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Review Article

Mimickers of urothelial neoplasia

Oleksandr N. Kryvenko[a,b,c], Jonathan I. Epstein[d,e,f,*]

[a] Department of Pathology and Laboratory Medicine, University of Miami Miller School of Medicine, Miami, FL, USA
[b] Department of Urology, University of Miami Miller School of Medicine, Miami, FL, USA
[c] Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Miami, FL, USA
[d] Department of Pathology, The Johns Hopkins Medical Institutions, Baltimore, MD, USA
[e] Department of Urology, The Johns Hopkins Medical Institutions, Baltimore, MD, USA
[f] Department of Oncology, The Johns Hopkins Medical Institutions, Baltimore, MD, USA

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ABSTRACT

Management of malignant urothelial tumors is often associated with extended costly treatments, some with significant morbidity. Advanced tumors are treated with radical cystectomy with neoadjuvant or adjuvant radiation or chemotherapy. Over and under interpretation of histological findings from biopsies and transurethral resections of urothelial lesions may either incur treatments with significant side effects or miss a possible window of cure, respectively. Herein we reflect our approaches and common diagnostic challenges of urothelial tumors and their mimickers, and highlight the diagnostic pitfalls and key histological and immunohistochemical differentiating features. It is useful to separate mimickers of bladder adenocarcinoma and mimics of urothelial carcinoma as the former can involve the muscularis propria, whereas the latter do not. Glandular mimickers discussed herein include cystitis cystica et glandularis with intestinal (colonic) metaplasia, endocervicosis and endometriosis, and nephrogenic adenoma. Common mimickers of urothelial carcinoma include polypoid cystitis, pseudocarcinomatous urothelial neoplasia, inverted urothelial papilloma, florid proliferation of von Brunn nests, and reactive urothelial metaplasia associated with prostatic infarction. We emphasize where clinical impression and history are important for the correct diagnosis. In some entities assessment of the entire histological picture is critical rather than focusing on isolated findings that out of context may be indistinguishable from cancer.

1. Introduction

Management of malignant urothelial tumors is often associated with extended costly treatments, some with significant morbidity. Advanced tumors are treated with radical cystectomy with neoadjuvant or adjuvant radiation or chemotherapy. Over and under interpretation of histological findings from biopsies and transurethral resections of urothelial lesions may either incur treatments with significant side effects or miss a possible window of cure, respectively. Herein we reflect our approaches and common diagnostic challenges of urothelial tumors and their mimickers, and highlight diagnostic pitfalls and key histological and immunohistochemical differentiating features. In this review we do not discuss the differential diagnosis of urothelial carcinoma from secondary tumors involving the bladder. It is useful to separate mimickers of bladder adenocarcinoma and mimics of urothelial carcinoma as the former can involve the muscularis propria, whereas the latter do not.

2. Mimickers of bladder adenocarcinoma

Pure primary adenocarcinomas arising in the urothelial system are relatively infrequent. However, divergent glandular differentiation is seen in approximately 30% of advanced urothelial carcinomas and may represent most or the entire diagnostic tissue specimen [1]. The differential diagnosis of adenocarcinoma arising in urothelium includes florid cystitis cystica et glandularis with intestinal (colonic) metaplasia; endocervicosis/endosalpingiosis/endometriosis (müllerianosis); and nephrogenic adenoma.

3. Cystitis cystica et glandularis with intestinal (colonic) metaplasia

Cystitis cystic et glandularis with intestinal metaplasia (CCGIM) is not rare and may be seen endoscopically as a broad based mass. As a general rule, CCGIM lacks cytological atypia, necrosis, signet ring cells, and brisk or atypical mitotic activity (Fig. 1A) [2]. The presence of

* Corresponding author at: The Johns Hopkins Hospital, The Weinberg Building, Rm. 2242, 401 N. Broadway Street, Baltimore, MD 21231, USA.
E-mail address: jepstein@jhmi.edu (J.I. Epstein).

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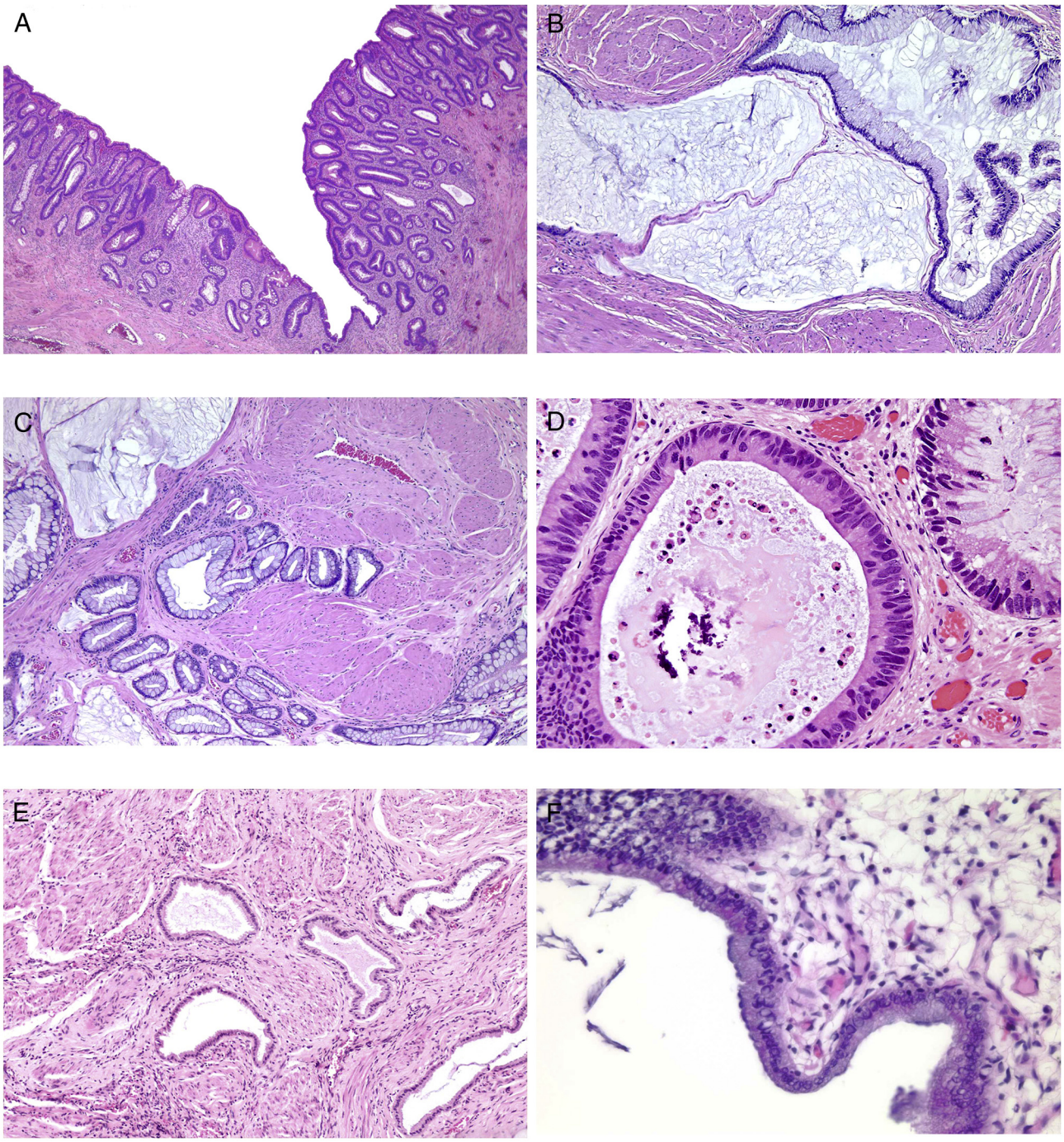

Fig. 1. A. Low-power magnification of cystitis cystica et glandularis. Note a linear non-infiltrative base. B. Mucus extravasation in cystitis cystica et glandularis with intestinal metaplasia. No cytological atypia or stromal reaction is present. C. Cystitis cystica et glandularis with intestinal metaplasia demonstrating the presence of benign glands in the muscularis propria. D. Intestinal type bladder adenocarcinoma with high-grade cytological atypia and frequent mitotic figures. E. Benign glands of endocervicosis involving the muscularis propria. No surrounding stromal reaction is seen. F. Benign endocervical mucinous glands in a bladder biopsy (endocervicosis).

intestinal metaplasia has been show to bear no increased risk of cancer [3]. CCGIM may demonstrate mucus extravasation, sometimes extensive, which may be mistaken for invasive adenocarcinoma (Fig. 1B) [4]. A feature seen less frequently but more often incorrectly regarded as invasive adenocarcinoma is the presence of benign CCGIM glands amidst muscularis propria thick muscle bundles (Fig. 1C). In contrast, adenocarcinomas arising in the bladder are usually intestinal type and feature significant cytological atypia and prominent mitotic activity, infiltrative growth pattern, and desmoplastic reaction (Fig. 1D). The only situation where we have seen relatively blander infiltrating adenocarcinomas involving the bladder have been secondary involvement from metastatic pancreatic adenocarcinoma or invasion from a uterine endocervical primary. In both these situations, there is still more atypia than CCGIM and also there is an associated desmoplastic reaction which is lacking in CCGIM. We have recently reported a short series of dysplasia (adenomatous change) in CCGIM and pure adenomatous polyps of the bladder [5,6]. The former lesion is associated with a high risk of concurrent carcinoma and warrants further work up. Despite their

urothelial origin, both primary bladder adenocarcinomas and CCGIM with adenomatous change stain positive for intestinal markers (CDX2 and CK20) and are often negative for urothelial marker (GATA3). In our practices, particularly in consultation cases with limited clinical information, we routinely comment on specimens composed of pure intestinal type adenocarcinoma that the distinction between bladder intestinal type adenocarcinoma and colorectal adenocarcinoma may not be made on morphology alone and further clinical correlation is required.

4. Endocervicosis, endosalpingiosis, and endometriosis (müllerianosis)

Endocervicosis, endosalpingiosis, and endometriosis are typically seen in women in their fourth to fifth decades of life and in some cases all three morphologies can be seen in the same case where it is referred to as müllerianosis. The lesions typically involve the posterior bladder wall and are rarely reported in the urethra [7]. The masses may be as large as 5 cm and extravesical involvement may occasionally accompany the bladder lesion [8]. The clinical presentation usually involves pelvic pain, frequency, dysuria, hematuria (including gross hematuria), dyspareunia, and dysmenorrhea. Similar to other benign glandular lesions of the urothelial origin, the müllerian derivatives may be present within muscularis propria muscle bundles (Fig. 1E). In foci of endosalpingiosis one may recognize the presence of luminal cilia at high-power magnification. The key distinction features of benign müllerian glandular lesions are lack of cytological atypia, infrequent mitotic activity, and no associated desmoplasia (Fig. 1F). Recognition of endometrial stroma may help in cases of endometriosis but it is not always present. Staining with PAX-8 and estrogen receptor is positive in all these lesions.

5. Nephrogenic adenoma

Nephrogenic adenoma is a relative frequent lesion in bladder biopsies. It mostly develops in patients with urinary stones, indwelling catheters, or prior bladder manipulations. Although older reports used the term nephrogenic metaplasia, this terminology may not exactly reflect the pathogenesis as was shown in a more recent study [9]. Researchers from the University of Vienna investigated the nature of nephrogenic adenoma in 14 female and 10 male recipients of orthotopic kidney transplant from male and female donors, correspondingly. Using fluorescent in situ hybridization (FISH) probes against centromeres of X and Y chromosomes, the authors demonstrated that in all patients the nephrogenic adenomas had the same sex-chromosome status as the donor kidney but not recipient and concluded that nephrogenic adenomas are derived from shed renal tubular cells that implant in areas of urothelial injury [10]. Most nephrogenic adenomas are asymptomatic and identified during surveillance cystoscopies. Although most lesions are inverted nodular proliferation, some lesions may have exophytic papillary architecture and often designated by urologist as papillary urothelial tumors (Fig. 2A). The senior author has reported a small series of nephrogenic adenomas that deeply infiltrated the renal pelvis wall and invaded hilar adipose tissue in areas of prior instrumentation, closely mimicking adenocarcinoma [11]. The cells lining nephrogenic adenoma usually have very scant cytoplasm and hobnail appearing nuclei resting on the thickened basement membrane (Fig. 2B). We have observed rare cases of nephrogenic adenoma involving non-invasive papillary urothelial carcinoma and in situ urothelial carcinoma where nephrogenic adenomas were incorrectly interpreted as evidence of glandular differentiation and invasion. The key to diagnosing nephrogenic adenoma is that it is has multiple patterns, typically many occurring in the same case. Consequently, if one pattern may be confused with adenocarcinoma, recognition of one of the other typical patterns can help direct one to the correct diagnosis. Patterns that are common in nephrogenic adenoma that are more readily recognizable as benign are tubules lined by cuboidal epithelium, atrophic tubules with dense eosinophilic cytoplasm and dense luminal contents resembling thyroid secretions, and tubules with flattened lining resembling vessels yet lacking red blood cells. Some of the patterns that are more typically confused with malignancy include tubules with reactive hobnail atypia and small tubules that in certain planes of resection mimic signet ring cell adenocarcinoma. Also, pathologists can misdiagnose a papillary nephrogenic adenoma lined by cuboidal epithelium as a papillary urothelial neoplasm if they are not aware that nephrogenic adenomas can present as papillary lesions. Additional useful morphological features in nephrogenic adenomas are the virtual absence of mitotic activity and the presence of a hyalinized rim of collagen around some of the tubules and signet ring cell-like structures.

Nephrogenic adenomas are positive for CK7, racemase, and PAX-8 and have < 5% proliferation rate assessed by Ki-67 nuclear labeling index (typically 1–2%).

A unique variant of nephrogenic adenoma is a fibromyxoid nephrogenic adenoma [12]. Unlike conventional nephrogenic adenoma, this variant is composed of compressed spindled cells within a fibromyxoid background, with only rare tubular and cordlike structures (Fig. 2C). Immunohistochemical profile of fibromyxoid variant is similar to conventional nephrogenic adenoma. This variant of nephrogenic adenoma nearly uniformly develops in patients with a prior pelvic irradiation, mostly seen in men with prior prostate cancer radiotherapy.

A common diagnostic question is the differential diagnosis of nephrogenic adenoma versus clear cell adenocarcinoma. We studied 12 classic clear cell adenocarcinomas (Fig. 2D) of the bladder and urethra, 7 clear cell adenocarcinomas reminiscent of nephrogenic adenoma (Fig. 2E), and compared those to 10 nephrogenic adenomas [13]. Differentiating clinical features are that clear cell adenocarcinoma has a strong female predominance and are large lesions. Nephrogenic adenomas more commonly occur in men and are usually small, although larger lesions exist. Most clear cell adenocarcinomas are histologically overtly malignant but there is a variant that mimics nephrogenic adenoma. In these cases, clear cell adenocarcinoma can be recognized by diffuse nuclear hyperchromasia (the nuclei in nephrogenic adenoma have uniform more open chromatin), solid foci, and clear cells, along with appreciable mitotic activity and elevated Ki-67 nuclear labeling index (Figs. 2F). Although nephrogenic adenoma can focally involve the muscularis propria, clear cell adenocarcinomas show a greater degree of infiltration (Table 1). In limited biopsies done in an outpatient setting where there are overlapping features, pathologists should recommend additional tissue sampling with a full transurethral resection.

6. Mimickers of urothelial carcinoma

Lesions that may mimic urothelial carcinoma include polypoid cystitis, pseudocarcinomatous urothelial hyperplasia, inverted urothelial papilloma, florid proliferation of von Brunn nests, and urothelial metaplasia associated with prostatic infarction.

7. Polypoid cystitis

Polypoid cystitis is believed to be an inflammatory reaction to injury often caused by indwelling catheter, calculi, enteric-vesicle fistulas, pelvic abscess, or long-standing urinary obstruction [14]. The polypoid (papillary) lesions are usually broad and edematous which is often recognized by urologists at cystoscopy as an inflammatory condition (Fig. 3A). Polypoid cystitis represents a diagnostic difficulty when isolated or, less frequently, branching papillae are present (Fig. 3B) [15]. In contrast to the classic histology, some or even most of the papillae may have a narrow base (Fig. 3C). Urothelium may be thickened and demonstrate reactive urothelial changes with scattered mitotic activity. In longer standing case there may be fibrosis (not edema) within polypoid stalks (Fig. 3D). The key to recognizing these lesions as

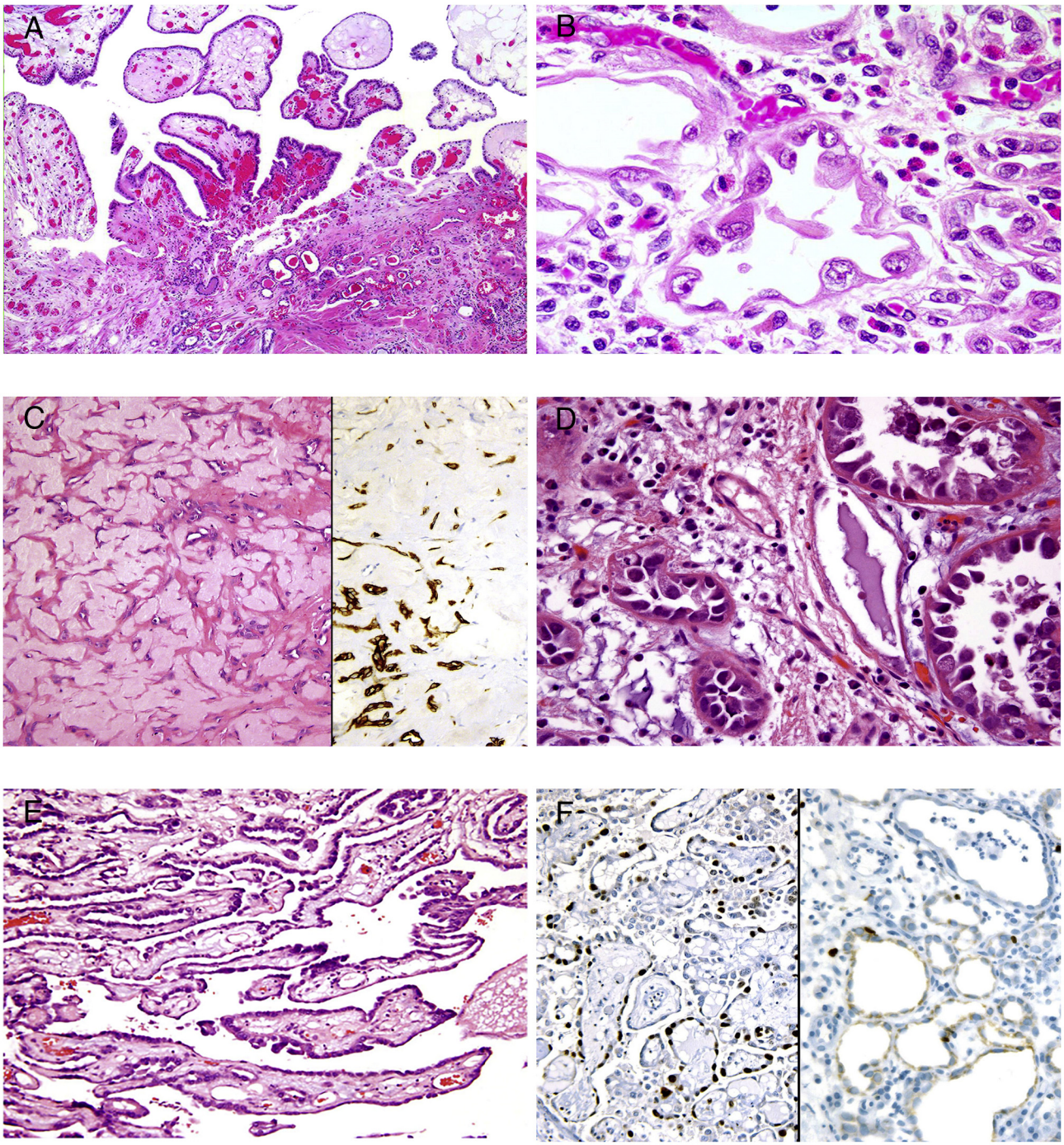

Fig. 2. A. Nephrogenic adenoma with papillary component. B. Hobnail cells in nephrogenic adenoma mimicking clear cell adenocarcinoma. Note the presence of thickened basement membrane. C. Fibromyxoid nephrogenic adenoma. The right hand of the picture shows a pancytokeratin immunostain highlighting renal tubular cells in myxoid matrix. D. Clear cell adenocarcinoma of the bladder demonstrating marked cytological atypia and nuclear hyperchromasia. E. Clear cell adenocarcinoma reminiscent of papillary nephrogenic adenoma. Note hyperchromatic nuclei. F. High proliferation rate assessed by Ki-67 nuclear labeling index in clear cell adenocarcinoma (left) and only focal immunoreactivity in nephrogenic adenoma (right).

inflammatory is to look at scanning magnification where the vast majority of the lesion has features of polypoid cystitis with edema and inflammation in the polypoid stalks and most of the fronds are simple projections as opposed to complex branching papillae. Where pathologists get into trouble is diagnosing the lesion as a papillary urothelial tumor based on one or two papillary fronds that out of context can mimic urothelial neoplasia. The diagnosis of polypoid cystitis rests on factoring in the entire lesion and in difficult cases contacting the urologist, as they are often better able to recognize the inflammatory nature of the process since at cystoscopy they are seeing the entire bladder and are aware of potential etiological factors of polypoid cystitis [15].

8. Pseudocarcinomatous urothelial hyperplasia

Pseudocarcinomatous urothelial hyperplasia (PCUH) is an entity less familiar to pathologists despite its increasing frequency because of increasing number of men with long follow-up who have had their

Table 1
Differential diagnosis of nephrogenic adenoma versus clear cell adenocarcinoma.

Nephrogenic adenoma	Clear cell adenocarcinoma
Usually < 1 cm. Rarely large	Typically large
20% multifocal	Solitary
Male:female 2:1	Rare in men
Prior injury to urothelial lining	No prior injury
Rare focal solid areas	Common solid areas
No mitoses	Common mitoses
No clear cells	Typically clear cells
PAX2/PAX8 positive	PAX2/PAX8 positive

prostate cancer treated with irradiation. The first series to report this mimicker of invasive urothelial carcinoma was by Baker and Young in 2000 [16]. The authors described four cases of PCUH in patients with prior pelvic irradiation. More recently the current authors assembled the largest to date series which included 70 cases of PCUH [17]. We questioned if PCUH had any increased risk of subsequent cancer diagnosis and if it could be seen in scenarios other than irradiation. There were 60 males and 10 females with average age of 67 years (range 33–85). Approximately three-quarters of patients had prior pelvic irradiation. PCUH developed on average 4.5 years (9 months to 13 years) after prior irradiation. Other causes of PCUH included systemic chemotherapy (n = 2), indwelling catheter (n = 3), intravesical chemotherapy (n = 2), prior radical prostatectomy (n = 1), severe peripheral vascular disease (n = 4), arteriovenous malformation of the bladder (n = 1), and sickle cell trait (n = 1). The unifying feature in these risk factors is that they result in chronic ischemia to the bladder that then results in PCUH. In two (2.9%) patients we could not identify any contributing factor but recognize the possibility of incomplete clinical information in consultation cases. Only 3 of 40 patients with significant follow-up (mean: 27 months) developed urothelial carcinoma – one with prior positive cytology and FISH, one with prior high-grade non-invasive papillary urothelial carcinoma, and one with unknown history. Consequently, PCUH is a mimicker of urothelial carcinoma but associated with no increased risk of subsequent carcinoma.

The classical histological appearance of PCUH includes irregular nests of urothelium in edematous stroma of the lamina propria associated with dilated vessels with hemorrhage, stromal fibrin accumulation, and stromal hemosiderin (Fig. 3E). Features mimicking urothelial carcinoma include extensive inverted urothelial proliferation occupying more than a low-power field view which is seen in nearly half of the cases, prominent nucleoli, mild-to-moderate cytological pleomorphism, and mitotic figures (Fig. 3F). The key to the correct diagnosis is to appreciate at scanning magnification the background of prominent irregular vascular dilation and congestion, stromal edema with hemorrhage and hemosiderin deposition, and most importantly extensive fibrin deposition encircling the urothelial nests. These features are lacking in invasive urothelial carcinoma. As with polypoid cystitis, overinterpretation of urothelial carcinoma occurs when pathologists focus on the irregular urothelial nests in the lamina propria that out of context mimic carcinoma without taking into account the overall picture. The other pitfall with PCUH is that the history of prior irradiation is in the distant past and typically not noted at the time of the specimen submission and must be solicited by the pathologist once they consider PCUH in the differential diagnosis. As with all urothelial mimickers, PCUH does not extend into the muscularis propria.

Vascular injury is considering to be a uniting factor for all contributing factors of PCUH. Typical patient is a man with prior prostate cancer irradiation but also other miscellaneous causes of ischemia. Our data indicate that PCUH is a mimicker of cancer and not associated with an increased risk of carcinoma.

9. Inverted urothelial papilloma

Inverted urothelial papilloma is a long recognized and distinct benign urothelial tumor [18]. Exophytic urothelial tumors, even benign exophytic papilloma, require regular cystoscopy and urine cytology follow-up because of their high likelihood of recurrence and possibility of grade and stage progression. In contrast, inverted papilloma is a completely benign lesion and if completely excided does not need routine cystoscopic follow-up [19,20]. Most inverted papillomas develop at the trigone yet may be anywhere urothelium is present [21]. Endoscopically, inverted urothelial papillomas are usually solitary and present as broad based sessile lesions with a smooth surface. Rare cases may be large (> 5 cm) but never invade the muscularis propria.

Typical histological findings include a benign smooth or undulating surface urothelium undermined by thin anastomosing trabeculae of urothelium (Fig. 4A). In contrast, non-invasive urothelial carcinomas with an inverted growth pattern are composed of large rounded nests. Lumina formation may be prominent in some cases of inverted papilloma (Fig. 4B). Central streaming and peripheral palisading of cells are additional architectural features that distinguish inverted papilloma from inverted variant of exophytic urothelial tumors (Fig. 4C). Occasional exophytic areas may be seen and probably an attribute of tangential histological sectioning of the tissue or in some cases can represent rare papillary structures typically lined by the same streaming urothelium seen elsewhere in the lesion. More than a rare fibrovascular frond, especially when branching, are not permitted for the diagnosis of inverted papilloma and exophytic lesion with extensive inverted component should be considered. Mitotic activity is usually absent or limited to the basal layer, and cytological atypia is absent with the exception of degenerative multinucleated giant cells. Inverted papillomas lack associated inflammation, stromal reaction, or retraction artifact around tumor nests. In occasional cases with squamous metaplasia the latter is non-keratinizing. Rare cases feature the presence of foamy or vacuolated cytoplasm which do not impact the behavior of inverted papilloma but is prone to be misdiagnosed as carcinoma [22]. The senior author studied 11 cases which have focal cytological atypia and elsewhere had typical appearance of inverted papillomas [23]. This study concluded that there was no increased risk of urothelial carcinoma and it was advised to designate these cases as inverted urothelial papillomas with cytological atypia and recommend close follow-up surveillance. However, these lesions are rare, controversial and need further study, with many experts not allowing any atypia in inverted papilloma.

10. Florid proliferation of von Brunn nests

Florid proliferation of von Brunn nests is a benign reactive condition with no increased risk of subsequent cancer. Endoscopically, the lesions are perceived as small broad based bumps and may be located anywhere in the urothelial tract. Microscopy demonstrates a proliferation of round regular nests that are not interconnected in the lamina propria, lack desmoplasia, and do not have an infiltrative growth pattern or retraction artifact. No mitotic activity or cytological atypia is usually seen (Fig. 4D). Circumferential proliferations of von Brunn nests can be prominent in cross sections of the ureter or in the renal pelvis. They have a linear or lobular growth pattern that can be appreciated in resection specimens yet no on biopsy. The diagnosis of nested variant of urothelial carcinoma in the ureter or renal pelvis should never be made on biopsy since very rare in these sites and overlap histologically with von Brunn nest hyperplasia (Fig. 4E). Unlike benign glandular mimickers of urothelial tumors, von Brunn nests may not be present in the muscularis propria. Cystic change may be seen in the von Brunn nests (Fig. 4F).

Distinction of florid von Brunn nest hyperplasia from nested variant of urothelial carcinoma is critical [24]. The latter is cytologically bland and does not demonstrate significant cytological atypia or mitotic

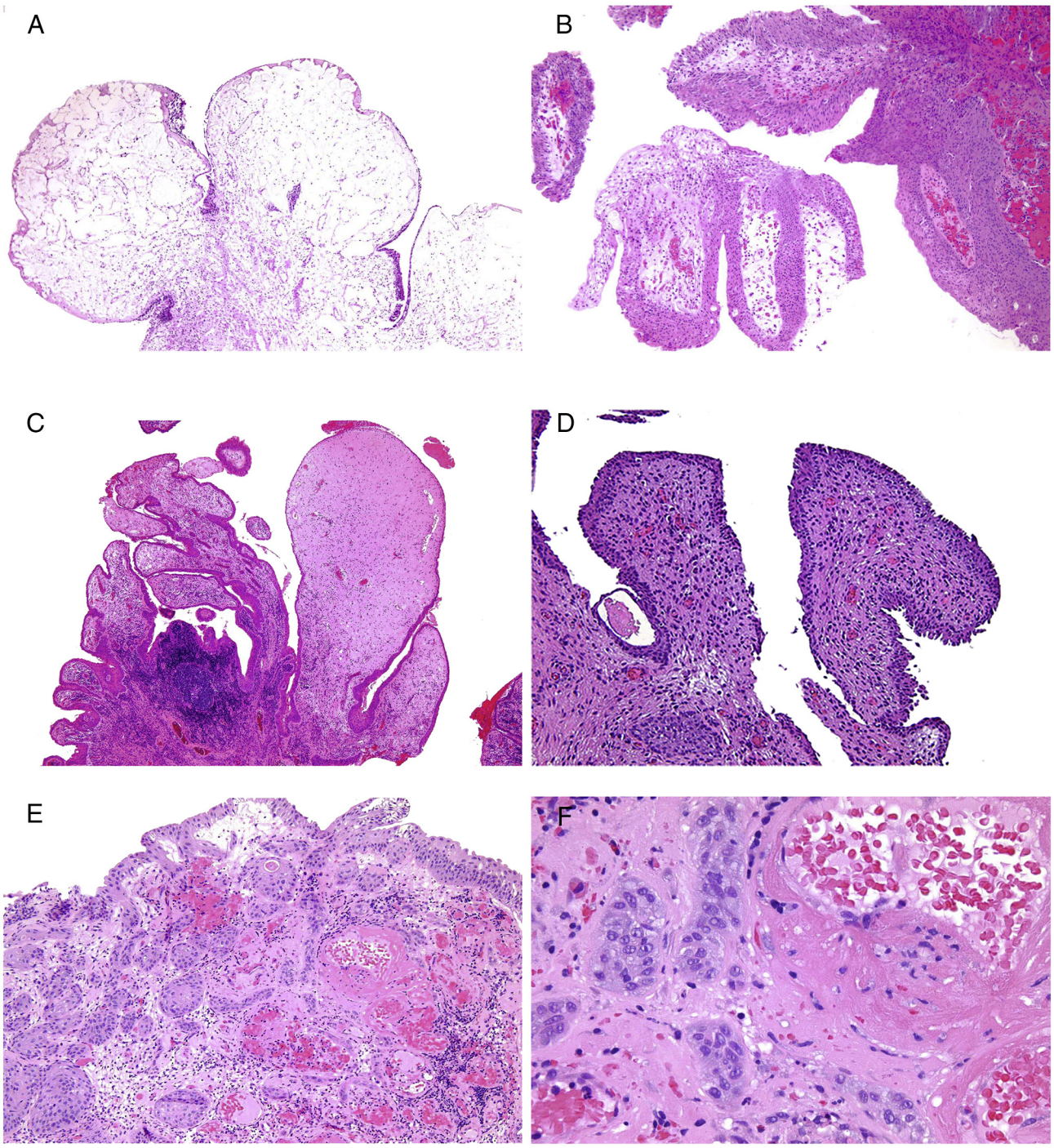

Fig. 3. A. Thick edematous broad based polypoid projections of polypoid cystitis. B. Tangential section of polypoid cystitis appearing as thinner and branching papillae and thickened urothelium. C. Low-power magnification of polypoid cystitis with some papillae having narrow base. This finding in isolation is a mimicker of exophytic papillary urothelial tumor. D. Polypoid cystitis with fibrotic stalks representing a later stage of the process. In contrast, papillary urothelial tumor has delicate loose collagen without prominent chronic inflammation. E. Low-power magnification of pseudocarcinomatous urothelial hyperplasia with irregular dilated vessels, hemorrhage, inflammation, and extensive fibrin deposition. F. High-power magnification of pseudocarcinomatous urothelial hyperplasia demonstrating cytological atypia and prominent nucleoli. The urothelial nests are encircled by extensive fibrin.

activity (Fig. 5A). A more recently described large nested variant of urothelial carcinoma has similar cytological findings [25]. In contrast to von Brunn nests, nested cancer in the bladder has smaller back-to-back nests with irregular infiltration. Muscularis propria invasion, if present, rules out von Brunn nests proliferation. In addition to the lack of atypia in nested carcinoma, other features that mimic von Brunn nests in nested carcinoma are the lack of retraction artifact or stromal reaction and the frequent absence of an overlying urothelial precursor lesion (i.e. CIS or papillary carcinoma). The distinction of florid proliferation of von Brunn nests and nested urothelial carcinoma may only be possible when sufficient amount of cancer is present in the specimen such that the architecture can be adequately assessed (Table 2). A request for additional tissue sampling may therefore be needed in select cases. The diagnosis is based on the H&E appearance only and immunohistochemical stains are of limited utility [26]. A potential ancillary test is TERT promoter mutation analysis. In our study of 20

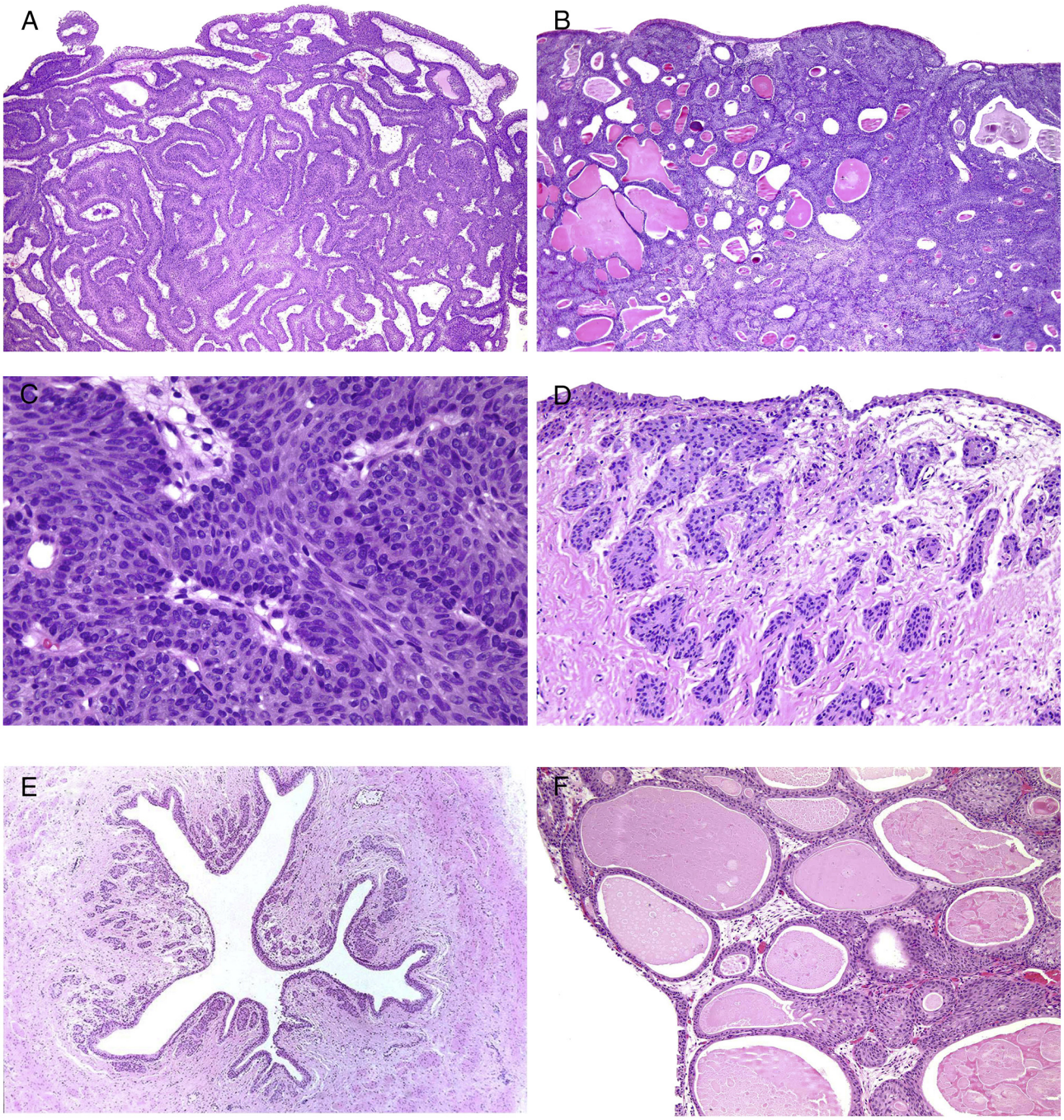

Fig. 4. A. Low-power magnification of inverted urothelial papilloma showing thin interconnected trabeculae of urothelium and smooth surface. B. Low-power magnification of inverted urothelial papilloma with prominent cyst formation. C. High-power magnification of inverted urothelial papilloma demonstrating central streaming and peripheral palisading of cells. Note the lack of cytological atypia or mitotic activity. D. A focus of florid proliferation of von Brunn nests mimicking nested variant of urothelial carcinoma. E. A cross-section of the ureter demonstrating circumferential florid proliferation of von Brunn nests. F. Florid proliferation of von Brunn nests with prominent cyst formation. Note the lack of anastomosing of urothelial nests in contrast to inverted urothelial papilloma with cyst formation.

nested and 10 large nested urothelial carcinoma, TERT promoter mutations were identified in 17 (85%) and 8 (80%) cases, correspondingly [27]. No mutation was found in 14 studied mimickers. It is critical to distinguish von Brunn nests from nested carcinoma as the latter's prognosis is usually dismal, related to a high stage at presentation [28]. However, the prognosis of nested carcinoma is similar to a conventional invasive urothelial carcinoma in stage matched patients.

11. Urothelial reaction associated with prostatic infarction

Prostatic infarction is usually seen in older men with benign prostatic hyperplasia and peripheral vascular disease [29]. Men with prostatic infarction on average present in the 8th decade of life. Prostatic infarction may give rise to a significant spike in serum PSA levels. However, most infarctions are detected incidentally on transurethral resection or needle biopsy. Microscopically, the lesions represent a central hemorrhagic infarction with the surrounding non-keratinizing squamous or urothelial metaplasia (Fig. 5D). The latter usually has at

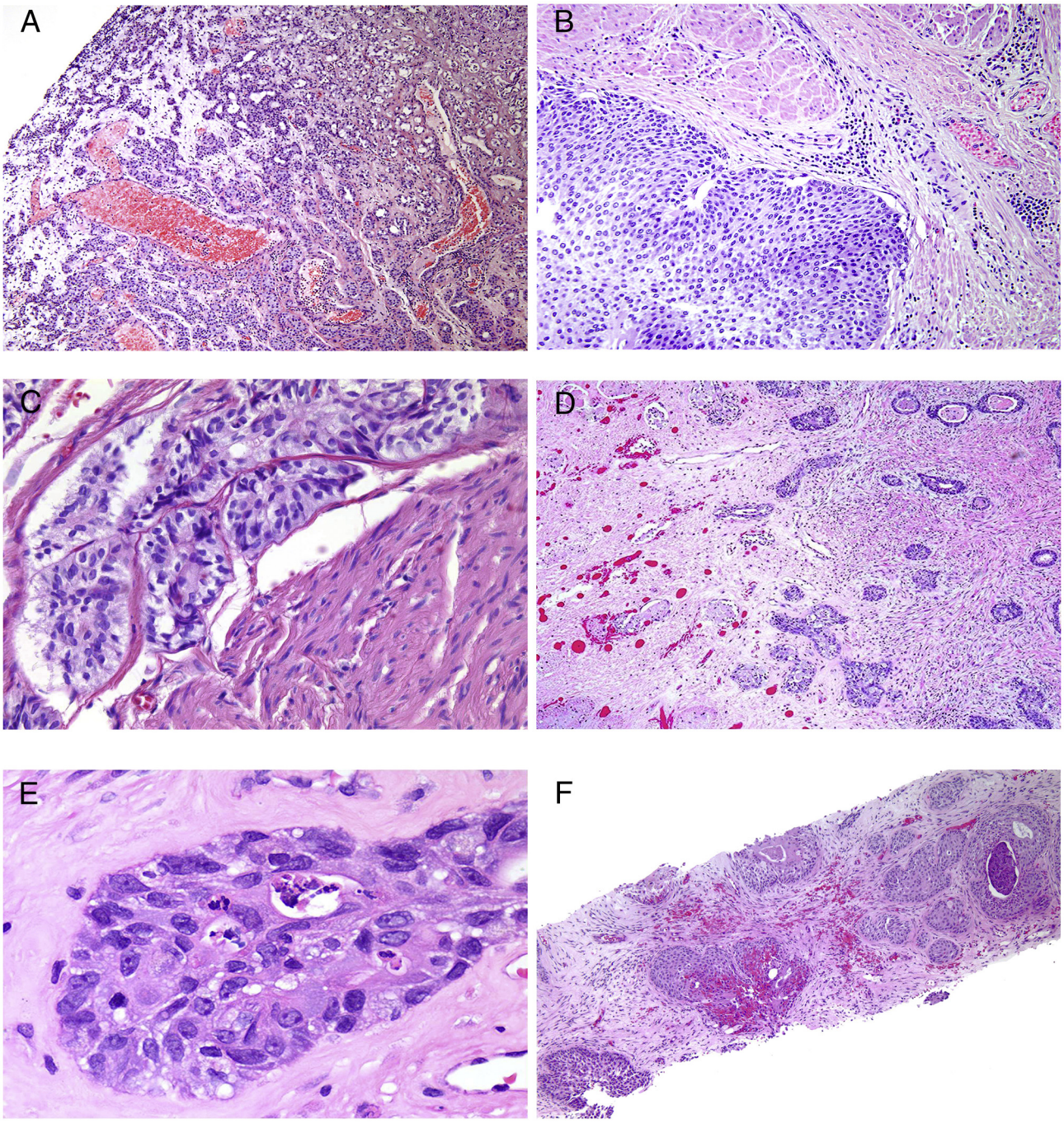

Fig. 5. A. Nested variant of invasive urothelial carcinoma. The architecture is irregular and infiltrative appearing. B. Large nested variant of invasive urothelial carcinoma. Despite bland cytology, the solid urothelial nest is present in the muscularis propria and diagnostic of cancer. C. Bland cytology of nested variant of invasive urothelial carcinoma. Presence of tumor nests in muscularis propria allows an unequivocal diagnosis. D. Transurethral resection with hemorrhagic prostatic infarction (left) with associated urothelial metaplasia (right). E. Reactive cytological atypia in urothelial metaplasia accompanying prostatic infarction. F. Low-power magnification of prostatic infarction in prostate needle biopsy. Although the findings are suspicious of invasive urothelial carcinoma, the nature of the stromal reaction is typical of prostatic infarction.

Table 2
Architectural characteristic of florid hyperplasia of von Brunn nests (VBN) in the ureter and bladder, and nested variant of invasive urothelial carcinoma.

Bladder VBN	Ureter VBN	Nested urothelial carcinoma
Larger, more uniform with even spacing.	Small crowded nests with liner or lobular arrangement.	Small crowded nests with variable shape and spacing.
Even base, no infiltration.	Even base, no infiltration.	Irregular base, infiltration (muscularis propria in particular).
Edematous stroma, some with delicate concentric layering.	Variable, edematous stroma is unusual.	Dense and collagenous, rarely edematous.

least focal cytological atypia and mitotic activity mimicking urothelial carcinoma (Fig. 5E). The key to its diagnosis if one cannot appreciate the central area of infarction due to the plane of section is, as with many of the other mimickers discussed above, to look at the overall picture and not focus on just the atypical urothelial nests. The background of prostatic infarcts is similar to what is seen with pseudocarcinomatous hyperplasia with stromal hemorrhage and hemosiderin (Fig. 5F), features not associated with invasive urothelial carcinoma.

12. Summary

There is a wide range of benign mimickers of both adenocarcinoma and urothelial carcinoma. In many entities, urologist's impression and clinical history may be revealing. In other conditions, it is critical to look at the overall histology, rather than focus on isolated features that out of context may be indistinguishable from cancer. In more superficial or doubtful cases, it is appropriate to convey the uncertainty and differential diagnosis to the urologist and request additional tissue.

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