【 CASE REPORT 】

Severe Visceral Obesity, Fatty Liver and Diabetes after Orchiectomy for Prostate Cancer

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Abstract:
    A 79-year-old man without a history of diabetes underwent orchiectomy for prostate cancer. Eight months after the operation, he suffered severe deterioration of visceral fat deposition, fatty liver and diabetes. Treatment for diabetes with canagliflozin and dulaglutide resulted in improvement in his glycemic control, visceral fat and fatty liver. Visceral fat-dominant deposition, which differs from the typical course after androgen deprivation therapy, may have been associated with severe exacerbation of diabetes and fatty liver. Glycemic management with a sodium glucose cotransporter 2 (SGLT2) inhibitor and glucagon-like peptide (GLP)-1 receptor agonist may help improve the glucose metabolism, visceral fat deposition and fatty liver after orchiectomy.

Key words: orchiectomy, diabetes mellitus, visceral fat, fatty liver, SGLT2 inhibitor, GLP-1 receptor agonist

Introduction

Androgen deprivation therapy (ADT) including orchiectomy is used to treat prostate cancer and is widely performed, from the metastatic state to locally advanced cancer. The risk of metabolic syndrome (1, 2), fatty liver (3) and diabetes (4) is reportedly increased after ADT. The incidence of diabetes in particular is reported to be equivalent between patients who have received orchiectomy and those who have undergone medical castration (5). At 1 year after orchiectomy, the body weight is reported to increase by 2.9% (6). Subcutaneous fat accumulation is dominant compared with visceral fat in patients who have received ADT (6-10) and is the main cause of weight gain. Fasting plasma glucose and hemoglobin A1c (HbA1c) levels are reported to increase by 3.9% and 2.7% from baseline, respectively (6). Severe deterioration of diabetes may occur after ADT (11), but the pathophysiology underlying the development of severe hyperglycemia remains unclear. Furthermore, therapeutic strategies for metabolic syndrome that develops after ADT have not been well established.

We herein report a patient who developed severe diabetes after orchiectomy with severe visceral fat accumulation and fatty liver. The typical change in body composition after orchiectomy is subcutaneous fat accumulation. However, it is suggested that glucose tolerance may be markedly deteriorated in castrated patients with visceral fat accumulation and deterioration of fatty liver, which are the typical changes seen in metabolic syndrome. Treatment with a sodium glucose cotransporter 2 (SGLT2) inhibitor and glucagon-like peptide (GLP)-1 receptor agonist successfully improved the glucose metabolism and fatty liver.

Case Report

A 79-year-old man was admitted to our hospital for the treatment of diabetes. He had undergone orchiectomy for prostate cancer (T2bN0M0 Stage B, Gleason score 8) eight months earlier. His preoperative body weight was 81 kg, and he had gained 4 kg of body weight within 6 months after the operation. He had not been diagnosed with diabetes mellitus before the operation, and his preoperative postprandial blood glucose and HbA1c were 115 mg/dL and 6.6%, respectively. His preoperative prostate-specific antigen (PSA) concentration was 8.334 ng/mL.

He had felt thirst and polyuria and lost 10 kg of body weight in the previous 2 months. He visited a clinic due to

Table 1. Laboratory Data on Admission.

Urinalysis		Glucose metabolism		Lipid profile	
pH	5.0	Fasting plasma glucose	210 mg/dL	TG	225 mg/dL
Protein	-	Fasting CPR	1.63 ng/mL	TC	145 mg/dL
Glucose	4+	HbA1c	12.3 %	HDL-C	32 mg/dL
Ketone	-	Glucagon stimulation test		LDL-C	68 mg/dL
Blood	-	Glucose (0 min)	172 mg/dL	Serology	
UACR	29.4 mg/gCr	CPR (0 min)	2.33 ng/mL	PSA	0.739 ng/mL
CBC		Glucose (6 min)	186 mg/dL	CEA	2 ng/mL
WBC	6,370 /μL	CPR (6 min)	6.68 ng/mL	CA19-9	10.9 U/mL
RBC	435 ×10^4/μL	Anti-GAD antibody	<5.0 U/mL	HBsAg	-
Hb	13.0 g/dL	Anti-insulin antibody binding rate	<0.4 %	HCVAb	-
Ht	42.8 %	Anti-insulin antibody level	<125 nU/mL	IgG	1,203 mg/dL
Plt	17.9 ×10^4/μL	Anti-IA2 antibody	<0.6 U/mL	IgA	356 mg/dL
Biochemistry		Endocrinology		IgM	107 mg/dL
TP	7.0 g/dL	Total testosterone	0.14 ng/mL		
Alb	4.1 g/dL	Free testosterone	1 pg/mL		
BUN	18 mg/dL	Estradiol	<10 pg/mL		
Cre	1.05 mg/dL	GH	0.54 ng/mL		
eGFR	37.7 mL/min/1.73m^2	IGF-1	76 ng/mL		
AST	21 IU/L	LH	28.4 mIU/mL		
ALT	21 IU/L	FSH	57.25 mIU/mL		
γ-GTP	36 IU/L	ACTH	48.2 pg/mL		
ChE	310 U/L	Cortisol	16 μg/dL		
		TSH	1.38 μIU/mL		
		FT4	1.23 ng/dL		

γ-GTP: gamma glutamyl transpeptidase, ACTH: adrenocorticotropic hormone, Alb: albumin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, CA19-9: carbohydrate antigen 19-9, CBC: complete blood count, CEA: Carcinoembryonic antigen, ChE: choline esterase, CPR: C-peptide immunoreactivity, Cre: creatinine, CRP: C-reactive protein, eGFR: estimated glomerular filtration rate, FSH: follicle stimulating hormone, FT4: free thyroxine, GAD: glutamic acid decarboxylase, GH: growth hormone, Hb: hemoglobin, HbA1c: hemoglobin A1c, HBsAg: hepatitis B surface antigen, HCVAb: Hepatitis C virus antibody, HDL-C: high-density lipoprotein cholesterol, Ht: hematocrit, IA2: insulinoma antigen 2, IGF-1: insulin-like growth factor-1, IgG: immunoglobulin G, IgA: immunoglobulin A, IgM: immunoglobulin M, LDL-C: low-density lipoprotein cholesterol, LH: luteinizing hormone, Plt: platelet, PSA: prostate-specific antigen, RBC: red blood cell, TC: total cholesterol, TG: triglyceride, TP: total protein, TSH: thyroid stimulating hormone, WBC: white blood cell

his thirst three days before admission and underwent laboratory tests. His postprandial plasma glucose was 518 mg/dL, and HbA1c was 11.9% at the test. Based on these findings, he was admitted to our hospital for the treatment of hyperglycemia.

He had taken medication for hypertension, dyslipidemia and paroxysmal atrial fibrillation. He had no family history of diabetes. His ethanol intake was under 30 g a day. His body temperature, blood pressure and pulse on admission were 35.6 °C, 113/65 mmHg and 88 bpm, respectively. His body weight and body mass index (BMI) were 75 kg and 25.6 kg/m², respectively. In the glucagon stimulation test, the C-peptide immunoreactivity (CPR) level increased from 2.33 ng/mL in the fasting state to 6.68 ng/mL at 6 minutes after the 1-mg glucagon injection; his endogenous insulin secretion was therefore deemed to be preserved. Anti-glutamic acid decarboxylase antibody and anti-insulin antibody were negative. His prostate-specific antigen (PSA) concentration on admission was 0.739 ng/mL. His postoperative serum free testosterone concentration was 1 pg/mL, and the serum level of estradiol was below detection. Thyroid and adrenal function test findings were normal (Table 1).

Abdominal computed tomography (CT) on admission showed a markedly lower liver intensity than preoperative CT; the liver-to-spleen ratio (L/S ratio) had decreased from 1.00 on preoperative CT to 0.37 on admission CT (Figure a, b). During the 8 months after surgery, the visceral fat area and subcutaneous fat area at the position of the omphalic portion calculated on CT had increased by 40.8% and 15.9%, respectively (Table 2). Liver function test findings were normal. Tests for viral hepatitis, anti-nuclear antibody and anti-mitochondrial M2 antibody were negative. Hypergammaglobulinemia was not found (Table 1).

We diagnosed him with severe diabetes after orchiectomy, and the rapid deterioration of visceral fat accumulation was attributed to the clinical course of diabetes and fatty liver. He was administered multiple daily insulin injection (MDI) therapy with the SGLT2 inhibitor canagliflozin at 100 mg/day and sitagliptin at 50 mg/day. His blood glucose was well controlled by one-week treatment with MDI. After his blood glucose level had been reduced, his insulin regimen was changed to insulin aspart/insulin degludec combination formulation twice daily, and sitagliptin was changed to du-
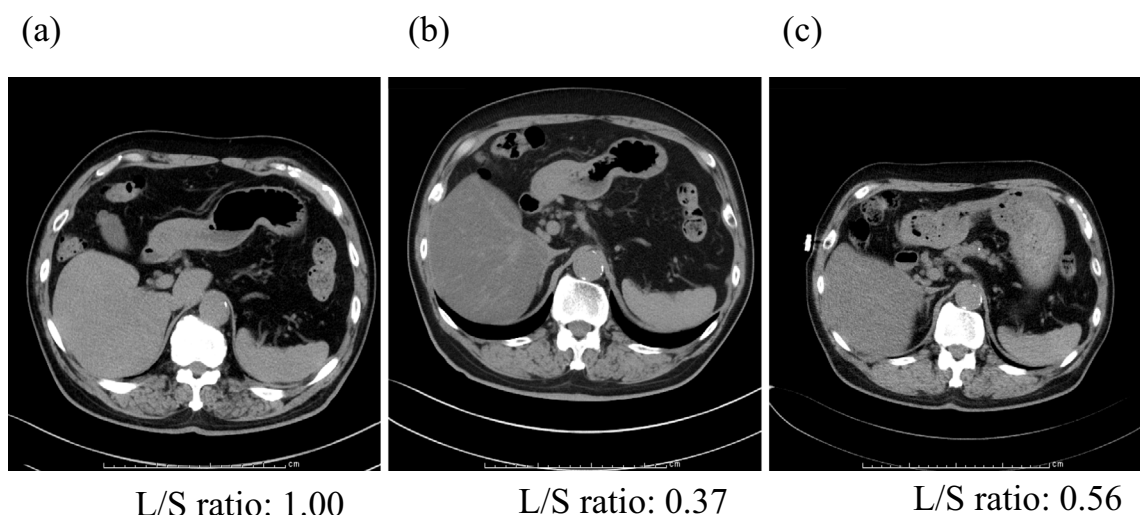
(a)   (b)   (c)

L/S ratio: 1.00   L/S ratio: 0.37   L/S ratio: 0.56

Figure. The time course of liver intensity on abdominal CT. Compared to preoperative CT findings eight months before admission (a), CT on admission (b) showed a markedly lower liver intensity. Two weeks after the initiation of treatment, the liver intensity showed an improving trend (c). CT: computed tomography, L/S ratio: the liver-to-spleen intensity ratio

Table 2. Time Course of the Visceral Fat Area of the Omphalic Portion on CT.

	Preoperative (cm^2)	Admission (cm^2)	Rate of change from operation to admission (%)	Two weeks after initiation of treatment (cm^2)
Total fat area	375.05	476.03	26.9	438.90
Visceral fat area	165.76	233.50	40.9	217.39
Subcutaneous fat area	209.29	242.54	15.9	221.51

CT: computed tomography

laglutide injection 75 mg once a week. CT performed two weeks after the initiation of treatment revealed obvious improvement in the L/S ratio (Figure c) and a reduction in both the visceral and subcutaneous fat area (Table 2).

Discussion

This is a valuable case highlighting the fact that patients after orchiectomy can develop marked visceral fat accumulation and fatty liver and severe deterioration of diabetes. This case also suggests that glycemic management with an SGLT2 inhibitor and GLP-1 receptor agonist is effective for managing metabolic side effects related to ADT.

Visceral fat accumulation is generally greater than that of subcutaneous fat in typical cases with metabolic syndrome (12), while subcutaneous fat accumulation is a major characteristic of patients who have received ADT. Visceral fat accumulation has thus far received only limited attention in men treated with ADT. Orchiectomy results in a rapid decrease in the serum concentrations of testosterone. Testosterone is involved in the enhancement of adiponectin in adipose tissue, insulin sensitivity in muscle and liver and insulin secretion in β cells via androgen receptor (13). Testosterone deficiency thus results in fat accumulation and systemic insulin resistance, subsequently increasing the risk of metabolic syndrome and diabetes. However, the mechanism un-

derlying the subcutaneous fat-dominant deposition after ADT remains unclear. A constant increase in subcutaneous fat is observed in mice who have undergone orchiectomy; however, visceral fat is increased only in high-fat-diet (HFD)-fed castrated mice; the Firmicutes/Bacteroidetes ratio and Lactobacillus species are also increased in the feces of HFD-fed castrated mice (14). Intestinal microbiota alteration, or "dysbiosis", has been implicated in type 2 diabetes and obesity. Energy-rich diets result in a reduction in the number of species that produce short-chain fatty acids (SCFAs). Reduced proportions of SCFAs can alter the body's energy absorption efficiency and promote fat accumulation. Furthermore, the gut microbiome in obese patients may be associated with chronic low-grade inflammation and endotoxemia through lipopolysaccharides. Fat deposition and chronic inflammation related to dysbiosis is thought to be related to insulin resistance. Some antidiabetic drugs, such as metformin and GLP-1 receptor agonist, can alter the microbiome and may thereby help improve obesity and insulin resistance (15). In patients who have received ADT, changes in the lifestyle, particularly due to diet therapy, may lead to alterations in the intestinal microbiota and exacerbation of visceral obesity.

Visceral fat accumulation is independently associated with insulin resistance rather than being a result of sex steroid deficiency in patients who have undergone ADT (16). In the

present case, the visceral fat area was obviously increased compared with the subcutaneous fat area, suggesting that the deterioration of visceral obesity was related to the severe exacerbation of diabetes and fatty liver. The patient's drinking habits might have been involved in the visceral fat accumulation and fatty liver. The rapid accumulation of visceral fat and fatty liver after orchiectomy may have been associated with severe insulin resistance and subsequent deterioration in diabetes. A longitudinal study should be conducted to investigate the relationship between variations in the fat distribution and glucose metabolism in patients who have received ADT.

There is no specific consensus concerning the treatment of metabolic disorders after ADT. Lifestyle modification is recommended for the prevention of metabolic disorders, and the treatment of individual diseases is performed according to local guidelines. However, metformin was able to prevent metabolic syndrome after ADT in non-diabetic men (17). Some anti-diabetic drugs may help improve the metabolic changes after ADT. Treatment with SGLT2 inhibitors is reported to improve fatty liver in diabetes (18). GLP-1 receptor agonists are reported to improve nonalcoholic steatohepatitis via adenosine monophosphate-activated protein kinase (AMPK) activation (19, 20) and reduce visceral and intrahepatic fat (21). In the present case, treatment with canagliflozin and dulaglutide may have influenced the improvement in the fatty liver as well as glycemic control. ADT is a known risk factor of cardiovascular disease. SGLT2 inhibitors (22) and GLP-1 receptor agonists (23, 24) have been shown to be useful for cardiovascular disease prevention, so the use of an SGLT2 inhibitor and GLP-1 receptor agonist in the present patient may have played an important role in the management of metabolic disorders after ADT.

In conclusion, we encountered a patient who developed severe diabetes after orchiectomy along with the rapid deterioration of visceral fat accumulation and fatty liver. The incidence of prostate cancer is likely to increase in aging Asia. The possibility of severe deterioration of metabolic conditions should therefore be noted. Appropriate treatment for metabolic side effects of ADT should also be evaluated; treatment with an SGLT2 inhibitor and GLP-1 receptor agonist may be effective for improving the glucose metabolism and fatty liver after ADT.

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