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【 CASE REPORT 】

Bilateral Testicular Metastases from Lung Adenocarcinoma Showing an Objective Response to Nivolumab: A Case Report and Review of the Literature

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Abstract:
A 69-year-old man who had undergone chemoradiotherapy for advanced pulmonary adenocarcinoma had bilateral testicular and adrenal gland masses on a routine follow-up examination. We performed left orchiectomy, and the histopathological examination confirmed metastatic pulmonary adenocarcinoma involving the extracted testis. He was treated for disease progression with nivolumab after unsuccessful cytotoxic chemotherapy, which resulted in regression of recurrent adrenal and right testicular tumors. We reviewed the existing literature on metastatic testicular tumors and found that testicular metastasis from lung cancer is rare and poses a chemotherapeutic challenge. Based on our experience, immune checkpoint inhibitors seem to have good efficacy for treating testicular metastasis.

Key words: non-small cell lung cancer, adenocarcinoma, testicular metastasis, immune checkpoint inhibitors, nivolumab

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Introduction

A majority of testicular cancers (>90%) are germ cell tumors derived from the epithelium of a mature testis, and only 5% are gonadal stromal tumors derived from cells that play a role in the development and maturation of spermatozoa (1). Thus, testicular metastasis is rare. Except for lymphoma and leukemia, the most common primary malignant tumors that metastasize to the testis are those of the prostate, followed by lung cancer (2). There have been a few reported cases of testicular metastasis of lung adenocarcinoma.

Nivolumab is an immune checkpoint inhibitor (ICI) that exerts antitumor activity by targeting programmed cell death protein-1 (PD-1) or programmed cell death ligand-1 (PD-L1). A recent clinical study showed that nivolumab was associated with a significantly longer progression-free and overall survival (3, 4). While nivolumab is widely used in patients with advanced or recurrent non-small cell lung cancer (NSCLC), the efficacy of the drug in those with lung cancer with testicular metastasis is unknown.

In this report, we describe the case of a patient with bilateral testicular metastases from lung adenocarcinoma who responded to nivolumab and additionally present a review of the existing literature on the topic.

Case Report

A 68-year-old man was admitted to our hospital in December 2016. He had a history of diabetes mellitus and gastric ulceration. He had been a smoker between 20 and 65 years of age. He had been in good health until approximately two months before admission, when he developed generalized fatigue and anorexia. Computed tomography (CT) of his chest performed at a nearby hospital revealed a mass in the left upper lobe along with mediastinal lymphadenopathy. A histopathological examination of a specimen obtained by a needle biopsy of the tumor under CT guidance revealed lung adenocarcinoma. The tumor tested negative for oncogenic mutations, such as epidermal growth fac-

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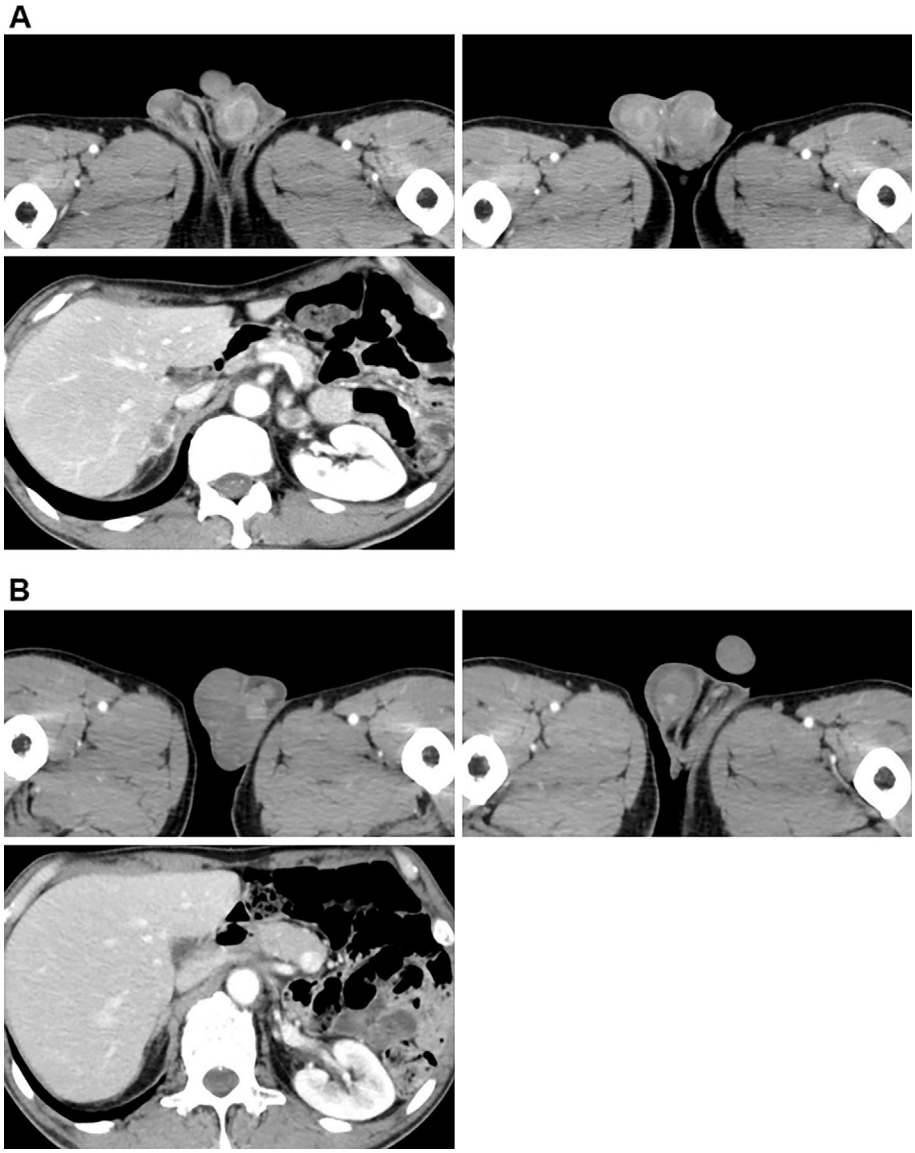

Figure 1. **(A) A radiographic review of the patient's contrast abdominal and pelvic CT scans performed in September 2017 incidentally revealed bilateral testicular and adrenal gland masses. (B) When reviewed retrospectively, the CT scan performed in May 2017 also showed a nodular shadow involving both testes, which was presumed to indicate testicular metastasis, although adrenal metastasis was not detected on that scan.**

tor receptor and echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase rearrangement. A staging work-up was performed using magnetic resonance imaging of the brain and whole-body fluorine-18 2-fluoro-2-deoxy-d-glucose positron emission tomography; the patient was revealed to have T2aN2M0, stage IIIA lung cancer.

The patient underwent chemotherapy consisting of carboplatin and paclitaxel along with concomitant thoracic irradiation according to a protocol established by the West Japan Oncology Group (5). The patient responded to the treatment to a certain extent and had been subsequently followed at our hospital without any additional treatment for his lung cancer.

In September 2017, during a routine surveillance checkup, a radiographic review of the patient's CT scans incidentally revealed bilateral testicular and adrenal gland masses (Fig. 1A). When reviewed retrospectively, the CT scan performed in May 2017 had already shown a small nodular shadow bilaterally placed within the testes that was presumed to indicate testicular metastasis, although no adrenal metastasis were detected on that scan (Fig. 1B). On a physical examination, we detected bilateral painless, firmly palpable masses in the testes that were almost the size of a quail's egg. A blood assay revealed elevation of the patient's carcinoembryonic antigen (CEA) and cytokeratin 19 fragment (CYFRA) levels compared to those recorded during the previous visits. Other laboratory findings were unremarkable. As these tumors were considered to have been caused by metastasis from the lung adenocarcinoma, we performed left orchiectomy in November 2017. On sectioning

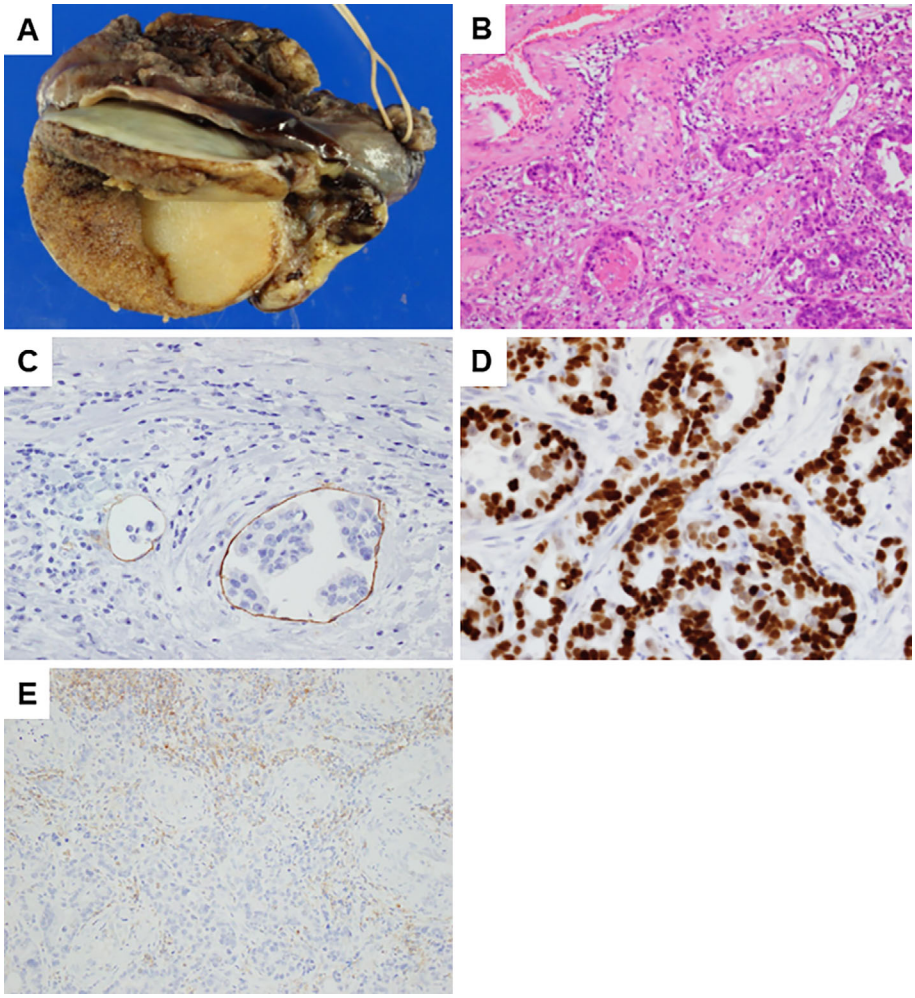

Figure 2. **(A) On sectioning of the left testis, a solid yellowish white tumor measuring 2.5×1.5×1.8 cm was found. (B) A histopathological examination of the mass showed atypical adenocarcinoma cells resembling a lung tumor that had multiplied to form a glandular pipe between the seminiferous tubules. The seminiferous tubules had partially disappeared due to tumor infiltration (200× magnification). (C) Immunohistochemical staining of D2-40 revealed tumor cells invading the lymphatic vessel. (D) The tumor was positive for thyroid transcription factor-1 staining. (E) Less than 1% of the tumor cells were found to express PD-L1 on immunohistochemistry.**

the left testis, a solid yellowish white tumor was found, measuring 2.5×1.5×1.8 cm (Fig. 2A). A microscopic examination of the growth showed atypical adenocarcinoma cells (like those observed in the lung biopsy histopathological examination), which had multiplied to form a glandular pipe between the seminiferous tubules and invaded the lymphatic vessel (Fig. 2B and C). The seminiferous tubules partially disappeared by tumor infiltration, suggesting that the blood-testis barrier had been broken. There was no sign of involvement of the excised stump of the spermatic cord. On an immunohistochemical examination, the tumor tested positive for thyroid transcription factor-1 (Fig. 2D), which supported the diagnosis of metastasis from the pulmonary adenocarcinoma. A ROS1 gene rearrangement analysis was negative, and PD-L1 was expressed in <1% of the cancer cells in the tumor (Fig. 2E). PD-L1 staining for the primary lung tumor was not performed.

The patient was administered five cycles of chemotherapy, consisting of carboplatin and pemetrexed, following orchiectomy. However, on follow-up, the metastatic tumors in the right testis and bilateral adrenal glands were found to have gradually increased in size. Therefore, we changed the chemotherapy regimen to nivolumab according to the guidelines established by the Japan Lung Cancer Society, and the metastatic tumors, including the bilateral adrenal metastases, regressed (Fig. 3). In addition, the patient's serum CEA and CYFRA levels decreased gradually. The patient has been maintained on nivolumab and is being followed up at our outpatient clinic regularly.

Discussion

Testicular metastasis is rare, with an incidence ranging from 0.06% to 0.46% according to a large unselected autopsy series (6, 7), and metastatic testicular cancer was found to comprise 3.6% of all testicular tumors (8). In their

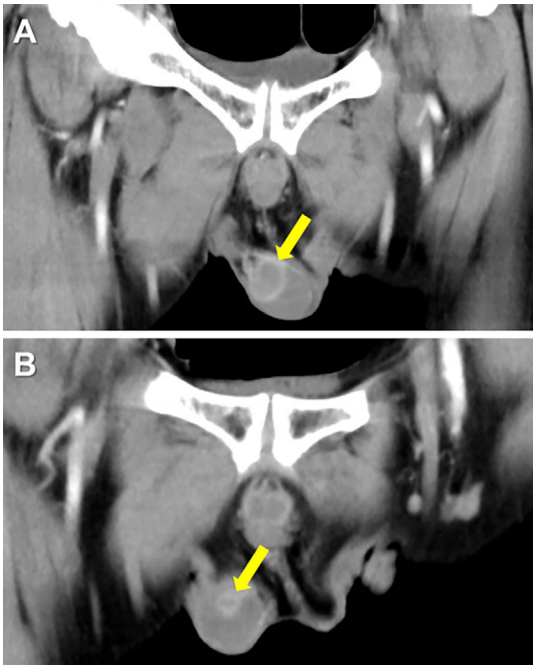

Figure 3. (A, B) The right-sided metastatic testicular tumor before and after regression was achieved following six cycles of nivolumab administration (arrow).

review of the worldwide literature on 209 patients with metastatic carcinoma to the testes, Patel et al. found that only 13 (6%) patients presented with a testicular lump that was diagnosed as an occult primary tumor, while 196 (94%) patients were incidentally diagnosed, with no evident clinical signs. In these cases, the most common primary malignancies were prostate cancers (34.6%), followed by lung carcinomas (17.3%) (8). Following this publication in 1989, we found 10 reported cases of testicular metastasis from primary lung cancers diagnosed during patients' lifetimes (Table) (1, 9-17). All patients were younger than 70 years of age, which is a relatively young age of presentation compared to the mean age at the diagnosis of lung cancer. The reason for this is unclear but may be related to the gonadal function. Metastasis to the testis from lung cancer has only been found to occur unilaterally in previous cases. However, our patient developed bilateral testicular metastases.

The reason for the rare occurrence of testicular metastasis is unclear. Metastasis to the testes is mainly dependent on two variables, the first of which is the ability of primary malignant cells to establish themselves in the testicular environment (9). Smallman and Odedra reported that the relatively low temperature of the scrotal tissue is the most important factor impeding the ability of neoplastic cells to thrive within the testis (18). The second variable is the mechanism of transportation of tumor cells to the testes. While any tumor cells can be potentially transported to the testicle (18), there are several routes for metastases, which are determined by the site of primary malignancy. For example, prostate cancer may spread along the vas deferens (19), gastrointestinal tract cancers may show a retrograde lymphatic spread, renal cell carcinoma may metastasize through the spermatic vein, and lung cancers spread via hematogenous routes (19, 20). Adrenal metastasis from lung cancer is also considered to be a form of hematogenous metastasis (21), strongly suggesting the possibility of hematogenous metastasis in our case. However, lymphatic metastasis cannot be denied, as tumor infiltration into the lymphatic vessels in the testis was observed, although this may have been the result of hematogenous transportation which resulted in the development of tumors in the testes.

Generally, patients with metastatic lung cancer receive systemic chemotherapy. However, there have been several reported cases, including those of small cell lung cancer metastasizing to the testes, that showed treatment failure even after the completion of adjuvant chemotherapy (9, 18, 20). Touroutoglou et al. reported that isolated testicular recurrences occurred in 1.7% to 13% of patients with acute lymphoblastic leukemia after they achieved complete remission. The testes are also the most common site of disease recurrence in acute lymphoblastic leukemia, with 40-45% of all relapses involving the testis or the central nervous system after complete remission (22). These findings suggest that the testes act as a sanctuary site for cancer cells, thwarting the therapeutic effectiveness of chemotherapy (23). Furthermore, several clinical observations suggest the existence of the blood-testis barrier. Beginning at puberty, the process of spermatogenesis involves the expression of novel cell-surface antigens after the immune system has gained the ability to recognize foreign cells. However, the spermatozoa within the testis do not elicit an immune response. In addition, although macrophages and lymphocytes are frequently observed within testicular interstitial spaces, these antigen-presenting cells are rarely seen within the seminiferous tubules. These observations support the theory of the testicles serving as an immune-privileged site (24).

During treatment, chemotherapeutic drugs have been found to attain lower concentrations within the testicular interstitium compared with their plasma levels, which suggests the existence of a filtering barrier between testicular capillaries and its interstitial space (25). Multiple studies have reported the inability of specific large- and small-sized molecules to cross between the testicular interstitial space and germinal tubules (24). Dhiren et al. studied the rate of the survival of a residual viable tumor within the testis after the completion of systematic chemotherapy. They reported that a viable testicular tumor persisted in 8.3% to 37.5% of patients, and several studies demonstrated the presence of a residual viable malignant mass in the testis even when the metastatic disease had otherwise disappeared. This suggests that the blood-testis-barrier influences the effect of systematic chemotherapy. In our case, it was surmised that the testicular metastases had already existed during the first visit and had been refractory to carboplatin and paclitaxel combination chemotherapy due to the blood-testis barrier. In contrast, the bilateral adrenal metastases seemed to arise after the first round of chemotherapy. At the time of relapse, the

Table. **Reported Case Series of Testicular Metastasis from Lung Cancer in the Literature.**

No	Age	Pathology	Primary site	Involved side	Time of detection	Orchiectomy	Ref.
1	46	Undiff.	Bronchus	right	at initial diagnosis	+	(10)
2	51	Ad	RM	right	at initial diagnosis	+	(11)
3	58	Sm	NA	right	at initial diagnosis	+	(12)
4	51	Sm	Left	left	after surgery and chemoradiotherapy	+	(9)
5	60	Ad	RU	right	after 3 cycles of cisplatin/irinotecan	+	(13)
6	61	Sq	LL	left	after surgery	+	(1)
7	48	Sq	RU	right	at initial diagnosis	+	(14)
8	52	NEC	LL	right	at initial diagnosis	+	(15)
9	58	Sq	RU	right	after 2 cycles of carboplatin/paclitaxel	+	(16)
10	29	Ad	LL	right	at initial diagnosis	+	(17)
11	69	Ad	LU	bilateral	after chemoradiotherapy	+	Present case

M: male, Undiff.: undifferentiated carcinoma, Ad: adenocarcinoma, Sm: small cell carcinoma, Sq: squamous cell carcinoma, NEC: neuroendocrine carcinoma, RM: right middle lobe, NA: not available, RU: right upper lobe, LL: left lower lobe, LU: left upper lobe

testicular metastases had grown to the same size as that observed during the previous orchiectomy, suggesting that the blood-testis barrier had already broken, as evidenced by the pathological findings. Therefore, second-line chemotherapy consisting of carboplatin and pemetrexed did not affect the blood-testis barrier, so the failure was likely due to the nature of the tumor itself.

Nivolumab is a fully human IgG4 PD-1 ICI approved for administration in metastatic or refractory NSCLC. The role of PD-L1 as a potential biomarker has been investigated, so it can be used to predict the therapeutic response to nivolumab in clinical settings (26). However, Phillips et al. reported PD-L1 mismatch between original lesions and metastatic foci in 30% of metastatic NSCLC cases (26). In addition, the tumor mutational burden is an emerging biomarker of response to anti-PD-L1 therapy. There is a significant correlation between the tumor mutational burden and the objective response rate to ICIs (27). In our patient, nivolumab administration achieved a remarkable response despite the complete absence of PD-L1 in the extracted right testicular mass. This phenomenon may be due to a difference in the expression of PD-L1 between the right and left testes or may have resulted secondary to a higher rate of tumor mutation. However, as we have noted, the testes serve as an immune-privileged site, which makes it difficult to predict the immunological mechanism and degree of response. In our case, in addition to the collapse of the blood-testis barrier, the infiltration of the tumor cells into the testicular interstitial spaces may have eliminated the immunotolerance mechanism of the testis.

In conclusion, we treated a patient with a rare diagnosis of bilateral testicular metastases from a primary lung adenocarcinoma that responded favorably to chemotherapy with nivolumab. These findings suggest that ICIs are an effective alternative to cytotoxic chemotherapy for lung cancer with testicular metastasis. However, further research is needed to support this treatment approach.

Author's disclosure of potential Conflicts of Interest (COI).

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