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Case report

A Case of Candidemia after Long-term Presence of Urethral Foreign Bodies

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ABSTRACT

A 52-year-old man presented to our hospital complaining of general malaise, cough, and fever. Total body computed tomography revealed scattered pneumonia and urethral foreign bodies that had been inserted during adolescence. *Candida glabrata* was detected in blood and urine cultures. Based on these findings, the patient was diagnosed with candidemia that developed due to *Candida* urinary tract infection, complicated by septic pulmonary embolism and severe diabetes mellitus. Candidemia likely persisted despite the initiation of intravenous antifungal therapy and control of blood sugar level. Therefore, surgical removal of the urethral foreign bodies was performed, which resulted in resolution of the patient's symptoms. Herein, we report a rare case of candidemia complicated by *Candida* urinary tract infection that developed due to the long-term presence of urethral foreign bodies. A multidisciplinary therapeutic approach, including surgical removal of the infected foreign bodies, is effective in such cases. This case indicates that long-term presence of foreign bodies and acquired immune dysfunction can be risk factors for candidemia. Therefore, detailed history should be obtained and systemic examination should be performed to identify the complicating risk factors on diagnosis of candidemia.

Introduction

Candidemia is an infectious disease whose frequency is increasing, and *Candida* species (spp.) is now the fourth most common pathogenic microorganism associated with nosocomial bloodstream infections in the United States [1,2]. The prognosis of candidemia is poor, with a reported mortality rate of 40%-50% [3–7]. Urinary tract infection (UTI) caused by *Candida* spp. is rare; however, it is one of the known causes of candidemia, and the risk for *Candida* UTI is higher in individuals with anatomical abnormalities of the urinary tract. It is well known that persistent infection due to an infected foreign body is a common scenario; however, to the best of our knowledge, there are no reports of candidemia due to the long-term presence of urethral foreign bodies. Herein, we report a rare case of candidemia caused by urethral foreign bodies that were inserted several decades before the onset of candidemia, which was then successfully treated with a combination of antifungal drugs and surgical removal of the foreign bodies.

Case Report

A 52-year-old man was transported to the ER of our hospital as he complained of difficulty in walking, general malaise, fever, and cough for more than two weeks. The weight and height of the patient were 53.6 kg and 157.3 cm, and physical examination revealed the following: blood pressure 102/91 mmHg, heart rate 127 regular beats per minute, body temperature 39.8 °C, percutaneous oxygen saturation (SpO_2) 97% breathing room air, and positive for tenderness on palpation of the right costovertebral angle. The laboratory investigations revealed a serum white blood cell count of 19,860 /μL (neutrophils, 94.7%), C-reactive protein level of 23.6 mg/dL, creatinine level of 2.17 mg/dL, hemoglobin A1c

Abbreviations: CRP, C-reactive protein; CT, computed tomography; MCFG, micafungin; MEPM, meropenem; PZFX, pazufloxacin; spp., species; SpO_2, percutaneous oxygen saturation; UTI, urinary tract infection; VRCZ, voriconazole.

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Table 1
Laboratory findings on admission

<Hematology>		<Biochemistry>		<Coagulation>	
WBC	19,860 /μL	TP	7.6 g/dL	PT	12.5 sec
Neutro.	94.7 %	AlB	2.0 g/dL	PT-INR	1.11
Lympho.	2.2 %	T-bil	1.0 mg/dL	APTT	28.2 sec
Mono.	2.8 %	AST	21 IU/L		
Eosino.	0.1 %	ALT	19 IU/L	<Urinalysis>	
Baso.	0.2 %	LDH	205 IU/L	Spec Gravity	1.012
RBC	346×10^4/μL	γ-GTP	244 IU/L	pH	5.0
Hb	9.9 g/dl	BUN	40.9 mg/dL	Protein	1+
Ht	28.8 %	Cre	2.17 mg/dL	Blood	2+
MCV	83.2 fl	Na	117 mEq/L	Glucose	2+
PLT	16.5×10^4/μL	K	4.9 mEq/L	Ketone	negative
		Cl	83 mEq/L	Urobilinogen	±
		BS	588 mg/dL	Nitrite	negative
		HbA1c	13.2 %	Leukocyte	4+
		CRP	23.6 mg/dL		

<Cultivation survey>					
Sputum		Urine		Blood	
Normal flora		*Candida glabrata*	10^5 CFU/mL	*Candida glabrata*	10^5 CFU/mL
		Lactobacillus spp.	10^5 CFU/mL		

Abbreviations: spp., species

of 13.2%, and positive results on urinalysis for uric protein, blood, and white blood cells (Table 1). Total body computed tomography (CT) revealed infiltrative shadows in the lower lobe of the right lung, bilateral perinephric stranding and thickening of Gerota's fascia, air space in the left renal pelvis, bilateral pelvic distension, thickening of the bladder wall, and two high absorption areas in the anterior urethra. Urethrography revealed two foreign bodies in the pendulum urethra that had been inserted during adolescence (Fig. 1).

Based on these findings, the patient was diagnosed with emphysematous pyelonephritis with urethral foreign bodies, urethral stones, and type 2 diabetes mellitus. Therefore, intravenous infusion of pazufloxacin (PZFX) (1000 mg, daily) and subcutaneous insulin injection were initiated for the management of emphysematous pyelonephritis and diabetes, respectively (Fig. 2). Additionally, percutaneous cystostomy was performed on the day of admission, which resulted in the outflow of urine with white precipitates. On day 4, *Candida glabrata* and *Lactobacillus* spp. were cultured from the admission urine sample, *C. glabrata* was cultured from the blood sample (Table 2), and the serum β-D glucan level was found to be elevated (84.8 pg/mL). Therefore, the patient was diagnosed with UTI caused by *C. glabrata* and *Lactobacillus* spp., complicated by *C. glabrata* candidemia. Subsequently, intravenous infusion of micafungin (MCFG) (150 mg, daily) was initiated. However, since high fever and blood inflammatory markers persisted on day 12, CT scan was performed to evaluate the cause of the latter. The results demonstrated multiple new nodular shadows in the bilateral lung fields, consistent with septic pulmonary embolism. Although echocardiography did not provide evidence for infective endocarditis and repeat blood culture analysis was not performed, we believe that persistent candidemia can be inferred due to the persistently high levels of blood inflammatory markers in combination with multiple new nodular shadows in the bilateral lung fields. Therefore, antifungal therapy was switched from MCFG to intravenous voriconazole (VRCZ) (300 mg, daily). Similarly, antibacterial therapy was switched from PZFX to meropenem (1500 mg, daily) considering the possibility of UTI and urosepsis complicated by PZFX-resistant bacilli. However, the inflammatory markers remained elevated; therefore, the urethral foreign bodies were considered the major cause of persistent inflammation. Hence, a surgical procedure was performed under general anesthesia by making a longitudinal incision on the ventral side of the penis to remove the urethral foreign bodies. Consequently, two cylindrical foreign bodies that resembled smoking cessation pipe-like plastics were removed successfully (Fig. 3). After the procedure, the serum β-D glucan concentration gradually decreased, and improvement was observed in the serum inflammatory markers and abnormal lung shadows (Fig. 4). Meropenem was continued for 2 weeks, and VRCZ administration was switched from intravenous to oral route on day 27. The patient was discharged on day 36 after recovery.

Discussion

In the present case, candidemia caused by *C. glabrata* was insufficiently controlled by antifungal agents and eventually necessitated surgical removal of the urethral foreign bodies for clinical improvement. Of note is the fact that candidemia developed decades after insertion of the urethral foreign bodies. It seems likely that the patient developed candidemia a long time after insertion of the urethral foreign bodies because the urethral stones had formed over time, leading to urinary retention. Furthermore, poorly controlled diabetes mellitus further increased the risk. It is difficult to clarify whether *Candida* infection of the urethral foreign bodies occurred primarily or secondarily to candidemia. However, we believe that the most plausible scenario is that long-term presence of the urethral foreign bodies was the primary cause of persistent candidemia.

In the present case, *C. glabrata* was cultured from the blood, leading to the diagnosis of candidemia, which is often caused by *Candida* infection in medical devices such as intravenous catheters. It has been reported that *C. albicans, C. glabrata*, and *C. parapsilosis* are the most common species causing candidemia, with percentiles of 45%, 26%, and 16%, respectively [8]. The causative microbe in our case, *C. glabrata,* has been associated with a poor prognosis and a high mortality rate of 57% [9]. Known risk factors for candidemia include hematologic malignancy, post-organ transplantation, neutropenia, corticosteroid use, post-chemotherapy for malignancy, use of broad-spectrum antibiotics, long-term central venous catheterization, dialysis, and post-gastrointestinal surgery [10,11].

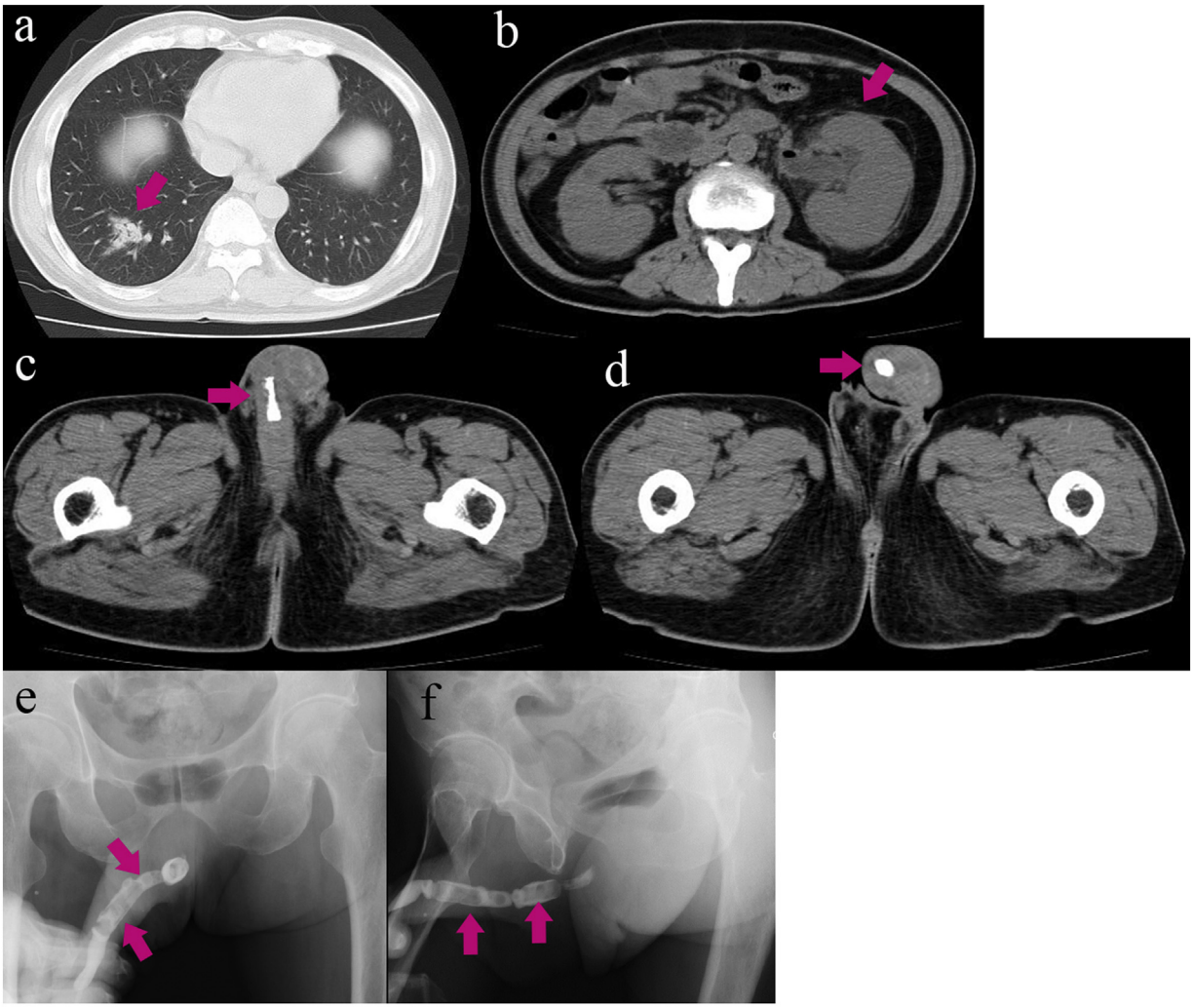

Fig. 1. Images of CT and urethrography on admission.
Infiltrative shadow in the lower lobe of the right lung was observed (a) (arrow). Bilateral perinephric stranding, thickening of Gerota's fascia, air in the left renal pelvis, and bilateral pelvic distension were observed (b) (arrow). Thickening of the bladder wall, and two areas of high absorption in the anterior urethra were observed on CT, and two foreign bodies in the pendulous urethra were revealed by urethrography (c-f) (arrows).

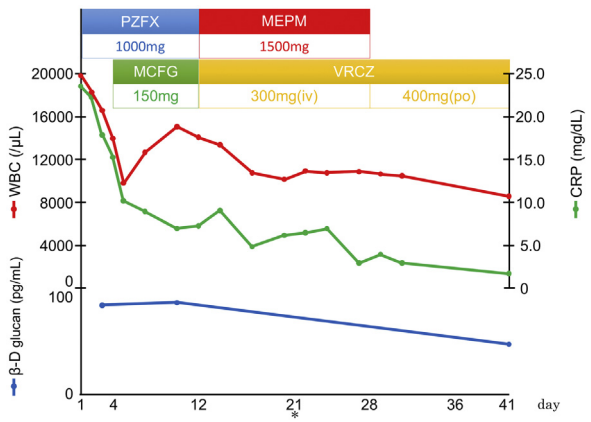

Fig. 2. Longitudinal display of treatment course and inflammatory markers.
WBC, white blood cells; CRP, C-reactive protein; PZFX, pazufloxacin; MEPM, meropenem; MCFC, micafungin; VRCZ, voriconazole; iv., intravenous; po., per oral; * , day of surgical procedure.

In the current case, the patient had persistent candidemia despite the initiation of MCFG, along with intensive diabetes control with insulin injections. Therefore, surgical removal of the urethral foreign bodies was required, suggesting that these were the major cause of persistent candidemia, and that control of the focus of UTI was critical. Candidemia often develops by microbial translocation from the gastrointestinal mucosa into the vasculature or by direct inoculation via intravascular catheters [12]. Candidemia is a relatively rare complication of *Candida* UTI, and it has been reported that only 0.81% of the patients with positive urine cultures for a fungal species also had positive blood cultures for the same species [13,14]. One study reported that 73% of the patients with candidemia caused by *Candida* UTI had urinary obstruction [14]. In addition, urinary catheterization and urinary tract obstruction are the known risk factors for *Candida* UTI [15,16]. Furthermore, *Candida* was cultured in the urine of 10% of the patients with complex UTI [17], suggesting that such abnormal conditions can be a major risk factor for candidemia. In the present case, endoscopic observation revealed tubular foreign bodies and stone formation in the urethra, suggesting urinary retention as a

Table 2
Antimicrobial susceptibility profile of *Candida glabrata* cultured from the blood cultures

Drug	MIC (μg/ml)	Susceptibility
Amphotericin B	0.25	S
Miconazole	0.5	S
Itraconazole	8	S
Flucytosine	<0.125	S
Fluconazole	1	R
Micafungin	0.06	S
Voriconazole	0.25	S

Abbreviations: MIC, minimum inhibitory concentration

likely cause of *Candida* UTI. Therefore, it is important to recognize that anatomic abnormalities in the urinary tract may be a causative risk factor when evaluating patients with candidemia.

In the present case, the urethral foreign bodies had been inserted for sexual purposes when the patient was an adolescent. A prior clinical study on 1504 cases of vesicourethral foreign bodies reported a male-to-female ratio of 1.7 to 1 and the presence of a broad range of foreign body types (listed in Table 3) [18]. Another study reported that the most common cases of foreign body occurrence were from the sexually active age group comprising individuals in their 20 s (28.8%), followed by those in their 10 s (20.4%) and 30 s (17.0%) [19]. Vesicourethral foreign bodies are usually detected and evaluated for their location and shape by radiography, CT scan, and urethrography. However, as shown in Table 4, vesicourethral foreign bodies are often attributed to sexual acts relating to preferences of the individual. Consequently, it is sometimes challenging to diagnose vesicourethral foreign bodies considering the sensitive nature of the issue, resulting in insufficient questioning by the physicians and a lack of historical information being provided by the patients. In the present case as well, accurate diagnosis was delayed after hospitalization until the patient provided the history of the foreign body insertion into the urinary tract. Although the patient inserted the foreign bodies for sexual purposes when he was an adolescent, they remained in place for years since he did not experience any pain or dysuria. The present case highlights the possibility that various foreign objects may be present in the body for prolonged periods because of sexual practices. Furthermore, other than central venous catheters, the presence of such foreign bodies for prolonged periods can be a risk factor for the development of candidemia, although they are not frequently recognized as a risk.

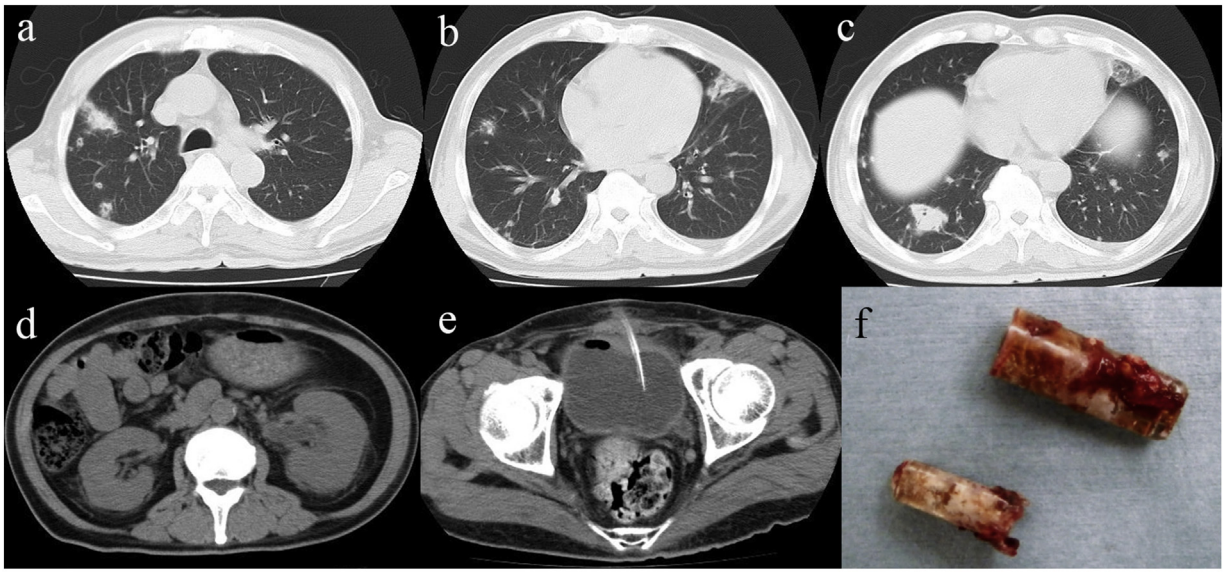

Fig. 3. Images of chest and abdomen CT on day 12 and foreign bodies after extraction.
Multiple nodular shadows were observed bilaterally in the lungs (a-c). After percutaneous cystostomy, the renal findings remained unchanged, and there was a large amount of urine retention in the bladder (d, e). Urethral foreign body findings: two cylindrical foreign bodies with the appearance of a smoking cessation pipe like plastics were extracted (f).

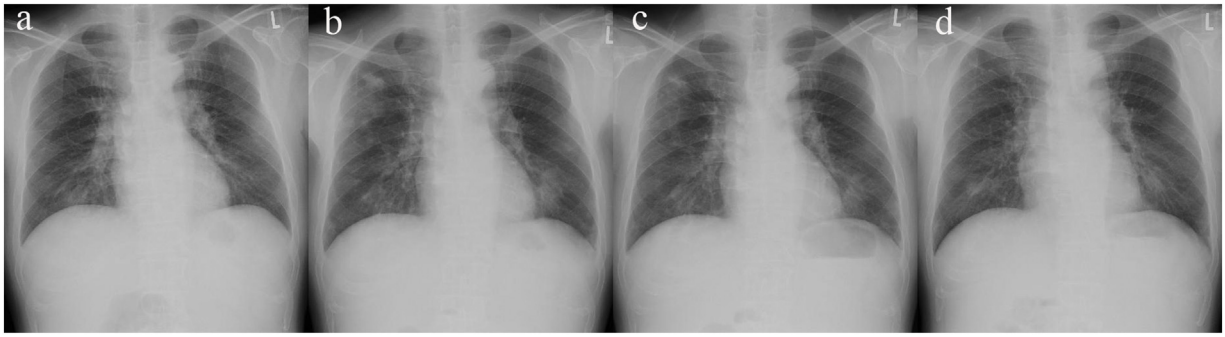

Fig. 4. Time course of chest x-ray imaging.
At the time of admission, there was only an invasive shadow in the lower right lung field (a), but multiple nodules and invasive shadow appeared bilaterally on day 12 (b). With anti-fungal drugs and surgery, these shades gradually improved by day 27 and 36 (c,d).

Table 3
Types of vesicourethral foreign body

Type	n	%
Thermometers, Pencils	231	15.4
Strings	227	15.1
Rubber products	154	10.2
Needles, Hairpins, etc.	145	9.6
Wax products	114	7.6
Vinyl Products	111	7.4
Plants	108	7.2
Metal products	108	7.2
Gauze and other products	307	20.3
Total	1505	100

A total of 1505 cases were obtained from combining Reference [18] and our one case here.

Table 4
Invasion pathways and causes of vesicourethral foreign body

Invasion pathways (causes)	n	%
Transurethral (subtotal)	919	61.0
Masturbation, Sex play	691	46.0
Urethral dilation	112	7.4
Others	116	7.6
Transbladder wall (subtotal)	405	27.0
Operation	297	19.8
Other iatrogenicities	30	2.0
Others	78	5.2
Unknown pathway (subtotal)	181	12.0
Total	1505	100

A total of 1505 cases were obtained from combining Reference [18] and our one case here.

Our patient also presented with severe diabetes mellitus at the time of diagnosis of candidemia. Diabetes mellitus promotes the growth of urinary fungi, decreases host resistance against fungal invasion, and promotes urinary stasis in the neurogenic bladder [20]. As a result, poorly controlled diabetes, which can also lead to the production of acidic urine, is a known risk factor for *Candida* UTI [21]. Therefore, severe diabetes mellitus was also likely a contributor to the development of candidemia in the current case.

Optimal treatment of candidemia requires the administration of appropriate antifungal agents and control of any underlying diseases that may cause immunosuppression. Echinocandins such as MCFG, caspofungin, and anidulafungin are recommended as the first-line antifungal agents for *C. glabrata* candidemia, which was detected in this case. In addition, it is important that the clinical efficacy and response be evaluated 3-5 days after the initiation of treatment [22,23]. It is also recommended that therapy be stepped down to oral VRCZ if the patient can tolerate oral intake and the fungal species is susceptible [22]. An alternative antifungal agent should be considered in case of resistance to VRCZ [23]. Regarding the duration of antifungal therapy, it is recommended that treatment be administered for two weeks after negative blood culture results are obtained and after the resolution of symptoms due to candidemia, in the absence of any apparent disseminated lesion [24–28]. Delay in the initiation of therapy has been shown to be a poor prognostic factor; wherein, the mortality rate was reported as 15.4% when treatment was initiated on the day of detection of *Candida* in the blood compared to 41.4% when initiated 3 days later [29]. In the present case, treatment with MCFG was initiated on the day of detection of *Candida* in the blood culture, which may have contributed to a better prognosis. It is important to emphasize that contamination of *Candida* in blood cultures is rare; therefore, treatment for candidemia should be initiated immediately after culturing the *Candida* spp. in blood samples [30].

Regarding the removal of urethral foreign bodies that have been present for an extended period, the transurethral approach may be difficult considering the chronic inflammation causing adhesion of the foreign bodies to the surrounding tissues and urethral stone formation. Therefore, an incisional surgical procedure may sometimes be necessary to remove the urethral foreign bodies, as was required in the present case.

In conclusion, we have reported a rare case of candidemia due to long-term presence of urethral foreign bodies complicated by severe diabetes mellitus. This case indicates that long-term presence of foreign bodies and acquired immune dysfunction are risk factors for candidemia. Therefore, detailed history should be obtained and systemic examination should be performed to identify the complicating risk factors on diagnosis of candidemia.

Authorship Statement

JN and TK performed the clinical assessments and finalized the manuscript. KI and FK provided feedback regarding treatment as experts of respiratory disease. MF and KM provided feedback regarding treatment as expert of the Urology department. TS, KY, JT, SD, and NT revised the manuscript critically for intellectual content. All the authors read and approved the final manuscript. All authors meet the ICMJE authorship criteria.

Declaration of Competing Interest

The authors report no declarations of interest.

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CRediT authorship contribution statement

Jun Nagata: Conceptualization, Data curation, Writing - original draft, Writing - review & editing, Supervision. **Takeshi Kawasaki:** Conceptualization, Writing - original draft, Writing - review & editing, Supervision. **Ken Iesato:** Writing - review & editing. **Toshihiko Sugiura:** Writing - review & editing. **Keita Yamauchi:** Writing - review & editing. **Junichi Tsuyusaki:** Writing - review & editing. **Masaaki Fujimura:** Writing - review & editing. **Fuminobu Kuroda:** Writing - review & editing. **Kazuo Mikami:** Writing - review & editing. **Steven M. Dudek:** Data curation, Writing - original draft, Writing - review & editing. **Nobuhiro Tanabe:** Writing - review & editing.

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