

CASE REPORT

Bilateral Multiple Lower Limb Tuberculous Aneurysms in a Pregnant Woman with Drug-Induced Liver Injury due to Tuberculosis Treatment

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ABSTRACT

Introduction: Tuberculosis (TB) is a long-term infectious disease caused by *Mycobacterium tuberculosis* (MTB). It can occur during pregnancy, in which its treatment can cause side effects, such as drug-induced liver injury (DILI). Tuberculous aneurysm due to TB infection is a rare occurrence, which can spread directly and hematogenously from the vascular wall. We report a case of bilateral multiple lower limb tuberculous aneurysms in a pregnant woman with DILI due to TB treatment.

Case: A 27-year-old pregnant woman at 14-15 weeks of gestation presented with painless lumps on the left side of her neck and both ankles. Fine needle aspiration biopsy (FNAB) of the left cervical lymph nodes confirmed tuberculous lymphadenitis. Vascular Doppler ultrasound of both lower limbs revealed multiple aneurysms, suspected to be infected tuberculous aneurysms with intramural thrombi, located on the lateral and anterior aspects of the distal leg extending to the left ankle, compressing the distal posterior and anterior tibial arteries. After one month of category one anti-TB drug (ATD) therapy, the patient developed elevated bilirubin levels (3.76 mg/dL). Following surgical intervention, the anti-TB regimen was resumed, leading to the resolution of the pseudoaneurysms by the fifth month of treatment.

Conclusion: Tuberculous aneurysm in pregnant patients with TB is a rare and potentially life-threatening condition. It is difficult to diagnose, but TB infection should be considered a possible cause in endemic countries. Surgery combined with anti-TB treatment improves outcomes.

INTRODUCTION

Tuberculosis (TB) is a chronic infectious disease caused by *Mycobacterium tuberculosis* (MTB), which primarily affects the lungs (pulmonary TB) but can also involve other parts of the body (extrapulmonary TB). It may arise as primary TB (at the initial site of infection) or as secondary TB, resulting from dissemination via hematogenous or lymphatic routes from the primary focus, reactivation of latent TB, or local extension from adjacent tissues. Common sites of extrapulmonary TB involvement include lymph nodes, meninges, pleura, pericardium, skin, the abdominal cavity, skeletal system, and the genitourinary tract, among others.

According to the World Health Organization (WHO) Global Tuberculosis Report 2024, an estimated 10.8 million people worldwide were diagnosed with TB in 2023.¹

Tuberculosis can also occur during pregnancy, with an incidence of 5-7% globally.² During pregnancy, TB refers to a range of conditions caused by (MTB) infections that either arise during pregnancy or continue due to untreated TB during this time. Tuberculosis infection can lead to more than 1 million deaths among women worldwide and can result in mortality during pregnancy.² The majority of TB cases were identified during the antenatal period, primarily in the second and third trimesters of pregnancy. This may be due to

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limited access to early antenatal care, the absence of TB screening in early pregnancy, or the potential reactivation of TB later in pregnancy.¹⁻³

Pregnant women suffering from TB are often diagnosed late due to nonspecific symptoms that are similar to normal pregnancy symptoms, such as malaise and fatigue, with extrapulmonary TB being the most common form. The most frequent risk factors for TB include contact with individuals who have active TB, residing in countries with high TB incidence, e.g., Asia and Africa, as well as living or working in environments with a high risk of TB transmission.^{2,4} Most of extrapulmonary TB does not pose a risk of transmission to the infant, except miliary TB, meningeal TB, or genital tract TB in the mother, which can result in congenital TB. Such transmission occurs in the uterus or during labor by transplacental hematogenous spread.^{2,5} If adequate and prompt therapy is received, TB does not affect pregnancy. However, complications such as chorioamnionitis, blood transfusion, intra-uterine growth retardation (IUGR), preeclampsia, antepartum hemorrhage, premature delivery, low birth weights, pneumonia, acute respiratory distress syndrome (ARDS), and perinatal death may occur as a result of incomplete treatment and advanced or extrapulmonary TB.^{2,6}

According to the United States (US) Federal Drug Administration (FDA), first-line TB medications such as isoniazid (H), rifampin (R), pyrazinamide (Z), and ethambutol (E) are classified as category C medications during pregnancy.⁴ Although the FDA classifies all TB drugs as class C, the benefits of treatment outweigh the potential risks, given the serious maternal and infant complications associated with untreated active TB.² Tuberculosis treatment in TB patients can cause some side effects, including gastrointestinal, neurological, and hepatotoxic disturbances, one of which can trigger drug-induced liver injury (DILI). Drug-induced liver injury is a potential side effect of TB treatment that can lead to treatment failure and even drug resistance. Globally, DILI occurs in 2-28% of patients receiving anti-TB drug (ATD) therapy, with manifestations ranging from mild, asymptomatic symptoms such as increased aspartate aminotransferase (AST)/alanine aminotransferase (ALT), acute hepatitis, to liver failure.^{7,8}

Tuberculous aneurysm due to MTB infection is a rare occurrence. *Mycobacterium tuberculosis*, *M. microti*, *M. bovis*, and *M. africanum* are part of the MTB complex that can cause tuberculous aneurysms. Aneurysms that develop in more than two anatomical locations or affect large and medium-sized arteries are called multiple aneurysms.⁹⁻¹¹ We report a case of

bilateral lower limb multiple tuberculous aneurysms in a pregnant woman with DILI due to TB treatment.

CASE

A 27-year-old woman presented with a painless lump on the left side of her neck that had been present for one month. She was pregnant, estimated at 14-15 weeks of gestation (G3P2A0). Previously, she had experienced weight loss over the past month but reported no other symptoms such as shortness of breath, cough, fever, or night sweats. Additionally, she noted lumps on both ankles that had begun enlarging over the past two weeks, along with visual impairment.

A chest radiograph revealed normal findings. A neck ultrasound demonstrated granulomatous lymphadenitis in the upper, middle, and lower regions of the left jugular chain. A fine needle aspiration biopsy (FNAB) of the left cervical lymph nodes subsequently confirmed the diagnosis of tuberculous lymphadenitis. The laboratory examination revealed a hemoglobin level of 9.9 g/dL (reference: 12.0-15.0 g/dL), platelet count of $363 \times 10^3/\mu\text{L}$ (reference: $150-450 \times 10^3/\mu\text{L}$), leukocyte count of $7.90 \times 10^3/\mu\text{L}$ (reference: $4.50-11.50 \times 10^3/\mu\text{L}$), mean corpuscular hemoglobin (MCH) of 24.2 pg (reference: adult range approximately 27-33 pg per cell), and mean corpuscular volume (MCV) of 72.2 fL (reference: adult range approximately 80-100 fL). Blood chemistry, including AST, ALT, albumin, urea, and creatinine, was within normal limits. Urinalysis revealed marked leukocyturia (++++) and positive bacterial findings. The patient was then initiated on category I ATD therapy.

After one month of ATD therapy, the patient presented to the emergency department with complaints of fatigue but denied cough, fever, nausea, or vomiting. Repeat laboratory evaluation revealed a hemoglobin level of 7.3 g/dL (reference: 12.0-15.0 g/dL), platelet count of $493 \times 10^3/\mu\text{L}$ (reference: $150-450 \times 10^3/\mu\text{L}$), leukocyte count of $11.86 \times 10^3/\mu\text{L}$ (reference: $4.50-11.50 \times 10^3/\mu\text{L}$), MCH of 23.1 pg (reference: 26.0-32.0 pg), and MCV of 69.0 fL (reference: 80.0-96.0 fL). Blood chemistry showed AST, ALT, urea, and creatinine within normal limits. However, total bilirubin was elevated at 3.76 mg/dL (reference: 0.3-1.2 mg/dL), direct bilirubin at 2.79 mg/dL (reference: <1.2 mg/dL), and indirect bilirubin at 0.97 mg/dL (reference: approximately 0.2-0.8 mg/dL). Urinalysis revealed bacteriuria, bilirubin +2, urobilinogen +2, and ketones +1.

One month later, the patient returned to the emergency department, reporting an enlarged lump on her left leg measuring 6 cm×5 cm, which was painful, warm, and itchy, accompanied by a tingling sensation in her feet. Repeat laboratory tests showed a hemoglobin

level of 7.6 g/dL (reference range: 12.0-15.0 g/dL), platelets at $602 \times 10^3/\mu\text{L}$ (reference range: $150-450 \times 10^3/\mu\text{L}$), leukocytes at $11.82 \times 10^3/\mu\text{L}$ (reference range: $4.50-11.50 \times 10^3/\mu\text{L}$), MCH of 23.8 pg (reference range: 26.0-32.0 pg), and MCV of 72.4 fL (reference range: 80.0-96.0 fL). Prothrombin time (PT) and activated partial thromboplastin time (aPTT) were typically within normal limits. Prothrombin time ranges from 11 to 13.5 seconds, and aPTT ranges from 25 to 35 seconds in healthy adults. Serologic tests were negative: the hepatitis B surface antigen (HBsAg) was negative, and the human immunodeficiency virus (HIV) test was non-reactive.

A vascular Doppler ultrasound examination of the bilateral lower extremities revealed multiple pseudoaneurysms, suspected to be infected (mycotic) pseudoaneurysms with intramural thrombi, located on the lateral and anterior aspects of the distal leg, extending to the left ankle. These lesions were compressing the distal posterior and anterior tibial arteries. A Doppler ultrasound examination of the neck region was not performed in this patient.



Figure 1. The chest X-ray revealed clear lung fields bilaterally

Initially, the patient was given an ATD treatment with the regimen two-month intensive phase of H, R, Z, and E, followed by a four-month continuation phase of H and R (2HRZE/4HR). After taking this regimen for one month, the patient complained of weakness without other symptoms and an increase in bilirubin levels (>2). As a result, the ATD treatment was changed to a DILI regimen nine months of R, H, and E (9RHE). A month later, when the patient returned to the hospital with complaints of an enlarged lump on the left ankle and was diagnosed with an aneurysm, ligation of the artery and clot removal were performed on the left anterior tibial artery.

After five months of ATD therapy, a follow-up color Doppler ultrasound of the lower extremities demonstrated resolution of pseudoaneurysms in the bilateral anterior tibial arteries and around both ankle regions. However, residual pseudoaneurysms persist in

the bilateral superficial femoral arteries and the left posterior tibial artery.

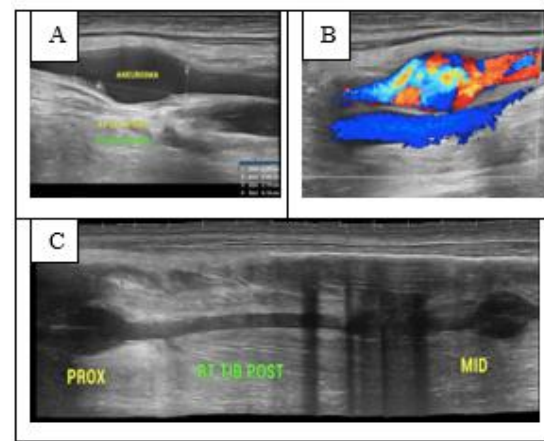


Figure 2. Ultrasound of the right lower limb. A, B) Pseudoaneurysms of the right superficial femoral artery, as seen on the transverse color Doppler; C) Multiple pseudoaneurysms in the right posterior tibial.

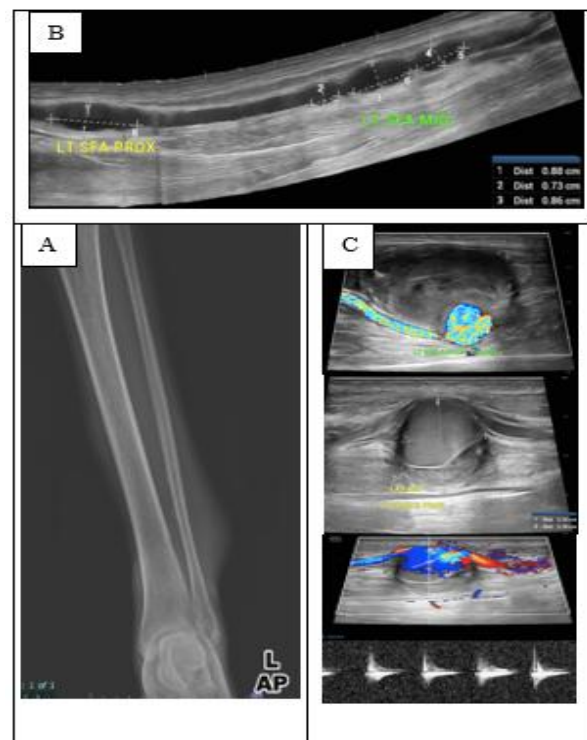


Figure 3. A) Anterior left leg radiograph showing soft tissue swelling in the lateral and medial aspects of the distal leg; B) Ultrasound of the left lower limb showed multiple pseudoaneurysms in the left superficial femoral artery; C) Color Doppler ultrasound showed classic yin-yang sign in the body of the pseudoaneurysm.

DISCUSSION

Tuberculous lymphadenitis has a better outcome during pregnancy compared to other extrapulmonary TB. The treatment for extrapulmonary TB in adults and pregnant women is the same approach as that for pulmonary TB, which involves a standard 6-month

regimen of 2HRZE/4HR. Streptomycin is not recommended for pregnant women with TB as it can be harmful to the fetus. The regimen has a good outcome for maternal and perinatal health and can cure 90% of TB cases during pregnancy with good medication adherence.¹² Isolation of the baby is not necessary if the mother has received ATD therapy for at least 2 weeks.¹²⁻¹⁴ In this case, the patient began TB treatment using the 2HRZE/4HR regimen, as indicated for pregnant women. This helps prevent complications from TB for both the mother and the baby.^{2,15}

After one month of taking the 2HRZE/4HR regimen, the patient complained of fatigue but did not experience nausea, vomiting, or jaundice. Laboratory tests revealed an increase in total bilirubin levels to >2 (3.76 mg/dL). In this case, the patient was identified with DILI. In patients with DILI, the most commonly observed symptoms are anorexia, nausea, and vomiting, although a small number of cases may occur without symptoms. Other conditions, such as malnutrition, diabetes, obesity, and pre-existing liver disease, can further increase the risk of DILI during pregnancy. Drug-induced liver injury is associated with an increase in AST, ALT, and/or bilirubin levels. Management includes discontinuation of ATD, periodic monitoring of clinical symptoms and laboratory parameters, and a re-challenge of ATD administration. Anti-TB drugs are usually given during early pregnancy for fetal safety, and DILI symptoms in pregnant women typically occur within the first 20 weeks of gestation.^{7,16,17} In this patient, DILI was detected at 18-19 weeks of gestation after one month of using the first-line ATD. The patient also experienced malnutrition, with a weight loss of nearly 10 kg. This malnourished state is one of the factors that increase the risk of developing DILI. Management of this patient involved temporary discontinuation of TB medications by the criteria of the absence of clinical symptoms, but an increase in total bilirubin levels >2.¹⁶ The patient then began the treatment with a non-hepatotoxic regimen 9RHE for TB management in the context of DILI. Pyrazinamide was discontinued because it was suspected to be the cause of DILI in this patient.

The limited literature on DILI in pregnancy is likely due to most cases occurring in developing countries with a high prevalence of TB, such as those in Southeast Asia, making it difficult to track and document cases for the literature.¹⁶⁻¹⁹ This patient also received 10 mg of pyridoxine once daily. Pyridoxine and vitamin K supplementation are necessary for pregnant women who are taking ATD medications because the administration of H can cause maternal hepatotoxicity (1%).¹² All first-line TB medications, except streptomycin, are considered safe during pregnancy.^{12,18,20} A tuberculous aneurysm occurs when

a bacterial infection spreads through the bloodstream and weakens the wall of an artery, causing it to bulge. A pseudoaneurysm occurs when one or two layers of a blood vessel wall bulge out. In comparison, a true aneurysm affects all three layers of the vessels: the inner (intima), middle (media), and outer (adventitia) layers. *Staphylococcus* and *Salmonella* are the most common pathogens, while MTB is rarely involved. The tuberculous aneurysm in the femoral artery is a rare case, accounting for only 0.8% of all aneurysms.¹⁷

A tuberculous aneurysm is a rare but serious condition that can develop as a complication of a body infection. Complications from large artery aneurysms are nearly twice as common as those from middle artery aneurysms.^{11,21,22} In pregnancy, no documented incidence rate or prevalence was available until this case report was submitted. In this patient, multiple pseudoaneurysms were found in the bilateral lower limbs, specifically in the superficial femoral artery, posterior tibial artery, and anterior tibial artery. Thus, it can be categorized as a rare case. The spread of a tuberculous aneurysm can occur in several ways, such as hematogenous, where bacteria invade the tunica and adventitia of the blood vessels, causing the formation of a pseudoaneurysm due to thinning or erosion of the vascular wall, or directly from the para-arterial lymph nodes, lungs, spine, or pericardium. In cases of tuberculous aneurysm, approximately 75% are caused by the spread of the disease through erosion of the vascular wall (hematogenous).^{23,24} In this case, the mechanism of possibility is hematogenous spread, as the aneurysms are located in nearly all the lower limb arteries, with multiple occurrences.

Tuberculous aneurysms can present with symptoms similar to TB, such as cough, fatigue, loss of appetite, fever, and weight loss. As the aneurysm enlarges, it may create a lump, often in the neck, which can potentially cause hoarseness or a visibly pulsating swelling. In some instances, bleeding may occur, resulting in anemia, vomiting blood (hematemesis), black stools (melena), coughing up blood (hemoptysis), or even severe blood loss that could lead to shock. Shortness of breath and pain are considered unusual symptoms.¹¹ In this patient, the initial complaint was a lump in the neck, accompanied by weight loss over the past month and lumps in both ankles. These symptoms indicated TB, and after performing an FNAB on the neck gland, the results confirmed TB lymphadenitis. Initially, the lump on the ankle was suspected to be normal swelling associated with pregnancy. However, the lump in the left ankle grew larger and became painful, warm, and itchy, accompanied by a tingling sensation, leading to suspicion of an abscess. Based on these complaints, a lower limb ultrasound was

performed, revealing multiple pseudoaneurysms in the bilateral lower limbs of the patient.

The treatment of a tuberculous aneurysm involves a combination of surgery and ATD medication.^{11,24,25} The first-line treatment for an infected pseudoaneurysm is managed with open surgery, involving debridement of the infected artery and vascular reconstruction.²⁵ For this patient, the treatment included a combination of ATD medication and ligation of the left anterior tibial artery, along with clot removal from the aneurysm in the left ankle region. This combined therapy yielded good results for the patient.



Figure 4. Clinical photos of the patient. A) Before ligation of the left anterior tibial artery and clot removal; B) After arterial ligation and clot removal.

On color Doppler ultrasound examination, a yin-yang sign was observed (Figure 3). This sign represents turbulent blood flow within a pseudoaneurysm vessel due to abnormal vascular dilation, appearing as red and blue colors on the monitor. Using color Doppler ultrasound to detect blood flow within the cystic structure is crucial to confirming the diagnosis. Ultrasound is a practical and non-invasive method for diagnosing pseudoaneurysms. It is affordable, easy to transport, and does not require contrast injection or expose patients to radiation.^{21,26}

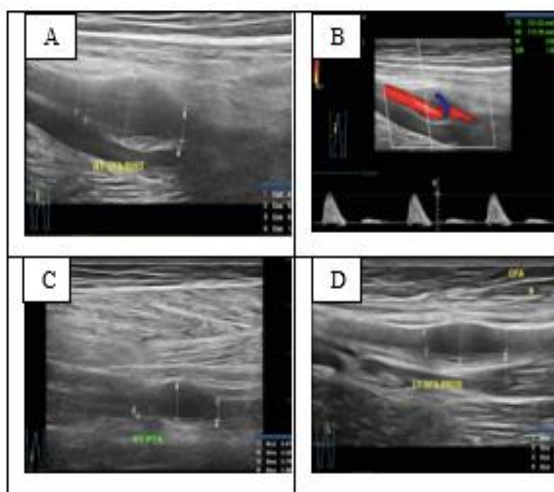


Figure 5. Follow-up ultrasound examination at five months after anti-tuberculosis treatment; A-D) Pseudoaneurysms in the bilateral superficial femoral artery and the left tibialis posterior.

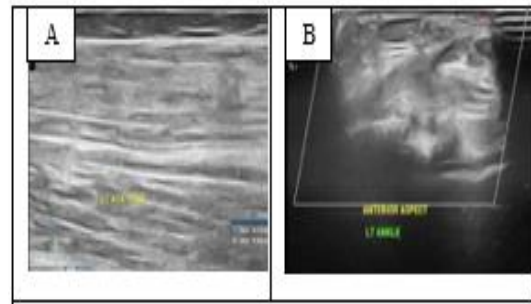


Figure 6. Follow-up ultrasound examination at five months after anti-tuberculosis treatment in the ankle region; A-B) No pseudoaneurysm in the tibialis anterior or ankle regions.

After two weeks of postoperative left anterior tibial artery ligation and clot removal, the patient's leg lump had shrunk. The patient had no pain or tingling, and no new lump appeared. After five months of ATD therapy, a follow-up color Doppler ultrasound was performed on both lower limbs, revealing no pseudoaneurysms in the bilateral anterior tibial arteries or the left and right ankle regions. However, there were still pseudoaneurysms in the bilateral superficial femoral artery and the left posterior tibial artery.

The spontaneous resolution of aneurysms in the right anterior tibial artery and right posterior tibial artery in this patient without surgical intervention is likely due to conservative management with ATD treatment. Several cases of tuberculous aneurysms have reported improvements in symptoms and regression of the aneurysm through consistent adherence to ATD treatment, even without surgical procedures. Anti-TB drug treatment plays a role in controlling the infection that causes damage to the vascular wall. However, it still requires a multidisciplinary approach. Factors related to the vascular wall and the size of the aneurysm also play a role. Surgery remains necessary if there is no improvement with conservative medical treatment.^{23,27,28}

Tuberculosis during pregnancy can lead to several complications, such as miscarriage, low birth weight (LBW), preterm birth, congenital abnormalities, and increased neonatal mortality.²⁹⁻³¹ In this case, the patient delivered a baby spontaneously through vaginal delivery at 33-34 weeks of gestation. The baby was born spontaneously, a female, weighing 1,630 grams. At birth, the baby cried immediately and was fully formed without any abnormalities. The baby was categorized as premature because she was born at less than 37 weeks of gestation. A baby with a birth weight of less than 2,500 grams is classified as LBW. Preterm birth and LBW in this patient's baby may be complications of TB during pregnancy. The specific way TB is linked to the reported adverse outcomes in newborns remains unclear. Treating active TB in the first trimester of pregnancy, rather than the second or third, can significantly reduce the risk of adverse outcomes in

newborns. However, in this case, the patient began TB treatment in the second trimester at 14-15 weeks of gestation.^{2,29,31}

During pregnancy, hormonal fluctuations and hemodynamic changes can increase the likelihood of aneurysm formation and rupture.³² The diagnosis of a tuberculous aneurysm depends on culturing and biopsy of the aneurysmal tissue. However, the cause of TB can be challenging to identify intraoperatively, as the macroscopic appearance of an aneurysm often lacks distinctive features that distinguish it from other causes, and cultures may not always be obtained. Even when tissue samples are submitted for culture, results can sometimes be negative.¹¹

Histopathological examination of tuberculous aneurysms reveals characteristic features, including a positive stain for acid-fast bacilli (AFB) or GeneXpert, which confirms the presence of mycobacteria. The formation of various types of granulomas (giant-cell, epithelioid, caseating, non-caseating, and necrotizing) is marked by infiltration of Langerhans-type multinucleated giant cells and/or epithelioid cells. Necrosis manifests as either classic caseous necrosis or granulomas with central necrosis, and the presence of fibrotic tissue, indicative of chronicity and tissue response. These histologic hallmarks are critical for confirming tuberculous involvement in aneurysmal lesions. Negative results from acid-fast staining, GeneXpert, or MTB culture cannot definitively exclude a diagnosis of tuberculous aneurysm.

In many cases, no tissue specimens are collected for culture or biopsy. Combined with the possibility of false-negative cultures and nonspecific histopathological findings, this significantly increases the risk of misdiagnosis. Therefore, maintaining a high index of clinical suspicion is essential. In patients presenting with arterial aneurysms and clinical features suggestive of TB, a tuberculous aneurysm should remain a diagnostic consideration until definitive confirmation is obtained, especially in high-burden countries.¹¹ In this patient, a pus culture was not performed. Nevertheless, the suspicion of a tuberculous aneurysm was further strengthened by the finding of TB infection in the form of tuberculous lymphadenitis on the FNAB examination and the improvement of the aneurysm with ATD therapy.

CONCLUSION

Tuberculous aneurysm in pregnant patients with TB is a rare yet potentially life-threatening condition. Unfortunately, research dedicated to this specific population is scarce. Further studies on this group remain an open area for future investigation. Surgical management and adequate ATD treatment resulted in a

favorable outcome for this patient. The tuberculous aneurysms in the left anterior tibial artery, right anterior tibial artery, and right posterior tibial artery disappeared after therapy, which was confirmed by a follow-up ultrasound five months after ATD treatment and left anterior tibial artery ligation. The patient gave birth to a preterm and LBW baby spontaneously through vaginal delivery.

Consent

Written informed consent was obtained from the patient.

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None declared.

Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Conceived and designed the study: FA. Collected clinical data: FA, KWAIP, DR. Wrote the manuscript: FA. Reviewed and revised: FA, KWAIP, DR. IS. All authors contributed and approved the final version of the manuscript.

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