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Original contribution

Diagnosis of urothelial carcinoma in situ using blue light cystoscopy and the utility of immunohistochemistry in blue light–positive lesions diagnosed as atypical[☆,☆☆,★]

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Summary Carcinoma in situ (CIS) is difficult to visualize with white light cystoscopy (WLC), whereas blue light cystoscopy (BLC) using photosensitizing agents improves detection rates. We retrospectively reviewed transurethral biopsies of bladder tumors in which both WLC and BLC evaluations were performed (n = 135 samples from 79 patients). Biopsies were classified based on the presence/absence of fluorescence under BLC and the final pathological report (CIS/benign/atypical). Forty-one (30%) cases were diagnosed as CIS; of those, 38 (93%) were BLC(+), including 23 that were WLC(−). Conversely, 51 (38%) lesions were BLC(+) but classified as non-CIS. Eleven BLC(+) cases were diagnosed as "atypical." These cases were anonymized and reviewed by 7 pathologists for concordance and then immunostained for CK20, p53, and Ki-67. Immunohistochemistry results were interpreted as consistent with CIS if there was full-thickness staining of CK20, more than 50% p53-positive cells, and more than 50% Ki-67–positive cells. Review of BLC(+)/atypical cases showed a mean agreement of 79%, and none of the cases showed staining pattern consistent with CIS. Therefore, all 11 cases of BLC(+)/atypical were considered non-CIS for the final analysis. All patients with BLC(+)/atypical lesions had a history of intravesical *Bacillus* Calmette-Guerin and/or mitomycin. Using final pathology as the reference, sensitivity, specificity, and negative predictive value of BLC were 93% (confidence interval [CI], 80.1%-98.5%), 46% (CI, 35.4%-56.3%), and 94% (CI, 82.5%-97.8%), respectively. The low specificity of BLC leads to BLC(+) lesions with atypical diagnosis.

Morphological classification of these lesions is fairly consistent among different pathologists. Immunohistochemistry for p53/CK20/Ki-67 in this setting is only helpful to potentially avoid overcalling CIS.

1. Introduction

Carcinoma in situ (CIS) of the urinary bladder is a high-grade, noninvasive urothelial carcinoma that poses the patients at an increased risk of recurrence and progression [1]. Although papillary lesions are relatively easy to identify and remove by transurethral resection, urothelial CIS is more difficult to visualize with traditional white light cystoscopy (WLC), especially if the patient has previously undergone intravesical therapies. On cystoscopy, they may appear as reddish or erythematous patches, with a velvety, granular appearance, sometimes difficult to distinguish from inflammation or reactive urothelium. Visualization of CIS is thought to be optimized by instilling of a photosensitizing drug, including 5-aminolevulinic acid or its derivative hexyl-aminolevulinate (HAL), in combination with blue light cystoscopy (BLC) [2,3]. BLC has been shown to improve tumor detection rates but may have a lower specificity than traditional WLC [4,5]. However, this has not been demonstrated in recent comparative multicenter phase III trial [6]. False positives can be due to the uptake of 5-aminolevulinic acid/HAL in areas of inflammation, as well as in case of recent transurethral resection of bladder tumor or intravesical therapies [7,8].

Flat urothelial lesions that are BLC(+) comprise a variety of different histopathologic entities including reactive changes, hyperplasia, urothelial atypia/dysplasia (atypical features falling short of diagnostic criteria for CIS), or CIS. Immunohistochemical (IHC) markers have been investigated as ancillary studies to aid in the diagnosis of CIS [9-12], but their utility in the setting of BLC(+) lesions has not been investigated. Here, we characterize the morphologic features of BLC(+) lesions that were diagnosed as "atypical" or "dysplasia." We tested the interpathologist reproducibility of this diagnosis and the utility of immunohistochemistry for cytokeratin 20 (CK20), Ki-67, and p53 in the classification of these lesions.

2. Materials and methods

2.1. Patients and tissue samples

Approval of this project was obtained from the Johns Hopkins Medicine Institutional Review Board. Patient records from January 2015 to May 2017 were retrospectively reviewed to identify all the bladder biopsies in which both white light and blue light evaluations were performed (n = 135, from 79 patients). We classified the biopsies based on the presence or absence of fluorescence at BLC [BLC(+)/BLC(−)] based on a single surgeon's (T. J. B.) operative notes. For example, lesions considered BLC(+) were those that showed fluorescence in an area suspicious of malignancy. For the purposes of our analysis, we collectively classified as "CIS negative" all the lesions reported by genitourinary pathologists as benign urothelium, urothelial dysplasia, or urothelial atypia. All cases that were BLC(+) with a non-CIS diagnosis on the final pathology report but that were reported as "urothelial atypia" or "dysplasia" (n = 11) were blindly reviewed by 7 different pathologists (only E;hematoxylin and eosin slides), including 3 general surgical pathologists and 4 fellowship-trained urologic pathologists. These cases were anonymized and blinded to the original diagnosis and circulated with a chart where the pathologist had to assign the diagnosis of "CIS," "benign," or "atypical" to each case. Fleiss κ interobserver agreement index was used to calculate the agreement among all 7 pathologists. The clinical history was retrieved from the electronic medical record.

2.2. Immunohistochemistry

Using 4-μm-thick tissue sections, immunohistochemistry was performed using a Ventana Benchmark Ultra automated staining system (Ventana Medical Systems, Tucson, AZ) using the Ventana reagents and the iViewDAB Detection kit (Ventana Medical Systems). Immunostains were performed for anti-CK20 monoclonal mouse antibody (clone Ks20.8, pre-dilute; CellMarque, Rocklin, CA), anti-p53 monoclonal mouse antibody (clone BP-53-11, pre-dilute; Ventana Medical Systems), and Ki-67 monoclonal rabbit antibody (clone 30-9, predilute; Ventana Medical Systems). Hematoxylin was used as a counterstain.

Results consistent with dysplasia/CIS included positivity of all 3 markers in the following distribution: full-thickness CK20 staining, strong nuclear staining for p53 in more than 50% of the cells, and Ki-67 higher than 50% of the cells and reaching the upper third of the urothelium [10,12,13]. If only 1 or 2 of the markers were positive, cases were not deemed to meet the criteria for CIS by immunohistochemistry [14].

3. Results

### 3.1. Blue light cystoscopy and CIS diagnosis

The cohort included 79 patients, accounting for a total of 135 bladder biopsies (parts) of flat lesions only. The information of

the cystoscopy result [BLC(+), BLC(−)] was specified by the urologic oncologist (T. J. B.) obtaining the sample. Examples of BLC(+) lesions are illustrated in Fig. 1. Of the 135 bladder biopsies, 41 (30%) lesions were diagnosed as CIS. Of those, 38 (93%) were BLC(+) including 23 (56%) that were only seen on blue light but not on white light. Conversely, 51 (38%) lesions did fluoresce on BLC but were classified as non-CIS (benign urothelium, dysplasia, or atypia). Using pathology as the reference standard, sensitivity, specificity, and negative predictive value of blue light cystoscopy (BLC) were 93%

(confidence interval [CI], 80.1%–98.5%), 46% (CI, 35.4%-56.3%), and 94% (CI, 82.5%-97.8%), respectively (Table 1).

3.2. BLC(+) lesions with pathology diagnosis of "atypical urothelium"

A total of 11 samples from 8 patients were BLC(+), and the pathology report was "atypical" (neither CIS nor benign). Pathology descriptions of the findings included "atypical," "dysplasia," "suspicious for CIS." All patients from this group had
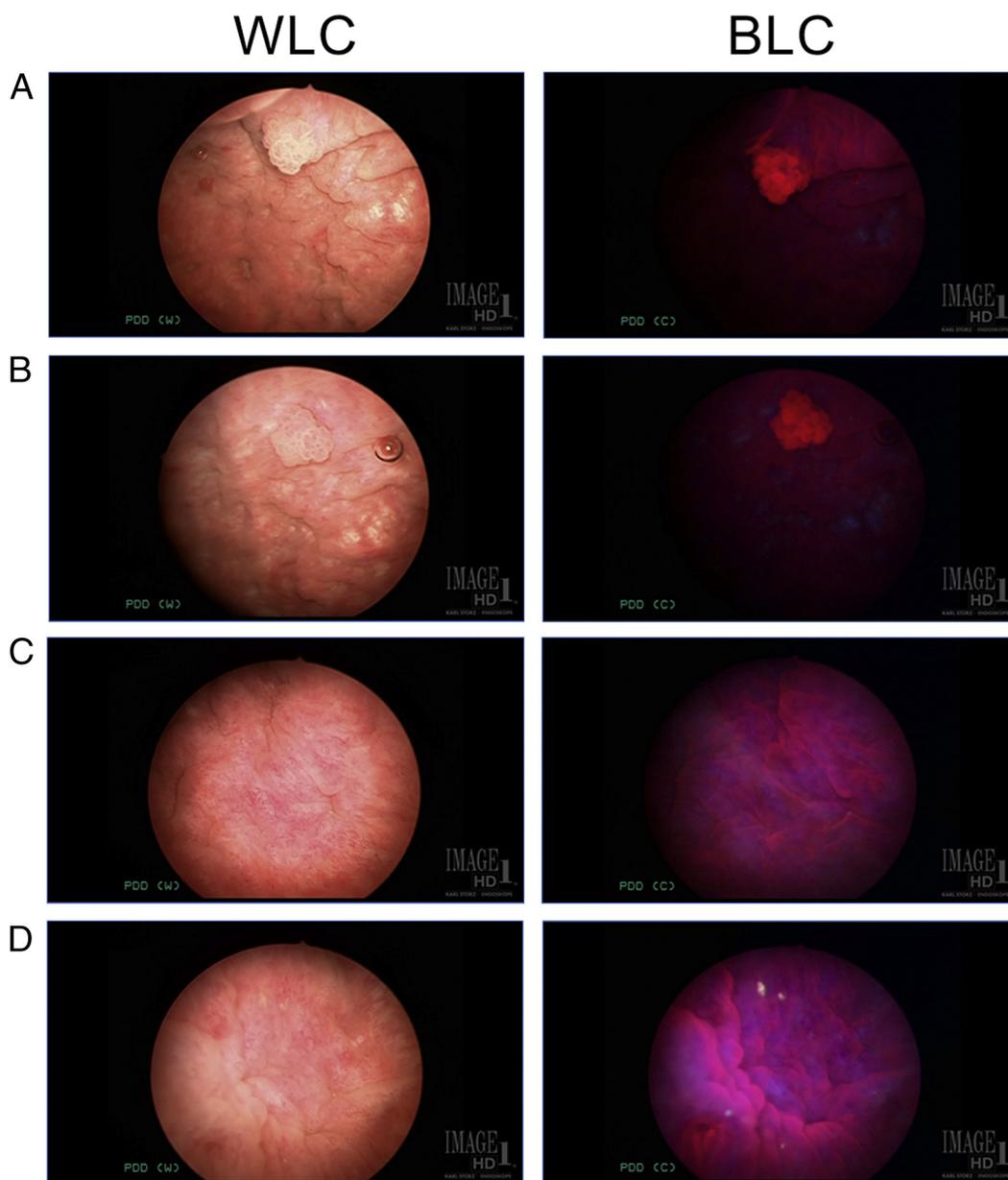
Fig. 1 A; and B, WLC view of an example of a small papillary lesion (left), highlighted by red fluorescence under BLC (;right). Note that the background urothelium around the small papillary lesions is seen dark and without fluorescence under BLC. C; and D, WLC of flat mucosa of areas that show red fluorescence under BLC (right), indicating to the urologist the area to be biopsied. The pathology of both these examples was benign.

Table 1   BLC detection of tumor lesions

	CIS+	CIS−	Total
BLC+	38	51	89
BLC−	3	43	46
Total	41	94	135

Abbreviations: CIS+, CIS at pathology; CIS−, no CIS at pathology (dysplasia, atypia, etc); (+), positive BLC; (−), negative BLC.

a history of intravesical *Bacillus* Calmette-Guerin (BCG), chemotherapy, or radiation therapy (Table 2). Morphologically, these lesions were characterized by (1) urothelium with intraepithelial lymphocytes, rare hyperchromatic urothelial cells, and/or urothelial cells with nuclear enlargement less than 3 times the size of the nuclei of a lymphocyte, and/or mild nuclear pleomorphisms (n = 6 ;), and (2) mostly denuded mucosa with residual von-Brunn nests with mild nuclear pleomorphism or rare atypical urothelial cells on the surface (n = 5) (Fig. 2).

To prove the interpathologist reproducibility of the "atypical" diagnosis, the slides from these cases were circulated among 7 pathologists, including 4 fellowship-trained urologic pathologists and 3 general pathologists, who were blinded to the original diagnosis and were provided with 3 options: CIS, benign, or atypical. The results of this survey are presented in Table 3. Overall, E;hematoxylin and eosin assessment of CIS versus non-CIS lesions reached a multirater κ score of 0.254 ($P < .001$), suggestive for a fair agreement between the different pathologists. In 9 of 11 (82%) cases, the most common diagnosis was "atypical," confirming the initial diagnosis. Lesion 9 had higher number of "benign" diagnoses (4/7), and lesion 10 had higher number of "CIS" diagnoses (6/7).

In addition, all 11 "atypical" lesions were immunostained with antibodies against CK20, p53, and Ki-67. Results consistent with dysplasia/CIS included full-thickness CK20 staining, strong nuclear staining for p53 in more than 50% of the cells, or Ki-67 higher than 30% of the cells and reaching the upper

third of the urothelium. None of the lesions presented IHC results consistent with CIS (Fig. 2; Table 3). Case 1 had discordant immunohistochemistry results with strongly positive p53 staining (50% staining), but negative CK20 and Ki-67. This case stayed as atypical as none of the 7 evaluating pathologists considered the morphology to be sufficient for the diagnosis of CIS.

4. Discussion

Diagnosis of a CIS lesion is of paramount importance for the prognosis and management of bladder cancer patients because most patients with CIS eventually recur and about 25% of them progresses to invasive disease [15]. Patients with diagnosis of CIS are classified as "high risk/highest risk" according to the European Association of Urology guidelines, and patients may be counseled to undergo additional intravesical therapy if they are BCG unresponsive versus early cystectomy [16]. Although pure urothelial CIS accounts for only 1% to 3% of new bladder cancer diagnoses, it is more commonly seen in association with high-grade papillary or invasive T1 (invasion of lamina propria) tumors [16].

CIS can be difficult to identify on WLC, as it often appears as an erythematous area, which can be focal, multifocal or diffuse. To increase tumor detection, in particular CIS, BLC with HAL instillation is currently used in many centers both in the United States and in Europe [17,18]. Several randomized controlled trials have demonstrated that BLC facilitates the detection of bladder cancer lesions [19-23]. In a large, multicenter randomized clinical trial, Stenzl et al [23] reported that BLC detected at least one additional lesion not visible at WLC in 16% of patients with Ta/T1 tumors. Moreover, the BLC group showed a 16% relative reduction in recurrence during the follow-up period compared with the group who underwent WLC only. Similarly, Grossman et al [20] showed that BLC detected at least one more tumor in 29% of patients, whereas

Table 2   Clinical characteristics of patients with blue light–positive lesions diagnosed as equivocal

Lesion no.	Age (y)	Sex	Pathology diagnosis in BCL(+) lesion	Clinical history	BCG	Intravesical mitomycin
1	69	M	Denudation and focal urothelial atypia	pT1 HGUCa	Yes, 6 cycles	Yes
2, 3	60	M	Dysplasia (×2)	pT1 HGUCa	Yes, 6 cycles	No
4, 5, 6	49	M	Urothelial atypia (×3)	pT1 HGUCa	Yes, 6 cycles	Yes, 3 mo prior
7	87	M	Urothelial atypia	Prostate cancer treated with external beam radiation and brachytherapy	No	No
8	81	M	Denudation and atypical cells suspicious for CIS	pT1 HGUCa with focal glandular differentiation	Yes, 6 cycles	No
9	62	M	Denudation and atypical cells	pT1 HGUCa	Yes	Yes, 3 mo prior
10	69	M	Urothelial atypia	pT1 HGUCa	Yes	No
11	83	M	Urothelial atypia	pT1 HGUCa	Yes	Yes

Abbreviation: HGUCa, high-grade urothelial carcinoma.
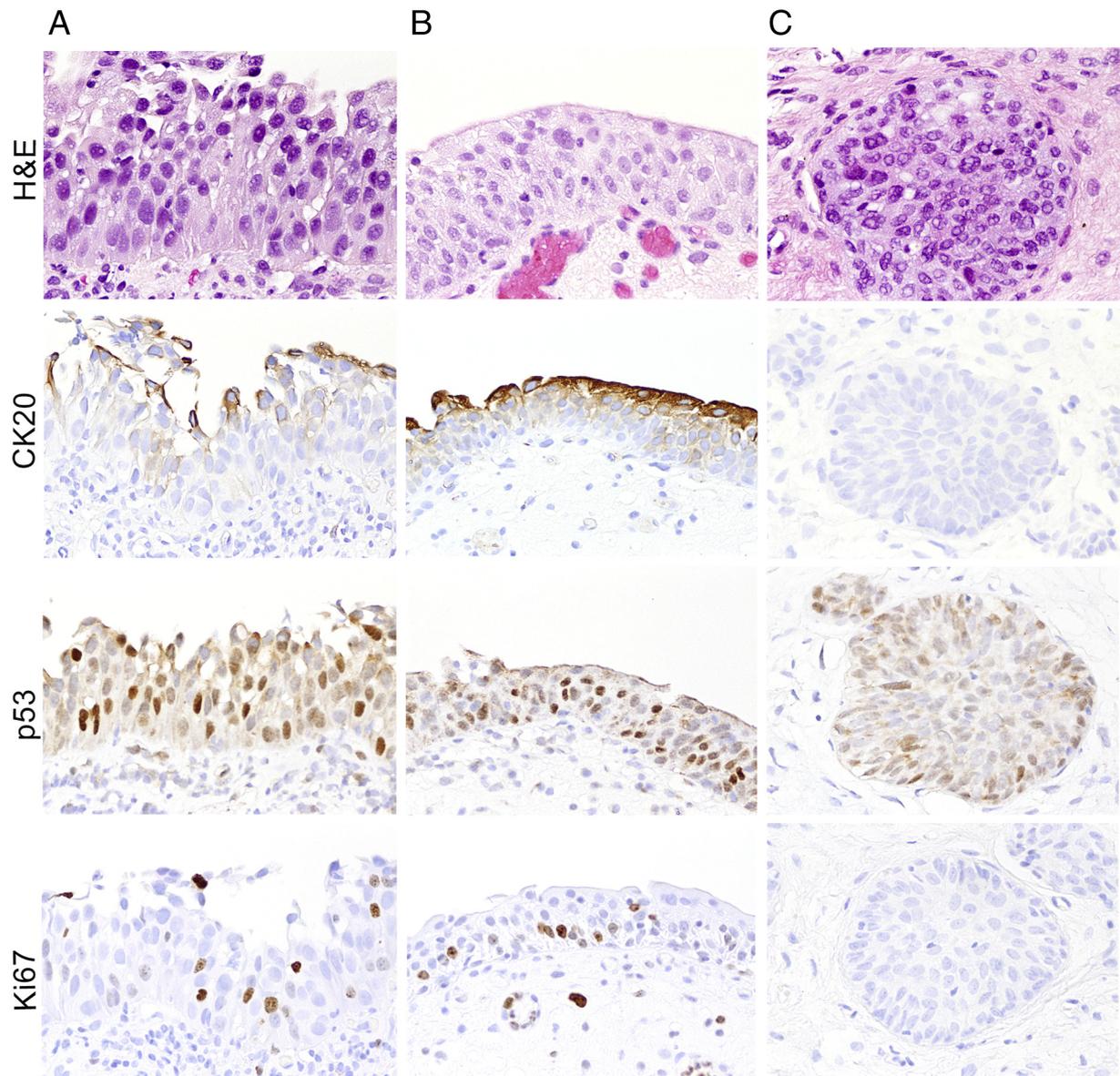
Fig. 2 Examples of flat lesions that were BLC(+) and with an "atypical" diagnosis and immunohistochemistry results supporting a non-CIS diagnosis. A, Lesion 10 is characterized by slightly thickened urothelium with multiple hyperchromatic nuclei and mild nuclear enlargement but without significant nuclear size variation. CK20 immunostain highlights only the top layer of cells and not "full thickness" as expected in dysplasia or CIS. P53 is positive with moderate staining in approximately 30% of urothelial cells; however, this finding is not specific for CIS. Ki-67 shows a low proliferation rate of approximately 20%. B, Lesion 7 shows urothelium of normal thickness with rare enlarged nuclei. CK20 immunostaining is positive in umbrella cells only, a pattern considered normal. P53 shows moderate nuclear staining in approximately 50% of cells and a Ki-67 proliferation rate of approximately 10%. C, Lesion 11 characterized by urothelial atypia in von-Brunn nests with overlying denuded mucosa. The von-Brunn nest is entirely negative for CK20 and shows mild nuclear staining for p53 in approximately 10% of nuclei and no labeling for Ki-67.

Jocham et al [21] reported that in their cohort BLC increased bladder cancer detection rate overall (19%), and especially of CIS (27%) and dysplastic (49%) lesions.

In our study, we demonstrated that BLC has a very high sensitivity (93%) and negative predictive value (94%) when compared with traditional WLC. These findings are clinically important because they highlight the very low probability to miss CIS during BLC. Even if the low specificity reported (46%) suggests a high number of unnecessary bladder biopsies, that additional sampling does not place the patients at significantly higher risk of complications or adverse effects, whereas they can be reassured that all potentially very aggressive lesions have been resected [24]. Indeed, systematic reviews and meta-analyses have shown that BLC has significantly higher sensitivity than WLC [4,25].

Table 3   Pathologists report and IHC staining interpretation of BLC(+)/atypical biopsies

	1 (GU)			2 (GU)			3 (GU)			4 (GU)			5 (GRL)			6 (GRL)			7 (GRL)			Total			P53	CK20	Ki-67 (%)	Int
	C	B	A	C	B	A	C	B	A	C	B	A	C	B	A	C	B	A	C	B	A	C	B	A				
1		X			X				X		X			X			X				X	0	2	5	>50% S	Neg	0	B
2		X			X				X			X		X				X			X	0	3	4	20% M	Neg	2	B
3		X			X				X			X		X				X			X	0	3	4	10% M	Neg	10	B
4		X			X				X	X					X			X			X	1	2	4	20% M	Neg	0	B
5		X			X		X					X			X			X			X	1	2	4	60% M	Neg	0	B
6		X			X				X			X			X			X			X	0	1	6	50% M	Neg	0	B
7	X				X				X			X		X		X					X	1	1	5	50% M	Neg	10	B
8		X		X		X			X					X				X			X	2	0	5	Den	Den	Den	-
9		X		X				X	X					X			X				X	1	4	2	20% M	Neg	20	B
10	X			X			X			X				X		X		X				6	1	0	30% M	Neg	20	B
11	X				X	X					X				X			X			X	2	1	4	10% M	Neg	0	B

Abbreviations: A, atypical; B, benign; ;C, CIS; Den, denudation; Int, immunohistochemistry interpretation; GRL, general pathologist; GU, genitourinary pathologist; ;IHC, immunohistochemistry; M, moderate; S, strong.

Despite the beneficial impact of the high negative predictive value of BLC for patient prognosis, the low specificity of BLC results in the removal of a number of BLC(+)/atypical lesions. Unfortunately, a clear-cut distinction between CIS and benign cannot always be made on histomorphology alone. Several studies have investigated the best IHC markers to discriminate between CIS and reactive lesions. A panel including CK20, CD44, p53, and Ki-67 antibodies produces relatively consistent results in differentiating benign urothelium versus CIS, even in cases with prior radiation or intravesical instillations [10,12,13,26,27]. Despite the growing literature and interest for IHC, the International Society of Urologic Pathology recommends a cautionary use, with interpretation of the findings always strict morphologic correlation [9].

In our study, we showed that the interobserver agreement between different pathologists reviewing BLC(+)/atypical lesions is good. None of these cases showed IHC results consistent with CIS, demonstrating that the only potential use for IHC in this context is to avoid overcalling CIS in cases with borderline morphology. It should also be noted that dysplasia can show an IHC pattern similar to the one described in CIS including full-thickness staining for CK20 [10]. Case 1 of our study showed discordant immunohistochemistry results with strong p53 staining in 50% of the nuclei but negative CK20 or Ki-67. A previous study by Arias-Stella et al [14] had shown that only 1 of 20 cases with equivocal atypia and discordant immunohistochemistry results developed diagnostic carcinoma on follow-up, emphasizing that caution should be used when interpreting immunohistochemistry when only one marker is supportive of CIS.

As the use of BLC becomes more widespread in clinical practice, pathologists will review a significant number of BLC(+) cases that are not diagnostic of CIS. These results should reassure practicing pathologists that morphology continues to be the criterion standard in the diagnosis of CIS, and although many specimens are labeled as BLC(+), they should not be feel compelled to make a diagnosis of CIS or dysplasia if the morphologic findings are insufficient.

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