Interstitial pneumonitis secondary to leuprorelin acetate for prostate cancer

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Abstract
Androgen blockade is standard treatment for advanced prostate cancer. We report an uncommon case of interstitial pneumonitis induced by leuprorelin acetate.

Introduction
Leuprorelin acetate is a gonadotropin-releasing hormone (GnRH) analog that acts as a potent antiandrogen when given continuously in therapeutic doses. It is often used following a course of androgen receptor antagonists such as cyproterone acetate, which serve to buffer the initial testosterone flare with GnRH analog therapy. Together, they form the maximal androgen blockade required to continually suppress the secretion of testosterone and thereby minimize the progression of prostate cancer. Antiandrogen-induced pneumonitis is extremely rare with only a handful of cases reported in current literature.

Case Report
A 66-year-old male with prostate cancer presented with a two-month history of gradual onset shortness of breath, cough, and fatigue after treatment with cyproterone and leuprorelin acetate. He was Caucasian, retired with no previous toxic chemical exposure, a non-smoker, and had past medical history of reflux and osteoarthritis.

The onset of his symptoms correlated with the use of androgen deprivation therapy. The patient first noticed a gradual onset of mild shortness of breath, malaise, and fatigue one week after starting cyproterone acetate (50 mg twice daily). His initial breathlessness on exertion scored 3 on the Modified Borg Dyspnoea Scale and gradually increased over the next few weeks (Fig. 1). At that stage, his chest X-ray and examination findings were normal, with no signs of infection or other lung disease. He presented afebrile, with normal inflammatory markers, and was managed as an outpatient. After five weeks of cyproterone, the patient received an intramuscular (IM) injection of leuprorelin (30 mg IM) planned to be administered four-monthly.

One day after receiving the IM leuprorelin, the patient experienced a sudden onset of severe shortness of breath (Modified Borg Dyspnoea Scale of 8) associated with extreme exhaustion and malaise. His exercise tolerance, previously several kilometers, decreased to 50 m. For five days, the patient remained immobile with no improvement. Presenting to hospital, he was admitted and treated for presumed pneumonia with a three-day course of oral azithromycin, and the dose of cyproterone acetate was reduced (from two to one
tablet daily). There were no lung crackles, and his arterial oxygen saturation was 95% on room air. He had no fevers, and infective markers (leucocyte count and C-reactive protein) were normal. A chest X-ray revealed diffuse bilateral patchy infiltrates, and computed tomography (CT) of the chest identified multifocal ground glass and air-space opacities bilaterally but no evidence of pulmonary emboli (lung bases on previous CT performed for prostate cancer staging showed no infiltrate) (Fig. 2). As there was no improvement, he was again treated for infection with intravenous therapy, and the cyproterone acetate was ceased.

Despite this, his shortness of breath worsened over the next month, and he re-presented to hospital with severe dyspnoea, cough, fatigue, and a further reduced exercise tolerance. At that time, he had noted no fevers, coryzal symptoms, pedal edema, or chest pain. Lung auscultation revealed bilateral fine crackles, and laboratory studies showed elevated lymphocytes and erythrocyte sedimentation rate. The chest X-ray revealed no interval change to previous imaging. Sputum cultures and autoimmune screening were negative. Pulmonary function tests showed a restrictive picture (forced vital capacity: 2.93 L [73% predicted], forced expiratory volume in one second: 2.23 L [81% predicted], diffusing capacity of the lung for carbon monoxide: 64% predicted), and his arterial oxygen saturation at rest and exercise on room air was 94% and 88%, respectively. Given the lack of infective symptoms, poor response to antibiotics, and lung function and radiological changes, it was felt an interstitial pneumonitis due to leuprorelin was most likely. A two-week course of oral prednisolone was given with symptomatic improvement, and serial CT of the chest three months from discharge revealed improvement in the infiltrates correlating to the patient’s clinical improvement.

Discussion

Administration of leuprorelin acetate, like other GnRH analogs, causes an initial increase in circulating levels of lutenizing hormone and follicle-stimulating hormone, in turn leading to a transient increase of testosterone and dihydrotestosterone. In some patients, this leads to a transient exacerbation of symptoms such as worsened bone pain, urinary obstruction, and spinal cord compression known as the “flare phenomenon” until castrate levels of testosterone are reached in two to six weeks. Although fatigue, hyperhidrosis, night sweats, and headache have been reported in up to 6% of patients of one clinical trial, respiratory side effects including dyspnoea, cough, or chest pain are extremely uncommon [1]. The diagnosis of drug-induced pulmonary toxicity is often a diagnosis of exclusion. In the case discussed, an infectious etiology for his dyspnoea was excluded based upon absent blood changes, negative sputum cultures, negative serology, and a lack of response to antibiotics. Other possibilities including pulmonary emboli (PE), airway disease, pulmonary hypertension, heart failure, and autoimmune pathology as common differentials for acute worsening of dyspnoea were also excluded. The exclusion of PE in this case was significant as men with prostate cancer, especially those undergoing antiandrogen therapy, are at greater risk of thromboembolic
disease [2]. The case for drug-induced interstitial pneumonitis was further strengthened by the temporal relationship and sequence of events demonstrating worsening and then improving dyspnoea following the initiation and cessation of leuprorelin and response to corticosteroids.

Three case reports link leuprorelin use with interstitial pneumonitis, and there are isolated but consistent reports of other antiandrogens used for prostate cancer inducing interstitial pneumonitis [3–5]. There is only one case report of cyproterone acetate induced pneumonitis [6]. The common theme found is the rapid improvement and complete resolution of symptoms and radiological findings after the cessation of antiandrogens. Importantly, antiandrogen therapy, including with cyproterone, can also be associated with dyspnoea through hormone effects on respiratory drive [7]. The respiratory stimulating effect of progesterone has been well documented in literature for over 50 years, explaining hyperventilation and low CO$_2$ in pregnancy and varying respiratory rates according to luteal cycle [8]. While the role of testosterone in the control of breathing has not been elucidated as clearly as progesterone, testosterone is a downregulator of prostaglandin receptors, which may explain, in part, an increasing sensation of dyspnoea with low testosterone levels [9].

This patient’s initial sensation of dyspnoea may have related to the hormone effect of antiandrogen therapy, but this mechanism cannot explain the lung parenchymal changes seen on the CT of his chest and ongoing symptoms despite cessation of cyproterone. The combination of causes may have resulted in the phases of worsening dyspnoea in the discussed case. The time frame suggests leuprorelin is more likely than cyproterone to be the cause of the interstitial changes, with leuprorelin depot taking roughly four months to be fully eliminated from the body, whereas the elimination half-life of cyproterone is less than 48 h.

The exact mechanism of how leuprorelin causes reversible, parenchymal changes is yet to be determined. Of the other few case reports linking leuprorelin with interstitial pneumonitis, they have found the gradual cessation of dyspnoea with the elimination of leuprorelin from the body, suggesting a relationship with tissue levels. Granted that prostate cancer is a common cancer in men, this case represents an important finding linking a commonly used prostate cancer drug and

Figure 2. Computed tomography scans of the chest taken at peak severity of dyspnoea demonstrating multifocal ground glass and air-space opacities bilaterally in February 2015 (A1 and A2). Repeat scans taken three months later (May 2015) demonstrating the marked improvement of bilateral opacities following cessation of cyproterone and leuprorelin acetate (matched images B1 and B2).
interstitial pneumonitis, and this complication should be considered in patients who develop breathlessness.

**Disclosure statements**

No conflict of interest declared.

Appropriate written informed consent was obtained for publication of this case report and accompanying images.

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