〈Case Report〉

Rapid Pulmonary Metastasis and Malignant Pleural Effusion during Follow-up in a Case of Stage I Non-Seminoma: A Case Report and Literature Review

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ABSTRACT Here, we report a case of stage I non-seminoma with vascular invasion that presented with rapid pulmonary metastasis and respiratory distress during follow-up. A 43-year-old male underwent high orchiectomy for a right testicular tumor at another hospital. Pathological examination revealed a mixed germ cell tumor with vascular invasion (non-seminoma, pT2N0M0S0; stage IB). The patient refused adjuvant chemotherapy and was scheduled for surveillance. Four months after surgery, CT at another hospital incidentally identified a right lung tumor. At that time, the AFP level was elevated to 1,384 ng/ml, and the lung tumor was diagnosed as metastasis from the testicular tumor. The patient also experienced respiratory distress and was urgently transferred to our hospital. Chest CT revealed an enlarged tumor in the right lung with a large pleural effusion, a significant mediastinal shift, and no visible normal lung tissue. Due to worsening respiratory distress, Bleomycin/Etoposide/Cisplatin (BEP) chemotherapy was immediately initiated. However, on the 6th day of treatment, the CT findings suggested drug-induced pneumonia. Therefore, Etoposide/Ifosfamide/Cisplatin (VIP) regimen was initiated as the 2nd cycle of chemotherapy. A gradual reduction in lung lesions was observed, and the patient eventually did not require oxygen therapy. Four cycles of VIP chemotherapy were administered with a combination of outpatient and inpatient care. Currently, AFP levels have normalized, and only minimal residual lung tumors remain. Subsequent surgical resection is planned.

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Key words：Testicular cancer, Non-seminoma, Metastatic testicular cancer, Mixed germ cell tumor, Lung metastasis, Vascular invasion

INTRODUCTION

Testicular cancer is most commonly diagnosed in relatively young individuals, typically in their 30s and 40s, and many of these patients are

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employed. The management of non-seminomatous testicular tumors following orchiectomy may include chemotherapy or retroperitoneal lymph node dissection, and it is crucial to focus on preventing recurrence. In particular, the presence of vascular invasion in stage I non-seminoma strongly correlates with recurrence rates and is a key factor in determining treatment strategies[1]. We report a case of stage I high-risk non-seminoma with vascular invasion, which was followed up by surveillance after surgery and subsequently developed rapid pulmonary metastasis and malignant pleural effusion.

CASE REPORT

A 43-year-old male had presented with scrotal enlargement at another hospital and a high orchiectomy was performed for a right testicular tumor. The pathological diagnosis was a mixed germ cell tumor, primarily composed of a yolk sac tumor component with vascular invasion. The tumor marker AFP level was elevated to 206.7 ng/ml at the initial visit but normalized to 4.6 ng/ml at 6 weeks postoperatively. The final diagnosis was non-seminoma, pT2N0M0S0, LVI+, stage IB. The patient refused postoperative chemotherapy and was, therefore, scheduled for surveillance.

Four months post-surgery, during a visit to another physician for the treatment of herniated disc, chest radiography and plain CT incidentally revealed a mass in the right lung and upper mediastinum along with pleural effusion (Fig. 1A, 2B). At that time,

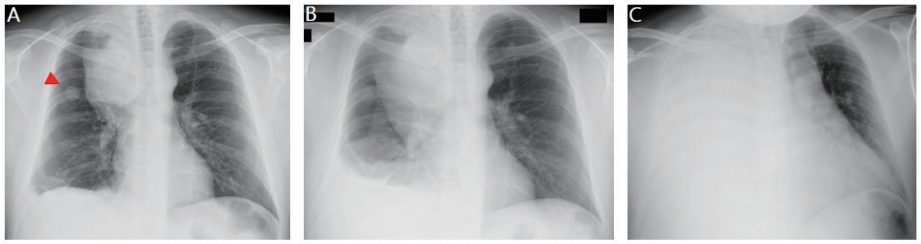

Fig. 1. Chest X-ray images showing the progression of pulmonary lesions
(A) 4 months post-surgery: a mass lesion is identified in the right lung and upper mediastinum. (B) 1 week after (A): enlargement of the mass and ipsilateral pleural effusion. (C) at the time of admission to our hospital: no normal right lung is visible, with mediastinal shift observed, 4 weeks after the initial identification.

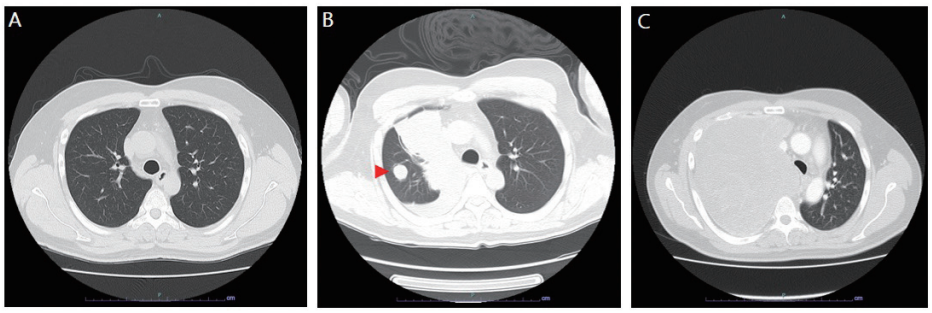

Fig. 2. CT images showing the progression of pulmonary lesions
(A) at the time of testicular tumor diagnosis: no significant abnormalities were observed. (B) 4 months post-surgery: a new mass measuring 18 mm is seen in the right upper lung lobe. (C) at the time of admission to our hospital: no normal right lung is visible, with mediastinal displacement toward the contralateral side.

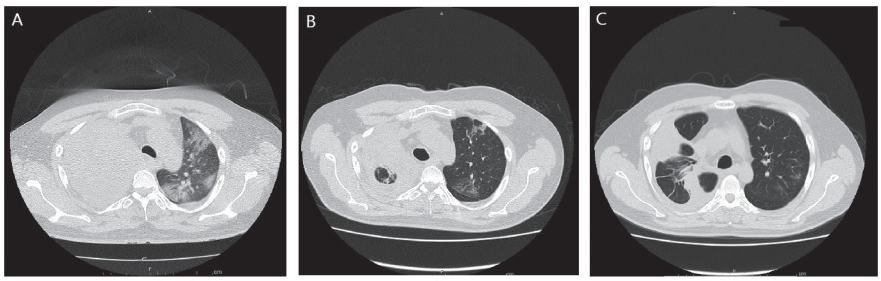

Fig. 3. Pulmonary lesions after chemotherapy
(A) Day 6 of treatment: ground-glass opacities suggestive of drug-induced pneumonia in the healthy lung. (B) Day 32 of treatment: resolution of ground-glass opacities in the healthy lung, with some normal lung tissue observed in the affected lung. (C) After 2 cycles of VIP therapy: further reduction of right lung lesions.

the AFP level had increased to 1,384 ng/ml, and the patient was diagnosed with pulmonary metastasis from the testicular tumor. The patient also experienced respiratory distress and was urgently transferred to our hospital. Vital signs were relatively stable, with a blood pressure of 125/75 mmHg, body temperature of 36.5 ℃, heart rate of 79 bpm, and SpO_2 of 95% (room air). Chest radiography revealed pleural effusion, tumor metastasis, and atelectasis in the right chest with no visible normal lung tissue (Fig. 1C). Contrast-enhanced CT revealed significant enlargement of the lung metastasis and mediastinal tumor, with a mediastinal shift to the opposite side (Fig. 2C). Additionally, a 21 mm mass with poor contrast enhancement was noted in the right hepatic lobe, which was diagnosed as hepatic metastasis on contrast-enhanced ultrasound. No metastasis was observed in other organs or lymph nodes. Upon presentation to our hospital, the patient was classified as having a poor risk according to the International Germ Cell Consensus Classification (IGCCC). On admission, the patient experienced worsening respiratory distress, and high-flow nasal cannula oxygen therapy and thoracic drainage were initiated. The aspirated pleural effusion was hemorrhagic and approximately 100 ml was drained. However, the following day, the drain became obstructed and was removed. Early intervention for pulmonary metastatic lesions was necessary to improve the respiratory status, and standard induction chemotherapy with BEP (bleomycin, etoposide, and cisplatin) was initiated. However, on the 6th day of treatment, CT findings suggested bleomycin-induced pneumonia (Fig. 3A), and bleomycin administration on days 8 and 15 was discontinued. Etoposide, ifosfamide, and cisplatin (VIP) therapy was initiated as the 2nd line therapy. On day 9 of treatment, chest CT showed improvement of drug-induced pneumonia and the appearance of some normal lung tissue in the right lung (Fig. 3B). The AFP level decreased to 69.9 ng/ml, and the respiratory condition improved, with the patient no longer requiring oxygen therapy. Subsequently, VIP therapy was continued, with repeated admissions and discharge. After completing four cycles, the AFP level normalized to 4.3 ng/ml, hepatic metastasis and mediastinal tumor disappeared, and only a minimal residual tumor remained in the right lung (Fig. 4). Grade 4 neutropenia was observed as a side effect during the third cycle but improved with G-CSF administration. Surgical resection is planned for the remaining pulmonary metastases.

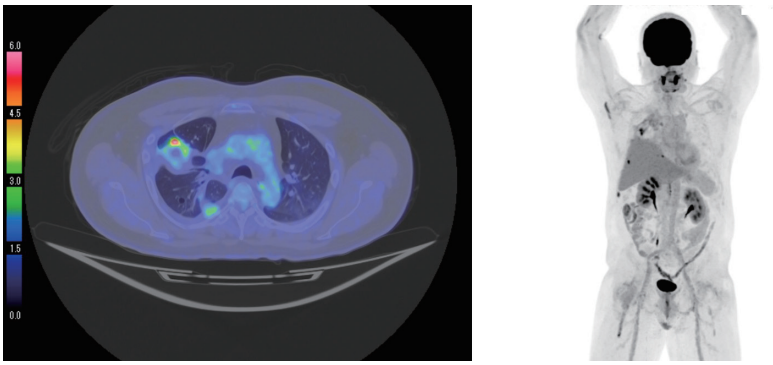

Fig. 4. PET/CT after completion of 4 cycles of VIP therapy
Right lung lesions have reduced over time, with FDG accumulation in some residual lesions measuring 34 mm, and resolution of hepatic metastasis.

DISCUSSION

Although testicular cancer is a relatively rare disease, it remains an important malignancy that predominantly affects young adults. It is also known for its tendency to metastasize early, necessitating close attention to the risks of recurrence and metastasis after high orchiectomy. Specifically, in stage I non-seminoma, it has been reported that 25.7% of patients experience recurrence with only postoperative surveillance[2], emphasizing the need for vigilance regarding the potential necessity for adjuvant treatment. Vascular invasion is considered a critical risk factor for recurrence in stage I non-seminomas. According to Choueiri *et al.*, the recurrence rate in patients without vascular invasion was 15%, whereas that in patients with vascular invasion was 50%[3]. The Japanese Testicular Cancer Clinical Guidelines recommend administering adjuvant chemotherapy (1 cycle of BEP therapy) to stage I non-seminoma patients with vascular invasion whenever possible[1]. Albers *et al.* reported that adjuvant chemotherapy reduced the recurrence rate to 0.5% over two years post-surgery[4], and the Swedish Testicular Cancer Project (SWENOTECA) also demonstrated a high recurrence prevention effect in a prospective study of 500 cases[5].

If a patient declines additional treatment after being aware of the risk of recurrence, strict outpatient surveillance is required. Divrik *et al.* reported that 78.8% of recurrence in stage I non-seminoma occurred within 1 year after surgery, and 16.7% occurred within 2 years in cases where no additional treatment was given[6]. In the current case, rapid pneumonia was observed four months postoperatively, leading to respiratory failure. Although the frequency of visits to the previous urology clinic is unknown, it is recommended that tumor markers (AFP, HCG, and LDH) be measured and imaging evaluations through plain CT be performed at least every 2 months during the first-year post-surgery. Effective communication with patients regarding their condition and cooperation during follow-up visits are essential for proper management.

For progressive testicular cancer with metastasis, the treatment strategy is selected based on the International Germ Cell Consensus Classification (IGCCC). In the present case, the patient was classified as having poor risk due to the presence of both pulmonary and hepatic metastases at the time of presentation. According to the guidelines, four cycles of BEP or VIP chemotherapy is recommended as standard induction chemotherapy (EP or VIP therapy should be selected in cases with

a high risk of bleomycin-induced lung toxicity)[1]. In this case, we chose the most common BEP regimen for induction chemotherapy. However, on the 6th day of treatment, drug-induced pneumonia was observed in the healthy left lung and bleomycin was discontinued. The Japanese Testicular Cancer Clinical Guidelines state that "EP or VIP therapy is weakly recommended as an alternative to BEP chemotherapy in patients with metastatic testicular cancer in whom bleomycin administration is undesirable"[1].

The risk factors for bleomycin-induced lung toxicity include age (> 40 years), cumulative bleomycin dose (> 300 IU), impaired renal function (GFR < 80 mL/min), and the presence of metastases to other organs. O'Sullivan *et al.* reported that when all four of these factors were present, 71.2% of patients develop pneumonia[7]. In this case, two risk factors, age and other organ metastases, were present, and the presence of lung metastasis, smoking history, and oxygen therapy contributed to the risk. Furthermore, Masayuki *et al.* reported that the incidence of bleomycin-induced lung toxicity in Japan is approximately 1,000 times higher than that in Western countries[8], highlighting the need to consider these risk factors when using bleomycin.

In this patient, VIP therapy was initiated from the 2nd cycle onward. The decision regarding the use of EP (etoposide and cisplatin) therapy, which excludes bleomycin, remains debatable. Although clinical studies comparing the effectiveness of BEP and VIP therapies have been published[9-10], there are no clinical reports comparing the efficacy of EP and VIP therapies. Furthermore, choosing VIP as the initial chemotherapy regimen results in fewer treatment options for 2nd-line or subsequent therapies. However, this patient had rapid progression with severe respiratory distress over a very short period, prompting the selection of VIP therapy, which included ifosfamide in addition to the two agents used in EP therapy, due to concerns about the potential failure of the initial treatment.

This patient was initially diagnosed with a stage I non-seminoma with vascular invasion at another hospital, but the patient opted for surveillance without adjuvant chemotherapy for personal reasons. When surveillance is chosen with a full understanding of the risk of recurrence, it is essential for the patient to cooperate with regular follow-up visits at least every 2 months during the 1st year after surgery. Although the follow-up status in this case was unclear, after approximately four months, rapid pulmonary metastasis and worsening cancer-related pleural effusion were observed, necessitating the prompt initiation of chemotherapy. The development of bleomycin-induced lung toxicity was prevented by careful CT monitoring, enabling the early detection of symptoms.

CONFLICT OF INTEREST

None declared

ABBREVIATIONS AND ACRONYMS

CT = Computed Tomography
AFP = α-fetoprotein
LVI = Lymphovasucular invasion
PET = Positron Emission Tomography

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