SAGE Open Medical Case Reports
Volume 10: 1–4

DOI: 10.1177/2050313X221084839
journals.sagepub.com/home/sco
SAGE

A case of paradoxical reaction after treatment of generalized tuberculous lymphadenopathy in a peritoneal dialysis patient

Farah Gul Khan[1] and Stanley Fan[2]

Abstract

Paradoxical reaction (also known as Jarisch–Herxheimer reaction) is a self-limited response to endotoxin released from dead bacteria after starting treatment and is characterized by constitutional symptoms such as fever, headache, dizziness and exacerbation of cutaneous lesions. We report a rare case of a 55-year-old gentleman, on peritoneal dialysis, who developed fever, dizziness and cloudy dialysate after starting anti-tuberculous treatment for disseminated tuberculous lymphadenitis. He was started on antibiotics for suspected peritoneal dialysis peritonitis and anti-tuberculosis treatment was continued. However, all his cultures turned out negative including peritoneal 16S ribosomal RNA. The diagnosis of paradoxical worsening following anti-tuberculosis treatment was made. His peritoneal dialysis was continued and he made full recovery after 8 months of therapy. This case highlights the fact that in a peritoneal dialysis patient, paradoxical reaction can present as cloudy dialysate with raised infective markers.

Keywords

Peritoneal dialysis, peritonitis, tuberculosis, paradoxical reaction

Date received: 9 August 2021; accepted: 10 February 2022

Introduction

Tuberculosis (TB) is a multi-system disease caused by bacilli *Mycobacterium tuberculosis*. Once infected, the individual is at risk of developing TB for life time, the risk being highest in the first 2 years. TB typically affects lungs; however, any part of the body can be affected and the most frequent extra-pulmonary site is lymph nodes, which accounts for approximately 15% of extra-pulmonary TB cases.[1] Most of the patients with TB lymphadenitis do not present with systemic signs and symptoms; nevertheless, these can occur especially after caseous necrosis.[2]

Paradoxical reaction after starting anti-tuberculosis treatment (ATT) is not very uncommon (6%–30%) and can present in a number of ways depending upon the site of primary involvement.[3] Although a well-known phenomenon in patients who are immunocompromised, it is increasingly being reported in immunocompetent patients as well. The timings and severity of these reactions may vary, from mild to severe, and can develop from days to months of starting ATT.[4]

We are reporting the case of paradoxical reaction in the form of cloudy peritoneal dialysate in a peritoneal dialysis (PD) patient after starting ATT for extensive tuberculous lymphadenopathy. To our knowledge, this is the first reported case of paradoxical reaction in a patient on PD.

Case

A 55-year-old gentleman, on PD for the last 2 years, presented with acute onset of dizziness, nausea, feeling sick along with passage of cloudy dialysate 3 days after beginning ATT for generalized tuberculous lymphadenopathy.

His chronic history includes long-term hypertension and diabetes mellitus. He developed end-stage kidney failure due to hypertension and was started on automated peritoneal dialysis (APD). A year ago, he had two exit site infections, both times with pseudomonas, with no peritonitis and was treated conservatively.

[1]Aga Khan University Hospital, Karachi, Pakistan
[2]The Royal London Hospital, Barts Health NHS Trust, London, UK

Corresponding Author:
Farah Gul Khan, Aga Khan University Hospital, Karachi 74800, Pakistan.
Emails: farah.gul@aku.edu; farahgulkhan@yahoo.com

On his routine kidney transplant screening, computed tomography (CT) abdomen and pelvis was done which revealed generalized para-aortic and mesenteric lymphadenopathy along with pre-cardiac lymph node mass. Subsequent CT chest with contrast also revealed mediastinal lymphadenopathy with lymph node mass in front of heart. The patient denied fever, weight loss and night sweats at the time of workup. He underwent CT-guided abdominal lymph node biopsy and while awaiting result, he started complaining of dry cough and attributed it to indigestion and bloating due to abdominal distension.

The biopsy showed necrotising granulomatous inflammation with negative Ziehl–Neelsen (ZN) and Grocott's Methenamine Silver (GMS) stain for acid-fast bacilli (AFB) and fungi, respectively. However, despite negative AFB staining, *M. tuberculosis* remained the top differential and the patient was started on Rifater (isoniazid (INH) 50 mg, rifampicin 120 mg and pyrazinamide 300 mg) six tablets, moxifloxacin 400 mg and pyridoxine 25 mg once a day. Ethambutol was not given due to the risk of optic neuritis.

However, 3 days after starting ATT, the patient presented to emergency department (ED) with cloudy peritoneal bags along with severe dizziness, low grade temperature and nausea.

On presentation, his blood pressure was 100/60 mmHg with a fast regular pulse of 110/min; oxygen saturation was 98% at room air and breathing was normal. The temperature was recorded at 38° C. On examination, he was alert and oriented in time, place and person. His abdomen was distended with dialysis fluid; however, it was non-tender with active bowel sounds. Physical examination did not reveal pedal oedema. The rest of his chest, cardiac and nervous system examination were within normal limits.

Laboratory investigation showed haemoglobin 12.9 g/dL, white cell count 9.7×10^9/L, platelets 322×10^9/L, sodium 125 mmol/L, potassium 3.7 mmol/L, chloride 79 mmol/L, bicarbonate 19 mmol/L; blood urea nitrogen (BUN) 13 mmol/L, creatinine 796 umol/L, C-reactive protein (CRP) 77 mg/L, liver function tests normal, cortisol 1104 nmol/L, peritoneal fluid microscopy revealed WBC 2752 with 60% neutrophils and 40% lymphocytes, peritoneal fluid culture (done twice) negative, peritoneal fluid 16S ribosomal RNA (done twice) negative for bacterial DNA, electrocardiogram (EKG) no new change, cardiac enzymes negative and lymph node culture: *M. tuberculosis* sensitive to isoniazid, rifampicin, ethambutol, pyrazinamide and quinolone.

The patient was treated with intravenous fluids and empirically started on a combination of intraperitoneal antibiotics (amikacin and ceftazidime) and oral ciprofloxacin for suspected peritonitis after sending peritoneal fluid cultures. His anti-TB drugs were continued; however, moxifloxacin was held. He started feeling better after few days with slow clearing of cloudy dialysate. His final peritoneal fluid cultures on day 5 came out negative including peritoneal fluid 16S ribosomal RNA and antibiotics were stopped. Subsequently, his ascitic fluid smear and culture for acid fast bacilli also came out negative. The diagnosis of paradoxical worsening following anti-TB drugs was made.

The patient continued four-drug ATT for the initial 2 months and then switched to two drugs (INH and rifampicin) for the next 6 months. At the end of the continuation phase, he developed signs and symptoms of peripheral neuropathy despite being on regular pyridoxine. His repeat CT scan abdomen revealed significant decline in the size of lymph nodes and ATT was stopped after a total of 8 months. He was reactivated on kidney transplant waiting list.

Discussion

Although this case looks like a simple case of PD peritonitis as it fulfils the criteria defined by International Society for Peritoneal Dialysis (IPSD),[5] it is very unlikely for a patient to develop infection after starting ATT for tuberculous lymphadenitis.

Paradoxical reaction (also known as Jarisch–Herxheimer Reaction (JHR)) is commonly characterized by constitutional symptoms such as diaphoresis, fever, hypotension, dizziness, headache and exacerbation of cutaneous lesions, if there are any, after starting therapy for a number of infections. It is a self-limited response to endotoxin released from dead bacteria, cytokines and immune complexes.[6]

In TB, JHR has been reported as aggravation of meningeal disease, tuberculous meningeal radiculitis, intracranial tuberculoma, abdominal TB and pleural effusion.[7] There is high tendency of paradoxical reaction in central nervous system due to its compact nature and it usually presents with worsening of neurological status with increase in the size of already existing or new tuberculomas.[8,9] Similarly, the most common presentation in respiratory system is either worsening of the pleural effusion or development of new contralateral effusion; patients can also present with signs of pleurisy or with aggravation of pulmonary infiltrates.[8,10]

Just like pleural effusion, the mechanism of development of cloudy PD fluid could be explained by the intense inflammatory response, as seen in our patient. In a case report published by Amit Kumar, a 9-year-old girl with disseminated TB developed pericardial effusion, followed by pleural effusion and papilledema a month after starting ATT which resolved with the continuation of ATT.[11] Similarly, another patient with TB ascites developed worsening of ascites 4 weeks after starting ATT, which subsequently improved when ATT was continued.[12]

Paradoxical worsening can occur at the same or different site; in one case report, a 77-year-old woman with biopsy-proven tuberculous lymphadenitis developed vitritis and chorioretinitis after ATT initiation which improved with addition of steroids and continuation of ATT.[13]

Our patient was asymptomatic when TB was diagnosed, and he developed symptoms only after taking ATT. One may argue that his presentation together with PD fluid analysis

and raised inflammatory markers support peritonitis; however, peritoneal fluid cultures along with 16S ribosomal RNA were negative. 16S ribosomal RNA can be effectively used to diagnose bacterial pathogen in conditions when cultures are negative, bacteria are difficult to cultivate or when bacteria are made non-cultivatable due to previous antibiotic therapy as in our patient who was already on rifampicin which has good gram-positive coverage.[14–16] Many studies have reported low sensitivity and specificity of 16S ribosomal RNA when compared with routine cultures; nevertheless, it is increasingly being used in evaluating culture-negative infections. One recently published retrospective analysis has reported highest yield (37%) in cardiovascular infections.[17] Similarly, another study from Indonesia reported positive nucleic acid amplification test (using 16S ribosomal RNA) with 83.1% sensitivity in AFB smear-negative patients with pulmonary TB.[18] With regard to PD patients, there are a number of case reports where pathogen was detected by 16S ribosomal RNA and cultures were negative.[19,20] The only downside is in some cases, it cannot differentiate between close genetically related organisms. Despite this limitation, 16S ribosomal RNA gene sequencing can be used as an add-on test to the routine peritoneal fluid culture.[21]

Finally, our patient developed peripheral neuropathy, a known side effect of isoniazid, towards the end of treatment despite being on pyridoxine. Underdosing of a drug is not a major problem as drug clearance is unlikely to be increased during PD; however, a patient may be exposed to excessive quantities which may result in undue side effects, and hence, frequent drug level monitoring may aid in more accurate dosing. This needs more research and patients should be regularly monitored for the potential side effects of anti-TB drugs, especially isoniazid and ethambutol.

Two years down the road, the patient is still on PD without any complication and tolerating it well.

Conclusion

To our knowledge, this is the first reported case of paradoxical reaction in a patient on PD. This case highlights the significance of paradoxical reaction to anti-TB therapy which can also present as cloudy dialysate with raised infective markers in a patient on PD.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship and/or publication of this article.

Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was taken from the patient for their anonymised information to be published in this article.

ORCID iD

Farah Gul Khan https://orcid.org/0000-0003-0394-2856

References

1. World Health Organization. Global tuberculosis report 2018 (Updated 28 February 2019), https://www.who.int/tb/publications/global_report/en/
2. Handa U, Mundi I and Mohan S. Nodal tuberculosis revisited: a review. *J Infect Dev Ctries* 2012; 6(1): 6–12.
3. Memish ZA, Mah MW, Mahmood SA, et al. Clinico-diagnostic experience with tuberculous lymphadenitis in Saudi Arabia. *Clin Microbiol Infect* 2000; 6(3): 137–141.
4. Breen RA, Smith CJ, Bettinson H, et al. Paradoxical reactions during tuberculosis treatment in patients with and without HIV co-infection. *Thorax* 2004; 59(8): 704–707.
5. Li PK, Szeto CC, Piraino B, et al. ISPD peritonitis recommendations: 2016 update on prevention and treatment. *Perit Dial Int* 2016; 36(5): 481–508.
6. Belum GR, Belum VR, Chaitanya Arudra SK, et al. The Jarisch-Herxheimer reaction: revisited. *Travel Med Infect Dis* 2013; 11(4): 231–237.
7. Gupta V, Gupta A and Rao N. Intraocular tuberculosis update. *Surv Ophthalmol* 2007; 52: 561–558.
8. Cheng V, Ho P, Lee R, et al. Clinical spectrum of paradoxical deterioration during antituberculosis therapy in non-HIV-infected patients. *Eur J Clin Microbiol Infect Dis* 2002; 21(11): 803–809.
9. AbdulJabbar M. Paradoxical response to chemotherapy for intracranial tuberculoma: two case reports from Saudi Arabia. *J Trop Med Hyg* 1991; 94(6): 374–376.
10. Al-Ali MA and Almasri NM. Development of contralateral pleural effusion during chemotherapy for tuberculous pleurisy. *Saudi Med J* 2000; 21(6): 574–576.
11. Dey AK and Shah I. Disseminated tuberculosis with varied paradoxical reactions. *J Family Med Prim Care* 2016; 5(1): 170–171.
12. Piryani RM, Sijapati MJ, Shrestha S, et al. Paradoxical ascites during anti-tuberculous chemotherapy. *J Coll Physicians Surg Pak* 2013; 23(4): 310–312.
13. Cheung CM and Chee SP. Jarisch–Herxheimer reaction: paradoxical worsening of tuberculosis chorioretinitis following initiation of antituberculous therapy. *Eye (Lond)* 2009; 23(6): 1472–1473.
14. Bador J, Nicolas B, Chapuis A, et al. 16S rRNA PCR on clinical specimens: impact on diagnosis and therapeutic management. *Med Mal Infect* 2020; 50(1): 63–73.
15. Larsen LH, Khalid V, Xu Y, et al. Differential contributions of specimen types, culturing, and 16S rRNA sequencing in diagnosis of prosthetic joint infections. *J Clin Microbiol* 2018; 56(5): e01351-17.
16. Mishra D, Satpathy G, Wig N, et al. Evaluation of 16S rRNA broad range PCR assay for microbial detection in serum specimens in sepsis patients. *J Infect Public Health* 2020; 13(7): 998–1002.
17. Fida M, Khalil S, Abu Saleh O, et al. Diagnostic value of 16S ribosomal RNA gene polymerase chain reaction/Sanger

sequencing in clinical practice. *Clin Infect Dis* 2021; 73(6): 961–968.
18. Sari NI, Mertaniasih NM and Maruyama F. Application of serial tests for *Mycobacterium tuberculosis* detection to active lung tuberculosis cases in Indonesia. *BMC Res Notes* 2019; 12(1): 1–5.
19. Song SH, Choi HS, Ma SK, et al. Micrococcus aloeverae-a rare cause of peritoneal dialysis-related peritonitis confirmed by 16S rRNA gene sequencing. *J Nippon Med Sch* 2019; 86(1): 55–57.
20. Yamada S, Sonoda Y, Sugimachi K, et al. A case of Stappia indica-induced relapsing peritonitis confirmed by 16S ribosomal RNA gene sequencing analysis in a patient undergoing continuous ambulatory peritoneal dialysis. *CEN Case Rep* 2021; 10(3): 402–408.
21. Ahmadi SH, Neela V, Hamat RA, et al. Rapid detection and identification of pathogens in patients with continuous ambulatory peritoneal dialysis (CAPD) associated peritonitis by 16s rRNA gene sequencing. *Trop Biomed* 2013; 30(4): 602–607.