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Case Report

Successful Conversion Surgery after Ceritinib Monotherapy in a Patient with Advanced Inflammatory Myofibroblastic Tumor Harboring SQSTM1-ALK fusion

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Abstract

Inflammatory myofibroblastic tumor (IMT) is an intermediate malignant neoplasm, and approximately 50% of patients are anaplastic lymphoma kinase positive (ALK$^+$). Given this unique trait, ALK tyrosine kinase inhibitors (TKIs), initially developed for ALK$^+$ nonsmall cell lung carcinoma, were expected to be effective. Subsequently, crizotinib, a first-generation ALK-TKI, was approved by the U. S. Food and Drug Administration, and other generations of ALK-TKIs have since been tested for their efficacy. In this study, we report a case of unresectable IMT who showed a partial response to ceritinib, a second-generation ALK-TKI, allowing conversion surgery to be performed. Furthermore, the patient was found to have a rare ALK translocation, sequestosome 1 (5)-ALK (20), detected by next-generation sequencing. In conclusion, this case presents real-world evidence to establish the role of ceritinib as a first-line treatment for ALK$^+$ IMT, which can contribute to further studies on ALK$^+$ IMT.

Keywords: Anaplastic lymphoma kinase, ceritinib, inflammatory myofibroblastic tumor, sequestosome 1-anaplastic lymphoma kinase translocation

Introduction

Inflammatory myofibroblastic tumor (IMT) has low rates of occurrence and metastasis,[1] with pathological characteristics of polymorphic inflammatory cell infiltration with a background of spindle cell proliferation under microscopy.[2] In terms of

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genetic alterations, anaplastic lymphoma kinase (ALK) rearrangements have been discovered in more than half of IMTs, with various fusion partners, such as RNA-binding protein 1, echinoderm microtubule-associated protein-like 4, and tissue inhibitor of metalloproteinases 3.[3]

Surgical resection is now considered the best way to treat local IMT, given that radiotherapy has only been reported as effective in sporadic case reports.[4,5] Nevertheless, systemic treatment should be considered for those with unresectable tumors.[6] Both conventional chemotherapy[7,8] and novel tyrosine kinase inhibitors (TKI)[9] may be used for advanced IMT. A retrospective analysis of 38 patients found that anthracycline-based regimens and methotrexate, and vincristine showed a response, with overall response rates of 47.6% and 53.8%, respectively.[8] In contrast, due to the rarity of IMT, ALK-TKIs have only been widely studied in ALK$^+$ nonsmall cell lung cancer (NSCLC), with limited studies on their use in IMT. Crizotinib, the first-generation ALK inhibitor, was officially approved for the treatment of ALK$^+$ IMT by the U. S. Food and Drug Administration (FDA) on July 14th, 2022.[9] However, the effectiveness of ALK inhibitors other than crizotinib has yet to be entirely determined.

This case report provides clinical evidence of the effectiveness of ceritinib, a second-generation ALK inhibitor, in a patient with IMT.

Case Report

This 42-year-old female patient had a liver tumor noted during a regular health checkup. Computed tomography (CT) imaging [Figure 1a-c] revealed a 7.3 cm mass at the hepatic hilum in December 2021, which was diagnosed as IMT through hepatic CT-guided needle biopsy. The pathology showed a spindle cell tumor with frequent nuclear atypia and heavy inflammatory cell infiltration [Figure 2a], and immunohistochemical (IHC) staining revealed strong positivity for ALK, which confirmed the diagnosis of IMT pathologically.

As complete surgical resection was impossible, the IMT was considered unresectable. Therefore, systemic treatment was suggested. Considering the financial status of the patient, systemic therapy with ceritinib (450 mg/day) was applied. After 2 months of treatment, CT [Figure 1d-f] showed a significant response with a reduction in size of approximately 50% from 7.3 cm to 4.0 cm, making surgical resection possible. No adverse events were reported throughout the course.

En bloc right lobectomy and cholecystectomy were performed in June 2022. The pathology showed aggregations of foamy histiocytes and chronic inflammatory cells, with no macroscopic venous invasion or microvascular invasion. Furthermore, IHC staining showed partial positivity for ALK [Figure 2b], indicating a "more than 50%" treatment effect.

After surgery, ceritinib was withheld due to financial considerations. No radiological evidence of tumor recurrence was noted at the last follow-up in August 2023. The good response to ceritinib implied that an ALK fusion was presented in the tumor, and so the surgical specimen was sent for next-generation sequencing (NGS, by ACTOnco, ACT Genomics, Taiwan) to identify the fusion partners with ALK. A translocation involving the ALK gene on exon 20 of

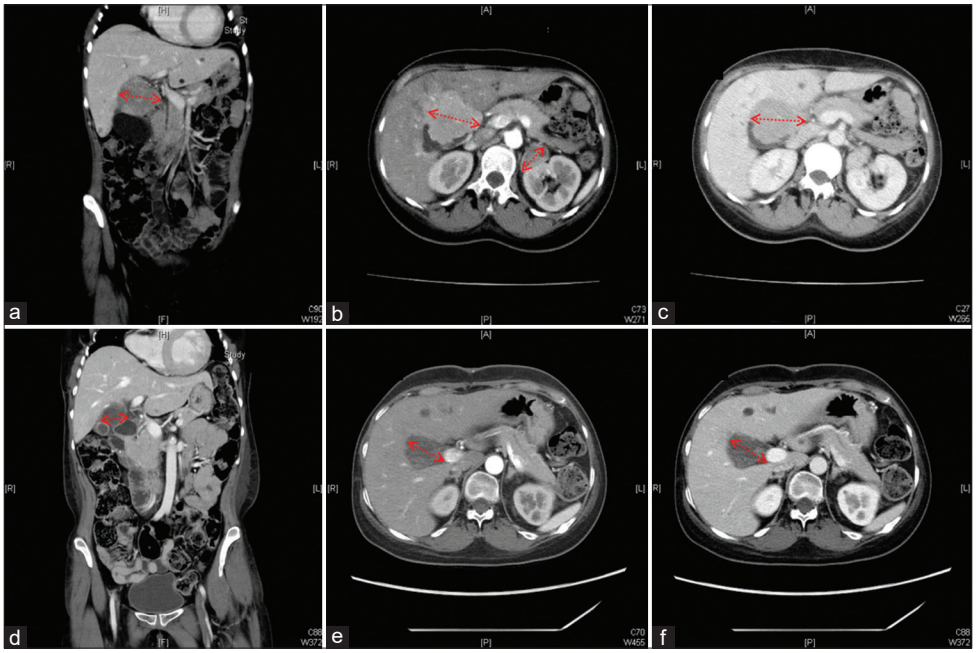

Figure 1: Computed tomography before (a-c) and after (d-f) ceritinib treatment. Coronal view (a), transverse view (b), and venous phase transverse plane (c) showed a 6.6 cm tumor at the hepatic hilum area before treatment. A 3.6 cm stationary mass at the suprarenal gland was also shown in the transverse view (b). Coronal view (d), transverse view (e), and venous phase transverse plane (f) showed a 3.9 cm tumor after 1 month of ceritinib treatment

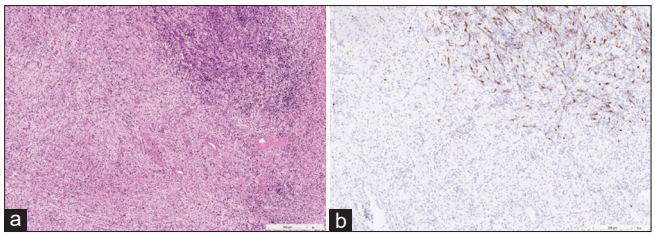

Figure 2: Pathological and IHC examinations| (a) Hematoxylin and eosin (H and E) stain (×4), revealed nuclear atypia in a spindle cell tumor with heavy inflammatory infiltration. (b) IHC stain (×4) showed partial positivity for anaplastic lymphoma kinase

chromosome 2 and the sequestosome 1 (SQSTM1) on exon 5 of chromosome 5 was subsequently identified.

Discussion

Given that ALK gene rearrangements have been confirmed in approximately 50% of IMTs,[10] ALK inhibitors have been used to treat IMT. The first such ALK inhibitor was crizotinib, which was shown to be efficacious and was approved by the U. S. FDA.[9] However, crizotinib-resistant IMTs have also been reported.[11] Therefore, second-generation ALK inhibitors were developed and showed success in treating ALK$^+$ NSCLC, overcoming tumors with ALK kinase domain mutations resistant to crizotinib.[12] In addition, another study also established that ceritinib could provide a better response than crizotinib in ALK$^+$ NSCLC, with 13.8 months and 8.3 months of progression-free survival (PFS) for ceritinib and crizotinib, respectively.[13] Based on the experience of ALK inhibitor treatment for ALK$^+$ NSCLC and no indication for crizotinib in Taiwan, ceritinib was suggested for this patient.

Regarding the genetic characteristics, NGS identified a translocation involving the ALK gene on exon 20 of chromosome 2 and SQSTM1 on exon 5 of chromosome 5. SQSTM1 is a gene that encodes the p62 protein, which can promote protein degradation through the ubiquitin-proteasome system and regulate cell survival through Nrf2 or NF-B. Sunga *et al*. reported the case of a female patient with SQSTM1-ALK IMT who was treated with alectinib as the first-line treatment and achieved more than 36 months of PFS.[14] However, to the best of our knowledge, the current report is the first to show the efficacy of ceritinib in a patient with SQSTM1-ALK translocation IMT.

In conclusion, this report provides real-world evidence of the use of ceritinib in a patient with ALK$^+$ IMT, and the results suggest that ceritinib may have potential not only as a second-line agent for crizotinib-resistant IMT but also as a first-line treatment for ALK$^+$ IMT. This may be a cornerstone for further studies on the sequential treatment of ALK$^+$ IMT.

Ethical approval

The study was approved by the Institutional Review Board of Linkou Chang-Gung Memorial Hospital, Protocol Number: IRB 202301009B0.

Declaration of patient consent

Patient consent to participate was not required because of the retrospective nature of this study, which was approved by the Institutional Review Board of CGMH (Protocol Number: IRB 202301009B0.) to conceal their identity, but anonymity cannot be guaranteed.

Data availability statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Nil.

Conflicts of interest

Dr. Chiao-En Wu , an editorial board member at *Journal of Cancer Research and Practice*, had no role in the peer review process of or decision to publish this article. The other authors declared no conflicts of interest in writing this paper.

References

1. Antonescu CR, Blay JY, Bovee JV, Bridge JA, Cunha IW, Dei Tos AP, *et al*. WHO Classification of Tumours: Soft Tissue and Bone Tumours. 5th ed., Vol. 3. Lyon: International Agency for Research on Cancer; 2020.
2. Rohrlich P, Peuchmaur M, Cocci SN, Gasselin ID, Garel C, Aigrain Y, *et al.* Interleukin-6 and interleukin-1 beta production in a pediatric plasma cell granuloma of the lung. Am J Surg Pathol 1995;19:590-5.
3. Siemion K, Reszec-Gielazyn J, Kisluk J, Roszkowiak L, Zak J, Korzynska A. What do we know about inflammatory myofibroblastic tumors? – A systematic review. Adv Med Sci 2022;67:129-38.
4. Najjar N, Patel H, Steinberg S, Baskovich B, Rothweiler S, Hoppe B. Very low-dose radiation therapy for management of inflammatory myofibroblastic tumor of the lung. Rare Tumors 2022;14:1-4.
5. Lisi R, Abate G, D'Urso P, Martinetti MT, Siniscalchi B, Marampon F, *et al.* Successful role of adjuvant radiotherapy in a rare case of tracheal inflammatory myofibroblastic tumor: A case report. Tumori 2019;105:P1-3.
6. Si X, Wang H, Zhang X, Wang M, You Y, Zhang L. Successful treatment of pulmonary inflammatory myofibroblastic tumor with platinum-pemetrexed: The first report of two cases. Thorac Cancer 2020;11:2339-42.
7. Kusunoki-Nakamoto F, Matsukawa T, Tanaka M, Miyagawa T, Yamamoto T, Shimizu J, *et al.* Successful treatment of an unresectable inflammatory myofibroblastic tumor of the frontal bone using a cyclooxygenase-2 inhibitor and methotrexate. Intern Med 2013;52:623-8.
8. Baldi GG, Brahmi M, Lo Vullo S, Cojocaru E, Mir O, Casanova M, *et al.* The activity of chemotherapy in inflammatory myofibroblastic tumors: A multicenter, European retrospective case series analysis. Oncologist 2020;25:e1777-84.
9. FDA Approves Crizotinib for Alk-Positive Inflammatory Myofibroblastic tumor; 2022. Available from: https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-crizotinib-alk-positive-inflammatory-myofibroblastic-tumor. [Last accessed on 2023 Mar 26].
10. Coffin CM, Patel A, Perkins S, Elenitoba-Johnson KS, Perlman E, Griffin CA. ALK1 and p80 expression and chromosomal rearrangements involving 2p23 in inflammatory myofibroblastic tumor. Mod Pathol 2001;14:569-76.
11. Tsakiri K, Kotoula V, Lakis S, Müller J, Fostira F, Bobos M, *et al.* Crizotinib failure in a TPM4-ALK-rearranged inflammatory myofibroblastic tumor with an emerging ALK kinase domain mutation. JCO Precis Oncol 2017;1:1-7.
12. Somasundaram A, Socinski MA, Burns TF. Personalized treatment

of EGFR mutant and ALK-positive patients in NSCLC. Expert Opin Pharmacother 2014;15:2693-708.
13. Tan DS, Araújo A, Zhang J, Signorovitch J, Zhou ZY, Cai X, *et al.* Comparative efficacy of ceritinib and crizotinib as initial ALK-targeted therapies in previously treated advanced NSCLC: An adjusted comparison with external controls. J Thorac Oncol 2016;11:1550-7.
14. Sunga CG, Higgins MS, Ricciotti RW, Liu YJ, Cranmer LD. Inflammatory myofibroblastic tumor of the mesentery with a SQSTM1:ALK fusion responding to alectinib. Cancer Rep (Hoboken) 2023;6:e1792.