Paraneoplastic Cholestasis in Prostate Carcinoma: A Case Report and Review of the Literature

Prostat Kanserinde Paraneoplastik Kolestaz: Bir Olgu ve Literatür Taraması

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ABSTRACT Intrahepatic cholestasis is a rare manifestation of paraneoplastic syndrome and has been reported to be associated with various malignancies. Intrahepatic cholestasis without a mechanical obstruction has been previously reported in only three prostate carcinoma cases in English literature. In this report, we described a new case of paraneoplastic intrahepatic cholestasis in a patient with prostate carcinoma treated only with bilateral orchiectomy. We also discussed the mechanisms of cholestasis in prostate carcinoma in the light of the pertinent literature. Paraneoplastic cholestasis should be kept in mind in the absence of biliary tract obstruction and hepatic involvement in prostate carcinoma. Patients with unexplained cholestasis should be investigated for a possible paraneoplastic syndrome. Paraneoplastic cholestasis resolves following orchiectomy in prostate carcinoma cases.

Key Words: Cholestasis, intrahepatic; paraneoplastic syndromes; prostatic neoplasms

ÖZET İntrahepatik kolestaz, paraneoplastik sendromun nadir bir göstergesi olup çeşitli malignitelerle birlikteliği bildirilmiştir. Prostat kanserinde mekanik obstrüksiyon olmaksızın gelişen intrahepatik kolestaz, İngiliz literatüründe daha önce sadece üç olguda sunulmuştur. Burada, sadece bilateral orşiektomi ile paraneoplastik intrahepatik kolestazı tedavi edilen, prostat kanserli yeni bir olgu sunduk. Ayrıca, bu konu ile ilgili literatürler eşliğinde prostat kanserinde kolestazın mekanizmalarını da tartıştık. Paraneoplastik kolestazın, prostat kanserinde hepatik tutulum ve biliyer obstrüksiyon olmaksızın gelişebileceği akılda tutulmalıdır. Açıklanamayan kolestazlı hastalar da paraneoplastik sendrom araştırılmalıdır. Paraneoplastik kolestaz prostat kanserli vakalarda orşiektomiyi takiben gerilemektedir.

Anahtar Kelimeler: İntrahepatik kolestaz; paraneoplastik sendrom; prostat neoplazmları

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Intrahepatic cholestasis is a rare manifestation of paraneoplastic syndrome and has been reported to be associated with various malignancies.[1-14] Systemic and/or local intrahepatic proinflammatory cytokines are assumed to inhibit hepatocellular bile secretion. There is evidence that those cytokines are potent inhibitors of hepatobiliary transporter gene expression, resulting in hyperbilirubinemia and cholestasis.[15]

Prostate carcinoma associated with cholestasis may be due to mechanical bile duct obstruction by the liver metastasis[16] or enlarged lymph

node compression.[17] Intrahepatic cholestasis without mechanical obstruction has been previously reported in only three prostate carcinoma cases in the English literature.[1-3] In this report, we described a new case of paraneoplastic intrahepatic cholestasis in a patient with prostate carcinoma. We also discussed the mechanisms of cholestasis in prostate carcinoma in the light of the pertinent literature.

CASE REPORT

A 70-year-old man was admitted to our clinic with the complaints of jaundice, pruritis, fatigue, dark urine and low back pain lasting for a month. His past medical history and family history were unremarkable. He denied using alcohol or any other drugs. On physical examination, the patient was normal except for jaundice and dullness in Traube's region. On rectal digital examination prostate was palpable with an irregular surface. Laboratory studies revealed the following: white blood cell count, 4.670 /mm^3; hemoglobin 10.0 g/dL; MCV 94 fl; platelets 282.000 /mm^3; alanine aminotransferase 69 U/L (0-40); aspartate aminotransferase 49 U/L (0-40); alkaline phosphatase 4032 U/L (38-155); gamma-glutamyltransferase 366 U/L (15-60); total bilirubin 26.07 mg/dL (0.1-2.0); direct bilirubin 18.97 mg/dL (0.1-0.8); albumin 3.9 g/dL (3.5-5); globulin 3.3 g/dL (2.3-3.5); amylase 87 U/L (28-100); erythrocyte sedimentation rate 58 mm/hr; prostate specific antigen 100 ng/ml (0-4); INR 1.1; HBsAg (-); anti HBc IgM (-); anti HAV IgM (-); anti HCV (-); anti HIV (-); antimitochondrial antibody (-). Abdominal ultrasonography and computed tomography showed mild splenomegaly and prostate hypertrophy. The liver parenchyma, portal system and biliary tree were normal. There was no lymphadenopathies. Technetium-methylene diphosphonate bone scan demonstrated extensive areas of increased uptake in vertebral column and pelvis, reflecting bone metastasis.

With a high suspicion of cancer, prostate biopsy was performed. Prostate adenocarcinoma with neural and capsule invasion was observed. A liver biopsy was compatible with hepatocanalicular cholestasis without a specific etiology (Figure 1).

Since other disorders leading cholestasis were eliminated, paraneoplastic intrahepatic cholestasis was considered. Chemotherapy was planned, however the patient could not get it because of a problem with his social assurance. Therefore, he preferred surgery and bilateral orchiectomy was performed by urosurgeons without any problems in the postoperative period. Two months after orchiectomy, he had no complaints and bilirubin levels returned to normal. He was advised to continue follow up in the department of Medical Oncology.

DISCUSSION

Neoplasms often cause intrahepatic or extrahepatic cholestasis as a result of widespread hepatic metastatic infiltration or mechanical bile duct obstruction by the primary tumor, compression by enlarged lymph nodes, liver metastasis, liver amyloidosis or disappearance of bile duct syndromes associated with malignant lymphomas.[18,19] In the absence of anatomic obstruction of the bile duct and metastatic hepatic involvement or in the absence of an infectious etiology and toxic side effects, a paraneoplastic intrahepatic cholestasis may be considered. This form of cholestasis has been rarely described in the course of some malignancies (Table 1).

No obvious etiologic factors for cholestasis were found in the initial evaluation of our patient. A thorough drug history was negative and liver function tests completely normalized after orchiectomy and did not recur. Furthermore, other etiologies of hepatitis (eg, alcohol, steatohepatitis, autoimmune hepatitis, viral hepatitis) were appropriately ruled out.

Paraneoplastic syndrome presents with various manifestations in cancer patients, and may be due to immune reactions related to a primary malignancy. The underlying pathophysiology of this phenomenon is not clear, but cholestasis has been ascribed to the effects of paraneoplastic mediators released by the tumor, in particular cytokines released by inflammatory cells surrounding/ infiltrating the tumor.[18,19] Evidence now exists that proinflammatory cytokines are potent inhibitors of hepatobiliary transporter gene expression which

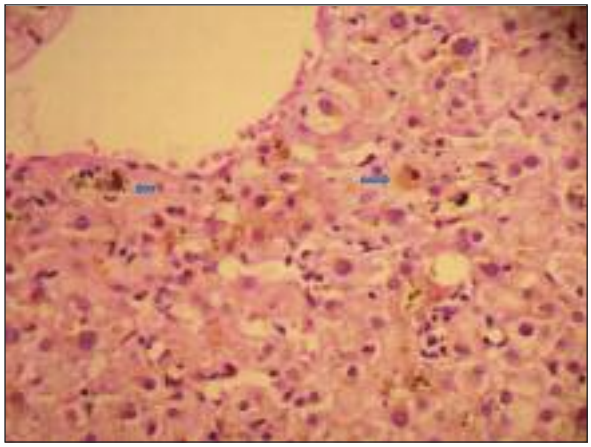

FIGURE 1: Hepatocanalicular cholestasis; bile plugs are seen in dilated canaliculi as well as in hepatocytes (arrows).

TABLE 1: Reported paraneoplastic cholestasis associated with malignancies

References	Malignancies (n)
4-7	Renal cell carcinoma (4)
1-3	Prostate carcinoma (3)
8	Bronchial adenocarcinoma (1)
9	Hodgkin's disease (1)
10	Non-Hodgkin's lymphoma (1)
11	Chronic lymphocytic leukaemia (1)
12	Medullary thyroid carcinoma (1)
13	Soft tissue sarcoma (1)
14	Pheochromocytoma (1)

may explain impaired transport function resulting in hyperbilirubinemia and cholestasis. Inflammation-induced cholestasis is mediated by cholestatic effects of endotoxins (i.e. lipopolysaccharides in the outer membrane of Gram-negative bacteria) and/or is mediated by lipopolysaccharide-induced proinflammatory cytokines, such as TNF-a and various interleukins (IL). For instance, IL-6 was found to be involved in the pathophysiology of paraneoplastic syndromes in patients with metastatic renal cell carcinoma.[20] Cytokine (IL-1, IL-6 and tumor necrosis factor-alpha) synthesis by Kupffer's cells (intrahepatic macrophages) in response to the release of endotoxins occurs in the course of various clinical syndromes.[21]

Prostate adenocarcinoma may cause extensive metastasis such as bone, lymph nodes and viscera. Liver metastasis is rare and paraneoplastic syndrome associated with prostate carcinoma is very uncommon. To the best of our knowledge, only eight cases of prostate adenocarcinoma-induced cholestasis were reported in the literature to date (Table 2). Three of those cases had paraneoplastic cholestasis.[1-3] Another three had main bile duct obstruction[16,17,26] and the others were diagnosed with secondary biliary cirrhosis[22] and sclerosing cholangitis.[23] Our case had no signs of obstruction of bile flow, neoplastic involvement of the liver, or infectious etiology. Moreover, liver biopsy showed nonspecific hepatocanalicular cholestasis presumed to have a paraneoplastic etiology.

It has been reported that malignancy associated intrahepatic cholestasis can be successfully resolved after treatment of the underlying malignancy.[18] Paraneoplastic cholestasis resolved completely following chemotherapy in the prostate carcinoma cases.[1,2,16,17,22] Unlike the literature, after orchiectomy (without chemotherapy) serum bilirubin levels returned to normal gradually in our case. It is also important to remember that jaundice may appear as a result of the treatment of prostate carcinoma. Cyproterone acetate, flutamide and bicalutamide used in treatment of prostate carcinoma have been associated with fulminant hepatitis and jaundice.[24,25,27]

In conclusion, paraneoplastic cholestasis should be borne in mind in the absence of biliary tract obstruction and hepatic involvement in prostate carcinoma. Patients with unexplained cholestasis should be investigated for a possible paraneoplastic syndrome. Paraneoplastic cholestasis resolves following orchiectomy in prostate carcinoma cases.

TABLE 2: Summary of cholestasis associated with prostate carcinoma.

Reference	Complaints	Metastasis	Cause of cholestasis	Therapy	Outcome
Ben-Ishay et al., 1975	Jaundice, pruritus, weight loss	Lung, bone, cervical lymph nodes	As a the result of secondary biliary cirrhosis	Antiandrogen therapy (stilbestrol) and bilateral orchiectomy	Liver function tests became normal after several months
Chen et al., 1990	Subicterus, dark colored urine	Omentum, gall bladder	Hilar biliary obstruction	Biliary stent, bilateral orchiectomy	Liver function tests became normal after several months
Bloch et al., 1992	Abdominal pain, vomiting, jaundice	Retroperitoneal mass (involving head of the pancreas)	Secondary to a large mass	Biliary stent, bilateral orchiectomy and antiandrogen therapy	Liver function tests became normal after several days
Taylor et al., 1993	Jaundice	Gall bladder supraclavicular lymph node	Multifocal strictures of both intrahepatic and extrahepatic biliary system consistent with sclerosing cholangitis	Biliary stent, gonadotropin-releasing hormone analog (leuprolide)	NA
Cole et al., 2000	Jaundice, pelvic pain	Bone, lymph nodes	Secondary to large retroperitoneal lymph nodes	Gonadotropin-releasing hormone analog (leuprolide) and antiandrogen (bicalutamide)	Liver function tests normalized rapidly
Reddy et al, 1977	Jaundice	No metastasis	Paraneoplastic syndrome	No therapy	Exitus
Karakolios et al., 2003	Jaundice, pruritus	NA	Paraneoplastic syndrome	Gonadotropin-releasing hormone analog (leuprolide) and antiandrogen (bicalutamide)	Liver function tests became normal after one month
Koruk et al., 2004	Low back pain jaundice, pruritus	Bone	Paraneoplastic syndrome	Goserelin, antiandrogen (flutamide, zolendronate)	Liver function tests became normal after two weeks
Our case	Jaundice, pruritis, fatique, low back pain	Bone	Paraneoplastic syndrome	Orchiectomy	Liver function tests became normal after two months

NA: Not available.

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