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Case Report

Arteriovenous thrombosis in a patient with miliary tuberculosis complicated by a left ventricular mass and its treatment

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Abstract

Introduction: Tuberculosis (TB) is considered one of the two greater long-term global public health threats than the coronavirus disease 2019 (COVID-19) pandemic. Although venous thromboembolism has a low prevalence of 3.5% among patients with active TB, miliary TB complicated by arteriovenous thrombosis is a rare and potentially life-threatening condition.

Case study: We present here an unusual case of a 32-year-old man with a two-month history of shortness of breath and painful swelling in the right lower extremity. In addition, elevated plasma levels of platelets, white blood cells, neutrophils, and D-dimer were observed upon his admission to the hospital. The patient was diagnosed with miliary TB complicated by arteriovenous thrombosis in the right lower extremity and a left ventricular mass measuring 3.5 × 1.7 cm. He was successfully treated with anti-TB drugs and low molecular weight heparin followed by warfarin, aspirin and clopidogrel.

Conclusions: This case study demonstrates that a patient with miliary TB complicated by arteriovenous thrombosis and a left ventricular mass can be cured with timely diagnosis and appropriate treatment. The implications of this report are to raise awareness about miliary TB and arteriovenous thrombosis, to improve diagnosis and treatment, and to reduce patient mortality through sharing our successful experience with clinicians and healthcare providers in the developing countries of the world.

Key words: Miliary tuberculosis; arteriovenous thrombosis; biomarker; treatment.

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Introduction

Tuberculosis (TB) was the leading cause of death from infectious diseases until the coronavirus disease 2019 (COVID-19) pandemic [1], and is considered one of the two greater long-term global public health threats than the COVID-19 pandemic [2]. TB normally affects the lungs but may affect other organs of the body including lymph nodes, kidneys, bones and joints, meninges, and brain (extrapulmonary TB, EPTB). New and relapse extrapulmonary TB cases accounted for 16% of the 7.1 million incident cases of TB reported to the World Health Organization (WHO) in 2019, ranging from 8% in the Western Pacific Region to 24% in the Eastern Mediterranean Region [3]. Miliary or disseminated TB occurs when a pulmonary TB lesion erodes into a blood vessel and disseminates throughout the body. Miliary TB is a potentially life-threatening disease and its diagnosis poses a major challenge due to its atypical clinical manifestations. Venous thromboembolism (VTE) is a chronic disease that affects nearly 10 million people globally every year and remains a major cause of cardiovascular mortality [4]. A recently published global epidemiology study of VTE in people with active TB suggested that VTE was not rare with the prevalence of 3.5% [5]. However, only limited cases of miliary TB complicated by VTE and a ventricular mass were reported [6-8]. Here we present a case of both venous and arterial thrombosis in a young man with miliary TB complicated by a left ventricular mass along with its successful treatment.

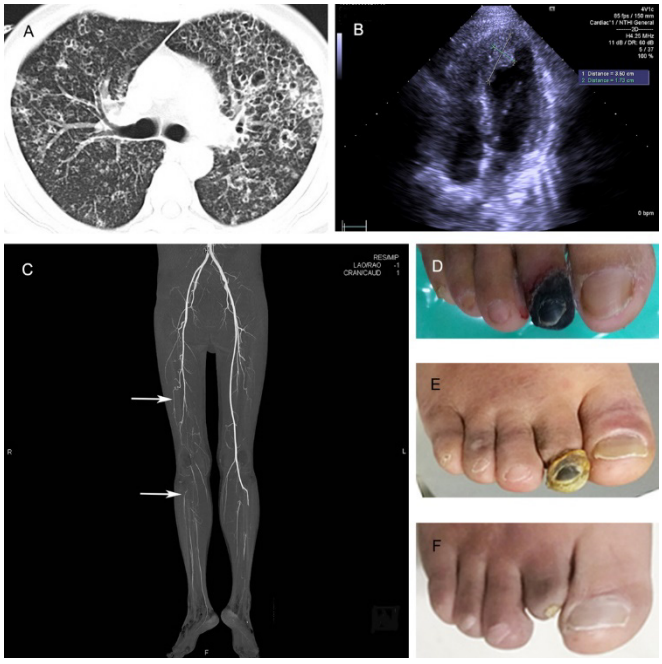
Case Report

A 32-year-old man presented at our hospital with a two-month history of shortness of breath and painful swelling in the right lower extremity, accompanied by night sweats, fatigue, anorexia, and weight loss. He was diagnosed with pulmonary TB at another hospital one week before being admitted to our hospital. The patient had no history of chest pain, hemoptysis, or diabetes, and denied any recent surgery or long-term bed rest. He had smoked one pack of cigarettes a day for the past ten years before quitting one month prior to admission. The patient was a farmer and his family history was unremarkable. Physical examination revealed that the

patient was underweight due to chronic malnutrition and had a blood pressure of 100/65 mmHg, heart rate of 124 beats/min, respiratory rate of 21 breaths/min, and temperature of 38°C (100.4°F). He reported decreased sensation in his right foot, had a diminished right pedal pulse and a dry black tip of the right second toe indicative of ischemic necrosis (Figure 1D). Respiratory examination of the patient revealed moist rales bilaterally.

Laboratory studies at the time of admission revealed decreased plasma levels of hemoglobin and lymphocytes and elevated plasma levels of platelets, D-dimer, white blood cells, and neutrophils. Additional laboratory tests evaluating kidney functions revealed elevated levels of urea, creatinine, and uric acid (Table 1). Serologic testing results for antibodies to HIV, hepatitis B surface antigen, hepatitis C virus, and *Treponema pallidum* were negative. Two sputum samples were strongly positive (4+) and one urine sediment was weakly positive (1+) for acid fast bacilli smear. Collected clinical specimens were cultured on Löwenstein-Jensen solid slants as described previously [9], and two sputum cultures were positive and one urine culture was negative for *M. tuberculosis*. The proportion method on Löwenstein-Jensen solid slants was used for drug susceptibility testing (DST) against four first-line (isoniazid, rifampicin, ethambutol and streptomycin) and one second-line (levofloxacin) anti-TB drugs with the standard *M. tuberculosis* strain H37Rv as the quality control. DST results showed that both *M. tuberculosis* isolates were susceptible to four first-line anti-TB drugs and levofloxacin.

Figure 1. Diagnostic imaging of the patient on admission and the appearance of the toes before and after treatment.



A: Chest CT scans of the patient showed multiple cavities and bronchiectasis lesions in bilateral lungs. **B:** Transthoracic echocardiograms of the patient showed a mass of cardiac tuberculoma/thrombosis measuring 3.5 × 1.7 cm in the left ventricular apex (arrowhead). **C:** CT angiography of both lower extremities showed the femoral and popliteal artery occlusions before the treatment. **D-F:** show the appearance of the right second toe on admission (D), at the end of 18-month treatment (E), and at the eight-month follow-up visit (F).

Computed tomography (CT) examinations of patient's chest and abdomen were performed to evaluate for EPTB. Abdominal CT revealed lesions in the patient's urinary system and heart, further examination of the urinary system and heart was performed by using a transthoracic echocardiogram (TTE) and color Doppler ultrasound (CDUS). CDUS and CT angiography (CTA) of both lower extremities were also performed because the patient had swelling and pain in the right lower extremity and an elevated D-dimer.

CT scans of the chest revealed multiple cavities and bronchiectasis lesions in both lungs indicating miliary or disseminated TB (Figure 1A). Magnetic resonance imaging (MRI) of the head showed softening lesions in the right parietal and occipital lobes. CT scans of the abdomen showed narrowed bladder section of the left kidney, hydronephrosis in the right kidney and multiple enlarged retroperitoneal lymph nodes, most likely caused by TB. Tumors and infectious lesions in kidneys were ruled out.

TTE of the heart revealed a mass measuring 3.5 × 1.7 cm in the left ventricular apex (Figure 1B). It was uncertain whether the heart mass in this patient was a cardiac tuberculoma or a cardiac thrombosis. Arteriovenous CDUS of both lower extremities showed thrombosis in the right superficial femoral artery, right popliteal artery, and the right peroneal vein. CTA of both lower extremities revealed that the right femoral and popliteal arteries were occluded (Figure 1C). CTA of the thoracic and abdominal aorta was unremarkable.

Based on imaging and laboratory studies, the patient was diagnosed with miliary TB (affecting his lungs, brain, and kidneys) complicated by arteriovenous thrombosis in the right lower extremity. A daily oral treatment regimen with four first-line anti-TB drugs (600 mg isoniazid, 450 mg rifampicin, 750 mg ethambutol, and 1500 mg pyrazinamide) combined with levofloxacin (500 mg) was initiated on the day of his admission in accordance with WHO guidelines for treatment of drug-susceptible tuberculosis and patient care [10]. Although levofloxacin was not one of the first-line antituberculosis drugs, we added it to the regimen based on our experience in treating severe

cases of TB such as this potentially lethal multiorgan TB. A recent prospective study from China demonstrated the efficacy and safety of short-term regimen containing levofloxacin in the treatment of newly diagnosed bacteria-positive TB [11]. The patient also received subcutaneous injections of low molecular weight heparin (2500 U q12h) for seven days followed by six-months of oral anticoagulation treatment with warfarin (4.375 mg daily), aspirin (100 mg daily) and clopidogrel (75 mg daily) to prevent additional thromboembolic events from occurring.

At the end of six-month treatment, symptoms of the patient were improved and the patient's levels of hemoglobin, white blood cells, lymphocytes, and neutrophils were back to normal; while the levels of platelets, urea, uric acid, creatinine and D-dimer remained elevated. At the end of 17-month treatment, urea and D-dimer were back to normal levels while the levels of platelets, white blood cells, lymphocytes, monocytes, neutrophils, uric acid, and creatinine were still elevated (Table 1).

At the end of 18-month treatment, lesions in the lungs and brain appeared to have been absorbed, local renal calices of both kidneys were dilated, the mass in the apex of the left ventricle disappeared, no abnormalities were seen in the right peroneal vein with ultrasound examination, and the right superficial femoral artery and popliteal artery remained occluded but developed collateral circulation. The patient's symptoms of shortness of breath, swelling and pain in the right lower limb resolved, and the distal end of the second toe fell off spontaneously (Figure 1F). A sputum smear and cultures of sputum samples and urine sediment were negative. At the 8-month follow-up visit, the patient had no symptoms of shortness of breath, cough, or swelling of the lower extremities. The sputum smear was negative and the lesions in the lungs, heart, brain and kidneys were stable. However, the levels of hemoglobin, white blood cells, monocytes, neutrophils, platelets, urea, and creatinine were above normal ranges (Table 1).

Discussion

The five risk factors for many new cases of TB are undernutrition, HIV infection, alcohol use disorders, smoking and diabetes [3], while risk factors for miliary TB are involved in immunosuppression including childhood infections, malnutrition, HIV infection, smoking, diabetes, organ transplantation, underlying malignancy and silicosis [12]. The harmful components in cigarettes can negatively influence the effectiveness of the immune system's response to a pathogen leading to continuous infection [13]. Meanwhile, chronic malnutrition can cause impairment of organ functions and immune dysfunction making it easy to turn into active TB and even miliary TB in severe cases once infected with *M. tuberculosis*. On admission, the patient had a ten-year history of smoking and was underweight due to chronic malnutrition, which could be possible reasons leading this patient to develop miliary TB in the absence of any immunocompromised condition.

The association between inflammation, infection, and VTE has been summarized in a recent review article trying to understand how the immune and coagulation systems interact and regulate each other to build up an effective response to injury and pathogen [14]. VTE comprises both deep vein thrombosis (DVT) and pulmonary embolism (PE), while DVT of the lower extremities is much more likely to cause PE when a blood clot formed in a deep vein breaks loose and travels to the lungs. DVT results from conditions that impair venous return leading to endothelial injury or dysfunction, or causing hypercoagulability. DVT may be asymptomatic or cause swelling, redness, and pain in

Table 1. Laboratory data before, during, and after treatment.

Variable	Before	Month 6	Month 17	Month 18	Month 8 after*	Reference range
Hemoglobin (g/L)	81.0	146.0	172.0	178.0	204.0	130-175
White blood cells (10^9/L)	10.43	8.48	15.48	14.06	16.24	3.5-9.5
Lymphocytes # (10^9/L)	0.73	2.71	4.02	3.23	3.25	1.1-3.2
Lymphocytes %	0.07	0.32	0.26	0.23	0.20	0.20-0.50
Monocytes # (10^9/L)	0.42	0.76	0.93	0.84	0.97	0.1-0.6
Monocytes %	0.04	0.09	0.06	0.06	0.06	0.02-0.08
Neutrophils # (10^9/L)	9.07	4.41	9.91	9.42	11.53	1.8-6.3
Neutrophils %	0.87	0.52	0.64	0.67	0.71	0.40-0.75
Platelet count (10^9/L)	415	389	364	334	371	100-300
D-dimer (μg/mL)	3.99	2.98	0.21	N/A	N/A	<1.0
Urea (mmol/L)	22.56	8.19	4.13	7.07	7.85	2.8-7.2
Uric acid (μ mol/L)	750	581	535	518	538	208-428
Creatinine (μ mol/L)	228	159	125	148	143	41-109

N/A: not available; *Eight months after the end of 18-month treatment.

an extremity. Risk factors for VTE include major surgery, malignancy, immobilization, use of oral contraceptives, obesity, smoking, chronic inflammation caused by active TB, and other environmental and generic factors [4,5,14-16].

A systematic review showed the prevalence of PE at 5.8% and DVT at 1.3% among people with active TB [5]. However, disseminated TB complicated by VTE is relatively rare [6,7] but is potentially life-threatening [8]. In our case, we successfully treated a 32-year-old male patient with miliary TB complicated by arteriovenous thrombosis and a 3.5 × 1.7 cm mass in his left ventricular apex, which is a rare and severe complication. This case is similar to a 2017 case where a 33-year-old female patient from South Africa with HIV-positive disseminated TB complicated by pulmonary thrombus formation was treated empirically with antiretroviral therapy and later with antituberculosis drugs. On day 10 of her admission, the patient died of a 3 × 0.5 cm occluding thrombus in her left main pulmonary artery [8].

Infection-associated thrombosis is caused by the pathogen and its products which induce inflammation, trigger platelet activation, and cause endothelial damages leading to thrombus formation [17]. Neutrophils, monocytes, and platelets play critical roles in the formation of VTE through interacting with each other and the endothelium in host defense [14]. Diagnosis of VTE requires a combined assessment of history, physical examination, D-dimer testing, and imaging [4]. Results from a recent study showed that the sensitivity in predicting VTE increased from 25% to 100% for the HIV-/TB+ patients in a South African setting when the modified Wells score adjusted for HIV/TB was used [18]. On admission, the patient had a history of smoking, which is one of the risk factors for VTE, and elevated levels of platelets, neutrophils, and D-dimer, which could be used as thrombosis markers for TB patients. Anticoagulants such as low molecular weight heparin (injectable) and warfarin (oral) are most commonly used to treat VTE. The experience gained from this case can be shared with clinicians in developing countries to raise awareness about miliary TB and arteriovenous thrombosis to reduce patient mortality.

Conclusions

To the best of our knowledge, this is the first reported case of arteriovenous thrombosis in a young man with miliary tuberculosis complicated by a left ventricular mass from Guizhou province of China. This case report demonstrates that a patient with miliary TB complicated by arteriovenous thrombosis and a left ventricular mass can be cured with timely diagnosis and treatment. Therefore, clinicians in high TB burden developing countries should consider the possibility of arteriovenous thrombosis while treating TB patients with risk factors for thrombosis in order to avoid misdiagnosis and delayed treatment.

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References

1. World Health Organization (2022) Global tuberculosis report 2022. Available: https://www.who.int/publications/i/item/9789240061729. Accessed: 6 March 2023.
2. The Lancet Infectious Diseases (2021) Tuberculosis and malaria in the age of COVID-19. Lancet Infect Dis 21: 1. doi: 10.1016/S1473-3099(20)30946-4.
3. World Health Organization (2020) Global tuberculosis report 2020. Available: https://www.who.int/publications/i/item/9789240013131. Accessed: 6 March 2023.
4. Khan F, Tritschler T, Kahn SR, Rodger MA (2021) Venous thromboembolism. Lancet 398: 64-77. doi: 10.1016/S0140-6736(20)32658-1.
5. Danwang C, Bigna JJ, Awana AP, Nzalie RN, Robert A (2021) Global epidemiology of venous thromboembolism in people with active tuberculosis: a systematic review and meta-analysis. J Thromb Thrombolysis 51: 502-512. doi: 10.1007/s11239-020-02211-7.
6. Ng BH, Andrea YLB, Nuratiqah NA, Faisal AH, Low HJ (2021) Clots in tuberculosis. Med J Malaysia 76: 953-955.
7. Hashmani S, Sultan FAT, Masood MQ (2016) Unusual presentation of a young man with disseminated tuberculosis and right ventricular mass. BMJ Case Rep 2016: bcr2016216964. doi: 10.1136/bcr-2016-216964.
8. Ugalde I, Pirela D, Presti SL, Bilderback M, Pirela A, Chan J (2017) Fatal pulmonary embolism in the setting of immune reconstitution inflammatory syndrome attributed to ovarian tuberculosis. J Investig Med High Impact Case Rep 5: 2324709617729690. doi: 10.1177/2324709617729690.
9. Li N, Liao X, Chen L, Wang J, Liu M, Zhang H (2015) Antibiotic susceptibility patterns of *Mycobacterium tuberculosis* isolates from Guizhou Province of China against 13 antituberculosis drugs. Microb Drug Resist 21: 292-296. doi: 10.1089/mdr.2014.0094.
10. World Health Organization (2017) Guidelines for treatment of drug-susceptible tuberculosis and patient care, 2017 update. Geneva: WHO; Licence: CC BY-NC-SA 3.0 IGO. Available: https://apps.who.int/iris/bitstream/10665/255052/1/9789241550000-eng.pdf?ua=1. Accessed: 6 March 2023.

11. Chen Z-H, Lin J-X, Zeng L-X (2022) Clinical effect of short-term regimen containing levofloxacin in the treatment of newly diagnosed bacteria-positive pulmonary tuberculosis. J Tuberculosis and Lung Disease 3: 19-21. doi: 10.19983/j.issn.2096-8493.20210145.
12. Sharma SK, Mohan A (2017) Miliary tuberculosis. Microbiol Spectr 5. doi: 10.1128/microbiolspec.TNMI7-0013-2016.
13. Karavitis J, Kovacs EJ (2011) Macrophage phagocytosis: effects of environmental pollutants, alcohol, cigarette smoke, and other external factors. J Leukoc Biol 90: 1065-1078. doi: 10.1189/jlb.031114.
14. Colling ME, Tourdot BE, Kanthi Y (2021) Inflammation, infection and venous thromboembolism. Circ Res 128: 2017-2036. doi: 10.1161/CIRCRESAHA.121.318225.
15. Maasdorp SD (2021) Venous thromboembolism and infection. Afr J Thorac Crit Care Med 27: 10.7196/AJTCCM.2021.v27i3.171. http://doi.org/10.7196/AJTCCM.2021.v27i3.171.
16. Crous-Bou M, Harrington LB, Kabrhel C (2016) Environmental and genetic risk factors associated with venous thromboembolism. Semin ThrombHemost 42: 808-820. http://doi.org/10.1055/s-0036-1592333.
17. Beristain-Covarrubias N, Perez-Toledo M, Thomas MR, Henderson IR, Watson SP, Cunningham AF (2019) Understanding infection-induced thrombosis: lessons learned from animal models. Front Immunol 10: 2569. doi: 10.3389/fimmu.2019.02569.
18. Keokgale T, van Blydenstein SA, Kalla IS (2022) Evaluation of the modified Wells score in predicting venous thromboembolic disease in patients with tuberculosis or HIV in a South African setting. S Afr J HIV Med 23: a1349. doi: 10.4102/sajhivmed.v23i1.1349.

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