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Diagnostic difficulties in cases of papillary urothelial neoplasm of low malignant potential, urothelial proliferation of uncertain malignant potential, urothelial dysplasia and urothelial papilloma: A review of current literature

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ABSTRACT

Tumours of the urinary tract are the fifth most frequent type of cancer. The most common types are urothelial tumours, among which, non-invasive urothelial neoplasms represent 45% of all cases. The 2016 WHO classification of urinary tract tumours introduced new classifications of non-invasive lesions. Besides urothelial papilloma (UP) and papillary urothelial neoplasm of low malignant potential (PUNLMP), as described in the former classification, the new classification also includes new entities such as urothelial proliferation of uncertain malignant potential (UPUMP) and urothelial dysplasia (UD). Of the aforementioned, UPUMP is the lesion that most commonly progresses, but solely to non-invasive carcinomas. UD is associated with a high risk of progression to invasive carcinoma. Understanding the biological character, and establishing the correct differential diagnosis in cases of non-invasive, non-cancerous lesions of the urinary bladder, will be of importance in establishing outcome predictions for future patients. A systematic review of the current literature allows us to systematize genetic, morphologic and prognostic factors of such lesions. Moreover, the collected data provide the basis for a proposed diagnostic algorithm which facilitates quick and effective differential diagnoses in cases of non-invasive non-cancerous urinary bladder lesions.

1. Introduction

Tumours of the urinary tract are the fifth most frequent type of cancer. Among all neoplasms of the urinary system, cancers of the urinary bladder are the most frequently lethal [1]. Of these, the most common types are urothelial tumours which can be further divided into infiltrating urothelial carcinomas and non-invasive urothelial neoplasms; the latter represent 70% of all bladder tumours [2]. Non-invasive urothelial neoplasms are characterized by the occurrence of lesions with differing molecular profiles but, in some cases, similar morphology, which makes the diagnosis challenging. According to the 2004 World Health Organization (WHO) classification of urinary tract tumours, these lesions can be subdivided into urothelial papilloma (UP), papillary urothelial neoplasm of low malignant potential (PUNLMP), non-invasive low grade papillary urothelial carcinoma (niLGC) and non-invasive high-grade papillary urothelial carcinoma (niHGC) [3]. Of clinical importance is the fact that UP and PUNLMP are characterized by different biological behaviours, compared to niLGC and niHGC, namely the potential for progression and recurrence [4,5]. Among all the subdivisions of non-invasive papillary urothelial neoplasms, PUNLMP is the most controversial group, since the term “low malignant potential” does not adequately express the biological behaviour of this type of tumour. Also, PUNLMP's histopathological variability often hinders its diagnosis [6].

The 2016 WHO classification of urinary tract tumours introduced new classifications for non-invasive lesions. In this new classification, urothelial proliferation of uncertain malignant potential (UPUMP) replaced an unofficial terminology of urinary bladder lesions that was not considered in former editions. Urothelial dysplasia (UD) was introduced to take account of molecular changes that promote more aggressive

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biological behaviour and progression, in comparison to other non-invasive lesions described by other authors [7-9].

Understanding the biological character, and establishing the correct differential diagnosis in cases of non-invasive, non-cancerous lesions of the urinary bladder, will be of importance in establishing outcome predictions for future patients.

2. Characteristics of non-invasive non-cancerous lesions of the urinary bladder

2.1. Urothelial papilloma

UP is a benign exophytic lesion most commonly localized in the posterior or lateral wall of the urinary bladder [3]. UP represents 13% of bladder lesions among children and adolescents (4 − 20 years) and 7.7% among adults [10-12]. UP is described as a papillary lesion with a fibrovascular core and with divided, occasionally branched fronds. UP cells are indistinguishable from normal urothelium, with no atypia and with rare mitoses [3]. In immunohistochemical examinations, UP cells are superficially stained by cytokeratin (CK) 20 as in normal urothelium [13] while the Ki-67 labelling index is positive in only 4% of UP cells [14].

Studies have revealed limited molecular changes in UP. In 75% of lesions, tumour growth is initiated by a mutation of the FGFR3 gene, resulting in overexpression of the FGFR3 protein [15]. There are also UP features that prevent invasive behaviour. Székely et al. reported a higher expression of tight junction proteins, such as claudin-1, − 2 and − 4, than may be observed in the normal urothelium [16]. UP's molecular profile thereby indicates a benign nature.

Numerous studies have indicated a low risk of recurrence in UP. Tumours recur in 6.9% of cases, usually appearing > 25 months after resection of the primary lesion [12,17,18,4]. In rare cases, one can observe UP progression to PUNLMP and niLGC, with frequencies of around 3.2% and 8.7% respectively [18,4,19]. The average progression time in reported cases varied from 84 to 141 months in PUNLMP and niLGC respectively [18,4,19]. Recurrent UP shows shorter progression times after resection of the primary lesion, amounting to 48 months for PUNLMP and 15 months in cases of niLGC [18,4]. Progression to invasive urothelial carcinoma has been reported in only one case. In that case, the patient was treated with immunosuppressive therapy, and the authors suggested that abnormalities of the immune system were an additional risk factor for the development of invasive carcinoma [17].

2.2. Papillary urothelial neoplasm of low malignant potential

PUNLMP is a non-invasive papillary urothelial lesion with a low risk of progression, but with the potential for recurrence [9]. Two independent studies have estimated PUNLMP frequency to be approximately 26.2% of all bladder tumours [15,16]. Incidence of PUNLMP depends on age and is summarized in Table 1 [20,21]. PUNLMP is defined as an exophytic papillary neoplasm. PUNLMP never disrupts the basement membrane of the urinary bladder and, that being the case, is categorized as pTa, with the appropriate clinical follow up [22]. PUNLMP has higher mitotic activity and increased thickness in comparison to normal urothelium. Papilli are discrete, with no fusion, and are covered with multi-layered urothelium, with minimal or no atypia (Fig. 1). Cell polarity is well observed, and rare mitoses are localized in the basal layer [3]. In 96% of cases, the proliferation marker Ki-67 is detected in no more than in 13% of tumour cells [23].

Table 1
Incidence of papillary urothelial neoplasm of low malignant potential frequency as a percentage of all urinary bladder neoplasms, according to age group [20,21].

< 18 years old	18–30 years old	> 30 years old
50.7%	40.3%	27.2%

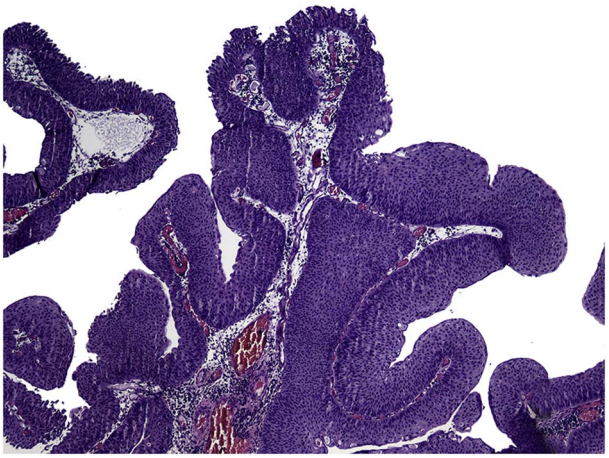

Fig. 1. Micrograph of papillary urothelial neoplasm of low malignant potential (PUNLMP). Hematoxylin and eosin staining. Primary objective magnification 4×. Microscopic description: exophytic, papillary kind of growth, increased thickness in comparison to normal urothelium and papilloma, papilli are discrete, with no fusion, cells exhibit minimal or no cytological atypia.

The development of PUNLMP is associated with several molecular pathways. The latest studies show that, in 85% of cases, self-sufficiency in growth signals results from the overexpression of the FGFR3 oncogene [24]. PUNLMP cells exhibit immunostaining for p63 in all cell layers, and no evidence for p53 mutation, which suggests normal functioning of suppressor genes [25-27]. A high expression of miR-125b accelerates the process of neoplastic transformation. PUNLMP frequently presents with a loss of heterozygosity (LOH) at 5 polymorphic microsatellite markers on chromosome loci 9q32–33, 9p22, 17p13.1, 12q14–24 and 3p25–26 [28]. Studies have also revealed defects in the DNA repair system, including a reduced expression of mismatch repair genes, mainly hMSH2, hMLH1 and hMSH6 [29]. Increased expression of the pro-angiogenic factor VEGF, and decreased expression of the anti-angiogenic pigment.

epithelium-derived factor (PEDF), promote tumour angiogenesis [30].

The clinical relevance of PUNLMP comes from its high tendency to recurrence. This introduces the necessity of monitoring patients and, in the case of tumour recurrence, additional clinical intervention [31]. Resected PUNLMP recurs in 35% of cases [24]. PUNLMP could be subdivided into recurrent and non-recurrent PUNLMP. The determination of PUNLMP cases with a risk of recurrence can be predicted by immunohistochemistry studies, but not by conventional histopathologic assessment [31]. Studies show that recurrent PUNLMP exhibits strong FGFR3 staining intensity, CK20 immunostaining throughout the whole depth of the urothelium, Ki-67 labelling above 5%, decreased Claudine-1 expression, and an increased level of serine/threonine kinase Aurora-A [32,16,33]. Recurrent PUNLMP is characterized by decreased methylation and acetylation of histones, with the histone acetylation-to-methylation ratio being significantly higher than in the non-recurrent form [34]. This progression may be induced by the shortening of telomeres and by chromosomal instabilities, such as diploidy, polyploidy, or hypoploidy [35]. The aforementioned data are summarized in Table 2, and could be used as a tool for the prediction of PUNLMP recurrence. Patients assessed as being at high risk of recurrence will undoubtedly require close observation but, on the other hand, cuts in expenditure should be expected for low-risk patients as there will be a reduction in unnecessary clinical procedures such as cystoscopy in these cases. The latest studies have also revealed that progression may be associated with chronic inflammation of the urinary tract, and that upregulation of lymphotoxin β receptor and nuclear factor-κB pathways could be key factors in these processes [36]. PUNLMPs progress to non-

Table 2
A comparison of recurrent and non-recurrent PUNLMP [32,16,33,34].

Features	Non-recurrent PUNLMP	Recurrent PUNLMP
FGFR3 staining intensity	Strong	Weak, moderate or strong
CK20 expression	Superficial staining pattern	Abnormal in different layers of cells
Ki-67 positive cells	< 5.2%[1]	> 5.2%[a]
Claudin-I's expression	> 22,6%[2]	< 22,6%[b]
Aurora-A expression	Normal	High
The percentage of changes in histone acetylation and methylation in comparison with normal urothelium	Decreased (by 5% of cells)	Decreased (by 15%–19% of cells)

PUNLMP = papillary urothelial neoplasm of low malignant potential.
FGFR3 = fibroblast growth factor receptor 3.
CK20 = cytokeratin 20.
[a] average percentage of Ki-67 positive cells in presented study.
[b] median area % positivity in presented study.

invasive carcinomas in 11% of cases, either as niLGC (85% of progressions) or niHGC (15%) [37]. There is no evidence of PUNLMP progression to invasive carcinoma [38].

2.3. Urothelial proliferation of uncertain malignant potential

UPUMP is a new term, introduced in the 2016 WHO classification of tumours of the urinary tract. This term systematizes the former terminology of urinary bladder lesions described as papillary or flat urothelial hyperplasia [9]. There are no reliable studies concerning the epidemiology of UPUMP. UPUMP is described as a lesion with thickened urothelium and with no true papillary fronds. The most common localization of these lesions is the right lateral wall of the urinary bladder [39]. Superficial undulations are frequently observed [9]. Cells exhibit minimal or no cytological atypia, and cell polarity is observed, with a normal nucleus-to-cytoplasm ratio (Fig. 2). Immunohistochemistry shows superficial CK20 and basal CD44 immunostaining, as in the normal urothelium [40].

The transformation of normal urothelium into UPUMP might be caused by LOH, namely deletions on chromosome 9, as observed in 54.5–71% of cases [35,37]. Chromosomal changes are most often associated with the Fanconi anemia complementation group C gene (FANCC) on chromosome arm 9q [8,39]. FANCC protein is responsible for the repair of damaged DNA [41]. Loss of the FANCC gene leads to disorders of the DNA repair process [8,39]. Alternations on chromosome 9p, by loss of one copy of the tumour suppressor gene CDKN2N, might also contribute to UPUMP development. Loss of the p53 gene, by deletion of chromosome 17p, can also impact UPUMP pathogenesis [39]. Other chromosomal changes affect chromosomes 2, 4, 8, and 11 [7,42]. Research has demonstrated FGFR3 oncogene overexpression in approximately 23% of lesions, coexisting with chromosome abnormalities in 93.4% of cases [7,43]. Nonetheless, the high expression of proteins responsible for cellular coherence, such as periplakin, suggests a benign biological outcome for UPUMP [44].

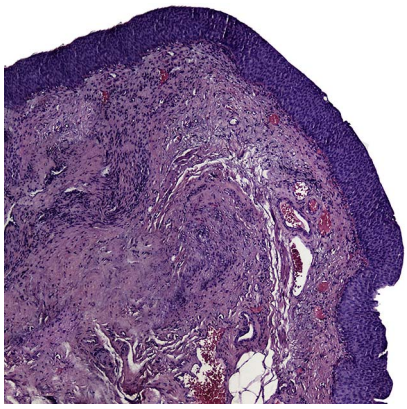

Fig. 2. Micrograph of urothelial proliferation of uncertain malignant potential (UPUMP). Hematoxylin and eosin staining. Primary objective magnification 4 ×. Microscopic description: superficial undulations or flat kind of growth, increased thickness in comparison to normal urothelium, cells exhibit minimal or no cytological atypia with a normal nucleus-to-cytoplasm ratio.

Animal studies have revealed a significant correlation with the occurrence of HRAS and CDKN2A gene mutations [45,46]. The HRAS and CDKN2A gene loci are localized on chromosome arms 11p and 9p, respectively, where deletions may be found in cases of UPUMP. Synchronic changes in both genes could contribute to a higher risk of progression. However, as shown in Fig. 3, independent of an HRAS gene mutation, the presence of at least one unchanged CDKN2A gene copy eliminates the possibility of progression to niLGC [45].

Hartmann et al. reported recurrence of UPUMP in 17% of cases, after removal of the primary lesion. The urothelium surrounding UPUMP lesions may exhibit molecular changes identical to UPUMP in 50% of cases [39]. This supports the possibility of recurrence after resection of UPUMP. One study also suggests that UPUMP may appear after resection of other bladder cancers, though mainly niLGC [47].

UPUMP undergoes progression to low grade non-invasive papillary carcinoma in approximately 67% of cases. The 5 year progression risk ranges between 47.8% for patients with previous bladder tumour episodes and 27.4% for patients without a history of bladder tumours [47]. There is no evidence to suggest that UPUMP may progress to dysplasia, carcinoma *in situ*, or to invasive carcinoma [47,48].

2.4. Urothelial dysplasia

The term “dysplasia” is commonly used by physicians and scientists, as well as pathologists, to describe an abnormal and precancerous epithelial growth. UD was officially included in the 2016 WHO classification of urinary tract tumours. The former nomenclature often led to misunderstandings as the same lesions were described in different ways, including low grade dysplasia, dysplasia, or low grade intraepithelial neoplasm.

Shirai et al. reported a UD prevalence of 6.8% for males and 5.7% for females [49]. UD is a flat lesion that cannot be recognized as carcinoma *in situ* [9] and is characterized by a slightly abnormal cell polarity, with homogenous cytoplasm and a slightly increased nucleus-to-cytoplasm ratio [40]. Ki-67 is positive in < 15% of nuclei [50]. The CK20 immunostaining pattern is normal in 10% of cases, whereas 90% of cases exhibit CK20 expression in 2/3 of the depth of the urothelium [51]. Furthermore, in approximately 70% of cases, immunostaining for the basal cell marker CK14 is positive in 51–75% of cells [52].

Studies have suggested that the P2RY5 gene polymorphism and germ line mutation may be responsible for an inherited tendency to develop UD [53]. Dysplastic cell proliferation may be induced by overexpression of the Her2/neu oncogene without its amplification [54]. Furthermore, in 67% cases of UD, the cell cycle is deregulated by the loss of p53 protein function [55]. Oncogenesis may also be promoted by mutation in the suppressor gene encoding protein, p16 [56]. E-cadherin and β-catenin also exhibit changed expression patterns, in comparison to normal urothelium [57].

There have been no studies which reveal the recurrence risk for UD [40]. Data shows that UD can undergo development to urinary bladder cancer in 15–20% of cases, with 75% of these tumours becoming invasive carcinomas [48,58]. Subsequent to a diagnosis of UD, the average time of progression to carcinoma is 4.5 years [48]. The high risk of progression might be associated with the abnormal expression of intercellular adherence proteins, such as E-cadherin and β-catenin. Qi Pan et al. revealed that metformin can inhibit invasive cancer

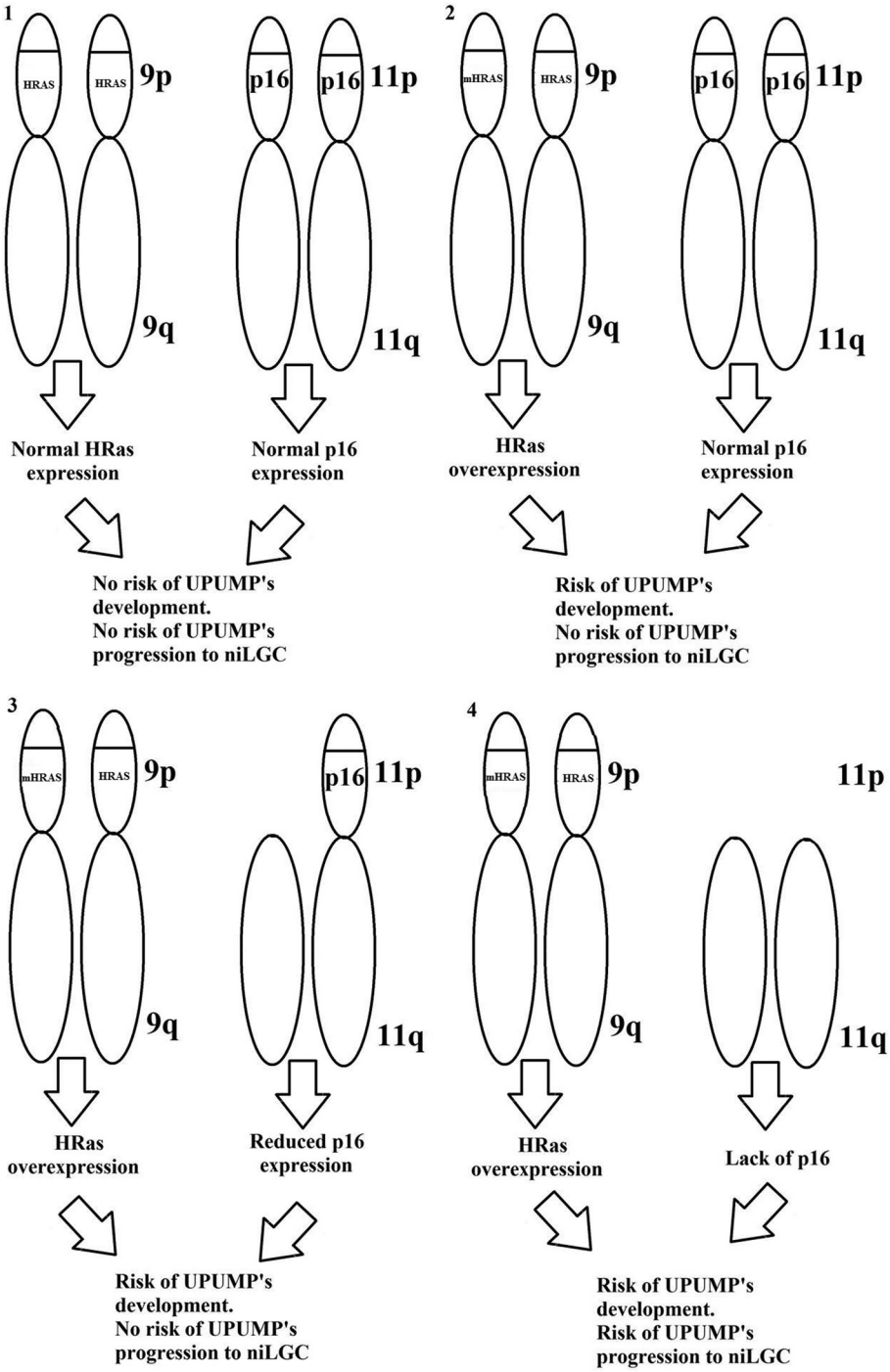

Fig. 3. Correlation between protein products of mutated genes and the likelihood of UPUMP and tumour development [45].
UPUMP = urothelial proliferation of uncertain malignant potential, niLGC = non-invasive low grade carcinoma, p16 = protein product of CDKN2A gene, HRas = protein product of HRAS gene, HRAS = normal HRAS gene, mHRAS = mutated HRAS gene.

development from urothelial dysplasia [59].

3. Differential diagnosis of non-invasive non-cancerous lesions of urinary bladder

The clinical manifestation of a bladder neoplasm, in three-quarters of patients, is painless haematuria [60]. Exophytic growths, without infiltration of the basement membrane or adjacent connective tissues, are characteristic of non-invasive, non-cancerous lesions [22]. The presence of papillary structures in these types of tumours discriminate between UP, PUNLMP, and UPUMP. In cases of UP, the urothelial epithelium does not exceed 7 layers and umbrella cells are present. Papillae of this tumour may not be able to fuse together. In contrast to this, PUNLMP consists of > 7 layers of cells and the absence of umbrella cells [61]. Non-invasive exophytic lesions of the bladder without true papillae, and with > 7 layers of cells, are categorized as UPUMP [43]. UPUMP can also occur as a flat lesion and, in such cases, precise differential diagnosis is needed to distinguish UPUMP from other non-malignant flat lesions. Microscopic examination of UPUMP samples shows a lack of the cytological atypia which is typically observed in histological examinations of UD. A simple immunohistochemistry test with CK20 confirms abnormality in UD lesions [3,62]. Correct diagnosis of UD is very important because, unlike other precancerous lesions, the risk of progression to invasive carcinoma in these cases is very high [48,58]. A diagnostic algorithm for non-invasive, non-cancerous lesions of the urinary bladder was made possible by a systematic review of the

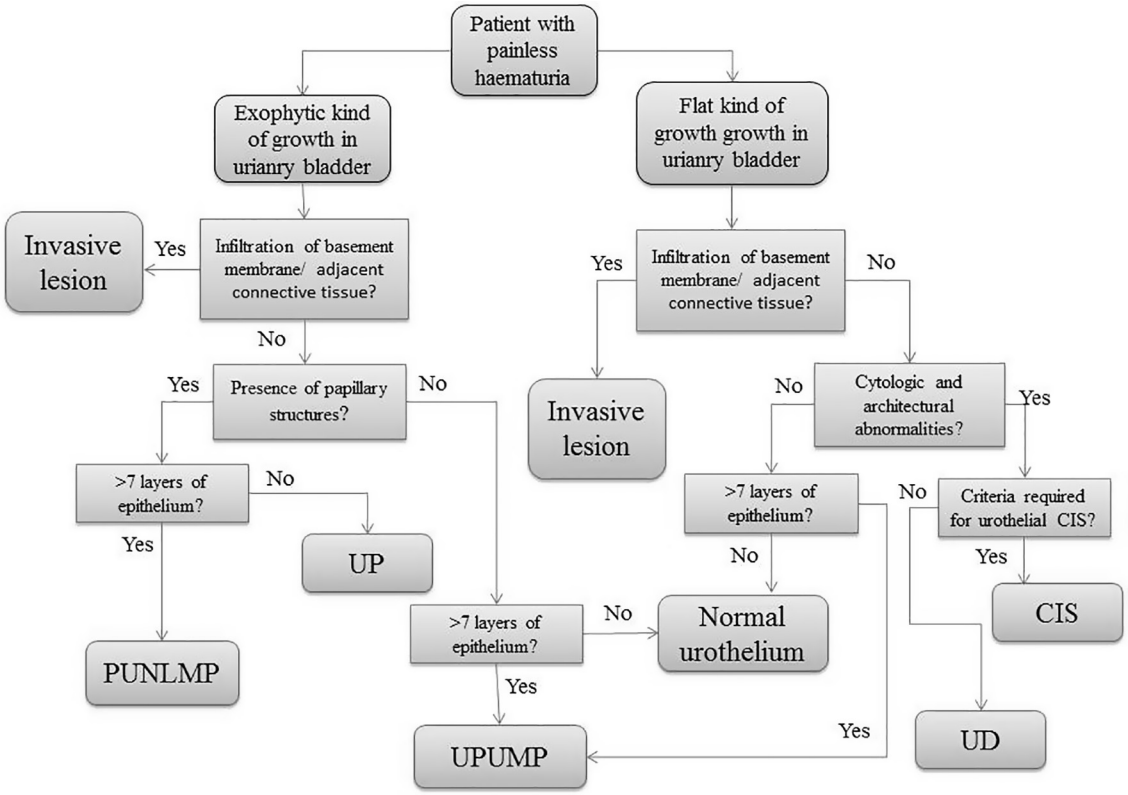

Fig. 4. Diagnostic algorithm for non-invasive non-cancerous lesions of the urinary bladder [3,22,48,58,60,61,62].
UP = Urothelial papilloma, PUNLMP = Papillary urothelial neoplasm of low malignant potential, UPUMP = uncertain proliferation of uncertain malignant potential, UD = urothelial dysplasia, CIS = Carcinoma *in situ*.

Table 3
Characteristics of non-cancerous and non-invasive neoplasms of the urinary bladder [4,7,10-15,17,18,19,23-28,32,37-40,42,43,47-51,55,58,63].

Features	Urothelial papilloma	PUNLMP	UPUMP	Urothelial dysplasia
Prevalence	13%	26%	No data available	6.25%
Frequency of recurrence	6.9% cases	35% cases	17% cases	Non data available
Risk of progression to non-invasive carcinoma	11.9%	11%	37.75%	4.4%
Risk of progression to invasive carcinoma	0%	0%	0%	13.1%
Ki-67 positive cells	< 4.3%	< 13%	No data available	< 15%
CK20 immunostaining pattern	Superficial	Superficial or abnormal[a]	Superficial	Abnormal[a]
FGFR3 overexpression	75% lesions	85% lesions	23% lesions	Absent
Loss of p53	Absent	29% lesions	absent	67% lesions
Loss of heterozygosity	Absent	81% lesions	62.75% lesions	Absent

PUNLMP = papillary urothelial neoplasm of low malignant potential.
UPUMP = uncertain proliferation of low malignant potential.
[a] 2/3 or all depth of urothelium.

current literature, and is presented in Fig. 4.

4. Final remarks

The bladder conditions UP, PUNLMP, UPUMP and UD are distinct lesions with diverse biological behaviours. UP is the most benign urinary bladder lesion, with a low risk of progression and a low recurrence frequency. PUNLMP shows the most frequent recurrence rate among the aforementioned lesions, and the tendency to recurrence can be predicted using immunohistochemistry. Among these lesions, UPUMP most commonly progresses, but solely to non-invasive carcinomas. The inclusion of UD in the 2016 WHO classification is justified given its high risk of progression to invasive carcinoma. The lesions are summarized in Table 3.

Conflict of interest

The authors declare that they have no conflict of interest.

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