INTERNAL MEDICINE

□ CASEREPORT □

An Elderly Case of Type 2 Diabetes which Developed in Association with Oral and Esophageal Candidiasis

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Abstract

A 75-year-old woman who had been healthy except for mild glycemia and lipidemia discovered three and a half months before admission experienced severe dysphagia secondary to oral and esophageal candidiasis. She eventually developed diabetic hyperosmolar syndrome and ketoacidosis. Since anti-GAD antibody was negative and her diabetes was controlled with a moderate dose of insulin, we made a diagnosis of type 2 diabetes. Her only risk factors for candidiasis were hyperglycemia, age, and continuous denture use. The fact that her diabetes developed in association with oral candidiasis supports the hypothesis that there is a bidirectional interrelationship between diabetes and oral infection.

Key words: denture, candidiasis, hyperosmolar syndrome, ketoacidosis

(DOI: 10.2169/internalmedicine.46.1898)

Introduction

Candidiasis is one of the most common infections associated with diabetes. Most of the cases of diabetes-related candidiasis reported in Japan have been associated with chronic poor glycemic control (usually for years) and secondary factors such as 1) use of immunosuppressants, 2) malignant disease, 3) administration of intravenous hyperalimentation, and 4) antibiotic use. Below we report a case of newly diagnosed type 2 diabetes accompanied by severe oral candidiasis and esophageal candidiasis (OC and EC, respectively), in which there was an evidence that the diabetes and clinically evident *Candida* infection both developed within a short interval in the absence of any of the well-known secondary factors mentioned above.

Case Report

The patient was a 75-year-old woman who was found to have mild glycemia (fasting plasma glucose 117 mg/dl), mildly elevated hemoglobin A1c level (6.0%), and moderate lipidemia (total cholesterol 234 mg/dl, and fasting triglyceride 329 mg/dl) during an annual health checkup in early January 2005, but who was otherwise healthy. Her height was 151 cm, and body weight was 47 kg at the time of the checkup. She never smoked, rarely drank alcohol, and had no noteworthy medical history except for cataract surgery at 70 years of age and a cutaneous herpes zoster infection at 65 years of age. Her father died of laryngeal cancer, but there was no other family history of major illness. Notably, she had hardly any teeth and wore dentures almost constantly.

In early April 2005, she started a series of domestic trips and began to experience fatigue, thirst, and dysphagia during her trips. She had lost 5 kg in one week. In mid-April, her dysphagia became so severe that she could not eat solid food and could only drink water. A few days later, she went to a clinic by herself, and the physician noted very dry skin, a white coating in her mouth, fissured tongue, and signs of extreme exhaustion. Esophageal cancer was suspected. Gastric fiberscopy was performed the next day, and glucose was infused (approximately 16 g of glucose) during the examination. The examination revealed severe candidiasis of oral mucosa, larynx, and entire esophagus. The diagnosis of candidiasis was confirmed by staining esophageal specimens, and amphotericin B syrup was prescribed. The next evening, the patient was transferred to our hospital because she was confused and had a gait disturbance.

The patient soon lapsed into hypovolemic shock, and a

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Received for publication June 20, 2006; Accepted for publication November 14, 2006
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DOI: 10.2169/internalmedicine.46.1898

Table 1. Summary of the Laboratory Findings

Blood chemistry (day 1)		Blood cell count (day 1)		Serology exam (day 2)	
Albumin	3.6 g/dl	White blood cells	11700 /μl	HIV antibody (–)	
AST	20 IU/l	Neutrophils	81.8%	HBV antigen (–)	
ALT	55 IU/l	Lymphocytes	12.1%	HCV antibody (–)	
Lactate dehydrogenase	297 IU/l	Monocytes	5.0%	Anti-nuclear antibody (–)	
Alkaline phosphatase	400 IU/l	Eosinophils	0.7%	Rheumatoid Factor (–)	
Creatine kinase	349 IU/l	Basophils	0.4%	Candida antigen (–)	
Amylase	67 IU/l	Red blood cells	402×10^4 /μl	Anti-GAD antibody (–)	
Blood urea nitrogen	65.5 mg/dl	Hemoglobin	12.9 g/dl	IgG	961.0 mg/dl
Creatinine	1.74 mg/dl	Hematocrit	40.1 %	TSH	0.423 IU/l
Uric acid	16.9 mg/dl	Platelet	22.2×10^4 /μl	Free T_4	0.77 ng/dl
Na	144 mEq/l			CEA	3.4 ng/ml
K	5.5 mEq/l	Blood gas analysis (day 1)		CA19-9	9 U/ml
Cl	105 mEq/l	pH	7.196	SPan-1	13.8 U/ml
Total Cholesterol	160 mg/dl	PaO_2	107 mmHg		
HDL-Cholesterol	73 mg/dl	$PaCO_2$	17.1 mmHg	Fasting serum C-peptide	
Triglyceride	127 mg/dl	HCO_3^-	6.6 mmol/l	(day 2)	0.3 ng/ml
C-reactive protein	0.81 mg/dl	Base Excess	–21 mmol/l	(day 17)	0.8 ng/ml
Glucose	1369 mg/dl	Lactate	1.5 mmol/l		
HbA1c	10.6%			Urinary C-peptide (24 hr)	
		Blood total ketone bodies		(day 3)	6.8 μg/day
Urinalysis (day 2)		(day 2)	2.1 mmol/l	(day 4)	7.0 μg/day
Protein	(–)	(day 3)	1.2 mmol/l	(day 5)	23.9 μg/day
Glucose	(±)			(day 17)	33.1 μg/day
Ketone	(–)				
Occult Blood	(–)			Urinary albumin excretion	
Red blood cells	1-4 /HPF	Stool (day 5)		(day 17)	6.95 mg/gCr
White blood cells	1-4 /HPF	Occult Blood	(–)		

Not all of the examinations were performed on admission; hospital days corresponding to the times of the examinations are indicated in parentheses. AST, aspartate aminotransferase; ALT, alanine aminotransferase; HIV, human immunodeficiency virus; HBV, hepatitis B virus; HCV, hepatitis C virus; TSH, thyroid stimulating hormone; CEA, cartinoembryonic antigen.

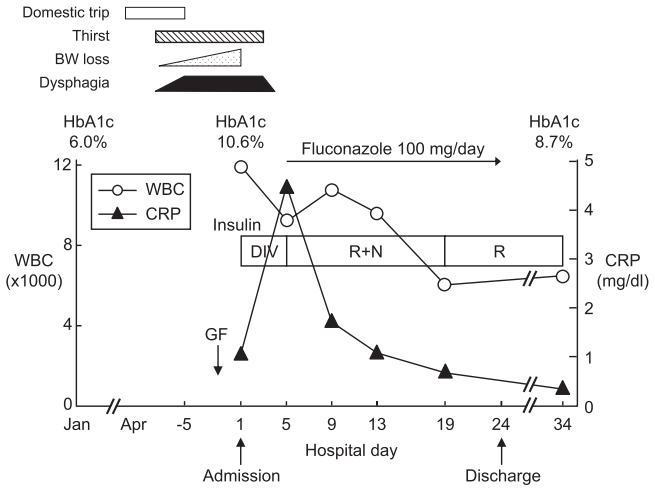

Figure 1. Clinical Course. The dysphagia improved and the patient resumed oral feeding prior to administration of fluconazole. However, the CRP level increased on hospital day 5, and the antifungal therapy was started. After day 34, she was referred to another hospital for follow-up. GF: gastric fiberscopy; DIV: drip infusion of regular insulin; R+N: three injections of regular insulin daily plus bedtime NPH insulin injection.

drip infusion was started immediately. Her body temperature was 36.5℃, and physical examination revealed a white coating of the oral cavity and severe dehydration. Her chest and heart were normal to auscultation, and no masses were found in the abdomen. We failed to notice the condition of her dentures because of the emergency admission.

Laboratory data showed severe hyperglycemia (plasma glucose 1,369 mg/dl), an elevated HbA1c level (10.6%), and renal dysfunction (Table 1). Serum lactate was mildly increased and the anion gap was very high (32.4 mEq/l). There was moderate acidemia (pH=7.196), and plasma osmotic pressure deduced from serum sodium, potassium, BUN, and glucose was very high (398 mOsm/l). Based on these findings, a diagnosis of diabetic hyperosmolar syndrome complicated by ketoacidosis was made.

Antinuclear antibody and rheumatoid factor were negative, and the immunoglobulin G level was within the normal range. A chest X-ray and abdominal CT scan did not show any abnormal findings, such as malignant disease or an abscess. An eye examination showed no evidence of diabetic retinopathy or fungal endophthalmitis, and *Candida* septicemia was ruled out by the blood culture and *Candida* antigen test. Anti-glutamic acid decarboxylase (GAD) antibody was negative. Urinary C-peptide excretion was impaired at first (8.3 μg/day), but after intensive insulin therapy it recovered to 33.1 μg/day (Table 1). The dysphagia improved even after discontinuation of amphotericin B syrup, and it was possible to resume oral feeding at the end of the month. However, the C-reactive protein value rose on day 5 (Fig. 1), and fluconazole was administered orally until the middle of the next month. Since glycemic control had improved, bedtime insulin was discontinued, and the patient was discharged on three injections of regular insulin a day (6 units before breakfast and 4 units each before lunch and dinner).

Her final visit to our hospital was on day 34, and she was referred to another local hospital at that time. Her diabetes has been well controlled with twice daily injections of a mixed type of insulin (30% of insulin aspart and 70% of insulin aspart protamine suspension), 8 units before breakfast and 4 units before dinner, and her hemoglobin A1c level was 6.5% at the 9-month follow-up examination. There have been no recurrences of the OC or EC. Since 1) anti-GAD antibody was not detected, 2) the urinary C-peptide excretion had recovered to a level that showed her diabetes was not insulin dependent, and 3) her diabetes control was stable on a moderate dose of insulin, the final diagnosis was type 2 diabetes.

Discussion

We have summarized the cases of glycemia-related OC and EC reported in Japan from 1995 to 2004 in Table 2. Except for case 9, in which there was impaired glucose tolerance (IGT), and case 10, in which diabetes was newly diagnosed, the OC and/or EC occurred in patients with long-term hyperglycemia (more than 2 years) or with repeated episodes of ketoacidosis (case 2 and case 7). Diabetes is considered as a risk factor for EC because of 1) impaired immunity and 2) stasis of esophageal contents as a manifestation of neuropathy (1). Although an oral glucose tolerance test was not performed in early January 2005 and latent dia-

DOI: 10.2169/internalmedicine.46.1898

Table 2. Summary of Case Reports of Diabetes-related Oral and/or Esophageal Candidiasis in Japan From 1995 to 2004

No.	Focus	Age	Sex	DM type	HbA1c (%)	Risk factor	Author	Year	Report type
1	EC	26	M	Type 1	15.1	DKA	Fujii M	1995	Abstract
2	EC	30	F	Type 1	12.7	DKA	Fujii M	1995	Abstract
3	EC	36	M	Type 1	?	Antibiotic	Akatsu S	1996	Abstract
4	EC	54	M	Type 2	?	Glycemia	Nishikawa S	1997	Abstract
5	EC	58	M	Type 2	?	Glycemia	Yamamoto H	2000	Abstract
6	OC+EC	38	M	Type 2	14.7	Glycemia	Ashidate K	2000	Article (ref.10)
7	OC+EC	25	F	Type 1	?	DKA	Okuno S	2000	Abstract
8	OC+EC	52	M	Type 2	?	DKA	Okuno S	2000	Abstract
9	OC	68	F	IGT	6.5	Denture	Maeda H	2003	Article (ref.4)
10	OC	42	M	Type 2	14.5	Glycemia?	Ashidate K	2004	Article (ref.16)

Information was obtained from abstracts or articles in Japanese journals. Only first authors are listed, and articles are cited in the references. 'DM type' denotes the type of glucose intolerance diagnosed. Abbreviations: EC, esophageal candidiasis; OC, oral candidiasis; DKA, diabetic ketoacidosis; and IGT, impaired glucose tolerance. In case 10, an antibiotic was administered prior to the diagnosis of OC, and no risk factor for OC was mentioned.

betes was not completely ruled out at that time, the fasting plasma glucose level and hemoglobin A1c value in the present case indicated that the duration of clinically overt diabetes was less than three and a half months, a duration that was unlikely to have been long enough to have caused chronic immune dysfunction or diabetic neuropathy.

OC in diabetes has recently been reviewed (2), and the evidence available is still limited. In several papers to address the correlation between OC and diabetes, we have had a deep interest in the hypothesis regarding the interrelationship between diabetes and oral infection that states that diabetes will trigger oral infection, and conversely that oral infection can promote insulin resistance and is also a risk factor for developing diabetes (3). Continuous denture wearing has been suggested to be a risk for OC (2), and our patient wore dentures almost all the time. We speculate that 1) her series of trips may have led to insufficient denture cleaning and increased contamination of her dentures, which was likely to have promoted *Candida* growth; 2) the clinical *Candida* infection may have promoted insulin resistance and worsened her diabetes; and 3) an increased glucose level in her saliva may have further encouraged *Candida* growth. This vicious cycle would contribute to the progression of type 2 diabetes and spread of candidiasis. Consistent with this speculation, a recent report described the case of an elderly Japanese woman whose only risk factors for OC were contaminated dentures and impaired glucose tolerance (IGT) (4). Dysphagia, especially in our aged patient, would easily lead to deterioration of nutritional status and dehydration, and that would have further contributed to insulin resistance and the spread of the *Candida* infection, and consequently, to extreme hyperglycemia. It was also likely that the patient consumed a substantial volume of glucose-containing beverages, which may have increased the glycemia and given rise to glucotoxicity, which causes pancreatic beta cell failure (5). It is not uncommon for type 2 diabetes to become complicated by ketoacidosis as a result of relative insulin deficiency, an increase in counterregulatory hormones, and severe dehydration (6).

Biological analyses have revealed mechanisms by which hyperglycemia triggers candidiasis specifically to diabetic patients; 1) neutrophil dysfunction, 2) impaired opsonization because of glucose binding to the third component of complement, and 3) virulence of the pathogens that enables them to grow rapidly in the hyperglycemic environment (7). *Candida albicans*, the most frequently detected *Candida* species in oral mucosa specimens from diabetic patients (8, 9), contains a glucose-inducible protein that inhibits phagocytosis (7). Thus, apart from the neutrophil dysfunction, hyperglycemia itself may be a risk factor for candidiasis. In fact, a middle-aged Japanese man who had repeated OC and EC was found to have no abnormalities of neutrophil function or lymphocyte proliferation, and it is noteworthy that his symptoms were not sufficiently controlled by antifungal drugs alone, but only in combination with insulin therapy (Table 2 case 6, ref. 10).

In light of the current review in odontology, however, whether or not hyperglycemia is an independent factor for OC remains a matter of controversy (2). Recent reports indicate that oral *Candida* carriage is not directly associated with age, denture wearing, gender, or glycemic control (8, 9). Even though glycemic control is not independently correlated with the *Candida* carriage, cases reported in Japan suggest a relationship between clinically evident OC and diabetes (Table 2 and this paper). The accumulation of multiple risk factors including hyperglycemia, denture wearing, improper tooth brushing, and aging may trigger OC and EC.

Many reports suggest that type 2 diabetes is a risk factor for periodontal disease (ref.11, for example), and conversely, a randomized controlled trial of the effectiveness of treatment of periodontal disease on glycemic control indicated that effective treatment of periodontal infection with doxycycline is associated with a reduction in the HbA1c level (12). Also, a Japanese study has indicated that poor glycemic control is associated with poor periodontal status, such as increased *Candida* on the tongue and that the oral microbial flora and salivary function improve after controlling fasting glycemia (13). Thus, there is increasing evidence for a bidirectional interrelationship between oral health and diabetes. Oral infection is common in the elderly, and poor dental health combined with systemic diseases such as diabetes may be associated with increased mortality (14). The present patient developed severe hyperglycemia and dehydration, and consequently a life-threatening diabetic complication. An oral hygiene program has shown significant improvement in colonization of the oral mucosa and dentures by *Candida* (15). Greater attention should be paid to oral health as a means of preventing serious systemic disease in the elderly.

We thank Dr M. Kishimoto for critical reading of this manuscript.

DOI: 10.2169/internalmedicine.46.1898

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