AINO JOURNAL, Vol. 5, 2006, pp. 73 – 76

Case Report

Interstitial pneumonia and *de-novo* onset of asthma induced by leuprorelin acetate for prostate cancer

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Abstract

We describe herein the first report of side effects induced by leuprorelin acetate (LA) administration. A 70-year-old man, with idiopathic pulmonary fibrosis (IPF), vasospastic angina, diabetes mellitus type 2, and arteriosclerosis obliterans was suffering from prostate cancer. LA administration (drug–)induced interstitial pneumonia based on IPF and the *de-novo* onset of bronchial asthma, both of which are thought to be Th 2-related diseases. Using 3-color flow cytometry, we analyzed the chemokine receptors CD4+CXCR3+/CD3+ and CD4+CCR4+/CD3+, and found that the CXCR3/CCR4 ratio changed in the Th 2 pattern.

It is important to be careful with LA administration, especially for underlying Th 2-related diseases, and clinicians should fully understand the possibilities of LA-inducing *de-novo* Th 1/Th 2-driven autoimmune diseases.

Key words: leuprorelin acetate, interstitial pneumonia, chemokine receptor, Th 1/Th 2 balance, bronchial asthma, prostate cancer

Introduction

Hormonal treatment is standard for prostate cancer, but the various side effects of this treatment should not be overlooked. We report herein a case involving drug-induced interstitial pneumonia based on idiopathic pulmonary fibrosis (IPF) and the *de-novo* onset of bronchial asthma induced by leuprorelin acetate (LA) for prostate cancer. Based on this case, we speculate as to how LA affects immunity.

Case Report

A 70-year-old man suffering from chronic respiratory failure based on IPF, vasospastic angina, diabetes mellitus type 2, and arteriosclerosis obliterans became aware of lumbago resistant to orthopedical therapies in October 2001. The patient was administered basic therapy, as shown in Fig. 1, for more than seven years, and his general condition, other than the worsening lumbago, remained stable. The patient was 178 cm in height and 70 kg in weight. He was a non-smoker and had no environmental history. Physical examination upon the first consultation in my clinic revealed fine crackles at the lower part of the bilateral lung field, and percussion pain at the lower part of the spine and bilateral sacro-iliac joints. Laboratory data demonstrated an elevation of alkaline phosphatase (Al-p) and prostate-specific antigen (PSA). The rate of Al-p was 766 IU/L (<340) and that of PSA was 2252 ng/mL (< 4.0). A spirometric test revealed decreased % VC at a rate of 65% and normal forced expiratory volume in 1.0 second/forced vital capacity. This prompted his hospital consultation for further diagnostic evaluation and he was diagnosed with advanced prostate cancer, Stage D2, by staff in the Department of Urology. The clinical course is shown in Fig. 1. The patient began to undergo bicalutamide

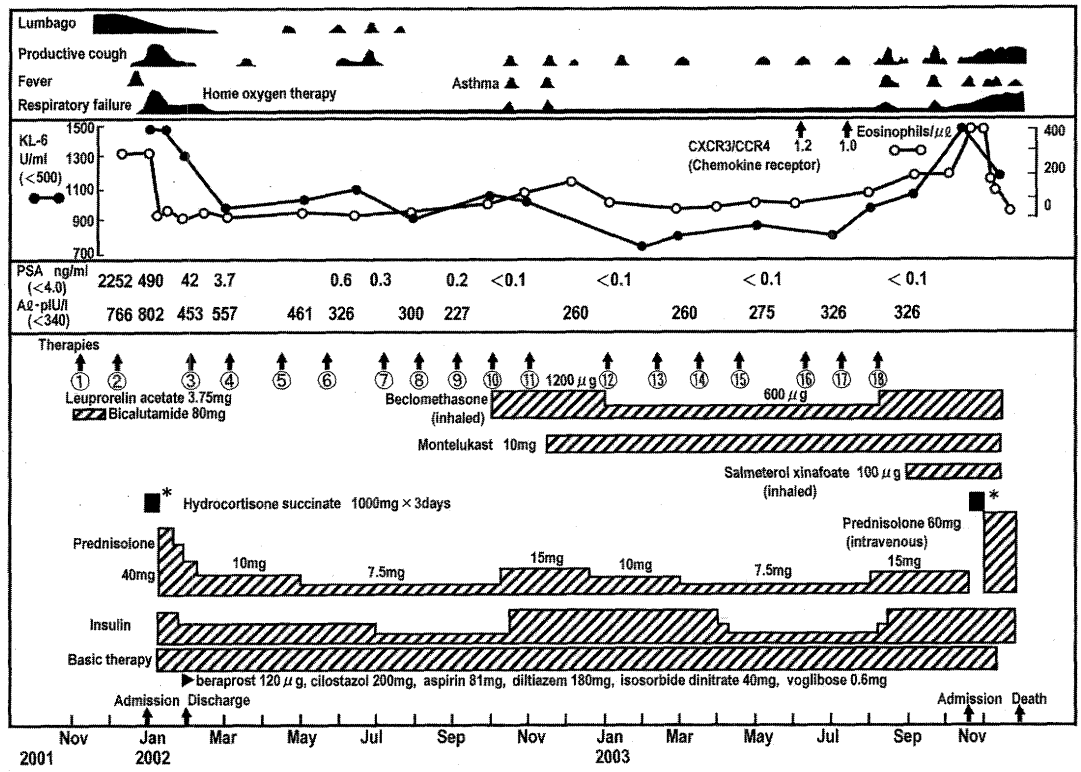

Fig. 1 Clinical course: A 70-year-old man suffered from drug-induced interstitial pneumonia of the lung based on idiopathic pulmonary fibrosis and the *de-novo* onset of bronchial asthma induced by leuprorelin acetate for prostate cancer

administration and subcutaneous injection of LA (maximal androgen blockade, MAB) in November 2001. The patient chose to cease the bicalutamide administration himself due to epigastric discomfort within a month. After two LA injections, a productive cough appeared in December 2001. The patient was suffering from cough, gradually progressive dyspnea, and fever, finally without responsiveness to antibiotics including azithromycin, and was admitted to the hospital due to an exacerbation of interstitial pneumonia at 2 -month intervals following the initial administration of LA. On admission, hematological examination showed an elevated white blood cell count without eosinophilia (WBC: 10900/ μL, eosinophils: 327/μL). Serological examinations revealed elevated C reactive protein (6.2 mg/dL) and no abnormalities regarding the anti-Sm antibody, anti-RNP antibody, anti-Scl 70 antibody, proteinase-3 anti-neutrophil cytoplasmic antibody, myeloperoxidase anti-neutrophil cytoplasmic antibody, anti-nuclear antibody, anti-DNA antibody, CH50, C3, and C 4. Urine analysis revealed no abnormalities including the Legionella antigen test. There were no significantly elevated titers of serological tests for chlamydia pneumoniae, mycoplasma pneumoniae, cytomegalovirus, pneumocystis carinii, and fungi (β-D-glucan). Sputum culture revealed no significant appearance of bacteria, tuberculosis and atypical mycobacterium (including PCR), and fungi. LK-6 in the serum increased to a level of 1500 U/mL, and chest CT and chest X-ray revealed a progressive, diffuse bilateral interstitial shadow, primarily involving the lower lung fields, based on the appearance of honey-comb lung, as shown in Fig. 2A (before)/2B (after)/2 C (honey-comb appearance). Arterial blood

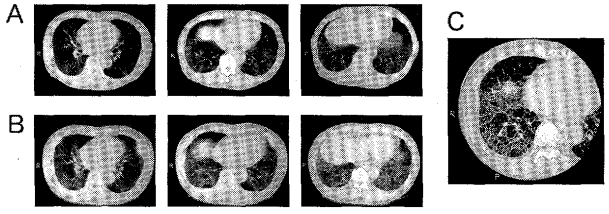

Fig. 2 (A) Chest CT scan shows bilateral honey-comb lung before leuprorelin acetate administration in August 2000. (B) Chest CT scan shows bilateral lung exacerbation induced by leuprorelin acetate. A metastatic lesion appeared on the left-sided chest wall in May 2002. (C) HRCT scan apparently shows honey-comb lung

gas analysis under inhaled oxygen at a rate of 12 L/min revealed a PaO_2 of 52 mmHg and a $PaCO_2$ of 38 mmHg with a pH of 7.43. Antibiotics were not effective, and steroid therapy was performed with hydrocortisone sodium succinate at a dosage of 1000 mg per day for 3 days, followed by 40 mg per day of oral prednisolone. Clinical symptoms were improved, and KL-6 levels decreased. The patient was discharged in approximately 1 month and followed up as an out-patient on home oxygen support. As he suffered from advanced prostate cancer accompanied by bone pains of metastatic lesions but he expressed a refusal to undergo radiation therapy or sole therapy for the pains, he did not abandon the LA injections. Third and fourth careful administrations of LA were carried out after obtaining his informed consent. A transient productive cough recurred after this treatment, followed by a transient elevation of KL-6. After the 10 th and 11th administrations of LA, *de-novo* bronchial asthma was present in addition to a productive cough, followed by an increase in KL-6 levels and eosinophils in the peripheral blood. No asthmatic episodes had occurred before in this patient. Examination by peak flow meter revealed recovery from a rate of 420 L/min to one of 520 L/min by some therapies described in Fig. 1. The prescribed dosage of prednisolone increased from 7.5 mg to 15 mg a day. After that, bronchial asthma did not occur, but the rate of eosinophils in the peripheral blood was higher than before. We analyzed the chemokine receptor using 3-color flow cytometry after the 16th and 17th administrations of LA. The percentages of CD4+CXCR3+/CD3+ changed from 13.7% to 15.1%, and those of CD4+CCR4+/CD3+ changed from 11.5% to 15.0%, while the ratio of CXCR3/CCR4 (Th 1/Th 2) changed from 1.2 to 1.0. After the 18th administration of LA, there was an increase in KL-6 levels and eosinophils in the peripheral blood, and bronchial asthma had also recurred. The asthmatic state was controllable by the administration of bronchodilators via peak flow meter monitoring. Respiratory failure due to the recurrent exacerbation of interstitial pneumonia worsened, resistant to the therapy, resulting in the eventual death of the patient.

Discussion

This is the first report to show the occurrence of interstitial pneumonia and *de-novo* onset of bronchial asthma definitely induced by LA, and to analyze the immunological background of this condition. Only a few cases with *de-novo* interstitial pneumonia associated with LA and/or antiandrogen have been previously reported, as summarized in Table 1 (Azuma et al., 1999; Shioi et al., 2003; Wieder et al., 1998). Interstitial pneumonia associated with non-steroidal antiandrogens has been reported in the literature (McCaffrey et al., 1998; Pfitzenmeyer et al., 1992). Interstitial pneumonia associated with nonsteroidal antiandrogens is presumed to be a class adverse effect occurring at a median rate of 5–8 weeks of treatment. Its estimated frequency of occurrence is considered to be 0.01%–0.07% (Bennett et al., 2002). Since MAB regimens are the standard therapy for advanced prostate

Table 1 Literature on interstitial pneumonia associated with hormonal therapy for prostate cancer

Reports	Age	IP	Clinical course	Leuprorelin ∧∨(possibility) Antiandrogen	CT	Labo. Data	Prognosis /autopsy
Wieder et al. (1998)	68	*de-novo* gradual	2-months later	3 injections leuprolide <nilutamide	Bilateral lower lung	PSA 4.5	Improved
Azuma et al. (1999)	75	*de-novo* acute	8-days later	1 injection leuprorelin >flutamide	Bilateral lung	PSA 202	Death 1-month /performed
Shioi et al. (2003)	79	*de-novo* acute or subacute?	1-month later	bicalutamide /leuprolerin?	Bilateral lung	PSA 18	Improved
Yamasaki et al. (2006)	70	Exacerbation gradual with asthma	2-months later	18 injections leuprorelin /bicalutamide ceased in a month	Bilateral lower lung 1.2 → 1.0	PSA 2252 KL-6 1500 CXCR3/CCR4	Death 2-years

IP: interstitial pneumonitis
Chomokine receptor: CD4+CXCR3+/CD3+(Th 1), CD4+CCR4+/CD3+(Th 2)

cancer, we can not determine which drug was responsible for interstitial pneumonia.

In this case, LA was thought to be the definite cause of the occurence of interstitial pneumonia, because the antiandrogen was ceased within a month and the recurrent clinical course related to LA was shown during the total clinical course. Before the administration of LA, interstitial pneumonia on the basis of respiratory failure in the present case was diagnosed with IPF based on typical honey-comb CT findings, no occupational history of pneumoconiosis, non-smoker, and negative laboratory findings, etc. The Th 1/Th 2 paradigm has recently been noted in the pathogenesis of interstitial lung disease (Lukas et al., 2001; Strieter et al., 2000). It has been found that the numbers of lymphocytes immunostained by IL-4 and IL-5 increase and those of lymphocytes immunostained by interferon-γ decrease in the lungs of patients with IPF. It has also been reported that the number of eosinophils in bronchoalveolar lavage fluid increases in patients with IPF compared to controls (Fujimoto et al., 1995). These findings demonstrate that Th 2-shifted immunity and, in consequence, eosinophilic inflammation might exist in small and large airways in patients with IPF. We used 3-color flow cytometry to analyze the chemokine receptors CD4+CXCR3+/CD3+ corresponding to Th 1 cells and CD4+CCR4+/CD3+ corresponding to Th 2 cells to examine the immunological conditions before and after LA administration. This flow cytometric data indicated that the immunological condition shifted to a Th 2 -dominant pattern after LA administration. This immunological data theoretically explains the comorbidity of drug-induced interstitial pneumonia based on IPF and the *de-novo* onset of bronchial asthma due to their Th-2 related pathogenesis. The rates of CD4+ CXCR3+/CD3+ cells and CD4+CCR4+/CD3 + cells were within normal ranges, but this patient had undergone oral steroid administration over a long period. In this case, the changes in the immunological condition were thought to be more important than the absolute rates of laboratory data. The acute onset of polymyositis induced by LA has also been reported (Crayton et al., 1991). The inflammatory myopathies including polymyositis have been identified as Th 1-driven autoimmune disease (Megens-de Letter et al., 1999). The present case shows that LA activated both Th 1 and Th 2 cells, similar to a previous report (Chen et al., 1999). It is inferred that if the ratio shifted to a Th 1-dominant pattern, Th 1-driven autoimmune disease might occur in contrast to this case with a Th 2-dominant pattern.

It is important, however, to be careful with LA administration, especially for underlying Th 2-related diseases, and clinicians should fully understand the possibilities of LA-inducing *de-novo* Th 1/Th 2-driven autoimmune diseases.

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