

Case report

Radiation-induced sarcoma in a 10-year survivor with stage IV EGFR-mutated lung adenocarcinoma

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ARTICLE INFO

Keywords:

Radiation-induced sarcoma
Epidermal growth factor receptor
Lung adenocarcinoma
Radiation therapy
Palliative radiation therapy

ABSTRACT

A 70-year-old Japanese man with stage IV EGFR-mutated lung adenocarcinoma complained of right mild back pain. The patient had been heavily treated with several cytotoxic or molecular targeted agents for 10 years and received a palliative radiation therapy of 2nd sacral vertebra 5 years ago. Computed tomography showed the abnormal lesion in right iliopsoas muscle. A pathological examination confirmed undifferentiated pleomorphic sarcoma, consistent with the diagnosis of radiation-induced sarcoma (RIS). Since RIS is a rare late-onset complication of radiation therapy, to our knowledge, this is the first report of RIS that was associated with advanced lung cancer and detected after palliative radiation therapy. The careful long-term follow-up is thus necessary even after palliative radiation therapy and we have to be aware of the existence of RIS.

1. Introduction

Lung cancer remains the leading cause of cancer death worldwide. Molecular targeted drugs such as epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors (TKIs), however, have remarkably improved the clinical course for non-small cell lung cancer (NSCLC) patients with *EGFR* mutations. In a real-world setting, unfortunately, 5-year survival rate with stage IV EGFR-mutated NSCLC patients is still 13.8–14.6% [1,2].

Radiation therapy has become an important part of cancer therapy, and the majority of cancer patients have the experience of radiation therapy during the course of their disease. Radiation-induced sarcoma (RIS) is a rare late-onset complication of radiation therapy, usually developed in 8.4–10 years [3,4]. Since patients with advanced lung cancers rarely survive more than 10 years, RIS may be very rare in advanced lung cancer. We here present a 10-year survivor with stage IV

EGFR-mutated NSCLC developing radiation-induced sarcoma 5 years after the palliative radiation therapy.

2. Case report

In 2008, a 60-year-old Japanese man was first diagnosed with cT2N0M1 stage IV adenocarcinoma of the lung and multiple metastases including the brain and the 12th thoracic vertebra (Th12) (Fig. 1). Irradiation of the Th12 with a total dose of 45 Gy and gamma knife radiosurgery for the brain was performed, followed by treatment with carboplatin and paclitaxel as first-line therapy, cisplatin and S-1 as second-line therapy. The patient next received treatment with erlotinib from 2009 to 2014. After the disease progression of lung lesion was detected in computed tomography (CT) in 2014, a lung rebiopsy revealed an activating *EGFR* mutation (exon 19 deletion) without a secondary mutation (T790M) in exon 20. The patient decided to receive

Abbreviations: EGFR, epidermal growth factor receptor; CT, Computed tomography; RIS, Radiation-induced sarcoma; TKIs, tyrosine kinase inhibitors; NSCLC, non-small cell lung cancer; PET, Positron emission tomography

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<https://doi.org/10.1016/j.rmcr.2019.100889>

Received 11 March 2019; Received in revised form 16 June 2019; Accepted 17 June 2019

Available online 18 June 2019

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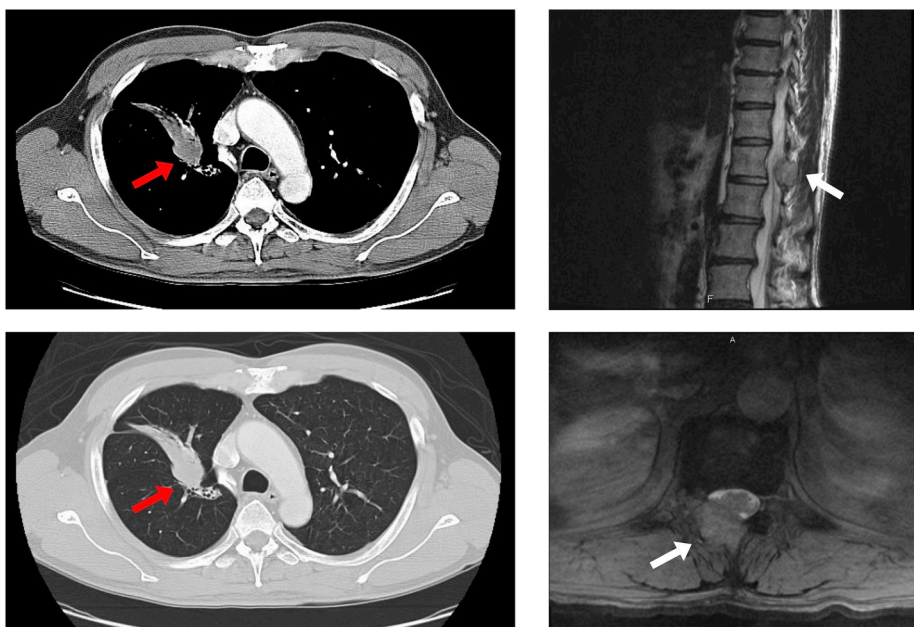


Fig. 1. Imaging findings of the initial diagnosis. Primary lung tumor in the right upper lobes on chest computed tomography (red arrow) and its metastatic lesion in 12th thoracic vertebra on spinal magnetic resonance imaging (white arrow). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

the treatment with afatinib in addition to docetaxel or pemetrexed from 2014 to 2017, even though EGFR-TKI failed to control the disease's progression.

Since pelvic pain, caused by bone metastases in 2nd lumbar vertebra (L2) and 2nd sacral vertebra (S2), was occurred in 2013, irradiation of L2 and S2 was performed with a total dose of 30 Gy, respectively (Fig. 2). In 2017, the disease progression of lung lesion was further developed in CT, and a liquid biopsy showed a secondary mutation (T790M) in exon 20 of *EGFR*. Treatment with osimertinib thus has been administered with partial remission.

In 2018, the patient, now aged 70 years, complained of right mild back pain, caused by the lesion with abnormally enhanced signals in right iliopsoas muscle in CT (Fig. 3A). Positron emission tomography (PET)-CT also confirmed the lesion with highly enhanced signals (Fig. 3B). Other lesion still showed partial remission with no change in serum tumor markers for lung cancer, whereas the lesion in right iliopsoas muscle progressed rapidly. A CT-guided biopsy and subsequent surgery of the tumor were performed.

A pathological examination revealed proliferation of atypical spindle cells in a random growth pattern (Fig. 4A). On immunohistochemical examination, most of the tumor cells were positive for CD34 (Fig. 4B), and only limited number of the tumor cells was faintly positive for EMA or desmin. By contrast, AE1/AE3, SMA and S-100 were negative. These findings indicate that the tumor does not have noticeable histologic features, and carcinoma with sarcomatous change is unlikely. In light of the morphological and immunohistochemical findings, undifferentiated pleomorphic sarcoma was diagnosed. Importantly, no *EGFR* mutations was detected by RT-PCR, indicating that the detected sarcoma is unrelated to the primary lung cancer. As the locoregional recurrence occurred 7 months later after the surgery, the patient received the radiation therapy, and is now under outpatient follow-up.

In summary, this patient had undergone radiation therapy, and the sarcoma histologically different from the primary tumor arose from the irradiated field, both of which are consistent with the disease definition of radiation-induced sarcoma.

3. Discussion

RIS is an uncommon late-onset complication of radiation therapy, with the risk ranges from 0.03% to 0.8% [4]. The common primary cancers were breast (34%), followed by lymphoma (18%) and genitourinary cancers (17%), but lung cancers represented only 2% [3]. As the mean latency period is 8.4–10 years [3,4], the patients with advanced lung cancer rarely survive long enough to arise RIS.

We here presented a 10-year survivor with stage IV EGFR-mutated NSCLC who had undergone palliative radiation therapy three times. RIS was located in the edge of irradiation region of S2. The total dose was 30 Gy in 10 fractions in the field of S2, but RIS arose in the region exposed to very low dose of around 2 Gy (Fig. 2C). Since there is no known safety threshold below which second malignancies do not occur, radiation-induced tumors could arise in tissues exposed to lower dose [5]. Although the aim of radiation therapy is to kill tumor cells, the cells in surrounding areas irradiated to sublethal cellular doses might survive with damage to double-strand DNA [6]. The resulting genomic instability could cause second malignancies including RIS. Indeed, one of the largest and longest studies based on Japanese atomic-bomb survivors has shown that the lower dose of radiation exposure less than 2 Gy developed soft-tissue sarcomas [7].

The histological characteristics of RIS were varied. Undifferentiated pleomorphic sarcoma (which previous term was malignant fibrous histiocytoma) was the most common diagnosis followed by angiosarcoma, fibrosarcoma and leiomyosarcoma [3,4]. It is difficult to histologically distinguish between RIS and sporadic soft-tissue sarcoma; however, the diagnostic criteria of RIS have been reported i) a history of radiation therapy at least three years prior to development of sarcoma, ii) the occurrence of sarcoma in the irradiation field and iii) the different histology between sarcoma and primary tumor [8,9]. Our case matches these criteria, although the latency period was relatively shorter than previous reports. Chemotherapy may shorten the interval to development of RIS [10]. Moreover, we have to distinguish whether the detected sarcoma is developed from the primary lung tumor or not. Epithelial-to-mesenchymal transition (EMT) including sarcomatous

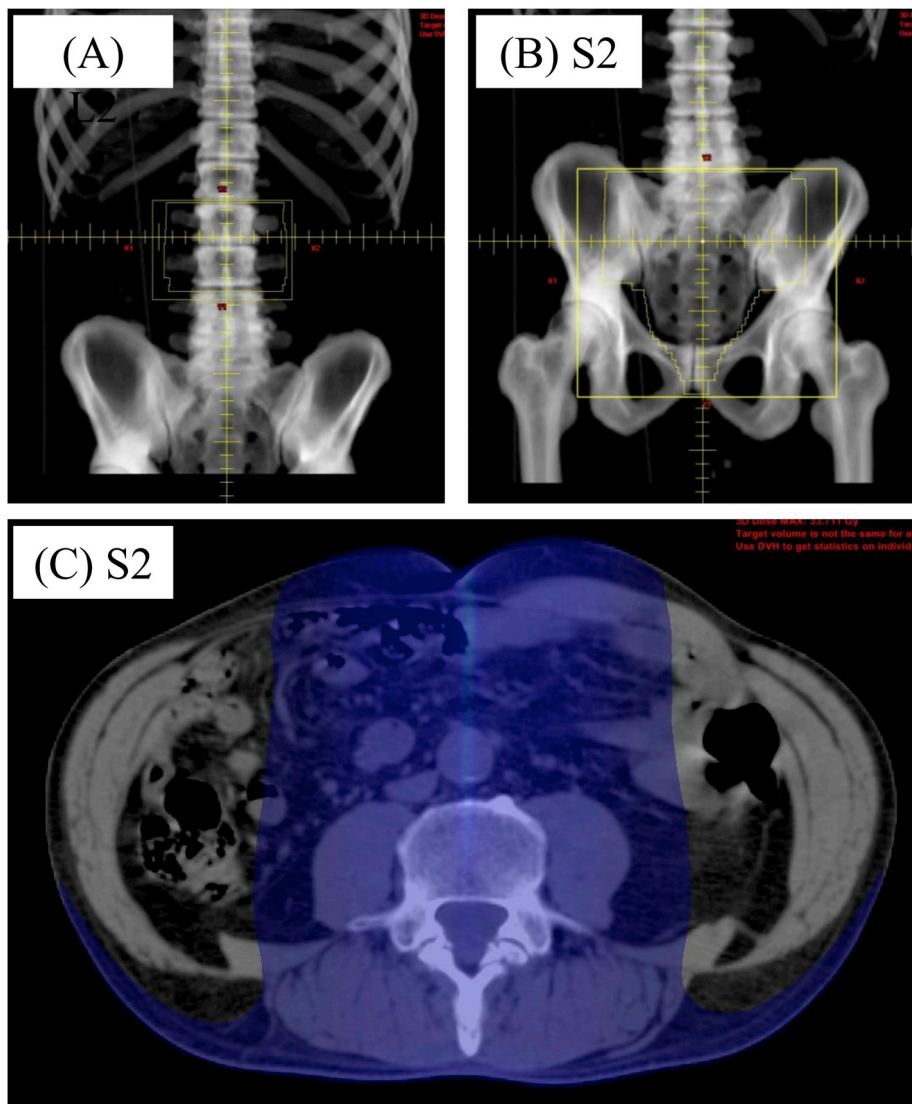


Fig. 2. Irradiation field of palliative radiation therapy. (A and B) Irradiation field of 2nd lumbar vertebra (L2) and 2nd sacral vertebra (S2). (C) Irradiation region of S2 with around 2 Gy including right iliopsoas muscle.

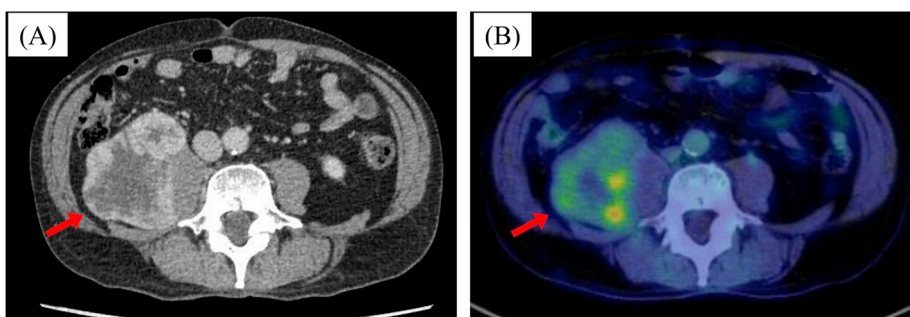


Fig. 3. Location of radiation-induced sarcoma (A) The lesion (red arrow) with abnormally enhanced signal in right iliopsoas muscle in computed tomography (CT). (B) The lesion (red arrow) with highly enhanced signal in right iliopsoas muscle in positron emission tomography (PET)-CT. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

transformation of metastatic lung adenocarcinoma has been reported as a cause of acquired resistance to EGFR-TKIs [11,12]; namely, the original genetic phenotype such as activating *EGFR* mutations is retained, despite EMT. In the present case, however, the genetic examination of the sarcoma revealed no mutations in *EGFR*, indicating that the detected sarcoma is not correlated with the primary lung cancer.

As immune therapy or molecular target therapy has shown

promising clinical activities in the treatment of advanced lung cancers, the patients with stage IV NSCLC can survive longer. Although several cases of RIS were reported in earlier-stage lung cancer [13–15], to our knowledge, this is the first report of RIS that was associated with advanced lung cancer and detected after palliative radiation therapy. The careful long-term follow-up is thus necessary even after palliative radiation therapy and we have to be aware of the existence of RIS.

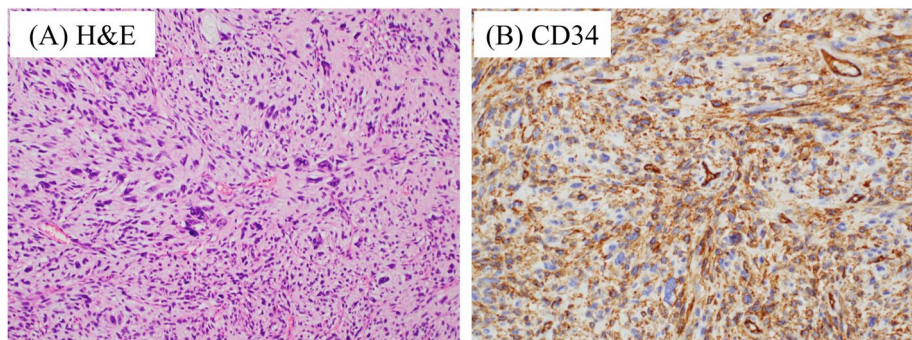


Fig. 4. Pathological and immunohistochemical examination.

(A) Tumor cells displaying proliferation of atypical spindle cells in a random growth pattern [Hematoxylin and eosin (H&E)]. (B) Most of the tumor cells displaying positive staining for CD34.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

The authors have no conflicts of interest.

Declarations of interest

None.

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