Cholestatic Jaundice as a Paraneoplastic Manifestation of Prostate Cancer Aggravated by Steroid Therapy

Min Kyu Kang · Jung Gil Park · Heon Ju Lee

Division of Gastroenterology and Hepatology, Department of Internal Medicine, College of Medicine, Yeungnam University, Daegu, Republic of Korea

Significance of the Study

- As a paraneoplastic manifestation of advanced prostate cancer, cholestatic jaundice can be exacerbated by the use of steroids and it can be improved by appropriate antiandrogen therapy.

Keywords

Androgen receptor · Bicalutamide · Jaundice · Prostate cancer · Prednisone

Abstract

Objective: To report a rare case of paraneoplastic jaundice as a manifestation of prostate cancer. **Clinical Presentation and Intervention:** We report on a case of paraneoplastic syndrome in a 72-year-old man with prostate cancer that manifested with idiopathic jaundice. Although steroids can be used as treatment in patients with prostate cancer, they could exacerbate paraneoplastic jaundice. The jaundice that flared up after treatment with 40 mg prednisone was improved with antiandrogen treatment. **Conclusion:** Physicians should be aware of the possibility of paraneoplastic jaundice in patients with prostate cancer. Appropriate antiandrogen therapy should be considered for paraneoplastic jaundice in these patients.

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Introduction

Paraneoplastic cholestasis in patients with prostate cancer, which has been previously shown to improve with the use of antiandrogen agents, has been rarely reported [1–9]. As maintenance therapy for metastatic prostate cancer, corticosteroids have been widely used for decades [10]. Here, we report a patient with metastatic prostate cancer in whom we observed deterioration of paraneoplastic jaundice after a short course of treatment with 40 mg prednisone. The patient showed improvement after antiandrogen treatment.

Case Report

A 72-year-old man visited our emergency department due to jaundice and anorexia which had persisted for 2 months. The results of his physical examination were unremarkable. Liver function tests revealed the following values: serum bilirubin level (SBL), 13.1 mg/dL; serum albumin level, 4.45 g/dL; serum aspartate ami-

Fig. 1. Abdominal computed tomography scan showing no evidence of biliary obstruction including common bile duct (arrow) and intrahepatic ductal dilatation.

Fig. 2. Transrectal prostate biopsy findings that led to the diagnosis of adenocarcinoma Hematoxylin and eosin stain. $\times 100$.

Fig. 3. Microscopic examination result showing mild infiltration of lymphocytes and bile plugs in the portal tract and bile canaliculi. Hematoxylin and eosin stain. $\times 200$.

notransferase level, 112 IU/L; serum alanine aminotransferase level, 146 IU/L; and prothrombin time-international normalized ratio, 1.1. Serum hepatitis B surface antigen and hepatitis C antigen tests were all negative. Abdominal computed tomography revealed enlargement of the prostate gland and no evidence of obstructive

jaundice including intrahepatic ductal dilatation (Fig. 1). The serum prostate-specific antigen level was as high as 7,895 ng/mL (normal range: 0–4 ng/mL). A prostate biopsy revealed adenocarcinoma (Fig. 2), and a liver biopsy revealed a canalicular type of cholestasis without evidence of liver metastasis (Fig. 3).

Despite 20 days of supportive care, the patient's SBL did not improve. After 3 days of 40 mg prednisone therapy, sudden deterioration of the jaundice was observed. Although the corticosteroid therapy was discontinued, his SBL increased to 25.25 mg/dL. Considering the jaundice to be a paraneoplastic manifestation of prostate cancer, antiandrogen treatments with 50 mg bicalutamide and 3.6 mg goserelin were started. Six days later, his jaundice improved dramatically, with his SBL decreasing to 7.22 mg/dL. Three months after the hormone therapy, his serum prostate-specific antigen level decreased from 7,895 to 311 ng/mL, and his bilirubin level was normalized without any adverse reaction (Fig. 4).

Discussion

Cholestatic manifestation of paraneoplastic syndrome in association with prostate cancer is rare. A few previous cases have been reported [1–9] and 7 cases showed improvement after hormone therapy (Table 1). From a therapeutic point of view, corticosteroids have been used to treat metastatic prostate cancer for decades [10]. In con-

Fig. 4. Clinical course of the patient. ALT, alanine aminotransferase; PSA, prostate-specific antigen (in mg/mL).

Table 1. Summary of cases of paraneoplastic cholestatic jaundice of prostate cancer

	Age, years	Peak bilirubin	Peak PSA, ng/mL	Liver biopsy	Treatment (cancer)	Prognostic outcome
Okano et al. [1]	68	23.4 mg/dL	15,018	Lymphocyte infiltration, cholestasis	Bicalutamide	Improved
Kuramoto et al. [2]	75	17 mg/dL	9,862	ND	Bicalutamide, leuprolide	Improved
Koruk et al. [3]	77	10 mg/dL	100	Normal	Bicalutamide, goserelin	Improved
Reddy et al. [4]	57	8 mg/dL	ND	Lymphocyte infiltration, cholestasis	ND	Intermittent worsening
Shah [5]	64	302 mmol/L	970	ND	Goserelin, cyproterone	Unknown
Nguyen et al. [6]	51	19 mmol/L	556	ND	Bicalutamide, goserelin	Improved
Karakolios et al. [7]	72	18.1 mg/dL	150	ND	Flutamide, leuprolide	Improved
Hinostroza-Yanahuaya et al. [8]	70	29 mg/dL	1,548	ND	Conservative treatment	Expired
Vieira et al. [9]	84	3.96 mg/dL	ND	ND	Conservative treatment	Expired
Vieira et al. [9]	78	12.3 mg/dL	>1,000	ND	Bicalutamide, goserelin	Improved
Our case	72	25.25 mg/dL	7,895	Lymphocyte infiltration, cholestasis	Bicalutamide, goserelin	Improved

PSA, prostate-specific antigen; ND, not done.

trast, we observed a deterioration of paraneoplastic jaundice in a patient with metastatic prostate cancer after a short course of prednisone, which improved after antiandrogen treatment.

Although no convincing pathogenesis was found, we suggest a hypothesis on the cause of the sudden deterioration. The use of corticosteroids in prostate cancer inhibits the secretion of adrenocorticotrophic hormone in the pituitary gland, thereby reducing the synthesis of the

adrenal androgen hormone, preventing cancer and improving the patient's symptoms [10]. However, in the literature, corticosteroid use has been associated with the development of resistance to prostate cancer treatment [10, 11]. The interaction of steroid hormones such as corticosteroids and androgens in prostate cancer has not been fully elucidated, especially in terms of growth receptors and androgen receptors (AR) [10]. In advanced stages of prostate cancer, the frequency of AR mutations

is significantly increased [12]. Corticosteroids can activate the mutated AR to manifest an androgenic effect in metastatic prostate cancer, which in turn activates the growth receptor to induce cancer growth and stimulate genes that overlap with AR targets [11]. We suggest that administration of steroids may cause a sudden flare of paraneoplastic cholestasis, with elevation of bilirubin levels.

Conclusion

Paraneoplastic cholestasis should be considered when unexplained cholestasis occurs in cancer patients. In addition, paraneoplastic cholestasis due to prostate cancer can be improved with appropriate antiandrogen therapy and may be exacerbated by steroid use.

Disclosure Statement

No conflict of interest is reported.

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