Exceptional Response to MEK Inhibition in a Patient With RAF1-Mutant Myxofibrosarcoma: Case Report and Mechanistic Overview

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Introduction

Myxofibrosarcoma (MFS) is a subtype of soft-tissue sarcoma (STS) that is characterized by slow-growing, painless masses. Treatment options are limited for advanced MFS, and patients with metastatic disease often have poor outcome with chemotherapy.[1] Integration of comprehensive genomic profiling (CGP) into the clinic provides alternative approaches these patients.[2,3] To date, several studies elucidated genomic landscape of MFS,[4-6] with frequent alterations in *TP53*, *CDKN2A/B*, *RB1*, and *ATRX* genes.[6] However, further investigations are required to assess the efficacy of targeted therapies in patients with MFS.

RAF1, encoding c-Raf protein, is a serine-threonine kinase involved in the mitogen-activated protein kinase (MAPK) signaling. MAPK signaling regulates diverse biological processes, such as cell proliferation, apoptosis, differentiation, and angiogenesis.[7] *RAF1* alterations are attractive targets for precision oncology because of the major contribution of MAPK pathway dysregulation in cancer pathogenesis and progression.[8,9] *RAF1* alterations are observed in 2.3% of the The Cancer Genome Atlas (TCGA) PanCancer Atlas samples.[10,11] Activating germline *RAF1* point mutations are also frequently observed in RASopathies, such as Noonan and LEOPARD syndromes.[12]

Activating *RAF1* alterations include fusions, amplifications, and point mutations.[13] Alterations that increase *RAF1* activity promote tumorigenesis through hyperactivation of the MAPK pathway.[14] Consequently, MAPK-targeted therapies have shown to be a rational treatment strategy in *RAF1*-altered tumors.[15,16] Although the clinical efficacy of MAPK-targeted therapies in melanomas harboring *RAF1* fusions has been demonstrated,[17-19] data regarding the activating *RAF1* point mutations in cancer are limited.[20]

Here, we present a case of a heavily pretreated, chemotherapy-refractory patient with advanced myxofibrosarcoma, whose tumor harbored *RAF1 S259P* mutation and *CDKN2A/B* loss and achieved complete radiological response on treatment recommended by our Molecular Tumor Board (MTB), that is, the MEK inhibitor trametinib and the CDK4/6 inhibitor palbociclib. The combination was well tolerated, and the patient showed impressive clinical improvement. Tumor clearance was confirmed by circulating tumor DNA monitoring. Our case suggests that activating *RAF1* point mutations may be biomarkers of MEK inhibitor response. Moreover, it demonstrates the pivotal role of the MTB for CGP interpretation in the clinics.

Methods

Informed Consent

The patient provided written informed consent for tests, treatment, and publication.

Western Blot

The cDNAs encoding RAF1 mutants were generated by PCR and inserted into pCDNA3.1(+) vector with N-terminal FLAG tag. Plasmids were transfected into 293T cells by using

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Data Supplement

Visual Abstract

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lipofectamine 2000 (Invitrogen), and 293T transfectants were lyzed at 48 hours after transfection for measuring ERK signaling by anti–phospho-ERK1/2 immunoblot. The S257L mutant of RAF1 serves as a positive control. The anti–phospho-ERK1/2 antibody was purchased from Cell Signaling Technologies (4370), anti-ERK1/2 antibody from Santa Cruz Biotechnology (c-514302), and anti-FLAG antibody from Sigma-Aldrich (F3165).

Case Presentation

This is a 60-year-old female patient with a history of breast cancer in 2013, for which she had bilateral mastectomy and received six cycles of docetaxel, doxorubicin, and cyclophosphamide, followed by radiotherapy and tamoxifen. In 2022, the patient went to an outside institution with left hip pain. She was diagnosed with myxofibrosarcoma accompanied by extensive liver metastasis. She received two cycles of ifosfamide/mesna/doxorubicin, but the tumor progressed. She switched to ifosfamide/gemcitabine/docetaxel, which was poorly tolerated; ifosfamide was discontinued. The tumor progressed on three cycles of gemcitabine and docetaxel. PD-L1 tumor proportion score was found to be 60%, and she received pembrolizumab; however, no response was observed, and she started receiving pazopanib.

On progression with pazopanib, she was admitted to our clinic, and FoundationOne Heme test (see Methods) was recommended. Tumor mutational burden 2 muts/mb, microsatellite stable, *RAF1* S259P mutation, *CDKN2A/B* loss, and *TP53* C229fs*1 were detected. She also had a PD-L1 score of 20% and combined positive score of 25% as measured by Ventana SP263 assay. *RAF1* mutation was confirmed to be somatic by additional germline testing. Our MTB recommended trametinib and palbociclib combination on the basis of the findings, which was initiated after informed consent.

Initially, the patient received 1 mg once daily trametinib and 3 weeks-on and 1 week-off 75 mg once daily palbociclib. She tolerated the combination well in the first 2 months; however, she developed neutropenia and upper airway infection; thus, palbociclib was discontinued for 20 days. 75 mg/day in palbociclib was reintroduced in a 1 day-on, 1 day-off manner and was well-tolerated. After 2 months, complete remission was observed with fluorodeoxyglucose positron emission tomography-computed tomography (Fig 1). Patient's performance status was improved (Eastern Cooperative Oncology Group [ECOG] 0) compared to initial presentation (ECOG 1-2). Further confirmation of the tumor regression was achieved with molecular residual disease (MRD) testing (Signatera [see Methods]). The latest check was done with MRD test and imaging studies in August 2023 which confirmed the complete response, ongoing for 11 months with 8-month disease-free survival.

To investigate the activity of RAF1 S259P mutant, we performed western blot. Constitutively, active RAF1 S257 mutant was used as a positive control. RAF1 S257L and RAF1 S259P mutants were expressed in HEK293T cells, and phospho-ERK1/2 (p-ERK1/2) levels were assessed. Overexpression of RAF1 S259P resulted in increased p-ERK1/2 levels, which was even higher than the S257L mutant.

Discussion

This case report demonstrates the critical role of next-generation sequencing/CGP in clinical practice and therapeutic decision making. Patients with rare tumor types can benefit immensely from targeted treatments, and the MTB should be an integral part of the CGP evaluation and treatment design. Our case also suggests that activating *RAF1* point mutations may be potential biomarkers for MEK inhibitor response. A synergy between MAPK pathway inhibitors and CDK4/6 inhibitors was possibly in play as well, supporting previous studies in patients harboring both MEK and cyclin pathway alterations.[21-23]

To the best of our knowledge, this case represents the first case of patient-tailored combination therapy in a patient

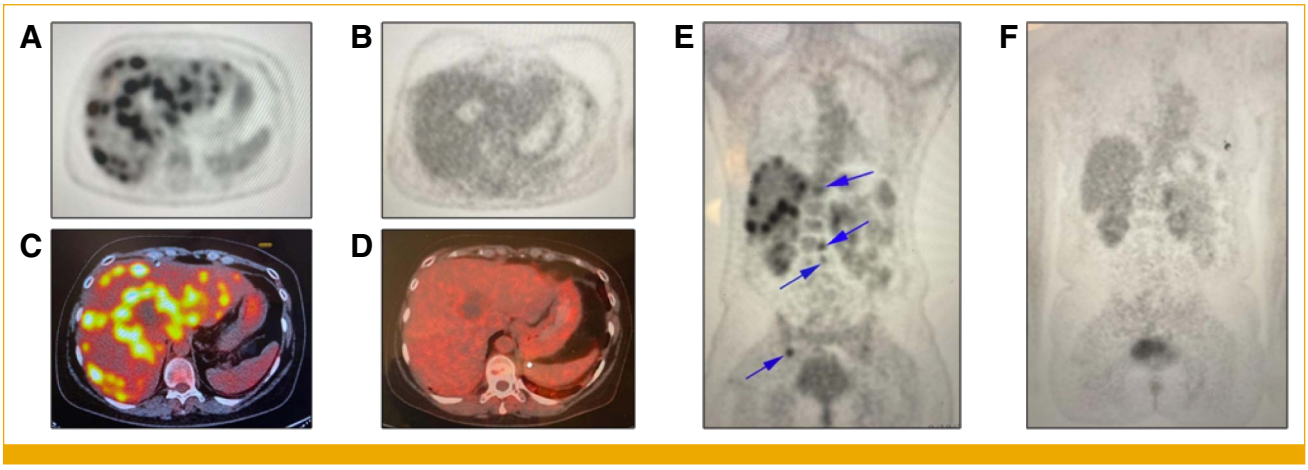

FIG 1. Radiological follow-up of the patient through 2 months of treatment course. (A, C, and E), Before and (B, D, F) after.

with STS harboring an activating *RAF1 S259P*. *RAF1 S259* mutations are especially prevalent in RASopathies, such as Noonan and LEOPARD syndromes,[12] and were shown to be activating.[24] Our MTB, composed of medical oncologists, molecular biologists, pathologists, and radiologists, evaluated the potential role of the *RAF1 S259P* mutation in tumorigenesis and treatment response. S259 is a critical residue that regulates the activity of RAF.[2] RAF1 is in autoinhibited state before activation of RAS. In this state, RAF1 S259 is phosphorylated and bound by 14-3-3 proteins, preventing activation of RAF1 and its recruitment to the plasma membrane.[25,26] On RAS activation (we refer to activated RAS as RAS-GTP), RAF1 interacts with RAS-GTP through its RAS-binding domain (RBD) and is recruited to the plasma membrane. This induces repositioning of cysteine-rich domain of the RAF1, which also modulates RAS-GTP:RAF1 interaction.[27] Through this interaction, S259 is dephosphorylated and RAF1 is primed for activation. SHOC2 complex is one of the diphosphatase complexes mediating this event. RAF1 forms dimers with other RAF proteins to become fully activated[28] (Fig 2).

Phosphorylation of the 259th residue was expected to be lost as proline is not a target for kinases, unlike serine. The presence of a phosphate group in S259 was shown to be required for RAF1 autoinhibition.[24] Moreover, crystal structure

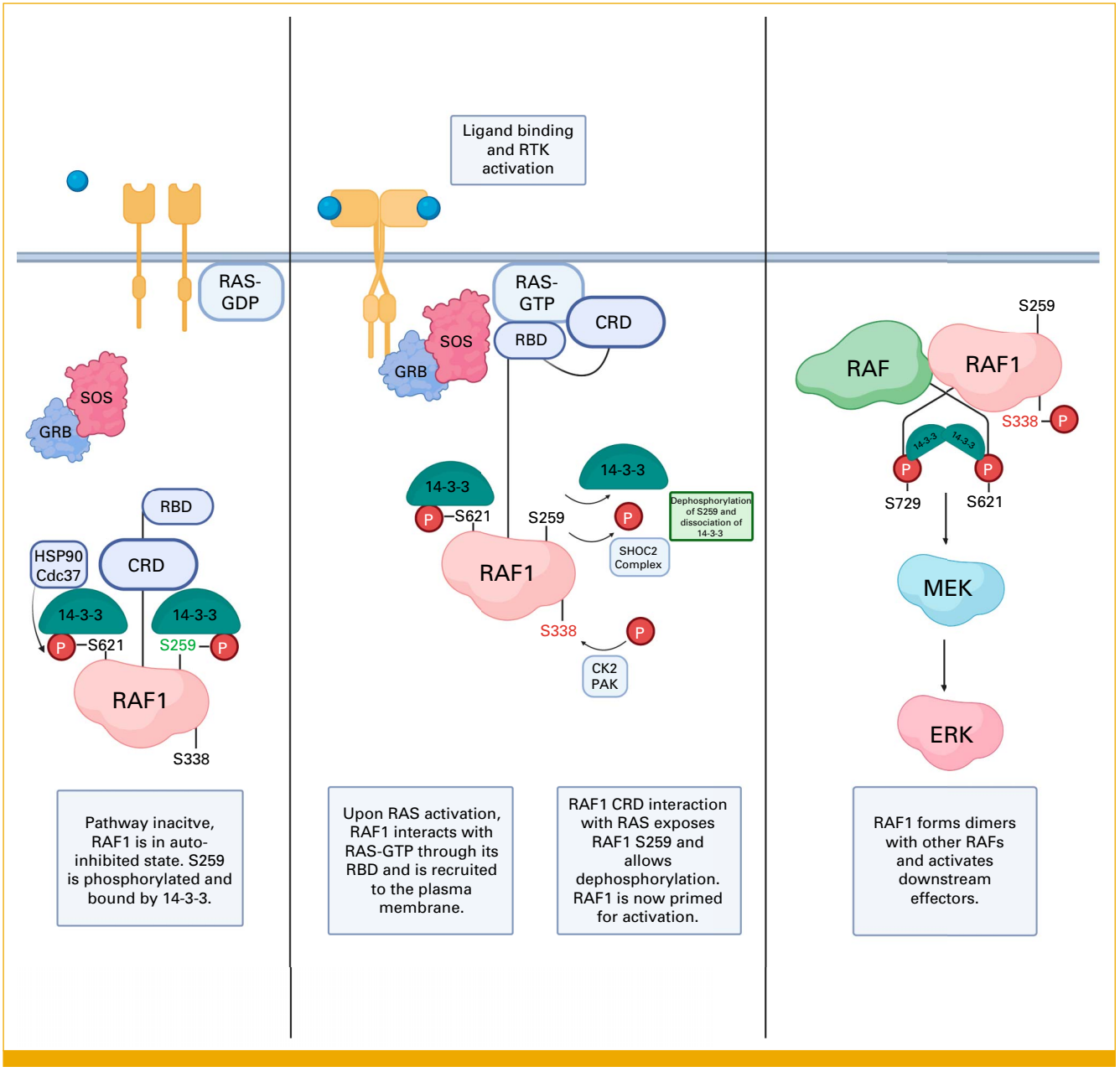

FIG 2. The role of S259 in the regulation of RAF1 activity. CRD, cysteine-rich domain; RBD, RAS-binding domain.

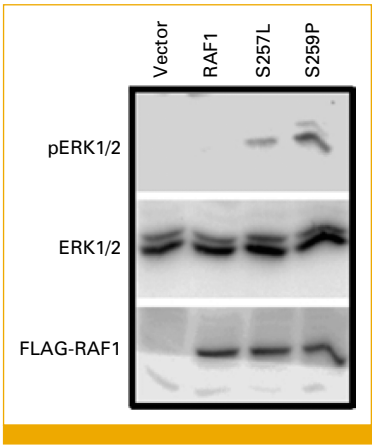

FIG 3. The S259P mutant of RAF1 is a constitutively active mutant, apparent from high levels of p-ERK1/2. The RAF1 S257L serves as a positive control.

of RAF1:14-3-3 revealed the requirement of the serine residue for the full interaction[29] (Data Supplement, Fig S1). S259P mutation is expected to abolish this interaction, allowing recruitment of phosphatases that can act on near-by residues, disrupting cytosolic partition (Fig 2). To note, there is no direct evidence for this hypothesis, and therefore experimental confirmation is needed, such as using peptide affinity assay. However, we showed by western blot that overexpression of RAF1 S259P results in increased ERK phosphorylation in HEK293T cells, indicating enhanced MAPK pathway activity (Fig 3).

Our patient also harbored a homozygous *CDKN2A/B* loss, which is a frequently occurring event in STS. *CDKN2A* encodes for p16 and p14, which regulates cell cycle and p53 pathway, respectively. p16 inhibits CDK4 in response to cellular cues, which acts as a checkpoint inhibitor that prevents G1-S progression.[30] Therefore, p16 loss may result in hyperactivation of cyclin-dependent kinases and may predict sensitivity to CDK4/6 inhibitors.[31,32] Multiple clinical studies showed benefit from CDK4/6 inhibitors in various cancers, and *CDKN2A* loss was found to have modest predictive value in few studies.[33,34] Loss of *CDKN2A* may contribute to tumorigenesis through dysregulation of the cyclin-dependent kinases and the cell cycle, and increased activity of CDK4 is a common event in sarcomas. Palbociclib showed antitumor activity in patients with STS with *CDK4* amplification.[35] Accordingly, our MTB recommended palbociclib to the patient.

Although *CDKN2A* loss is common in cancer, coalteration of *CDKN2A* and *RAF1* is extremely rare. In 13.867 samples from MSK-IMPACT Clinical Sequencing Cohort (MSK[38]) and Pan-cancer analysis of whole genomes (International Cancer Genome Consortium [ICGC]/TCGA[39]), only eight samples had coalteration of *RAF1* and *CDKN2A* which corresponds to 0.057% of the samples in MSK-IMPACT Clinical Sequencing Cohort (MSK, Nat Med 2017) and ICGC/TCGA (Nature 2020) pan-cancer studies. Moreover, none of the samples harbored RAF1 S259 mutation.[10,11] In general, very few studies investigated MEK inhibitor and CDK4/6 inhibitor combination in patients harboring both cyclin and RAS pathway alterations. In one study, this combination elicited responses in various cancer types with concurrent cyclin and RAS pathway alterations. Interestingly, the clinical benefit rate was 56%, with most patients having a stable disease for more than 6 months.[21] Our data further support the synergism between MAPK pathway inhibitors with CDK4/6 inhibitors in specific molecular backgrounds.

A limitation to our study was the lack of adequate tissue to perform p-ERK1/2 staining by immunohistochemistry (IHC). CGP and MRD testing were performed in the biopsy from the liver metastasis; however, this tissue was not available for IHC analysis. The primary tumor specimen was deemed inadequate and poor quality for IHC staining. Therefore, we could not show the p-ERK1/2 levels directly in the patient's tumor tissue.

Although we cannot exclude the possibility of the observed response because of the antitumor effect of palbociclib, CDK4/6 inhibitors have shown modest benefit in various cancers harboring *CDKN2A/B* loss.[33,34] Therefore, it is likely that the combination of trametinib with palbociclib augmented the antitumor activities of both drugs or, less likely, that trametinib alone was solely responsible for the observed tumor regression. Indeed, previous studies have suggested tailoring treatments targeting as many alterations as possible is associated with better outcomes.[4,36,37] It is plausible to consider *RAF1 S259P* mutation as a potential driver that may predict response to MEK inhibition. Further studies are required to confirm our findings.

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DATA SHARING STATEMENT

The authors state that all the data that support the conclusions of this research are accessible within the article.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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