



Paraneoplastic hyperbilirubinemia in metastatic prostate cancer and review of the current literature

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ABSTRACT

Paraneoplastic syndromes are functional clinical disorders caused by the direct effect of the primary tumor or metastasis. The initial presenting symptom of the patients may be associated with paraneoplastic manifestations. Paraneoplastic cholestasis is most frequently defined in association with renal cell carcinoma (Stauffer's syndrome), but it is an extremely rare clinical entity seen in association with prostate cancer. Etiology of cholestasis was investigated in the case diagnosed as metastatic prostate cancer who applied to the gastroenterology outpatient clinic due to complaints of ascites and jaundice that established the diagnosis of paraneoplastic hyperbilirubinemia. We observed improvement of his cholestasis with hormonotherapy used for prostate cancer.

Keywords: Cholestasis; paraneoplastic syndrome; peritonitis carcinomatosa; prostate cancer.

Introduction

Manifestations of cholestasis arising due to the malignant tumors may occur via different mechanisms. Obstruction of the primary tumor on the bile duct, pressure effect of large lymph nodes or the infiltration of the liver are responsible mechanisms.^[1] When the mechanical causes are excluded, the concept of tumor-associated paraneoplastic hyperbilirubinemia is defined as a rare cause for cholestasis. Paraneoplastic cholestasis is most frequently defined as "Stauffer's syndrome" related to renal cell carcinoma (RCC), soft tissue sarcomas and lymphoproliferative diseases and the occurrence of paraneoplastic syndrome related to prostate cancer is an extremely rare clinical entity.^[2] There are only eight cases known in the literature and regression of cholestatic manifestations has been observed thanks to hormonal treatment of prostate cancer.^[3]

We present clinic picture and treatment of the paraneoplastic cholestasis that developed in a patient diagnosed with metastatic prostate cancer while he was being examined in terms of the etiology of cholestasis.

Case presentation

A 65-year-old male patient applied to the gastroenterology outpatient clinic with the complaints of jaundice and abdominal distention that had started two months before and gradually increased. Within the last 20 days, a weight loss of approximately 20 kg was noticed. He was under follow-up for six years due to type 2 Diabetes Mellitus and he was receiving insulin detemir treatment. In his physical examination, vital findings were stable and skin and scleras were extremely icteric. In his abdominal examination, hepatosplenomegaly and ascites were determined. Any abnormality was not observed in his

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hemogram and coagulation examinations. Some of his biochemical test values were as follows: alkaline phosphatase (ALP): 600 U/L (30-120), alanine aminotransaminase (ALT): 70 U/L (0-50), aspartate aminotransaminase (AST): 130 U/L (0-50), gamma glutamyl transpeptidase (GGT): 494 U/L (0-55), total bilirubin: 14.14 mg/dL (0.3-1.2) and direct bilirubin: 7.86 mg/dL (0.0-0.2). His urinalysis was normal except for the bilirubin positivity. Antinuclear antibodies (ANA) and anti-mitochondrial antibodies (AMA) were not found, and his viral examinations were unremarkable. Immunoglobulin and complement levels were within normal levels. Gastrointestinal tumor markers were normal and prostate specific antigen (PSA) level was observed as high as >150 ng/mL (0-4). Results of biochemical analysis of ascites fluid were as follows: total protein, 4.20 g/dL; total albumin, 3.0 g/dL; serum albumin, 3.48 g/dL (3.5-5.2); serum total protein, 5.61 g/L (6.6-8.3); 650 leucocyte/mm³ (90% mononuclear leukocytes, 10% polymorphonuclear leukocyte). Serum ascites albumin gradient (SAAG) was calculated as 0.48 and evaluated as an exudate. Bacterial growth was not observed in the microbiological examinations of the ascites fluid, neither mycobacterium species nor tbc-DNA could be identified. In the abdominal ultrasonography, widespread free fluid and peritoneal implant were observed. Any abnormality was not observed in esophagogastroduodenoscopy and colonoscopy. In contrast tomography, numerous lymphadenopathies in the right paracaval area and typical "omental cake" appearance in the omentum were remarkable (Figure 1). The sizes of the prostate gland were measured as 5x4x4.5 cm which was larger than normal. In the lung, bilateral hilar and paratracheal metastatic lymphadenopathies were observed. Any abnormality could not be found in MRCP (magnetic resonance cholangiopancreatography) and ERCP (endoscopic retrograde cholangiopancreatography). In positron emission tomography/computed tomography (PET/CT) it was considered that the metastases in mesenterium had a character that did not show FDG involvement. As a result of the transrectal biopsy that was done due to high PSA; adenocarcinoma, acinar type, gleason score was reported as 4+4. In the peritoneal biopsy; PSA was found as positive and high molecular weight keratin (HMWSK), podoplanin (D2-40) and thyroid transcription factor 1, (TTF-1) negative malignant epithelial tumor and thus considered as prostate adenocarcinoma metastasis. No involvement was observed in bone scintigraphy. It was thought that the reason of cholestasis was paraneoplastic syndrome related to prostate cancer. Anti-androgen treatment was started with oral 50 mg/day bicalutamide and after 10 days, goserelin acetate 3.6 mg/month subcutaneous treatment was started. Three months after the treatment, it was observed that bilirubin levels and cholestasis enzymes decreased rapidly to normal limits and PSA value reduced to 109.96 ng/mL.



Figure 1. Computed tomography of the abdomen showing typical omental cake appearance

Discussion

Paraneoplastic syndromes present with clinical manifestations of the functional disorders caused by the primary tumor or metastasis and they recover with treatment of the tumor. Prostate cancer is the second urological malignancy that is mostly related to paraneoplastic syndrome after renal cell carcinoma. Hong et al.^[4] classified the paraneoplastic syndromes related to prostate cancer as endocrine, hematological, dermatological, neurological and inflammatory types according to the clinical symptoms. Paraneoplastic syndromes are generally seen in the cases at advanced stage and appear as the first symptom of malignancy. The first presenting symptoms in our case were ascites and jaundice.

Paraneoplastic cholestasis is a reversible type of cholestasis that is frequently seen in the absence of hepatic metastasis and in the course of renal cell carcinoma. This situation, defined as Stauffer's syndrome, is notified at varying rates in RCC as 0.7-40%. Biochemically increases in ALP, erythrocyte sedimentation rate, α -2 globuline, and GGT levels, hypoalbuminemia, thrombocytosis, prolonged prothrombin time are observed.^[5] On the other hand, even though prostate cancer is the most frequently seen urological malignancy, paraneoplastic cholestasis related to prostate cancer is extremely rare. The mostly accepted pathophysiologic mechanism of paraneoplastic cholestasis is the systemic and intrahepatic release of proinflammatory cytokines. It is thought that these cytokines are the potent inhibitors of hepatocellular bile secretion. Also, it is emphasized that interleukin 6 (IL-6) is the possible pathogenic

factor that may explain its correlation with paraneoplastic syndrome in prostate cancer.^[6] In *in vitro* studies; it is considered that IL-6 is a paracrine growth inhibitor. However, it functions as an autocrine growth stimulator in prostate cancer and this situation takes part in the progression of the cancer to its refractory phase.^[7] However in our case, IL-6 level was not studied.

In the case-based inspections in the literature, Okano et al.^[3] examined eight cases with paraneoplastic cholestasis related to prostate cancer according to their age, bilirubin, ALP, PSA levels. In none of the cases, metastatic hepatic infiltration, bile duct obstruction and infection were observed. In our case, lung metastases were present and mechanical factors involving in the etiology of cholestasis were excluded. Liver biopsy was performed in half of the patients. In our case, liver biopsy was not performed and in the literature nonspecific findings have been reported in cases in whom liver biopsies were performed.^[8] The treatment of paraneoplastic syndrome depends on the treatment of the underlying malignancy and it has been observed that clinic manifestations of cholestasis recovered, liver enzymes and bilirubin levels rapidly returned to normal levels by adding luteinizing hormone-releasing hormone (LHRH) analogues to the anti-androgen treatment administered with bicalutamide.^[9] In all the cases receiving hormonal treatment, the resolution of cholestasis was observed. Because it is present in the publications in which since anti-androgen treatment in prostate cancer is correlated with fulminant hepatitis and cholestasis; close follow-up of the outcomes of the treatment gains importance.^[10]

As a conclusion, it should be kept in mind that malignancies may take part in the etiology of unexplained forms of cholestasis and we may encounter rare malignancies in association with manifestations of paraneoplastic cholestasis.

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