

CASE REPORT

Metastatic Prostate Cancer Presented with Stauffer Syndrome-Like Paraneoplastic Cholestasis: A Case Report

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ABSTRACT

Prostate cancer is common cancer diagnosed in men, primarily affecting those older than 60 years. Bone metastasis, which is the most frequent metastatic site, significantly reduce survival time. We present the case of an 83-year-old Thai male diagnosed with advanced prostate cancer and bone marrow metastasis who developed jaundice. Laboratory results show anemia, thrombocytopenia, and unexplained cholestasis. Viral hepatitis and autoimmune hepatitis were excluded. Magnetic resonance imaging with magnetic resonance cholangiopancreatography showed no biliary obstruction. Bone marrow biopsy confirmed metastatic prostate cancer. Due to anemic symptoms and fatigue, only medical castration was chosen as first-line treatment. 2 months after treatment, the patient had significantly improved in anemia, thrombocytopenia, bilirubin level, prostate-specific antigen levels, and clinical status. The patient can well tolerate the treatment. This improvement is consistent with Stauffer syndrome-like; a paraneoplastic syndrome most often associated with renal cell carcinoma but rarely reported in prostate cancer.

Keywords: paraneoplastic syndrome, prostate cancer, Stauffer syndrome

INTRODUCTION

Prostate cancer is the most common cancer among men and the fourth most frequent cancer globally. predominantly diagnosed in men over 65, its clinical presentation ranges from indolent localized tumors to highly aggressive metastatic disease. Bone metastasis, especially to the axial skeleton, is a hallmark of advanced disease that significantly compromises quality of life and reduces overall survival.

Paraneoplastic syndromes are systemic disorders that occur before or during cancer diagnosis. Their symptoms are not directly related to the primary tumor

site but result from cancer-secreted hormones or cytokines that affect other organ systems. Stauffer syndrome first described in 1961 by Stauffer, is a rare paraneoplastic syndrome characterized by abnormal liver function tests without evidence of biliary obstruction from radiologic imaging and exclude other possible causes. Its hallmark is cholestatic jaundice, sometimes accompanied by hepatitis-like features. The syndrome is commonly associated with renal cell carcinoma, occurring in about 3–6% of patients.¹ Primary cancer treatment, regardless of disease staging, improve the symptoms.² However, the presence of Stauffer

syndrome is a negative prognostic factor.³ Although prostatic cancer with confirmed Stauffer syndrome has been reported rarely.^{4,5} Cholestasis without obstructive jaundice pattern is diagnostic hallmark. The proposed mechanism involves cytokine release, particularly interleukin-6 (IL-6), leading to cholestasis.⁶ From report, Pathological reports of liver biopsy show foci of bile stasis, with acute inflammation of the bile duct in the portal triad, and absent evidence of granulomatous inflammation or malignancy.⁷ For classical Stauffer syndrome, Latest proposed diagnostic criteria suggest liver biopsy may be necessary for definite diagnosis whereas no known liver pathological pathognomonic features.⁸ However, without liver pathology, Stauffer syndrome-like can diagnosed in the context of diagnosed malignancy other than renal cell carcinoma. Treatment of the underlying malignancy usually improves the syndrome.

CASE REPORT

An 83-year-old Thai male, retired government officer lived in rural area of Bangkok. He had history of well-controlled hypertension on amlodipine. He denied history of smoking, alcohol drinking or other over the counter medication used. He visited local government hospital with chief complaints of chronic neck pain with fatigue. His general physical examination was unremarkable but pale conjunctiva. He was initially diagnosed with cervical spondylosis. Blood tests revealed anemia, thrombocytopenia, and elevated liver enzymes with cholestatic pattern without recent baseline tests. Whole abdominal computer tomography was done and showed neither significant liver mass nor biliary system dilatation. Enlarged prostate gland was noted without other intra-abdominal mass or lymph node. Diffused heterogeneous background of visualized bony structure was also shown. Magnetic resonance imaging with Cholangiopancreatography was performed later and reported no evidence of biliary tract obstruction. He was referred to Charoenkrung Pracharak Hospital for further evaluation. Physical examination on first visit showed neither lymphadenopathy, hepatomegaly, splenomegaly nor sign of chronic liver disease. Digital rectal examinations showed hard consistency prostate.

Due to laboratory showing unexplained multilineage cytopenia, consultant hematologist performed bone marrow biopsy and revealed metastatic adenocarcinoma consistent with prostate origin. Described as cuboidal malignant cells with enlarged hyperchromatic nuclei

and clear cytoplasm, with depletion of myeloid, erythroid, and megakaryocytic lineages (Figure 1). Immunohistochemistry was positive for prostate-specific antigen (PSA) and alpha-methyl acyl-CoA racemase, pathological result confirms bone marrow metastasis from prostate adenocarcinoma (Figure 2). The initial PSA level was 6344 nanograms (ng)/milliliter (mL) (normal range 0–4 ng/mL).

Further evaluation of cholestasis causes, Gamma-glutamyl transferase (GGT) level was 514 unit (U)/liter (L) showed marked elevation, viral serology (negative for hepatitis A, B, C, and E), autoimmune markers (antinuclear antibody, antimitochondrial antibody, and smooth muscle antibody negative), and

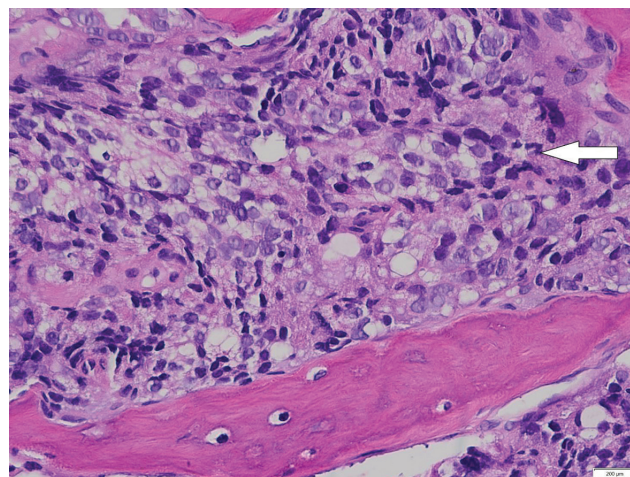


Figure 1 Bone Marrow Biopsy (H&E staining slide) Showed Metastatic Sheets of Malignant Cells Along Bone Marrow Cavity (scale bar = 200 μ m.)

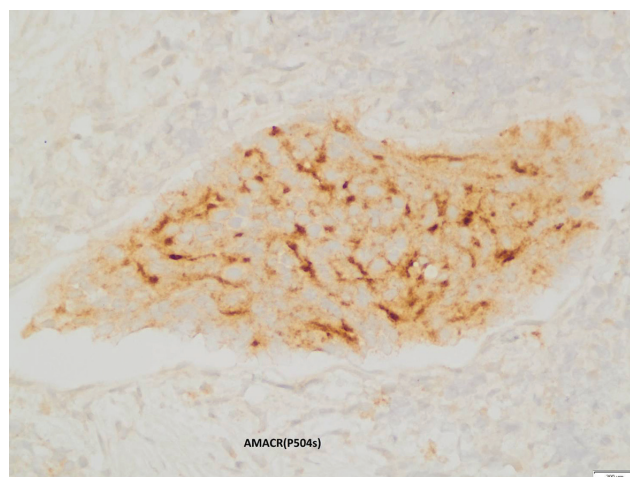


Figure 2 Alpha-Methyl Acyl CoA Racemase (AMACR) Showed Granular Cytoplasmic Staining of Malignant Prostatic Acinar Cells (scale bar = 200 μ m.)

magnetic resonance imaging with magnetic resonance cholangiopancreatography (**Figure 3**) showed neither biliary obstruction nor intraabdominal mass. Due to

severe thrombocytopenia risk for procedural bleeding tendency, liver biopsy and prostatic biopsy were deferred.

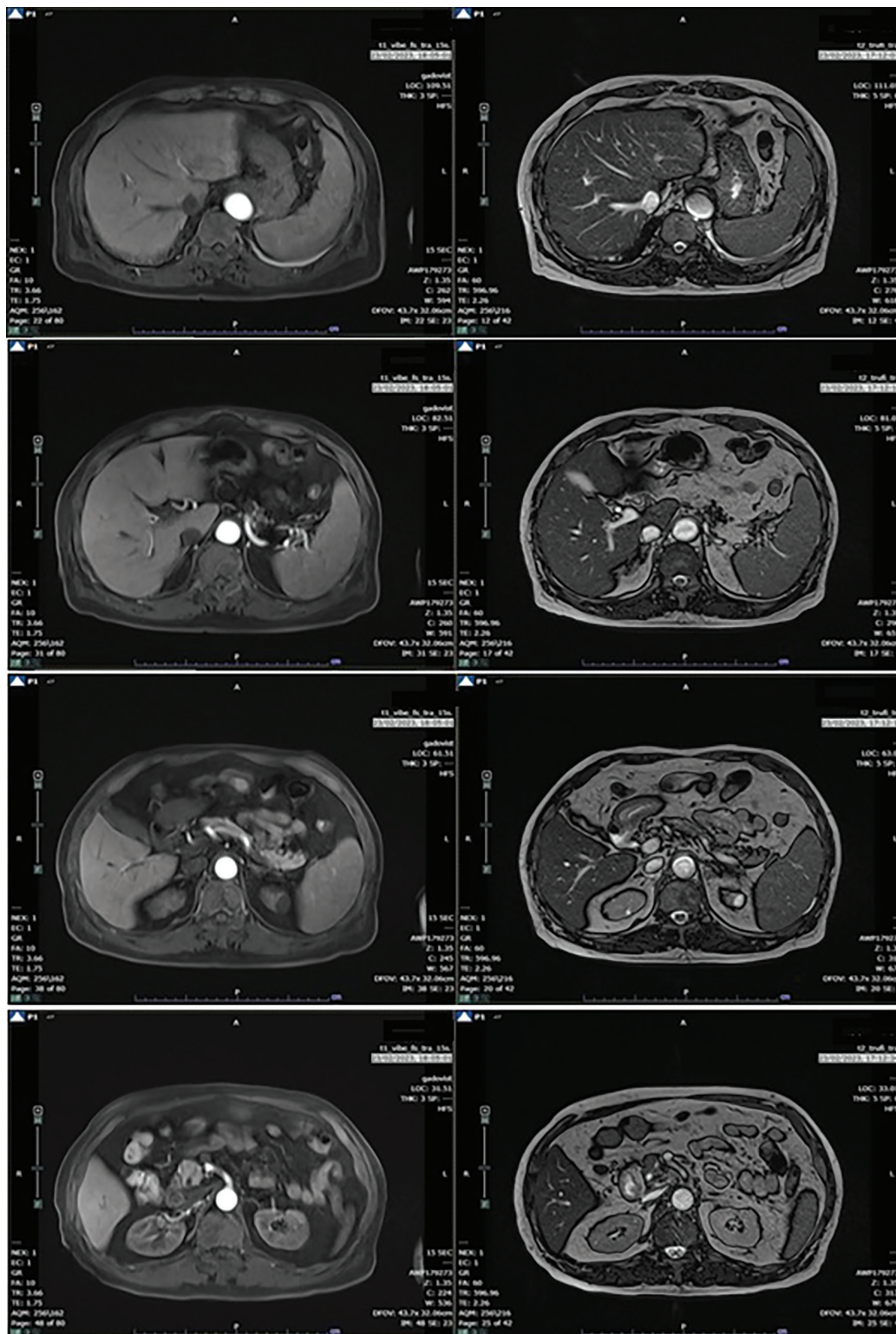


Figure 3 MRI Upper Abdomen with Gadolinium with MRCP in Axial T1 and T2 Showed Normal Size, Shape and Parenchymal Signal Intensity of Liver. Patent Portal Vein and Hepatic Veins. No Significant Evidence of Biliary Tract Obstruction on This Study.

The patient was diagnosed with advanced metastatic prostate cancer with paraneoplastic Stauffer syndrome. His Eastern Cooperative Oncology Group (ECOG) performance status was 2. Initial treatment with leuporelin acetate 11.25 mg intramuscular alone was started (baseline = T0), anti-androgen was not prescribed concurrently due to concerned about fatigue and abnormal liver function test. Zoledronic acid was started soon after dental examination.

Due to severe anemia, the following up appointment was made every 2 weeks for symptoms evaluation (T+2 weeks, T+4 weeks, T+6 weeks). He complained only about his fatigue as previously without either bleeding or other pain. His complete blood count showed same level of hemoglobin and thrombocytopenia. Two pack red blood cells were transfused to alleviate symptoms in every visit. Total bilirubin level was improved whereas alkaline phosphatase was rising instead. GGT level showed 326 U/L. This paradoxical change resulted from flared up of alkaline phosphatase (ALP) which typically occur within 1 month after treatment started.

At T+2 months, his anemia, thrombocytopenia, and cholestatic jaundice improved significantly. PSA dramatically decreased (Table 1). Testosterone level was still at the castration level and leuporelin acetate was prescribed every 12 weeks interval. ALP level started to decrease after flared up episode.

At T+7 months, Platelet counts reached normal level. PSA level was 7 ng/mL (nadir level). Bilateral orchiectomy was performed and had no complication. At T+13 months, PSA level continues rising for 2 consecutive times with 4 weeks apart above the nadir level (7 → 15 → 23 ng/mL). Confirmed testosterone level was still in castrated level. The patient's ECOG was 1 without any disturbance symptoms. He denied further imaging from personal reasons. Castration resistance prostate cancer was diagnosed and abiraterone with prednisolone was started. PSA level was stabilized for 8 months. Thereafter PSA level continued to rise again. Only oral medication was chosen by patient's decision to control disease.

DISCUSSION

Abnormal liver function in cancer patients requires careful evaluation to distinguish between biliary tract obstruction from liver metastasis, viral hepatitis,

drug-induced liver injury, sepsis-associated cholestasis, and paraneoplastic syndromes. In this case, liver dysfunction was presented before the diagnosis of prostate cancer. Imaging and laboratory studies excluded mainly biliary tract obstruction and other causes. The patient's cholestasis consistent with Stauffer syndrome-like after primary prostate cancer was diagnosed and treated.

Stauffer syndrome is a paraneoplastic liver dysfunction usually seen in renal cell carcinoma but rarely described as prostate cancer. The pathogenesis presumed from cytokine release, particularly IL-6.⁶ Treatment of the underlying malignancy typically leads to improvement. Histopathology of liver biopsy shows intrahepatic cholestasis with bile stasis and portal inflammation, but biopsy was not performed in this patient due to thrombocytopenia.

The specific management focused on palliative aim treatment. Although from imaging, CT scan shows diffuse bone lesion and marked elevated initial PSA level was compatible with high-risk patient. According to the LATITUDE trial,⁹ addition of abiraterone to androgen deprivation therapy (ADT) in high-risk metastatic prostate cancer significantly improves overall survival (53.3 vs. 36.5 months). Another alternative treatment is adding docetaxel to ADT from GETUG-AFU 15 trial, CHAARTED trial, STAMPEDE trial docetaxel arm.¹⁰⁻¹² The result mostly shows survival benefit except for GETUG-AFU only showed progression free survival. In this patient, only medical castration with leuporelin acetate was chosen due to modest tolerability and patient's coverage scheme.

CONCLUSION

Stauffer syndrome is a rare paraneoplastic manifestation of prostate cancer, characterized by cholestatic jaundice without biliary obstruction. Definite Diagnosis requires exclusion of liver metastasis, viral hepatitis, autoimmune, and other obstructive causes and monitor response after cancer treatment. Although no liver biopsy was yielded to confirm diagnosis, effectively control of tumor with ADT was associated with significant reversal hematologic and hepatic abnormalities, this highlights specific manifestation of paraneoplastic Stauffer syndrome-like in prostate cancer patients presented with unexplained liver dysfunction.

Table 1 Baseline and Follow Up Laboratory Investigation after Initiate Treatment

	Normal Range	*	T0 **	T+2w	T+4w	T+6w	T+2m	T+3m	T+4m	T+6m	T+13m
Hemoglobin	14-17.4 g/dL	9.2	5.8	6.5	6.9	5.7	9.1	10.3	12.3	12.0	12.3
Hematocrit	42-52%	27.3	17.2	19.4	21	17.5	28.5	32.6	36.4	35.6	35.5
Platelet	140-400x 10 ⁹ /L	74	50	50	68	82	126	124	163	165	182
SGOT	0-40 U/L	41	53	52	87	60	71	44	38	34	29
SGPT	0-41 U/L	23	33	39	98	71	94	71	55	59	37
ALP	40-129 U/L	899	681	644	3673	5930	3714	2192	919	391	135
Total Bilirubin	0-1.2 mg/dL	18.3	9.0	5.3	2.7	1.6	0.8	0.5	0.4	0.5	0.4
Direct Bilirubin	0-0.2 mg/dL	9.92	9.0	5.1	2.7	1.2	0.7	0.3	0.5	0.3	0.2
PT/INR	10-13 sec/0.8-1.2		12.9/1.12					12.4/1.05			
GGT	15-85 U/L	271	514		326						
PSA	0-4 ng/mL		6344	4576	2224	791	155	40	18	7	23
Management	Supportive		LPRC	LPRC	LPRC	LPRC					
	ADT		Leuprorelin Acetate (1 st dose 7/4/2566)								Orchiectomy

Abbreviations: ADT, androgen deprivation therapy; ALP, alkaline phosphatase; dL, deciliter; g, grams; GGT, gamma-glutamyl transferase; INR, international normalized ratio; L, liter; LPRC, leuprorelin; m, month; mg, milligrams; mL, milliliter; ng, nanograms; PSA, prostate-specific antigen; PT, prothrombin time; sec, second; SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; T, time; U, units; w, week

* Investigation from refer out hospital, ** Baseline Investigation in Charoenkrung Pracharak Hospital

Conflict of Interest

The authors declare no conflicts of interest regarding this manuscript.

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