Candida Glabrata Fungemia After Amputation of an Infected Diabetic Foot

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A 58-year-old woman suffered from left pyelonephritis with diabetic triopathy on admission at which time a double J stent was inserted in the left ureter and was left untreated for a year. She was admitted due to fever, thirst, polydipsia, polyuria and, left 1,2-toe ulcer and vacuole. We diagnosed diabetic foot infections. We used 6 g of ampicillin-sulbactam and 40 μ g of alprostadil alfadex daily in addition to diet and insulin therapy for diabetes mellitus. As the toe lesion deteriorated, a left foot amputation was performed at the 11th day. The subfever continued and the consciousness level deteriorated from alert to 100 on the Japan coma scale and acute respiratory failure occurred 21 days after operation. Whole body computed tomography showed invasive lesions in bilateral pulmonary lower lobes and renal pelvic dilatation and perirenal abscess in left kidney indicating renal abscess. Milk-like urine was excreted. Urine and blood culture detected *Candida glabrata*. Fundoscopic exam showed retinal exudates indicating mycotic endophthalmitis. We diagnosed *Candida glabrata* sepsis from pyelonephritis. After using 200mg of micafungin daily, the patient recovered. In addition to exchanging the stent, treatment of diabetes mellitus is important for the prevention of severe infection. (Kitakanto Med J 2010 ; 60 : 259~263)

Key Words : diabetic gangrene, renal abscess, *Candida glabrata*

Introduction

The incidence of infection is higher than normal in diabetic patients and infectious complications resulting in death are more frequent.^{1,2} Impaired leukocyte functions such as chemotaxis and bactericidal activity in diabetic patients have been shown.³ Impaired monocyte chemotaxis has also been reported.⁴ Abnormalities in the microvascular circulation of diabetic patients generally result in decreased tissue perfusion.⁵ These abnormalities may increase the risk of infection and make treatment more difficult. Foot infections are common in diabetic patients and are associated with high morbidity and risk of lower extremity amputation.⁶ Diabetes mellitus is present in 39% of patients with fungal urinary tract infection.⁷ Urinary tract abnormalities occur in 37.7% and malignancy in 22.2%. *Candida albicans* is found in 51.8%

of patients and *Candida glabrata* in 15.6%.⁷ *Candida glabrata* is the second most common isolate of candidemia and the emergence of non-*albicans* species of *Candida* is the major cause of candidemia among diabetic patients.⁸ Here, we report a case of *Candida glabrata* fungemia after amputation of an infected diabetic foot.

Case report

A 58-year-old woman was admitted due to fever, thirst, polydipsia, polyuria, and left 1,2-toe injury and vacuole. She had suffered from left 1,2-toe injury for the previous 14 days and from fever, thirst, polydipsia and polyuria for the previous 3 days. Her weight was 52 kg at age 20. Her maximal weight was 87 kg at age 24. She was normally delivered at age 25. Diabetes mellitus was indicated at age 30, but thereafter she had not been treated. She suffered from left pyelone-

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phritis with diabetic triopathy at age 57. At that time a double J stent was inserted in the left ureter because the retrograde pyelography indicated intraureter polyp lesion. She then remained untreated for a year. Other diseases had not been indicated. She smoked 10/day and drank about 20g of alcohol daily. Her father and mother also had diabetes mellitus. Her physical examination showed the following: height 158.9cm, weight 47kg (body mass index: 18.6kg/m²), blood pressure 135/83mmHg, pulse rate 93/min, respiratory rate 24/min, temperature 38.4°C, consciousness alert. Fundoscopic examination showed background diabetic retinopathy. There were no abnormalities in the pharynx, chest or abdomen. There was no skin eruption. Diminished deep tendon reflexes and bilateral foot paresthesia indicated diabetic neuropathy. Left 1,2-toe ulcerative lesion with necrosis was detected. Laboratory data were as follows: chest X-ray film showed normal. Chest x-ray film showed normal

Fig. 1a Chest x ray film shows normal pulmonary field at the admission.

Fig. 1b Chest x ray film shows cardiomegaly and bilateral homogenous lesions in the bilateral middle to lower pulmonary field in the prone position.

pulmonary field (Fig. 1a). Electrocardiogram was within the normal range. Abdominal echogram showed a bright liver. Urinalysis showed proteinuria (100mg/dl), glycosuria (+) and blood + with sediment (red blood cell count 10/hpf, white blood cell count 30/hpf). The white blood cell count was 24700/ μ l (basophil 0%, eosinophil 0%, segmented leukocyte 65%, lymphocyte 25%, monocyte 10%). Albumin was 2.6g/dl, BUN; 29.8mg/dl, creatinine; 2.0mg/dl and C-reactive protein (CRP); 27.4mg/dl. Fasting blood glucose was 257mg/dl and HbA1c; 12.2%. The urinary C-peptide was 31 μ g/day. Creatinine clearance was 25.1ml/min. The urinary albumin excretion rate of 761mg/gCr indicated diabetic nephropathy. Toe wound culture revealed Staphylococcus aureus and blood culture was negative (Table 1). We diagnosed diabetic foot infections followed by Staphylococcus aureus due to untreated diabetes mellitus. We used 6g of ampicillin-sulbactam daily and 40 μ g of alprostadil alfadex daily in addition to diet and insulin therapy (Humalog mix 50) for diabetes mellitus. Although the Staphylococcus aureus was sensitive to ampicillin-sulbactam, the toe lesion did not recover and the fever continued. The left foot amputation was performed at the 11th day. After that the subfever continued and slight exudates were excreted from the operative lesion. We changed

Table 1 laboratory data on the 1st day

Urinalysis		ZTT	8.1u
protein	100mg/dl	TTT	4.2U
glucose	1.0g/dl	BUN	29.8mg/dl
blood	+	Cr	2.0mg/dl
acetone	(-)	UA	5.2mg/dl
RBC	10/hpf	Na	134mEq/l
WBC	30/hpf	K	4.2mEq/l
Hematology		Cl	97mEq/l
RBC	380 $\times 10^4$ / μ l	Ca	8.4mg/dl
Hb	11.1g/dl	amylase	35su/dl
Ht	32.6%	T-CH	146mg/dl
platelet	38.7 $\times 10^4$ / μ l	HDL-CH	40mg/dl
WBC	24700/ μ l	TRG	119mg/dl
Baso	0%	CRP	27.4mg/dl
Eosino	0%	FBG	257mg/dl
Seg	65%	HbA1c	12.2%
Lymph	25%	urine CPR	31 μ g/day
Mono	10%	Ccr	25.1ml/min
Chemistry		Urine protein	761mg/gCr
AST	24mU/ml	Serology	
ALT	16mU/ml	STS	(-)
LDH	223mU/ml	HBsAg	(-)
ALP	221mU/ml	anti-HCV Ab	(-)
γ -GTP	11mU/ml	Abscess culture	
total protein	7.6g/dl	St. aureus	
albumin	2.6g/dl	Blood culture	
T-Bil	0.7mg/dl	negative

Fig. 2a Chest computed tomography shows invasive lesions in bilateral pulmonary lower lobes.

Fig. 2b Abdominal computed tomography shows renal pelvic dilatation and perirenal abscess in the left kidney.

from ampicillin-sulbactam to 2g of cefozopran hydropchloride daily for covering gram-negative pathogen. The CRP decreased ranging from 11.3–12.5mg/dl to 5.1–6.2mg/dl. However, the subfever continued. The consciousness level deteriorated from alert to 100 on the Japan coma scale and acute respiratory failure occurred 21 days after operation (pH 7.407, pCO₂ 29.5 Torr, pO₂ 43.9Torr and HCO₃ 18.2mEq/l after the inhalation of 6l/min oxygen). Chest x-ray film showed cardiomegaly and bilateral homogenous lesions in the bilateral middle to lower pulmonary field in the prone position (Fig. 1b). Whole body computed tomography showed invasive lesions in bilateral pulmonary lower lobes (Fig. 2a) and renal pelvic dilatation and perirenal abscess in the left kidney indicating renal abscess (Fig. 2b). The electrocardiogram subsequently showed sinus tachycardia while axis deviation or STT change was not shown. The ultra cardiogram did not show abnormal valve and wall motion, or right ventricular dilatation. The white blood cell (WBC) count was 26900/ μ l (basophil 1%, eosinophil 2%, stab leukocyte 2%, segmented leukocyte 90%, lymphocyte 4%, monocyte 1%); hemoglobin; 10.1 g/dl and platelet count; 47.6 $\times$ 10⁴/ μ l. Renal function showed BUN; 26.2mg/dl and creatinine; 1.9mg/dl. Fasting blood glucose was 138 mg/dl and HbA1c 8.9%. The CRP was 14.7mg/dl. Urine pneumococcal Ag and legionella Ag were negative. Milk-like urine was excreted. Although the sputum culture showed normal flora, urine and blood culture detected *Candida glabrata*. β -D-glucan was 230pg/ml and mannan antigen 2u/ml (Table 2). Fundoscopic exam showed retinal exudates indicating mycotic endophthalmitis. We diagnosed candida glabrata sepsis from renal abscess. The patient was

Table 2 laboratory data 21 day after operation

Urinalysis		K	4.6mEq/l
protein	30mg/dl	Cl	98mEq/l
glucose	(-)	FBG	138mg/dl
blood	+	HbA1c	8.9%
acetone	(-)	CRP	14.7mg/dl
Hematology		Blood gas	
RBC	340 $\times$ 10 ⁴ / μ l	(nasal O ₂ 6l/min)	
Hb	10.1g/dl	pH	7.407
Ht	31.5%	pCO ₂	29.5 Torr
platelet	47.6 $\times$ 10 ⁴ / μ l	pO ₂	43.9 Torr
WBC	26900/ μ l	HCO ₃	18.2mEq/l
Baso	1%	Infection	
Eosino	2%	Urine pneumococcal Ag	negative
Stab	2%	Urine legionella Ag	negative
Seg	90%	β -D-glucan	230pg/ml
Lymph	4%	mannan Ag	2u/ml
Mono	1%	Sputum culture	normal flora
Chemistry		Urine culture	<i>Candida glabrata</i>
AST	37mU/ml	Blood culture	<i>Candida glabrata</i>
ALT	21mU/ml		
LDH	241mU/ml		
ALP	211mU/ml		
BUN	26.2mg/dl		
Cr	1.9mg/dl		
Na	130mEq/l		

moved to the intensive care unit where in addition to 100mg of amikacin sulfate and 1g of meropenem trihydrate for empiric therapy, a central vein pressure catheter was inserted and she was put on a respirator at low tidal volume ventilation and given 250mg of sivelestat sodium hydrate for acute respiratory failure. Administration of regular insulin aimed for a blood glucose range of 80 to 140mg/dl for intravenous hyperalimentation. After using 200mg of micafungin daily, the patient's fever gradually decreased and her respira-

Fig. 3 Clinical course of the patient

tory condition improved. The patient did not need the respirator after 5 days and she became alert. We stopped intravenous hyperalimentation and started diet therapy and subcutaneous insulin infusion therapy (Humalog mix 50) again. The patient's fever normalized with decrease in the white cell count, CRP and β -D-glucan levels (Fig. 3). We then exchanged the double J stent and have exchanged it every 6 months. Fundoscopic exam showed background diabetic nephropathy alone 3 weeks after mycotic endophthalmitis occurrence.

Discussion

The patient had clinical manifestations featuring *Candida glabrata* sepsis after amputation of an infected diabetic foot and untreated diabetes mellitus with microangiopathy. The patient suffered from left renal pyelonephritis and a double J stent was inserted in the left ureter a year previously. She was then left untreated for diabetes mellitus and the stent had remained for a year. *Staphylococcus aureus* induced diabetic foot infections may occur in cases of hyperglycemia and diabetic neuropathy.^{3,4,5} *Staphylococcus aureus* and β hemolytic streptococci are the most common pathogens in previously untreated diabetic foot infections.⁶ The *Staphylococcus aureus* was sensitive to Ampicillin-sulbactam in our case. However, the subfever continued after the amputation had been performed. Patients with severe diabetic foot lesions show a

polymicrobial etiology.^{6,9} After we changed from ampicillin-sulbactam to cefazopran hydrochloride for covering gram-negative pathogen, the CRP decreased but the subfever continued. At that time *Candida glabrata* surrounding the double J stent may have proliferated and caused left renal abscess. Urine and blood culture detected *Candida glabrata*. β -D-glucan was elevated and mannan antigen was positive. Fundoscopic exam showed retinal exudates indicating mycotic endophthalmitis. Therefore, we diagnosed *Candida glabrata* sepsis from renal abscess. Candidemia in critically ill patients is a significant source of mortality.¹⁰ Patients with prior surgery are at a higher risk fatality than others.¹¹ This is compatible with our case. *Candida glabrata* is the second most common isolate of candidemia and the emergence of non-albicans species of *Candida* is the major cause of candidemia among diabetic patients.⁸ The patient had suffered from hyperglycemia and diabetic neuropathy, and the double J stent had been inserted in the ureter for a year. Therefore, *Candida glabrata* may have remained alive surrounding the stent. An immunocompromised condition after leg amputation and broad-spectrum antibiotics such as cefazopran hydrochloride may have caused *Candida glabrata* to proliferate and may have induced left renal abscess following candidemia induced mycotic endophthalmitis and pulmonary infiltration. Therefore, we administered micafungin and then the condition improved. Treat-

ing *Candida glabrata* urinary tract infections can be difficult because the organism may be resistant to fluconazole. A newer antifungal agent, micafungin, provides an alternative and effective therapy against *Candida glabrata*.¹² It is important for the prevention of severe infection to treat diabetes mellitus in addition to exchanging the stent in the ureter regularly.

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