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ORIGINAL ARTICLE

Squamoid and glycogen-rich-like clear-cell change in low-grade papillary urothelial carcinoma: a clinicopathologic analysis

Ece Ozturk[1] · Ali Akin[2] · Busra Yaprak Bayrak[3] · N. Alperen Yildirim[4] · Kemal Kosemehmetoglu[2] · Mahmut Akgul[5,6]

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Abstract

Background: Low-grade papillary urothelial carcinoma (LGPUC) is the most common form of non-muscle-invasive bladder cancer and is typically associated with frequent recurrence but limited progression. While focal squamoid morphology and clear-cell change may occasionally be encountered in LGPUC, their clinicopathologic significance remains poorly defined. Design: We retrospectively reviewed all LGPUC cases diagnosed at a tertiary academic center between 2015 and 2025. Hematoxylin and eosin (H&E)-stained slides were reassessed for squamoid morphology and H&E-suspected glycogen-rich-like clear-cell change. Cases with suspected glycogen-rich-like morphology underwent PAS and PASD staining for histochemical evaluation. Clinicopathologic features and clinical outcomes were analyzed. Results: A total of 514 patients with LGPUC were included. Squamoid morphology was identified in 6 cases (1.2%). Four additional tumors (<1%) showed focal glycogen-rich-like clear-cell change. During follow-up, recurrence occurred in 1 of 6 patients (16.7%) with squamoid morphology, whereas no progression was observed in this subgroup. One patient with glycogen-rich-like clear-cell change subsequently developed invasive low-grade urothelial carcinoma (pT1). Conventional LGPUC showed recurrence in 57 of 504 patients (11.3%) and subsequent progression in 27 of 504 patients (5.4%). Conclusion: Squamoid morphology is an uncommon finding in LGPUC and was not associated with adverse clinical outcomes in this cohort. Glycogen-rich-like clear-cell change could not be definitively confirmed on corresponding deeper PAS/PASD levels, underscoring the importance of careful histochemical correlation before diagnosing glycogen-rich morphology in LGPUC. These findings suggest that focal squamoid morphology and glycogen-rich-like change should be interpreted cautiously and do not appear to justify tumor upgrading in the absence of conventional high-grade features.

Keywords Low-grade papillary urothelial carcinoma · Squamoid morphology · Glycogen-rich-like clear-cell change · Bladder cancer

Introduction

Urothelial carcinoma is the most common malignancy of the urinary tract [1], with several histologic subtypes of urothelial carcinoma recognized in the World Health Organization (WHO) 2022 classification. These morphological subtypes may coexist with conventional UC and may hold diagnostic and prognostic significance [1, 2]. The need for accurate recognition of urothelial carcinoma subtypes and detailed reporting in clinical practice are well-established [2–4].

Papillary urothelial carcinoma (PUC) is graded as low grade or high grade based on the degree of architectural disorder and cytologic atypia. Low-grade PUC (LGPUC) is characterized by relatively orderly papillary architecture and only mild cytologic atypia, whereas high-grade tumors show marked architectural disorder, significant nuclear

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pleomorphism and increased mitotic activity. The WHO 2022 classification specifies that any papillary urothelial tumor containing a high-grade component comprising ≥ 5% of the lesion should be classified as high grade [1]. In addition, several authors have reported that even tumors with a focal high-grade component below this threshold may exhibit more aggressive biological behavior [5, 6]. LGPUC represents the most common form of non-muscle-invasive bladder cancer [7–10]. Reported five-year recurrence rates for Ta low-grade tumors range from 30% to 60%, and stage progression is uncommon, usually reported at approximately 6% or lower, although grade progression rates may vary depending on cohort composition and outcome definitions [11–13]. Although the disease course of LGPUC is usually indolent, its propensity for recurrence requires vigilant long-term surveillance.

Squamoid morphology has been rarely addressed in the context of otherwise conventional LGPUC and may overlap morphologically with whorled growth patterns, or early squamous differentiation [14–19]. Similarly, clear-cell change within urothelial neoplasia encompasses a broad differential diagnosis, including glycogen accumulation, degenerative alterations, fixation-related changes, and cautery-related artifact. True glycogen-rich urothelial carcinoma is exceptionally rare and has been described in invasive tumors [20]. Consequently, focal clear-cell change identified on routine H&E sections should not be assumed to represent glycogen-rich morphology without histochemical confirmation.

The prevalence, clinicopathologic significance, and histochemical correlates of these uncommon morphologic findings in LGPUC remain poorly characterized. Therefore, we analyzed a large cohort of LGPUC to determine the frequency of squamoid morphology and glycogen-rich-like clear-cell change and to assess whether the latter could be confirmed as glycogen-rich morphology using corresponding deeper PAS/PASD-stained sections.

Materials and methods

Study design and case selection

This retrospective clinicopathologic study included urinary bladder biopsy and transurethral resection specimens diagnosed as LGPUC at a tertiary academic referral center between January 2015 and January 2025. The pathology database was systematically searched to identify all eligible cases during the study period. Eligibility was assessed at the patient level. Patients aged ≥ 18 years whose initial urothelial neoplasm was diagnosed as non-invasive LGPUC were eligible for inclusion. Exclusion criteria were age < 18 years; an initial, prior, or concurrent diagnosis of high-grade urothelial carcinoma; a prior or concurrent diagnosis of invasive urothelial carcinoma (pathologic stage pT1 or higher); and tumors arising in the trigone. Trigonal lesions were excluded because squamous differentiation-like epithelial alterations may occur as site-related non-neoplastic phenomena in this region, potentially confounding morphologic assessment. After application of the exclusion criteria, 988 eligible biopsy or transurethral resection specimens from 514 unique patients remained. The patient, rather than the individual specimen, was used as the unit of analysis, and multiple specimens from the same patient were grouped as a single case. Subsequent specimens were evaluated for recurrence and progression. Cases containing only detached squamous epithelium, cauterized epithelial fragments, or metaplastic epithelial elements without unequivocal intratumoral involvement were also excluded.

These criteria were applied to establish a morphologically homogeneous cohort and to minimize potential diagnostic confounders.

Pathologic review and morphologic classification

All available hematoxylin and eosin (H&E)-stained slides were independently reviewed by two pathology residents (EO and AA) and two attending uropathologists (KK and MA) who were blinded to clinical outcomes. Discrepant interpretations were resolved by multiheaded consensus review.

Cases were assessed for squamoid morphology and glycogen-rich-like clear-cell change. Squamoid morphology was defined as focal nests, whorls, or compact solid aggregates of polygonal urothelial cells exhibiting distinct cell borders and abundant eosinophilic cytoplasm, in the absence of overt keratinization or keratin accumulation. Glycogen-rich-like clear-cell change was defined as tumor cells exhibiting optically clear cytoplasm on routine H&E examination, morphologically reminiscent of glycogen-rich change.

All cases with H&E-suspected glycogen-rich-like clear-cell change underwent PAS and PASD staining on deeper levels.

Clinical data and outcome definitions

Clinical variables included age at diagnosis, sex and follow-up information obtained from institutional electronic medical records. Overall follow-up was calculated from the index diagnosis to the last documented clinical evaluation or death. Time to recurrence and time to progression were calculated separately from the index diagnosis to the corresponding first event.

Patients without documented surveillance or follow-up were recorded as having no available follow-up. Recurrence was defined as the development of any subsequent urothelial neoplasm following complete resection of the index lesion. Disease progression was defined as progression in histologic grade (development of high-grade urothelial carcinoma) and/or pathologic stage (lamina propria invasion or higher).

Statistical analysis

Clinicopathologic variables and clinical outcomes were compared among conventional LGPUC, LGPUC with squamoid morphology, and LGPUC with glycogen-rich-like clear-cell change. Continuous variables were summarized using medians and ranges and compared using appropriate parametric or non-parametric methods according to data distribution. Categorical variables were compared using the chi-square test or Fisher's exact test, as appropriate.

Given the rarity of the investigated morphologic patterns and the limited number of non-conventional cases, all subgroup analyses were considered exploratory and interpreted cautiously. Statistical significance was defined as a two-sided p value < 0.05. All analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA).

Results

Clinicopathologic characteristics

The final cohort comprised 514 patients, aged 18–95 years, with a median age of 63 years. The cohort was predominantly male, including 415 men (80.7%) and 99 women (19.3%), and included 988 biopsy or transurethral resection specimens. Six patients with squamoid morphology (1.2%) had a median age of 68 years (range: 52–75 years); four were male and two were female. The morphologic features of focal squamoid morphology in LGPUC are illustrated in Fig. 1. At low power, the tumor showed otherwise typical LGPUC with a focal area showing squamoid morphology (Fig. 1A). On higher-power examination, this area was composed of polygonal urothelial tumor cells arranged in compact nests and small solid aggregates, with sharp cell borders and dense eosinophilic cytoplasm, without definite keratinization (Fig. 1B, C). Adjacent conventional LGPUC is shown for comparison at corresponding magnifications (Fig. 1D-F).

Four additional cases showed focal glycogen-rich-like clear-cell change, generally involving less than 5% of the tumor volume. PAS and PASD stains were performed in all four cases. Representative paired H&E and PAS-stained sections from two cases are shown in Fig. 2. In the first case, focal clear-cell change is identified on the initial H&E

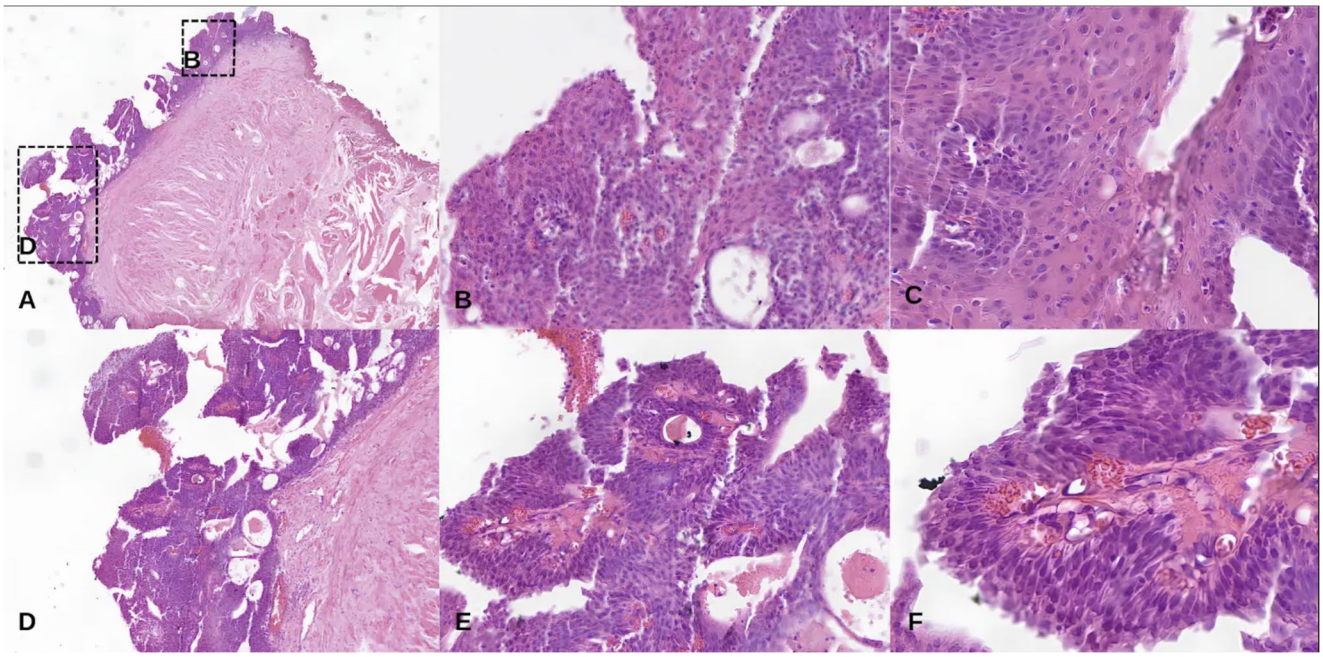


Fig. 1 Squamoid morphology in low-grade papillary urothelial carcinoma. Low-power examination demonstrates a focal squamoid area within an otherwise conventional low-grade papillary urothelial carcinoma (LGPUC) (**A**). Intermediate- and high-power views show polygonal urothelial tumor cells arranged in compact nests and small solid aggregates, with distinct cell borders and abundant eosinophilic cytoplasm, without definite keratinization (**B**, **C**). Conventional LGPUC is shown at corresponding low-, intermediate-, and high-power magnifications for comparison (**D**–**F**)

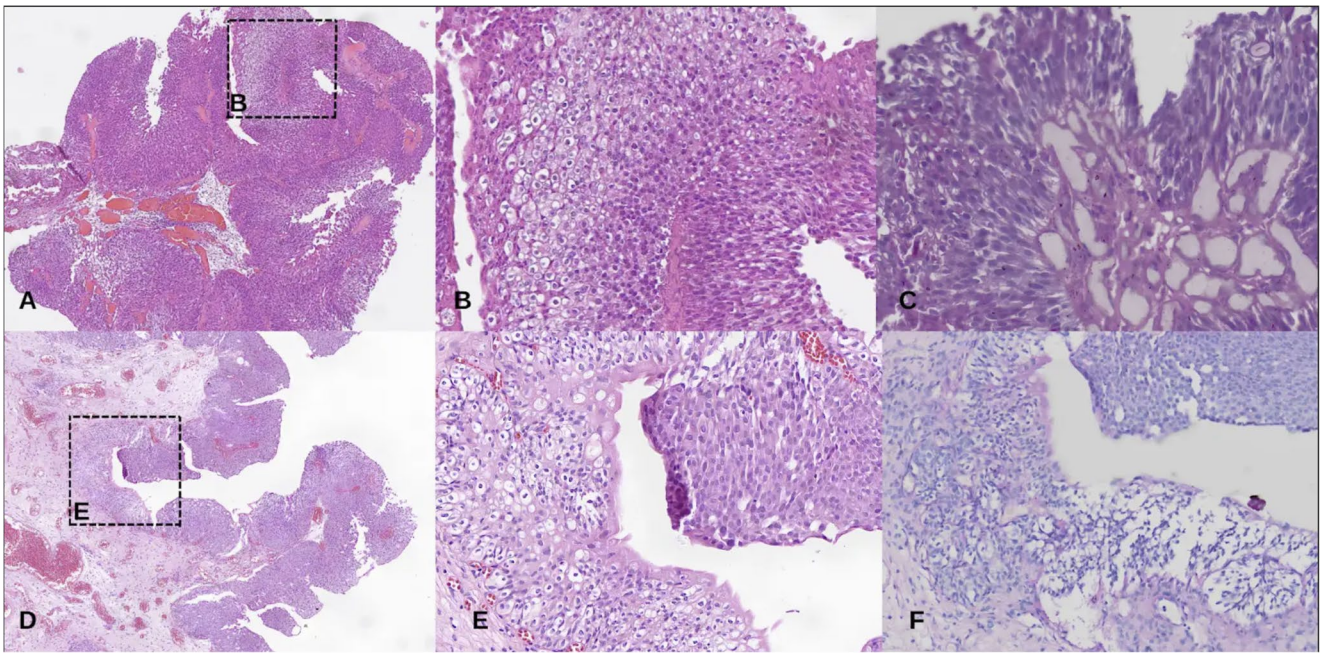


Fig. 2 Glycogen-rich-like clear-cell change in low-grade papillary urothelial carcinoma. Representative paired H&E and PAS-stained sections from two cases. In the first case, focal clear-cell change is identified on the initial H&E section (**A**, **B**), but the corresponding focus is not adequately represented on the deeper PAS-stained level (**C**). A similar finding is present in the second case (**D**–**E**), precluding definitive histochemical confirmation of intracytoplasmic glycogen (**F**)

section (A-B), but the corresponding focus is not adequately represented on the deeper PAS-stained level (C). A similar finding is present in the second case (D-E), precluding definitive histochemical confirmation of intracytoplasmic glycogen (F).

These cases were therefore classified as glycogen-rich-like clear-cell change rather than definitive glycogen-rich clear-cell morphology in LGPUC.

All tumors were non-muscle invasive at initial diagnosis. In cases with squamoid morphology or glycogen-rich-like clear-cell change, these findings were focal and generally involved less than 5% of the tumor volume. None showed concomitant carcinoma in situ or lymphovascular invasion at diagnosis.

Follow-up and clinical outcomes

Among the 514 patients, 276 (53.7%) had documented follow-up of at least 6 months or until an outcome event. The median follow-up duration for the entire cohort was 18 months. Among the six patients with squamoid morphology, one (16.7%) developed recurrence, and none progressed to high-grade or invasive disease. No cancer-specific deaths occurred in this group. Among the four cases with glycogen-rich-like clear-cell change, one patient subsequently developed invasive low-grade urothelial carcinoma (pT1). Representative images of the subsequent pT1 low-grade urothelial carcinoma are provided in Supplementary Fig. S1.

Among the 504 patients with conventional LGPUC, 57 (11.3%) experienced recurrence and 27 (5.4%) progressed. These progression events included 17 cases of invasive high-grade urothelial carcinoma, 8 cases of non-invasive high-grade papillary urothelial carcinoma, and 2 cases of invasive low-grade urothelial carcinoma (pT1) without high-grade features. Including the single invasive low-grade event in the glycogen-rich-like group, 28 patients (5.4%) in the overall cohort experienced a subsequent progression event. Five patients ultimately underwent radical cystectomy or other definitive therapy. Two patients died of bladder cancer-related causes, both after progression to invasive high-grade disease (disease-specific mortality, 0.4%). Most recurrences remained low grade. Median times to recurrence and progression were 12 and 17 months, respectively. Outcome comparisons are summarized in Table 1.

Discussion

While divergent differentiation and unusual histologic features are well documented in invasive urothelial carcinoma, their relevance in non-invasive tumors remains less clear. Our study systematically evaluated squamoid morphology and glycogen-rich-like clear-cell change in LGPUC and correlated these findings with clinical outcomes.

Table 1 Clinicopathologic features and clinical outcomes of LGPUC stratified by morphologic pattern. H&E-suspected glycogen-rich–like cases were classified as histochemically unconfirmed when the corresponding foci were absent, depleted, or not adequately represented on deeper PAS/PASD levels

Parameter	Conventional LGPUC ($n=504$)	Squamoid LGPUC ($n=6$)	Histochemically unconfirmed GR-like change ($n=4$)	p-value
Age, median (range)	63 (18–95)	68 (52–75)	61.5 (44–81)	>0.4
Sex (M/F)	408 / 96 (81.0% / 19.0%)	4 / 2	3/ 1	0.3
Recurrence, n (%)	57 / 504 (11.3%)	1 / 6 (16.7%)	0 / 4 (0%)	0.52 (SQ) / 1.00 (GR-like)
Subsequent progression event, total, n (%)	27 / 504 (5.4%)	0 / 6 (0%)	1 / 4 (25.0%)	1.00 (SQ) / 0.20 (GR-like)
Invasive high-grade, n (%)	17 / 504 (3.4%)	-	-	-
Non-invasive high-grade, n (%)	8 / 504 (1.6%)	-	-	-
Invasive low-grade, n (%)	2 / 504 (0.4%)	-	1 / 4 (25.0%)	-
Cancer-specific mortality, n (%)	2 (0.4%)	0 (0%)	0 (0%)	-
Median follow-up, months (range)	18 (0-273)	40 (12–72)	21 (10–42)	-

*SQ = squamoid morphology; GR-like = H&E-suspected glycogen-rich-like clear-cell change

*PAS/PASD stains were performed in all four GR-like cases; however, the corresponding H&E-suspected foci were absent, depleted, or not adequately represented on deeper histochemical levels in some cases, precluding definitive confirmation of glycogen accumulation

*The single invasive low-grade event in the GR-like group occurred in a histochemically unconfirmed case and was not interpreted as progression of definitive glycogen-rich clear-cell morphology in LGPUC

**P*-values represent comparisons of each morphologic subgroup with conventional LGPUC

Both squamoid morphology and glycogen-rich-like clear-cell change were rare. True squamous differentiation in urothelial carcinoma has been associated with adverse clinicopathologic features and worse outcomes, particularly in invasive and/or high-grade disease. However, the relevance of focal squamoid morphology in non-invasive LGPUC remains unclear and, to our knowledge, its prognostic significance has not been specifically investigated in this setting [15–17]. Related low-grade squamoid patterns have been described in papillary urothelial neoplasms, including the low-grade whorled pattern reported by Patriarca et al. and the "urothelial eddies" described by Kim et al. These patterns appear to behave indolently and should be distinguished from true squamous differentiation [18, 19]. In our cohort, squamoid LGPUC showed a recurrence rate of 16.7%, which was not significantly higher than the 11.3% seen in conventional LGPUC, and notably, no patients experienced disease progression (Table 1). These findings support the interpretation that focal squamoid morphology, when present in an otherwise conventional LGPUC, is not clearly associated with adverse clinical outcomes in the present cohort.

Clear-cell or glycogen-rich morphology in urothelial carcinoma has largely been described in high-grade invasive tumors. In the present cohort, four LGPUC cases raised the possibility of glycogen-rich-like clear-cell morphology because of focal clear cytoplasmic change on H&E sections. The differential diagnosis of focal clear-cell change in urothelial neoplasia is broad and includes glycogen accumulation, fixation-related artifact, cautery-related change, and degenerative cytoplasmic clearing. To minimize potential overinterpretation, cases composed exclusively of cauterized epithelial fragments were excluded from the study cohort, and glycogen-rich morphology was not diagnosed in the absence of histochemical confirmation.

An important practical implication of our findings is the risk of diagnostic overinterpretation. Minor squamoid foci or H&E-suspected glycogen-rich-like clear-cell change may raise concern for divergent differentiation or higher-grade disease, particularly in limited biopsy specimens. Our results suggest that, in the absence of high-grade architectural or cytologic features, focal squamoid morphology or glycogen-rich-like change should not by itself prompt tumor upgrading or altered clinical management.

Limitations

We acknowledge several limitations. The number of squamoid cases was small, limiting statistical power for subgroup comparisons. The number of H&E-suspected glycogen-rich-like cases was also small, and the foci were extremely limited. Most importantly, deeper sections prepared for PAS/PASD did not consistently contain the same H&E-suspected foci, precluding definitive histochemical confirmation of glycogen in the corresponding tumor cells. Accordingly, this study cannot determine the prognostic significance of definitive glycogen-rich clear-cell morphology

in LGPUC; rather, it highlights the practical difficulty of correlating very focal H&E findings with deeper histochemical levels.

Before the biological significance of glycogen-rich-like morphology can be fully assessed, definitive histochemical confirmation on sections corresponding to the H&E-suspected focus is required. Future studies should ideally incorporate a prospective or protocolized histochemical approach in which PAS and PASD are performed on immediately adjacent serial sections once the suspicious focus is identified on H&E, or unstained intervening sections are reserved at the time of initial sectioning. Such an approach would minimize level-related tissue loss and permit more reliable H&E-to-PAS/PASD correlation.

Our analysis was also limited by incomplete follow-up in a subset of patients. Because recurrence and progression rates were calculated using the entire morphologic subgroup as the denominator, patients without documented follow-up were treated as event-negative unless an outcome event was recorded. Therefore, the reported event rates should be interpreted as descriptive and potentially conservative estimates.

Additionally, no molecular analyses were performed. Future studies incorporating protocolized PAS/PASD evaluation of immediately adjacent levels together with molecular profiling may help determine whether these uncommon morphologic findings represent true biologic variation or merely sampling-related heterogeneity. In this setting, molecular markers should be viewed as complementary to, rather than replacements for, careful morphologic and histochemical assessment.

Conclusion

Squamoid morphology and glycogen-rich-like clear-cell change are rare in LGPUC and not associated with increased recurrence or progression in this cohort. In the absence of high-grade architectural or cytologic features, focal squamoid morphology or glycogen-rich-like clear-cell change should be interpreted cautiously and, based on the present data, does not appear to justify tumor upgrading.

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Data availability Data are not publicly available; however, they are available upon reasonable request.

Declarations

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Competing interests The authors declare that they have no competing interests.

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