15. IgG4-related diseases and the liver

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ABSTRACT

IgG4-related disease (IgG4-RD) is a systemic illness including autoimmune pancreatitis and IgG4-related sclerosing cholangitis (IgG4-SC). Although hepatic presentation of IgG4-RD has been reported, whether intrahepatic small bile ducts and hepatocytes are direct targets of IgG4-RD is uncertain. IgG4-RD is pathologically characterized by the numerous $IgG4^+$ cells found in affected organs, but this IgG4 positivity is also frequently found in extrahepatic cholangiocarcinoma and is prominent, albeit rarely, in other hepatobiliary diseases including primary sclerosing cholangitis and autoimmune hepatitis. Moreover, cholangiocarcinoma arising from precedent IgG4-SC and IgG4-SC accompanying precursor lesions of cholangiocarcinoma (biliary intraepithelial neoplasia) are also reported. Diagnostic criteria for IgG-RD and IgG4-SC were recently proposed, but each individual case should be diagnosed clinicopathologically on the basis of its individual features.

Chapter keywords: cholangiocarcinoma, IgG4-sclerosing cholangitis, IgG4-hepatopathy, IgG4-associated autoimmune hepatitis, primary biliary cirrhosis

15.1 Introduction

IgG4-related disease (IgG4-RD) and its systemic nature were first described in Japan (1-5). IgG4-RD most profoundly affects the pancreas but involves most organs in the human body, including the pituitary gland, lacrimal glands, salivary glands, lungs, breast, bile duct, aorta, kidney, lymph nodes, retroperitoneum, and prostate. Initial or secondary presentation in the liver, skin, peripheral nerves, and gastrointestinal tract has also been reported. Infiltrates of numerous $IgG4^+$ plasma cells in affected organs are important pathological findings of IgG4-RD. Obliterative phlebitis, storiform-type sclerosing fibrosis, and sometimes mass-forming type sclerosing fibrosis in the lung, pancreas, and liver are also characteristics of this disease. Regardless of the organ in which IgG4-RD develops, elevated serum IgG4 (≥135 mg/dL) and marked efficacy of steroid therapy are common characteristics. The prototype IgG4-RD disease is type I autoimmune pancreatitis (AIP). IgG4-related sclerosing cholangitis (IgG4-SC) involves sclerosing cholangitic lesions that arise as complications of AIP or, rarely, are isolated in the biliary tract system. IgG4-SC lesions share the characteristic features of AIP. Hepatic presentation of IgG4-RD has also been described in the literature (6-8); whether such disease is a primary liver manifestation or simply the extension of IgG4-SC into intrahepatic bile ducts is unclear. In this chapter, we summarize the present knowledge of IgG4-SC and several inflammatory and neoplastic hepatobiliary diseases accompanied by $IgG4^+$ cells.

15.2 IgG4-SC

IgG4 is a minor immunoglobulin subtype composing 3%–6% of the total IgG circulating in adults (1). Systemic IgG4-RD features elevated serum IgG4 levels and abundant infiltration with $IgG4^+$ plasma cells in affected organs (1, 9, 10). IgG4-SC can be viewed as a manifestation of IgG4-RD in the bile duct. In the differential diagnosis of IgG4-SC, primary sclerosing cholangitis (PSC, another prototype of sclerosing cholangitis), and cholangiocarcinoma are also clinicopathologically important. Each of these diseases requires an appropriate diagnosis and therapy, but their differentiation is not always easy.

IgG4-SC exhibits severe inflammatory cell infiltrates containing abundant IgG4-bearing plasma cells and biliary sclerosis as a result of progressive fibrosis within the bile duct wall that leads to bile duct stenosis (Fig.1). These diffuse or localized sclerotic and stenotic lesions are found in the large bile ducts of the hepatic hilus, extrahepatic bile ducts, and, in some cases, the gall bladder. These biliary lesions show circumferential wall thickening and are prominent at stenotic sites. Similar inflammatory lesions are also common at non-stenotic biliary sites. IgG4-SC cases not involving other organs are rare; most cases are associated with AIP, particularly those with lesions in the intrapancreatic bile ducts. As with IgG4-RD in other organs, serum IgG4 values of IgG4-SC patients are usually elevated to ≥135 mg/dL, and the lesions are reversible and responsive to steroid therapy.

Similar to the pancreatic ducts, the extrahepatic bile duct and gallbladder are covered by a single layer of epithelium and have peribiliary glands (11). Histologically, bile duct lesions in IgG4-SC resemble the inflammatory and sclerosing lesions found in the pancreatic duct of AIP. Characteristics of IgG4-SC lesions are as follows: 1) inflammation, mainly affecting the bile duct wall (chronic cholangitis) but also particularly prominent around peribiliary glands; the biliary epithelium is relatively preserved; 2) marked lymphoplasmacytic cell infiltration, fibrosis, and luminal stenosis in affected regions of the bile ducts; 3) storiform fibrosis, a characteristic of AIP, is observed in IgG4-SC cases with marked fibrosis; 4) numerous IgG4-bearing plasma cells, as revealed by immunohistochemical staining; and 5) obliterative phlebitis and perineural infiltration of $IgG4^+$ cells (Fig.1). As seen in mass-forming pancreatitis, exacerbated inflammation from the hilum to the intrahepatic large bile duct can lead to inflammatory pseudotumors in the liver and hepatic hilus. Before the first report of IgG4-related AIPby Hamano et al. in 2001 (1), Nonomura et al. had reported in 1997 on a case of hepatic hilar inflammatory pseudotumor with cholangitis and phlebitis mimicking cholangiocarcinoma (12). We later confirmed that the lesions in this case were IgG4-related (Fig.2). At present, 2 types of inflammatory pseudotumors, fibrohistiocytic and lymphoplasmacytic, have been proposed. The latter is thought to be representative of IgG4-RD (13, 14).

As mentioned above, most IgG4-SC cases accompany IgG4-related AIP, but rare cases without the involvement of other organs are encountered. IgG4-SC cases

without pancreatic lesions are surely present. But whether the presence or absence of pancreatic lesions reflects differences in the pathological features of the IgG4 reaction in IgG4-SC or merely reflects differences in the pathological phenotype of systemic IgG4-RD is unclear. The characteristics of IgG4-SC not associated with pancreatic lesions have been described as follows (15, 16): 1) mainly affects middle-aged to elderly men; 2) serum IgG4 is normal or only slightly elevated in most cases; 3) cases with IgE and soluble IL-2 receptor elevation and antinuclear antibody^{+} status are frequent; 4) affected bile ducts show relatively long and flat narrowing, but peripheral bile duct stenosis is mild; and 5) affected bile ducts show marked IgG4^{+} plasmacytic cell infiltration. However, cases of IgG4-SC alone are clinically very hard to differentiate from biliary tumor, particularly cholangiocarcinoma. Although the cases of isolated IgG4-SC mainly display hilar biliary strictures, isolated intrapancreatic IgG4-SC is also reported (16). Of the five cases included in this report, all patients were male, with a mean age of 74.2 years. Bile duct wall thickening in lesions without luminal stenosis was detected using abdominal computed tomography in all the five cases. Interestingly, in three of the cases, serum IgG4 levels were within normal limits. The mean serum IgG4 level measured before surgery was 202.1 mg/dL (four cases). Isolated intrapancreatic IgG4-SC is difficult to diagnose, particularly if the IgG4 level remains normal (15, 17). Diagnostic criteria for IgG4-SC have been proposed by two groups in Research on Measures for Intractable Diseases supported by a Health Labour Sciences Research Grant in Japan. Characteristic and diagnostically-useful histological findings of bile duct tissue specimens include: 1) IgG4^{+} plasmacytic cell infiltration

(≥10/high power field (hpf); IgG4/IgG positive cell ratio of ≥40%); 2) marked lymphoplasmacytic cell infiltration and fibrosis, without neutrophil infiltration; 3) obliterative phlebitis or swirling fibrosis; and 4) storiform fibrosis. However, identification of these characteristics in small biopsy specimens obtained from the surface of the bile duct is difficult. Alternatively, the Diagnostic Criteria for AIP (the HISORt Criteria) proposed by the Mayo Clinic (18) have been applied to the diagnosis of IgG4-SC (19). These criteria emphasize $IgG4^+$ plasmacytic cell infiltration, although abundant $IgG4^+$ cell infiltration is important in the histology of IgG4-RD. Because the infiltration of $IgG4^+$ cells is of varying degrees in the cases of cholangiocarcinoma described, care must be taken not to be overly influenced by diagnostic criteria that overemphasize $IgG4^+$ cell infiltration in affected organs. Therefore, no single diagnostic criteria should be strictly followed; rather, each individual case should be clinicopathologically diagnosed on the basis of its own individual features.

In the pathogenesis of IgG4-RD including IgG4-SC, the activation of the Th2 immune response has been confirmed by several studies (20-24). Two regulatory cytokines, IL-10 and transforming growth factor-beta, are also significantly overexpressed in IgG4-RD (20). IL-10, a regulatory cytokine mainly produced by $Foxp3^+$ regulatory T cells (Treg cells), Th2 cells, and IL-10-producing regulatory T cells, is thought to induce the differentiation of $IgG4^+$ plasma cells and favor B-cell switching to IgG4 in the presence of IL-4 (25-27). In the presence of this cytokine

milieu, the induction of $IgG4^+$ cells and fibrous sclerosing lesions could occur in other diseases and in coexisting inflammatory lesions in addition to IgG4-RD (28).

15.3 Biliary distribution of $IgG4^+$ cells in IgG4-SC

In IgG4-SC, numerous $IgG4^+$ cells are found in the affected regions of bile ducts. These cells accompany other characteristic findings such as a predominance of $IgG4^+$ cells among IgG^+ cells and a unique pattern of sclerosing fibrosis. In addition, other regions of the biliary tree are affected. Therefore, biopsies from the Papilla of Vater to the peripheral intrahepatic small bile ducts, which are relative easily obtained, are useful for diagnosing IgG4-SC.

Inflammation of the Papilla of Vater (papillitis) is commonly found in several inflammatory and neoplastic pancreatiobiliary diseases. Although duodenitis, including papillitis, is generally thought to be non-specific in IgG4-SC and AIP, papillitis accompanying $IgG4^+$ plasmacytic cell infiltration is speculated to be an evidence of IgG4-SC and AIP (Fig.3). Moreover, the $IgG4^+$ cell infiltration found in the papilla of Vater in IgG4-SC and AIP is severe compared with that of PSC, pancreatic cancer, and bile duct cancer, but the swelling and magnitude of $IgG4^+$ cell infiltration do not correlate (29).

Moreover, the site of the biliary tree opposite to the affected bile duct is also involved in IgG4-SC. Therefore, a liver needle biopsy obtained from the periphery of the liver is also useful for diagnosing IgG-SC and AIP (8). Closed pathological examination of partially hepatectomized or autopsied liver specimens reveals an infiltration of $IgG4^+$ cells that are continuously and broadly distributed among intrahepatic bile ducts; $IgG4^+$ cells are scattered in the small portal tracts containing the interlobular and septal bile ducts found in needle liver biopsies (Fig.4). Although intrahepatic small bile ducts as well as large bile ducts may be the target organs of IgG4-SC, the portal inflammation including $IgG4^+$ cells is thought to result from $IgG4^+$ cells spreading along the biliary tree from IgG4-SC lesions in the hepatic hilus.

15.4 IgG4 hepatopathy

Varying degrees of liver dysfunction are found in 50%–70% of patients with IgG4-related AIP (8, 30). Clinicopathological studies reveal an intrahepatic $IgG4^+$ cell infiltration of ≥5/hpf in approximately 50% of AIP patients; the degree of infiltration correlates with serum IgG4 values (8, 30). A correlation is observed between parenchymal inflammation and AST values and between cholestasis and serum bilirubin levels. The hepatic lesions observed in AIP patients are known as IgG4-hepatopathy (8). Whether the pathogenesis of IgG4-RD, including IgG4-SC, involves an autoimmune response, and whether hepatic parenchymal cells such as hepatocytes and

cholangiocytes of intrahepatic small bile ducts are target organs of IgG4-RD are unknown. However, the serum IgG4 levels and the incidence of IgG4-bearing cells in affected organs is higher in patients with IgG4-RD than in patients with other autoimmune-mediated liver diseases such as AIH, primary biliary cirrhosis (PBC), and PSC (8). On pathological analysis, liver biopsy specimens from patients with AIP reveal a marked infiltration of inflammatory cells, including $IgG4^+$ plasma cells, in small intrahepatic portal tracts (5, 8, 31). Umemura et al. (8) specifically surveyed the histology of liver biopsies from patients with AIP to clarify the pathogenesis of clinical liver injury, noting 5 intrahepatic histological patterns: portal inflammation, large bile duct damage, portal sclerosis, lobular hepatitis, and cholestasis (Fig.5). Multiple histological patterns were found to coexist. The portal inflammation pattern consists of an intense infiltration of mononuclear cells containing plasma cells, with or without interface hepatitis. If these intrahepatic findings are isolated in the liver without IgG4-SC, they are presumed to be a liver manifestation of IgG-RD in AIP patients. In contrast, if the histological lesions of IgG4-SC are always present in AIP patients, despite the absence of clinical or radiological findings, all intrahepatic findings identified in AIP patients can be considered secondary to extrahepatic bile duct damage associated with IgG4-SC. Portal inflammation may be involved in IgG4-SC, causing the progression of periductal inflammation along the biliary tracts and the smaller tracts encountered in needle liver biopsies. Moreover, based on our experience of patients with serum IgG4 >1000 mg/dL, interface hepatitis and hepatitis-associated bile duct injury are also found, suggesting a correlation between the severity of inflammation in

the affected extrahepatic bile ducts and the degree of inflammatory extension along intrahepatic bile ducts. The pattern of large bile duct damage is characterized by ductular proliferation, neutrophil infiltration, and edematous change in the portal areas. These findings are well known to occur secondarily to stenosis and the obstruction of extrahepatic bile duct, irrespective of any biliary diseases. The portal sclerosis pattern is consistent with dense fibrosis. In general, portal inflammation is scarce in sclerotic portal tracts; however, the sclerotic change may be just a remnant of portal inflammation after the active inflammation subsides, and/or secondary portal tract fibrosis may be associated with sclerosing cholangitis involving the large or extrahepatic bile ducts. The lobular hepatitis pattern may resemble that of viral hepatitis. Pathology reveals a parenchymal inflammation pattern in conjunction with hepatocellular focal necrosis in the parenchyma. Mild parenchymal inflammation is observed in a variety of biliary diseases and is thought to be caused by cholestasis as a non-specific reactive change. The cholestatic pattern is a canalicular cholestasis found predominantly in the centrilobular area and is consistent with extensive stenosis and obstruction of the affected extrahepatic bile ducts, including intrapancreatic bile ducts. Although the combined findings of parenchymal inflammation (lobular hepatitis) and portal inflammation with an interface hepatitis may indicate a primary liver manifestation (32), all five pathological findings could be explained as secondary to sclerosing cholangitis or obstruction of the extrahepatic biliary tract and may not be specifically related to the histopathogenesis of IgG4-RD.

The liver-related manifestations of IgG4-RD are heterogeneous and not well described within the literature (8, 32, 33). Whether IgG4-hepatopathy is a primary liver manifestation of systemic IgG4-RD or an excess of $IgG4^+$ cells along the biliary tract due to IgG4-SC is unknown. However, IgG4-hepatopathy is an important finding for the diagnosis of IgG4-RD. Diagnosing IgG4-SC in the setting of AIP can be accomplished using the diagnostic criteria for AIP. In cases of IgG4-SC without pancreatic lesions, the presence or absence of IgG4-hepatopathy may be useful to differentiate it from conditions such as PSC and cholangiocarcinoma.

15.5 IgG4-associated autoimmune hepatitis

Elevated serum IgG4 levels have been reported in several patients diagnosed with AIH (6, 7, 34). IgG4-associated AIH is an identified disease entity characterized by definitive AIH according to the International Autoimmune Hepatitis Group (IAIHG) scoring system (35) and the histopathological features of IgG4-RD. IgG4-associated de novo AIH after liver transplantation has also been reported (36). In a survey of 60 patients with type 1 AIH, Umemura et al. reported that 2 out of 60 (3.3%) showed features suggesting IgG4-RD, with elevated serum IgG4 (≥135 mg/dL) and increased IgG4 positive cells in the portal tracts (≥10/hpf); however, liver histology indicated chronic active hepatitis accompanied by liver cell rosette formation, indistinguishable from classic AIH (7). Bile duct injury and cholestasis found in IgG4-hepatopathy, as

mentioned above, were not prominent in these two cases of IgG4-associated AIH (7). Additionally, Chung et al. (37) reported in a study of 26 AIH patients that AIH can be classified as either IgG4-associated or non–IgG4-associated. IgG4-associated AIH is characterized by higher infiltration of $CD3^+$ T cells, $CD20^+$ B cells, $CD38^+$ plasma cells, and IgG^+ cells as well as $IgG4^+$ cells in the liver. In contrast to classic AIH, these IgG4-associated AIH cases showed a marked response to prednisolone therapy, with improvements in serum IgG4 values, liver function, and liver histology (6, 36, 37). Some patients developed IgG4-SC during follow-up observation, and others had $IgG4^+$ cell infiltration in both the liver and the gallbladder (6). The scoring system of the International AIH Group has been widely used to diagnose AIH. Simplified criteria were adopted in 2008 (38), using parameters including autoantibodies, serum IgG values, hepatitis viruses, and pathological hepatic findings of lymphoplasmacytic cell infiltration in the portal tracts, interface hepatitis, hepatocytic rosette formation, and emperipolesis. On the basis of these simplified criteria, most IgG4-associated AIH cases are likely diagnosed as definite AIH. For both AIH diseases, regardless of the presence or absence of prominent $IgG4^+$ cells, immunosuppression with steroids is the mainstay of therapy. Future studies are needed to determine the significance and importance of differentiating between these diseases.

15.6 Overlap syndrome of IgG4-SC and PBC

PBC mainly affects middle-aged females. Histologically, the interlobular bile ducts are damaged and show characteristic findings of chronic nonsuppurative destructive cholangitis followed by progressive bile duct loss via apoptosis (39-41). Serologically, the presence of autoantibodies (antimitochondrial antibody (AMA) and anti-M2 antibody) is a specific indicator of PBC. The major proteins recognized by AMA are subunits of the 2-oxo acid dehydrogenase complexes, including the E2 components of the pyruvate dehydrogenase complex (PDC), the 2-oxo-glutarate dehydrogenase complex, the branched-chain 2-oxo acid dehydrogenase complex, and the E3 binding protein (E3BP or Protein X) (42). The etiopathogenesis of PBC remains speculative, but the cross-reaction of human and bacterial PDC-E2 with AMA and autoreactive T cells in PBC patients suspects the association of molecular mimicry in the pathogenesis of PBC (43-45). $CD4^+$ helper T cells are essential regulators of immune responses and inflammatory diseases. Immunoreactivity to intra- and extracellular antigens is primarily regulated by two different types of memory $CD4^+$ helper T cells. These Th1 and Th2 cells are principally distinguished by their production of different cytokines as well as their ability to induce either cellular (Th1) or humoral (Th2) immune reactions. Most studies on the Th1/Th2 balance in liver diseases have been based on the profile of cytokines using peripheral blood lymphocytes or liver tissues; such studies have classified PBC as a Th1-predominant disease (41, 46-48).

Whereas IgG4-SC is associated with systemic IgG4-RD diseases such as AIP, PBC is associated with a variety of autoimmune diseases, irrespective of liver involvement, such as AIH, Sjogren syndrome, rheumatoid arthritis, and Hashimoto thyroiditis. Although seemingly inconsistent, four cases of concurrent IgG4-RD and PBC have been reported (49-52). Two of these cases involved PBC and AIP, with elevated serum IgG4 and AMA positivity. One of these cases involved IgG4-SC (49, 50) in a 65-year-old male. In this case, the pathological lesions of PBC and IgG4-SC are speculated to affect the intrahepatic small bile ducts and the large bile ducts of the hepatic hilus, respectively (50). Moreover, unique overlap cases of isolated IgG4-SC without any other IgG4-RD lesions and of PBC have been reported (51, 52). Although IgG4-SC and PBC commonly affect older men and middle-aged women, respectively, these overlap cases involved a 61- and a 45-year-old man(51, 52). Figure 6 shows the case of 61-year-old man.(52)

With respect to PBC, these patients are not typical, though approximately 15% of PBC patients are male (53, 54). Because PBC differs from IgG4-associated AIH as described above, the occurrence of PBC is unlikely to be related to IgG4-RD. In addition, the cytokine milieu differs between PBC (Th1) and IgG4-RD (Th2) (20, 55, 56). The concomitance of the two diseases associated with opposing cytokine networks is unique. By one interpretation, PBC and IgG4-SC affect bile ducts at different anatomical levels; thus, the peripheral intrahepatic small bile ducts (PBC) and extrahepatic bile ducts (IgG4-SC) are damaged by different mechanisms. However, Li

et al. (50) speculate that according to the systemic nature of AIP and PBC, the coexistence of AIP and PBC is not a coincidence. Review of the pathogenesis of both diseases reveals several common features, including genetic susceptibility conferred by HLA-DQB1 (57, 58), dysregulation of cytotoxic T-lymphocyte antigen-4, T-cell mediated pathogenesis (59, 60), and the involvement of B cells associated with circulating autoantibodies and infiltration of plasma cells (59, 61-63). The association between the pathogenesis of IgG4-RD and PBC has not been further elucidated. Successful treatment of concomitant disease requires combination therapy with prednisolone for the IgG4-SC and ursodeoxycholic acid for the PBC (51).

Elevated serum IgG subclasses are associated with numerous autoimmune diseases, including primary Sjogren syndrome, systemic sclerosis, systemic lupus erythematosus, and PBC (64). Serum IgG1 (IgG1/IgG) and/or IgG3 (IgG3/IgG) are significantly increased in these autoimmune diseases, with serum IgG subclass levels presenting distinct patterns in different autoimmune diseases. For IgG4-RD, 6.34% of patients have serum IgG4 >135 mg/dL, but there are no significant differences in the frequency of elevated serum IgG4 levels between patients and healthy controls. We should reconsider the pathological significance of increased serum IgG4 levels. Further studies of serum IgG subclass distribution will help to elucidate the immunopathogenesis of autoimmune diseases, including IgG4-RD (64).

15.7 Cholangiocarcinoma with histological IgG4 positivity

Differentiating between IgG4-SC and cholangiocarcinoma is clinically important but very difficult, even with the use of recent modalities. The infiltration of $IgG4^+$ cells is very characteristic and useful in the diagnosis of IgG4-RD, but histological IgG4 positivity is found in several other inflammatory and neoplastic lesions, including PSC (24, 65). Moreover, patients with pancreatic adenocarcinoma accompanied by histological IgG4 positivity and/or elevated serum IgG4 levels (66-69) and those with pancreatic and biliary cancers arising from IgG4-RD (68, 70, 71) have been reported. However, a cause-and-effect relationship between histological IgG4 positivity and these cancers has not been demonstrated. Our retrospective survey (72) of 68 surgical specimens from patients with extrahepatic biliary cancers including common bile duct cancers, gallbladder cancer, and cancers of the papilla of Vater reports that 10 or more $IgG4^+$ cells/hpf were observed in 37% of cases. Cases resembling IgG4-RD and having marked infiltration ($\geq$50 $IgG4^+$ cells/hpf) made up 9% of the total (Fig.7). In contrast, intrahepatic bile ducts and hepatocellular carcinoma mostly lack the prominent $IgG4^+$ cells (unpublished data), although the reason is unknown. $IgG4^+$ cells are found within and around the tumor area, predominantly in the invasive front of the carcinoma tissue. Therefore, the presence of $IgG4^+$ cells is not a histological hallmark of IgG4-RD, and histological IgG4 positivity is speculated to occur non-specifically in carcinoma tissues (72). Several cancers involving remarkable infiltration of $IgG4^+$ cells ($\geq$50 cells/hpf) are speculated to originate from precedent

IgG4-SC, but data collected before the diagnosis of each cancer is needed to demonstrate the presence of IgG4-SC.

Patients with IgG4-SC are generally older men (85%) (19), but this male preponderance is not found in histological IgG4 positivity concomitant with cholangiocarcinoma according to our survey (72). As a histological characteristic of cholangiocarcinoma, irrespective of intra- vs. extrahepatic location, desmoplastic change consisting of fibrosis occurs. However, storiform fibrosis and obliterative phlebitis, other characteristics of IgG4-RD, are not prominent in cholangiocarcinoma. These observations indicate that IgG4-SC and cholangiocarcinoma share features, including increased fibrosis and histological IgG4 positivity, but the pathogenetic mechanisms underlying these features are speculated to differ.

The expression of the Th2-type cytokine milieu and IL-10 produced by Treg cells is assumed to involve IgG4 class switching and/or the progressive proliferation/differentiation of $IgG4^+$ plasma cells (20, 24, 26, 73, 74). The induction of $IgG4^+$ cells is directly regulated by IL-10 (25). This known regulatory/inhibitory cytokine plays the main role in the inhibition of the general immune reaction and possibly in IgG4-RD. The clinicopathological significance of histological IgG4 positivity in biliary tract cancers is still unknown, but our studies suggest that IgG4 positivity in cancer reflects the immune escape from cancer immunity (28, 72). In fact, the degree of $IgG4^+$ infiltration in biliary tract cancers correlates with the degree of $CD8^+$ cytotoxic T cell invasion into cancer cell layers (72). Moreover, patients with

IgG4-rich tissues in biliary tract cancers have a poor prognosis compared with those having IgG4-poor tissues (72). Because the cancer cells as well as Treg cells produce IL-10, the cancer cells themselves take part in the IL10-induced milieu (28).

In biliary cancers, $IgG4^+$ cells are not only found in cancer nests but are also scattered in the non-neoplastic biliary mucosa adjacent to the cancerous mucosa (75, 76). As shown in Fig. 8, many $IgG4^+$ cells are found within and peripheral to the invasive regions of submucosal layers. A similar IgG4 positivity is prominent in the non-neoplastic mucosa around the primary cancer lesion. Although a biopsy of the bile duct is the best modality for diagnosing cholangiocarcinoma, such examination is unfortunately limited in the superficial biliary mucosa using biopsy specimens. Therefore, if a biopsy specimen is obtained from this IgG4-rich, non-neoplastic biliary mucosa in patients with increased serum IgG4 levels, the condition could be diagnosed as “cholangitis with $IgG4^+$ cells, consistent with IgG4-SC.” Another informative case involves that of a 70-year-old male with serum IgG4 of 113 mg/dL, the borderline zone for IgG4-RD. Radiologically, IgG4-SC, PSC, and cholangiocarcinoma of the hepatic hilus were included in the differential diagnosis. Cytologically, no atypical cells were detected in bile specimens. Biopsies of the Ampulla of Vater and liver revealed infiltration of numerous $IgG4^+$ cells (Fig.9), consistent with IgG4-SC. However, the biopsy of the stenotic biliary region indicated the presence of adenocarcinoma (cholangiocarcinoma) (Fig.9). The bile duct biopsy from the stenotic region is the cornerstone of differential diagnosis; the pathological diagnosis of cancer is very easy in

appropriate specimens. This case emphasizes the importance of using appropriate specimens for pathological diagnosis and understanding the distribution of $IgG4^+$ cells in cholangiocarcinoma. That is, histological IgG4 positivity is not only localized in and around the primary cancer but also broadly distributed into the distal and proximal regions of the biliary tree. Although few in number, cholangiocarcinoma cases arising from preceding IgG4-SC have been reported (68, 70, 71); in addition, the precursor lesions of cholangiocarcinoma (BilIN lesions) are often encountered in IgG4-SC (Fig.10) (77). Therefore, in practice, it is impossible to completely exclude the possibility of cholangiocarcinoma in the diagnosis of IgG4-SC. Elevated serum IgG4 values are an important finding when diagnosing AIP and IgG4-SC, but are not sufficient to definitively diagnose IgG4-RD. Rather, a danger lurks that IgG4-RD may be diagnosed or excluded too readily, and serum IgG4 values should not be regarded as more than an adjuvant diagnostic clue.

15.8 Concluding remarks

IgG4-RD is a systemic disease that affects most organs. Most patients synchronously or metachronously suffer from multiple organ involvement. AIP is the prototype of IgG4-RD, and extrahepatic biliary tracts, including the gall bladder, are also surely a manifestation of IgG4-RD. However, whether intrahepatic small bile ducts and hepatocytes are direct targets in IgG4-RD is unknown. Moreover, an increase in

$IgG4^+$ cells is highly sensitive but not highly specific for IgG4-DR. In contrast, several cases of IgG4-RD with low serum IgG4 levels and/or scant $IgG4^+$ cell infiltration in target organs have also been reported. Although IgG4-related lesions present numerous oddities, further studies will surely resolve these challenges by accumulating more cases and experience.

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FIGURE LEGENDS

Figure 1. Representative IgG4-related sclerosing cholangitis (IgG4-SC) associated with autoimmune pancreatitis (AIP). A and B: Macroscopic and semi-macroscopic findings, respectively. Arrows and arrowheads denote the stenotic bile duct and pancreatic duct with wall thickening, respectively. C: Inflammation and edema are found in the fibrous-thickened wall and are particularly prominent around the peribiliary gland (arrows). The mucosa is relatively preserved, with scant inflammation. D: Higher magnification of inflammatory area. Many scattered plasma cells and eosinophils are seen. E: Immunohistochemistry for IgG4. Abundant positive plasma cells are seen. F: Storiform fibrosis and perineural inflammation (arrow) are prominent.

Figure 2. Inflammatory pseudotumor with many $IgG4^+$ liver cells. A: Semi-macroscopic findings. Fibrous nodule (arrow) is seen. B: Nodule consists of typical storiform fibrosis and inflammation. C: Chronic cholangitis in adjacent portal tract.

Figure 3. Inflammation of Papilla of Vater (papillitis) in IgG4-related sclerosing cholangitis (IgG4-SC) associated with autoimmune pancreatitis (AIP). A: Inflammation is prominent, but differentiating between non-specific and IgG4-related papillitis is

difficult. B: Immunohistochemistry for IgG4 reveals the presence of many $IgG4^+$ cells and IgG4 deposition in the stroma and on epithelial cells.

Figure 4. Autopsied live specimens of systemic IgG4-related disease with IgG4-related sclerosing cholangitis. A: In subcapsular area of liver, mild to moderately inflamed portal tracts (arrows) are seen. B: Portal tract is mildly sclerotic and a minor scattering of inflammatory cells is seen. C: Immunohistochemistry for IgG4. Many positive cells are found within portal tracts.

Figure 5. Representative findings of IgG4-hepatopathy. A: Prominent portal inflammation with interface hepatitis (arrow). B: Inflamed portal tracts contain many $IgG4^+$ cells. Immunohistochemistry for IgG4. C: Lobular hepatitis. Some focal necroses are found (arrows). D: Canalicular cholestasis. Bile plugs are found in dilated bile canaliculi (arrows).

Figure 6. Overlap syndrome of IgG4-related sclerosing cholangitis and primary biliary cirrhosis (PBC) in a 61-year-old man. A: In inflamed portal tracts, moderate inflammatory cell infiltrate, and chronic, nonsuppurative destructive cholangitis (CNSDC, arrow) are seen. B: Immunohistochemistry for IgG4. Many positive cells are

seen. Their distribution is mainly in the peripheral portal tract, but scant cells are located around CNSDC.

Figure 7. Extrahepatic cholangiocarcinoma. A: Primary carcinoma nest consists of adenocarcinoma with abundant inflammatory cells. B: Immunohistochemistry for IgG4 reveals the presence of many $IgG4^+$ cells within cancer nests.

Figure 8. Gall bladder cancer. A: Section adjacent to the primary cancer area, but a cancer nest (T) invades the subserosal layer with marked inflammatory cells. Non-neoplastic surface mucosa (M) also accompanies inflammation. B and C: Immunohistochemistry for IgG4. In the cancerous region (B) and the non-neoplastic superficial mucosa (C), many $IgG4^+$ cells are intermixed with inflammatory infiltrate.

Figure 9. Cholangiocarcinoma of the hepatic hilus accompanying IgG4 positivity in the Ampulla of Vater and peripheral liver. A. Biopsy of the Ampulla of Vater. Immunohistochemistry for IgG4 demonstrates the presence of several positive cells within papillitis. B and C: Liver needle biopsy. Mild portal inflammation (B) and several $IgG4^+$ cells (C) are found in peripheral small portal tracts. D: Biopsy from the

stenotic large bile duct in the hepatic hilus. Well- (arrow) and poorly (arrowhead) differentiated adenocarcinomas (cholangiocarcinoma) are present.

Figure 10. IgG4-related sclerosing cholangitis affecting the common bile duct. A: Biliary intraepithelial neoplasia (BilIN) is found in the preserved biliary epithelium (arrows). B: Immunohistochemistry for IgG4. Several positive cells are scattered.

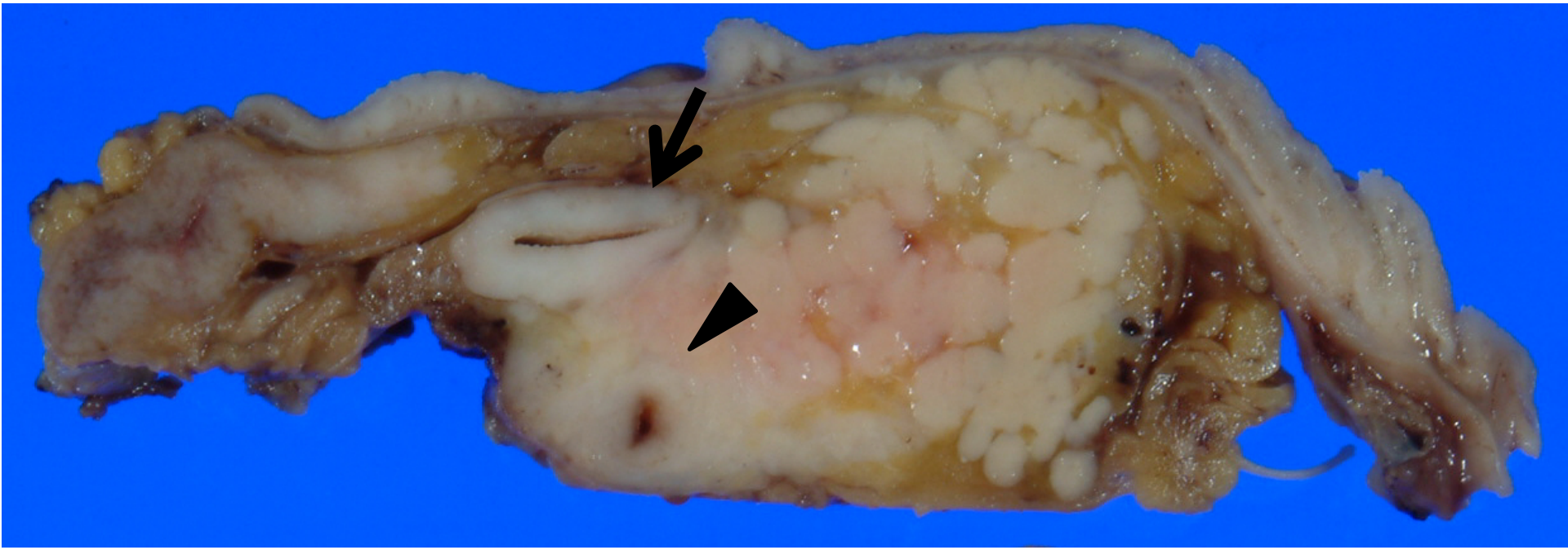
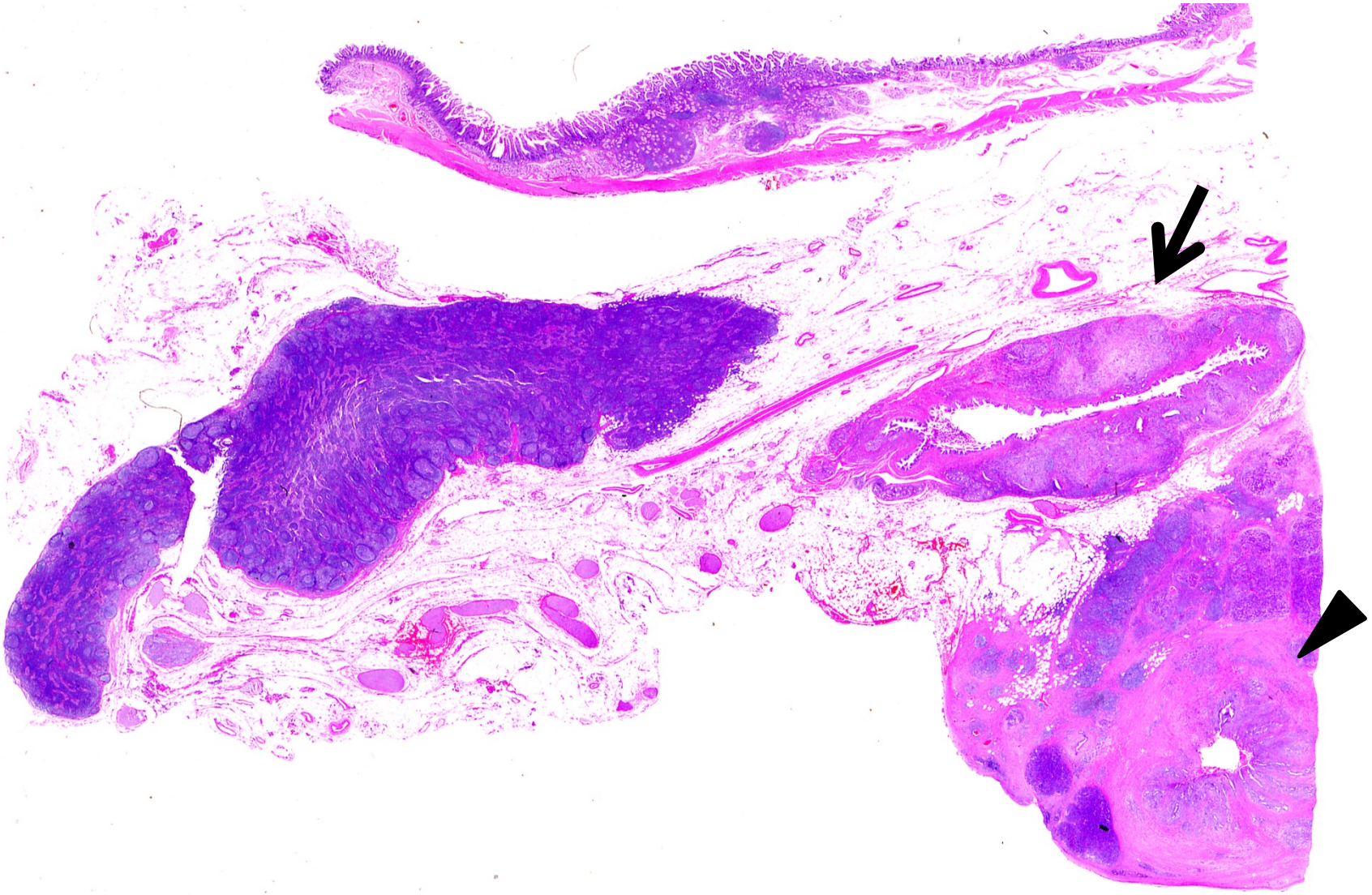


Fig 1A



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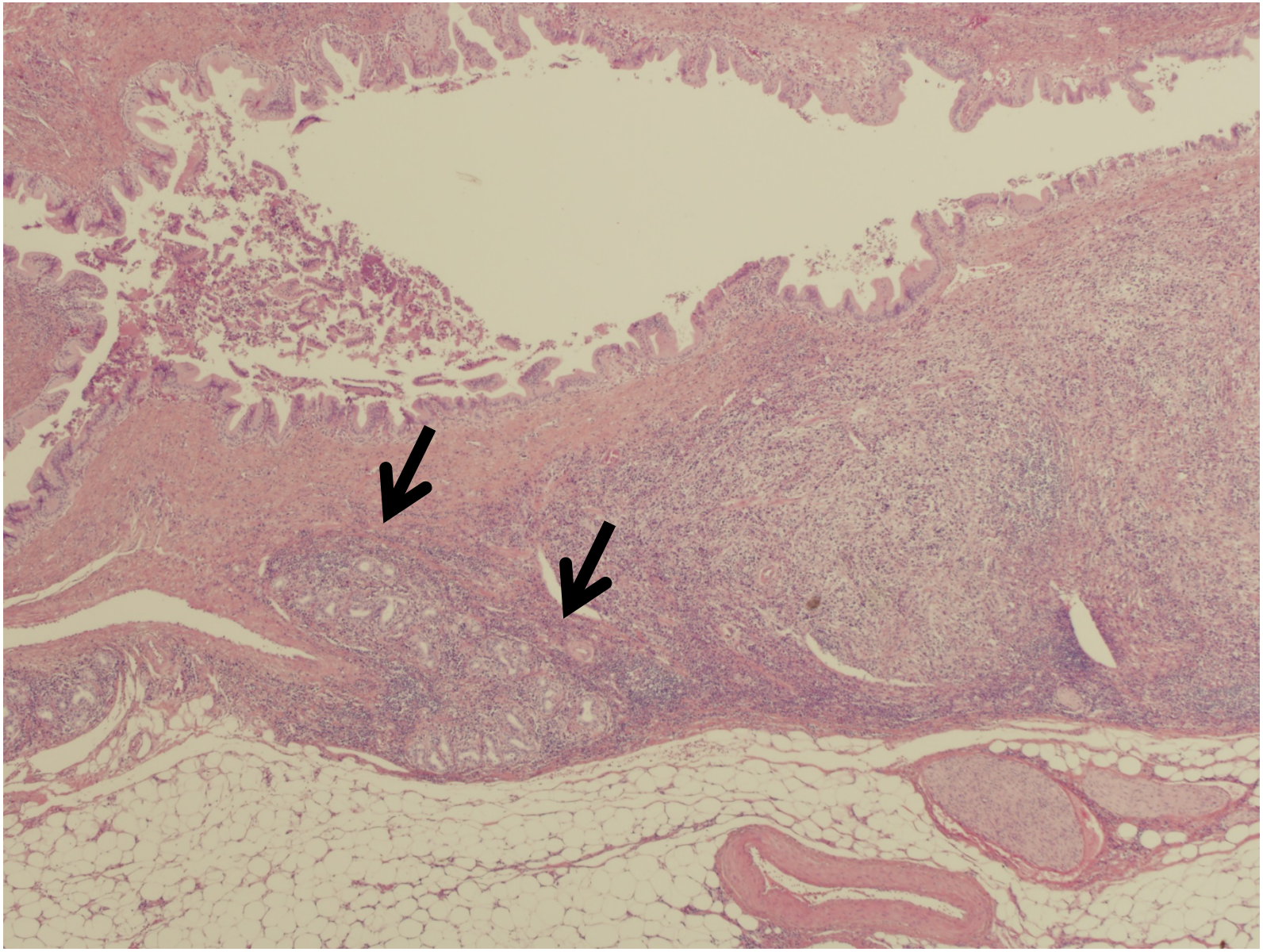


Fig 1C

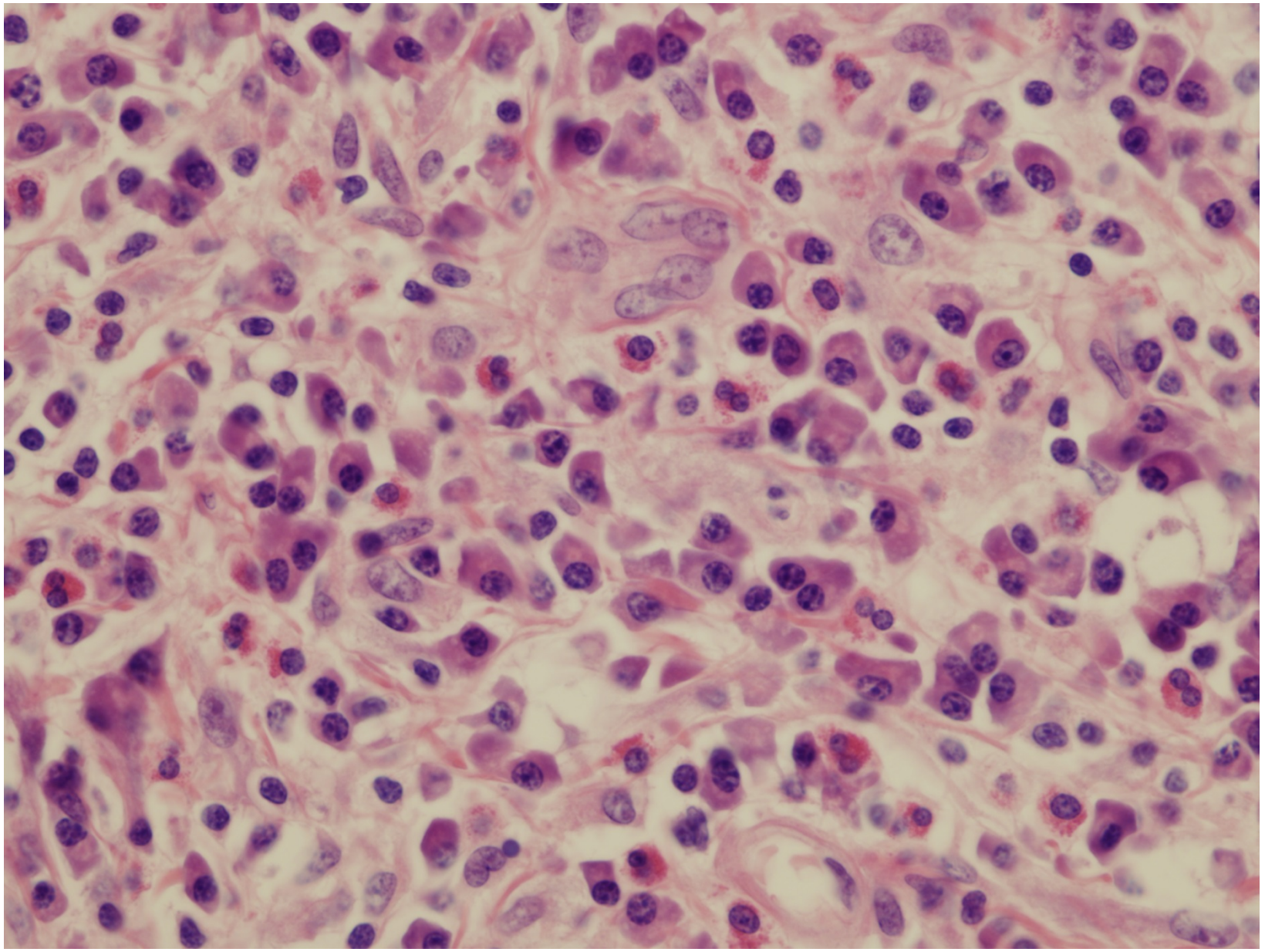
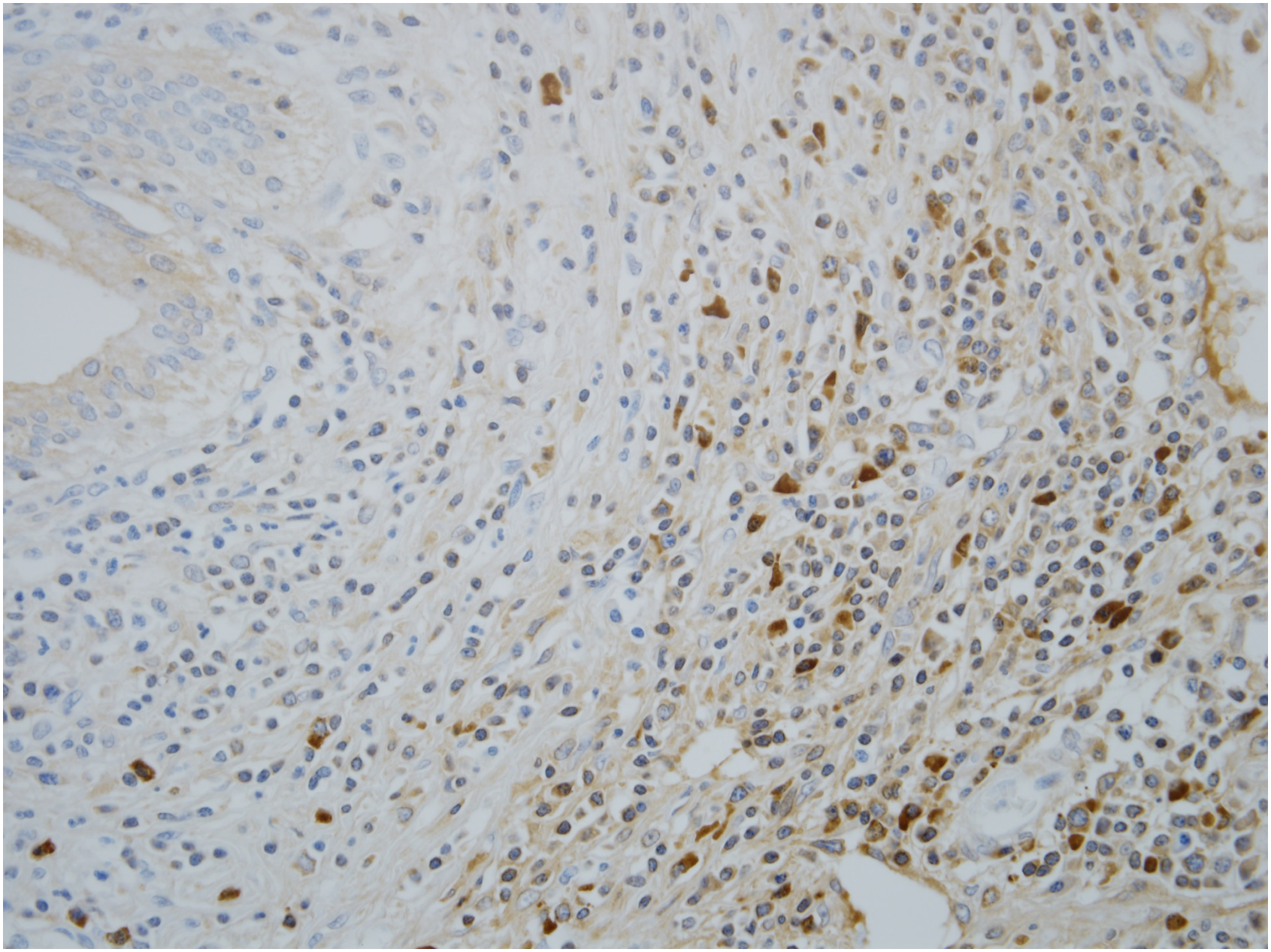


Fig 1D



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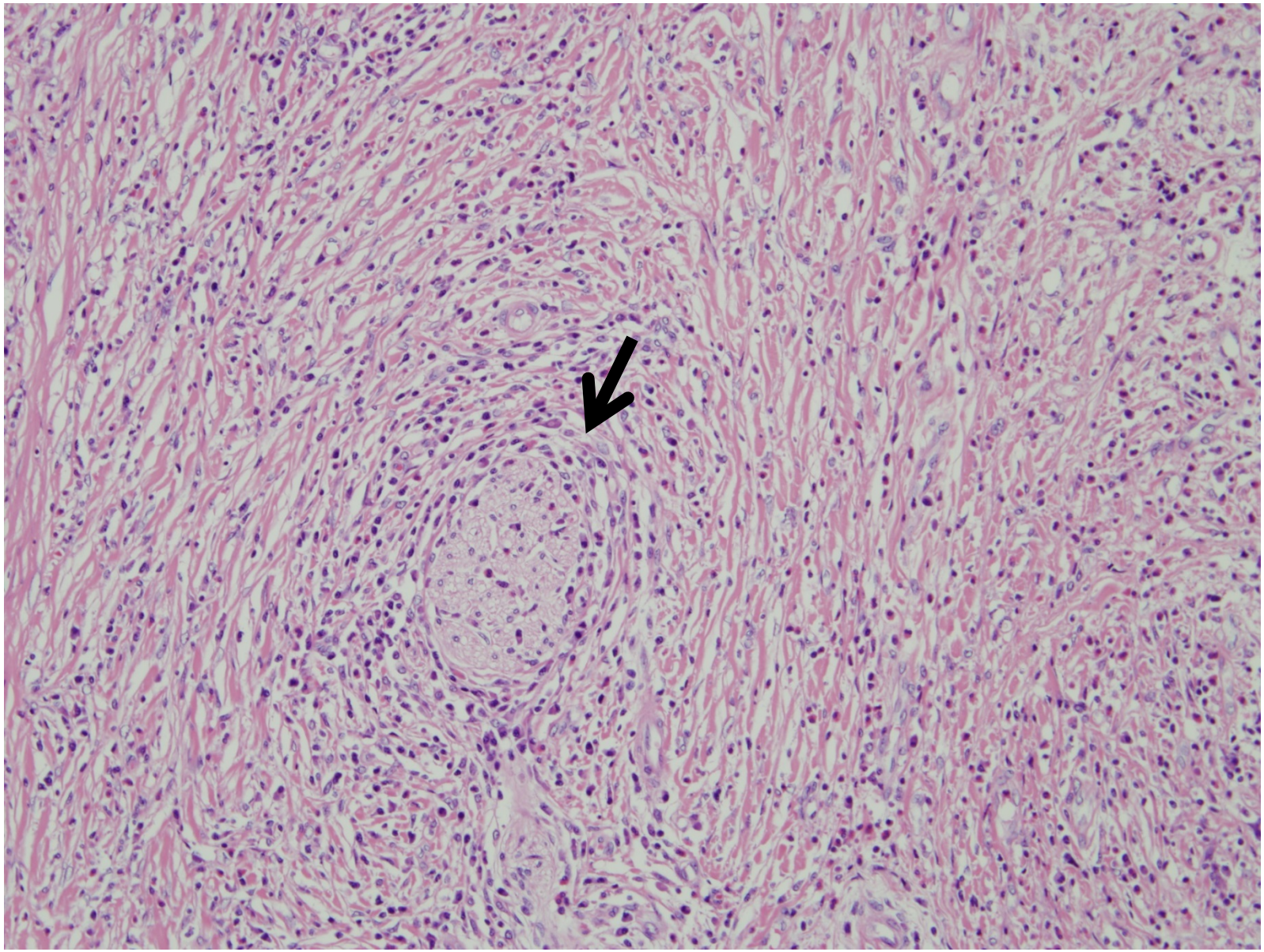

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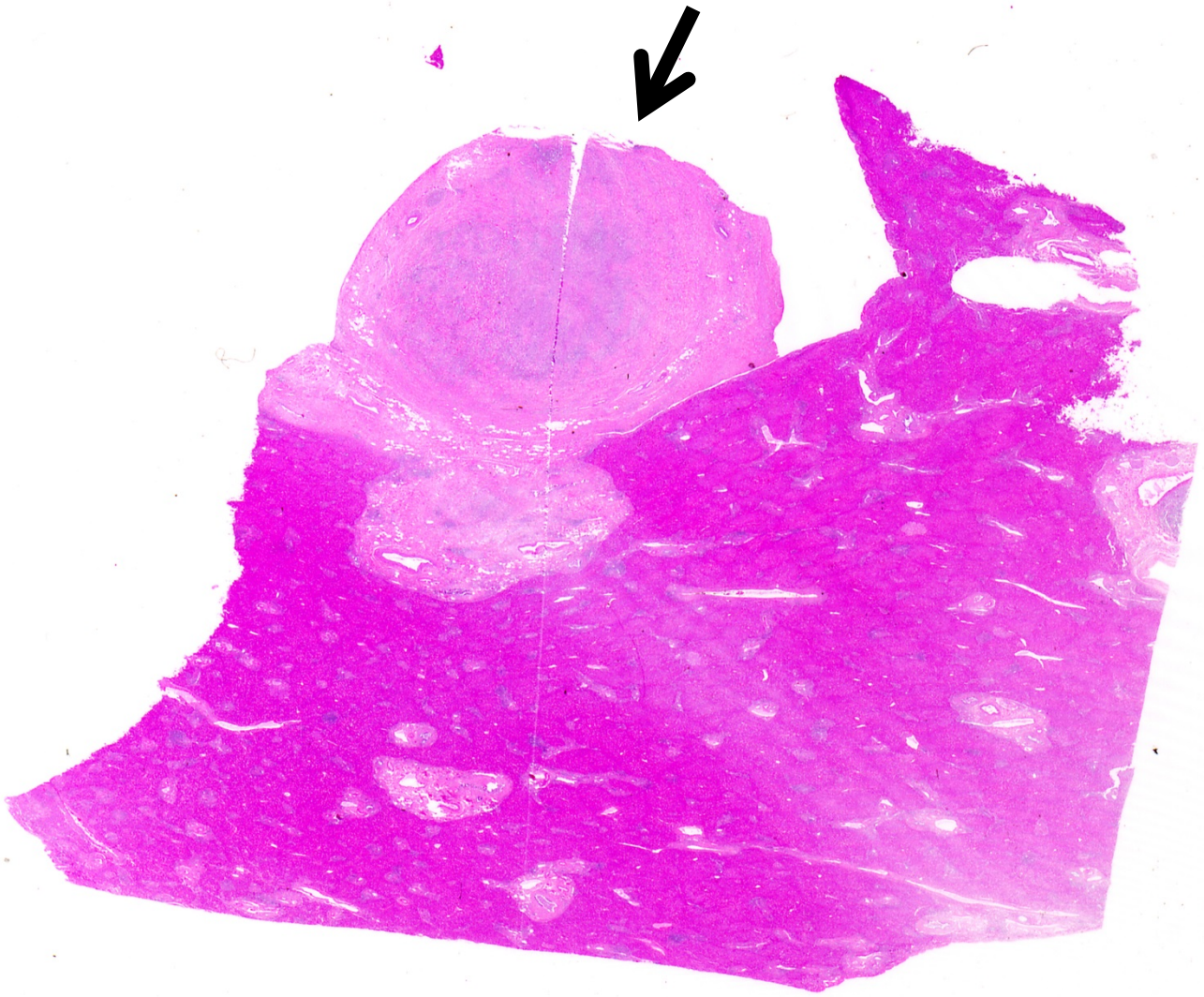
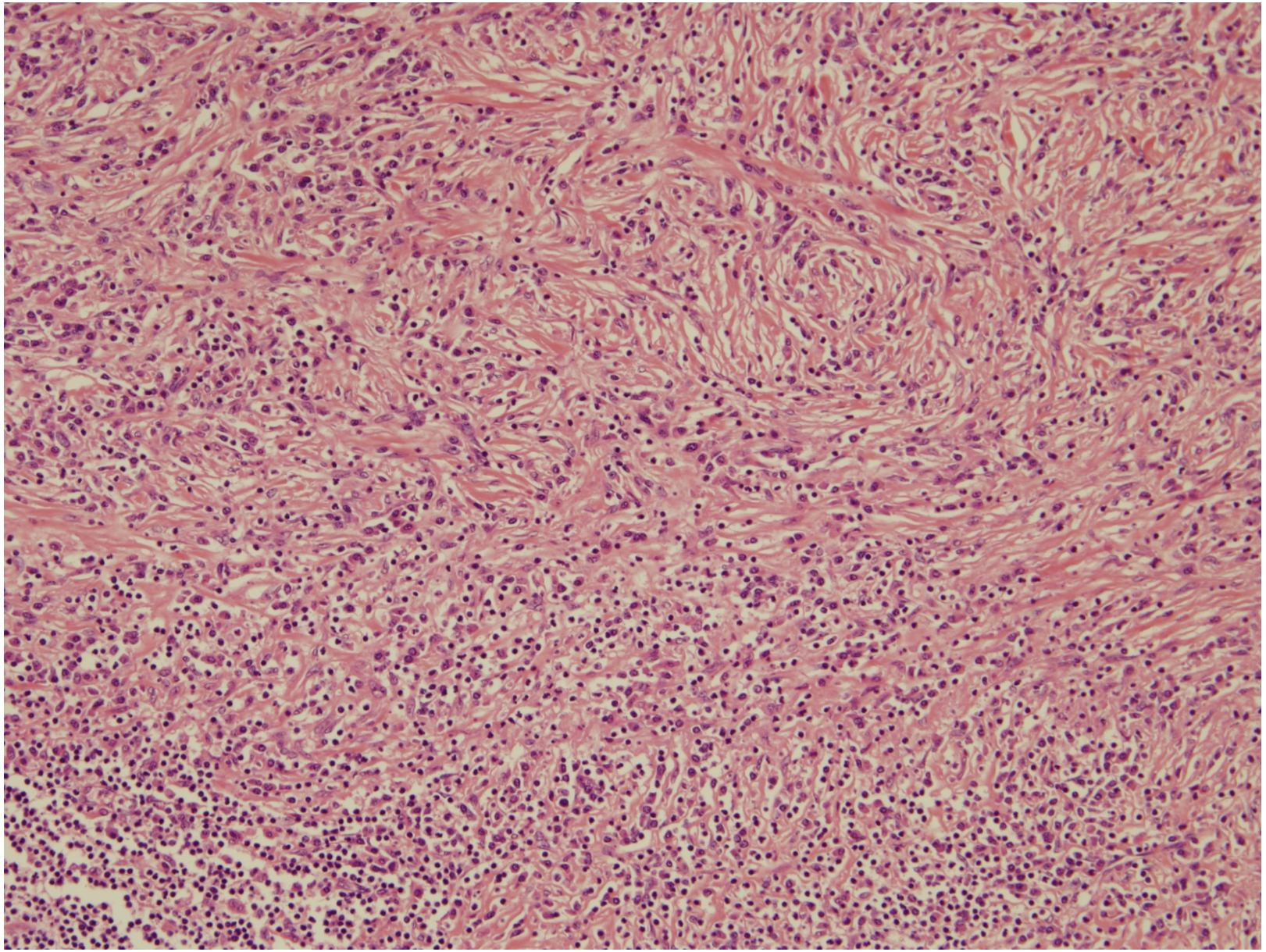


Fig 2A



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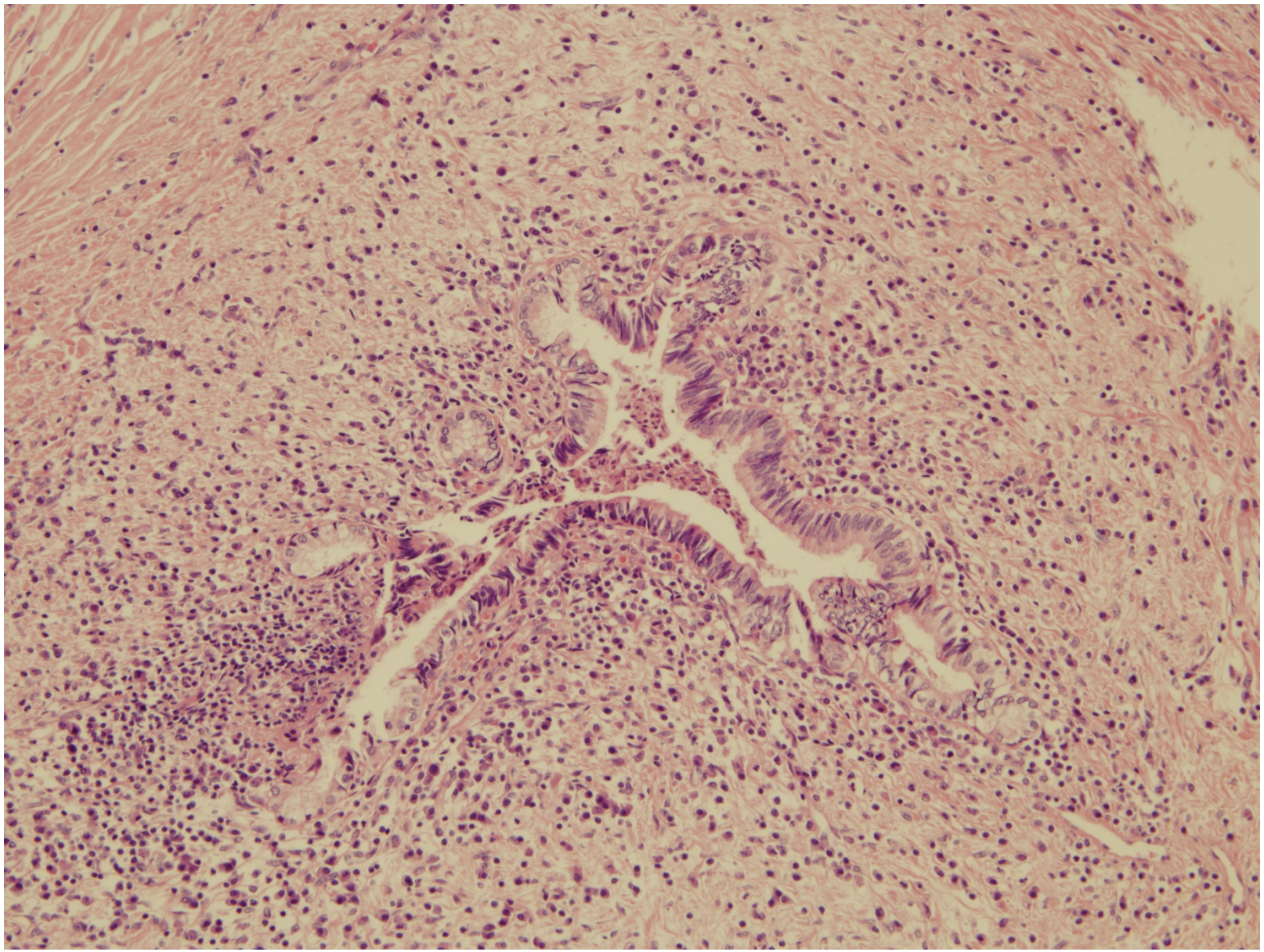

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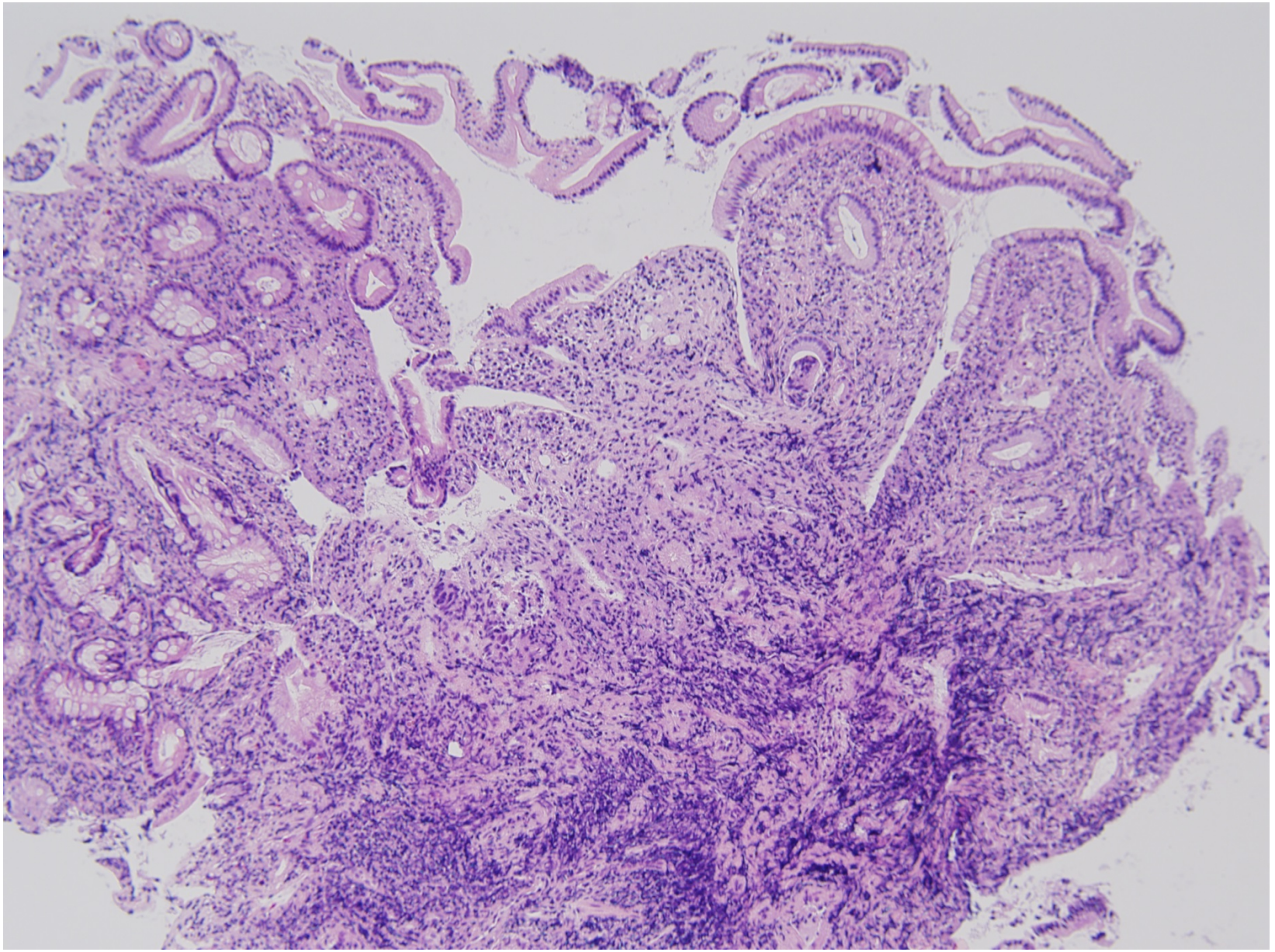

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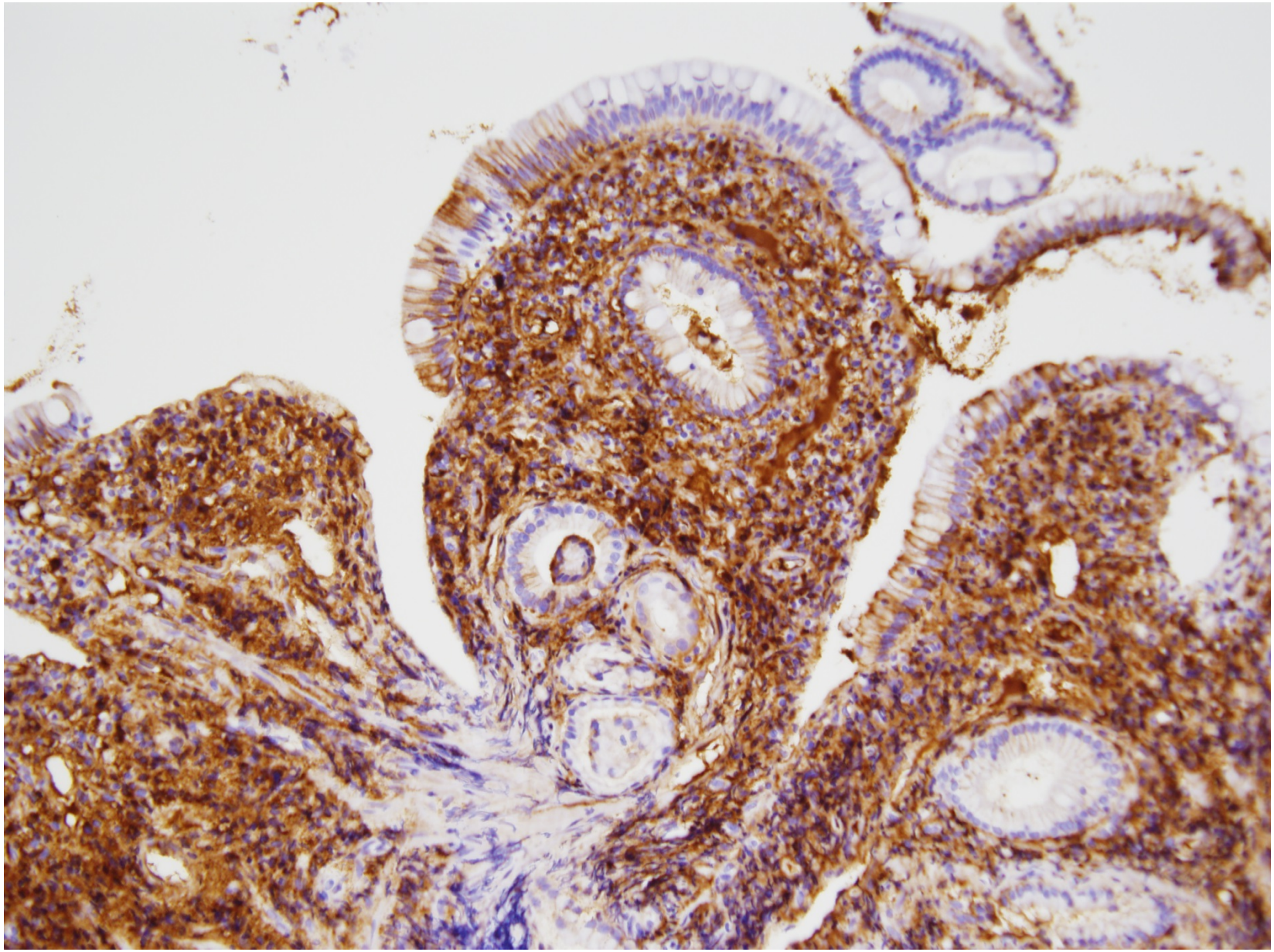

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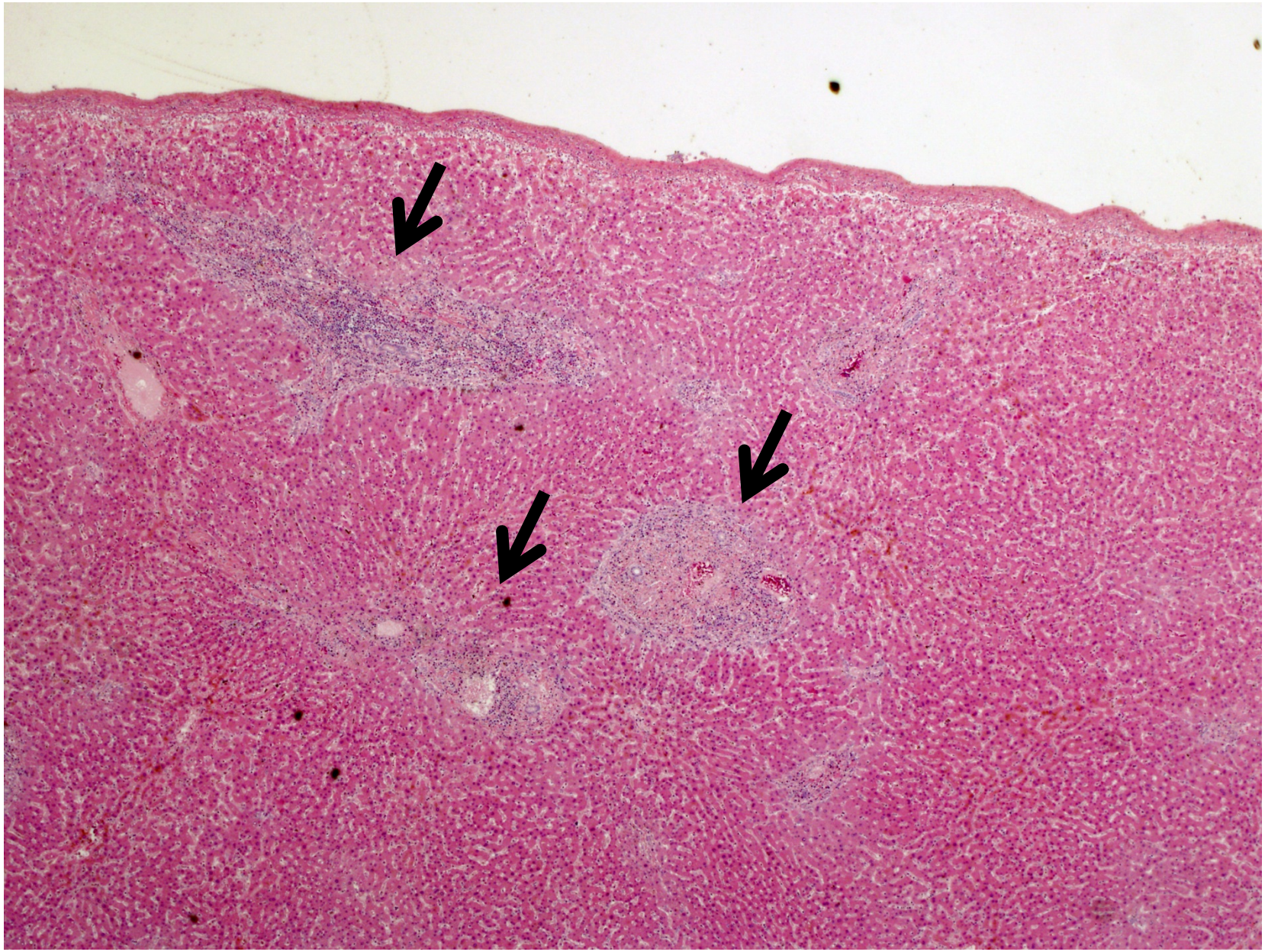

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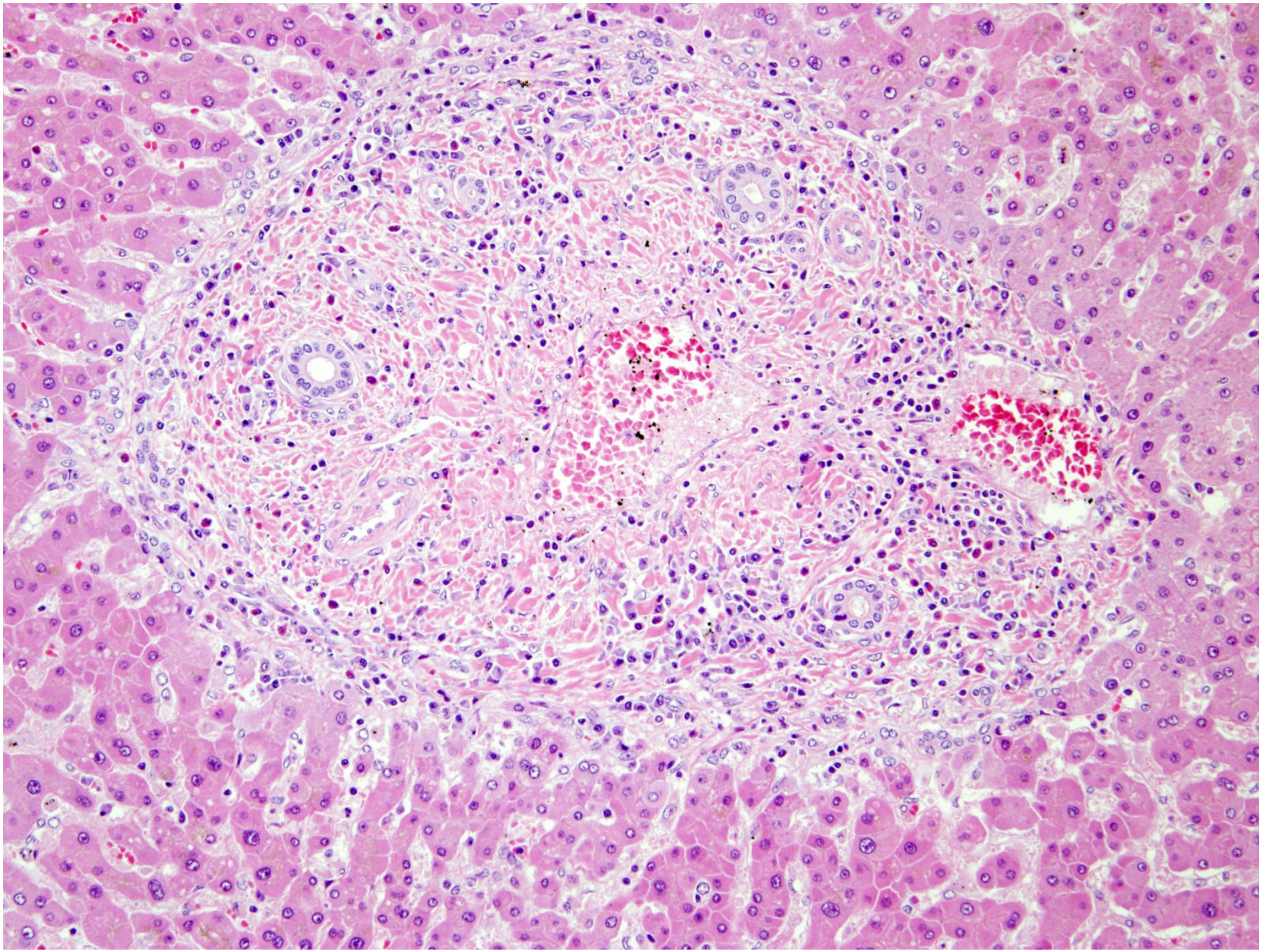

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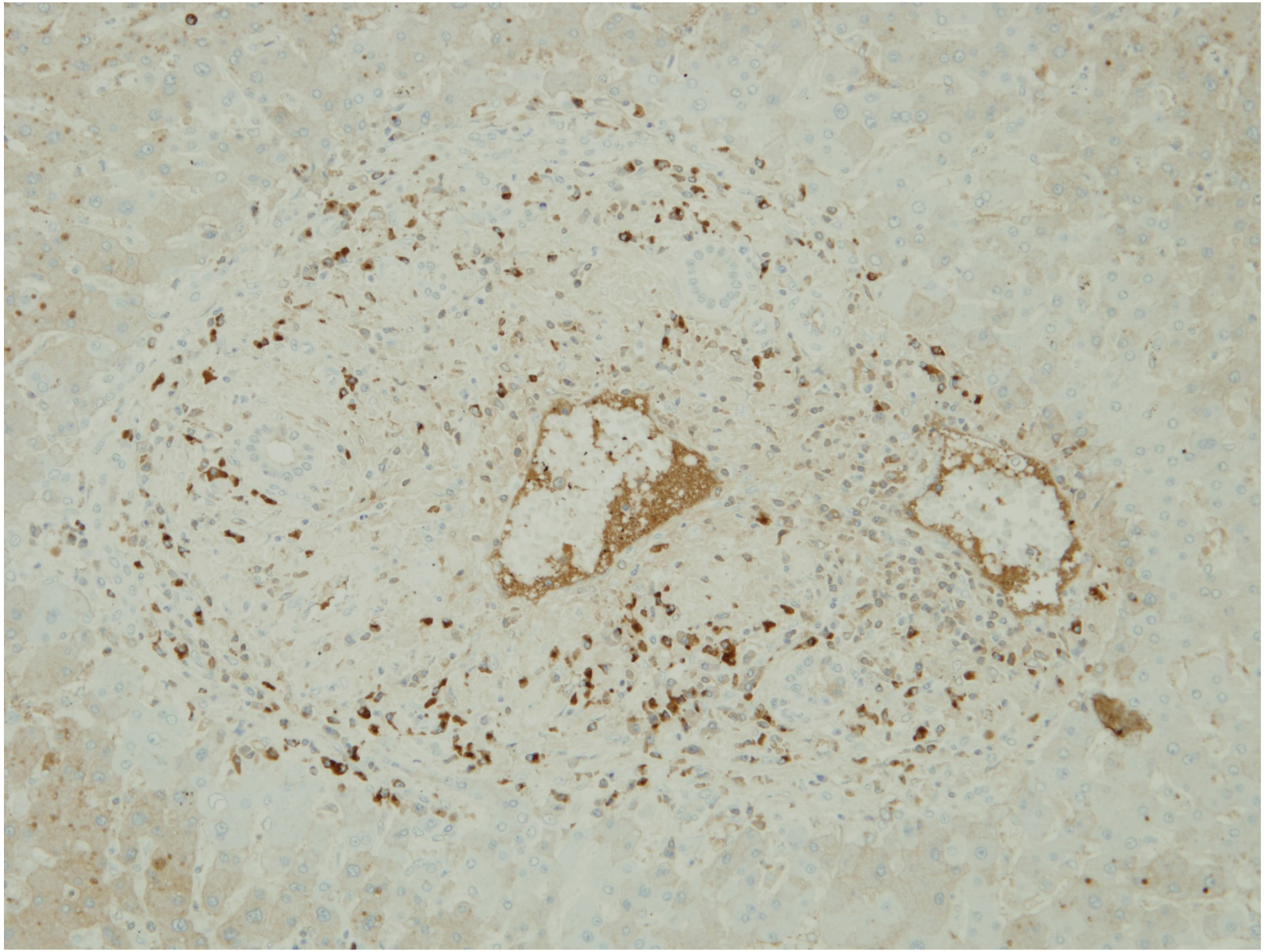

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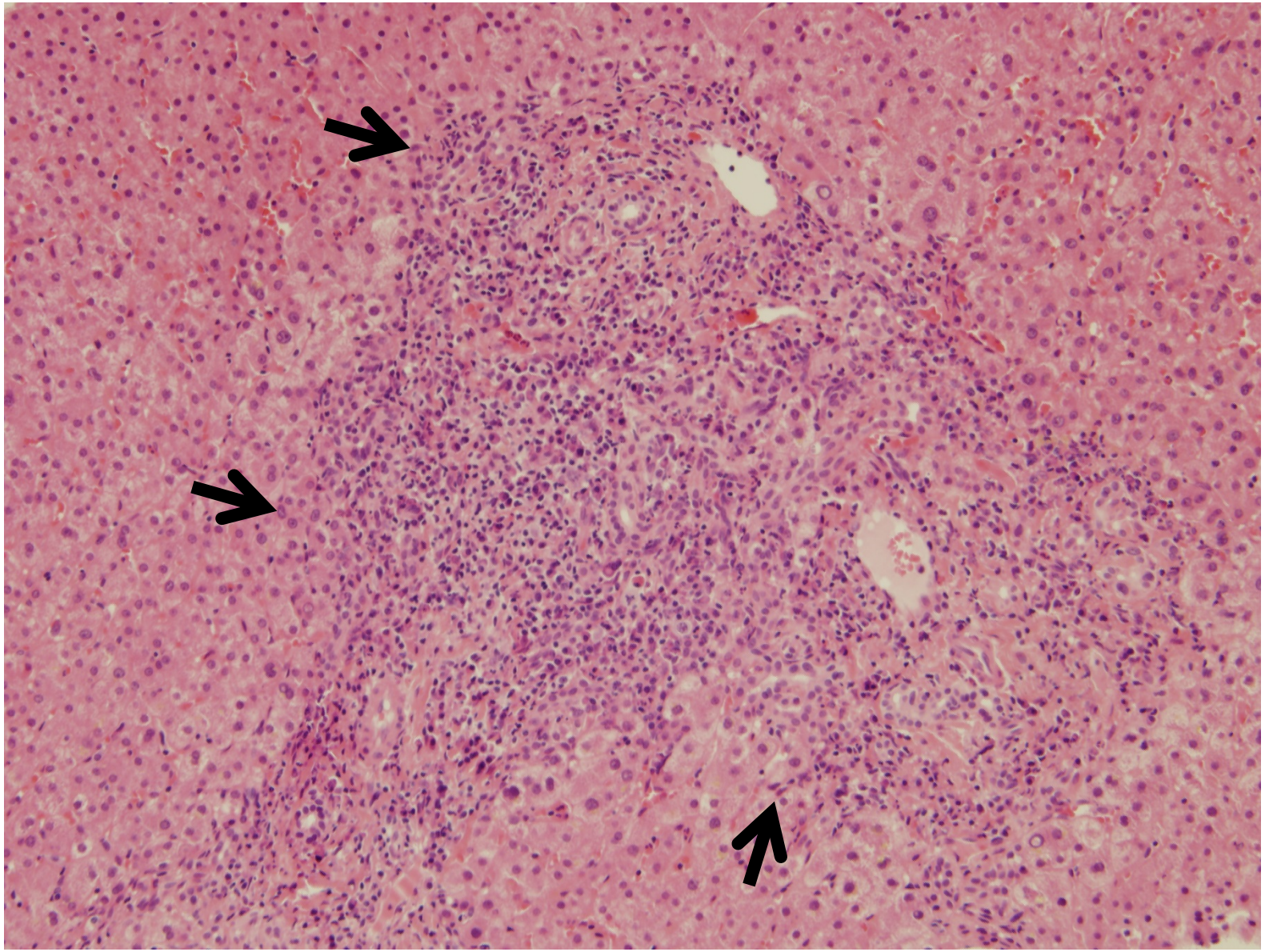

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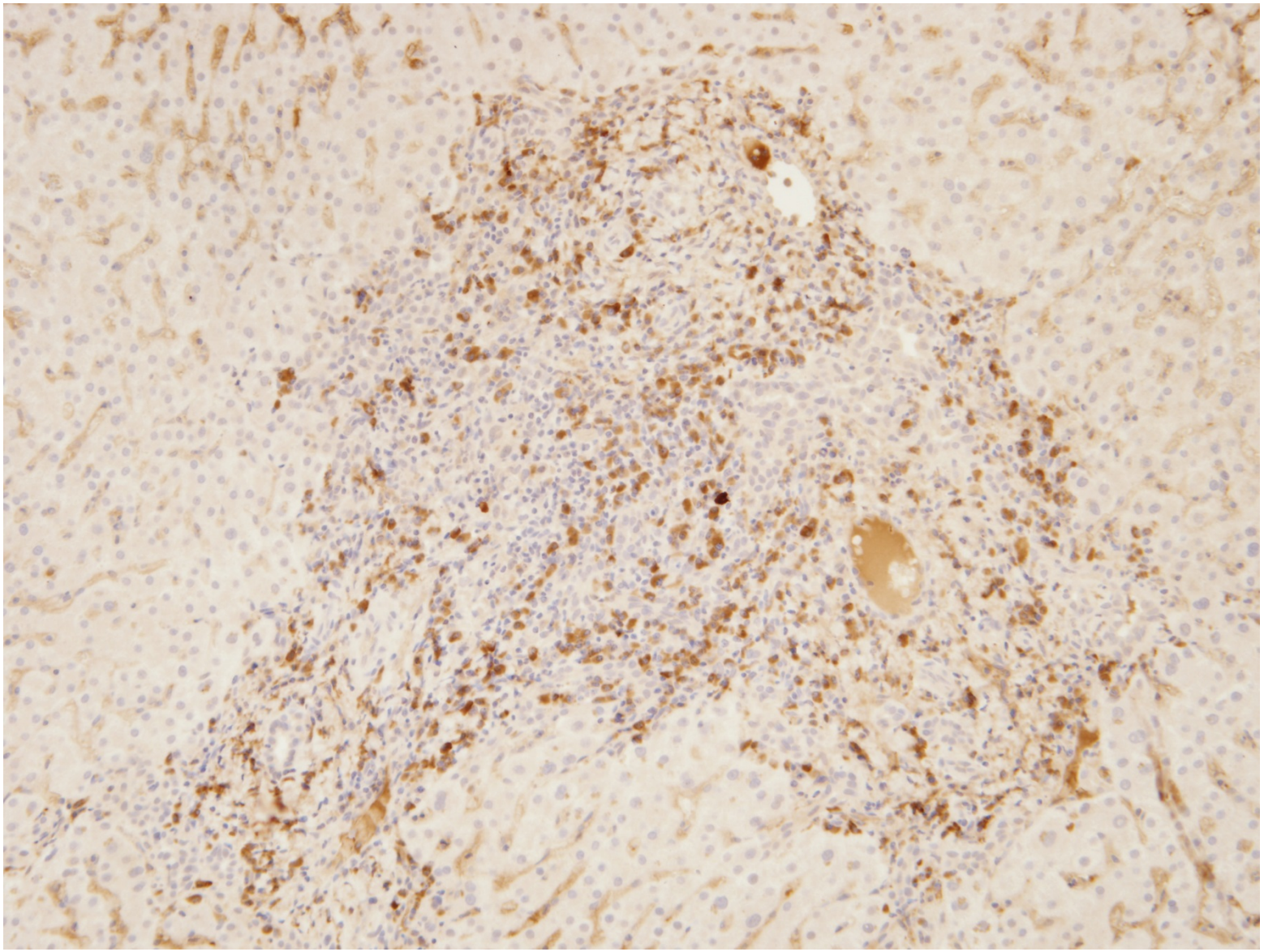

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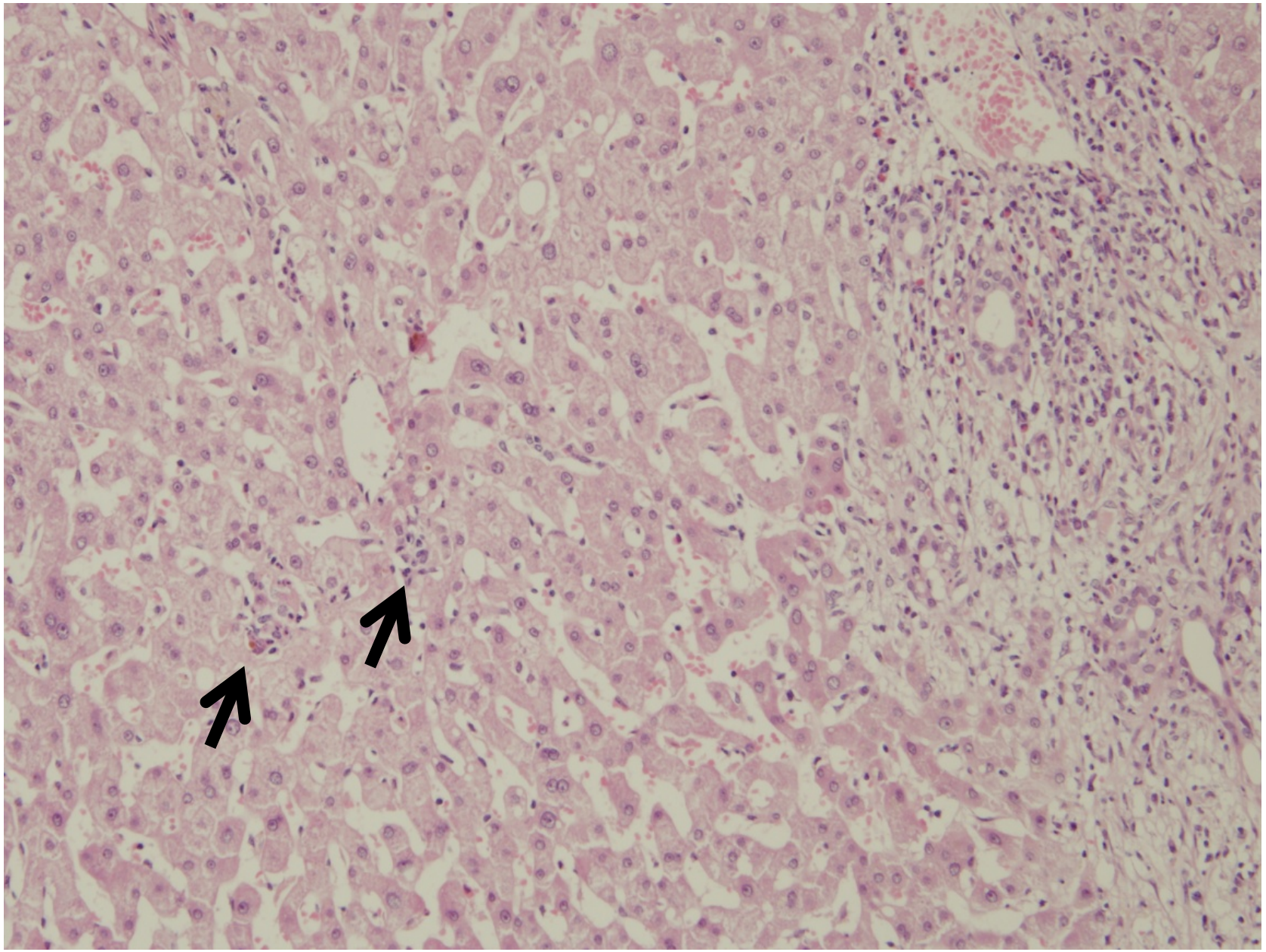

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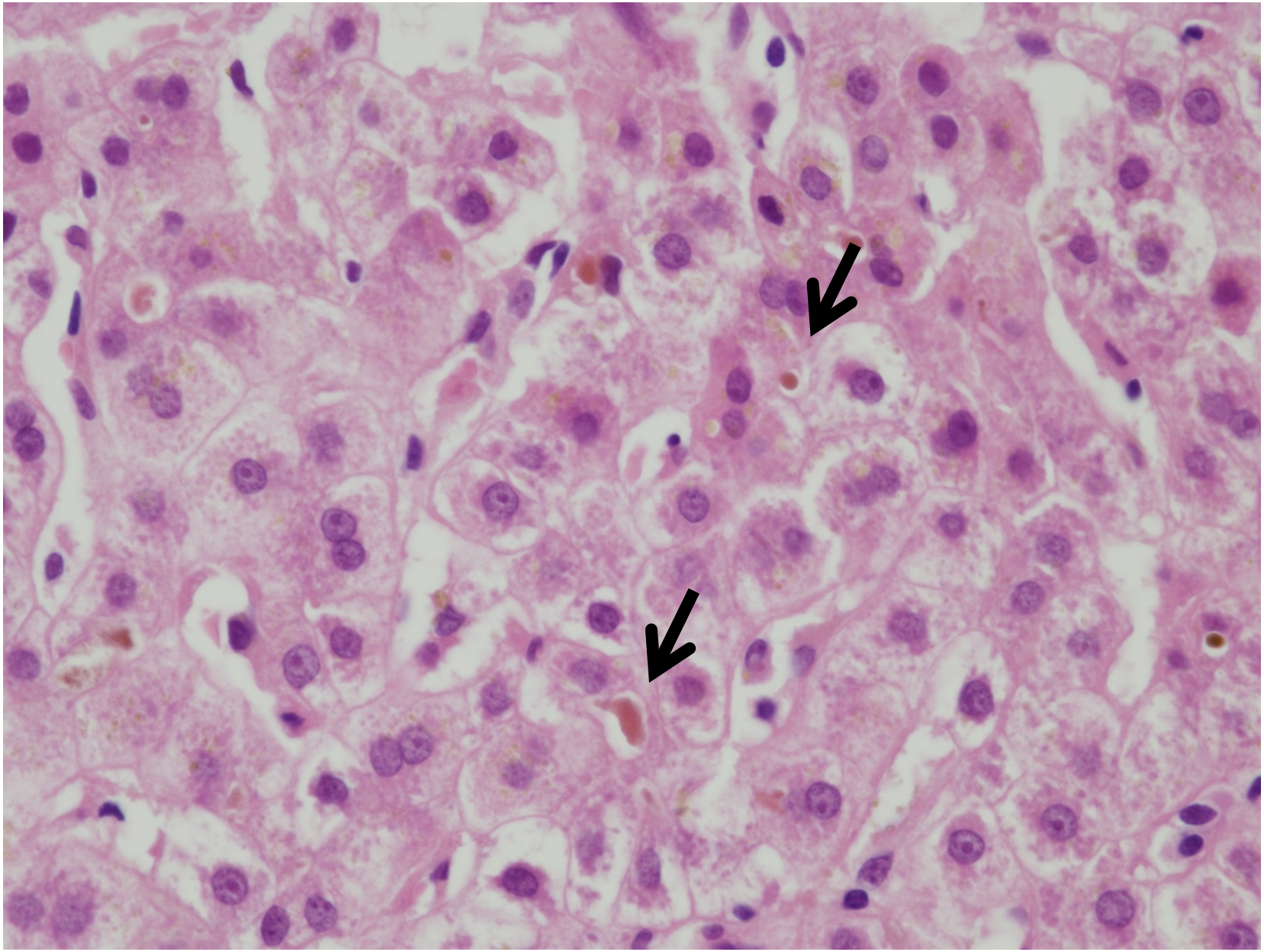


Fig 5D

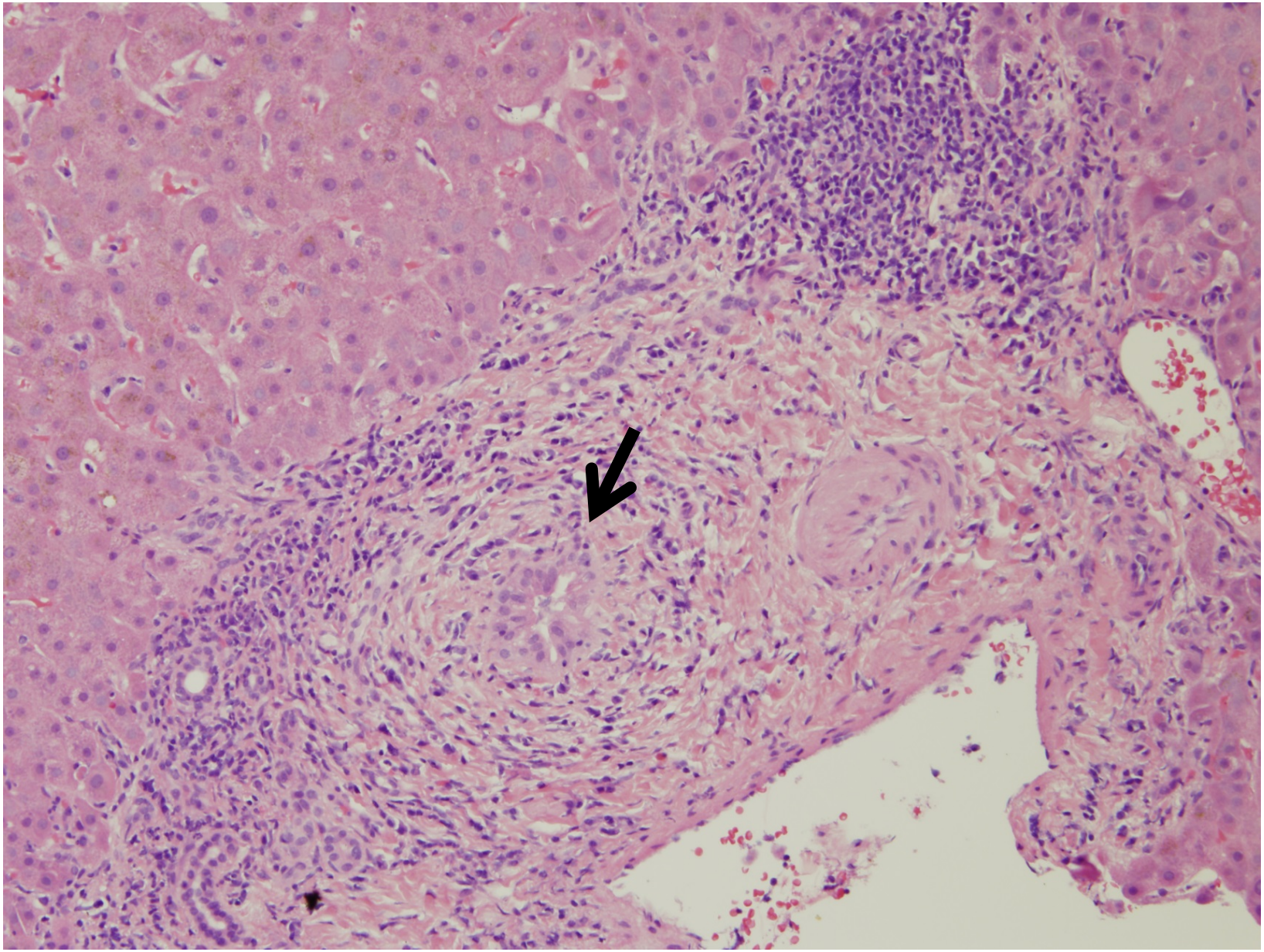


Fig 6A

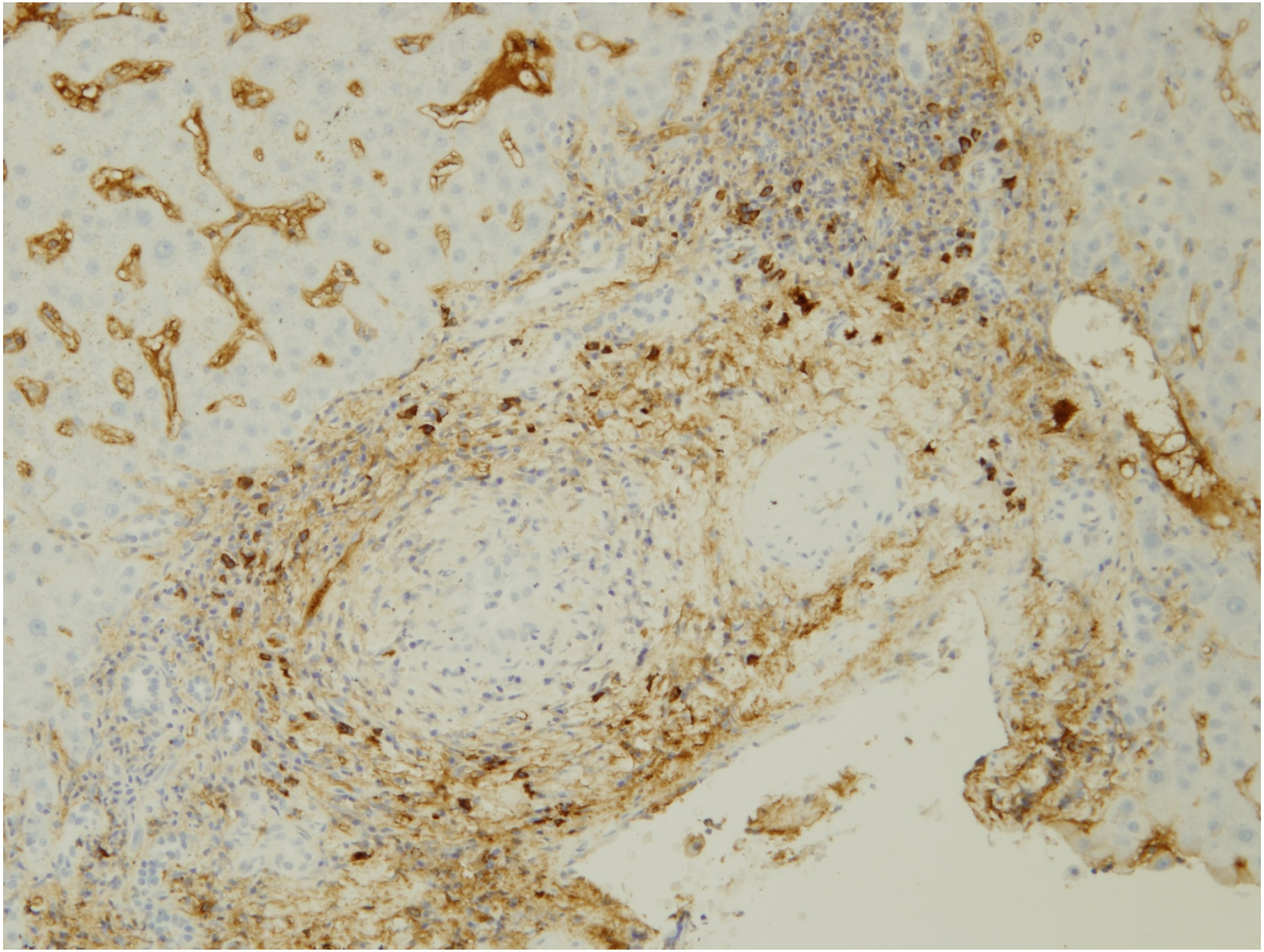
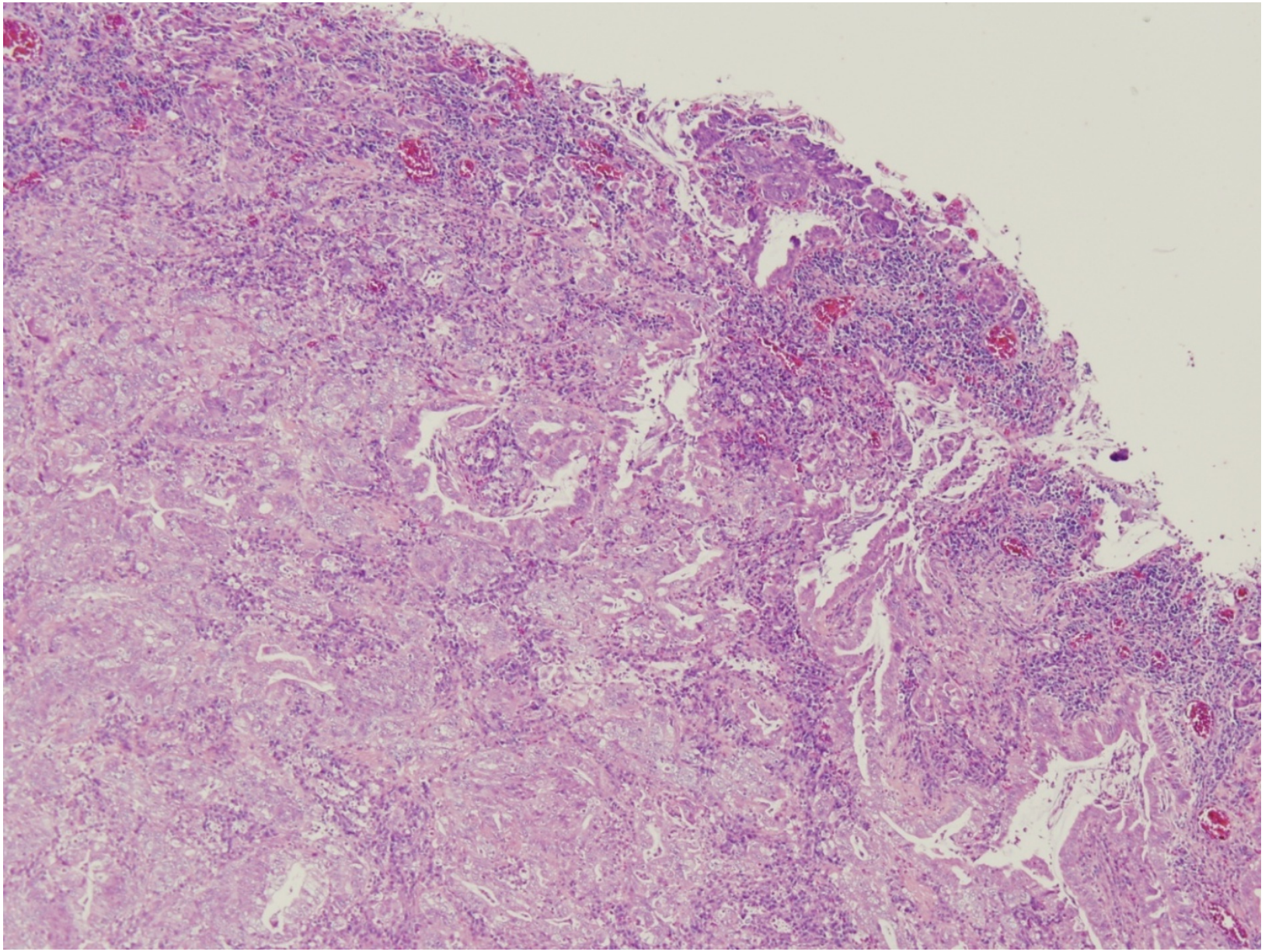


Fig 6B



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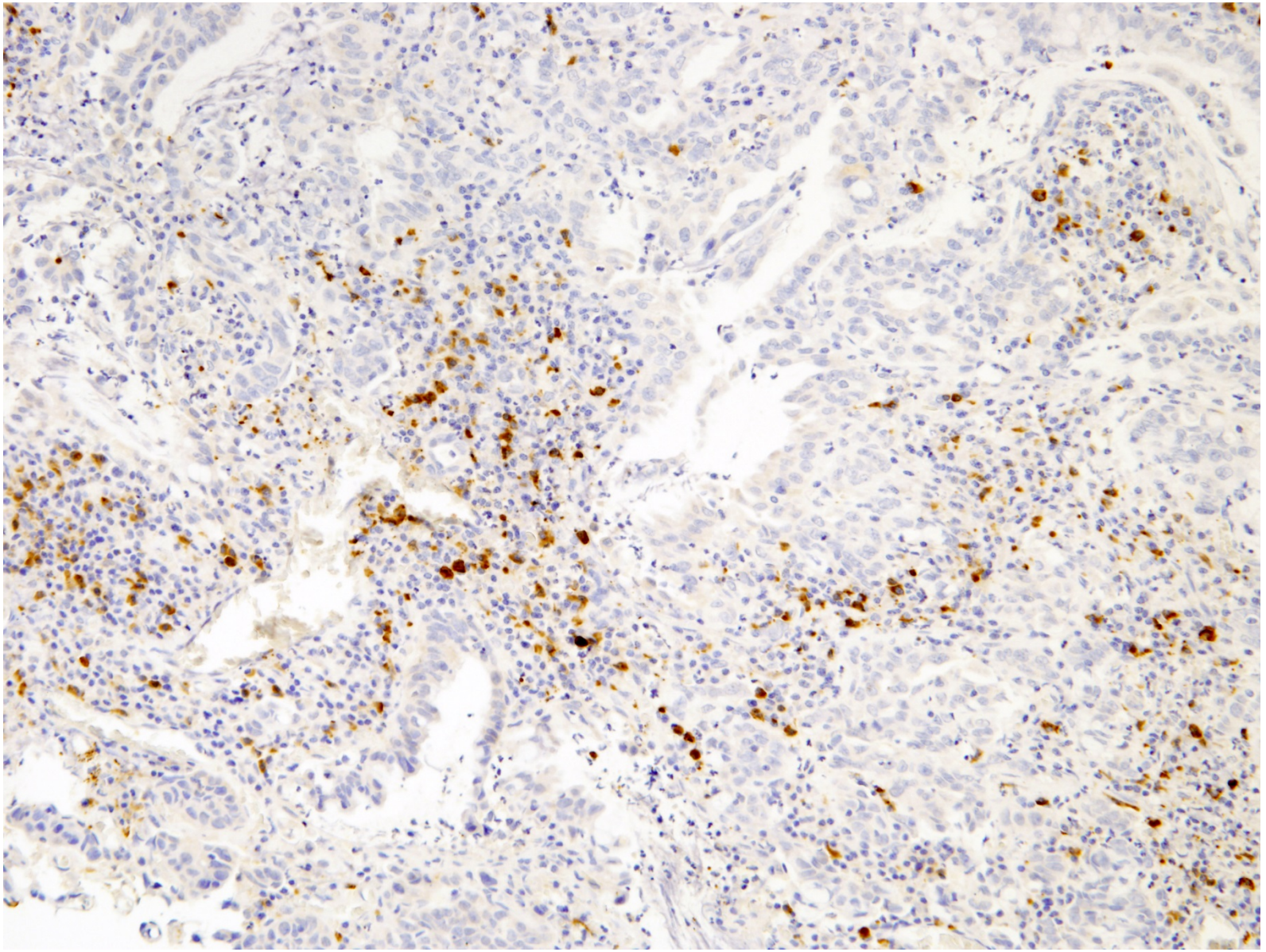

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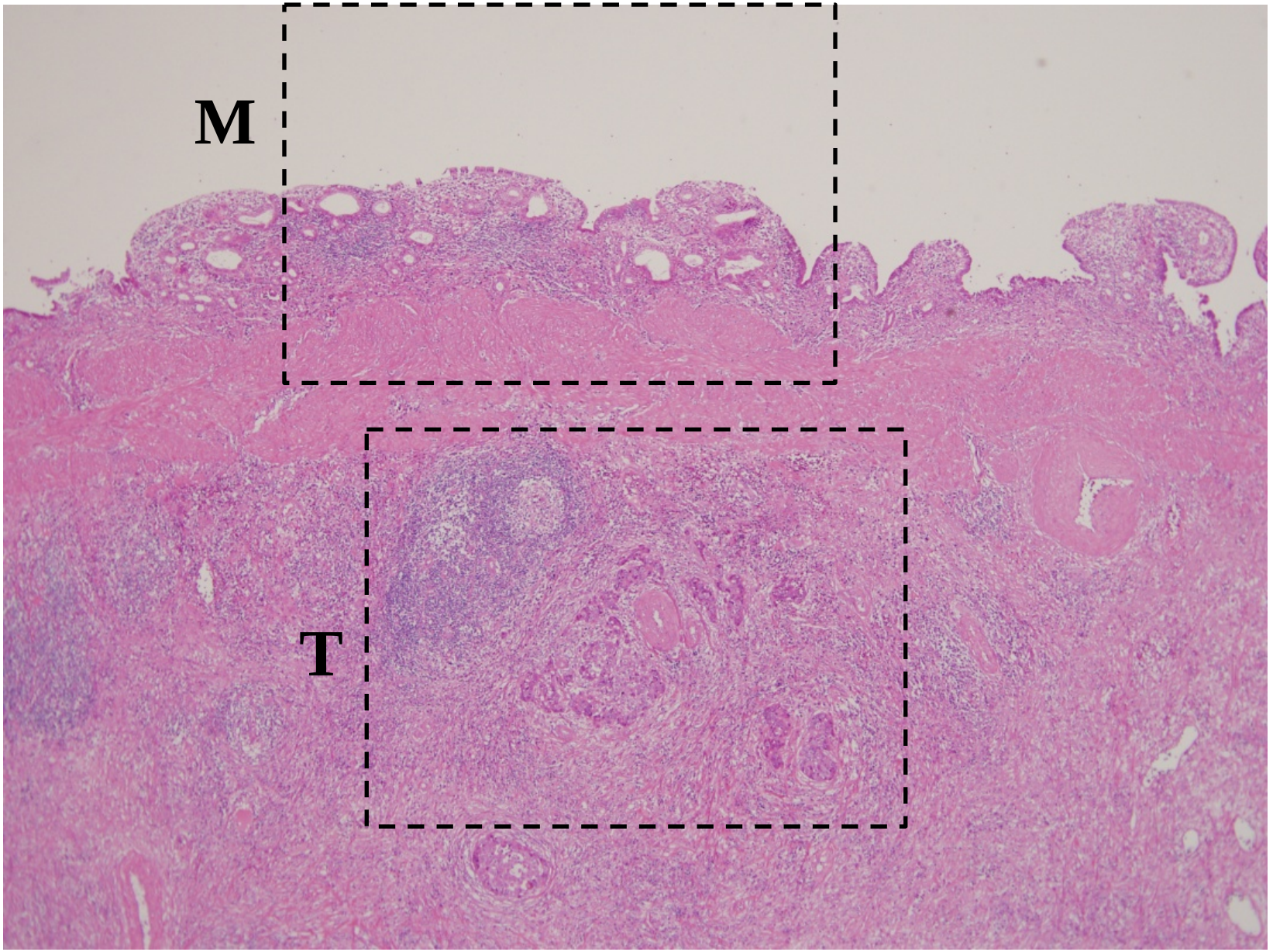
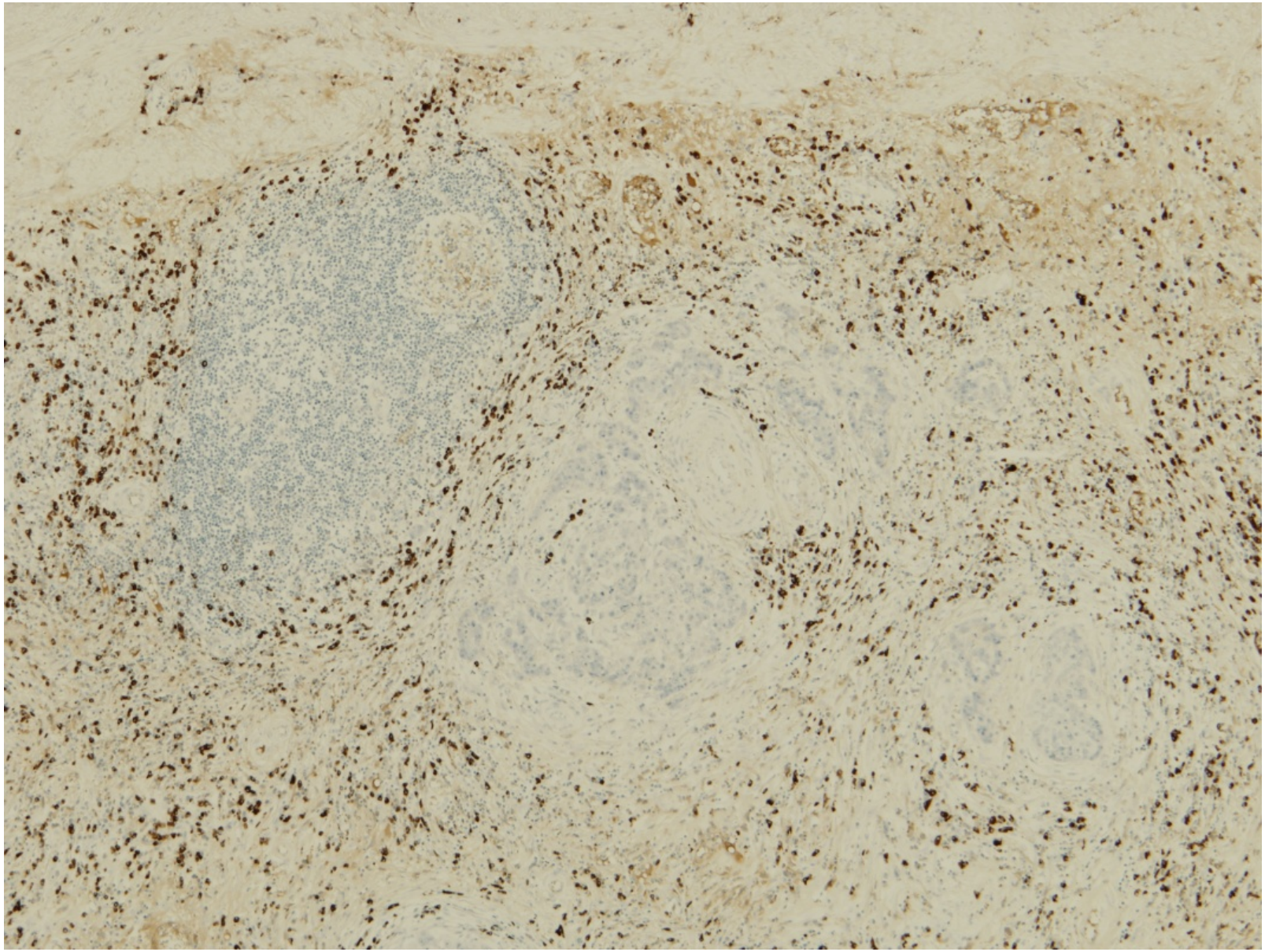


Fig 8A



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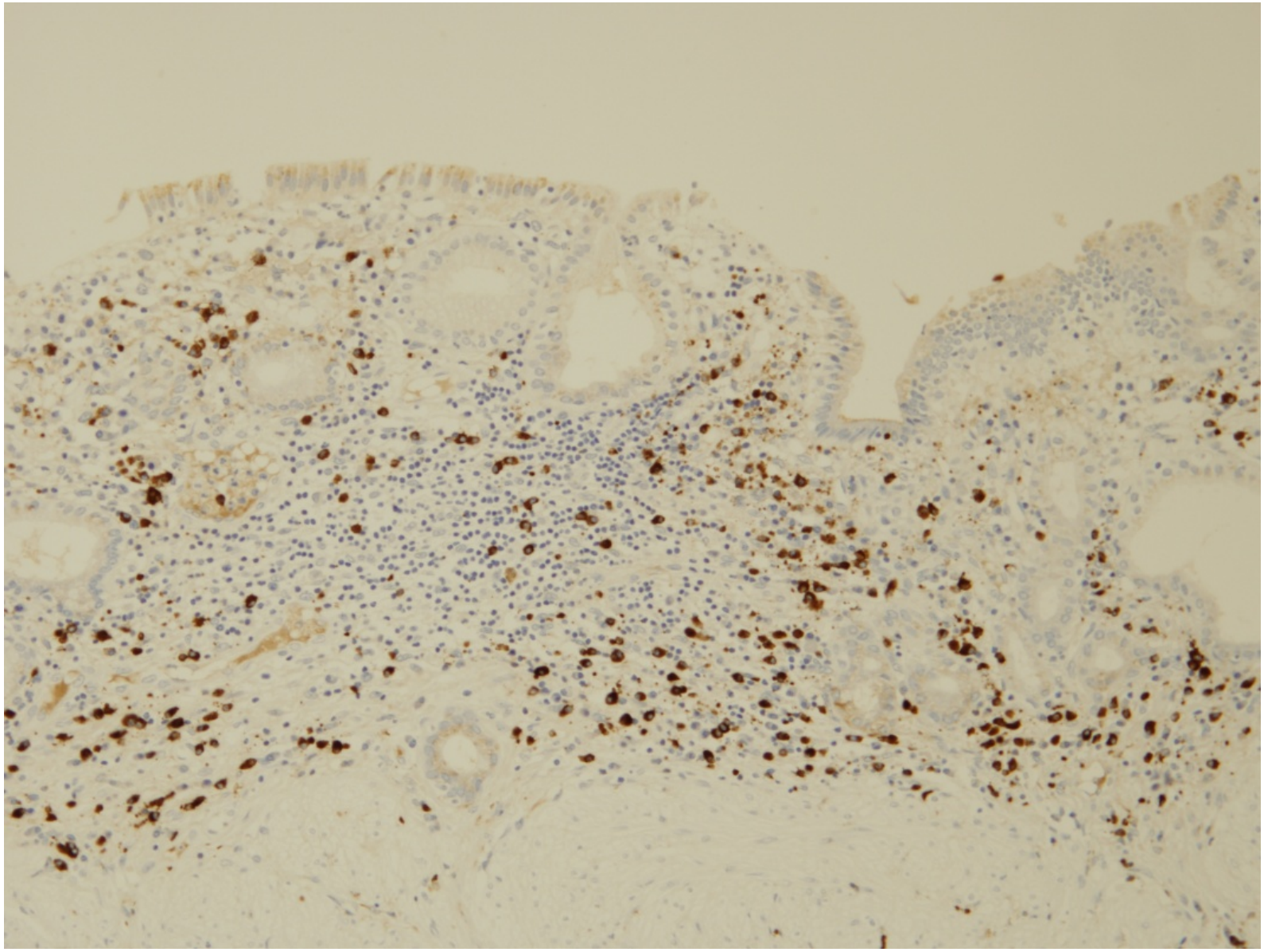

Fig 8C

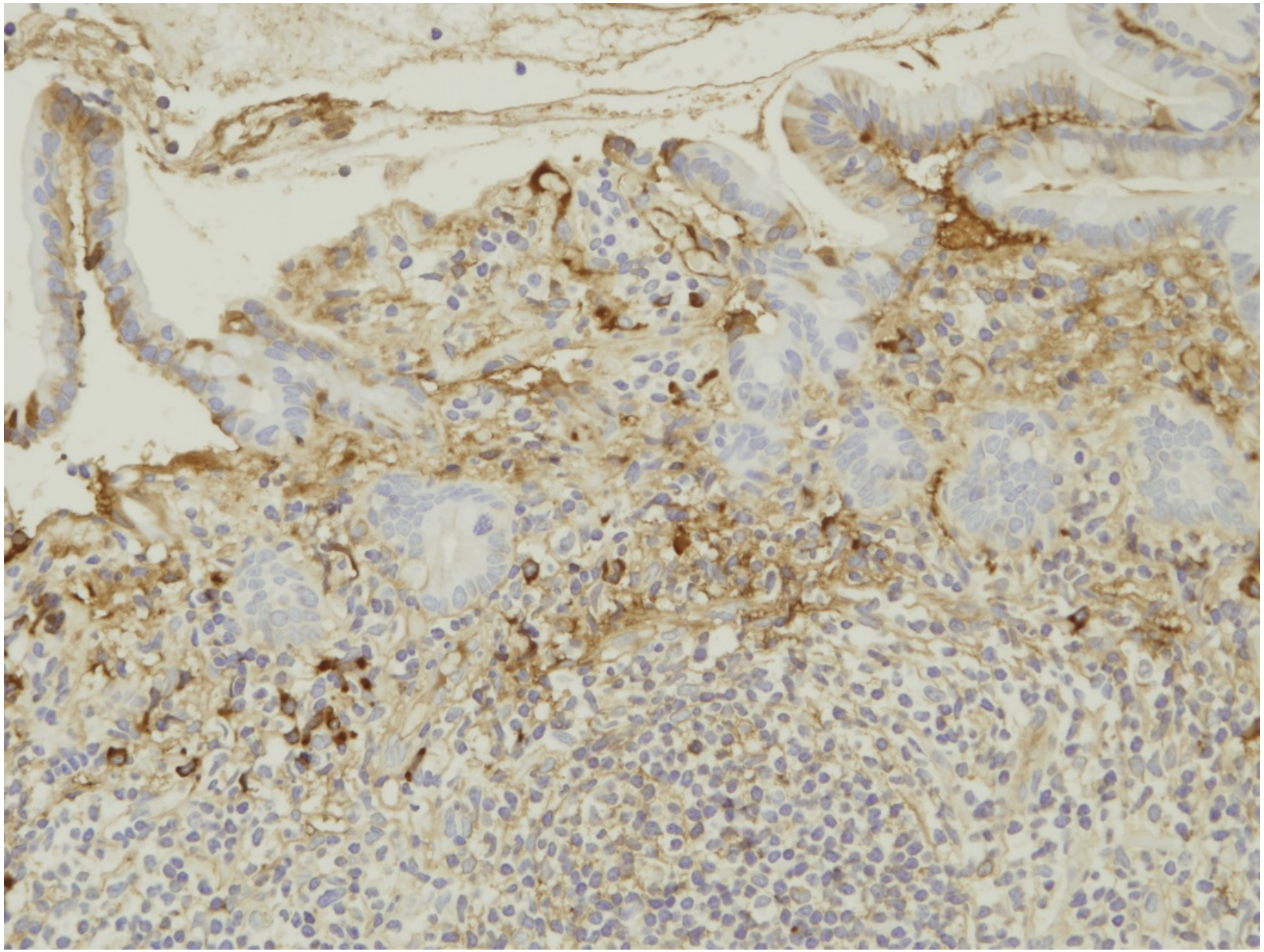

Fig 9A

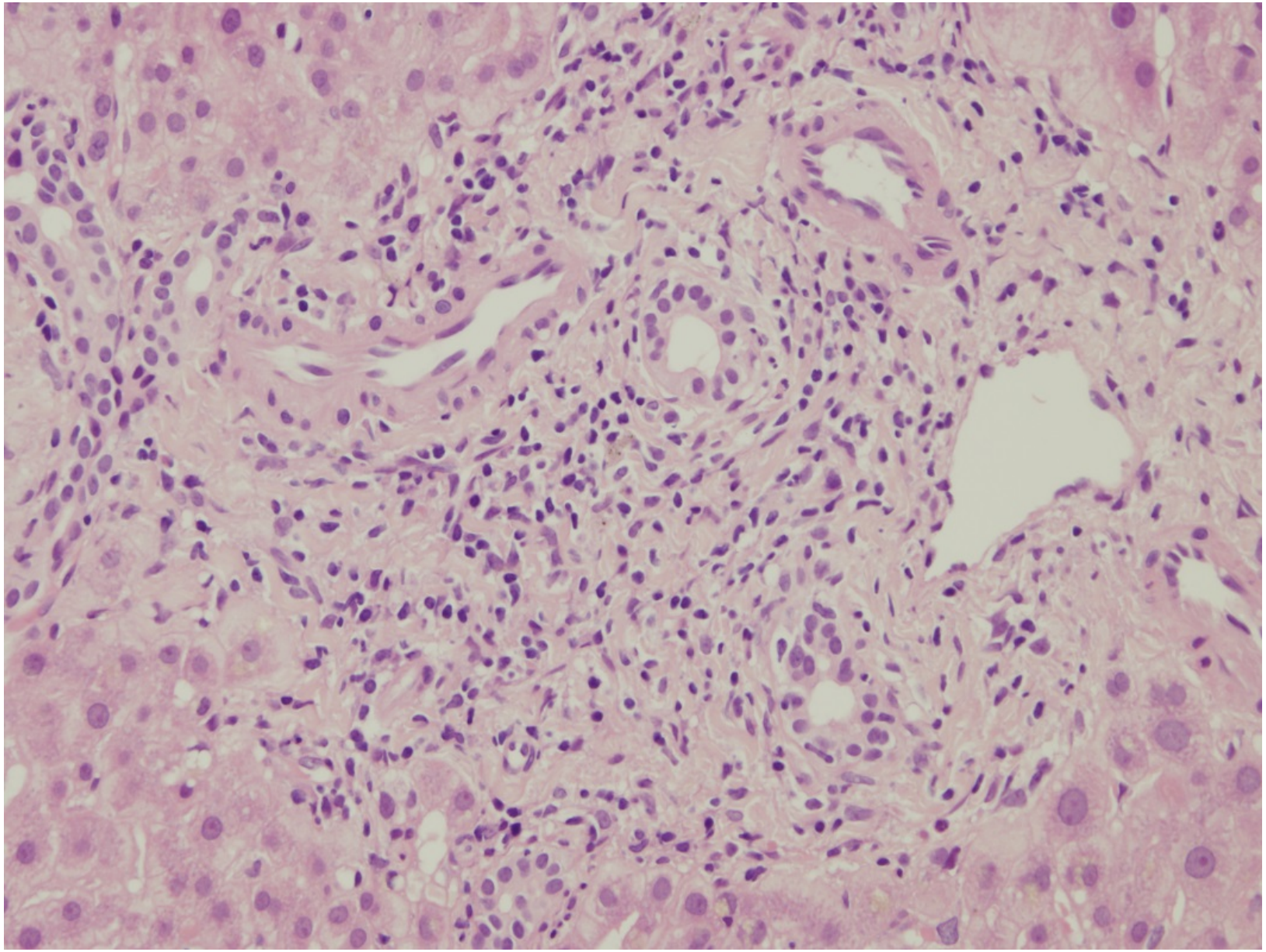

Fig 9B

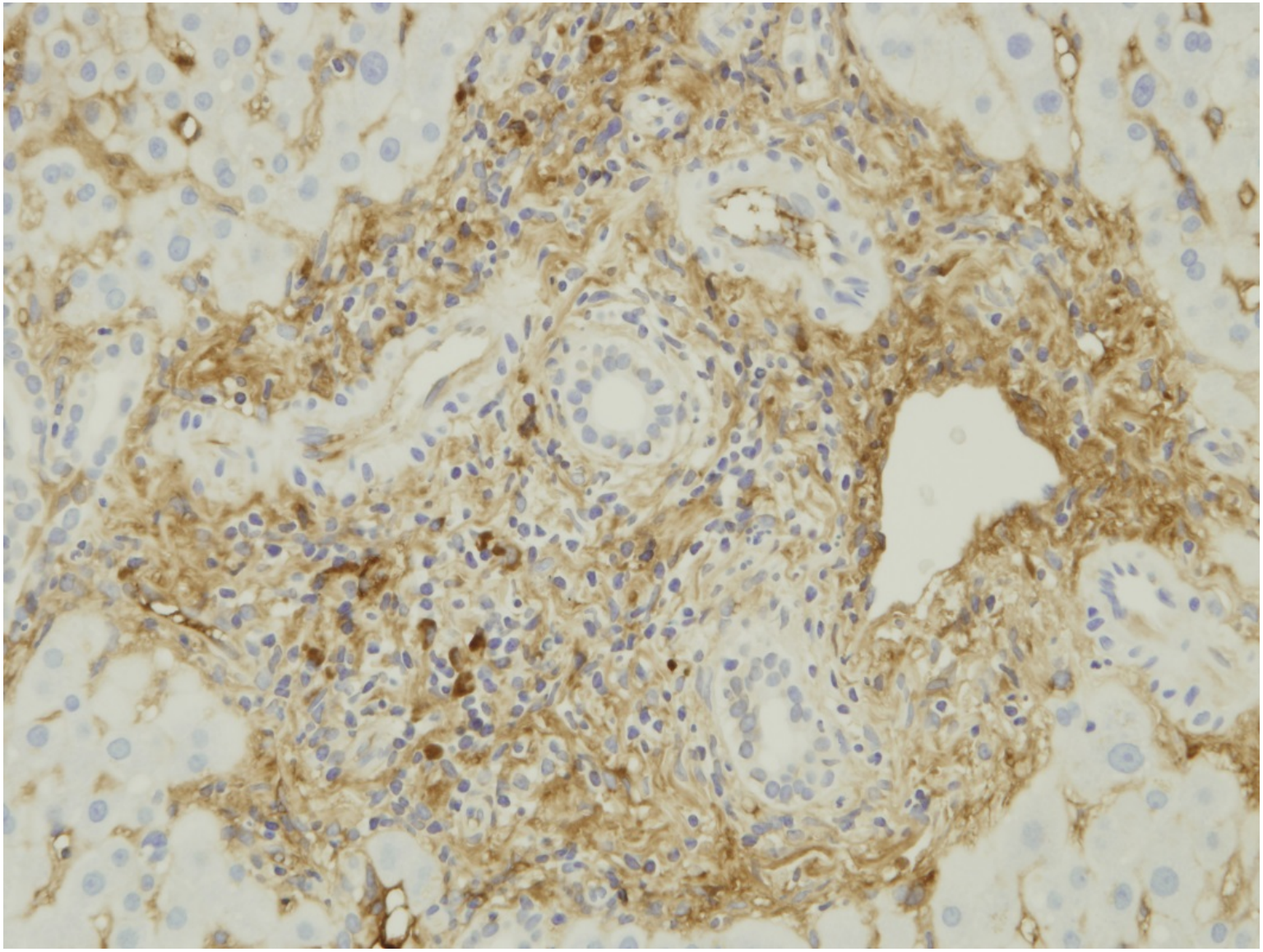

Fig 9C

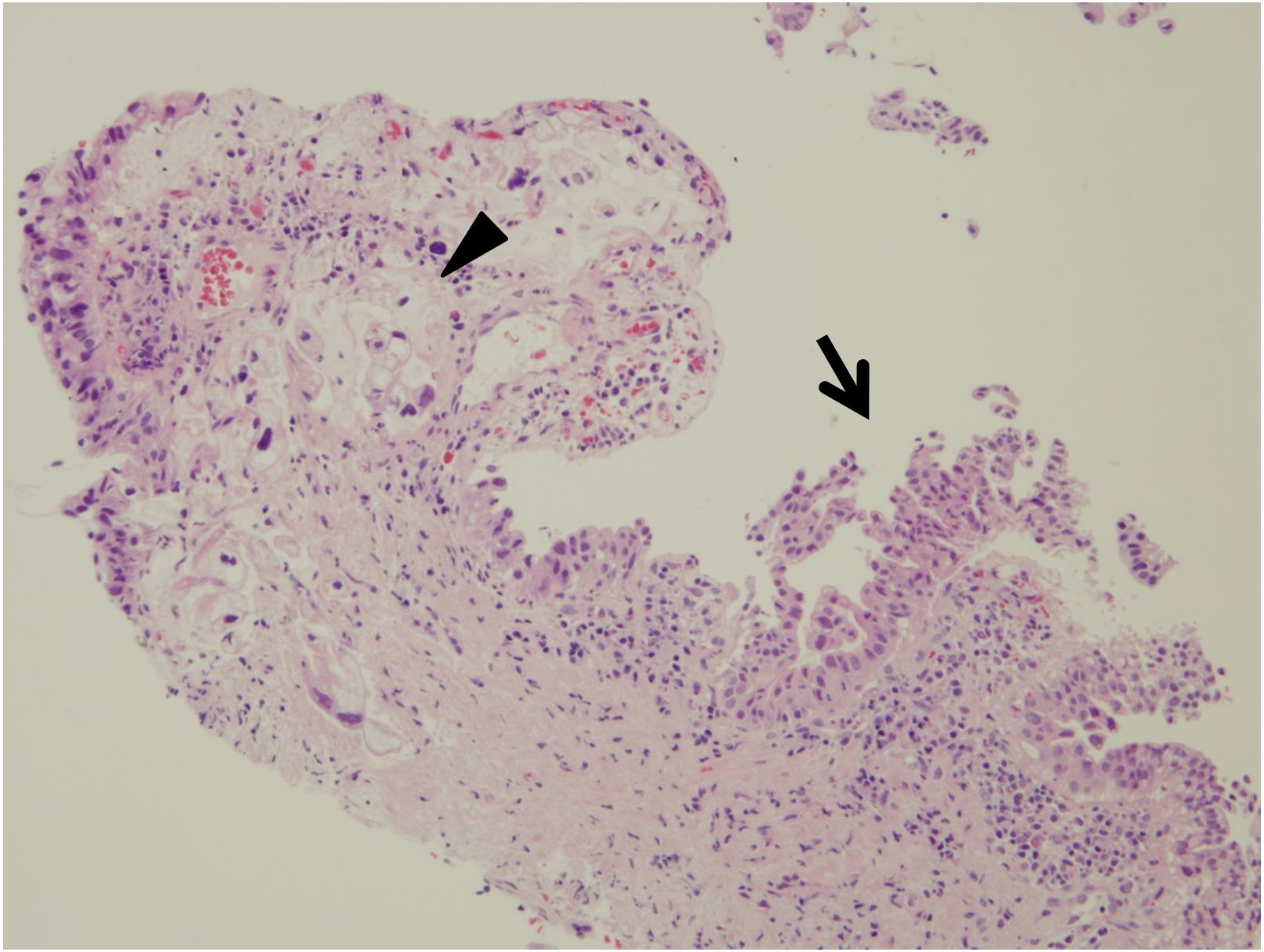

Fig 9D

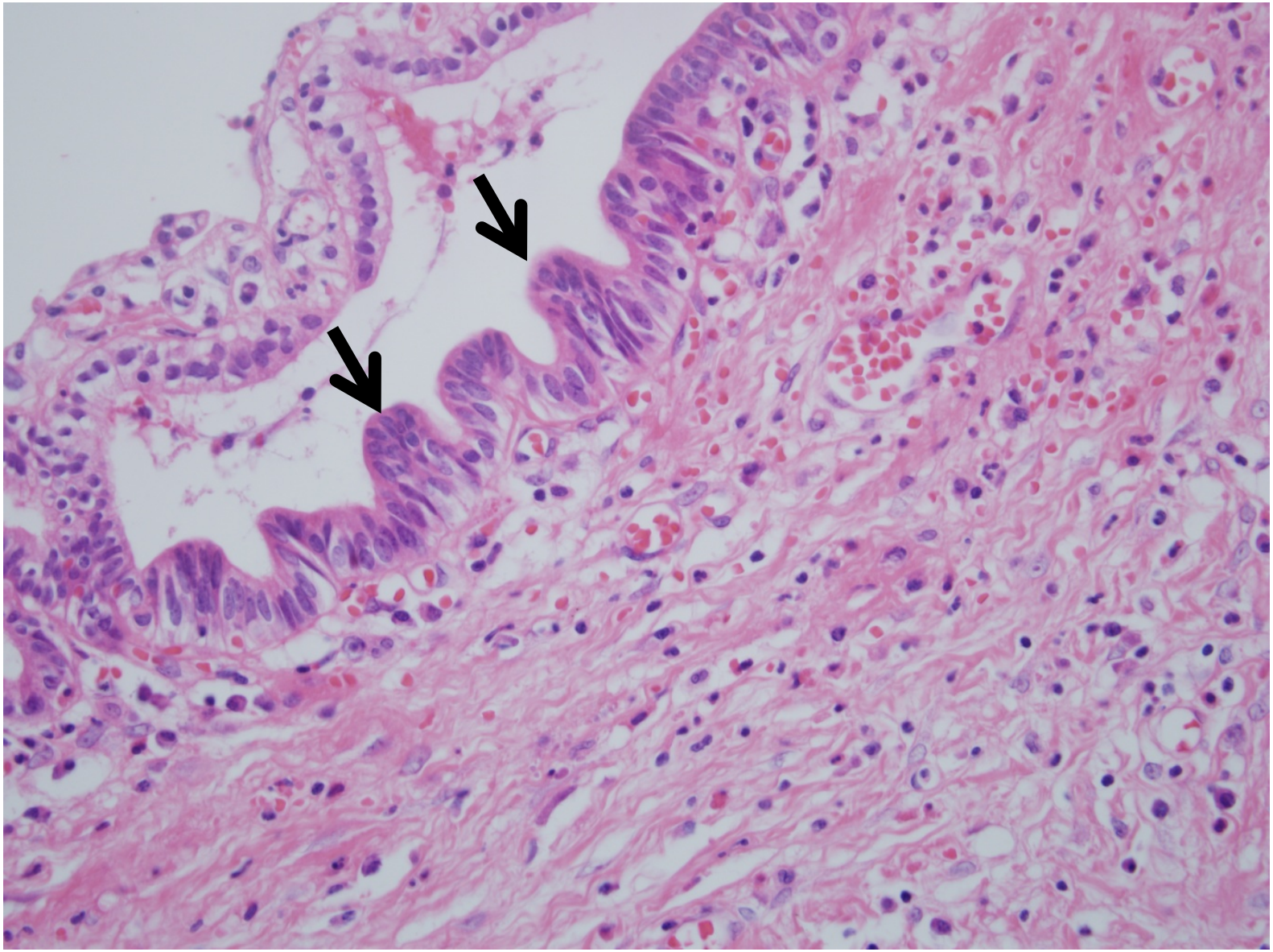

Fig 10A

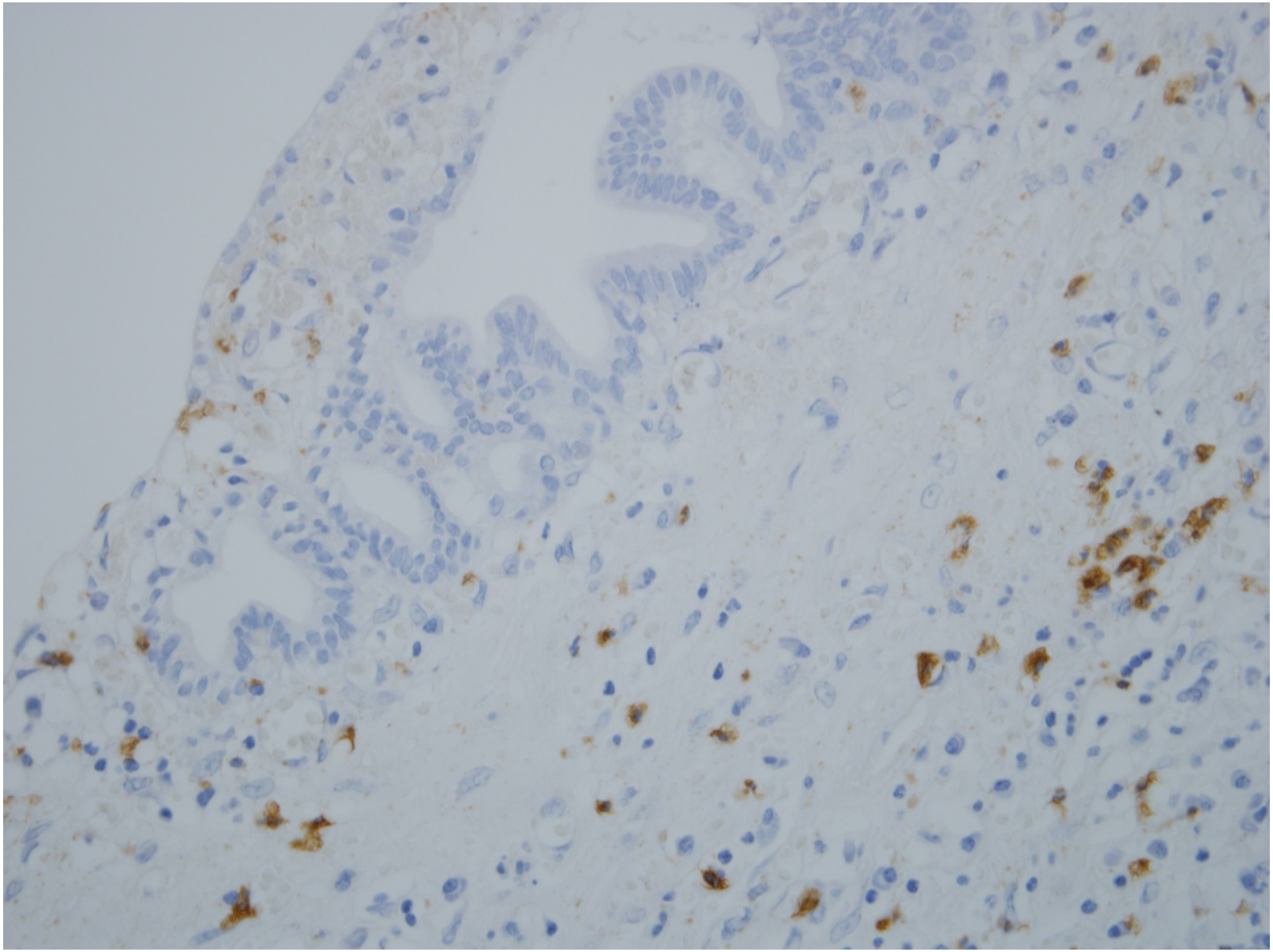

Fig 10B