Osimertinib for the Treatment of EGFR Mutation-Positive Lung Adenocarcinoma Complicated With Dermatomyositis

El osimertinib como tratamiento del adenocarcinoma de pulmón con mutación positiva del EGFR complicado con dermatomiositis

Dear Editor:

Dermatomyositis (DM) is a well-known inflammatory myopathy usually associated with malignant diseases, including lung cancer. However, there are few reports on epidermal growth factor receptor (EGFR) mutation-positive non-small cell lung cancer (NSCLC) complicated by DM; EGFR mutations in these cases are uncommon.[1,2] Osimertinib is a third-generation EGFR-tyrosine kinase inhibitor (TKI) generally used as first-line treatment for common EGFR mutation (i.e., exon 19 deletion/L858R)-positive NSCLC. Osimertinib therapy for DM-associated NSCLC has not been reported previously. Here, we report a case of EGFR exon 19 mutation-positive DM-associated lung adenocarcinoma treated with osimertinib. Informed consent was obtained from the patient, and the study was conducted in accordance with the Helsinki Declaration.

A 45-year-old Asian woman with a 26-pack-year smoking history presented with edema on her face and dorsal surface of her hands and feet, erythema over both eyelids (heliotrope rash, Fig. 1A), papules on the dorsal surface of the hands (Gottron's papules, Fig. 1B), and muscle weakness in both legs. She had a low-grade fever and both legs were tender to the touch. She had left cervical lymphadenopathy. Her serum creatine phosphokinase level was elevated (161 U/L), and magnetic resonance imaging of her legs showed myositis and fasciitis. Although the serum myositis-specific autoantibody levels were normal, she was diagnosed with DM.

Computed tomography and [18F]-fluorodeoxyglucose positron emission tomography showed a pulmonary nodule in the right lung; bilateral neck, supraclavicular, mediastinal, and hilar lymphadenopathy; and multiple hepatic nodules (Fig. 1C, D). Her serum carcinoembryonic antigen level was elevated (122.2 ng/mL). A biopsy of a left cervical lymph node revealed an adenocarcinoma. Immunohistochemical staining of the tumor specimen was positive for CK7 and TTF-1 and negative for p63 and the estrogen receptor. These results suggested that the lung was the primary site of the adenocarcinoma. Additional analysis of the tumor specimen revealed an EGFR mutation (exon 19 deletion).

After further investigation, the patient was diagnosed with primary lung adenocarcinoma, cT1bN3M1c, stage IVB, and DM. Treatment with osimertinib and prednisolone 20 mg per day was initiated. On follow-up three months later, the tumor lesions had shrunk markedly, and her serum carcinoembryonic antigen level was normal. The symptoms of DM also improved. She developed a mild rash as a side effect of osimertinib use but did not develop interstitial lung disease (ILD).

In this case report, we have presented two important clinical observations. First, common EGFR mutation-positive lung adenocarcinoma may occur in patients with DM. To our knowledge, this is the first English case report of common EGFR mutation-positive DM-associated NSCLC. The most common histopathological type of DM-associated lung cancer is small-cell lung cancer (44%); adenocarcinoma accounts for only 17% of the cases.[1] EGFR mutations are commonly associated with adenocarcinoma, which may be the reason EGFR mutation-positive DM-associated NSCLC is extremely rare.

Second, osimertinib may be safely used for EGFR mutation-positive NSCLC complicated with DM. EGFR-TKIs have been reported to induce ILD at a higher rate than cytotoxic anticancer drugs.[3] Moreover, in a large multicenter clinical trial, the incidence of ILD was reported to be higher in patients who received osimertinib than in those who received gefitinib,[4] especially in the Japanese subset.[5] As severe acute interstitial pneumonia often develops in DM patients, clinicians may hesitate to use osimertinib for DM-associated NSCLC. Our patient did not have DM-related ILD and did not develop osimertinib-induced ILD. Therefore, osimertinib may be used cautiously for patients with DM-associated NSCLC without DM-related ILD.

It is speculated that the mechanism underlying osimertinib-induced ILD is different from that underlying first or second generation EGFR-TKIs and may be associated with T cell activity.[6] More data should be accumulated to evaluate the safety of osimertinib therapy for NSCLC complicated with autoimmune diseases, including DM.

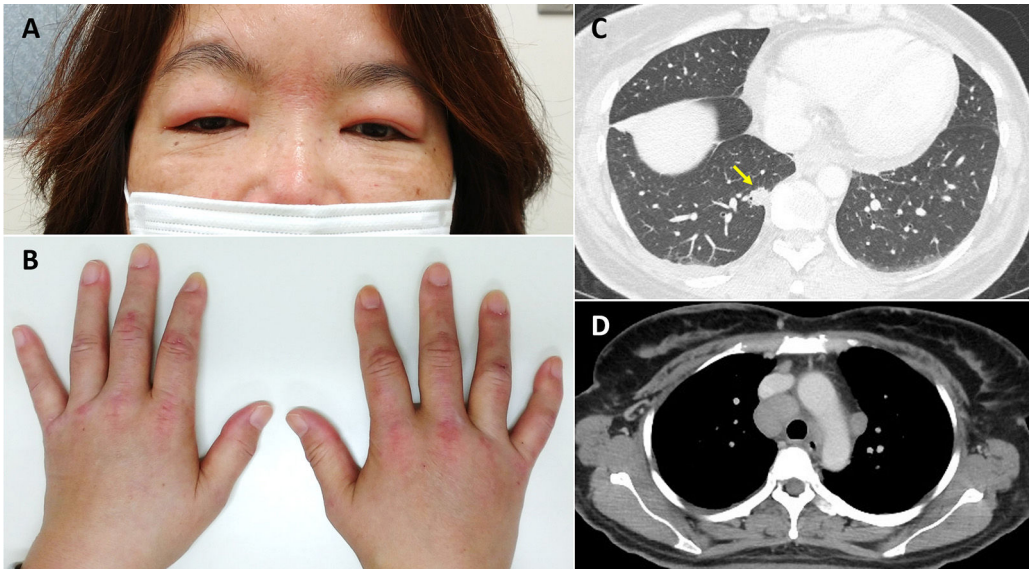

Fig. 1. (A, B) Dermatological findings after the first examination of the patient. (A) Visible erythema over both eyelids (heliotrope rash) with facial edema. (B) Papules (Gottron's papules) and edema on the dorsal surface of the hands are visible. (C) Chest computed tomography (CT) scan showing primary lesion in the right lung, lower lobe (arrow). (D) Chest CT scan showing mediastinal lymphadenopathy.

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Conflict of interest

The authors declare no conflict of interest.

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Adverse Events Associated With New Injectable-Free Multidrug-Resistant Tuberculosis Drug Regimens

Efectos adversos asociados a los nuevos tratamientos farmacológicos sin inyectables contra la tuberculosis multirresistente

Dear Editor,

Multidrug-resistant tuberculosis (MDR-TB) represents a global challenge. In 2018, 186,772 new cases of MDR-TB or TB resistant to rifampicin (RR-TB) were notified globally, resulting in an estimated incidence of 484,000 (95% confidence interval 417,000–556,000).[1] Mathematical modelling studies estimate the number of MDR-TB in children as between 25,000 and 32,000 annually, although it is suspected that <5% are identified and even less are correctly treated.[2]

Treatment outcomes for MDR-TB remain suboptimal. In the last 40 years only two new drugs for TB treatment have been licensed (bedaquiline and delamanid).[3] However, the World Health Organization (WHO) has recently updated its guidelines on MDR-TB treatment, as well as the SEPAR guideline updated in 2017.[4,5] They propose new drug combination regimens which exclude the second-line injectable agents and include bedaquiline, delamanid and other repurposed drugs such as linezolid and clofazimine in order to optimize safety and efficacy.[4] Bedaquiline is considered highly effective and is recommended in all MDR-TB regimens for adults and children > 6 years; however, it is expensive and not currently available in many European countries such as Spain. Bedaquiline dosing and safety studies are yet to be done in young children (<6 years). Linezolid is also recommended as a core agent with good activity against *M. tuberculosis* including extensively drug-resistant (XDR) strains. Fluoroquinolones (levofloxacin and moxifloxacin) complete the group of the most effective agents (Group A).[4] The major advantage is that they are all-oral regimens, increasing treatment feasibility and reducing severe adverse events such as ototoxicity and nephrotoxicity caused by the aminoglycosides. However, these new drug regimens are not exempt from adverse events and data on safety and efficacy in children are scarce.[2] We present a case of probable cycloserine-associated behavioural disturbance with neuromuscular symptoms, as well as intracranial hypertension secondary to levofloxacin in a child with MDR-TB.

A previously healthy, not BCG-vaccinated, Spanish six-year-old girl was diagnosed with tuberculosis (TB) following active household contact tracing. Her father, diagnosed with infectious MDR pulmonary TB, was the index case.

At diagnosis she was asymptomatic, with normal physical examination and a positive tuberculin skin test (induration of 13 mm). Left hilar enlarged lymph nodes were suspected on her chest-X-ray and bilateral enlarged mediastinal and hilar lymph nodes with bilateral lung nodules were detected on chest computed tomography (CT) (Fig. 1). Serial gastric aspirate specimens for acid-fast bacilli smear microscopy, PCR and mycobacterial culture were negative in the patient; however, *M. tuberculosis* cultures were positive in both her father and four-year old brother, with isolates showing resistance to isoniazid, rifampicin, pyrazinamide, ethionamide and streptomycin. These findings were sufficient for the diagnosis of MDR pulmonary TB, reserving the bronchoscopy in the event that the patient did not have a known TB contact or antimicrobial sensitivity pattern. Therefore, an injectable-free treatment regimen was initiated with levofloxacin (18.5 mg/kg/day), linezolid (14 mg/kg/day), clofazimine (100 mg every second day), cycloserine (18.5 mg/kg/day) and ethambutol (18.5 mg/kg/day).