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A Case of Significant Fibrosis in Irradiation Field After Salvage Radiation Therapy for Postprostatectomy Biochemical Recurrence

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An 80-year-old man received salvage radiation therapy for prostate-specific antigen recurrence of prostate cancer after prostatectomy. Urinary retention and edema of both legs developed 1 year and 3 months after initiation of radiation therapy. Imaging showed significant fibrosis in the radiation field. Histological findings were characteristic of ischemic changes, but not retroperitoneal fibrosis or fibrosarcoma. Development of significant fibrosis with accompanying symptoms after postoperative radiation therapy is rare in prostate cancer. The patient's history of heavy smoking and arteriosclerotic diseases（e.g., cerebral infarction and carotid artery stenosis）, in addition to an elevated D-dimer level confirmed by blood test, suggested the presence of underlying advanced vascular endothelial disorders and microvascular circulatory disorders. Significant fibrosis was likely caused by the patient's underlying condition in addition to surgery and extensive radiation to the pelvis.

Keywords: prostate cancer, postoperative, prostate-specific antigen recurrence, salvage radiotherapy

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INTRODUCTION

It is widely known that fibrosis develops within the radiation field in the skin, subcutaneous tissue, lungs, gastrointestinal tract, and genitourinary tract after radiation therapy［1, 2］. We encountered a patient who developed fibrosis in the radiation field and accompanying symptoms after salvage radiation therapy for prostate-specific antigen（PSA）recurrence that occurred after prostatectomy for prostate cancer. Salvage radiation therapy for PSA recurrence is explained in guidelines［3］and widely used as a standard therapy, but rarely associated with marked fibrosis with accompanying symptoms. Here we report our case with a literature review.

CASE REPORT

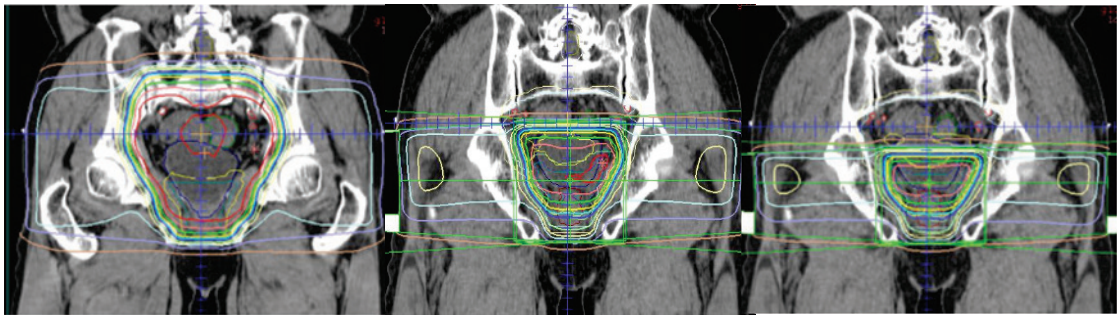
The patient was an 80-year-old man who had a past medical history and comorbidities that included prostatic hypertrophy, cerebral infarction, carotid artery stenosis, hypertension, and hyperlipidemia. He also had a history of heavy smoking（80 cigarettes a day for 60 years）. Robot-assisted laparoscopic radical prostatectomy（RALP）and extended lymphadenectomy were performed to treat the prostate cancer. Pathology revealed that the tumor was pT3bN1M0 and pStageIV, and the surgical margin was positive. PSA recurrence of prostate cancer was diagnosed 1 year and 5 months after surgery and treated by salvage radiation therapy with hormone therapy. The patient provided written informed consent after hearing detailed explanation about radiation therapy and being informed of their right to reject the therapy.

The prostate bed, seminal vesicles bed, and regional lymph node area were irradiated with 50.4

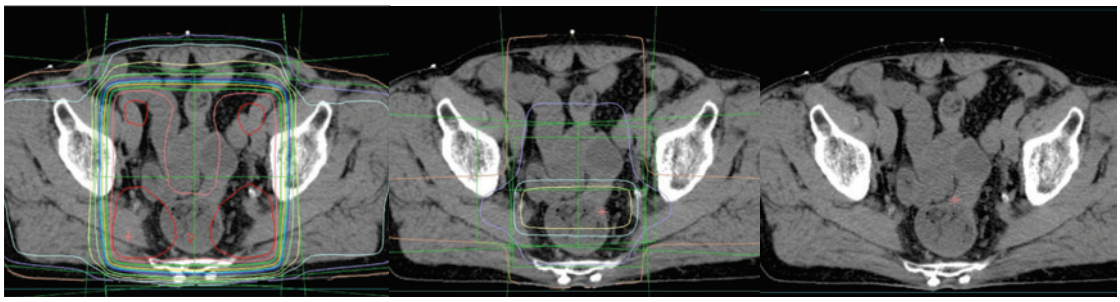
Gy/28 fractions (treatment 1; Fig. 1a and 1d), followed by irradiation of the prostate bed and seminal vesicles bed with 9 Gy/5 fractions (treatment 2; Fig. 1b and 1e), and irradiation of the prostate bed only with 7.2 Gy/4 fractions (treatment 3; Fig. 1c and 1f). The total dose was 66.6 Gy. All treatments were performed using 10 mega-volt X-rays.

The PSA level remained low, but urinary retention and edema of both legs developed 1 year and 3 months after initiation of radiation therapy. Blood test results at this point are shown in Table 1. Computed tomography (CT) confirmed wall thickening of the rectum, bladder, and ureters, and a retroperitoneal tumor in the position corresponding to the radiation field (Fig. 2a and 2b). ^{18}F-fludeoxyglucose (FDG) positron emission tomography (PET)/CT confirmed FDG accumulation (SUVmax of 4.0 in the early phase, and 4.1 in the delayed phase) in the position corresponding to the tumor. No other abnormal FDG uptake was observed (Fig. 2c). T2-weighted magnetic resonance (MR) images demonstrated most of these regions showed hyperintense, suggesting edematous changes. And some showed hypointense like pieces of string, suggesting fibrosis. Diffusion-weighted imaging showed mildly high signal and apparent diffusion coefficient (ADC) was mildly decreased (Fig. 2d-2f).

We checked irradiated dose in these regions using radiation therapy planning system. Around the rectum and bladder were irradiated with 60-67 Gy at the level of the prostate and seminal vesicle bed, and about 50 Gy more cephalad. Retroperitoneal area including anterior surface of sacrum was irradiated with 50-57 Gy.



(a) (b) (c)

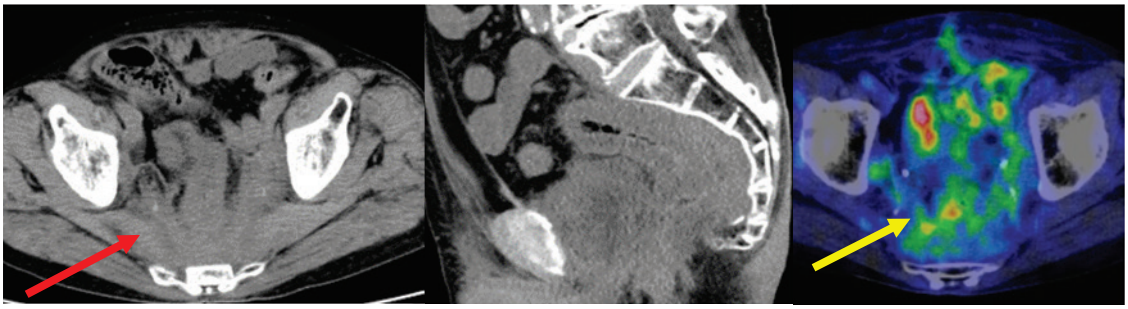


(d) (e) (f)

Figure 1: Dose distribution of salvage radiation therapy
a: Dose distribution on a coronal image, taken in treatment 1
b: Dose distribution on a coronal image, taken in treatment 2
c: Dose distribution on a coronal image, taken in treatment 3
d: Dose distribution on an axial image at the same slice level as Figure 2a, taken in treatment 1
e: Dose distribution on an axial image at the same slice level as Figure 2a, taken in treatment 2
f: Dose distribution on an axial image at the same slice level as Figure 2a, taken in treatment 3

Malignancies, amyloidosis, and IgG4-related disease were suspected. Cystoscopy with bladder biopsy and rectal endoscopy with biopsy were performed to examine wall thickening of the bladder and the rectum, respectively. Open biopsy was performed to examine the retroperitoneal tumor. Bladder biopsy showed only edema, fibrosis, and mild inflammatory cell infiltration (Fig. 3a). Rectal biopsy showed lymphocytic infiltration and increases in collagenous fibers between rectal crypts, with some crypts exhibiting a ghost-like appearance. These results suggested ischemic changes, which were consistent with finding of radiation proctitis (Fig. 3b). Biopsy of the retroperitoneal tumor indicated replacement of adipose tissue with connective tissue comprising collagenous fibers. Fibroblasts and mild lymphocytic infiltration, but not neoplasms, were observed, which were different from findings associated with retroperitoneal fibrosis and fibrosarcoma (Fig. 3c).

These pathological findings indicated post-



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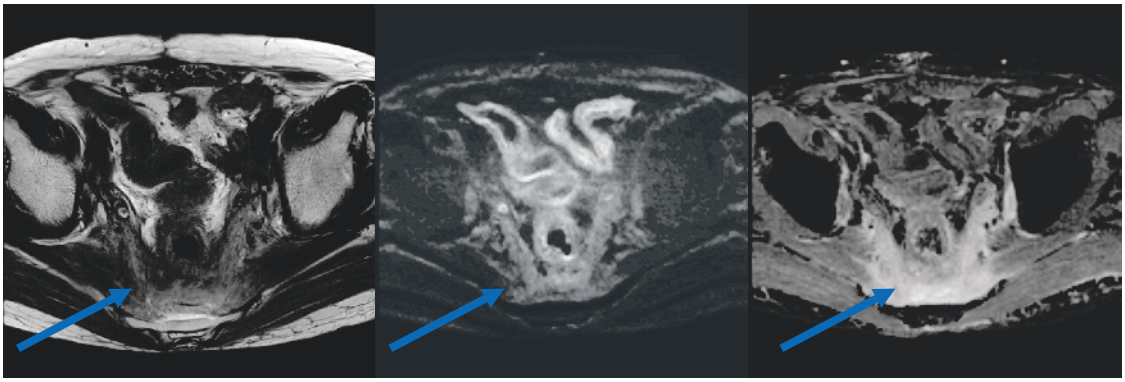


(d) (e) (f)

Figure 2: Computed tomography (CT) taken 1 year and 3 months after initiation of radiation therapy confirmed wall thickening of the rectum, bladder, and ureters, and a retroperitoneal tumor in the position corresponding to the radiation field (red arrow). FDG-position emission tomography (PET)/CT confirmed FDG accumulation (yellow arrow). T2-weighted magnetic resonance (MR) images demonstrated most of these regions showed hyperintense, suggesting edematous changes. And some showed hypointense like pieces of string, suggesting fibrosis. Diffusion-weighted imaging showed mildly high signals, and apparent diffusion coefficient (ADC) map showed mildly low signals (blue arrows).

a: A CT image acquired in the axial plane
b: A CT image acquired in the sagittal plane
c: FDG-PET/CT, fusion image acquired in the axial plane
d: A T2-weighted MR imaging acquired in axial plane
e: A Diffusion-weighted imaging acquired in axial plane
f: An ADC map acquired in axial plane

Table 1. Labolatory findings

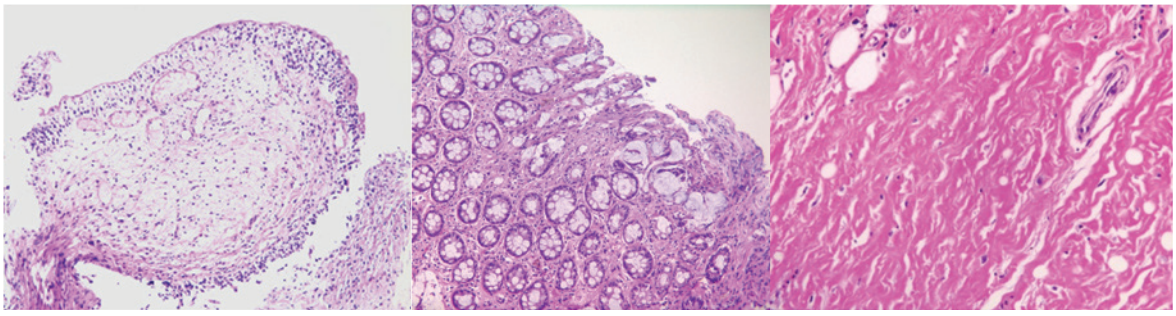
Blood cell count		**Coagulation**	
WBC	5,790 /μL	PT (sec)	12.6 sec
RBC	357×10^6 /μL	PT (%)	87.3 %
Hb	10.8 g/dL	PT-INR	1.08
Ht	33.6 %	APTT	31.8 sec
Plt	21.4×10^4 /μL	Fib	776 mg/dL
		D-dimer	1.6 μg/mL
Blood chemistry			
TP	6.9 g/dL		
Alb	3.4 g/dL		
T-Bil	0.5 mg/dL		
AST	25 IU/L		
ALT	20 IU/L		
LDH	226 IU/L		
BUN	22.2 mg/dL		
Cr	1.39 mg/dL		
Na	141 mmol/L		
K	4.2 mmol/L		
Cl	109 mmol/L		
Ca	8.9 mg/dL		
CRP	2.72 mg/dL		

radiation change, not malignancy. Bilateral ureteral stents placement was performed for urinary retention caused by bilateral ureteral stenoses, and the patient was put on observation. Urinary retention was alleviated but edema of both legs persisted.

DISCUSSION

Fibrosis is one of the late adverse events that occur after radiation therapy and has been reported as radiation-induced fibrosis (RIF) [1, 2]. According to these previous reports, recruitment of mesenchymal stem cells and mesenchymal fibroblasts to the radiation field is enhanced by cytokine production in response to DNA damage caused by radiation and cell injury caused by radiation-generated free radicals; these cells become myofibroblasts via TGF-b signals released from macrophages. An excess of myofibroblasts causes tissue fibrosis.

There are many risk factors for RIF. Therapy-related factors include total radiation dose, single dose, volume of tissue irradiated, combination with chemotherapy, and combination with surgery [4-6]. Patient-related factors include the presence of systemic scleroderma, systemic lupus erythematosus, and Marfan syndrome [7, 8]. Thus, radiation therapy to the wide pelvic area with previous surgery



(a) (b) (c)

Figure 3: Biopsy images 1 year and 3 months after initiation of radiation therapy
a: Bladder biopsy, hematoxylin-eosin (HE) staining, low-power magnification
b: Rectal biopsy, HE staining, low-power magnification
c: Open biopsy of a retroperitoneal tumor, HE staining, high-power magnification

might have increased the risk of RIF in our case. However, it is rare to develop significant fibrosis, as observed in this case, with these two factors only.

There are three possible factors for significant RIF in our case. The first factor is that the patient had a history of heavy smoking. Steinberger et al. reported that smoking contributed to increases in urinary late adverse events in patients who had undergone radical irradiation for prostate cancer [9]. Furthermore, smoking is said to cause functional impairment of vascular endothelial cells [10], and microvascular circulatory disorder is implicated in increases in acute and late adverse events associated with radiation therapy [11].

The second factor is that the patient had a history of arteriosclerotic diseases such as cerebral infarction and carotid artery stenosis. Because disorders of vascular endothelial cells have been considered an important element of atherosclerosis [12], arteriosclerotic disease might have caused functional impairment of vascular endothelial cells in the patient.

The third factor is that the patient had an elevated D-dimer level, indicative of the presence of secondary fibrinolysis, suggesting the preexistence of thrombi, in other words, thrombogenic tendency. Given the close relationship between D-dimer increases and peripheral atherosclerosis [13], thrombogenic tendency and peripheral atherosclerosis might have caused microvascular circulatory disorder in the patient. In such a situation, the tissue is in a hypoxic state where generation of active oxygen species, activation of inflammatory cytokines, and consequent enhancement of fibrosis occur [14, 15].

Taken together, it is likely that significant fibrosis was caused by preexisting advanced vascular endothelial disorder (suggested by the patient's history of heavy smoking and arteriosclerotic disease) and microvascular circulatory disorder based on thrombogenic tendency and peripheral atherosclerosis in addition to surgery and extensive radiation to the pelvis.

CONCLUSION

We encountered a patient with significant fibrosis after radiation therapy for postoperative PSA recurrence of prostate cancer. Findings suggested involvement of advanced vascular endothelial disorder, indicated by the patient's history of heavy smoking and arteriosclerotic disease, and microvascular circulatory disorder in the development of the fibrosis.

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