

BRIEF REPORT

Synovial Sarcoma With *BRAF* V600E Mutation: A Case Report and Literature Review

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ABSTRACT

Synovial sarcoma (SS) is a genetically defined soft tissue sarcoma driven by the pathognomonic *SS18::SSX* fusion and is generally characterized by a low burden of secondary genomic alterations. We report a 42-year-old man with metastatic SS harboring both the *SS18::SSX1* rearrangement and the *BRAF* V600E mutation. The patient developed metastatic disease following standard multimodal therapy. Comprehensive genomic profiling using DNA and RNA based next-generation sequencing identified the *SS18::SSX1* fusion and the activating *BRAF* V600E mutation. The *SS18* rearrangement was further confirmed by fluorescence in situ hybridization (FISH), and immunohistochemistry supported the histologic diagnosis. Treatment with combined BRAF and MEK inhibition (dabrafenib and trametinib) resulted in a clinical response. In addition to this index case, a literature review identified multiple additional SS harboring *BRAF* V600E, supporting its role as a recurrent, potentially targetable alteration in a small subset of SS. These findings highlight the value of comprehensive genomic profiling in SS, particularly in advanced or refractory cases, to identify rare but actionable molecular events that may expand therapeutic options.

1 | Introduction

In more than 95% of cases, the t(X;18)(p11;q11) translocation, which produces the *SS18::SSX* fusion oncoprotein, defines oncogenesis in synovial sarcoma (SS) [1]. This fusion protein is a complex disruptor of gene regulation rather than a kinase [2, 3]. *SS18::SSX* fusion protein drives sarcoma by hijacking the mammalian BAF (SWI/SNF) chromatin remodeling complex, evicting the tumor suppressor BAF47/SMARCB1, and retargeting the complex to polycomb (PcG)-repressed domains [3, 4]. This mistargeting and PRC1.1 recruitment disrupt the BAF-PcG balance, causing epigenetic dysregulation and abnormal activation of developmental genes [5].

A direct result of this epigenetic driver is that the SS genome is “quiet,” with a low tumor mutation burden and targetable kinase mutations [4, 6]. Unlike the epigenetically driven oncogenic program of SS, *BRAF* V600E is a typical kinase-activating mutation. The V600E change keeps BRAF active, resulting in constitutive stimulation of the MAPK pathway and continuous downstream signaling that promotes proliferation and survival [7]. This mechanism underpins highly effective targeted therapies in various cancers, in which BRAF and MEK inhibitors are included in standard clinical practice.

In this study, we report a patient with metastatic SS whose genomic profiling revealed *SS18::SSX1* and a concurrent *BRAF*

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V600E mutation. A literature review identified six additional cases of SS harboring *BRAF* V600E, suggesting that this may represent a recurrent secondary alteration. This subgroup of SS appears to be associated with a poor prognosis, with increased risk of metastasis and local recurrence. Notably, because *BRAF* V600E and its downstream MAPK pathway can be targeted with clinically available inhibitors, this mutation represents a potential therapeutic target.

2 | Materials and Methods

2.1 | Immunohistochemistry (IHC)

The tissue samples were fixed, embedded, and cut into 4 μ m-thick sections. IHC staining was performed using a standard automated staining system (Benchmark GX, Ventana Medical Systems, USA). While the panel varied by case, key antibodies

evaluated included Vimentin, pan-cytokeratin (AE1/AE3, CK), Desmin, Ki-67, TLE1, EMA, and SS18-SSX. Positivity was defined as any unequivocal staining in tumor cells, and the distribution (e.g., diffuse, focal) and intensity were reviewed by two pathologists to confirm the histologic features.

2.2 | Fluorescence In Situ Hybridization (FISH)

FISH analysis was performed on 4 μ m FFPE sections using dual-color, break-apart probes for *SS18* (18q11) (Anbiping Pharmaceutical Technology Co. Ltd., Guangzhou, China) according to the manufacturer's instructions. Slides were evaluated under a fluorescence microscope, and signals from 200 tumor nuclei were counted. A case was considered positive for gene rearrangement if > 5% of cells displayed a break-apart signal pattern, defined as one fusion signal and one pair of separate red and green signals (1F1R1G).

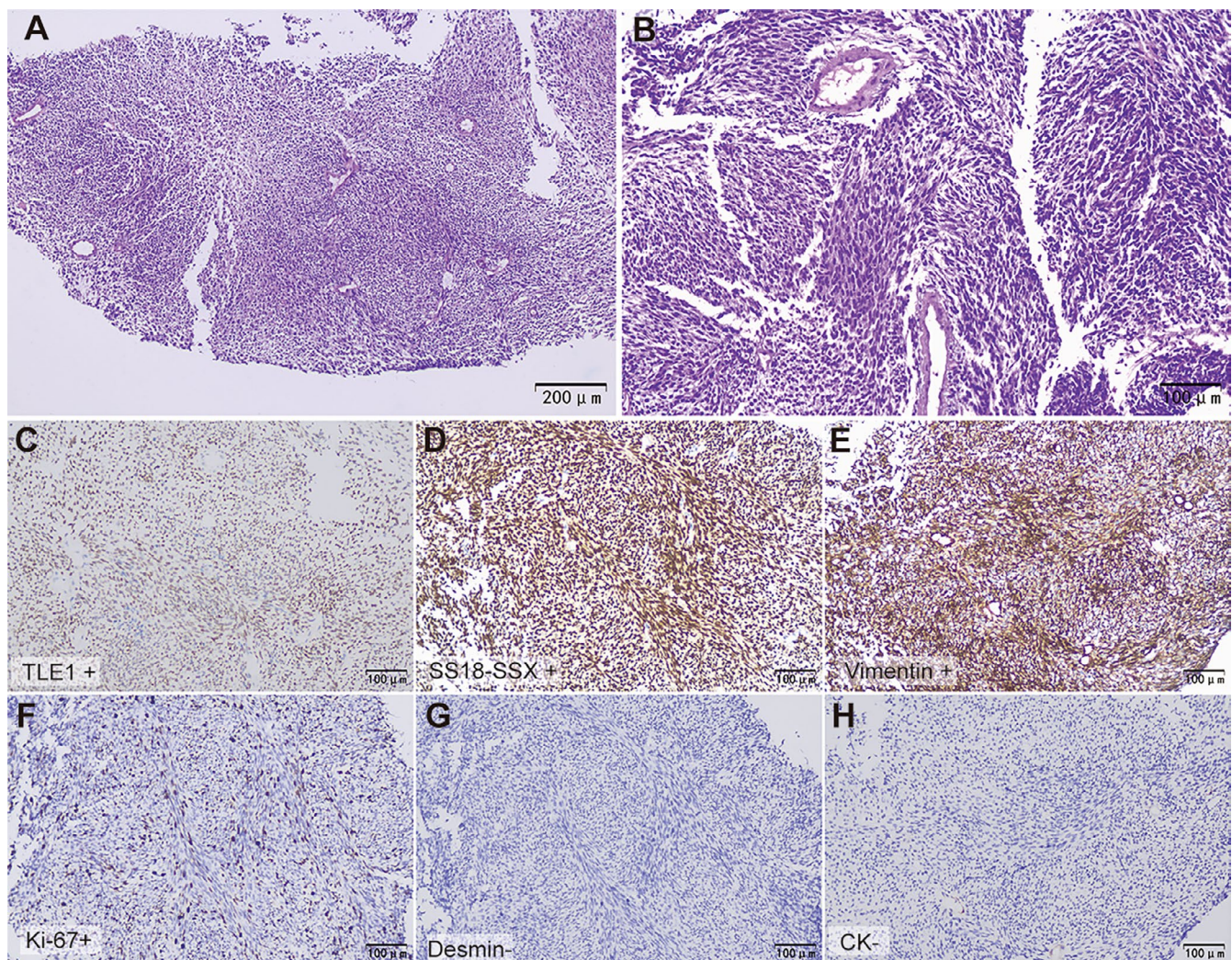


FIGURE 1 | Histopathological features and immunohistochemical profile of the tumor. (A and B) H&E staining of the primary tumor tissue sections showed a monotonous population of spindle cells arranged in fascicles, consistent with a monophasic fibrous pattern; IHC was positive for TLE1 (C), SS18-SSX (D), Vimentin (E), and Ki-67 (40%, F); negative for Desmin (G) and CK (pan-cytokeratin, AE1/AE3) (H). H&E images $\times 10$, $\times 20$; IHC images $\times 20$.

2.3 | DNA/RNA Next-Generation Sequencing (NGS)

Our cases underwent targeted NGS for comprehensive genomic and transcriptomic profiling using formalin-fixed, paraffin-embedded (FFPE) tumor tissue. In all instances, a hybrid-capture-based approach targeting a large panel of cancer-related genes was performed for both DNA and RNA sequencing. Briefly, DNA and RNA were co-extracted from FFPE sections. Sequencing libraries were prepared according to each institution's validated protocols and subsequently sequenced on an Illumina platform. The sequencing data were analyzed through institution-specific, validated bioinformatics pipelines. The DNA sequencing analysis was designed to detect single-nucleotide variants (SNVs), small insertions and deletions (indels), and copy number variations (CNVs). The RNA sequencing data were analyzed primarily for the detection of gene fusions.

3 | Results

3.1 | Case Presentation

A 42-year-old male was admitted to the hospital due to cervical pain. The diagnostic imaging revealed a 5.2×4.6 cm mass in the para-atlantoaxial region. Histopathology examination revealed a densely cellular tumor composed of uniform, spindle-shaped cells (Figure 1A,B). The tumor displayed a monophasic fibrous pattern and lacked obvious epithelial

structures. Immunohistochemical analysis was positive for TLE1, SS18-SSX, Vimentin, and Ki-67 (40%); negative for Desmin and CK (Figure 1C-H). FISH with a SYT (*SS18*) split-apart probe set showed *SS18* rearrangement (Figure 2A), and a diagnosis of SS was established. The patient underwent five sessions of stereotactic radiosurgery (CyberKnife) followed by the multi-targeted tyrosine kinase inhibitor anlotinib. This combined therapeutic approach initially resulted in a reduction in tumor volume.

Four months after therapy, a PET-CT scan found new widespread tumors in the axial skeleton, limb bones, and both lungs. The patient then received four cycles of systemic chemotherapy, which included liposomal doxorubicin, dacarbazine, and the PD-1 inhibitor toripalimab. Radiographic evaluation after four cycles showed stable disease (SD), with minor symptomatic improvement.

3.2 | Molecular Findings and Targeted Treatment

A biopsy of the chest wall metastatic lesion was done when a PET-CT showed metastasis. A targeted DNA NGS and RNA NGS were performed on the biopsied specimen, which confirmed *SS18::SSX1* rearrangement, with the breakpoint of *SS18* in exon 9 (chr18: 23612363) and the *SSX1* breakpoints in exon 7 (chrX:48123217) (Figure 2B). In addition, a *BRAF* p.V600E (c.1799T>A) mutation (Figure 2C) with a variant allele frequency (VAF) of 47.9% was detected.

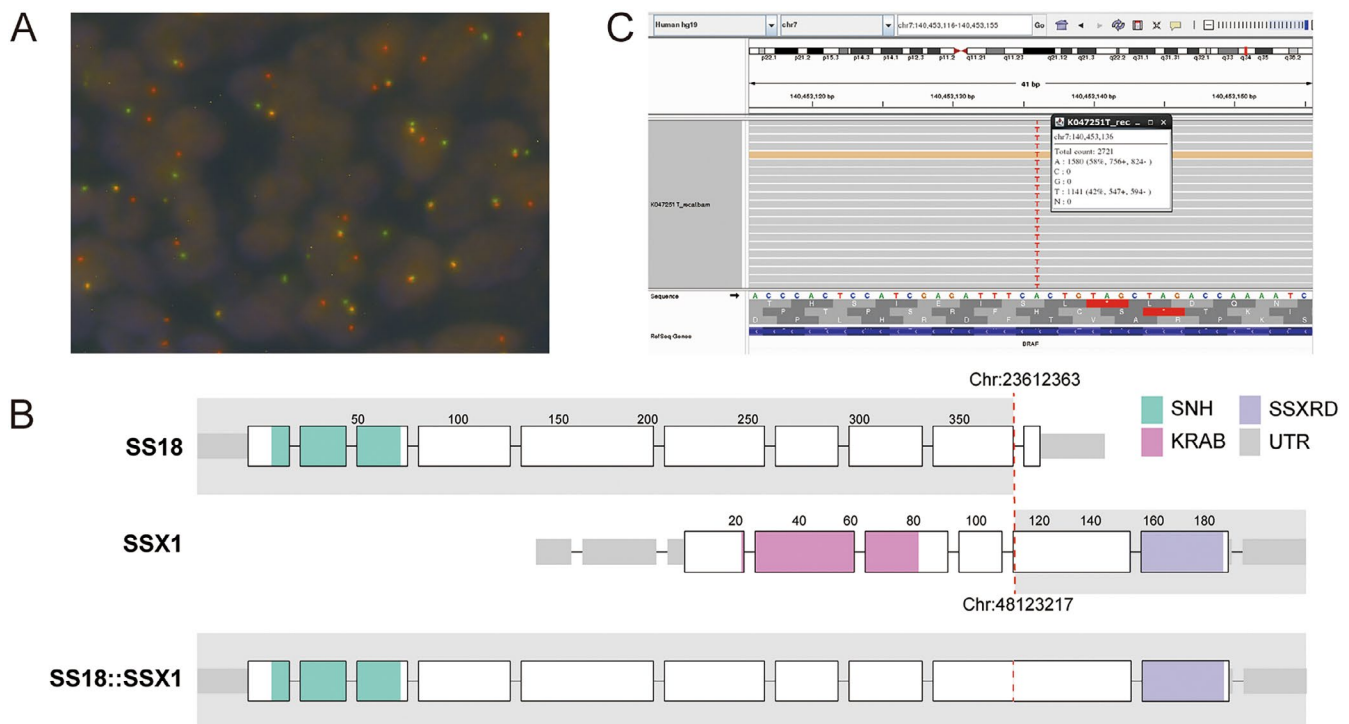


FIGURE 2 | Molecular characterization of the tumor. (A) Fluorescence in situ hybridization (FISH) with a SYT split-apart probe set showed the rearrangement in the SYT (*SS18*) gene. (B) Targeted RNA NGS showed an in-frame fusion between *SS18* exon 9 and *SSX1* exon 7. The main functional domains and exon position are illustrated. The location of the breakpoints was marked by dotted lines. SNH, SYT N-terminal homology domain; KRAB, Krüppel-associated box; SSXRD, SSX repression domain. (C) Next-generation sequencing (NGS) of the FFPE tumor sample from a biopsy of the chest wall metastatic lesion showed a *BRAF* p.V600E (c.1799T>A) mutation on chromosome 7.

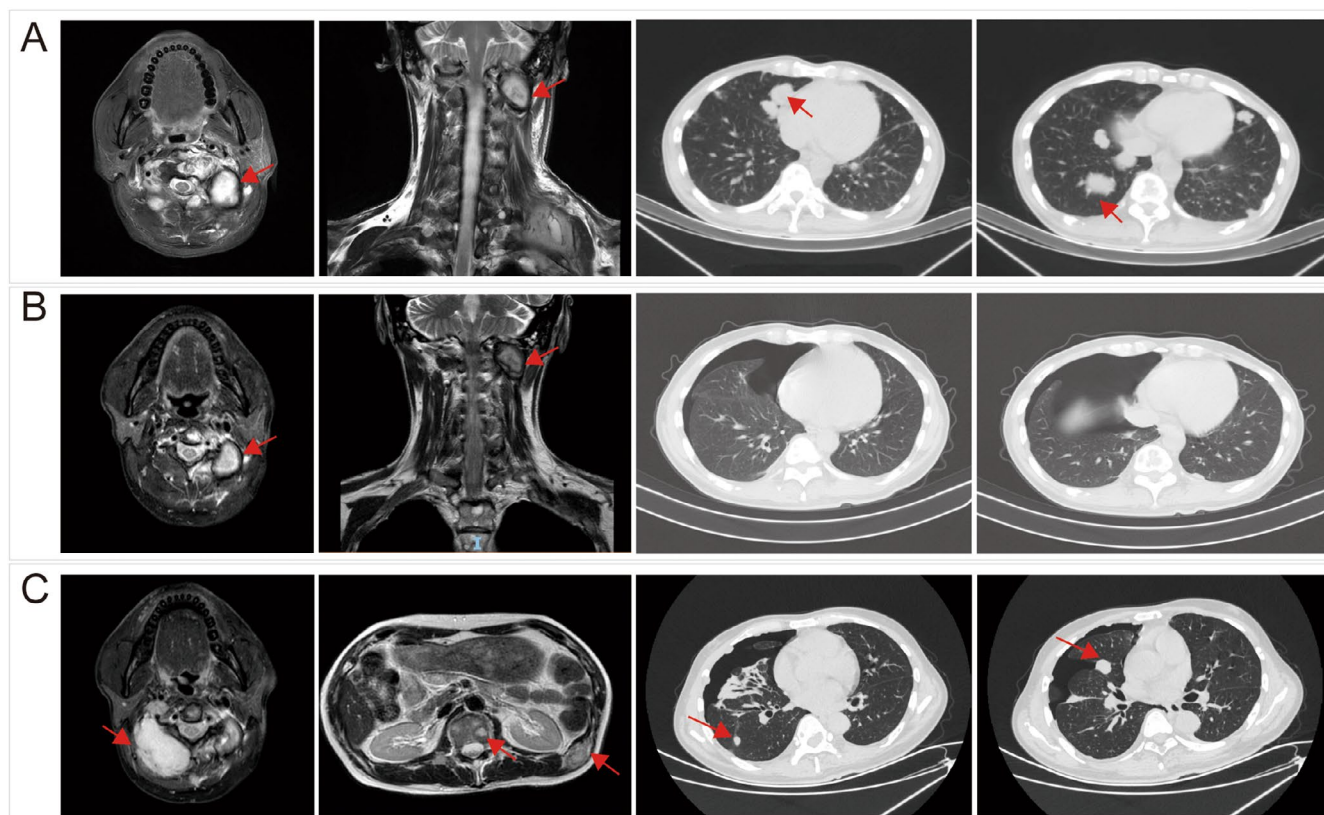


FIGURE 3 | Radiological response and disease progression during targeted therapy. Serial MRI and CT imaging demonstrating treatment response and subsequent progression. (A) Baseline imaging showing the primary cervical lesion and multiple pulmonary metastases (red arrows). (B) Imaging after 4 months of dabrafenib plus trametinib therapy. Marked reduction in primary and metastatic lesions following 4 months of dabrafenib plus trametinib therapy, consistent with a partial response (PR). (C) Follow-up imaging revealed new metastatic lesions in the cervical region, abdomen/left lumbar area, and lungs indicating disease progression.

The patient started targeted therapy with dabrafenib (150 mg twice daily) and trametinib (2 mg once daily). He achieved a rapid and significant clinical response, with substantial shrinkage of both the primary and metastatic lesions confirmed by imaging (Figure 3A,B). The duration of the response was 6.5 months. The patient started to feel pain in the left lumbar area again. Follow-up imaging showed that the disease had relapsed, with new lesions in the cervical, abdomen/left lumbar area, and lungs (Figure 3C). A rebiopsy confirmed the presence of *SS18::SSX1* and *BRAF V600E*, with no other genomic alterations identified that could explain the drug resistance.

Due to the poor overall condition of the patient, he declined high-dose ifosfamide and instead received the anti-angiogenic agent apatinib. His health continued to deteriorate, eventually leading to coma and death. The total survival time from initial diagnosis was 24 months.

4 | Discussion

We report an SS harboring an *SS18::SSX1* rearrangement and a *BRAF V600E* mutation. *BRAF V600E* is a classic constitutively activating mutation that drives the MAPK (RAS–RAF–MEK–ERK) signaling pathway. *SS18::SSX* fusion acts primarily

through epigenetic dysregulation rather than direct MAPK activation. The fusion retains the *SS18* (*SSXT*) domain and the *SSX1* *SSXRD* domain, while lacking the *SSX1* *KRAB* transcriptional repression domain (Figure 2C). It incorporates into the BAF (*SWI/SNF*) chromatin-remodeling complex and aberrantly redirects it to polycomb-repressed genomic loci. This process leads to transcriptional reprogramming, most prominently involving *Wnt/β-catenin* signaling.

By literature search, only 6 additional cases of SS with *BRAF V600E* have been reported (Table 1). The initial report by Watanabe et al. [8] identified two thoracic SS cases with concurrent *SS18::SSX2* fusion and *BRAF V600E* mutation. Both tumors showed classic monophasic morphology and were confirmed to be associated with increased pERK expression through immunohistochemistry. One patient demonstrated a marked but transient response to combined BRAF/MEK inhibition, followed by disease progression associated with an acquired *NRAS Q61K* mutation, while the other patient did not receive targeted therapy and died of disease. Further cases identified in the VEBASKET trial [9] involved two adult patients with metastatic SS who showed primary resistance to single-agent BRAF inhibition and rapid mortality. More recently, Russo et al. [10] reported an intrathoracic SS in a pediatric patient in whom *BRAF V600E* mutation was identified at relapse. Despite aggressive clinical behavior and resistance to conventional treatment, the

TABLE 1 | The clinical information for SS patients with BRAF V600E.

Author/Year	Sex, age	Tumor characteristics at onset	First-line treatment	Relapses/further line treatments	Targeted therapy with BRAF +/- MEK inhibitors	Response to targeted therapy	PFS/outcome
Watanabe (2020) [8]	F, 32 y	Right thoracic cavity mass (12 cm), N0, M0. Monophasic SS, SS18::SSX2 fusion.	Neoadjuvant IFO/DOX CT; surgery; adjuvant IFO/DOX CT	Pulmonary mets after 18 months; trabectedin; IFO mono; pazopanib	Not done	N.A.	N.A./died of disease 43 mo after diagnosis.
Watanabe (2020) [8]	F, 23 y	Superior mediastinum mass (4.3 cm), N0, M0. Hemiothorax. Monophasic SS, SS18::SSX2 fusion.	Surgery	Local recurrence after 5 months; IFO/DOX CT; local RT; pazopanib; IFO mono.	Dabrafenib 150 mg BID + trametinib 2 mg QD	CR	7.5 mo/local recurrence (acquired NRAS Q61K mutation). Outcome N.A.
Subbiah (2020) [9]	F, 59 y	N.A.	Vemurafenib	N.A.	Vemurafenib 960 mg BID	PD	1.6 mo/died of disease 2 mo after diagnosis.
Subbiah (2020) [9]	M, 47 y	N.A.	N.A.	N.A.	Vemurafenib 960 mg BID	PD	1.2 mo/died of disease 3.7 mo after diagnosis.
Russo (2023) [10]	M, 15 y	Left thoracic cavity mass, Nx, M0. Monophasic SS, SS18::SSX1 fusion.	Neoadjuvant IFO/DOX CT; surgery; adjuvant proton therapy + IFO CT	Local relapse; pazopanib (stopped early); gemcitabine	Vemurafenib 240 mg BID initially, increased to 480 mg BID	PR	6 mo/alive at 19 months after diagnosis.
Kobayashi (2023) [11]	M, 50 y	Left thigh	N.A.	N.A.	N.A.	N.A.	N.A.
Current case	M, 42 y	Para-atlantoaxial mass (5.2 cm), N0, M0 → M1. Monophasic SS, SS18::SSX1 fusion.	Radiosurgery; anlotinib	Multiple-site mets; lipo-DOX/DTIC/toripalimab	Dabrafenib 150 mg BID + trametinib 2 mg QD	PR	6.5 months/died of disease approx. 24 mo after diagnosis.

Abbreviations: BID, twice a day; CR, complete response; CT, chemotherapy; DOX, doxorubicin; DTIC, dacarbazine; F, female; Gem/Doce, gemcitabine/docetaxel; IFO, ifosfamide; Lipo-DOX, liposomal doxorubicin; M, male; M, metastasis; mets, metastases; mo, months; N.A., not available; N, node; PD, progressive disease; PFS, progression-free survival; PR, partial response; QD, once a day; Ref, reference number corresponding to the manuscript's reference list; RT, radiotherapy; SS, synovial sarcoma; y, years.

patient achieved a partial response to BRAF inhibitor therapy. In a large genomic cohort, Kobayashi et al. [11] identified an SS patient harboring *BRAF* V600E and a *TERT* promoter mutation, with no available clinical details.

These reported cases, spanning ages 15–59, were uniformly classified as monophasic SS. The anatomic distribution spans thoracic sites and extra-thoracic locations. Immunophenotypic differences were observed. While focal CK and EMA positivity can be detected in Watanabe's case, our patient lacked CK and EMA expression entirely. These variations underscore the well-recognized immunohistochemical heterogeneity of SS.

Identifying the *BRAF* V600E mutation elucidated a treatment pathway for the disease. The standard treatment for metastatic melanoma and non-small cell lung cancer with the *BRAF* V600E mutation is both BRAF and MEK inhibitors. This method leads to high response rates and greater survival than chemotherapy or single-agent BRAF inhibition [12, 13]. This combination strategy offers a more substantial and lasting inhibition of the constitutively active signaling pathway induced by the mutation. In reported cases of *BRAF* V600E mutant SS with available clinical data, targeted therapy was administered after progression on multiple prior treatment lines. One patient in the VE-BASKET trial represents an exception; however, detailed information on treatment and clinical outcome was not available.

Comparing the treatment strategies employed across the reported cases, dual BRAF/MEK inhibition appears particularly effective. Case 2 reported by Watanabe et al. [8], a 23-year-old woman, achieved a complete response lasting 7.5 months on the same dabrafenib/trametinib combination. In contrast, two patients treated with vemurafenib monotherapy within the VE-BASKET trial experienced rapid disease progression (PFS 1.2 and 1.6 months) [9]. Another case reported by Russo et al. achieved a partial response lasting 6 months with vemurafenib monotherapy initiated [10]. Indeed, the dual-blockade strategy has shown efficacy in other *BRAF* V600E-mutant sarcoma types. Gounder et al. documented a fast and nearly complete response to vemurafenib and trametinib in a refractory sarcoma with a *BRAF* V600E mutation [14]. These results indicate that dual BRAF/MEK inhibition appears more active in selected cases; however, the overall incidence of reported *BRAF* V600E mutant sarcoma cases is still extremely rare. Consequently, no conclusive determination regarding the superiority of combination therapy can be established, needing further validation in a more extensive patient cohort.

The eventual emergence of resistance, as observed in our patient after 6.5 months, is a recognized constraint of targeted therapy aimed at the MAPK pathway. Notably, the resistant tumor in the responsive Watanabe et al. case acquired a secondary *NRAS* Q61K mutation [8]. *NRAS* mutations are a well-documented mechanism of acquired resistance to BRAF/MEK inhibition in melanoma, leading to MAPK pathway reactivation independent of BRAF [15]. We were unable to identify a resistance mechanism in this case; however, our analysis was limited to DNA-level genomic alterations. Other mechanisms, including post-transcriptional and post-translational regulation, may still influence MAPK signaling activity.

Another interesting question is the timing of *BRAF* V600E acquisition, that is, whether this occurs at the time of diagnosis or later at disease relapse. Unfortunately, DNA NGS was not done at the initial diagnosis in our case, preventing this determination. The primary tumor tissue was unavailable, and additional testing, such as *BRAF* V600E immunohistochemistry, could not be performed. In vitro cell models, such as introducing *SS18::SSX* fusion alone or in combination with *BRAF* V600E, may help clarify the biological impact of added BRAF/MAPK signaling on SS tumor behavior.

In summary, we present a rare case of metastatic SS harboring an *SS18::SSX1* fusion and a *BRAF* V600E mutation, which showed a clinical response to a therapy targeting BRAF/MAPK signaling. A review of six additional similar cases suggests an emerging pattern of clinically aggressive tumors with poor prognosis. Although our patient responded to combined dabrafenib and trametinib therapy, disease progression ultimately relapsed, and the patient succumbed to the disease. These findings highlight the need for further therapeutic innovation, including exploration of combination strategies targeting both MAPK and Wnt/ β -catenin signaling pathways.

Author Contributions

Conceptualization: Tian Gao and Zhengfu Fan. Methodology: Fan Yang and Sheng Xiao. Data curation: Tao Deng and Yunfei Shi. Writing – original draft: Tian Gao and Tao Deng. Writing – review and editing: Tian Gao, Tao Deng, Yunfei Shi, Fan Yang, Sheng Xiao, and Zhengfu Fan.

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The authors have nothing to report.

Ethics Statement

The study was approved by the Institutional Review Board. All procedures were carried out in accordance with institutional guidelines and the principles outlined in the Declaration of Helsinki.

Consent

Patient consented to participate in research.

Conflicts of Interest

The authors declare no conflicts of interest.

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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