Pulmonary lymphangitic carcinomatosis with ground-glass opacities as presentation of prostate cancer

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Keywords
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Abstract
There is a broad differential diagnosis for interstitial shadows on chest computed tomography in rheumatoid arthritis patients, especially those previously treated with immunosuppressant drugs. We report an immunocompromised rheumatoid arthritis patient in respiratory failure with diffuse ground-glass opacities (GGOs), who was diagnosed with pulmonary lymphangitic carcinomatosis as the initial presentation of prostate cancer. He was successfully treated with chemohormonal androgen deprivation therapy, including bicalutamide, leuprolelin acetate, denosumab, and docetaxel. Metastatic pulmonary lymphangitis, rarely from the prostate, should always be considered in the differential diagnosis of GGOs, even when the patient has no known prior malignancies.

Introduction
Rheumatoid arthritis is a systemic inflammatory disease that can involve other tissues and organs as well as the synovial joints. The lung is also a frequent site of extra-articular involvement, and interstitial lung disease is the most common pulmonary manifestation of rheumatoid arthritis. Generally, it is a laborious task to appropriately treat the rheumatoid arthritis patient—especially in an immunosuppressed state—with diffuse ground-glass opacities (GGOs) and ensuing respiratory failure because there is a broad differential diagnosis for rheumatoid arthritis and lung disease, including rheumatoid arthritis-associated lung disease, drug-induced pneumonitis, infection secondary to immunosuppression, and coexistent medical conditions. Here, we report a rheumatoid arthritis patient with pulmonary lymphangitic carcinomatosis (PLC) as the initial presentation of prostate cancer, who was pathologically diagnosed with respiratory failure and treated with chemohormonal therapy without delay.

Case Report
A 68-year-old Japanese man and current smoker with an 11-year history of rheumatoid arthritis (functional class 4 with high disease activity at the time of diagnosis) was referred to our department due to a four-month history of dry cough, a two-week history of anorexia, weight loss (4 kg), and progressive dyspnoea. His joint symptoms were worsening 17 months before admission, at which time he was treated with prednisolone, methotrexate, and golimumab. After a month, infliximab was commenced (switching from golimumab) and resulted in minimal disease activity. He had no history of allergy, bronchial asthma, drug use (including herbal medicine and illegal drugs), changes in bowel habits, recent travel abroad, or inhalation exposure.

The patient’s temperature was 37.0°C, and he was tachypnoeic (respiratory rate, 27) and had an oxygen saturation of 91% at rest, which decreased to 80% on mild exertion. Physical examination showed no abnormality.
other than bilateral ulnar drift deformity of the hands. Laboratory findings were normal, except for slightly elevated serum lactate dehydrogenase (473 IU/L), alkaline phosphatase (550 IU/L), C-reactive protein (3.57 mg/dL), and carcinoembryonic antigen (7.2 U/mL) levels. A chest roentgenogram revealed an infiltrative shadow in both lung fields. A high-resolution computed tomography (CT) scan of the lungs revealed extensive GGOs and emphysematous changes; a partially irregular, thickened interlobular septum and bronchovascular interstitium; slight pleural effusion; and mediastinal lymphadenopathy (Fig. 1A–C). Electrocardiography and echocardiography revealed no abnormality.

Screening tests for opportunistic infection were negative, including cytomegalovirus pp65-antigenemia, serum β-D-glucan, anti-Aspergillus antibody, and galactomannan antigen. A bronchoalveolar lavage fluid examination was unremarkable; loop-mediated isothermal amplification tests for *Mycoplasma pneumoniae* and *Legionella pneumophila* and a real-time polymerase chain reaction test for *Pneumocystis jirovecii* were negative; smears and cultures for fungus, bacteria, and acid-fast bacilli were negative; and a cytological test was negative for malignancy. Transbronchial lung biopsy (TBLB) revealed adenocarcinoma within the lymphatics and small vessels (Fig. 2A,B). There was no primary tumour in the thorax; therefore, additional tests were performed as follows: a digital rectal examination revealing a rough, firm, and slightly enlarged prostate; elevated prostate-specific antigen (PSA, 4072.434 ng/mL); a prostatic biopsy showing adenocarcinoma; and bone scintigraphy suggesting multiple bone metastases. The tumour cells in the lung (Fig. 2C) and prostate (not shown in the figure) were immunohistochemically positive for PSA. Based on these findings, PLC associated with stage IV prostatic adenocarcinoma (T4N0M1c) was diagnosed.

Chemohormonal androgen deprivation therapy, bicalutamide, leuprorelin acetate, and docetaxel (70 mg/m² of body surface area once every four weeks) were started, followed by denosumab. Four courses of docetaxel resulted in symptomatic relief, with considerable improvement in the GGOs (Fig. 2D–F) and a decrease to 531.081 ng/mL in PSA, and treatment currently continues in the outpatient clinic.

**Discussion**

Prostate adenocarcinoma, the most common cancer in males, is often diagnosed in a non-metastatic setting. In its

![Figure 1. Axial chest high-resolution computed tomography at the time of admission demonstrating extensive ground-glass opacities with emphysematous changes, thickened bronchovascular interstitium, and slight right-sided pleural effusion (A: At the level of the aortic arch, B: At the level of the right middle lobe branch). A thickened interlobular septum was most obviously present in the right lower lobe (C). Mediastinal lymphadenopathy is also evident (not shown) with no primary lesion in either lung. After four courses of docetaxel, the abnormal shadows, except for emphysematous changes, were almost completely resolved (D–F).](image-url)
late stage, it can metastasize to the lungs, often with nodular involvement, but rarely with lymphangitic involvement. Pulmonary lymphangitic carcinomatosis refers to tumour spread to the lymphatic system of the lungs. Primary lesions commonly associated with PLC include breast, stomach, lung, and pancreas. PLC due to prostate cancer is estimated at 3% of all PLC cases [1]. Pre-mortem diagnosis of PLC with respiratory symptoms at initial presentation, before the diagnosis of primary prostatic adenocarcinoma, is extremely rare [2]. In the previous report, a patient with PLC from undiagnosed prostatic adenocarcinoma was initially treated with bicalutamide; however, the patient’s condition deteriorated rapidly, and death ensued, as a result of poor response to hormonal therapy and exacerbation of PLC [2]. In the present case, the patient was successfully treated with hormonal therapy and chemotherapy, which was added during the early phase of treatment. Generally, prostatic adenocarcinoma may respond to hormonal therapy alone; however, it may progress despite hormonal therapy. Thus, chemohormonal therapy, as first-line systemic therapy, could be beneficial for preventing potentially fatal PLC from prostatic adenocarcinoma, as described in the present case [3,4].

In this case, extensive GGOs were the characteristic findings on CT. Initially, it was difficult to determine the cause of the extensive GGOs because PLC seldom produces extensive, diffuse GGOs in both lungs, and various entities are possible in an immunocompromised rheumatoid arthritis patient, including opportunistic infection, drug-induced pneumonitis, or rheumatoid arthritis-associated interstitial pneumonia [5]. However, specific abnormalities, such as a thickened interlobular septum and bronchovascular interstitium, suggested perilymphatic-distributed disease and led to a definitive diagnosis of PLC from undiagnosed prostatic adenocarcinoma without delay, despite the rarity of this condition. Metastatic tumours, rarely from the prostate, should always be considered in the differential diagnosis of GGOs, even when the patient has no known prior malignancies.

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

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