Conversion Surgery for Advanced Thoracic SMARCA4-Deficient Undifferentiated Tumor With Atezolizumab in Combination With Bevacizumab, Paclitaxel, and Carboplatin Treatment: A Case Report

Kei Kunimasa, MD, PhD, a,* Jiro Okami, MD, PhD, b Satoshi Takenaka, MD, PhD, c Keiichiro Honma, MD, PhD, d Yoji Kukita, PhD, e Shigenori Nagata, MD, PhD, d Takahisa Kawamura, MD, PhD, a Takako Inoue, MD, a Motohiro Tamiya, MD, a Hanako Kuhara, MD, PhD, a Kazumi Nishino, MD, PhD, a Hideaki Tahara, MD, PhD, f,g Toru Kumagai, MD, PhD a

aDepartment of Thoracic Oncology, Osaka International Cancer Institute, Osaka, Japan
bDepartment of General Thoracic Surgery, Osaka International Cancer Institute, Osaka, Japan
cMusculoskeletal Oncology Service, Osaka International Cancer Institute, Osaka, Japan
dDepartment of Diagnostic Pathology and Cytology, Osaka International Cancer Institute, Osaka, Japan
eLaboratory of Genomic Pathology, Osaka International Cancer Institute, Osaka, Japan
fDepartment of Cancer Drug Discovery and Development, Research Center, Osaka International Cancer Center, Osaka, Japan
gProject Division of Cancer Biomolecular Therapy, Institute of Medical Science, The University of Tokyo, Tokyo, Japan

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ABSTRACT

A SMARCA4-deficient undifferentiated tumor (SMARCA4-UT) is a rapidly progressing subtype of lung cancer with a poor prognosis and causes early postoperative recurrence among operable patients. In this study, we present a case of SMARCA4-UT with vertebral and chest wall invasion that successfully underwent conversion surgery after treatment with atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin. The surgical specimen comprised SMARCA4-deficient and SMARCA2-positive adenocarcinoma, confirming intratumor heterogeneity. Gene panel analysis revealed no substantial differences in mutant gene profiles among tumors and no differences in SMARCA2 mutations. Furthermore, no recurrence occurred for 9 months after surgery. Thus, this case illustrates the possibility of multidisciplinary treatment including...
neoadjuvant therapy with immunotherapy and conversion surgery for SMARCA4-UT.

Keywords: SMARCA4-deficient undifferentiated tumor; Conversion surgery; Neoadjuvant therapy; Immunotherapy; Case report

Introduction

Thoracic SMARCA4-deficient undifferentiated tumor (SMARCA4-UT) is a lung cancer newly classified in the fifth edition of the WHO classification of thoracic tumors published in 2021. Initially published as SMARCA4-deficient thoracic sarcoma, it was later classified as a subtype of undifferentiated lung cancer of pulmonary epithelial origin. Most cases of SMARCA4-UT exhibit advanced stage at presentation, with poor prognosis and epithelial origin. Most cases of SMARCA4-UT exhibit subtype of undifferentiated lung cancer of pulmonary de

In addition to residual SMARCA4-UT, SMARCA4-deficient, SMARCA2-retained, and TTF-1–positive adenocarcinoma (SMARCA4-deficient adenocarcinoma [SMARCA4-DA]) were found at a distant site. The programmed death ligand-1 tumor proportion score of both components was 0% (Fig. 3C).

Genomic analysis of SMARCA4-UT specimen and two surgical resected specimens of SMARCA4-UT and SMARCA4-deficient adenocarcinoma was performed using the Illumina TruSight Oncology 500 (TSO500) panel (Supplementary Method) (Fig. 3D). Similar mutations were detected in SMARCA4 D1161fs* and in TP53 V157L in all three specimens. The oncogenic mutations of TET2 and PHOX2B were less than 10% in variant allele frequency. Moreover, the whole-exome sequence of the SMARCA2 gene was performed separately from the TS0500 panel, and the SMARCA2 Q235P mutation was detected from all three samples.

Discussion

SMARCA4-UT often occurs in advanced stages, presenting early postoperative recurrence and poor prognosis among operable patients. In the present case, the patient was diagnosed with clinical stage IVA with vertebral invasion and pleural dissemination; however, ABCP treatment markedly reduced the tumor and paved the way for conversion surgery. Postoperative adjuvant therapy was not performed, and no recurrence was observed for 9 months.
Figure 1. Chest plain enhanced CT images and histopathological analysis of CT-guided biopsy specimen. (A) Transverse chest CT images depict lung mass and parenchymal emphysema. (B) Transverse and sagittal enhanced CT images reveal tumor invasion into vertebrae and ribs. (C) Coronal CT image suggests pleural dissemination (yellow arrowheads). (D) Immunohistopathologic analysis of the biopsy specimen. HE staining presents undifferentiated round to plasmacytoid cells with prominent nucleoli and overall monomorphism. Immunohistochemical features indicate the complete loss of SMARCA4 and SMARCA2 in tumor cells with retained expression in normal inflammatory and stromal cells, lack of TTF-1, p40, and Claudin-4. The PD-L1 TPS using the 22C3 pharmDx assay is 0%. COSMIC, Catalogue Of Somatic Mutations In Cancer; CT, computed tomography; HE, hematoxylin and eosin; PD-L1, programmed death ligand-1; TPS, tumor proportion score.

Figure 2. Changes in transverse and sagittal enhanced CT images of the chest during the ABCP treatment. ABCP, atezolizumab in combination with bevacizumab, paclitaxel, and carboplatin; CT, computed tomography.
SMARCA4-UT is caused by heavy smoking, and mutations such as STK11, KEAP1, ARID1A, KRAS, and NF1 may occur as comutations after the TP53 mutation. In the present case, TP53 V157L mutation was recognized in addition to the SMARCA4 L1161fs* mutation, and the oncogenic mutation was not recognized otherwise. Mutations in STK11 and KEAP1 have been implicated for resistance to immunotherapy, but the absence of these mutations may exhibit an excellent response to ABCP therapy. Moreover, no major adverse events were associated with ABCP treatment, and the ability to complete six courses without dose reduction may have contributed to the successful conversion surgery.

SMARCA4 mutations and loss of expression occur in approximately 5% of NSCLC. Although it is unclear whether SMARCA2 deletion affects pathomorphologic differences between undifferentiated carcinoma and adenocarcinoma, the hypothesis that SMARCA4-UT is formed by additional SMARCA2 deletion has been proposed. In the present case, we confirmed the heterogeneity of SMARCA4-UT and SMARCA4-DA in the resected specimen. In this study, we investigated SMARCA2 mutations by adding the whole-exome sequence of SMARCA2. The detected SMARCA2 Q235P mutation is a nonsynonymous mutation registered in the Catalogue Of Somatic Mutations In Cancer database, but its oncogenicity is unknown, and it is also detected in the components of SMARCA2-positive SMARCA4-DA. Therefore, it is highly unlikely that it is involved in the loss of SMARCA2 function. Although SMARCA2 is rarely included in the mutations to be analyzed in gene panels and its mutations are rarely evaluated, analysis in small cell carcinoma of the ovary, hypercalcemic type, which is characterized by SMARCA4 inactivating mutations, revealed that SMARCA4 and SMARCA2 are rarely mutated together. Both SMARCA4 and SMARCA2 are subunits of the BAF complex and their conformational analysis suggests that they exist in combination, and SMARCA2
deletion may occur by a mechanism that is not mediated by gene mutation, such as a loss of SMARCA4 by inactivating mutation resulting in an inability to maintain SMARCA2 conformationally.

Analysis of the TSO500 panel revealed no substantial difference in the mutation profile between SMARCA4-UT and SMARCA4-DA. Although PHOX2B I280fs* and TET2 Q810* mutations were detected as new oncogenic mutations in SMARCA4-DA, their variant allele frequencies were less than 10%, and it is unclear whether they are major drivers mutations or not. The present analysis was performed on surgical resection specimens after ABCP therapy, and it is unclear whether these differences occurred as a result of the treatment or during the development of SMARCA4-UT. The results of the TSO500 panel analysis, together with the results of the SMARCA2 sequencing, did not reveal a mechanism for the differentiation of SMARCA4-DA to SMARCA4-UT.

Clinical studies of neoadjuvant therapy with immunotherapy are in progress. Although careful follow-up is necessary, we believe that this case illustrates the potential application of ABCP and multidisciplinary treatment including surgery for SMARCA4-UT.

Conclusions
SMARCA4-UT is a rapidly progressing subtype of lung cancer with a poor prognosis. In many cases, SMARCA4-UT is in an advanced stage at the time of diagnosis and is not amenable to surgical treatment; furthermore, it is said that it often recurs even if surgery is performed. Immunotherapy including ABCP treatment may lead to conversion surgery, as in this case. The effects of immunotherapy and the possibility of conversion surgery in SMARCA4-UT need to be evaluated in the future.

CRediT Authorship Contribution Statement
Kei Kunimasa: Conceptualization, Methodology, Investigation, Writing—original draft.
Jiro Okami: Investigation, Supervision, Writing—review & editing.
Takahisa Kawamura, Takako Inoue, Motohiro Tamiya, Hanako Kuhara, Kazumi Nishino, Satoshi Takenaka: Investigation.
Shigenori Nagata, Keiichiro Honma: Pathologic Investigation.
Yoji Kukita: Next-generation sequencing, Investigation, Software.

Hideaki Tahara, Toru Kumagai: Supervision.

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Supplementary Data
Note: To access the supplementary material accompanying this article, visit the online version of the JTO Clinical and Research Reports at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2021.100235.

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