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CASE REPORT

WILEY

Sarcoid-like reaction of the extrathoracic lymph node in a patient with lung adenocarcinoma treated with pembrolizumab

Shinkichi Takamori[1] | **Nobuki Furubayashi**[2] | **Kenichi Taguchi**[3] | **Taichi Matsubara**[1] | **Takatoshi Fujishita**[1] | **Kensaku Ito**[1] | **Masafumi Yamaguchi**[1] | **Ryo Toyozawa**[1] | **Takashi Seto**[1] | **Takahito Negishi**[2] | **Motonobu Nakamura**[2] | **Tatsuro Okamoto**[1]

[1]Department of Thoracic Oncology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan

[2]Department of Urology, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan

[3]Cancer Pathology Laboratory, National Hospital Organization Kyushu Cancer Center, Fukuoka, Japan

Correspondence
Shinkichi Takamori, Department of Thoracic Oncology, National Hospital Organization Kyushu Cancer Center, 3-1-1 Notame, Minami-ku, Fukuoka 811-1395, Japan.
Email: takamori@surg2.med.kyushu-u.ac.jp

Abstract

Immune checkpoint inhibitors (ICIs) have become the standard of care for the treatment of non-small cell lung cancer (NSCLC). With the increasing use of ICIs, clinicians should be familiar with their immune-related adverse events, including sarcoid-like reactions, which have been associated with the use of ICIs in patients with cancer. Sarcoid-like reactions are caused by uncontrolled T helper 1-mediated immune responses resulting from ICIs, but their pathophysiology is not fully understood. Sarcoid-like reactions are often clinically important because they mimic metastases from treated cancer. According to previous reports, sarcoid-like reactions are typically observed in intrathoracic locations (lung and/or mediastinal lymph nodes) and the skin. In this study, we report an extremely rare case of extrathoracic sarcoid-like reaction in the right external iliac lymph node following two cycles of pembrolizumab therapy in a patient with lung adenocarcinoma. The laboratory data and computed tomography images suggested that infectious and autoimmune diseases were not considered to be the causative agents. Residual bone metastasis might have caused T helper 1-mediated immune responses by pembrolizumab, and contributed to sarcoid-like reactions in the right external iliac lymph node. Sarcoid-like reactions should be considered in the differential diagnosis of patients with lung cancer treated with ICIs who exhibit worsening extrathoracic lymph node swelling. Clinicians should be cautious not to mistake extrathoracic sarcoid-like reactions of the lymph nodes for progression of the treated disease.

KEYWORDS

lung adenocarcinoma, lymph node metastasis, programmed death-ligand 1, sarcoid reaction

INTRODUCTION

Lung cancer is one of the most devastating neoplasms, and patient prognosis remains poor.[1] Immune checkpoint inhibitors (ICIs) targeting programmed death-1 and programmed death-ligand 1 have become the standard of care in the treatment of non-small cell lung cancer (NSCLC).[2–5] With the increasing use of ICIs, clinicians should be familiar with their immune-related adverse events such as sarcoid-like reactions, which have been associated with the use of ICIs in patients with cancer.[6] Sarcoid-like reactions are often clinically important because they mimic metastases from treated cancer.[6] According to previous reports, sarcoid-like reactions are typically observed in the lungs, thoracic lymph nodes, and skin.[7–11] In this study, we report an extremely rare case of extrathoracic sarcoid-like reaction of the lymph nodes following pembrolizumab administration mimicking oligometastasis from treated primary lung adenocarcinoma.

CASE REPORT

The patient was a 62-year-old woman with a 38-pack-year smoking history. In May 2018, the patient experienced left upper limb weakness and back pain. Brain magnetic resonance imaging (MRI) revealed a tumor in the right frontal lobe of the brain. In July 2018, she underwent resection of the tumor in the right frontal lobe of the brain. The pathological diagnosis was metastasis from lung adenocarcinoma. Epidermal growth factor receptor (EGFR) status was wild-type, and ≥95% of tumor cells expressed programmed death-ligand 1 (22C3). Chest computed tomography (CT) revealed a mass in the right upper lobe of the lungs (maximum diameter: 5.6 cm) and swollen right hilar and mediastinal lymph nodes (Figure 1(a); cT3N2M1c [BRA, OSS], cStage IVB). Baseline abdominal CT showed no lymph node swelling (Figure 1(b)). Lumbar MRI revealed extensive bone metastasis of the spine into the spinal canal from the level of the eleventh thoracic spine to the first lumbar spine. In August 2018, the patient underwent palliative radiotherapy (30 Gy/10 fractions) for the bone metastasis of the spine because of her back pain. In October 2018, the patient completed two cycles of pembrolizumab (200 mg/bodyweight) and achieved a partial response (tumor shrinkage rate: 33.6%). Owing to an immune-related adverse event (diarrhea; grade 2), pembrolizumab was discontinued. However, the effects of the drug had been monitored without any treatment for 1.25 years. In January 2020, CT revealed worsening of right external iliac lymph node swelling (Figure 1(c)). Positron emission tomography (PET) illustrated that the maximum standardized uptake value was 9.56 in the right external iliac lymph node (Figure 1(d)), and the accumulation of ^{18}F fluorodeoxyglucose activity in the primary lesion and bone metastasis of the spine was negative. The laboratory data showed no inflammatory findings, and CT images showed no abnormal findings in the bilateral lung fields. Infectious diseases (i.e., bacteria, fungi, and tuberculosis) as well as autoimmune diseases were not considered to be the causative agents. The right external iliac lymph node was suspected to be a metastasis from the primary lung adenocarcinoma. The patient underwent surgical resection of the right external iliac lymph node because the right external iliac lymph node was considered a single metastatic lesion. The pathological diagnosis was sarcoid-like reaction carrying no carcinoma cells (Figure 2). The patient has received no treatment, and she has visited our hospital with no recurrence for one year.

DISCUSSION

To the best of our knowledge, this is the first report of a case of extrathoracic sarcoid-like reaction of the lymph node following ICI administration in a patient with lung cancer.

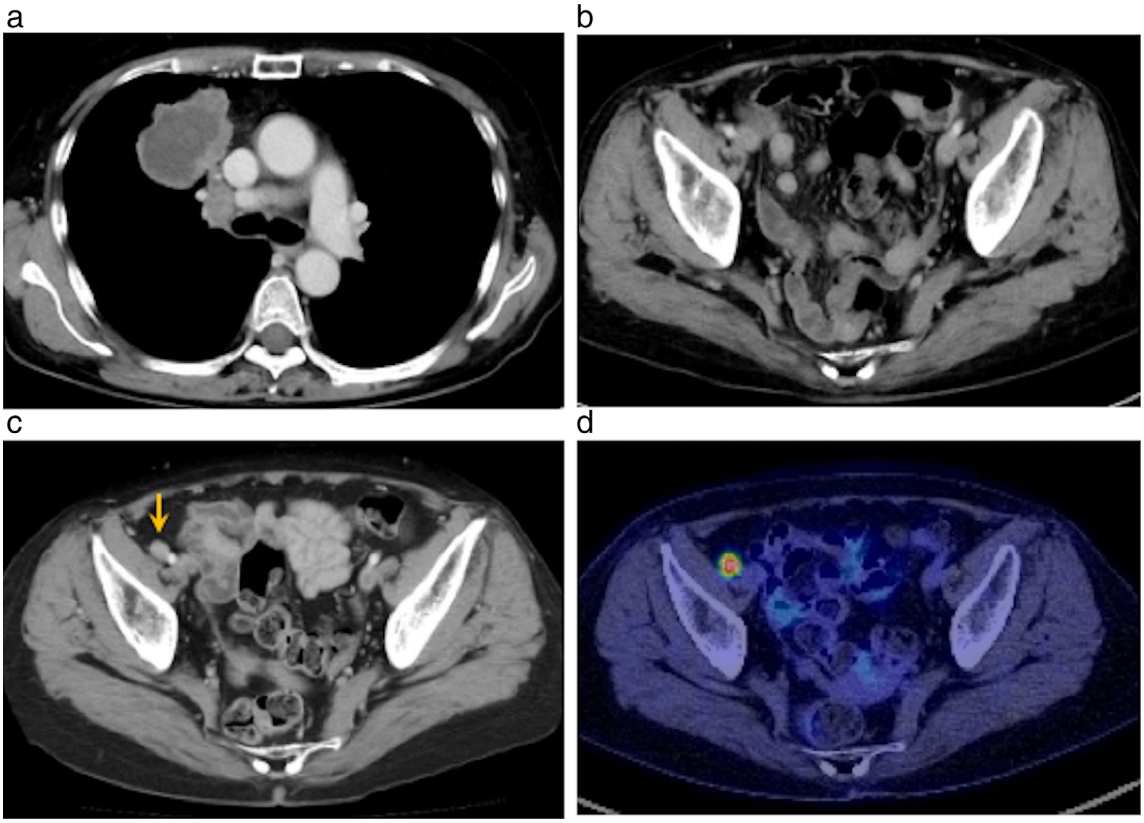

FIGURE 1 (a) Chest computed tomography (CT) revealed a mass in the right upper lobe of the lungs. (b) Baseline abdominal CT showed no lymph node swelling. (c) Abdominal CT and (d) positron emission tomography (PET) images revealed worsening of the right external iliac lymph node swelling (yellow arrow) with the accumulation of ^{18}F fluorodeoxyglucose activity

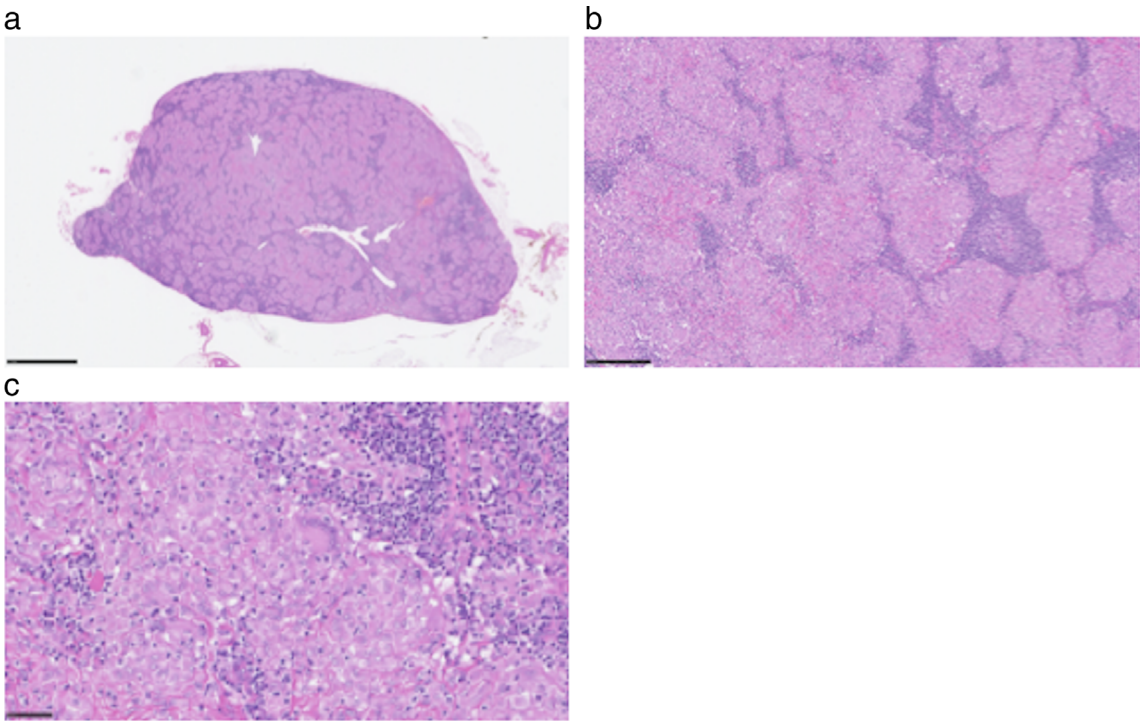

FIGURE 2 (a) Surgically resected right external iliac lymph node showing nodular lesions of epithelioid granulomata (scale bar: 2.5 mm, H&E). (b, c) The lymph node comprised lymphocytes and multinucleated giant cells without foreign bodies (scale bar: [b] 250 μm, [c] 50 μm, H&E). H&E, hematoxylin and eosin

Regarding the underlying pathophysiology of sarcoid-like reactions, uncontrolled T helper 1-mediated immune responses caused by ICIs may contribute to their occurrence, but their pathophysiology is not fully understood.[12] Several previous articles have reported ICI-associated sarcoid-like reactions in patients with lung cancer,[7–11] and all of the reactions arose in intrathoracic locations (lung and/or mediastinal lymph nodes) and the skin.[6] In this case, metastatic tumors were observed in the bone metastases from the level of the eleventh thoracic spine to the first lumbar spine, which means that cancer cells existed in the extrathoracic lesion. According to the previous report, bone metastasis is an independent worse prognostic factor in NSCLC patients treated with ICIs.[13] Residual bone metastasis might have caused T helper 1-mediated immune responses by pembrolizumab, and contributed to sarcoid-like reactions in the right external iliac lymph node in this case. In our search of the previous literature, we identified only one case of extrathoracic sarcoid-like reaction of the lymph nodes in a patient with melanoma who received nivolumab and ipilimumab.[14] In patients with lung cancer, extrathoracic sarcoid-like reactions of the lymph nodes following ICI therapy are extremely rare. Nevertheless, sarcoid-like reactions should be considered in the differential diagnosis of patients with lung cancer treated with ICIs who have developed ^{18}F fluorodeoxyglucose-avid extrathoracic lymph node swelling. Regarding a method to distinguish between a sarcoid-like reaction and metastasis from cancer, a blood test investigating tumor DNA may be helpful in diagnosing whether or not the swelling lymph node is metastasis from cancer given that the residual cancer cells could be detected by circulating tumor DNA.[15] In conclusion, clinicians should be cautious not to mistake extrathoracic sarcoid-like reactions of the lymph nodes for progression of a treated lung cancer.

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CONFLICT OF INTEREST

All authors declare no conflicts of interest in association with the present study.

ORCID

Shinkichi Takamori https://orcid.org/0000-0001-8175-6798
Takashi Seto https://orcid.org/0000-0002-2960-4364

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