Clinical Case Report

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# Reversible recurrent profound thrombocytopenia due to linezolid in a patient with multi-drug resistant tuberculosis

## A case report

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**Abstract**

**Rationale:** Thrombocytopenia caused by linezolid (LZD) is common, with a reported prevalence as high as 11.8%. Platelets typically reach normal levels 7 days after LZD withdrawal. However, recurrent profound thrombocytopenia due to LZD usage and a persistent profound drop in platelet count after LZD withdrawal have not been reported.

**Patient concerns:** We report a case of a 75-year-old woman, who presented with recurrent profound thrombocytopenia induced by LZD treatment for multidrug-resistant tuberculosis (MDR-TB).

**Diagnoses:** Laboratory data and symptoms during and after LZD usage and reusage indicated severe thrombocytopenia.

**Interventions:** LZD was discontinued due to recurrent thrombocytopenia and the platelet count continued to drop for 9 days and returned to normal gradually 16 days after LZD withdrawal and supportive care including platelet transfusion.

**Outcomes:** There was no recurrence of thrombocytopenia during 10 months of follow-up during treatment for MDR-TB with a regimen without LZD.

**Lessons:** Recurrent profound thrombocytopenia can happen after several doses of LZD rechallenging. Therefore, reuse of LZD should be avoided after recovery from severe thrombocytopenia due to LZD.

**Abbreviations:** HB = hemoglobin, LZD = linezolid, MDR-TB = multidrug-resistant tuberculosis, PLT = platelets, PMN = polymorphonuclear neutrophils, RBC = red blood cell, WBC = white blood cell, XDR-TB = extensively drug-resistant tuberculosis.

**Keywords:** linezolid, multidrug-resistant tuberculosis, thrombocytopenia

## 1. Introduction

Linezolid (LZD) is an oxazolidinone-class antibacterial agent, which interrupts protein synthesis by binding to the 50S ribosomal subunit.[1] It is used for the treatment of nosocomial pneumonia, community-acquired pneumonia, complicated skin infections, methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant *Enterococcus faecium* infection.[2] Recently, LZD has been used for the treatment of multidrug-resistant tuberculosis (MDR-TB, defined as resistance to at least isoniazid and rifampicin) or extensively drug-resistant tuberculosis (XDR-TB, defined as MDR-TB with additional bacillary resistance to any fluoroquinolone and at least one second-line injectable anti-TB drug),[3] and previous studies have shown an excellent efficacy for MDR-TB and XDR-TB.[4,5] The common adverse effects of this drug include diarrhea, nausea, headache, vomiting, tongue discoloration and oral candidiasis, and other effects, such as peripheral neuropathy, anemia, and thrombocytopenia have also been reported.[4,6] With the increase of dosage, the list of adverse effects of this drug is growing and more and more adverse events are being reported. The prevalence of thrombocytopenia due to LZD in an MDR/XDR-TB regimen is common,[4,7,8] and it has been reported to be as high as 11.8%.[4] It has been reported that platelets reached normal level 7 days after LZD withdrawal.[9] Here we present a case of an old woman, diagnosed with MDR-TB who developed profound thrombocytopenia after 10 days of treatment with an LZD based regimen; profound thrombocytopenia recurred after rechallenging with a short course of low dose LZD after the platelet count was normalized, and platelet count continued to drop 9 days after LZD withdrawal.

## 2. Case report

A 70-year-old woman with pulmonary TB (PTB) and extra-PTB was admitted to a tertiary hospital on December 20, 2016 due to a mass with tenderness in her lower right thoracic wall. Her first diagnosis of PTB, tuberculous pleurisy and extra-PTB were made in July 2016. At that time, the tender mass in her lower right

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thoracic wall was 2 cm in diameter. She was started on treatment with isoniazid, rifampicin, pyrazinamide and ethambutol for 2 months followed by isoniazid and rifampicin for 3 months. After treatment for 5 months, the mass in her lower right thoracic wall was enlarged although her PTB and tuberculous pleurisy showed improvement. On physical examination, she presented with mild pallor, without jaundice on the sclera. A tender mass about 5.0 × 5.0 cm in greatest dimension with normal temperature was palpated in her lower right thoracic wall, which did not show fluctuation. Laboratory results on admission indicated: white blood cell ($6.55 \times 10^9$/L; normal range, 3.5–9.5), hemoglobin (105 g/L; normal range, 115–150 g/L), platelet ($290 \times 10^9$/L; normal range, $100–300 \times 10^9$/L), albumin (34.5 g/L; normal range, 40.0–55.0 g/L), globulin (36.3 g/L; normal range, 20.0–40.0 g/L), total bilirubin (9.2 μmol/L; normal range, 5.0–28.0 μmol/L), direct bilirubin (4.1 μmol/L; normal range,< 8.8 μmol/L), aspartate aminotransferase (8 U/L; normal range, <35 U/L), alanine aminotransferase (7 U/L; normal range, <40 U/L), lactate dehydrogenase (98 U/L; normal range, 110–220 U/L), serum urea nitrogen (2.7 mmol/L; normal range, 3.34–8.75 mmol/L), creatinine (47.0 μmol/L; normal range, 37.0–110.0 μmol/L), erythrocyte sedimentation rate (84 mm/h; normal range < 38 mm/h), C-reactive protein (55.2 mg/L; normal range, <5 mg/L), T-SPOT result was positive. Serologic markers were negative for acute or chronic viral hepatitis, and HIV. Acid fast stain, real-time polymerase chain reaction analysis for *Mycobacterium tuberculosis* and culture for bacteria and tuberculosis on puncture fluid from her thoracic wall mass were negative. Chest computed tomography (CT) after admission (January 2, 2017) (Fig. 1) showed infiltrates on the lower lobe of the right lung, right pleural thickness, and calcification with small amount of effusion, accompanied by enlargement of mediastinal lymph nodes. Ultrasound revealed a large soft tissue heterogeneous mass in her lower right thoracic wall (measuring 5.2 × 2.2 × 5.3 cm), the mass had an irregular shape but clear boundary. After admission, she was diagnosed with MDR-TB, started on an anti-MDT-TB regimen of amikacin, moxifloxacin, protionamide, and cycloserine on January 27, 2017, then she was discharged with these medications. After 2 months of treatment, the mass became small (about 2 cm in diameter). Unfortunately, amikacin was withdrawn at this time due to hearing loss. The mass in her lower right thoracic wall worsened and new lymphadenopathy appeared in her left cervical and fossa axillaris regions 7 months after treatment. Therefore she was readmitted on August 25, 2017. Laboratory results on admission indicated: white blood cell ($4.88 \times 10^9$/L; normal range, 3.5–9.5), hemoglobin (90 g/L; normal range, 115–150 g/L), platelet ($197 \times 10^9$/L; normal range, $100–300 \times 10^9$/L), albumin (27.2 g/L; normal range, 40.0–55.0 g/L), serum urea nitrogen (3.8 mmol/L; normal range, 3.34–8.75 mmol/L), creatinine (46.2 μmol/L; normal range, 37.0–110.0 μmol/L), erythrocyte sedimentation rate (74 mm/h; normal range < 38 mm/h), C-reactive protein (26.7 mg/L; normal range, <5 mg/L). Hematologic parameters related to the usage of LZD, as shown in Table 1. In addition to the original anti-TB medications, LZD was initialized at a start dose of 600 mg/q12 h on Aug 31, 2017.[6,7,10] Ten days after initiation with LZD, her complete blood count revealed the platelet count decreased from $197 \times 10^9$/L to $5 \times 10^9$/L (normal range, $100–300 \times 10^9$/L) on Sept 9, 2017 (Fig. 2). Petechiae and ecchymosis were observed in her lower limbs, and the LZD was stopped immediately and supportive care including platelet transfusion was given. As shown in Figure 1, 13 days after LZD was discontinued, the patient's platelet count recovered to $121 \times 10^9$/L on September 22, 2017, and normal values were maintained for a week. LZD was added again (300 mg/qd)[11] on September 28, 2017 after the platelets were normalized and platelet count was monitored closely. Thrombocytopenia was seen on the third day after recommencement of LZD treatment, the platelet count was $75 \times 10^9$/L on October 1, 2017 and LZD was discontinued again. However, her platelet count continued to drop to the nadir of $5 \times 10^9$/L on the 9th day (October 10, 2017) after LZD withdrawal. Her platelet count returned to normal ($153 \times 10^9$/L) after 2 weeks of LZD withdrawal (October 16, 2017), and clofazimine was added at the same time. The patient left hospital with moxifloxacin, protionamide, cycloserine, and clofazimine on October 17, 2017. There was no recurrence of thrombocytopenia during 10 months of follow-up (once a month) and her mass on

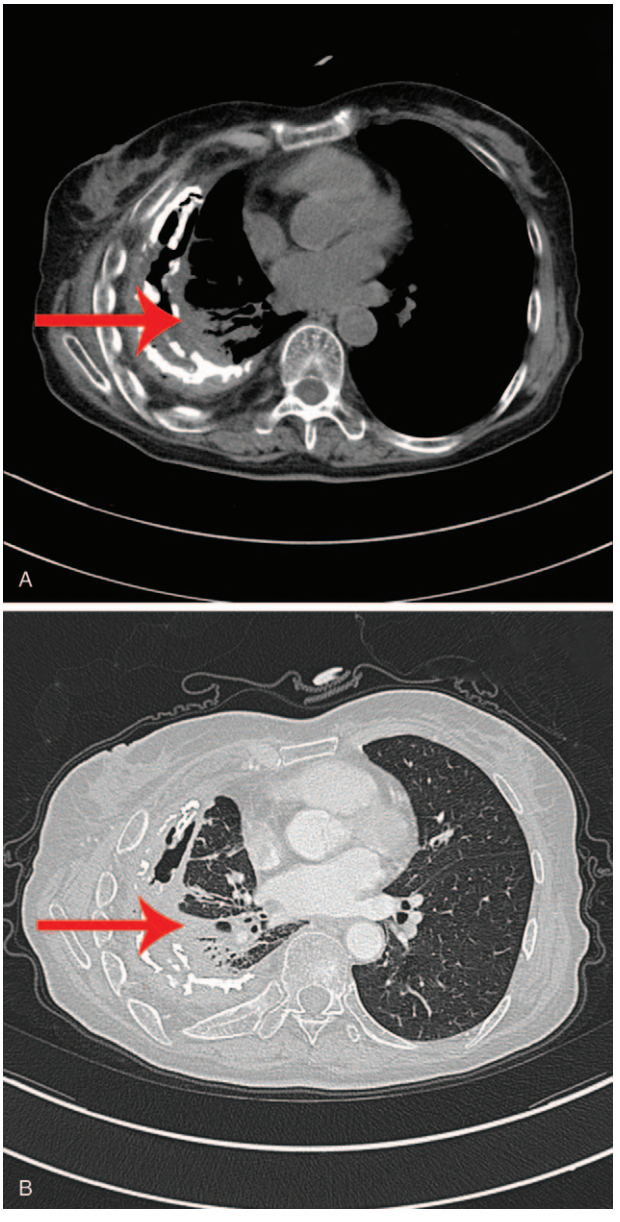


**Figure 1.** The chest computed tomography images of the patient. The figure shows the images of chest computed tomography (CT) of the patient 14 days after admission (January 12, 2017). The images show infiltrates on the left lobe of the right lung, right pleural thickness, and calcification with a small amount of effusion, accompanied by enlargement of mediastinal lymph nodes. CT = computed tomography.

**Table 1**

**Hematologic parameters related to the usage of linezolid.**

| Day | Parameter (normal range) | | | | |
|---|---|---|---|---|---|
| | PLT (100–300 × $10^9$/L) | RBC (350–450 × $10^9$/L) | HB (120–165 g/L) | WBC (4.0–10.0 × $10^9$/L) | PMN (4.0–10.0 × $10^9$/L) |
| August 25, 2017 | 197 | 3.17↓ | 90↓ | 4.88 | 56.4 |
| September 02, 2017 | 52↓ | 3.63↓ | 102↓ | 5.24 | 58.0 |
| September 09, 2017 | 5↓ | 3.20↓ | 92↓ | 5.19 | 43.9 |
| September 19, 2017 | 98↓ | 2.99↓ | 88↓ | 5.19 | 58.0 |
| September 22, 2017 | 121 | 3.21↓ | 90↓ | 5.49 | 54.1 |
| October 01, 2017 | 75↓ | 3.47↓ | 100↓ | 6.44 | 57.4 |
| October 10, 2017 | 5↓ | 3.34↓ | 95↓ | 5.30 | 53.0 |
| October 12, 2017 | 24↓ | 3.17↓ | 90↓ | 6.90 | 61.5 |
| October 16, 2017 | 153 | 3.03↓ | 86↓ | 6.53 | 77.7 |

HB = hemoglobin, PLT = platelets, PMN = polymorphonuclear neutrophils, RBC = red blood cell, WBC = white blood cell.

the chest wall disappeared. Unfortunately, she refused to perform a chest CT and a chest wall ultrasound examination although she is still on the anti-MDR-TB regimen.

## 3. Discussion

LZD is a member of the oxazolidinone class of drugs, which have been approved in the United States more than a decade ago. Recently, LZD has been widely used in multidrug-resistant bacterial infections, such as MRSA and vancomycin-resistant *E faecium* infections.[2] In vitro studies have shown that LZD has good activity against *M tuberculosis*, including MDR and XDR strains.[12,13] Previous retrospective analysis and randomized controlled trials have suggested that LZD may be effective in treating MDR-TB and XDR-TB.[7,8,11,14,15] Meta-analyses have also shown an excellent efficacy of LZD among MDR-TB and XDR-TB patients.[4,5] According to guidelines for drug-resistant TB published in 2016 by the World Health Organization, LZD was reclassified as one of the 4 core second-line agents in group C, due to the growing evidence of its anti-TB efficacy.[16] However, despite its excellent efficacy in drug resistant TB treatment, serious adverse events have been observed, which include gastrointestinal side effects, headache, myelosuppression, optic neuropathy, thrombocytopenia, peripheral neuropathy, and so on.[4,5,8,11,15]

This report is the first to document reversible recurrent profound thrombocytopenia due to LZD. Thrombocytopenia occurred after LZD was added, and resolved with drug discontinuation.[7–9] Although thrombocytopenia has been reported earlier with LZD, our case is unique in several ways.

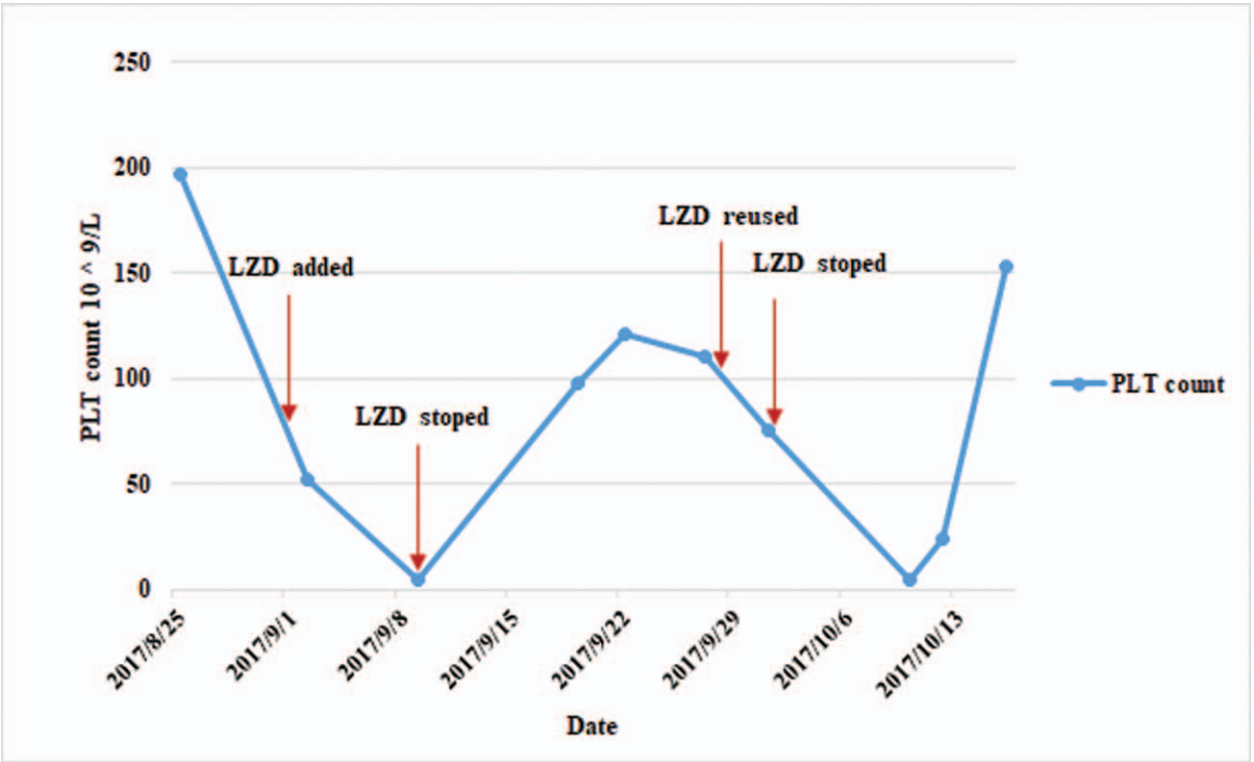


**Figure 2.** Curve of platelet count change. LZD = linezolid, PLT = platelet.

First, our patient was diagnosed as MDR-TB with extra-PTB based on ineffective first-line anti-TB treatment. Second, our patient developed profound thrombocytopenia after 10 days of treatment with LZD rather than after prolonged use as reported in literature.[6] Although, several cytotoxic drugs were used in anti-TB treatment, the thrombocytopenia recovered gradually after LZD was discontinued while other agents were being continued. Third, and most importantly, profound thrombocytopenia reoccurred after restarting a lower dose of LZD at 300 mg/day for only 3 days, which recovered again after withdrawal of LZD. There can be no doubt of a causal relationship between thrombocytopenia and usage of LZD. Fourth, and most alarmingly, the platelet count continued to decline after LZD withdrawal. Thus, close attention should be paid to patients who reuse LZD after withdrawal. When the thrombocytopenia occurs again, the drug should be stopped immediately. Thus, it needs to be kept in mind that LZD reuse, even at a decreased dosage and only for a few doses, can cause recurrent profound thrombocytopenia. Even worse, despite the withdrawal of the drug, platelets may still progressively decrease.

The mechanisms of LZD-induced thrombocytopenia remain unclear. Platelets are produced from megakaryocytes and are then released into the blood. Platelet numbers are maintained by modulation of the production and destruction processes, that is to say thrombocytopenia can be caused by 2 mechanisms: increased consumption/destruction or reduced production of platelets. A previous study has shown that LZD could cause the inhibition of the release of platelets from mature megakaryocytes, thus resulting in the development of thrombocytopenia.[17] Similarly, other studies suggested that thrombocytopenia was caused by the inhibition of platelet formation.[18] In contrast, a case report found an immune-mediated mechanism of platelet destruction may be the mechanism.[19] Numerous factors have been thought to be associated with LZD-induced thrombocytopenia, such as LZD therapy for ≥14 days, low body weight, and low creatinine clearance.[20–23] In addition, a study performed in Chinese adults identified the following risk factors: low pretreatment platelet count, low serum albumin concentration, and concomitant use of caspofungin, levofloxacin, and meropenem.[24] In our case, the following risk factors may associate with developing thrombocytopenia: initial high dosage of LZD, old age (75 years old), decreased albumin (27.2 g/L), and probably concomitant use of moxifloxacin.

There are some limitations in this case report. First, no bacteriological evidence was found in this case and therefore a drug sensitivity test could not be carried out. The result of a drug sensitivity test can assist in the formulation of a definitive diagnosis and is very helpful for the choice of therapeutic regimen. Second, because of the patient's advanced age and respect for the choice of the patient and her dependants, no bone marrow biopsy was performed. Therefore, to determine the mechanisms of LZD-induced thrombocytopenia in this case is a challenge. Although there are some risk factors such as old age, decreased albumin and so on, we did not explore the mechanism of thrombocytopenia that occurred in this patient. Additional studies such as platelet antibody for LZD and bone marrow examination are needed to investigate the mechanisms of LZD-induced thrombocytopenia.

## 4. Conclusion

Thrombocytopenia is a major side effect of LZD therapy, which appears to occur with greater severity than reported in clinical trials. It usually occurs after LZD is added and resolves with temporary drug withdrawal. Since LZD plays an important role in the treatment of M/XDR-TB, it is necessary to monitor platelet count closely during M/XDR-TB treatment including LZD in the regimen, reuse of LZD should be avoided after recovery from severe thrombocytopenia due to LZD.

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## Author contributions

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**Writing – original draft:** Ming-Gui Wang.
**Writing – review & editing:** Jian-Qing He.

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