Case Reports in Oncology

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Case Report

Solitary Lung Metastasis of Prostate Cancer with a Long Disease-Free Interval and Normal Prostate-Specific Antigen Level

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Keywords
Long disease-free interval · Normal PSA level · Prostate cancer · Solitary lung metastasis

Abstract
An 83-year-old man with core needle biopsy-proven Gleason score 5 prostate cancer had received radiotherapy including 18 Gy brachytherapy to the prostate cancer, leading to no locoregional and distant recurrence for more than 5 years with the normalization of elevated prostate-specific antigen (PSA) level before the radiotherapy. Due to the enlargement of coexisting ground glass nodule (GGN) in the left lung from 1 to 2.1 cm, the patient underwent wide resection of the GGN 7 years later. Under the diagnosis of adenocarcinoma in situ of the lung, follow-up computed tomography 6 months after the wide resection showed a rapid enlargement of a solid nodule having been judged as a presumed inflammatory nodule in the middle lobe, highly suggesting a malignant neoplasm of the lung. Due to both the tall columnar atypical cells with trabecular pattern on frozen section and no elevation of serum PSA level, we judged the nodule as a primary adenocarcinoma of the lung and further resected the middle lobe with lymph node dissection. Immunostaining of the tumor showed all the CK7, CK20, TTF-1, napsin A, synaptophysin, chromogranin, CD56, CDX2, p53, beta-catenin, and MUC2 negative, and PSA highly positive, clearly showing the solid nodule as a solitary lung metastasis of the prostate cancer. Physicians should note the possible solitary lung metastasis of prostate cancer, especially bearing indolent biology, with no elevation of the PSA level even after the completion of standard 5-year follow-up.

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Introduction

Prostate cancer is the 2nd most common cancer in men worldwide [1] and generally shows more favorable prognosis than those of lung, colon, gastric, and liver cancers. Prostate cancer, however, often spreads to the lymph nodes and distant organs like other solid malignancies. Of the three organs mainly affected by hematogenous spread, bone is the main target of hematogenous metastasis of the prostate cancer. On the other hand, lung is much less often involved without simultaneous or preceding bone metastasis by the prostate cancer.

Prostate-specific antigen (PSA) is a glycoprotein that is expressed by nearly all recurrent and even very early prostate cancers. PSA measurement, therefore, plays an important role both in the prostate cancer screening program [2] and in the postoperative follow-up scheme of the prostate cancer [3].

We report here a case of lung metastasis of prostate cancer with a disease-free interval of more than 8 years, normal PSA levels, and no extrapulmonary metastases.

Case Report

An 83-year-old man with an elevated PSA level, i.e. 8.47 ng/mL, was referred to the Urology Department in our Hospital in September 2012. Magnetic resonance images showed a hypointense mass on T2-weighted images and hyperintense signals on diffusion-weighted images in the left peripheral zone of the prostate (Fig. 1). Pathological examination of the 12 core needle biopsy specimens showed atypical cell growth with tubular architecture in 3 cores, i.e. 2 cores of Gleason score 5 and one core of Gleason score 4. Under the diagnosis of prostate cancer of Gleason score 5, the patient underwent radiotherapy (i.e., external radiotherapy 50 Gy/25 fractions and brachytherapy 18 Gy/2 fractions) to the prostate cancer in September 2012. Elevated PSA level normalized promptly after the radiotherapy. Due to the enlargement of ground glass nodule (GGN; Fig. 2B) in the left upper lung (i.e., from 1 cm, at the time of radiotherapy to the prostate cancer, to 2.1 cm), the patient was referred to our Department and underwent wide resection of the nodule in December 2019. Both frozen section and postoperative permanent section showed atypical cuboidal cell lining in a lipidemic fashion, leading to the diagnosis of adenocarcinoma in situ. Follow-up computed

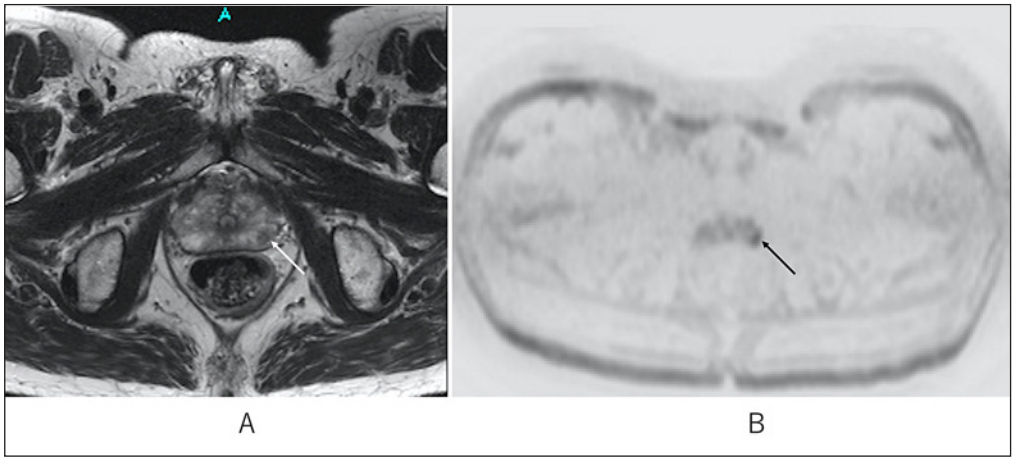

Fig. 1. Magnetic resonance imaging of the prostate. **A** MRI showed a mainly hypointense mass (arrow) with heterogenous internal intensities on T2-weighted images. **B** Diffusion-weighted images showed faintly hyperintense signals (arrow) in the left peripheral zone of the prostate.

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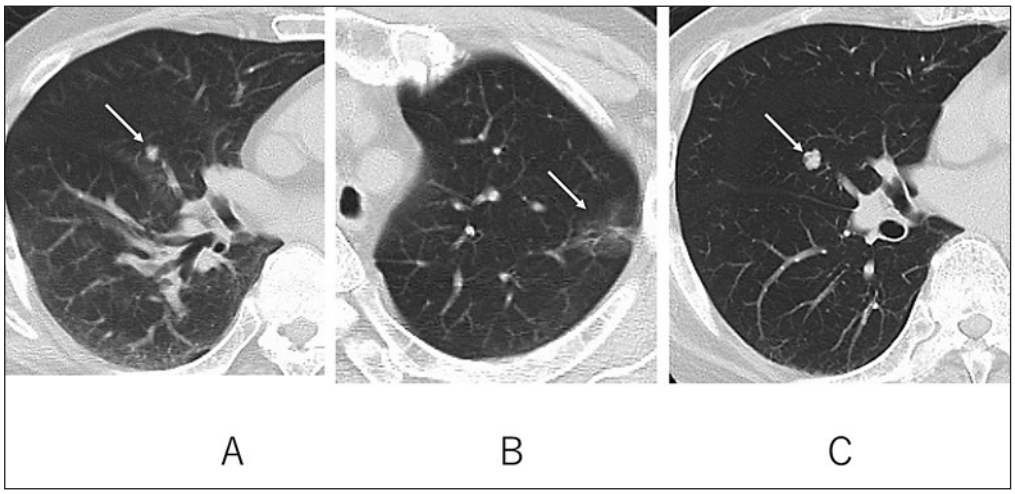

Fig. 2. Computed tomography (CT) of the lung. **A** CT of the right lung showed a small nodule (arrow), then judged as an inflammatory nodule or an intrapulmonary lymph node at the time of wedge resection of the left ground glass nodule, located just peripherally to the pulmonary artery. **B** Enlarged ground glass nodule (arrow) located just beneath the visceral pleura in the left upper lung. **C** Postoperative follow-up CT 6 months after the operation showed a rapid enlargement of the presumed inflammatory nodule (arrow).

tomography 6 months after the wide resection showed a rapid enlargement of a solid nodule (Fig. 2C) judged as a presumed inflammatory nodule in the right middle lobe at the time of wide resection of the GGN (Fig. 2A), highly suggesting a primary malignant neoplasm of the lung. The preoperative serum PSA level was still within normal range. Intraoperative frozen section of the solid nodule showed tall columnar atypical cells with trabecular pattern, leading to the tentative diagnosis of adenocarcinoma of the lung. The patient, therefore, underwent immediate middle lobectomy and hilar and mediastinal lymph node dissection. No other malignant foci including the dissected nodes were observed in the postoperative pathological examination. Immunostaining of the tumor showed all the CK7, CK20, TTF-1, napsin A, synaptophysin, chromogranin, CD56, CDX2, p53, beta-catenin, and MUC2 negative, and PSA highly positive, clearly showing the solid nodule as a lung metastasis of the prostate cancer (Fig. 3). The patient recovered uneventfully and was discharged on the 8th day after the operation. The patient received no systemic therapy after the operation due to his 83 years of age, presumed indolent biology of the metastatic and completely resected tumor, and the patient's preference.

Discussion

It is well known that prostate cancer frequently spreads to the bone in an osteoblastic fashion [4]. Prostatic venous plexus, also called Santrini's plexus [5], is a venous network around the prostate and bladder, draining into the internal iliac veins. Valveless Batson's venous plexus [6] connects the deep pelvic veins including the internal iliac veins and the internal vertebral venous plexus, leading to the high prevalence of bone metastasis of prostate cancer. It, however, seems highly feasible for prostate cancer to hematogenously spread to the lung like to the bone. Lung-only metastasis, however, consists of less than 1% of all metastatic prostate cancers [7]. Anatomical connection mentioned above does not well explain the marked difference in the metastatic frequency between bone and lung. Like breast cancer,

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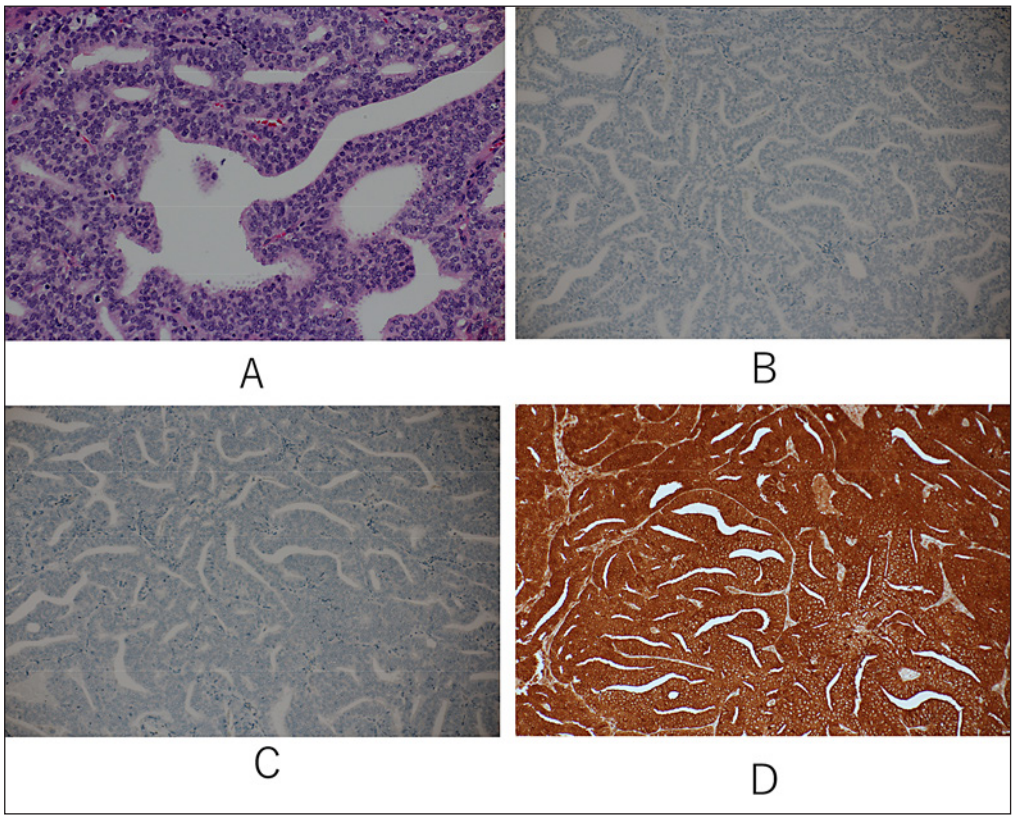

Fig. 3. Pathological examination of the right lung nodule. **A** HE staining showed tall columnar atypical cells proliferating in a trabecular fashion. **B**, **C** Neither TTF-1 (**B**) nor napsin (**C**) immunostaining was positive in the atypical ells. **D** Atypical cells showed extremely high positivity for PSA.

prostate cancer cells highly secrete osteoclast-activating cytokines, e.g. parathyroid-related protein, probably contributing to this marked metastatic preference to the bone. In other words, many prostate cancer cells flowing into the lungs, mainly due to the apoptosis of the cancer cells, do not establish lung metastasis.

Elevation of the PSA level generally precedes the symptoms or radiologic findings of local or distant recurrence of prostate cancer. Therefore, rising serum PSA level without detectable cancer recurrence is expressed as a biochemical recurrence [8] in the field of urologic oncology. Why no elevation of the PSA level occurred in this case remains uncertain. Oncologists should note the presence of prostate cancer recurrence without PSA elevation. In addition to the normal PSA level, this patient had a very long disease-free interval of more than 8 years, no other presumed metastatic foci except for the lung metastasis, and the history of lung cancer operation only 9 months ago. All these findings and condition markedly pressured the attending physicians to make a definitive diagnosis of the nodule.

The patient underwent wedge resection of the lung nodule followed by lobectomy of the middle lobe with lymph node dissection. Much less amount of lung volume of the middle lobe than other lobes fortunately lead to the possible preservation of the vital capacity of the patient. If the nodule had been located in other lobes, it should have caused much harm to the patient. In addition, full preoperative communication between the pathologist and the surgeons, if it had been done, could have led to much more harmless operation, i.e. wedge resection without further lobectomy and lymph node dissection.

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Pathological examination of the left GGN resected 9 months ago showed atypical cuboidal cells proliferating in a lepidic fashion with no stromal invasion, resulting in the final diagnosis of lung adenocarcinoma in situ. GGN itself highly suggests the presence of non-invasive component, i.e. lung primary, on one hand, but the absence of ground glass opacity does not negate the lung primary on the other hand. We, therefore, should have proceeded to lobectomy if only non-invasive cancer had been detected on frozen section.

Approximately half of the breast cancer recurrences occur in the following decade after the 5-year postoperative follow-up period. Prostate cancer, generally showing better survival outcome than that of breast cancer, also often develops recurrences after 5 years of follow-up despite the much lower frequency of the late recurrence compared with that of breast cancer [9]. Physicians, therefore, should note the recurrence of prostate cancer beyond the disease-free interval of 5 years, especially in case of prostate cancer bearing more favorable biology, e.g. Gleason score ≤5. In addition, physicians should note the fact that radiotherapy including brachytherapy without surgical resection induces more lung metastasis than surgical intervention [10].

In conclusion, prostate cancer can recur with no elevation of PSA level even after the standard follow-up period of 5 years. Surgical intervention to the possible lung metastatic tumor(s) should be cautiously planned.

Statement of Ethics

We have reported this case in compliance with the Declaration of Helsinki. Written informed consent was obtained from the patient for the publication of this case report and any accompanying images.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Not applicable.

Author Contributions

H.Y. contributed to the design of the report and collected the data. S.O. drafted the manuscript. T.Y. decided how to treat the patient. S.M. revised the manuscript. All authors have read and approved the final version of the manuscript.

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