CASE REPORT

가려움증 및 담즙정체로 발현한 전립선암

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Prostate Cancer Presenting with Pruritus and Cholestasis

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Jaundice is a rare symptom of the paraneoplastic syndrome associated with prostate cancer. We report a case of metastatic prostate cancer that presented as jaundice. There was an absence of biliary obstruction and hepatic metastasis; therefore, the paraneoplastic syndrome was suggested as the etiology of cholestasis. Jaundice improved with the treatment of prostate cancer. In the literature, interleukin-6 has been suggested to be associated with paraneoplastic syndrome. (*Korean J Gastroenterol* 2021;78:59-64)

Key Words: Prostatic neoplasms; Cholestasis; Paraneoplastic syndromes; Interleukin-6

INTRODUCTION

An extrahepatic malignant tumor can be associated with cholestasis. When hepatic metastasis, bile duct obstruction, or other causes are ruled out, cholestasis may be attributed to the remote effect of a tumor. This is called paraneoplastic syndrome.

We report a case of a man who presented with paraneoplastic jaundice as a manifestation of prostate cancer. Cholestasis improved with androgen deprivation therapy.

CASE REPORT

An 81-year-old man visited Kangwon National University Hospital with complaints of pruritus and jaundice. He developed

pruritus 2 months ago and visited the dermatology department. Subsequently, jaundice was confirmed, and he was referred to department of internal medicine for further evaluation.

He had a weight loss of 9 kg over 2 months and complained of dark urine for the previous 2 weeks. He had no abdominal pain and fever. He had undergone left total hip replacement arthroplasty surgery 9 years ago. There was no other medical history, including hypertension, diabetes, and chronic liver disease.

He was a current smoker (40 pack-years) and had stopped drinking alcohol 1 year ago. He did not take any toxic substances or herbal medication.

Physical examination revealed icteric sclera, and there was no mass or tenderness observed on abdominal examination. The results of laboratory tests were as follows: white blood

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cell count $6,800/\mu\text{L}$ (reference range $3.8\text{--}10.0\times 10^3/\mu\text{L}$), hemoglobin 12.1 g/dL ($13.3\text{--}16.5\text{ g/dL}$), platelet count $529,000/\mu\text{L}$ ($140\text{--}400\times 10^3/\mu\text{L}$), total bilirubin 23.0 mg/dL ($0.3\text{--}1.2\text{ mg/dL}$), direct bilirubin 16.84 mg/dL ($0\text{--}0.40\text{ mg/dL}$), GGT 81 U/L ($0\text{--}73\text{ U/L}$), AST 50 U/L ($0\text{--}34\text{ U/L}$), ALT 32 U/L ($10\text{--}49\text{ U/L}$), ALP 678 U/L ($45\text{--}129\text{ U/L}$), and CRP 0.524 mg/dL ($0\text{--}0.500\text{ mg/dL}$). BUN, creatinine, sodium, potassium, chloride, glucose level, and prothrombin time were within their normal limits. The serologic tests for viral hepatitis were negative. Anti-nuclear and mitochondrial antibodies were negative. The ceruloplasmin level was 42.0 mg/dL ($15.0\text{--}30.0\text{ mg/dL}$) and the IgG level was 783 mg/dL ($700\text{--}1,600\text{ mg/dL}$).

CT did not reveal a hepatic mass, bile duct dilatation, or obstruction (Fig. 1A). It showed a heterogeneous enhancement of the prostate, lymph node enlargement in bilateral iliac chains, and diffuse presence of osteoblastic lesions in the axial skeleton, which were suggestive of prostate cancer

with metastasis (Fig. 1B). The whole body bone scan with technetium-99m was suggestive of multiple bone metastases (Fig. 1C).

The serum prostate-specific antigen (PSA) level was elevated (59.68 ng/mL , reference range $0\text{--}4\text{ ng/mL}$), and the carbohydrate antigen 19-9 level was within the reference range. Ultrasonography-guided prostate biopsy revealed adenocarcinoma. The Gleason score was 7 (4+3) (Fig. 2A). A liver biopsy was also performed, and it showed marked cholestasis and nodular inflammation. However, fatty change, interface hepatitis, bile duct damage, granuloma, and malignant cell infiltration were not present (Fig. 2B).

PET/CT revealed diffuse osteosclerotic change with hypermetabolism along the axial and appendicular skeletons, which was suggestive of metastasis. However, no abnormal hypermetabolic lesion was found in the liver and biliary tree.

We made the diagnosis of paraneoplastic jaundice with

Fig. 1. Computed tomography showed (A) no findings of metastasis, hepatic infiltration, and no bile duct dilation or obstruction (B) heterogeneous enhancement of the prostate. (C) The whole body bone scan was suggestive of multiple bone metastases.

Fig. 2. (A) Prostate biopsy revealed adenocarcinoma (hematoxylin and eosin stain, $\times 100$). (B) Liver biopsy showed cholestasis and nodular inflammation (hematoxylin and eosin stain, $\times 200$).

prostate cancer. From the 14th day of hospitalization, the patient was started on leuporelin 22.5 mg subcutaneous injections, (to be administered every 3 months) and oral bicalutamide 50 mg daily. However, hepatotonics were not prescribed. Total bilirubin and ALT levels gradually decreased. The ALP level decreased initially, but it increased again. After the second leuporelin injection, the ALP level finally decreased. The

PSA level rose to 3,319.91 ng/mL after 2 weeks, and then it decreased to 2,260 ng/mL at the time of the second leuporelin injection (Table 1, Fig. 3). Contrast-enhanced MRI of the prostate was performed three weeks after the first leuporelin injection. It revealed diffuse involvement of prostate cancer in both lobes of the prostate gland. Other follow-up imaging tests were not performed.

Table 1. Interval Change of the Laboratory Findings

	On admission	4th day	11th day	14th day	18th day (discharge)	27th day	41th day	55th day	85th day	104th day	108th day
				1st leuporelin SC			2nd leuporelin SC				
	Oral bicalutamide administered daily										
Total bilirubin (mg/dL)	23	21.7	17.7	15.4	12	6.4	3	1.8	1	1	0.7
Direct bilirubin (mg/dL)	16.84	16.76	14.32	12.53	9.82	6.17	2.39	1.31	0.39	0.39	
AST (U/L)	50	44	50	57	54	64	83	49	37	31	68
ALT (U/L)	32	29	28	33	32	41	63	44	21	21	40
ALP (U/L)	678	593	453	396	357	320	689	946	602	328	222
GGT (U/L)	81	78	63	64	77	146	350	374	200	134	
PSA (ng/dL)	60					3,320				2,260	

AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyl transpeptidase; PSA, prostate-specific antigen; SC, subcutaneous injection.

Fig. 3. Clinical course of the patient. From the 14th day of hospitalization, leuporelin was injected every 3 months, and bicalutamide was administered daily. Total bilirubin level gradually decreased.

Table 2. Summary of Cases of Paraneoplastic Cholestasis in Prostate Cancer

Study	Age (years)	Total bilirubin (mg/dL)	ALP (U/L)	PSA (ng/dL)	Liver biopsy	Prostate cancer	Treatment	Outcome (cholestasis)
Reddy et al. (1977) ³	57	6.2	1,835	Unknown	Fibrosis, inflammatory infiltration, cholestasis	Known	Radiation, diethylstilbestrol	Improved
Karakolios et al. (2003) ⁴	72	18.1	4,679	150	No	ND	Flutamide, leuprolide	Improved
Koruk et al. (2004) ⁵	77	10	5,631	100	Normal	ND	Goserelin, bicalutamide	Improved
Shah (2006) ⁶	64	9	86	643.8	No	ND	Cypoterone	Not Improved
Nguyen et al. (2011) ⁷	51	16	579	556	Normal	ND	Goserelin, bicalutamide	Improved
Hinostroza-Yanahua et al. (2013) ¹	70	29	1,713	1,548	No	Known	Goserelin, estramustine	Not improved
	84	3.96	581	WNL	No	ND	Leuprolide	Not improved
Kuramoto et al. (2013) ⁸	75	17	44	9,862	No	ND	Leuprolide, bicalutamide	Improved
Okano et al. (2014) ⁹	68	23.4	2,182	15,018	Inflammation, cholestasis	ND	Bicalutamide	Improved
Kato et al. (2014) ¹⁰	60	9.3	1,803	41.4	No	ND	Bicalutamide, leuprolide	Improved
Walter et al. (2015) ¹¹	72	8.2	4,364	1,061	Cholestasis, hematopoiesis	Known	Leuprolide	Improved
Vieira et al. (2017) ¹²	78	12.3	950	>1,000	No	ND	Bicalutamide, goserelin	Improved
Bhangoo et al. (2018) ¹³	67	26.3	988	4,130	No	ND	Leuprolide, bicalutamide	Improved
Ravindranathan et al. (2018) ¹⁴	47	15.3	524	>1,300	Inflammation, cholestasis	ND	Degarelix, leuprolide, doxetalet	Improved
Kang et al. (2018) ¹⁵	72	13.1	Unknown	7,895	Cholestasis	ND	prednisone, Bicalutamide, goserelin	Improved
Romašovs et al. (2019) ¹⁶	80	165	2,513	66.01	No	Known	ADT	Not Improved
Liu et al. (2019) ¹⁷	88	3.8	654	3,030	No	Known	Enzalutamide	Not Improved
Gökçen et al. (2018) ¹⁸	65	14.14	600	>150	No	ND	Bicalutamide, goserelin	Improved
Present case	81	23	678	59.68	Inflammation, cholestasis	ND	Leuprolerelin, bicalutamide	Improved

ALP, alkaline phosphatase; PSA, prostate-specific antigen; WNL, within normal limits; ND, newly-diagnosed; ADT, androgen deprivation therapy.

Four days after the second leuporelin injection, the patient was readmitted due to myocardial infarction and was managed with percutaneous coronary intervention. He did not have any hepatobiliary problem during hospitalization and was discharged 12 days later. After 2 months, he suffered a cardiac arrest while working in the field and expired.

DISCUSSION

This is a case of a metastatic prostate cancer patient presenting with jaundice and pruritus. Jaundice showed a cholestatic pattern; however, the etiology was unclear. There was an absence of extrahepatic biliary obstruction. Viral, toxic hepatitis, and other rare causes were also excluded. Based on the imaging based diagnostic tests, we concluded that cholestasis was the most likely cause.

tasis was paraneoplastic jaundice associated with metastatic prostate cancer.

Stauffer's syndrome is a rare paraneoplastic syndrome, which is characterized by cholestasis, in which the patient may present with pruritus, jaundice, elevated liver enzymes, hepatosplenomegaly without liver metastases, bile duct obstruction, and other hepatocellular disorders. It disappears when the tumor is controlled.¹ This disease entity was first reported in renal cell carcinoma (RCC) by an American gastroenterologist Maurice H. Stauffer. Prostate cancer, soft tissue sarcoma, pancreatic cancer, bladder cancer, malignant lymphoproliferative diseases, bronchogenic carcinoma, and gastrointestinal neuroendocrine tumor have also been reported to be associated with this syndrome. Prostate cancer is the second most common malignancy associated with paraneoplastic jaundice.²

However, Stauffer's syndrome has been rarely reported in prostate cancer. A thorough search of medical literature revealed only 17 case reports published in the English language (Table 2).^{1,3-18} Of these, 13 cases were of newly diagnosed prostate cancer, and cholestasis which improved after treatment, and five cases where improvement was not seen. There was accompanying distant metastasis in all cases. To the best of our knowledge, this case is the second reported case of prostate cancer with Stauffer's syndrome in South Korea.

The pathophysiology of Stauffer's syndrome is unknown. An association between IL-6 and paraneoplastic manifestations has been observed in RCC, including cholestasis, although the causality is less well established.² The association between IL-6 and cholestasis may be mediated by systemic inflammation. Pro-inflammatory cytokines, including IL-6, are involved in the up-regulation of inflammation and inhibition of the expression of the hepatobiliary transporter gene possibly accounting for biliary outflow.¹³

In a study, the anti-IL-6 monoclonal antibody was found to reverse most of the biochemical abnormalities in patients with Stauffer's syndrome with RCC.¹⁹ Kuramoto et al.⁸ reported that the serum IL-6 levels decreased after anti-androgen therapy. Unfortunately, IL-6 was not measured in this case. The correlation between the IL-6 level and cholestasis needs further investigation.

Stauffer's syndrome is characterized by paraneoplastic cholestasis, which is rarely seen in prostate cancer. It is necessary to consider the possibility of paraneoplastic cholestasis

in cases of prostate cancer with cholestasis of unknown etiology.

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