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Pulmonary vasculitis due to infection with *Mycobacterium goodii*: A case report

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ABSTRACT

A 57-year-old Caucasian woman suffered from dyspnea on exertion. One year following a supposed pulmonary embolism event, a chronic thromboembolic vasculopathy was diagnosed and a pulmonary thromboendarterectomy was performed. However, a granulomatous pulmonary arterial vasculitis was identified upon examination. DNA of *Mycobacterium goodii* was detected as the most likely causative agent. Anti-inflammatory and anti-mycobacterial therapy was initiated for more than 12 months. Regular PET-CT scans revealed improvement under therapy. The last PET-CT did not show any tracer uptake following 10 months of therapy.

Introduction

Mycobacterium goodii (*M. goodii*) is a rare, rapidly growing and nontuberculous mycobacterium (Brown et al. 1999) and can be found in soil, dust and drinking water (Griffith et al. 2007; Mohajeri et al. 2017). It causes nosocomial infections such as secondary wound infections (Ferguson et al. 2004; Salas and Klein 2017). Nontuberculous mycobacteria (NTM) causing any form of vasculitis are uncommon in literature. There are case reports of small-vessel vasculitis due to NTM infection (Asano et al. 2016; Lee et al. 2016), but an induced large vessel disease has not yet been reported.

Case presentation

A 57-year-old woman with Caucasian ethnicity reported dyspnea and chest pain since June 2016. She had been cleaning up a flooded basement a few weeks earlier. On CT scan in September 2016, pulmonary embolism (PE) was diagnosed and therapy with rivaroxaban was initiated. The only comorbidity at that time was previous hypothyroidism, which had been sufficiently treated for years.

In October 2016, the patient presented to the specialized outpatient clinic for pulmonary hypertension at the Medical Mission Hospital (Würzburg, Germany). Transthoracic echocardiography and lung function testing did not show any abnormal results. Signs of gas exchange disturbance and massive hyperventilation were noticed during cardiopulmonary exercise testing, which were interpreted as part of the recently diagnosed PE. Due to persistent dyspnea, a lung-scintigraphy was performed in April 2017, revealing a ventilation-perfusion mismatch. Pulmonary

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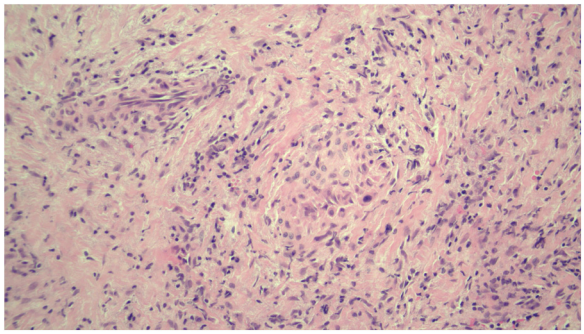

Figure 1. Resectate showing lymphocellular inflammation of the media of the right pulmonary artery with epithelioid granuloma (hematoxylin and eosin stain).

angiography showed several obstructions of the right pulmonary artery. Chronic thromboembolic pulmonary hypertension was diagnosed by right heart catheter, with a pulmonary artery pressure of 22 mmHg, and the patient was admitted for pulmonary thromboendarterectomy (PEA) in September 2017.

The surgical dissection of the right artery during PEA was difficult. The resected tissue appeared atypical compared with usual thrombus material. Histology revealed lymphocellular inflammation of the intima and media of the right pulmonary artery with epithelioid granuloma (Figure 1). Gram and Warthin-Starry stain of the samples did not detect bacteria. The patient had no symptoms of any systemic infection, with negative tests for HIV, *Treponema pallidum*, *Mycobacterium tuberculosis* or other pathogens on serological and microbiological screening of different materials, including blood cultures out of the right pulmonary artery. The laboratory results including auto-antibodies were unspecific (Supplementary Table 1).

Molecular methods were applied for bacterial species identification. DNA was extracted from the tissue samples by using the QiaAmp DNA Mini Kit (Qiagen, Hilden, Germany), and a 510-bp fragment of the ribosomal 16S rDNA was amplified and sequenced. Data were analyzed with the Integrated Database Network System (SmartGene Services, Lausanne, Switzerland; www.smartgene.com). The resulting sequence was assigned to *M. goodii*. Sequence identity to GenBank accession no. Y12872.1 was complete without any mismatches in the sequenced segment of 448 bp. An 18F-FDG-PET-CT in December 2017 showed high tracer activity rates in the thoracic aorta and right pulmonary artery, indicating a localized vasculitis. Due to the DNA detection of *M. goodii* and the exclusion of other differential diagnoses, a pulmonary vasculitis due to *M. goodii* was concluded.

Treatment and follow-up

Combination therapy consisting of prednisolone (0.5 mg/kg body weight), amikacin, doxycycline and moxifloxacin was initiated in July 2018. Due to a moderate deterioration in renal function, amikacin was replaced by cotrimoxazole. Dyspnea improved very slowly during the first months. In December 2018, a PET-CT depicted an unchanged accumulation of the tracer but revealed a decrease in the pulmonary artery wall thickness. Since then, prednisolone therapy was reduced stepwise. In May 2019, another PET-CT did not show any tracer activity in the pulmonary artery (Supplementary Figure 1 for CT sequences). Corticosteroids were tapered down and finally stopped. At that time, the patient was on prednisolone for 10 months and unchanged therapy with cotrimoxazole, moxifloxacin and doxycycline, which was continued for the following 11 months.

Discussion

Mycobacterium goodii is still an uncommon pathogen (Griffith et al. 2007). This is the first published case of a large vessel vasculitis caused by *M. goodii*. *M. goodii* was only proven by PCR. However, the reference standard for mycobacterial infections is still mycobacterial culture (Griffith et al. 2007), which could not be tested in the paraffin-embedded resectate. A contamination of the paraffin-embedded resectate could have been possible but seems unlikely as paraffin was tested negative by DNA sequencing for mycobacteria species. A reoperation to gain native material for cultivation was not performed due to procedural risk, but detection of *M. goodii* by PCR was confirmed by Germany's National Reference Center for mycobacteria (Borstel). Due to the exclusion of other differential diagnoses, it is believed that *M. goodii* might have caused this vasculitis. The underlying pathomechanism of this vasculitis is still unclear. Case reports describing vasculitis in patients with *Mycobacterium tuberculosis* infections can be found in the literature (Walters et al. 2013; Reshkova et al. 2016). A cross-reactivity between mycobacteria and a human heat shock protein (HSP) has been suggested (Aggarwal et al. 1996). A mycobacterial HSP-induced immune response may cross-react with human HSP, which leads to autoimmune reactions and inflammation (Kumar et al. 2004). A similar mechanism may have induced the vasculitis in the current case.

The adequate therapeutic procedure of how to treat a vasculitis associated with mycobacterial infection is unclear. Anti-inflammatory therapy may result in an aggravation of an active mycobacteriosis. In a case report of Takayasu arteritis accompanied by tuberculosis, the exclusive immunosuppressive therapy with steroids did not lead to an improvement in the disease (Duzova et al. 2000). A solely antimycobacterial therapy in a vasculitis with a high inflammatory activity, as in this case, seemed to be insufficient. It was decided to treat the patient with both anti-inflammatory and antimycobacterial drugs.

There are no guidelines for the treatment of NTM associated with vasculitis. However, therapeutic strategies in this case were based on ATS recommendations for NTM lung disease. Combination therapy with amikacin, doxycycline and trimethoprim-sulfamethoxazole is recommended for *M. goodii* (Griffith et al. 2007). The few reported pulmonary infections due to *M. goodii* have recommended therapy with at least two drugs for >12 months (Martinez-Gonzalez et al. 2011; Waldron et al. 2019). *M. goodii* could not be cultivated and a molecular resistance test was not available; therefore, empiric therapy was induced. The necessary treatment duration was unclear. Therapy response measured by culture conversion, as recommended by the guidelines, was not possible in this case (Griffith et al. 2007); therefore, the treatment response was evaluated by 18F-FDG-PET. Tracer uptake in the right pulmonary artery in the first 18F-FDG-PET in December 2017 could have been affected by the PEA, which was performed 3 months before imaging. Nevertheless, the 18F-FDG-PET in June 2018 remained unchanged, so it seems unlikely that the tracer uptake was caused by the previous surgical intervention.

This is the first published case of large vessel disease caused by *M. goodii*. The combination therapy of antimycobacterial and anti-inflammatory drugs was able to induce remission of the inflammatory alterations of the affected pulmonary arteries. 18F-FDG-PET served as the main disease monitoring tool. The antimycobacterial therapy has been continued for more than 18 months. The systemic steroid therapy was gradually reduced during this time. Currently, the patient seems to be in a stable situation without any inflammatory activity.

Conflict of interest

Dr. Pfeuffer-Jovic reports fees for travel/accommodation from Actelion, Boehringer Ingelheim, Novartis and OMT, outside the submitted work. PD Dr. Heyckendorf reports honoraria for independent lectures at symposia sponsored by Chiesi and Astra Zeneca. Prof. Dr. Reischl has nothing to declare. Prof. Dr. Bohle has nothing to declare. Prof. Dr. Bley reports fees from Chugai, GSK, Roche and Novartis and grants from German Research Foundation (DFG) and from Siemens Healthineers, outside the submitted work. Prof. Dr. Buck has nothing to declare. Prof. Dr. Wilkens has received personal fees for lectures and/or advisory board activities from Actelion, Janssen, Bayer Healthcare, Boehringer Ingelheim, GSK, MSD, Pfizer and Roche. Prof. Dr. Schäfer has nothing to declare. Prof. Dr. Langen has nothing to declare. PD Dr. Held reports grants from Actelion, honoraria for lectures from Actelion, Bayer HealthCare, Berlin Chemie, Boehringer Ingelheim, GSK, Novartis, Pfizer, honoraria for advisory board activities from Actelion, Bayer HealthCare, GSK, MSD, and participation in clinical trials of Actelion, Bayer HealthCare, GSK, Pfizer, United Therapeutics, outside the submitted work.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards.

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Contribution: Writing - original draft: Elena Pfeuffer-Jovic, Matthias Held**. Writing - review and editing:** Elena Pfeuffer-Jovic, Matthias Held, Jan Heyckendorf, Udo Reischl, Heinrike Wilkens, Heinz-Jakob Langen, Rainer M. Bohle, Thorsten Bley, Andreas Buck, Hans-Joachim Schäfers. All authors were actively contributing to interpretation of the results and discussion of the findings. They all approved the final version of the manuscript.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2020.12.074.

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