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Single Case

Bicalutamide-Associated Acute Liver Injury and Migratory Arthralgia: A Rare but Clinically Important Adverse Effect

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Keywords

Bicalutamide · Liver injury · Liver failure · Migratory polyarthralgia · Prostate cancer · Drug safety

Abstract

We describe a case of acute liver injury and migratory arthralgia in a patient receiving bicalutamide treatment for prostate cancer. A 67-year-old male with metastatic prostate cancer presented with a 6-day history of migratory arthralgia. He had been undergoing treatment with bicalutamide for 4 months; 3 weeks prior to symptom appearance the bicalutamide dose had been increased. He had no other symptoms. Liver tests and inflammatory markers were markedly elevated. Serology for hepatitis viruses A, B, and C, CMV, and EBV and autoimmune causes were all negative, and an ultrasound of the upper abdomen was normal. There was no history of blood transfusion, intravenous drug abuse, or alcohol abuse. Due to the suspicion of a drug-induced symptomatology, bicalutamide was discontinued and the patient started on 30 mg prednisolone daily. Three weeks later he was symptom free and after 6 weeks his liver tests were almost normal. The Roussel Uclaf Causality Assessment Method (RUCAM) suggested a

high probability of liver injury. Bicalutamide has very rarely been reported as a causative agent for liver injury and to our knowledge never for migratory polyarthralgia. The migratory polyarthralgia was attributed to bicalutamide due to the absence of other etiological factors and the disappearance of symptoms after discontinuation of the drug. To our knowledge, this is the first published case report of migratory arthralgia and concomitant liver injury attributed to bicalutamide.

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Introduction

Prostate cancer is an important health care issue and is the second leading cause of cancer in men worldwide. Most cases of prostate cancers are now being diagnosed at an early disease stage and in younger men, due in part to the widespread measurements of serum prostate-specific antigen [1]. Management of the prostate cancer confined to the prostate gland includes watchful waiting, radical prostatectomy, radiation therapy, or hormonal therapy [2]. Once the cancer extends beyond the prostate gland (stages T3–4, N+, M+) hormonal therapy is the mainstay of treatment [1]. The most commonly used agents are medical castration with luteinizing hormone-releasing hormone agonists, maximum androgen blockade, and anti-androgen monotherapy including bicalutamide [1].

We describe a case of an acute liver injury and migratory arthralgia in a patient receiving bicalutamide treatment for prostate cancer without an underlying arthritic or hepatic disease. To our knowledge, this is the first published case report of migratory arthralgia and concomitant liver injury attributed to bicalutamide.

Case Report

A 67-year-old Caucasian male with a history of hypertension and kidney stones was diagnosed with locally advanced prostatic cancer. The cancer was in Gleason scale 4 + 3 adenocarcinoma (cT3bN0M0) with a prostate-specific antigen level of 46 ng/mL (normal <4 ng/mL). His only other medication included enalapril (ACE inhibitor) and angelica root (*Angelica archangelica*), a dietary supplement, both of which he had been taking for a few years. He was started on treatment with 50 mg ×1 bicalutamide (a nonsteroidal antiandrogen), goserelin (a luteinizing hormone-releasing hormone agonist), 3.6 mg s.c. every 28 days, and radiation therapy which he tolerated well. Four months after starting bicalutamide (125 days) the dose was increased to 150 mg ×1. Twenty-three days later he developed an intensive pain in the left shoulder that later moved to the right shoulder, leaving the left shoulder symptom free, followed by migration to the left hip and right hand, ending only with jaw pain. The pain became so severe that he sought assistance in the emergency room. He had no fever, respiratory symptoms, or gastrointestinal symptoms accompanying the arthralgia. Both liver tests and inflammatory markers were found to be elevated with alkaline phosphatase 468 U/L (normal <105 U/L), alanine aminotransferase 263 U/L (normal <70 U/L), CRP 187 mg/L (normal <3 mg/L), and an erythrocyte sedimentation rate of 73 mm/h (Table 1). An ultrasound of the upper abdomen showed no pathological changes in the liver or biliary tree. Hepatitis serology against

hepatitis A, B, and C were negative as were tests for immunoglobulin M antibodies to EBV and CMV. Furthermore, antinuclear, anti-cyclic citrullinated peptide antibodies and rheumatoid factor testing were also negative. There was no history of blood transfusion, intravenous drug abuse, or alcohol abuse. Due to the suspicion of a drug-induced symptomatology, bicalutamide was discontinued after a week of migratory arthralgia symptoms. The patient was started on prednisolone 30 mg per day to treat the arthralgia. He continued on both his enalapril and dietary supplement (see above) during the course and after the reaction.

His symptoms gradually decreased, being pain free 3 weeks later. Six weeks later his liver tests were almost normal, except for a slightly elevated alkaline phosphatase (Table 1), and the patient remained pain free. According to the Roussel Uclaf Causality Assessment Method (RUCAM) [2] the liver injury was highly probable.

Discussion

Monotherapy with bicalutamide, an orally active nonsteroidal antiandrogen, is an attractive alternative in the treatment of prostate cancer as it does not suppress testosterone production, offering potential advantages to castration [1]. It inhibits the growth of prostate tumors by antagonizing the action of androgens at the receptor level of both the testis and adrenal gland [1]. Bicalutamide is readily absorbed with a linear steady-state concentration with a dose over 10–50 mg [1]. If a higher dose is used, the steady-state increase is slightly less than dose proportional [3]. It is cleared by both phase I and phase II hepatic metabolism with oxidation and glucuronidation, and eliminated both through bile and by the kidney [3]. The pharmacokinetics of bicalutamide are not affected by age, renal function, or mild hepatic impairment [3]. The most commonly reported side effects of bicalutamide are gynecomastia, mastitis, and hot flushes [3]. Liver injury has very rarely been reported in association with the use of bicalutamide, although it has been on the market for more than 20 years [1, 4]. According to a recent review only 3 cases of liver injury have been published that were convincingly related to the use of the drug [4–7]. Another case was reported but not found to fulfill the causality assessment criteria for a possible relationship [4, 8]. Since then 2 cases have been reported [9, 10]. In Table 2, all cases reported and found to have at least a possible causal relationship are illustrated in terms of demographics, type of liver injury, and outcome. The majority of the patients presented in the case reports (Table 2) were similar in age, had no prior history of liver disease, and were previously healthy. All of the patients survived except for one who died of multiorgan failure after 4 days of bicalutamide treatment [6].

Migratory polyarthralgia can be seen in various conditions including reactive arthritis, rheumatic fever, or crystalline arthropathies [11–14]. Cases have also been reported on migratory polyarthralgias as a paraneoplastic phenomenon such as carcinomatous polyarthrititis, which is a diagnosis of exclusion [12]. Several medications have been reported as causative agents for migratory polyarthrititis including clopidogrel and propylthiouracil [11, 13].

The migratory polyarthralgia was attributed to bicalutamide because of the absence of other etiological factors and the disappearance of symptoms after discontinuation of the drug. The reaction appeared approximately 3 weeks after the dose of bicalutamide was increased. Interestingly, idiosyncratic liver injury has been found to be dose dependent [15].

Conclusion

Bicalutamide is commonly used in the treatment of prostate cancer and seems to be better tolerated than other antiandrogens. This case report underlines the possible hepatic complications associated with bicalutamide but also draws attention to the other possible side effects such as the migratory arthralgia seen in our patient. To our knowledge, this is the first presented case where migratory polyarthralgia with concomitant liver injury has been associated with bicalutamide.

Statement of Ethics

The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors declare that there is no conflict of interest regarding the publication of this paper.

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Table 1. Results of laboratory tests at onset and follow-up

Days from presentation	ALP, U/L	AST, U/L	ALT, U/L	Bilirubin, $\mu\text{mol/L}$	CRP, mg/L
Admission	468	107	225	11	187
Day 3	462	81	167	7	108
Day 17	184	37	72	–	–
Day 46	112	22	29	7	–

ALP, alkaline phosphatase (normal <105 U/L); AST, aspartate aminotransferase (normal <31 U/L); ALT, alanine aminotransferase (normal <70 U/L); bilirubin (normal <25 $\mu\text{mol/L}$); CRP, C-reactive protein (normal <3 mg/L).

Table 2. Cases reported in the literature of bicalutamide-induced liver injury

Reference	Age, years	Dose	Duration of treatment	Type of injury	Outcome
Dawson et al. [5]	60	50 mg	2 days	HC	survived
O'Bryant et al. [6]	59	–	4 days	HC	death
Yun et al. [9]	62	100 mg	133 days	HC	survived
Hussain et al. [10]	81	150 mg	21 days	mixed	survived
Current report	67	150 mg	23 days	mixed	survived

HC, hepatocellular liver injury.