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RESEARCH ARTICLE

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Complete remission following icotinib administration in an advanced ectopic thymic carcinoma patient harbouring the *EGFR* exon 19 deletion

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Abstract

Background: Ectopic thymic carcinoma (TC) is an extremely rare disease with a poor prognosis. The main treatment for early TC is surgery, although an effective treatment for advanced TC is lacking.

Methods: We present the case of a 61-year-old man with advanced posterior mediastinum thymic squamous cell carcinoma. Amplification refractory mutation system (ARMS)–polymerase chain reaction (PCR) analysis was used to investigate the molecular and mutational characteristics of this tumour.

Results: After chemotherapy and radiotherapy, the tumour showed disease progression. Immunohistochemistry revealed that the tumour was positive for CD117 (specific for primary TC), CK19, CD56 and Ki67. ARMS-PCR analysis revealed an *EGFR* exon 19 deletion in the patient. The patient subsequently received icotinib treatment and achieved complete remission for 3 years.

Conclusions: This case report suggests that tyrosine kinase inhibitors are a potential treatment strategy for patients with TC harbouring *EGFR* alterations.

KEYWORDS

EGFR, icotinib, thymic carcinoma, tyrosine kinase inhibitor

1 | INTRODUCTION

Thymic carcinoma (TC) is a rare disease that occurs in the anterior mediastinum. Accounting for only 0.06% of all malignancies, TC is highly aggressive with a poor prognosis. Few case reports have been published on ectopic TC.[1,2] The main treatment for early TC is surgery, although treatments for advanced thymic neoplasms have presented poor outcomes and no consistent benefit.[3] Targeted therapy has recently made great progress in treating solid tumours, whereas targeted therapies against TC are limited (because of its relative rarity). Epidermal growth factor receptor (EGFR) is a transmembrane tyrosine kinase that plays an important role in tumour development and progression.[4] Several studies have shown that the overexpression of *EGFR* is associated with poor progression-free survival (PFS) and poor overall survival in thymomas and TCs.[5,6] However, *EGFR* mutations have rarely been reported in TC. Icotinib,

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a highly selective EGFR-tyrosine kinase inhibitor (EGFR-TKI), has been approved as a first-line monotherapy in non-small-cell lung cancer (NSCLC) patients with somatic *EGFR* mutations.[7] Here, we report the first case of a posterior mediastinal TC with an *EGFR* exon 19 deletion that was successfully treated with icotinib.

2 | MATERIALS AND METHODS

In December 2015, a 61-year-old man with a cough and shortness of breath visited our hospital. The patient went on to develop life-threatening dyspnoea. The timeline of disease progression is shown in Figure 1. A chest computed tomography (CT) scan revealed a 10 × 3.6 × 2.6 cm area of soft tissue in the posterior superior mediastinum that had invaded the trachea and oesophagus, resulting in airway stenosis (Figure 1A). A tracheal stent was placed to relieve shortness of breath. Immunohistochemical staining for CD117 (specific for primary TC), CK19, CD56 and Ki67 was positive (Figure 2). The patient was diagnosed with stage IIIB poorly differentiated thymic squamous cell carcinoma. He was treated with four cycles of carboplatin (500 mg/day intravenously) and paclitaxel (250 mg/day intravenously), followed by radiotherapy (60 Gy) for 6 weeks. During re-examination, the CT scan showed a reduced mass, and the clinical efficacy was evaluated as a partial response (Figure 1B). In May 2016, the patient again experienced shortness of breath and cough, and a CT scan revealed tumour recurrence in the posterior superior mediastinum (Figure 1C). Although chemotherapy was repeated, the patient withdrew from the treatment because of the severe adverse effects of leukopenia. Then, an amplification refractory mutation system–polymerase chain reaction (PCR) using a collected pathological paraffin tissue section sample suggested a deletion mutation of *EGFR* exon 19 (Figure 3) and the patient was started on icotinib (375 mg/day) monotherapy.

3 | RESULTS

In June 2016, the productive cough and shortness of breath were relieved, and a CT scan showed remarkable shrinkage of the tumour and even disappearance of the masses. Clinical efficacy was evaluated as complete remission (CR) (Figure 1D). During treatment with icotinib, the patient experienced a skin rash adverse event, whereas no abnormalities in blood and major organ indexes were identified.

The patient was continually treated with icotinib until the last follow-up in October 2019 and showed no evidence of recurrence.

4 | DISCUSSION

Patients with advanced TC are not eligible for surgical resection. The 5-year overall survival of patients with unresectable TC is 0%, with a median survival rate of 28 months.[8] Although concurrent chemoradiation might be a more beneficial treatment, there is a potential risk of pulmonary damage.[9] The benefits of targeted therapy for solid tumours have been widely reported following the discovery of cancer driver genes. Shitara et al.[10] reported TC-specific mutations in several tyrosine kinase genes (including *KIT*, *DDR2*, *PDGFRA*, *ROS1* and *IGF1R*). Mutation analysis of EGFR pathway genes revealed that the EGFR pathway mutation was an independent factor leading to a low overall survival rate.[11] The low overall survival rate in patients with *EGFR* mutations might be improved with EGFR TKIs. However, although *EGFR* overexpression is common in TC, *EGFR* mutations are rare.[12]

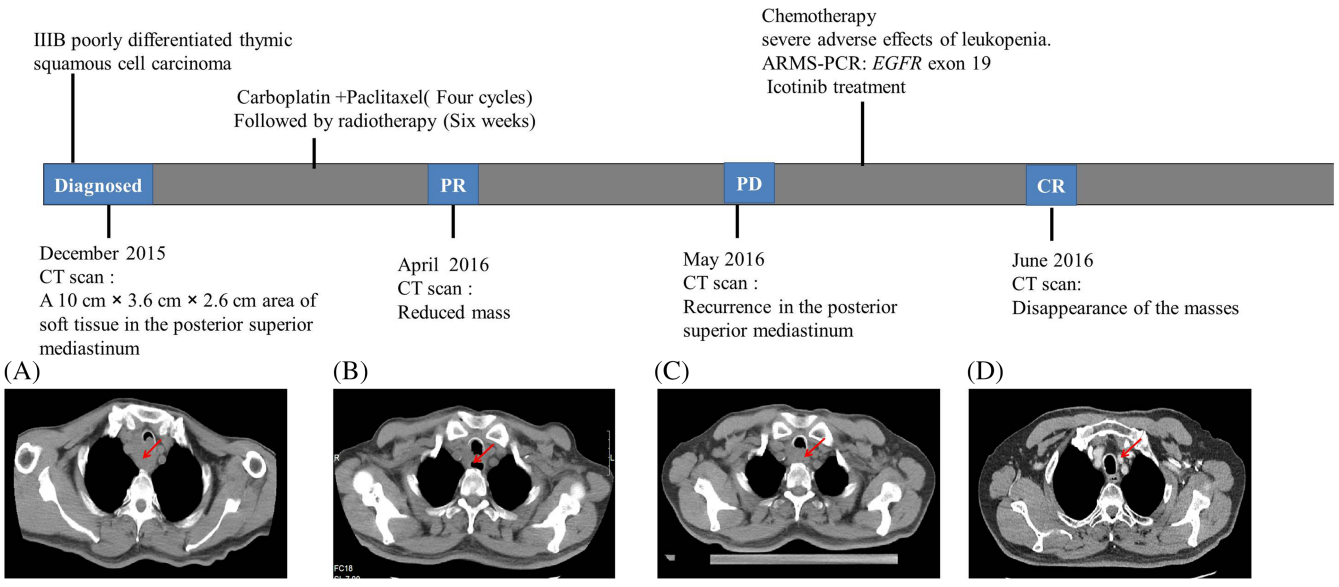

FIGURE 1 The timeline of disease progression. (A) Chest CT scan before carboplatin and paclitaxel treatment. (B) CT scan after four cycles of carboplatin and paclitaxel treatment and 6 weeks of radiotherapy treatment; the clinical efficacy was evaluated as a partial response. (C) CT scan at tumour recurrence in May 2016. (D) CT scan of complete remission after icotinib treatment

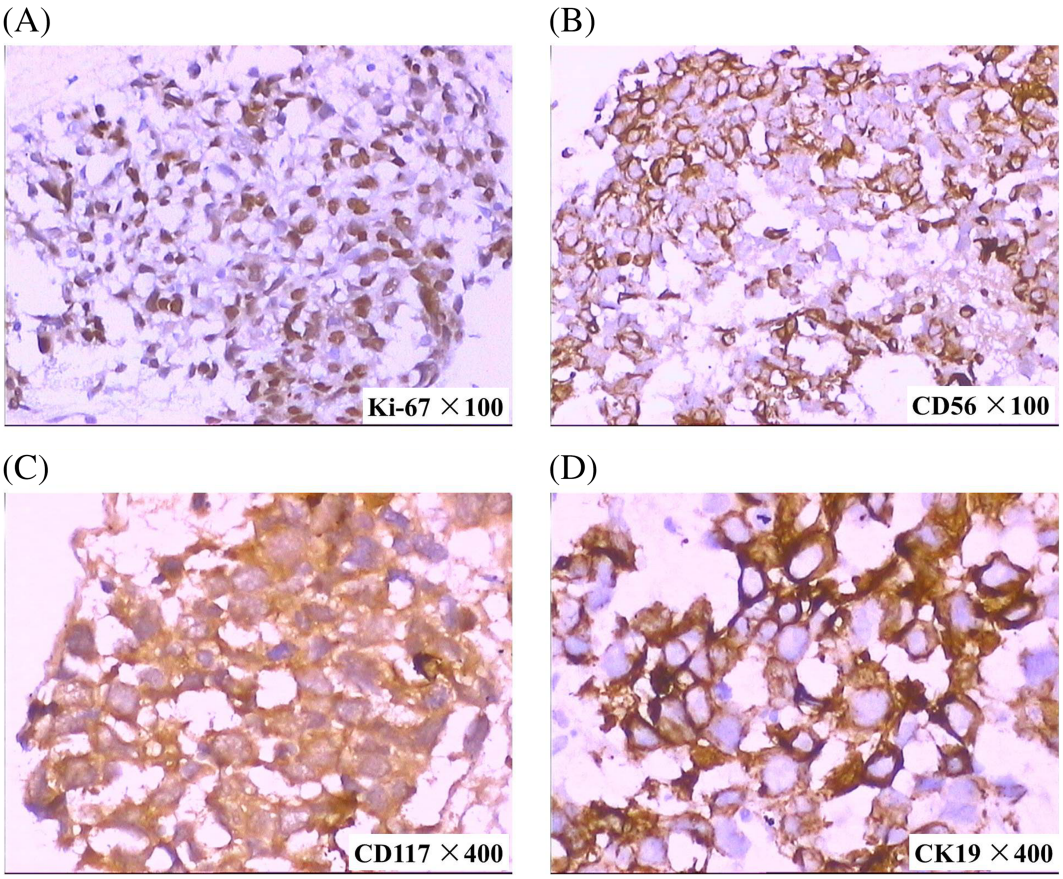

FIGURE 2 Biopsy pathology demonstrating thymic squamous cell carcinoma. Positive immunohistochemistry results for (A) Ki67 (100×), (B) CD56 (100×), (C) CD117 (400×) and (D) CK19 (400×)

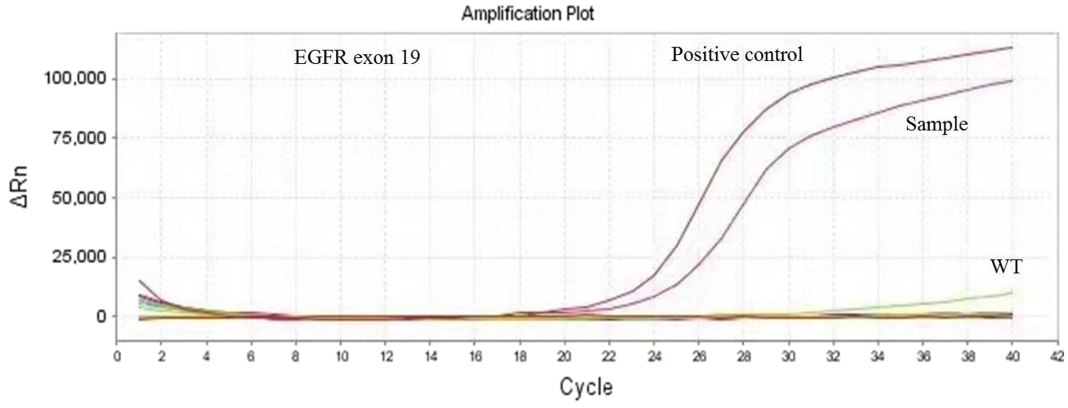

FIGURE 3 Amplification refractory mutation system–polymerase chain reaction suggested a deletion mutation of *EGFR* exon 19

EGFR overexpression has been shown to play an important role in the pathogenesis of TC and *EGFR* inhibitors have been successfully used to treat patients with TC.[13] Advanced thymic squamous cell carcinoma patients with an *EGFR* exon 20 insertion mutation were reported to respond to apatinib, achieving a PFS of 10 months.[14] He et al.[15] also reported that an advanced TC patient treated with apatinib after chemotherapy failure and multiple lung metastases achieved partial remission (PR) and PFS was 6.3 months. In a phase II study, 26 patients with advanced thymoma or TC were treated with gefitinib, with one patient achieving PR and 15 patients achieving stable disease; however, no patients achieved CR. DNA sequencing revealed no mutations in *EGFR* exons 18–21.[16] In another study, 18 patients with TC were enrolled to determine the effects of combined treatment with erlotinib plus bevacizumab on patients with

progressive malignant thymic tumours; however, limited activity was observed in thymic malignancies.[17] Co-mutations in *EGFR*-driven NSCLCs have been widely observed, and a shorter PFS was related to *ERBB2* and *MET* amplification or *TP53* mutation.[18] Further experiments are warranted to confirm that co-mutations, such as in *TP53*, will affect the response to *EGFR* inhibitors in TC. However, currently reported inhibitors targeting *EGFR* have not shown a consistent benefit for TCs.

Icotinib (Conmana, Betta Pharmaceuticals Co., Ltd, Hangzhou, China) is a self-developed first-generation EGFR-TKI and has been widely used in clinics in China.[19] A phase III ICOGEN trial confirmed its non-inferiority to gefitinib in terms of PFS, and it was approved for patients with NSCLC by the China Food and Drug Administration.[20] Preliminary experience suggests that cetuximab might be a useful therapeutic choice for advanced pre-treated thymic tumours with EGFR expression.[21] Anlotinib, a novel small molecule tyrosine kinase multitarget inhibitor, was approved by the China Food and Drug Administration as a third-line treatment for advanced NSCLC in May 2018. Anlotinib is a new oral small molecule multitarget TKI that can strongly inhibit signal pathways mediated by vascular EGFR (VEGFR), platelet-derived growth factor receptor (PDGFR) and fibroblast growth factor receptor (FGFR), as well as block tumour angiogenesis completely. A previous report demonstrated a case of an advanced thymic squamous cell carcinoma patient harbouring an *EGFR* exon 20 insertion who achieved stable disease with grade 2 hypothyroidism.[22] Further investigations are warranted to ascertain whether icotinib is associated with a more favourable outcome for TC compared to that with other first-generation EGFR-TKIs. Acquired resistance to first-generation EGFR-TKIs is common, and several resistance mechanisms, including T790M, *MET* amplification, *PIK3CA* and *BRAF* mutations, have been reported in NSCLC.[23] However, the mechanism underlying acquired resistance to *EGFR*-mutated TC has not been elucidated. Continuous follow-up of *EGFR*-mutated TC patients who respond well to EGFR TKIs might be helpful to clarify whether the mechanism of EGFR TKIs in TC is the same as that reported previously. In summary, we report an advanced TC patient with an *EGFR* exon 19 deletion who responded to icotinib, achieving CR for almost 40 months. This new therapeutic strategy could be used to treat TC patients harbouring *EGFR* mutations and might provide insights into the molecular mechanism of TC.

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AUTHOR CONTRIBUTIONS

All authors contributed to the study conception and design. XL designed the research study. YZ and YL performed the research and collected data. CL analysed the data and performed the investigation. JZ and XS wrote and revised the manuscript. TH revised and submitted the manuscript.

CONFLICT OF INTEREST STATEMENT

JZ, TH and XS declare personal fees from OrigiMed. The remaining authors declare that they have no conflicts of interest. The authors declare no conflicts of interest regarding drug selection.

DATA AVAILABILITY STATEMENT

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

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