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Ground-glass opacity as a paradoxical reaction in miliary tuberculosis: A case report and review of the literature

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ABSTRACT

A paradoxical reaction (PR) is an excessive immune response occurring during antitubercular therapy (ATT), but is rare in patients with miliary tuberculosis. A 78-year-old woman complained of general malaise, loss of appetite, and fever for 10 days. Chest computed tomography (CT) showed diffuse, bilateral, discrete miliary nodules. The patient was treated with ATT for miliary tuberculosis. Nine days after starting the treatment, she developed a spiking fever and worsening malaise. Repeat CT showed new localized ground-glass opacity (GGO) in the right upper lobe. After excluding possible etiologies, she was diagnosed with PR due to ATT. She was successfully managed with oral prednisolone while continuing ATT. The GGO diminished and did not recur after discontinuation of the steroids. We reviewed 28 reported cases of miliary tuberculosis with a PR in patients not infected with human immunodeficiency virus. Those not on immunosuppressive therapy were likely to develop a PR early. This case illustrates that a PR may present as localized GGO in miliary tuberculosis in the lung of patients treated with ATT. In cases of a PR with marked symptoms, steroid therapy may be valuable.

Introduction

Tuberculosis remains a common disease in both developing and developed countries. Although the global incidence of tuberculosis has been on the decline, the worldwide disease burden remains a major health problem. One-third of the world's population is estimated to be infected with *Mycobacterium tuberculosis*, and 10% of these individuals develop active tuberculosis during their lifetime [1]. While treatment with appropriate antitubercular drugs is important, they have some characteristic complications. A paradoxical reaction (PR) is defined as transient worsening of pre-existing symptoms or appearance of new signs, symptoms, or radiographic manifestations of tuberculosis that occur after treatment initiation [2]. A PR can be diagnosed only after ruling out treatment failure, poor compliance, drug resistance, side effects of antitubercular therapy (ATT), or another infection. This phenomenon often occurs in individuals infected with human immunodeficiency virus (HIV), but it is not common in individuals who are HIV-negative [3]. A PR has been reported to occur in 2.4% of cases with pulmonary tuberculosis [4]. However, it is rare in miliary tuberculosis and has only been reported sporadically in case reports. Here we report a case of miliary tuberculosis in a HIV- negative patient who developed a PR during appropriate ATT and also discuss similar cases reported in the literature.

Case report

A 78-year-old woman presented to our hospital complaining of general malaise, loss of appetite for 2 weeks, and fever for 10 days. She had been diagnosed with pulmonary tuberculosis when she was in elementary school and had been treated with ATT, although the specific details of the therapy were unknown. She was admitted to our hospital for further investigation.

Physical examination revealed a heart rate of 78 beats/min; blood pressure of 153/80 mmHg; body temperature of 38.4 °C; and SpO_2 of 97% (on room air). Chest auscultation revealed no rhonchi, crackles, or wheezes. A chest radiograph showed diffuse reticular nodule (Fig. 1), and computed tomography (CT) showed diffuse, bilateral, discrete miliary nodules (Fig. 2a). Laboratory findings revealed a hemoglobin level of 10.0 g/dl, white blood cell count of 4300 cells/mm^3 with 67.6% neutrophils, and C-reactive protein level of 6.6 mg/dl.

Bronchoscopy was performed on the 2nd day after admission and revealed no specific abnormalities of the bronchial walls.

Abbreviations: PR, paradoxical reaction; ATT, antitubercular therapy; HIV, human immunodeficiency virus; CT, computed tomography; GGO, ground-glass opacity.

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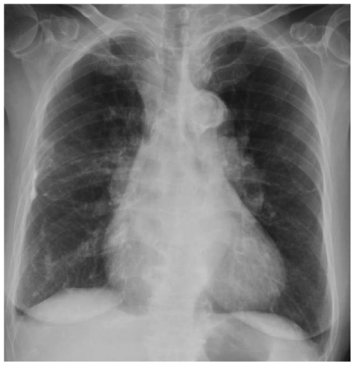

Fig. 1. Chest X-ray on admission showing diffuse reticular nodule.

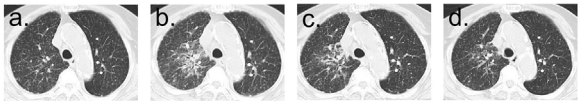

Fig. 2. (a) Chest CT on admission showing diffuse, bilateral, discrete miliary nodules. (b) On day 9 of ATT, chest CT showing a new localized GGO in the right upper lobe. (c) On day 18, chest CT showing improvement of the GGO. (d) On day 28, chest CT showing no recurrence of the GGO after discontinuation of steroid therapy. Abbreviations: CT, computed tomography; ATT, antitubercular therapy; GGO, ground-glass opacity.

Bronchial washings of the right upper lobe and transbronchial lung biopsies in subsegments B2b, B3a and B9 were performed. Sputum, blood, urine, bronchial lavage fluid, and lung tissue smears were negative for acid-fast bacilli. Polymerase chain reaction for *M. tuberculosis* DNA isolated from the bronchial lavage fluid was also negative.

Despite negative test results for acid-fast bacilli, the patient was diagnosed with miliary tuberculosis on the basis of clinical history and radiological findings. She was subsequently started on a four-drug ATT comprising isoniazid (200 mg/day), rifampicin (300 mg/day), ethambutol (500 mg/day), and pyrazinamide (1000 mg/day), which temporarily improved her fever (Fig. 3). However, 9 days after starting ATT, she developed a spiking fever and worsening malaise. Repeat CT showed new localized ground-glass opacity (GGO) in the right upper lobe (Fig. 2b).

Sputum Gram staining and sputum and blood cultures were negative for secondary bacterial infection. Additional laboratory investigations revealed the following results: Krebs von den Lungen-6 level, 306 U/ml (normal level; <500 U/ml); surfactant protein-D level, 69.5 ng/ml (normal level; <110 ng/ml); procalcitonin level, 0.1 ng/ml; HIV-1 and -2 antibody, negative; and cytomegalovirus antigen, negative. Krebs von den Lungen-6 and surfactant protein-D are serum markers indicating the disease activity of interstitial pneumonia. Considering the clinical course and radiological worsening after initiation of ATT, she was considered to have a PR as a result of the therapy.

Because of her increased general fatigue, repeat bronchoscopy was waived, and she was managed with oral prednisolone at a dose of 25 mg/day while continuing ATT. Her fever and malaise gradually resolved. Eight days after the initiation of steroid therapy (18 days after the initiation of ATT), CT showed improvement in the GGO (Fig. 2c). Oral prednisolone was then tapered over a period of 2 weeks. Even after discontinuation of the steroid therapy, there was no recurrence of the GGO on follow-up CT (Fig. 2d).

She again experienced fever accompanied by eosinophilia and elevated liver enzyme levels; these findings were attributed to the drug fever. The ATT was ceased for 1 week, after which a modified regimen was administered (Fig. 3). She was discharged on day 63, and hyposensitization therapy for rifampicin was initiated. ATT with isoniazid (300 mg/day) and rifampicin (450 mg/day) was continued. On follow-up CT, the GGO had disappeared and the miliary nodule was improving.

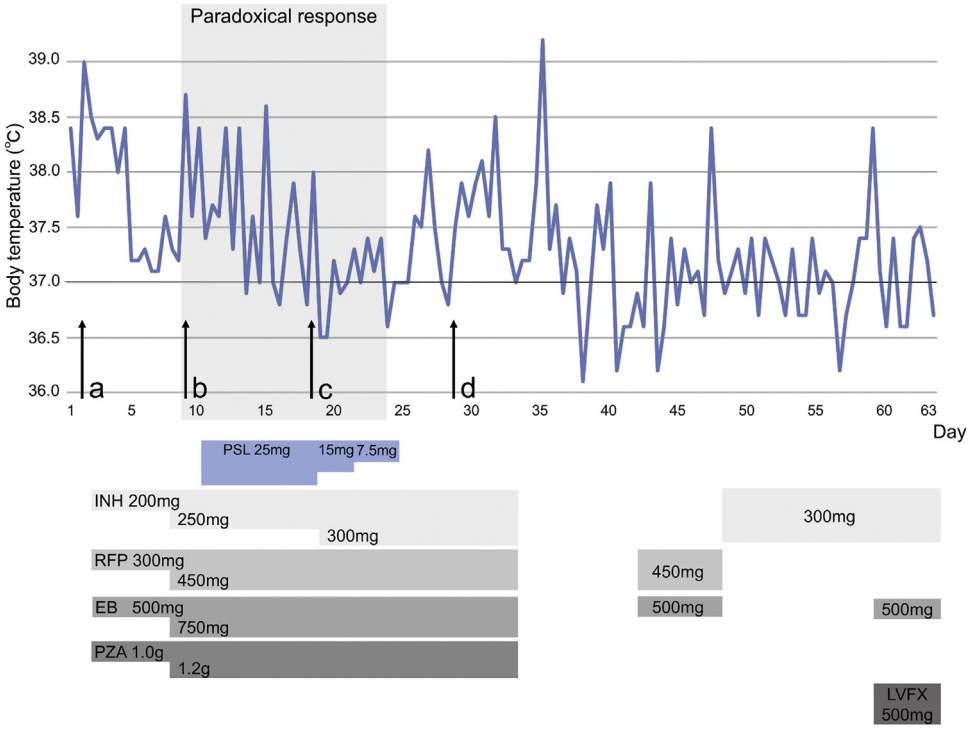

Fig. 3. Hospital course depicting the patient's fever and antitubercular therapy regimen. On day 33, because of a drug fever with eosinophilia and elevated liver enzyme levels (AST 176 U/l, ALT 120 U/l), antitubercular therapy was withdrawn for 1 week. Arrows and letters indicate when chest CT described in Fig. 2 was performed. Abbreviations: AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 1
Summary of paradoxical reactions in miliary tuberculosis among non-HIV infected patients.

Author	Age/sex	Immunodeficiency	Presentation of PR	Onset after initiation of ATT	Additional treatment	Outcome
Chambers et al. [7]	34/M	None	Convulsions and increase in previously noted brain lesions	7 months	Anticonvulsants	Improved
Rietbroek et al. [8]	64/F	Prednisone and azathioprine for scleroderma and polymyositis	Subcutaneous abscesses	17 days	Drainage	Improved
Chen et al. [9]	32/F	Systemic lupus erythematosus	Subcutaneous abscesses	1 month	None	Improved
Valdez et al. [10]	28/M	None	Subcutaneous abscesses	2 months	Aspiration	Improved
Berg et al. [11]	23/F	Azathioprine and prednisone for dermatomyositis	Fever and abscesses of both thighs	13 weeks	Fluid aspiration	Improved
Mert et al. [12]	37/F	Prednisolone and methotrexate for rheumatoid arthritis and dermatomyositis	Subcutaneous abscesses	5 months	Drainage	Improved
Garcia Vidal et al. [13]	49/F	Infliximab for rheumatoid arthritis	Fever and lymphadenopathy	5 weeks	Surgery	Improved
Garcia Vidal et al. [13]	48/F	Infliximab for rheumatoid arthritis	Lymphadenopathy	8 weeks	Surgery	Improved
Toutous-Trellu et al. [14]	81/F	Prednisone and methotrexate for rheumatoid polyarthritis	Fever and skin ulcer	6 weeks	Prednisone	Improved
Yoon et al. [15]	38/M	Infliximab and methylprednisolone for Crohn disease	Right supraclavicular lymphadenopathy	3 months	Surgery	Improved
Melboucy-Belkhir et al. [16]	56/F	Infliximab for ankylosing spondylitis	Right supraclavicular lymphadenopathy	3 months	Prednisolone and surgical excision	Improved
Matsuyama et al. [17]	72/F	Diabetes mellitus Prednisolone for systemic sclerosis	Left femur pain and swelling of lateral great adductor muscle abscess	3 months	Prednisolone increased	Improved
Hassan et al. [18]	29/F	Vitamin D deficiency	Abscess of left knee	4 months	Oral steroid	Improved
Chaudhry et al. [19]	31/F	None	Spastic ataxia	3 weeks	Prednisolone	Improved
Jorge et al. [20]	20/M	Methotrexate and infliximab for Juvenile idiopathic arthritis	Severe cerebrospinal fluid and brain inflammatory reaction in pre-existing tuberculous meningitis	NA	Corticosteroids and infliximab	Improved
Morioka et al. [21]	78/F	Prednisolone for tuberculous meningitis	Dizziness and right temporal lobe infarct	40 days	Existing prednisolone	Improved
Gupta et al. [22]	18/M	None	Fever, cough, dyspnea, and pulmonary infiltration	10 days	Prednisone	Improved
Das et al. [23]	22/F	None	Headache, vomiting, photophobia, and pain and erythema of the left eye; multiple small nodular and ring-enhancing lesions with edema in both cerebral hemispheres	1 month	Dexamethasone and lamotrigine	Improved
Das et al. [23]	10/F	None	Generalized tonic clonic seizures with right temporal conglomerated nodules and perilesional edema	2 months	Oral phenytoin and prednisolone	Improved
Yilmaz et al. [24]	20/M	None	Diminished visual acuity in the left eye due to a pre-existing choroidal tuberculoma	7 days	None	Persistent decrease in visual acuity
Kim et al. [25]	76/F	None	Right hemiparesis and increased size of pre-existing brain lesions	1 month	Stopped pyrazinamide and craniotomy and mass resection	Improved
Falkenstern-Ge et al. [26]	37/M	Adalimumab for psoriatic arthritis	Fever and progressive bilateral pulmonary infiltrates	6 weeks	Prednisolone	Improved
Xie et al. [27]	55/F	High-titer anti IFN-γ autoantibodies	Lytic lesions in the left humeral head	14 weeks	Prednisolone	Improved
Saitou et al. [28]	61/M	Methotrexate, tacrolimus, and prednisolone for dermatomyositis	Bowel perforation	97 days	Surgery	Improved
Bacha et al. [29]	21/M	None	Left cervical lymphadenopathy, pulmonary, pleural, costal and spinal location tuberculosis	8 months	None	Improved
Min et al. [30]	47/M	None	Sudden hearing loss, tinnitus in right ear, and multiple nodule in the brain parenchyma	7 days	Added pyrazinamide and prednisolone	Persistent hearing loss
Wakamiya et al. [31]	63/M	Cyclosporine and mycophenolate mofetil for heart transplantation	Fever and confusion Cerebral tuberculomas in the subarachnoid space	1 month	Dexamethasone	Improved
Kim et al. [32]	65/F	Tacrolimus, mycophenolate mofetil, and prednisolone for kidney transplantation	Intramedullary enhancing spinal mass with sensory loss below T10 and marked motor weakness in both legs	14 days	Surgical resection of the spinal mass and prednisolone	Partial motor paralysis
Our case	78/F	None	Pulmonary GGO	9 days	Prednisolone	Improved

Abbreviations: ATT, antitubercular therapy; GGO, ground-glass opacity; NA, not available.

Discussion

A PR to ATT is a well-recognized phenomenon. In this case, an individual who was HIV-negative developed a localized GGO as a PR to ATT. Although her sputum smear was negative for acid-fast bacilli, the diagnosis of miliary tuberculosis was based on the clinical and radiological features as the sputum smear is reported to be positive in only one-third of patients with miliary

tuberculosis [5]. The PR was successfully treated with a short course of steroids while ATT was continued, and the complication did not recur thereafter.

Our patient developed worsening clinical and radiological features on day 9 of ATT. Bacteriological and serologic testing did not indicate any secondary infection. Drug-induced pneumonia secondary to the ATT seemed unlikely because the new GGO was unilateral and limited to the right upper lobe. It also supports the idea that serum markers, Krebs von den Lungen-6 and surfactant protein-D were normal. It did not recur with continuation of ATT even though the steroid therapy was discontinued. Exacerbation of miliary tuberculosis was also unlikely because the miliary nodule was seen to be improving with ATT. Therefore, we clinically diagnosed this phenomenon as a PR even though the patient's condition did not allow bronchoscopy to be performed.

It has been postulated that the mechanism underlying a PR is local rebound immunological response. The destruction of mycobacteria and release of tubercular proteins invoke mixed type 1 and type 2 helper T-lymphocyte inflammatory responses [6]. The inflamed tissue becomes extremely sensitive to tumor necrosis factor-α, releasing cytokines that cause necrosis, first of the microvasculature and subsequently the whole tissue [6].

To our knowledge, besides our case, 28 cases of a PR in miliary tuberculosis in non-HIV-infected patients have been reported in the past 40 years (Table 1) [7–32]. The manifestations described depended on the site of involvement. It occurred most commonly in the central nervous system (39%), followed by skin (25%), lymph nodes (18%), bone and muscles (7%), lung (7%), and gastrointestinal tract (4%). However, there may be selection bias in the spectrum of findings in the PRs identified in these reports because unusual or severe cases are more likely to be reported. The occurrence of PR varied from a few days to a few months after initiation of ATT, although it was likely to occur earlier in patients not on immunosuppressive therapy. The outcome was generally good, although sequelae could occur with a central nervous system PR. Treatments included surgery and steroid administration. A PR in the lung is comparatively atypical and localized GGO is especially rare, although some cases of acute respiratory distress syndrome in miliary tuberculosis have been reported [33–35]. Our case illustrates that a PR in the lung may present with localized GGO. As in the other reports, our patient's PR improved following administration of steroids with continued ATT.

In summary, we must recognize that in miliary tuberculosis being treated with ATT, a PR may present with a localized GGO in the lung. Patients without immunosuppression may be prone to developing a PR earlier than those who are immunosuppressed. In cases of PR with marked symptoms, steroid therapy may be valuable. More studies are necessary to decide the treatment course for a PR to ATT in miliary tuberculosis.

Author contributions

Contribution to the study design: Y.T., T.M., Y.K., N.Y., K.A., S.Y., M.M.; Drafting the manuscript: Y.T., T.M.; Revising the manuscript critically: Y.T., T.M., Y.K., N.Y., K.A., S.Y., M.M.; Approval of the final version of manuscript: Y.T., T.M., Y.K., N.Y., K.A., S.Y., M.M. All authors meet the ICMJE authorship criteria.

Declaration of Competing Interest

The authors have no conflict of interest.

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References

[1] Dheda K, Barry 3rd CE, Maartens G. Tuberculosis. Lancet 2016;387:1211–26.
[2] Burman WJ, Jones BE. Treatment of hiv-related tuberculosis in the era of effective antiretroviral therapy. Am J Respir Crit Care Med 2001;164:7–12.
[3] Brown CS, Smith CJ, Breen RA, Ormerod LP, Mittal R, Fisk M, et al. Determinants of treatment-related paradoxical reactions during anti-tuberculosis therapy: a case control study. BMC Infect Dis 2016;16:479.
[4] Cheng SL, Wang HC, Yang PC. Paradoxical response during anti-tuberculosis treatment in hiv-negative patients with pulmonary tuberculosis. Int J Tuberc Lung Dis 2007;11:1290–5.
[5] Kim JH, Langston AA, Gallis HA. Miliary tuberculosis: Epidemiology, clinical manifestations, diagnosis, and outcome. Rev Infect Dis 1990;12:583–90.
[6] Grange JM, Stanford JL, Rook GA. Tuberculosis and cancer: parallels in host responses and therapeutic approaches? Lancet 1995;345:1350–2.
[7] Chambers ST, Hendrickse WA, Record C, Rudge P, Smith H. Paradoxical expansion of intracranial tuberculomas during chemotherapy. Lancet 1984;2:181–4.
[8] Rietbroek RC, Dahlmans RP, Smedts F, Frantzen PJ, Koopman RJ, van der Meer JW. Tuberculosis cutis miliaris disseminata as a manifestation of miliary tuberculosis: Literature review and report of a case of recurrent skin lesions. Rev Infect Dis 1991;13:265–9.
[9] Chen CH, Tsai JJ, Shih JF, Perng RP. Tuberculous subcutaneous abscesses developing during chemotherapy for pulmonary tuberculosis. Scand J Infect Dis 1993;25:149–52.
[10] Valdez LM, Schwab P, Okhuysen PC, Rakita RM. Paradoxical subcutaneous tuberculous abscess. Clin Infect Dis 1997;24:734.
[11] Berg J, Leonard A, Clancy CJ, Nguyen MH. Subcutaneous abscesses due to mycobacterium tuberculosis: Paradoxical expansion of disease during therapy for miliary tuberculosis. Clin Infect Dis 1998;26:231–2.
[12] Mert A, Bilir M, Ozturk R, Tabak F, Ozaras R, Tahan V, et al. Tuberculous subcutaneous abscesses developing during miliary tuberculosis therapy. Scand J Infect Dis 2000;32:37–40.
[13] Garcia Vidal C, Rodriguez Fernandez S, Martinez Lacasa J, Salavert M, Vidal R, et al. Paradoxical response to antituberculous therapy in infliximab-treated patients with disseminated tuberculosis. Clin Infect Dis 2005;40:756–9.
[14] Toutous-Trellu L, Charlet I, Hirschel B, Prins C, Masouye I, Vischer UM, et al. Tuberculous cutaneous ulcers associated with miliary tuberculosis in an elderly woman. Case Rep Dermatol 2009;1:23–8.
[15] Yoon YK, Kim JY, Sohn JW, Kim MJ, Koo JS, Choi JH, et al. Paradoxical response during antituberculous therapy in a patient discontinuing infliximab: A case report. J Med Case Rep 2009;3:6673.
[16] Melboucy-Belkhir S, Flexor G, Stirnemann J, Morin AS, Boukari L, Polliand C, et al. Prolonged paradoxical response to anti-tuberculous treatment after infliximab. Int J Infect Dis 2010;14(Suppl 3):e333–4.
[17] Matsuyama T, Sadamura Y, Kawabata T, Momi H, Higashimoto I. [a case of tuberculous lateral great adductor muscle abscess during treatment of miliary tuberculosis]. Nihon Kokyuki Gakkai Zasshi 2010;48:702–5.
[18] Hassan TM, Keane J, McLaughlin AM. Paradoxical reaction causing tuberculous arthritis and soft-tissue abscess in a non-hiv infected, lymphopenic, vitamin d deficient patient with disseminated tuberculosis. A coincidence or an immunological conundrum? Joint Bone Spine 2011;78:322–3.
[19] Chaudhry LA, Ebtesam B-E, Al-Solaiman S. Milliary tuberculosis with unusual paradoxical response at 3 weeks of antituberculous treatment. J Coll Physicians Surg Pak 2012;22:43–5.
[20] Jorge JH, Graciela C, Pablo AP, Luis SH. A life-threatening central nervous system-tuberculosis inflammatory reaction nonresponsive to corticosteroids and successfully controlled by infliximab in a young patient with a variant of juvenile idiopathic arthritis. J Clin Rheumatol 2012;18:189–91.
[21] Morioka H, Matsumoto S, Kojima E, Takada K, Iwata S, Okachi S. Paradoxical infarct in tuberculous meningitis: a case report. Intern Med 2012;51:949–51.
[22] Gupta A, Srivastava VK, Khanna VN, Rizvi I. Paradoxical reaction to antitubercular therapy in miliary tuberculosis. BMJ Case Rep 2012;2012:.
[23] Das A, Das SK, Mandal A, Halder AK. Cerebral tuberculoma as a manifestation of paradoxical reaction in patients with pulmonary and extrapulmonary tuberculosis. J Neurosci Rural Pract 2012;3:350–4.
[24] Yilmaz T, Selcuk E, Polat N, Mutlu K. Choroidal tuberculoma showing paradoxical worsening in a patient with miliary tb. Ocul Immunol Inflamm 2015;23:97–9.
[25] Kim JK, Jung TY, Lee KH, Kim SK. Radiological follow-up of a cerebral tuberculoma with a paradoxical response mimicking a brain tumor. J Korean Neurosurg Soc 2015;57:307–10.
[26] Falkenstern-Ge RF, Husemann K, Kohlhaufl M. Prolonged paradoxical reaction to anti-tuberculous treatment after discontinuation of tnf-alpha- blocker therapy with adalimumab. Rare clinical documentation. Open Med (Wars) 2015;10:39–43.
[27] Xie YL, Rosen LB, Sereti I, Barber DL, Chen RY, Hsu DC, et al. Severe paradoxical reaction during treatment of disseminated tuberculosis in a patient with neutralizing anti-ifngamma autoantibodies. Clin Infect Dis 2016;62:770–3.

[28] Saitou M, Suzuki T, Niitsuma K. Intestinal perforation due to paradoxical reaction during treatment for miliary tuberculosis. Respirol Case Rep 2016;4:e00196.
[29] Bacha S, Khemiri M, Racil H, Hantous S, Chaouch N, Cheikhrouhou S, et al. paradoxical reaction following antituberculosis therapy in immunocompetent patient. Rev Pneumol Clin 2016;72:367–72.
[30] Min SK, Shin JH, Mun SK. Can a sudden sensorineural hearing loss occur due to miliary tuberculosis? J Audiol Otol 2018;22:45–7.
[31] Wakamiya A, Seguchi O, Shionoiri A, Kumai Y, Kuroda K, Nakajima S, et al. Paradoxical reaction of tuberculosis in a heart transplant recipient during antituberculosis therapy: A case report. Transplant Proc 2018;50:947–9.
[32] Kim Y, Kim SP, Han S. Multiple tuberculomas invading the central nervous system as a paradoxical reaction in a kidney transplantation recipient. Saudi J Kidney Dis Transpl 2018;29:719–22.
[33] Kim JY, Park YB, Kim YS, Kang SB, Shin JW, Park IW, et al. Miliary tuberculosis and acute respiratory distress syndrome. Int J Tuberc Lung Dis 2003;7:359–64.
[34] Mohan A, Sharma SK, Pande JN. Acute respiratory distress syndrome (ards) in miliary tuberculosis: A twelve year experience. Indian J Chest Dis Allied Sci 1996;38:157–62.
[35] Piqueras AR, Marruecos L, Artigas A, Rodriguez C. Miliary tuberculosis and adult respiratory distress syndrome. Intensive Care Med 1987;13:175–82.