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Case Report

Tubulointerstitial Nephritis in an Advanced Melanoma Patient Treated with Encorafenib plus Binimetinib Combination Therapy

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Keywords
Tubulointerstitial nephritis · BRAF/MEK inhibitor · Adverse event · Rheumatoid arthritis · Melanoma

Abstract
Encorafenib plus binimetinib combination therapy is one of the first-line therapies for advanced melanoma, and it is known to cause a different profile of adverse events (AEs) than dabrafenib plus trametinib combination therapy. Of such AEs, tubulointerstitial nephritis caused by BRAF plus MEK inhibitors combination therapy is limited. In this report, a case of tubulointerstitial nephritis that developed in a rheumatoid arthritis patient with advanced melanoma treated with encorafenib plus dabrafenib combination therapy is presented.

Introduction

As many guidelines for melanoma have suggested, BRAF plus MEK inhibitors, including encorafenib plus binimetinib (E + B), combination therapy is one of the optimal chemotherapies for BRAF-mutated advanced melanoma as a first-line therapy [1, 2]. Although various drug-induced adverse events (AEs) are reported in patients with E + B combination therapy [3, 4],

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cases of tubulointerstitial nephritis as an AE are limited [5]. In this report, a case of tubulointerstitial nephritis that developed in a rheumatoid arthritis patient with advanced melanoma treated with E + B combination therapy is described.

Case Report

A 74-year-old Japanese woman visited a private clinic with a history of resection of a black nodule on the left shoulder. Radical resection of the nodule with a 3-cm surgical margin was performed by a general surgeon, and it was histologically diagnosed as malignant melanoma (tumor thickness of 7 mm). She had been treated for rheumatoid arthritis with abatacept for 3 years. On her initial visit, positron emission tomography CT showed no lymph node and organ metastases. Additional sentinel lymph node biopsy of the axillary lymph node was performed, but no sentinel lymph node was found because of the previous radical resection with wide margin. The diagnosis was cutaneous malignant melanoma (pT4bNxM0: stage IIC). The THxID kit for BRAF mutation showed that the primary tumor was positive for $BRAF^{V600E}$ mutation. Four months after the radical resection, positron emission tomography CT showed left axillary lymph node and lower right lung involvement (Fig. 1a). Thereafter, encorafenib (450 mg/day) plus binimetinib (45 mg/day) combination therapy was given. Three days after the initial treatment, she complained of visual impairment. An ophthalmologist found serous retinal detachment. Moreover, the estimated glomerular filtration rate decreased 46–25 (mL/min/1.73 m^2) 1 week after the initial administration. Urinalysis did not show microhematuria nor proteinuria. Serum B2MG was above the normal range (5.6 mg/L). Renal biopsy showed that about 30% of glomeruli were sclerosing and collapsing but remaining glomeruli were intact (Fig. 1b). Tubular atrophy and interstitial fibrosis with lymphocyte infiltration were observed in about 30% of the tubular interstitial area (Fig. 1c, d). From these findings, the diagnosis was tubulointerstitial nephritis due to E + B combination therapy. The combination

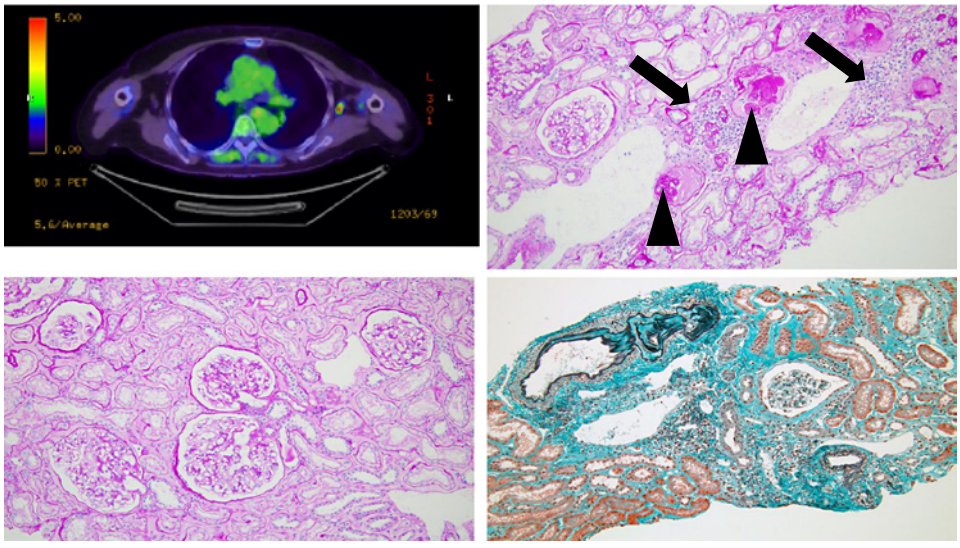

Fig. 1. PET-CT findings: left axillary lymph node (**a**) Histopathological findings of the renal biopsy: about 30% of glomeruli were sclerosing and collapsing but remaining glomeruli were intact (**b**), affected area: tubular atrophy (allow) and interstitial fibrosis with lymphocyte infiltration (allow) were observed in the tubular interstitial area (**c**, **d**). (H&E staining (**b**, **c**), Elastica Masson staining (**d**)). PET-CT, positron emission tomography CT.

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therapy was stopped, and 3 months later, her serum creatinine had gradually decreased (1.06 mg/dL) without additional treatment.

Discussion

E + B combination therapy is one of the first-line therapies for advanced melanoma that is recommended by several guidelines for cutaneous melanoma [1, 2], and it is known to develop a different profile of AEs compared with dabrafenib plus trametinib (D + T) combination therapy [3, 6]. For example, one of the characteristic AEs of E + B combination therapy is serous retinal detachment [3–5], whereas a characteristic AE of D + T combination therapy is pyrexia [6–8]. However, a case of tubulointerstitial nephritis as an AE of E + B combination therapy was limited in all of these clinical studies [3–5].

Little is known about the mechanisms of interstitial nephritis in E + B combination therapy. A case of tubulointerstitial nephritis that developed in a rheumatoid arthritis patient with advanced melanoma treated with E + B combination therapy was described. Notably, as we previously reported, increased serum CXCL5 could be one of the biomarkers for AEs by BRAF plus MEK inhibitors in advanced melanoma patients [9]. Since circulating CXCL5 is correlated with the activity of rheumatoid arthritis [10] and could even be a biomarker for the prediction of immune-related AEs of anti-PD1 antibody in melanoma patients [11], rheumatoid arthritis-related factors, such as CXCL5, might have triggered the tubulointerstitial nephritis in the present case. Since only a single case was presented, further cases are needed to confirm the correlation between E + B combination therapy and the onset of tubulointerstitial nephritis in rheumatoid arthritis with advanced melanoma.

Statement of Ethics

Written, informed consent was obtained from the patients for publication of this case report and any accompanying images. The protocol for this human study was approved by the Ethics Committee of Tohoku University Graduate School of Medicine, Sendai, Japan (permit no. 2019-1-417).

Conflict of Interest Statement

The authors have no conflicting interests to declare.

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Author Contributions

Yumi Kambayashi, Hiromi Chiba, Erika Tamabuchi, Kentaro Ohuchi, Tasuku Nagasawa, Yoshihide Asano, and Taku Fujimura treated the patient and acquired the clinical data. Yumi Kambayashi and Taku Fujimura wrote the manuscript. Yoshihide Asano and Taku Fujimura supervised the study.

Data Availability Statement

All data generated or analyzed during this study are included in this article.

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