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CASE SERIES

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Malignant involvement of the iliopsoas muscle associated with non-small cell lung cancer: Two case reports

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Key Clinical Message

Under the current progression of molecular targeting or immune therapy, early detection and radiation therapy of iliopsoas metastasis will not only improve performance status but also enable the continuation of effective systemic cancer treatment.

KEYWORDS

ALK inhibitors, malignant psoas syndrome (MPS), non-small cell lung cancer (NSCLC), pembrolizumab, radiation therapy

1 | INTRODUCTION

The iliopsoas muscle has a wide origin, with the psoas major portion originating from the twelfth thoracic and all five lumbar vertebrae, and the iliacus portion arising mainly from the iliac fossa of the pelvis. The iliopsoas muscle joining the lesser trochanter of the femur is the main flexor of the hip joint. The iliacus is innervated by branches of the femoral nerve (L2, L3). The psoas major is innervated by the anterior rami of the lumbar spinal nerves, mainly L1 and L2, with some contributions from L3 and L4.

Malignant psoas syndrome (MPS) was first described by Stevens and Gonet in 1990 and is unique cancer-related syndrome characterized by ipsilateral proximal lumbosacral (LS) plexopathy and painful hip flexion caused by radiographically or pathologically evident malignant involvement of the psoas major muscle.[1,2] Female genital tract malignancies are the most common diseases causing MPS, followed by gastrointestinal and urinary tract malignancies.[3] MPS-causing non-small cell lung cancer (NSCLC) is extremely rare. Recently, we encountered two patients who developed MPS during treatment for NSCLC. The clinical significance of this syndrome involving NSCLC is discussed.

2 | CASE PRESENTATION

2.1 | Case 1 (Figure 1)

In February 2019, a 46-year-old nonsmoking woman presented at Yao Tokusyukai General Hospital with anterior chest and shoulder pains and face edema. Whole-body contrast-enhanced computed tomography (CT) showed a 70-×50-×47-mm heterogeneous solid/cystic lesion in the left pulmonary hilar region. The lesion directly invaded the mediastinum and connected with swollen

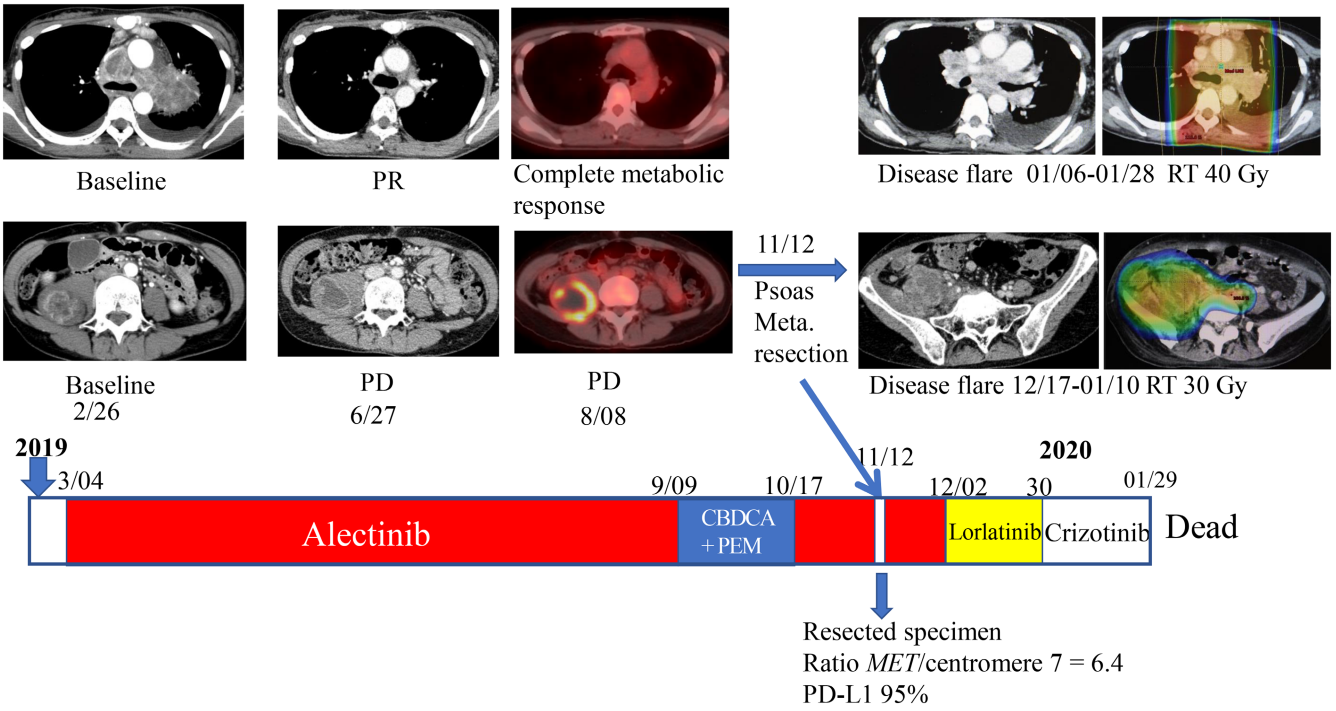

FIGURE 1 A timeline summarizing the main diagnostic and therapeutic switches in Case 1. PR, partial response; PD, progressive disease; RT, radiation therapy; CBDCA, carboplatin; PEM, pemetrexed; PD-L1 TPS, programed cell death 1-Ligand 1 tumor proportion score. The baseline image was quoted from Okazaki et al.[4]

right superior mediastinal lymph nodes that completely occluded the superior vena cava. In addition, multiple enlarged lymph nodes were seen in the mediastinum. Concomitantly, CT showed a 42-×37-×44-mm cystic mass within the right psoas muscle. She had no symptoms associated with this intramuscular mass. Her thoracic lesion was biopsied via endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and revealed adenocarcinoma with surrounding lymph node metastasis. Cytology of the left pleural effusion revealed malignant cells consistent with adenocarcinoma. Thus, the diagnosis of stage T3N2M1a but not M1b, stage IVA adenocarcinoma of the lung, was achieved according to the 8th edition of the TNM classification because the mass within the right psoas muscle was regarded as a different entity on diagnostic imaging at that point. Further testing using reverse transcription-polymerase chain reaction (RT-PCR) revealed echinoderm microtubule-associated protein-like 4 (EML4) and the anaplastic lymphoma kinase (ALK) fusion gene, variant 1, and the patient was started on the oral administration of alectinib at a dose of 300 mg twice a day immediately.

In June 2019, the patient was transferred to Yao Municipal Hospital to continue treatment with alectinib. As a result, fluorodeoxyglucose positron emission tomography (FDG-PET) showed a complete metabolic response to alectinib. However, the tumor in the right psoas muscle enlarged with a standardized uptake value (SUV max) of 10.1. At this point, she complained of severe low back pain. The pain was right-sided, extending from the lower back through hip and thigh to inside the knee, and it worsened in August. Physical examination identified painful flexion of her right hip and gait disturbance. CT-guided core needle biopsy for this tumor was performed, and undifferentiated carcinoma with positive immunostaining for ALK (D5F3) and thyroid transcription factor 1 (TTF-1) was consistent with lung cancer metastasis (Figure 2). For this oligo-progression against alectinib, surgical removal was performed on November 12. However, surrounding lymph node metastases were confirmed at the time of the operation, resulting in incomplete resection. She developed disease flare at both psoas and intrathoracic lesions shortly afterward. To manage the lower back pain, a high dose of analgesics plus opioids (oxycodone up to 100 mg/day) and continuous intravenous infusion of oxycodone plus ketamine hydrochloride through Legacy® infusion pump were introduced, achieving mild pain control.

To control the disease flare of cancer, alectinib was changed to lorlatinib. As a fluorescence in situ hybridization (FISH) test of excised psoas metastasis revealed MET gene amplification, loratinib was changed to crizotinib. Concurrently, external beam radiation therapy (EBRT) was added to either the psoas muscle metastasis and thoracic recurrence, but the disease could not be controlled, and she developed uncontrollable bilateral cancerous pleurisy and died 10 months after the start of alectinib.

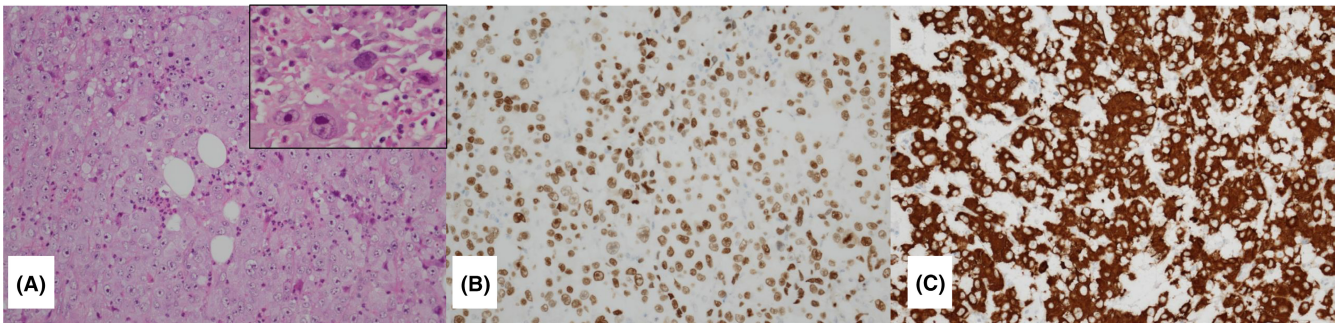

FIGURE 2 Case 1. Morphology of the psoas tumor (object lens 20×). (A) Hematoxylin and eosin stain showing metastatic carcinoma, compatible with metastasis from solid type pulmonary adenocarcinoma. High power magnification (inset, 40×) shows tumor cells with giant bizarre nucleus including prominent nucleolus. TTF-1 (B) and ALK (C) immunohistochemical stains are positive.

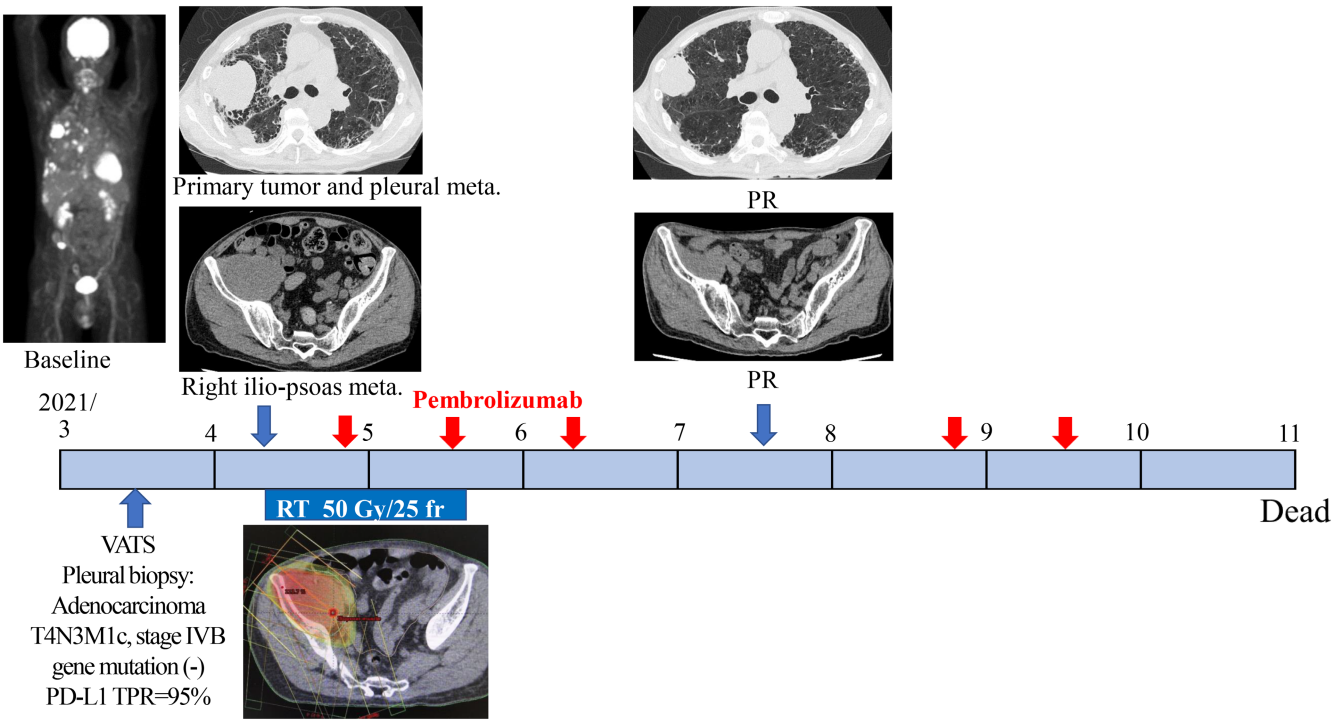

FIGURE 3 A timeline summarizing the main diagnostic and therapeutic switches in Case 2. PR, partial response; PD, progressive disease; RT, radiation therapy; PD-L1 TPS, programed cell death 1-Ligand 1 tumor proportion score.

2.2 | Case 2 (Figure 3)

In February 2021, a 65-year-old man was referred to our hospital with a 45×36×43-mm mass in the upper lobe of the right lung and right pleural effusion on chest radiography and CT. Emphysema and fibrosis were also observed. FDG-PET showed intense uptake in the pulmonary tumor, pleura, mediastinal lymph nodes, and the right ilium. The patient had a heavy smoking history of 40 pack years. Body weight loss was remarkable. The Eastern Cooperative Oncology Group performance status score (P.S. ECOG) was 2. Laboratory values were significant for CRP 0.92 (normal < 0.03), LDH 307 IU/L (normal < 245 IU/L), ALP 384 U/L (normal < 104 U/L), KL-6 906 U/mL (normal < 500 U/mL), and CEA 188.8 ng/mL (normal < 5 ng/mL).

On March 16, 2021, diagnostic and staging video-assisted thoracic surgery (VATS) was performed, and the tumor was diagnosed as poorly differentiated adenocarcinoma with pleural dissemination and malignant effusion and classified pathologically as T4N3M1c, stage IVB (Figure 4). There was no driver gene mutation. The programmed cell death ligand 1 (PD-L1) tumor proportion score (TPS) was 95%.

On April 7, 2021, he had a complaint of spontaneous, burning, and lancinating pain radiating from his right

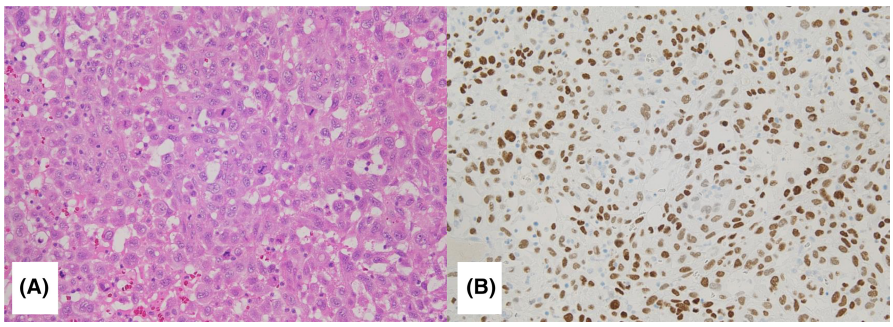

FIGURE 4 Case 2. Morphology of the primary tumor (object lens 20×). (A) Hematoxylin and eosin staining showing poorly differentiated (grade 3) adenocarcinoma proliferating atypical cells with irregular and eccentric nuclei. (B) TTF-1 immunohistochemical stain is positive.

lower back to his lower leg. The pain was associated with an inability to extend the right hip and consistent with symptoms of MPS, and thus, the patient was forced to rest with the hip in flexion. Concomitantly, his respiratory condition became distressed. Total body CT taken on April 12 revealed ground-glass opacities presenting with peripheral distribution in the bilateral lung and a huge mass shadow in the right iliopsoas muscle, which was not noted on PET conducted on February 27. This time, his P.S. ECOG was 4.

Assuming rapid exacerbation of combined pulmonary emphysema and fibrosis due to cancer progression in the lung, on April 12, pulse steroid therapy with intravenous methylprednisolone 1,000 mg/day for 3 days, nasal high flow therapy, and oral tolvaptan at 15 mg/day in addition to furosemide 20 mg/day were administered in combination. To manage the lower back pain, EBRT to the iliopsoas lesion was initiated with a dose of 50 Gy in 25 fractions from April 12 to May 20 under the prescription of analgesics and opioid (hydromorphone up to 4 mg/day).

Consequently, his respiratory symptoms gradually recovered, and the dose of prednisolone was successfully tapered to 10 mg/day, and then he was started on pembrolizumab 200 mg intravenously every 3 weeks from April 26. His pain gradually reduced. Finally, he recovered a normal gait and was discharged with good PS. ECOG of 1 from the hospital on June 1. After three courses of pembrolizumab, CT taken on July 19 showed a partial response of the primary lesion in the right lung and no regrowth at the right iliopsoas muscle. Pain was completely resolved.

After 3 courses of pembrolizumab, he developed grade 3 diarrhea as an immuno-related adverse event (irAE) and was administered prednisolone at 60 mg/day. After tapering prednisolone to 10 mg/day, we rechallenged the pembrolizumab from August 26. Despite two additional courses of pembrolizumab being administered, chest pain increased due to the progressive lung lesion but was well-controlled with the administration of opioids. The symptoms of MPS never recurred; however, he died of progressive disease in the lung 6 months after symptom onset of MPS.

3 | DISCUSSION

ALK rearrangement lung cancer accounts for 5% of all lung cancers, and the absolute number is small. Therefore, according to our best knowledge, there have been no reports of ALK rearrangement cases exhibited MPS to date. In our *Case 1*, although the primary lesion of the lung had shown a marked response to alectinib, the lesion in the right psoas muscle that had existed since the initial diagnosis was resistant to alectinib. Therefore, we had regarded this lesion as a different entity like a neurogenic tumor based on the initial image findings. Ishizuka et al.[5] reported an ALK rearrangement case with different responses to alectinib between the primary lesion and gastric metastatic lesion. Because immunostaining of the gastric lesion revealed that it retained ALK rearrangement even after the lesion had developed resistance to alectinib, the same as the psoas metastasis in our case, they hypothesized that the bypass of the signaling pathways might have been related to the development of resistance by the metastatic lesion. In our *Case 1*, intrathoracic lesions showed a marked response to ALK inhibitors, but the psoas lesion showed no sensitivity from the beginning of treatment. In retrospect, even if the lesion was asymptomatic, oligo-progression of metastatic lesion should have been taken into consideration, and aggressive pathologic diagnosis[6] and complete excision or RT should have been performed first. Recently, we reported the unique cytologic characteristics of the primary tumor in *Case 1*.[4] On the other hand, Zhang P et al.[7] reported a case diagnosed with NSCLC with concomitant intramuscular myxoma of the right psoas mimicking intramuscular metastasis based on the CT appearance, showing low-density, well-circumscribed, and homogenous but mild enhancement and the complaint of lumbar pain. They also emphasized the importance of histopathological diagnosis before starting definitive treatment.

Case 2 never showed abnormal findings in the iliopsoas muscles on CT or PET at the time of the initial diagnosis. However, during the following 2 months, a huge mass appeared with severe and difficult pain. Emergency EBRT was employed to control the pain and tumor growth while using continuous intravenous opioid administration.

Pembrolizumab monotherapy was initiated after pulse therapy with methylprednisolone for acute deterioration of combined pulmonary emphysema and fibrosis, and an oncological partial response was achieved with PS recovery to grade I. Although the patient finally died of progression of the pulmonary lesion, his MPS was well-controlled until he died. This may have been attributable to the antitumor effect of radiotherapy.[8]

Malignant psoas syndrome is a rare malignant condition presenting as lumbosacral plexopathy and painful fixed flexion of the hip. The syndrome presents as refractory lower back pain with several other neurological symptoms. The pain is difficult to control because it is a mixture of nociceptive and neuropathic pain, which indicates that treatment requires a versatile approach.[9]

Pain due to MPS is often refractory to multimodal analgesic treatment, including opioid analgesics.[10] If pain is uncontrolled with multimodal analgesic treatment, physicians should consider the use of neuraxial analgesia in cases of MPS to provide the best possible quality of life.[11] Takase et al.[12] reported that methadone (fourth-line opioid) may be considered a treatment option for MPS patients in whose pain is difficult to control.

Lung cancer was reported as rare primary sites for developing iliopsoas muscle metastasis through the treatment course. The metastasis develops quickly and causes a sudden decline in PS due to pain and motor disturbances, so early detection and, if possible, early complete resection of the intramuscular metastasis might be effective. However, the opportunity to encounter psoas muscle involvement as oligo-progression or oligo-metastasis like in our *Case 1* may be extremely rare; thus, symptom mitigation with opioids and/or radiation is usually recommended to improve PS and enable the continuation of systemic cancer treatment.

The treatment of MPS was achieved with the combination of pain control and control of the original malignant disease. The iliopsoas muscle metastasis associated with lung cancer may be sensitive to radiation therapy,[13] being effective in combination with opioid analgesic treatment. If a patient has difficulties in maintaining a supine position because of back pain and a problem receiving radiotherapy, epidural analgesia may be effective to maintain a supine position and complete radiotherapy without increasing opioid administration.[9]

4 | CONCLUSION

Early detection and aggressive pain control of iliopsoas metastasis in lung cancer patients may lead to significant improvement in the quality of life and further continuation of cancer therapy such as tyrosine kinase inhibitors (TKIs) or ICIs.

AUTHOR CONTRIBUTIONS

Ken Kodama: Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; supervision; visualization; writing – original draft; writing – review and editing. **Toru Momozane:** Investigation; resources; writing – review and editing. **Kaichi Shigetsu:** Investigation; resources; writing – review and editing. **Hiroshi Takehara:** Investigation; resources; writing – review and editing. **Takamasa Toyofuku:** Investigation; resources; software; visualization; writing – review and editing. **Kinji Nishiyama:** Data curation; supervision; writing – review and editing. **Genju Koh:** Investigation; supervision; writing – review and editing. **Kiyoaki Uryu:** Investigation; supervision; writing – review and editing.

FUNDING INFORMATION

None of the authors have any financial disclosures.

CONFLICT OF INTEREST STATEMENT

All authors have declared no conflict of interest.

DATA AVAILABILITY STATEMENT

Data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

This report was approved by ethics committee of Yao Municipal Hospital (approval no. 241122-173).

CONSENT

As this is case reports and patients died, written informed consents was obtained from patient's mother (Case 1) and patient's wife (Case 2) in accordance with the journal's patient consent policy.

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