Eosinophilic Lung Disease Induced by Bicalutamide*

A Case Report and Review of the Medical Literature

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A 69-year-old man with advanced prostate cancer was receiving antiandrogen therapy (bicalutamide [Casodex]). He developed dyspnea, peripheral eosinophilia and bilateral pulmonary interstitial infiltrates. Transbronchial biopsy confirmed pulmonary eosinophilia. Withdrawal of bicalutamide and initiation of steroid therapy resulted in clinical improvement. (CHEST 1998; 113:548-50)

Key words: antiandrogen agent; drug-induced eosinophilic lung disease; pulmonary infiltrates and eosinophilia (PIE)

Bicalutamide (Casodex) is the most recent nonsteroidal antiandrogen agent developed as a once-daily oral medication for treating advanced prostate cancer. The most frequent adverse effects of bicalutamide treatment are comparable to those of other nonsteroidal antiandrogen agents, and they include hot flushes, gynecomastia, impotence, nausea, diarrhea, constipation, and asthenia. Although a recent review mentioned an increased incidence of dyspnea in patients receiving this medication as compared with control subjects, no explanation was offered.2 Herein is the first reported case of a patient taking this medication who developed dyspnea, peripheral blood eosinophilia, and bilateral interstitial infiltrates, evidenced on chest x-ray film, in whom clearing of all aspects of illness occurred after cessation of bicalutamide therapy and initiation of a course of oral corticosteroid therapy.

REPORT OF A CASE

A 69-year-old man had a history of prostate cancer since 1991 with osseous metastasis to the pelvic bones. The patient visited his physician with symptoms of 5 weeks of productive cough with progressive dyspnea on exertion. There were no fever, chills, or rashes. A week prior to admission, a chest x-ray film and a CT scan of the chest were done; these revealed bilateral interstitial infiltrates (Figs 1, 2), and he was empirically treated with oral clarithromycin for 1 week without clinical improvement. This prompted his hospital admission for further diagnostic evaluation.

His past history included radical prostatectomy in 1991 for prostate cancer followed by radiation therapy for vertebral metastasis. Six months prior to his present illness, bicalutamide therapy was started for increasing prostatic specific antigen (PSA) level. He also had a history of Marfan’s syndrome and aortic arch repair for dissection in 1993. Current medications included bicalutamide, 200 mg orally once a day; clarithromycin, 500 mg twice a day for 1 week; triamcinolone acetonide (Azmacort), 2 puffs 4 times a day; and colace, 100 mg orally 3 times a day. He had been smoking 5 years earlier and had no significant occupational exposures. There was no known medical history of parasitic infection, prior food or drug allergies, or symptoms of atopy.

On admission, the physical examination revealed the following vital signs: BP, 120/70 mm Hg; pulse, 80 beats per minute; respiratory rate, 18 breaths per minute; temperature, 37.2°C. Chest examination showed bibasal velcro rales. Cardiac examination showed soft sounds, regular rate, and rhythm with grade 3/6 systolic murmur at the aortic valve area. There were no edema, cyanosis, or clubbing.

Significant laboratory findings included a WBC count of 10.7×10^3/mL with a differential cell count of 31% polymorphonuclear leukocytes, 13% band cells, 10% lymphocytes, 7% monocytes, and 39% eosinophils. Osimetry revealed an SaO_2 of 94% with the patient breathing room air. The ECG demonstrated normal sinus rhythm, normal axis with nonspecific ST segments, and T wave changes. The admission chest x-ray film showed new bilateral interstitial shadows.

During the hospital stay, peripheral eosinophilia was confirmed with repeated blood cell counts. A Gram’s stain of a sputum sample showed few neutrophils and eosinophils. Fungal culture obtained from the patient’s home humidifier grew no organisms. Serum protein electrophoresis revealed mildly broadened gamma band fraction, and quantitative study showed increased IgA (636 mg/dL) and IgE (464 mg/dL) with normal IgG and IgM. T complement, C3, and C4 were normal. Pulmonary function testing demonstrated normal spirometry and lung volumes but a significant decrease in diffusing capacity for carbon monoxide to 62% of predicted. The resting arterial blood gas level determination revealed mild hypoxemia (Po_2, 70 mm Hg) which worsened to Po_2 of 57 mm Hg after 6 min of exercise.

The echocardiogram showed mild aortic root dilatation (5.2 cm), mild aortic insufficiency, and mild decreased left ventricular ejection fraction with no evidence of dissection. Subsequent
bronchoscopy disclosed no endobronchial lesions with moderate amounts of secretions. The BAL and brushings grew no bacterial, fungal, or acid-fast organisms but showed preponderance of eosinophils. Transbronchial biopsy showed interstitial pneumonitis with eosinophilic infiltration (Fig 3).

With a presumptive diagnosis of eosinophilic pneumonia due to bicalutamide, the medication was stopped, and therapy was started with methylprednisolone sodium succinate (Solu-Medrol), administered intravenously. There was subsequent complete clinical improvement with an end to the cough and dyspnea, decrease of the peripheral blood eosinophil level to less than 1%, and clearing shown on the chest x-ray film. The patient was discharged on a regimen of oral prednisone; the dosage was tapered and stopped over a 3-week period. He has remained symptom-free during the next 3 months of follow-up while he was not receiving steroid treatment.

**Figure 1.** Chest x-ray film demonstrating bilateral interstitial shadows.

**Figure 2.** CT scan of the chest showing bilateral infiltration of the interstitium.

**Figure 3.** Transbronchial biopsy section shows markedly reactive alveolar pneumocytes with diffuse interstitial thickening and fibrosis. Collections of histiocytes and giant cells are found in the alveolar spaces with scattered eosinophils (hematoxylin-phloxine B-safranine stain, original ×450.

**Discussion**

Bicalutamide is a nonsteroidal antiandrogen agent which exerts its action by competitive inhibition of androgen binding to cytosol androgen receptors in the target tissue. Prostatic cancer is known to be androgen-sensitive and responds to treatment that counteracts the effect of androgen or removes the source of androgen, or both.

There are currently three nonsteroidal antiandrogens available on the market. 2 These agents have comparable efficacy but differ in their side effects. Flutamide, the first nonsteroidal antiandrogen released, has a short half life of 5 h, and causes gynecomastia, severe diarrhea, and reversible hepatic insufficiency. The second nonsteroidal antiandrogen, nilutamide (Canada), has a longer half life of about 2 days with reported adverse reactions of light-dark adaptation, alcohol intolerance, and noneosinophilic interstitial pneumonitis. The case reports3,4 describing nilutamide-induced lung diseases reported dyspnea and bilateral interstitial infiltrates on a chest x-ray film. The CBC count showed no peripheral eosinophilia. BAL demonstrated eosinophilia in one case. Clinical improvement took place after discontinuation of nilutamide, and without steroid therapy in either case.

Blackledge5 reviewed the adverse events with bicalutamide compared with those from flutamide and placebo. He reported a higher incidence (11%) of dyspnea in patients taking bicalutamide when compared with that of those taking flutamide (7.9%) or placebo (5.7%). No diagnostic data to confirm the cause of the dyspnea were discussed. Based upon the inquiry to the manufacturer of bicalutamide, there have been no similar unreported cases.

The current case differs from those produced by nilutamide in that the patient presented with peripheral eosinophilia in addition to dyspnea and bilateral interstitial infiltrates. Bronchoscopy showed eosinophilia on BAL and eosinophilic pneumonitis on biopsy. All studies for infection or malignant tumors showed neither entity. The
patient was treated with corticosteroids and bicalutamide therapy was discontinued; prompt resolution of symptoms and laboratory abnormalities followed. The patient refused a challenge study with this medication to see if the clinical picture would return.

This case strongly suggests a drug-induced eosinophilic lung disease as supported by the temporal relationship of events, the exclusion of all other causes, and the prompt clinical improvement following withdrawal of causative agent and institution of corticosteroid therapy.

Drug-induced lung injury is thought to be either a direct toxic effect of the drug or due to a hypersensitivity reaction. The clinical signs and symptoms usually are variable and nonspecific. Development of such an injury does not appear to be related to cumulative drug dose or duration of therapy. Chest roentgenographic findings are variable and nonspecific. The most common pattern is bilateral peripheral alveolar infiltrates with or without a migratory component and is often similar to other interstitial lung diseases. The usual pulmonary function deficit is a restrictive pattern with a reduction in diffusing capacity. Lung biopsy may reveal poorly defined granuloma formation, hyperplastic type II alveolar cells, and lymphocytic or eosinophilic infiltration affecting peribronchial, septal, and intra-alveolar spaces. Peripheral blood eosinophilia occasionally is noted. Therapy entails discontinuation of the offending agent. Clinical symptoms rapidly resolve, but clearing shown on a chest x-ray film usually lags behind the clinical improvement with less than 10% of patients having residual infiltrates. Corticosteroid therapy usually hastens recovery.

CONCLUSIONS

The data presented demonstrate that a new nonsteroidal antiandrogen agent, bicalutamide, is capable of causing drug-induced eosinophilic lung diseases. As more patients with advanced prostate cancers receive antiandrogen chemotherapy, more cases of drug-induced lung diseases may be encountered. Awareness of this entity is important since treatment entails simple withdrawal of the drug and institution of corticosteroid therapy in severe cases.

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ARDS Associated With Tumor Lysis Syndrome in a Patient With Non-Hodgkin’s Lymphoma*

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ARDS developed in association with tumor lysis syndrome (TLS) in a patient with non-Hodgkin’s lymphoma. Although a number of life-threatening complications have been noted to occur following TLS, this appears to be the first report of ARDS developing in association with TLS.

(CHEST 1998; 113:550-52)

Key words: acute respiratory distress syndrome; non-Hodgkin’s lymphoma; tumor lysis syndrome

Abbreviation: TLS=tumor lysis syndrome

Tumor lysis syndrome (TLS) is characterized by several metabolic derangements resulting from rapid lysis of tumor cells and is seen most frequently following chemotherapy for neoplasms with a high mitotic rate. Cardiac arrhythmias and renal failure are both well described fatal complications of the syndrome.1,2 A patient with high-grade lymphoma complicated by acute TLS developed ARDS. An extensive MEDLINE search (1966-1997) leads one to believe this is the first report of ARDS occurring in association with TLS.

CASE REPORT

A previously healthy 26-year-old man presented with a 10-day history of abdominal pain, night sweats, and shortness of breath. A radiograph of the chest revealed bilateral pleural effusions, and cytologic analysis of the pleural fluid was consistent with lymphoma. CT scans of the chest, abdomen, and pelvis revealed massive pericardial, epicardial, and retroperitoneal lymphadenopathy. A staging laparotomy was performed and demonstrated ascites with multiple tumor nodules present throughout the abdominal cavity. Results of an omental biopsy confirmed the diagnosis of a high-grade lymphoma.

His immediate postoperative course was complicated by hyperpyrexia and failure to wean from the ventilator. Significant levels of positive end-expiratory pressure and a high fraction of inspired oxygen were needed to maintain adequate systemic oxygenation. A chest radiograph taken at this time revealed bilateral pulmonary infiltrates consistent with ARDS (Fig 1).

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