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[Bozhidar Vergov](#)^{*}, Andreana Angelova, [Yordan Kalchev](#), [Alexandra Baldzhieva](#), [Marianna Murdjeva](#), Georgi Tsochev

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Case Report

Gordonia sputi as an Arising Causative Agent of Bacteremia in Immunocompromised Comorbid Dialysis Patients—A Case Report

Bozhidar Vergov ^{1,2,*}, Andreana Angelova ^{3,4,5}, Alexandra Baldzhieva ^{3,5,6}, Yordan Kalchev ^{3,4,5}, Georgi Tsochev ² and Marianna Murdjeva ^{3,4,5}

¹ Department of Medical Biology, Faculty of Medicine, Medical University of Plovdiv, Plovdiv, Bulgaria

² Department of Dialysis Treatment, St George University Hospital, Plovdiv, Bulgaria

³ Department of Medical Microbiology and Immunology “Prof. Dr. Elissav Yanev”, Faculty of Pharmacy, Medical University of Plovdiv, Plovdiv, Bulgaria

⁴ Laboratory of Microbiology, St George University Hospital, Plovdiv, Bulgaria

⁵ Research Institute at Medical University of Plovdiv, Plovdiv, Bulgaria

⁶ Laboratory of Clinical Immunology, St George University Hospital, Plovdiv, Bulgaria

* Correspondence: bozhidar.vergov@mu-plovdiv.bg

Abstract: Improvement in medical care has turned severe diseases into chronic conditions, but often their treatment and use of medical devices are related to specific complications. Here we present a clinical case of a long-term dialysis patient, who is infected with a rare opportunistic infectious agent – *Gordonia sputi*. In recent years the incidence of *Gordonia spp.* infections in immunocompromised patients with central venous catheters (CVC) appear to rise. Their isolation and identification are challenging and require modern techniques. In addition, the treatment is usually persistent and often results in CVC extraction, which is associated with further risk and costs for the patient. We also studied the alternations in the immune status of the patient caused by long-term renal replacement therapy and persistent HCV infection. Antibiotic therapy and immunostimulation with Inosine pranobex lead to successful eradication of the infection without the need for CVC replacement.

Keywords: *Gordonia sputi*; dialysis; catheter-associated infection

1. Introduction

Long-term hemodialysis is a life-supporting procedure, but it has many complications for the patient. Chronic inflammation due to the contact of blood with artificial materials and uremia affects the immune status of the patient. Consequently, the leading causes of mortality in the hemodialysis population are infections and cardiovascular diseases [1,2].

Here we present a clinical case of a hemodialysis patient with bacteremia caused by the opportunistic pathogen *Gordonia sputi*. Furthermore, we tried to investigate if long-term renal replacement therapy (more than 35 years) affected the immune status of the patient.

Gordonia spp. are aerobic actinomycetes, found in soil and water, and are first described as a separate genus by Tsukamura in 1971[3]. Some species are reported to cause infections in humans [4]. Even the rare incidences, their identification and treatment may be challenging. Colonization of medical devices appears to be a potential risk as some species are reported to adhere and to degrade rubber [5]. Often successful treatment requires medical device extraction, which is related to higher risk and healthcare costs.

2. Case Presentation

We report a 59-year-old female dialysis patient with a double-lumen tunneled venous catheter. Her dialysis treatment was initiated in 1985 due to 4 hypotrophic kidneys with superposed chronic

glomerulonephritis. After multiple blood transfusions back then, the patient was infected with hepatitis C virus.

From November 2021 the patient reports malaise, weight loss, and febrile episodes with 37,5 to 38°C the night after the dialysis procedure and the next day. No febrile episodes or chills during the procedure were noted. Multiple blood culture sets were tested but no explicit bacterial agent was isolated. No leukocytosis was observed, only a slightly elevated C-reactive protein (CRP) was found. After every microbiology test antibiotic treatment was applied, which resulted in temporary improvement of the symptoms. No clinical or laboratory findings, echocardiography including, were in favor of endocarditis. The patient refuses multiple times a withdrawal of the dialysis catheter.

In September 2022, upon a new relapse of symptoms, another blood culture set was sent to the microbiology laboratory. On the fifth day of incubation, it yielded gracile Gram-positive rods, that grew on sheep blood agar as small non-hemolytic white colonies. Phenotypic identification was performed using 4h semi-automated biochemical testing with RapID™ CB PLUS (Thermo Scientific, the USA) and the microorganism was identified as *Corynebacterium striatum*. Since no leukocytosis was found, and CRP was 37, another blood culture sample was taken to rule out contamination or to confirm the result. Upon 4 days of incubation of the new blood culture set, the aerobic blood culture vial became positive. Direct microscopy revealed mid-sized actinomycete-like rods and upon cultivation at 37° C, in an aerobic environment, small white colonies on sheep blood agar appeared. They were subjected to Matrix-Assisted Laser Desorption Ionization–Time Of Flight Mass Spectrometry (MALDI-TOF MS, Vitek MS, bioMérieux, France) identification and the protein profiles obtained were characteristic of *Gordonia sputi*. The antimicrobial susceptibility testing (AST) according to EUCAST revealed the isolate was susceptible to Vancomycin, Gentamycin, Linezolid, Imipenem, Ceftriaxone, and Ciprofloxacin. After antibiotic treatment with Gentamycin and Meropenem for 21 days, all symptoms disappeared, and the improvement of the patient's condition remained constant. On the second and the fourth week after the end of the antibiotic course blood culture samples were negative. Meanwhile, on July 22nd of 2022, *Candida tropicalis* from a throat swab was isolated. The candida infection persisted for about 6 months despite the peroral fluconazole therapy.

In March 2023, the patient was referred to the Clinical immunology unit for further immune status investigation. For assessment of humoral immunity the levels of serum IgA, IgG, IgM and complement fractions C3 and C4 were measured by an automated immunoturbidimetry analyzer (BA200, Biosystems, Spain). Laboratory investigations showed normal levels of the three immunoglobulins and the complement fractions. For evaluation of the cellular immune status lymphocyte subpopulation counts (LSc) were measured by 6-color TBNK reagent in a peripheral venous blood sample within 2 h of blood draw by BD FACSCanto II, BD, USA. Flowcytometric testing revealed impairment of the cell-mediated immunity with lymphopenia and decreased absolute number of immunocompetent CD3+ T cells, helper/inducer CD4+ T cells and cytotoxic/suppressor CD8+ T cells, and borderline low B and NK (Natural Killer) cells. CD4/CD8 T cell ratio was normal. Additionally, cytokine analysis was conducted using a human Th1/Th2/Th17 cytokines Cytometric bead array kit which allowed for the simultaneous detection of IL-2, IL-4, IL-6, IL-10, TNF- α , IFN- γ and IL-17A cytokines in serum. The altered function of immune cells resulted in an intriguing dysregulation of cytokine production characterized by elevated levels of Th2 cytokines (IL-4, IL-6, and IL-10) and slightly detectable Th1 (IFN- γ , TNF- α , and IL-2) and Th17 (IL-17A) cytokines.

3. Discussion

The clinical and laboratory changes consistent with infection were weakly manifested, probably because of the patient's comorbidity and deprived immune status. Clinical presentation was additionally concealed by the empirical antibiotic courses and later by the superposed fungal infection. The refusal for catheter removal interfered with the prompt identification and eradication of the infection.

Dialysis patients with central venous catheters are reported to have higher rates of mortality and complications i.e., endocarditis, septic shock, and abscesses, compared to other vascular accesses:

arterio-venous fistulas and vascular grafts. The same article pointed out that despite the many problems of catheters, their placement may be inevitable and because of the profile of patients that begin hemodialysis they are widely used– i.e., older patients often with many comorbidities. The construction of arterio-venous fistula and its maturation in these cases may be difficult [6].

A bibliographic review indicates that the use of catheters for long-term intravenous access is a notable risk factor for bloodstream infections caused by *Gordonia* species [7–11]. The *Gordonia* genus has a complicated taxonomic history of several reclassifications. Moreover, due to the close relation to other genera within the *Mycobacteriales* order like *Dietzia*, *Corynebacterium*, *Rhodococcus*, and *Tsukamurella*, the *Gordonia* spp. identification has been challenging, as other authors have noted cases of misidentification [11,12]. In our case, for the time between Nov. 2021 and Sept. 2022, the patient had multiple febrile episodes where conventional blood culture testing didn't yield a definitive causative agent and the applied antimicrobial treatment had a temporary effect. The first possible causative agent in our patient, detected in Sept. 2022 was identified by semi-automated biochemical testing (RapID CB Plus) as *Corynebacterium striatum*. The mentioned test doesn't include *Gordonia* spp. in its diagnostic spectrum. Because of this fact and due to the close relativity and overlapping of some morphological and biochemical characteristics of *Gordonia* spp. and its other neighboring genera, similar to the other authors, we cannot exclude the possibility for the first isolate to have been *Gordonia sputi* misidentified as *Corynebacterium striatum*. This goes to show that routine methods are insufficient and more complex and modern techniques are needed e.g., proteomic analysis with mass-spectrometry or molecular genetic assays like polymerase-chain reaction (PCR) or 16S ribosomal RNA sequencing.

Also, it is crucial to underline the significance of opportunistic isolates as *Gordonia sputi* in immunosuppressed patients. For adequate immune response towards infectious agents, a sufficient number of immune competent cells are needed and, in our patient, the flowcytometry testing indisputably confirmed lymphopenia with suppression of major subsets of cells with the most remarkable decrease in CD3+ T-cells count. This is an important factor supporting the invasiveness of infections. Such findings regarding the cellular immune status are also present in various studies [13,14]

Another reason for impaired immune response is the dysregulation of cytokine production resulting in imbalanced differentiation of Th lymphocytes to Th1 or Th2 cells. Each of the corresponding subpopulations secretes distinct cytokines – Th1 cytokines are IL-2, TNF- α , IFN- γ , etc. while to the group of Th2 cytokines belong IL-4, IL-6, IL-10, etc. [15]. Our patient's immune status demonstrates impairment of cell-mediated immunity which is sustained by Th1 cells (slightly detectable levels of Th1 cytokines) with preserved humoral immunity marked by normal levels of total immunoglobulins and complement fractions C3 and C4) sustained by Th2 cells (increased levels of Th2 cytokines). It is known that IL-4 as well as IL-10 enhance Th2 and inhibit Th1 development [16,17]. According to some other authors, the levels of Th2 cytokines in hemodialyzed patients are increased [15,18] which corresponds to the results in our patient. A study of Szabo et al. demonstrates that IL-4 inhibits the expression of the signal-transducing $\beta 2$ subunit of IL-12 receptor and thus the ability of the latter to induce Th1 response [19]. Additionally, both IL-4 and IL-10 possess direct anti-inflammatory properties [20–23]. The hindrance of Th1 cytokines may result in complex defects of cell-mediated effector functions, including phagocytic elimination of infectious agents, macrophage inflammatory cytokine production, natural killer cell– and CD8+ T-cell-mediated cytotoxicity [24]. Moreover, chronic hepatitis C infection is associated with impaired function of helper/inducer CD4+ T cells and cytotoxic/suppressor CD8+ T cells and overactive Th2 immune response [25–30] Thus, comorbidity presented by chronic liver infection, longtime hemodialysis, cancer in her adolescence correspond for the immune suppression in this patient.

Immune stimulation is an important therapeutic measure in such patients. Due to the intact levels of total immunoglobulins in this case, the administration of intravenous immunoglobulin (IVIG) is not taken into consideration. A therapeutic approach for this patient is Inosine pranobex (IP), commonly known as Isoprinosine which is known to enhance T-cell lymphocyte proliferation and activity of NK cells leading to restoration of the deficient responses in immunosuppressed patients with advantageous effect also on HCV infection [31].

4. Conclusions

Clinical presentation of catheter-associated bacteremia in polymorbid hemodialysis patients may be vague because of a depressed immune system. Prophylaxis of infections by these patients is crucial because of the many life-threatening complications. These patients must be closely followed-up and even when mild symptoms are presented physicians should be encouraged to take blood cultures.

This case illustrates that some rapid commercially available microbiological identification systems may provide inaccurate results, and the precise identification to the species level can be achieved by more complex but still accessible for most laboratories assays like MALDI-TOF mass spectrometry.

We may also conclude that the treatment of immunocompromised comorbid hemodialysis patients should always include a consideration of the constant risk of opportunistic infections. Their management should involve protective measures against the latter, prophylaxis of fungal infections, and appropriate immune stimulation.

Author Contributions: B.V. and A.A. were responsible for the conceptualization. B.V. and G. T. were responsible for patient treatment and follow-up. B.V. wrote mainly the manuscript but all the authors contributed to writing, reviewing, and editing the manuscript. A.B. and M. M. contributed to the immunological analyses and interpretations. Microbiological evaluation and interpretations were performed by A.A. and Y. K. In addition, M.M. was also responsible for supervision and final correction. All authors have read and agreed to the published version of the manuscript. All authors approved the submitted version.

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Informed Consent Statement: Written informed consent was obtained from the patient involved in the study. All procedures performed in the presented study were in accordance with the ethical standards of the institution and with the 1964 Helsinki Declaration and its later amendments.

Data Availability Statement: The raw clinical and laboratory data associated with the current study are available by the corresponding author, without undue reservation on a reasonable request.

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