ORIGINAL ARTICLE

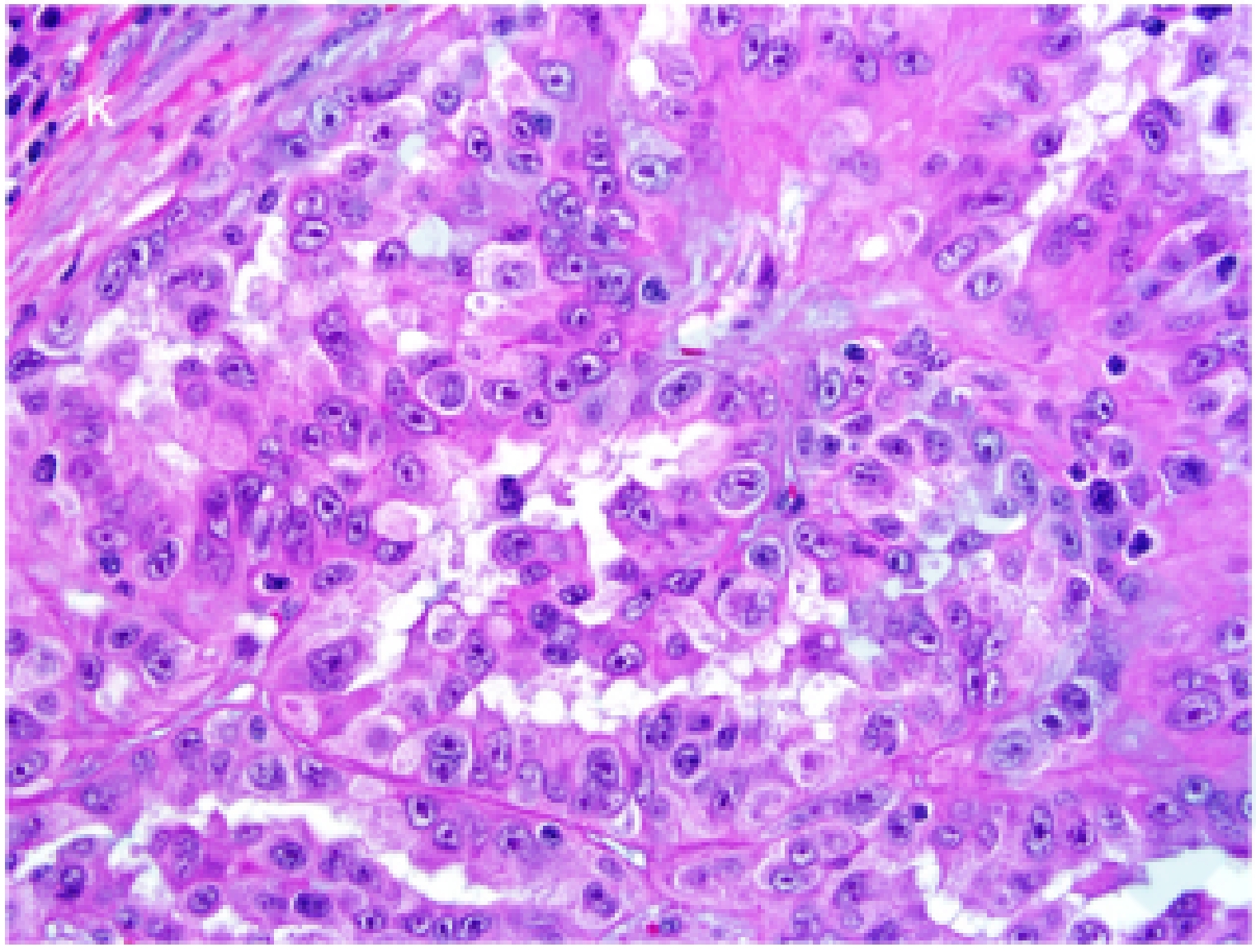
Biphasic Hyalinizing Psammomatous Renal Cell Carcinoma (BHP RCC)

A Distinctive Neoplasm Associated With Somatic NF2 Mutations

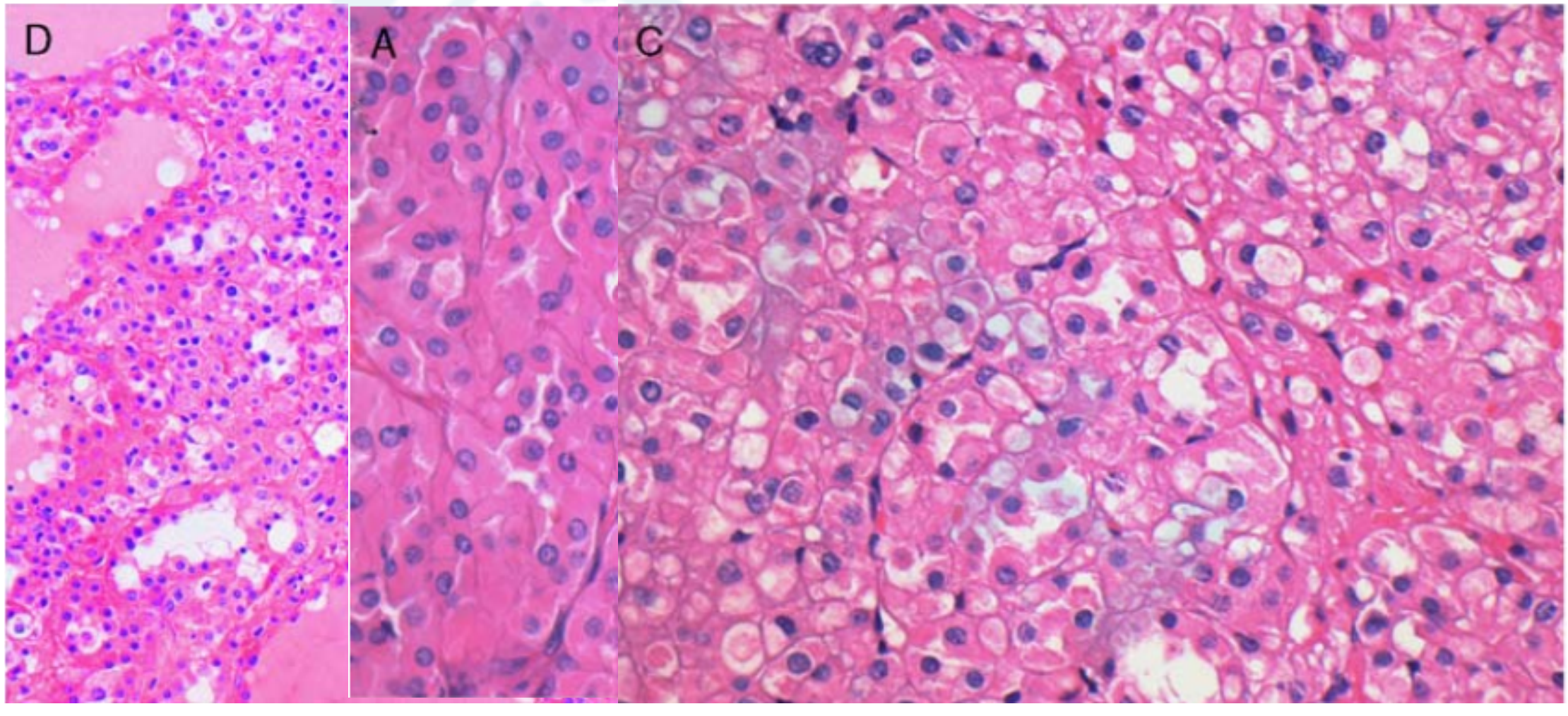
Pedram Argani, MD. Am J Surg Pathol. Volume 44, Number 7, July 2020

汇 报 人：　　魏　洁

- Perhaps more than any other cancer, distinctive morphologic features of renal cell carcinomas (RCCs) correlate with specific genetic alterations.
    - ✓ fumarate hydratase deficiency: prominent nucleoli with a perinucleolar halo

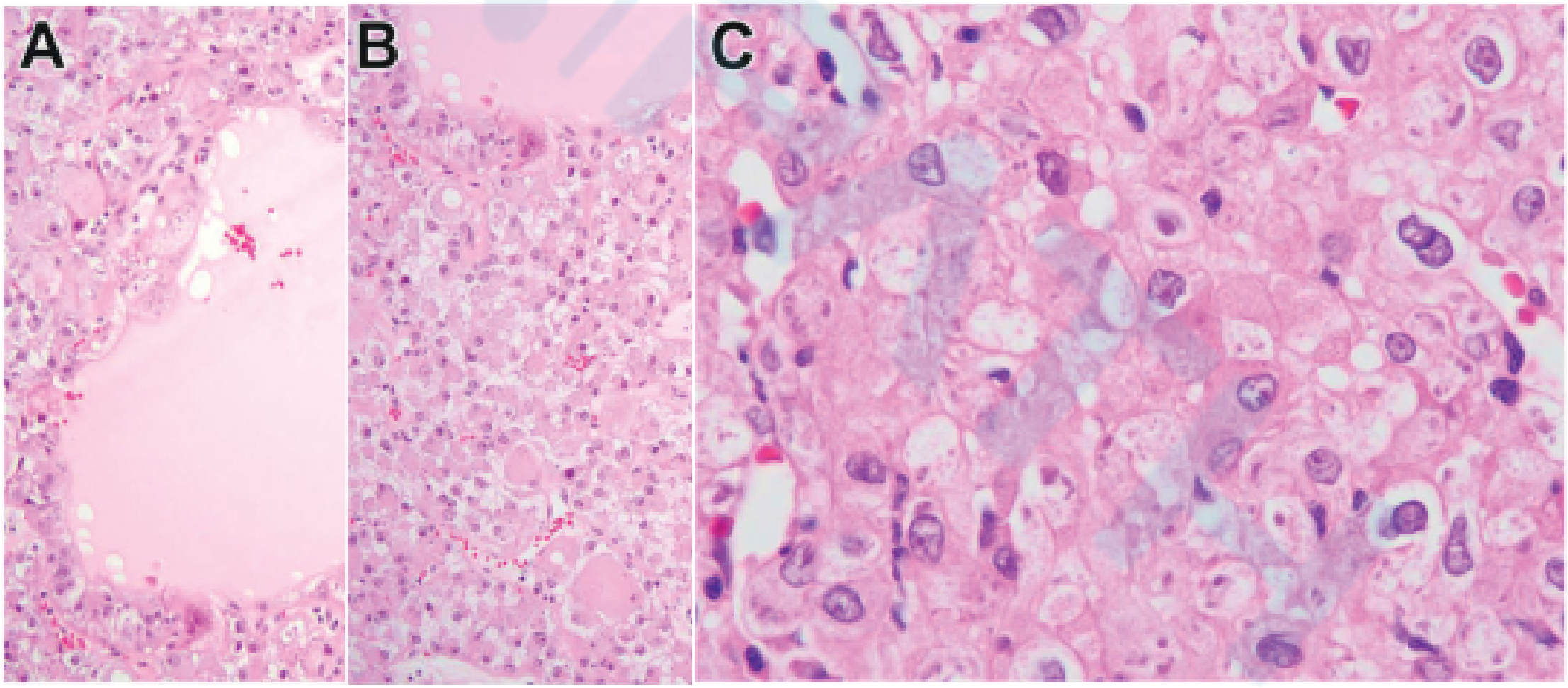


- Perhaps more than any other cancer, distinctive morphologic features of renal cell carcinomas (RCCs) correlate with specific genetic alterations.
    - ✓ succinate dehydrogenase deficiency:solid or focally cystic growth, uniform cytology with eosinophilic flocculent cytoplasm, intracytoplasmic vacuolations and inclusions, and round to oval low-grade nuclei.

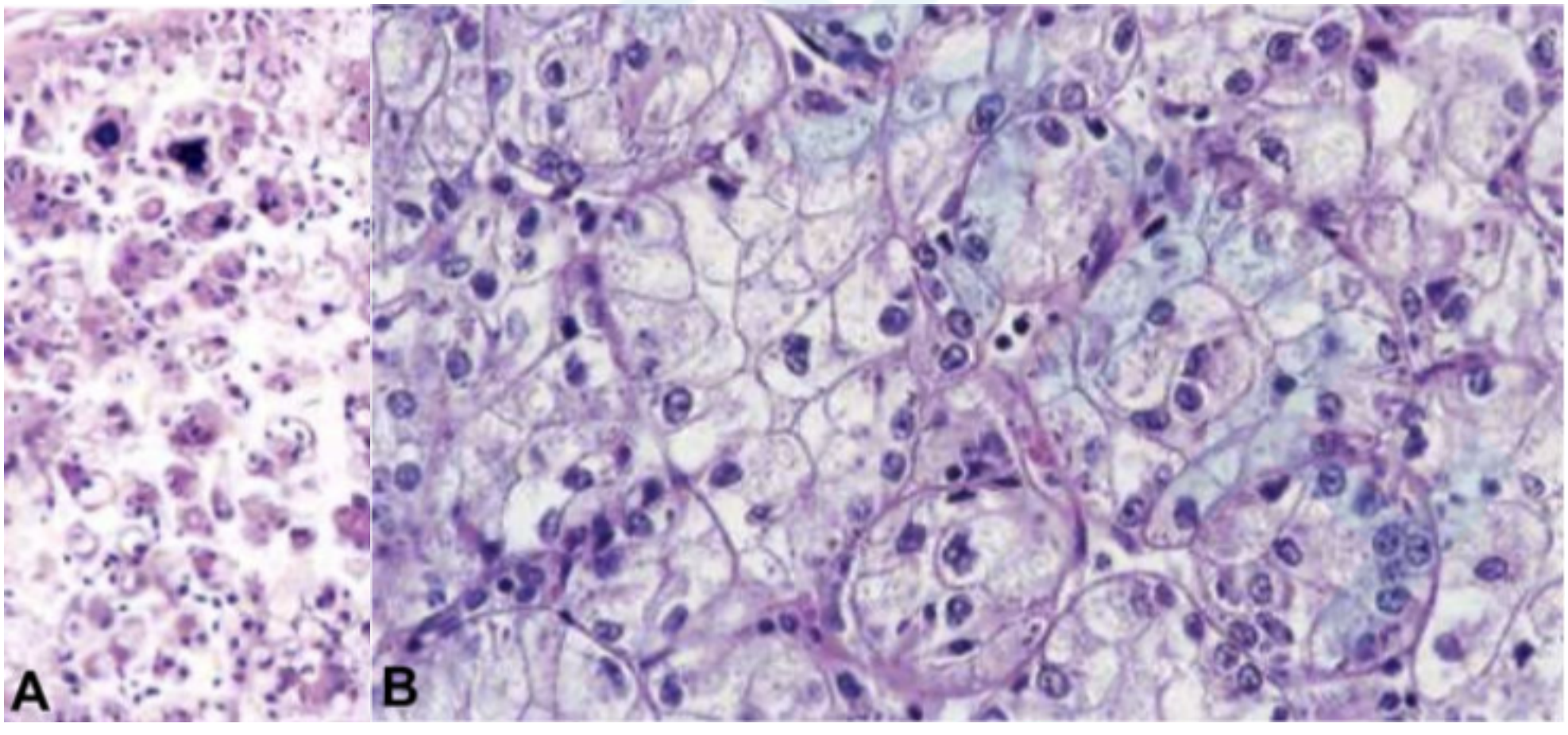


Am J Surg Pathol • Volume 38, Number 12, December 2014

- Perhaps more than any other cancer, distinctive morphologic features of renal cell carcinomas (RCCs) correlate with specific genetic alterations.
    - ✓ tuberous sclerosis complex (TSC) gene mutations: These neoplasms typically demonstrate solid and cystic architecture, and the neoplastic cells contain voluminous eosinophilic cytoplasm with granular cytoplasmic stippling .



- Perhaps more than any other cancer, distinctive morphologic features of renal cell carcinomas (RCCs) correlate with specific genetic alterations.
    - ✓ translocations involving chromosome Xp11 resulting in gene fusions involving the TFE3 transcription factor gene: the constellation of clear cells with papillary architecture, voluminous cytoplasm.



MATERIALS AND METHODS

•Cases

The 8 cases reported herein were retrieved from the files of 3 authors (P.A., V.E.R., J.N.E.) during a review of unclassified primary renal carcinomas.

•Immunohistochemistry

HMB45 , cathepsin K , AE1/3 , Cam5.2 ,EMA , PAX8, S100, melan A, desmin, SF-1, GATA3, SMA , TFE3

•DNA and RNA Sequencing

•Photomicrographs

RESULTS

TABLE 1. Clinical, Pathologic, and Genetic Features of Cases

Case #	Age/Sex	Tumor Size/Stage	IHC^{+}	IHC^{-}	Comment	*NF2* Variant	Other Molecular Findings
1	78/male	4.2 cm; pT1bNX	HNF1-beta, PAX8, CK7, EMA (focal)	WT-1, Melan A, cathepsin k^{-}, GATA3, SF-1, inhibin; FH, SDHB intact	TFE3/B FISH^{-}; died of complications 1 mo after operation	p.Tyr66*	Chr loss: 1p, 6, 22q; Chr gain: 16, 20 *XPO1* p.Asn735Lys; *POLQ* p. Phe944Val; *SPTBN1* p. Trp1893*; *EXT2* p.Tyr421*; *NPM1* p.Asp165_Glu169del; *NCOA1* p.Met476Ile; *AUTS2* p.Gly216Arg; *ARID2* p. Arg314Ser; *LMO7* p. Pro715Ser; *CYLD* p. Pro78Thr; *MIB1* p. Ser408Asn; *CSNK1G2* c.187 +1G>T
2	60/U	7 cm; pT2NX	PAX8, EMA, CK7	WT-1, TFE3, cathepsin k, TFEB, HMB45, Melan A chromogranin, synaptophysin, GATA3, SF-1, inhibin	TFE3/B FISH^{-}; ESRD; tumor in native kidney 21 y after transplant	p.Asn293fs	Chr loss: 1p, 6, 22q; Chr gain: 16, 20 *WNT4* p.Val97Ile; *RAD54L* p. Arg202Cys; *MRE11A* p. Asp495His; *ERBB2* p. Asp880Tyr; *PI4KA* p. Pro514Leu
3	69/male	4 cm; pT1cNXM1 (bone metastasis)	CK7, racemase, HNF1-beta	TFE3, HMB45, Melan A, cathepsin K, AR, ER, CA-IX, GATA3	Lung metastasis; died of disease 2 mo later	p.Gln111*	Chr loss: 9; Chr gain: 20 *GLI1* p.Gly1097fs; *RB1* p. Glu539_Thr543del; *TERT* promoter variant g.1295228C>T

RESULTS

TABLE 1. Clinical, Pathologic, and Genetic Features of Cases

Case #	Age/Sex	Tumor Size/Stage	IHC^{+}	IHC^{-}	Comment	*NF2* Variant	Other Molecular Findings
4	53/female	2.5 cm; pT1NX		GATA3, WT-1, cathepsin K, inhibin, SF-1	TFE3/B FISH^{-}; h/o bilateral ovarian cystectomy	c.600-1G > A	Chr loss: 1p, 4, 6, 21q, 22q; Chr gain: 1, 7, 20 *ARID1A* p.Pro1619fs; *CDK6* p. Thr198fs; *RAD50* p. Gln479Arg; *MLLT6* p. Ser608Tyr; *SUGP2* p. Ala75Ser; *THBS1* p. Arg458Gly; *LRIG3* p. Asp56Glu; *PLCG2* p. Glu567Lys; *KMT2B* p. Gly100Asp
5	73/male	3 cm; pT1aNX	CK7	CA-IX, cathepsin K, GATA3, WT-1, inhibin, SF-1^{-}; FH, SDHB intact	TFE3/B FISH^{-}	p.Lys364*	Chr loss: 1, 6, 9q, 15q, 19q; Chr gain: 9p, 16 *CHD6* p.Asn2152Ser; *NUP98* p. Ser103*; *SAMD9* p.Phe801fs; *MIB1* c.2211+1G > A; *CIITA* p.Gly174Arg; *MECOM* p. Glu81Gln; *FLT4* p. Trp1233Cys; *ABL2* p. Asn152fs; *ASPSCR1* p. Asp217fs; *HIST1H2AG* p. Pro81Arg; *FBXW7* p. Arg505His; *KDM1A* p. Val400Ile; *SQSTM1* p. Cys27Ser
6	71/male	1.5 cm; pT3NX (perirenal fat and vascular invasion)	PAX8, CK7	Cathepsin k, GATA3, WT-1, inhibin, SF-1^{-}; FH intact	Concurrent clear cell RCC; TFE3/B FISH^{-}	p.Leu316fs	Chr loss: 1p, 6, 9, 15q; Chr gain: 16,17q,20 *SMARCA4* c.3546+3A > T; *FANCD2* p.Ser352Leu; *BCL2* p.Leu185Met; *PAK5* p. Ala120Val; *PPP2R1B* p. His661Leu; *NOTCH2* p. Phe2091Ser; *PICALM* p. Val183Gly; *HIP1* c.2891-2A > G; *AKAP9* p. Glu2697Gln; *STAT1* p. Ala531Thr; *DLEC1* p. Gln1740Arg; *PRICKLE1* p. Pro786Thr; *LAMA5* p. Asn479Ser

RESULTS

Case #	Age/Sex	Tumor Size/Stage	IHC$^+$	IHC$^-$	Comment	*NF2* Variant	Other Molecular Findings
7	52/male	1 cm; pT1NX	PAX8	Chromogranin, synaptophysin, cathepsin K, Melan A, WT-1, inhibin, SF-1, calretinin, GATA3	Renal-adrenal fusion; concurrent renal cyst	p. Arg516_Lys523-delinsGln	Chr loss: 14q, 19q, 22q; Chr gain: 2p, 5, 13q, 20 *PPP2R2B* p.Arg129fs; *RPL22* p. Lys13fs; *BICC1* p.Val254Leu; *WDFY3* c.1591+4A > C; *TFEB* p.Arg4Pro; *FZD3* p. Gly595Ala; *TNC* p. Phe1196Tyr
8	51/male	1.5 cm; pT1NX			Concurrent renal cyst	p.Lys130fs	Chr loss: 1p, 3, 6, 11, 14q, 19, 22q; Chr gain: 20 *ERCC5* p.Leu844*; *CLTC* p. Asp662fs; *WHSC1* c.1674 +6dupT; *SNX29* p.Lys513Ile; *CNTN1* c.2185-4T > A; *SGK1* p.Lys338Glu; *ITGA7* p. Glu120Val; *GNAI1* p. Arg142Ile; *TPR* p. Glu1594Asp; *RASGRF1* p. Asn1075Tyr; *LIFR* p. Met773Leu

*Stop codon.
Chr indicates chromosome; FH, fumarate hydratase; FISH, fluorescence in situ hybridization; SDHB, succinate dehydrogenase subunit B; U, unknown sex.

age: 51-78y
F:M=6:1

5 underwent partial nephrectomy
2 underwent radical nephrectomy
size:1-7cm; solid

RESULTS

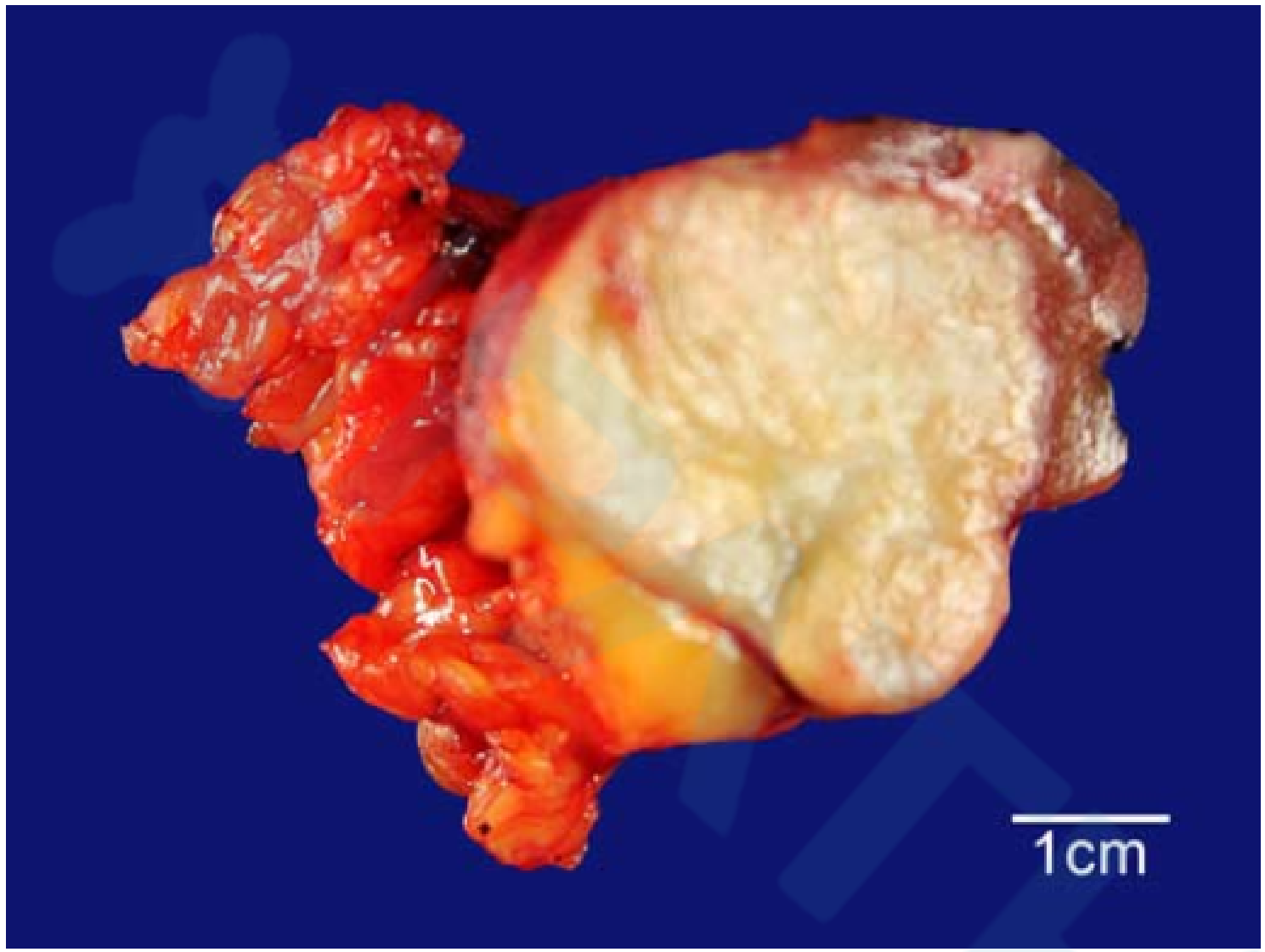


FIGURE 1. BHP RCC case #3. The 4 cm neoplasm has a white, fibrous appearance, which contrasts with the yellow perinephric fat lobules to the left and the maroon-red native renal parenchyma to the upper right.

RESULTS

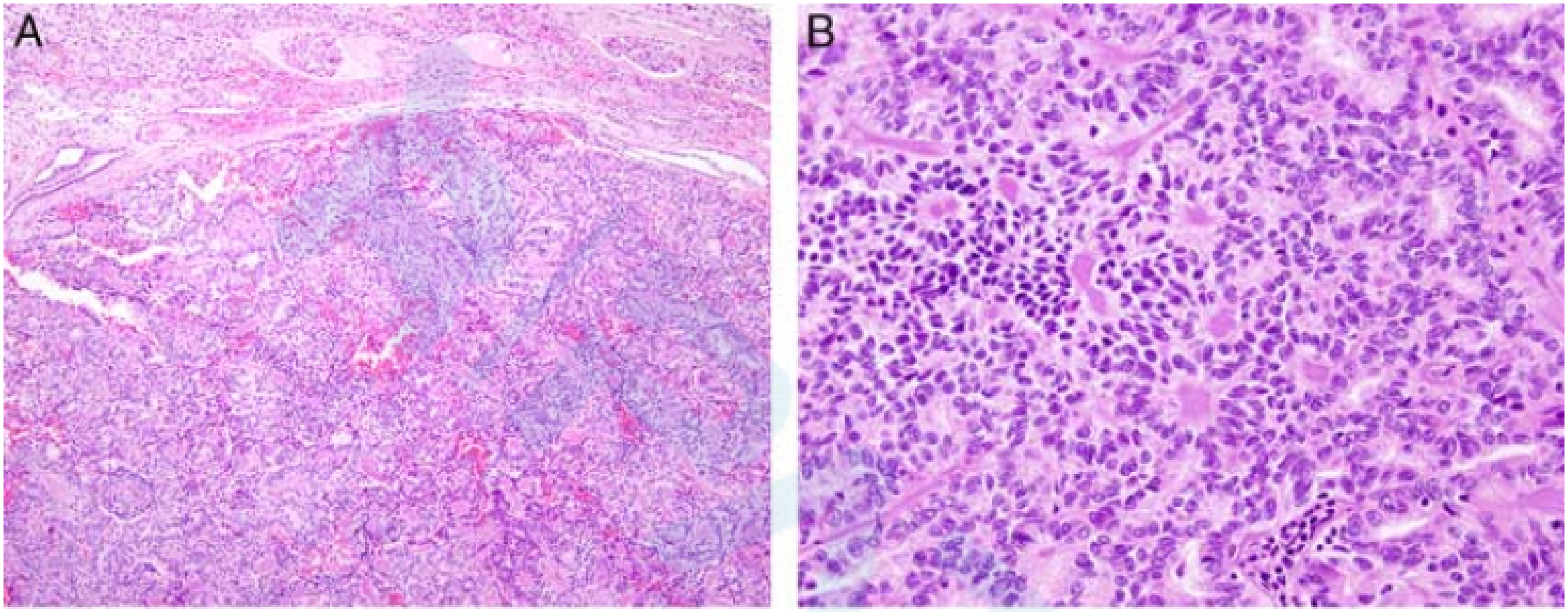
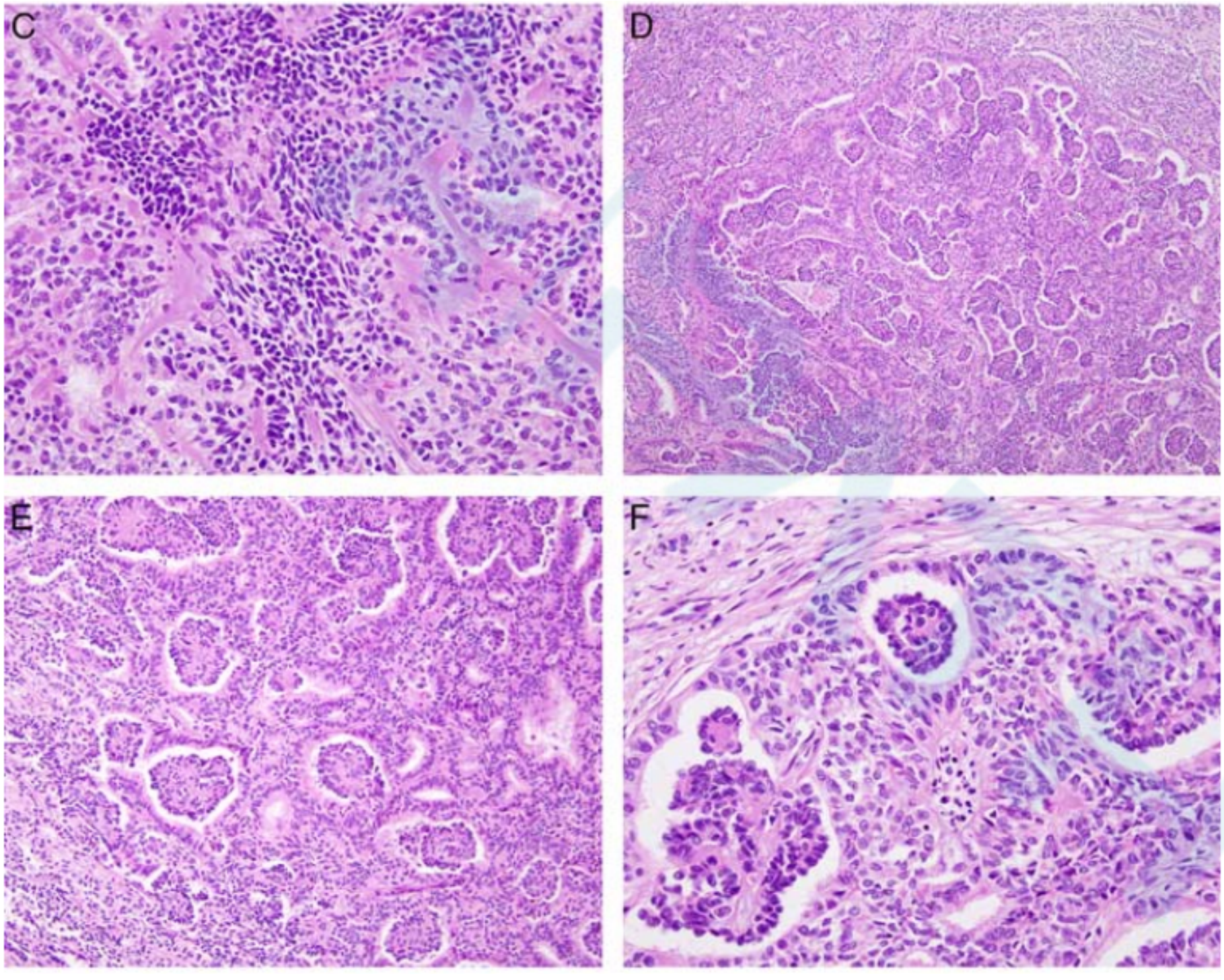


FIGURE 2. BHP RCC case #1. The neoplasm is unencapsulated and has a rounded, nodular border with the native kidney at the top of the figure (A). The biphasic pattern is evident, as smaller cells with condensed chromatin cluster around hyalinized material while larger cells with vesicular chromatin form tubules and larger acini (B).

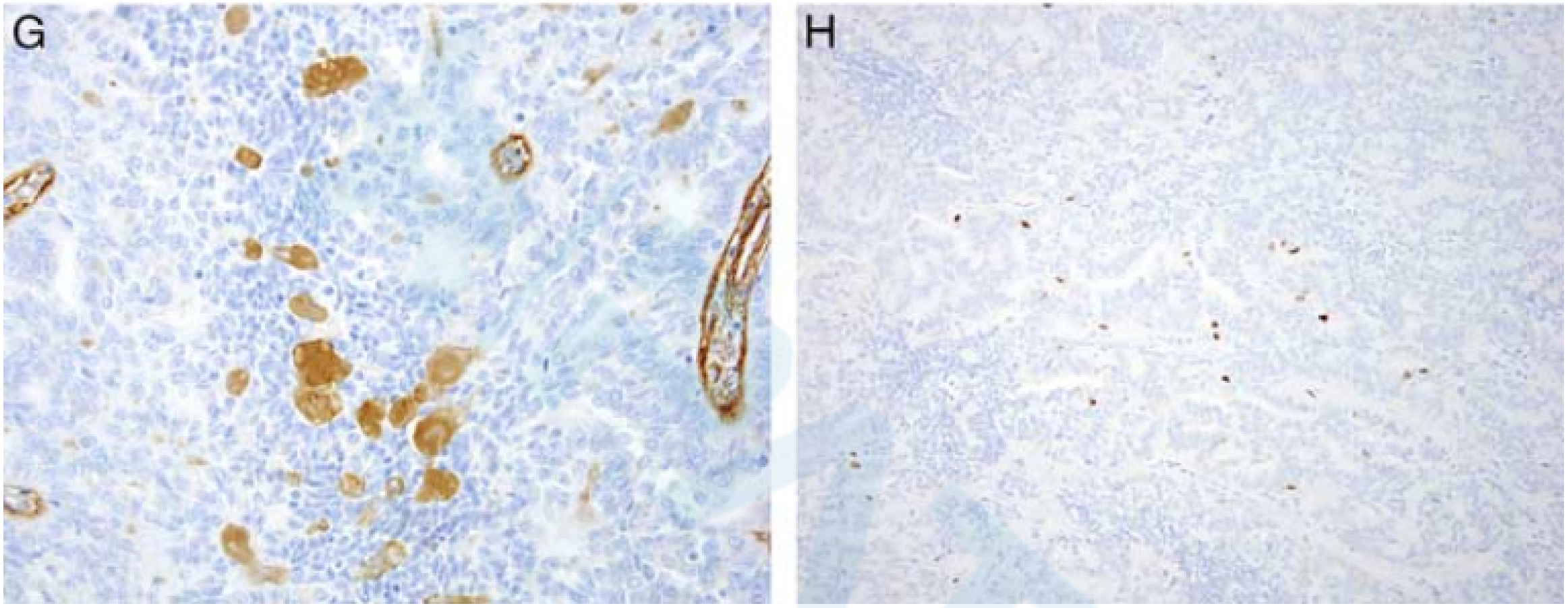
RESULTS



The smaller cells also form solid spindle cell foci unassociated with basement membrane material (C). The small cells on papillae associated with the basement membrane branch within larger acini, resulting in a glomeruloid pattern (D–F).

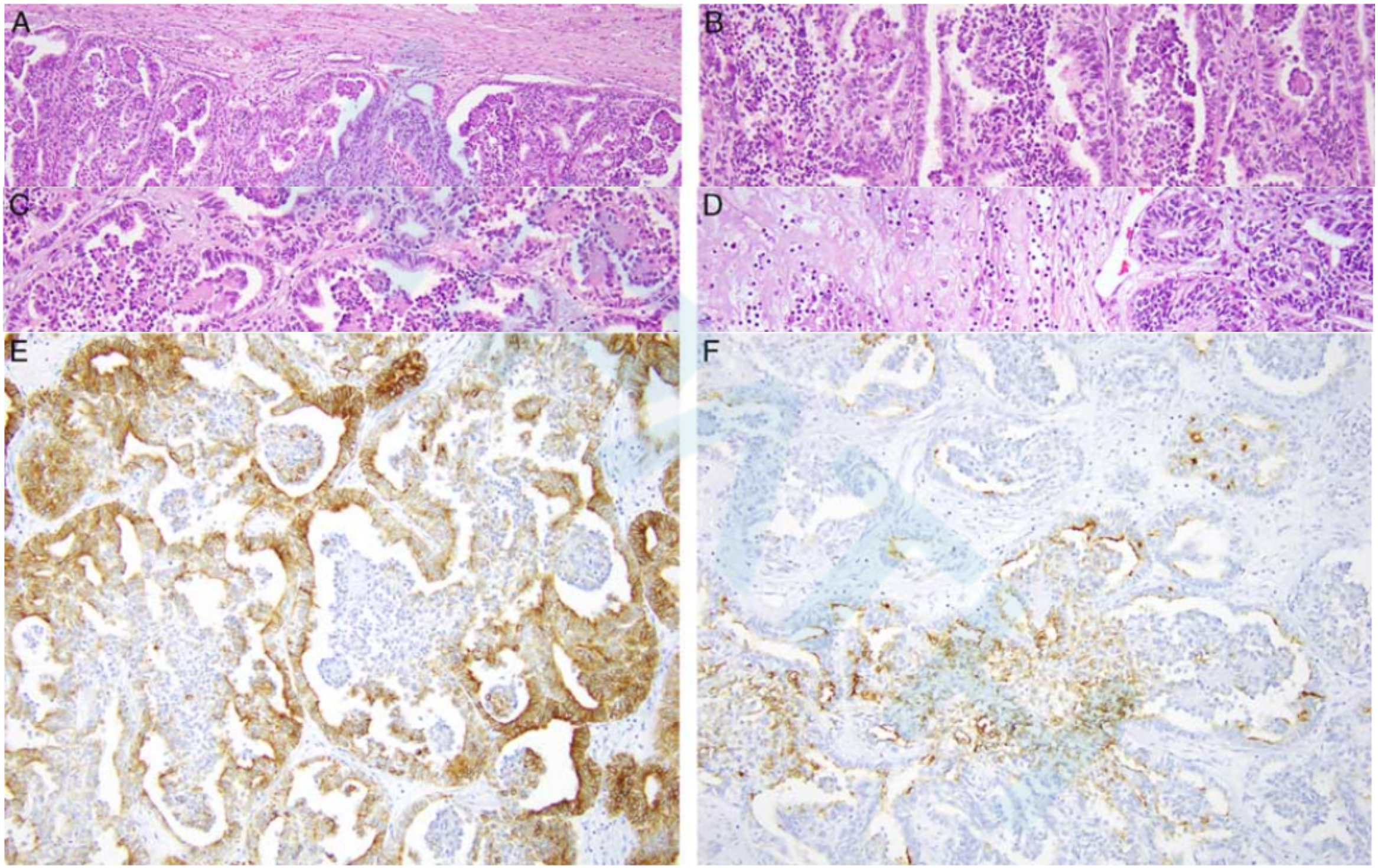
case 1

RESULTS



The hyalinized material labels with type IV collagen, consistent with basement membrane material (G). The neoplasm has a low proliferative index as measured by Ki-67 IHC, particularly in the smaller cells (H).

RESULTS



Cytokeratin 7 preferentially labels the larger cells forming the larger acini (E). EMA preferentially labels the smaller cells in the glomeruloid bodies (F).

case 2

RESULTS

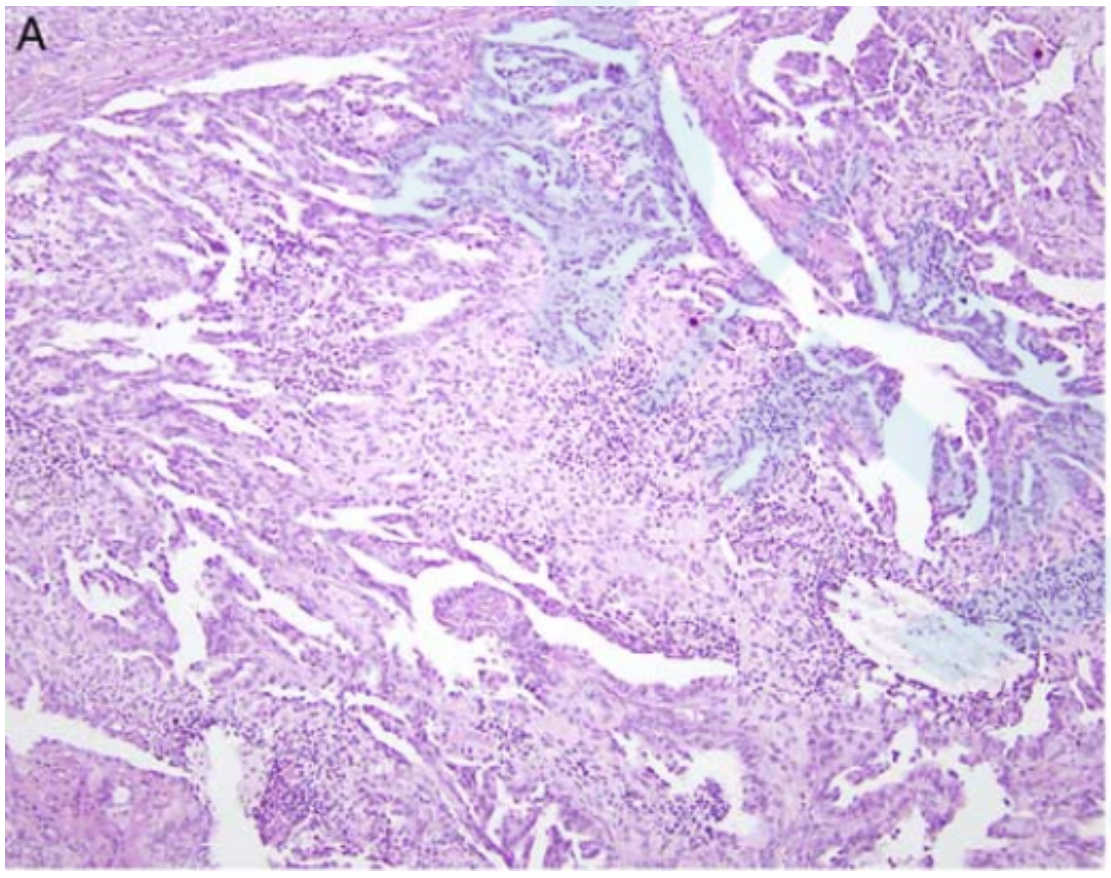
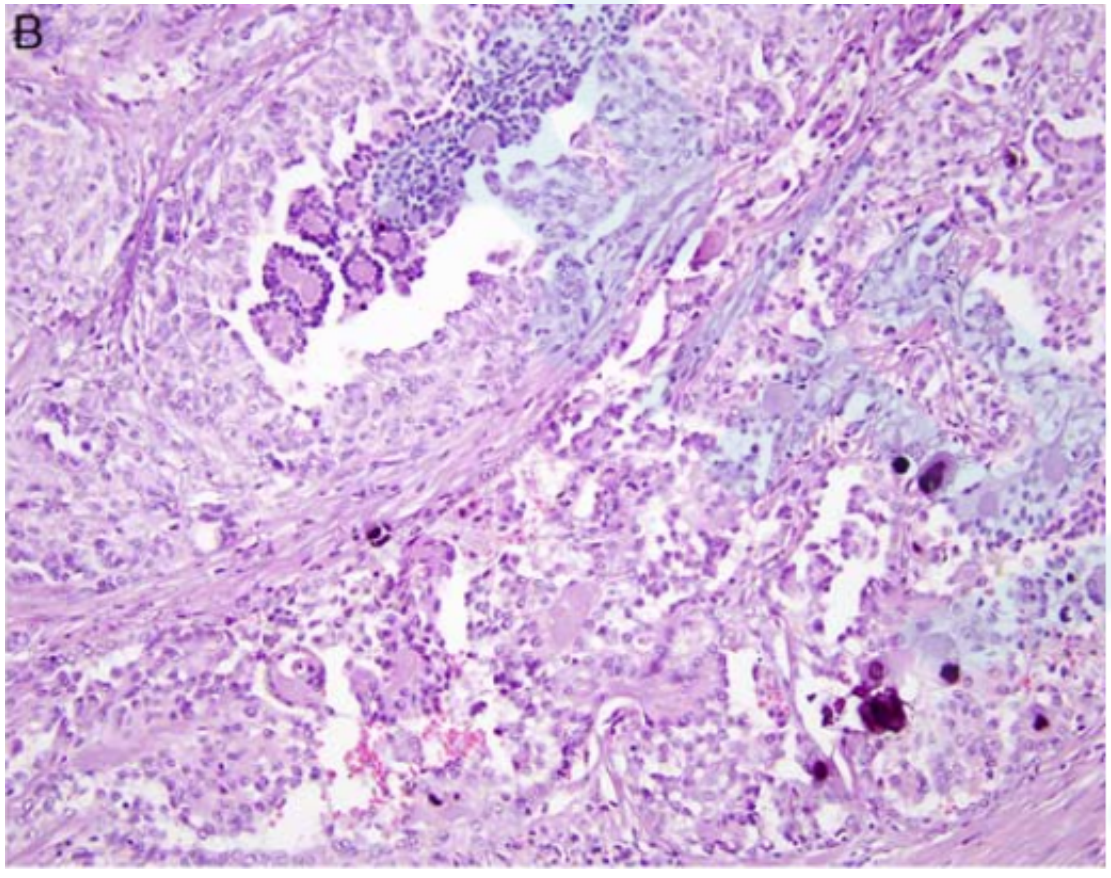
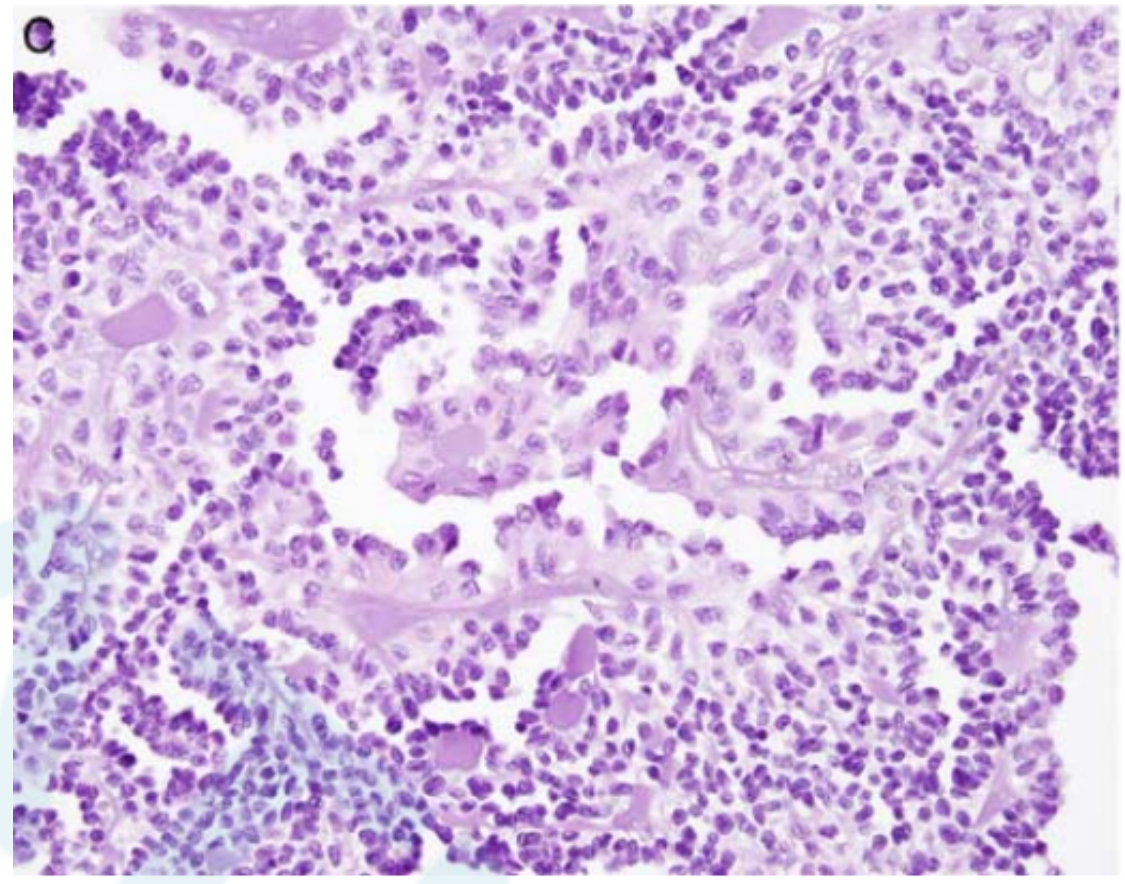


FIGURE 4. BHP RCC case #3. The neoplasm is unencapsulated; note the native renal parenchyma at the upper left. The neoplasm has a striking biphasic appearance, with solid clusters of larger epithelioid clear cells and smaller cells forming branching papillae(A).

case 3

RESULTS

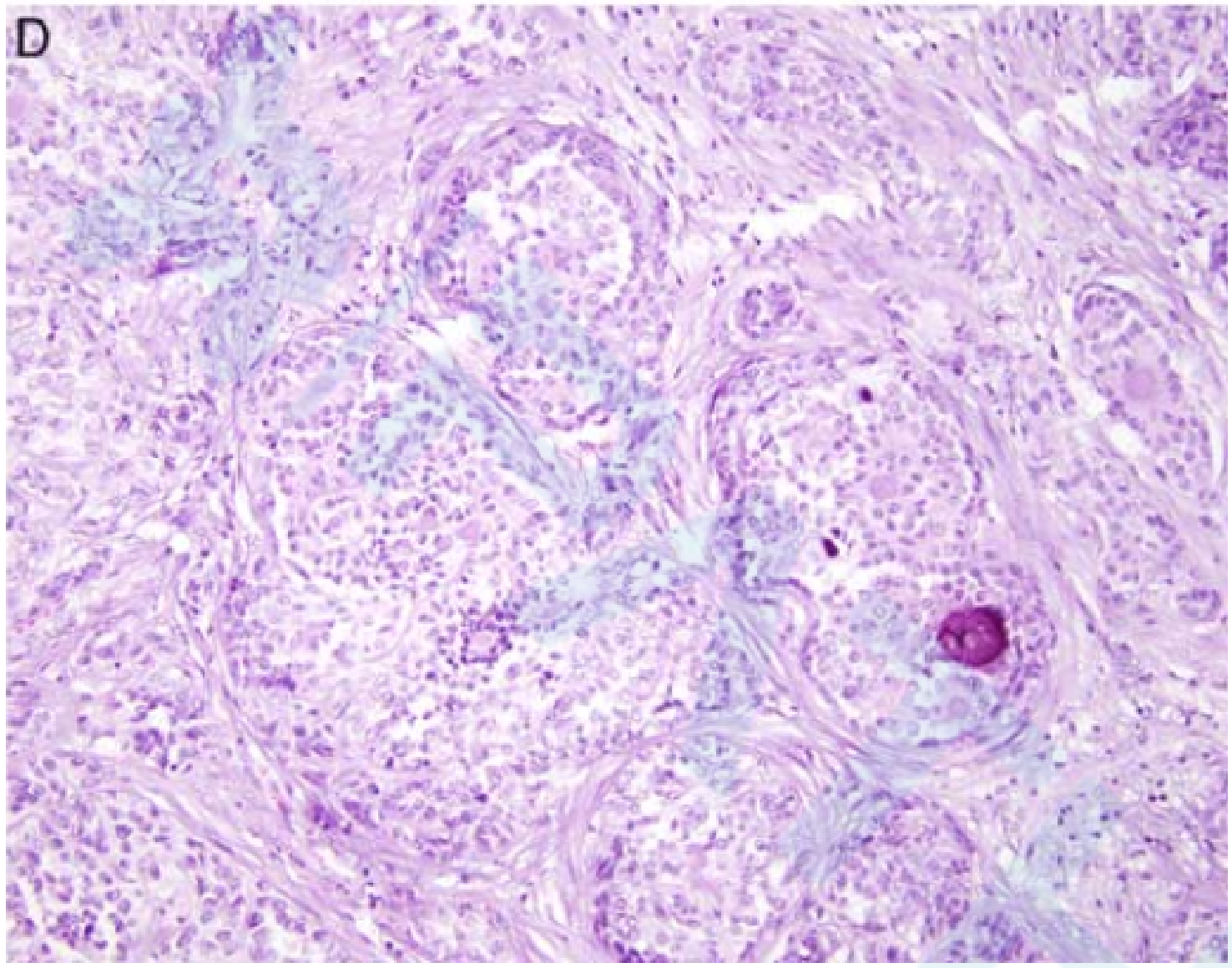




At higher power, one can appreciate the smaller cells with condensed chromatin clustered around basement membrane material, the larger cells with vesicular chromatin, as well as extensive psammomatous calcification (B, C).

case 3

RESULTS



In other areas, the neoplasm has more fibrotic stroma and the architecture is more solid with epithelioid cells surrounding smaller cells around hyalinized material and psammomatous calcifications (D).

RESULTS

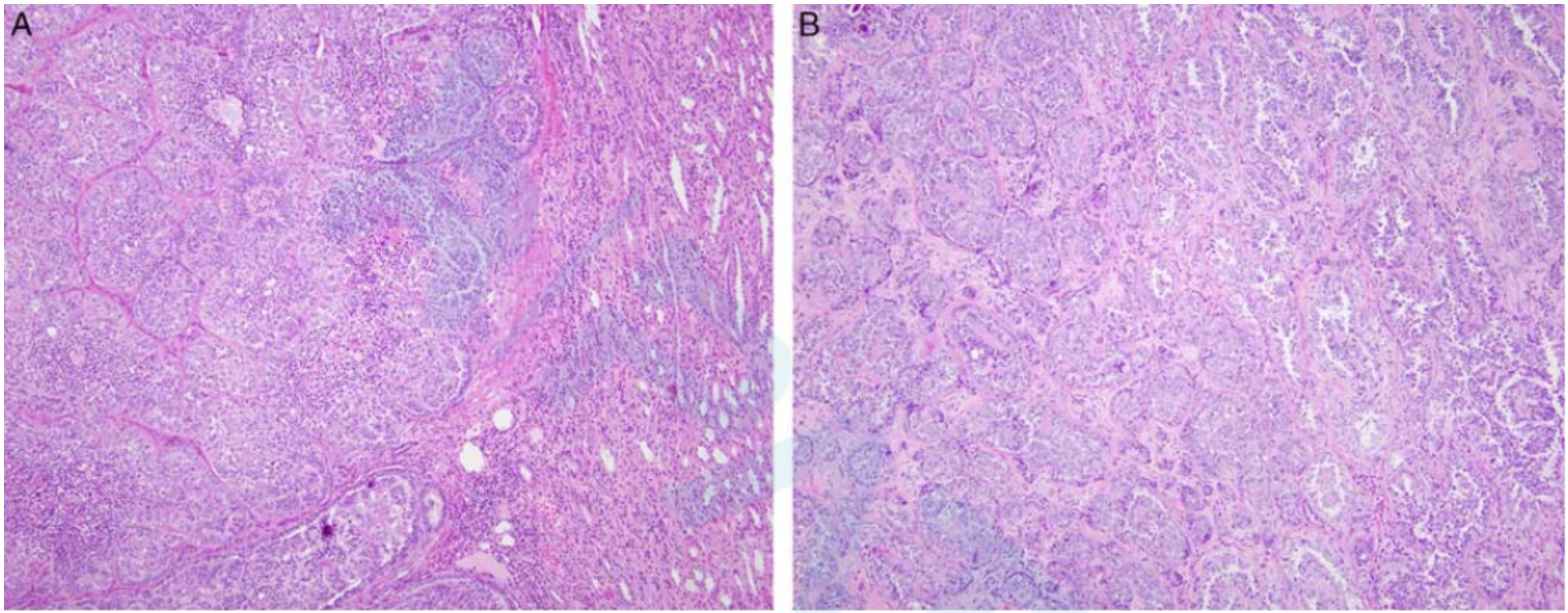
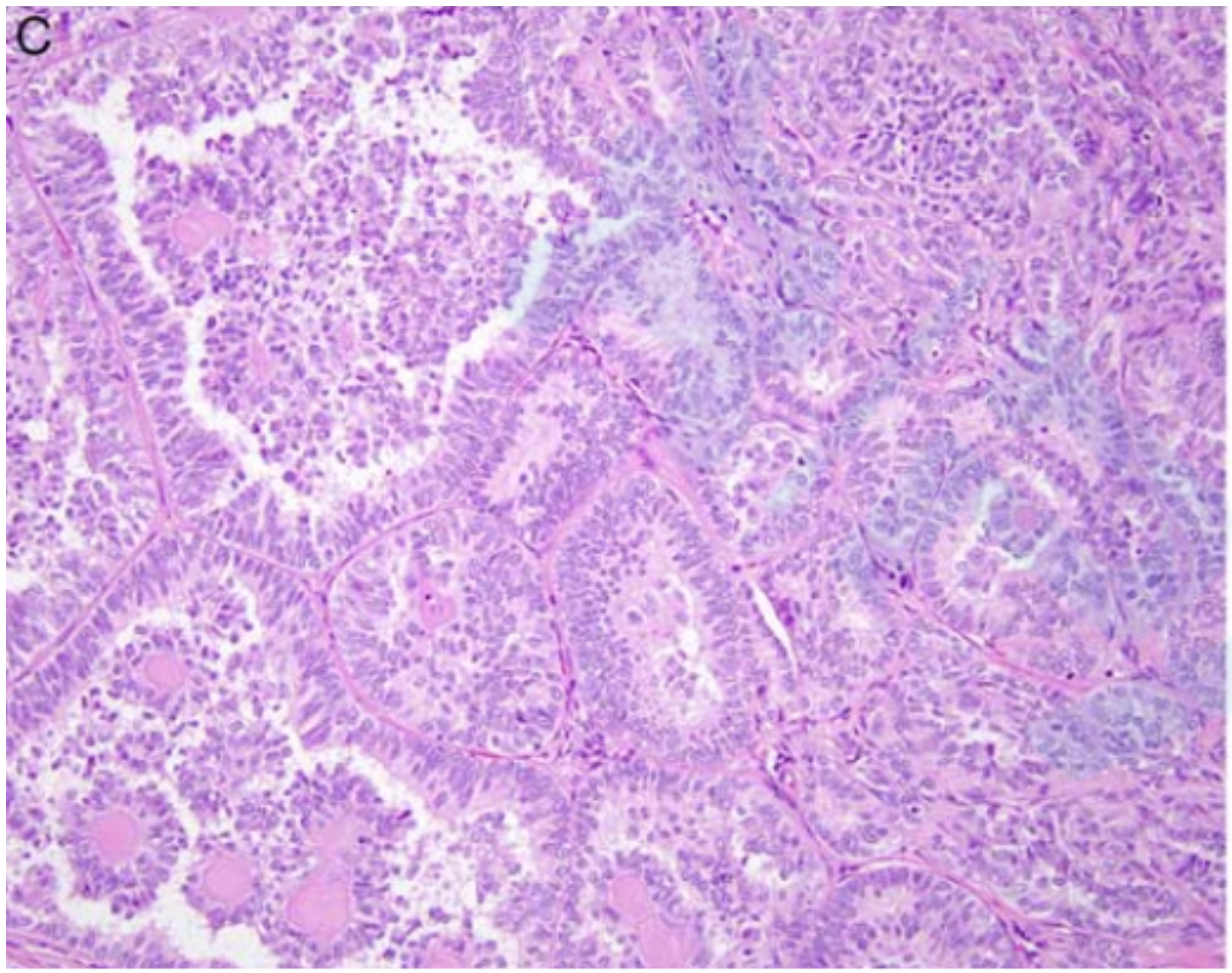
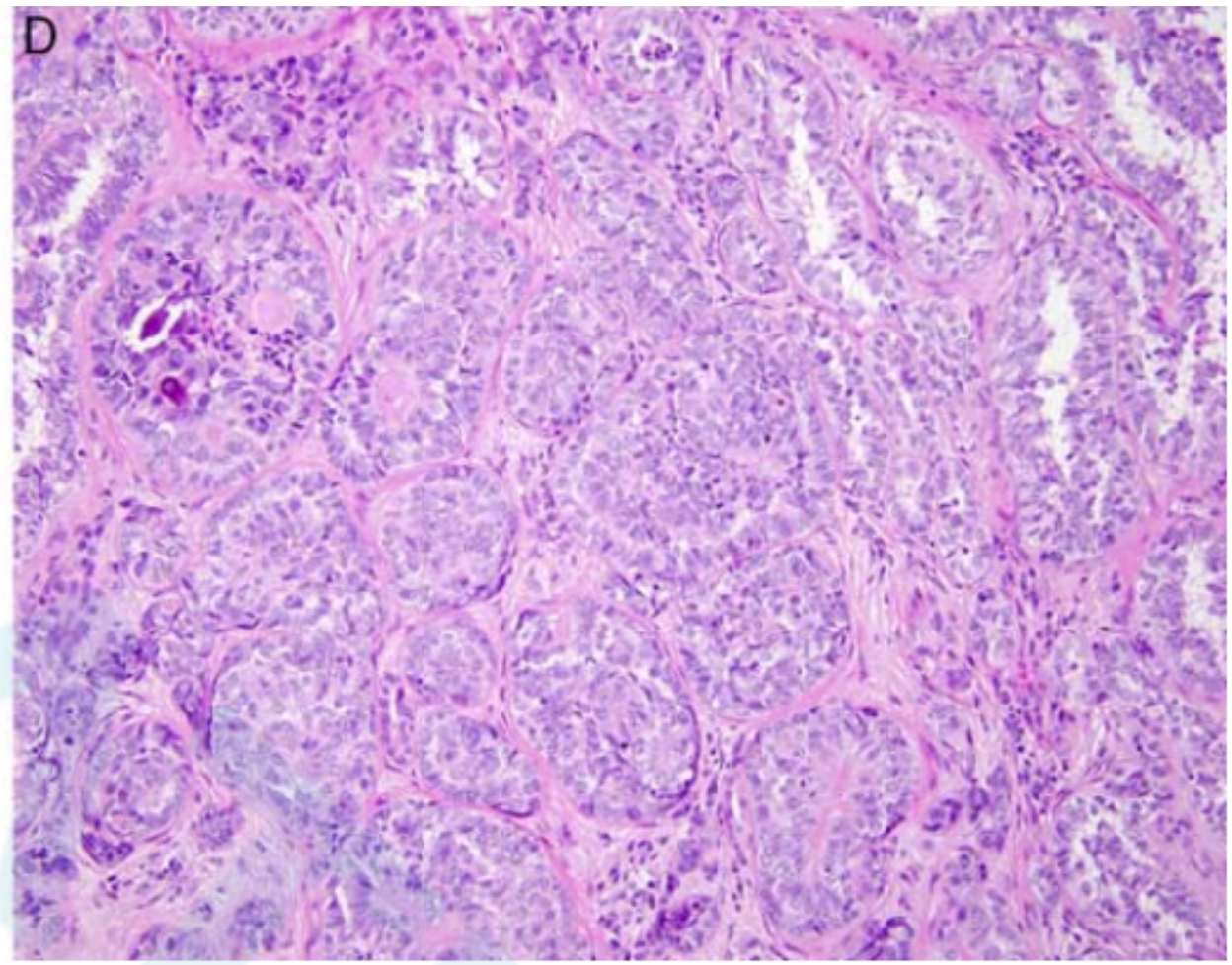


FIGURE 5. BHP RCC case #4. At lower power, one can appreciate the unencapsulated nature of the neoplasm that borders the native kidney at the right (A). At intermediate power, one can appreciate both the tubulopapillary pattern at the right and the solid tubular pattern at the left (B).

RESULTS





The tubulopapillary pattern demonstrates smaller cells clustered around basement membrane material in larger acini, yielding a glomeruloid pattern (C). The more solid areas feature sclerotic stroma in which there are tubules, more cribriform structures clustered around basement membrane material, and psammomatous calcification (D).

case 4

RESULTS

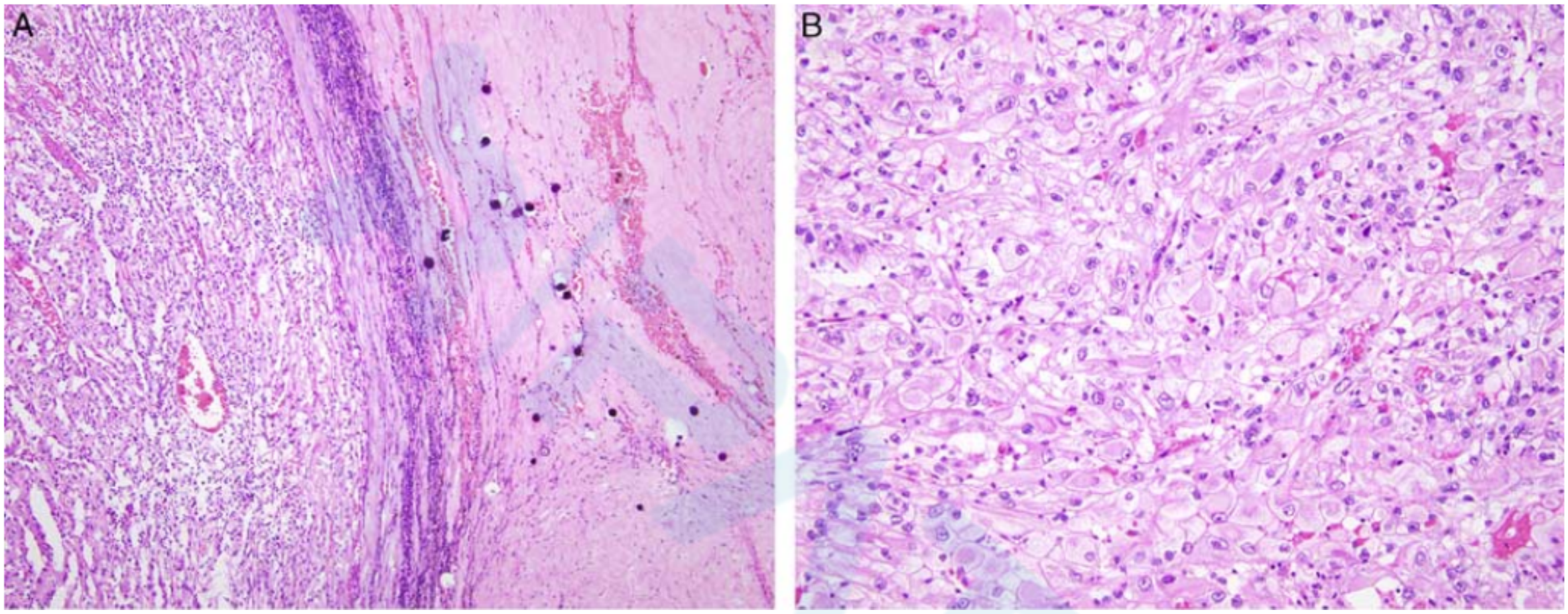
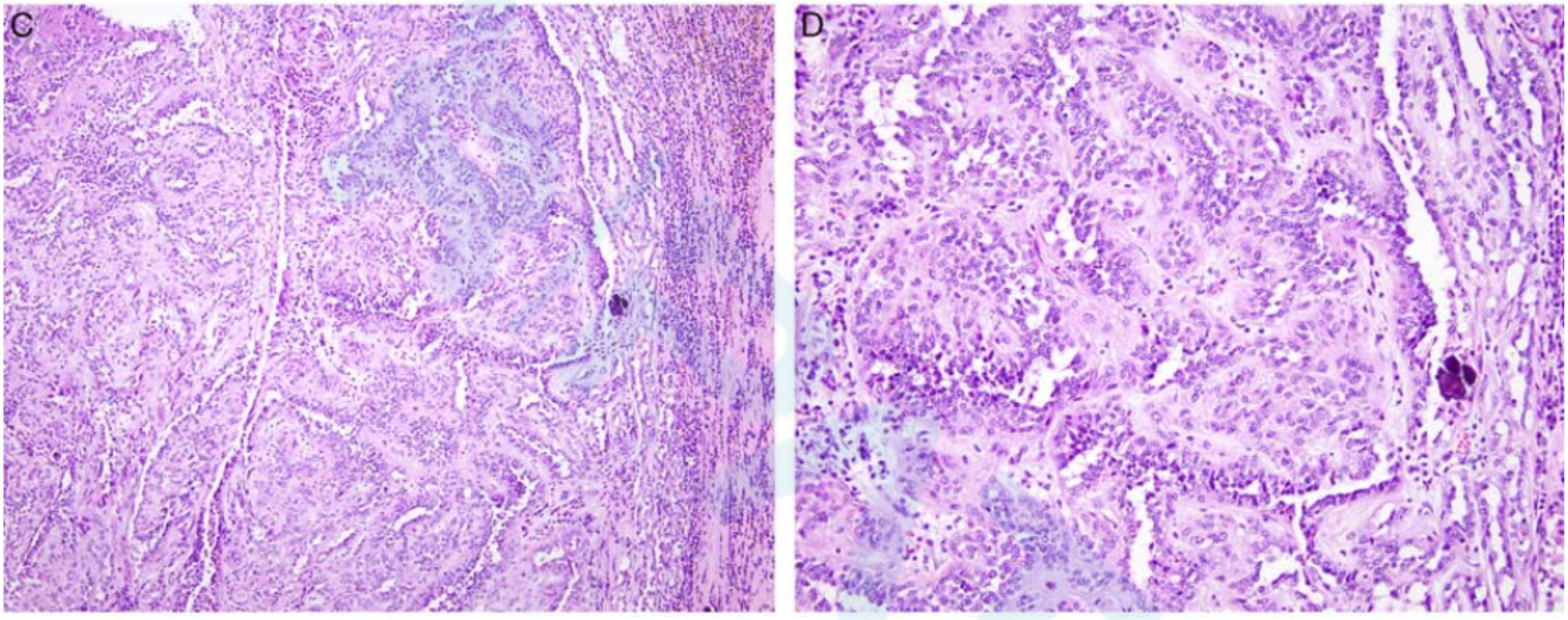


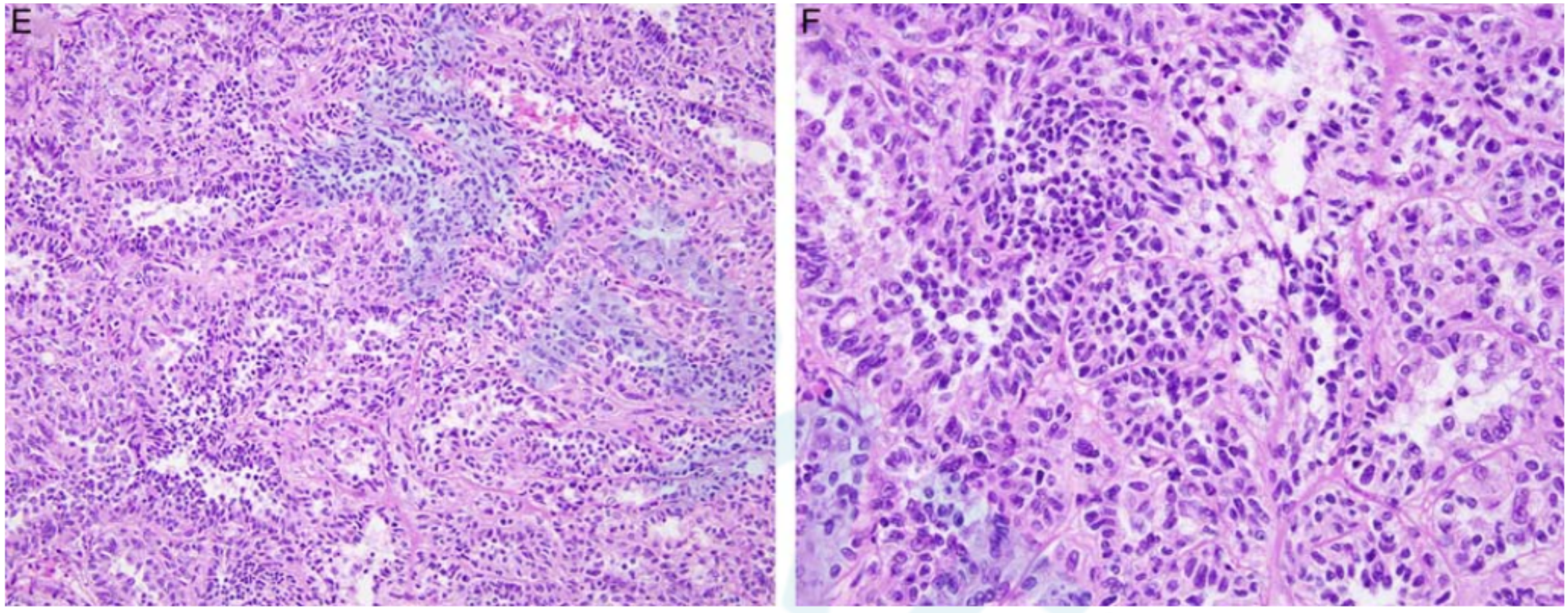
FIGURE 6. BHP RCC case #5. Much of this neoplasm had the appearance of an unclassifiable RCC. At low power, the neoplasm demonstrates hyalinization with prominent psammomatous calcifications to the right, and a clear cell appearance to the left (A). A higher power view of the clear cell area reveals a nondescript solid clear cell proliferation that would be difficult to distinguish from high-grade conventional clear cell RCC (B).

RESULTS



Other areas of the neoplasm demonstrate an anastomosing tubular pattern in the myxoid stroma that is reminiscent of MTSC (note the psammomatous calcification to the right of both figures) (C, D).

RESULTS



In other areas, one can appreciate tubular architecture and biphasic cytology (E). Higher power view of these areas reveals larger epithelioid cells with open chromatin and eosinophilic cytoplasm and smaller cells with condensed chromatin and minimal basophilic cytoplasm (F).

RESULTS

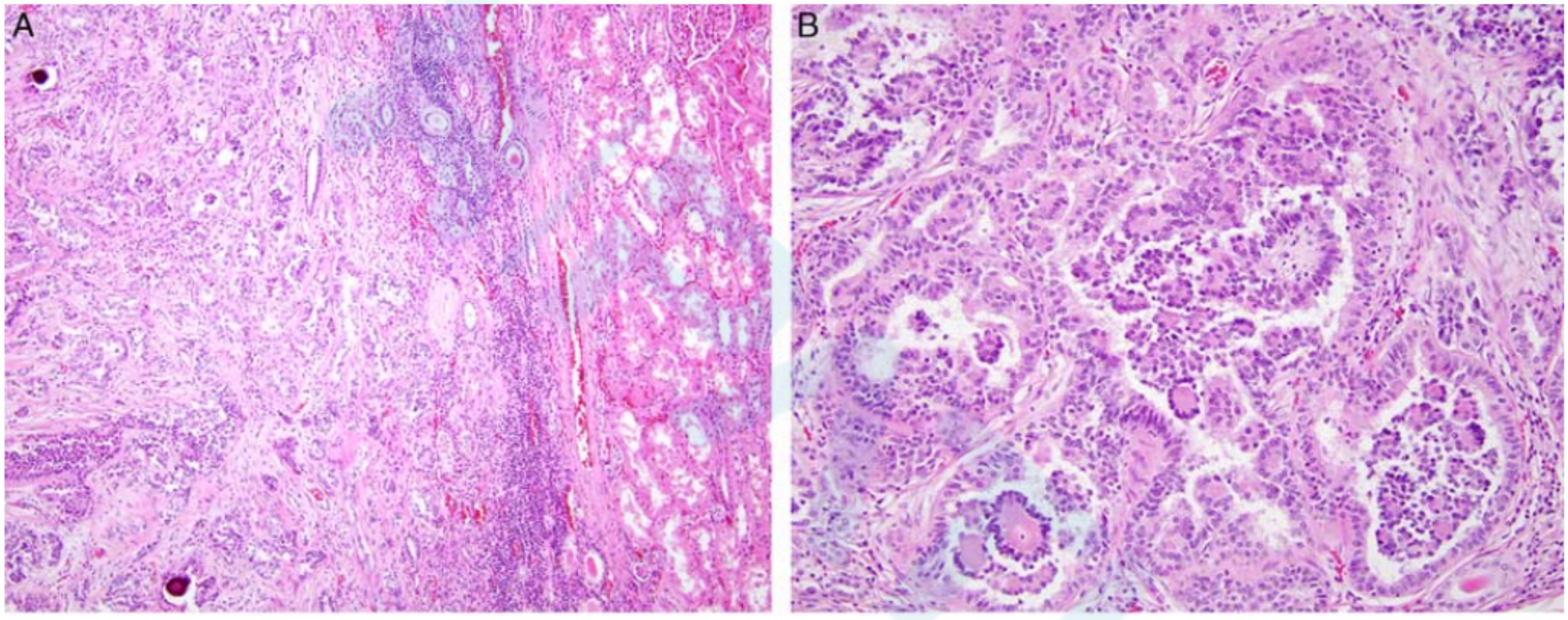
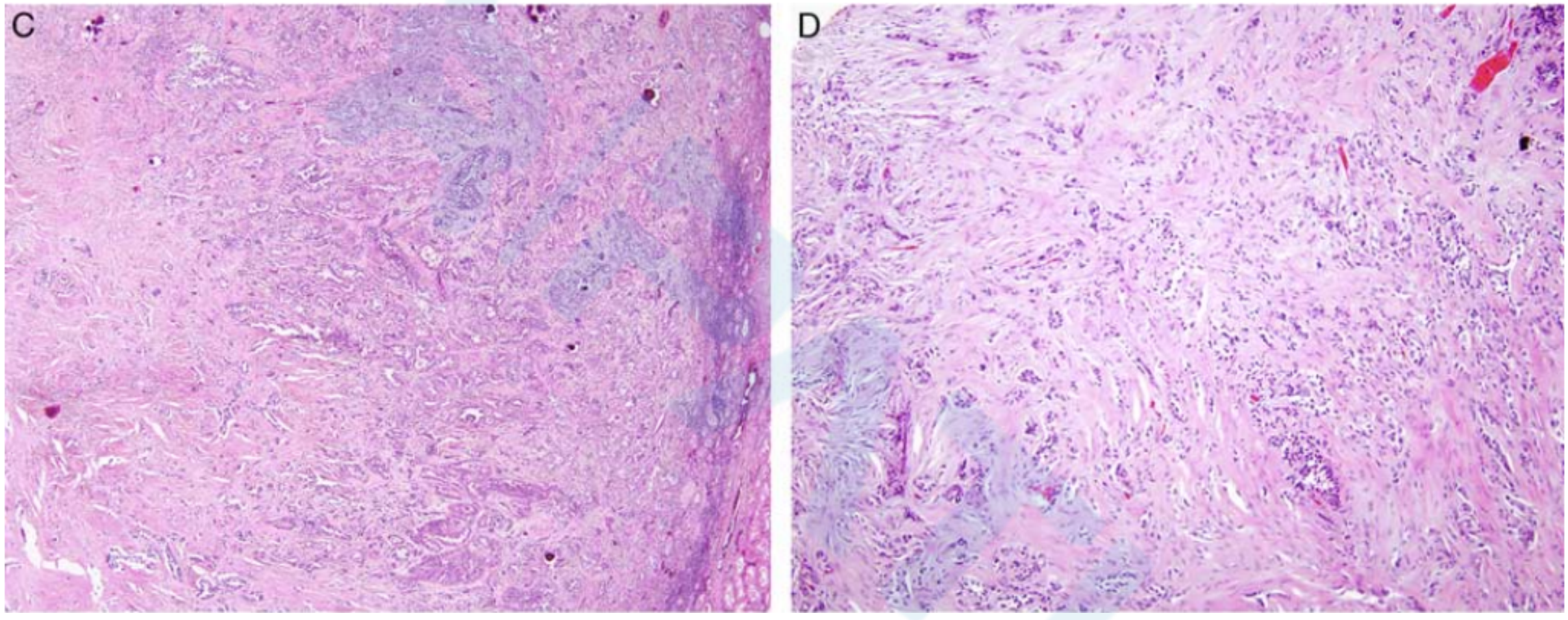


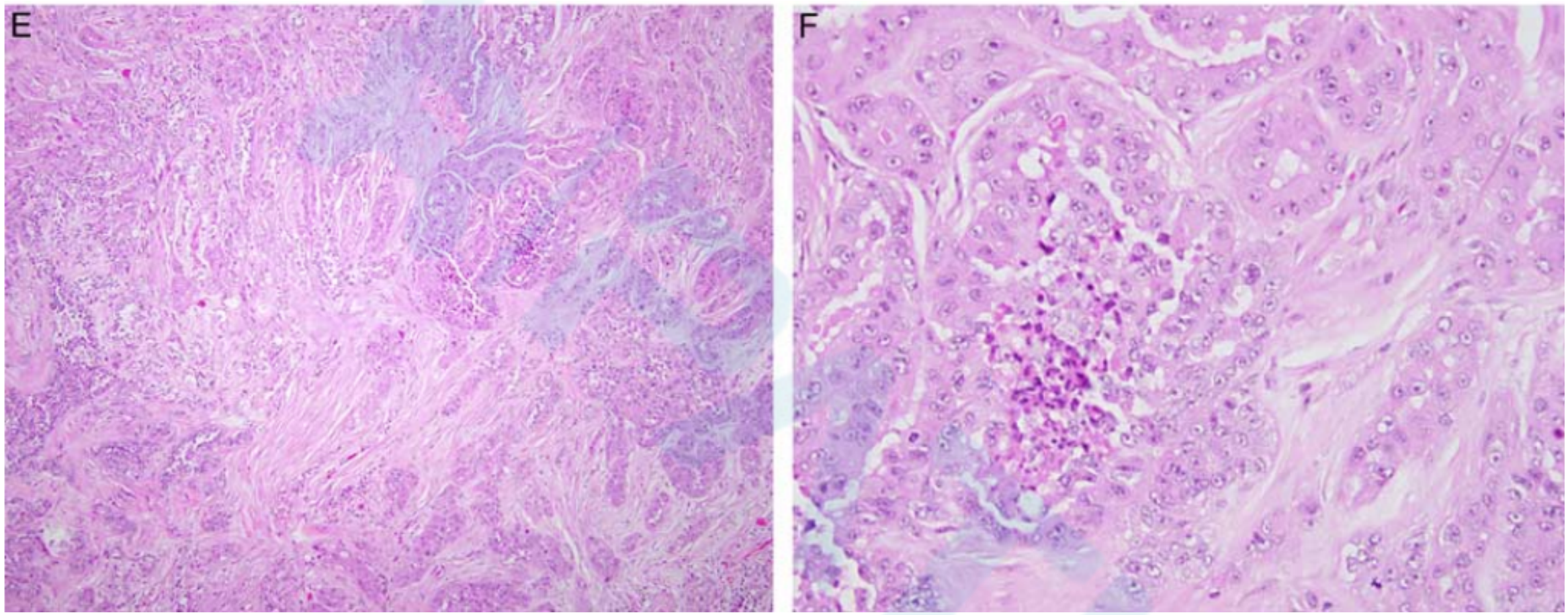
FIGURE 7. BHP RCC case #6. The neoplasm demonstrated an unencapsulated border with the native kidney to the right (A). The majority of the neoplasm demonstrates the typical biphasic appearance with small cells forming glomeruloid bodies within larger acini lined by larger cells (B).

RESULTS



Centrally, the neoplasm demonstrates extensive sclerosis (C). Neoplastic epithelium within this sclerotic and desmoplastic stroma has a cord-like and tubular appearance that raises the differential diagnosis of collecting duct carcinoma (D).

RESULTS



The more typical biphasic areas (left bottom) merge with areas having a more prominent eosinophilic cytoplasm (upper right) (E). The neoplastic cells in the latter areas have abundant eosinophilic cytoplasm, vesicular chromatin, and prominent nucleoli and are associated with necrosis (F).

RESULTS

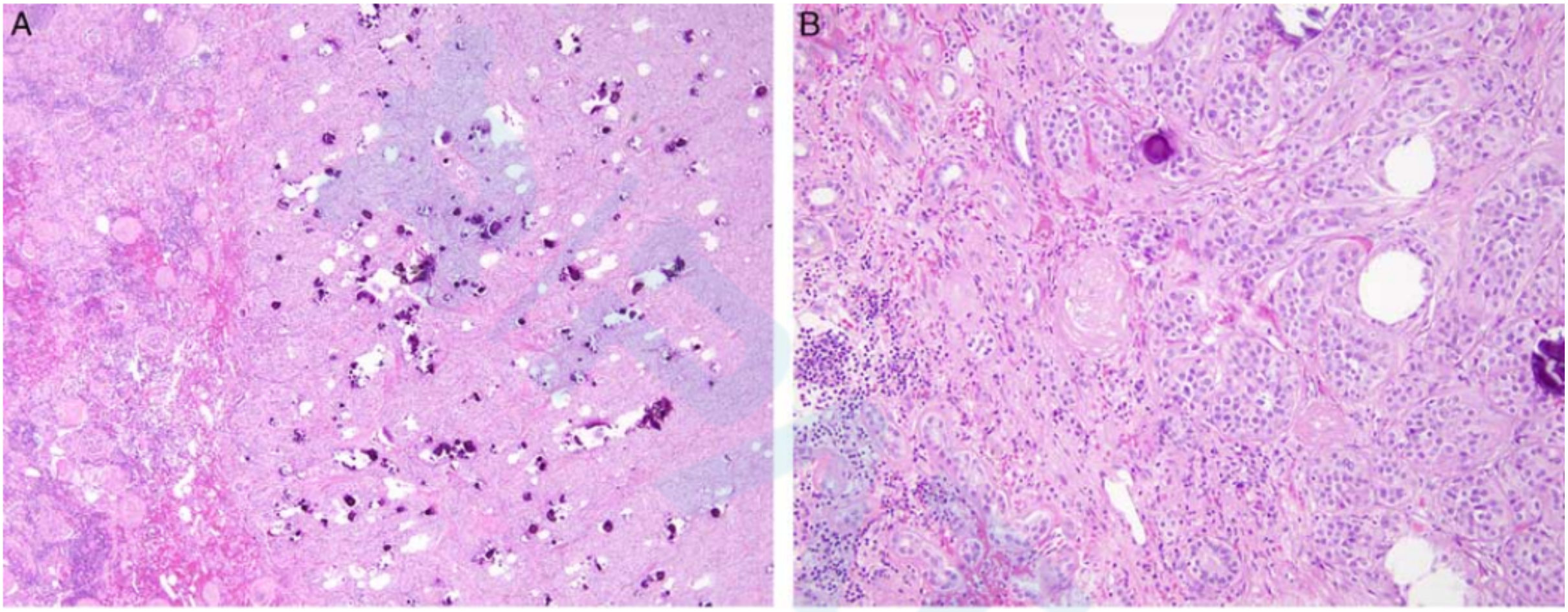
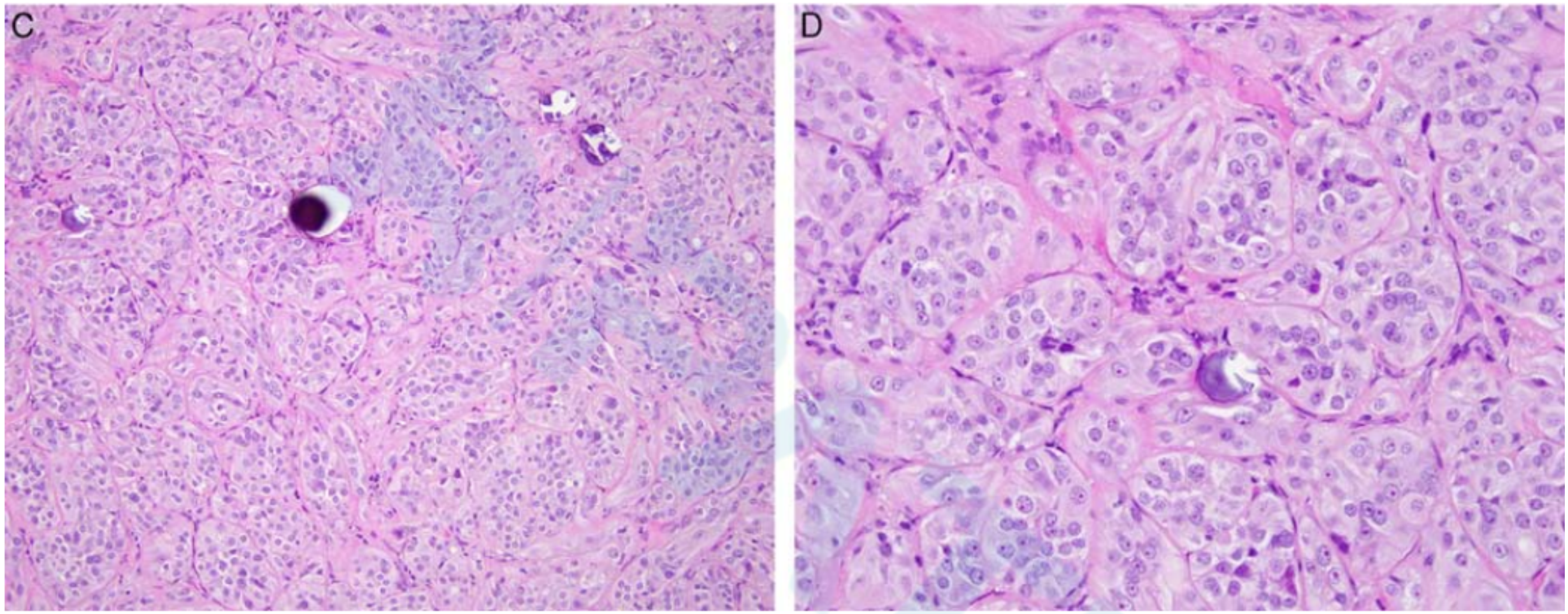


FIGURE 8. BHP RCC case #7. This neoplasm has an unencapsulated border with the native kidney. The dominant appearance is that of a solid tubular lesion with extensive psammomatous calcifications (A). The neoplasm intermingles among native renal elements at its border to the left (B).

RESULTS



At higher power, one can appreciate solid nests of neoplastic cells with vesicular chromatin, prominent nucleoli and abundant eosinophilic cytoplasm forming solid nests, frequently associated with psammomatous calcification (C, D).

RESULTS

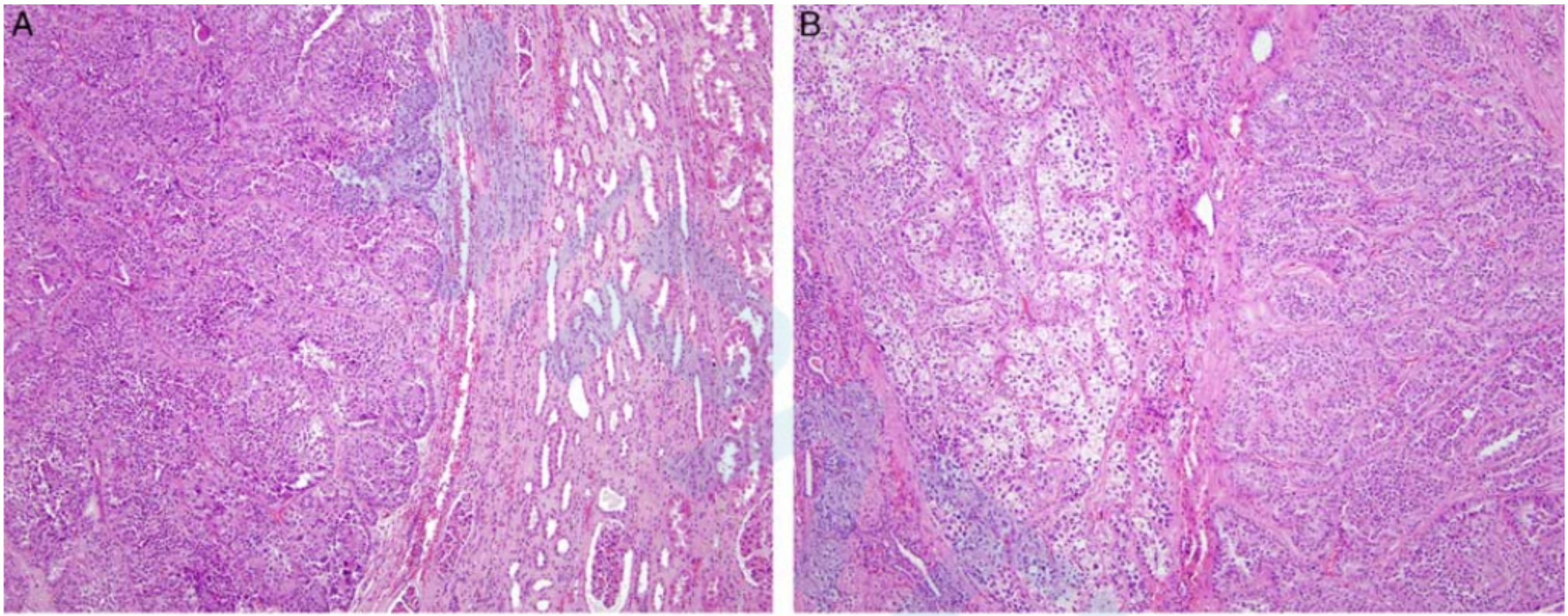
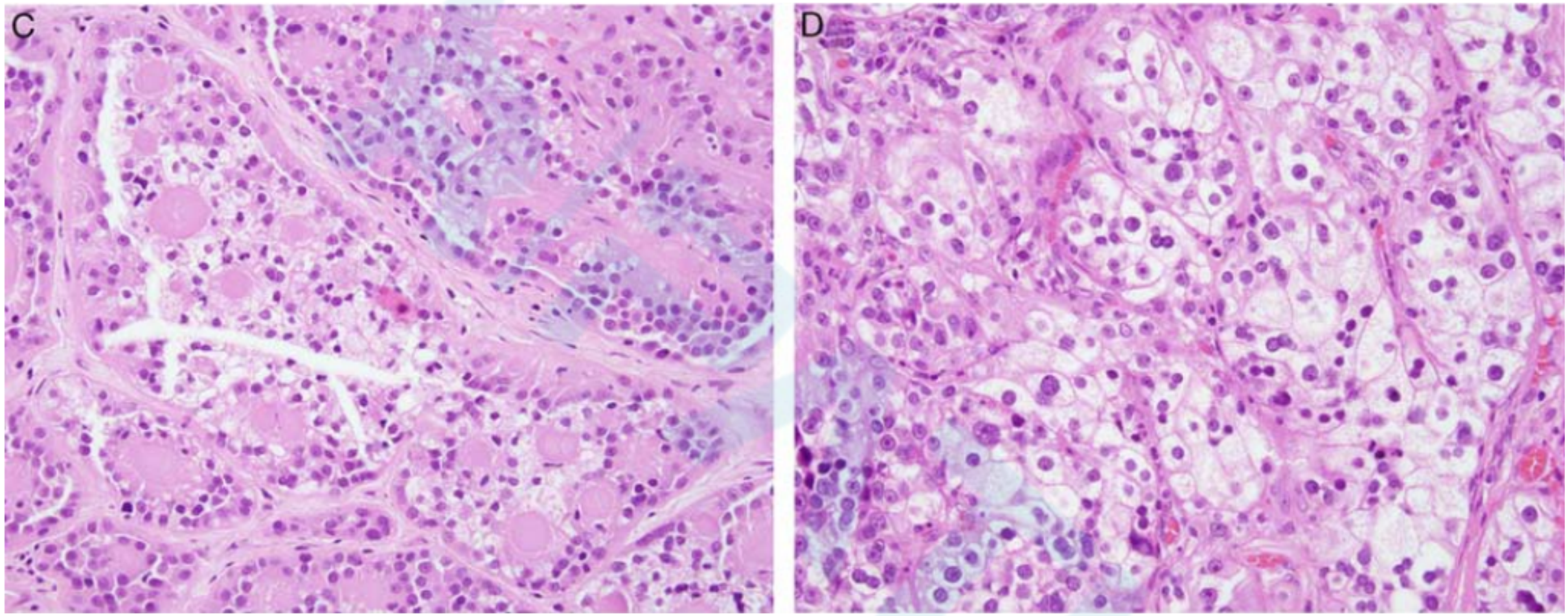


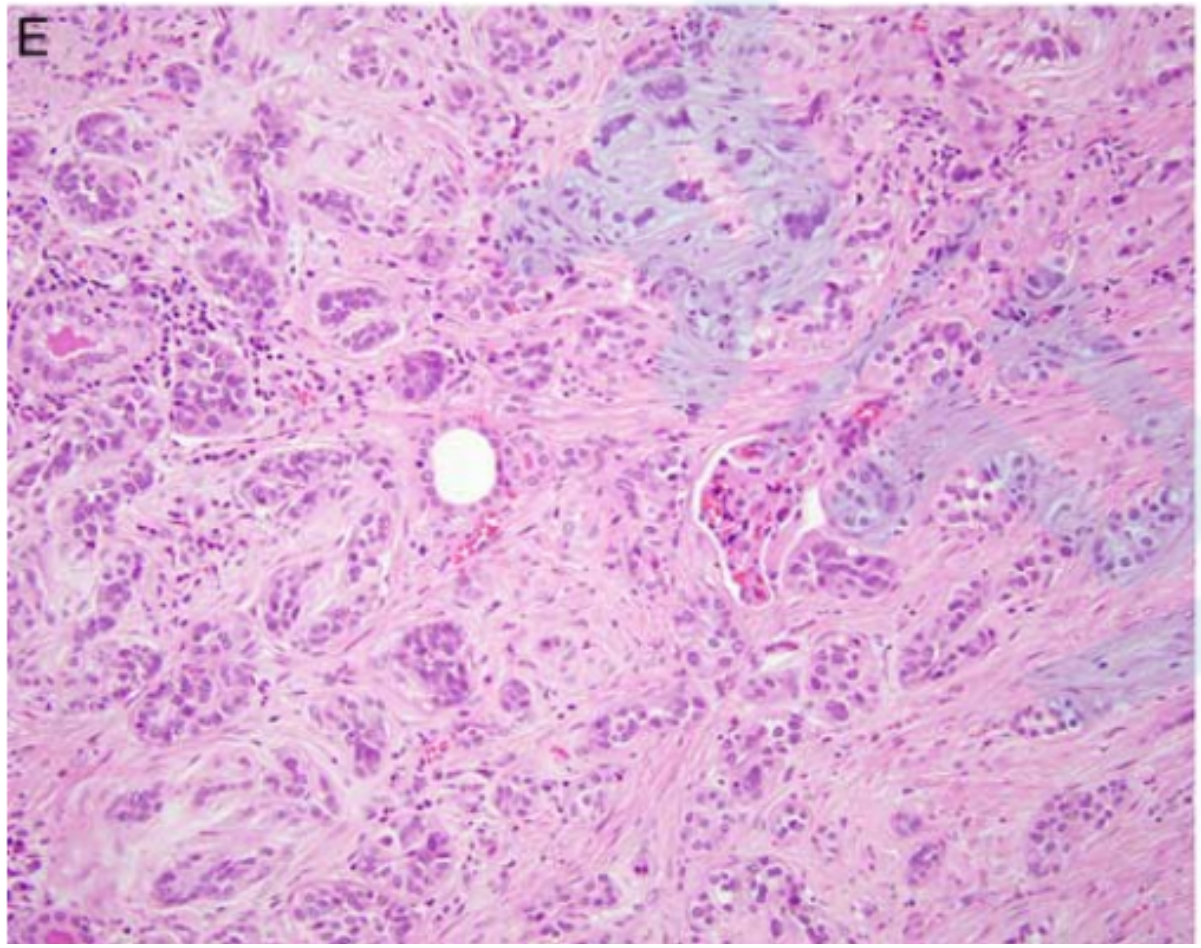
FIGURE 9. BHP RCC case #8. At low power, the neoplasm has a solid and papillary architecture and has an unencapsulated border with the native kidney to the right (A). The neoplasm has a biphasic appearance, with solid, tubular, and papillary areas to the right and a nested clear cell area to the left (B).

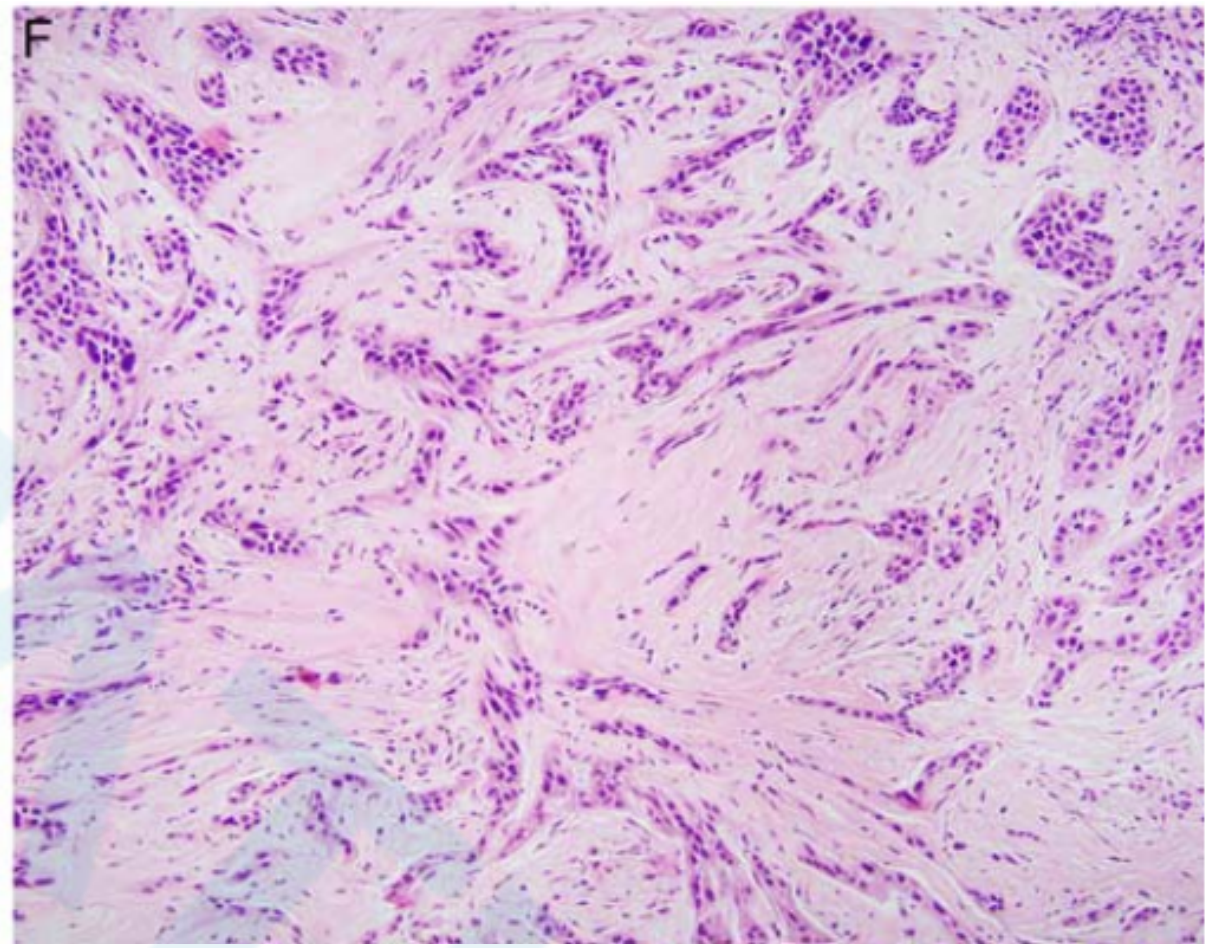
RESULTS



The solid papillary areas demonstrate the typical biphasic appearance with smaller cells clustered on basement membrane material and larger cells at the periphery (C). The solid clear cell areas are indistinguishable from clear cell RCC (D).

RESULTS





Other areas of this neoplasm demonstrated sclerotic and desmoplastic stroma, as cords and tubules of neoplastic cells permeate among renal native tubules and glomeruli (E). In other areas, the neoplastic cells form linear cords in a desmoplastic and sclerotic stroma (F).

RESULTS

TABLE 2. Morphologic Features of Cases

Case #	Slides	Capsule	Vaguely Nodular	Biphasic	Basement Membrane Nodules	Small Cell Spindling	Papillary	Glomeruloid Bodies	Sclerotic Stroma	Psammoma Bodies	Other
1	3	−/+	+	+	+	+	+	+	+	+	
2	3	−	+	+	+	+	+	+	+	+	Necrosis
3	1	NA	+	+	+	+	+	+	+	+	
4	2	−*	+	+	+	+	+	+	+	+++	Necrosis
5	3	+	+	+	Minimal	+	+	−	+	+++	Clear cells, pink cells, MTSC-like
6	2	−/+*	+	Minimal	+	Minimal	+	+	+	+	Pink cells, entraps tubules
7	4	−/+	+	+	++	−	−	−	+	+++	All tubular
8	2	−	+	+	++	−	+	+	+	+	Clear cells, entraps tubules

*−prominent peritumoral chronic inflammation.
+ indicates present; ++, well-developed; +++, prominent; NA, not available.

RESULTS

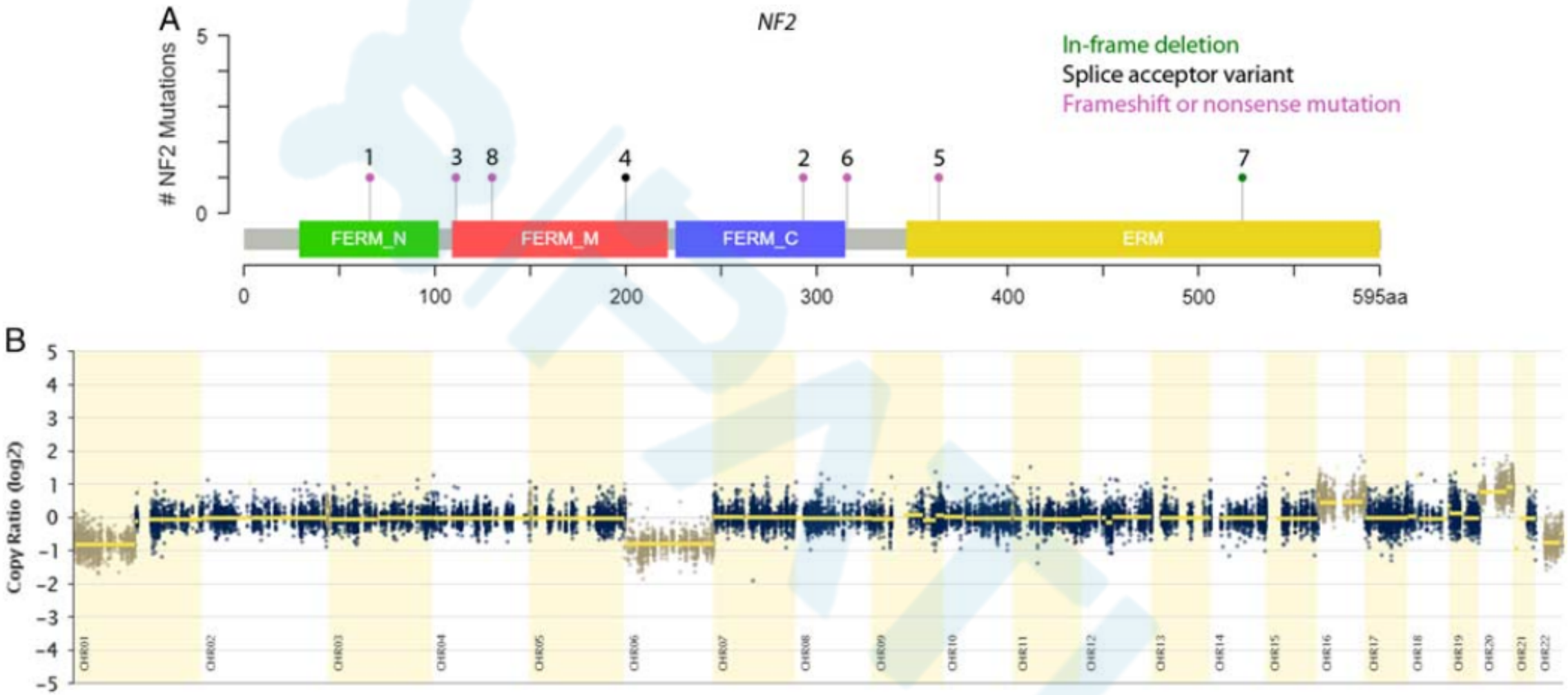


FIGURE 10. Recurrent molecular findings in BHP RCC. A, Lollipop plot of the NF2 gene (ENST00000338641, NM_000268) showing the distribution of alterations identified. Each mutation is plotted with the corresponding case number. In-frame deletion—green; splice acceptor variant—black; frameshift or nonsense mutation—magenta. B, CNV scatter plot of case #2 showing broad copy number alterations in chromosomes 1p, 6, 16, 20, and 22q.

DISCUSSION

- NF2基因：
  - ✓ 肿瘤抑制基因
  - ✓ 定位与22q12.2，由17个外显子组成
  - ✓ 编码蛋白Merlin，维持细胞骨架的稳定性，在细胞接触时抑制细胞增殖。
- ✓ NF2基因还可抑制Ras所介导的肿瘤恶性变。
- ✓ NF2基因的缺乏会导致钙粘蛋白介导的细胞连接的不稳定。

DISCUSSION

- NF2基因：
  - ✓ Inactivation of NF2 has been described in many tumor types.
  - ✓ Patients with neurofibromatosis type 2 syndrome are not known to develop RCCs at an increased frequency.
  - ✓ Five of our 8 NF2 mutant RCC demonstrated loss of chromosome 22q where NF2 resides, consistent with biallelic inactivation of this tumor suppressor gene.

DISCUSSION

TABLE 3. *NF2* Mutated Clear Cell RCC in TCGA PanCancer Atlas Database

Case	*NF2* Variant	Age/Sex	Tumor Size/ Stage	Morphology	Outcome	Other Notable Genetic Anomalies
TCGA-CJ-4901-01	R341*	47/male	14 cm/pT3b	Clear cell	Alive 47 mo	*VHL*, *MLH1*, *BAP1* deletions; loss of 3p: partial gain of 5q
TCGA-CJ-4638-01	X172_splice	46/male	15 cm/ pT3aN1M1	Clear cell	DOD 14 mo	*VHL*, *BAP1* mutations; *CDKN2A* deletion; partial loss of 3p: partial gain of 5q
TCGA-B8-4153-01	D494N	74/male	5 cm/pT3a	Clear cell	Alive 25 mo	*VHL*, *ARID1B* mutations; *PBRM1* deletion; partial loss of 3p
TCGA-B8-5098-01	X200_splice	53/female	4 cm/pT1	Unclassified, rhabdoid features	Died 52 mo (ESRD)	*CDK12*, *NF1*, *TP53*, *MLH1*, *APC*, *EP400*, *SMARCA4* mutations: partial loss of 3p
TCGA-B0-5084-01	X121_splice	33/male	8 cm/pT3N1M1	Unclassified, possibly clear cell	DOD 7 mo	*NSD1*, *NOTCH1* mutations
TCGA-B0-4698-01	X81_splice	75/male	10.5 cm/pT4	Unclassified with rhabdoid features	DOD 1 mo	*KRAS*,*TP53*, *ARID3A*, *EP300* mutations

*Stop codon.
ESRD indicates end-stage renal disease.

DISCUSSION

TABLE 4. *NF2* Mutated Papillary RCC in TCGA PanCancer Atlas Database

Case	*NF2* Variant	Age/Sex	Tumor Size/ Stage	Morphology	Outcome	Other Notable Genetic Anomalies
TCGA-BQ-5875	Y132*	68/female	13 cm/pT3a	Oncocytic, reverse polarity	Alive 36 mo	*SETD2*, *STAG2* mutations; probable 16q and 17q gain; 22q loss
TCGA-EV-5902	R359Kfs*11	58/male	3 cm/pT1N0	Biphasic, hyaline nodules	Alive 19 mo	Probable 5, 16, 20 gain
TCGA-SX-A7SL	G151Vfs*23	7/male	4 cm/pT1	Biphasic hyaline nodules	Alive 27 mo	Probable 16,17q,20 gain; 6 loss
TCGA-Y8-A896	D277Gfs*20	62/male	6 cm/pT3aNX	Unclassified but suggestive of biphasic morphology	Alive 18 mo	Probable 7 gain; 6, 9, 15q, 22q loss
TCGA-G7-6797	X200_splice	46/male	2.6 cm (multifocal)/ pT1a	Solid papillary NOS	Alive 25 mo	*BAP1*, *MSH2*, *FANCD2*, *BCL11B* mutations; probable 16, 20 gain and 1, 6p, 22q loss
TCGA-BQ-5877	K171*	60/male	3 cm/pT3aN1M1	Papillary NOS	DOD 8 mo	*SETD2*, *BAP1* mutation; *CDKN2A/B* deletion; probable 12 gain and 1p,3p,11,18, 22q loss
TCGA-GL-7966	L295Rfs*14	28/female	6.5 cm/pT3N1	Tubulopapillary NOS	Alive 3 mo	*FH* and *B2M* nonsense mutations; probable partial 6p gain and 1p, 4, partial 5p, 10, 13q, 15q, 18,22q loss
TCGA-P4-A5EA	X270_splice	54/female	8 cm/pT3N1	Papillary NOS	DOD 6 mo	*CREBBP*, *MAP3K1*, *RASA1*, *BCOR* nonsense or frameshift mutations
TCGA-B1-A47M	P134H	79/male	4.5 cm/pT3a	Papillary NOS	Alive 21 mo	*SMARCB1*, *NIFE2L2*, *ERRFI1*, *TET1* mutations; probable 7 gain

*Stop codon.
DOD indicates dead of disease; NOS, not otherwise specified.

Differential Diagnosis

- ✓ Papillary RCC
- ✓ Collecting Duct Carcinoma
- ✓ MiTF Family Translocation Renal Cell Carcinoma
- ✓ Gonadal Sex Cord-Stromal Tumors
- ✓ Wilms Tumor

SUMMARY

We report a novel, morphologically distinctive subtype of RCC associated with NF2 mutations. The latter suggests the potential for targeted therapy.

THANK YOU