Original Article

Immunohistochemical Expression of HER2/neu and β-catenin in Urothelial Carcinoma: "A Dawn of Hope"

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Abstract

Background: Urothelial carcinoma is the 10th most commonly occurring and 13th most common cause of cancer-related deaths worldwide. The major prognostic factors in urothelial carcinomas are the depth of invasion into the bladder wall and the degree of differentiation of the tumour. However, there is no reliable prognostic marker, and thus molecular markers are required to estimate the individual prognosis of patients as well as for effective treatment.
Methods: To evaluate HER2/Neu and β-catenin immunohistochemical (IHC) expression in urothelial carcinoma and their correlation with tumour grade and stage, thus contributing as prognostic factors. Fifty formalin-fixed TURBT specimens of urinary bladder carcinoma were collected from our hospital during the period from January 2023–June 2024. Hematoxylin and Eosin stained sections were done, along with microscopical examination, and immunohistochemistry for HER2/Neu and β-catenin were done. A p-value of <0.05 was considered statistically significant.
Results: A total of 38 (82%) out of 46 cases of high-grade urothelial carcinoma and 24 (92.3%) out of 26 cases of muscle-invasive urothelial carcinoma expressed strong HER2/Neu membranous positivity (score 3). HER2/Neu expression was found to be statistically significant with respect to histological grade and pathological stage ($p < 0.001$). 42/46 cases of high-grade urothelial carcinoma showed β-catenin positivity, and intensity increased with an increase in pathological stage ($p < 0.001$).
Conclusion: A positive association between HER2/Neu and β-catenin expression with tumour grade and pathological stage of urothelial carcinoma was found, contributing to prognostic assessment and thereby guiding targeted therapy.

Keywords: Immunohistochemistry; Grade; Muscle invasive; TURBT

Introduction

Urothelial carcinoma is the 10th most commonly occurring and 13th most common cause of cancer-related deaths worldwide. The estimated new number of cases and deaths are 5,73,278 and 2,12,536 respectively [1]. In India, it is ranked 17th in incidence and 19th in mortality with a varying incidence across the Indian population [2]. According to the involvement of muscularis propria of the bladder, it is categorized as muscle-invasive and non-invasive groups. Transitional cell carcinoma (TCC) accounts for about 92% of bladder malignancies [3]. Smoking, exposure to arylamines, aniline dyes, auramines, phenacetin, cyclophosphamide, and Schistosoma haematobium infections are considered as the known risk factors involved in urothelial carcinoma [4]. High levels of arsenic present in water have also shown an increased risk of bladder cancer.

Hematuria is the presenting symptom in 90% of patients with bladder cancer. Other symptoms at presentation may include urinary frequency, urgency, dysuria, and ureteral obstruction. Systemic manifestations indicate metastatic disease and portend a poor prognosis [5, 6].

Cystoscopy with tissue biopsies is typically done for diagnosis. Cancer staging is determined by medical imaging such as MRI, CT scan, and bone scan along with histopathological grading.

The transurethral resection of bladder tumour (TURBT) is a diagnostic, prognostic, and often therapeutic procedure followed. The treatment of bladder cancer depends on the grade and stage of the tumour [7]. Different parameters determine the prognosis of bladder carcinoma, including stage, grade, patient's age, and lymph node status [8].

Human Epidermal Growth Factor (HER2/Neu) is a proto-oncogene located on chromosome 17q21 that encodes ErbB-2. Over-expression of HER2/Neu has been notably associated with increased cellular survival, increased proliferation, and decreased apoptotic potential of cells, leading to malignant transformation and maintenance of the associated malignancy.

Amplifications of the HER2/Neu gene have been observed in Adenocarcinomas in different sites like breast, colon, bladder, ovarian, endometrial, lung, uterine cervix, and esophagus [9].

Antitumor antigen-specific immunotherapeutic strategies (tumour vaccines) and modulators of HER2/Neu expression such as inhibitors of HSP90 and targeting of the HER2/Neu gene product by the monoclonal antibody trastuzumab (Herceptin) have led to advances in the treatment of certain carcinomas, including breast carcinoma [10, 11].

Regulation of intercellular adhesion is settled by homotypic interaction of cadherin (a cell-cell adhesion molecule), which are attached to the cytoskeleton via various cytoplasmic proteins including β-catenin (β-catenin) [12]. β-catenin is an oncoprotein, encoded by the CTNNB1 gene and responsible for anchoring the cadherin with the cytoskeleton. Loss of cadherin-mediated adhesion and activation of the Wnt/β-catenin signaling pathway are important steps in the development and progression of many neoplasms [13, 14]. Urakami et al. had also found that β-catenin nuclear accumulation was significantly higher in bladder tumour than normal bladder mucosa [15], and Kastritis E et al. concluded that either APC mutations and/or aberrant expression of β-catenin are associated with a worse outcome [16].

The need of the hour is a better understanding of the pathogenesis of bladder neoplasm immunohistochemical markers to facilitate early diagnosis, prognostic assessment, and targeted therapy.

In our study, we performed the HER2/Neu and β-catenin immunohistochemistry study in bladder malignancy, thereby guiding the surgeons for prognostic protocols and the formulation of the best and optimized treatment.

Materials and Methods

This was a cross-sectional, observational study conducted after receiving the Institutional Medical Ethics Committee approval (BMC/I.E.C/548), dated 24th Nov 2022, on 50 cases over 1 and a half years from January 2023–June 2024 at a tertiary care hospital in the department of pathology.

TURBT (trans urethral resection of bladder tumours) specimens from clinically suspected bladder neoplasm were sent from the department of surgery. Formalin-fixed specimens were processed for histopathological examination. Hematoxylin and Eosin (H&E) stained sections were observed microscopically for diagnosis and classification. The pathological stage was determined on the basis of the degree of tumour invasion, while the histological grade was determined by examining cell architecture, polarity, thickness, and cohesiveness (Figure 1 and Figure 2). Immunohistochemical staining for HER2/Neu and β-catenin was done (Figure 3, Figure 4, and Figure 5). Rabbit Anti-c-erbB2 Monoclonal Antibody to HER2/Neu surface antigen (clone SP3) was used for IHC evaluation of HER2/Neu. The antibodies and chemicals were obtained from Master Diagnostica, Spain. [REF: MAD-000308 QD-R-7; LOT: 03080026S].

Data collection and interpretation

The data was collected using the pro-forma that had information regarding patient particulars, history, complaints, and other parameters throughout the period of study. TURBT was performed more frequently than bladder resection because it is the first-line procedure for diagnosing, staging, and treating bladder tumours.

Inclusion criteria: Trans urethral resection of bladder tumor (TURBT) specimens.

Exclusion criteria:

- Inflammatory conditions of the bladder.
- Those who are unwilling to undergo surgery.
- Debilitated and critically ill patients.

Evaluation of HER2/Neu expression: The immunohistochemical expression of HER2/Neu was evaluated by ASCO scoring (Wolff AC et al., 2009) [17] and was scaled from 0 to 3+ score. For assessment of HER2/Neu, score 0 and score 1+ are taken as negative; score 2+ is taken as equivocal positivity, which needs further HER2/Neu demonstration by FISH; and score 3+ is taken as strong positive [18].

Evaluation of β-catenin Expression: Positive and ectopic nucleocytoplasmic β-catenin expression ($>$10% positivity for β-catenin in the cell cytoplasm and/or nucleus) [19].

Statistical Analysis: The data are tabulated in Microsoft Excel and analysed with SPSS V.24 software (IBM, Armonk, NewYork, USA). The continuous variables are presented with mean and standard deviation. The categorical variables are presented with frequency and percentage. The Chi-square test is used for statistical analysis. The p-value $\leq$0.05 is considered statistically significant.

Results

Urothelial carcinoma was universally observed in all the cases, and the majority of the cases were high grade, belonging to Invasive Urothelial Carcinoma. The age of the patients ranged between 22 and 73 years with a mean age of 57.72 $\pm$ 10.55 years.

Gender distribution of the cases showed that 42/50 (84%) of cases were males compared with 8/50 (16%) female cases. Males outnumbered the females with a male-to-female ratio of 5.25:1.

Histological examination of hematoxylin and eosin (H&E) stained sections confirmed that the maximum number of cases were high-grade invasive urothelial carcinoma, comprising 46 (92%) cases, and the rest 4 (8%) cases were low-grade non-invasive urothelial carcinoma. The distribution of tumour configuration in the present study showed mostly of nested variant in 36 (72%) out of 50 cases, followed by Micropapillary variant in 10 (20%) cases, and papillary variant in 4 (8%) cases. Lymphovascular invasion was present in 6 (12%) cases and not identified in 44 (88%) cases. Among the 50 cases, the most commonly encountered pathological stage was T2NxMx stage, which was seen in over 26 (52%) cases, followed by T1NxMx stage seen in 18 (36%) cases, stage pTa seen in 4 (8%) cases, and stage T4NxMx seen in 2 (4%) cases.

Muscularis propria was present in 42 out of 50 cases and absent in the remaining 8 cases. Twenty-six (52%) cases showed tumour extension to muscularis propria, 18 (36%) cases showed tumour extension upto lamina propria, 2 (4%) cases showed invasion to prostatic chips in prostatic stroma, and non-invasive papillary carcinoma was seen in 4 (8%) cases.

Among 46 high-grade urothelial carcinoma, 2 (4.3%) cases were negative (score 0 to +1) for HER2/Neu expression. 6/46 cases (13%) revealed an equivocal (weak positive) staining pattern (score 2), and 38/46 cases (82.6%) expressed strong membranous positivity (score 3). Out of 4 low-grade Non-invasive urothelial carcinoma cases, none showed negative staining (score 0), 2 (50%) cases showed negative (weak membranous) score +1, and 2 cases (50%) showed an equivocal (weak positive) staining pattern.

The inference from this study was that most low-grade urothelial carcinomas were negative for HER2/Neu staining. HER2/Neu expression scores +2 and +3 were maximum in patients of high-grade tumours as compared to that of low-grade tumours, and the difference was highly significant statistically ($p < 0.001$) (Chi-square value: 29.620). Hence, it was noted that as the grade of the tumour increased, the expression of HER2/Neu also increased (Table 1).

HER2/Neu positive cases were seen most commonly in the T2 stage, comprising 26 cases, where 2/26 (7.7%) cases scored +2 and 24/26 (92.3%) cases scored +3, followed by the T1 stage where positivity was seen in 18 cases, where 6/18 (33.3%) cases scored +2 and 12/18 (66.7%) cases scored +3. None of the cases of stage pTa scored HER2/Neu positivity, with 2 pTa cases scoring 0 and the other 2 cases scoring +1. All 4 cases (100%) of the T4 stage were HER2/Neu expression positive, with 2 cases (50%) scoring +2 and the other 2 cases (50%) scoring +3.

With increasing tumor stage, there was an increase in the intensity score of HER2/Neu expression. A statistically significant association was observed between the pathological stage and HER2/Neu expression ($p < 0.001$) (Chi-square value: 55.769) (Table 2).

Immunohistochemistry expression of β-catenin was seen to be positive in 42 (84%) cases overall. 42/46 cases (91.3%) of Infiltrating urothelial carcinoma were β-catenin positive, and the remaining 4 cases were negative. All 4 cases of non-invasive urothelial carcinoma were β-catenin negative. The association is statistically significant ($p < 0.001$) (Chi-square value: 22.826) (Table 3).

All 26 (100%) cases of the T2 stage and 2 (100%) cases of the T4 stage were β-catenin positive. 14/18 cases (77.8%) of the T1 stage were β-catenin positive. All 4 cases belonging to the pTa stage and 4 cases of the T1 stage were negative for β-catenin expression. The association is statistically significant ($p < 0.001$) (Chi-square value: 26.852) (Table 4).

Thus, all 42 β-catenin positive cases were of high-grade urothelial carcinomas, with the majority belonging to higher

pathological stages.

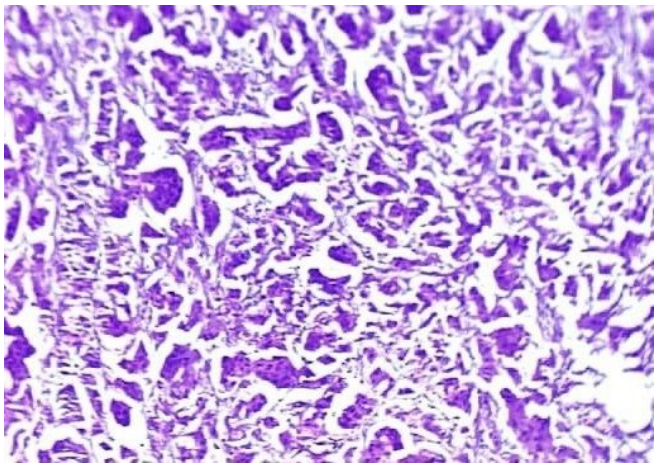

Figure 1: Nested Urothelial carcinoma, high grade, invading lamina propria; H&E (400X magnification).

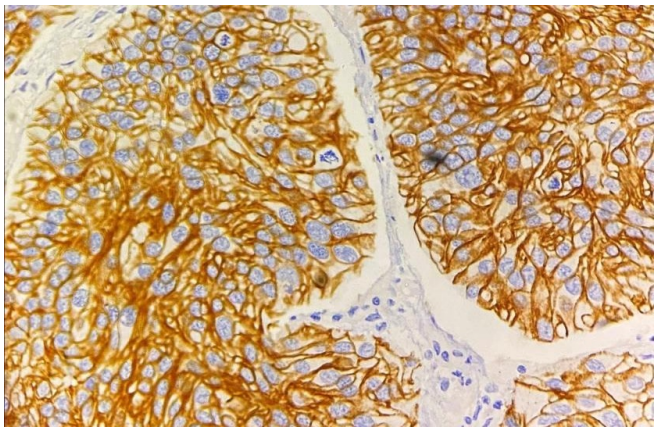

Figure 2: Micropapillary subtype of urothelial carcinoma; H&E (100X magnification).

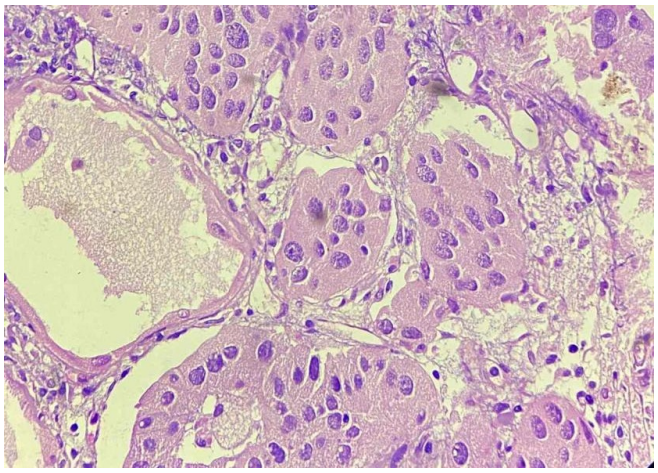

Figure 3: High grade urothelial carcinoma; Her2/neu score 3+, circumferential membrane staining by IHC >10% tumor cells (100X magnification).

Discussion

The mean age of the patients was 57.72 ± 10.55 years, which was similar to Badawia B Ibrahim et al. (2017), who stated a mean age of 59.57 ± 9.39 years [20], and similar reports were given by Zeb et al. [21], Noora Ali Jawad et al. [22], and Sukhmani Samra et al. [23]. The male-to-female ratio of 5.25:1 was similar to the findings of Mahmoud S. Abdelhalim Salem et al. (2021) [24], Muhammad Kashif Sarfraz et al. (2019) [25], and Haque S et al. (2018) [26].

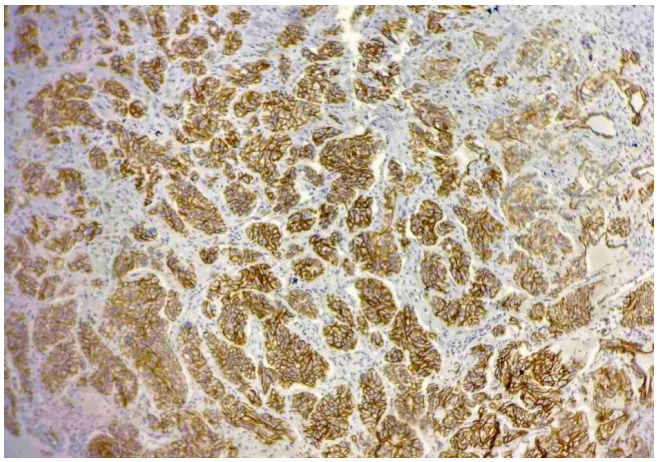

Figure 4: High grade urothelial carcinoma, Her2/neu stain positive, score 3+ (400X magnification).

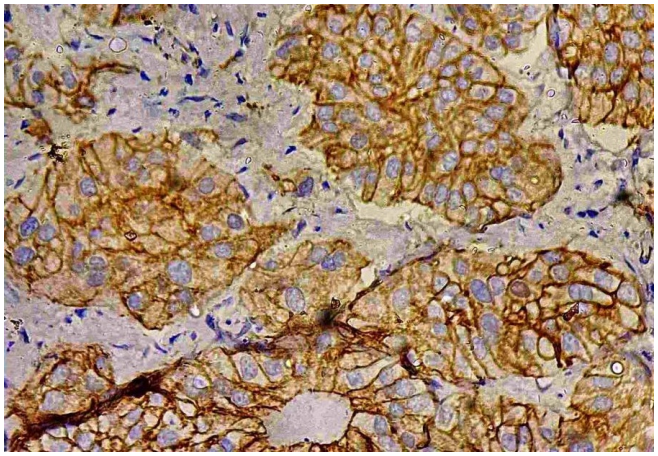

Figure 5: High grade urothelial carcinoma, β-catenin positive (400X magnification).

Table 1: Association of Her2/neu score with Histologic grade

Parameter		High Grade	Low Grade	Total
Her2/neu score	0	N=2 (4.3%)	N=0 (0.0%)	N=2 (4.0%)
	1+	N=0 (0.0%)	N=2 (50.0%)	N=2 (4.0%)
	2+	N=6 (13.0%)	N=2 (50.0%)	N=8 (16.0%)
	3+	N=38 (82.6%)	N=0 (0.0%)	N=38 (76.0%)
Total		**N=46 (100.0%)**	**N=4 (100.0%)**	**N=50 (100.0%)**
Chi-square value: 29.620				**P-value**: <0.001

Table 2: Association of Her2/neu score with TNM Staging

Her2/neu score	pTa	T1NxMx	T2NxMx	T4NxMx	Total
0	N=2 (50.0%)	N=0 (0.0%)	N=0 (0.0%)	N=0 (0.0%)	N=2 (4.0%)
1+	N=2 (50.0%)	N=0 (0.0%)	N=0 (0.0%)	N=0 (0.0%)	N=2 (4.0%)
2+	N=0 (0.0%)	N=6 (33.3%)	N=2 (7.7%)	N=0 (0.0%)	N=8 (16.0%)
3+	N=0 (0.0%)	N=12 (66.7%)	N=24 (92.3%)	N=2 (100.0%)	N=38 (76.0%)
Total	**N=4 (100.0%)**	**N=18 (100.0%)**	**N=26 (100.0%)**	**N=2 (100.0%)**	**N=50 (100.0%)**
Chi-square value: 55.769					**P-value**: <0.001

Table 3: Association of β-catenin with Histologic grade

β-catenin	**High Grade**	**Low Grade**	**Total**
Negative	N=4 (8.7%)	N=4 (100.0%)	N=8 (16.0%)
Positive	N=42 (91.3%)	N=0 (0.0%)	N=42 (84.0%)
Total	**N=46 (100.0%)**	**N=4 (100.0%)**	**N=50 (100.0%)**
Chi-square value: 22.826			**P-value**: <0.001

Table 4: Association of β-catenin with TNM Staging

β-catenin	**pTa**	**T1NxMx**	**T2NxMx**	**T4NxMx**	**Total**
Negative	N=4 (100.0%)	N=4 (22.2%)	N=0 (0.0%)	N=0 (0.0%)	N=8 (16.0%)
Positive	N=0 (0.0%)	N=14 (77.8%)	N=26 (100.0%)	N=2 (100.0%)	N=42 (84.0%)
Total	**N=4 (100.0%)**	**N=18 (100.0%)**	**N=26 (100.0%)**	**N=2 (100.0%)**	**N=50 (100.0%)**
Chi-square value: 26.852					**P-value**: <0.001

Table 5: Association of Her2/neu score with β-catenin

Her2/neu score	**Negative β-catenin**	**Positive β-catenin**	**Total**
0	N=2 (25.0%)	N=0 (0.0%)	N=2 (4.0%)
1+	N=2 (25.0%)	N=0 (0.0%)	N=2 (4.0%)
2+	N=4 (50.0%)	N=4 (9.5%)	N=8 (16.0%)
3+	N=0 (0.0%)	N=38 (90.5%)	N=38 (76.0%)
Total	**N=8 (100.0%)**	**N=42 (100.0%)**	**N=50 (100.0%)**
Chi-square value: 35.119			**P-value**: <0.001

This study was similar to the studies done by Sukhmani Samra et al. (2023), who reported that the majority of high-grade invasive urothelial carcinomas (82.6%) cases showed positive HER2/Neu expression. HER2/Neu expression increased with increasing grade with a statistically significant p-value of <0.0001 [23]. Concordant findings were also seen by Kumar S et al., who found HER2/Neu positivity of 75.9% in high grade tumors and 63% low grade tumour [27].

Findings were similar to the reports of Muhammad Sanusi Haruna [28], who found a statistically significant difference in HER2/Neu protein with overexpression detected only in the high-grade and invasive tumours [28].

This was similar to the studies done by Mahak Agarwal et al. (2019), who reported HER2/Neu positive cases were seen most commonly in the pT2 stage, comprising 72.22% (n=13) of all cases, followed by the pT1 stage, where positivity was 16.67% (n=3) [29]. Danaei et al. reported a similar significant association with histological grade (p=1.27) and pathological stage ($p < 0.001$ in both) [30].

Urakami et al. [15] had also found that the nuclear β-catenin accumulation was significantly higher in bladder tumors than in normal bladder mucosa, similar to the study done by Maurya N et al. (2019) [31]. Several studies had also shown that cytoplasmic β-catenin expression was associated with a poorer prognosis in patients with cancers of breast, liver, and colon. We found that maximum β-catenin positive cases belonged to high-grade and high pathological stage muscle-invasive urothelial carcinomas.

Finally, 38 (90.5%) cases of score +3 and 4 (9.5%) cases of score +2 HER2/Neu expression were also positive for β-catenin, all belonging to high-grade urothelial carcinoma. Thus, the association is statistically significant ($p < 0.001$) (Chi-square value: 35.119) (Table 5).

Urothelial carcinoma has been widely studied for the expression of HER2/Neu and β-catenin markers. In bladder neoplasms, its clinical significance remains under-investigated and poorly linked to the patients' clinicopathological features. The need of the hour is a better understanding of the pathogenesis of bladder neoplasm with immunohistochemical markers to facilitate early diagnosis, prognostic assessment, and targeted therapy.

This study evaluates both HER2/neu and β-catenin expression together, unlike most Indian studies that focused on a single marker. We used a well-defined cohort of 50 cases with detailed clinicopathological correlation. Our findings highlight co-expression patterns and their diagnostic relevance and a more comprehensive insight into tumor biology. This study helps bridge gaps in biomarker-based research within the Indian context.

In spite of every sincere effort, the present study has lacunae. The notable shortcomings of this study are: The study has been done in a single-centre in a tertiary care hospital. Reliability and reproducibility of the IHC technique may be a limitation. Fluorescent in situ hybridization (FISH) could not be done for the equivocal cases due to financial limitation and constraints of resources. Confirmation of HER2/neu status, especially for equivocal cases, by FISH for gene amplification should be done in view of better patient stratification for potential anti-HER2 therapy as this may lead to potential misclassification and limit diagnostic accuracy. Multicentre studies for further elaboration of the pattern of overexpression of HER2/Neu and β-catenin in a larger sample size of urothelial carcinomas are recommended.

Conclusion

Thus, a strong association was made by seeing an increasing frequency of HER2/Neu and β-catenin positive expression with an increase in tumour grade as well as pathological stage. This suggests that assessment of Her2/neu status would be helpful in formulating the treatment plan for patients of urothelial carcinoma by estimating the accurate biological behavior of urothelial carcinoma, and it also can be used to assess controversial cases. The development of target therapies using anti-HER2 and further studies are required by identifying patients who may benefit from these therapies. It can give the clinician the platform to study the response of trastuzumab therapy in HER2/neu positive bladder neoplasms as a therapeutic immunomarker in bladder neoplasms. Results obtained in those studies can set the foundation for a new generation of genetic screening tests.

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Conflicts of Interest: None declared.

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