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

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A R T I C L E   I N F O

Article history:
Received 14 October 2019
Received in revised form 28 November 2019
Accepted 28 November 2019

Keywords:
Paradoxical reaction
Miliary tuberculosis
Mycobacterium tuberculosis

A B S T R A C T

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.

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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 SpO2 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/mm³ 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.
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.

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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.

**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     |
| Toutou-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-Belhik 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 and infliximab | 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 | Prednisolone | Improved     |
| Morieka et al. [21]         | 78/F    | Prednisolone for tuberculous meningitis | Left femur pain and swelling of lateral great adductor muscle abscess | 3 months                     | Prednisolone increased | Improved     |
| Gupta et al. [22]           | 38/M    | None                      | Dizziness and right temporal lobe infarct | 10 days                      | Dexamethasone and lamotrigine | 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                      | Improved             | 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 tuberculum | 7 days                      | None                 | Improved     |
| 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     |
| Falkenstein-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 | Lymphatic 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, pulmonar, 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 | Improved     |
| Wakamiya et al. [31]        | 63/M    | Cyclosporine and mycophenolate mofetil for heart transplantation | Fever and confusion Cerebral tuberculosis 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 | Improved     |
| 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 tuberculoprotein 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 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 cranial 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.

Acknowledgement

The authors thank Enago (www.enago.jp) for the English language review.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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