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Case Report

Effectiveness Treatment of a BRAF-ZKSCAN5 Fusion Gene Melanoma Case with Dabrafenib/Trametinib

Hiroshi Kato Shinji Kano Yukiko Yasui Yuka Nojiri Maki Yoshimitsu
Motoki Nakamura Akimichi Morita

Department of Geriatric and Environmental Dermatology, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

Keywords
Melanoma · Fusion gene · BRAF · BRAF-ZKSCAN5 · Dabrafenib

Abstract
The most important driver gene in malignant melanoma is the BRAF mutation, and molecularly targeted therapies targeting mutations, mainly V600E and V600k, are used in clinical practice. In this report, we treated a patient with malignant melanoma expressing a rare BRAF-ZKSCAN5 fusion gene with dabrafenib/trametinib. The patient was a 71-year-old female. She was diagnosed with malignant melanoma (pT4aN3M0, STAGE IIIC) of the abdomen with axillary lymph node metastasis. She underwent extended resection and axillary lymph node dissection and was treated with adjuvant therapy, but lung and mediastinal lymph node metastases developed. The patient was treated with immune checkpoint inhibitors for metastatic lesions and achieved complete remission, but relapsed and metastatic lesions appeared in the cervical lymph nodes. Next-generation sequencing revealed the BRAF-ZKSCAN5 fusion gene, and treatment with dabrafenib/trametinib was initiated. After 1 month of treatment, tumor growth stopped and the length of the tumor shrank by 22.2%, but she developed grade 3 adverse events of nausea, fatigue, and diarrhea and had difficulty exercising, forcing her to discontinue treatment after 6 weeks. The tumor continued to shrink during drug administration. This case report may provide insight into treatment options for cases in which the BRAF fusion gene was observed, which is expected to be detected in large numbers by next-generation sequencing in the future.

Correspondence to:
Hiroshi Kato, hkato43@gmail.com

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Introduction

Several genetic mutations have been reported in malignant melanoma that are targets for therapy, the most important of which are BRAF mutations, which are driver genes for tumor cell growth and are generally expressed in the V600 region [1]. This gene mutation is known to be found in cancers other than melanoma, such as biliary tract and lung cancer, and the benefit of molecularly targeted therapies has also been reported [2, 3]. The most common of these mutations is in the V600E region, but several other mutations have been reported in recent years [4]. In this study, we report a case of melanoma expressing the BRAF-ZKSCAN fusion gene that was successfully treated with dabrafenib/trametinib.

Case Report

With the development of cancer genome research, has identified various melanoma driver genes have been identified [5]. We report a case of melanoma expressing the BRAF-ZKSCAN5 fusion gene that was treated with dabrafenib/trametinib. The patient was a 71-year-old female. She underwent extended resection and axillary lymph node dissection for abdominal malignant melanoma in the abdomen with axillary lymph node metastasis (pT4aN3M0, STAGE IIIC) and received peginterferon-α as postoperative adjuvant therapy (Fig. 1). Lung and mediastinal lymph node metastases were detected 2 months after surgery, and she was treated with nivolumab. Her metastatic lesions remained stable for 2 years, but then increased in number 2 years after the initial treatment. The combination of treatment with ipilimumab and nivolumab was started as second-line therapy. Although the patient achieved a complete response at the first posttreatment evaluation, she developed bullous pemphigoid with a mucocutaneous rash after the second administration, and the ipilimumab/nivolumab treatment was discontinued. After remission of the bullous pemphigoid, treatment with pembrolizumab was started. No tumor relapse was observed during the first year of treatment, but cervical lymph node metastases appeared and gradually increased. At that time, the other lesions continued to shrink. Therefore, radiotherapy (electron beam, 66 Gy) was applied to the cervical lymph node, leading to a partial response (Fig. 2). At 4 months after the completion of radiotherapy, the tumor was enlarged (Fig. 3). Next-generation sequencing with FoundationOne® CDx detected the gene for the BRAF-ZKSCAN5 fusion protein, leading to treatment with dabrafenib/trametinib. At 1-month posttreatment, the tumor had stopped growing and the long diameter was reduced by 22.2% (Fig. 4). The patient developed grade 3 adverse events of nausea, fatigue, and diarrhea, which caused movement difficulties and forced the discontinuation of treatment 6 weeks. A chronology was created from a timeline of events that occurred with this patient (Table 1).

Discussion

BRAF mutations, involving the driver gene for tumor cell growth, are usually observed in the V600 region [6]. In this case, a fusion gene related to BRAF was expressed. The efficacy of BRAF/MEK inhibitors in such cases is well established [7]. In addition, the efficacy of the BRAF/MEK inhibitor for brain metastases from melanoma was also reported in BRAFi naive patients with an overall response rate of 67.3%, median overall survival of 20.0 months, and median progression-free survival of 7.5 months compared to previous treatment modalities [8].

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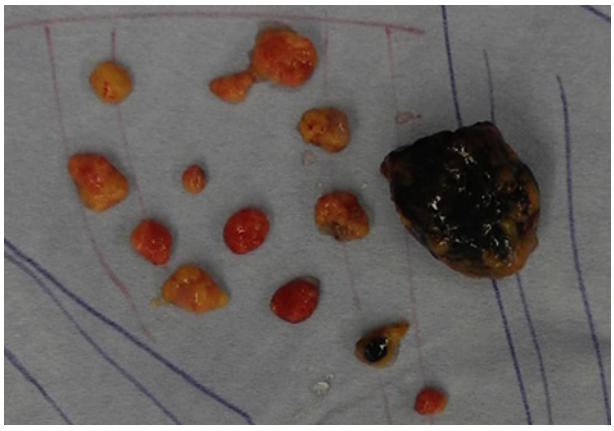

Fig. 1. Dissected right axillary lymph nodes showing gross metastasis.

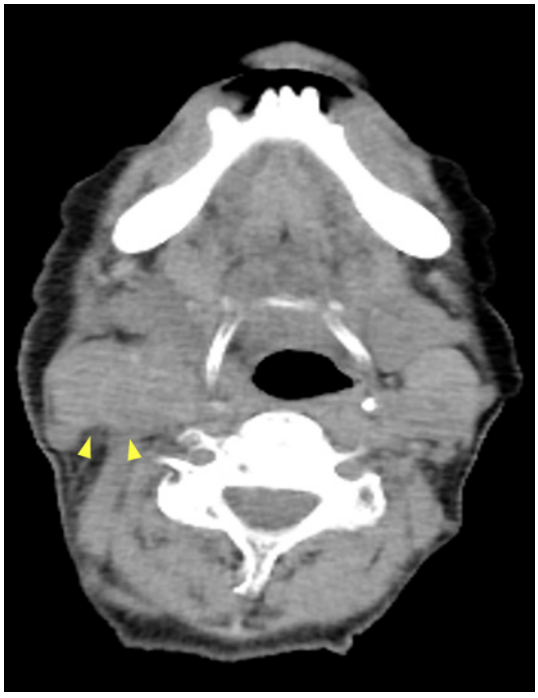

Fig. 2. CT scan of the neck after radiotherapy: arrow indicates lymph node with a long diameter of 23.5 mm.

Although there are some case reports of BRAF fusion genes in various tumors other than melanoma, no BRAF-targeted therapies for melanoma have been reported [9, 10]. Previous basic research on melanoma cells reported that the efficacy of BRAF inhibitors is specific to the fusion gene type [11]. In another case report, a MEK inhibitor was administered to a case of malignant melanoma expressing the GOLGA4-RAF1 fusion gene, and efficacy was achieved [12]. Similarly, in our case, the efficacy of dabrafenib/trametinib was observed during short-term administration in our case, and the results suggest that the BRAF-ZKSCAN5 fusion gene is a potential target gene for the treatment of melanoma. Although many variations of BRAF fusion genes are known, the effects of molecularly targeted therapeutics on each fusion gene remain unclear. As cancer genomic testing becomes more widespread in the future, it is expected that multiple such genes will be detected. This case

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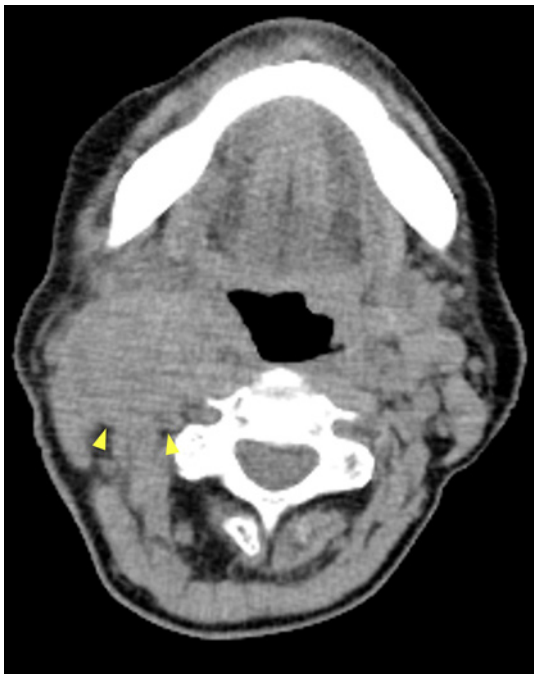

Fig. 3. CT scan of the neck 4 months after the completion of radiotherapy; lymph node diameter increased to 35.3 mm.

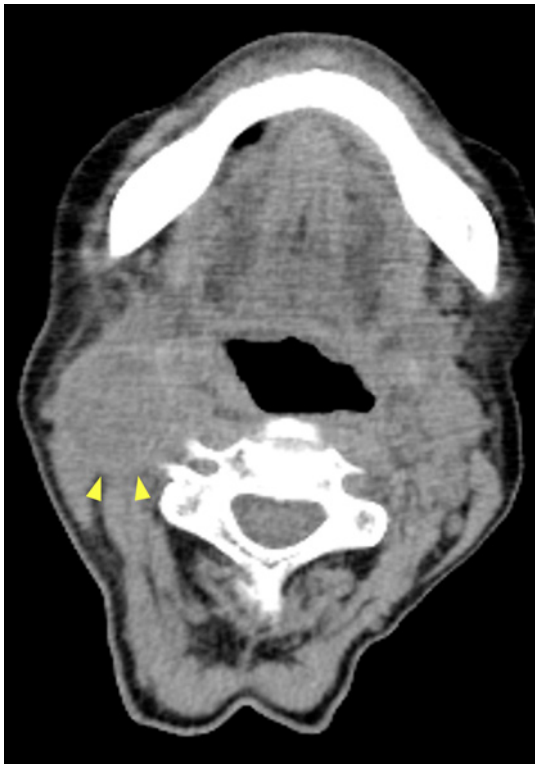

Fig. 4. Cervical CT 1 month after dabrafenib/trametinib administration; lymph node long diameter reduced to 27.5 mm.

report may provide evidence for treatment options for cases with BRAF fusion gene detection, which is expected to be detected in large numbers by next-generation sequencing in the future. It is important to accumulate such reports while conducting basic research to

Table 1. Time line of events that occurred with this patient

Date	Event
Aug/20XX	Initial medical evaluation
Sep/20XX	Extended resection, axillary lymph node dissection
Oct/20XX	Peginterferon-alpha started
Dec/20XX	Pulmonary metastasis and mediastinal lymph node metastasis appear
Jan/20XY	Nivolumab started
	Multiple subcutaneous metastases were resected, but no metastases other than subcutaneous for 3 years
Feb/20XZ	Multiple lung metastases appeared
Mar/20XZ	Started ipilimumab and nivolumab
May/20XZ	Onset of bullous pemphigoid
Jun/20XZ	Started pembrolizumab
	No disease progression for 1 year
Jun/20XA	Onset of cervical lymph node metastases
Aug/20XA	Started radiation therapy to cervical lymph nodes
Dec/20XA	Shrunken cervical lymph nodes re-enlarged, dabrafenib/trametinib started
Jan/20XB	Dabrafenib/trametinib discontinued due to nausea symptoms

deepen our understanding of the effects of drugs on each target molecule. The CARE Checklist has been completed by the authors for this case report, available online at https://doi.org/10.1159/000533822.

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Statement of Ethics

Written informed consent was obtained from the patient for publication of the details of their medical case and any accompanying images. In addition, the administration of dabrafenib/trametinib in this case was reviewed and approved review by the Ethics Committee of Nagoya City University Hospital (approval #2021-33).

Conflict of Interest Statement

Kato H. has received speakers' bureau from Novartis Pharma K.K.

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Author Contributions

Kato H. wrote the case report. Kato H., Kano S., Yasui Y., Nojiri Y., Yoshimitsu M., and Nakamura M. contributed to the clinical management of this patient. Morita A. contributed to critical review of the manuscript for important intellectual content.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material. Further inquiries can be directed to the corresponding author.

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