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NAVIGATING A COMPLEX CASE OF *MYCOBACTERIUM XENOPI* IN A PATIENT WITH BLUE RUBBER BLEB NEVUS SYNDROME

Muhammad Umer Riaz Gondal[1], Luke Rovenstine[2], Fawwad Ansari[3], Zainab Kiyani[4], Devi Parvathy Jyothi Ramachandran Nair[1], Toqeer Khan[5], Anthony Donato[1]

[1] Department of Internal Medicine, Tower Health, Reading Hospital, West Reading, USA
[2] Department of Internal Medicine, Drexel University, West Reading, USA
[3] Department of Internal Medicine, Piedmont Athens Regional, Athens, USA
[4] Department of Internal Medicine, Islamabad Medical and Dental College, Islamabad, Pakistan
[5] Department of Internal Medicine, Lincoln Medical Center, New York, USA

Corresponding author: Muhammad Umer Riaz Gondal **e-mail:** umer_rz@hotmail.com

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ABSTRACT

Introduction: Blue rubber bleb nevus syndrome is a rare disorder of venous malformations, with around 200 cases reported. We present a case of *Mycobacterium xenopi* infection in a patient with blue rubber bleb nevus syndrome.

Case Description: A 40-year-old female with blue rubber bleb nevus syndrome, asthma, and bronchiectasis came to the pulmonology clinic with shortness of breath and a cough. She was recently admitted for a bronchiectasis exacerbation but continued to have a worsening productive cough and fevers. The most recent CT scan of the chest showed interval stable right upper lobe fibrocavitary disease, demonstrating gradual progression over two years. She had occasional positive cultures for *Mycobacterium Avium Complex* and *M. xenopi* one year previously, assumed to be a colonizer and not treated. Most recent hospital cultures were negative for bacteria and an acid-fast bacilli smear. She was sent to the emergency department for bronchiectasis exacerbation and returned to the clinic six weeks later with two sputum cultures growing *M. xenopi*. It was decided to treat *M. xenopi* as this was likely the cause of her cavitary lung lesion and frequent infections. Azithromycin, rifampin, and sulfamethoxazole/trimethoprim were initiated. Intravenous amikacin was added later on. She finally had a right partial lung resection done after one year at an outside hospital. She was on and off antibiotics for *M. xenopi* for approximately three years with negative repeat cultures for non-tuberculous mycobacteria.

Conclusion: Due to the high mortality of *M. xenopi* infections (which can be as high as 69%), treatment of at least twelve months is recommended. To our knowledge, this is the first reported case of *M. xenopi* in a patient with blue rubber bleb nevus syndrome.

KEYWORDS

Blue rubber bleb nevus syndrome, *Mycobacterium xenopi*, bronchiectasis

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LEARNING POINTS

- The decision to initiate treatment for non-tuberculous mycobacterium infections is often challenging with prolonged treatment.
- Lifetime monitoring is required in patients with blue rubber bleb nevus syndrome, which can have pulmonary complications.
- *M. xenopi* has the highest mortality among non-tuberculous mycobacterium infections and requires at least 12 months of treatment.

INTRODUCTION

Mycobacterium xenopi is often a commensal organism associated with the highest mortality among pulmonary nontuberculous mycobacterial infections. The risk of infection is higher in immunocompromised patients, particularly with structural lung disease. Blue rubber bleb nevus syndrome is a rare disorder of venous malformations, with around 200 cases reported[1]. It frequently involves multiple organs, including the lungs. We present a case of *M. xenopi* infection in a patient with blue rubber bleb syndrome. The decision to initiate treatment for infections is often challenging.

CASE DESCRIPTION

A 40-year-old female with a history of blue rubber bleb nevus syndrome, asthma, and bronchiectasis presented to the pulmonology clinic in respiratory discomfort. Of note, her blue rubber bleb nevus syndrome case is uniquely severe. As a 3-month-old, she underwent surgery for a giant neck hemangioma, and a hemidiaphragm complicated her postoperative course. As a child, she received small bowel resections for severe gastrointestinal bleeds and, later in life, a hysterectomy for menorrhagia resistant to therapy. She had venous malformations appearing in her skin, small intestine, liver, pancreas, spleen, joints, paraspinal muscles, and neck. Her neck hemangioma was significant, causing recurring obstruction of her trachea and requiring multiple surgical interventions. She was hospitalized on several occasions for blue rubber bleb nevus syndrome complications, received many regimens of antibiotics and blood transfusions, and underwent various therapeutic procedures and operations. Magnetic Resonance Imaging (MRI) imaging in 2004 was documented to exhibit multiple haemangiomas of the chest wall, diaphragm, and lungs, and computed tomography (CT) scans in 2007 showed right apical scarring with cystic changes.

She was seen in our pulmonology clinic and had concomitant chronic asthma and bronchiectasis. She had been experiencing two weeks of shortness of breath and a cough. She was recently admitted for a bronchiectasis exacerbation, treated with cefepime, and discharged on cefpodoxime, but continued to have a worsening productive cough. An indwelling peripheral line for intravenous antibiotics was not placed because of her vascular malformations; she had also been having low-grade fevers to (37.8°C). She was using ipratropium, fluticasone, and albuterol inhalers regularly with guaifenesin. Physical examination revealed diffuse rhonchi and wheezing. Her most recent chest CT scan showed interval stable right upper lobe fibro cavitary disease, demonstrating gradual progression over two years, as seen in *Fig. 1*.

She had had occasional positive cultures for *M. avium complex* and *M. xenopi* one year previously, assumed to be a coloniser and not treated. Most recent hospital cultures were negative for bacteria and acid-fast bacilli (AFB) smear, with negative antifungal and unremarkable immunoglobulin

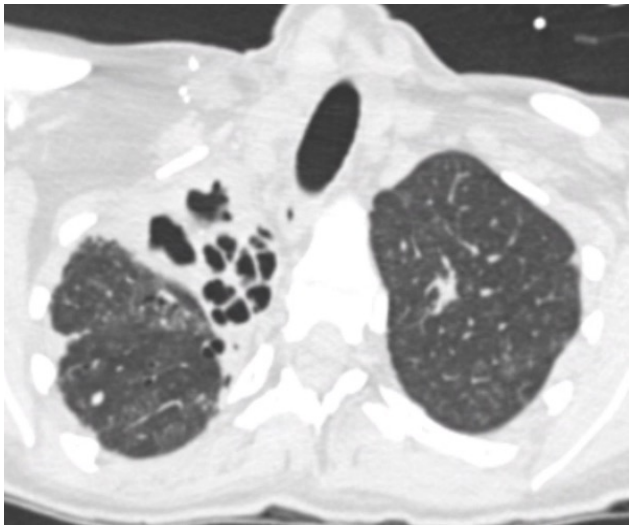

Figure 1. CT chest showing interval stable right upper lobe fibro-cavitary disease.

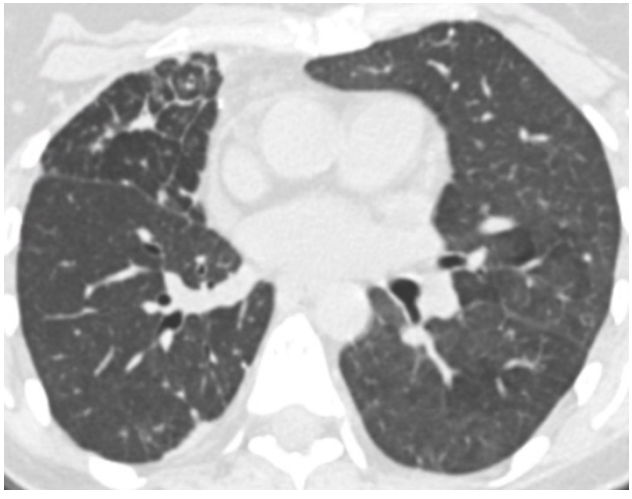

Figure 2. A CT scan of the chest shows reticulonodular opacities in the right upper lobe, linear opacity in the para mediastinal upper right lung, probable sutures, and evidence of partial right pneumonectomy.

testing. Most recent pulmonary function testing revealed severe respiratory impairment with a decrease in forced expiratory volume in one second (FEV1) of 0.83 l (30%) and a forced vital capacity (FVC) of 0.99 (30%), with an FEV1/FVC ratio of 83%. A decision was made to send the patient to the emergency department for a bronchiectasis exacerbation, intravenous antibiotics, and systemic steroids. Sputum cultures were obtained with a negative AFB smear. The patient returned to the pulmonology clinic six weeks later as she had two sputum cultures growing *M. xenopi*. It was decided to treat *M. xenopi* as this was likely the cause of her cavitary lung lesion and frequent respiratory infections. She had allergies to doxycycline and all fluoroquinolones and was therefore started on azithromycin, rifampin, and sulfamethoxazole/trimethoprim. She also did not tolerate sulfamethoxazole/trimethoprim, and intravenous amikacin was added in its stead, with rifampin replaced with rifabutin. In the interim, she had episodes of haemoptysis and was referred to cardiothoracic surgery for a right upper lobectomy. After months of coordination between various specialties, she finally had a right partial lung resection done after one year at an outside hospital, with her amikacin switched to nebulisation *(Fig. 2)*.

She was on and off antibiotics for *M. xenopi* for approximately three years with various interruptions due to complications with negative repeat cultures for non-tuberculous mycobacteria.

DISCUSSION

Blue rubber bleb nevus syndrome, or bean syndrome, is a rare and severe condition caused by multifocal cutaneous and pathognomonic internal venous malformations in various organs. Blue rubber bleb nevus syndrome is nominally rare, only appearing in 200 reported cases throughout the literature[1]. The pathophysiology of this disease results from double-activating mutations in the TIE2 endothelial cell tyrosine kinase receptor, a crucial and multifactorial component of orchestrating the migration of epithelial cells, formation of tubes, stability of new tubes, and destabilisation of old vessels. Therefore, constitutive active TIE2 leads to profoundly dysregulated angiogenesis[2,3]. This mutation has primarily been found to be due to sporadic mutations on chromosome 9p, but some cases have exhibited an autosomal dominant pattern[2]. From an epidemiological standpoint, Caucasians are more affected, and there is no preference for affecting one gender over the other[1]. Lesions present as tender, large, tortuous, dilated vessels 5 mm up to 5 cm in diameter and notably more swollen in gravity-dependent areas, and hyperhidrosis may also occur over the skin lesions[1]. In early childhood, these lesions will present as blue to purple soft nodules on the skin or mucosal surfaces, and their quantity and size will increase over their lifetime, often leading to disfigurement[3]. As individuals age, venous malformations develop in the gastrointestinal tract. Rarely does the disease involve the liver, lungs, heart, eyes, bladder, and parotid glands, and symptoms depend on the lesions' location and size. The reported number of cases in which venous malformations impacted the lungs is exceedingly rare. These malformations have been reported to mainly involve endobronchial involvement and bilateral and pulmonary vascular malformations[4-6]. The changes may consequently destroy the lung parenchyma and lead to bronchiectasis.

In this study, the patient had a rare conglomerate of conditions, including hemidiaphragm, asthma on inhaled corticosteroids, multiple hospitalisations for blue rubber bleb nevus syndrome management, and numerous antibiotic regimens leading to immunosuppressed states. Therefore, the blue rubber bleb nevus syndrome cannot be ruled out as a likely cause of her bronchiectasis, thus creating a nidus for opportunistic *M. xenopi* infection. Therefore, this may be a rare example of blue rubber bleb nevus syndrome manifesting in the lungs, leading to *M. xenopi* infection as a severe complication.

M. xenopi is a thermophile bacterium growing in optimal conditions at 42–45°C and is slow-growing and resistant to common disinfectants. It is commonly found in hot water systems and hospitals, leading to nosocomial infections or pseudo infections, contaminating equipment such as bronchoscopes and specimens. Unfortunately, the differentiation between an actual infection and a contamination is challenging and must be determined clinically after ruling out other disease aetiologies. *M. xenopi* is the second leading cause of non-tuberculous mycobacterium lung disease in Canada, the United Kingdom, and other regions of Europe; however, it is rarely isolated in the United States[7]. This particular non-tuberculous mycobacterium is opportunistic, developing in immunocompromised individuals or those with lung diseases such as chronic obstructive pulmonary disease or bronchiectasis. Beyond lung infection, *M. xenopi* can manifest in the joints and soft tissues. On radiographic imaging, apical cavitary lesions are observed on chest X-rays. A definitive diagnosis can be made by culturing sputum, bronchoalveolar lavage, or pulmonary biopsies showing AFB; however, the predicament of *M. xenopi*'s growth resulting from contamination is highly relevant in the United States.

Treatment guidelines for *M. xenopi* infection, established by the Journal of Clinical Infectious Diseases in 2020[8], state that initial treatment can be one of two regimens: 1) moxifloxacin or macrolide, 2) a combination of rifampin, ethambutol and either a macrolide or fluoroquinolone. If severe disease is apparent, parenteral amikacin should be added, and the patient must be referred to an infectious disease specialist. Treatment for *M. xenopi* should continue for 12 months past the culture conversion to negative. Regardless of the potential risks of treatment, the benefit of preventing recurrent *M. xenopi* infection is far more significant[8]. Our patient received azithromycin, rifampin, and trimethoprim/sulfamethoxazole (TMP-SMX) initially, and given the severe disease, intravenous amikacin was added.

CONCLUSION

Non-tuberculous mycobacterium pulmonary disease is diagnosed by nodular or cavitary opacities on chest imaging with positive cultures from at least two separate sputum samples according to guidelines, such as in our case. Due to the high mortality of *M. xenopi* infections (which can be as high as 69%), treatment of at least twelve months is recommended. Given the rarity of blue rubber bleb nevus syndrome and the various complications associated with the syndrome, a multidisciplinary team approach with multiple specialties is needed to manage these patients. To our knowledge, this is the first case reported of *M. xenopi* in a patient with blue rubber bleb nevus syndrome.

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