CDK12 and HER2 coamplification in two urothelial carcinomas with rapid and aggressive clinical progression

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Abstract
Cyclin-dependent kinase 12 (CDK12), one of the key factors associated with DNA damage response pathways, is located on chromosome 17 proximal to Erb-B2 receptor tyrosine kinase 2 (ERBB2). In this report, CDK12 and ERBB2 coamplification was detected by targeted next-generation sequencing in two urothelial carcinomas. The staining intensity of the CDK12 and human epidermal growth factor receptor-2 proteins was associated with the prognosis of each urothelial carcinoma case. Our results suggest that CDK12 coamplification with ERBB2 might be associated with tumor aggressiveness and contribution to cancer pathogenesis. Therapies targeting CDK12 should be developed for these patients.

KEYWORDS
CDK12 amplification, DNA repair gene, ERBB2, prostate cancer, urothelial carcinoma

1 | INTRODUCTION
Cyclin-dependent kinase 12 is an important kinase necessary for modulating transcription in various cellular processes, including DDR, cell growth regulation, and differentiation, similar to HER2.1,2 Loss of CDK12 function could cause genomic instability, suggesting the need for PARP inhibitor treatment. CDK12 mutation could predict sensitivity to targeted treatments against BRCA-mutant tumors, such as PARP1 inhibitors.3,4 In breast cancer, CDK12 gene amplification often coexists with ERBB2 amplification because both are colocated at locus Ch17q12, and CDK12 overexpression correlates with aggressive tumor progression and anti-HER2 therapy resistance through the activation of ErbB-PI3K-AKT or WNT-signaling cascades; given this colocation, CDK12 could act as an oncogenic driver and a prognostic biomarker in breast cancer.5 However, CDK12 and ERBB2 coamplification in urological cancers remains unreported. In this study, we report on two patients with urothelial carcinoma showing CDK12 and ERBB2 coamplification.

2 | CASE PRESENTATIONS
2.1 | Patient 1
An 89-year-old man had been diagnosed with prostatic adenocarcinoma, with a PSA level of 7.7 ng/mL at presentation and a Gleason score of 6 in prostate biopsies. He underwent radical...
prostatectomy and adjuvant radiotherapy at 73 years of age. His recurrence-free survival rate reached more than 10 years. However, he complained of hematuria. Urine cytology samples were reported as suspicious (class III), and CT, as well as cystoscopy, detected a bladder tumor (Figure S1). After undergoing TURBT and eight consecutive weekly intravesical instillations of BCG, the patient was diagnosed with bladder carcinoma in situ. One year after TURBT, tumor recurred and was then resected. The pathological diagnosis was high-grade invasive urothelial carcinoma without lymph node or distant metastases (pT1N0M0). Five cycles of weekly intravesical instillations of BCG were provided. One month later, the patient had bilateral hydronephrosis caused by bladder cancer. Despite undergoing percutaneous nephrostomy to improve renal function, the patient died because of the progressive worsening of pleural effusions.

Targeted next-generation sequencing of the resected bladder specimen with recurrent tumor was carried out using an in-house assay during treatment (Appendix S1 and Table S1). Meanwhile, ERBB2 amplification (estimated CN, 61.3) and CDK12 amplification (estimated CN, 38.2) were found. Furthermore, we detected TP53 somatic point mutation (p.F113C) with LOH as an actionable variant in the tumor, and EP300 somatic point mutations (p.G672R and p.T2391M) as VUS. In addition, SMARCA4 showed LOH without mutation. In the samples, the TMB calculated from our pipeline was 5.4 SNV/Mbp. Moreover, the CN variation box revealed that CDK12 coamplified with ERBB2 (Figure 1), and the tumor cells showed a strong positive staining for HER2 and CDK12 (Figure 2).

2.2 | Patient 2

A 72-year-old man was diagnosed with prostatic adenocarcinoma, with a PSA level of 7.0 ng/mL at presentation and a Gleason score of 7 in prostate biopsies. He underwent radical prostatectomy and obtained a PSA nadir of 0.04 ng/mL. After 3 months postoperatively, he complained of hematuria. Contrast-enhanced CT scan showed an enhancing mass and filling located in the right renal pelvis (Figure S1). He was diagnosed with primary right renal pelvic carcinoma incidentally. Thus, he underwent right radical nephroureterectomy. The pathological diagnosis was high-grade invasive urothelial carcinoma with pT3 (infiltration of the renal parenchyma). He then received three cycles of adjuvant chemotherapy. Nine months after nephroureterectomy, he underwent instrumented lumbar fixation surgery and palliative radiotherapy for the lumbar spine metastasis of renal pelvic carcinoma. The patient was then treated with five cycles of intravenous pembrolizumab every 3 weeks. Two months later, however, the patient died because of pancytopenia due to multiple bone marrow metastases.

Targeted next-generation sequencing of the resected prostate specimen and renal specimen was separately carried out. FANCD2 and NOTCH1 point mutations (VUS) were detected in the prostate specimen, with no gene CN alteration, whereas ERBB2 amplification (estimated CN, 4.5) and CDK12 amplification (estimated CN, 4.3) were observed in the renal specimen. Two VUS point mutations (p.S633F and p.A763D) were additionally detected in the ERBB2 gene. Furthermore, TP53 somatic frameshift mutation (p.Y236*), FANCD2 VUS mutation, and LOH without mutation in

![Figure 1](image-url)  
**Figure 1** Examined genes (horizontal axis) and the copy number in each case (vertical axis) of two men (Patient 1, 89 years old) and (Patient 2, 72 years old) with urothelial carcinomas with rapid and aggressive clinical progression.
WT1, SMAD4, KDM6A, FANCA, PBRM1, BAP1, and SETD2 were detected in the sample. The TMBs in the prostate and renal samples were 4.0 and 2.7 SNV/Mbp, respectively. The CN variation box indicated that CDK12 coamplified with ERBB2 in the renal sample (Figure 1). Furthermore, the tumor cells showed moderate positive staining for HER2 and CDK12 (Figure 2). Overall, the patient had multiple primary cancer.

3 | DISCUSSION

CDK12 is one of the key factors associated with DDR pathways. Cyclin-dependent kinase alteration is reportedly associated with PARP inhibitors,3,4 which are effective in patients with DDR mutation-positive prostate cancer according to a well described synthetically lethal effect.6 However, CDK12-altered prostate cancer is an aggressive subtype that poorly responds to PARP inhibitors or to hormonal and taxane therapies.7 In addition, this subtype has a distinct immunological microenvironment and is associated with programmed cell death-1/programmed cell death-ligand 1 inhibitor response.

Recent topics shed light on CDK12 coamplification with ERBB2. CDK12 is located on chromosome 17, 165-267 kb proximal to ERBB2.9 In the two patient cases, CDK12 amplification accompanied with ERBB2 amplification was detected by targeted next-generation sequencing in urothelial carcinomas. For patients with HER2-positive advanced breast, gastric, or lung cancer, an anti-HER2 Ab (trastuzumab deruxtecan) is reportedly effective.10-12 However, the effectiveness of anti-HER2 therapy for breast cancers with CDK12 and ERBB2 coamplification is still unconfirmed.13,14 For these patients, anti-CDK12 therapy will be effective because it induces self-renewal of breast cancers and reduces susceptibility to anti-HER2 therapy.5 Furthermore, CDK12 kinase activity inhibition facilitates anticancer efficacy of the anti-HER2 therapy in HER2-positive tumors, and mice bearing trastuzumab-resistant HER2-positive tumors are reportedly sensitive to CDK12 inhibitor.5 Mechanistically, the catalytic activity of CDK12 is required for the expression of genes involved in the activation of ErbB-PI3K-AKT or WNT signaling cascades.5

In the present cases, immunohistochemistry validated that the CDK12 and HER2 proteins were highly expressed. The staining intensity differed because the degrees of amplification of CDK12 and ERBB2 genes also varied; such intensity is associated with the prognosis of each urothelial carcinoma case. The first patient had a low-risk prostate cancer but a fatal urothelial bladder tumor. The bladder tumor was BCG-resistant, and it progressed exponentially. The second patient, who also had a prostate cancer, achieved excellent long-term cancer control after prostatectomy. The patient also had a primary renal pelvic carcinoma and died despite treatment with multidisciplinary therapy, including nephroureterectomy, radiotherapy, and systemic therapy. Anti-HER2 therapy might not be effective for treating patients with CDK12 and ERBB2 coamplification, and therapy targeting CDK12 can be a therapeutic option for these patients.

To the best of our knowledge, CDK12 and ERBB2 coamplification in urothelial carcinoma has not been reported. Our results suggest that CDK12 coamplification with ERBB2 could be associated with tumor aggressiveness and could contribute to cancer pathogenesis. The present report provides important data for the future study of precision medicine for urothelial carcinoma.

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CONFLICT OF INTEREST

The authors have no conflicts of interest.

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SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section.

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