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Dual Burden of MDR-TB and COVID-19 in a Previously Treated Tuberculosis Case: Diagnostic and Therapeutic Dilemmas

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ABSTRACT

The presence of both MDR-TB and COVID-19 complicates diagnosis and treatment, as their symptoms can overlap, resulting in possible delays in receiving the appropriate care. This study aimed to investigate whether COVID-19 plays a role in the initiation or progression of latent or current tuberculosis (TB) infection, especially MDR-TB, through immunosuppression or lung injury. On May 19, 2022, a retired black African 40-year-old woman was admitted to the emergency room. She had a history of persistent cough, fever, muscle weakness, and weight loss. Reverse transcription polymerase chain reaction (RT-PCR) confirmed the presence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), indicating a positive COVID-19 diagnosis. GeneXpert MTB/RIF identified *Mycobacterium tuberculosis* (Mtb) and detected rifampicin resistance, confirming MDR-TB. An oral daily antituberculosis regimen consisting of 4 months of kanamycin 1220 mg, moxifloxacin 800 mg, prothionamide 750 mg, clofazimine 100 mg, pyrazinamide 1200 mg, high-dose isoniazid (HH) 600 mg, ethambutol 1200 mg, and for 5 months moxifloxacin 800 mg, clofazimine 100 mg, pyrazinamide 1200 mg, and ethambutol 1200 mg. She received ≈5000 IU of low-molecular-weight heparin (80 IU/kg for her 61 kg body weight) every 12 h to prevent prothrombotic episodes.

1 | Introduction

Mycobacterium tuberculosis strains that are resistant to at least two of the most potent anti-TB medications, isoniazid (INH) and rifampicin (RIF), cause multidrug-resistant tuberculosis (MDR-TB) [1]. MDR-TB therapy presents serious public health issues because it is complicated, expensive, and time-consuming [2]. The coronavirus disease 2019 (COVID-19) pandemic has made controlling tuberculosis (TB) more difficult, which may increase the incidence of MDR-TB because of a number of direct and indirect reasons [3]. The two most common infectious diseases that cause death right now are TB and COVID-19 [4]. COVID-19 pandemic exposed significant health disparities, particularly with regard to diseases that are directly linked to socioeconomic circumstances [5]. The determinants linked to MDR-TB include age, sex, educational level, behavioral (addiction, smoking, and alcoholism), clinical (HIV), prior treatment history, type of resistance, accessibility to health services, reduction in social protection policies, and social contexts of poverty [6].

GeneXpert and culture are essential methods for the diagnosis of MDR-TB. GeneXpert provides rare results, whereas culture confirms the diagnosis with susceptibility profiles [7]. Second-line anti-TB medications, such as bedaquiline, linezolid, delamanid,

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Summary

- The co-occurrence of multidrug-resistant tuberculosis (MDR-TB) and corona virus disease 2019 (COVID-19) in patients with a history of treated tuberculosis presents significant diagnostic challenges.
- It also complicates treatment, making disease management more difficult.
- Overlapping symptoms, such as cough, fever, and difficulty breathing, can hinder prompt and accurate diagnosis, leading to delays in initiating appropriate therapy.
- Tailored and integrated treatment plans are essential to address the dual burden of MDR-TB and COVID-19, to promote treatment adherence, and to reduce the risk of adverse outcomes.

clofazimine, levofloxacin or moxifloxacin, amikacin or kanamycin, cyclomerize or terizidone, and ethionamide or prothionamide, are commonly used to treat MDR-TB for 18–24 months [8]. This study illustrates how COVID-19 contributed to the development of MDR-TB in individuals with a preexisting TB diagnosis.

2 | What This Study Adds

This study examined the use of imaging modalities, such as chest X-ray, for coinfection diagnosis and diagnostic techniques, such as GeneXpert for MDR-TB confirmation in conjunction with RT-PCR for SARS-CoV-2. This emphasizes the importance of integrated care strategies for addressing delays in diagnosis and guaranteeing that TB treatment continues during the pandemic. This highlights the significance of differential diagnosis and identifies overlapping symptoms, such as cough, fever, or weariness, which make diagnosis more difficult.

3 | Case/Examination

On May 19, 2022, a 40-year-old HIV-negative retired Black African woman with a history of prolonged cough, fever, and muscle weakness was admitted to the emergency room. She had neither been vaccinated nor previously contracted COVID-19. She was familiar with recent travel and explained that she had visited her family's house without wearing a face mask, using public transit. She presented with low-grade fever, cough, lethargy, a further 25-pound (11.34 kg) weight loss, progressive night sweats, and new-onset dyspnea on the fourth day.

She was unaware of any medical or pharmaceutical history in her family. She had pulmonary TB seven years ago and had previously received first-line antituberculosis medication, which included two months of intensive phase treatment with rifampicin (R) 300 mg, isoniazid (H) 600 mg, pyrazinamide (Z) 1600 mg, and ethambutol (E) 1100 mg, followed by four months of continuous phase treatment with rifampicin 225 mg and isoniazid 450 mg. She consistently adhered to her antitubercular treatment plan and fully recovered from TB four years ago.

She lived in an overcrowded environment with poor living conditions. Her home lacked proper ventilation, further exacerbating her exposure to airborne TB bacteria. Additionally, she resided in an area with high levels of air pollution, which may have compromised her lung function, making her more susceptible to TB recurrence. Furthermore, her living environment had a cold and humid climate, creating favorable conditions for the survival and transmission of Mtb, contributing to the persistence of the disease.

Her vital signs indicated a blood pressure of 124/79 mmHg, a heart rate of 116 beats per minute, a body temperature of 38.3°C, a respiratory rate of 18 breaths per minute, and an oxygen saturation ($Sp0_2$) of 89% on room air. Her weight and height were 61 kg and 1.59 m, respectively.

4 | Differential Diagnosis, Investigations, and Treatment

Her blood count showed 11,950 cells/mm^3 white blood cells and 14% lymphocytes. Creatinine was 0.9 mg/dL, blood urea nitrogen 11 mg/dL, a hemoglobin concentration of 15.3 g/dL, hematocrit of 37%, and fasting blood sugar level of 149 mg/dL with glycosylated hemoglobin (HbA1c) of 5.1%. The metabolic panel measured alanine aminotransferase at 91 U/L and aspartate aminotransferase at 84 U/L. In this case of MDR-TB, sputum microscopy using Ziehl-Neelsen staining detected acid-fast bacilli (AFB), confirming active TB, including MDR-TB, within 24 h. The GeneXpert assay (Xpert MTB/RIF, Cepheid, USA) identified Mtb within 48 h, indicating potential rifampicin resistance and establishing MDR-TB. Drug susceptibility testing (DST) using liquid culture revealed high-level resistance to isoniazid and rifampicin within 22 days. RT-PCR confirmed SARS-CoV-2 infection, verifying a positive COVID-19 diagnosis in 24 h. For TB culture, the Mycobacteria Growth Indicator Tube (MGIT) 960 system (Becton Dickinson, USA) utilized Middlebrook 7H9 liquid medium and detected bacterial growth through a fluorescence-based technique. In DST, the MGIT 960 system (liquid culture) assessed bacterial growth in drug-containing tubes compared to drug-free control tubes.

Active TB was confirmed through a positive sputum microscopy result, and treatment was initiated immediately. A second-line MDR-TB regimen was prescribed on the basis of the GeneXpert MTB/RIF assay's detection of rifampicin resistance. Subsequent DST confirmed resistance to both isoniazid and rifampicin, guiding the selection of appropriate second-line drugs. The determination of susceptibility to second-line tuberculosis drugs (SL-DST) could not be conducted because there was not enough viable bacterial culture grown using the MGIT 960 system (a liquid culture method) to perform the necessary phenotypic testing for drug susceptibility. She was considered at high risk for MDR-TB due to a prior TB diagnosis. Therefore, an empirical MDR-TB regimen was initiated while awaiting confirmation of culture results. According

to WHO guidelines prior to 2020, she took moxifloxacin 800 mg, prothionamide 750 mg, clofazimine 100 mg, pyrazinamide 1200 mg, ethambutol 1200 mg, and high-dose isoniazid 600 mg, all once daily. Once the culture results became available, her regimen was adjusted accordingly.

In COVID-19, chest x-ray showed a peripheral distribution, predominantly in the lower lobes. These may be accompanied by interlobular septal thickening, indicative of organizing pneumonia or acute respiratory distress syndrome (ARDS). The chest X-ray for TB revealed an enlarged hilar lymph nodes, opacification in the lung tissue, and a broad mediastinum because of enlarged mediastinal lymph nodes. Additionally, there is evidence of miliary mottling in the lung tissue, cavitation, and effusion in both the pleural and pericardial spaces. She was diagnosed with MDR-TB (pulmonary) and a COVID-19.

She started receiving 1000 mL of fluid resuscitation (0.9% normal saline) in the intensive care unit of a hospital. She was administered 4 L of oxygen per minute through a nasal cannula to correct moderate hypoxemia ($Sp0_2$ of 89%). After three hours, her oxygen saturation increased to 95%, which falls within the normal range. The oral daily antituberculosis regimen consists of 4 months of kanamycin 1220 mg (20 mg/kg × 61 kg), moxifloxacin 800 mg, prothionamide 750 mg, clofazimine 100 mg, pyrazinamide 1200 mg, high-dose isoniazid (HH) 600 mg, and ethambutol 1200 mg. For the next 5 months, the regimen includes moxifloxacin 800 mg, clofazimine 100 mg, pyrazinamide 1200 mg, and ethambutol 1200 mg. She received ≈5000 IU of low-molecular-weight heparin (80 IU/kg for her 61 kg body weight) every 12 h to prevent prothrombotic episodes. To prevent secondary bacterial infection, 1 g of ceftriaxone was administered intravenously every day for three days. To reduce the fever caused by COVID-19, 500 mg of acetaminophen was administered as needed.

5 | Outcomes and Follow-Up

For both infections, lung function and treatment response were regularly evaluated. The problems related to COVID-19 and the side effects of TB drugs were carefully monitored. The SARS-CoV-2 PCR test returned negative results after three weeks. Plans for outpatient care were made to ensure adherence to treatment and to closely monitor for reinfection or relapse. She also had two consecutive negative sputum acid-fast bacilli smear tests for TB after two months. She continued to attend the TB clinic for monthly follow-up sessions.

6 | Discussion

Globally, the COVID-19 pandemic has had a major impact on TB care, causing delays in its surveillance, diagnosis, and treatment. Recognizing the coexistence of both infection and comprehending the possible overlap in symptoms, diagnostic difficulties, and laboratory results is essential for diagnosing MDR-TB caused or aggravated by COVID-19 [9]. Patients with respiratory symptoms and MDR-TB risk factors should be prioritized for GeneXpert MTB/RIF or other molecular TB tests. In all suspected COVID-19 cases, especially in areas where TB is endemic, PCR is used for SARS-CoV-2. Chest imaging was used to identify the unique and overlapping patterns. Drug resistance testing was performed to verify MDR-TB. The symptoms of COVID-19 and MDR-TB may overlap, making diagnosis difficult [10].

Typical signs include chronic cough, fever, exhaustion, dyspnea, or weight loss (which is particularly severe in TB), which are overlapping symptoms of TB and COVID-19. Hemoptysis is one of the distinguishing characteristics of TB. COVID-19 is more likely to cause anosmia and an acute onset of symptoms [11]. Headaches, night sweats, shortness of breath, weak muscles, fever, productive cough, and sore throat were some of the patient's symptoms in this study. In addition, there was a lack of appetite. She displayed clinical symptoms of both TB and COVID-19, including fever, coughing, shortness of breath, and weak muscles.

Patients with TB who contract COVID-19 are more likely to experience negative outcomes because underlying pulmonary infection is linked to higher mortality in individuals with COVID-19 [12]. In this study, fluid was found to significantly affect the patient's lungs because of leakage from the small blood vessels in the lungs, which reduces the ability of the patient's lungs to absorb oxygen and causes dyspnea, coughing, and shortness of breath. She experienced moderate COVID-19 symptoms. The SARS-CoV-2 pandemic, which has spread alarmingly, shares numerous similarities with TB, an older and considerably more neglected airborne disease. In addition to having a higher risk of contracting SARS-CoV-2, patients with TB are more likely to experience negative effects from infection [13, 14].

In comparing this case report on the dual burden of MDR-TB and COVID-19 with previously published literature, it becomes evident that coinfection poses significant challenges in clinical management and outcomes. Similar to other studies, this case report highlights the risk of severe respiratory complications and prolonged SARS-CoV-2 positivity in patients with underlying MDR-TB. These findings align with existing literature, which indicates a higher likelihood of adverse outcomes in patients with dual infection (Table 1).

HIV significantly contributes to the reactivation of TB by impairing immune function, whereas diabetes promotes the transition from latent TB infection to active disease by modulating the expression of resuscitation-promoting factors RpfB and RpfD, which are involved in reviving dormant mycobacteria [19]. COVID-19 can exacerbate TB progression by disrupting immune function, potentially triggering the reactivation of latent TB or hastening the development of active disease. On the other hand, TB can heighten the risk of severe COVID-19 because of persistent inflammation and a compromised immune system [20]. The COVID-19 pandemic has severely affected TB diagnosis and treatment, leading to significant diagnostic delays. These delays have been linked to reduced hospital admissions and more severe clinical presentations when patients were eventually diagnosed [21]. The development or exacerbation of MDR-TB is linked to COVID-19 through a complicated web of pathophysiological processes [22, 23]. COVID-19 does not directly induce MDR-TB. Based on the case presented, it is not possible to establish the temporal sequence between COVID-19 and MDR-TB. Without knowing which condition came first, it is difficult to establish a direct causal relationship. A person

TABLE 1 | The comparison between previously published studies and the findings of this manuscript.

Case number	Author (years)	Patient demographics	Comorbidities and previous TB history	Main diagnosis	Key findings
Findings from some earlier published literature (review) studies					
1	Sinaga BYM., et al. 2022	60-year-old HIV-negative Indonesian man	Diabetes mellitus (7 years) and had previous TB history	COVID-19, and pulmonary MDR-TB	The case highlights the challenges of diagnosing and treating such coinfections in resource-limited settings, emphasizing the need for integrated healthcare strategies and increased clinical awareness to address these issues effectively [15]
2	Yadav S., et al. 2021	26-year-old HIV-negative Indian female	None reported and had no previous TB history	Primary multidrug-resistant pulmonary TB with COVID-19	The report emphasizes the importance of healthcare providers recognizing concurrent infections during the pandemic and recommends integrated treatment approaches for effective management [16]
3	Vilbrun SC., et al. 2020	26-year-old HIV-negative Haitian man	None reported and had previous MDR-TB history	Pulmonary MDR-TB and COVID-19	The report emphasizes the need for a multidisciplinary approach and personalized treatment strategies to effectively manage coinfections and address the challenges faced by patients with multiple concurrent diseases [17]
4	Hassan-Moosa R., et al. 2023	(31-year-old man, 37-year-old woman, and 24-year-old woman) unemployed from Kwa-Zulu Natal, South Africa	HIV infection and had previous TB history	Pulmonary MDR-TB and COVID-19	The case demonstrates that regular SARS-CoV-2 screening for MDR-TB patients experiencing new or worsening respiratory symptoms is essential for early detection and effective management [18]
Finding of this manuscript					

(Continues)

TABLE 1 | (Continued)

Case number	Author (years)	Patient demographics	Comorbidities and previous TB history	Main diagnosis	Key findings
1	Bereda G., 2025	40-year-old HIV-negative retired Black African	None reported and had previous TB history	Pulmonary MDR-TB and COVID-19	This case illustrates the difficulties posed by the coexistence of MDR-TB and COVID-19, emphasizing the necessity for customized and integrated treatment strategies to effectively manage both conditions, enhance treatment adherence, and mitigate adverse outcomes

with latent TB may develop active TB over time, and if they later contract COVID-19, it could complicate TB management but not cause MDR-TB. Additionally, the mere coexistence of COVID-19 and MDR-TB in a patient does not imply causality. Various factors, such as preexisting conditions, immune status, and the timing of infection, must be considered, as the co-occurrence could be coincidental or related to common risk factors, such as weakened immunity [24].

However, COVID-19 may impact the development or progression of MDR-TB through the following mechanisms (Figure 1): Dysregulation of the immune system and COVID-19: Cytokine storm is a major immunological dysregulation driven by COVID-19, which is induced by SARS-CoV-2. Overproduction of proinflammatory cytokines such as TNF-α and IL-6 causes immunological fatigue and hyperinflammation [25]. SARS-CoV-2 reduces the body's capacity to regulate latent Mtb infection by depleting $CD4^+$ and $CD8^+$ T cells. The capacity of the immune system to contain Mtb is affected by impaired macrophage function, which may result in reactivation or advancement of latent TB [26].

TB infection worsens: Latent Mtb can become active in an environment that is conducive to immunological suppression caused by COVID-19. The risk of MDR-TB may increase because of COVID-19-induced lung damage (fibrosis, consolidation, etc.), which may hinder the delivery of TB medications to infected tissues. Through a number of pathways, COVID-19 may indirectly aid in the development of MDR-TB [27]. COVID-19-related limits, healthcare access restrictions, and isolation measures may result in poor treatment adherence, which increases the risk of resistance. Antimicrobial resistance, especially MDR-TB, may be exacerbated by the widespread administration of broad-spectrum antibiotics for suspected bacterial coinfections during COVID-19 [28].

Lung pathology and coinfection: SARS-CoV-2 infection results in fibrosis, vascular injury, and alveolar destruction, which intensifies TB pathology. Coinfection with Mtb and COVID-19 causes increased bacterial load and synergistic inflammation, making illness management more difficult [29].

In the above figure, the main cause of MDR-TB includes COVID-19, which can disrupt the immune system, particularly through a cytokine storm, triggering an excessive immune response that can worsen preexisting TB infection [26]. This inflammatory response weakens the immune system's ability to control TB, potentially leading to the reactivation of latent TB or the exacerbation of existing TB. Severe COVID-19 cases often result in lymphopenia, a reduction in lymphocytes, which impairs the body's ability to fight TB infection and may contribute to the development of MDR-TB, particularly in individuals already infected with resistant strains [28]. Additionally, COVID-19-induced macrophage dysfunction can impair the immune system's ability to control TB, complicating treatment and promoting bacterial resistance. The pandemic has also led to inappropriate antibiotic use, contributing to antimicrobial resistance and potentially suboptimal TB treatment. COVID-19-related lung damage and the increased risk of coinfection can further compromise the immune response and facilitate the spread of TB, worsening the disease [27]. The combination of these factors can lead to poorer outcomes and an increased risk of developing MDR-TB in coinfected individuals [29].

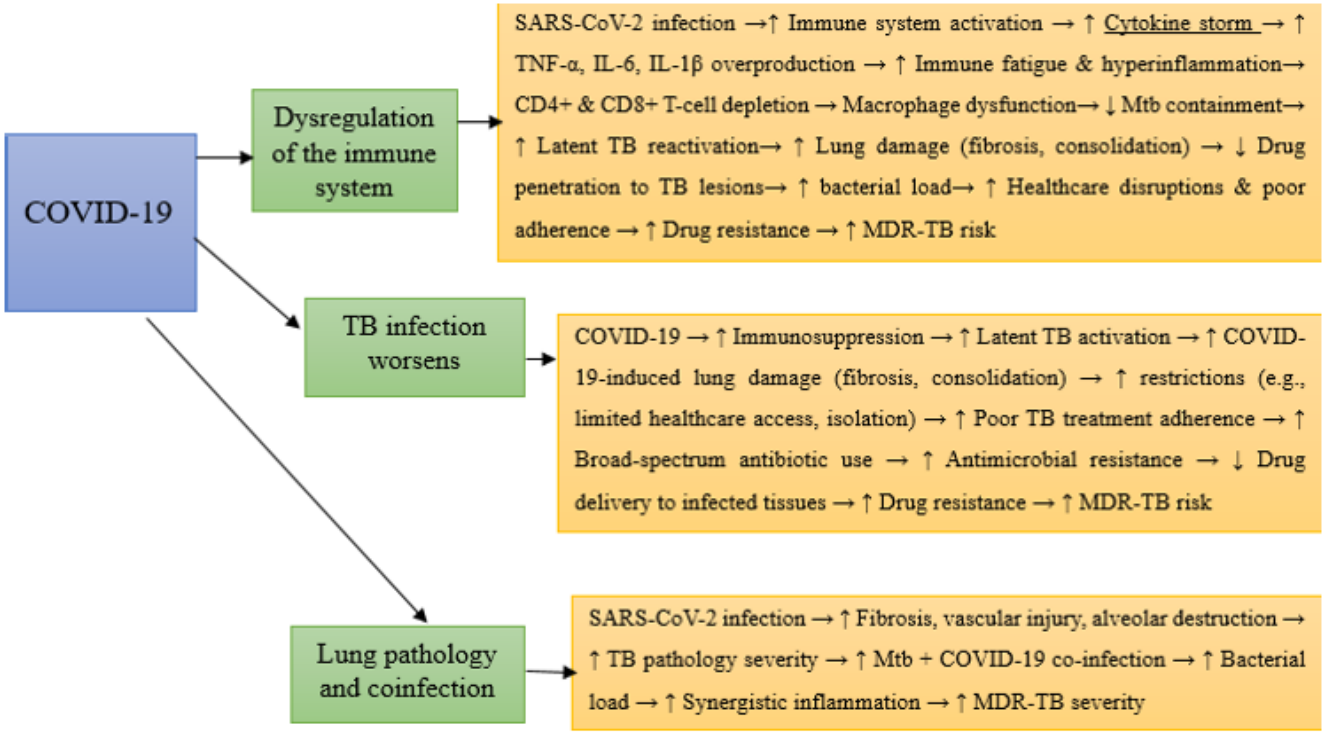

FIGURE 1 | In Figure 1, the arrow symbols (→) indicate processes that are worsened by COVID-19, ultimately leading to the progression and aggravation of multidrug-resistant tuberculosis (MDR-TB).

The speed of TB onset and progression differs the most in the early stages. The symptoms of TB, when they manifest, typically have a more gradual onset and proceed over a period of weeks or months [30, 31]. Treating patients with both MDR-TB and COVID-19 is complicated and requires a multidisciplinary approach. Drugs for MDR-TB might interfere with COVID-19 therapies; thus, careful management and monitoring are required [32]. The treatment of MDR-TB includes 9-month standardized regimen of 4 months of intensive phase kanamycin, moxifloxacin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid (HH), and ethambutol, and for 5 months moxifloxacin, clofazimine, pyrazinamide, and ethambutol. The intensive phase may be prolonged up to 6 months, if the patient remains smear-positive after four months of treatment [33]. Given the complexity of treating both conditions, managing MDR-TB and COVID-19 together requires close monitoring of drug interactions, side effects, and treatment efficacy. Drug interactions example, rifampicin may reduce the effectiveness of paxlovid (due to enzyme interactions). Paxlovid (nirmatrelvir/ritonavir) contains ritonavir, which strongly inhibits CYP3A, affecting the metabolism of second-line MDR-TB drugs such as bedaquiline, fluoroquinolones, clofazimine, and linezolid. This increases the risk of QT prolongation, myelosuppression, and neurotoxicity. Significant screening, management, and infection control problems are presented by COVID-19 and MDR-TB [34].

7 | Strengths and Limitations of the Study

This case presentation draws attention to a complicated coinfection that may help clinicians in circumstances like COVID-19 and MDR-TB. It discusses diagnostic difficulties such as overlapping symptoms like fever, cough, or exhaustion and makes a distinction between COVID-19 complications, active TB recurrence, and MDR-TB progression. It clarifies the dual burden of COVID-19 and MDR-TB, which can help guide policies for integrated surveillance and care during pandemics. The results may not apply to larger populations with coinfection of MDR-TB and COVID-19 because they are based on a single case. Assessing the longevity of therapy success might be challenging if the patient's long-term outcomes are not well investigated.

8 | Conclusion

The coexistence of MDR-TB and COVID-19 causes significant diagnostic and therapeutic challenges because of overlapping clinical symptoms, such as cough, fever, and fatigue, which make early detection and accurate diagnosis more difficult. Additionally, the dual burden may worsen disease severity, compromise immune response, and increase the risk of poor outcomes. A multidisciplinary approach is necessary for effective management, including timely diagnosis, careful treatment selection to avoid drug interactions, and adherence to infection control measures to prevent further transmission and reduce mortality.

Author Contributions

Gudisa Bereda: conceptualization, investigation, validation, visualization, writing – original draft, writing – review and editing.

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The author has nothing to report.

Ethics Statement

The author has nothing to report.

Consent

A written informed consent was obtained from the patient to publish her information. The patient's private information remained confidential with the researcher.

Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

The author has nothing to report.

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