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Case Report
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Disseminated *Rhodococcus* Sp Infection with Central Nervous System Involvement in a Patient with AIDS Case Report and Literature Review

Giomi CV[1]*, Altamiranda CG[2], García JL[1], Benchetrit A[1], Echazarreta SE[1], Corti M[1], Wallach J[1] and Rollet R[1]

[1]*Department of Infectious Diseases, F. J. Muñiz Hospital, Buenos Aires, Argentina*

[2]*Department of Infectious Diseases, Interzonal General Acute Hospital Abraham F. Piñeyro, Argentina*

Abstract

Rhodococcus sp. is a microorganism historically known as a cause of zoonotic diseases. It is an infrequent human pathogen that typically manifests as cavitary pneumonia. However, *Rhododoccus* gene can also produce systemic disease with multi-organic involvement. In the past decades, it has emerged as an opportunistic bacteria affecting predominantly immunocompromised patients. Here, we report a case of an HIV-positive patient who developed a disseminated disease due to *Rhodococcus* sp. with central nervous system involvement.

Keywords: *Rhodococcus*; Cerebral mass lesion; HIV; AIDS

Introduction

Since it was first isolated from a Swedish foal on 1923, *Rhodococcus* sp. (originally named *Corynebacterium equi*) has become a well-known pathogen in veterinary medicine as the causative agent of chronic granulomatous pneumonia and pulmonary abscesses in equines and other animals [1-3]. *Rhodococcus* sp. is a pleomorphic, strictly aerobic, acid-fast variable, Gram-positive coccobacillus. It forms mucoid salmon-pink to red colonies when grown on solid culture media. Unlike pathogenic corynebacteria, it lacks carbohydrate fermentation capabilities. On Gram staining it may resemble contaminant diphtheroids; smears of clinical specimens stained by modified Kinyoun or Ziehl-Neelsen methods may show partial-acid fast bacilli [4]. We describe the clinical case of an HIV-positive patient with disseminated *Rhodococcus* sp. infection with central nervous system (CNS) involvement as multiple brain mass lesions.

Case Presentation

A 44 year-old HIV-positive woman, that not received Highly Active Antiretroviral Therapy (HAART), CD4+ T lymphocyte count of 5 cells/ul (1%) and viral load of 39,383 copies/ml (4.6 log) was admitted in the reference hospital of Infectious Diseases of Buenos Aires city. The patient was diagnosed with pulmonary tuberculosis in 2008 and pneumonia caused by *Rhodococcus sp.* with microbiological isolation in blood, sputum and Bronchoalveolar Lavage (BAL) cultures in 2012 (Figure 1), with irregular treatment compliance. In 2013, a Computerized Tomography (CT) showed space-occupying lesions of the CNS (Figure 2). Empiric treatment for toxoplasmosis with pyrimethamine and sulfadiazine and *Rhodococcus* sp. with ciprofloxacin, imipenem and vancomycin was started, showing a favorable clinical and imaging evolution. The patient was discharged with ciprofloxacin and rifampicin treatment which she continued with poor compliance.

Patient was newly admitted on August 2014 due to febrile syndrome associated to generalized tonic-clonic seizures, sensory impairment, mixed aphasia and right-sided hemiparesis. A brain Magnetic Resonance Imaging (MRI) showed multiple space-occupying lesions located in the left cerebral hemisphere, with peripheral enhancement after the administration of intravenous contrast, perilesional edema and mild mass effect on the midline structures (Figures 3 and 4). Empiric treatment for toxoplasmosis was started wih pyrimethamine and sulfadiazine with adjunctive glucocorticoids, and for CNS involvement due to *Rhodococcus* sp. with meropenem-vancomycin. A CT-guided brain biopsy was performed for diagnosis (Figure 5). Histopathology analysis showed positive Periodic Acid-Schiff stain (PAS) inclusions within macrophages which were morphologically compatible with *Rhodococcus* sp (Figures 6 and 7). Also, a lumbar puncture

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Correspondence:
Giomi CV, Francisco J. Muñiz Hospital, Uspallata 2272, Ciudad Autónoma de Buenos Aires, Argentina, Tel: +54 9 11 4304-5555;
E-mail: cinthia.giomi@hotmail.com

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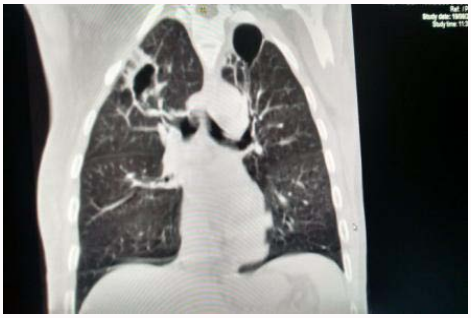

Figure 1: High-resolution thorax CT with evidence of a consolidation with area of cavitation affecting the right upper lobe.

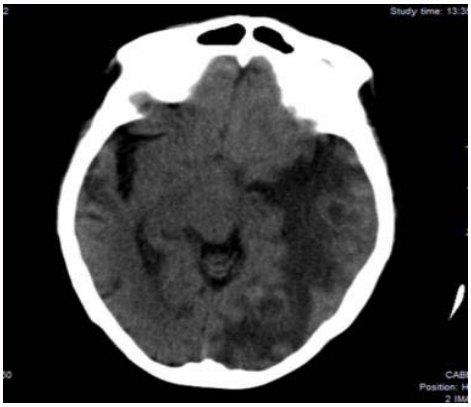

Figure 2: Cerebral CT showing multiple ring-enhancing lesions with perifocal oedema and mass effect on the midline structures in the left hemisphere.

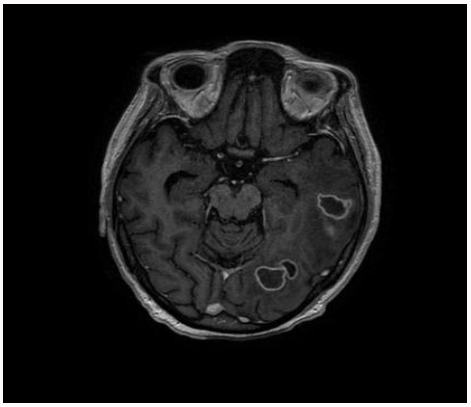

Figure 3: Axial brain MRI with gadolinium showing multiple ring-enhancing cerebral lesions with perifocal oedema and mass effect in the left hemisphere.

was performed and the analysis showed normal Cerebro Spinal Fluid (CSF) physical-chemical characteristics and *Rhocococcus* sp. isolation in culture. Chest CT showed bilateral cavitary lesions. A Fibrobronchoscopy with bronchoalveolar lavage was performed which was positive for the same microorganism. Blood cultures were negatives.

HAART based on emtricitabine, tenofovir, atazanavir and ritonavir was started, and antibiotic therapy was switched to an oral scheme with ciprofloxacin, azithromycin and trimethoprim/sulfamethoxazole with a favorable evolution of the neurologic condition. Nevertheless, the patient continued with irregular follow-up and treatment with the development of new opportunist infections

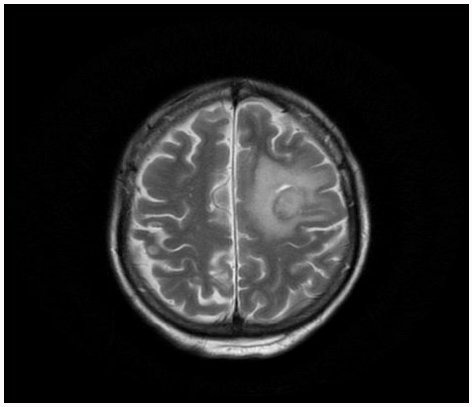

Figure 4: Sagittal view of MRI showing large nodular lesions with ring-enhancing, and perifocal oedema.

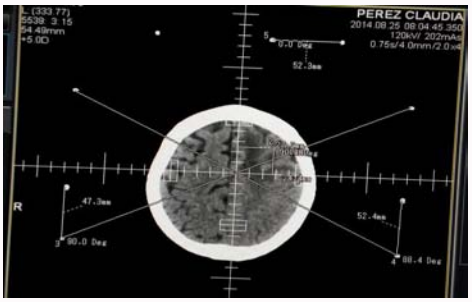

Figure 5: Pre-biopsy brain CT.

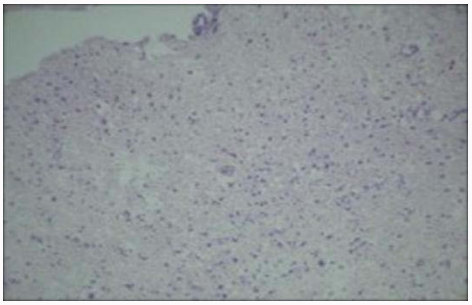

Figure 6: Histopathology of the brain biopsy smears: dense histiocytic infiltrate with abundant granular eosinophilic cytoplasm.

with poor prognosis followed by death in the succeeding months.

Discussion

Rhodococcus sp. is an environmental microorganism with universal presence that is found in soil and water or colonizing the intestinal tract of some omnivores and herbivores [4,5]. It is a facultative intracellular pathogen that infects macrophages and polymorphonuclear cells most commonly affecting patients with altered cell-mediated immunity. The first human infection was reported in 1967 in Minnesota, United States, and only few other were reported until early 1980's [6] when the amount of cases were reported as a result of the spread of Human Immunodeficiency Virus (HIV) infection, new immunosuppressive therapies, organ transplants recipients, and others [7-9]. Although widespread, *Rhodococcus* disease continues to be uncommon, even among patients with advanced HIV infection. A multicentric study that was conducted in Spain since the beginning of the HIV pandemic until

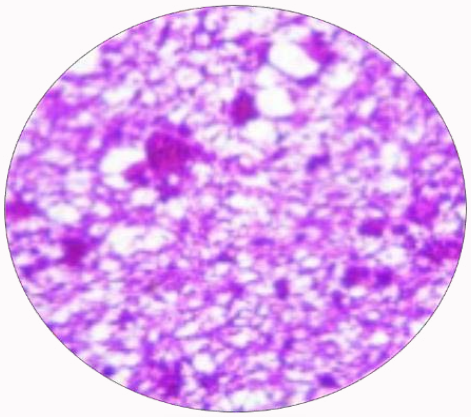

Figure 7: Brain biopsy: infiltrate with abundant polymorphonuclear leukocytes; the periodic acid-Schiff staining procedure reveals highly positive histiocytes. Gram-positive *coccobacilli* were seen in the tissue staining.

1998 that included samples of 19,374 HIV-positive patients showed that only 96 developed *Rhodococcus* sp. as an opportunictic disease, with only a 4.5% involvement of the CNS [10]. Even though the number of cases of *Rhodococcus* sp. infection has increased in the past decades, it remains uncommon. Immunocompromised patients comprise 80% to 90% of the cases and approximately two thirds of the aforementioned presents HIV infection with a low CD4+ T lymphocyte count, as the case that we describe [9,10]. Different studies conducted in Spain and Argentina with HIV-positive population show that *Rhodococcus* sp. disease prevalence is below 2%. However, prevalence of *Rhodococcus* sp. in patients with cavitary pneumonia rises to 7.7%. For this reason, infectologists should consider this complication in the differential diagnosis of patients with cavitary lung lesions [11,12]. The main route of transmission is through inhalation but it may also occur by inoculation into mucosal surfaces or wounds, or by ingestion. Also nosocomial and human transmission have been reported [9,13,14]. The epidemiologic data of exposure to animals potentially infected with *Rhodococcus* sp. should not be overestimated as it is present in only 15% to 58% of HIV-positive patients and 53% of immunocompetent subjects [10,15,16]. Two publications that report cases of HIV-positive patients in our country show an epidemiologic connection in only 8% and 11% of the cases, respectively [12,17]. In HIV-positive population with *Rhodococcus* sp. infection, pulmonary involvement is over 95% with the majority of the cases occurring as pneumonia with no pathognomonic clinical or radiological signs; however, 69% of patients presents with cavitary pneumonia as the initial manifestation of the disease, as in our patient. Other clinical forms include pulmonary abscesses, pleural effusions and empyema. Extrapulmonary involvement reaches 20% of the patients but only 5% of these manifestations correspond to brain abscesses, as in our case. Other extrapulmonary infection sites that should be involvement are skin and soft tissues, pericardium, lymph nodes and osteoarticular system [18]. Local publications show a CNS involvement in only 8% of the patients (1/13) and 22% (4/18), respectively [12,17]. Diagnosis was confirmed only in the first case by isolation of the bacteria from CSF and the diagnosis of the four remaining cases was suspected due to clinical features, imaging and response to treatment [12,17]. Reports show that CNS involvement with space-occupying lesions due to *Rhodococcus* sp. is infrequent in HIV-positive patients with etiology confirmed through stereotactic biopsies or necropsies [19,20,21]. Differential diagnosis should be proposed due to clinical and imaging feature similarities between the infections caused by *Rhodococcus* sp. and *M. tuberculosis*. Da Silva et al. [13] analyzed the sputum of patients with suspected tuberculosis in Brazil and found that 12.6% of the infections corresponded to *Rhodococcus* sp. A study conducted in Uganda showed a 36:1 ratio of a population of HIV-positive patients infected with *M. tuberculosis vs. Rhodococcus* sp. [14]. Due to the high frequency of respiratory involvement, it is no surprise that most of the isolations are obtained from respiratory samples (sputum, bronchoalveolar lavage, thoracentesis, etc.), with blood culture isolates following in frequency. Microbiological diagnosis in patients with CNS involvement is mostly obtained by biopsy smears. CSF isolations are rare and, during the literature review done for this report, only 2 cases were reported [12,18]. Given the low prevalence of the disease, there is no standard of care and current recommendations are based upon reports or series of cases, and no controlled trial for the treatment of this complication has been found. It is suggested to complete a combined antibiotic treatment with two or three drugs in order to prevent the development of resistance and, if possible, drainage of the abscesses [19]. The antibiogram is mandatory due to the variability in sensitivity patterns of *Rhodococcus* sp. and it is recommended to use drugs with a large volume of distribution, activity to intracellular bacteria and a good passage through the brain blood barrier, such as macrolides, rifampicin, tetracyclines and quinolones. Since it is found at a high bacteremia rate, it is suggested to start intravenous therapy and later switch to oral treatment. Treatment duration is not defined and varies according to the etiology of the immunocompromise; at least four months for transplant patients, and up to immune reconstitution and negative cultures for HIV-positive patients [12,19]. Early start of HAART for HIV-positive patients is essential since its absence is an independent variable associated to higher mortality [10]. The attributable mortality rate for the infection by *Rhodococcus* sp. in HIV-positive patients varies from 17.3% to 34.3%, with the absence of HAART being the only factor associated to mortality. A higher number of relapses can be found in the HAART era but it is probably related to a higher survival of HIV-positive patients [10-18]. Unfavorable evolution has been associated to delay in diagnostic and treatment and the absence of HAART [17].

In conclusion, infection by *Rhodococcus* sp. should be included in the differential diagnosis of cavitary pneumonia, mainly in patients with severe cellular immunity compromise. CNS involvement is uncommon but should be considered in patients with a pulmonary infection caused by this pathogen and cerebral mass lesions. If suspected, a thorough laboratory analysis search should be conducted due to Gram or Zielhn Nielsen staining similarities to other microorganisms. Once the infection is confirmed, a combined antibiotic treatment with intracellular effect is suggested which should be initially administered intravenously. We consider the antibiotic sensitivity test to be essential for all isolations in order to guide the therapeutic approach.

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