Case Report

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Value of Prostate-Specific Antigen Elevated in Transudative Pleural Effusion for Diagnosis of Prostate Cancer-Induced Paramalignant Pleural Effusion

Naoko Fujiwara[a], Hitoshi Sugawara[a, d], Hiroki Yabe[a], Akira Ishii[a], Hiroshi Matsubayashi[a], Tamami Watanabe[a], Masafumi Kakei[a], Yutaka Kobayashi[b], Yoh Dobashi[c]

Abstract

When evaluating pleural effusion of undetermined etiology, malignant disease cannot be ruled out even if the effusion is transudative. Measurement of tumor markers in transudative pleural effusion (TPE) may aid in diagnosis, but the exact utility of these markers is unclear. We report the case of a 78-year-old man with paramalignant pleural effusion (PMPE) due to prostate cancer diagnosed by measuring prostate-specific antigen (PSA) in TPE. Androgen blockade therapy was effective in treating the PMPE. We discuss the value of PSA elevated in TPE for diagnosis of prostate cancer induced-PMPE.

Keywords: Prostate cancer; Prostate-specific antigen; Transudative pleural effusion; Paramalignant pleural effusion; Malignant pleural effusion

Introduction

Although pleural effusion (PE) is common, diagnosis of its precise etiology is difficult in some cases with possible malignancy, irrespective of pathology, particularly in cases of transudative pleural effusion (TPE). Because TPE is caused by malignant disease in 3-10% of cases [1], the distinction between TPE due to benign conditions or to malignancy with concomitant disease such as heart failure may be difficult.

Malignant PE is diagnosed based on the presence of malignant cells by cytology or pleural biopsy. PE in cases of known malignancy without cytological evidence of malignancy is termed paramalignant pleural effusion (PMPE) [2].

In one report, the cause of PMPE could be only established in 88 (59%) of 150 patients, major causes being lung cancer (41%) and breast cancer (13%) [3].

In diagnosis of the etiology of TPE, no single tumor marker has exceptional diagnostic accuracy [4]. The sensitivity of prostate-specific antigen (PSA) for evaluating the etiology of TPE in patient with prostate cancer is not yet known.

Here, we measured PSA in TPE of a man with prostate cancer and diagnosed prostate cancer-induced PMPE. Further, we discuss the possible mechanisms of prostate cancer-induced PMPE.

Case Report

A 78-year-old man had experienced exertional dyspnea for 1 year prior to admission. He had well-controlled hypertension. Bilateral PE was detected at a local clinic. Treatment with diuretics did not improve the dyspnea. Six months before admission, he was referred to our medical center, where thoracentesis was performed. The PE was transudative but physical examination, brain natriuretic peptide (BNP) tests, and echocardiography did not indicate heart failure. Following thoracic drainage, the dyspnea improved and he discontinued hospital visits.

One week before admission, the patient again developed exertional dyspnea and was admitted for further examination. He reported a weight loss of 10 kg over the previous year without appetite loss and had no urinary voiding symptoms. His body mass index was 19 kg/m^2; body temperature, 36.5°C; blood pressure, 118/80 mmHg; heart rate, 93 beats/min (regular); and respiratory rate, 18 breaths/min. His general appearance was good. Physical findings included weakness of respiratory sounds in both lower lung fields, no heart murmur, and edema in both lower extremities. Digital rectal

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[a]Division of General Medicine, The First Department of Comprehensive Medicine, Saitama Medical Center, Jichi Medical University, Saitama, Japan
[b]Division of Urology, The Second Department of Comprehensive Medicine, Saitama Medical Center, Jichi Medical University, Saitama, Japan
[c]Department of Pathology, Saitama Medical Center, Jichi Medical University, Saitama, Japan
[d]Corresponding author: Hitoshi Sugawara, FACP, Division of General Medicine, The First Department of Comprehensive Medicine, Saitama Medical Center, Jichi Medical University, 1-847, Amanuma-cho, Omiya-ku, Saitama-city, Saitama 330-8503, Japan.
Email: hsmdfacp@omiya.jichi.ac.jp

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Table 1. Summary of the Investigations Performed: All Positive and Relevant Negative Results are Shown

Urinalysis:			**Biochemistry:**			**Pleural effusion analysis:**	
Urinary protein	-		TP	6.9	g/dL	Color of fluid	Pale yellow
Occult blood	-		Alb	3.4	g/dL	Cloudiness	Slightly turbid
CBC:			T-Bil	0.55	mg/dL	Specific gravity	1.025
WBC	7,270	/μL	AST	29	U/L	pH	7.2
RBC	585×10^4	/μL	ALT	17	U/L	Protein	3.4 g/dL
Hb	15.5	g/dL	LDH	204	U/L	Glucose	172 mg/dL
Plt	39.6×10^4	/μL	CK	115	U/L	LDH	101 U/L
Serum PSA series:			ALP	274	U/L	ADA	6.4 IU/L
HD 1	166.0	ng/mL	CRP	0.17	mg/dL	Cell numbers	320 /μL
HD 30 (discharge)	65.0	ng/mL	Na	140	mmol/L	Cytology	Class II
30 days AD	21.6	ng/mL	K	4.2	mmol/L	**Echocardiogram:**	
120 days AD	4.4	ng/mL	Cl	105	mmol/L	LAD	33 mm
Pleural PSA series:			BUN	19	mg/dL	LVDd	46 mm
HD 1	192.0	ng/mL	Cr	1.06	mg/dL	LVDs	24 mm
HD 30 (discharge)	109.0	ng/mL	FPG	104	mg/dL	EF	79 %
BGA under room air on admission:			BNP	44.1	pg/mL	TEI index	0.4
pH	7.475					E/A	0.71
PaO_2	49.4	mmHg				DT	190 msec
$PaCO_2$	29.2	mmHg				**Pathology of prostate:**	
HCO_3^-	21.0	mmol/L				adenocarcinoma (positive PSA stain)	

Abbreviations; CBC: complete blood count, PSA: prostate-specific antigen, HD: hospital day, AD: after discharge, FPG: fasting plasma glucose, BNP: brain natriuretic peptide, ADA: adenosine deaminase, LAD: left atrium diameter, LVDd: left ventricular end-diastolic diameter, LVDs: left ventricular end-systolic diameter, EF: ejection fraction, TEI index: left ventricular total ejection isovolume index, E/A: peak early diastolic LV filling velocity/peak atrial filling velocity ratio, DT: deceleration time

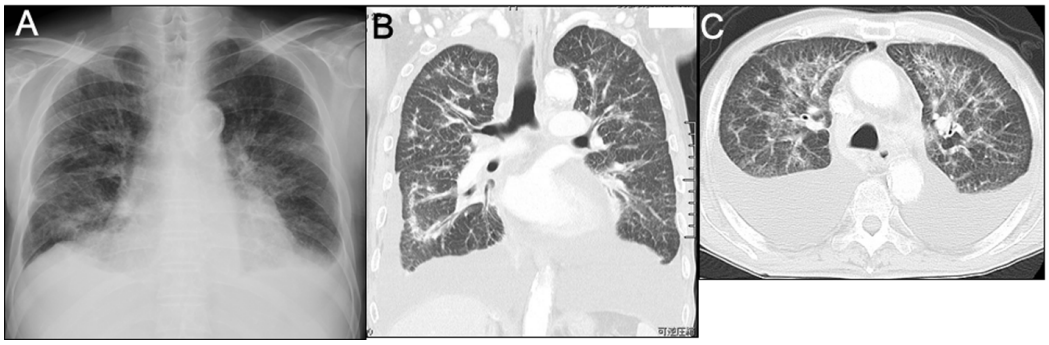

Figure 1. Imaging studies on admission. A) Plain chest radiography showed the cardiothoracic ratio was 55%, bilateral costophrenic angles were dull, and diffuse bilateral reticulonodular opacification was present. B, C) Plain chest computed tomography showed bilateral large amounts of pleural fluid, slight pericardial effusion, patchy consolidation sparing the subpleural regions, and thickenings of both the interlobular septum and pleura.

examination revealed an elastic hard 5-cm prostate with induration.

Laboratory tests (Table 1) revealed absence of proteinuria, slight hypoalbuminemia, slightly elevated serum creatinine and BNP levels, hypoxemia, and respiratory alkalosis.

Chest radiography (Fig. 1A) and computed tomography (Fig. 1B, C) showed changes indicative of pulmonary lymphangitis carcinomatosa. Echocardiography confirmed absence of heart failure (Table 1).

Because of the indurated prostate and elevated serum PSA (166.0 ng/mL), transrectal prostate biopsy was done and revealed Gleason's grade 4 adenocarcinoma. Immunohistochemical detection of PSA confirmed the diagnosis. Bone scintigraphy showed several bone metastases in both humeri, right iliac bone, and sternum.

Because the PE protein-to-serum protein ratio was 0.49 (3.4/6.9) and the PE lactate dehydrogenase (LDH)-to-serum LDH ratio was 0.49 (101/204), < 0.6 and 0.5, respectively, it was classified as transudative [5]. Additionally, absolute PE LDH was 101 mU/mL, less than two-thirds of the normal serum LDH upper limit. Though repeated cytology of the PE did not show malignant cells, the PSA level in PE was elevated (192.0 ng/mL). Therefore, TPE was diagnosed with prostate cancer-induced PMPE.

On hospital day 17, we initiated androgen blockade therapy: 80 mg oral bicalutamide daily and 3.75 mg subcutaneous leuprorelin acetate once every week.

On hospital day 30, 2 weeks after starting treatment, the PaO_2 level had increased to 72 mmHg with room air, and serum and PE PSA values had decreased to 65.0 ng/mL and 109 ng/mL, respectively. The patient was discharged on day 30.

The serum PSA level decreased to 21.6 ng/mL 30 days after discharge and to 4.4 ng/mL 120 days after discharge.

Discussion

The diagnosis of prostate cancer was clear from the physical examination and elevated PSA. But the etiology of TPE was uncertain, especially whether benign or not. According to the classical algorithmic approach for diagnosis of PE,

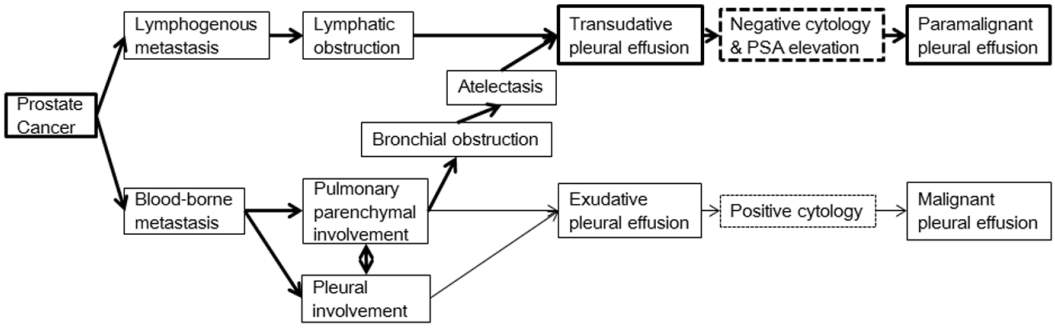

Figure 2. Possible mechanisms of prostate cancer-induced paramalignant pleural effusion. Lymphatic obstruction causes transudative pleural effusion (TPE), and usually exhibits negative cytology. When there is prostate tumor-related lymphatic obstruction, prostate-specific antigen (PSA) will be high in TPE. Blood-borne metastases cause pulmonary parenchymal or pleural involvement, resulting in exudative pleural effusion in most cases. Atelectasis attributed to bronchial obstruction either due to parenchymal or pleural involvement could increase PSA levels in TPE of some cases.

usual TPE etiologies include congestive heart failure, liver cirrhosis, nephrotic syndrome, acute atelectasis, and congestive pericarditis.

When TPE of undetermined etiology suggests the possibility of malignant disease, PSA levels in TPE should be measured in prostatic cancer patients, even in cases without malignant cytology. Brown et al. reported a case of prostate cancer diagnosed based on elevated PSA despite negative cytology in PE, normal age-adjusted serum PSA, and no radiographic evidence of metastatic disease [6].

High PE PSA levels suggest that PMPE is due to prostate cancer. PSA, a glycoprotein expressed specifically in the cytoplasm of prostatic cells but not in other normal tissues or tumors, is the most sensitive marker of prostate cancer [7]. Cascinu measured malignant effusion PSA levels in 89 patients with primary malignancies in the colon, stomach, breast, liver, prostate, lung, and kidney tissues. PSA in PE was positive in 5 of 5 prostate cancer cases, and negative in other cancers [8].

PMPE due to prostate cancer may be from either lymphatic or hematogenous origin (Fig. 2). Lymphatic obstruction may cause TPE [9] and usually shows negative cytology. PSA production by prostate cancer with tumor-related lymphatic obstruction results in high PSA levels in TPE. In contrast, blood-borne metastases cause pulmonary parenchymal or pleural involvement and usually cause exudative PE. However, atelectasis attributed to bronchial obstruction, either due to parenchymal or pleural involvement, can raise TPE PSA levels in some cases.

Androgen blockade therapy was effective in this case. Carrascosa reported the case of a 73-year-old man with prostate cancer-induced malignant PE, which resolved with flutamide and leuprorelin acetate [10]. Intrathoracic metastasis is indicative of advanced disease with remote metastasis, which typically has no effective treatment. However, hormonal therapy is often effective for advanced prostate cancer.

In conclusion, measurement of PSA in TPE is a helpful adjunct for diagnosis when TPE is of uncertain etiology and lacks malignant cytology in patients with prostate cancer.

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Conflict of Interest

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