Leifsonia aquatica: Case report and literature review

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Abstract. Non-diphtheria *Corynebacterium* species have been increasingly recognized as multidrug resistant pathogens that also infect immunocompromised patients. Automated and semi-automated phenotypic tests have been used by clinical laboratories for detection of these gram-positive rods. The present case report describes the rare pediatric case of *L. aquatica* isolated in central venous catheter blood cultures during chemotherapy treatment for Wilms tumor and adds to the knowledge on this infection with regard to pediatric cancer. The clinical aspects of this patient and opportunities for improving treatment were reviewed. Additionally, a review of the literature revealed no other case report involving cancer and a pediatric patient with documented *L. aquatica* bacteremia. Corynebacterial infections are considered uncommon, but in recent decades' reports on infection with bacterium are increasing in frequency, particularly in nosocomial immunocompromised patients.

Introduction

Toxigenic *Corynebacterium Diphtheriae* is a major cause of morbidity and mortality in regions of the world where immunization against diphtheria is not universally available. Coryneform bacteria are a diverse group of aerobically growing non-spore forming, irregularly shaped gram-positive rods. Geographical variations in the frequency of isolated species and variations in natural and acquired antimicrobial resistance have been described (1). Diagnosis of coryneform bacteria remains a challenge for routine checks, due to the large number of different species belonging to this group (2,3). Isolates of coryneform gram-positive rods are often difficult to identify for diagnostic laboratories. Modern technologies such as MALDI-TOF MS and/or RNA sequencing molecular detection methods for bacterial pathogens in fluids provide sensitive, specific and rapid results (4).

The incidence of *Corynebacterium spp.* as pathogens of nosocomial infections associated with septicemia, endocarditis, infections of surgical wounds and infections related to the use of invasive medical devices is increasing. Blood culture is considered the gold standard for diagnosis of bacteremia. The incidence and clinical presentations of *Corynebacterium spp.* infections differ in children and adults (5).

Non-diphtheria *Corynebacterium* species have been increasingly recognized as multidrug resistant (MDR) pathogens that also infect immunocompromised patients (5), and Vancomycin is still considered the primary drug of choice in the control of this infection. The indication of the removal of catheters is recommended in guidelines, such as the Clinical and Laboratory Standards Institute 2017 (CLSI, 2017), with the aim of avoiding bacteremia or sepsis of in immunocompromised patients. Antimicrobial susceptibility testing of clinical isolates is also recommended by the CLSI guidelines (6). Additional studies of actions and medications that influence in the bacterial adherence may contribute to more effective drugs and new guidelines.

In the present article, the case of an *L. aquatica* infection (before *Corynebacterium aquaticum* infection) isolated from a pediatric patient with a Wilms tumor who was kept on a catheter long term is described. This bacteria is a bacilli gram positive, and has a natural affinity for moist surfaces and or water-based solutions and can infect animals and plants, including human beings (7). This paper should be of interest to a broad readership including those interested in demonstrated that treatment of these infections may contribute to significant changes in clinical and epidemiological features of corynebacterial infections in nosocomial environments.

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Case report

This study received Institutional Review Board approval from the National Cancer Institute (INCA/HCI, Rio de Janeiro, Brazil; approval no. CAAE- 0121.0.007.000-11).

The present report describes the of a 4-year-old boy, white, with hematuria, dysuria and abdominal pain. He had a palpable abdominal mass, and this underwent physical examination. In the contrast-enhanced computerized tomography, the right kidney was normal whereas the left kidney presented a mass (7.4x6.2 cm) in the upper third of the right kidney. Following the New Wilms Tumor Study (NWTS) protocol, surgical intervention was recommended (8,9). Surgical enquiry showed the presence of a large tumor in the left kidney with renal homolateral vein thrombosis. Nephro-adrenalectomy was carried out with retroperitoneal lymphadenectomy and thrombectomy. Subsequently, the tumor was classified as stage EIII (referring to a Wilms tumor that has most likely not been removed completely, for example, in the case where a disease has spread to lymph nodes). On 9th of February 2002, under the NWTS EE4A protocol, the patient was treated with doxorubicin and vincristine. During the first cycle of treatment, the patient presented with pneumopathy, and thus, the treatment was changed to ciprofloxacin. Subsequently, other infections occurred, including pultaceous tonsillitis (treated with amoxicillin) and urinary infection on the 12th of February 2003 (treated with Bactrim until 24th of April 2003.

During ambulatorial follow-up on the 10th of January 2004 due to chest pain, he was diagnosed with a recurring thoracic tumor, and was thus prescribed chemotherapy under NWTS for EV protocol with doxorubicin, vincristine and cyclophosphamide. Radiotherapy of the thorax and thoracic spine column was recommended and was performed between 8th of January 2004 until 2nd of February 2004. A Venous Catheter of Long Permanency (CVC LP SI) was inserted on the 29th of January 2004, in the humeral vein under institutional protocol. On 17th of February 2004, the patient developed an *Enterobacter cloacae* urinary infection in the right kidney, which was treated with ciprofloxacin antibiotic for 10 days (15 mg/kg/day). During the chemotherapy cycle, he exhibited fever. On 23rd of February 2004, he had a venous prothesis, and was treated with cefalexin. As hemocultures were negative, the catheter was maintained. On the 15th of April 2004, he was diagnosed with pancytopenia and right pneumopathy, and was thus treated with cefepime; on the 21st of April 2004, he was considered neutropenic and he presented with herpes zoster in the perineal area, thus fluconazole was used for 10 days. On 21 May 2004, within 5 months of CVC, he had fungemia. Fluconazole was given, and the CVCLP SI (LSM) was removed. A peripheric intravenous central catheter was inserted on 3rd of June 2004. However, after 7 days, he had local hyperemia and pain, and thus it was removed. On 24th of June 2004, a new CVC LP SI was inserted in the RSM, and chemotherapy treatment was maintained. After 8 days, the patient presented with a new fever with neutropenia, and thus ceftriaxone was started. During doppler ultrasound examination, a thrombus in the right atrium and cultures from the insertion ostium of the CVC was identified. On 9th of July 2004, a non-solid mass in the lung associated with disseminated intravascular coagulation occurred. Culturing and analysis confirmed the growth of *L. aquatica* associated a member of the *Staphylococcus spp*. taxa. Thus, the catheter was removed, and the patient was administered amikacin and vancomycin in the intensive therapy. Coagulation examinations showed: Antithrombin III-112%, anticardiolipin (+), C reactive protein 50.2 mg/dl and lupus anticoagulant (-); thus, anti-coagulation therapy was started on enoxaparin 20 mg/day for anti-phospholipidic syndrome (condition of oncogenic origin, and due to a family history of hereditary hemostasis). A third CVC LP catheter was inserted on the 5th of August 2004, which was removed on 24th of March 2005, after sufficient control of hemostasis was achieved. Patient underwent ambulatorial follow-up on 23rd of July 2014, were co-axial tomography showed a relapse of thoracic disease on the right side, and a venous chemotherapy cycle was started under the Vincristine, Irinotecan, Temozolomide and Bevacizumab protocol with a new CVC LP inserted in the right subclavian on the 18th of July 2014, and a reduction of the mass was achieved. He remained under thoracotomy until 12th of January 2015 (10). During the post-surgery period, he presented with the following complications: Suture dehiscence in the surgical wound, and infection by Methicillin-resistant *Staphylococcus aureus* and *Acinetobacter spp*. pathogens. He was treated with linezolid and ciprofloxacin. After bandaging and surgical interventions, the wound completely healed. Chemotherapy was ended on 16th of November 2015. Subsequently, the patient came back for ambulatorial follow-up, and there was no evidence of disease and/or infection.

Discussion

In the last two decades, *Non-diphtheria Corynebacterium* species have been increasingly recognized as MDR pathogens that also infect immunocompromised patients, which may be caused by inappropriate outpatient prescription of antibiotics (3,5,11-13). There are reports of isolation of coryneform bacteria causing nosocomial infections, such as endocarditis, and orthopedic bone and joint infections (14). Isolates of coryneform gram-positive rods are often difficult to identify for diagnostic laboratories (15).

There are only a few reports describing an *L. aquatica* infection in an individual under long-term catheter use (14-19). An integrative review was performed based on the following guiding question: How common is an *L. aquatic* infection? And what is best antibiotic approach to treat it, primarily in immunocompromised patients?

A literature review was performed by searching SCOPUS and MEDLINE, using the key words in medical subject heading (MeSH): '*Leifsonia aquatica*', 'catheter', 'neoplasms'. Key words were combined using the Boolean operator 'AND'.

The inclusion criteria were as follow: Original articles, letters to the editor and bibliographic reviews published in English. No timeframe was set in this research. The evaluated aspects were: Documents by type, documents by country/territory, documents by affiliation, documents by author, periodic research and publication by year. Articles that were considered other aspects of *L. aquatica* infections related were excluded from this review.

Table I. Case reports on *L. aquatic* infections between 1975 and 2017.

First author, year	Continent	Age/ Sex	Pathology	Symptoms and signs	Site of infection	Laboratory findings	Culture	Others microorganisms	Antibiotics administered	Technique	Outcome	(Refs.)
Lau *et al*, 2002	Asiatic	39/F	Chronic myeloid leukemia	Fever	CVC	Normal white cells	Blood	No	Penicilin/ vancomycin	API Coryne system	Catheter removed/ good response	(14)
Porte *et al*, 2012	South America	79/M	Kidney disease	Hemodalysis	CVC	High C-reative protein levels	Blood	No	Pen G/ cefotaxane/ vancomycin	API Coryne system/DNA sequenced[a]	Catheter removed	(19)
Gardenier *et al*, 2012	North American	50/F	Hemodialysis	Peritonitis	Abdominal	Neutrophilia	Peritoneal	*Sthapylococcus aureus*/ *Haemophilus parainfluenzae*/ *Gordonia spp*.	Amoxicillin acid clavulanic/ trimethoprim-sulfamethoxazole/ vancomycin	Blood agar culture	Good response	(22)
Han *et al*, 2013	Asiatic	60/M	No comorbidities	Septic shock/y Yellowish pigmentation	Ocular	Leucocitosis/ high C-reative protein levels	Blood	No	Meropenem/ vancomicin/ linezolid	API Coryne system/DNA sequenced[a]	Good response	(26)
Sulpher *et al*, 2008	North American	58/M	Kidney polycystic/ diabetes/ Heart disease	Surgical infection	CVC	No significant findings	Blood	No	Vancomycin	API Coryne system	Change catheter/ good response	(17)
Weiner *et al*, 1975	North American	85/F	Diabetic ketoacidosis	Septicemia	CVC	Ketoacidosis/ diabetic	Blood	No	Ampicillin/ cephalothin/ erythromycin/ gentamicin/ tetracycline	Blood agar culture	Good response	(16)
Morris *et al*, 1986	Australia	33/F	Diabetic/ peritonitis	Renal failure/ CAPD	Abdominal	Leucocitosis	Dialysis fluid	No	Vancomycin/ co-trimoxazole/ doxycline/ piperaciclin	Stoke's method	Tenchkoff catheter removed	(23)

Table I. Continued.

First author, year	Continent	Age/ Sex	Pathology	Symptoms and signs	Site of infection	Laboratory findings	Culture	Others microorganisms	Antibiotics administered	Technique	Outcome	(Refs.)
Beckwith *et al*, 1986	North American	4 weeks /F	Natural new born/ meningitis	Vomiting/ irritability	Spinal Fluid	Leucocitosis	Blood/ spinal fluid	No	Ampicillin/ cephalothin/ penicillin/ chloramphenicol/ erythromycin/ vancomycin	BACTEC/ CTA sugar/ API 20S/ EBC +Card	Good response	(24)
Casella *et al*, 1988	Europe	79/M	Angionephro sclerosis	Cloudy peritoneal effluent	Peritonitis	Normal blood cell count	Peritoneal fluid	No	Vancomycin	Schedler agar plates	No CAPD removed 4 relapses/ good response	(25)
Tendler *et al*, 1989	North American	8 days/ M	Natural new born	Vomiting/ diarrhea/ irritability	Urinary	Leucocitosis	Urine Sample	No	Vancomycin/ cefazolin/ cefuroxime/ cefotaxime/ ceftriaxone/ gentamicin	BBL microbiologi cal system	Good response	(27)
Fischer *et al*, 1994	Europe	13/M	Lymphoblastic leukemia	Fever tonsilytis	No identified	Aplasia low granulocytes/ elevated C-reactive protein levels	Blood	No	Cefaclor/ cefatazidime/ vancomycin	API Coryne system	Good response	(21)
Moore *et al*, 1995	Australia	74/F	Polycythaenia rubra vera	Anaemia/ fever	CVC	High packed cell volume, platelets and white cell counts	Blood	*Staphylococcus aureus*	Penicilin	BACTEC NR860	Catheter removed	(15)
Larsson *et al*, 1994	Europe	24/M	No comorbidities/ accidental	Lymphangitis	Right foot		Swab of foot fluid lesion	*No*	Benzylpenicillin/ rifampicin/ tetracycline/ ceftazidime/ vancomycin	API Coryne system	Good response	(7)

Table I. Continued.

First author, year	Continent	Age/ Sex	Pathology	Symptoms and signs	Site of infection	Laboratory findings	Culture	Others microorganisms	Antibiotics administered	Technique	Outcome	(Refs.)
Levitski-Heikkila *et al*, 2005	North American	41/M	Peritoneal dialysis	Drug addict	Abdominal	No significant findings	Peritoneal fluid/cuff catheter	No	No test used. Empiric antibiotics	-	Tenchkoff removed/ death, but with no relation to the infection	(28)
Giammanco *et al*, 2006	Europe	44/M	Heart transplantation	Rejection/ pulmonary disease	Pleural effusion	Low CD4 and CD8 cell counts	Bronch alveolar aspiration	No	Cefepime/ ceftriaxone/ cefuroxime/ cephalothin/ imipenem/ erythromicin/ vancomycin	Vitek 2/API Corryne system/DNA sequenced[a]	Good response	(29)
Corona *et al*, 2008	Europe	39/M	HIV	Renal failure/ septic	No identificated	Low CD4 cell counts	Blood	No	Penicillin/ ampicillin/ tetracycline/ amikacin/ vancomycin	Bactec 9240/API Coryne	Good response	(18)
Fujinaga *et al*, 2009	Asiatic	17/M	Hypoplastic kidneys	Cloudy peritoneal effluent	Peritoneal fluid	Little high white count cell and C-reactive protein levels	Peritoneal fluid	*Sthapylococcus pidermitis*	Vancomycin	API Coryne system	APD catheter removed/ good response	(30)

[a]16SrRNA DNA was sequenced. M, male; F, female; CAPD, continuous ambulatory abdominal catheter peritoneal dialysis; CVC, central venous catheter.

Information on the cause of the case that was defined as being of importance for discussion in this integrative review. The description in the title and abstracts were assessed in the filtered articles obtained. Evaluation and critical analysis of the articles involved classifying them by case reports in immunocompromised patients.

A review of the literature revealed a case report involving dialysis patients with documented *L. aquatica* bacteremia (19) Searching the two databases, SCOPUS and MEDLINE. In SCOPUS, 15 articles were retrieved; and 3 were discarded as they were deemed irrelevant based on either the title or the abstract. Thus 12 articles were obtained. In MEDLINE, 17 articles were selected but articles were the written language was not English were discarded, and 1 article was a duplicate between the two databases. The case reports selected after filtering out irrelevant articles are shown in Table I. The source basis, signals and symptoms, the laboratory results, comorbidities associated, equipment used to identify *L. aquatic* infection, the susceptible antibiotic tests used in each related case report and the outcome of each case patient is described. This review of the literature did not reveal any other case report describing the case of an *L. aquatica* infection in a patient with cancer or a pediatric patient.

In the present report, the rare case of an *L. aquatica* infection isolated from a pediatric patient with a Wilms tumor is described. To the best of our knowledge, this is the only report of an *L. aquatica* infection in Brazil associated with long term catheter use. This report highlights the possibility of a rare case of *L. aquatica* infection isolated during chemotherapy treatment for Wilms Tumor, and the clinical aspects of this patient, and the subsequent developments for improving treatment were analyzed.

A study by Adderson *et al* describes some cases of Coryneform bacterial infections in a pediatric oncological setting. They proposed that the incidence and presentation of these infections differed in children and adults (20).

In the present study, *L. aquatica* was responsible for central venous catheter related infection in the pediatric patient with solid malignant tumor. Most reports of corynebacterial infections describe single patients, and thus the characteristics of these infections are poorly defined (17,21-26). Certain articles highlight the pathogenicity of this bacterium as the primary causative agent of bacteremia in patients on dialysis and is not considered a simple episode of opportunistic infection (27-30).

Vancomycin has been considered the treatment of choice for management of corynebacterial infections (11,31). Indeed, the majority of reports from Europe show *C. Jeikeium* as susceptible to vancomycin, but resistant to other antibiotics (5,32). The biofilm on catheter surfaces formed by this agent complicates eradication of this bacteria (33). Additional complications, such as longer hospitalization periods, use of other catheters or a non-competent patient increase the necessity of catheter removal. Thus, introducing vancomycin for management of these infections may be a sensible approach to reduce the risk of worsening of infections. Vancomycin remains the better option as empiric treatment of catheter *Corynebacterium* infection (34,35). This approach reduces the risk of making an assumption of the nature of the pathogen based on 'common sense', which could increase the risk to the patient. Instead, correct identification and treatment can prevent further complications.

In Conclusion, infections by *Corynebacterium* species are increasingly being recognized as causative agents of bloodstream and venous catheter-related infections in immunocompromised patients. With the development and advancement of novel technologies and improvement in diagnostic approaches, and the possibility of using new medications guided by accurate clinical laboratory identification with suitable sensitivity, non-Corynebacterium may be implicated in an increasing number of deaths in immunocompromised patients. This literature review highlights the increasing importance of the potential for infections and the problems they can cause in patients using catheters.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

ALMG designed the study, analyzed and interpreted the data, and assisted in writing the manuscript. RVDC performed the experiments, interpreted the results, drafted the manuscript, performed the surgical procedure and logged the patient's data/results, and performed the analysis. MFG was responsible for patient treatment and welfare. FFL and LSDSSA performed the experiments, interpreted the results and drafted the manuscript. CSS and RHJ assisted in writing the manuscript, and performed the microbiological data analysis and interpretation. All authors have read and approved the final manuscript. ALMG, CSS and RVDC confirm the authenticity of all the raw data.

Ethics approval and consent to participate

This study received Institutional Review Board approval from the National Cancer Institute (INCA/HCI, Rio de Janeiro, Brazil; approval no. CAAE- 0121.0.007.000-11).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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