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Cytoplasmic Expression of AXL Is Associated With High Risk of Postoperative Relapse of Conventional Renal Cell Carcinoma

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Abstract. *Background/Aim: Despite early detection by widespread use of abdominal imaging more than 40% of patients with conventional renal cell carcinoma (RCC) will die due to metastatic disease. Small kinase inhibitors for AXL receptor tyrosine kinase may delay the progression of metastatic cRCC. Patients and Methods: We analysed AXL expression by immunohistochemistry on tissue multi arrays of 691 conventional RCC without metastasis at the time of nephrectomy. Results: The Kaplan-Meier survival analysis indicated a poor disease-specific survival rates for patients with tumour showing cytoplasmic AXL staining, whereas expression on the cell membrane is associated with excellent disease outcome. Multivariate Cox regression analysis identified cytoplasmic AXL expression as an independent prognostic factor indicating a five-times higher risk of postoperative tumour progression (RR=5.048; 95% CI=2.391-10.657; p<0.001). Conclusion: Detecting cytoplasmic expression of AXL can be used to define a subset of conventional RCC with high risk of progression, thus identifying patients for more aggressive surveillance and adjuvant AXL inhibitor treatment as early as possible.*

Approximately 40% of patients with conventional renal cell carcinoma (RCC) have already a metastasis at the time of operation or will develop one during the postoperative course (1, 2). Despite early detection by imaging techniques approximately 15% of pT1, pT2 tumours operated with curative intent will develop metastases with in 5 years of follow-up (3, 4). Especially, patients with bone metastases have a limited overall survival (5). There is a need for biomarkers to estimate the outcome of disease (6, 7). Recent targeted therapies can prolong the survival of patients with metastatic disease, but earlier or later drug resistence may develop (8, 9). Therefore, increasing attention has been paid to biological and immunmodulatory therapies including kinase inhibitors and specific antibodies.

Recently, small kinase inhibitors for AXL receptor tyrosine kinase have entered clinical trials. AXL is a member of the Tyro3-Axl-Mer (TAM) receptor tyrosine kinase (RTK) subfamily. Increased expression of AXL is associated with invasive growth and metastasis of several types of tumours including glioblastoma multiforme, urothelial, prostate, lung, gastric and breast cancer (10-15). The correlation between expression of AXL and progression of conventional RCC is yet unknown. Two previous studies applying RT-PCR (reverse transcription-polymerase chain reaction) technique to detect AXL expression in conventional RCC yielded controversial results (16, 17). The only study using immunohistochemistry on tumour tissues did not evaluate the correlation between AXL expression and tumour progression (18).

The aim of this study was to analyze a large cohort of conventional RCC by immunohistochemistry, and establish the prognostic significance of AXL protein expression. A significant correlation between localisation of AXL to different cellular compartements of tumour cells and postoperative disease relapse, was found.

Patients and Methods

Patients and tissue samples. For evaluation of AXL expression we retrospectively analysed tumour samples from patients who undervent radical or partial nephrectomy due to conventional RCC between 2000 and 2014 at the Department of Urology, University of Pecs, Hungary. Data on regular follow-up and tumour-specific death were obtained from the Tumor Registry of the Department of Urology. Follow-up was defined as a time from operation until the last recorded control or cancer-specific death. Patients who died from causes other than RCC within 5 years are not counted in this measurement. Preoperative clinical staging included abdominal and chest computed tomography scans (CT). Bone scans and brain CT scans were carried out only when indicated by clinical signs. The presence of nodal metastasis was

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confirmed by histological, whereas distant metastases by radiographic examination. In the postoperative period patients were observed every 6 months by abdominal ultrasound and measurement of serum creatinine and eGFR, and yearly by CT. The histological diagnosis and TNM classification was reevaluated by a genitourinary pathologist (GK) according to the Heidelberg and TNM classification systems by applying our 1-3 tumour grading system (19, 20). We restrained to the Heidelberg Classification because it is based on specific genetic alterations. According to this classification approximately 70-80% of conventional RCCs are composed of "clear" cells and the rest of "eosinophilic" (earlier "granular") cells (21).

Tissue microarrays (TMA) and immunohistochemistry. Haematoxylin and eosin (H&E)-stained slides were reviewed to select representative paraffin blocks for TMA construction. From each tumour a minimum of three core biopsies with a diameter of 0.6 mm were placed in the recipient block using a Manual Tissue Arrayer (MTA1, Beecher Instruments, Inc., Sun Prairie, USA). For marking the TMAs foetal and adult kidney biopsies were included. Paraffin blocks of fetal and adult kidneys and TMAs containing conventional RCC were used for immunohistochemistry. After deparaffinisation and rehydration the 4 μm thick sections were subjected to heat-induced epitope retrieval in citrate buffer, pH 6.0 in 2100-Retriever (Pick-Cell Laboratories, Amsterdam, The Netherlands). Endogenous peroxidase activity and unspecific binding sites were blocked with 3% hydrogen peroxide containing 1% normal horse serum for 15 min at room temperature. Slides were incubated overnight at 40C in a moist chamber with the anti-AXL antibody (PA5-28850, Thermo Fisher, Budapest, Hungary) at the dilution of 1:200. Horse-radish-peroxydase conjugated anti-rabbit secondary antibody (HISTOLSMR, Histopathology Kft, Pecs, Hungary) was applied for 30 min at room temperature and colour was developed using the DAB substrate (DAKO, Glostrup, Denmark). Tissue sections were counterstained with Mayer's haematoxylin. The immune reaction as membranous or cytoplasmic staining or lack of staining was evaluated twice at different times by one of the authors (GK)

Statistical analysis. Correlations between categorical variables were estimated with Fisher's exact test. Estimates of cumulative survival distributions were calculated by the Kaplan-Meier method, and the differences between the groups were compared using the log-rank test. The significance of clinico-pathological variables was evaluated using the univariate and multivariate Cox proportional hazard regression model. Analysis was performed using IBM SPSS Statistics v.25 for Windows (Inc. Chicago IL, USA). A p-value <0.05 was considered the limit of statistical significance.

Results

We included 691 patients having conventional RCCs without clinically detectable metastasis at first observation. The pertinent clinical and pathological data are presented in Table I. Of the 691 patients, 406 (59%) were males and 285 (41%) females, the mean age of the cohort was 61.3±11.2 years (range=23-88 years). The average tumour size was 50.2±25.8 mm. During the median follow-up of 73±28 months, tumour relapse was observed in 107 patients (15%). Of 691 tumours 511 (74%) were classified as pT1 including 308 (45%) pT1a tumour. The overwhelming majority of RCCs (456 of 691) displayed G1 tumour grade. Regarding to the tumour stage, 671 (97%) of tumours were designed to stage I and II. The pertinent clinical and pathological data are presented in Table I.

Table I. *Association of AXL expression with clinico-pathological parameters of conventional RCCs without metastasis at the time of operation (n=691).*

	N (691)	AXL expression			p-Value
		Mem (321)	Neg (227)	Cyt (143)	
Gender					0.229
Male	406	184	129	93	
Female	285	137	98	50	
Status					<0.001
AWD	584	311	193	80	
PTR	107	10	34	63	
Size					<0.001
<4 cm	272	153	93	26	
4<x<7 cm	269	125	86	58	
>7 cm	150	43	48	59	
T Stadium					<0.001
pT1	511	273	173	65	
pT2	94	38	29	27	
pT3	86	10	25	51	
Grade					<0.001
G1	456	263	163	30	
G2	180	51	57	72	
G3	55	7	7	41	
Necrosis					<0.001
No	608	305	213	90	
Yes	83	16	14	53	
Stage					<0.001
I	504	270	171	63	
II	167	48	50	69	
III	20	3	6	11	

Mem: Membranous; Neg: negative; Cyt: cytoplasmic; AWD: alive without disease; PTR: postoperative tumor relapse.

Immunohistochemistry failed to detect AXL expression in normal foetal and adult kidney samples. No AXL expression was seen in 227 (33%) conventional RCCs (Figure 1A). In 321 (46%) tumours a weak to strong membrane attenuated immunoreaction was detected (Figure 1B), whereas a weak to strong cytoplasmic staining was observed in 143 (21%) of the 691 tumours (Figure 1C-D). AXL staining patterns were significantly correlated with tumour size, grade and T-classification of conventional RCC as well as postoperative cancer relapse (Table I, all p<0.001).

Kaplan-Meier analysis revealed that patients having a conventional RCC with cytoplasmic expression or lack of expression of AXL protein have a significantly shorter disease-free survival compared to those with membranous AXL expression (Figure 2). In the group of tumours with membranous AXL expression 97.5%, with negative tumour 89.6% whereas with cytoplasmic positivity only 65.9% of patients were disease-

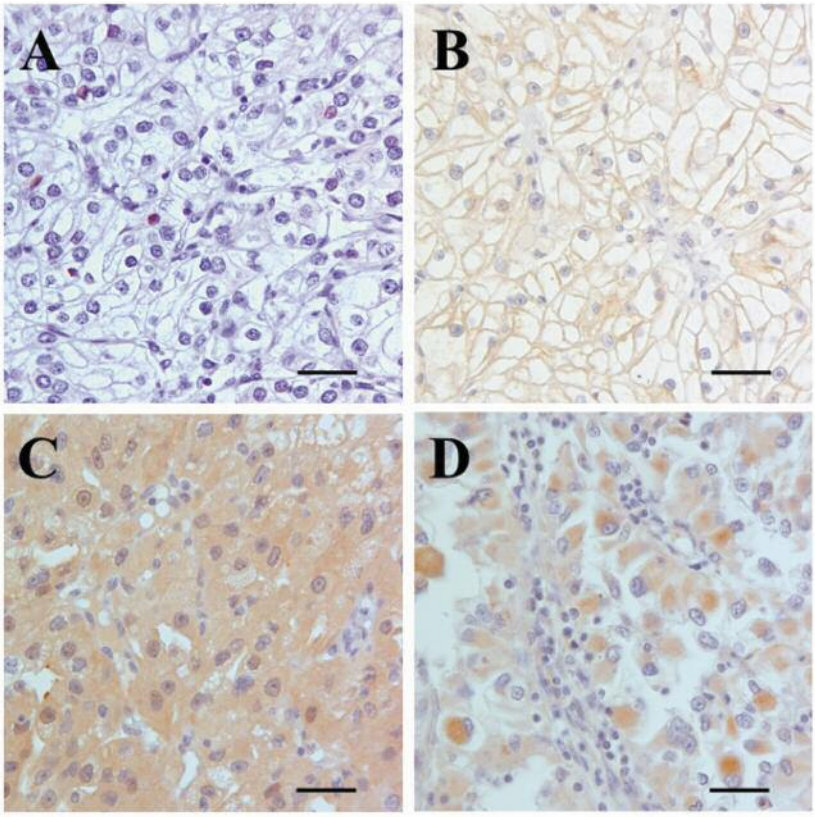

Figure 1. *Expression of AXL in conventional RCC. (A) No immunoreaction was detected with the anti-AXL antibody in a grade 2 "clear cell" conventional RCC. (B) Membranous AXL staining in a conventional RCC with similar morphology. (C) Diffuse cytoplasmic staining in a "eosinophilic" conventional RCC and (D) globular cytoplasmic staining in a conventional RCC with rhabdoid changes. Scale bar: 35 μm.*

free during follow-up. Univariate Cox regression analysis revealed that tumor size, grade, T classification, necrosis as well as cytoplasmic AXL positivity or lack of expression were significantly associated with postoperative tumour progression (all $p<0.001$). In multivariate Cox regression analysis only necrosis (RR=2.139; 95% CI=1.351-3.386; $p<0.001$) and AXL remained as independent predictor of cancer progression. The lack of expression or cytoplasmic expression of AXL was an independent negative survival factor showing four- or five-times higher risk of disease relapse and subsequent cancer-specific death (RR=4.110; 95% CI=1.999-8.449; $p<0.001$ and RR=5.048; 95% CI=2.391-10.657; $p<0.001$), respectively.

Discussion

We analysed the expression of AXL protein in conventional RCCs without detectable metastasis at the time of operation. Based on cellular localisation we identified three groups of tumours, one with membranous, one with cytoplasmic AXL positivity and a group of AXL-negative tumours. The Kaplan-Meier survival analysis indicated that patients having conventional RCC with membranous staining of AXL protein have an excellent prognosis. Patients with tumours dysplaying

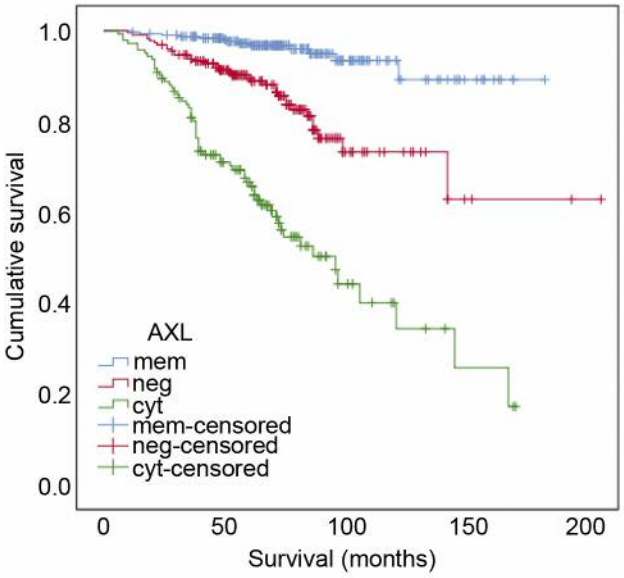

Figure 2. *Kaplan-Meier analysis of survival rate in 691 patients having conventional RCC with membranous (n=321), negative (n=227) and cytoplasmic (n=143) AXL expression. Censored data are marked by crosses. Evaluation of the data indicates the prognostic value of cytoplasmic AXL expression (log-rank test, p<0.001).*

cytoplasmic expression have five-times higher risk to develop metastatic disease during the mediam follow-up of 73 months. The only immunohistochemical study on AXL expression in RCC separated membranous and cytoplasmic staining, evaluated the two forms together as positive result but did not correlate to disease outcome (18). In glioma cells it was reported that only membrane attenuated AXL staining, whereas other studies on distinct types of tumours applied an intensity and proportion score, staining intensity and per cent of positive cells or noticed simple as AXL positivity (10-15).

The protein encoded by AXL tyrosine kinase is composed of two immunoglobulin-like motifs and two fibronectin type-III moieties at the N-terminal, a single pass transmembran domain and a conserved cytoplasmic tyrosine kinase domain (22). The TAM family including AXL is involved in several biological processes. Activation of AXL in tumor is linked to cell proliferation, survival, migration and invasion by activating oncogenic signaling pathways (23). The extracellular immunoglobulin-like and fibronectin-type III-like domains of AXL, which occur in the adhesion molecules of cadherin and immunoglobulin superfamily, suggest that AXL might regulate cell adhesion as well (24). AXL is expressed in tumor-infiltrating macrophages and dendritic cells and has a function in limiting the innate immune response (25). And finally, up-regulation of AXL leads to drug resistance of tumor cells, a function which makes AXL attractive for targeted therapy (26).

AXL has expressed in kidney cancer but not in normal kidneys. Several mechanisms are involved in the regulation of AXL in cancer including the hypoxemic microenvironment leading to expression of HIF-1 and HIF-2 (27). Binding of growth arrest-specific 6 (Gas6) to AXL results in receptor dimerisation, tyrosine phosphorylation and activation of the downstream pathways (22). Phosphatidylinositol 3 kinase (PI3K) recruitment by AXL leads to activation of AKT kinase (protein kinase B), a central node in signalling downstream of growth factors, cytokines and many other cellular processes (26). However, the 786-O AXL dependent RCC cell line does not express Gas6 suggesting that AXL may undergo an autocrine signalling in absence of its ligand (18, 29).

Recently, novel tools for inhibition of AXL signaling by anti-AXL antibodies, by soluble AXL ectodomain or by small-molecule inhibitors have been elaborated and small kinase inhibitors for AXL have entered clinical trials (18, 23, 29, 30). Cabozantinib, an AXL, MET and VEGFR2 inhibitor has been tested in the phase III METEOR trial and the therapy resulted in delayed RCC progression, and improved an objective response compared with everolimus (31). This finding lead to inclusion of cabozantinib in treatment of patients with metastatic conventional RCC.

Our study demonstrated a significant correlation between the expression pattern of the receptor tyrosine kinase AXL and relapse-free survival of patients with conventional RCC. Cytoplasmic expression of AXL seems to be a powerful biomarker to define a set of tumours with a five-times higher risk of developing metastasis, whereas patients having tumours with membranous localisation of AXL protein have an excellent prognosis. AXL immunohistochemistry may help to optimize active surveillance with the aim to detect tumor relapse as early as possible and direct anti-AXL adjuvant therapy with the ultimate goal to achive a delayed progression of metastatic tumours.

Conflicts of Interest

The Authors have no conflicts of interest to declare.

Authors' Contributions

LP, and DB designed the study, GK constructed the tissue microarrays, LP, TB performed the immunohistochemistry and GK analyzed the data, MVY performed the statistical analysis, LP, DB wrote the manuscript and GK reviewed the manuscript. All Authors read and approved the final version of the manuscript.

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