Case Report

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Miliary tuberculosis and pregnancy

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Abstract:

Miliary tuberculosis (TB) is a disseminated form of TB resulting from the lymphohematogenous spread of *Mycobacterium tuberculosis* (MTb). Since pregnancy-related TB lacks the typical respiratory symptoms, clinicians might overlook the condition, complicating early diagnosis and treatment. This is a case of a 39-year-old multigravida, who presented with vaginal bleeding in the second trimester. She was admitted for tocolysis and correction of severe anemia. On the 6th hospital day, there was a note of febrile episodes accompanied by productive cough. Chest X-ray revealed miliary spread, eventually detecting MTb on sputum GeneXpert. At 19-week age of gestation, she delivered to an abortus. Histopathology of the endometrial tissues revealed caseating granulomas, consistent with tuberculous etiology. The disease's severity, stage of the pregnancy at the time of diagnosis, and the existence of extrapulmonary dissemination might influence the outcome of pregnancy.

Keywords:

Extrapulmonary tuberculosis, miliary tuberculosis, pregnancy

Introduction

Miliary tuberculosis (TB) is a disseminated form of TB resulting from the lymphohematogenous spread of *Mycobacterium tuberculosis* (MTb).[1] It is uncommon during pregnancy. Since pregnancy-related TB does not exhibit the usual respiratory symptoms, this makes it more likely for unsuspecting clinicians to ignore the condition, making early diagnosis and treatment even more challenging.

Several variables might influence the outcome of TB in pregnancy. Obstetric morbidity and the risk of premature labor may increase with late diagnosis of TB.[2]

This case discusses a 39-year-old multigravida diagnosed with miliary TB, resulting in a miscarriage, one of the complications of TB in pregnancy.

Case Report

This is a case of 39-year-old gravida 9 para 8 (8-0-0-8), married, from Malate Manila, who came in with a chief complaint of vaginal bleeding. The patient has no known comorbidities and unremarkable family history. She is married and has been living with her husband since 2020, while her eight children have been staying with her mother in the province.

Her last menstrual period was from February 14–20, 2023, giving her an amenorrhea of 16 weeks. She has one lifetime sexual partner. All her pregnancies were carried to term and delivered via normal spontaneous delivery. There were no fetomaternal complications noted. This is her ninth pregnancy. She was not cognizant of this pregnancy and hence had no prenatal check-ups, no baseline laboratories and imaging studies, and no intake of prenatal medications. A review of systems showed unintentional weight loss, no febrile episodes, no night sweats, no easy fatigability, and no shortness of breath.

One month prior to consult, at 13-week age of gestation, the patient consulted at a tertiary government hospital for a preemployment check-up. Despite her being pregnant, she was given clearance for radiographic imaging and underwent

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chest X-ray (CXR). Results allegedly showed pulmonary TB. The patient was referred to a TB DOTS clinic where GeneXpert was done; however, no MTb was detected; hence, no active management was done.

Three weeks prior to consult, at 14-week age of gestation, the patient noted vaginal bleeding amounting to one pantyliner per day. She consulted at a tertiary hospital and was assessed as a case of threatened abortion and was given isoxsuprine 10 mg tablet every 8 h which she took for 7 days. Vaginal bleeding persisted for 2 weeks despite compliance with the given medication; hence, she consulted at our institution. There was no passage of meaty tissues noted, no abdominal pain, no febrile episodes, no easy fatigability, no colds and cough, no night sweats, and no changes in bowel and urinary habits.

On the day of consultation, the patient only had vaginal spotting but reportedly used one fully soaked baby diaper the day before presenting at the emergency department. There were no other accompanying symptoms. The patient was normotensive at 100/60 mmHg, tachycardic at 110 beats per minute, nontachypneic at 20 cycles per minute, afebrile at 36.5°C, and with good oxygen saturation at 98%. The patient stands at 170 cm, and weighs 58 kg, with a normal body mass index of 20.1 kg/m^2. She had pale palpebral conjunctivae, no cervical lymphadenopathies noted. Abdominal examination showed no abdominal tenderness, absence of tenderness, and noted good fetal heart tones at 150 beats per minute at the hypogastric area. Speculum examination was done revealing a clean-looking cervix with no pooling of blood. On internal examination, the vagina admitted two fingers with ease, the cervix was smooth, soft, and closed, and the uterus was enlarged to 16-week size. The patient was then admitted as a case of threatened abortion.

Complete blood count (CBC) showed severe anemia (hemoglobin of 6.7 g/dl), while coagulation studies were normal [Table 1]. She was admitted and started on tocolytics nifedipine 10 mg tablet thrice daily and oral progesterone 200 mg capsule once daily. She was transfused with three units of packed red blood cells. Weekly biometry was planned for fetal surveillance. CBC, prothrombin time, and activated partial thromboplastin time every 3 days were requested [Table 1]. Other baseline laboratories revealed normal results [Tables 2 and 3].

The patient underwent baseline pelvic ultrasound with cervical length and funneling revealing a single, live, intrauterine pregnancy, transverse presentation, 19-week and 4-day age of gestation by fetal biometry, with good somatic and cardiac activities; placenta posterofundal, grade 1, high-lying; normohydramnios; cervical score of 5 indicating a high risk for preterm delivery. There was an incidental finding of a subplacental hemorrhage at the right lateral portion of the placenta measuring 7.5 cm × 8.2 cm × 4.0 cm (vol=129.4 cc), cannot totally rule out abruptio placenta [Figure 1]. During this time, the plan was to continue tocolysis and fetal and subplacental hemorrhage surveillance.

On the 6th hospital day, she was noted to be febrile with the highest temperature at 38.5°C. This was accompanied by cough with whitish sputum and night sweats. Rapid antigen test for COVID-19 revealed negative results. CXR revealed pulmonary TB with miliary spread [Figure 2]. She was then referred to the Infectious Disease service, and GeneXpert was requested which eventually detected MTb, with no rifampicin resistance. The patient was referred to ophthalmology for baseline assessment of visual acuity and color vision before starting with anti-TB medications. The patient was also referred to TB-DOTS for management of miliary TB and was started on the intensive phase regimen for TB with HRZE

Table 1: Hematology

Parameters	6/14/23	6/17/23	6/19/23	6/22/23	6/25/23	6/28/23
Hemoglobin	6.7 (L)	10.1 (L)	9.2 (L)	8.4 (L)	10.7 (L)	12
Hematocrit	19 (L)	30.4 (L)	26 (L)	24.3 (L)	31.5 (L)	35.6
WBC	8.2	11.5	10.8	9.6	12.1 (H)	16.9 (H)
Neutrophils	70.4 (H)	76.5 (H)	70.7 (H)	69	78.7 (H)	82.7 (H)
Lymphocytes	17.7 (L)	13.4 (L)	15.3 (L)	16.4 (L)	11.6 (L)	9.7 (L)
Monocytes	10.9	9	11.6 (H)	12.7 (H)	8.8	7
Eosinophils	0.7 (L)	0.7 (L)	1.7	1.6	0.3 (L)	0.2 (L)
Basophils	0.3	0.4	0.7	0.3	0.6	0.4
Platelets	393	370	323	314	287	359
PTc	12.1			12.1	12.1	12.1
PT	11.8			11.3 (L)	11.9	11.5 (L)
INR	0.93			0.89	0.94	0.91
%Activity	109.5 (H)			117.9 (H)	107.9 (H)	114.4 (H)
APTT	29.7			25.8 (L)	31.8	26.8
D-Dimer (mg/L)			1.38 (H)			

(150/75/400/275 mg), four tablets daily based on a 58 kg body weight, and Vitamin B complex once daily.

Uterine quiescence and resolution of vaginal spotting was eventually achieved on the 10th hospital day. However, on the 12th hospital day, the patient noted moderate uterine contractions lasting for 10 min occurring 3 times a day. On internal examination, the cervix was dilated to 2 cm, beginning effacement, cephalic, intact bag of waters, station 3. Nifedipine was increased to 30 mg tablet twice daily and oral progesterone to 200 mg capsule twice daily. There was no note of vaginal spotting.

Irregular uterine contractions persisted until the 15th hospital day when there was a note of regular uterine contractions despite increasing the tocolytics. This subsequently led to the spontaneous expulsion of an abortus male fetus, weighing 340 g [Figure 3]. She then underwent postexpulsion curettage. The endometrial tissues and placenta were then sent for histopathologic examination [Figure 4]. The patient was then sent home on the 2nd postpartum day and was advised to follow up after a week with strict compliance to anti-TB medications.

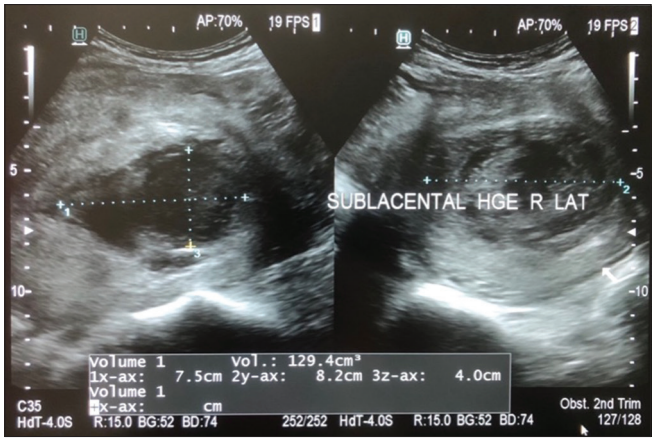

Figure 1: Ultrasound picture of the subplacental hemorrhage

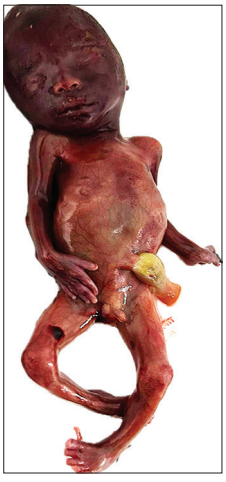

Figure 3: Abortus

Histopathology report of the endometrial specimen revealed deciduitis and chronic endometritis with central caseation necrosis and chronic granulomatous and multinucleated giant cell formation (Langhans type), consistent with tuberculous etiology [Figure 5]. It also revealed a singleton placenta with 15% infarction and moderate chorioamnionitis.

Discussion

Maternal infections are known to increase the risk of early pregnancy loss, as illustrated in this case report, where an overwhelming tuberculous infection led to the spontaneous expulsion of a nonviable fetus. According

Table 2: Iron Studies

Parameters	6/15/23
% reticulocytes	1.3%
Ferritin	212 (H)
Iron	41.6 (H)
TIBC	46.1

Table 3: Peripheral Blood Smear

6/15/23	RBC: Mild microcytosis, mild hypochromia, mild poikilocytosis (elliptocytes)
	WBC: within normal limits, with neutrophilic predominance
	Platelets: adequate
	No immature/blast cells seen.

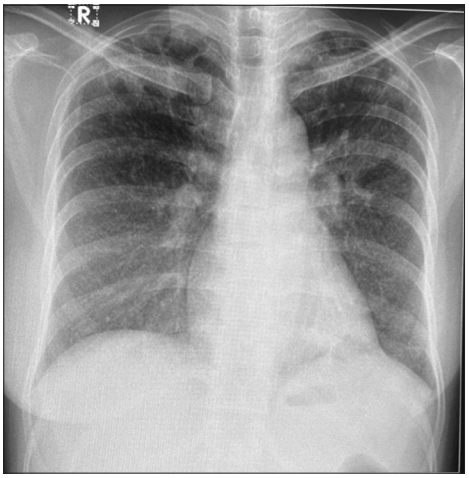

Figure 2: Chest X-ray

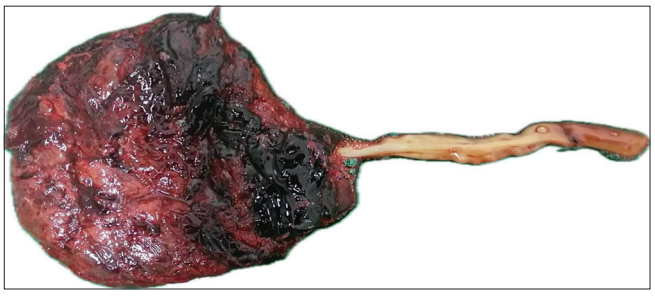

Figure 4: Placenta

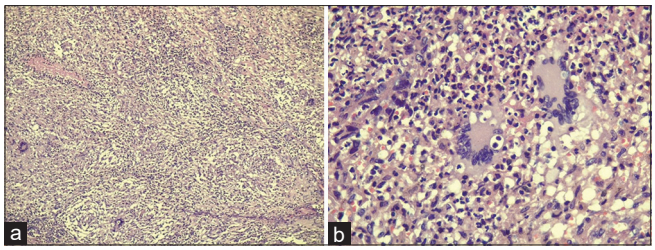

Figure 5: (a) Deciduitis and chronic endometritis with central caseation necrosis, (b) Chronic granulomatous and multinucleated giant cell formation (Langhans type)

to the World Health Organization's Global Tuberculosis Report 2023, the Philippines is among the 30 high TB burden countries, contributing 7% of the world's TB cases in 2022 and accounting for 87% of cases globally when combined with the other high-burden nations.[3] The TB incidence in the Philippines stands at 500 cases per 100,000 population, placing it among the countries with the highest TB burden worldwide.[4]

In the Philippines, individuals aged 15 years and older are considered presumptive TB cases if they present with a cough lasting at least 2 weeks or any of the following symptoms: significant and unintentional weight loss, unexplained fever, night sweats, chest pain not referable to musculoskeletal causes, hemoptysis, or easy fatigability. A CXR showing findings suggestive of pulmonary TB, even in the absence of symptoms, also qualifies an individual as a presumptive TB case and warrants further evaluation. Based on the National Tuberculosis Control Program Manual of Procedures published in 2020, the primary diagnostic test for both pulmonary and extrapulmonary TB is the Xpert® MTB/Rif, a WHO-endorsed rapid diagnostic test, preferred for its high sensitivity and specificity. If Xpert is not available, alternatives such as direct sputum smear microscopy or Tuberculosis Loop-Mediated Isothermal Amplification (TB-LAMP) may be used [Figure 6].[5] For patients with negative bacteriologic results or those unable to produce sputum, the diagnosis may be based on clinical and radiographic assessment. In the case presented, although the patient's febrile episodes, cough, and night sweats had not yet met the duration threshold of 2 weeks, the performance of a CXR – which revealed miliary spread – prompted immediate bacteriologic confirmation using GeneXpert, which subsequently confirmed the diagnosis of TB.

MTb can spread lymphohematogenously, resulting in the disseminated type of TB known as "miliary TB."[2] TB most often affects the lungs but its widespread dissemination via hematogenous route, also known as miliary TB, is possible, although rare. Currently, there are no available data regarding the incidence of disseminated TB internationally and locally. In nations with high TB incidence, there has been evidence of an elevated risk of active TB during pregnancy and the postpartum period.[6]

Miliary TB frequently manifests clinically as fever, dyspnea, cough, headache, stomach pain, and chest pain.[7] The index patient eventually presented with an acute onset of fever and cough during the second trimester. Miliary TB is uncommon during pregnancy and the postpartum phase. Its nonspecific clinical presentation, which includes symptoms such as tachypnea and tiredness, is frequently associated with pregnancy itself, making it more likely for unsuspecting healthcare professionals to ignore the condition and make early identification and treatment more challenging.[1] In this case, the patient initially presented with vaginal bleeding due to threatened abortion which is not a common manifestation of TB. The hallmark symptoms of TB which include night sweats, cough, and fever only occurred on the 6th hospital day. The acute presentation of the symptoms in this patient cannot explain the disseminated form of TB which tend to be more chronic in nature, allowing for the spread of foci. However, pregnant women may be more susceptible to the development of symptoms of TB since the agent can enter the bloodstream through increased microvascular permeability, leading to miliary TB, which typically manifests in the second trimester. The increased levels of chorionic gonadotropin, estrogen, and progesterone during pregnancy are primarily responsible for the pathogenesis of pregnant women's high susceptibility to TB.[8]

The diagnosis of TB is made using sputum culture and (acid-fast bacillus) AFB, sputum for GeneXpert, and the presence of a diffuse miliary mottling on a CXR or high-resolution computed tomography (CT) scan. While CT and CXRs are valuable diagnostic tools for miliary TB, some doctors may not be considering their use at this time due to concerns about the prudent use of ionizing radiation, especially in pregnancy.[2]

Numerous variables, such as the disease's severity, the stage of the pregnancy at the time of diagnosis, and the existence of extrapulmonary dissemination, might influence the outcome of TB in pregnancy. A higher incidence of spontaneous miscarriage, intrauterine growth restriction, inadequate weight gain throughout pregnancy, premature labor, and higher infant mortality have all been reported in these women.[9] This was also evident in this case given the malevolent stage of TB that the mother is currently in, it can be deduced that this condition has been present already even before pregnancy, and an earlier treatment of the condition could have prevented the dismal outcome of this pregnancy. The Centers for Disease Control and Prevention supports this finding as they advocate that people who are diagnosed with active TB disease during

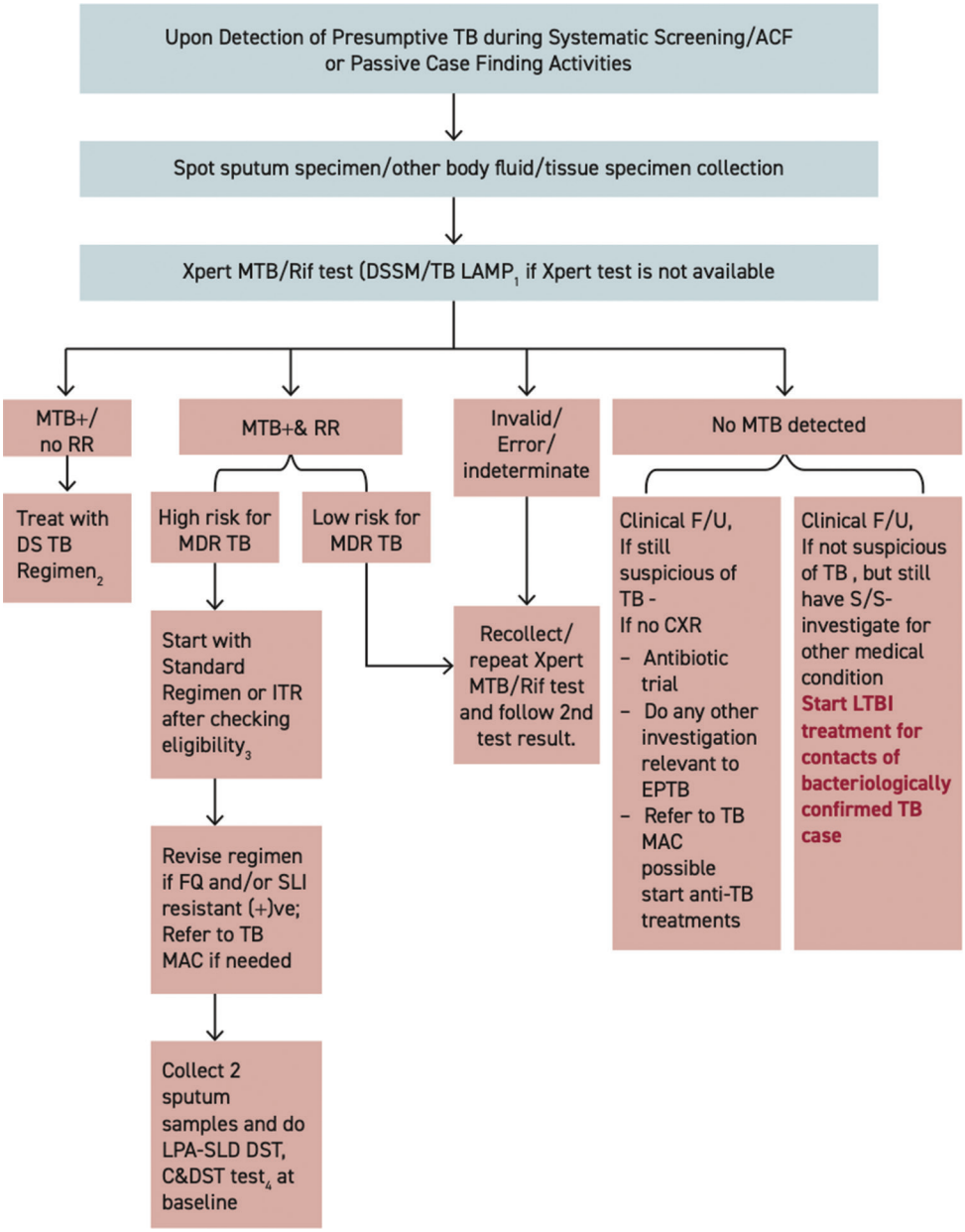

Figure 6: National Tuberculosis Control Program algorithm. TB: Tuberculosis, DSSM: Direct sputum smear microscopy, TB-LAMP: Loop-mediated isothermal amplification, DS-TB: Drug-susceptible tuberculosis, MDR-TB: Multidrug-resistant tuberculosis, ITR: Individualized treatment regimen, CXR: Chest X-ray, EPTB: Extrapulmonary tuberculosis, TB-MAC: Tuberculosis-*Mycobacterium avium* complex, FQ: fluoroquinolones, SLI: Second Line Injectable LPA-SLD DST: Line Probe Assay-Second Line Drug Susceptibility Test, C and DST: Culture and Drug Susceptibility Test, LTBI: Latent Tuberculosis Infection, ACF: Active Case Finding, RR: Rifampicin Resistant

pregnancy should start treatment right away.[9] Based on the National Tuberculosis Control Program Manual of Procedures from 2023, the successful treatment of TB with the recommended standardized treatment regimen is important for a successful outcome of pregnancy. Pregnant women taking isoniazid should be given pyridoxine (Vitamin B6) at 25 mg/day.[7]

Although the fetus is rarely affected, tuberculous bacillemia can infect the placenta. Maternal TB affecting the vaginal tract or placenta can cause congenital TB, an uncommon consequence of TB infection in gestation. The hematogenous transfer of TB bacilli from the infected placenta to the fetal liver and lungs through the umbilical vein can result in a congenital transmission of TB in an untreated mother. Aspiration or ingestion of contaminated amniotic fluid during pregnancy or before delivery canal entry is a less frequent cause of congenital TB and can result in primary complexes in the lungs and gastrointestinal tract.[9] Approximately half of the cases are found in each route. Neonatal TB presents with fever, lymphadenopathy, respiratory distress, and hepatosplenomegaly, mimicking other congenital illnesses.[4] Complications from TB may be prevented in both the mother and the fetus with an early diagnosis and appropriate treatment.[2] If the mother is

treated for her active illness before delivery, or if her sputum culture is negative, the likelihood of a neonatal infection is low.[4]

All diagnosed drug-susceptible TB cases shall be provided with appropriate anti-TB treatment within 5 working days from collection of sputum.[5] TB is treated with a multidrug antibiotic regimen consisting of isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E). The patient was started on HRZE at 19 weeks of gestation, within 3 days of diagnosis of miliary TB.

While it is not rare to find TB granulomas on routine endometrial histopathologic examination, especially in regions wherein TB is already endemic, its presence is consistent with systemic dissemination of the disease, and it supports current data regarding the severity of the disease burden in the Philippines. Genital TB may contribute to tubal blockage and eventual infertility in patients inflicted with the disease. It damages genital organs, which results in abnormal menstruation and infertility. Cases of genital TB including the fallopian tubes, and endometrium totally render patients infertile. Surgery in the form of abscess drainage via the laparoscopic route may be necessary in more severe cases. However, even after receiving multimodal therapy for TB, infertile women with genital TB have low conception rates and a significant risk of complications such as ectopic pregnancy and pregnancy loss.[10] In this multigravida patient wherein prior fertility is presumed, the occurrence of a disseminated TB may have occurred only during the present pregnancy or through the previously mentioned susceptibility and subsequent pathogenesis of TB in pregnancy.

Conclusion

The difficulty in the diagnosis of TB in pregnancy leads to delays in its treatment and subsequent harmful effects on the outcomes of pregnancy. The burden rests on the healthcare professionals having a high index of suspicion to bridge the gap between diagnosis and prompt treatment in pregnancies affected by TB.

The disease severity, the stage of the pregnancy at the time of diagnosis, and the existence of extrapulmonary dissemination might influence the outcome of TB in pregnancy. In this case, should early identification of pulmonary TB and prompt treatment have been employed, a much more favorable outcome could have been achieved, instead of resulting in a miscarriage.

Given the global political support for TB elimination, it should be a collective goal of Filipino healthcare workers to make the Philippines prepared and strengthened in the fight against TB.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Authorship contributions

Dr. Jiane Queliza F. Francia - Involved in the conceptualization, resources, writing of the original draft, visualization.

Dr. Mariel S. Nevado-Gammad - Involved in the conceptualization, review and editing of the draft, and supervision.

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Conflicts of interest

There are no conflicts of interest.

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