Hepatic Failure-induced Hypogonadism in a Prostate Cancer Patient

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Hypogonadism owing to systemic diseases in prostate cancer is rare. Here, we present a patient with metastatic prostate cancer to the pericardium who had low serum testosterone level due to hepatic failure. The patient had cardiac tamponade, and pericardiocentesis revealed sanguineous exudate. Cytology revealed adenocarcinoma. High serum prostate-specific antigen level of 244 ng/mL was detected. The patient experienced complications of stress gastric and duodenal ulcer perforation and underwent subtotal gastrectomy. Perioperative intra-abdominal inflammatory process caused subsequent cholestasis and hepatic dysfunction. Transrectal ultrasound-guided prostate biopsy confirmed prostate cancer. Hypogonadism and a gradual decline in prostate-specific antigen were detected without any hormone therapy. The patient died due to hepatic failure in the 12th postoperative week. [*J Chin Med Assoc* 2010;73(7):389–392]

Key Words: hypogonadism, liver failure, prostate cancer

Introduction

Hypogonadism induced by systemic illness is not uncommon.[1,2] The pathogenesis of hypogonadism is not well understood. Herein we report a rare case with metastatic prostate cancer to the pericardium who experienced hypogonadism during the complicated treatment course.

Case Report

A 68-year-old male had progressive dyspnea and productive cough for 1 week. Chest radiography revealed cardiomegaly (Figure 1) and cardial echography showed massive pericardial effusion. Cytology from pericardiocentesis showed adenocarcinoma, and serum prostate-specific antigen (PSA) was 244 ng/mL. Pericardial effusion recurred in 1 week, and perforation of the duodenum developed. Preoperative hepatic dysfunction was found: total bilirubin was 6.2 mg/dL (normal range, 0.1–1.2 mg/dL), direct bilirubin was 3.6 mg/dL (normal range, 0–0.2 mg/dL), aspartate aminotransferase (AST) was 544 U/L (normal range, 8–38 U/L), alanine aminotransferase (ALT) was 1,142 U/L (normal range, 4–44 U/L), alkaline phosphatase (ALK-P) was 259 U/L (normal range, 50–190 U/L), and albumin was 2.5 g/dL (normal range, 3.5–5.0 g/dL). Surveys of hepatitis A, B and C were all negative. Follow-up PSA was 97.55 ng/mL.

The patient underwent subtotal gastrectomy and Billroth II gastrojejunostomy. Pathology revealed severe gastric and duodenal ulcer with perforation. Postoperative duodenal stump leakage developed, and localized peritonitis caused delayed enteral feeding. Parenteral nutrition was given and jaundice persisted. Two weeks after the operation, total bilirubin rose to 29.1 mg/dL and direct bilirubin rose to 17.0 mg/dL. AST was 31 U/L, ALT was 8 U/L, and ALK-P was 307 U/L. Gamma-glutamyl transpeptidase was 70 U/L (normal range, 8–61 U/L).

Enteral feeding started after 4 weeks of starvation, at which time the liver function tests were still abnormal. Total bilirubin was 24.2 mg/dL, direct bilirubin was 11.9 mg/dL, AST was 259 U/L, ALT was 138 U/L, ALK-P was 579 U/L, and γ-glutamyl transpeptidase

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was 339 U/L. Abdominal computed tomography did not show any abscess, intra-abdominal tumor or dilated biliary tracts except for small retroperitoneal lymphadenopathy and bone metastases to the spine and sacroiliac joint. The heart shadow from chest radiography was normal. The sizes of the testicles on physical examination were both 2.2 cm. Transrectal ultrasound-guided biopsy showed adenocarcinoma of the prostate with a Gleason score of 3 + 4. Bone scan revealed multiple bone metastases to the sacroiliac joint, spine and ribs. PSA declined to 3.82 ng/mL and 1.94 ng/mL in the 8th and 12th postoperative weeks, respectively. Hypogonadism was also detected, with testosterone level of 0.79 ng/mL. The patient died due to hepatorenal syndrome in the 12th week after surgery. The complete treatment paradigm is shown in Figure 2.

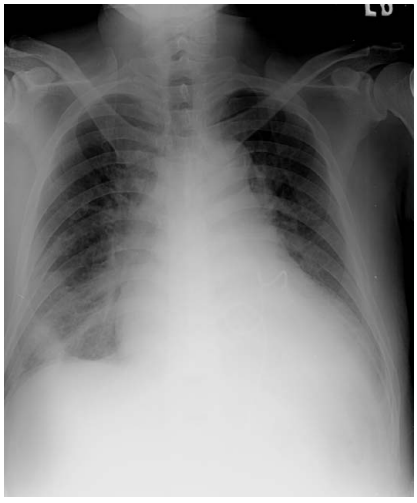

Figure 1. Preoperative chest radiography shows cardiomegaly and pericardial effusion.

Discussion

This is the first case report describing the PSA decline effect in a newly diagnosed advanced prostate cancer patient through hypogonadism induced by hepatic failure. Two key points determined the diagnosis and treatment in this case. First, what was the cause of liver failure? During diagnosis, computed tomography, radiography and endoscopy had excluded the sources of obstructive jaundice and other intra-abdominal infections or tumors. Therefore, cholestasis induced by any entity was the major pathway to liver damage. Table 1 lists the common differential diagnoses of cholestasis.[3] In this patient, biliary obstruction, biliary sludge and acalculous cholecystitis were excluded after imaging studies. Acute cholangitis less likely developed in this condition owing to lack of underlying liver disease history. Viral hepatitis was excluded after blood tests, and autoimmune hepatitis was not likely due to the rapidly erupting disease process.[4] Malignancy-induced cholestasis has been reported in advanced prostate cancer as a paraneoplastic syndrome.[5] In our case, the decline in serum PSA level did not correlate with

Table 1. Differential diagnoses of cholestasis

1. Biliary obstruction
2. Biliary sludge
3. Acalculous cholecystitis
4. Acute bacterial cholangitis
5. Unrecognized liver disease
6. Malignancy (e.g. lymphoma)
7. Drug-induced cholestasis
8. Total parenteral nutrition
9. Sepsis

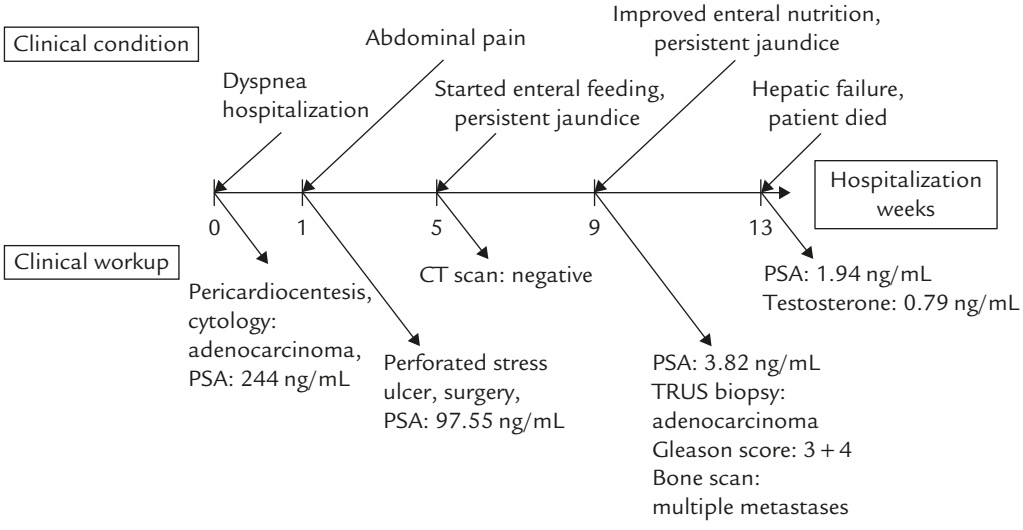

Figure 2. Summary of the patient's hospitalization course.

improvement of liver function. This clinical manifestation differs from that shown in a paraneoplastic syndrome. Based on the history of postoperative leakage of the duodenal stump, subsequently localized peritonitis and prolonged ileus, we regarded the liver failure as a combined result of sepsis and medical treatment.

The mechanism of cholestasis induced by sepsis is considered to be mediated systemically by proinflammatory cytokines.[3] These cytokines, such as tumor necrosis factor-α, interleukin (IL)-1 and IL-6, are released in response to the systemic inflammatory process induced by lipopolysaccharides. Total parenteral nutrition and some medications have been reported to be hepatotoxic.[6,7]

Reviewing the medication used in this patient, total parenteral nutrition with hepatic modification was prescribed, antibiotics such as amoxicillin-clavulanic acid were avoided, and other medications such as nonsteroidal anti-inflammatory drugs, opioids, antihypertensives and antidiabetic agents were not consistently used.[7,8] Table 2 lists the systemic medications used in the patient. However, with cautious treatment, hepatic failure eventually developed due to irreversible damage. The second key point: how did hypogonadism develop during treatment? The mechanism of hypogonadism in cirrhotic patients has been attributed to malnutrition, and increasing estrogen conversion from androgens.[9] Vicentini et al observed low serum testosterone and PSA levels among cirrhotic patients, which corresponded to this theory.[2] Furthermore, hepatic dysfunction reduces the synthesis of insulin-like growth factor-1 in the liver and subsequently decreases testosterone synthesis. Another mechanism causing hypogonadism is sepsis-induced organ injuries. Yang et al described testis injuries in a sepsis rat model from observing an increased concentration of nitric oxide-derived nitrate anion in tissues.[10] Nitrate anion can facilitate vasopressin secretion and subsequently induce vascular contraction and tissue hypoperfusion. Moreover, medications such as norepinephrine and octreotide used to maintain blood pressure and control duodenal stump leakage may have compromised the peripheral circulation and also impaired the testes function in this patient. These considerations corresponded to the smaller testicles of the patient. In summary, the possible mechanisms leading to hypogonadism in this patient are presented in Figure 3.

The treatment of this patient was mainly focused on the prevention of hepatotoxicity and the restoration of enteral nutrition. Serum PSA declined gradually without any treatment. In summary, we have reported a rare case of malignant pericardial effusion due to metastatic prostate cancer. Hepatic failure developed during treatment and induced hypogonadism and spontaneous decline of serum PSA level.

Table 2. Possible hepatotoxic or hypogonadism medications used in the patient

Antibiotics
Fluconazole
Nonsteroidal anti-inflammatory drugs
Ketorolac
Diclofenac
Hypnotics
Midazolam
Miscellaneous
Octreotide
Norepinephrine
Total parenteral nutrition

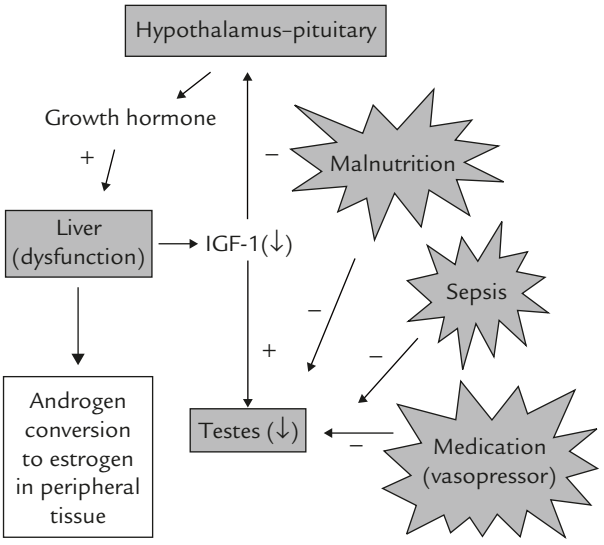

Figure 3. Illustration of endocrine control axis leading to hypogonadism. In hepatic dysfunction, the sensitivity of growth hormone receptors decrease and reduce the synthesis of insulin-like growth factor-1 (IGF-1). Subsequently, the stimulation of the testes decreases. Hepatic dysfunction increases the conversion of androgen to estrogen in peripheral tissue. Malnutrition, sepsis and medication compromises testicular function through decrease of nutrition and perfusion.

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