Bicalutamide-induced Eosinophilic Pneumonitis - A Serendipitous Diagnosis

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Abstract
Bicalutamide is a first-generation non-steroidal anti-androgen. Interstitial lung disease is a rare side effect of bicalutamide. Centres in the United States of America and Japan have previously reported bicalutamide-induced interstitial lung disease. This has not been reported in the United Kingdom.

An 86-year-old Caucasian man with a history of advanced prostate cancer, on oral bicalutamide, presented to the emergency department with sudden onset dyspnoea and chest tightness.

Bicalutamide-induced eosinophilic pneumonitis co-existing with community acquired pneumonia, and left ventricular systolic dysfunction were suspected, based on physical examination findings and investigation results that include blood tests, chest radiographs, echocardiogram, in addition to computed tomography pulmonary angiogram performed to rule out pulmonary embolism.

There was a marked clinical, biochemical and radiological improvements after discontinuation of bicalutamide, initiation of a high-dose steroid, intravenous antibiotics, and diuretic. Prostate cancer retains a high incidence in the Western population. Recognising toxicities due to anti-androgen therapies is relevant to clinical practice.

Introduction
Bicalutamide is a first-generation non-steroidal competitive inhibitor of androgen, which exerts its effects by binding to cytosolic androgen receptors in the target tissues [1]. It is the most recent once daily oral anti-androgen drug used in the treatment of advanced prostate cancer [2-3].

Interstitial lung disease is an uncommon but significant side effect of bicalutamide [3]. Bicalutamide-induced interstitial lung disease developed within months of bicalutamide therapy, has previously been reported by centres in the United States of America and Japan, [2,4] however, this has not been reported in the United Kingdom. We report a case of eosinophilic pneumonitis developed after many years of bicalutamide therapy, co-existing with community acquired pneumonia, and moderate left ventricular systolic dysfunction.

Case Presentation
An 86-year-old Caucasian man was brought to the emergency department (ED) by an ambulance due to sudden onset dyspnoea associated with chest tightness, cough productive of yellowish sputum, diaphoresis, and palpitations. He also described a 3 months history of ankle swelling, and reduced exercise tolerance to 200 metres over the past 1 year. However, he denied any fever, weight loss, orthopnoea, or paroxysmal nocturnal dyspnoea.

Past medical history included moderately well differentiated adenocarcinoma, Gleason 3+4 of prostate diagnosed in 2012, previous ureteric carcinoma in 2000, hypertension, chronic kidney disease (Stage II), glaucoma, left total hip replacement surgery, and previous cataract surgery.

Current medications included bicalutamide 150 mg OD, nebivolol 5 mg OD, amlo dipine 10 mg OD, dorzolamide 2% + timolol 0.5% eye drop i BD, latanoprost 50 micrograms/ml i nocte, omeprazole 20 mg OD, aspirin 75 mg OD, and atorvastatin 10 mg nocte.

He does not have any allergies or history of atopy.

His father died at the age of 67 years due to prostate cancer.

He has 30 pack years of smoking history. He does not drink alcohol.

He was a retired ship engineer. He denied any recent foreign travel.

On examination, he appeared unwell. Observations revealed a respiratory rate of 30 breaths per minute, oxygen saturation 91% on 15 litres of oxygen, heart rate 103 beats per minute, blood pressure 107/76 mmHg, temperature 37.0°C. He had no finger clubbing. Chest auscultation revealed reduced breath sound bilaterally with coarse inspiratory crackles in the lower and mid-zones, heart sound was normal (irregular) with a raised jugular venous pressure 4 cm above the clav-
icle, abdomen was soft non-tender, as well as soft non-tender calves with bilateral pitting oedema.

In-patient investigations include serial bedside arterial blood gases (ABG), electrocardiogram (ECG), blood tests, series of chest x-rays (CXR), computed tomography pulmonary angiogram (CTPA), and echocardiogram.

He was subsequently admitted to the medical high dependency unit (HDU) due to severe type 1 respiratory failure, where oxygen was administered using a continuous positive airway pressure (CPAP) machine. He was stepped down to a respiratory ward when he improved clinically.

Eventually, he was discharged home after spending 25 days in the hospital (Table 1).

<table>
<thead>
<tr>
<th>Date</th>
<th>Event</th>
</tr>
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<tbody>
<tr>
<td>September 16</td>
<td>Presented to the ED with shortness of breath</td>
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<tr>
<td>September 16</td>
<td>Admitted to the medical HDU</td>
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<tr>
<td>September 18</td>
<td>X2 MET CALLS, haemoptysis, bicalutamide stopped, high dose prednisolone started</td>
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<tr>
<td>September 19</td>
<td>Continued oxygen delivery using a CPAP machine</td>
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<tr>
<td>September 21</td>
<td>CXR</td>
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<tr>
<td>September 23</td>
<td>Antibiotic escalation</td>
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<tr>
<td>September 25</td>
<td>CXR</td>
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<tr>
<td>September 26</td>
<td>Step down to a respiratory ward</td>
</tr>
<tr>
<td>October 1</td>
<td>CXR</td>
</tr>
<tr>
<td>October 1</td>
<td>Antibiotics stopped</td>
</tr>
<tr>
<td>October 10</td>
<td>Discharged from the hospital</td>
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</tbody>
</table>

Table 1: The timeline from hospital admission to discharge

Diagnostic focus and assessment

The results of the initial investigations performed in the ED are as follows: ABG on room air showed pH 7.43 (normal 7.35-7.45), pCO₂ 4.1 kPa (4.7-6.4), pO₂ 5.2 kPa (11.1-14.4), HCO₃ 22.2 mmol/L (20-26), BE - 3.0 mmol/L (-2.0-3.0), lactate 2.3 mmol/L (0.5-2.2). ECG showed new onset of atrial fibrillation (AF) with a mild prolonged QTc interval (Figure 1). Blood results showed white blood cells (WBC) 22.5 * 10^9/L (4.0 - 11.0) with a differential WBC count showing neutrophil count 14.4 *10^9/L (2.0 - 8.0), lymphocyte count 2.3 *10^9/L (1.0 - 4.0), monocyte count 2.5 *10^9/L (0.1 - 1.0), eosinophil count 3.2 *10^9/L (0.0 - 0.4), basophil count 0.1 *10^9/L (0.0 - 0.3). Haemoglobin 109.0 g/L (130 - 170), platelet count 271 *10^9/L (140 - 400 *10^9/L), sodium 139 mmol/L (137-145), potassium 4.0 mmol/L (3.5 - 5.1), urea 10.9 mmol/L (2.5 - 7.8) creatinine 134 µmol/L (59 - 104), C-reactive protein 164 mg/l (< 10 mg/l), troponin I 331 ng/L (< 20). CXR showed bilateral upper and mid-zone opacification (Figures 2,3). CTPA showed bilateral consolidation, bilateral lower zone ground-glass opacities, bilateral pleural effusion, and mediastinal adenopathy with no evidence of pulmonary embolism (Figures 4-11). He was started on treatment for community acquired pneumonia (CAP) according to the local protocol using intravenous benzylpenicillin 2.4 g QDS, and oral clarithromycin 500 mg OD, as well as diuresis with intravenous furosemide 40 mg OD.
Figure 4: CTPA showed bilateral consolidation and pleural effusion in the upper zone

Figure 5: CTPA showed bilateral consolidation and pleural effusion in the upper zone

Figure 6: CTPA showed bilateral consolidation, bilateral mid-zone ground glass opacities, and bilateral pleural effusion

Figure 7: CTPA showed bilateral consolidation, bilateral mid-zone ground glass opacities, and bilateral pleural effusion

Figure 8: CTPA showed bilateral consolidation, bilateral mid-zone ground glass opacities, and bilateral pleural effusion

Figure 9: CTPA showed bilateral consolidation, bilateral lower zone ground glass opacities, and bilateral pleural effusion
Serial troponin I blood tests performed showed a decreasing troponin I of 328 ng/L and 68 ng/L two days later. The features of congestive cardiac failure present were thought to be heart rate-related after the cardiologist reviewed him. Whilst in the HDU, he had a few episodes of haemoptysis. He continued to trigger medical emergency team (MET) call due to ongoing tachypnoea and tachycardia. Repeat ABG on 60% of oxygen using CPAP with a setting of 5 cmH₂O showed pH 7.51, pCO₂ 3.7 kPa (4.7 - 6.4), pO₂ 11.0 kPa (40 - 50), HCO₃ 25.2 mmol/L (20 - 26), BE - 0.4 mmol/L (-2.0 - 3.0), lactate 1.8 mmol/L (0.5 - 2.2). Bicalutamide was stopped after urology consult. High-dose oral prednisolone 60 mg was started and a tapering dose commenced after 7 days. Anticoagulation due to AF was not started due to haemoptysis, and HAS-BLED score of 3 despite CHA2DS2-VASC score of 4.

Echocardiogram showed mild aortic stenosis, moderately impaired left ventricular systolic function with ejection fraction of 45%, impression of global hypokinesis, mild bi-atrial dilatation, and persistent AF. He was started on oral ramipril 1.25 mg OD and oral furosemide 20 mg OD continued after consult with the cardiology team.

Repeat CXR few days later showed bilateral consolidation with pleural effusion (Figure 12). Blood results showed high but improving inflammatory markers (albeit slowly) but patient continued to require oxygen therapy using a CPAP machine. Blood culture had no bacteria growth after 48 hours. No acid-fast bacillus (AFB) was seen in 3 sputum cultures, however coliform was isolated from the sputum culture. Pneumococcal urinary antigen test was negative, as well as legionella pneumophila antigen. The results of the vasculitic screen are as follows: anti-glomerular basement membrane (GBM) antibody < 7 U/ml (7 - 10), cytoplasmic anti-neutrophil cytoplasmic antibody (cANCA) negative, anti-neutrophil antibody (ANA) negative, anti Jo-1 antibody negative, anti Ro antibody negative, anti La antibody negative, anti RNP antibody negative, anti Scl-70 antibody negative, and anti-centromere antibody negative. Antibiotics were escalated to oral levofloxacin 500 mg BD initially, then 250 mg BD due to estimated glomerular filtration rate (eGFR) varying between 46 - 52 mL/minute/1.73 m² (normal range > 90) on the advice of the local microbiologist after 7 days of benzylpenicillin and clarithromycin.
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Figure 13: CXR on day 10 of hospital admission showed bilateral consolidation with pleural effusion

Figure 14: CXR on day 15 of hospital admission showed significant improvements in the consolidations, and resolution of the pleural effusion

Follow-up and outcomes

1. He was discharged home with 30 mg of prednisolone to be tapered until stopped, and follow-up in the respiratory outpatient clinic in 4 weeks with a CXR

2. PSA monitoring and outpatient follow-up with the urology team in 3 months with the aim of surgical castration if PSA relapses

3. Outpatient cardiology follow-up in 3 months

Discussion

Raised peripheral blood eosinophil count and evidence of ground-glass opacities on a CTPA, points towards the diagnosis of eosinophilic pneumonitis, in a patient with biochemical and radiological evidence of CAP and left ventricular systolic dysfunction (Figures 4-11). Having excluded other causes of blood eosinophilia and pneumonitis, bicalutamide therapy remains the only plausible explanation for these findings. This is consistent with previously published case reports by Wong, et al. and Masago, et al. [2, 4]. Wong, et al. reported peripheral and pulmonary eosinophilia, with evidence of bilateral pulmonary interstitial infiltrates on a CT thorax, which was confirmed with a transbronchial biopsy and bronchoalveolar lavage. These were in a 69-year-old man with advanced prostate cancer, 6 months after starting treatment with bicalutamide [2]. In addition, Masago, et al. reported interstitial pneumonitis confirmed on a CT scan in a 78-year-old man with prostate cancer, 8 months after bicalutamide therapy was initiated, though there was no eosinophilia [4].

Adenocarcinoma of the prostate retains a high incidence in the Western population [5]. Bicalutamide is one of the three first-generation non-steroidal anti-androgen agents available on the markets. Other members of this class include flutamide and nilutamide [1]. They are widely used as the first-line drugs to achieve combined androgen blockade in advanced and castrate-resistant prostate cancer [6]. Their main and common side effects include gynaecomastia and hepatic dysfunction, however, eosinophilic and non-eosinophilic pneumonitis are their rare/uncommon side effects [3,7-8].

The pathogenesis of bicalutamide-induced interstitial lung disease remains poorly understood.

It is noteworthy that the patient has been on bicalutamide therapy for 6 years and has not presented to the hospital with dyspnoea. Importantly, there was no previous CXR to compare his initial CXR with because he did not have a baseline CXR prior to the initiation of bicalutamide therapy. This prompted a literature search for clinical guidelines on initiation of bicalutamide therapy. We did not find any National Institute for Health and Care Excellence (NICE) guideline, however, a guideline by Dorset Cancer Network requires clinicians to monitor liver function tests every 6 months and PSA as appropriate without baseline CXR [9].

Interstitial pneumonitis was considered after he had a CTPA to rule out pulmonary embolism. It is therefore difficult to establish whether interstitial pneumonitis has been on the background before the development of CAP and left ventricular systolic dysfunction.

It could be argued that bronchoalveolar lavage and tissue diagnosis were not obtained, however, he was too unwell to undergo a bronchoscopy. Importantly, tissue diagnosis after stopping bicalutamide therapy might not be sufficient to confirm the diagnosis unless the patient undergoes bronchoscopy after a re-challenge with bicalutamide. This however is unethical.

Conclusions

Clinical improvement after discontinuation of bicalutamide therapy and initiating treatment with a high-dose prednisolone, together with biochemical resolution of peripheral blood eosinophilia, in the absence of no other plausible causes of eosinophilic pneumonitis,
strongly suggest bicalutamide-induced eosinophilic pneumonitis.

Finally, the incidence of prostate cancer remains high with increasing number of patients on first generation non-steroidal anti-androgen therapy. Recognising toxicities because of these therapies may become increasingly relevant to clinical practice. Take home messages include:

2. Baseline CXR should be performed before initiating a bicalutamide therapy.
3. Clinical guidelines should be updated to include performing baseline CXR before initiating bicalutamide therapy as this is currently not included in any clinical guidelines despite interstitial lung disease being a side effect of this medication.
4. High-dose steroid can be started in patients with severe infection if indicated.
5. Consent for treatments should be informed - including explaining rare but significant side effects of medications.

Patient perspective

It is quite upsetting that treatment for my prostate cancer may have caused my breathing problems. I did not really notice any difference in my breathing since I have been taking this tablet called bicalutamide. I only took 1 tablet a day. I am confused that the tablet may have caused it. I never really thought about it until I was told. There is not much I can do about it now.

It was not explained to me that this tablet could cause breathing problems. If it was explained to me, I would not have made the decision to take it. I am not a medical person. But I understand that all tablets have side effects. Using my experience as an example and writing this might help someone else.

I am happy and believe that now the tablet has been stopped that my breathing problems will get better.

Conflict of Interest

The authors declare that there is no conflict of interest.

References