




CASE REPORT

EGFR-mutant lung adenocarcinoma associated with antisynthetase syndrome successfully treated with osimertinib

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Abstract

Here, we report a rare case involving a 66-year-old man with epidermal growth factor receptor (EGFR)-mutant lung adenocarcinoma and antisynthetase syndrome (ASS) treated with osimertinib. The patient presented with respiratory failure and bilateral pulmonary opacities; he was diagnosed with ASS accompanied by interstitial lung disease (ILD), consistent with paraneoplastic syndrome. After steroid pulse therapy, osimertinib was administered for lung adenocarcinoma without ILD exacerbation. Osimertinib could therefore be a treatment option for EGFR-mutant lung cancer with paraneoplastic ILD.

KEYWORDS

aminoacyl transfer RNA synthetase, interstitial lung disease, lung cancer

INTRODUCTION

For non-small cell lung cancer (NSCLC) harboring epidermal growth factor receptor (EGFR) mutations, tyrosine kinase inhibitors (TKIs) are superior to cytotoxic agents, mainly in terms of progression-free survival.^{1–5} Osimertinib is a third-generation EGFR-TKI approved for the first-line treatment of EGFR-mutant NSCLC and later-line treatment for EGFR T790M-positive NSCLC.

Pre-existing interstitial lung disease (ILD) is a risk factor for TKI-related ILD.⁶ While studies have shown that cytotoxic agents are relatively safe for lung cancer patients with ILD,⁷ evidence on the safety of TKIs is scarce.

Antisynthetase syndrome (ASS) is characterized by the presence of serum anti-aminoacyl-transfer RNA synthetase (anti-ARS) antibodies, myositis, fever, polyarthritis, Raynaud's phenomenon, mechanic's hand, and ILD.⁸ ILD is observed in 75%–95% of ASS cases, sometimes being its only initial manifestation.⁹ Patients positive for anti-ARS antibodies could have complex cancers, with a reported prevalence rate of 12%.¹⁰ In such cases, ASS is considered a paraneoplastic syndrome.

Here, we report a case involving a 66-year-old man with lung adenocarcinoma (cT2aN3M1c, stage IVB, EGFR gene mutation exon 21 L858R) accompanied by ASS-ILD, who was successfully treated with osimertinib.

CASE REPORT

A 66-year-old man with dyspnea was admitted to Osaka Toneyama Medical Center (day 1). He was a former smoker. His body temperature was 36.6°C. He had tachypnea and percutaneous oxygen saturation of 95% (with oxygen supply via a nasal cannula at a flow rate of 2 L/min). Physical examination revealed Raynaud's phenomenon in his limbs and fine crackles in both lungs, but there was no cutaneous manifestation or muscle weakness. Blood samples showed elevated C-reactive protein (CRP), lactate dehydrogenase (LDH), sialylated carbohydrate antigen (KL-6), carcinoembryonic antigen (CEA), and cytokeratin 19 fragment (CYFRA) levels. The creatine kinase (CK) level was normal, and antinuclear antibodies were not detected. The test for anti-ARS antibody was positive (anti-glycyl-tRNA

TABLE 1 Results of blood analysis and respiratory function test at the first admission

Blood analysis			Arterial blood gas analysis		
WBC	10 000/ μ l	CEA	315 ng/ml	pH	7.42
Neu	74.2%	CYFRA	16.9 ng/ml	PaCO ₂	35.1 mmHg
Eos	1.6%	BNP	8.1 pg/ml	PaO ₂	91.9 mmHg
RBC	495 \times 10 ⁴ / μ l	β -D-glucan	17.7 pg/ml	HCO ₃ ⁻	22.3 mmol/l
Hb	14.8 g/dl	CMV antigen	(-)	ABE	-1.1 mmol/l
Plt	34.3 \times 10 ⁴ / μ l	ANA	80	Respiratory function test	
AST	33 U/L	RF	5 IU/ml	FEV ₁	1.75 L
ALT	27 U/L	SS-A/Ro	(-)	%FEV ₁	56.3 %
LDH	338 U/L	PR3-ANCA	(-)	FEV ₁ %	84.5 %
BUN	20.1 mg/dl	MPO-ANCA	(-)	VC	2.03 L
Cre	1.05 mg/dl	ARS	120	%VC	52.1 %
Na	142 mEq/L	EJ	(3+)	FVC	2.07 L
K	5 mEq/L	SRP	(1+)	%FVC	54.6 %
Cl	105.6 mEq/L	MDA-5	(-)		
Ca	8.6 mg/dl	Scl-70	(-)		
TP	6.8 g/dl	Centromere	(-)		
Alb	3.3 g/dl	RNP	(-)		
CRP	2.38 mg/dl	ss-DNA	(-)		
CK	249 U/ml	ds-DNA	(-)		
KL-6	1903 U/ml				

Abbreviations: ABE, actual base excess; Alb, albumin; ALT, alanine transaminase; ANA, antinuclear antibody; ARS, anti-aminoacyl-tRNA synthetase antibody; AST, aspartate transaminase; BNP, brain natriuretic peptide; BUN, blood urea nitrogen; Ca, calcium; CEA, carcinoembryonic antigen; centromere, anticentromere antibody; CK, creatine kinase; Cl, chloride; CMV, cytomegalovirus; Cre, creatinine; CRP, C-reactive protein; CYFRA, cytokeratin 19 fragment; ds-DNA, anti-double stranded DNA antibody; EJ, anti-glycyl-tRNA synthetase antibody; Eos, eosinophils; FEV₁%, forced expiratory volume in 1 second percentage; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; Hb, hemoglobin; K, potassium; KL-6, sialylated carbohydrate antigen; LDH, lactate dehydrogenase; MDA-5, anti-melanoma differentiation-associated gene 5 antibody; MPO-ANCA, anti-myeloperoxidase-antineutrophil cytoplasmic antibody; Na, sodium; Neu, neutrophils; Plt, platelet count; PR3-ANCA, anti-proteinase 3-antineutrophil cytoplasmic antibody; RBC, red blood cell count; RF, rheumatoid factor; RNP, anti-ribonucleoprotein antibody; Scl-70, anti-scleroderma-70 antibody; SRP, anti-signal recognition particle antibody; ss-DNA, anti-single stranded DNA antibody; TP, total protein; VC, vital capacity; WBC, white blood cell count.

synthetase [anti-EJ] antibody [3+] and anti-signal recognition particle [anti-SRP] [1+], *EUROLINE* Myositis Profile 3, *EUROIMMUN*, Germany) (Table 1). A computed tomography (CT) scan of the chest revealed bilateral ground-glass opacities (GGOs) with consolidations, right lung pleural effusion, a nodule in the upper lobe of the right lung, and

mediastinal lymphadenopathies (Figure 1). Bronchoscopy was performed, and bronchoalveolar lavage fluid analysis at the right middle lobe (S4) showed that lymphocytes accounted for 80% of the total cells. Furthermore, histopathological examination of the mediastinal lymph node (4R) specimen revealed tumor cells with papillary structures

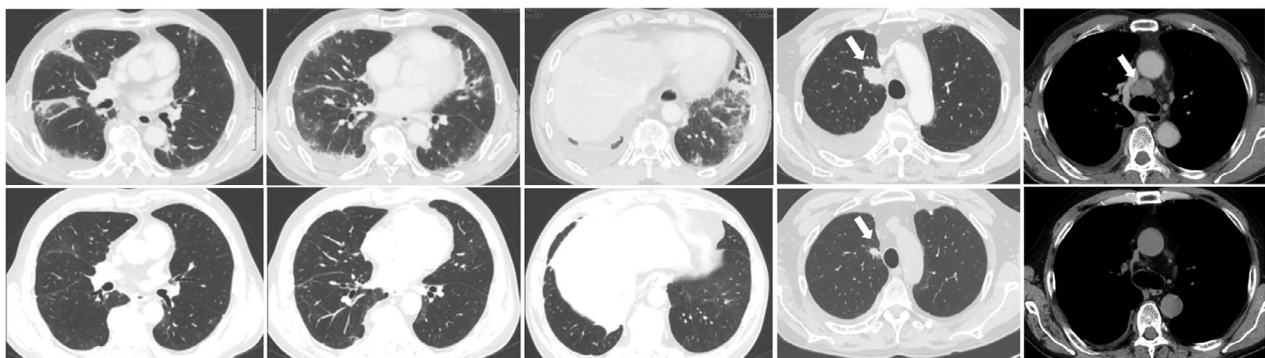


FIGURE 1 Chest computed tomography images from day 1 (upper row) and day 133 (lower row). First to the third column: bilateral ground grass opacities with mixed consolidations. Fourth column: nodule in the right upper lobe (arrow) and ipsilateral pleural effusion. Fifth column: enlarged mediastinal lymph node (arrow). All the above lesions showed an improvement on day 133 compared with that on day 1

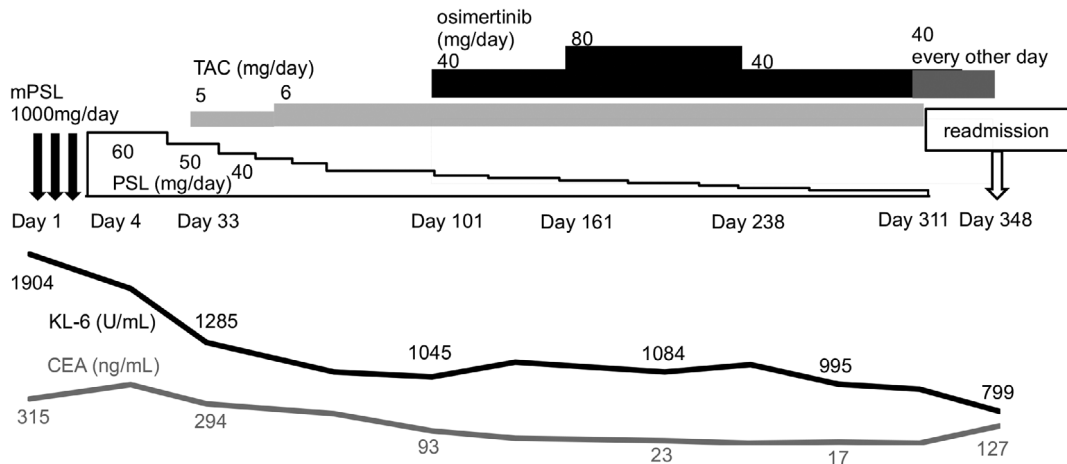


FIGURE 2 Clinical course of the patient. Steroid pulse therapy was initiated on day 1, followed by oral corticosteroid therapy. Tacrolimus was added on day 33 and terminated on day 314, and corticosteroid administration was stopped on day 342 after tapering. The KL-6 level gradually declined. Osimertinib was administered on day 101. After readmission on day 348, steroid pulse therapy and subsequent oral corticosteroid therapy combined with tacrolimus were administered again. Second-line chemotherapy was initiated on day 387. mPSL, methylprednisolone; PSL, prednisolone; TAC, tacrolimus; KL-6, sialylated carbohydrate antigen; CEA, carcinoembryonic antigen

that were positive for thyroid transcription factor-1 (TTF-1) and napsin A, determined by immunohistochemistry. He was diagnosed with adenocarcinoma (cT2aN3M1c, stage IVB, bone and brain metastases, and *EGFR* gene mutation exon 21 L858R), and ASS-ILD.

Methylprednisolone (1000 mg) was administered for three days, followed by oral prednisolone (60 mg/day) and tacrolimus (5 mg/day) (Figure 2). Subsequently, normalization of the CRP and LDH levels, decrease in the KL-6 and CEA levels, and radiological improvement on chest X-ray were observed. After stereotactic radiosurgery for brain metastases, osimertinib was initiated at 40 mg/day, and the patient was discharged. A CT scan was performed on day 133 (day 33 of osimertinib treatment), when the primary lesion showed a partial response, and bilateral interstitial opacities showed an

improvement. Thereafter, he developed renal dysfunction attributable to osimertinib; and the osimertinib dose was subsequently decreased to 40 mg every other day. Tacrolimus was terminated on day 314, and prednisolone was discontinued on day 342 after tapering.

On day 348, the patient was readmitted with fever and desaturation. Bilateral lung opacities and enlarged primary lung tumors consistent with progressive disease were observed (Figure 3). A blood test revealed elevated levels of the following which reflected tumor progression and recurrence of inflammation: CRP, 4.07 mg/dl; LDH, 357 U/L; KL-6, 799 U/ml; and CEA 12.7 ng/ml. After steroid pulse therapy followed by oral prednisolone and tacrolimus, second-line chemotherapy was initiated with carboplatin and nab-paclitaxel. The patient is currently receiving treatment.

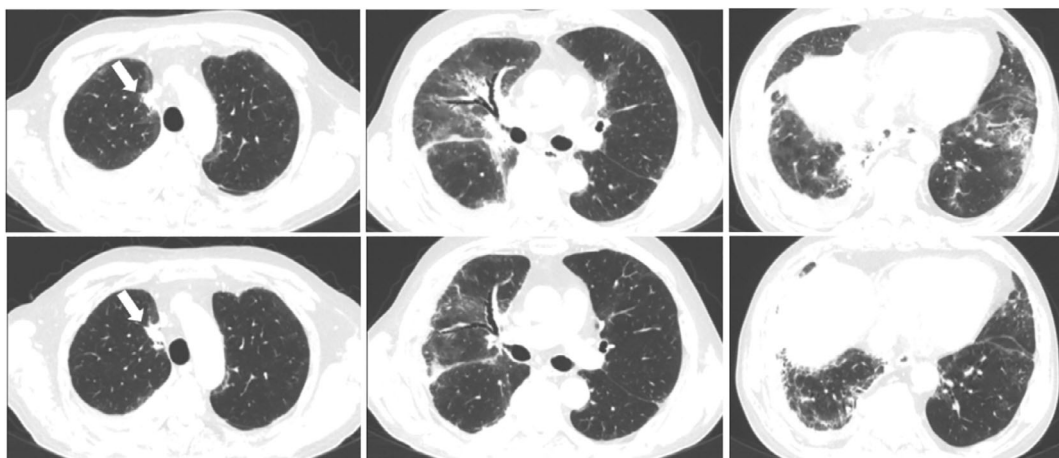


FIGURE 3 Chest computed tomography (CT) images from day 348 (upper row) and day 387 (lower row). Enlarged primary tumor of the lung (arrow) and recurring bilateral ground-glass opacities (GGOs) with consolidations were observed on day 348. On day 387, the primary lesion remained unchanged, and bilateral opacities resolved

DISCUSSION

The rate of cancer occurrence in patients with ASS is 1.7%–19.4%,^{11, 12} which is equivalent to, or higher than, that in the general population. According to a retrospective analysis of 165 Japanese patients with ASS, 19 had cancer, of which three had lung cancer.¹⁰ In case reports of ASS patients with NSCLC, ASS behavior was in parallel with that of tumors.^{13–15} In these cases, systemic corticosteroids were first administered to stabilize ILD. NSCLC was subsequently treated, and both complete tumor resection and cytotoxic chemotherapy with or without radiotherapy were effective. In our case, ASS, which was detected simultaneously with lung cancer, was considered a paraneoplastic syndrome. The patient was also first treated for ASS with corticosteroids and subsequently with systemic chemotherapy. As ASS was expected to be controlled by effective lung cancer treatment, we treated the patient with osimertinib because of its efficacy in systemic lesions. Consequently, tumor shrinkage was achieved without apparent drug-induced ILD. Although ASS-ILD remained under control after the discontinuation of corticosteroids, ASS-ILD recurred simultaneously with tumor progression, supporting the paraneoplastic origin of ILD.

Contrarily, a fatal exacerbation of ASS-ILD following nivolumab administration has been previously reported,¹⁴ indicating that chemotherapeutic use with ILD risks, such as immune checkpoint inhibitors, requires caution. In patients with NSCLC treated with osimertinib, the frequency of drug-related ILD has previously been reported to be 2%–4%.^{16, 17} In our case, we chose osimertinib owing to its efficacy in systemic lesions, after informing the patient about potential drug-induced ILD exacerbation. The patient did not experience drug-induced ILD until ASS-ILD recurrence with tumor progression.

Although TKI use in patients with ILD requires careful consideration, our case suggests that osimertinib could be a treatment option for *EGFR*-mutant NSCLC with paraneoplastic ILD.

CONFLICT OF INTEREST

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REFERENCES

- Maemondo M, Inoue A, Kobayashi K, Sugawara S, Oizumi S, Isohe H, et al. Gefitinib or chemotherapy for non-small-cell lung cancer with mutated *EGFR*. *N Engl J Med*. 2010;362:2380–8.
- Mitsudomi T, Morita S, Yatabe Y, Negoro S, Okamoto I, Tsurutani J, et al. Gefitinib versus cisplatin plus docetaxel in patients with non-small-cell lung cancer harbouring mutations of the epidermal growth factor receptor (WJTOG3405): An open label, randomised phase 3 trial. *Lancet Oncol*. 2010;11:121–8.
- Zhou C, Wu YL, Chen G, Feng J, Liu XQ, Wang C, et al. Erlotinib versus chemotherapy as first-line treatment for patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (OPTIMAL, CTONG-0802): A multicentre, open-label, randomised, phase 3 study. *Lancet Oncol*. 2011;12:735–42.
- Rosell R, Carcereny E, Gervais R, Vergnenegre A, Massuti B, Felip E, et al. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced *EGFR* mutation-positive non-small-cell lung cancer (EURTAC): A multicentre, open-label, randomised phase 3 trial. *Lancet Oncol*. 2012;13:239–46.
- Yang JC, Wu YL, Schuler M, Sebastian M, Papat S, Yamamoto N, et al. Afatinib versus cisplatin-based chemotherapy for *EGFR* mutation-positive lung adenocarcinoma (LUX-lung 3 and LUX-lung 6): Analysis of overall survival data from two randomised, phase 3 trials. *Lancet Oncol*. 2015;16:141–51.
- Yoneda KY, Shelton DK, Beckett LA, Gandara DR. Independent review of interstitial lung disease associated with death in TRIBUTE (paclitaxel and carboplatin with or without concurrent erlotinib) in advanced non-small cell lung cancer. *J Thorac Oncol*. 2007;2:537–43.
- Asahina H, Oizumi S, Takamura K, Harada T, Harada M, Yokouchi H, et al. A prospective phase II study of carboplatin and nab-paclitaxel in patients with advanced non-small cell lung cancer and concomitant interstitial lung disease (HOT1302). *Lung Cancer*. 2019;138:65–71.
- Yoshifuji H, Fujii T, Kobayashi S, Imura Y, Fujita Y, Kawabata D, et al. Anti-aminoacyl-tRNA synthetase antibodies in clinical course prediction of interstitial lung disease complicated with idiopathic inflammatory myopathies. *Autoimmunity*. 2006;39:233–41.
- Nakashima R, Imura Y, Hosono Y, Seto M, Murakami A, Watanabe K, et al. The multicenter study of a new assay for simultaneous detection of multiple anti-aminoacyl-tRNA synthetases in myositis and interstitial pneumonia. *PLoS One*. 2014;9:e85062.
- Hamaguchi Y, Fujimoto M, Matsushita T, Kaji K, Komura K, Hasegawa M, et al. Common and distinct clinical features in adult patients with anti-aminoacyl-tRNA synthetase antibodies: Heterogeneity within the syndrome. *PLoS One*. 2013;8:e60442.
- Hervier B, Devilliers H, Stanciu R, Meyer A, Uzunhan Y, Masseau A, et al. Hierarchical cluster and survival analyses of antisynthetase syndrome: Phenotype and outcome are correlated with anti-tRNA synthetase antibody specificity. *Autoimmun Rev*. 2012;12:210–7.
- Marie I, Hatron PY, Dominique S, Cherin P, Mouthon L, Menard JF, et al. Short-term and long-term outcome of anti-Jo1-positive patients with anti-Ro52 antibody. *Semin Arthritis Rheum*. 2012;41:890–9.
- Daido W, Yamasaki M, Morio Y, Funaishi K, Ishiyama S, Deguchi N, et al. A rare combination of dermatomyositis, interstitial pneumonia, and lung cancer in a patient treated with immunosuppressive therapy and chemotherapy. *Intern Med*. 2018;57:849–53.
- Mackintosh D, Islam MF, Ng J, Basham J. Immune checkpoint inhibitor use in antisynthetase syndrome. *Asia Pac J Clin Oncol*. 2019;15:266–9.
- Boletto G, Perotin JM, Eschard JP, Salmon JH. Squamous cell carcinoma of the lung associated with anti-Jo1 antisynthetase syndrome: A case report and review of the literature. *Rheumatol Int*. 2017;37:1203–6.
- Goss G, Tsai CM, Shepherd FA, Bazhenova L, Lee JS, Chang GC, et al. Osimertinib for pretreated *EGFR* Thr790Met-positive advanced non-small-cell lung cancer (AURA2): A multicenter open-label, single-arm, phase 2 study. *Lancet Oncol*. 2016;17:1643–52.
- Mok TS, Wu Y-L, Ahn M-J, Garassino MC, Kim HR, Ramalingam SS, et al. Osimertinib or platinum-pemetrexed in *EGFR* T790M-positive lung cancer. *N Engl J Med*. 2017;376:629–40.

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