IDCases 22 (2020) e00999

Contents lists available at ScienceDirect

IDCases

journal homepage: www.elsevier.com/locate/idcr

Mycobacterium malmoense: an unusual pathogen causing endocarditis, a case report and literature review

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ARTICLE INFO

Article history:
Received 25 August 2020
Received in revised form 21 October 2020
Accepted 22 October 2020

Keywords:
Endocarditis
Mycobacteria
Infectious diseases
Case report
Rheumatologic diseases

ABSTRACT

Non-tuberculous mycobacterias (NTM) are important pathogens responsible for a broad spectrum of diseases in humans. Although exposure is widespread since they are distributed in the environment, the development of the disease is rare. It will depend on the specific species, their virulence (only 50 have been found to cause disease), and the host's immune response. M Mycobacterium Malmoense is a NTM first reported in 1977 at Malmö, Sweden, based on four cases of lung infections. After these, other infections have been reported mainly involving the respiratory tract. Extrapulmonary infections are limited to cervical adenitis, and rarely to tenosynovitis and disseminated disease. We are hence reporting, to our knowledge, the first case of M. malmoense as the cause of bacterial endocarditis in the world.

Case report

A 61-year-old patient with a 5-year history of dermatomyositis and rheumatoid arthritis of 3 years onset, in management with methotrexate, chloroquine, and prednisolone, replacement of mitral valve with biological prosthesis due to stenosis secondary to rheumatic valve disease (7 years before admission) and left hepatic lobectomy due to haemangioma (three years before admission) presented to the emergency department with generalized myalgia and sporadic fever episodes up to 39 °C associated with chills. Physical examination revealed vital signs in the normal range: heart rate: 75 BPM, respiratory rate: 18, the temperature of 36 °C, and blood pressure of 120/70 mmHg. The rest of the physical examination was unaltered. The initial laboratory tests were normal, normal CPK, leukocytes: 5600 / μL, neutrophils: 1900 /μ L, lymphocytes: 2070 /μ L, PCR: 0.5 mg / dL.

As part of the febrile syndrome approach that the patient referred to, and given the history of valvular prosthesis and immunosuppression, a transesophageal echocardiogram was performed to rule out the presence of endocarditis. It reported: "bioprosthesis in mitral position with thickening of its veils and slight alteration in mobility, and multiple highly mobile echodense images between 2 and 5 mm in diameter adhered to the atrial aspect suggestive of vegetations". Blood cultures resulted negative.

Taking the modified Duke criteria as a guide, the patient presented 1 (one) major imaging criteria, and 2 (two) minor criteria (fever and risk factor), which is why possible endocarditis was considered. Because he had initial negative cultures and a history of immunosuppression, suspicion of atypical germs arose, which is why an immunodiffusion test was initially indicated for Histoplasma and cultures for fungi/mycobacteria (which are reported on average 14–15 days after taking it); PET-CT was also shown and which was negative for presence of hypermetabolic foci suggestive of neoplastic and/or another infectious process, without hypermetabolism in mitral valve.

During the time that the patient remained hospitalized, there was no increase in acute phase reactants, even though febrile peaks rise to 38.7 °C. He persisted with negative blood cultures and no other symptoms associated with endocarditis, so the possibility of a diagnosis of non-bacterial thrombotic endocarditis due to autoimmune pathology was considered. A new echocardiogram was then taken that reported no variations concerning the first

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https://doi.org/10.1016/j.idcr.2020.e00999

one. Immunosuppressive therapy with rituximab was initiated, with which the patient presented a significant clinical improvement without febrile peaks. The patient was discharged.

Four days after the patient's discharge, the blood cultures for mycobacteria were reported as positive for resistant acid-alcohol bacilli, so the patient was located and re-admitted to the emergency department, the patient was asymptomatic at the moment.

The diagnosis of mycobacterial endocarditis was made while typification of the specific microorganism was still in process. Antibiotic treatment was started with Clarithromycin (500 mg every 12 h), Moxifloxacin (400 mg every day), Rifampicin (900 mg every day), and Amikacin (1 g intravenously every day). - in a compatible scheme for the management of slow-growing NTM. The patient was seen by cardiovascular surgery who consider it pertinent to perform valve replacement; the surgery was carried out without complications, and a biological valve was implanted.

The mitral biological valve was taken to pathology where Ziehl-Neelson and hematoxylin eosin stain was performed, and acid-alcohol-resistant bacilli were reported (Images 1 and 2); subsequent culture was positive for Mycobacterium malmoense, so the same antibiotic scheme was maintained. Following control of blood cultures were negative. The patient was discharged two weeks later due to the good clinical evolution. He received antimicrobial treatment for six months with adequate response and finally attained criteria for the cured disease. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Discussion

NTM are important pathogens that can cause a broad spectrum of diseases, which will depend on the interaction between the specific mycobacteria and the host's immune system. [1]. NTM infections have been reported since the 1930s, and 50 species are currently considered etiological agents responsible for causing disease [2]. The NTM is found in soil, in environmental water, drinking water, and in aerosols. The reservoir in animals has been considered less important, although species have been isolated in animals such as birds, fish, and some amphibians. Although contact with mycobacteria is quite frequent, developing a disease is difficult because of the low virulence of these pathogens [1]. In our patient, the infection occurred because he was immunosuppressed with steroids and methotrexate, among other medications, given his underlying pathologies.

The most common risk factors for developing mycobacterial infections include medical procedures and surgical maneuvers (central venous accesses, prosthetic materials, hemodialysis, particularly in patients with acquired immunodeficiency syndrome (AIDS), patients with COPD, malignant hematological neoplasia or immunosuppressant treatments and, more recently, the use of tumor necrosis factor-α inhibitors [2,3]. In our case, the patient also had a biological valve.

Diseases caused by NTM are usually divided into six different groups: lung diseases; lymphadenitis; dermatological and soft tissue diseases; bone, joint and tendon infections; foreign body infections and central venous catheter; and infection by disseminated NTM [1]. Endocarditis due to these types of microorganisms is quite infrequent, and cases are rarely reported; however, an association with foreign bodies has been described, for example, prosthetic valves. The most common etiology being M. fortuitum and M. chelonae; cases of M. gordonae have also been reported [4,5]. To our knowledge, there are nine reported cases of endocarditis caused by *Mycobacterium fortuitum* in medical literature, of which seven are associated with prosthetic valves [5]. M. malmoense, the isolated species in our patient has not been reported so far as a cause of bacterial endocarditis.

M. malmoense was reported for the first time as a pathogenic species by Schroder and Juhlin based on four cases of lung infections in Malmö, Sweden, in 1977, for which the microorganism receives its name [6,7]. Subsequently, in 1979, 11 cases were described in England and Wales, 9 of which were responsible for lung disease and 2 for cervical adenitis; the latter, described in female pediatric patients. So far, 61 strains of M. malmoense had been isolated [8].

In 1984, the first case of *Mycobacterium malmoense* was reported in the United States. This was a 43-year-old man from Virginia, from whom the organism was isolated from sputum and bronchoalveolar lavage [9]. In 1987, France et al. studied cases of pulmonary infections due to M. malmoense reported in Scotland between 1982–1984. They found 20 cases, most of them associated with chronic lung diseases such as COPD; also, with a prevalence twice as high in men as in women [10].

By 1993 there were more than 180 reported cases of M. malmoense in the world, of which only 5 were causative of disseminated infection [11]. Between 1967–1992, 15 reports of extrapulmonary and disseminated infections were published describing 21 cases [11]. Of the 21 cases, five were disseminated infections, 13 lymphadenitis, more frequently cervical, and 3 were tenosynovitis [11].

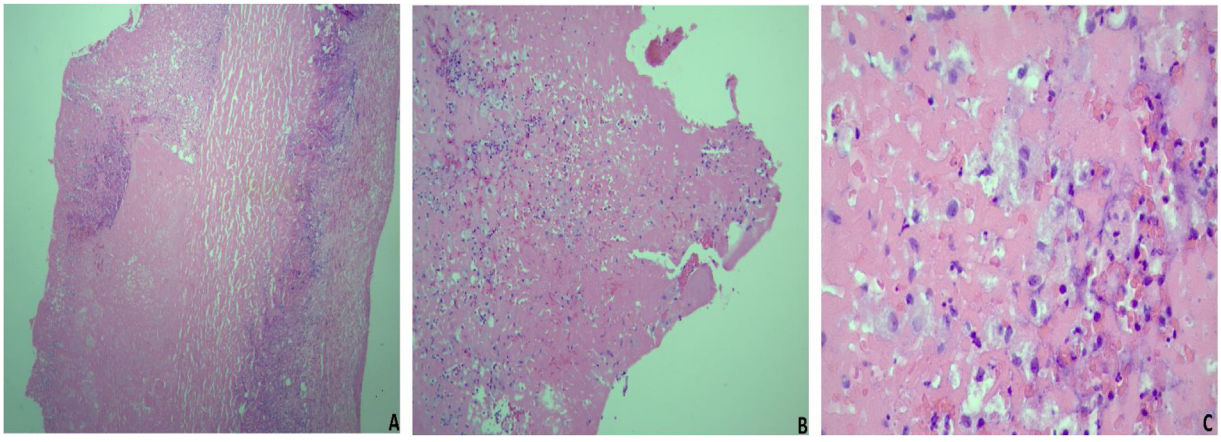

Image 1. Microphotography on hematoxylin eosin(H&E) stain (A,B,C). In the H&E staining (A. 4X; B. 10X, C. 40X), connective fibrous tissue is identified with some areas of calcification. There is a presence of necrosis with inflammatory cells of polymorphonuclear neutrophil type. Histocytes are observed.

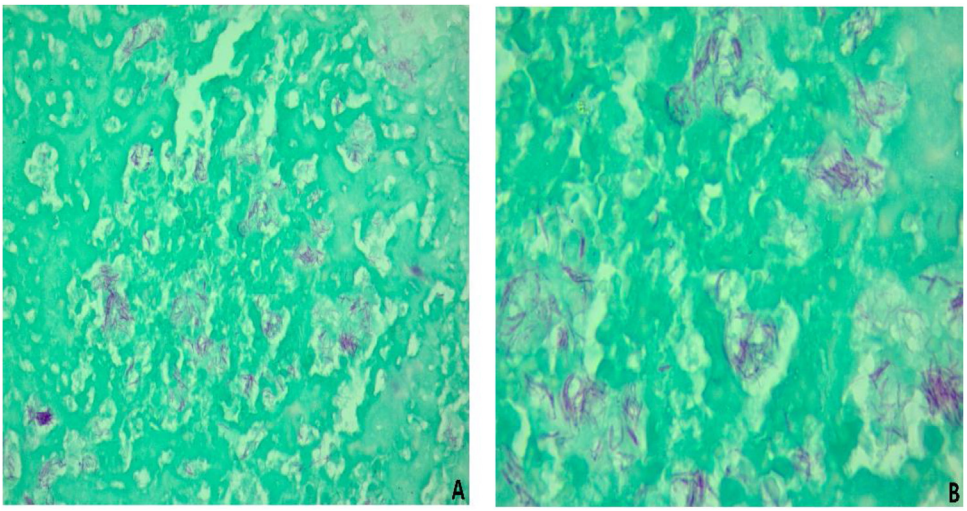

Image 2. Microphotography on Ziehl-Neelsen (Z&N) stain (A,B). (A. 40X; B. 100X).In the N&Z staining aggregates of elongated formations, representing acid-alcohol-resistant bacilli are identified. Some of them undulated within the histocytes without granuloma formation.

In 1994 Henriques et al. collected global reports from 1968 to 1989, where 221 patients were identified, of which 171 (79 %) had respiratory tract infection, 36 of cervical lymphadenitis, and 14 had other infections [12].

In the United States, 73 cases of M. malmoense were reported to the CDC during the years 1993–1995; however, when Buchholz et al. evaluated 60 of these patients, only 6 had disease according to the American Chest Society criteria. Of these, 5 had lung disease, and 1 had cervical lymphadenitis [13].

In 2009, a retrospective study was published that analyzed cases in the Netherlands from 2002 to 2006, where 51 patients were identified, of which 40 (70 %) had lung involvement. Of these cases, 80 % met the American Society of Chest criteria [14].

This way, reports in the medical literature regarding M. malmoense are limited mainly to pulmonary infections. Extrapulmonary infections are limited to lymphadenitis and rarely tenosynovitis. This would be the first reported case of M. malmoense as the cause of bacterial endocarditis in the world.

Endocarditis due to mycobacteria is a rare but dangerous pathology. Its etiology is generally related to non-tuberculous mycobacteria rather than tuberculous mycobacterium [4]. Rapidly growing mycobacteria (M. chelonae, M. abscessus, and M. fortuitum) are the main pathogens since they represent 68 % of the cultures isolated from mycobacteria, with M. chelonae being the most common; this is why antibiotics such as amikacin, ciprofloxacin, and clarithromycin are used. However, these bacteria have shown resistance to these drugs, and that is why they are associated with high mortality. Only two of the nine reported cases of endocarditis due to M. fortuitum have survived [5] (15). Fortunately, the prognosis of this disease has improved thanks to the molecular techniques of rapid identification of strains, high doses of antibiotics, and multidrug therapies guided by a profile of susceptibility to drugs and surgical interventions. (15)

A review of mycobacterial endocarditis that analyzed data from 2000 to 2013 found that the positivity of the cultures varied according to the affected valves. For example, cultures were positive in 75 % of mechanical valves, 20 % in biological valves, and 100 % in native valves. The removed valvular prostheses showed a high positivity in cultures of mycobacteria [15]. Due to the difficult identification of microorganisms, after the growth of colonies, gram stain and Zhiel Neelsen stain for acid-fast bacilli should be performed. Then, if and when the blood cultures are negative, Zhiel Neelsen staining and histological examination of the removed prosthetic valve should be performed, followed by subcultures [15].

With respect to treatment, the best agent to treat non-tuberculous mycobacteria is amikacin and other alternatives such as ciprofloxacin, clarithromycin, imipenem, and linezolid. Clarithromycin has proven to be a good agent against M. abscessus / chelonae. Moxifloxacin is the best to treat M. fortuitum and is very active against M. chelonae when used alone and more effective against all strains when used in combination with clarithromycin and amikacin. It has also been proven that the use of clarithromycin with moxifloxacin or linezolid at high concentrations (16 μg/mL) has good activity against M. abscessus [15].

It is important to bear in mind that patients who have deep infections of rapidly growing NTM often justify a surgical intervention such as extraction of prosthetic material, this has been associated with a better prognosis [15].

Conclusion

Endocarditis due to mycobacteria is a rare but dangerous pathology. Its etiology is generally related to NTM, especially the fast-growing mycobacteria chelonae, fortuitum, and abscesses. Now that we know that *Mycobacterium malmoense* is a pathogen that can cause bacterial endocarditis, we suggest heightened vigilance for correct isolation of the microorganism in order to establish prudent management that will ensure the best results for the patient.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Iván Posso-Osorio: Conceptualization, Investigation, Methodology, Writing - original draft, Writing - review & editing. **Alejandra De Las Salas:** Conceptualization, Investigation, Methodology, Writing - original draft. **Gabriel J. Tobón:** Conceptualization, Investigation, Supervision, Validation, Writing - review & editing. **Melibea Sierra-Ruiz:** Project administration, Supervision, Validation, Writing - review & editing. **Carlos A. Cañas:**

Conceptualization, Investigation, Supervision, Validation, Writing - review & editing. **Juan Carlos Bravo:** Conceptualization, Investigation, Supervision, Validation, Writing - review & editing. **Pablo A. Moncada:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgments

We thank the Centro de Investigaciones Clínicas (CIC) – Fundación Valle del Lili for their support in this case report.

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