

Case Report

BRAF and MEK Inhibitor Treatment for Metastatic Undifferentiated Sarcoma of the Spermatic Cord with BRAF V600E Mutation

Ken Saijo^a Hiroo Imai^a Hiromichi Katayama^b Fumiyoshi Fujishima^c
Kenichi Nakamura^d Yuki Kasahara^a Kota Ouchi^a Keigo Komine^a
Hidekazu Shirota^a Masanobu Takahashi^a Chikashi Ishioka^a

^aDepartment of Medical Oncology, Tohoku University Hospital, Sendai, Japan; ^bDepartment of Urology, Tohoku University Hospital, Sendai, Japan; ^cDepartment of Pathology, Tohoku University Hospital, Sendai, Japan; ^dClinical Research Support Office, National Cancer Center Hospital, Tokyo, Japan

Keywords

Sarcoma · *BRAF* V600E · Comprehensive genomic profiling · Dabrafenib · Trametinib

Abstract

An 18-year-old Japanese man was diagnosed with an undifferentiated sarcoma of the spermatic cord, with multiple distant metastases to the lungs and bones. The patient received doxorubicin-based standard chemotherapy. Although the chemotherapy was effective, it induced severe adverse events, which led to treatment discontinuation. A comprehensive genomic profiling test using resected tumor tissue revealed the *BRAF* V600E mutation. Based on the result, the patient received combination therapy with dabrafenib and trametinib. The combination therapy achieved a good response with few adverse events. However, 6.5 months later, pleural metastases and meningeal dissemination had emerged. A liquid comprehensive genomic profiling test was performed after the progression to identify the resistance mechanism, which resulted in the detection of no actionable gene alterations other than *BRAF* V600E. This report shows that the *BRAF* V600E mutation may be a promising therapeutic target and that resistance to the targeted therapy could also occur in soft tissue sarcoma. The significance of *BRAF* mutations across different types of cancer should be validated, and it is necessary to apply targeted therapies and develop methods to overcome resistance based on the optimal use of comprehensive genomic profiling tests.

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Correspondence to:
Chikashi Ishioka, chikashi@tohoku.ac.jp

Introduction

Soft tissue sarcoma (STS) is a rare mesenchymal neoplasm with heterogeneous histological subtypes [1]. STS can occur everywhere in the body, including the head, neck, extremities, internal organs, and reproductive organs. Chemotherapy is the primary treatment option for recurrent and metastatic STS [2]. Doxorubicin, with or without add-on ifosfamide, is widely used to treat STS. However, the response rate is less than 20% [3]. Therefore, an urgent need exists to develop additional treatment options for patients with STS. In response to this need, the use of comprehensive genomic profiling tests in solid cancers has led to a better understanding of molecular mechanisms underlying the pathogenesis of cancers and to the discovery of treatment-targeted molecules. Indeed, targeted therapies based on genomic profiling tests have been accepted in clinical practice and resulted in unprecedented outcome improvement in the treatment of some solid cancers, such as non-small-cell lung cancer and biliary tract cancer [4, 5]. Generally, targeted therapy has a better tolerated toxicity profile than conventional chemotherapy [4]. A number of clinical trials are being conducted aimed at evaluating targeted therapies. The *BRAF* V600E mutation is a promising therapeutic target because *BRAF* V600E can potentially drive oncogenic cell proliferation. In addition, specific BRAF inhibitors are currently available. Oncogenic *BRAF* mutations occur in various malignancies, including malignant melanoma (50%), thyroid cancer (30%–50%), and colorectal cancer (10%) [6]. However, only a few cases of STS with *BRAF* mutation have been described [7]. Studies examining treatment outcomes with the use of specific BRAF inhibitors are scarce [8]. The significance of *BRAF* mutations in patients with STS remains unclear. This report describes a case of *BRAF*-mutated undifferentiated sarcoma successfully treated with BRAF and MEK inhibitors and suggests the potential of the *BRAF* V600E mutation as a therapeutic target in patients with STS.

Case Report

In December 2020, an 18-year-old Japanese man presented with swelling of the right scrotum due to an approximately 5-cm tumor in the spermatic cord (Fig. 1a). The patient had no previous history of illness or familial history of cancer. Chest radiography revealed multiple lung metastases (Fig. 1b). In addition, computed tomography (CT) revealed multiple metastases to the bones in the spine, ribs, and pelvis. Bone scintigraphy revealed tracer uptake in the same bone lesions (Fig. 1c). In January 2021, he developed paraparesis due to spinal cord compression at the 12th thoracic vertebra (Fig. 1d).

The tumor of the spermatic cord was resected at the Department of Urology. Pathologically, the resected tumor was composed of proliferating large polygonal cells with focal desmin-positive rhabdoid cells. Venous invasion was prominent, and the mitotic figure count was at least 7–8 per 1 high-power field. Immunohistochemically, the cells were negative for AE1/AE3, S100, CDK4, MDM2, CD99, and NKX3.1. The Ki-67 index was 60–70%. No gene fusions involving *EWS*, *CHOP*, *FUS*, *FKHR*, or *MDM2* were detected. Based on the abovementioned findings, the tumor was diagnosed as a high-grade undifferentiated sarcoma of the spermatic cord (Fig. 2). The patient was referred to our department. He received steroids and urgent radiotherapy to the thoracic and lumbar spines consisting of 25 Gy for each lesion. The patient also underwent chemotherapy with doxorubicin and ifosfamide. He developed severe anorexia, neutropenia, febrile neutropenia, and hematuria. These treatment-related adverse events led to a reduction in the chemotherapy dose. He had received four cycles of doxorubicin and ifosfamide therapy until May 2021. A CT scan showed tumor shrinkage in the lung metastasis (Fig. 3a, b). However, as those adverse events recurred even at reduced doses, it was difficult to continue the same chemotherapy regimen.

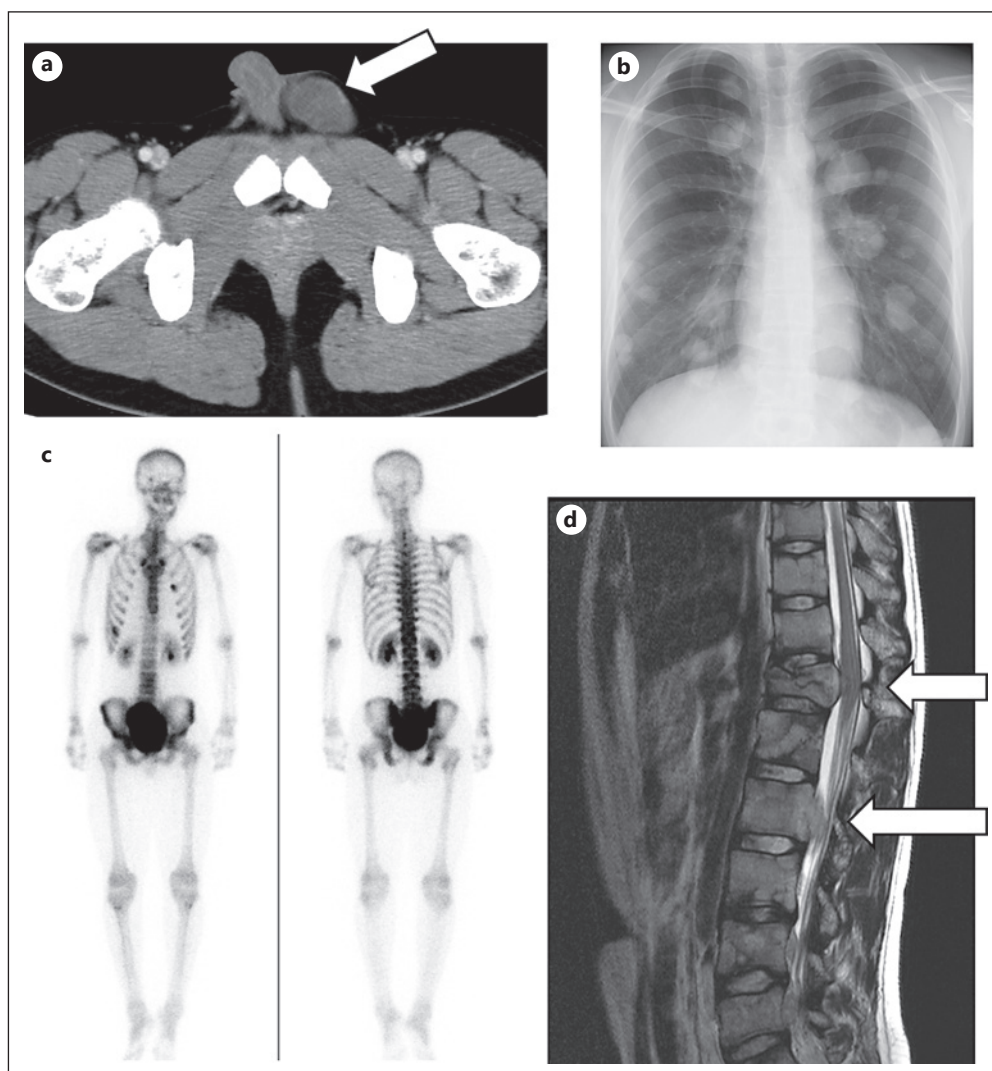


Fig. 1. Clinical imaging findings. **a** CT imaging of the testicular tumor. **b** Chest X-ray. **c** Bone scintigraphy imaging. **d** T2-weighted MRI of the thoracic and lumbar spines.

During chemotherapy, the resected tumor tissue was examined using a comprehensive genomic profiling test (FoundationOne® CDx, FOUNDATION MEDICINE, INC., MA, USA). The *BRAF* V600E mutation was detected (Table 1). A prospective trial of patient-proposed healthcare services with multiple targeted agents based on the results of gene profiling by multigene panel testing (NCCH1901, jRCTs031190104) is being conducted for patients who have no available clinical trials, even though the test showed actionable mutations, in 12 designated core hospitals for cancer genomic medicine in Japan. In June 2021, according to the trial protocol, the patient started combination therapy with the BRAF inhibitor dabrafenib (300 mg twice a day) and the MEK inhibitor trametinib (2 mg once a day). Both drugs were provided by Novartis Pharma K.K. (Tokyo, Japan).

Six days after starting the combination therapy, the patient developed grade 2 anorexia and fatigue. Both drugs were withheld for 8 days and restarted with a reduced dose of dabrafenib, 200 mg twice daily, and trametinib, 1.5 mg once daily. Two weeks later, the patient developed a fever of 39°C, exanthema of the trunk and extremities, and grade 2 leukocytopenia.

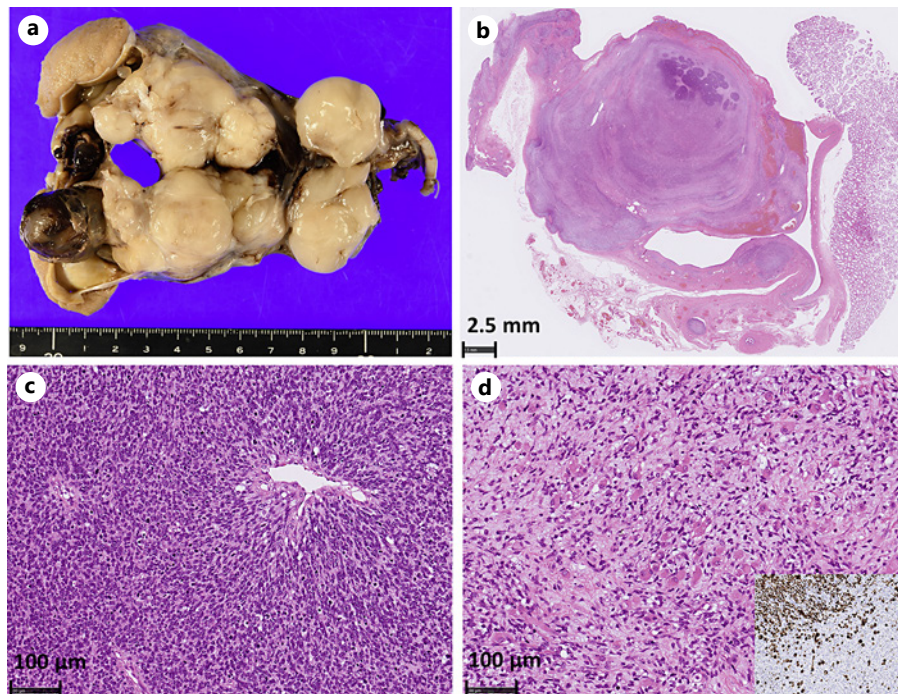


Fig. 2. Macroscopic and pathological findings of the resected spermatic cord tumor. **a** Macroscopic view of the resected specimen demonstrating a 10-cm multinodular mass. **b** Loupe image of the tumor without continuity to testis. **c** Pathological examination revealed proliferation of large polygonal cells. **d** The partial presence of rhabdoid cells with desmin positivity.

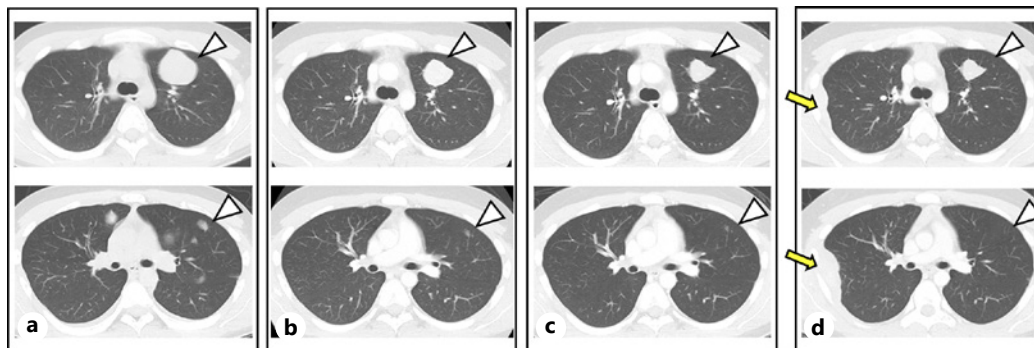


Fig. 3. Serial CT images of lung metastasis and pleural metastasis. **a** At the time of diagnosis (January 2021). **b** On doxorubicin plus ifosfamide (May 2021). **c** On dabrafenib plus trametinib with response (September 2021). **d** On dabrafenib plus trametinib with the refractory lesion (December 2021). Newly emerged pleural metastatic lesions are indicated by yellow arrows.

No clinical signs of infection were observed. Both drugs were discontinued. The patient's condition and white blood cell count recovered smoothly. After 8 days, both drugs were resumed. The dose of dabrafenib was further reduced to 100 mg twice daily. In September 2021, a CT scan revealed regression of the lung metastasis and no deterioration of the bone metastasis (Fig. 3c). Since then, both drugs were continued without worsening adverse events. The patient regained the ability to ambulate with the assistance of a stick.

Table 1. The result of comprehensive genomic profiling tests performed in this case

	Sample	Tumor-containing rate	Gene alteration (allele frequency)
FoundationOne®	Tumor tissue sample resected before treatment	40%	Microsatellite Stable TMB 9 mutations/megabase BRAF V600E (0.35) KEL M1T (0.60) BCOR loss
Guardant360®	Blood sample after treatment	–	BRAF V600E (0.30)

TMB, tumor mutational burden.

In December 2021, the patient complained of right-sided chest pain. A CT scan showed a newly emerged right pleural dissemination despite further regression of lung metastasis (Fig. 3d). Combination therapy was determined to be refractory, and chemotherapy with doxorubicin and ifosfamide was resumed. In February 2021, after an additional two cycles of chemotherapy, the patient developed diplopia and bilateral lower limb paralysis. Magnetic resonance imaging revealed multiple meningeal disseminations. Palliative radiation to the brain and thoracic and lumbar spinal cord was conducted. In March 2022, a liquid genomic profiling test was performed using the Guardant360® (Guardant Health, Inc. CA, USA). Only the *BRAF* V600E mutation was detected without additional gene mutations (Table 1). Approximately 1 month later, the patient died of respiratory failure due to the progression of pleural dissemination.

Discussion

The frequency of *BRAF* gene mutations in patients with sarcoma is 0–9% [7, 9]. As sarcoma is a rare type of cancer, the number of patients with *BRAF*-mutated sarcomas is extremely small. The presence of *BRAF* mutations and treatment outcomes with *BRAF*-targeted therapy have been reported in only a few cases of different types of sarcomas [8]. The significance of *BRAF* mutations differs among specific cancer types [10]. Because STS includes various histological subtypes, its significance would also differ among the histological subtypes. Thus, case reports describing the relationships between each STS subtype and *BRAF* mutation carrier status are meaningful. This case report shows that the *BRAF* V600E mutation could be a potential therapeutic target for undifferentiated STS.

BRAF-targeted therapy has been developed for cutaneous melanoma associated with the *BRAF* V600E mutation but not for mucosal melanoma [11]. *BRAF* inhibitor monotherapy is vulnerable to various resistance mechanisms. Combination therapies have been investigated to circumvent resistance. Based on this concept, the combination of *BRAF* and *MEK* inhibitors has shown to be more effective and safer than *BRAF* inhibitor monotherapy in patients with melanoma [12]. In this case, dabrafenib and trametinib were used as part of a prospective trial of NCCH1901. The progression-free survival time of combination therapy with dabrafenib and trametinib was 6.5 months. The combination therapy induced adverse events such as anorexia, fatigue, pyrexia, exanthema, and leukocytopenia, which have already been reported [13]. However, these adverse effects were less severe than those induced by doxorubicin-based chemotherapy. Furthermore, combination therapy did not require hospitalization, which certainly benefited the patient and family.

Acquired resistance to the combination therapy also developed in this case, showing that, like melanoma, *BRAF*-targeted combination therapy could be resistant even in STS. To identify the genomic mechanisms of acquired resistance to BRAF and MEK inhibitors, circulating tumor DNA analysis of plasma samples after tumor progression was performed using Guardant360[®] CDx. Several mechanisms of BRAF inhibitor resistance have been proposed [7]. The major one is the paradoxical activation of the RAS-RAF-MAPK pathway caused by secondary mutations of *BRAF* or *RAS*, amplification of *RAS*, and overexpression of *EGFR* [7, 14]. Another is the activation of alternative pathways, such as the PI3K-AKT pathway [7]. Liquid biopsy analysis provides real-time information on tumor heterogeneity [15]. Therefore, it is sometimes used to identify resistance mechanisms. No acquired gene alterations other than *BRAF* V600E were detected in this case. Sub-clonal groups with *BRAF* mutations thus remained, and other alterations that could not be detected were likely acquired. Guardant360[®] CDx detects mutations and amplification in 74 and 18 genes, respectively, including most of the BRAF inhibitor resistance-related gene alterations mentioned above. However, the number of gene alterations that can be detected by Guardant360[®] CDx is only about one-third of those detectable by FoundationOne[®] CDx. Other minor gene mutations or amplifications related to resistance mechanisms may not be detected in this liquid analysis. There are still several problems associated with liquid biopsy analysis. Liquid biopsy analysis is performed by several different techniques which reduce its reproducibility, and it may provide false negatives when circulating tumor DNA or allele frequency of genetic alterations is low [4]. Identifying the mechanism of resistance in individual cases may not be easy, even with liquid biopsy analysis. In this case, the resistance mechanism may be more complicated than that for BRAF inhibitors because resistance emerged against the combination of BRAF and MEK inhibitors treatment.

Another concern is the heterogeneous response to *BRAF*-targeted treatment. The resected tumor was histologically heterogeneous, as shown in Figure 2. *BRAF* mutation may have also been biased in the tumor tissue. We could not detect the relationship between histological features and *BRAF* mutation. The uneven distribution of *BRAF* mutation may have led to heterogeneous treatment responses and resistance to the targeted therapy.

The increasing use of comprehensive genomic profiling tests is expected to accumulate findings on molecular targets, especially in rare cancers. In addition, it is hoped that optimized and improved use of liquid biopsy analysis will efficiently reveal resistance mechanisms to the targeted therapy in individual cases.

Conclusion

We reported that a patient with *BRAF* V600E-mutated undifferentiated sarcoma was successfully treated with a combination of BRAF and MEK inhibitors. A comprehensive genomic profiling test led to the use of molecularly targeted drugs and brought clinical benefits that would not otherwise be considered. This report shows that the *BRAF* V600E mutation may be a promising therapeutic target and that resistance to targeted therapy could also occur in STS.

Acknowledgments

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Statement of Ethics

The prospective study (NCCH1901) and this case report were approved by the Ethics Committee of Tohoku University Graduate School of Medicine (approval numbers 2019-30-01 and 25514, respectively). Written informed consent was obtained from the patient's next of kin for publication of the details of their medical case and any accompanying images.

Conflict of Interest Statement

Chikashi Ishioka was funded by the Tokyo Cooperative Oncology Group and obtained financial support from Chugai Pharmaceutical, Ono Pharmaceutical, MSD, Pfizer, AstraZeneca, Bristol-Myers Squibb, Janssen Pharmaceutical, Taiho Pharmaceutical, Daiichi Sankyo Company, Limited, and Takeda Pharmaceutical; it is a representative of the Tohoku Clinical Oncology Research and Education Society, a specified nonprofit corporation. Masanobu Takahashi received research funding from Ono Pharmaceutical Co., Ltd. Kenichi Nakamura received research funding from the Chugai Pharmaceutical and Taiho Pharmaceutical company. The other authors have no conflicts of interest to declare.

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There is no funding source relevant to this report.

Author Contributions

Ken Saijo conducted this study. Ken Saijo, Hiroo Imai, Hiromichi Katayama, Yuki Kasahara, Kota Ouchi, Keigo Komine, Hidekazu Shirota, and Masanobu Takahashi treated the patients. Fumiyoshi Fujishima performed the histopathological analysis. Kenichi Nakamura is a member of the coordinating office of the NCCH1901. Chikashi Ishioka reviewed the study.

Data Availability Statement

All data in this case are included in this article. Further inquiries can be directed to the corresponding authors.

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