遠位胆管部腫瘍

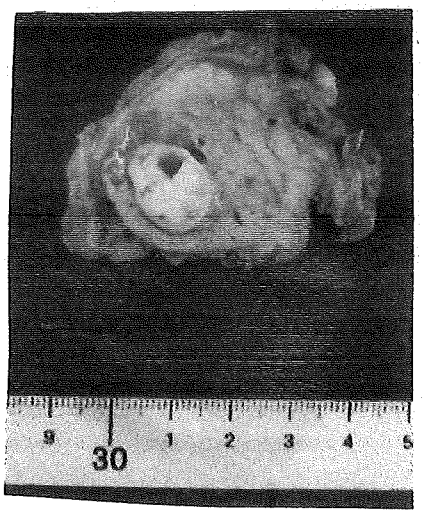
高知赤十字病院
病理診断科部
黒田直人

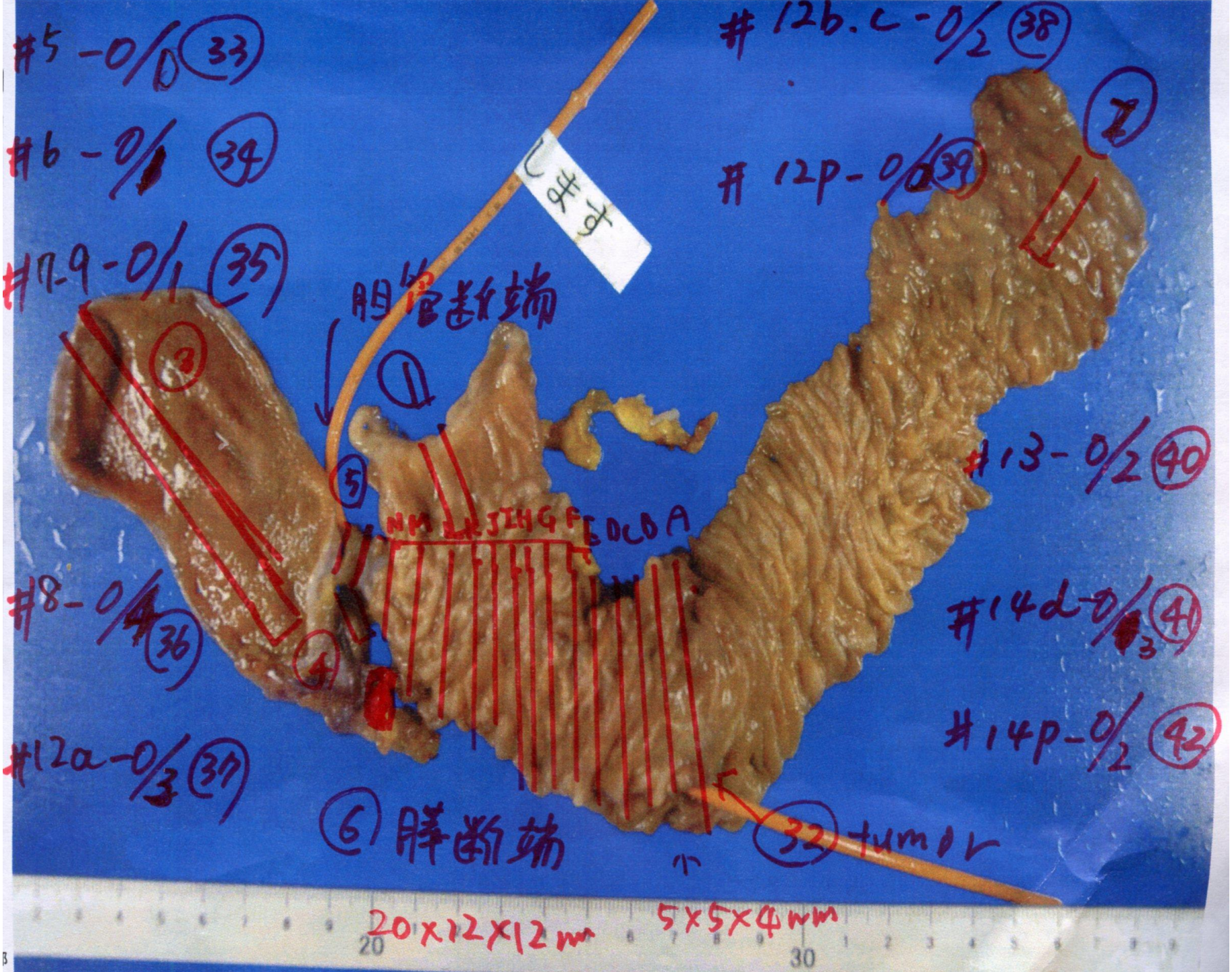
症例：70歳代後半、男性。

臨床経過：嘔気、腹痛の精査で遠位胆管とVater乳頭部に腫瘍がみつかり、膵頭十二指腸切除術が施行された。術前では連続性は明らかではなかった。

配布標本：遠位胆管部腫瘍。

問題点：病理診断。

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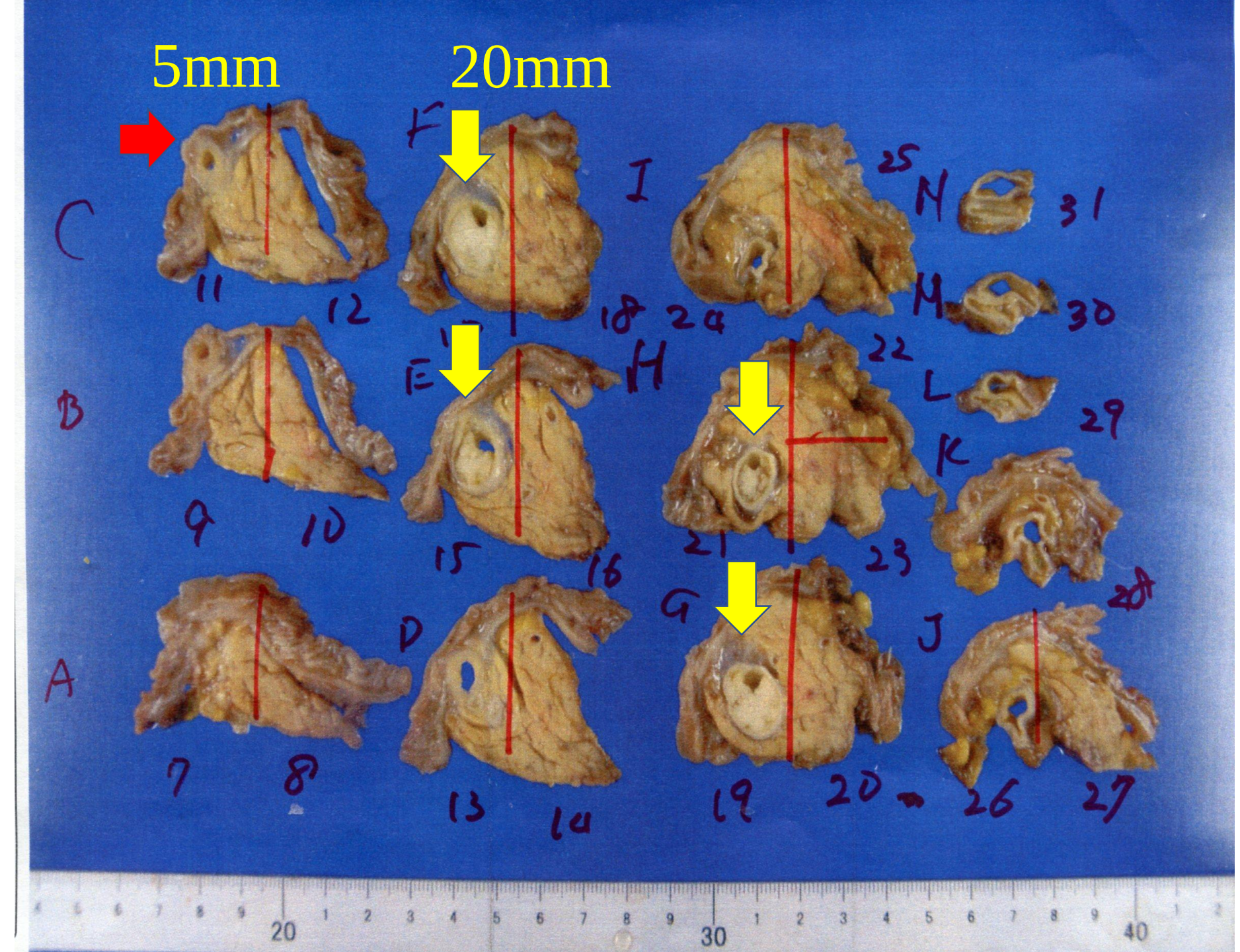
#6 -0/1 (34)
#7-9 -0/1 (35)
#8 -0/4 (36)
#12a -0/3 (37)
#12b.c -0/2 (38)
#12p -0/2 (39)
#13 -0/2 (40)
#14d -0/3 (41)
#14p -0/2 (42)
膽管断端
膵断端
tumor
20×12×12mm
5×5×4mm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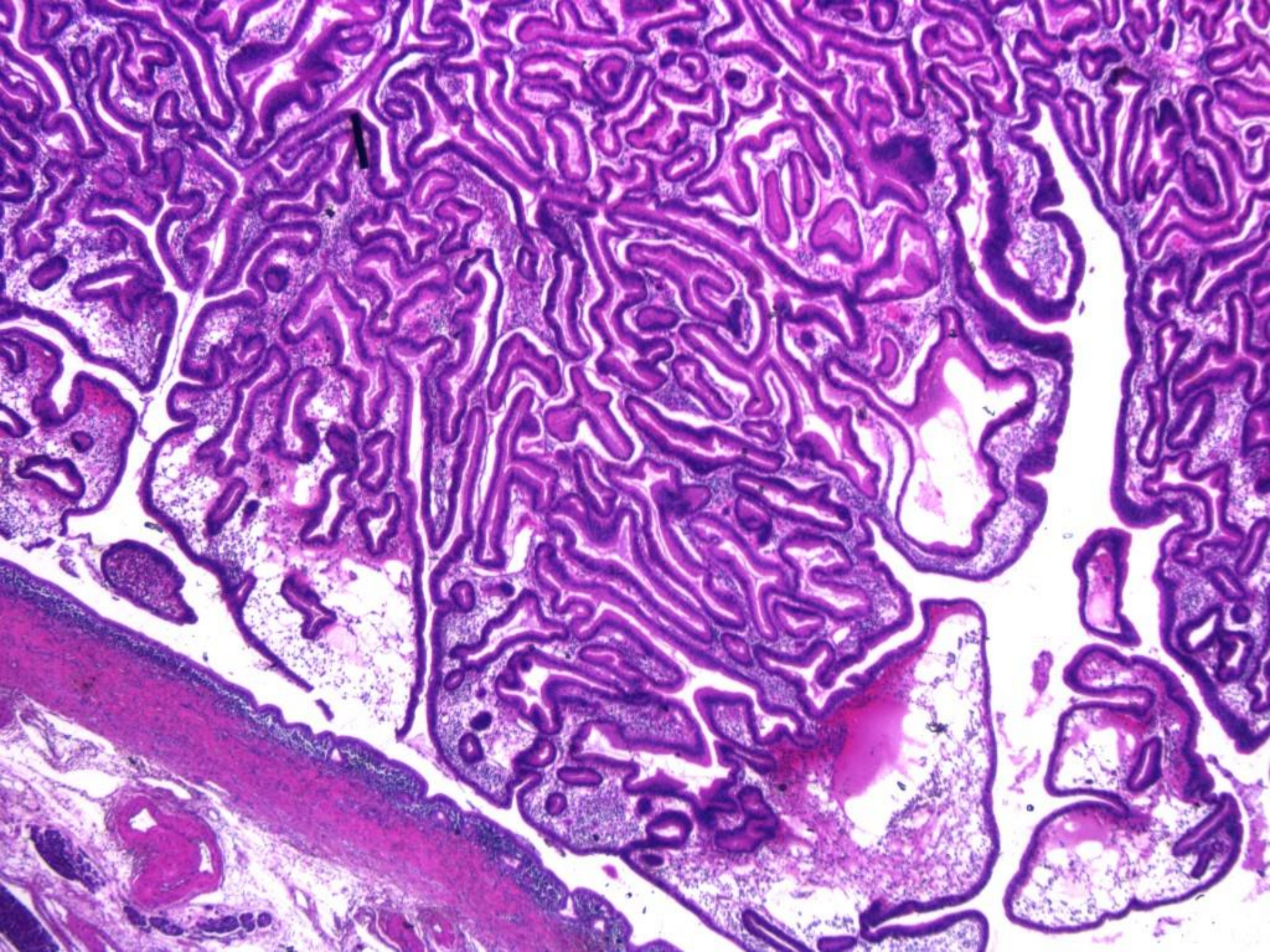

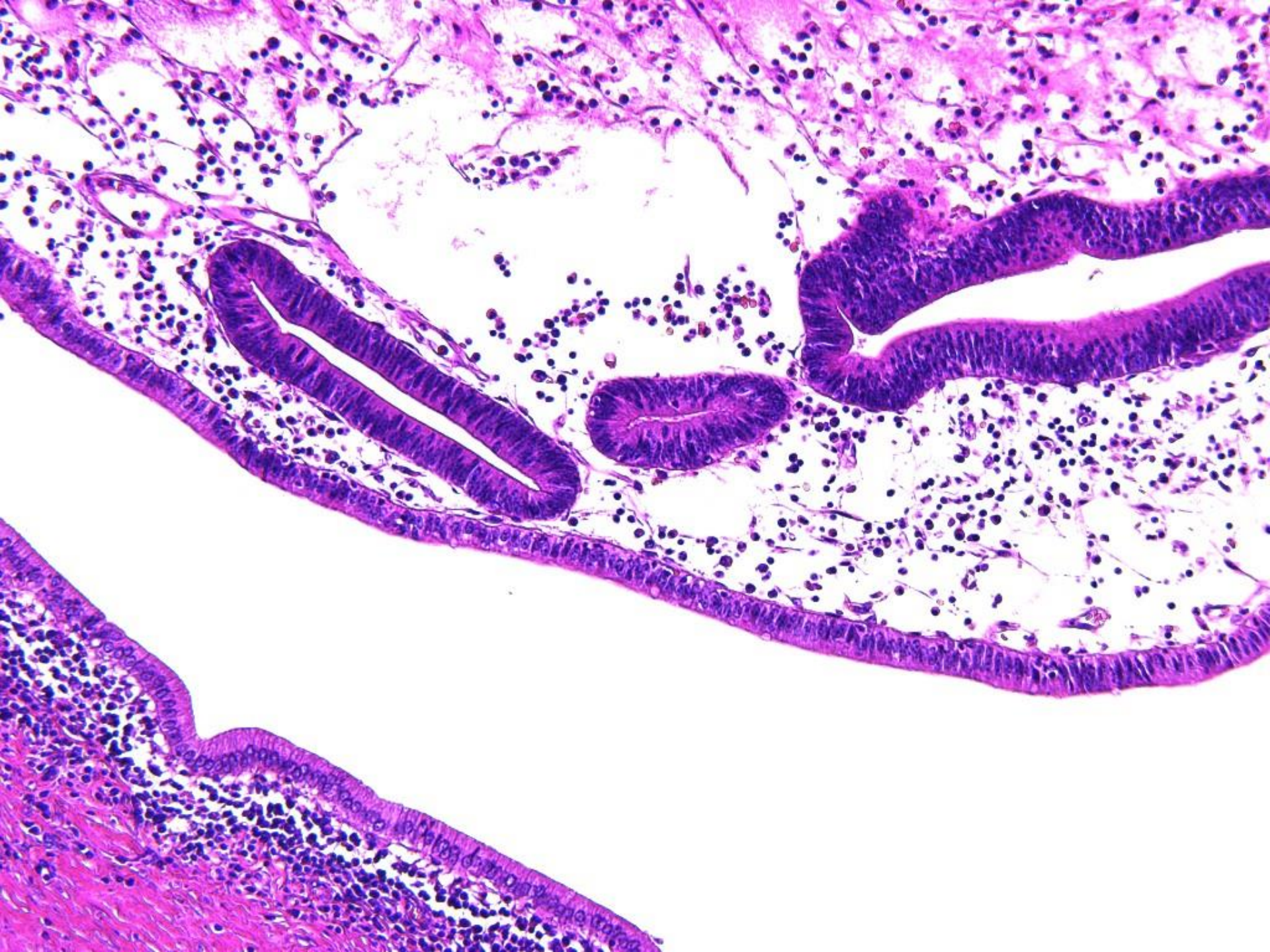

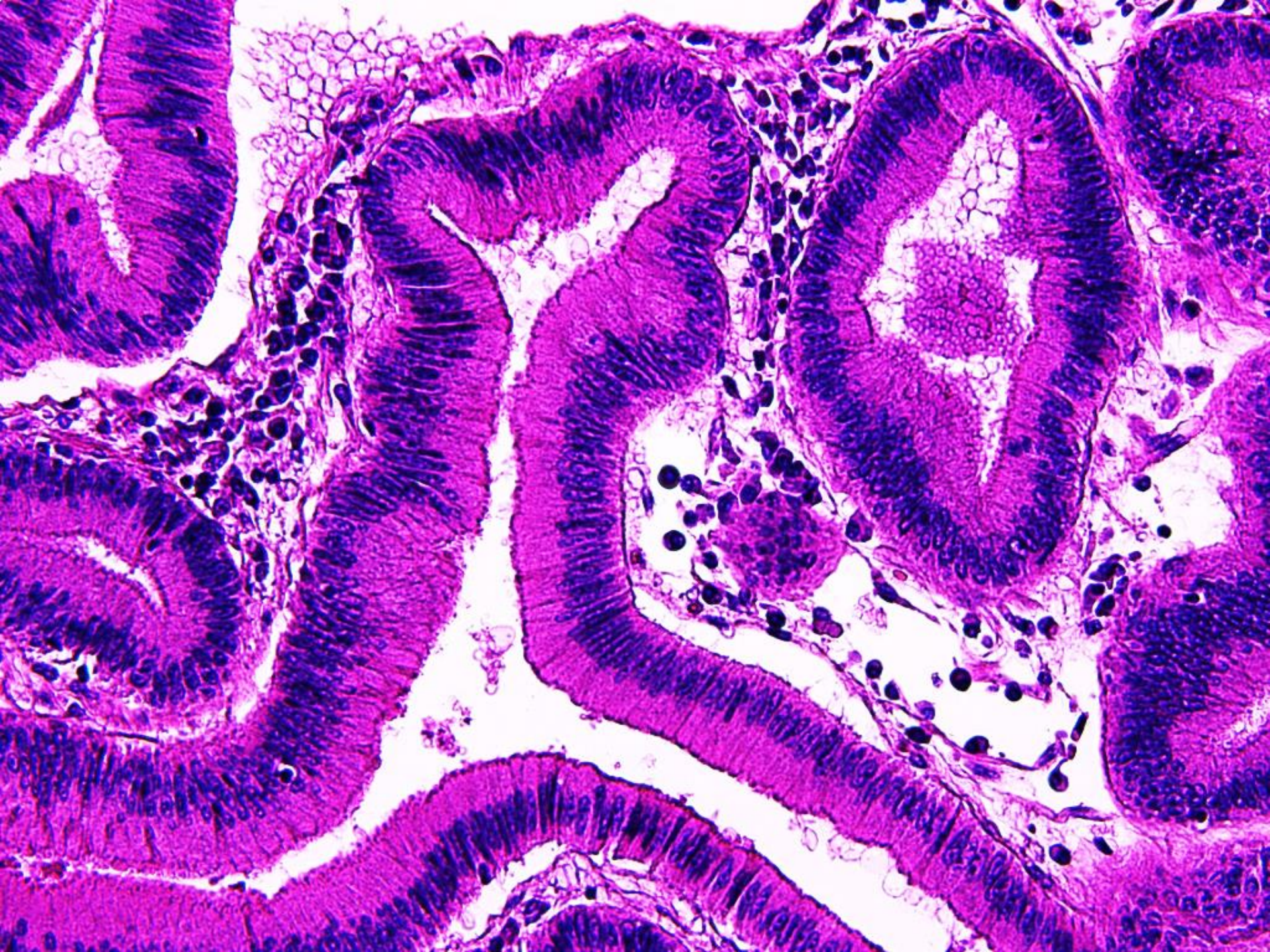

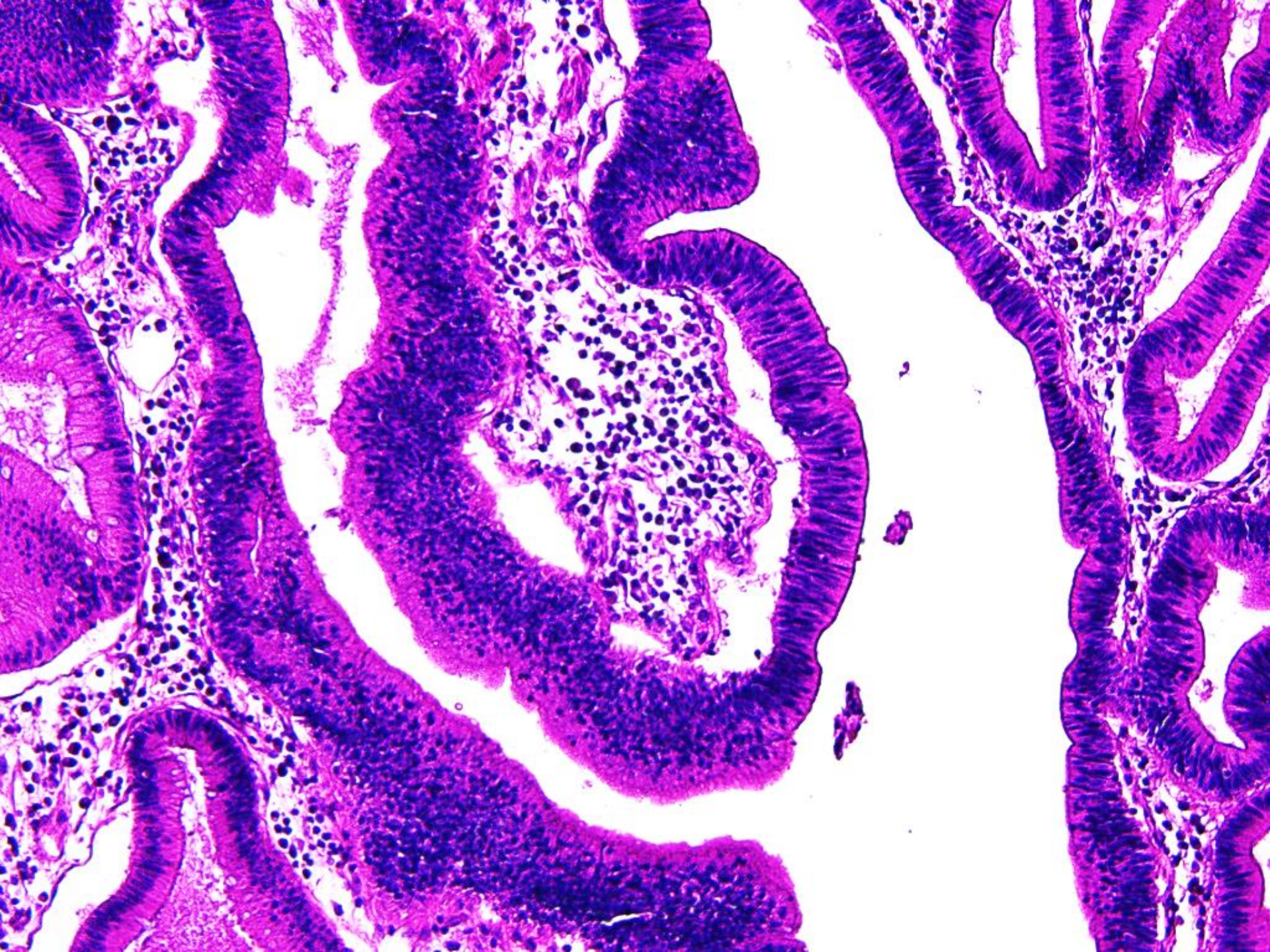

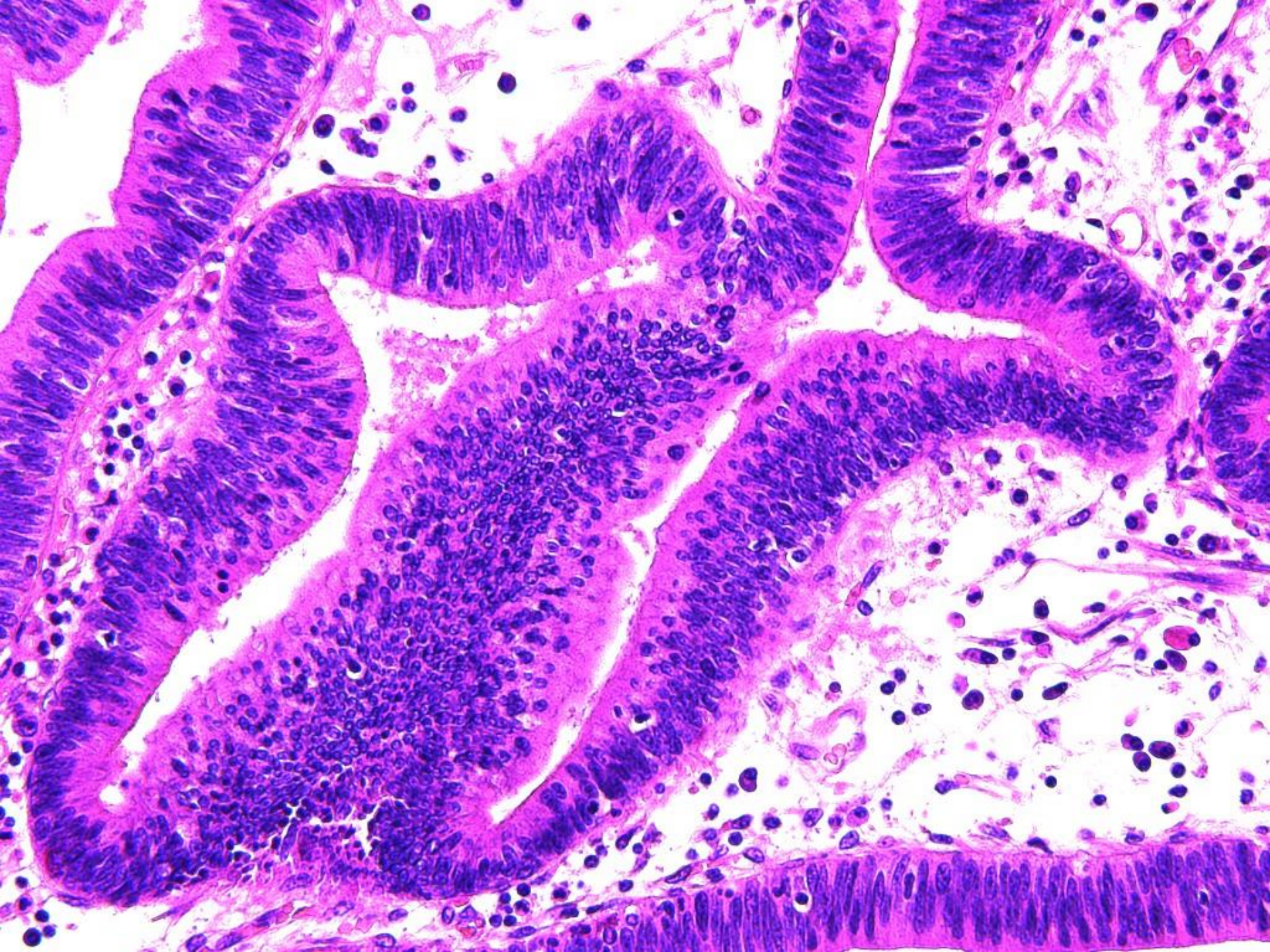

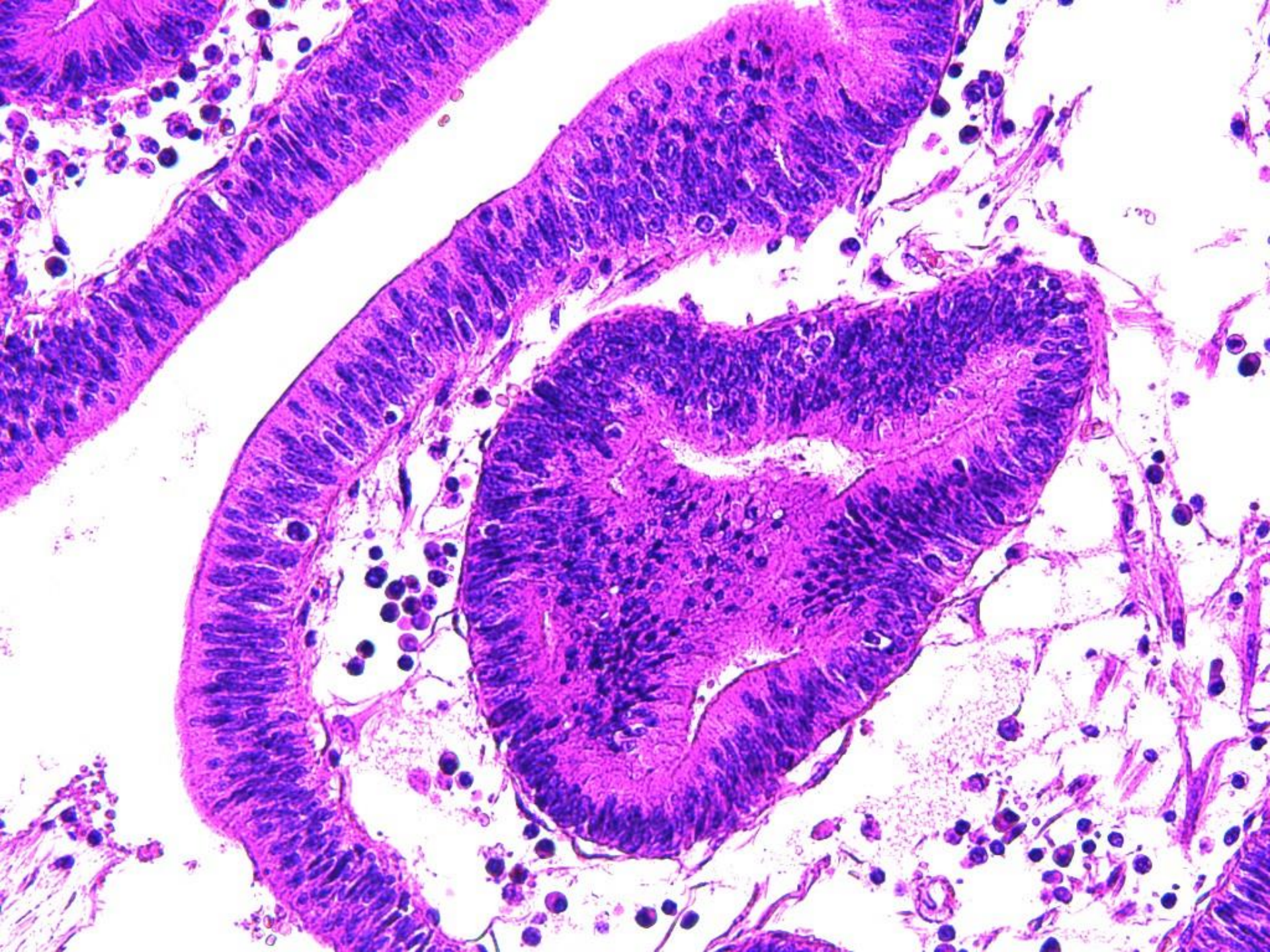

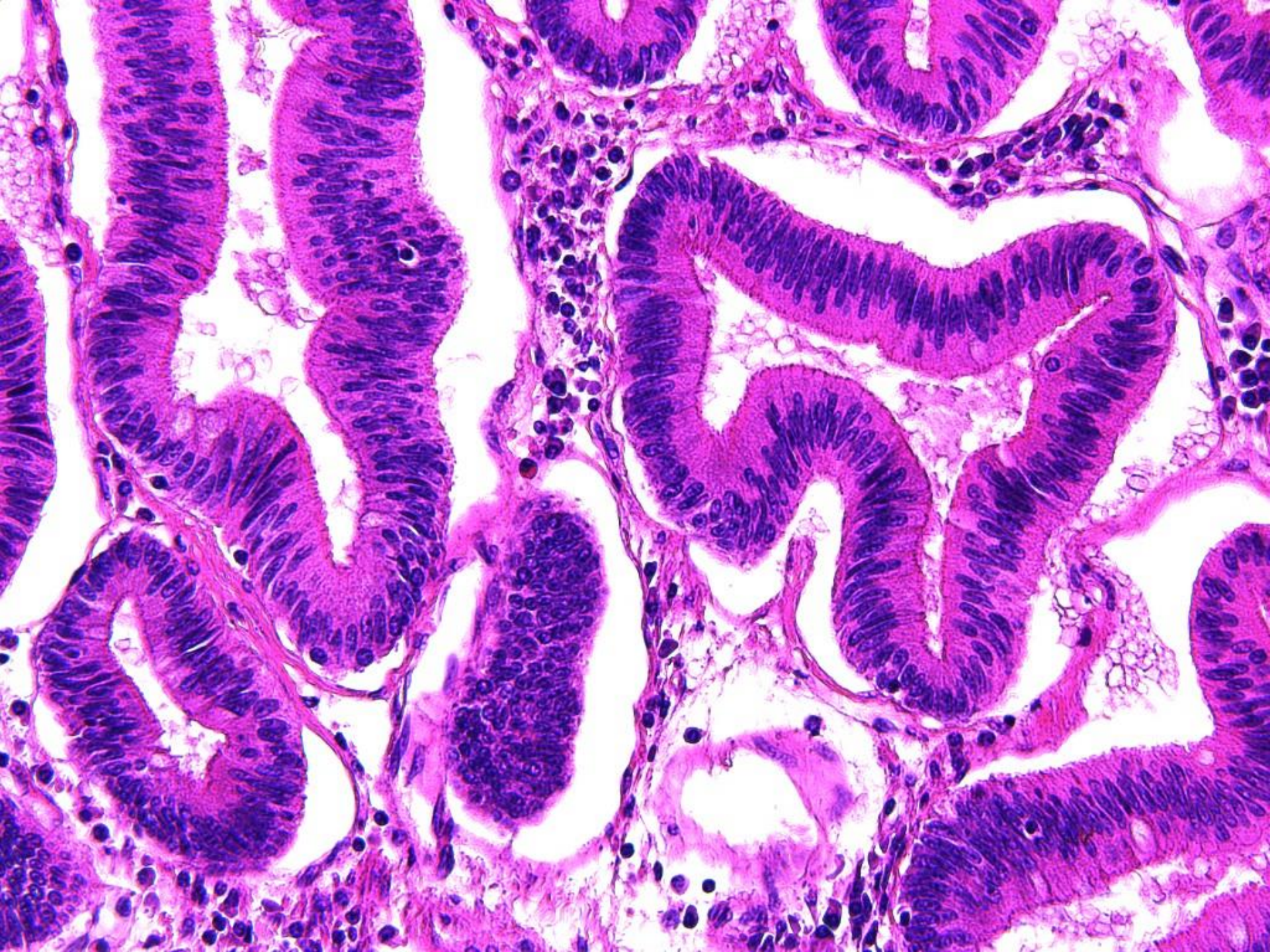

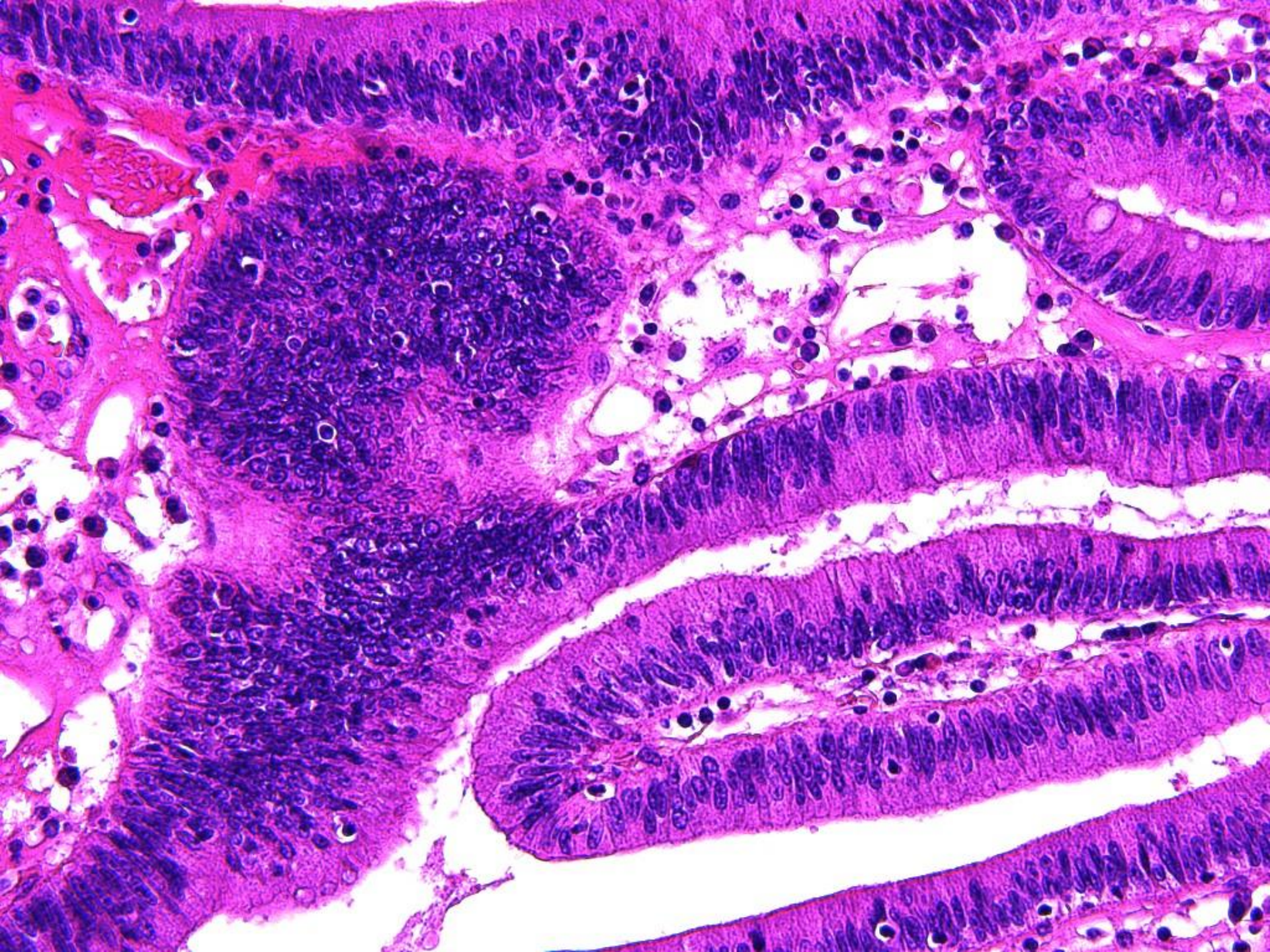

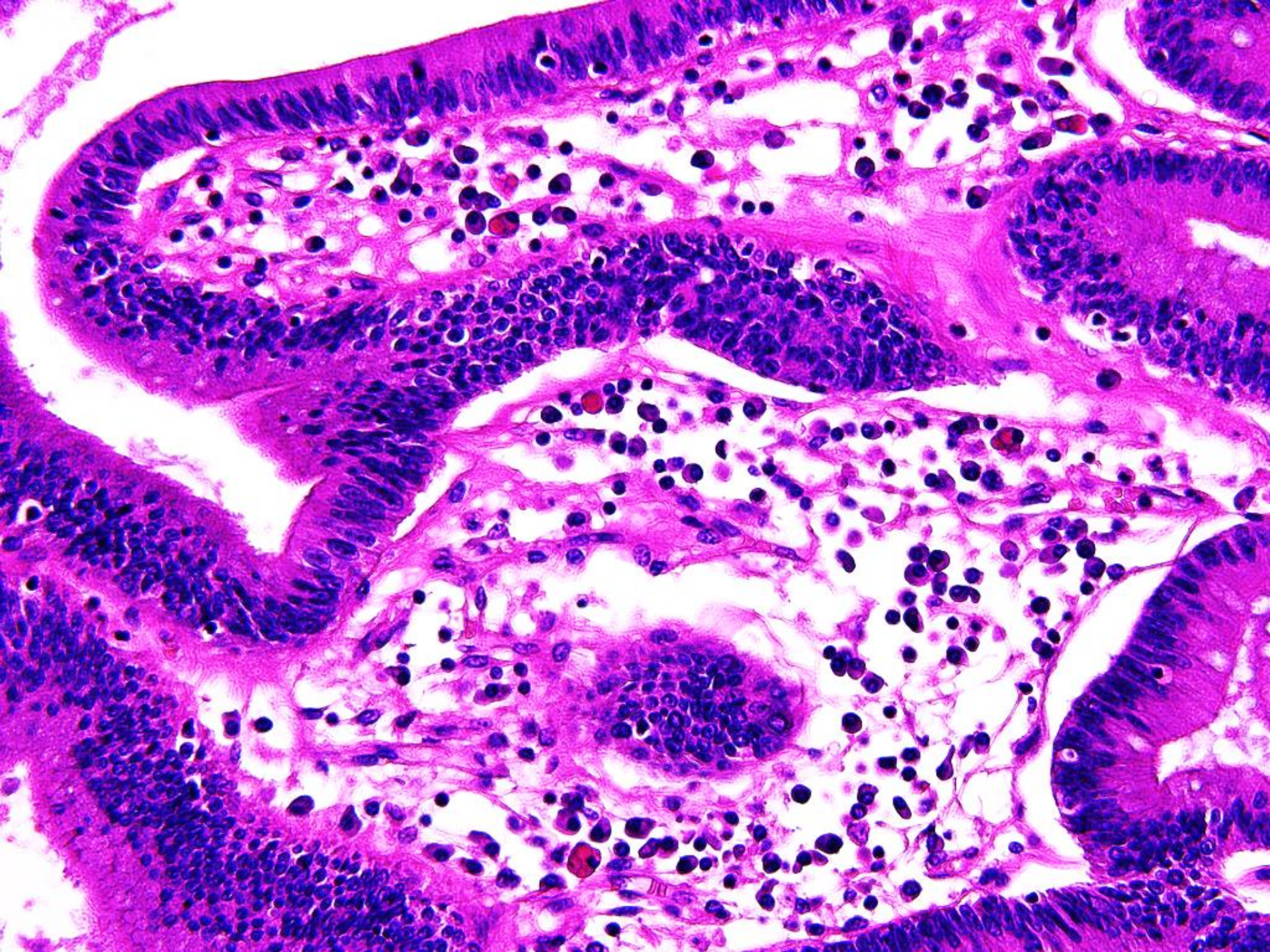

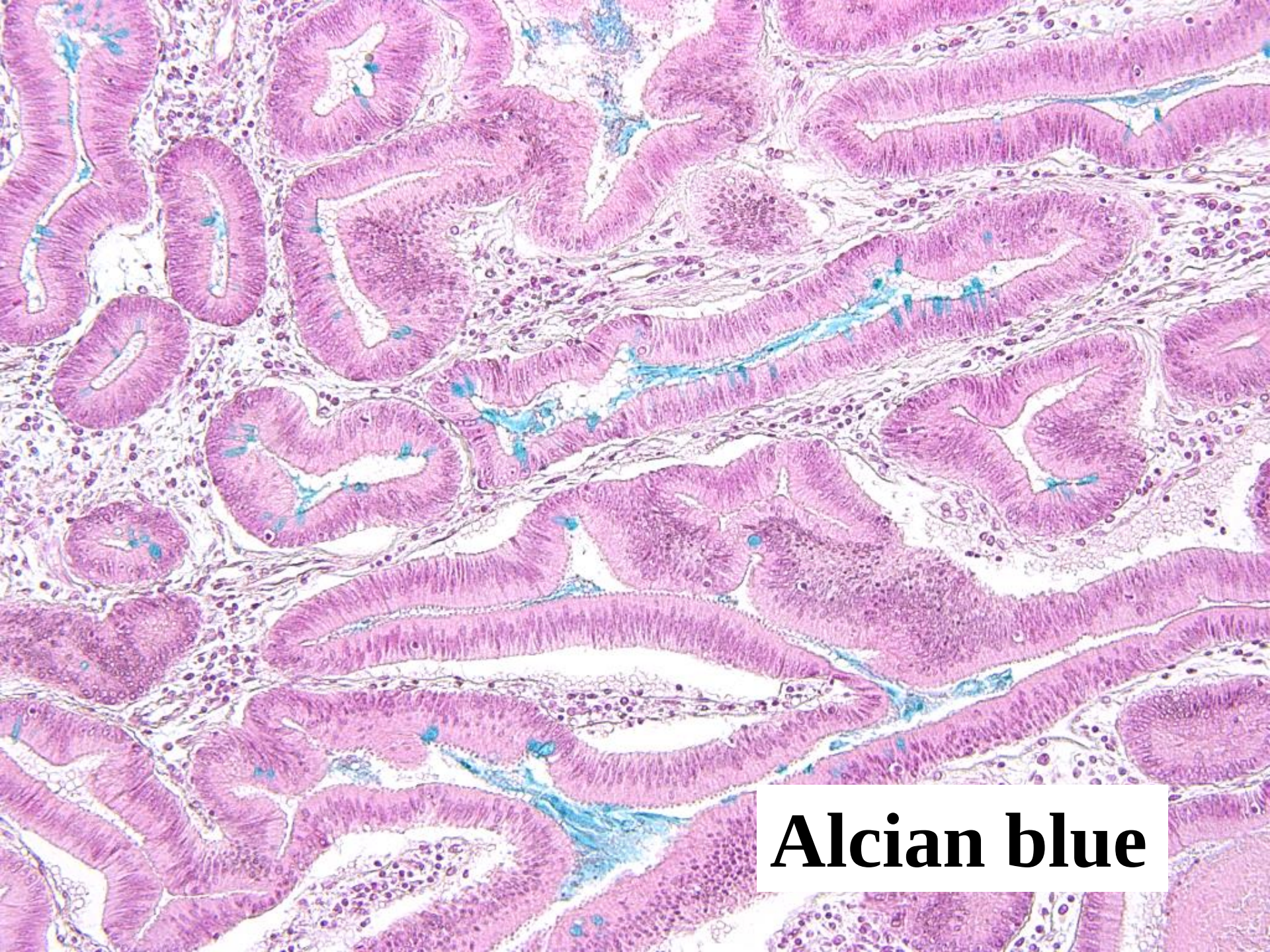
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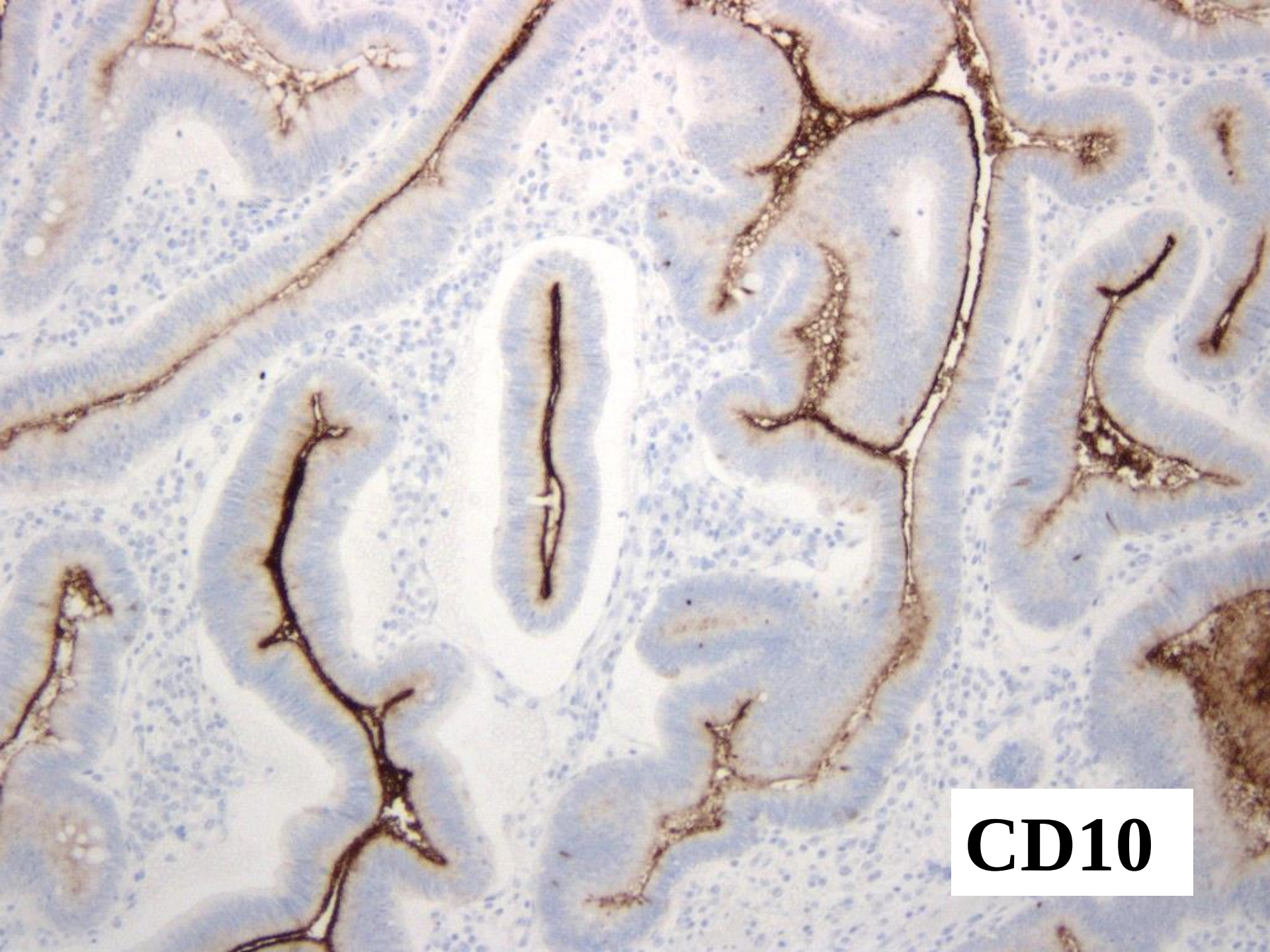
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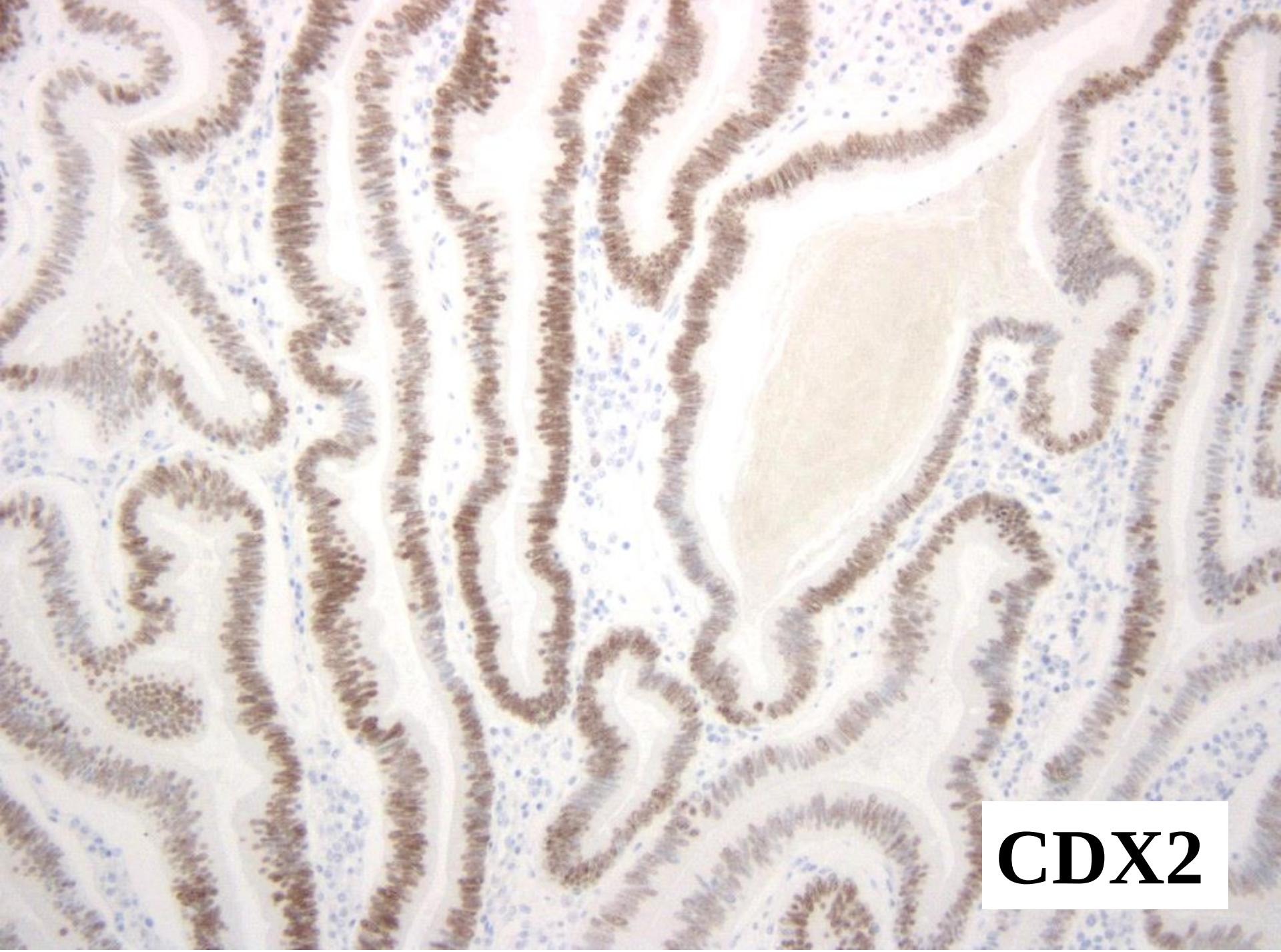
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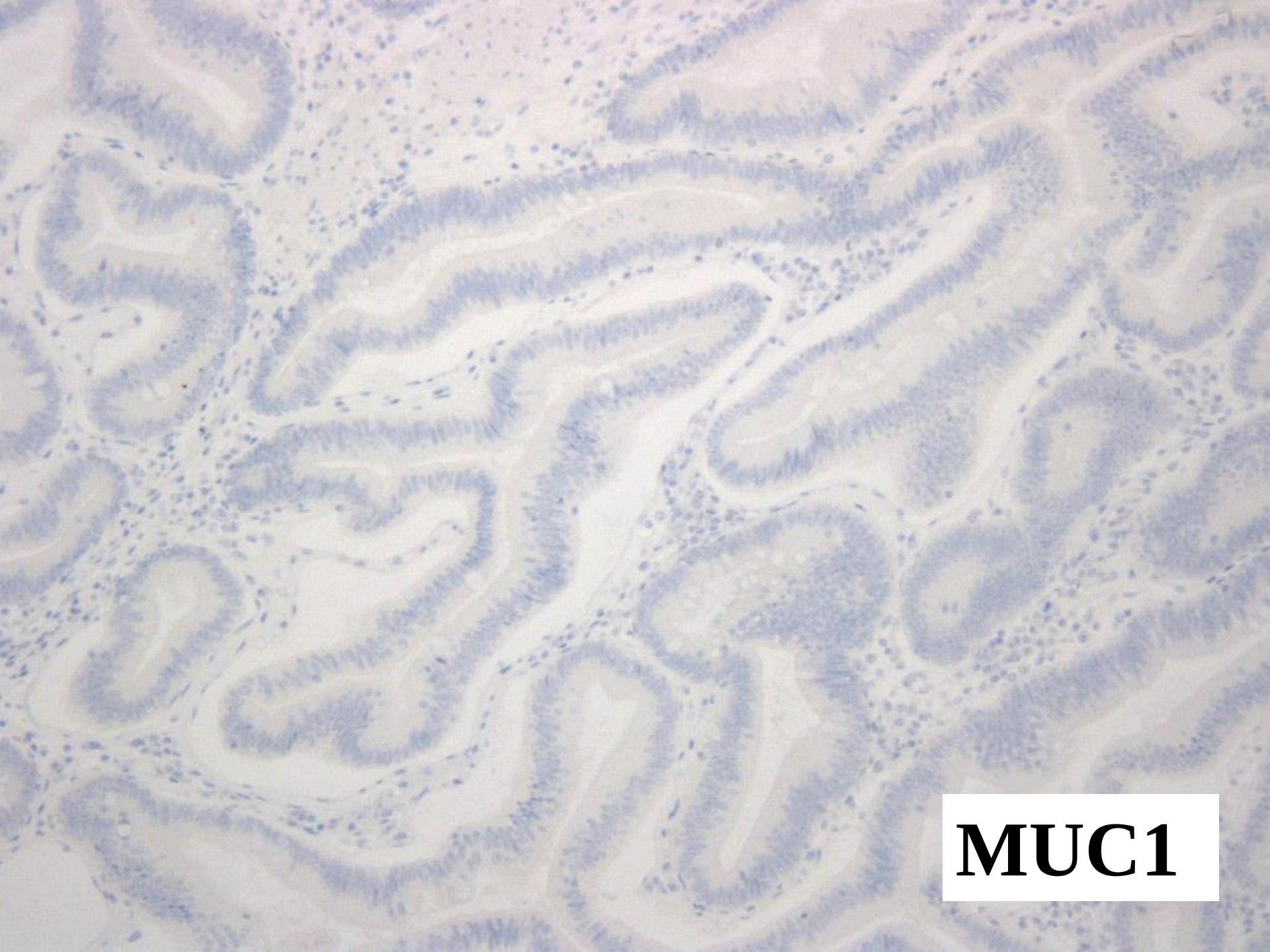
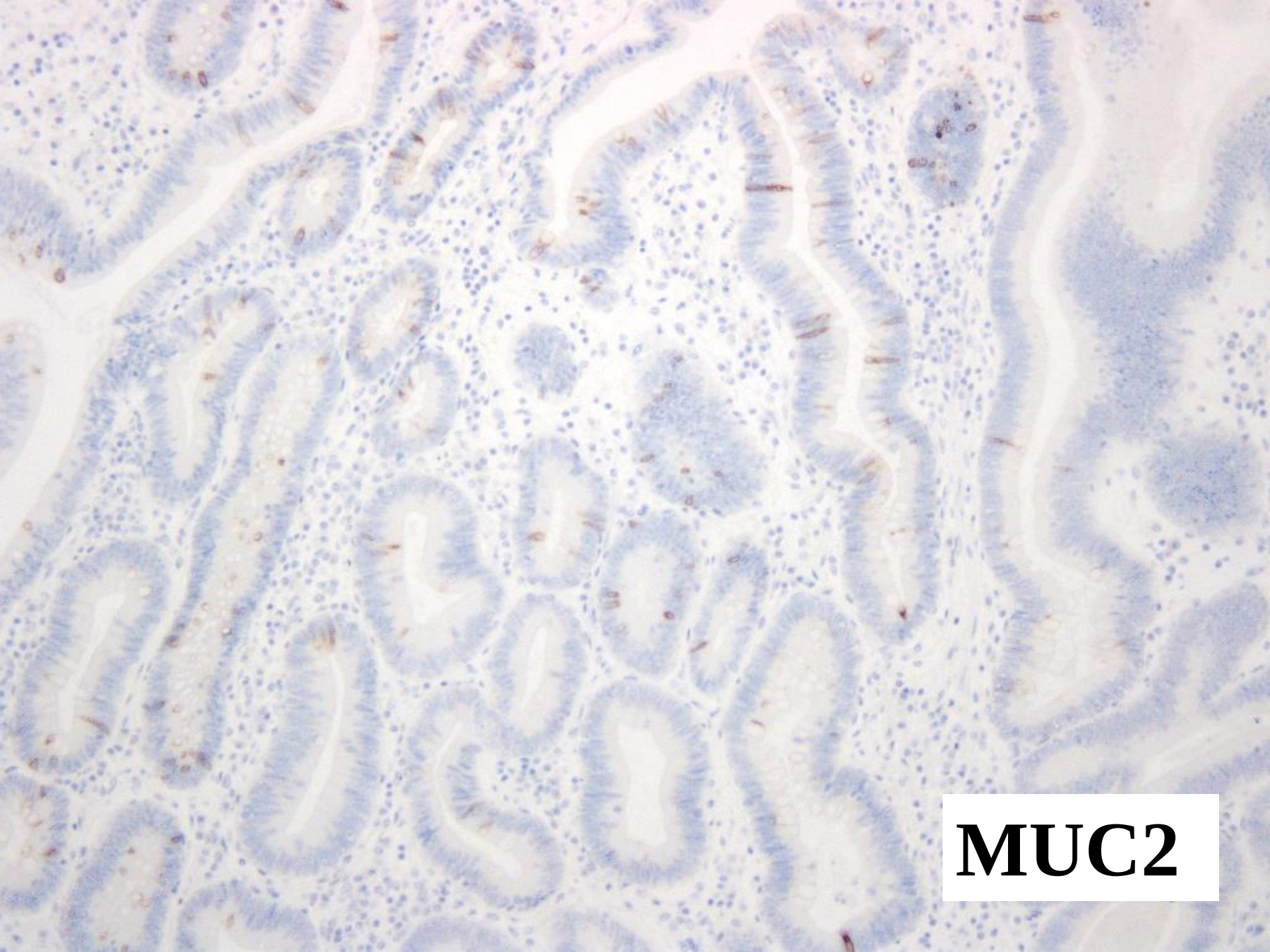

MUC1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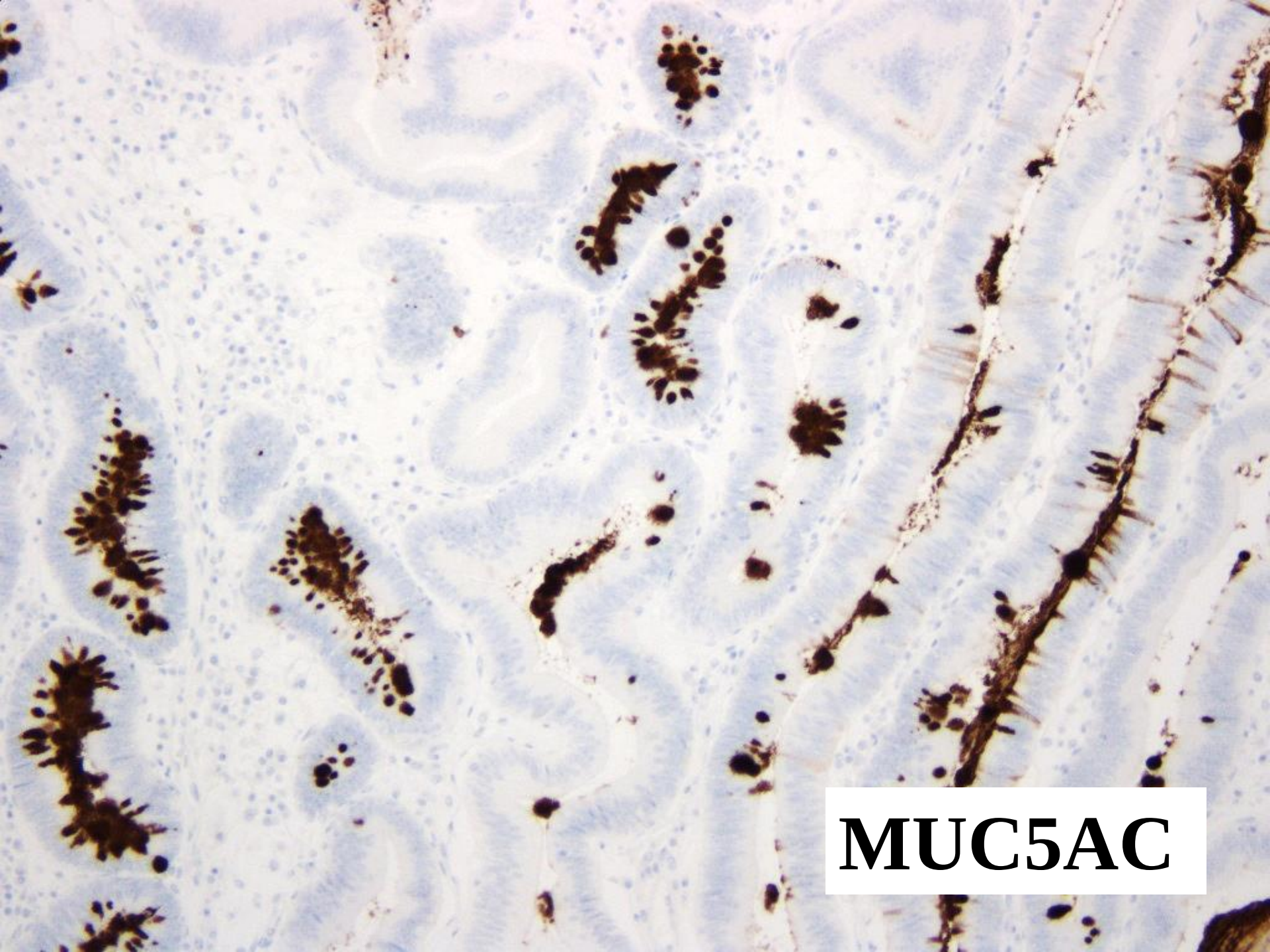
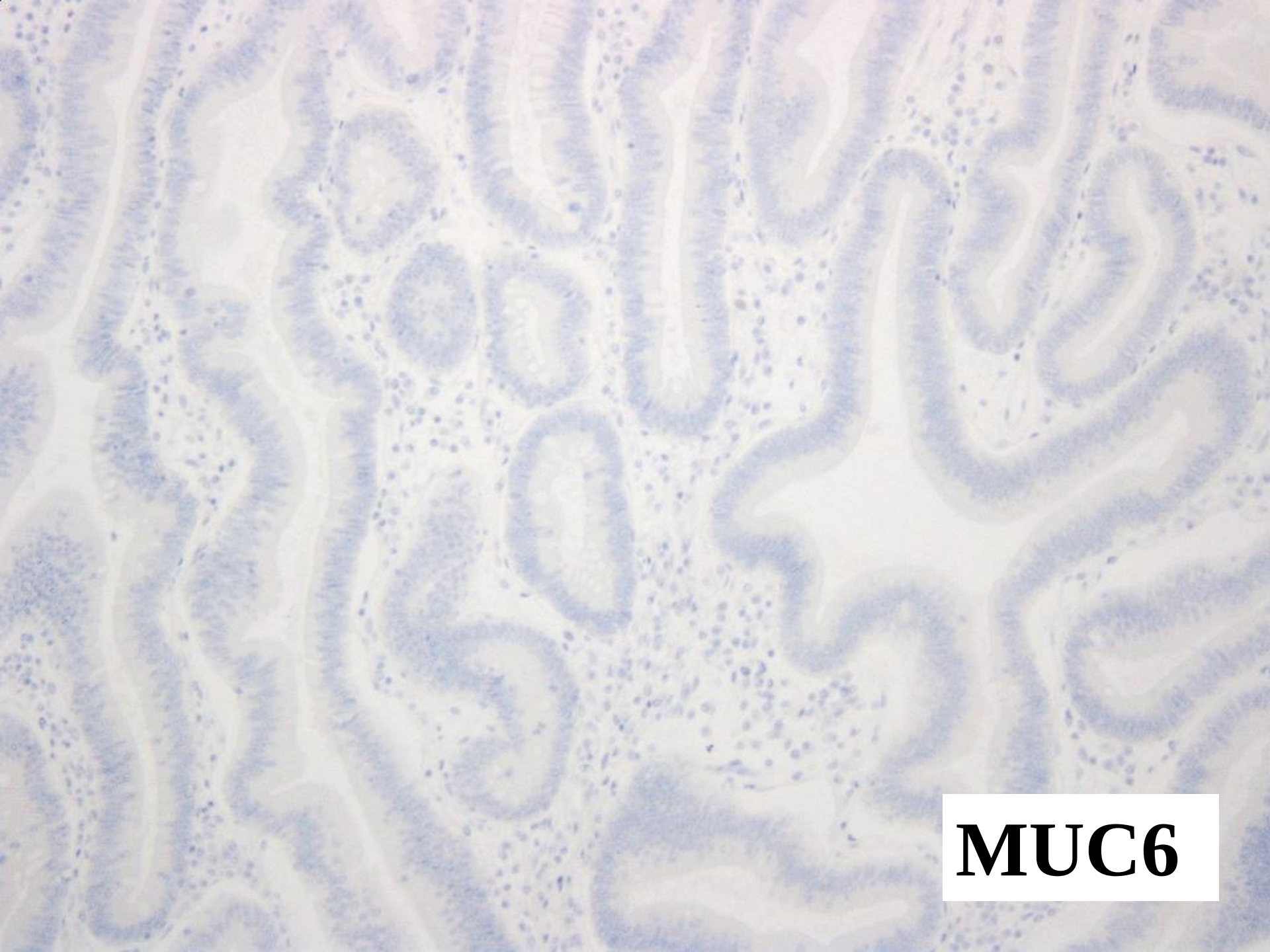

MUC5AC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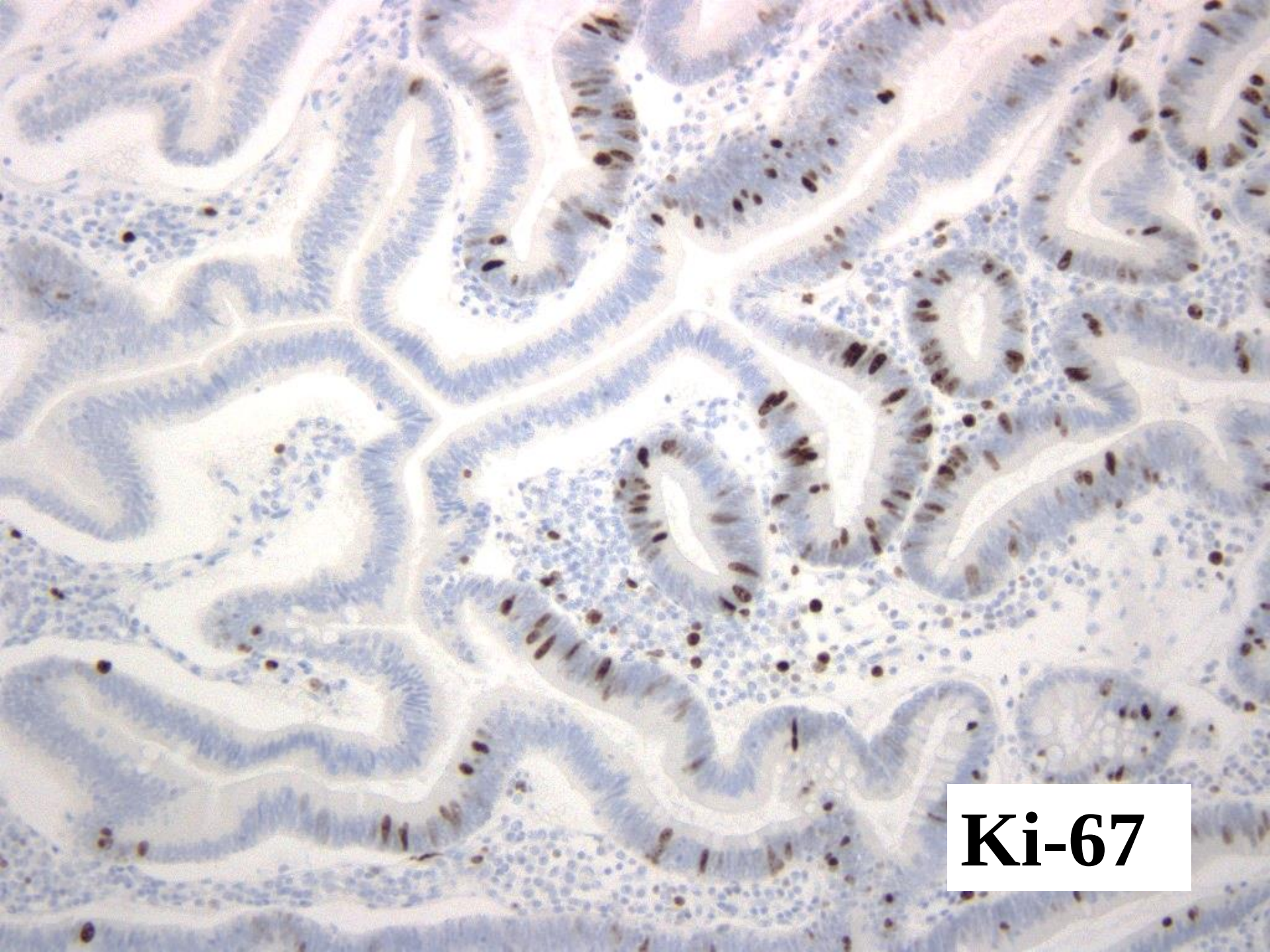
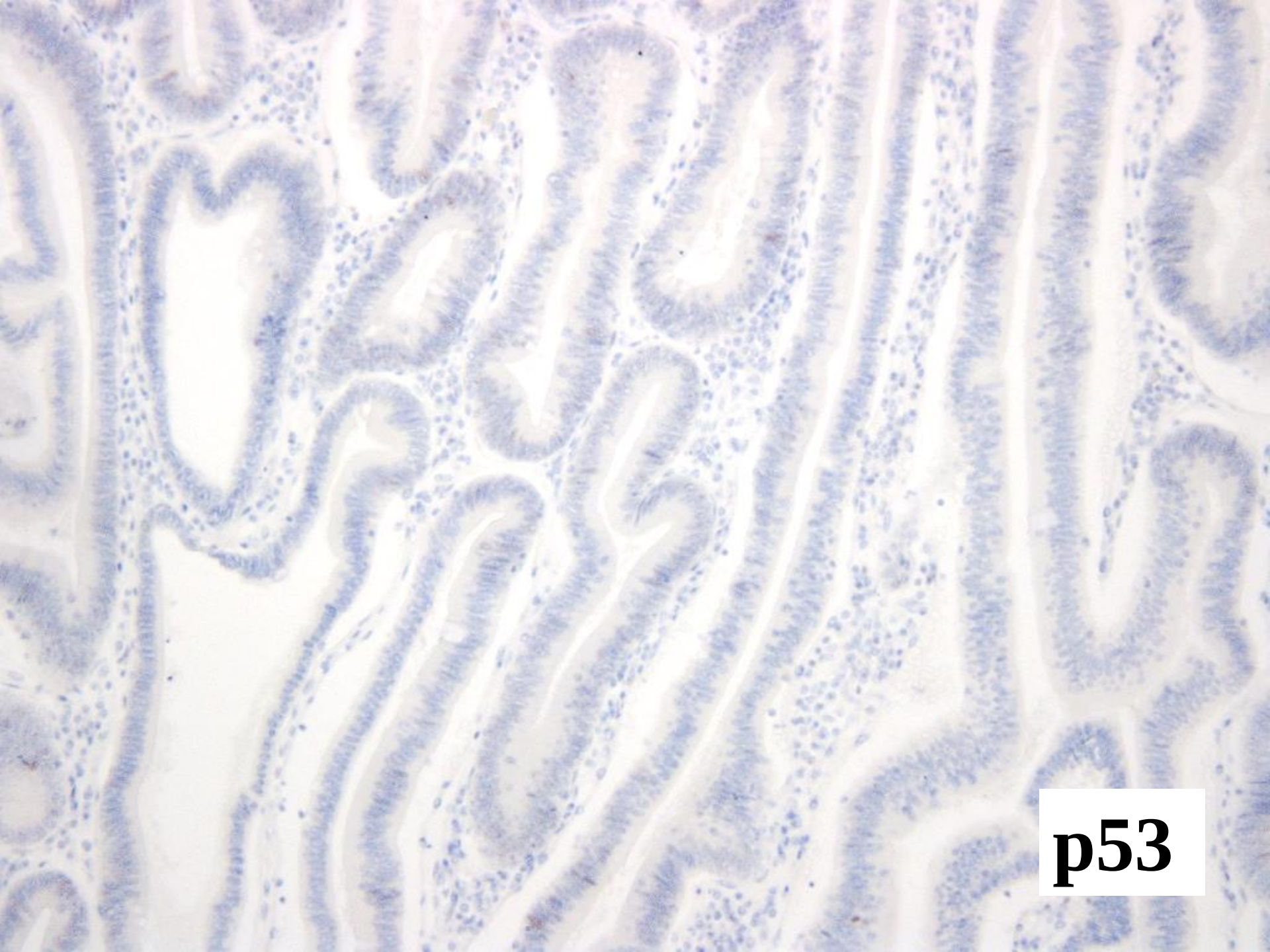
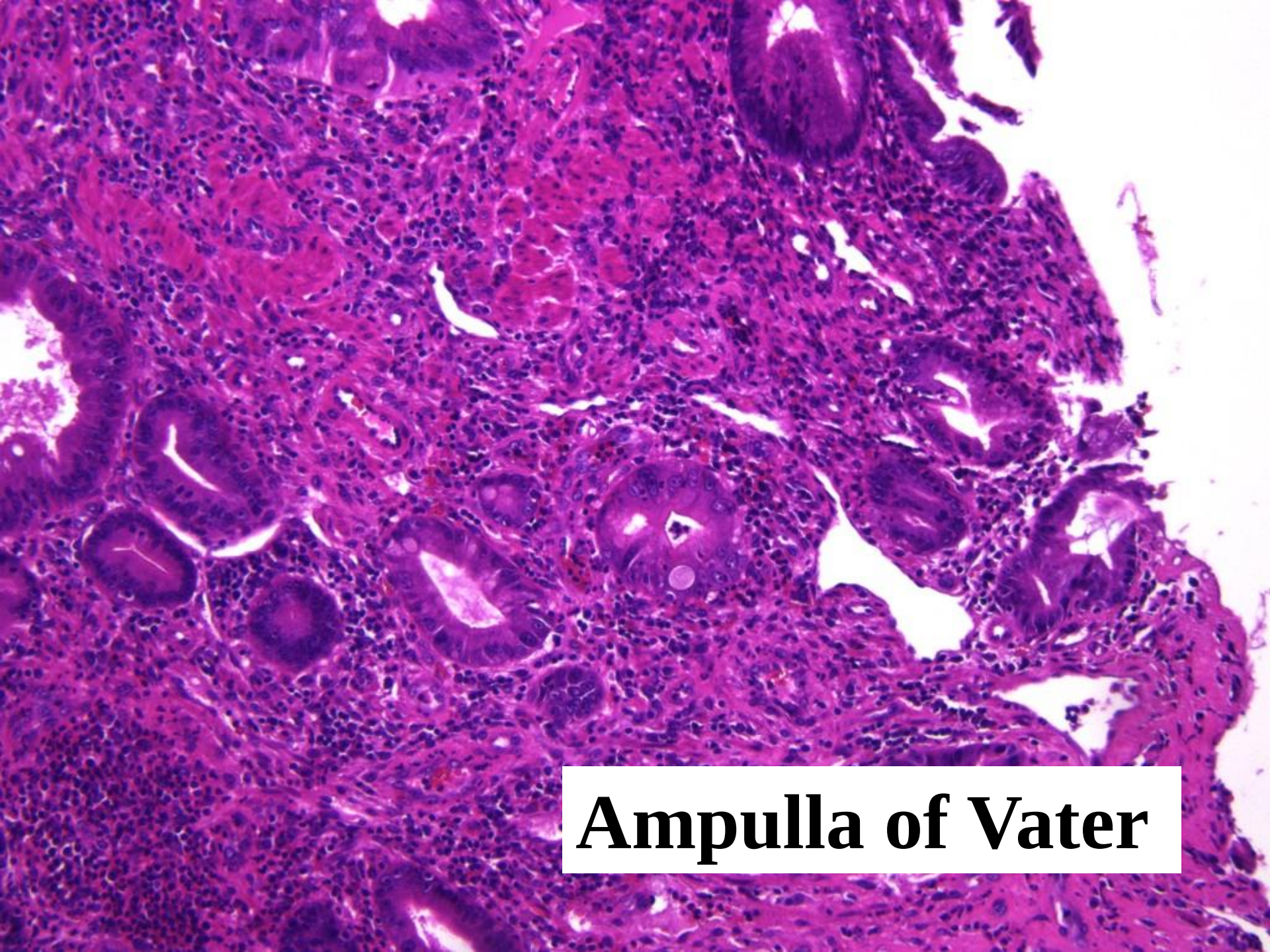
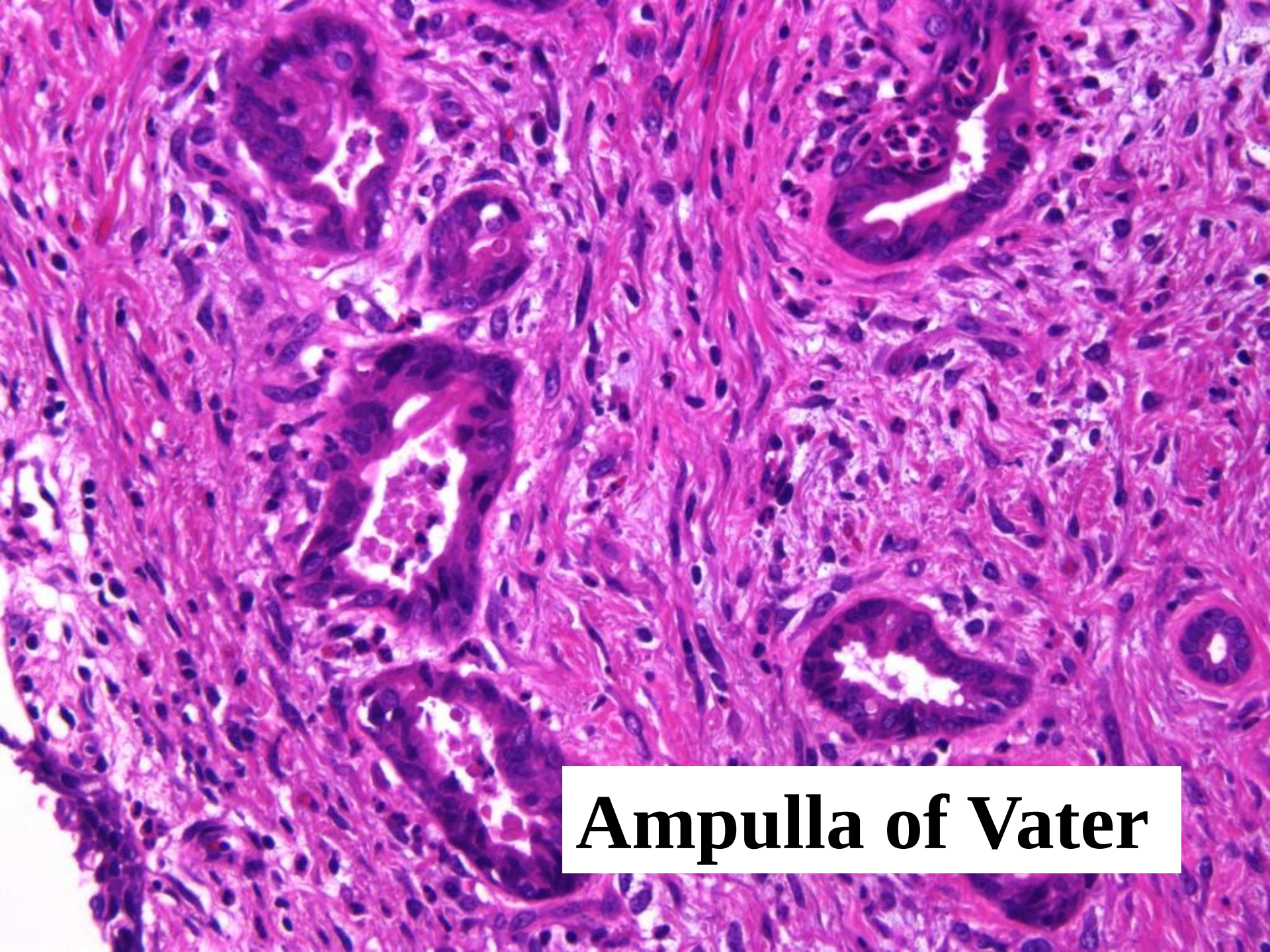

Ki-67


p53

Final Diagnosis

Intraductal papillary neoplasm, intestinal type, of the bile duct


Ampulla of Vater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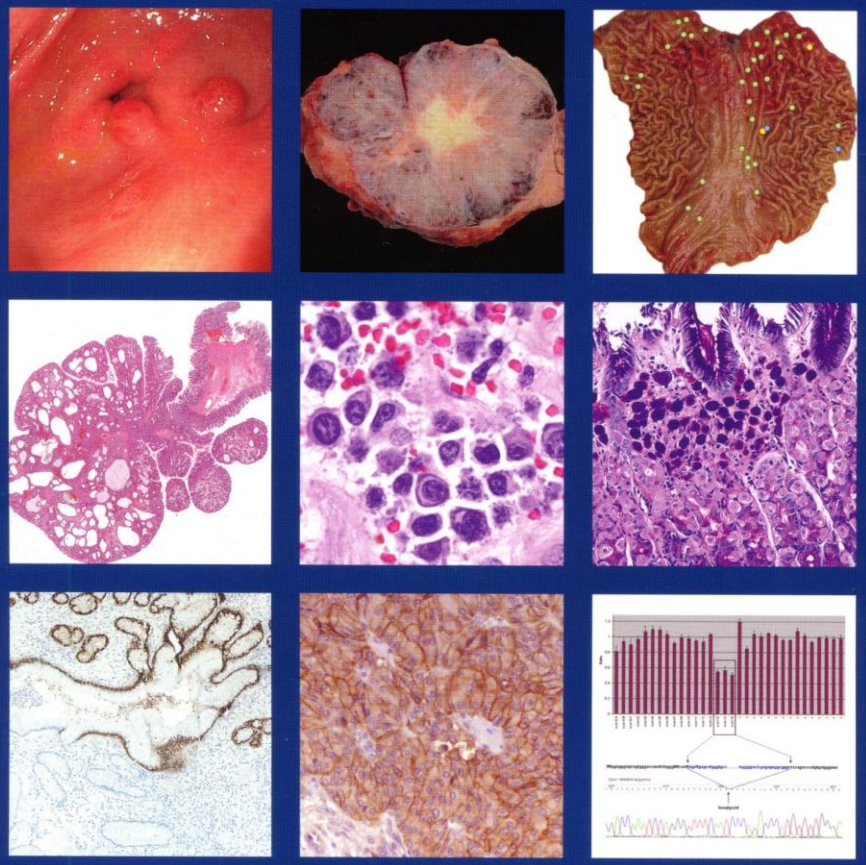
WHO Classification of Tumours • 5th Edition

Digestive System Tumours

Edited by the WHO Classification of Tumours Editorial Board



World Health Organization

Intraductal papillary neoplasm of the bile ducts (IPNB)

1) 定義：肝臓、胆管内に肉眼的に観察しうる乳頭状、絨毛状増殖を示す前癌病変。浸潤癌を伴う場合には浸潤癌を伴う IPNと呼ぶ。
2) 発生部位：報告により異なる。肝内胆管に80%まで発生するという報告もあれば、肝外胆管に 70%まで発生するという報告もある。
3) 発生年齢：50-70歳代に多く、男性に多い。
4) 症状：間欠性の腹痛、胆管炎。
5) 画像所見：cholangiographyで、filling defect。ポリープ状の腫瘤と粘液産生による。乳頭状までは画像ではわからない。
6) 病因：たいていは不明。PSC, 肝内結石、肝の感染症が病因という報告がある。

Table 9.02 Radiopathological correlation of intraductal papillary neoplasm of the bile ducts (IPNB)

Radiological pattern	Pathological characteristics
Intraductal mass and proximal ductal dilatation	Cast-like intraductal mass with upstream dilatation due to ductal obstruction by IPNB and absence of mucin
Intraductal mass and proximal and distal ductal dilatation	The most common and characteristic type Due to mass and excessive mucin secretion, the ducts containing mass and the proximal and distal bile ducts are markedly dilated
Cystic dilatation with mass	Unilocular or multilocular cystic lesions Mass on the internal surface of the cystic lesion or adjacent bile duct
Intraductal mass with macroinvasive lesion	In any of the above three types with grossly visible parenchymal invasion

7) 肉眼所見：ポリープ状の腫瘤。大きさは 5-20mm。単発も多発もありえる。浸潤しても限局性のことが多いが、腫瘤を形成することもありえる。

8) 組織所見：胆管上皮で被覆される立方状、円柱状細胞が線維血管性の間質を軸として乳頭状に増殖し、管状増殖も混在する。間質は浮腫状、炎症を伴うこともある。約 40-80%は浸潤癌を伴い、たいていはtubular adenocarcinomaないしは colloid carcinomaである。上皮内進展もみられることがある。細胞異型と構造異型に基づいて glow-gradeと high-gradeに分けられる。卵巣様間質を欠く。

9) 組織亜型と免疫染色：intestinal, biliary, oncocytic, gastric typeの4つに分類される。2つ以上の成分を有するものが半分以上を占めるので、優勢なものを亜型とする。MUC2-intestinal, biliary-MUC5AC, MUC6, MUC1-pancreatobiliaryで分類。アジアは intestinal typeと gastric typeが多い。最近新しい分類が提唱されている。

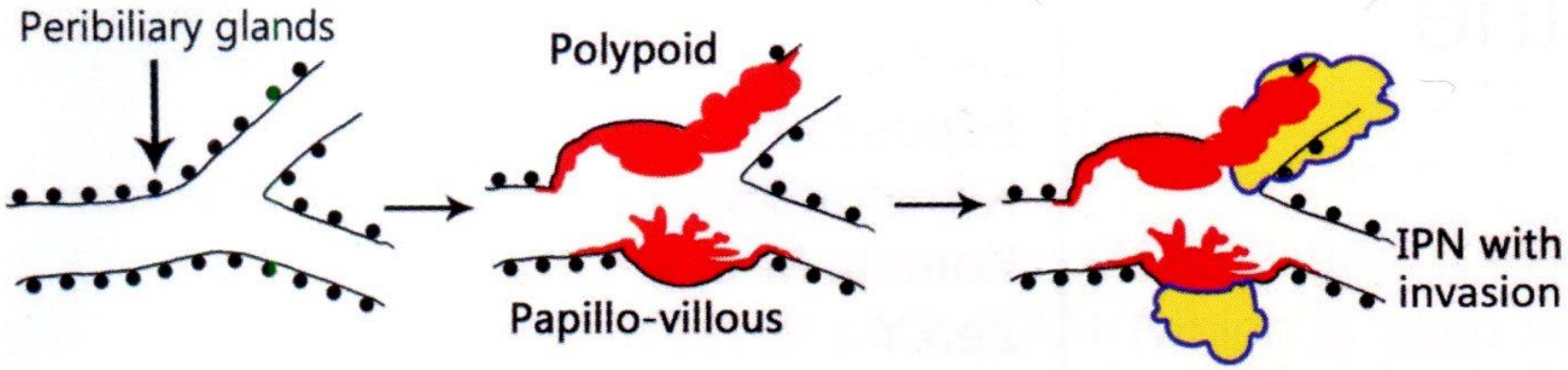


Fig. 9.08 Intraductal papillary neoplasm (IPN) of the bile ducts. Schematic representation of IPN presenting with polypoid and/or papillovillous growth (red) arising in the intrahepatic large bile duct and progressing to invasive carcinoma (IPN with invasion; orange).

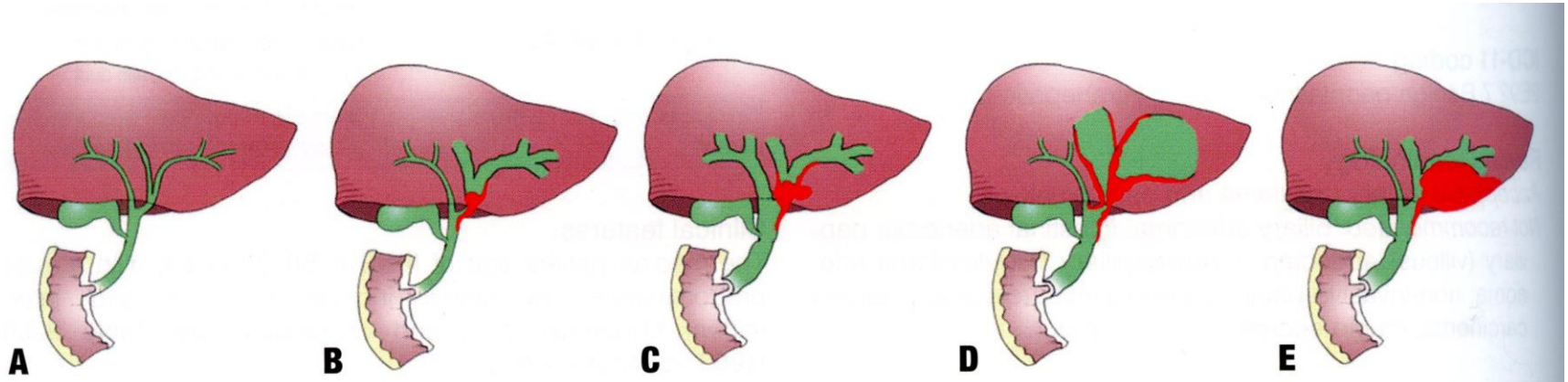


Fig. 9.09 Intraductal papillary neoplasm of the bile ducts (IPNB). Schematic representation of several pathoradiological patterns of IPNB (shown in red). **A** Normal hepatobiliary system. **B** Mass-forming IPNB with secondary dilatation of proximal bile ducts. **C** IPNB with proximal and distal bile duct dilatation due to excessive mucin hypersecretion. **D** Cystic dilatations of the proximal and distal bile ducts due to excessive mucin hypersecretion of the IPNB. **E** Cholangiocarcinoma derived from IPNB with marked invasion into the adjacent hepatic parenchyma (red).

Table 9.03 Characteristics of intraductal papillary neoplasms of the bile ducts based on similarities to their pancreatic counterparts, according to the Japan–Korea Cooperative Study Group {2295}

Characteristic	Type 1	Type 2
Preferential location	Intrahepatic bile ducts	Extrahepatic bile ducts
Gross features of ducts	Cystic, cylindrical dilatation	Cylindrical, fusiform dilatation
Excessive mucin	Frequent	Rare
Histology		
Lining epithelia	Regular, homogeneous Papillary > tubular	Irregular, complex Papillary > tubular; foci of cribriform and solid pattern
Fibrous core	Fine fibrovascular stroma	Fine vascular, focally fibrotic stroma
Subtype	Gastric, intestinal	Intestinal, pancreatobiliary
Grade	Mostly high grade, with foci of low/intermediate grade; infrequently low/intermediate grade	Always high grade, sometimes with foci of low/intermediate grade
Stromal invasion	Less common (< 50%) and minimal, occasionally nodular	Common (> 80%) and minimal, mild
Similarity to IPMN	Similar	Variably different
Aggressiveness	Less aggressive	More aggressive than type 1
Postoperative course	More favourable	Worse than type 1

IPMN, intraductal papillary mucinous neoplasm.

Box 9.02 Differential diagnosis of intraductal papillary neoplasm of the bile ducts

Micropapillary biliary intraepithelial neoplasia (BilIN)

- Microscopically recognizable lesions in the intrahepatic large bile ducts
- < 3 mm in height
- Constantly intermixed with flat or pseudopapillary BilIN

Intraductal tubulopapillary neoplasm

- Cast-like lesion composed of densely packed neoplastic tubular glands in the duct
- Unequivocal architectural and cytological atypia (high grade)
- No mucinous content, negative for MUC5AC

Intraductal polypoid metastasis from extrahepatic organs

- Metastasis from colorectal carcinoma is common

10) 予後：low-grade dysplasiaは完全に切除されれば、再発、転移しない。IPNBに由来する浸潤癌の再発率と生存率は 47.0%, 68.8%で、通常の肝内胆管癌や肝外胆管癌と比較して予後が良い。浸潤の深さや割合は生存率と相関する。Pancreatobilliary type のもの gastric, intestinal typeと比較し、 high gradeで、リンパ節転移が多く、再発率も高く、予後も悪い。
Colloid carcinomaは tubular adenocarcinomaより予後が良い。

Pathologic Features of Mucin-producing Bile Duct Tumors

Two Histopathologic Categories as Counterparts of Pancreatic Intraductal Papillary-mucinous Neoplasms

Hiroaki Shibahara, MD,† Shugo Tamada, MD,* Masamichi Goto, MD,* Koji Oda, MD,† Masato Nagino, MD,† Tetsuro Nagasaka, MD,‡ Surinder K. Batra, PhD,§ Michael A. Hollingsworth, PhD,§ Kohzoh Imai, MD,¶ Yuji Nimura, MD,† and Suguru Yonezawa, MD**

Abstract: Tumors with clinically recognizable mucin production arising from bile duct, "mucin-producing bile duct tumors (MPBTs)," have not been studied yet for their pathologic features and classification in details. The clinical findings of MPBT have a lot of similarities to those of pancreatic intraductal papillary-mucinous neoplasm. In the present study, we examined 30 MPBTs and classified them into two distinct morphologic categories: 22 cases of "columnar type" composed of pseudostratified columnar cells with basophilic cytoplasm and columnar nuclei and 8 cases of "cuboidal type" composed of pancreaticobiliary and/or oncocytic pattern. Pancreaticobiliary pattern showed abundantly branched papillae lined by acidophilic cuboidal cells with round nuclei, whereas oncocytic pattern was characterized by intraepithelial lumina and cribriform pattern composed of abundant oxyphilic cells with round nuclei, and these patterns overlapped frequently. There were significant differences in the clinicopathologic findings including macroscopic findings, morphometric data, mucin expression profiles (MUC2 expression in columnar type and MUC6 expression in cuboidal type), and cell proliferative activities between columnar type and cuboidal type. Patients with columnar type showed significantly poorer survival than those with cuboidal type. We concluded that columnar type and cuboidal type of MBPTs belong to different lineage of neoplasm and that they are counterparts of "intestinal type" and "pancreaticobiliary type" of pancreatic intraductal papillary-mucinous neoplasm, respectively.

Key Words: bile duct neoplasms, classification, immunohistochemistry, nuclear morphometry, prognosis

(*Am J Surg Pathol* 2004;28:327–338)

Tumors with clinically recognizable mucin production arising from bile duct have been reported as "mucus producing bile duct carcinoma,"[25] "mucin-producing cholangiocarcinoma,"[31,32] "mucin-producing cholangiocellular carcinoma,"[10] "mucin-producing biliary papillomatosis,"[28] "mucin ball-producing extrahepatic bile duct carcinoma,"[17] "intraductal mucosal-spreading mucin-producing peripheral cholangiocarcinoma,"[22] "mucin-hypersecreting intrahepatic biliary neoplasms,"[21] "mucin-hypersecreting bile duct tumor,"[19] and "mucin-hypersecreting papillary cholangiocarcinoma"[20] as clinical entities. Sakamoto et al reported a characteristic feature of mucin-producing cholangiocarcinoma, which showed an apparent mucin production radiographically with cystic or ductectatic tumor growth pattern.[31,32] The clinical entities of

TABLE 3. Ki-67 Labeling in Columnar-Type and Cuboidal-Type

Classification	n	Mean ± SD*	*P*
Columnar-type (CL)	22	34.1 ± 21.5	0.0462
Cuboidal-type (CB)	8	16.6 ± 13.5	

*Number of Ki-67-positive cells/number of tumor cells (%).

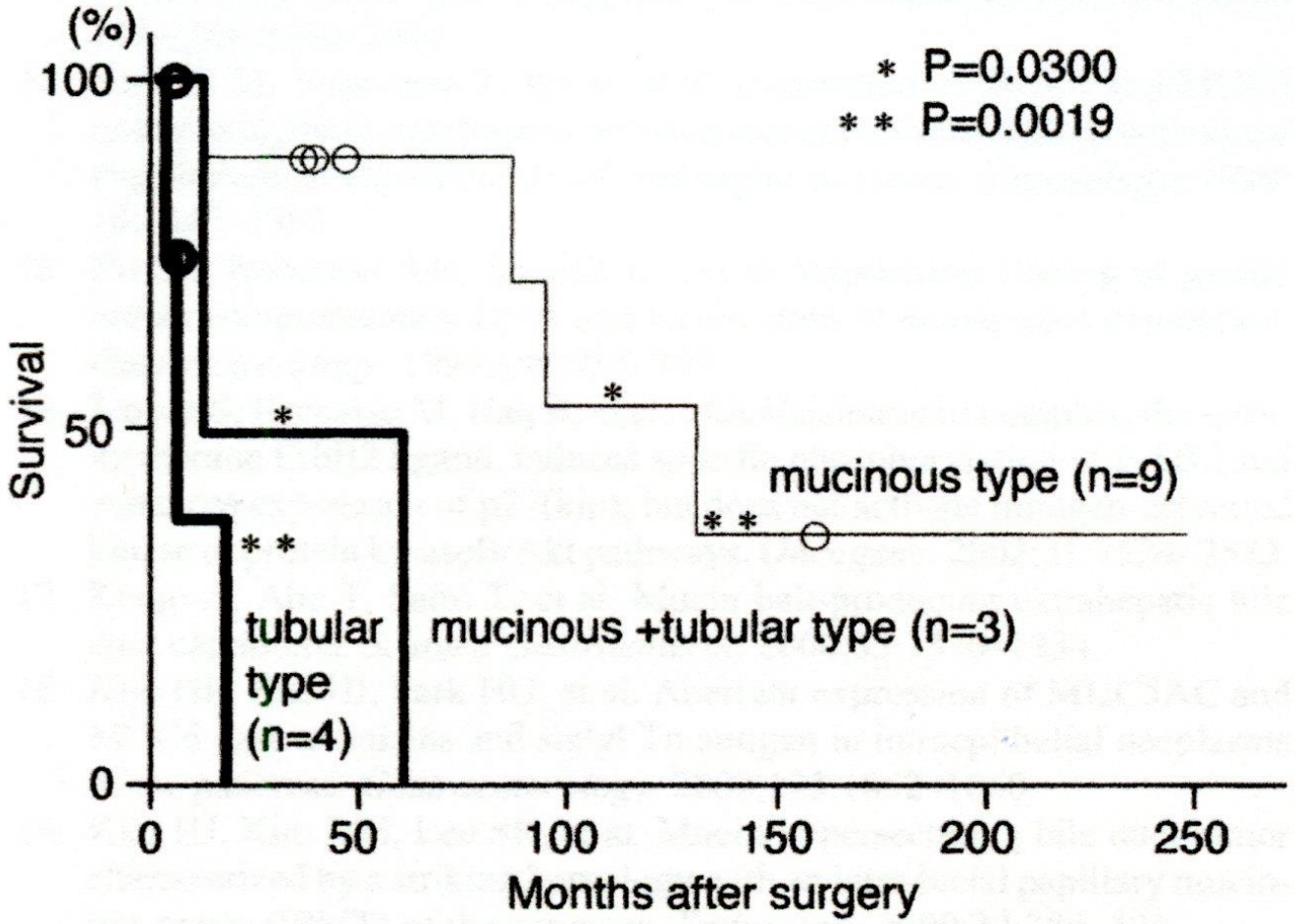


FIGURE 8. Survival status of 16 patients with different types of invasive carcinoma. The patients with tubular type showed significantly poorer survival than those with mucinous type ($P = 0.0019$) or than those with mucinous and tubular type ($P = 0.0300$).

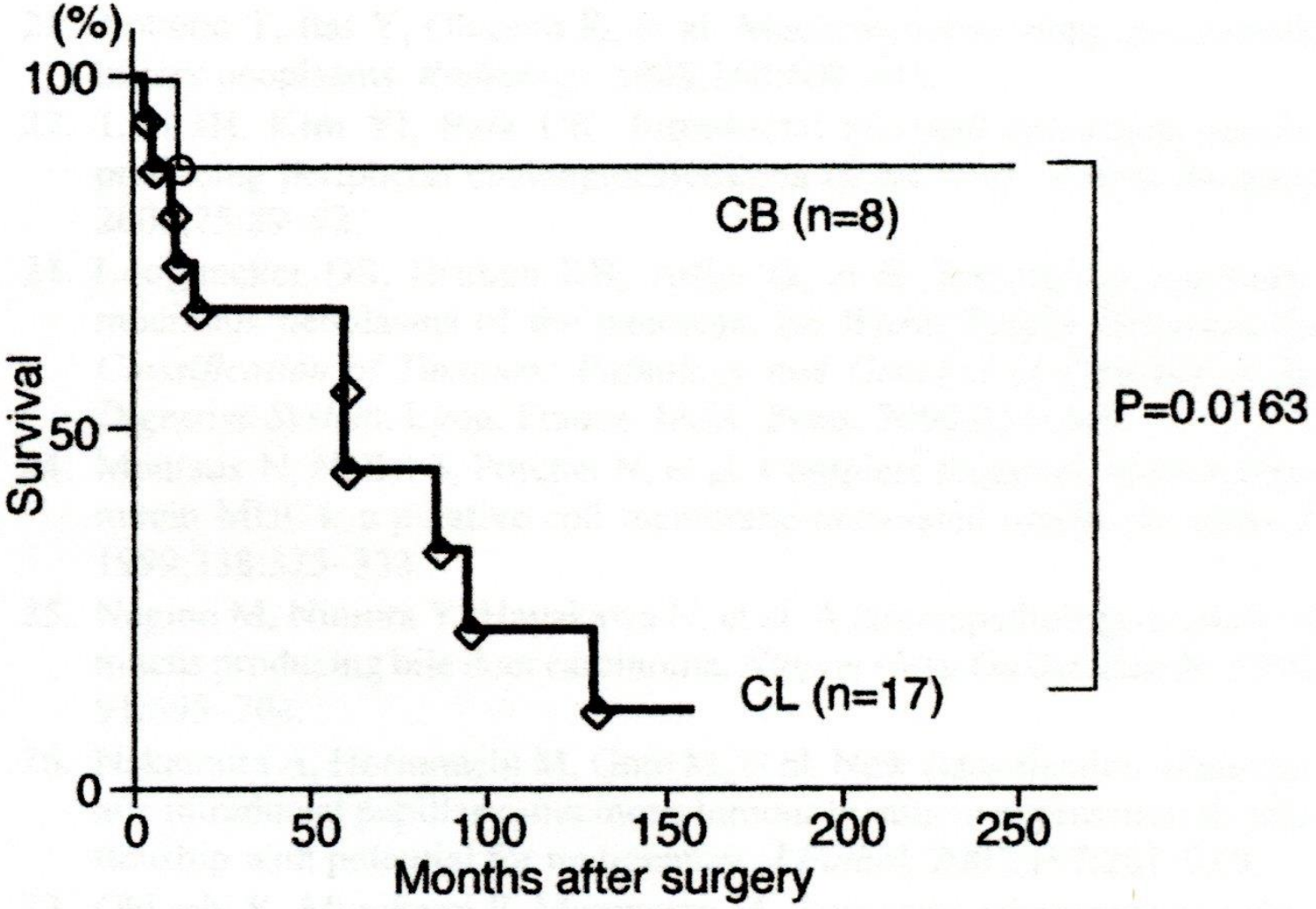


FIGURE 9. Correlation of survival rate between columnar-type (CL) and cuboidal-type (CB) in carcinoma (25 patients) demonstrated by the Kaplan-Meier method.

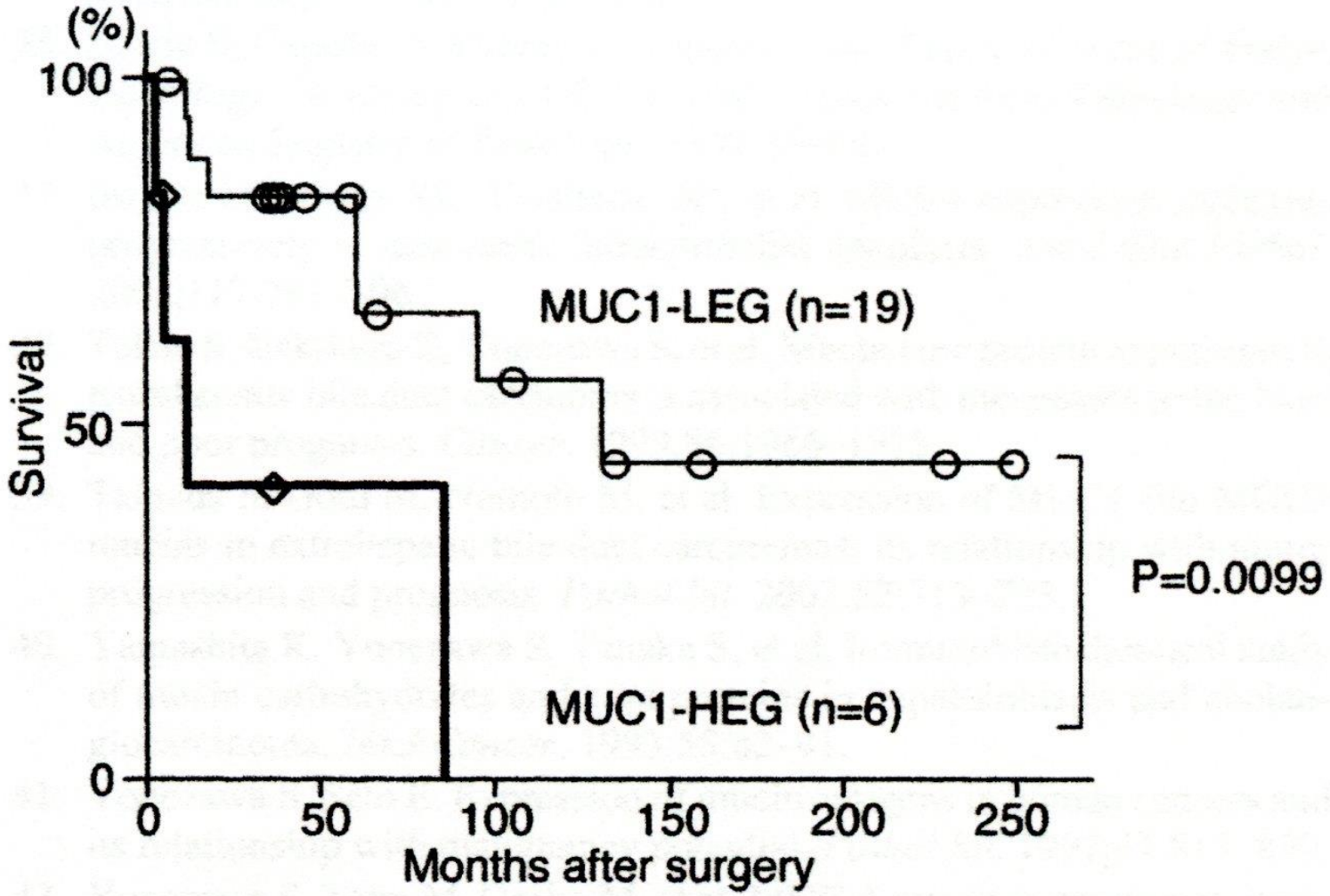


FIGURE 10. Correlation of survival rate between high expression group (HEG) and low expression group (LEG) of MUC1 in carcinoma (25 patients) demonstrated by the Kaplan-Meier method.

Similarities and Differences Between Intraductal Papillary Tumors of the Bile Duct With and Without Macroscopically Visible Mucin Secretion

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Abstract: Intraductal papillary neoplasms of the bile duct (IPNB) have been recently proposed as the biliary counterpart of intraductal papillary mucinous neoplasms of the pancreas (IPMN-P). However, in contrast to IPMN-P, IPNB include a considerable number of the tumors without macroscopically visible mucin secretion. Here we report the similarities and differences between IPNB with and without macroscopically visible mucin secretion (IPNB-M and IPNB-NM). Surgically resected 27 consecutive cases with IPNB were divided into IPNB-M (n = 10) and IPNB-NM (n = 17), and their clinicopathologic features were examined. Clinically, both tumors were similar. Pathologically, the most frequent histopathologic types were pancreatobiliary in IPNB-NM and intestinal in IPNB-M. Various degrees of cytoarchitectural atypia within the same tumor were exhibited in 8 IPNB-M, but only 3 in IPNB-NM. Although the tumor size was similar, 9 IPNB-NM were invasive carcinoma, whereas all but 1 IPNB-M with carcinoma were in situ or minimally invasive. Immunohistochemically, positive MUC2 expression was significantly more frequent in IPNB-M than in IPNB-NM, whereas MUC1 tended to be more frequently expressed in IPNB-NM compared with IPNB-M. Among IPNB-NM with positive MUC1 expression, 3 had negative MUC2 and MUC5AC expressions. These tumors showed a tubulopapillary growth with uniform degree of cytoarchitectural atypia. All IPNB-M were negative for p53, and the frequency of positive p53 protein in IPNB-NM was at the middle level of that in IPNB-M and nonpapillary cholangiocarcinoma. In conclusion, IPNB-M showed striking similarities to IPMN-P, but IPNB-NM contained heterogeneous disease groups.

Key Words: bile duct neoplasm, pathology, mucins, p53, cholangiocarcinoma

(*Am J Surg Pathol* 2011;35:512–521)

Bile duct tumors with macroscopically visible mucin secretion are a rare form among bile duct neoplasms. These tumors show predominantly papillary or, rarely, flat growth within the dilated bile duct lumen, and secrete a large amount of mucin, which is often seen draining from a patulous orifice of the duodenal papilla. As these features are similar to those in intraductal papillary mucinous neoplasms of the pancreas (IPMN-P), it is speculated that this type of tumor is a biliary counterpart of IPMN-P.[11,17,19] Microscopically, both types of tumor are composed of papillary fronds with fine vascular cores. Neoplastic epithelial cells of both tumors can be of the pancreatobiliary type or can show gastric or intestinal differentiation, and show a spectrum of cytoarchitectural atypia ranging from none to borderline to marked and can be associated with invasive carcinoma as well. On the basis of these results, the nomenclature, "intraductal papillary mucinous tumor of the bile ducts" has been used for such tumors.[12]

In contrast, biliary intraductal tumors without macroscopically visible mucin secretion are also encountered more frequently than tumors with mucin secretion. Similar to tumors with macroscopically visible mucin secretion, these tumors have a macroscopically recognizable papillary or granular structure, but no clinically visible mucin secretion. As certain morphologic features of these tumors, especially intraductal papillary growth patterns, are also similar to those of IPMN-P, Zen et al[24] recently proposed that they, together with tumors with macroscopically visible mucin secretion, may belong to a single tumor entity, "intraductal papillary neoplasms of

GNAS Is Frequently Mutated in a Specific Subgroup of Intraductal Papillary Neoplasms of the Bile Duct

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Abstract: Intraductal papillary neoplasms of the bile duct (IPN-Bs) share clinicopathologic features with intraductal papillary mucinous neoplasms (IPMNs) of the pancreas. Approximately two thirds of IPMNs have activating point mutations of *GNAS* at codon 201. The role of *GNAS* mutation is unclear in IPN-B. In this study, we evaluated 41 patients diagnosed with IPN-B for clinicopathologic characteristics and follow-up information. Mutation analyses of *GNAS* and *KRAS* were performed. Twenty-three cases (56.1%) of IPN-B were categorized as the intestinal subtype, and 18 (43.9%) were considered the gastric/pancreatobiliary subtype. IPN-Bs showing intestinal differentiation demonstrated high immunohistochemical expressions of CK20, CDX2, and MUC2, as well as a significant association with macroscopic and microscopic mucin hypersecretions and villous architecture. *GNAS* and *KRAS* mutations were detected in 29% and 32% of IPN-Bs, respectively. All IPN-Bs with *GNAS* mutation showed intestinal differentiation. *GNAS*-mutated IPN-B was highly significantly associated with certain pathologic characteristics, including macroscopic and microscopic mucin hypersecretion and villous architecture. IPN-B with *GNAS* mutation tended to more frequently harbor *KRAS* mutation than those without *GNAS* mutation. IPN-Bs with intestinal differentiation, villous architecture, and mucin hypersecretion constitute a distinct subgroup of IPN-B, which frequently has *GNAS* mutation. This subtype shares common genetic alterations with IPMN of the pancreas.

Key Words: GNAS, KRAS, mucin, intraductal papillary neoplasm of the bile duct

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Intraductal papillary neoplasms of the bile duct (IPN-Bs) are rare neoplasms of the bile duct and are characterized by intraductal tumorous growth of the dysplastic biliary epithelium with fibrovascular cores. IPN-B is a precursor lesion of cholangiocarcinoma distinct from biliary intraepithelial neoplasms.[1] It is considered to be the biliary counterpart of intraductal papillary neoplasm of the pancreas.[2,3] The prognosis for patients with IPN-B is excellent when the tumor is surgically resectable and not associated with an invasive component.[4] When an invasive carcinoma is present, the survival is related to tumor stage and histologic type.[5] Thus far, the molecular pathogenesis of IPN-B is still unknown.

A subset of IPN-B is characterized by excessive mucin secretion and is described using the terms "mucin-producing bile duct tumor," "mucin-hypersecreting bile duct tumor," or "IPN-B with macroscopically visible mucin secretion.[6–8] This subset of IPN-Bs is associated with hepatolithiasis[9] and has a tendency to show intestinal differentiation[6,7,10,11] and has $MUC1^-/MUC2^+$ immunophenotypes.[6,7] Most reports of mucin-producing bile duct tumors come from East Asian countries, including Japan, South Korea, China, and Taiwan.[3,6,8,10,11] These observations suggest that IPN-B is a heterogenous disorder with different epidemiologies, morphologies, and pathogeneses.

Recently, a high percentage of intraductal papillary mucinous neoplasms (IPMNs) of the pancreas were found to harbor activating mutations of *GNAS*.[12,13] *GNAS* encodes the α subunit of stimulatory guanine nucleotide–binding protein (Gsα), which regulates adenylate cyclase activity upon activation of G-protein-coupled receptors.[14] Postzygotic mutation of *GNAS* results in McCune-

Recurrent Mutations in *APC* and *CTNNB1* and Activated Wnt/β-catenin Signaling in Intraductal Papillary Neoplasms of the Bile Duct

A Whole Exome Sequencing Study

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Abstract: This study aimed to elucidate the genetic landscape of biliary papillary neoplasms. Of 28 cases examined, 7 underwent whole exome sequencing, while the remaining 21 were used for validation studies with targeted sequencing. In the whole exome sequencing study, 4/7 cases had mutations in either *APC* or *CTNNB1*, both of which belong to the Wnt/β-catenin pathway. Somatic mutations were also identified in genes involved in RAS signaling (*KRAS*, *BRAF*), a cell cycle regulator (*CDC27*), histone methyltransferase (*KMT2C*, *KMT2D*), and DNA mismatch repair (*MSH3*, *MSH6*, *PMS1*). Combined with discovery and validation cohorts, mutations in *APC* or *CTNNB1* were observed in 6/28 subjects (21%) and were mutually exclusive. When the cases were classified into intraductal papillary neoplasms of the bile duct (IPNBs, n = 14) and papillary cholangiocarcinomas (n = 14) based on the recently proposed classification criteria, mutations in *APC* and *CTNNB1* appeared to be entirely restricted to IPNBs with 6/14 cases (43%) harboring mutations in either gene. These genetic alterations were detected across the 3 nonintestinal histologic types. In immunohistochemistry, the aberrant cytoplasmic and/or nuclear expression of β-catenin was found in not only 5/6 IPNBs with *APC* or *CTNNB1* mutations, but also 6/8 cases with wild-type *APC* and *CTNNB1* (total 79%). In addition, *APC* and *CTNNB1* alterations were exceptional in nonpapillary cholangiocarcinomas (n = 29) with a single case harboring *CTNNB1* mutation (3%). This study demonstrated recurrent mutations in *APC* and *CTNNB1* in nonintestinal-type IPNBs, suggesting that activation of the Wnt/β-catenin signaling pathway is relevant to the development and progression of IPNBs.

Key Words: intraductal papillary neoplasm, cholangiocarcinoma, bile duct, exome sequencing, Wnt/β-catenin

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Intraductal papillary neoplasm of the bile duct (IPNB) is a distinct type of tumor with unique clinicopathologic features.[1] According to the World Health Organization Classification of Tumours of the Digestive System published in 2010, it is defined as a noninvasive papillary or villous neoplasm covering delicate fibrovascular stalks.[1] The affected bile ducts are often extensively dilated, and, thus, mimic cystic neoplasms. Another pathologic feature is mucin overproduction. This recently proposed entity encompasses previous categories including biliary papilloma (tosis),[2,3] mucin-producing bile duct tumors,[4,5] and biliary cystadenocarcinomas with no ovarian-like stroma.[6] IPNBs are more common in East Asia than in Western countries.[7] The higher prevalence of hepatolithiasis and clonorchiasis in Korea and Taiwan is partly responsible for this demographic difference, particularly the higher incidence of intestinal-type cases in those Asian countries.[2–5,7] In contrast, IPNBs reported from Japan, the United States, and European countries are mainly sporadic and not associated with chronic biliary diseases.[7–9]

Although the current definition of IPNBs covers nearly all papillary tumors developed in the bile duct, we recently

The Pathologic and Genetic Characteristics of the Intestinal Subtype of Intraductal Papillary Neoplasms of the Bile Duct

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Abstract: The present study aimed to identify the pathologic and genetic characteristics of intestinal subtype of intraductal papillary neoplasm of the bile duct (iIPNB) showing columnar cells with pseudostratified, cigar-shaped nuclei, and basophilic or amphophilic cytoplasm with the diffuse immunohistochemical expression of CK20 and/or CDX2. A total of 34 cases of iIPNB were pathologically examined according to their anatomic location (the bile duct) and were then compared with the intestinal subtype of intraductal papillary mucinous neoplasm (iIPMN) of the pancreas (n = 22). Mutations of 26 somatic genes were examined in formalin-fixed paraffin-embedded tissue specimens from 21 cases of iIPNB using the TruSight Tumor 26 gene panel and next-generation sequencing. iIPNB cases were divided into intrahepatic (n = 6) and extrahepatic (n = 28) categories. Intrahepatic IPNBs showed a less-complicated villous-papillary pattern, while extrahepatic IPNBs showed a papillary pattern with tubular and/or villous components and predominant high-grade dysplasia with complicated architectures. MUC5AC was frequently and extensively expressed in intrahepatic iIPNBs and iIPMNs but not in extrahepatic iIPNBs. CD10 was frequently expressed in extrahepatic IPNBs but not in intrahepatic iIPNBs or iIPMN. Genetic mutations of *TP53* and *PIK3CA*, which were infrequent or absent in iIPMNs, were frequently detected in extrahepatic iIPNBs, while *KRAS* and *GNAS*, which were commonly observed in iIPMNs, were frequently detected in intrahepatic iIPNBs. Intrahepatic iIPNBs showed villous-papillary growth with features reminiscent of iIPMNs, while extrahepatic iIPNBs showed papillary growth with tubular and/or villous components, complicated histology and variable differences from iIPMNs, suggesting differences in the tumorigenesis of iIPNBs along the biliary tree.

Key Words: biliary tree, intraductal papillary neoplasm of bile duct, intestinal subtype, intraductal papillary mucinous neoplasm of pancreas, next-generation sequencing

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Recently, several types of intraductal neoplasm of the bile duct, including intraductal papillary neoplasms of the bile duct (IPNBs) and intraductal tubulopapillary neoplasms (ITPNs), have been recognized at a preinvasive stage.[1–5] IPNBs are a unique type of biliary tumor showing grossly visible, intraductal predominant papillary or villous growth covered by a neoplastic epithelium with fine fibrovascular cores in the dilated bile ducts. IPNBs are known to show heterogenous morphologies and different biological and clinical behavior,[6–9] suggesting that they may exhibit diversity in their pathology and tumorigenesis. Such variations are one source of controversy in relation to the clinicopathologic recognition and diagnosis of IPNB.[10–12]

Interestingly, intraductal neoplasms of the bile duct and intraductal neoplasms of the pancreas reportedly share many features, and the concept that IPNB is the biliary counterpart of intraductal papillary mucinous neoplasm (IPMN) of the