INTERNAL MEDICINE

□ CASE REPORT □

Eosinophilic Pneumonia and Thoracic Metastases as an Initial Manifestation of Prostatic Carcinoma

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Abstract

We herein report an 80-year-old man with prostatic carcinoma who developed eosinophilic pneumonia and intrathoracic metastases. He presented with shortness of breath, cough, and fever as a chief complaint. Chest X-ray and computed tomography showed bilateral pulmonary nodules, intrathoracic lymphadenopathy, and right-sided consolidation. Positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose (FDG) showed poor uptake in these nodules and lymph nodes. The patient subsequently received a pelvic computed tomography scan, which revealed a massively enlarged prostate. The serum prostate specific antigen level was elevated to 4,181.2 ng/mL, and a transrectal biopsy revealed prostatic adenocarcinoma. Based on the morphological and immunohistochemical findings, the nodules in the lung and the lymph nodes were diagnosed as secondary neoplasm from the prostate. As for right-sided consolidation, remarkable bronchoalvelar lavage fluid eosinophilia was detected, that was compatible with eosinophilic pneumonia. Eosinophilic pneumonia in this case disappeared and has not recurred by treatment of prostatic carcinoma and steroid therapy for a week, and was regarded to be tumor-associated. Although prostatic carcinoma with an initial manifestation of intrathoracic metastases and eosinophilic pneumonia is uncommon, physicians should suspect the condition. In addition, we should also keep in mind that prostatic carcinoma sometimes shows poor uptake in FDG-PET.

PET: Positron emission tomography, FDG: ^{18}F-flouorodeoxyglucose

Key words: prostatic carcinoma, lung metastasis, eosinophilic pneumonia, eosinophilia

(Inter Med 47: 1419-1423, 2008)
(DOI: 10.2169/internalmedicine.47.1124)

Introduction

Here, we report an 80-year-old man suffering from prostatic carcinoma with eosinophilic pneumonia (EP) and thoracic metastases. Secondary neoplastic involvement of the lung is extremely common because blood flow or lymphatic fluid produced by body tissues passing through the pulmonary vascular system. However, prostatic carcinoma with an initial manifestation of pulmonary nodules, and hilar lymphadenopathy is uncommon.

In the present case, peripheral blood eosinophilia and EP developed, both of which are known to occur in patients with malignant tumor such as gastric cancer (1) and lymphoma (2). To our knowledge, however, cases with prostatic carcinoma who develop tumor-associated EP have not been reported, and we believe that this case is worth reporting.

Case Report

An 80-year-old man developed shortness of breath, cough, and fever for a month until he consulted a physician. He did not experience difficulty with urination. A chest X-ray revealed multiple nodules, and hilar and mediastinal lymphadenopathy (Fig. 1a), and he was subsequently referred to our hospital in October 2006. A chest CT showed

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Received for publication March 16, 2008; Accepted for publication May 9, 2008
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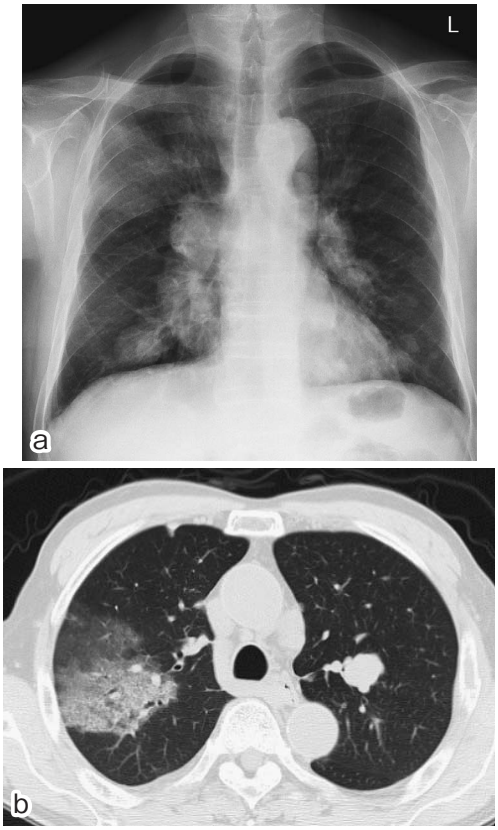

Figure 1. **a. An X-ray on admission. An X-ray showed massive, swollen hilar lymph nodes and some nodules in the lung field. The consolidation shadow observed in the upper right field was diagnosed as eosinophilic pneumonia by bronchoalveolar lavage. b. Chest CT on admission. CT on admission showed right-sided consolidation.**

Table1. **Laboratory Data on Admission**

Hematology		CRP	4.6 mg/dL
WBC	6700/μL	IgG	1550 mg/dL
Neutrophil	49.4%	IgA	448 mg/dL
Eosinophil	28.8%	IgM	58 mg/dL
Basophil	0.3%	IgE	406 IU/mL
Lymphocyt	17.2%	ANA	< 20 titers
Monocyte	4.3%	sIL-2R	626 U/mL
RBC	394×10^4/μL	Anti HIV Ab	(-)
Hb	12.3 g/dL	tumor marker	
Ht	37.6%	CEA	0.6 ng/mL
Plt	29.8×10^4/μL	CYFRA	1.8 ng/mL
ESR	132 mm/h	ProGRP	11.5 pg/mL
Biochemistry and Serology		CA19-9	7 U/mL
TP	6.8 g/dL	PSA	4181.2 ng/mL
BUN	12 mg/dL	BAL (right upper lobe)	
Cre	0.6 mg/dL	Recovery	44% (66/150)
T-bil	0.4 mg/dL	total cell count	$4.0\text{x}10^5$ cells/mL
AST	26 IU/L	Macrophage	13.0%
ALT	19 IU/L	Lymphocyte	11.0%
LDH	253 IU/L	Neutrophil	2.3%
ALP	268 IU/L	Eosinophil	73.3%
βD-glucan	5.0 pg/mL	CD4/CD8 ratio	1.8
ACE	13.5 IU/L	Grocott stain	(-)

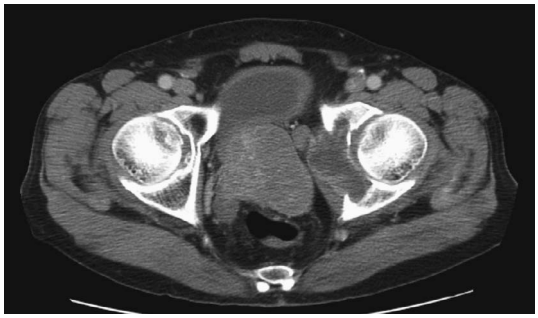

Figure 2. **Pelvic CT. Pelvic CT showed an enlarged prostate with spotty calcification and an enlarged pelvic lymph node.**

multiple pulmonary nodules, hilar and mediastinal lymphadenopathy, and right-sided consolidation (Fig. 1b). Then he was admitted for further examination. Regarding the patient profile, there was no history of dust exposure including silica. He never smoked or drank alcohol. On physical examination, there was no enlargement of superficial lymph nodes and his skin was free of eruption or unusual pigmentation. An ocular examination showed no abnormal findings. The patient had an increased respiratory rate (28 breaths per minute), normal blood pressure of 127/58 mmHg, heart rate 79 beats per minute, and body temperature of 38.0℃. Cardiac auscultation revealed no murmur, and wheezes were audible throughout the entire lung field. His respiratory symptoms were consistent with symptoms of asthma. His abdomen was flat and soft, and palpitation of the prostate disclosed an enlargement that was roughly the size of a hen's egg with an elastic consistency. Microscopic examination of repeated sputum smears and cultures revealed no acid-fast bacilli. As shown in Table 1, peripheral blood showed increased number of eosinophils (1,929/μL). Serum IgE level was elevated to 406 IU/mL. Serum tumor markers for lung carcinoma were within the normal range, and soluble interleukin (IL)-2 receptor for malignant lymphoma was slightly elevated at 626 U/mL. We performed FDG-PET-CT, which showed poor uptake in the nodules, swollen lymph nodes, and other organs with the exception of several ribs. Then, we performed bronchoscopy. As for pulmonary consolidation, bronchoalveolar lavage (BAL) through the right upper lobe (B1a) showed a total cell count of 4.0×10^5 cells/mL with an increase in the number of eosinophils (73.3%). Cytology of BAL fluid did not show malignant cells. There were no evident diseases which show BAL eosinophilia (3) including drug-induced lung disease, *Pneumocystis jiroveci* pneumonia associated with acquired immunodeficiency syndrome; then, a diagnosis of EP was established. As for pulmonary nodules and lymphadenopathy, transbronchial biopsy of the pulmonary nodules or transbronchial aspirated cytology of subcarinal lymph node specimens showed moderately differentiated adenocarcinoma (Fig. 3). Considering the CT findings and the high sensitivity and specificity of FDG-PET scans in detecting abnormalities related to lung cancer (4), we considered that the pulmonary nodules or enlarged lymph nodes in this case

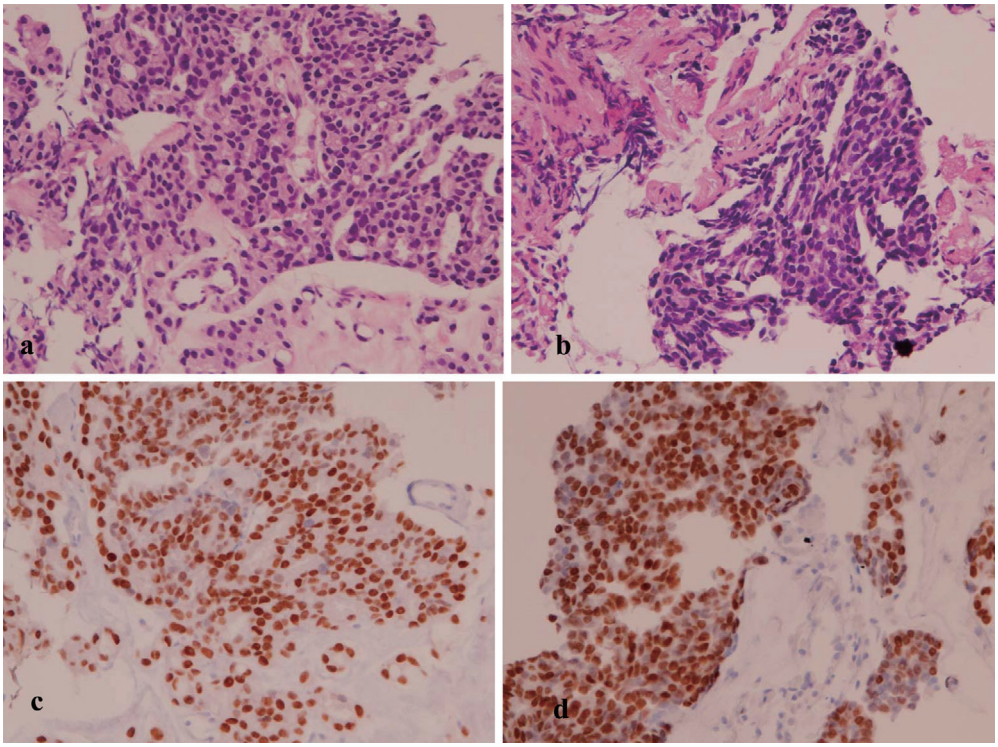

Figure 3. **A biopsy specimen of the prostate (a) showed moderately differentiated adenocarcinoma (Hematoxylin and Eosin staining, ×200). Its morphology was similar to that in the carcinoma cells in the lung biopsy specimens (b) (Hematoxylin and Eosin staining, ×200). Biopsy specimens of the prostate (c) and the lung (d) were immunohistochemically positive for androgen receptors (AR, ×200).**

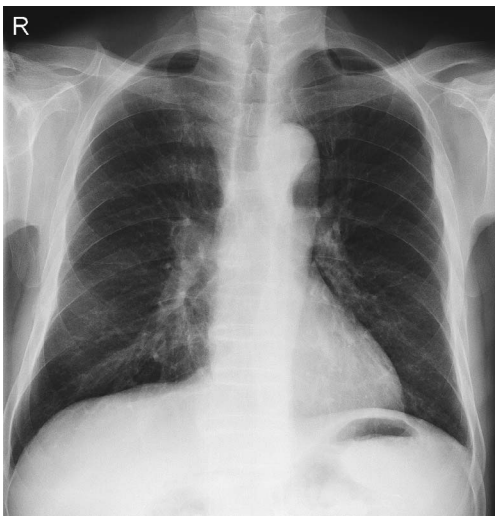

Figure 4. **An X-ray during thrapeutics of bicartamide and leuprorelin acetate. Right-sided consolidation of eosinophilic pneumonia disappeared after initiation of 4 week therapy of bicartamide 80 mg daily and leuprorelin acetate 3.75 mg.**

could be a metastatic tumor from a remote site. With a large number of reports and observations of the potential pitfalls in FDG-PET oncologic imaging, we performed a gastric endoscopy and a total colonoscopy, which did not reveal any malignant lesions. FDG-PET is not sensitive enough to facilitate the diagnosis of primary or recurrent tumors in prostate or urinary bladder cancer, so we performed a pelvic CT scan (Fig. 2), which showed an enlarged prostate with local invasion of adjacent pelvic structures and swelling of the paraaortic and pelvic lymph nodes. The serum prostate specific antigen level was 4,181.2 ng/mL (the normal level is less than 4.0 ng/mL). A transrectal biopsy of the prostate (Fig. 3a) was performed and histological examination of the specimens showed moderately differentiated adenocarcinoma with a cribriform pattern and glandular structures (Gleason's score 4+4=8). Its morphology was similar to that in the carcinoma cells in the pulmonary biopsy specimens (Fig. 3b) and in the aspirated specimens of the mediastinal lymph node. Biopsy specimens of the pulmonary lesions were immunohistochemically positive for androgen receptor (AR) (Fig. 3d), but were negative for CEA, thyroid transcription factor-1 (TTF-1), cytokeratin (CK) 7, CK 20, or PSA. The adenocarcinoma of the prostate showed a similar pattern of immunoreactivity (Fig. 3c) except for focal positivity with PSA. Although the PSA levels were negative in the tumor cells of the lung, the expression of AR and the negativity for CK 7, CK 20, TTF-1, and CEA strongly suggested that the tumor had a prostatic origin. Based on the clinical, morphological, and immunohistochemical findings, the diagnosis of lung metastases of prostatic adenocarcinoma with EP was established. Dexamethasone 16 mg daily was used for 7 days for bronchial asthma and EP, then, consolidation in an X-ray improved, and wheezes disappeared. The number of

peripheral blood eosinophils decreased to within normal range. We introduced this patient to urologists, and androgen blockade therapy with the oral administration of bicalutamide 80 mg daily and leuprorelin acetate 3.75 mg per four weeks was initiated. After 4 months, PSA level decreased to 8.5 ng/mL and an X-ray improved as shown in Fig. 4. In January 2008, he is now alive and is regularly followed up on an outpatient basis. Serum PSA level is within normal limits (0.5 ng/mL).

Discussion

We herein report a case of prostatic carcinoma in an 80-year old man who presented with chest symptoms with the presence of multiple pulmonary nodules, hilar lymphadenopathy, and consolidation in a chest X-ray.

As for pulmonary metastases from the prostate, the reported incidence found during autopsy ranges from 23 to 74% (4); however, the premortem identification of pulmonary metastasis is much less common and is found on chest radiographs in - 5 % of patients. This low premortem detection rate is possibly due to the presence of microscopic metastasis that can be detected at autopsy but cannot be consistently identified on radiographs. The metastatic pathways of lung metastases from the prostate are suggested to occur via the lymphatic or hematogenous routes, and it takes the form of lymphangitic metastasis, nodular metastasis, malignant effusions, or lymphadenopathy (5). The frequencies of the various thoracic metastatic findings have been reported as follows: pleural effusion 22%, reticular opacities 16%, nodules 8%, reticulonodular shadows 3.5%, and lymphadenopathy 4.5%. Metastatic findings of the present case were pulmonary nodules and bulky lymphadenopathy.

We performed FDG-PET-CT on this patient. FDG-PET-CT has been shown to be a highly sensitive and specific imaging modality in the diagnosis of primary and recurrent tumors (4). However, many benign conditions including inflammatory, infective, or granulomatous processes are known to cause a high uptake of FDG. By contrast, there are some tumors that are not easily detected by FDG-PET as shown in this case. FDG-PET-CT is not sensitive enough to aid the diagnosis of primary or recurrent tumors in prostatic carcinoma due to the low glycolytic rate of most primary prostate tumors and their metastatic lesions (6). In the present case, FDG uptake was found in pulmonary consolidation of EP, however, the thoracic metastatic lesion showed poor FDG uptake. Understanding these pitfalls is essential for the accurate interpretation of FDG-PET.

Cases with lung metastatic or primary lung tumor are considered advanced, and the prognosis is considered severe; however, it is not uncommon that cases of prostatic carcinoma with lung metastasis show responsiveness to androgen blockade therapy, and the appropriate treatment will lead to a prolonged survival. The patient we presented is now alive without any symptoms one year and 4 months after diagnosis. Therefore, prostatic carcinoma should always be considered in the differential diagnosis of men with pulmonary nodules or intrathoracic lymphadenopathy.

In this case, peripheral blood and BAL fluid eosinophilia was shown. Peripheral blood eosinophilia is found in several conditions such as allergic diseases, several skin diseases, and parasitic infestations, then malignancy is also known as a cause of peripheral blood eosinophilia. As for BAL fluid eosinophilia, there are several diseases (3) which show pulmonary eosinophilic infiltration or BAL eosinophilia: EP, drug-induced lung disease, and *Pneumocystis jiroveci* pneumonia associated with acquired immunodeficiency syndrome. Drug-induced lung disease was not suggested because of the absence of a drug history. β-D glucan, which is known to be increased in patients with *Pneumocystis jiroveci* pneumonia, was not elevated. Grocott stain of BAL fluid or lung tissue did not show *Pneumocystis jiroveci* itself. These findings suggested that the present case had EP (7). In this case, peripheral blood eosinophilia and pulmonary consolidation of EP were attenuated with daily dexamethasone 8 mg for a week, and has not recurred with only a treatment of prostatic carcinoma. The association may be coincidental; however, we believe that peripheral blood eosinophilia and EP in this case was secondary to prostatic carcinoma.

The incidence of peripheral blood eosinophilia associated with malignant tumors ranges from 0.8% to 26.3% (8, 9). Various causes of tumor-associated eosinophilia have been postulated as follows: tumor necrosis (10), extensive dissemination (10), vagal reflexes (11), local stimulation of connective tissue around the tumor (11), and eosinophil chemotactic or proliferating factor (12), or colony stimulating factor produced by the tumor (1). To our knowledge, peripheral blood eosinophilia with prostatic carcinoma has not been reported. Asano and Ohsawa investigated peripheral blood findings in 576 patients with malignancy (8), and the primary site of the tumor with peripheral blood eosinophilia (>1,000/mm^3) was limited to stomach, pancreas, thyroid, and brain. They also listed 13 cases of GM-CSF (granulocyte macrophage-colony stimulating factor) producing tumor, and there were no cases with prostatic carcinoma. Isaacson and Rapoport reported that malignant tumor accompanying blood eosinophilia generally occurs in the degenerative system [16 cases of total 34 cases (47%): stomach, colon, pancreas, gall bladder, and bile duct] (10). Other primary sites of the tumor was uterus, breast, penis, bronchus, and so on; however, there were no cases with prostatic carcinoma.

Cases of EP associated with malignant tumor have been reported. Some mechanisms of EP development with malignancy have been suggested, and Horie and colleagues reported that GM-CSF and IL-5 producing gastric cancer develop EP (1). In the present case, we did not investigate the production of these cytokines because of methodological limitation. To our knowledge, EP due to prostatic carcinoma has not been reported. Prostatic carcinoma may differ in a complex way such as cellular characteristics (ability to produce several cytokines) or local reactions from other malig-

nancy, and further studies are needed to clarify the matter.

In conclusion, we encountered a case of prostatic carcinoma with peripheral blood eosinophilia, EP, and thoracic metastatic lesion. There are fears that some other similar cases might be treated with chemotherapy as lung cancer or tumor of unknown origin without immunohistochemical staining. Although cases of prostatic carcinoma with an initial manifestation of intrathoracic metastases are uncommon, physicians should suspect the condition when multiple pulmonary nodules and lymphadenopathy are detected, since appropriate treatment will lead to a prolonged survival. In addition, we suggest that EP should be considered as a possible diagnosis in patients with prostatic carcinoma who have respiratory complaints, especially those who have peripheral blood eosinophilia.

Acknowledgement

We thank Yuko Waseda and Akihito Okazaki (Respiratory Medicine, Kanazawa University Hospital) for his detailed comments regarding the present report.

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