HHS Public Access

Author manuscript

Hum Pathol. Author manuscript; available in PMC 2020 August 01.

Published in final edited form as:

Hum Pathol. 2019 August ; 90: 1–7. doi:10.1016/j.humpath.2019.04.018.

Diagnosis of urothelial carcinoma in situ using blue light cystoscopy and the utility of im-munohistochemistry in blue light-positive lesions diagnosed as atypical

Filippo Pederzoli, MD[1,3,6], **Belkiss Murati Amador, MD**[2,6], **Iryna Samarska, MD**[2], **Kara A. Lombardo, BS**[2,5], **Max Kates, MD**[3,4,5], **Trinity J. Bivalacqua, MD, PhD**[3,4,5], **Andres Matoso, MD**[2,3,4,5]

[1]Vita-Salute San Raffaele University, Milan, Italy, 20132

[2]Department of Pathology The Johns Hopkins Medical Institutions, Baltimore, MD, 21231.

[3]Department of Urology The Johns Hopkins Medical Institutions, Baltimore, MD, 21231.

[4]Department of Oncology, The Johns Hopkins Medical Institutions, Baltimore, MD, 21231.

[5]Johns Hopkins Greenberg Bladder Cancer Institute, Baltimore, MD, 21231.

[6]These authors contributed equally

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 Ki67. Immunohistochemistry results were interpreted as consistent with CIS if there was full-thickness staining of CK20, more than 50% p53-positive cells, and over 50% Ki67-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 history of intravesical BCG and/or mitomycin. Using final pathology as the reference, sensitivity, specificity and negative predictive value (NPV) of BLC were 93% (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/Ki67 in this setting is only helpful to potentially avoid overcalling CIS.

Corresponding author: Andres Matoso, M.D. The Johns Hopkins Hospital, The Weinberg Building, Rm. 2242, 401 N. Broadway Street, Baltimore, MD 21231, U.S.A. Telephone: (410) 955-5082, Fax: (410) 367-3223, amatoso1@jhmi.edu.

Conflict of interest: The authors declare no conflict of interest

Keywords

urothelial carcinoma in situ; blue light cystoscopy; photosensitizing agents

1. Introduction

Carcinoma in-situ (CIS) of the urinary bladder is a high-grade, non-invasive urothelial carcinoma that poses the patients at an increased risk of recurrence and progression [1]. While papillary lesions are relatively easy to identify and remove by transurethral resection (TURBT), urothelial carcinoma in-situ (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 (5-ALA) 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-ALA/HAL in areas of inflammation, as well as in case of recent TURBT or intravesical therapies [7, 8].

Flat urothelial lesions that are BLC(+) comprise a variety of different histopathological 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 inter-pathologist reproducibility of this diagnosis and the utility of immunohistochemistry for cytokeratin-20 (CK20), Ki67 and p53 in the classification of these lesions.

2. Methods

2.1. Patients and tissue samples

Approval of this project was obtained from the Johns Hopkins Medicine Institutional Review Board (IRB). 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 blue-light cystoscopy [BLC(+)/BLC(−)] based on a single surgeon’s (TJB) operative notes. For example, lesions considered BLC(+) where 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 a genitourinary pathologists as benign urothelium, urothelial dysplasia, 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 seven

different pathologists (only H&E slides), including three general surgical pathologists and four 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’ kappa interobserver agreement index was used to calculate the agreement among all seven 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. 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 for Ki67 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 three markers in the following distribution: full thickness CK20 staining, strong nuclear staining for p53 in more than 50% of the cells and Ki67 higher than 50% of the cells and reaching the upper third of the urothelium [10, 12, 13]. If only one or two 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 carcinoma in-situ 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 (TJB) obtaining the sample. Examples of BLC(+) lesions are illustrated in figure 1. Out 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 (NPV) of blue light cystoscopy were 93% (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 eight 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 prior history of intravesical 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 3x the size of the nuclei of a lymphocyte, and/or mild nuclear pleomorphisms (n=6); 2) mostly

denuded mucosa with residual von-Brunn nests with mild nuclear pleomorphism or rare atypical urothelial cells on the surface (n=5). (Figure 2).

To prove the inter-pathologist reproducibility of the “atypical” diagnosis, the slides from these cases were circulated among seven pathologists, including four fellowship-trained urologic pathologists and three general pathologists, who were blinded to the original diagnosis and were provided with three options: CIS, benign, or atypical. The results of this survey is presented in Table 3. Overall, H&E assessment of CIS vs. non-CIS lesions reached a multi-rater kappa score of 0.254 ($p < 0.001$), suggestive for a fair agreement between the different pathologists. In 9/11 (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).

Additionally, all 11 “atypical” lesions were immunostained with antibodies against CK20, p53 and Ki67. Results consistent with dysplasia/CIS included full thickness CK20 staining, strong nuclear staining for p53 in more than 50% of the cells or Ki67 higher than 30% of the cells and reaching the upper third of the urothelium. None of the lesions presented IHC results consistent with CIS. (Figure 2; Table 3). Case #1 had discordant immunohistochemistry results with strongly positive p53 staining (50% staining), but negative CK20 and Ki67. 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 the majority of 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 (EAU) guidelines, and patients may be counselled to undergo additional intravesical therapy if they are BCG unresponsive vs. early cystectomy [16]. While pure urothelial CIS accounts for only 1–3% 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 U.S. 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. reported that BLC detected at least one additional lesion not visible at WLC in 16% of patients with Ta/T1 tumors [23]. Moreover, the BLC group showed a 16% relative reduction in recurrence during the follow-up period, compared to the group who underwent WLC only. Similarly, Grossman et al. showed that BLC detected at least one more tumor in 29% of patients, while Jocham et al. reported that in their cohort BLC increased bladder cancer detection rate overall (19%), and especially of CIS (27%) and dysplastic (49%) lesions [20, 21].

In our study, we demonstrated that BLC has a very high sensitivity (93%) and negative predictive value (94%), when compared to 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, while 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].

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, Ki67 antibodies produces relatively consistent results in differentiating benign urothelium vs. CIS, even in cases with prior radiation or intravesical instillations [10, 12, 13, 26, 27]. In spite of 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 Ki67. A previous study by Arias-Stella et al 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 [14].

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 gold standard in the diagnosis of CIS and while 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.

Acknowledgements:

This work was supported by the Department of Pathology at Johns Hopkins University and by the NIH Institutional Research Training Grant T32 CA193145 to BMA. This work has been accepted as an abstract at the USCAP 2019 Annual Meeting in National Harbor, MD.

References

1. Cheng L, Cheville JC, Neumann RM, et al. Survival of patients with carcinoma in situ of the urinary bladder. Cancer 1999; 85, 2469–2474. [PubMed: 10357420]
2. Lee CS, Yoon CY, Witjes JA. The past, present and future of cystoscopy: the fusion of cystoscopy and novel imaging technology. BJU Int 2008; 102, 1228–1233. [PubMed: 19035886]
3. Kolodziej A, Krajewski W, Matuszewski M, Tupikowski K. Review of current optical diagnostic techniques for non-muscle-invasive bladder cancer. Cent European J Urol 2016; 69, 150–156.
4. Mowatt G, N'Dow J, Vale L, et al. Photodynamic diagnosis of bladder cancer compared with white light cystoscopy: Systematic review and meta-analysis. Int J Technol Assess Health Care 2011; 27, 3–10. [PubMed: 21262078]
5. Kutwin P, Konecki T, Cichocki M, Falkowski P, Jablonowski Z. Photodynamic Diagnosis and Narrow-Band Imaging in the Management of Bladder Cancer: A Review. Photomed Laser Surg 2017; 35, 459–464. [PubMed: 28537820]
6. Lapini A, Minervini A, Masala A, et al. A comparison of hexaminolevulinate (Hexvix((R))) fluorescence cystoscopy and white-light cystoscopy for detection of bladder cancer: results of the HeRo observational study. Surg Endosc 2012; 26, 3634–3641. [PubMed: 22729704]
7. Ray ER, Chatterton K, Khan MS, et al. Hexylaminolaevulinate fluorescence cystoscopy in patients previously treated with intravesical bacille Calmette-Guerin. BJU Int 2010; 105, 789–794. [PubMed: 19832725]
8. Draga RO, Grimbergen MC, Kok ET, Jonges TN, van Swol CF, Bosch JL. Photodynamic diagnosis (5-aminolevulinic acid) of transitional cell carcinoma after bacillus Calmette-Guerin immunotherapy and mitomycin C intravesical therapy. Eur Urol 2010; 57, 655–660. [PubMed: 19819064]
9. Amin MB, Trpkov K, Lopez-Beltran A, Grignon D, Members of the IIiDUPG. Best practices recommendations in the application of immunohistochemistry in the bladder lesions: report from the International Society of Urologic Pathology consensus conference. Am J Surg Pathol 2014; 38, e20–34. [PubMed: 25029121]
10. Mallofre C, Castillo M, Morente V, Sole M. Immunohistochemical expression of CK20, p53, and Ki-67 as objective markers of urothelial dysplasia. Mod Pathol 2003; 16, 187–191. [PubMed: 12640096]
11. Sun W, Zhang PL, Herrera GA. p53 protein and Ki-67 overexpression in urothelial dysplasia of bladder. Appl Immunohistochem Mol Morphol 2002; 10, 327–331. [PubMed: 12607601]
12. McKenney JK, Desai S, Cohen C, Amin MB. Discriminatory immunohistochemical staining of urothelial carcinoma in situ and non-neoplastic urothelium: an analysis of cytokeratin 20, p53, and CD44 antigens. Am J Surg Pathol 2001; 25, 1074–1078. [PubMed: 11474293]
13. Aron M, Luthringer DJ, McKenney JK, et al. Utility of a triple antibody cocktail intraurothelial neoplasm-3 (IUN-3-CK20/CD44s/p53) and alpha-methylacyl-CoA racemase (AMACR) in the distinction of urothelial carcinoma in situ (CIS) and reactive urothelial atypia. Am J Surg Pathol 2013; 37, 1815–1823. [PubMed: 24225842]
14. Arias-Stella JA 3rd, Shah AB, Gupta NS, Williamson SR. CK20 and p53 Immunohistochemical Staining Patterns in Urinary Bladder Specimens With Equivocal Atypia. Arch Pathol Lab Med 2018; 142, 64–69. [PubMed: 28967804]
15. Moch H, Humphrey P, Ulbright T, Reuter V. WHO Classification of Tumours of the Urinary System and Male Genital Organs. Lyon, France: International Agency for Research on Cancer, 2016.
16. Rieken M, Shariat SF, Kluth L, et al. Comparison of the EORTC tables and the EAU categories for risk stratification of patients with nonmuscle-invasive bladder cancer. Urol Oncol 2018; 36, 8 e17–18 e24.
17. Daneshmand S, Bazargani ST, Bivalacqua TJ, et al. Blue light cystoscopy for the diagnosis of bladder cancer: Results from the US prospective multicenter registry. Urol Oncol 2018; 36, 361 e361–361 e366.

18. Smith AB, Daneshmand S, Patel S, et al. Patient-reported outcomes of blue-light flexible cystoscopy with hexaminolevulinate in the surveillance of bladder cancer: results from a prospective multicentre study. BJU Int 2019; 123, 35–41. [PubMed: 29979488]

19. Fradet Y, Grossman HB, Gomella L, et al. A comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of carcinoma in situ in patients with bladder cancer: a phase III, multicenter study. J Urol 2007; 178, 68–73; discussion 73. [PubMed: 17499291]

20. Grossman HB, Gomella L, Fradet Y, et al. A phase III, multicenter comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of superficial papillary lesions in patients with bladder cancer. J Urol 2007; 178, 62–67. [PubMed: 17499283]

21. Jocham D, Witjes F, Wagner S, et al. Improved detection and treatment of bladder cancer using hexaminolevulinate imaging: a prospective, phase III multicenter study. J Urol 2005; 174, 862–866; discussion 866. [PubMed: 16093971]

22. Hermann GG, Mogensen K, Carlsson S, Marcussen N, Duun S. Fluorescence-guided transurethral resection of bladder tumours reduces bladder tumour recurrence due to less residual tumour tissue in Ta/T1 patients: a randomized two-centre study. BJU Int 2011; 108, E297–303. [PubMed: 21414125]

23. Stenzl A, Burger M, Fradet Y, et al. Hexaminolevulinate guided fluorescence cystoscopy reduces recurrence in patients with nonmuscle invasive bladder cancer. J Urol 2010; 184, 1907–1913. [PubMed: 20850152]

24. Traxer O, Pasqui F, Gattegno B, Pearle MS. Technique and complications of transurethral surgery for bladder tumours. BJU Int 2004; 94, 492–496. [PubMed: 15329099]

25. Chou R, Selph S, Buckley DI, et al. Comparative Effectiveness of Fluorescent Versus White Light Cystoscopy for Initial Diagnosis or Surveillance of Bladder Cancer on Clinical Outcomes: Systematic Review and Meta-Analysis. J Urol 2017; 197, 548–558. [PubMed: 27780784]

26. Oliva E, Pinheiro NF, Heney NM, et al. Immunohistochemistry as an adjunct in the differential diagnosis of radiation-induced atypia versus urothelial carcinoma in situ of the bladder: a study of 45 cases. Hum Pathol 2013; 44, 860–866. [PubMed: 23199526]

27. Yin H, He Q, Li T, Leong AS. Cytokeratin 20 and Ki-67 to distinguish carcinoma in situ from flat non-neoplastic urothelium. Appl Immunohistochem Mol Morphol 2006; 14, 260–265. [PubMed: 16932015]

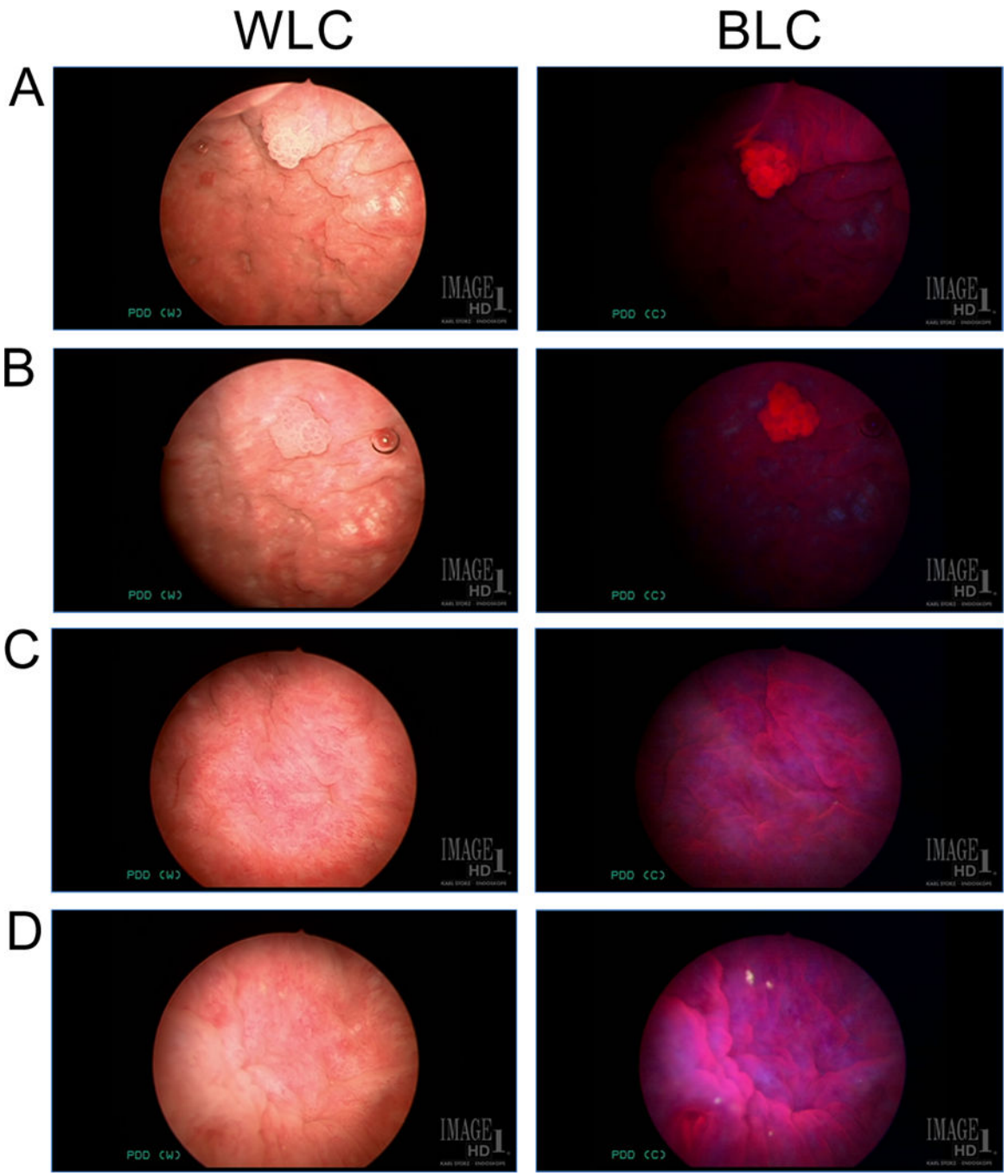

Figure 1.

A&B. White light cystoscopy (WLC) view of an example of a small papillary lesion (left), highlighted by red fluorescence under blue light cystoscopy (BLC; right). Note the background urothelium around the small papillary lesions is seen dark and without fluorescence under BLC. *C&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 were benign.

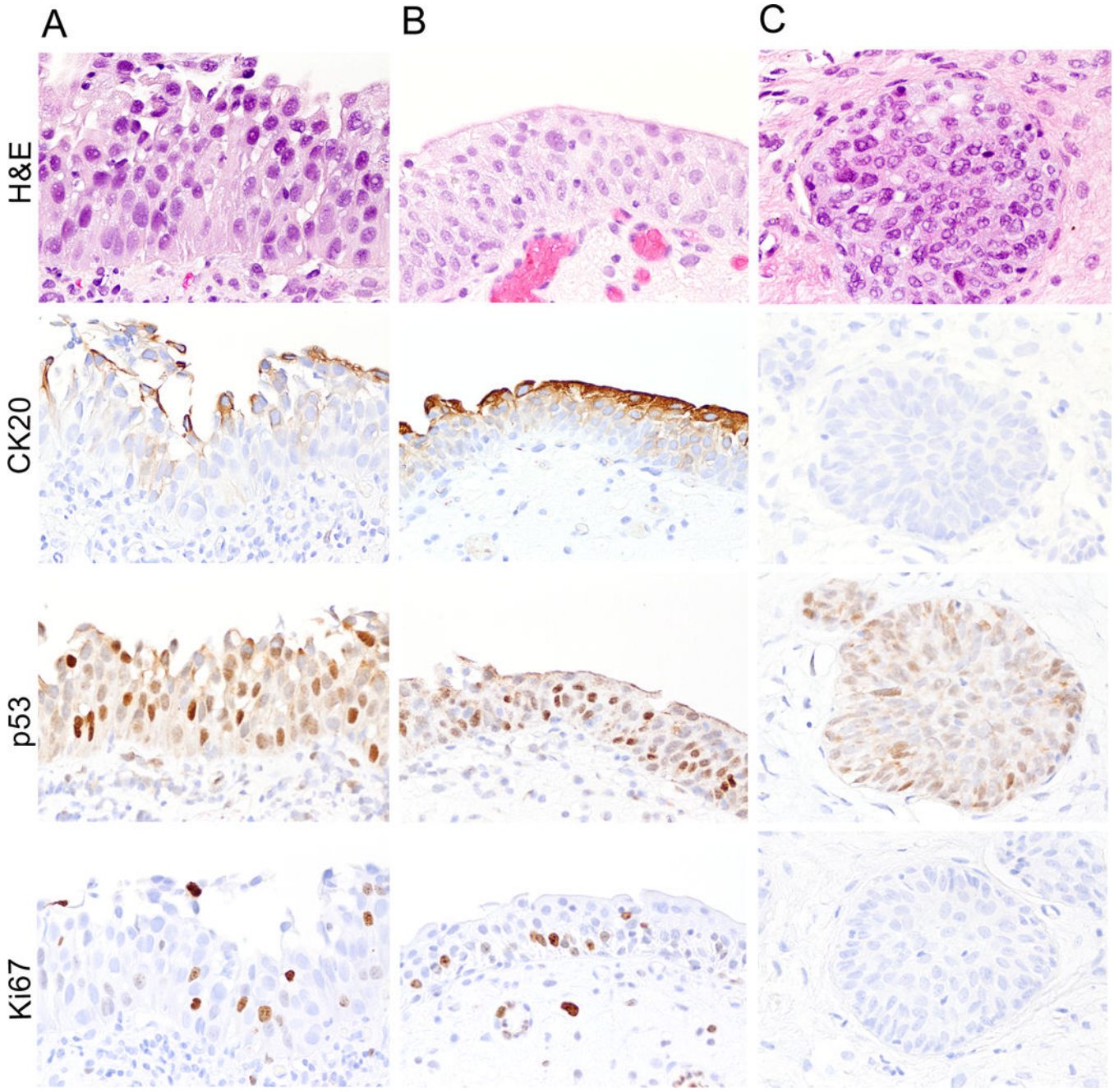

Figure 2.

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 carcinoma in-situ. P53 is positive with moderate staining in approximately 30% of urothelial cells, however this finding is not specific for CIS. Ki67 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 ki67 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, shows mild nuclear staining for p53 in approximately 10% of nuclei and no labeling for Ki67.

Table 1:

Blue light cystoscopy detection of tumor lesions.

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

CIS+ = CIS at pathology; CIS− = no CIS at pathology (dysplasia, atypia, etc…); (+) = Positive blue light cystoscopy; (−) = Negative blue light cystoscopy

Table 2.

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

Lesion #	Age	Gender	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 (x2)	pT1 HGUCa	Yes, 6 cycles	no
4, 5, 6	49	M	Urothelial atypia (x3)	pT1 HGUCa	Yes, 6 cycles	Yes, 3 months 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 months prior
10	69	M	Urothelial atypia	pT1 HGUCa	Yes	No
11	83	M	Urothelial atypia	pT1 HGUCa	Yes	Yes

HGUCa: high-grade urothelial carcinoma.

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	Ki67	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

A:atypical; B:benign; BLC:blue light cystoscopy; C : carcinoma in situ; Den: denudation; Int: immunohistochemistry interpretation; GU: genitourinary pathologist; GRL: general pathologist; IHC: immunohistochemistry; M:moderate; S:strong.