IgG4-related kidney diseases and conditions: renal pelvic and ureteral diseases

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Abstract

In IgG4-related urinary tract diseases, the renal pelvis and ureters are rarely involved; however, the number of reported cases with this involvement has been increasing.

IgG4-related renal pelvic and ureteral lesions accompany extra-renal organ involvement, including IgG4-related type 1 autoimmune pancreatitis, and are characterized by common pathological features of IgG4-related diseases, including substantial numbers of IgG4-positive plasma cells, sclerosing fibrosis, and stenosis in the affected organs. Similar to other mucosal organs affected in IgG4-related disease, these inflammatory findings are observed within the fibroadipose tissue in the renal hilum and around the ureters, and the urothelial epithelium covering the renal pelvis and ureter is preserved. Nodular lesions such as pseudotumors can also form and it is important to differentiate these from malignant tumors. At present, comprehensive diagnostic criteria that include pathological parameters have been proposed for IgG4-related diseases; however, obtaining diagnostic findings in small biopsy specimens is usually challenging. Therefore, the diagnosis must be made on a case-by-case basis, with careful consideration of the clinical, serologic, radiologic, and pathologic features in light of the potential manifestations of IgG4-related disease in other organs.

Keywords: IgG4, renal pelvis, ureter, pseudotumor, retroperitoneal fibrosis

1. Introduction

Hamano et al. (1) first reported the presence of elevated serum IgG4 concentrations in autoimmune pancreatitis (AIP) patients as a prototype of IgG4-related diseases in 2001, and Kamisawa et al. (2) proposed the existence of IgG4-related systemic disease as a new clinicopathologic entity affecting a wide variety of organs in 2003. Increased serum IgG4 levels ($\geq$135 mg/dl), the presence of IgG4-positive cells in affected organs, and effective disease control with steroid treatment are unique clinicopathological features of IgG4-related diseases, irrespective of the affected organs; however, additional organ-specific histological findings are frequently observed. In particular, IgG4-related kidney disease encompasses renal and renal pelvic lesions, and tubulointerstitial nephritis in the renal cortex is a well-described, major manifestation of the disease. However, the glomeruli, renal pelvis, and ureter are also affected in IgG4-related renal diseases, mostly in association with retroperitoneal fibrosis. Moreover, pseudotumor-like nodular lesions mimicking urothelial carcinoma may also form in the renal pelvis and ureter. Most reported cases of IgG4-related kidney diseases have a history of prior IgG4-related pancreatitis or sialoadenitis; however, several cases of patients with IgG4-related urinary tract disease in the absence of other organ involvement have also been reported. In this chapter, renal pelvic and ureteral lesions in IgG4-related diseases have been described.

2. Clinical features of renal pelvic and ureteral lesions

Involvement of the renal pelvis and ureter in IgG4-related diseases is rare. Our review of the literature using the search engines for Japanese and English medical articles, ICHUSHI (Web. Japana Centra Revuo Medicina) and PubMed, respectively, revealed a

total of 35 reported cases of such involvement (3-30), including a renal pelvic case that was reported by our group (Case 12); all cases are summarized in Table 1. In addition, a review article on IgG4-related renal diseases has recently been reported (31). The age of patients ranged from 39 to 84 years, and older patients as well as males constituted the majority. Most of the cases involved isolated renal pelvic or ureter diseases; however, continuous distributions from the pelvic to the ureter as well as inflammatory pseudotumors were also observed in some cases. Moreover, synchronous and metachronous involvement was found in bilateral pelvises and ureters. In all cases the serum IgG4 levels were found to be above 135 mg/dl, with the exception of one case in which the serum IgG4 levels were analyzed after the operation. Retroperitoneal fibrosis as well as autoimmune pancreatitis is often accompanied with IgG4-related renal pelvic and ureteral diseases.

3. Renal pelvic lesions

The renal pelvic lesions of IgG4-related diseases are radiologically visualized as thickening of the renal pelvic wall without luminal irregularity and tumorous lesions in the renal hilum. As shown in Figures 1–3, unlike renal pelvic mucosal lesions, the lesions in IgG4-related kidney diseases are recognizable as nonspecific nodular lesions within the fibroadipose tissue of the renal hilum. The disease histology shows dense lymphoplasmacytic infiltration of the lymphoid follicle and loss of adipose tissue within the renal hilum. Sclerosing fibrosis with occasional hyalinization and storiform and swirling fibrosis are found (Fig. 3F). However, the degree of sclerosing changes is comparatively milder than that observed in autoimmune pancreatitis, a prototypical IgG4-related disease; furthermore, some cases show only a prominent inflammatory

change without any sclerosing changes (Case 11 in Table 1) (13). Similar to the histological characteristics of other affected organs in IgG4-related diseases, eosinophilic infiltration, obliterative phlebitis (Fig. 1E), and perineural inflammatory infiltration (Fig. 3D) are also observed in some cases. This infiltration extends beyond the subepithelial layer of the renal pelvic urothelial mucosa; however, involvement of the urinary epithelial layer and epithelial injury are not prominent. Similar to IgG4-related autoimmune pancreatitis and sclerosing cholangitis, therefore, epithelial layer is well-preserved without any erosive changes. This lack of epithelial layer involvement underlies the general difficulties in obtaining valuable pathological information from superficial mucosal specimens by renal pelvic biopsy procedures. However, specimens from most of the patients show an absence of inflammation extending into the renal parenchyma, with a clear border between the renal pelvic pathology and renal parenchyma, in some cases, inflammatory invasion of the renal parenchyma (Fig. 3) and interstitinal nephritis were observed (Case 3 in Table 1) (5).

Immunohistochemical staining for IgG4 has revealed substantial numbers of diffuse IgG4-positive cells in inflammatory lesions even though IgG4 is a minor immunoglobulin subtype comprising only 3%–6% of the total circulating IgG in adults (1). In cases with prominent lymphoid follicle formation, IgG4-positive cells tend to be localized in the interfollicular area, with several IgG4-positive cells scattered in the germinal centers of lymphoid follicles. As expected, these cases fulfill the comprehensive pathological diagnostic criteria for IgG4-related disease (32) that is based on the presence of >40% of IgG-positive plasma cells as IgG4-positive and the presence of >10 cells/high powered field in the biopsy sample. The predominance of IgG4-positive cells instead of IgG1-positive cells also supports the diagnosis of

IgG4-related diseases (Fig. 2E and F).

3. Ureteral diseases

Ureteral involvement in IgG4-related disease has been found in 42% of the IgG4-related retroperitoneal fibrosis cases (13). In some patients, renal pelvic involvement, as discussed above, or bilateral ureteral lesions are also observed. Irrespective of the involvement of other organs, ureteral IgG4-related disease is characterized by the thickening of ureteral wall or the presence of nodular lesions involving the affected ureter, and these are usually associated with hydronephrosis resulting from ureteral stenosis of the affected portion. Therefore, in most IgG4-related ureteral cases, the initial presentation is of hydronephrosis associated with retroperitoneal fibrosis or renal dysfunction with unknown etiology, and a diagnosis is established following the finding of serological data indicating increased serum IgG4 levels and hypocomplementemia (33). As an example, in one case shown in Table 1 (Case 10), the definitive diagnosis of IgG4-related ureteral disease was preceded by a ureteral calculus (12).

IgG4-related ureteral disease displays the common pathological features of other IgG4-related diseases: in addition to marked lymphoplasmacytic infiltration, eosinophilic infiltration and sclerosing fibrosis are also observed in the lesions. Advanced fibrosis eventually results in ureteral sclerosis that in turn induces ureteral stenosis and obstruction. Lymphoid follicle formation can also be detected, albeit to a lesser extent than that observed in renal pelvic lesions. The extension of the inflammatory reaction into the adipose tissue around affected organs is an important feature of IgG4-related diseases, including autoimmune pancreatitis, reflecting their

characteristic radiological findings. Similarly, periureteral fibroadipose tissue as well as the ureteral wall harbor inflammatory and fibrosclerotic reactions (Fig. 4A), and in some cases, these reactions extend into the lesions of retroperitoneal fibrosis. Immunohistochemical staining for IgG1 and IgG4 reveals a predominantly IgG4-positive plasma cell infiltration in this disease (Fig. 4D and E).

5. Diagnosis

The diagnosis of IgG4-related renal pelvic and ureteral diseases is relatively easy and is based on the common clinicopathological features of IgG4-related disease in cases where there is either a concurrent or preceding diagnosis of IgG4-related disease in other organs, such as the pancreas or the salivary glands. However, if the initial lesions are within the renal pelvis or ureters with no overt involvement of other organs, differentiation of the lesions from malignant masses or stenosis in the affected area is crucial. Moreover, inflammatory pseudotumors not related to IgG4, inflammatory myofibroblastic tumors (15), and Cattleman's disease in cases with limited fibrosclerosis (13) should also be considered in differential diagnosis.

Increased serum IgG4 levels and infiltration of IgG4-positive plasma cells are important in the diagnosis of IgG4-related renal pelvic and ureteral diseases. According to the current comprehensive diagnostic criteria for IgG4-related disease (32), elevated serum levels of IgG4 (≥135 mg/dl) and predominantly IgG4-positive plasma cell infiltration (≥10 cells/high-power field with an IgG4-positive:total IgG-positive plasma cell ratio of ≥40%) are pathologically necessary for the diagnosis of IgG4-related disease. However, as mentioned above, biopsied specimens from the surface of renal pelvic and ureteral mucosa are unlikely to contain the characteristic features of

IgG4-related disease such as abundance of IgG4-positive cells and sclerosing fibrosis. Although the number of IgG4-positive cells that can be detected in small renal pelvic and ureteral specimens is not known, the biopsy of stenotic lesions is definitively recommended, as demonstrated in Case 13 in Table 1 where the IgG4-related ureteral disease was diagnosed by ureteral biopsy (14).

To complicate matters, IgG4-related ureteral disease in association with carcinoma *in situ* (urothelial carcinoma) (18), as seen with Case 21 in Table 1, raises the possibility of ureteral cancer to precede IgG4-related disease. While the infiltration of numerous IgG4-bearing plasma cells is important for the pathogenesis of IgG4-related disease, patients with pancreatic adenocarcinomas accompanying IgG4 infiltration in the cancerous area and/or elevated serum IgG4 levels (34-38) as well as patients with pancreatic and biliary cancers arising from IgG4-related disease (36, 39, 40) have been reported. However, a cause-and-effect relationship between IgG4 infiltration and cancer is yet to be demonstrated. It is imperative to examine the role of IgG4 in renal pelvic and ureteral cancers. Further, potential malignancies should be ruled out before the comprehensive criteria for IgG4-related disease are evaluated. Renal pelvic and ureteral biopsies and cytological examination are invariably important in the exclusion of malignancies prior to the diagnosis of IgG4-related disease.

6. Conclusion

Renal pelvic and ureteral lesions associated with IgG4-related disease are rare; however, their clinicopathological distinction from malignancy is crucial. In this chapter, we reviewed IgG4-related renal pelvic and ureteral diseases in the light of previous reports. Consequently, these diseases are often associated with IgG4-related diseases of

other organs such as the pancreas and present with increased serum IgG4 levels and substantial numbers of IgG4-positive cells in the affected areas that show the typical clinicopathological features of IgG4-related disease. Several cases with a potential association with malignancy have also been reported. Therefore, care must be taken not to be overly influenced by the comprehensive diagnostic criteria because fulfilling them does not rule out concomitant cancer.

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Figure legends

Figure 1. IgG4-related renal pelvic disease (Case 2 in Table 1). A: Macroscopic image of the cut surface of the resected kidney. A whitish mass was found in the renal hilum. B: Semi-macroscopic image. Asterisk denotes an inflammatory nodular lesion resembling a lymphoid organ with a clear border in the renal parenchyma. Arrow denotes renal pelvic mucosa. C; Inflammatory lesion containing several

lymphoid follicles and marked inflammatory cells. Note that the renal pelvic epithelium is well-preserved (arrow). D: Fibrotic area (*) and inflammatory invasion into the adipose tissue of the renal pelvis (lower side). E: Arrow denotes obliterative phlebitis using Elastica van Gieson staining. F: Numerous IgG4-positive cells dispersed throughout the interfollicular area, as determined by immunohistochemical staining for IgG4.

Figure 2. IgG4-related renal pelvic disease (Case 12 in Table 1). A: Computed tomography showing the presence of a mass within the renal pelvis (arrow). B: Semi-macroscopic image of the resected kidney. Lymphoid follicle-like inflammatory nodular lesions were found in the renal hilum. The renal pelvic mucosa was slit-like indicating stenosis (arrow). C: Renal pelvic mucosa, albeit stenotic, was well-preserved with the absence of inflammation (arrow). Fibrosis was not prominent. D: Inflammation consisting mostly of lymphocytes and plasma cells. E: Immunohistochemical staining for IgG4. Many IgG4-positive cells were found in the interfollicular area. F: Semi-serial sectioning of the area shown in (E). Immunohistochemical staining for IgG1. Several IgG1-positive cells were observed, albeit in smaller numbers than those of the IgG4-positive cells observed in (E).

Figure 3. IgG4-related renal pelvic disease (Case 1 in Table 1). A: Macroscopic image of the cut surface of the resected kidney. Whitish sclerotic changes were found in the adipose tissue of the renal hilum (arrows). B. Semi-macroscopic image of the resected kidney. Scar-like, broad fibrosis (*) was prominent, and lymphoid

follicles were scattered in the periphery facing the renal parenchyma. C: Fibrosis and inflammation extend from the adipose tissue of the renal hilum into the renal parenchyma (*). D: Nerve bundles are intact. Note the perineural inflammation. E: Inflammation and hyalinized fibrosis are shown. F: Note the mild inflammation but prominent fibrosis.

Figure 4. IgG4-related ureteral disease (Case 15 in Table 1). A: Semi-macroscopic image of the cross-section of the resected ureter. Distinct areas of prominent inflammation and fibrotic areas were found in the ureteral wall. Inflammation partially invades into adipose tissue of renal hilum (arrow). B: In inflammatory areas, a follicle-like inflammatory formation and extension of inflammation into the adipose tissue were found. C: Fibrosis was prominent, and sclerotic change was present; however, the inflammatory foci remained. D: Immunohistochemical staining for IgG4. Many IgG4-positive cells were found around the inflammatory area. E: Semi-serial section of the area shown in (D). Immunohistochemical staining for IgG1. Several scattered IgG1-positive cells, albeit in smaller numbers than those of the IgG4-positive cells, were seen.

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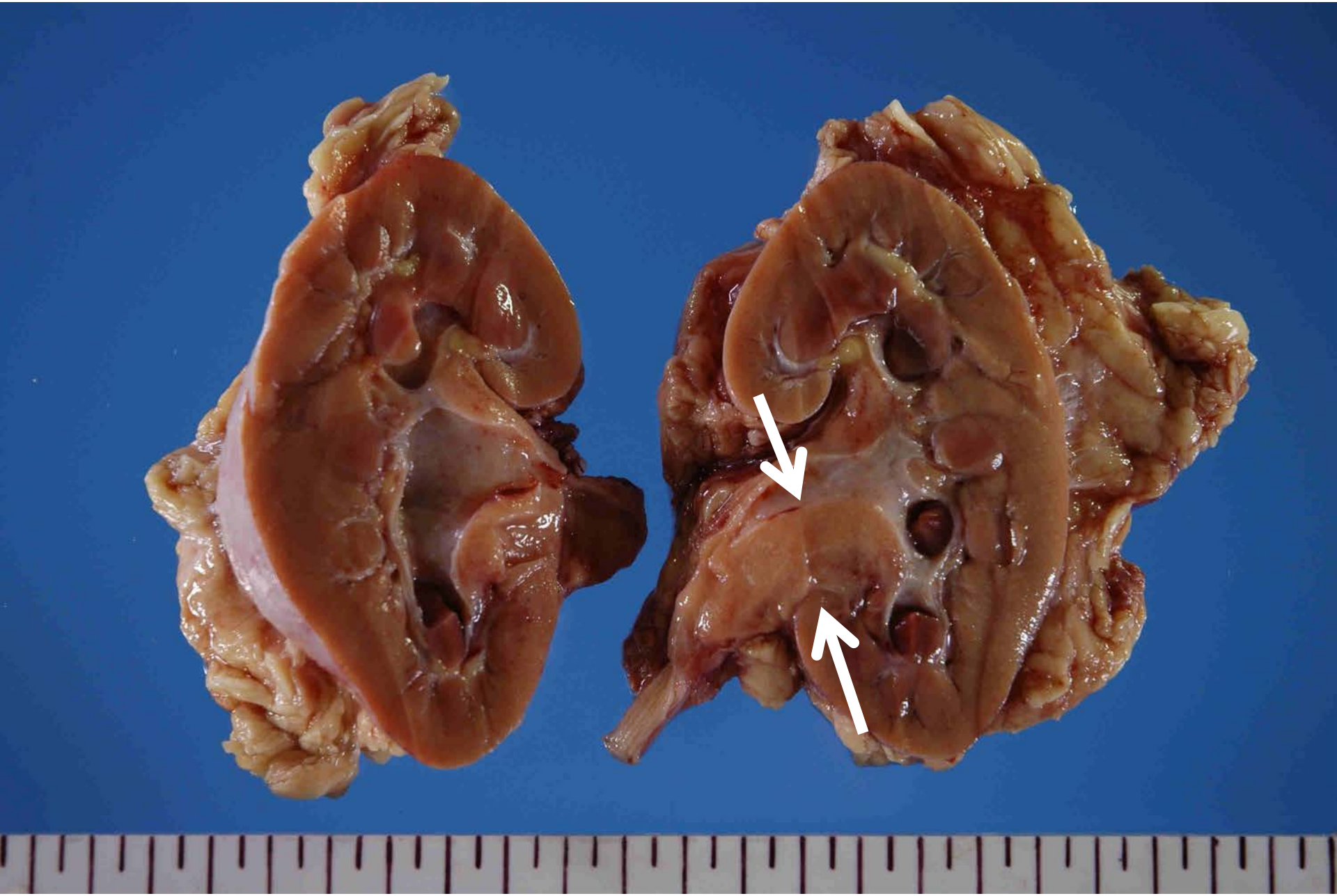
Table 1 Clinical summary of reported cases of IgG4-related pelvic and uretheral lesions

	Age (years)	Sex	Location of lesion
Case 1	63	Male	Left renal pelvis
Case 2	49	Female	Left renal pelvis to ureter
Case 3	76	Male	Right renal pelvis to ureter
Case 4	61	Male	Left renal pelvis
Case 5	70	Male	Left renal pelvis + Right renal pelvis (metachronous)
Case 6	70s	Male	Left renal pelvis + Right renal pelvis (metachronous)
Case 7	70s	Male	Left renal pelvis to ureter
Case 8	65	Male	Left renal pelvis
Case 9	78	Male	Left renal pelvis + Right renal pelvis (metachronous)
Case 10	53	Male	Bilateral renal pelvis
Case 11	60s	Female	Left renal pelvis
Case 12	52	Female	Left renal pelvis
Case 13	59	Male	Bilateral ureters
Case 14	51	Female	Left ureter
Case 15	39	Male	Left ureter
Case 16	60	Male	Left ureter
Case 17	74	Male	Right ureter
Case 18	75	Male	Left ureter
Case 19	45	Male	Left ureter (psudotumor)
Case 20	47	Male	Left ureter (psudotumor)
Case 21	84	Female	Right ureter ＋urothelial carcinoma (in situ)
Case 22	53	Female	right renal pelvis
Case 23	69	Male	Left renal pelvis+Right renal hilus (metachronous)
Case 24	49	Female	Bilateral renal pelvis
Case 25	79	Female	Ureter
Case 26	68	Male	Right renal mass
Case 27	80	Male	Right renal pelvis
Case 28	71	Male	Left renal pelvis
Case 29	71	Male	Right ureter + Left renal hilus (metachronous)
Case 30	54	Female	Left renal pelvis
Case 31	49	Male	Right ureter
Case 32	68	Male	Bilateral renal pelvis to ureters
Case 33	70	Male	Left renal pelvis to ureter
Case 34	82	Female	Left ureter
Case 35	77	Male	Left ureter

Blanks, to be specified

Size of lesion	Serum IgG4
40 × 30 × 25 mm	within normal range (post-operative)
35 mm	555 mg/dl
33 mm	376 mg/dl
	936 mg/dl
17 × 14 × 8 mm	
	1980 mg/dl
	295 mg/dl
	615 mg/dl
22 × 15 mm	404 mg/dl
	Elevated
	Elevated
30 × 11 mm	233 mg/dl
	265 mg/dl
	965 mg/dl
	240 mg/dl
15 × 7 × 7 mm	
10 × 40 mm	
20 mm	
	3250 mg/dl
30 mm (left renal pelvis)	847 mg/dl
	469mg/dl
30 mm long	206mg/dl
	202mg/dl
	220mg/dl
	847 mg/dl
	936 mg/dl
50 × 25 mm	1860 mg/dl
30 mm	
	420 mg/dl
40 mm long	

Extrarenal lesions	Reference
Retroperitoneal fibrosis	3)
Sialoadenitis,dacryoadenitis	4)
interstitial nephritis	5)
Autoimmune pancreatitis	6)
	7)
Sialoadenitis, Autoimmune pancreatitis	8)
renal hilar lymph node swelling	9)
	10)
	11)
	12)
	13)
	unpublished observation
	13)
Sialoadenitis	14)
Retroperitoneal fibrosis	15)
Autoimmune pancreatitis, Retroperitoneal fibrosis	16)
Autoimmune pancreatitis, Retroperitoneal fibrosis	16)
Autoimmune pancreatitis, Retroperitoneal fibrosis	17)
None	18)
None	18)
None	18)
	19)
None	20)
	21)
para-aortic lymph node swelling	22)
piuitary gland	23)
	23)
Retroperitoneal fibrosis	24)
Autoimmune pancreatitis, Sclerosing cholangitis	25)
Systemic lymph node swelling	26)
	27)
urinary bladder	28)
	29)
	30)
	30)



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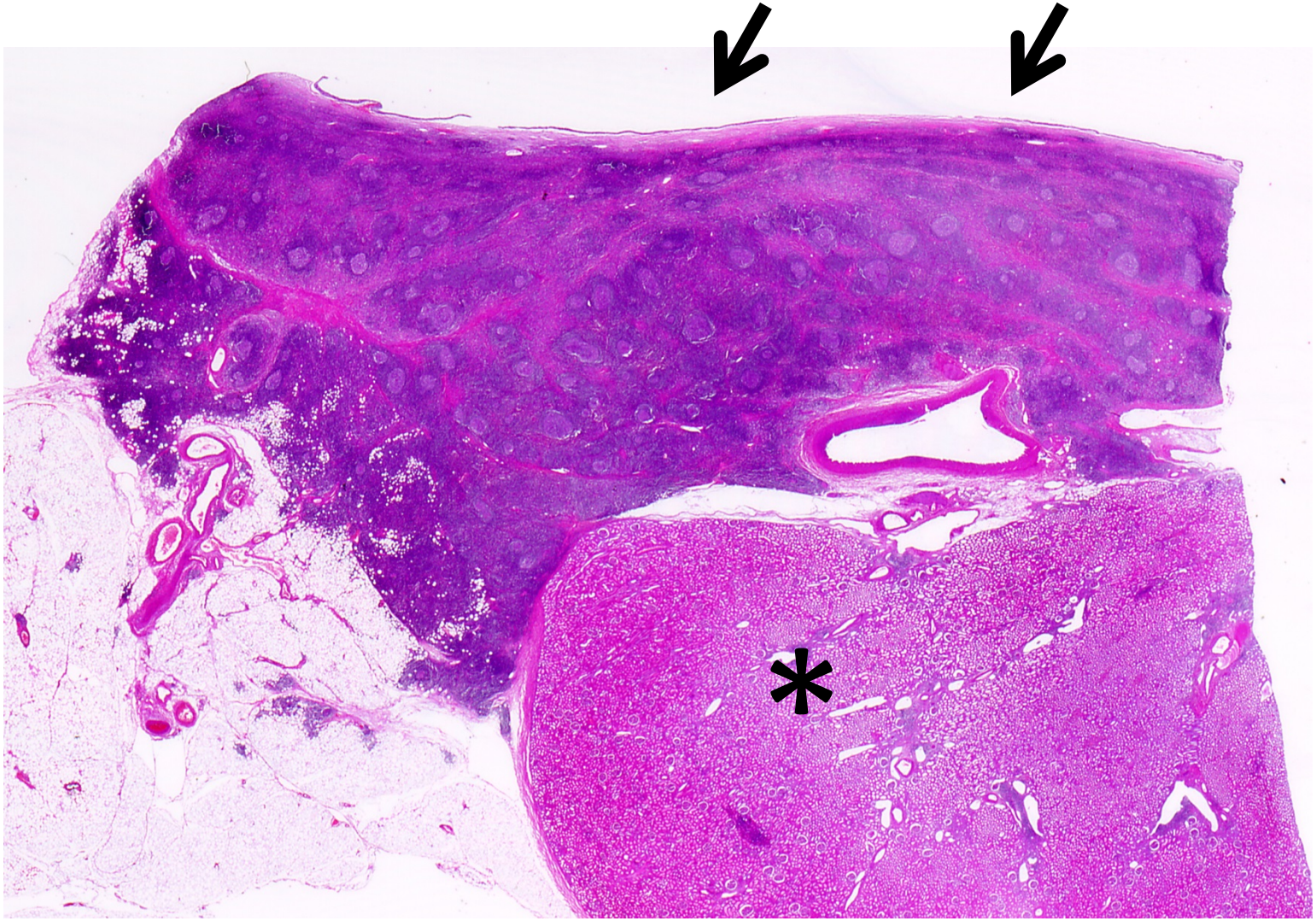

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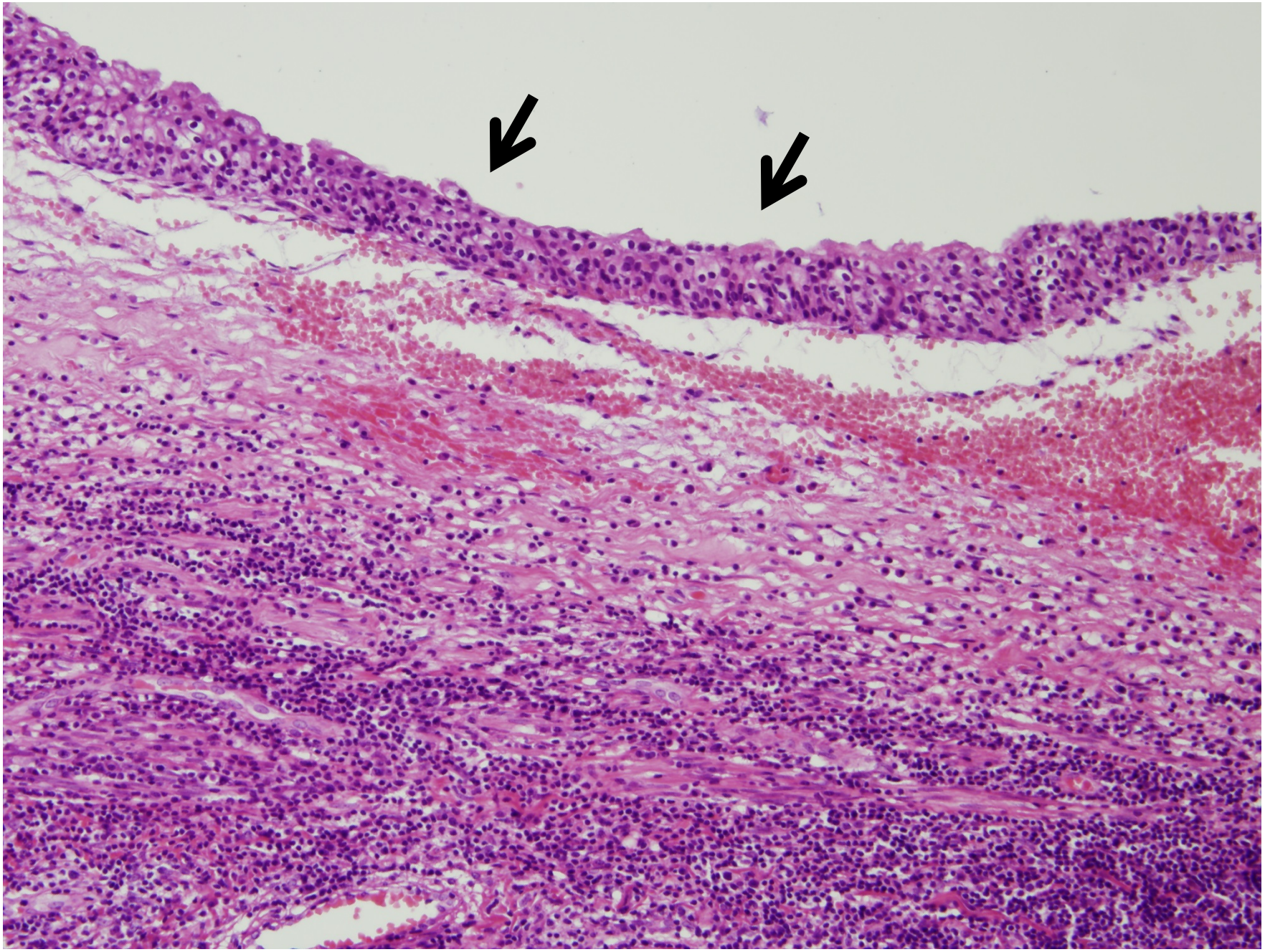

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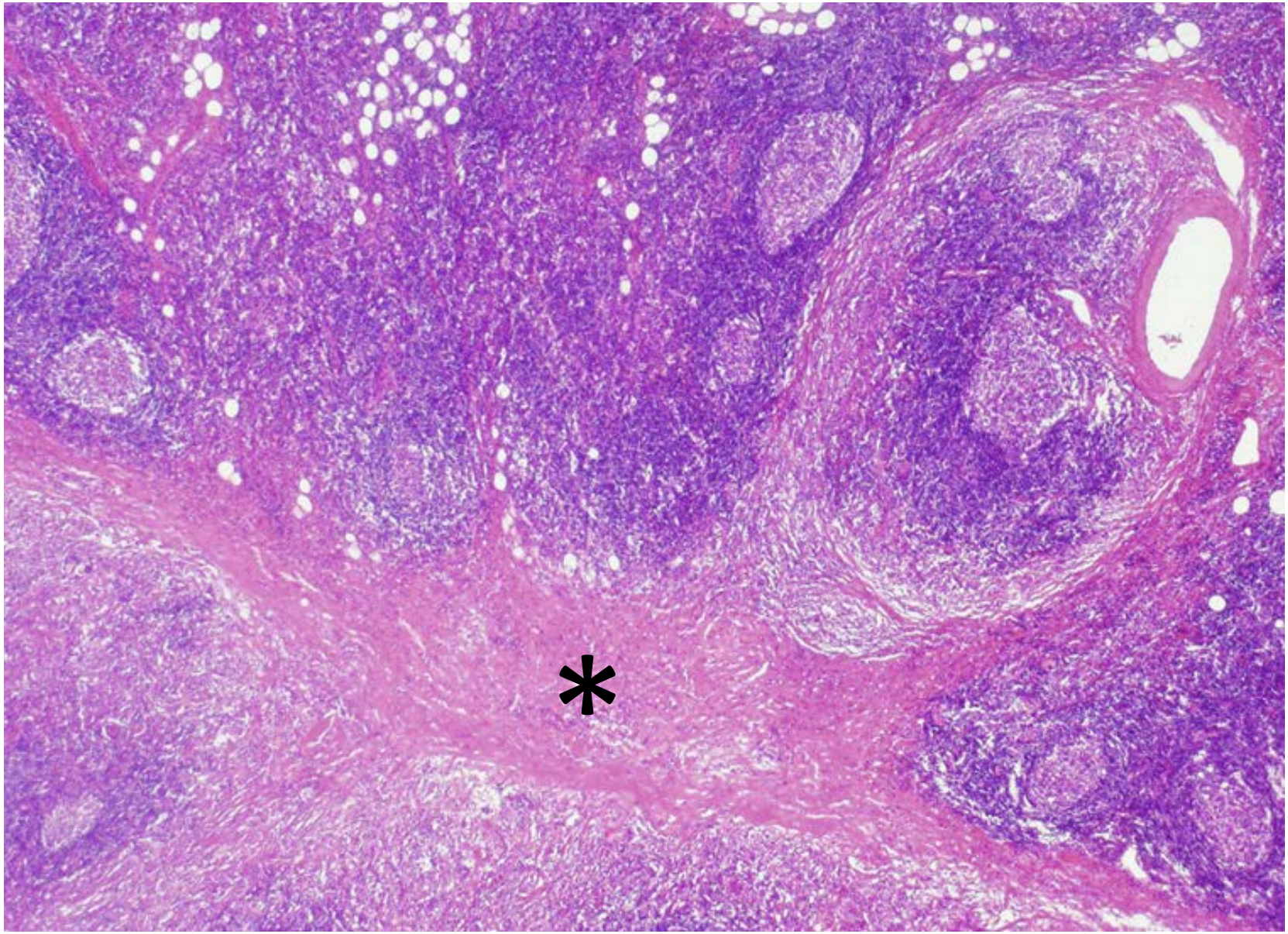

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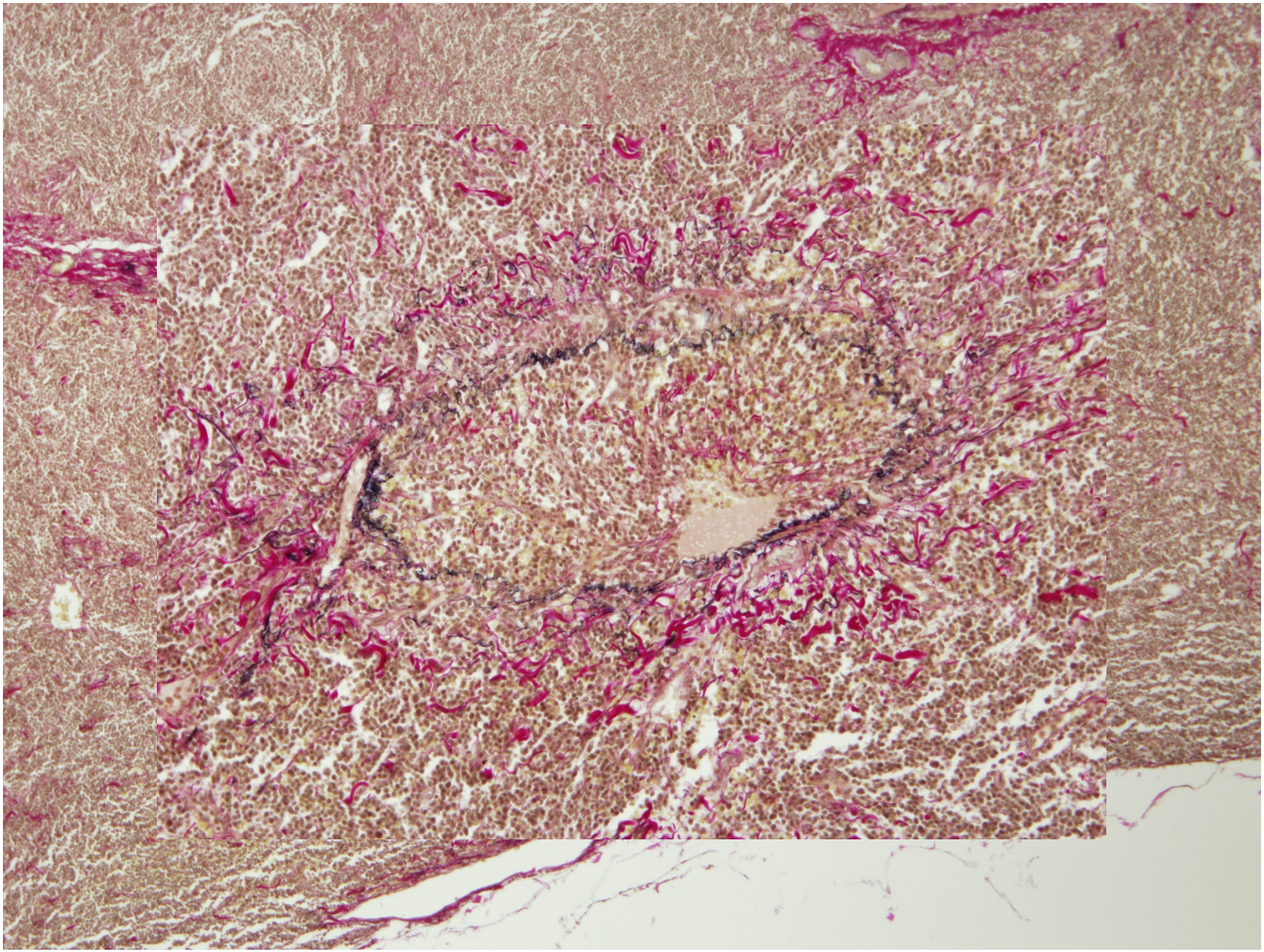
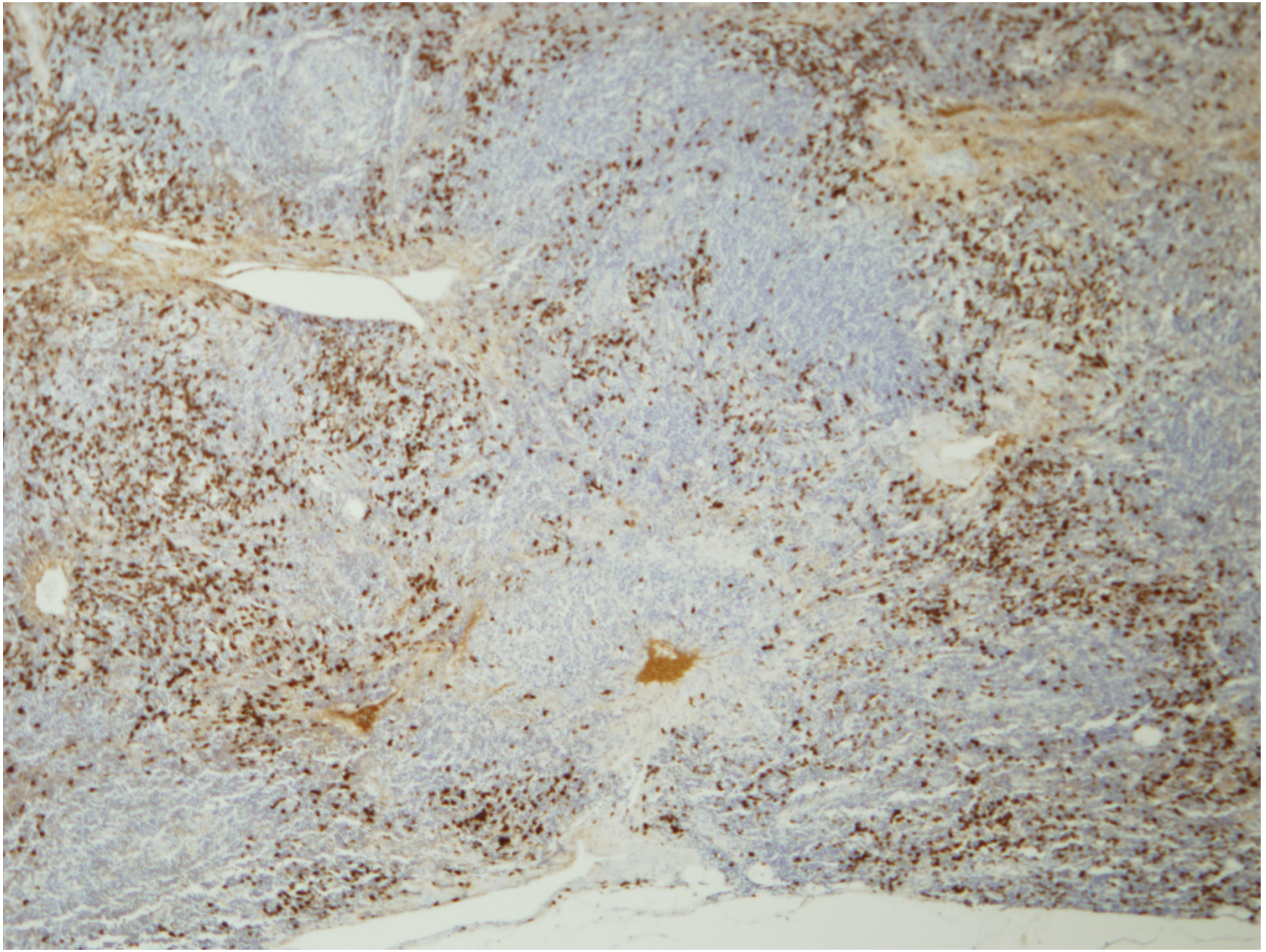


図1E



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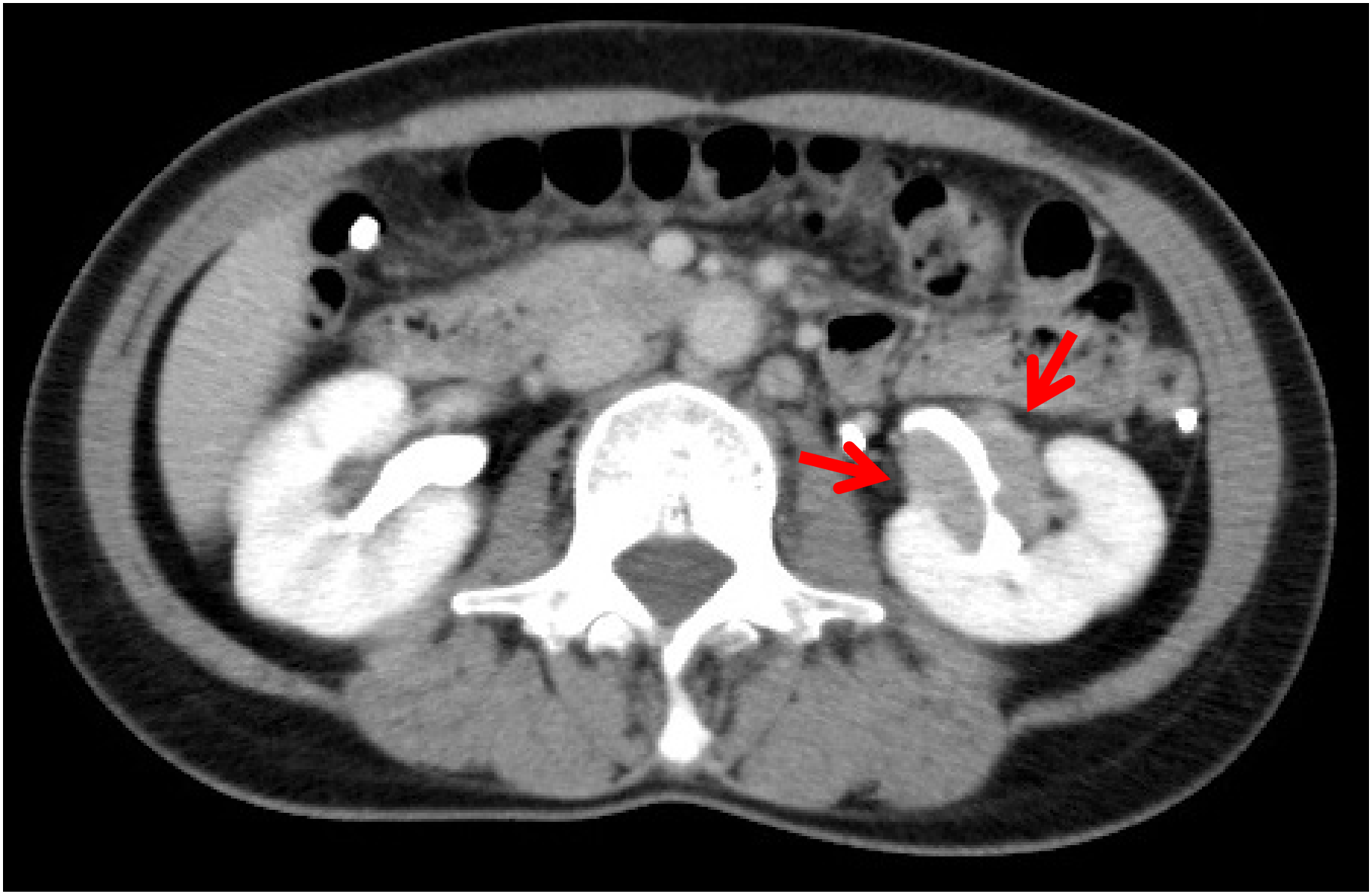

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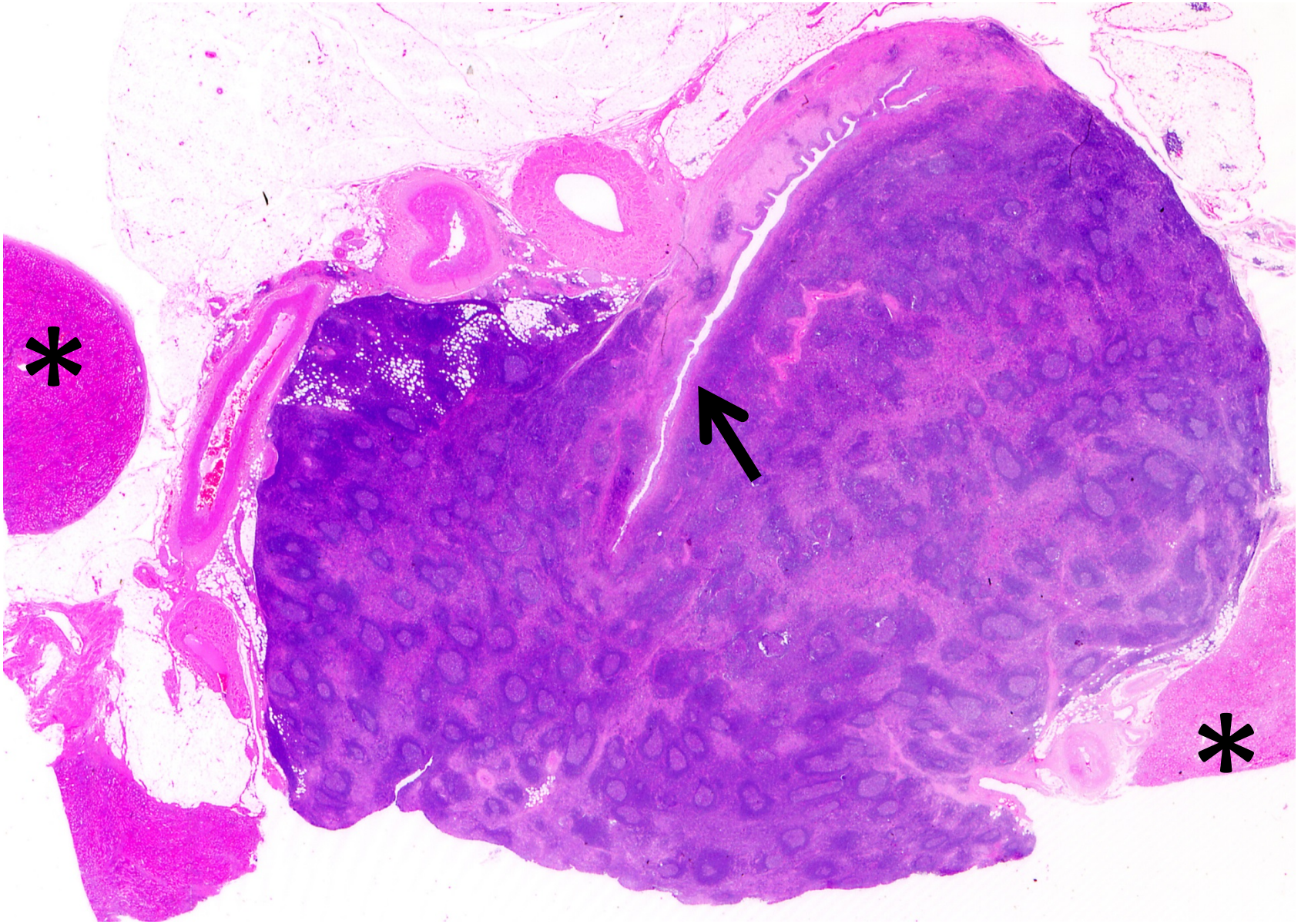

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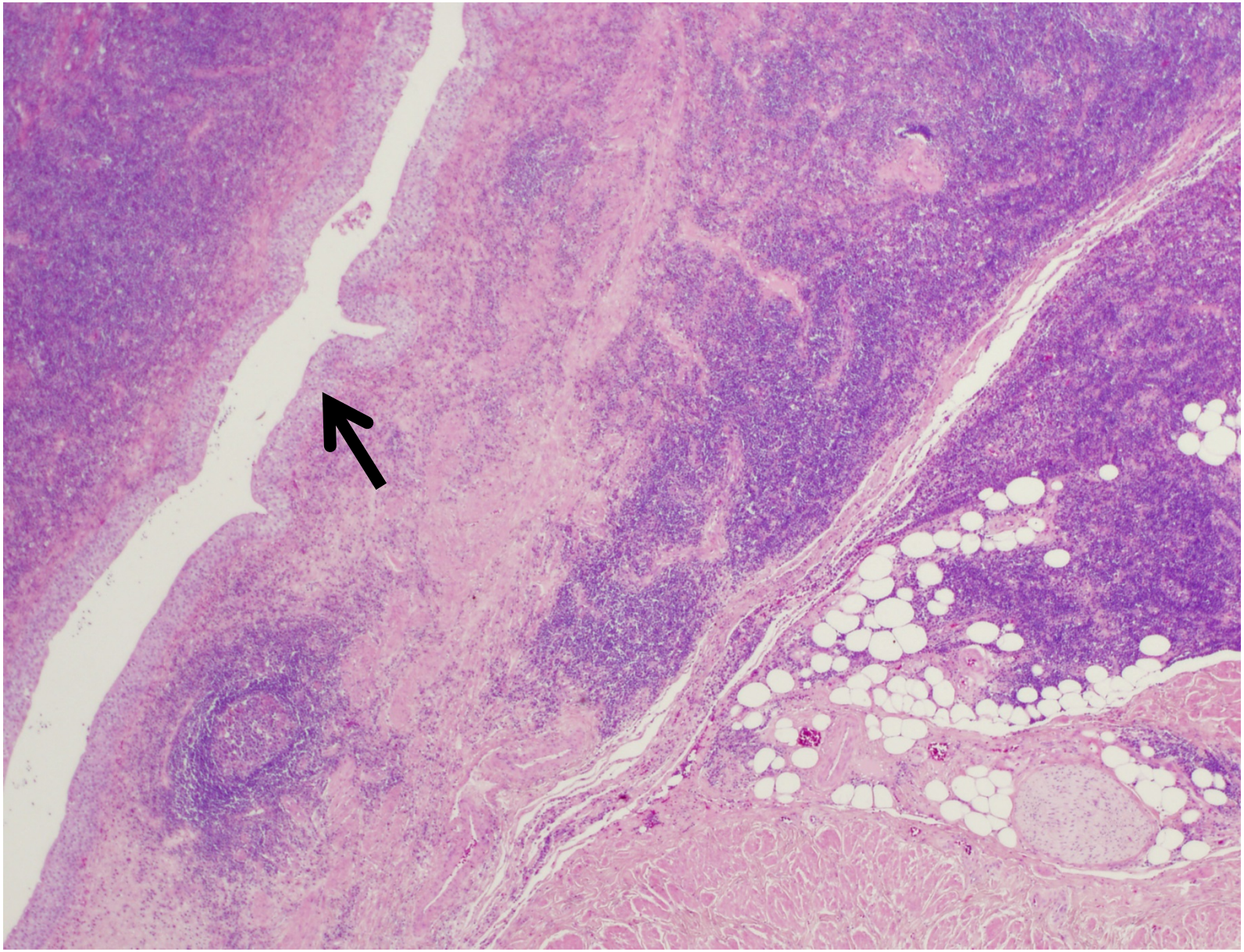

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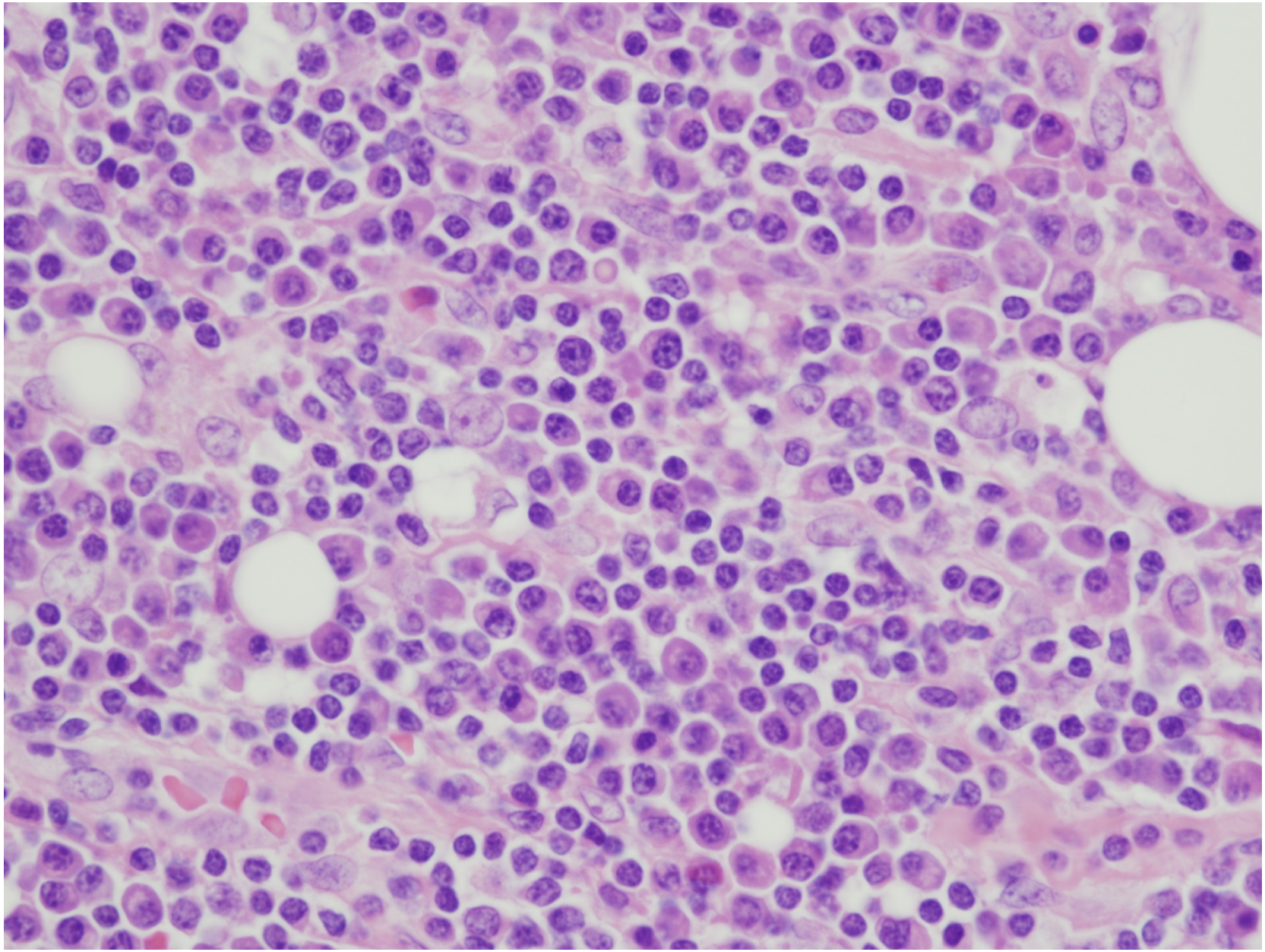

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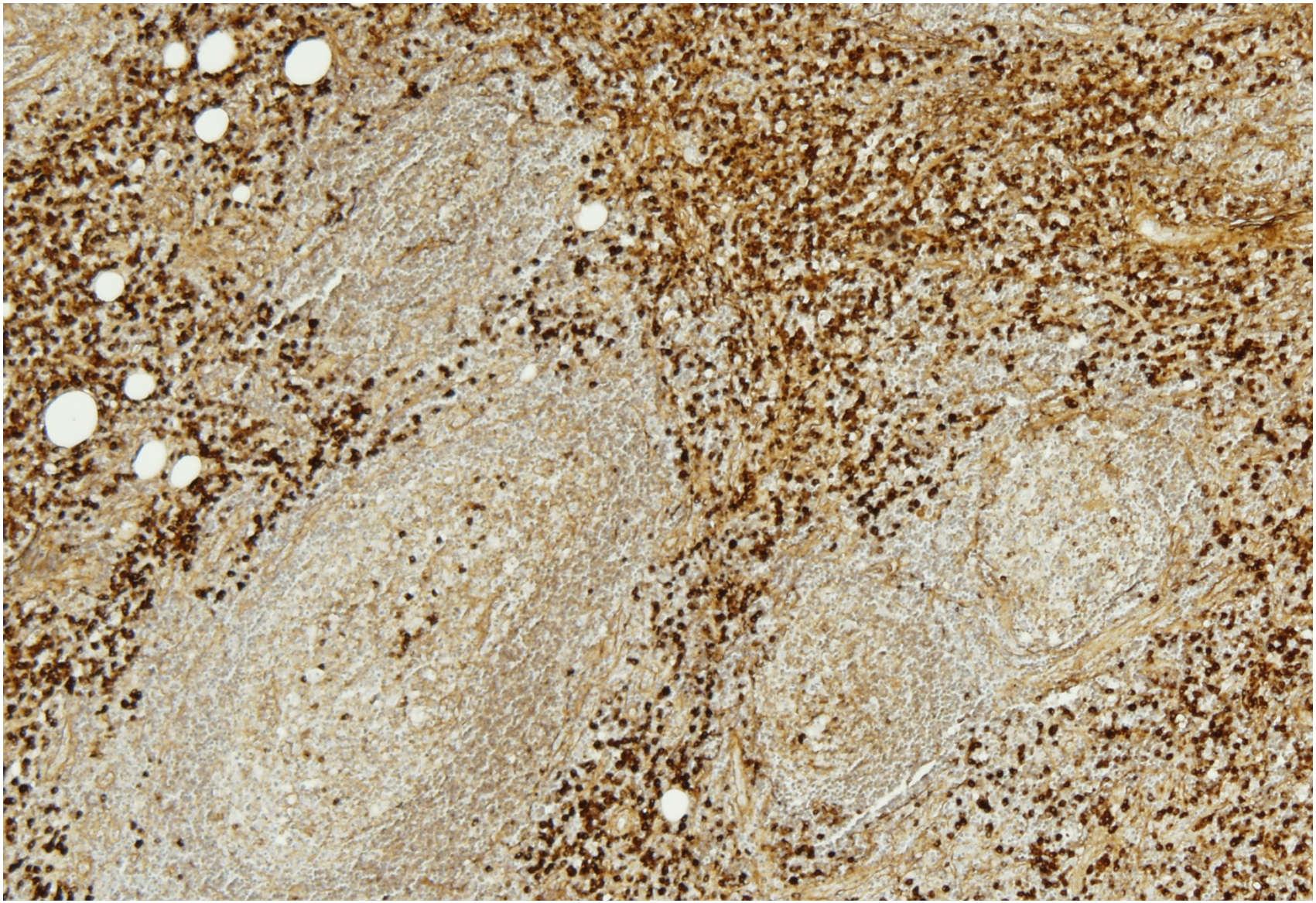

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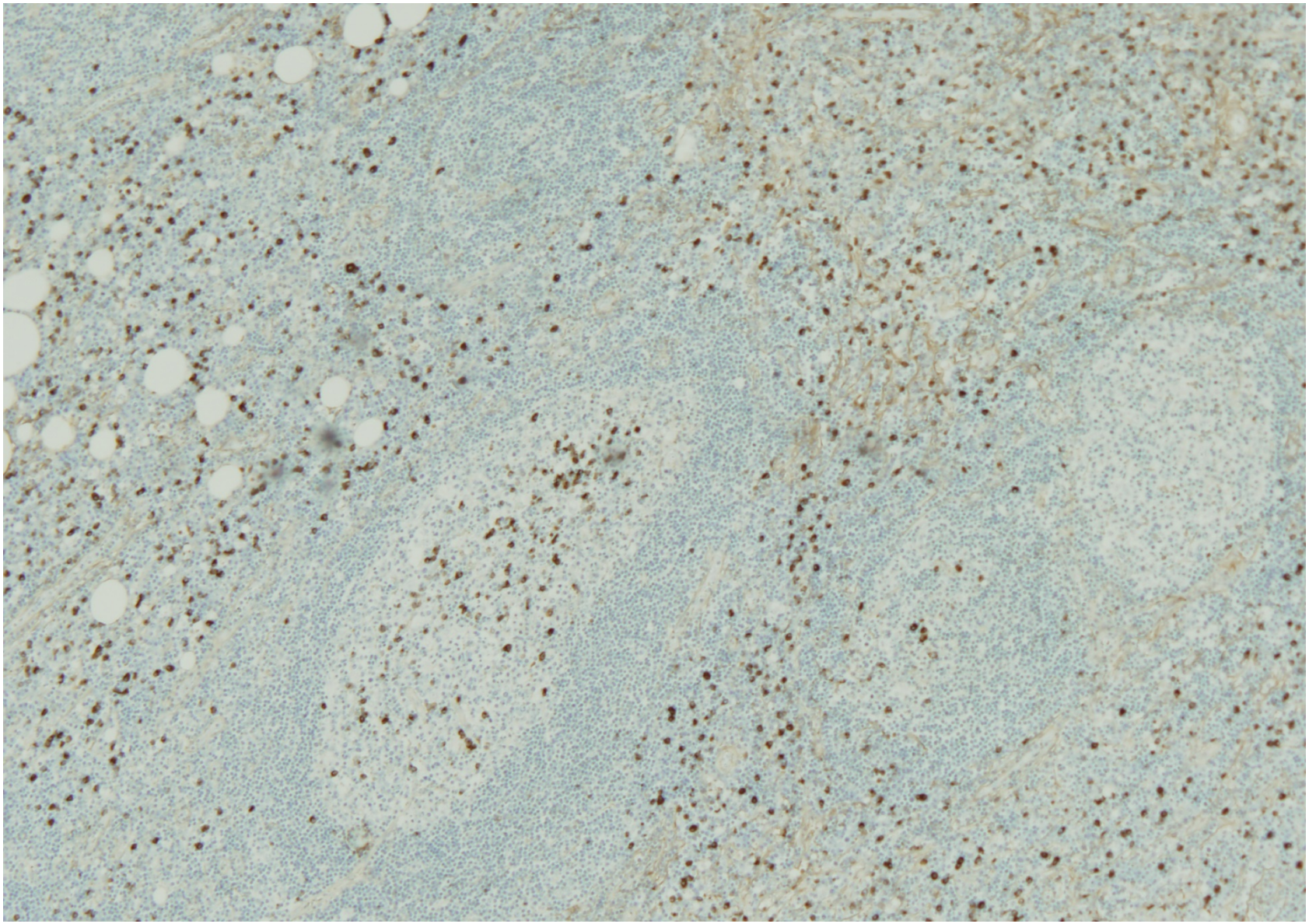

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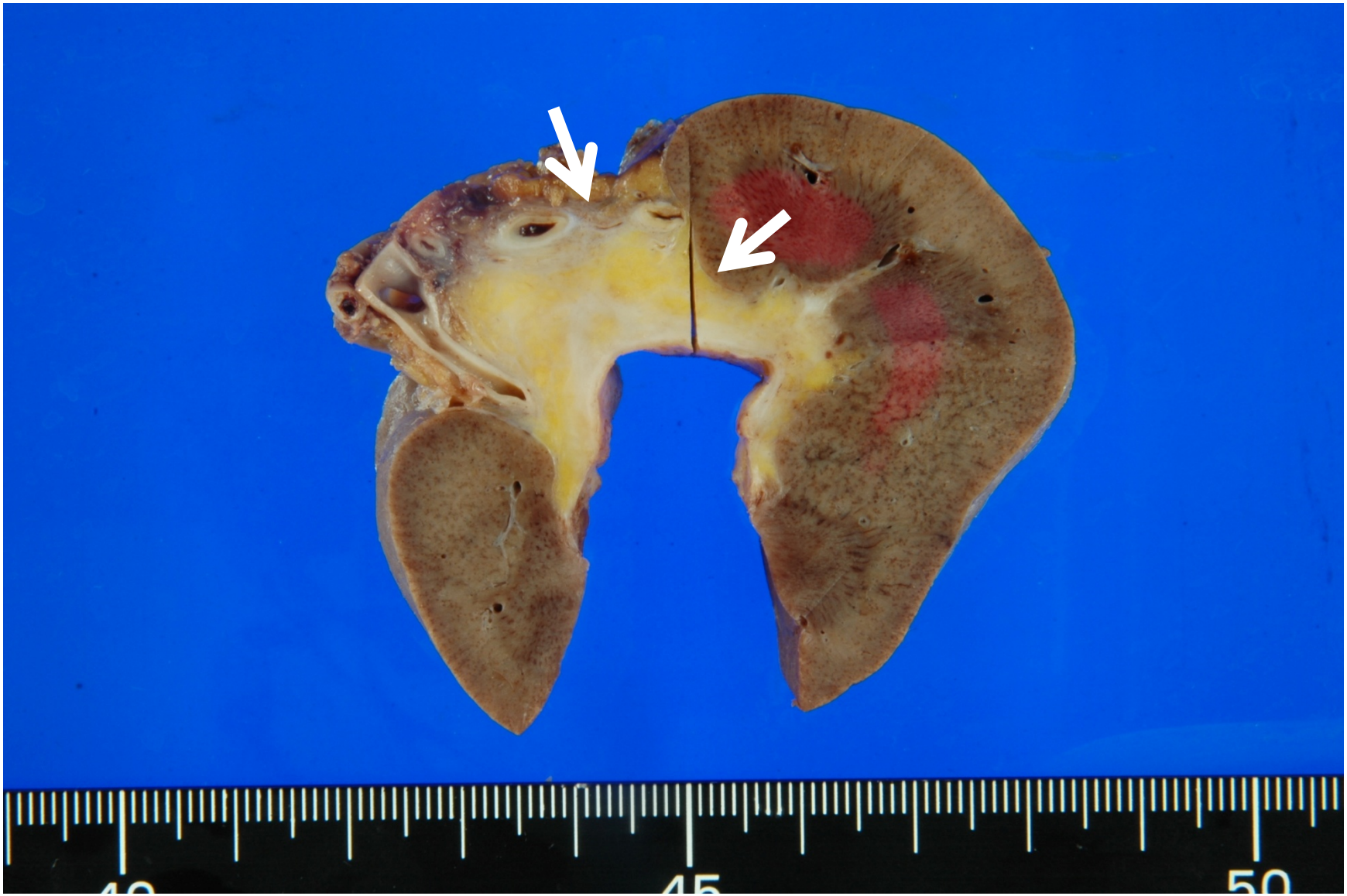

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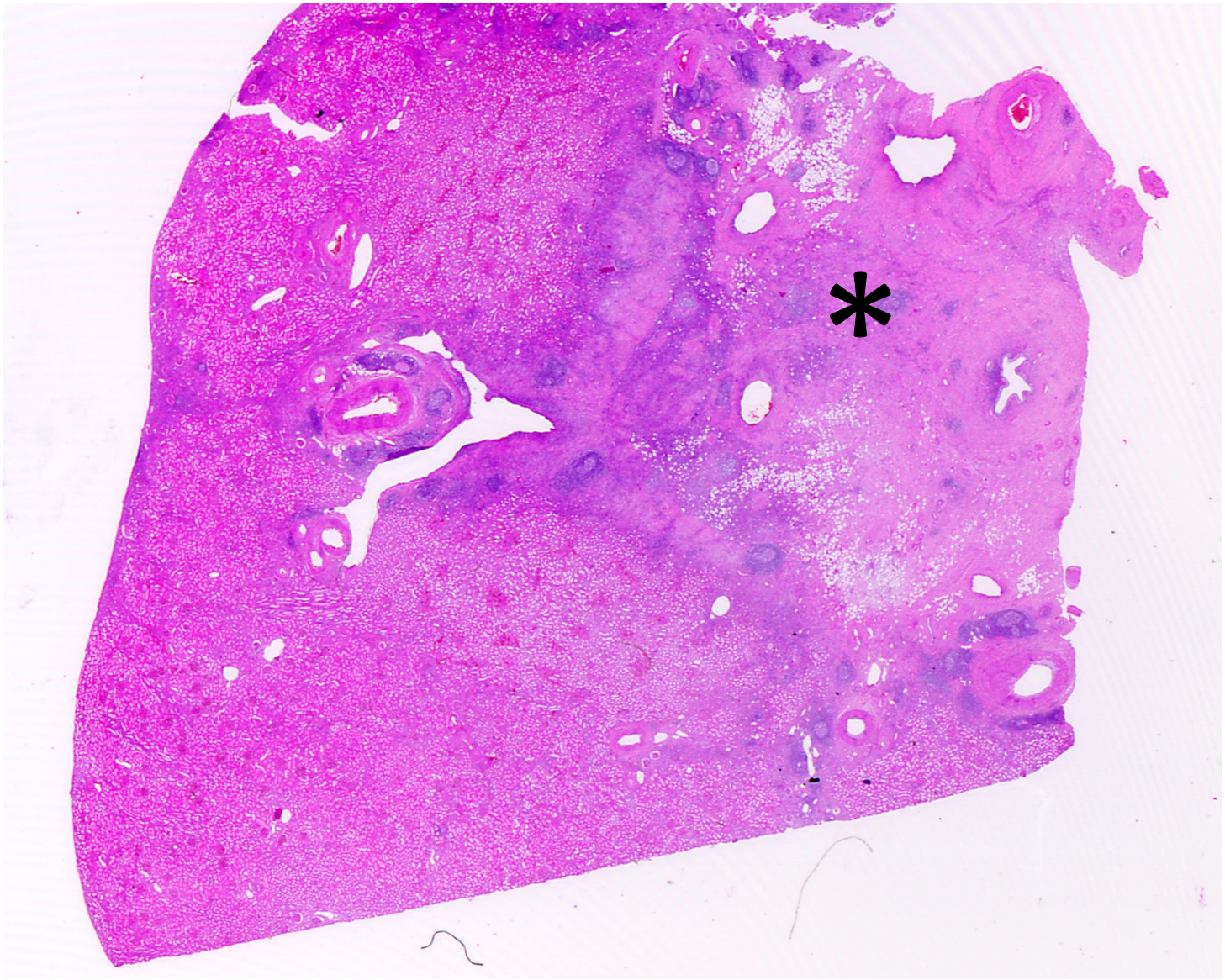

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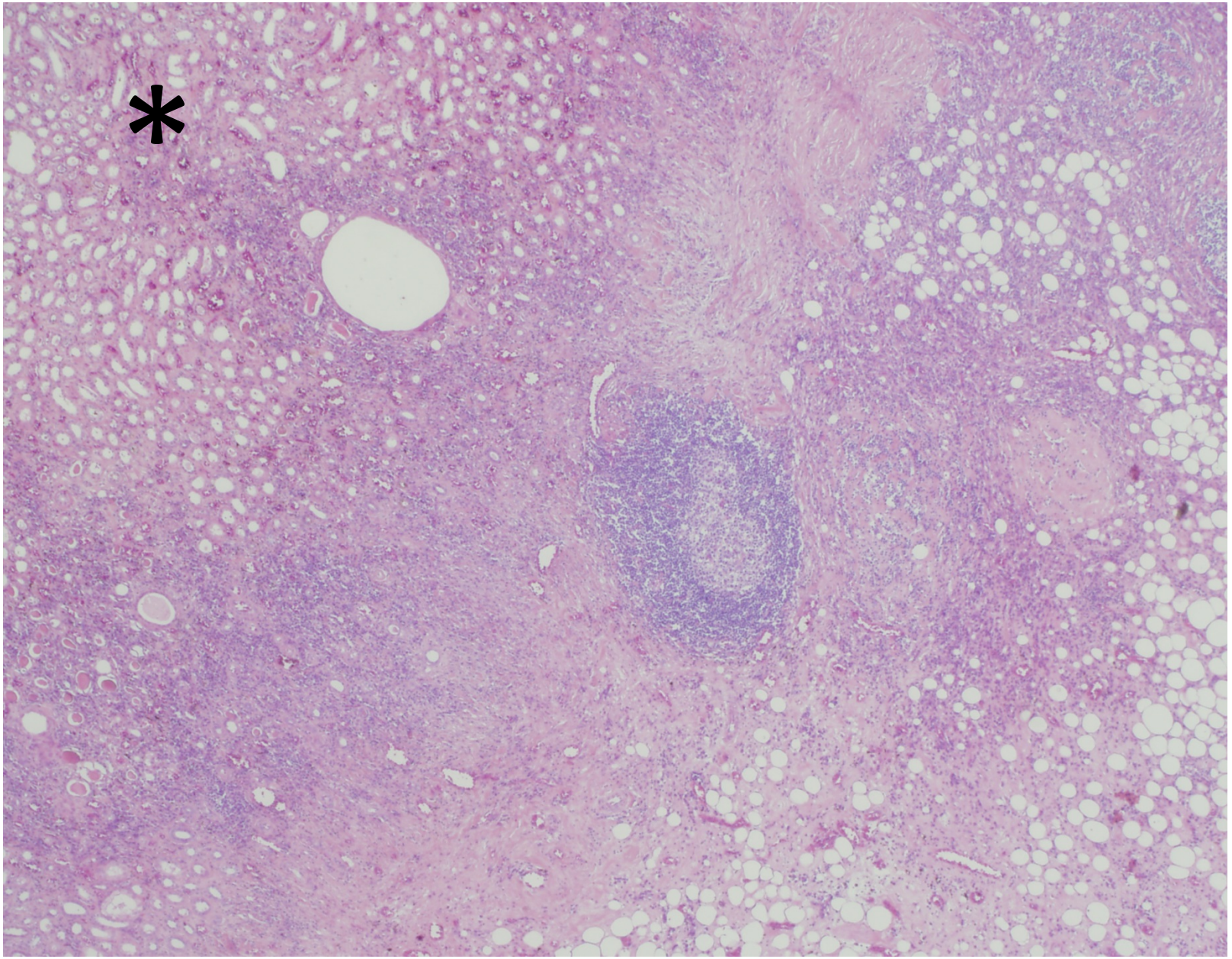

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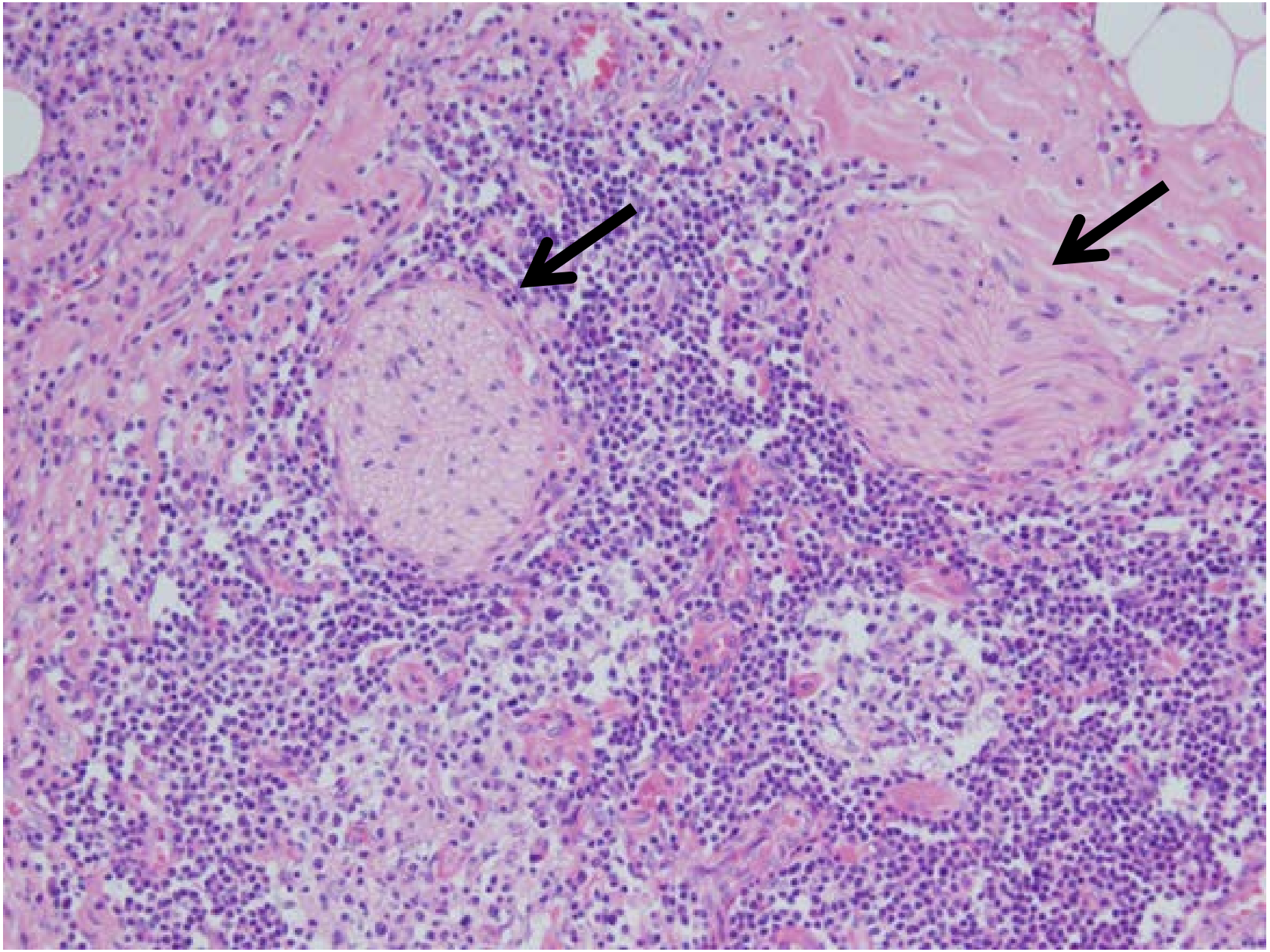

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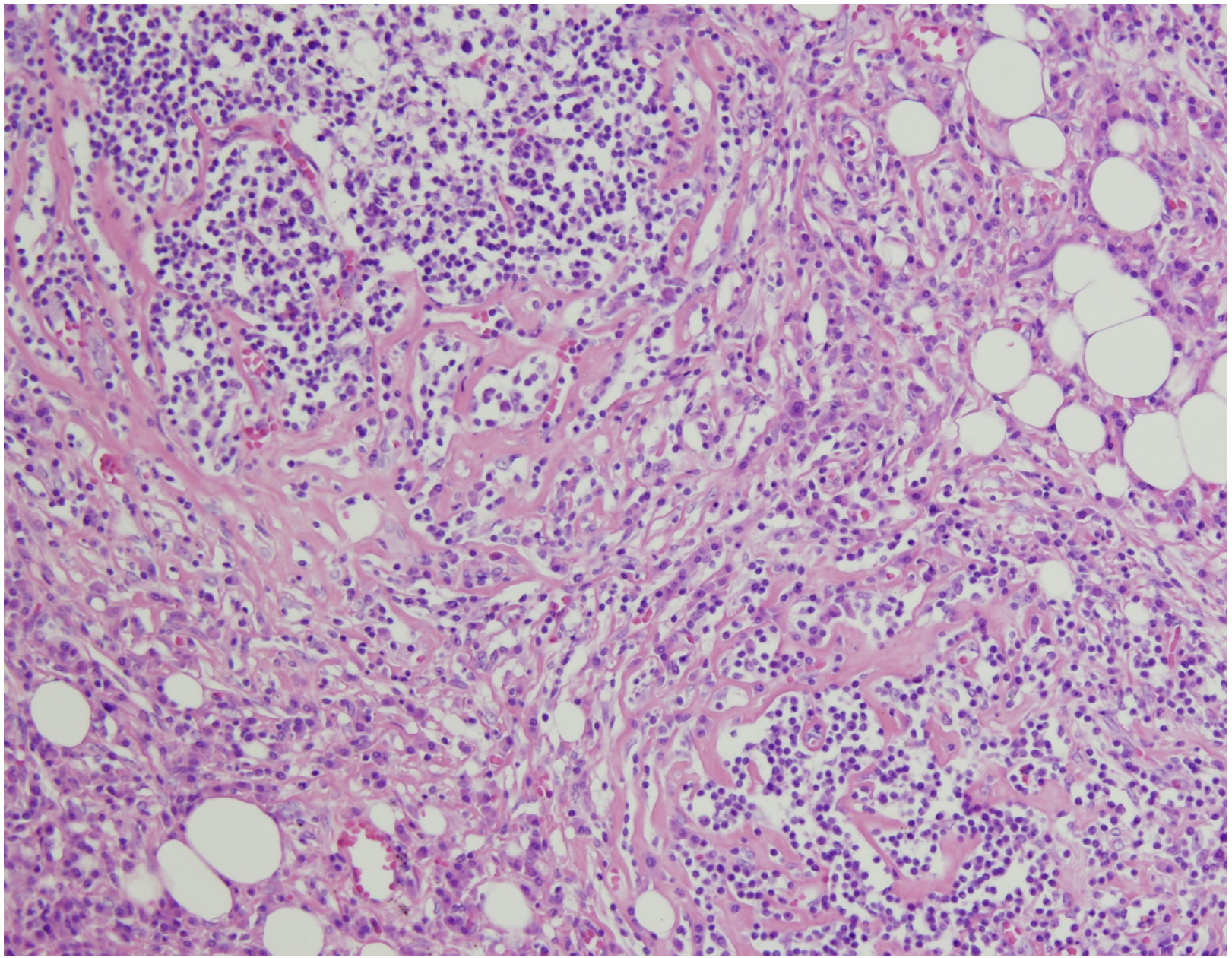

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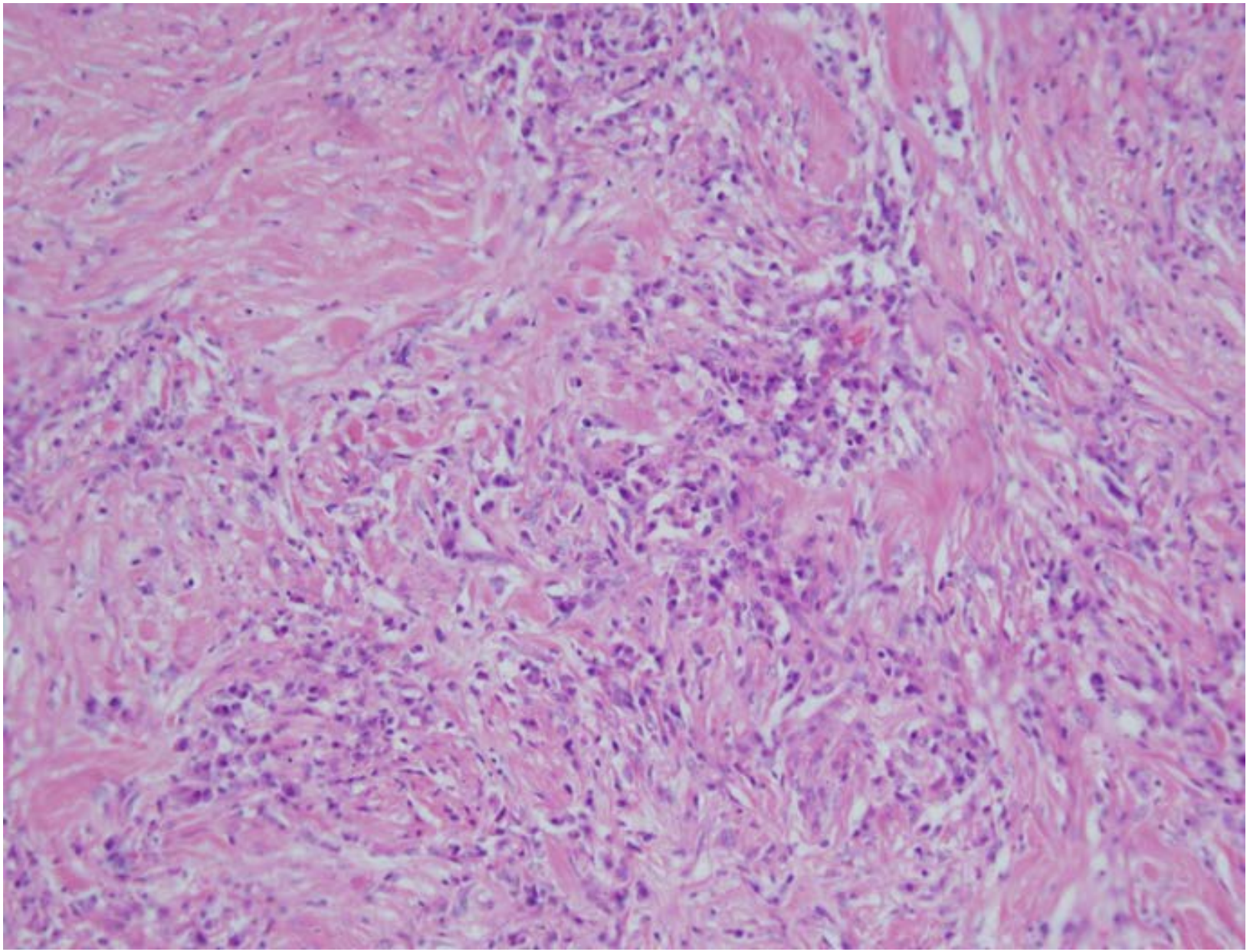

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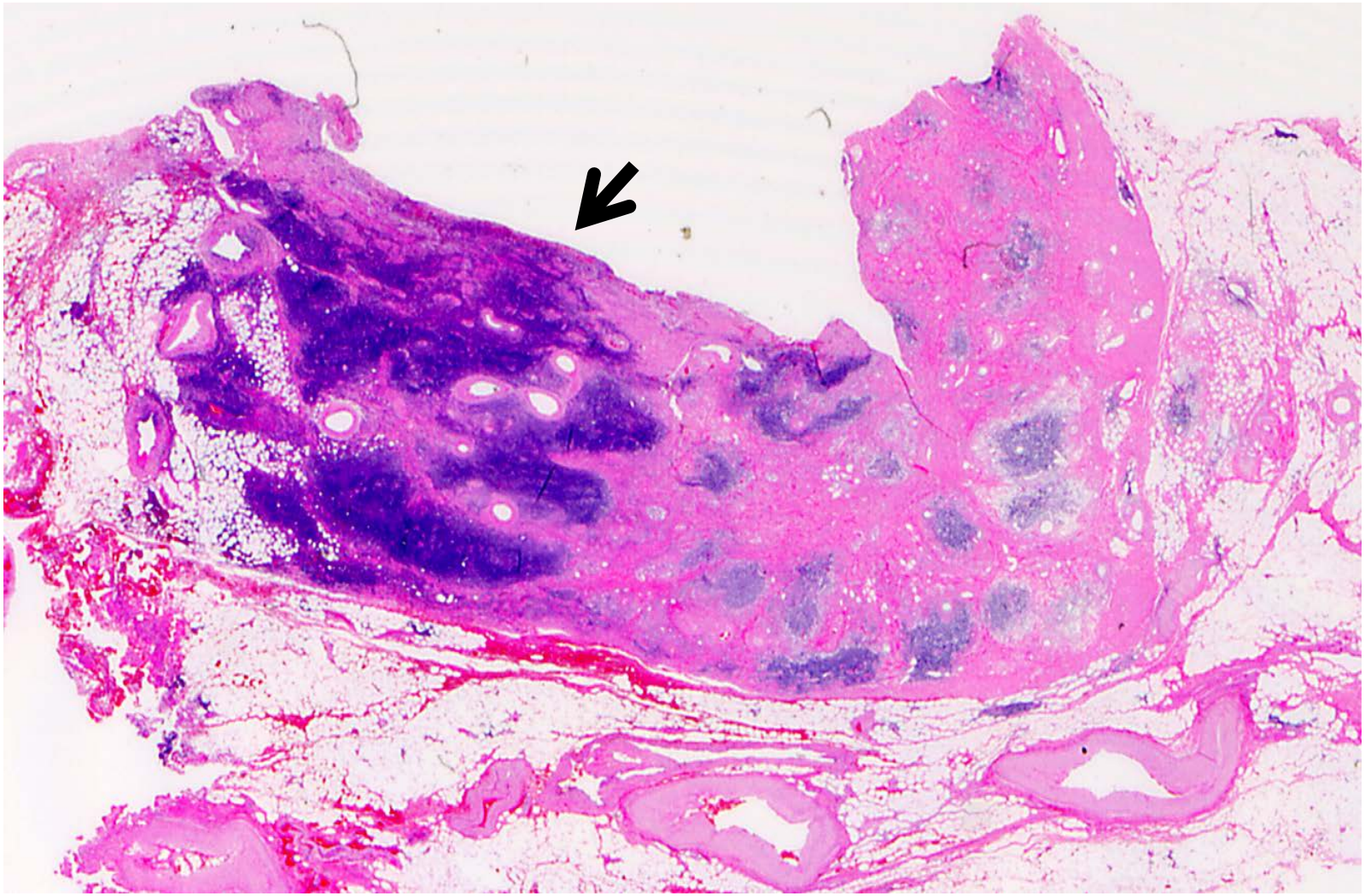

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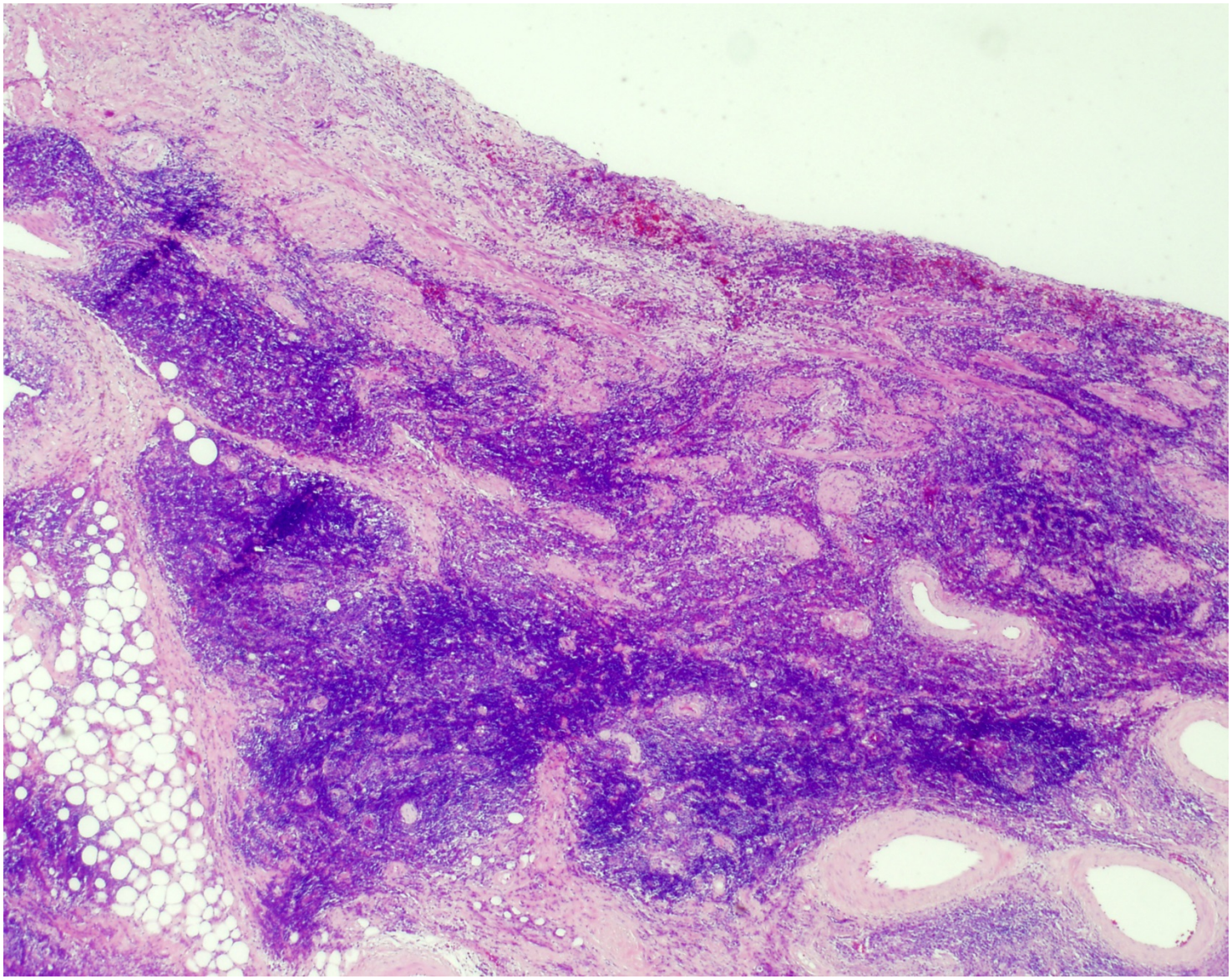

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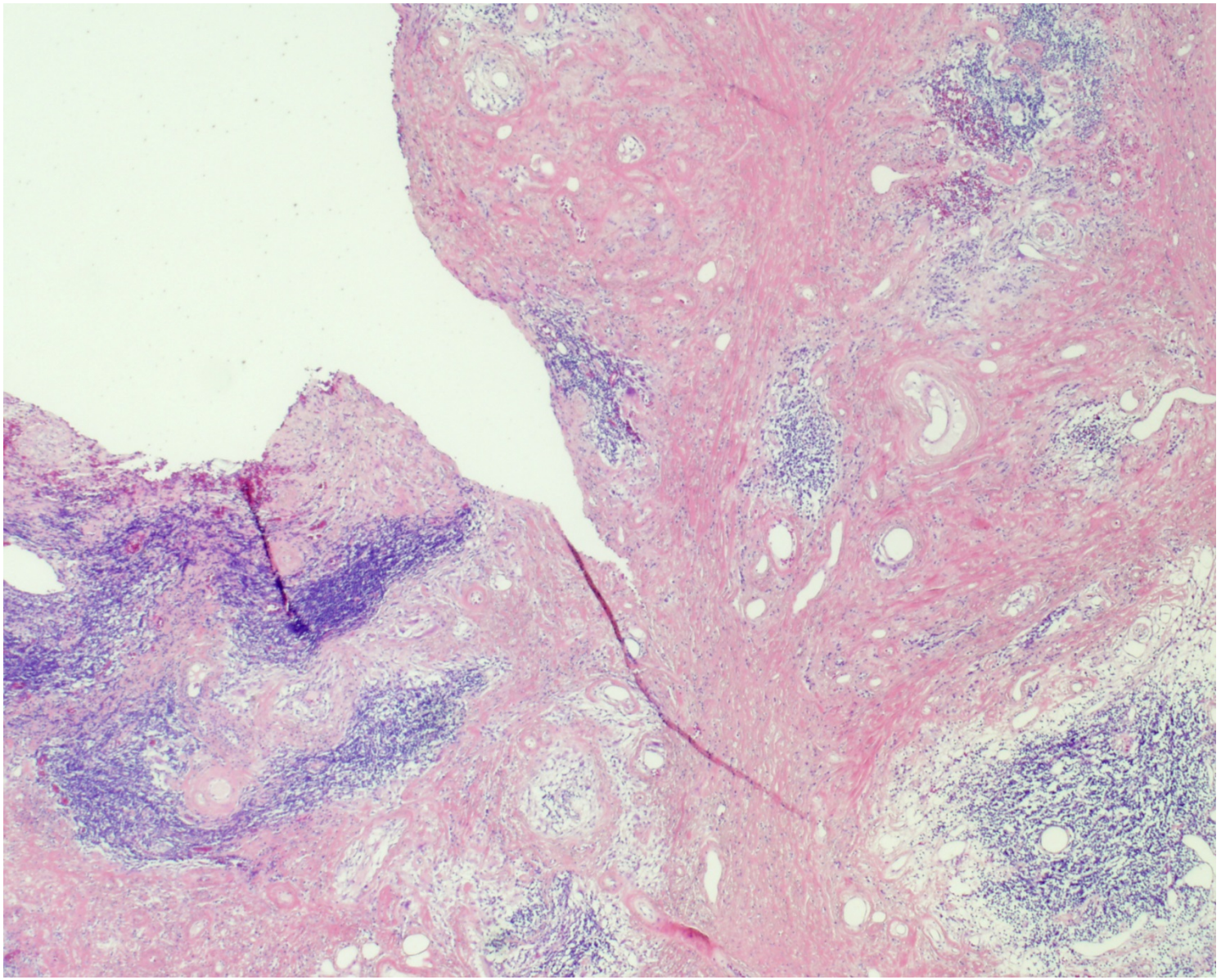

図4C

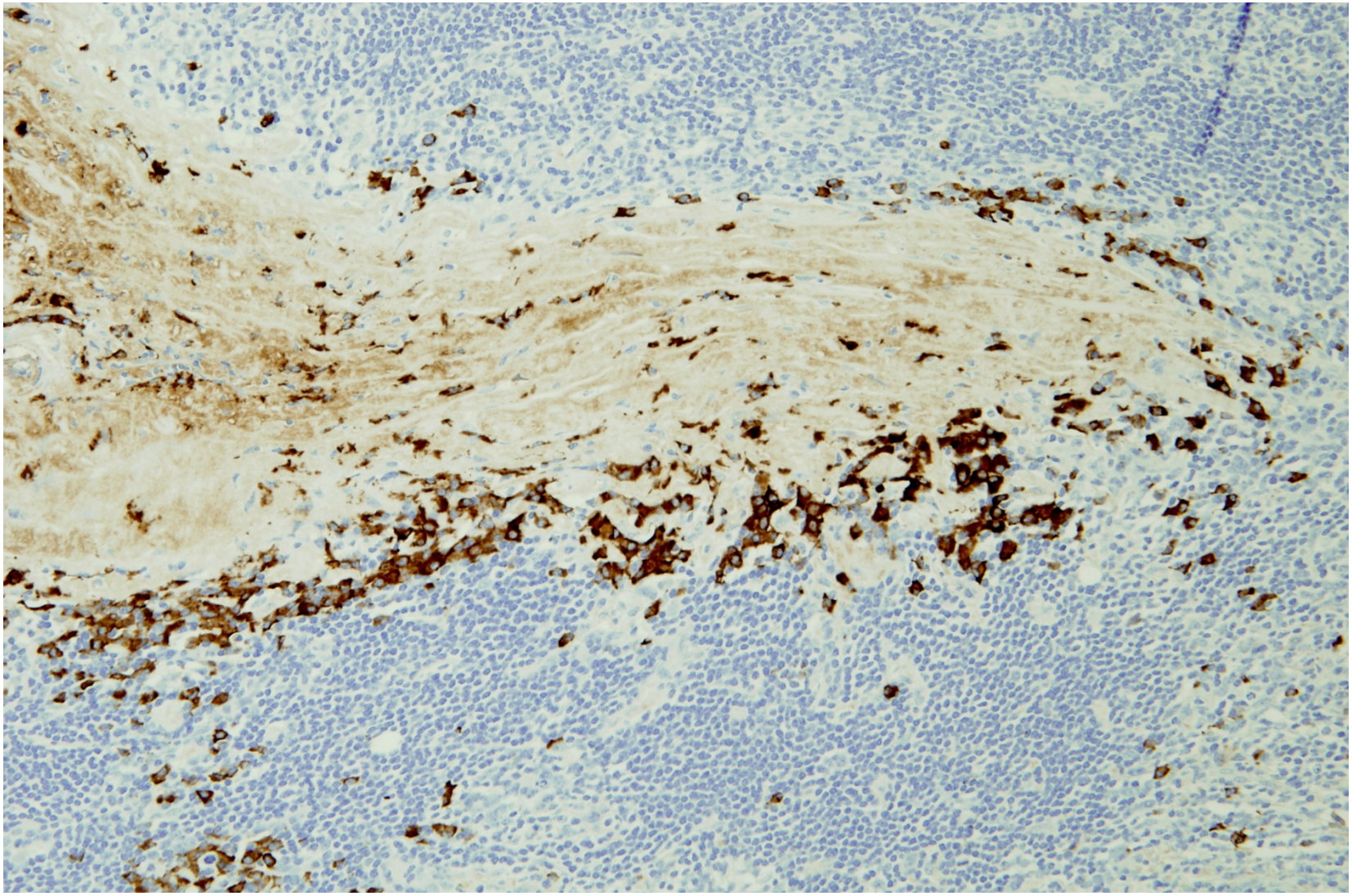

図4D

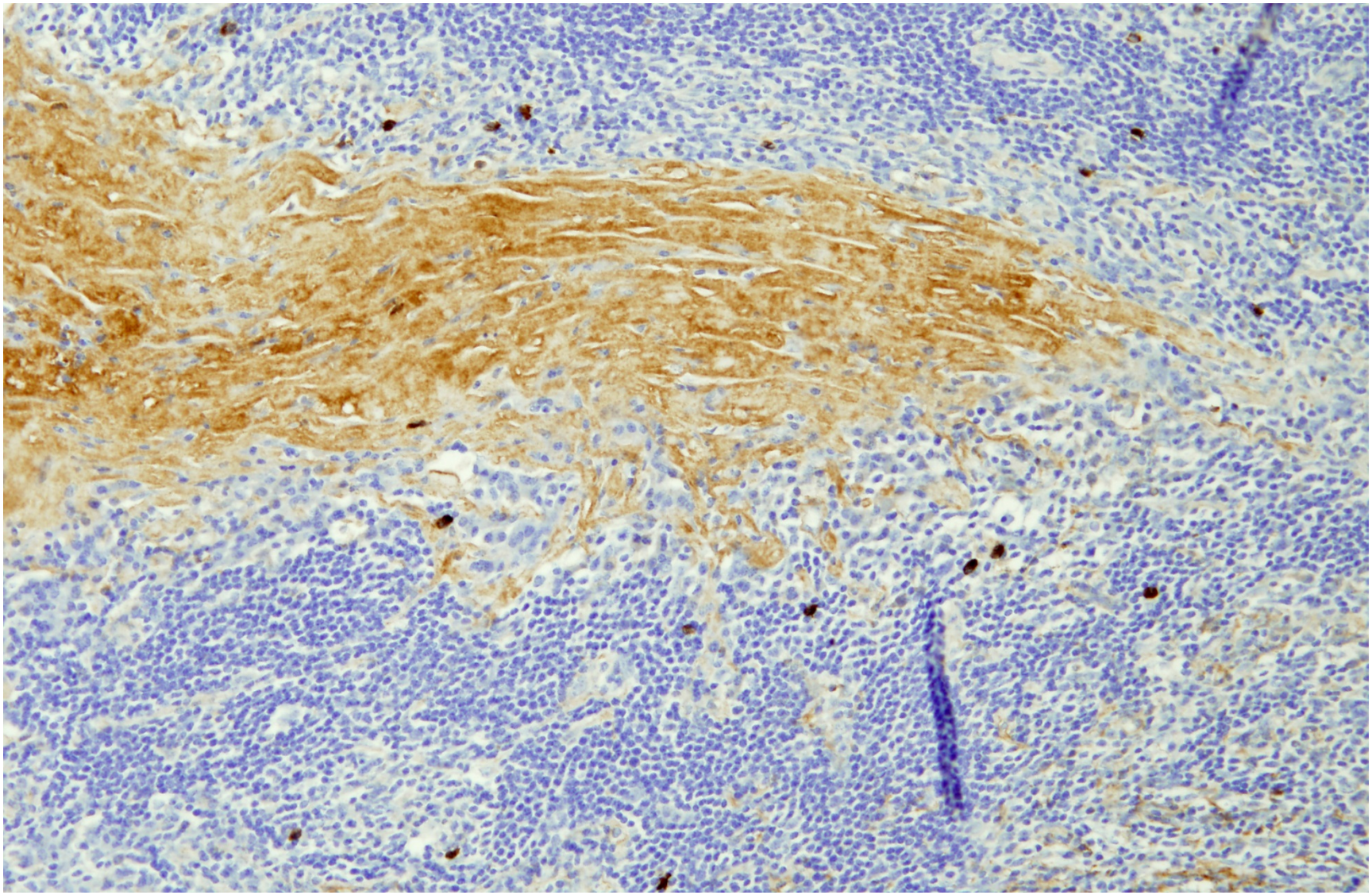

図4E