

# Borderline Mucinous Neoplasm of the Renal Pelvis with Osseous Metaplasia

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**Abstract:** Primary mucinous cystic tumours of the renal pelvis are extremely rare neoplasms. Herein, we describe the case of a 63-year-old man with a chronic history of nephrolithiasis, presented with long-standing flank pain and progressive abdominal distension. Radiological investigations demonstrated a multicystic, lobulated lesion extensively involving the left kidney. The laparoscopic nephrectomy specimen showed a mucin-containing multicystic tumour that involved the renal pelvis and medulla. Histologically, the cystic spaces were lined with stratified, multi-layering, mucin-containing columnar neoplastic epithelium with no evidence of an invasive growth pattern into the kidney parenchyma. An osseous metaplasia was evident in the tumour. A pathological diagnosis of a borderline mucinous tumour arising from mucinous metaplasia of the renal pelvis was rendered. No adjuvant therapy was given. The patient showed no evidence of recurrent or metastatic disease 58 months after surgery. This case highlights clinical and radiological diagnostic difficulties and contributes to the histopathological spectrum of an extremely rare kidney tumour.

**Keywords:** Mucinous tumours, cystic, borderline, renal pelvis, osseous metaplasia, kidney

## 1. Introduction

Urothelial carcinoma is the most common tumour of the renal pelvis. Other tumours of the renal pelvis include squamous cell carcinoma, adenocarcinoma and large and small cell neuroendocrine carcinoma. Adenocarcinomas are rare, account for <1% of renal pelvic tumours [1], and are believed to be associated with and arise from pyelitis cystica/pyelitis glandularis and glandular/intestinal metaplasia of the urothelial lining of the renal pelvis [2-4]. Adenocarcinoma of the renal pelvis exhibits different morphogenesis that includes adenocarcinoma with enteric (intestinal) features, tubulovillous, papillary non-mucinous, signet-ring, mucinous non-cystic and cystic mucinous types [5]. While primary invasive mucinous non-cystic adenocarcinomas have been sufficiently described in the literature [1], mucinous cystic neoplasms (MCNs) of the renal pelvis still exceedingly rare [4]. Similar to MCNs in other organs, these tumours can be malignant [6], borderline [4, 7] or benign [8]. We present the case of a 63-year-old man with a borderline MCN of the renal pelvicalyceal system originating from an extensive intestinal metaplasia of the urothelial lining of the renal pelvis secondary to long-standing nephrolithiasis. We describe the clinical, radiological and histopathological findings of this rare tumour, discuss its pathological differential diagnosis and review the literature.

## 2. Case Report

A 63-year-old man, known case of long standing type II diabetes mellitus, hypertension, dyslipidemia, bilateral

nephrolithiasis with severe obstructive uropathy, hydronephrosis and chronic renal failure, presented with a long-term history of flank pain and progressing abdominal distension. There was no history of haematuria or mucusuria. The physical examination was remarkable for left-sided flank tenderness. Abdominal ultrasonography, non-enhanced computed tomography (CT) scanning and magnetic resonance imaging (MRI) demonstrated multiple, bilateral, renal stones and cystic dilatation of the collecting system, severe hydronephrosis in the right kidney and extensive involvement of the left kidney by a multicystic, lobulated lesion in the renal pelvis and medulla, measuring 25 x 30 cm in two dimensions (Figure 1). Foci of parenchymal calcification were seen in both kidneys and in the left-sided cystic lesion. There was no evidence of a solid component or an invasive growth pattern. No lymphadenopathy or focal lesions in other abdominal organs were radiologically seen. The favoured radiological diagnosis was bilateral medullary cystic disease / medullary sponge kidney. The patient underwent left laparoscopic nephrectomy.

Grossly, the specimen consisted of a fragmented kidney with variably-sized, mucin- and blood-containing cystic spaces, extensively involving the renal pelvis and medulla, and rimmed by a compressed renal cortical tissue (Figure 2A). The inner lining of the cystic spaces was smooth in some areas and rubbery, variegated with variably-sized papillary structures in other areas (Figure 2B). Evaluation of the integrity of the renal capsule and the hilar vascular and ureteric resection margins was not possible due to the fragmented nature of the specimen.

Sections from the tumour were fixed in 10% buffered formalin, paraffin-embedded, sectioned at 5 µm, mounted on coated glass-slides and stained by routine haematoxylin and eosin stain. A panel of diagnostic immunohistochemical (IHC) stains was performed (Table 1). All immunoassays were performed according to the manufacturer's guidelines, using an automated platform (Ventana Benchmark XT, Tucson, AZ, USA), and heat antigen retrieval by ultracell condition solution PH 8.4. An ultra view universal DAB detection kit was used for reaction visualisation. Proper positive and negative controls were utilised for all special and IHC stains.

Histopathological examination showed borderline MCN of the renal pelvicalyceal system. The tumour extensively involved the renal pelvis and calyces, and consisted of variably-sized, multicystic, spaces that were surrounded by a variable amount of a plasma cell-rich, non-ovarian-type connective tissue stromal component. The inner lining of the cysts consisted of a single-cell layer and multi-layered neoplastic columnar epithelial cells that exhibited villo-papillary configurations and invaginations (Figure 3A & 3B). These neoplastic cells were moderate in size, showed a mild to moderate degree of pleomorphism and have hyperchromatic and vesicular nuclei, small nucleoli, amphophilic cytoplasm, and visible cell membranes. In the monolayer lining epithelium, the nuclei appear basally located. Focal cytoplasmic pale eosinophilia was noted. Abundant, predominantly apical, intracytoplasmic periodic acid Schiff and Alcian Blue-positive mucin content was evident in most cells (Figure 3C). Focal intracytoplasmic hyaline globules were noted (Figure 3D). Focal strips of neoplastic cells exhibited significant nuclear hyperchromasia, depletion of intracytoplasmic mucin content and increased nuclear-to-cytoplasmic ratio were identified (Figure 3E). No neoplastic cells with signet-ring morphology were identified. Scattered mitoses were noted, but no atypical mitotic figures were seen. Strips of glandular cells localised between attenuated urothelium were identified, representing metaplastic changes. No squamous metaplasia was seen. Abundant extracellular mucin, devoid of a neoplastic epithelial component, was present in the cystic spaces and connective tissue septae. Foci of extensive calcification and areas of osseous metaplasia were noted (Figure 3F). Meticulous examination showed no evidence of an epithelial or mucinous invasive component into the surrounding kidney parenchyma, or extra capsular extension or tumour extension into the renal sinus fat. There was no lymphovascular or perineural invasion. Two unremarkable lymph nodes were histologically identified.

Immunohistochemically, the neoplastic cells exhibited positive cytoplasmic and membranous staining for pan cytokeratin (CK), CK7 (Figure 4A), CK19, CK20 (Figure 4B), epithelial membrane antigen (EMA), carcinoembryonic antigen (CEA) (Figure 4C), BER-EP4 and CD10 (Figure 4D). Nuclear positivity for CDX2 (Figure 4E) and the KI-67 proliferation index (Figure 4F) was evident in >90% and approximately 25-30% of the neoplastic cells respectively. IHC for CA19-9, CA125, α-methylacyl-CoA racemase, PAX-8, vimentin and p53 was negative. IHC evaluation of MLH1, MSH2, MSH6 and PMS2 mismatch repair proteins

(MMR) demonstrated intact nuclear expression in neoplastic cells (not shown).

The uninvolved kidney showed histological features compatible with nodular diabetic nephropathy with severe interstitial fibrosis and tubular atrophy, significant arteriolar sclerosis and hypertensive arterial sclerosis.

The post-operative clinical course was uneventful. No adjuvant therapy was given to the patient after surgery. Fifty-eight months after nephrectomy, the patient was alive and a post operative bone scan, periodic chest and abdominal CT scans and MRIs demonstrated no evidence of recurrent disease.

### 3. Discussion

The urothelial lining of the renal pelvis can undergo phenotypical changes in the form of squamous or glandular metaplasia, typically in reaction to chronic irritation secondary to infection or nephrolithiasis. These metaplastic changes can be precancerous. Glandular neoplasms of the renal pelvis, including MCNs are believed to develop from the progressive transformation of the metaplastic epithelium in a stepwise carcinogenic (dysplasia-carcinoma) sequence [2]. Primary MCNs of the renal pelvicalyceal system are rare [9]. Similar to MCNs in other organs such as the ovary, pancreas and vermiform appendix, these tumours exhibit a heterogenous morphogenesis that ranges from simple benign mucinous cystic adenoma to invasive mucinous cystic carcinoma invading the renal parenchyma and associated with pseudomyxoma peritonei and distant metastasis [1, 4, 6-11]. To date, including the current case, only 5 cases of borderline MCN have been reported [4, 7, 12, 13]. Analysis of the literature demonstrates confusion in classification and the lack of diagnostic criteria of MCNs of the renal pelvis. While the diagnosis of malignancy requires histopathological examination of extensive sampling to identify an invasive component of the tumour into the renal parenchyma, the distinction between mucinous cystadenomas and borderline MCNs is blurred and both diagnostic terminologies are used in an interchangeable manner. Contrary to ovarian MCNs, it is not clear how the degree of nuclear atypia and pleomorphism, mitotic activity, and the complexity and degree of the villo-papillary growth pattern of the intracystic glandular proliferation can be applicable in separating benign cystadenomas from borderline tumours (tumours of low malignant potential) and intraepithelial/intracystic carcinomas [14]. For instance, the diagnosis of mucinous cystadenoma of the renal pelvis was designated to tumours with a single cell layer of mucin-containing neoplastic epithelial cells [15] as well as tumours with epithelial stratification and papillary projections configurations [16]. On the other hand, MCNs lined by a single layer of columnar epithelium with scattered goblet cells and focal papillary structures without intracystic epithelial complexity or stromal invasion were labelled as mucinous cystadenocarcinoma [17]. Furthermore, Roa et al. [4] diagnosed a case of mucinous borderline tumour, which one year later was complicated by pseudomyxoma peritonei; most of the tumour was lined with a simple mucinous epithelium and only <5% of the tumour epithelial lining showed nuclear stratification. In our case, the tumour

showed significant epithelial multi layering and focal nuclear pleomorphism without stromal invasion renders the diagnosis of a borderline MCN of the renal pelvis.

An intriguing histopathological finding in the current case was the presence of well-developed osseous metaplasia (OM). The pathogenesis of OM is not clear, but mucin, stromal and cellular inflammatory mediators and growth factors are considered to be relevant factors [18]. Osseous metaplasia was described in various mucin-producing tumours such as tumours of the appendix [18], colon [19], rectum [20], pancreas [21] and ovary [22]. To the best of our knowledge, the current case is the first case of MCN of the renal pelvis with OM.

CDX2 is a homeobox gene that encodes an intestine-specific transcription factor, which is important in the development and differentiation of the intestine and expressed in the nuclei of small and large intestinal epithelial cells [23, 24]. While CDX2 is a sensitive marker for intestinal phenotype and expressed in the vast majority of intestinal neoplasms, it is also expressed in various epithelial tumours, including ovarian mucinous adenocarcinomas and adenocarcinomas of the urinary bladder [23, 25]. Furthermore, CDX2 expression in intestinal metaplasia of the urinary bladder is well documented [26]. While the borderline MCN of the renal pelvis described by Rao et al. [4] showed no IHC positivity for CDX2, our case demonstrated nuclear positivity in >90% of the cases, which is in keeping with the intestinal immunophenotype; we believe that this is the first documentation of CDX2 expression in this tumour.

Microsatellite instability (MSI) is a form of genetic instability that results from a defect in DNA mismatch repair (MMR) genes such as *MLH1*, *MSH2*, *MSH6* and *PMS2*, and can occur in tumours of many organs [27]. This genetic hypermutability has been described in various mucin-producing tumours including colonic [28], appendiceal [29], pancreatic [30] and ovarian [31] tumours. In our case, IHC analysis of MMR proteins demonstrated an intact nuclear expression in the neoplastic cells, indicating a lack of MSI.

The cystic nature of MCNs distinguishes them from adenocarcinomas with enteric features, signet-ring adenocarcinomas and mucinous non-cystic carcinomas, which exhibit widespread and destructive invasion into the renal parenchyma. In addition, it is important to differentiate borderline MCNs from mucinous cystic adenocarcinoma, which share similar histological features with borderline tumours but show invasion into the renal parenchyma; extensive histological examination of a thorough sampling of a borderline MCN is needed to exclude foci of invasion.

Reported borderline MCNs of the renal pelvis [4, 7, 12, 13] affected both sexes equally and the patients' ages ranged between 52 and 69 years (median 62 years). Similar to our patient, all patients had nephrolithiasis. Clinical presentation included flank pain and swelling, dysuria, haematuria, mucusuria, chills and fever. Our patient presented with flank pain and abdominal swelling, but there was no history of haematuria or mucusuria. Radiological diagnostic modalities, including abdominal ultrasonography, intravenous pyelography, CT scanning and magnetic

resonance imaging, might not differentiate MCNs from other renal cystic lesions [6], and the diagnosis of MCNs is usually made from surgically resected specimens [1]. Because local recurrence can result from the downward seeding and surgical spillage of tumour cells, radical nephrectomy and complete ureterectomy is the recommended treatment of suspected MCNs of renal pelvis [1, 6]. In the current case, the diagnosis of non-neoplastic cystic lesion was preferred; thus the patient underwent laparoscopic nephrectomy, which resulted in a fragmented surgical specimen and suboptimal gross examination and prevented histological assessment of the ureteric resection margin. The possibility of mucin and neoplastic cell spillage and local recurrence could not be dismissed. However, 58 months after surgery, the patient showed no evidence of local recurrence, distant metastasis or new onset lesion in other abdominal organs, which is in keeping with the indolent clinical course of the tumour and confirms the renal pelvis as the primary location.

#### 4. Conclusion

In summary, we reported a rare case of borderline MCN of the renal pelvis with OM and nuclear expression of the CDX2 transcription factor, which was diagnosed after laparoscopic nephrectomy. Mucinous tumours of the renal pelvis should be radiologically considered in the differential diagnosis of renal cystic diseases and treated with radical nephrectomy and ureterectomy, and adequate precautions to prevent spillage and implantation of tumour cells should be practiced. Reporting of MCNs of the renal pelvis should certainly help with understanding the pathogenesis and biological behaviour, establishing proper histological classification and suggesting a follow-up on and surveillance of these rare tumours.

#### 5. Authors Contribution

Ms. Maram S. Al Turki & Ms. Areej R. Alqahtani: Clinical data collection and writing the manuscript. Dr. Noura Aloudah, Dr. Reem Al Zahrani and Dr. Deena T. Boqari: Reviewing the pathology, obtaining images for publication and editing the pathology text.

Dr. Khaled O. Alsaad: Histopathological analysis and diagnosis, and writing the manuscript.

#### 6. Conflict of Interest

The authors disclose no financial interest in the products or companies described in this article. No funding or financial support was granted for this manuscript.

Conflict of interest: None

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**Tables**

**Images**

**Table 1:** Primary Antibodies Used for IHC, their Clone and Source

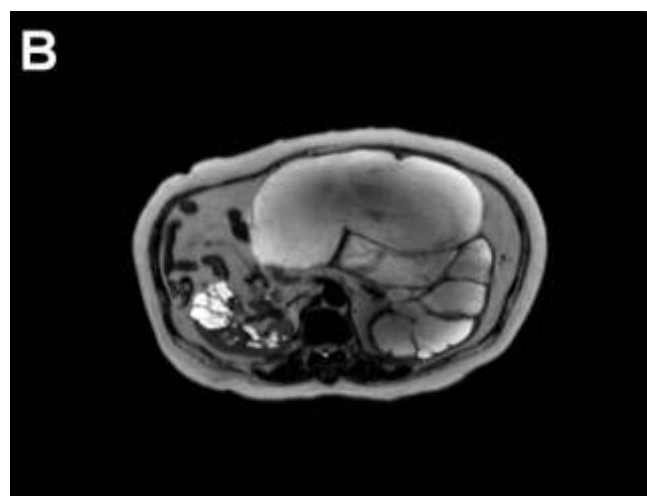
Antibody	Clone	Source
Pan CK	AE1/AE3	Ventana
CK7	SP52	Ventana
CK19	A53-B/A2.26	Ventana
CK20	SP33	Ventana
CA19-9	121SLE	Ventana
CA125	OC125	Ventana
EMA	E29	Ventana
CEA	TF-3H8-1	Ventana
BER-EP4	BER-EP4	Ventana
AMCR	13HA	Dako
Vimentin	V9	Ventana
CD10	5SP67	Ventana
CDX2	EPR2764Y	Ventana
PAX-8	MRQ-50	Ventana
p53	D0-7	Ventana
KI-67	30.9	Ventana
MLH1	M1	Ventana
MSH2	G219-1129	Ventana
MSH6	44	Ventana
PMS2	MRQ-28	Cell Marque

**Legends**

**Figure 1.** Coronal (A) and axial (B) magnetic resonance images demonstrating large multicystic, lobulated lesion involving most of the left kidney.



**Figure 1A**



**Figure 1B**

**Figure 2.** Gross pathology: (A) the renal pelvis and medulla were involved by variably-sized cystic spaces that compressed the renal cortical tissue, (B) the inner lining of the cystic spaces showing papillary growth.

**Figure 3.** Histopathological examination of borderline mucinous tumour of the renal pelvis: (A) & (B) the lining of the cystic spaces ranging from single to multiple layers of mucin-containing neoplastic epithelial cells, (B) areas of epithelial lining demonstrating epithelial pseudostratification and a villo-papillary growth pattern, (C) conspicuous amount of apical intracytoplasmic mucin in the neoplastic epithelial cells, (D) focal intracytoplasmic hyaline globules, (E) areas of which the neoplastic cells exhibit nuclear atypia in the form of nuclear hyperchromasia, increased nuclear-to-cytoplasmic ratio and inconspicuous amount of intracytoplasmic mucin, (F) calcification and osseous metaplasia; note the pool of extracellular mucin (haematoxylin-eosin, original magnification x10 [A, B, and F], x40 [D] and x20 [E], periodic acid Schiff [PAS] and Alcian Blue [AB] special stains, original magnification x10 [C]).



**Figure 2A**

**Figure 4.** Neoplastic cells of borderline mucinous tumour of the renal pelvis expressing diffuse positivity for CK7 (A), CK20 (B), carcinoembryonic antigen (CEA) (C), CD10 (D) and CDX2 (E). Immunostaining for KI67 proliferation index showing nuclear positivity in approximately 25-30% of the neoplastic epithelial cells (F) (original magnification x 10 [A – F])

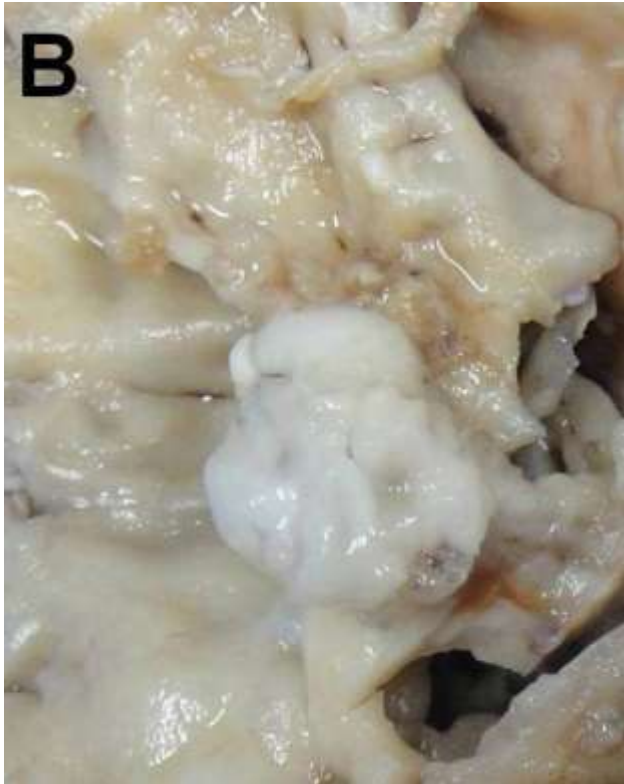


Figure 2B

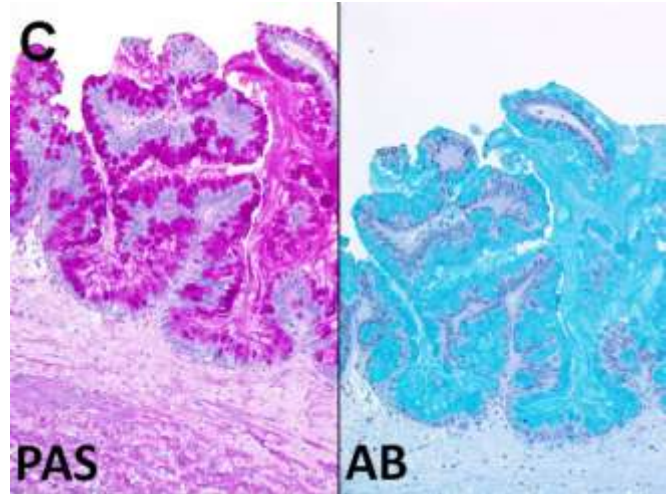


Figure 3C

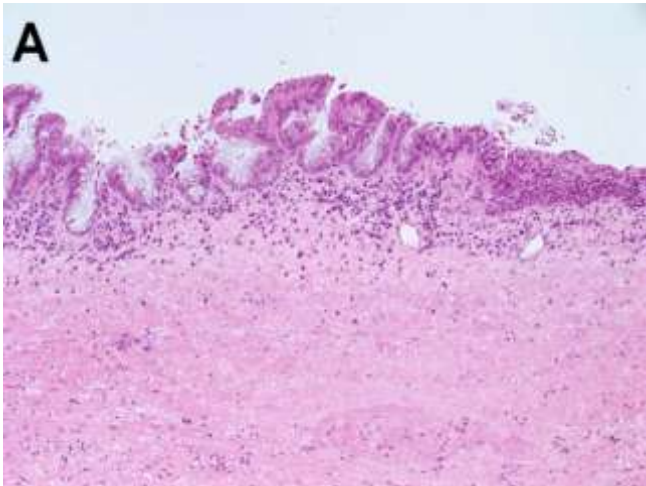


Figure 3A

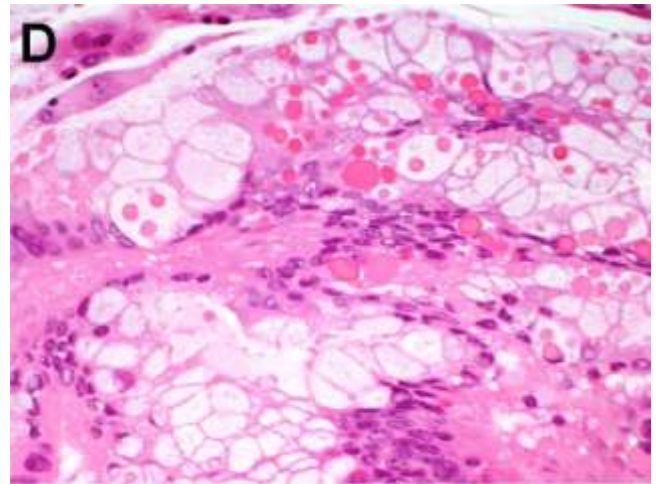


Figure 3D

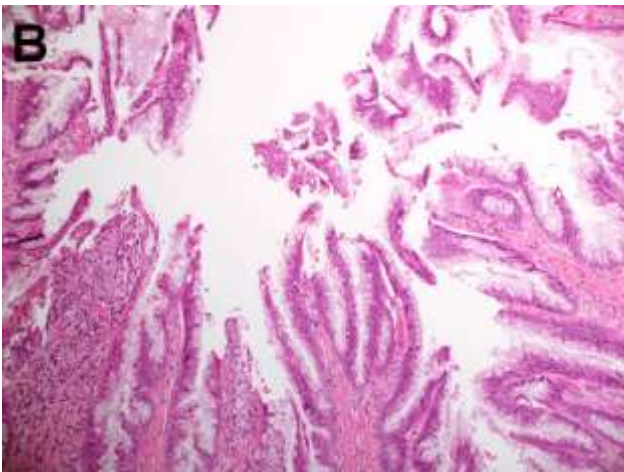


Figure 3B

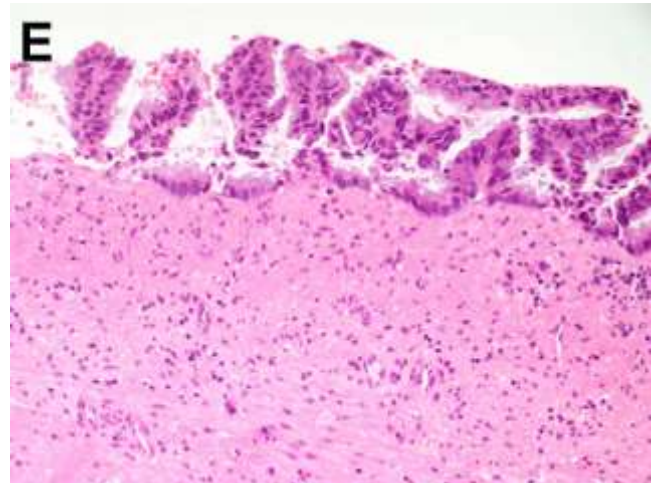


Figure 3E

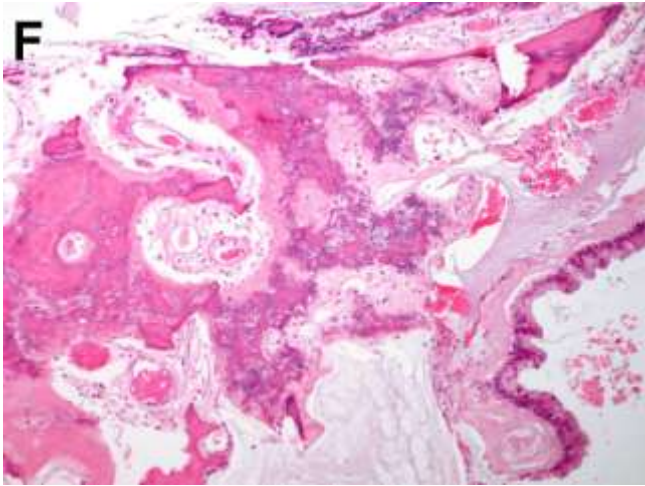


Figure 3F



Figure 4C



Figure 4A



Figure 4D



Figure 4B



Figure 4E



**Figure 4F**