

PRESENTACIÓN DE CASO

Disseminated mycobacteriosis affecting a prosthetic aortic valve: first case of *Mycobacterium peregrinum* type III reported in Colombia

Carlos A. Torres-Duque^{1,2,3}, Claudia Díaz^{1,2,3}, Leslie Vargas^{1,2,3}, Elsa María Serpa⁴, Walter Mosquera⁴, María Consuelo Garzón⁵, Graciela Mejía⁵, Luz Mary García⁵, Liliana Andrea González⁵, Claudia Marcela Castro^{5,6}, Wellman Ribón^{5,7}

¹ Departamentos de Investigación y Médico, Fundación Neumológica Colombiana, Bogotá, D.C., Colombia

² Servicio de Neumología, Fundación Cardioinfantil-Instituto de Cardiología, Bogotá, D.C., Colombia

³ Facultad de Medicina, Universidad de La Sabana, Chía, Colombia

⁴ Fundación Cardiovascular de Colombia, Bucaramanga, Colombia

⁵ Grupo de Micobacterias, Instituto Nacional de Salud, Bogotá, D.C., Colombia

⁶ Laboratorio de Referencia e Investigación en Enfermedades Tropicales, Dirección de Sanidad del Ejército, Bogotá, D.C., Colombia

⁷ Grupo de Inmunología y Epidemiología Molecular, Universidad Industrial de Santander, Bucaramanga, Colombia.

Rapidly growing mycobacteria are non-tuberculous mycobacteria amply present in the environment. Although they are not usually pathogenic for humans, they are opportunistic in that they can cause disease in people with disadvantageous conditions or who are immunocompromised. *Mycobacterium peregrinum*, an opportunistic, rapidly growing mycobacteria, belongs to the *M. fortuitum* group and has been reported as responsible for human cases of mycobacteriosis.

A case of *M. peregrinum* type III is herein reported as the first in Colombia. It presented as a disseminated disease involving a prosthetic aortic valve (endocarditis) in a seventeen-year-old girl with a well-established diagnosis of prosthetic aortic valve endocarditis who was referred for a surgical replacement. Due to a congenital heart disease (subaortic stenosis with valve insufficiency), she had two previous aortic valve implantation surgeries. One year after the second implantation, the patient presented with respiratory symptoms and weight lost indicative of lung tuberculosis.

A chest X-ray did not show parenchymal compromise but several Ziehl-Neelsen stains were positive. An echocardiography showed a vegetation on the prosthetic aortic valve. In blood and sputum samples, *M. peregrinum* type III was identified through culture, biochemical tests and *hsp65* gene molecular analysis (PRA). The patient underwent a valve replacement and received a multidrug antimycobacterial treatment. Progressive recovery ensued and further samples from respiratory tract and blood were negative for mycobacteria.

Key words: *Mycobacterium*, *Mycobacterium peregrinum* infections, aortic valve, endocarditis, Colombia.

Micobacteriosis diseminada con compromiso de válvula aórtica protésica: primer caso de *Mycobacterium peregrinum* de tipo III reportada en Colombia

Las micobacterias de rápido crecimiento son microorganismos pertenecientes a las micobacterias no tuberculosas que tienen amplia distribución ambiental. Aunque usualmente no son patógenas para los humanos, en condiciones desfavorables, pueden causar enfermedad en la población general o en huéspedes inmunocomprometidos, por lo cual se consideran oportunistas. *Mycobacterium peregrinum* es una micobacteria de rápido crecimiento perteneciente al complejo *fortuitum* que ha sido reportado como responsable de casos de micobacteriosis en humanos.

Se presenta el caso de una micobacteriosis por *M. peregrinum* de tipo III, el primero reportado en Colombia, en una paciente de 17 años de edad con una endocarditis de una válvula aórtica protésica, implantada inicialmente por estenosis subaórtica congénita con insuficiencia y, posteriormente, por estenosis aórtica relacionada con la válvula inicialmente implantada. Un año después del segundo implante, presentó síntomas respiratorios y pérdida de peso sugestivos de tuberculosis pulmonar.

Las coloraciones de Ziehl-Neelsen del esputo fueron positivas aunque la radiografía de tórax no mostró compromiso del parénquima. En el ecocardiograma se encontró una vegetación en la válvula aórtica. En las muestras de sangre y de esputo, se identificó *M. peregrinum* de tipo III por cultivo, pruebas bioquímicas y análisis molecular del gen *hsp65* por PCR-restriction pattern analysis (PRA).

La paciente se sometió a cambio de válvula y recibió tratamiento combinado contra la micobacteria, con rápida recuperación. Las muestras tomadas del sistema respiratorio y sanguíneo se tornaron negativas para micobacterias.

Palabras clave: *Mycobacterium*, *Mycobacterium peregrinum*, válvula aórtica protésica, endocarditis, micobacterias de rápido crecimiento, infecciones por *Mycobacterium*, Colombia.

The genus *Mycobacterium* comprises strictly pathogenic, opportunistic (potentially but not usually pathogenic), and non-pathogenic species. Opportunistic mycobacteria are commonly recovered from natural and human-influenced environments and can cause disease in humans and animals, especially birds. These characteristics reference them as environmental opportunistic mycobacteria or non-tuberculous mycobacteria (1,2). Environmental opportunistic mycobacteria include slowly growing mycobacteria (colonies usually visible after seven days, such as the *Mycobacterium avium intracellulare* complex) and rapidly growing mycobacteria (colonies usually visible less than seven days) (1,3).

Rapidly growing mycobacteria are classified in three groups: *M. fortuitum*, *M. chelonae*-*M. abscessus* and *M. smegmatis* (3). In clinical conditions, rapidly growing mycobacteria have been related to skin and soft tissue infections (frequently postsurgical wound infections), pulmonary disease, and colonization of implanted materials such as prosthetics, catheters and sutures; these infections could result in sepsis and disseminated disease (3-7). Clinical cases of environmental opportunistic mycobacteria, including rapidly growing mycobacteria, have been reported in Colombia (8-11).

Mycobacterium peregrinum, a rapidly growing mycobacterium belonging to the *M. fortuitum* group, has been reported as causing opportunistic disease in humans (3,12). Several past cases have had *M. peregrinum* designated as the causative agent as a consequence of the reclassification of microorganisms initially described as *M. fortuitum* (3).

Herein, the first report of mycobacteriosis caused by *M. peregrinum* type III in Colombia is presented and, to the best of our knowledge, the first one affecting a prosthetic cardiac valve.

Correspondencia:

Wellman Ribón, Universidad Industrial de Santander, Carrera 32 N° 29-31, oficina 106, edificio Roberto Serpa, Bucaramanga, Colombia

Teléfono: (057) 634 4000, extensión 3140

wribon@uis.edu.co, wellmanribon@yahoo.es

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Clinical case

A seventeen-year old female patient, born in Arauca (Colombia), was referred to the Fundación Neumológica Colombiana-Fundación Cardioinfantil-Instituto de Cardiología (Bogotá, Colombia) with a diagnosis of prosthetic aortic valve endocarditis. Fifteen years before, the patient had been diagnosed with a persistent ductus arteriosus and a mild perimembranous interventricular communication and 5 years later, with a subaortic stenosis with moderate insufficiency of the aortic valve. These abnormalities were corrected by surgical closure of the ductus and interventricular communication, subaortic ring widening and implantation of a mechanical aortic valve.

Four years later, she began to develop a progressive relative aortic valve stenosis, and at age 14, 12 years after her initial diagnosis, her aortic valve was replaced by a mechanical valve. Two years later, the patient consulted because of persistent cough with hemoptoic sputum. A serial Ziehl-Neelsen (ZN) stain of the sputum was positive and an antituberculosis treatment with isoniazid (H), ethambutol (E) and rifampicin (R) was started. However, since the chest X-ray showed no parenchymal abnormalities and the ZN stain and culture of bronchoalveolar lavage was negative, the antituberculosis treatment was withdrawn. Eleven months later she presented with weakness and cough. A new ZN stain of the sputum was positive, again without parenchymal abnormalities. Antituberculosis treatment was restarted but complicated by a medicamentous hepatitis.

Six months later, the patient consulted because of lower limb pain, purpuric lesions suggesting vasculitis, left eye amaurosis, convulsive crisis, cough, and hemoptoic sputum. She was hospitalized at Fundación Cardiovascular de Colombia in Bucaramanga. An infectious endocarditis of her prosthetic valve was suspected and later confirmed by echocardiography. Direct stains and cultures for common microorganisms in blood, cerebral spinal fluid and sputum samples were negative. Collagen diseases were ruled out. A drug-resistant tuberculosis or non-tuberculous mycobacteria

infection were suspected. A treatment with ciprofloxacin, claritromycin and trimethoprim-sulfamethoxazole was initiated, and due to non-medical reasons, the patient was referred to the Fundación Neumológica Colombiana-Fundación Cardioinfantil-Instituto de Cardiología for a new aortic valve replacement. A clinical diagnosis of infectious endocarditis was evident.

The physical examination showed a patient with deteriorated general condition, tachycardia, cardiac murmur, normal breath sounds, painful edema of the right knee, and purpuric lesions in the legs. No neurological abnormalities were found.

The hemogram showed normocytic normochromic anemia and normal count of white blood cells. Creatinine and transaminases levels were normal. The immunological profile and HIV serology were negative. A serial ZN stain of the sputum and blood cultures for common bacteria were also negative. The chest X-ray showed mild cardiomegaly with a mechanical aortic valve; neither lung abnormalities nor pleural effusions were found. The echocardiogram showed a 5 x 5 mm vegetation on the mechanical aortic valve, paravalvular leak and a saccular image suggesting abscess. The fiberoptic bronchoscopy was normal. The routine stains, including ZN stain, of the bronchoalveolar lavage were negative, but a significant lymphocytosis (81%) was found.

A rapidly growing mycobacteria was isolated in cultures from blood and sputum samples and sent to the Colombian National Institute of Health for phenotypical identification; pigment production was determined, as well as growth speed at 45°C, 37°C, 32°C and 22°C. Enzymatic tests for catalases, nitrates, arylsulphatase, pyrazinamidase, urease, acid phosphatase, tween hydrolysis and niacin detection were performed. Additionally, growth or inhibition capacity was determined in MacConkey medium, 0.2% picric agar and Lowenstein Jensen (LJ) medium for 10 µg/L tifen-carboxylic acid hydrazide (TCH), 250 µg/L hydroxylamine (HA), and 5% sodium chloride; Molecular identification was done through gene *hsp65* restriction analysis (PRA) (13,14), the patterns found for the BstEII enzyme were 240/130/85 and 145/140/100/60 for the HaeIII enzyme, resulting in *M. peregrinum* type III identification in blood and sputum samples.

A disseminated mycobacteriosis with aortic valve endocarditis due to *M. peregrinum* type III was diagnosed.

The treatment was adjusted including amikacin, imipenem, clarithromycin, trimethoprim-sulfamethoxazole, rifampicin, and doxycycline and, a few days after, the patient was undergone to an implantation of a biological aortic valve with replacement of the ascending aorta and coronary re-implantation. Histopathologic findings of the resected material were compatible with mycobacteria infection but ZN stains were negative.

The patient's condition slowly improved and she was finally discharged at the end of 2006. She continued improving but appearing hypoacusia probably due to amikacin which was withdrawn. She completed the antimycobacterial treatment prescribed for twelve months. Subsequent bacteriological tests, during and after the treatment, were negative (follow-up until 2008). During 2008, she required a reintervention related with her previous ascending aortic replacement.

Table 1 shows a summary of the clinical presentation and management of the patient.

Discussion

Rapidly growing mycobacteria are microorganisms belonging to the non-tuberculous mycobacteria amply present in natural (water, soil) or human-influenced environments (3). Rapidly growing mycobacteria are not usually pathogenic for humans but they can cause several type of infections including skin and soft tissue infections, osteomyelitis, lymphadenitis, disseminated disease, meningitis, postsurgical wound infections, infections of prosthetic devices, and chronic lung disease (3-7,15-18). Some cases have been described in Colombia (8,11).

M. peregrinum type III is a rapidly growing mycobacteria belonging to the *M. fortuitum* group (3) which also includes *M. fortuitum*, *M. fortuitum* third variant (19), *M. mucogenicum*, and *M. senegalense*. Although *M. peregrinum* was first proposed in 1962, only in the last years has been systematically included (20-22). Like other rapidly growing mycobacteria, *M. peregrinum* has been reported as causing skin and soft tissue infections, peritonitis (after cancer gastric surgery), primary bacteremia, pneumonia, tonsillar abscess, catheter-related bacteremia, and implantable cardioverter device infection (12,23-27). Recently, Nagao informed 11 cases reported in the literature (12). However, it is possible that some other cases had been misclassified as *M. fortuitum* and previously reported (3).

The presence of foreign artificial material (catheter, implantable devices) or immunocompromising

Table 1. Summary of clinical presentation.

Year	Condition	Intervention
1989	Birth – murmur found	None
1991	Persistent ductus arteriosus Interventricular communication	Surgical PDA closure No IVC closure (small)
1996	Interventricular communication Aortic valve and subaortic stenosis	Surgical IVC closure Mechanical aortic valve implantation
2003	Relative prosthetic aortic valve stenosis	Surgical change of the mechanical aortic valve
2005	Transient respiratory symptoms Positive Ziehl-Neelsen stain of the sputum	Antituberculosis treatment discontinued because of negative bronchoalveolar lavage ZN stain and no parenchymal abnormalities
2006	Endocarditis involving prosthetic valve Positive ZN stain of the sputum Positive cultures for rapidly growing mycobacteria (sputum, blood) <i>M. peregrinum</i> type III identification	Biological aortic valve implantation with ascending aortic replacement Treatment for rapidly growing mycobacteria-18 months
2008	No infectious manifestations Ascending aortic reintervention Slow recovering and rehabilitation process Severe hypoacusia Negative ZN and mycobacteria cultures	Rehabilitation Ascending aortic reintervention Follow-up

PDA: persistent ductus arteriosus; IVC: interventricular communication; ZN: Ziehl-Neelsen

conditions (HIV infection, infliximab treatment) confirm the opportunistic character of *M. peregrinum* and suggest that those conditions favour the adherence, colonization, and posterior progression of the mycobacteria infection.

Non-tuberculous mycobacteria colonization and infection of intracardiac devices such as prosthetic valves, catheters, pacemaker wires or defibrillators have been known for long time (15-18). The presence in water sources and soil favors the colonization and infection of predisposed patients. *M. fortuitum* group may represent 1% to 2% of sporadic community-acquired or health care-associated infections due to rapidly growing mycobacteria (3) and up to 2% of in-hospital opportunistic infections (4).

The *M. fortuitum* group is more sensitive to several drugs than other rapidly growing mycobacteria making the treatment generally effective (3,7,12,28). Some of the effective drugs are: amikacin, imipenem, ciprofloxacin, gatifloxacin, levofloxacin, linezolid, clarithromycin, trimethoprim-sulfamethoxazole, cefoxitin, and doxycycline (3,7,12,28). However, the best treatment for *M. peregrinum* has not been established and significant differences may be expected among the *M. fortuitum* group. For example, in the case reported by Nagao (12) the *M. peregrinum* was resistant to clarithromycin and minocycline. Rapidly growing mycobacteria are

usually resistant to the common antituberculous drugs (isoniazide, for example).

As it has been described for disseminated cases (3), our patient was treated with two injectable drugs: amikacin and imipenem, in addition to clarithromycin, trimethoprim-sulfamethoxazole, rifampicin, and doxycycline.

This is the first case of mycobacteriosis due to *M. peregrinum* type III described in Colombia and the first one reported as resulting in a prosthetic valve endocarditis, accepting that it is possible that some cases previously attributed to *M. fortuitum* may have been caused by *M. peregrinum*.

In our report, the disseminated condition was demonstrated by the isolation of the microorganism in sputum and blood samples. The repeatedly positive ZN stains of the sputum, with lymphocytosis in the bronchoalveolar lavage, and without lung parenchymal abnormalities suggests a colonization and infectious compromise of the upper respiratory tract or the tracheobronchial tree (tracheobronchitis). The conventional treatment for tuberculosis, as expected, was not effective, favoring the subsequent dissemination with colonization and infection of the prosthetic aortic valve (endocarditis due to *M. peregrinum*). Other manifestations such as the purpuric lesions in the legs, arthritis (right knee), amaurosis and convulsive crisis can be attributed to

the endocarditis rather than direct infection due to the mycobacteria. It is difficult to establish the exact moment when the respiratory colonization evolved into a disseminated disease affecting mainly the prosthetic valve (endocarditis).

The persistent presence of positive ZN stain without positive cultures for *M. tuberculosis*, should suggest a diagnosis of microorganism containing mycolic acids in their walls like non-tuberculous mycobacteria, *Corynebacterium*, *Nocardia* and *Rhodococcus* (22).

Non-tuberculous mycobacteria, especially rapidly growing mycobacteria including *M. peregrinum*, should be considered in patients with insidious conditions and chronic use of catheters, prosthetic valves, or implantable devices.

Conflict of interest

None of the authors declare conflicts of interest.

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