Original Article

Human epidermal growth factor receptor 2 expression in urothelial carcinoma of the renal pelvis: correlation with clinicopathologic parameters

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Abstract: The significance of human epidermal growth factor receptor 2 (HER2) overexpression in breast cancer is well established, and these patients are subsequently treated with Trastuzumab. Although HER2 expression in urothelial carcinoma of the urinary bladder has also been recently characterized, it has not been well studied in urothelial carcinoma of the renal pelvis. We investigated the relationship between HER2 overexpression in urothelial carcinoma of the renal pelvis and clinicopathologic parameters. Forty six cases were identified. HER2 overexpression was present in 34/46 (74%) cases. Mean patient age with HER2 overexpression was 68 years (range: 42-87 years). There was a male predominance with 28/34 (82%) patients. High grade urothelial carcinoma was present in 32/34 (94%) cases and 2/34 (6%) cases had low grade urothelial carcinoma. Pathologic staging was as follows; 9/34 (26%) cases were pTa, 10/34 (29%) cases were pT1, 2/34 (6%) cases were pT2, 12/34 (35%) cases were pT3, and 1/34 (3%) cases was pT4. An inverted growth pattern was present in 23/46 (50%) cases. HER2 overexpression was present in 15/23 (65%) cases of urothelial carcinoma with an inverted growth pattern. Our study showed that HER2 overexpression is more common in male patients with high grade urothelial carcinoma, especially those with an inverted growth pattern. It is highly conceivable that patients with urothelial carcinoma of the renal pelvis may be further stratified based on HER2 overexpression, and may also be potential candidates for Trastuzumab therapy in the neoadjuvant or adjuvant setting.

Keywords: Urothelial carcinoma, renal pelvis, immunohistochemistry, HER2, targeted therapy

Introduction

Upper urinary tract urothelial carcinoma is defined as a tumor that arises from the urothelium that lines the calyx, renal pelvis or ureter [1]. Urothelial carcinoma of the renal pelvis is relatively uncommon and accounts for 5-7% of urothelial carcinomas with an estimated incidence of 1-4 cases per 100 000 individuals per year [2-4]. The overall incidence has increased over the past several decades due to the increased use of ureteroscopy [5]. Urothelial carcinoma of the renal pelvis occurs twice as frequently as urethral tumors [4]. Compared to bladder cancers, upper urinary tract urothelial carcinoma are usually more invasive tumors at diagnosis and are associated with a worse prognosis [6]. Potential prognostic roles of tumor stage, tumor grade, lymphovascular invasion, and lymph node involvement are well established in this setting [7-9].

Despite advances in endoscopic and minimally invasive treatments, the gold standard procedure remains radical nephroureterectomy with excision of a bladder cuff and retroperitoneal lymph node dissection [10, 11]. However, upper urinary tract urothelial carcinoma is known to have a high recurrence rate including intravesical recurrence, even after radical surgery [12]. Patient survival is mainly influenced by stage, and 5-year survival rates range from 90% in early pathologic stages (pTa/pT1) to less than 5% in stages with lymph node involvement or metastatic disease [13]. The high recurrence and mortality rates in high-risk patients indicate the essential role of choosing the effective additional adjuvant treatment. Cisplatin-based
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The HER2 proto-oncogene which was previously called HER2/neu or (C-)ErbB-2, is located on chromosome 17q21 and encodes the 185 kDa transmembrane tyrosine kinase receptor HER2. The HER2 receptor is part of the EGF receptor (EGFR) family, which is important in several biochemical pathways including activation of signal transduction pathways controlling epithelial cell growth and differentiation, and possibly angiogenesis [14, 15]. Overexpression of HER2 protein products is observed in approximately 20% of human breast cancers [16]. It leads to an increase in HER2 messenger RNA levels and a concomitant overexpression of the HER2 receptor on the tumor cell surface [17]. In breast cancer it is crucial for both prognosis and prediction of the response to targeted therapies, and HER2 testing is recommended in all newly diagnosed cases of invasive breast cancer [18, 19]. The introduction of trastuzumab (Herceptin®), a recombinant humanized monoclonal Ab to the extracellular domain of HER2, has dramatically changed the treatment of HER2-amplified breast tumors in the adjuvant and metastatic setting [20-22]. HER2 is also overexpressed in some patients with bladder cancer [23].

Unlike breast cancer, where the role of HER2-targeting agents has been well established in both metastatic and adjuvant settings, no strategies of this type have yet been approved for use in urothelial carcinoma of the bladder and urothelial carcinoma of the renal pelvis.

In this study we investigated the relationship between HER2 overexpression in urothelial carcinoma of the renal pelvis and clinicopathologic parameters.

Material and methods

Case selection

A search was made through the surgical pathology and consultation files of our institution for radical nephroureterectomy cases with urothelial carcinoma of the renal pelvis from 2008-2012. Only cases with available tissue blocks were selected for the study. The hospital records of each patient were retrospectively reviewed. Clinicopathologic parameters including: sex, age, grade, stage, and inverted growth pattern were documented.

Immunohistochemistry

Immunohistochemistry was performed on 5 micron sections cut from routinely processed
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formalin-fixed, Paraffin-embedded tissue blocks. The tissue sections were deparaffinized and rehydrated, pretreated with 0.01 M citrate buffer (pH 6), and then stained for HER2 (Dako, Monoclonal Mouse Anti-Human, Carpinteria, Ca; RTU). Appropriate positive and negative controls were employed throughout. HER2 positivity was assessed using the ASCO scoring system, evaluating only membranous staining. [18] The level of HER2 protein expression was assessed semiquantitatively by the intensity and percentage of staining and scored on a scale of 0 to 3+. Scores of 0 and 1+ are categorized as negative, 2+ as equivocal, and 3+ as positive. A score of 1+ was defined as barely perceptible membrane staining in >10% of cells, a score of 2+ was defined as weak-to-moderate complete membrane staining present in >10% of tumor cells, and a score of 3+ was defined as strong complete membrane staining in >30% of tumor cells. A cytoplasmic staining was considered nonspecific. We consider only 3+ staining as a HER2 overexpression. This study was completed following the guidelines of and with approval from our institutional review board.

Results

Forty six cases were identified. HER2 overexpression was identified in 34/46 (74%) cases (Figure 1A and 1B). Mean patient age with HER2 overexpression was 68 years (range: 42-87 years). There was a male predominance with 28/34 (82%) patients and 6/34 (18%) patients were female. High grade urothelial carcinoma was present in 32/34 (94%) cases and 2/34 (6%) cases had low grade urothelial carcinoma (Figure 2A and 2B). Pathologic staging was as follows; 9/34 (26%) cases were pTa, 10/34 (29%) cases were pT1, 2/34 (6%) cases were pT2, 12/34 (35%) cases were pT3, and 1/34 (3%) cases was pT4. (Table 1) An inverted growth pattern was present in 23/46 (50%) cases. HER2 overexpression was present in 15/23 (65%) cases of UCA with an inverted growth pattern (Figure 2A and 2B).

Discussion

Due to relatively low incidence of urothelial carcinoma of the renal pelvis compared to urothelial carcinoma of the bladder, more studies regarding HER2 amplification and HER2 overexpression have been published on the latter. However these studies have yielded conflicting results, with extensive variability in the incidence rates of HER2 gene amplification ranging from 0% to 59% and HER2 receptor protein overexpression ranging from 21% to 89% [28]. The variability in immunohistochemical assays, were likely related to the heterogeneity between kits, antibodies, protocols, interpretations or cut-off values. Additionally, variability in gene amplification has been related to differences in the evaluation criteria and laboratory methods, since various target molecules related to HER2 amplification/overexpression, including DNA, mRNA, and receptor protein, have been used in different assays. Among the diagnostic techniques used, immunohistochemistry and fluorescence in situ hybridization (FISH) are both useful and practical. Immunohistochemistry is
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Table 1. Correlation of clinicopathologic parameters with overexpression of HER2 (3+ staining)

<table>
<thead>
<tr>
<th>Clinicopathologic data</th>
<th>Breakdown of cases with HER2</th>
<th>Total number of cases with HER2 overexpression (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>28</td>
<td>34(^a) (82%)</td>
</tr>
<tr>
<td>Female</td>
<td>6</td>
<td>34 (18%)</td>
</tr>
<tr>
<td>High grade UCA</td>
<td>32</td>
<td>34 (94%)</td>
</tr>
<tr>
<td>Low grade UCA</td>
<td>2</td>
<td>34 (6%)</td>
</tr>
<tr>
<td>pTa</td>
<td>9</td>
<td>34 (26%)</td>
</tr>
<tr>
<td>pT1</td>
<td>10</td>
<td>34 (29%)</td>
</tr>
<tr>
<td>pT2</td>
<td>2</td>
<td>34 (6%)</td>
</tr>
<tr>
<td>pT3</td>
<td>12</td>
<td>34 (35%)</td>
</tr>
<tr>
<td>pT4</td>
<td>1</td>
<td>34 (3%)</td>
</tr>
<tr>
<td>Inverted growth pattern</td>
<td>15</td>
<td>23(^b) (65%)</td>
</tr>
</tbody>
</table>

\(^a\)34/46 (74%) cases had HER2 overexpression (3+ staining); \(^b\)23/46 (50%) cases had an inverted growth pattern; UCA: urothelial carcinoma.

Four studies have investigated HER2 expression in upper urinary tract urothelial carcinoma [24-27]. Two of the four studies evaluated HER2 overexpression by immunohistochemistry. In the study by Bjerkehagen et al, they did not document HER2 expression in 20 cases of urothelial carcinoma of the renal pelvis, but in a study by Imai et al., HER2 expression was present in 11/20 (37%) cases of urothelial carcinoma of the renal pelvis and ureteral tumors [24, 25]. In the study by Imai et al. it was suggested that the immunohistochemical detection of the expression of EGFR and c-erbB-2 in upper urinary tract urothelial carcinoma may be a useful in predicting the likelihood of secondary bladder cancer recurrences [25]. Langner et al. performed a systematic analysis of HER2 status in upper urinary tract urothelial carcinoma using both IHC and FISH with respect to the associations with tumor stage and grade, as well as prognostic significance [26]. They found HER2 expression in about 50% of tumors with weak expression (HercepTest score 2+) and also an amplification of HER2 in 9% of the cases (4/53) but with a low amplification ratio in all cases. In addition, they noted a correlation between HER2 expression with tumor stage and grade, comparable to results obtained in bladder urothelial carcinoma, but other investigators have found these associations [30-35]. Due to low rate of HER2 overexpression and HER2 gene amplification in their studies, they concluded that only a small number of patients with upper urinary tract urothelial carcinoma might benefit from HER2-targeted (Herceptin) therapy [26]. Vershasselt-Crinquette et al. investigated the frequency of HER2 overexpression and amplification in upper urinary tract urothelial carcinoma using dual-color in situ hybridization (ISH) and immunohistochemistry. In their study, all tumors with HER2 gene amplification were high grade and high stage with a HER2 overexpression 2+/3+ score [27]. They did not observe any prognostic value for HER2 overexpression or amplification, but found a correlation between HER2 amplification and lymph node invasion. They concluded that HER2 gene amplification is a rare event in upper urinary tract urothelial carcinoma and is correlated with high-grade tumors and lymph node invasion, thus selected patients with aggressive tumors might benefit from adjuvant anti-HER2 therapies [27]. Our study showed HER2 overexpression in 34/46 (74%) cases of urothelial carcinoma of the renal pelvis with high frequency in high grade urothelial carcinoma 32/34 (94%).

Urothelial carcinoma of the renal pelvis and ureter may develop as a manifestation of hereditary nonpolyposis colorectal cancer syndrome, a disorder characterized by mutation or inactivation of a number of DNA mismatch repair genes and detectable as microsatellite instability. Hartmann et al. showed that inverted growth in urothelial carcinoma of the upper urinary tract may serve as a marker lesion for microsatellite instability (with a sensitivity and specificity of .82) and may help identify patients who should be offered testing for hereditary nonpolyposis colorectal cancer syndrome [36].

Our study, the first to investigate the correlation between HER2 overexpression with inverted growth pattern, showed that HER2 overexpression is more common in male patients with high grade urothelial carcinoma, especially those...
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with an inverted growth pattern. It is highly conceivable that a select group of patients may benefit from HER2-targeted (Herceptin) therapy. Additional multi-institutional studies are needed to confirm the potential diagnostic and prognostic utility of HER2 expression in upper urinary tract urothelial carcinoma.

Disclosure of conflict of interest

None.

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