discontinuation of biological anti TNF- α therapies in Crohn's disease patients.⁷

This reaction is more frequently seen among HIV infected persons who develop immune reconstitution syndrome after initiating therapy with highly active anti retroviral therapy (HAART). The frequency of PR in immunocompetent persons fluctuates around 2.4 to 11% and it varies according to the affected organ,^{3,4} being more frequent in disseminated or extra pulmonary TB.^{4,5}

The most frequent extra pulmonary location associated with PR is lymph node TB, where it can occur up to 25% of patients under treatment and it is characterized by the onset of new enlarged lymph nodes, which can be tender. Fifty percent of patients with central

nervous system (CNS) TB receiving anti TB treatment can develop PR, which is noticeable for the growth of new masses (tuberculomas).⁴

In the gastrointestinal tract PR is reported in about 2% of cases⁴ and it usually occurs between the first and sixth month of therapy.³ In a study reported by Church et al the mean time between the initiation of anti TB treatment and the occurrence of PR was 60 days.⁴ Risk factors associated with PR include young age, high serum albumin, peripheral lymphadenopathies, absolute lymphocyte count less than 1000/mm³ and a hemoglobin concentration less than 10.5 g/dL.^{5,6} Our patient was young, with peripheral lymphadenopathies, anemia, high serum albumin and with lymphopenia.

Differential diagnosis of PR include multi drug resistant TB and the onset of another extra pulmonary infection such as histoplasmosis or paracoccidoidomycosis.⁴ Pathology specimens may show AFB although these are usually non-viable organisms.³

Gastrointestinal manifestations of PR are usually associated with fibrotic complications which can generate stenosis and obstructive

symptoms.⁸ Buhkaire et al.⁹ report a patient similar to ours, with right lower quadrant pain with tenderness.⁹ Intestinal perforation has been reported as a complication of PR. Table 2 summarizes the case reports of intestinal perforation associated with PR, the average age of reported cases including ours is 47.6 years (22-78).^{3,10,11} Five of the six cases presented disseminated TB with abdominal and pulmonary involvement, and only one presented isolated abdominal TB. Intestinal perforation occurred between 3 weeks and 12 months after the initiation of anti TB treatment. The most frequent perforation site was the distal ileum. One of the cases had a perforation in the ileocecal valve and our patient had it in the cecum.^{3,10,11}

Mortality rate in patients with TB associated intestinal perforation is around 30%.⁽²⁾ Factors associated with increased morbidity and mortality in this group of patients include delay in surgical treatment, presence of multiple perforations, primary closure of perforations, corticosteroid therapy, anastomotic leaks, advanced age and comorbidities.^{3,10}

Table 2 Reported cases of intestinal perforation secondary a paradoxical reaction in intestinal TB.

Patient	1 ¹¹	2 ³	3 ¹⁰	4 ¹⁰	5 ¹⁰	Our case
Gender	Male	Male	male	male	Female	Female
Age	61	63	36	26	78	22
HIV status	Negative	Negative	Negative	Negative	Negative	Negative
Tuberculosis	Pulmonary and abdominal	Pulmonary and abdominal	Laryngeal, abdominal and miliary	Pulmonary and abdominal	Abdominal	Pulmonary, abdominal and ganglionic
Comorbidities	Dermatomyositis		Malnutrition DM	vitamin D deficiency	Acute MI GERD	
Treatment	INH, Rifampin, Ethambutol and Pyrazinamide	INH, Rifampin, Ethambutol and Pyrazinamide	IRPE Moxifloxacin Ciprofloxacin Amikin streptomycin	INH, Rifampin, Ethambutol and Pyrazinamide	IRP Moxifloxacin	INH, Rifampin, Ethambutol and Pyrazinamide
Time from treatment to perforation	97 days	3 weeks	6 months	6 months	12 months	3 months
Perforation site	Ileo cecal region	Distal Ileon perforation	Ileon perforation	Jejunum perforation	Distal ileon perforation	Cecal perforation
Evolución	Favorable	Favorable	Favorable	Favorable	death	Favorable
Cirugía:		Right Hemicolectomy plus ileocolonic anastomosis.	laparotomy	resection	resection	Right hemicolectomy plus ileostomy

The best surgical approach for the management of TB-associated intestinal perforations is resection of the involved segment followed by an end-to-end anastomosis.^{3,10} Primary closure of the lesion is not recommended because it is associated with a high rate of leaks and fistulae.³ Anti TB treatment should be completed thereafter for a period of 6 to 9 months.³

Corticosteroid use is recommended for TB of the CNS which is associated with a high mortality and neurological sequelae, or in severe PR.^{6,8} The recommended dexamethasone dose is 12 mg/day or 0,4 mg/kg/d for the first three weeks of treatment, with progressing tapering over the next 3-5 weeks.⁸ Bukharie et al.⁹ reported a patient with abdominal pain associated to intestinal TB and PR who improved

with the use of corticosteroids.⁹ However, there no sufficient data to recommend adjuvant corticosteroid therapy in patients with peritoneal TB since it has not been shown to decrease the risk of complications like fibrosis leading to intestinal obstruction.⁸

Conclusion

Gastrointestinal paradoxical reaction should be suspected in patients with intestinal TB who develop reappearance of symptoms or new manifestations after initial improvement with anti TB therapy. Intestinal perforation is the most serious manifestation of PR. Prompt recognition of perforation and timely surgical intervention decreases mortality in these patients.

Acknowledgments

We are grateful for the patient and family consent to allow us for the publication of the case details.

Conflicts of interest

Specific author contributions: ABC, JER, LPE, JA contributed to the drafting of the case report JER, JCG, JLP, MTA contributed to the critical revision of the manuscript. All authors reviewed and approved the final version of the case report.

References

1. Global tuberculosis report 2017. Geneva: World Health Organization; 2017. License: CC BY-NC-SA 3.0 IGO.
2. Jullien S, Jain s, Ryan H, et al. Six-month therapy for abdominal tuberculosis. *Cochrane Databases Syst Rev*. 2016;11: CD012163.
3. Leung VKS, Chu W, Lee VHM, et al. Tuberculosis intestinal perforation during anti-tuberculous treatment. *Hong Kong Med J*. 2006;12(4):313–315.
4. Church LWP, Chopra A, Judson MA. Paradoxical reactions and the immune reconstitution inflammatory syndrome. *Microbiol Spectrum*. 2017;5(2):1–15.
5. Jung JW, Shin JW, Kim JY, et al. Risk factors for development of paradoxical response during anti-tuberculosis treatment in HIV - negative patients with pleural tuberculosis. *Tohoku J Exp Med*. 2011;223(3): 199–204.
6. Geri G, Passeron A, Heym B, et al. Paradoxical reactions during treatment of tuberculosis with extrapulmonary manifestations in HIV-negative patients. *Infection*. 2013;41(2):537–543.
7. Unlu M, Cimen P, Ayranci A, et al. Disseminated tuberculosis infection and paradoxical reaction during antimycobacterial treatment related to TNF-alpha blocker agent infliximab. *Respirology Medicine Case reports*. 2014;13:43–47.
8. Lee JY. Diagnosis and treatment of extrapulmonary tuberculosis. *Tuberc Respir Dis*. 2015;78(2):47– 55.
9. Buhkarie Huda. Paradoxical response to anti-tuberculous drugs: Resolution with corticosteroid therapy. *Scand J Infect Dis*. 2000;32(1):96–97.
10. Lee M, Cresswell F, John L, et al. Diagnosis and treatment strategies of tuberculous intestinal perforations: a case series. *Eur J Gastroenterol Hepatol*. 2012;24:594–599.
11. Saitou M, Suzuki T, Nitsuma K. Intestinal perforation due to paradoxical reaction during treatment for military tuberculosis. *Respirol Case Rep*. 2016;4(6):e00196.