A case of metastatic Xp11.2 translocation renal cell carcinoma successfully managed by cytoreductive nephrectomy followed by axitinib therapy

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Abstract. Targeted medications for metastatic adult Xp11.2 translocation renal cell carcinoma (RCC) remain to be identified. We herein report a case of metastatic Xp11.2 translocation RCC controlled with cytoreductive nephrectomy (CN) and axitinib therapy. A 57-year-old woman complained of fatigue and low back pain. Imaging studies revealed a right renal tumor, with multiple lung and mediastinal lymph node metastases. Although the patient received 10 mg axitinib therapy for 5 months at the hospital she was initially admitted to, the size of the primary and metastatic lesions was not reduced. Thus, she was referred to the Tokyo Women's Medical University Hospital (Tokyo, Japan) for further treatment, where she underwent CN. On macroscopic examination, almost the entire kidney was replaced by a yellowish brown tumor >80 mm in diameter. Immunohistochemical examination confirmed the diagnosis of Xp11.2 translocation RCC. One month after surgery, axitinib therapy was resumed and the size of the metastatic lesions gradually decreased. These findings suggest that axitinib therapy is effective for adult Xp11.2 translocation RCC.

Introduction

Xp11.2 translocation renal cell carcinoma (RCC) involves fusion between the transcription factor binding to IGHM enhancer 3 (TFE3) in chromosome Xp11.2 and various partners, and was classified as a separate subset of RCCs by the World Health Organization in 2004 (1). According to a published article, 1.6% of adult RCCs involve Xp11.2 translocation and 15% of patients aged <45 years had translocation RCC (2). Compared with conventional RCC, this type of RCC is mostly diagnosed at an advanced stage, as it exhibits an aggressive course (3-7). However, a systemic therapy for metastatic adult Xp11.2 translocation RCC has not yet been established. We herein report a case of metastatic Xp11.2 translocation RCC that was oncologically controlled with cytoreductive nephrectomy (CN) and axitinib therapy.

Case report

A 57-year-old woman presented to a local hospital with fatigue and low back pain in October 2014. The laboratory tests revealed high levels of aspartate aminotransferase, alanine aminotransferase and lactate dehydrogenase. Ultrasonography and computed tomography revealed a right renal tumor, 80 mm in diameter, extending to the renal vein. Multiple lung nodules, lymphadenopathy of the mediastinal lymph nodes and pulmonary hilar lymph nodes were also identified (Fig. 1). The patient was diagnosed with RCC of clinical stage T3aN0M1, with intermediate risk according to the Memorial Sloan-Kettering Cancer Center risk classification (8). Although axitinib treatment was administered for 5 months at the initial hospital, the status of the primary and metastatic lesions remained unchanged. Thus, the patient was referred to the Tokyo Women's Medical University Hospital for further treatment in January 2015. CN was planned, followed by targeted therapy. On macroscopic examination following CN, almost the entire kidney was replaced by a yellowish brown tumor >80 mm in diameter. Histological examination of hematoxylin and eosin-stained sections revealed that the tumor was composed of cells with a voluminous clear cytoplasm and pleomorphic nuclei with prominent nucleoli (Fig. 2A). In addition, TFE3 immunostaining was positive (Fig. 2B). Thus, the pathological diagnosis was Xp11.2 translocation RCC. Axitinib treatment was resumed 1 month after surgery. At 11 months after surgery, follow-up computed tomography revealed that the size of the metastatic lung lesions was decreased by 11%, despite the limited effectiveness of the preoperative axitinib therapy (Fig. 3). Adverse events included grade 2 hypertension, grade 2 digestive symptoms and grade 2 hand-foot syndrome, assessed according to the Common Terminology Criteria

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Abbreviations: RCC, renal cell carcinoma; CN, cytoreductive nephrectomy

Key words: metastasis, molecular-targeted therapy, renal cell carcinoma, nephrectomy

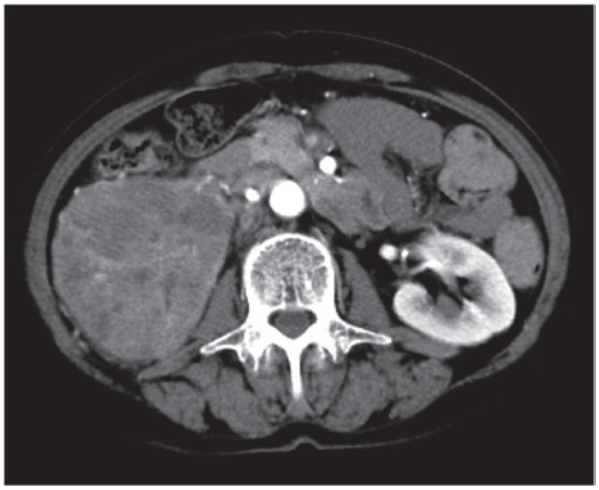

Figure 1. Computed tomography image showing a right renal tumor, 80 mm in diameter, with a thrombus in the right renal vein.

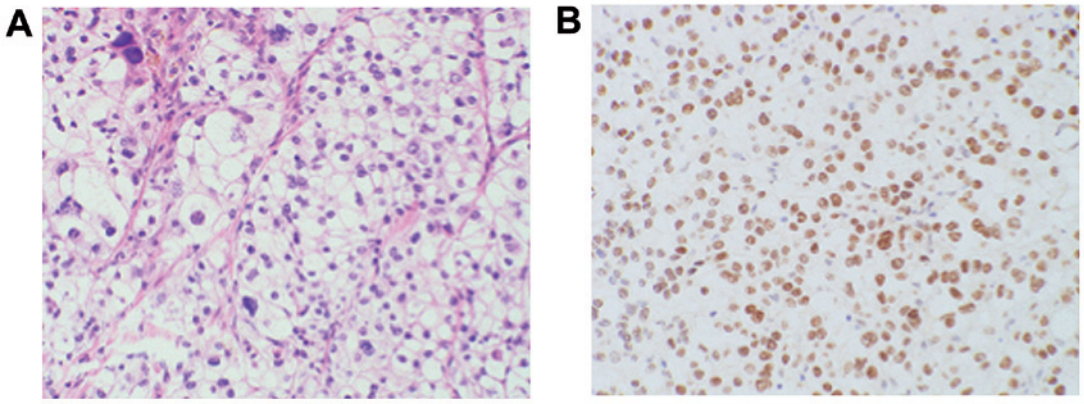

Figure 2. (A) Hematoxylin and eosin staining of a surgical specimen showing that the tumor was composed of cells with a voluminous clear cytoplasm and pleomorphic nuclei with prominent nucleoli (original magnification, x400). (B) Immunostaining for transcription factor binding to IGHM enhancer 3 was positive (original magnification, x400).

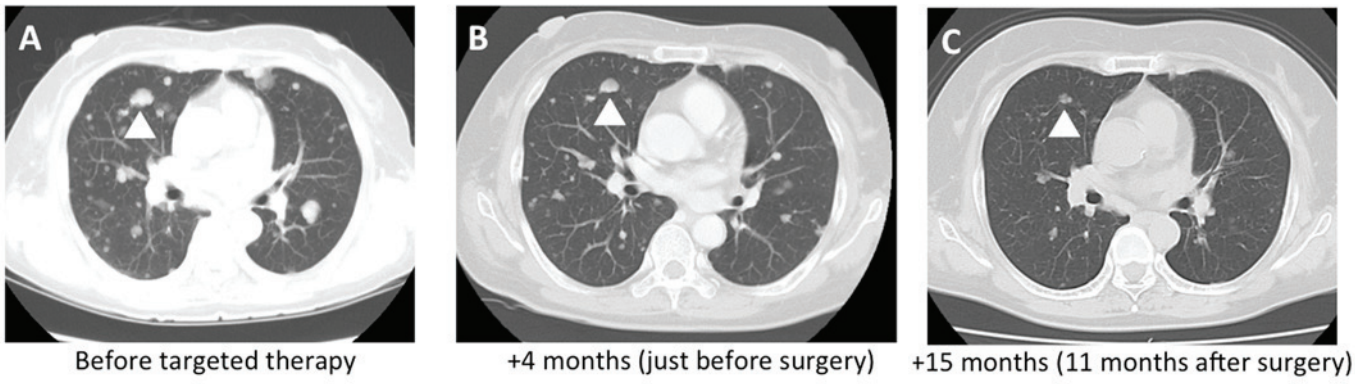

Figure 3. (A) Computed tomography revealed lung metastasis prior to the administration of axitinib. (B) The measurable metastatic pulmonary lesion (arrowheads) exhibited a 1% increase in size at 4 months after the initiation of axitinib (just prior to surgery). (C) The lesion showed a size reduction of 11% at 15 months after the initiation of axitinib (11 months after surgery).

for Adverse Events, version 4.0 (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf). The patient maintained stable disease for >12 months after the surgery and received the last ambulatory treatment in October 2016.

Discussion

We herein report a case of metastatic Xp11.2 translocation RCC that was oncologically controlled with CN and axitinib therapy for >12 months. In addition, CN may have

enhanced the effectiveness of the axitinib therapy in this case. Xp11.2 translocation RCC includes a translocation that activates the MET protein owing to the TFE3 gene on the X chromosome or the microphthalmia-associated transcription factor (MiTF) on chromosome 6 (6). Several reports investigated the management of metastatic Xp11.2 translocation RCC by immunotherapy (2,5), but the response to this type of therapy was poor. Regarding targeted therapy, previous multicenter retrospective studies of sunitinib reported a median progression-free survival time of 7.1-8.2 months (9,10). One pediatric case of metastatic Xp11.2 translocation RCC was controlled with axitinib therapy (11); however, to the best of our knowledge, reports of adult cases oncologically controlled with axitinib therapy are not available in the literature. The benefit of CN was evaluated by previous prospective randomized research studies in the cytokine therapy era (12,13). By contrast, the usefulness of CN in the new era of targeted therapy has not been confirmed in a large randomized trial, although several retrospective studies have demonstrated the effectiveness of CN (14,15). Heng *et al* assessed the overall survival benefit of CN in comparison with targeted therapy without CN in metastatic RCC (mRCC) patients according to the International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria (16); the authors demonstrated that CN is beneficial in patients with synchronous mRCC treated with targeted therapy, even in cases of non-clear cell histology. In addition, they found that the majority of the patients benefited from CN, except for those with ≥4 IMDC risk factors (17). In the present case, axitinib therapy was commenced prior to nephrectomy at the initial hospital, despite the presence of one IMDC risk factor; the time from diagnosis to initial treatment was <1 year. Five months of axitinib therapy did not reduce the size of the primary or metastatic lesions. However, CN followed by axitinib therapy resulted in reduction of the size of the lung and lymph node metastases, suggesting that CN may enhance the effectiveness of axitinib therapy. However, whether CN prolongs survival in the targeted era remains unclear and, if so, it should be performed before or after targeted therapy. The results of two ongoing prospective randomized trials, the Clinical Trial to Assess the Importance of Nephrectomy (CARMENA; NCT0093033) and the European Organization for Research and Treating Patients with Metastatic Kidney Cancer trial (SURTIME; NCT01099423), are expected.

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