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► **To cite this version:**

Jean-Jacques Boffa, Emmanuel Esteve, David Buob. Renal involvement in IgG4-related disease. La Presse Médicale, 2020, 49 (1), pp.1-6. 10.1016/j.lpm.2020.104017 . hal-03490381

HAL Id: hal-03490381

<https://hal.science/hal-03490381>

Submitted on 22 Aug 2022

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LPM

IgG4-related Disease

Renal involvement in IgG4-related disease

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Abstract

IgG4-RD may affect several organs including kidneys. The kidney is involved in approximately 20% of patient with IgG4-RD. The most common intrinsic kidney disease is tubulointerstitial nephritis (IgG4-TIN). Retroperitoneal fibrosis (IgG4-RPF) may induce obstructive acute renal failure. More rarely, IgG4-RKD can manifest as a glomerular disease, in particular as a membranous nephropathy (MN). It mostly affects middle-aged to elderly men and causes acute or chronic renal dysfunction, multiple hypodense lesions on CT-Scan and various extra-renal lesions. Increased serum IgG4 and hypocomplementemia are the most important serological findings for the diagnosis of IgG4-RD and thus should be systematically assessed when IgG4-RKD is suspected. Specific diagnosis criteria for IgG4-TIN including interstitial infiltration of IgG4-positive plasma cells, storiform fibrosis and tubular basement membrane immune complex deposits have been proposed. Corticosteroids are effective and remain the first line therapy but relapses or severe forms could respond to immunosuppressive therapy.

Introduction

IgG4-RD may affect several organs including kidneys. Renal involvement may manifest itself as an intrinsic kidney disease (IgG4-RKD) or as a consequence of ureteric obstruction from retroperitoneal fibrosis (IgG4-RPF). The most common intrinsic kidney disease is tubulointerstitial nephritis (IgG4-TIN). More rarely, IgG4-RKD can manifest as a glomerular disease, i.e. almost exclusively membranous nephropathy (MN). The renal parenchymal involvement shares the epidemiological, clinical, biological, radiological and histological features common to all other affected organs in the IgG4-related diseases. In addition, kidney specific diagnosis criteria have been proposed by the Mayo Clinic and the Japanese Society of Nephrology [1, 2]. Here, we will focus on the specific features of IgG4-RKD.

Demographic and clinical characteristics

Epidemiology of the disease remains poorly described, but kidney involvement is associated with striking demographic features. IgG4-RKD mostly affects middle-aged or elderly men. In the first series of 153 patients with suspected IgG4-RD, 23 patients (15%), had an IgG4-RKD with a renal parenchymal lesion [3]. Based on the Japanese kidney biopsy registry, the histological diagnosis frequency for IgG4-RKD was 0.67% of the total biopsied cases [4]. In this series, the average age was 66.8 ± 9.3 years, and 95% of the patients newly diagnosed were male. A retrospective monocentric study in Australia reveal that over the course of 10 years, IgG4-TIN made up 1% of all renal biopsy [5]. In the North American experience, the average age of the 35 patients with IgG4-TIN was 65 years and 86% were men [1]. In the multicentric French registry, kidney involvement was reported in 30 % of patient with IgG4-RD [6, 7]. The prevalence of renal and retroperitoneal involvement in the cohort of 154 IgG4-RD patients from the United Kingdom was 18.2%; 9.1% had intrinsic renal disease and 6.5% had RPF, and 2.6% had both intrinsic renal disease and RPF [8]. Of 28 patients, 20 patients (92.9%) were male.

Clinical symptoms are diverse, depending on the type and the number of organs affected, but most patients have only mild or no symptoms. Various manifestations can evolve simultaneously, sometimes metachronously, over months to years. Also, spontaneous improvement or resolution has been observed. Most patients with IgG4-RKD display other organ involvement of IgG4-RD, of 83 to 96% in different cohorts [3, 8]. Extra-renal involvement includes: pancreatitis, sialadenitis, lymphadenitis, dacryoadenitis, interstitial pneumonitis, prostatitis... Cluster analysis method to identify distinct phenotype groups in

patients with IgG4-RD displayed that patients with IgG4-RKD have preferentially a Mikulicz syndrome, higher serum IgG4 concentration and more extensive disease than other groups [9].

Laboratory and radiological features

At presentation, the two main revealing signs of IgG4-RKD are acute or progressive renal function decline and imaging abnormalities. Renal failure was present in 77% patients from the Mayo Clinic and the mean serum creatinine was 3.6 mg/dl. Glomerular filtration rate (eGFR) was lower (27.9 ml/mn/1.73m²) in intrinsic renal disease patients compared with those without (60.9 ml/mn/1.73m²) in the United Kingdom cohort [8]. The rise in serum creatinine is typically insidious but can be rapidly progressive. Proteinuria is variable, but urinary excretion of low molecular weight proteins, retinol binding protein or α 1-microglobulin is suggestive of IgG4-TIN [10]. Nephrotic range proteinuria with albuminuria is observed in rare cases of IgG4-RKD associated with MN. Mild hematuria was present only in 8 patients (34%) in the Japanese cohort. In contrast to other causes of TIN, in particular drug-induced TIN, urinary excretion of white blood cell is absent in IgG4-RKD.

Increased serum IgG and hypocomplementemia are the most important serological findings for the diagnosis of IgG4-RD and thus should be systematically assessed when IgG4-RKD is suspected. Indeed, elevated serum concentrations of IgG and IgG4 were present in all cases of IgG4-RKD in the Japanese cohort, in 88% in the Mayo Clinic cohort and from the United Kingdom. Follicular helper T cells (cThf), which are known to promote humoral immunity, may play a pivotal role in the pathogenesis of IgG4-RD. cThf cells were found significantly expanded in the peripheral blood, and even more in the involved tissues of patient with IgG4-RD [10-13]. They facilitate B cell proliferation, as the differentiation of naïve B cells into switched memory B cells and plasmablasts/plasma cells, resulting in increased secretion of IgG4. Interestingly, cThf cells subsets have been found expanded in both IgG4-TIN but also in patients with idiopathic membranous nephropathy suggesting a common pathophysiologic mechanism [14]. However, elevated serological IgG4 is not specific of IgG4-RD, and, on the other hand, a normal serum IgG4 does not exclude a diagnostic of IgG4-RD. Hypocomplementemia, which is present in approximately 60% of IgG4-RKD patients seems more prevalent if the kidney is involved. Both complement C3 and C4, are decreased, and may represent a biomarker to monitor recurrence of IgG4-TIN [15]. High IgE levels and eosinophilia are other common features of IgG4-RKD. Antinuclear antibodies and rheumatoid factor are positive in 30%, but more specific antibodies are usually negative, including anti-DNA, anti-SSA, anti-Sm and anti-RNP [16, 17]. Elevation of C-reactive protein is unusual.

Radiological abnormalities of the kidneys are often observed in patients with IgG4-RKD. On ultrasound, the kidneys may be enlarged. Contrast-enhanced computed tomography is considered the most useful tool to detect renal lesions (figure 1). Radiographic abnormalities were present in 70% and 78% in the Japanese and Mayo Clinic cohorts [1, 3]. Imaging displays multiple lesions, often bilateral, hypodense, either round or wedge-shaped lesions, or patchy lesions [18]. Solitary lesion can mimic malignant tumor leading to unnecessary nephrectomy. MRI is an efficient alternative in detecting renal lesions in IgG4-RKD (figure 2) [19]. Renal parenchymal nodules appear iso-intense (93.5%) on T1-weighted images, hypo-intense (77.4%) on T2-weighted images, hyper-intense (100%) on diffusion-weighted MRI. FDG-PET is increasingly used (figure 3, 4). It represents a useful tool for assessing organ involvement, for diagnostic biopsy-site selection, and for monitoring therapeutic response [20].

Histopathological features

1) Tubulointerstitial nephritis (TIN).

The characteristics of renal histological changes are similar to other organ involvement during IgG4-RD i.e. inflammatory infiltrate with numerous IgG4 plasma cells and peculiar fibrosis. TIN is the most dominant renal pattern of IgG4-RKD. Light microscopy shows an interstitial inflammatory infiltrate made of mononuclear cells with increased number of IgG4-positive plasma cells (figure 5). More than 10 infiltrating IgG4 and plasma cells per high-power field or at least 40% of the ratio of IgG4 and plasma cells to IgG and plasma cells are employed as the cutoff values for diagnostic criteria (figure 6) [1, 2]. Nevertheless, IgG4-positive plasma cell infiltrate is a necessary, but not a specific, finding for the diagnosis of IgG4-TIN. Comparison of renal lesions of IgG4-TIN with other causes of TIN showed that cell infiltration extending into and beyond the renal capsule was observed only in IgG4-related TIN. Conversely, neutrophil infiltration, severe tubulitis, severe peritubular capillaritis, granulomatous inflammation and necrotizing angitis were evident only in non-IgG4-related TIN [21]. Eosinophilic infiltration can accompany mononuclear interstitial inflammation. Fibrosis is typically qualified as storiform and consists of a pattern of collagen fibers arranged pell-mell, in multiple directions (figure 7). Fibers may surround the cellular infiltrates resembling a “bird’s eye pattern” [22]. Usually, glomeruli are normal. Obliterative phlebitis is less common in kidney compared with other involved organs.

Another important pathological feature of IgG4-TIN is the presence of immunoglobulin and complement deposit, in the tubular basement membrane (TBM) at immunofluorescence

(figure 8). These TBM immune deposits were present in 83% of patients from the Mayo Clinic [1] and in 75% of patients from the British cohort. Analysis of IgG subclasses revealed IgG1 and IgG4 deposition in the TBM and interstitium [22].

Differential diagnosis of IgG4-TIN are mostly represented by drug-induced TIN, chronic pyelonephritis, sarcoidosis, other auto-immune TIN, granulomatosis with polyangeitis (GPA) and multicentric Castleman disease. In allergic TIN and chronic pyelonephritis, granulomatous inflammation and marked neutrophilic infiltration predominate. Conversely, they do not show plasma cells infiltration and storiform fibrosis. Clinical symptoms including sialadenitis, lymphadenopathy, dacryoadenitis, and hypergammaglobulinemia could be encountered in sarcoidosis and Sjogren syndrome. Determination of serum IgG4 level and IgG4-positive plasma cells infiltration will lead to the diagnosis. Plasma cell-rich infiltrate may be a feature of GPA, Castleman disease, and lymphoproliferative disorders. Presence of necrotizing and/or crescentic glomerulonephritis and the absence of TBM immune complex deposits will be crucial. Castleman disease with renal involvement can closely mimic IgG4-TIN but TBM deposits are absent [23].

Based on serology, renal imaging, histology and involvement of other organs findings, the Mayo Clinic group and the Japanese Society of Nephrology defined diagnostic criteria for IgG4-TIN and IgG4-RKD (Table) [1, 2].

2) Membranous nephropathy (MN)

MN, the most common form of glomerulonephritis associated with IgG4-RKD has been reported in 7-27% of patients with IgG4-TIN [1, 8]. Usually, MN coexists with TIN. First, it was thought that MN without concurrent TIN was not IgG4-RD. Lately, isolated MN cases without TIN have been observed in 4 of the nine patients reported by Alexander [24]. Now, both TIN and MN could be considered IgG4-RD, either they occur concurrently or metachronously. Nevertheless, distinguishing between incidental coexistent primary MN or MN secondary to IgG4-RD can be difficult. Indeed, MN is a pattern of glomerular injury that may be primary ('idiopathic') or secondary. Most primary MN are associated with the presence of M-type PLA2R antibodies and IgG4 subclass IgG deposit on renal tissue. The renal pathological findings of IgG4-MN are generally compatible with the features of secondary MN: serum anti-PLA2R antibodies and the immunostaining for PLA2R on histology were negative in all reported cases of concurrent MN to IgG4-RD. In addition, positive deposition of IgG4 has been observed in IgG4-MN, either predominantly or together

with other IgG subclasses [24-28]. Thus, immunoprofile of IgG subclasses would likely not distinguish between primary MN and IgG4-MN [29]. It is worth noting that TBM immune complex deposits are less common in IgG4-MN than in IgG4-TIN. They were present in only 33% of IgG4-MN compared with >80% in IgG4-TIN. A differential diagnosis of concurrent IgG4-TIN and MN is sarcoidosis. In this case, the inflammatory infiltrate does not contain significant IgG4-staining plasma cells and more importantly granulomatous lesions are observed.

The pathogenesis of IgG4-MN is unclear, and appears to have a different pathophysiology from the rest of IgG4-RD. MN is secondary to immune complex deposition rather than the usual destructive inflammatory process that characterizes other organ involvement in this condition. Typically, IgG4 does not activate complement via the classical pathway, but it has been shown that IgG4 against PLA2R in primary MN activates complement via lectin pathway. Alternatively, other classes of IgG, mostly IgG1 and IgG3, that are co-deposited may activate the classical pathway of complement. In addition, IgG4 have the capacity to form aggregates which can cause inflammatory lesions in the absence of antigen [30].

Other glomerulopathies have been rarely reported including IgA nephropathy, mesangioproliferative glomerulonephritis [1, 3, 31, 32]. All of these glomerular lesions were concurrent to IgG4-TIN. One case of renal AA amyloidosis apparently secondary to IgG4-RD has been reported [33].

3) Retroperitoneal fibrosis (RPF)

IgG4-RPF is a rare disease and represents 60% of all idiopathic RPF from two series [34, 35]. The male-to-female ratio was 3.3 and the average age was 66 years old (range 52-79) in a series from China [36]. Clinical symptoms include general signs, malaise, weight loss, abdominal pain, and swelling of legs in case of compression of inferior vena cava. Retroperitoneal fibrosis may surround aorta, kidney and ureteric duct, pancreas and vena cava. It may lead to hydronephrosis and acute renal failure. Aortitis or periaortitis might be associated if fibrosis encases the aorta. Hydronephrosis is first detected by ultrasound but CT or MRI will diagnose FRP. FDG-PET is used to assess the activity and evaluate therapeutic response. Similar histological lesions as IgG4-RD are observed in RPF, but an extraperitoneal biopsy is often easier to perform. A differential diagnosis of IgG4-RPF is Erdheim-Chester disease. This multiorgan disease can manifest with retroperitoneal and periaortic involvement but has specific immunohistochemical profile [37].

Treatment and outcome

Steroid is the first-line therapy and 0.6 mg/kg/day of prednisolone is the recommended dose to induce remission [38]. Corticosteroid therapy quickly improves serum creatinine; increases complement concentration; and normalizes IgG4 level, into a few weeks [15]. Moreover, the ratio as well the absolute number of IgG4-positive plasma cells decreased after corticosteroid therapy on repeat renal biopsy in patients with IgG4-TIN [39, 40]. Although cell infiltration improved over time, fibrosis became more marked with the development of renal atrophy. Renal radiological abnormalities also resolve with treatment. Thus, prompt responsiveness to corticosteroid therapy is a characteristic feature of IgG4-RD. After this early improvement at 1 month, renal function was maintained at a similar level afterward in the Japanese cohort of IgG4-RKD [15]. However, recovery of renal function is not total in several patients, suggesting that early diagnosis and treatment are essential. Interestingly, there was no correlation between histologic pattern and response to therapy, and even patients with extensive fibrosis on biopsy showed response to steroid treatment in the Mayo Clinic experience. Steroid-sparing agents are used in patients with refractory or recurrent disease. Relapses occurred in 20 to 46% of treated patients with IgG4-RKD [8, 15]. Baseline concentrations of serum IgG4, IgE and circulating eosinophils were found as predictors of relapse IgG4-RD [41]. Treatment with Rituximab has been shown to be effective in patients with IgG4-RD and IgG4-TIN. In a prospective single-arm pilot trial using Rituximab as a single agent for IgG4-RD, 97% of patients (n=30) achieved disease response that was maintained at 6 months [42]. In the French retrospective multicenter study with 30% patients with kidney involvement, Rituximab was highly effective in inducing disease remission, with 93.5% of patients presenting a clinical response after therapy, but also for treatment of relapses [7]. Severe IgG4-TIN in patients with reduced GFR, showed a remarkable response to rituximab [40]. Despite the series cases reported, there are no randomized controlled studies to guide the management of IgG4-RD so far. In clinical practice, rituximab is usually considered the first steroid sparing agent after relapse and with severe disease. After kidney transplant, a recurrence of IgG4-TIN may occur [43]. It is important to remember that IgG4-RD is believed to have a close association with the development of malignancy. Indeed, the overall standardized incidence ratio of cancer was 2.01 (95% CI 1.34–2.69) in a Japanese cohort from 1992 to 2012 [44].

In contrast, glomerular lesions of IgG4-RKD are usually refractory to corticosteroid monotherapy [28, 29]. Most cases required combination therapy with immunosuppressive agents to

achieve a complete or partial response. Of the 6 treated patients with various regimens, 3 had a complete response of proteinuria ($<1\text{g/d}$), and 3 had a partial response, defined as $>50\%$ decrease in proteinuria but not reaching $<1\text{g/d}$. In the context of IgG4-MN, using Rituximab in combination with corticosteroid seems the treatment of choice. Glucocorticoids have been the gold standard treatment for idiopathic RPF but Rituximab even without additional glucocorticoids led to resolution of symptoms in all patients and radiologic improvement in the majority of American cohort of either idiopathic or IgG4-RPF [45].

In conclusion, IgG4-TIN is the main renal presentation of IgG4-RD, discovered on a recent rise of serum creatinine, an abnormal imaging or in someone with already known disease with multiple organs involved. The diagnostic criteria of IgG4-TIN and IgG4-RKD include relative specific histologic features. IgG4-MN is more rarely observed and its pathogenesis different. Although, steroids treatment is promptly efficient, total renal function recovery remains unusual and relapse frequent. Further understanding the pathogenesis of the disease may improve treatment and prognosis.

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Table 1: Diagnostic criteria for IgG4-TIN proposed by the Mayo Clinic group

Histology	Plasma cell-rich TIN with > 10 IgG4 + plasma cells/HPF Tubular immune complex deposits by IF, IHC, and/or EM
Imaging	Small peripheral low-attenuation cortical nodules, round or wedge-shaped lesions, or diffuse patchy involvement
Serology	Elevated serum IgG4 or total IgG level
Other Organ involvement	Characteristic findings of IgG4-RD in other organs

TIN: tubulointerstitial nephritis; HPF: high-power field; IF immunofluorescence; IHC immunohistochemistry; EM electron microscopy.

LEGENDS:

Figure 1: Transverse contrast-enhanced computed tomography (CT) image shows multiple low-attenuation lesions in a patient with IgG4-related tubulointerstitial nephritis. None of the lesions were visible on non-enhanced CT scans.

Figure 2: Transverse fat-saturated T2-weighted fast spin-echo magnetic resonance image (MRI), shows several renal lesions with a low-hyposignal intensity lesions of both kidneys.

Figure 3: Positron emission tomography-computed tomography (PET-CT) image shows of bilateral cortical lesions in a patient with IgG4-TIN.

Figure 4: PET-CT image of retroperitoneal fibrosis with presacral inflammation in an IgG4-RPF patient.

Figure 5: Representative light microscopic findings of renal biopsy in an IgG4-TIN patient (Masson trichromic stain). Note tubular atrophy, expansive interstitial fibrosis and inflammation.

Figure 6: Immunohistochemistry for IgG4 in a patient with an IgG4-TIN. Numerous interstitial IgG4-positive plasma cells are visible.

Figure 7: Characteristic fibrosis in IgG4-TIN (Periodic acid-methenamine silver stain). Swollen plasma cell nests encircled by collagenous tissue, with diffuse fibrosis.

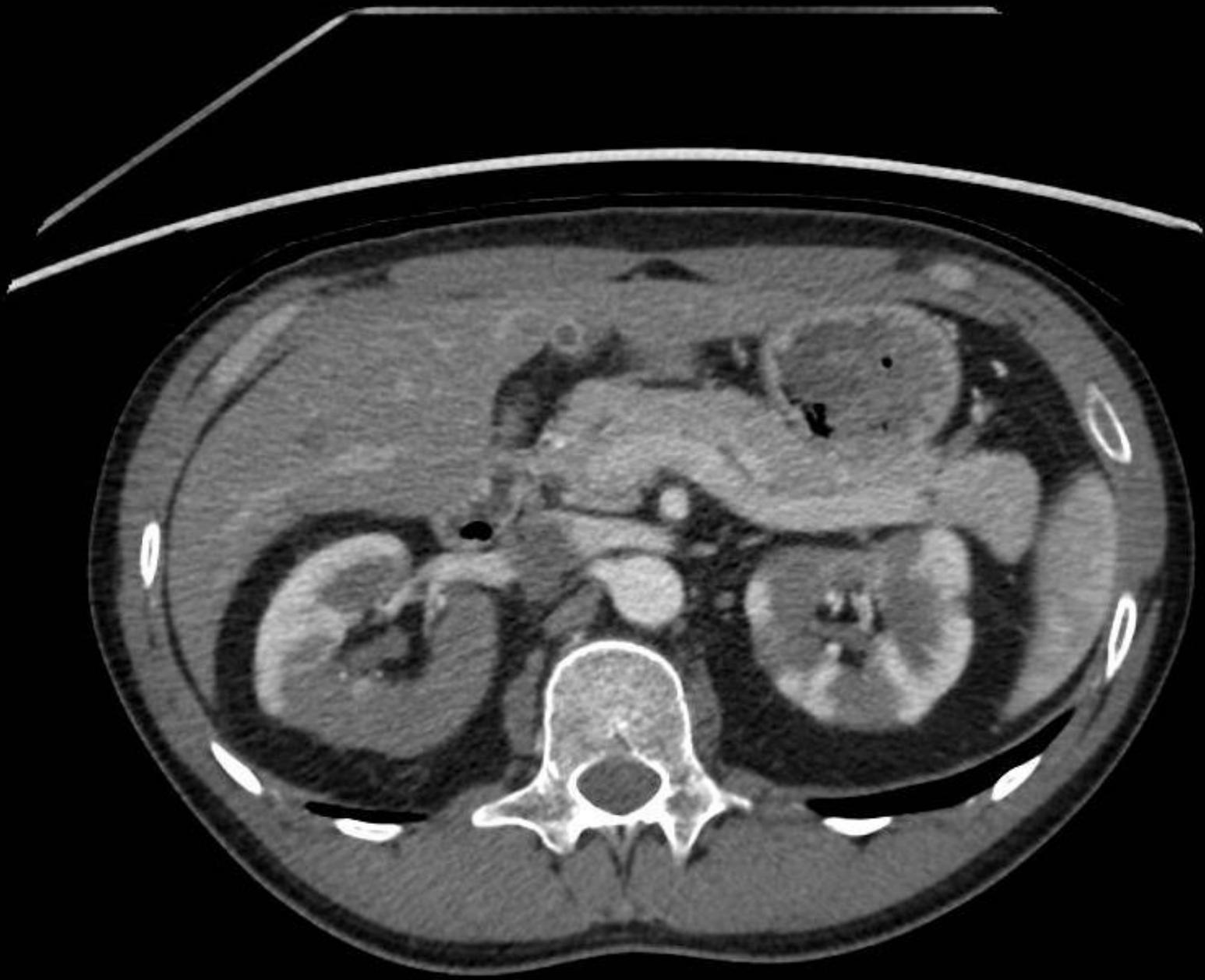
Figure 8: Immunofluorescence for IgG. Granular IgG deposits observed along the TBM.

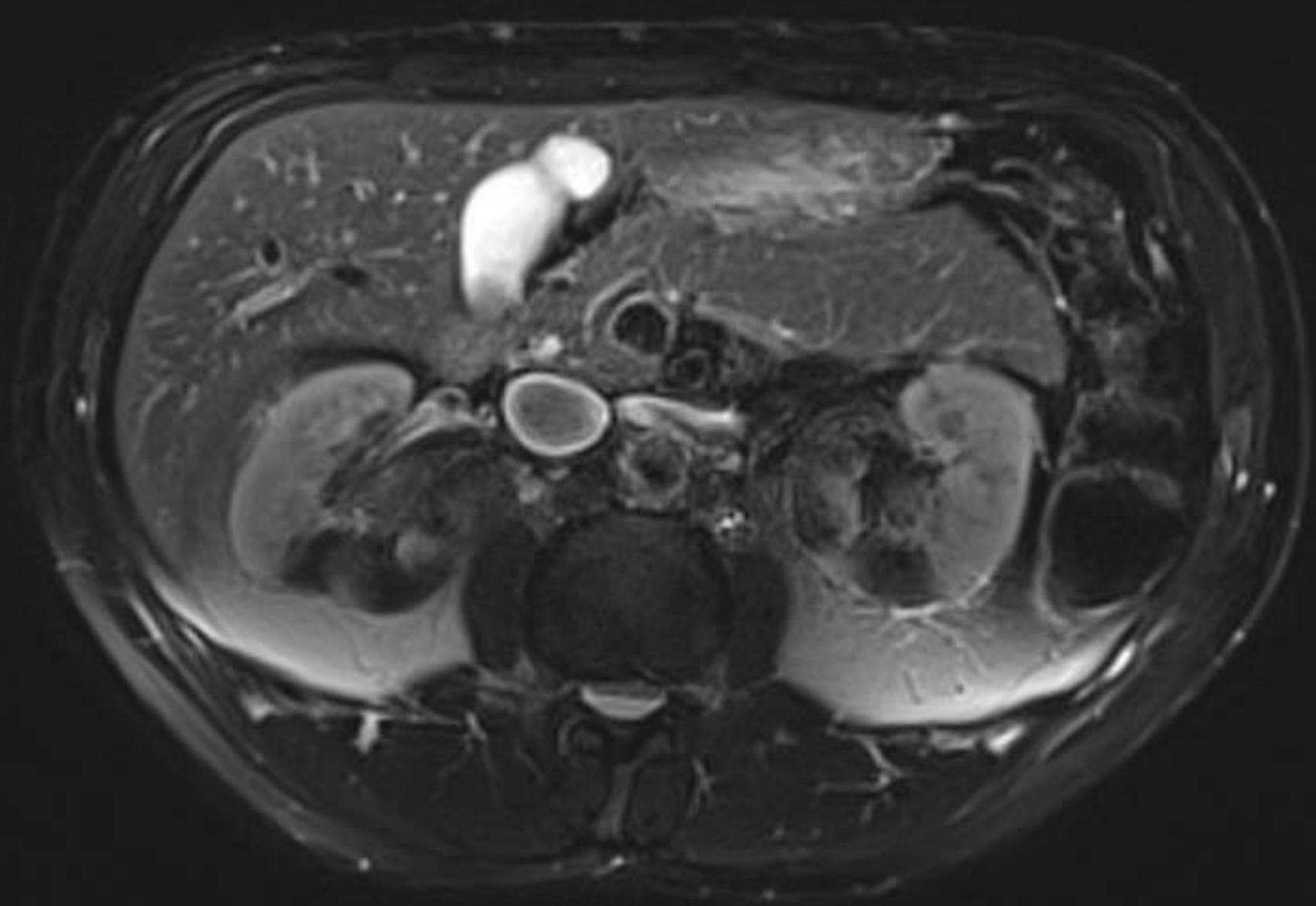
ACKNOWLEDGEMENT

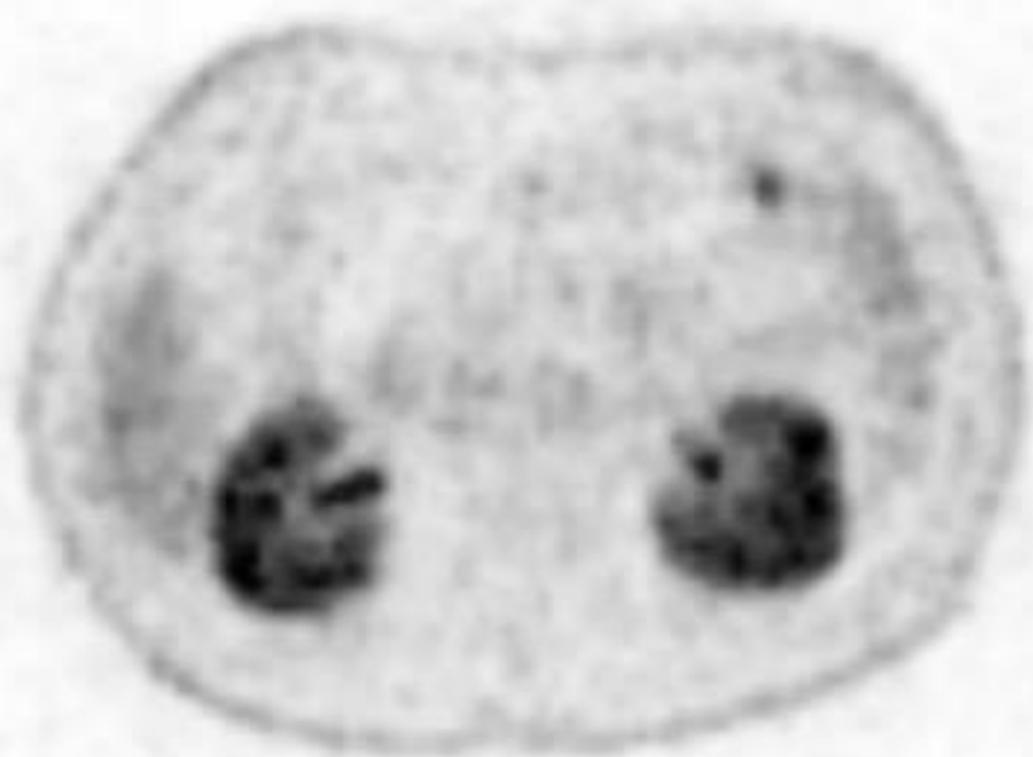
We are grateful to Daniel Birnbaum for the linguistic assistance and article review.

DISCLOSURE

All authors declared no competing interests









L4VOI1 PT
Max: 4,11 SUV-bw

F

Figure 5

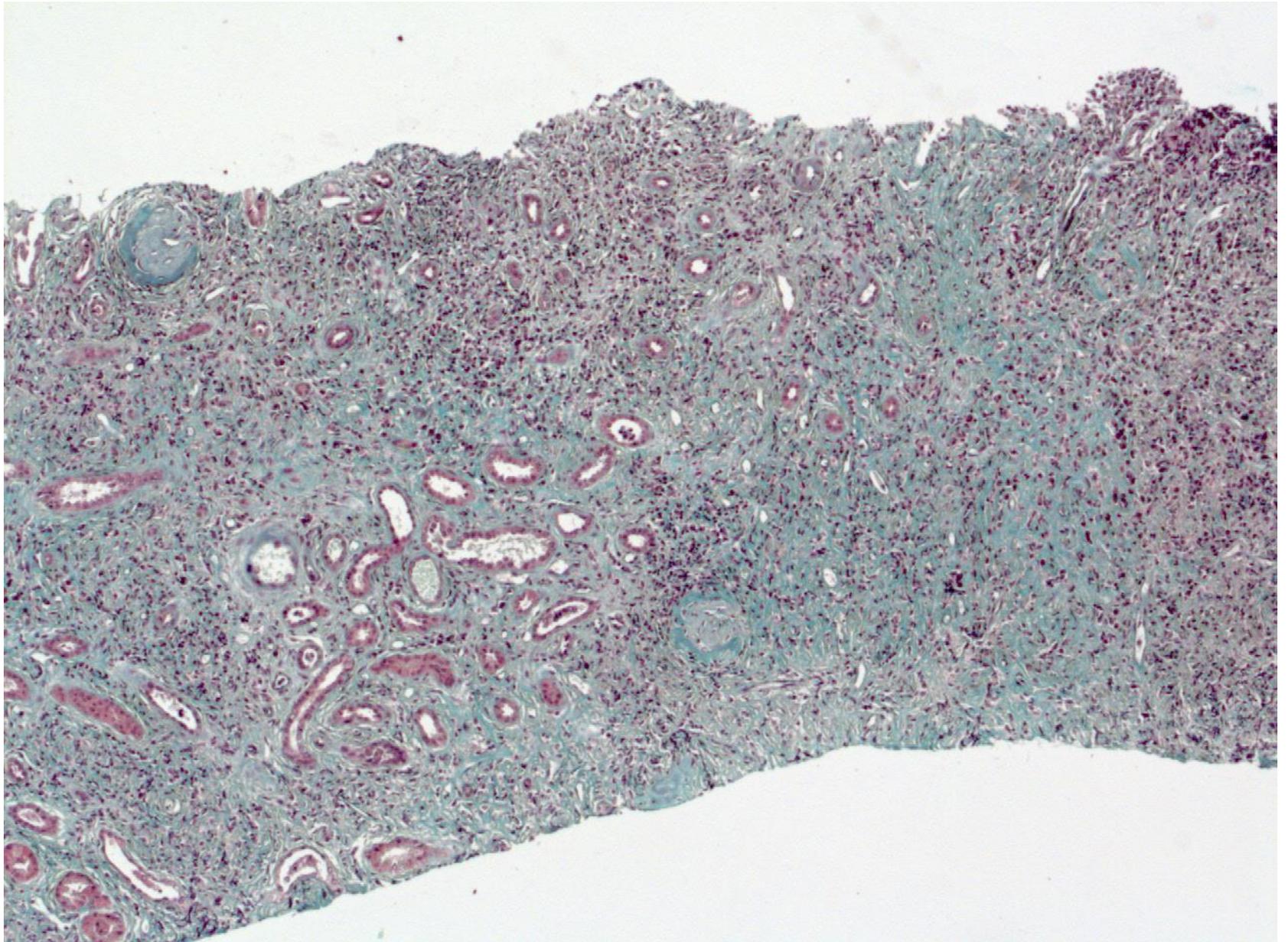


Figure 6

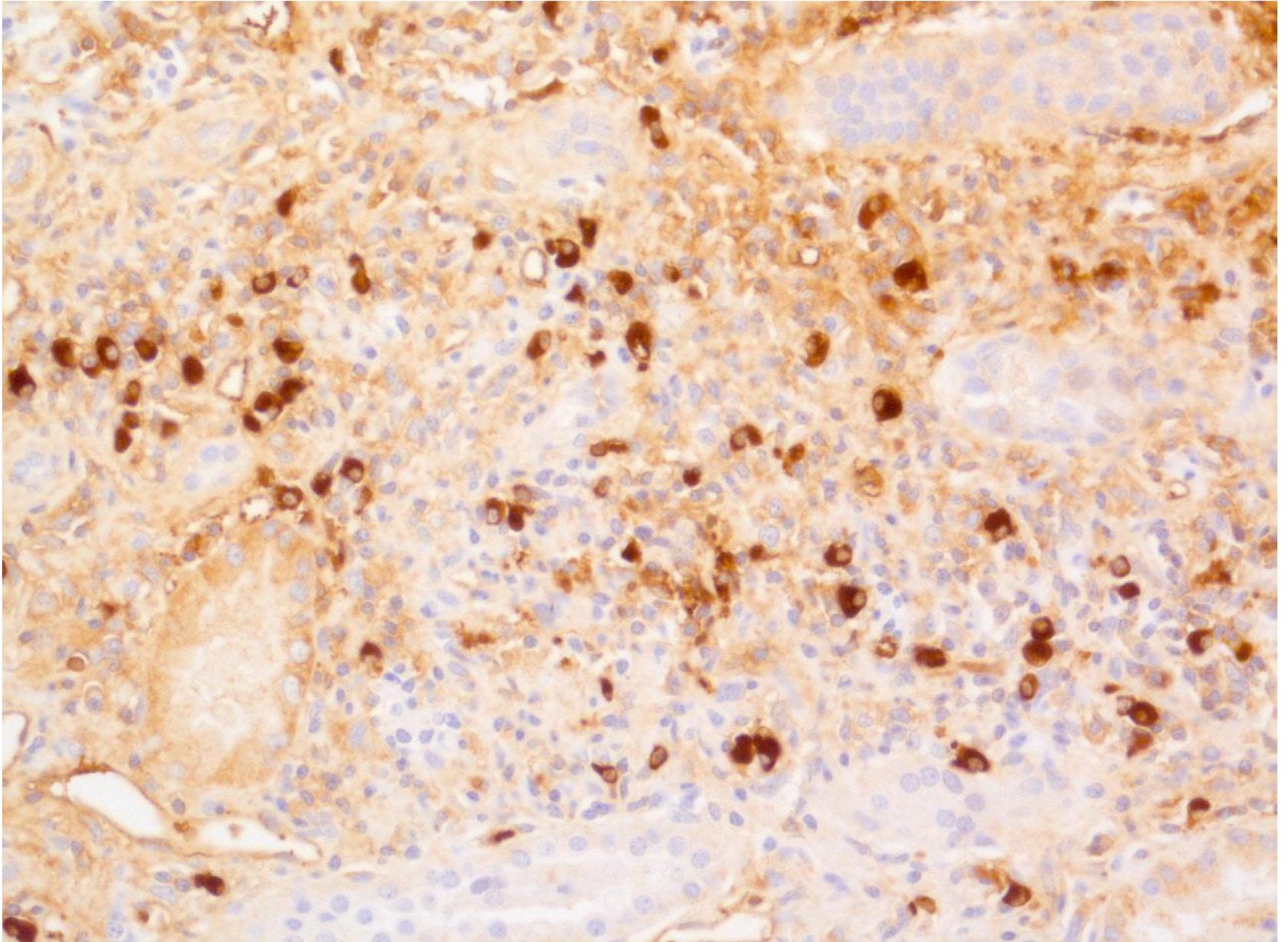


Figure 7

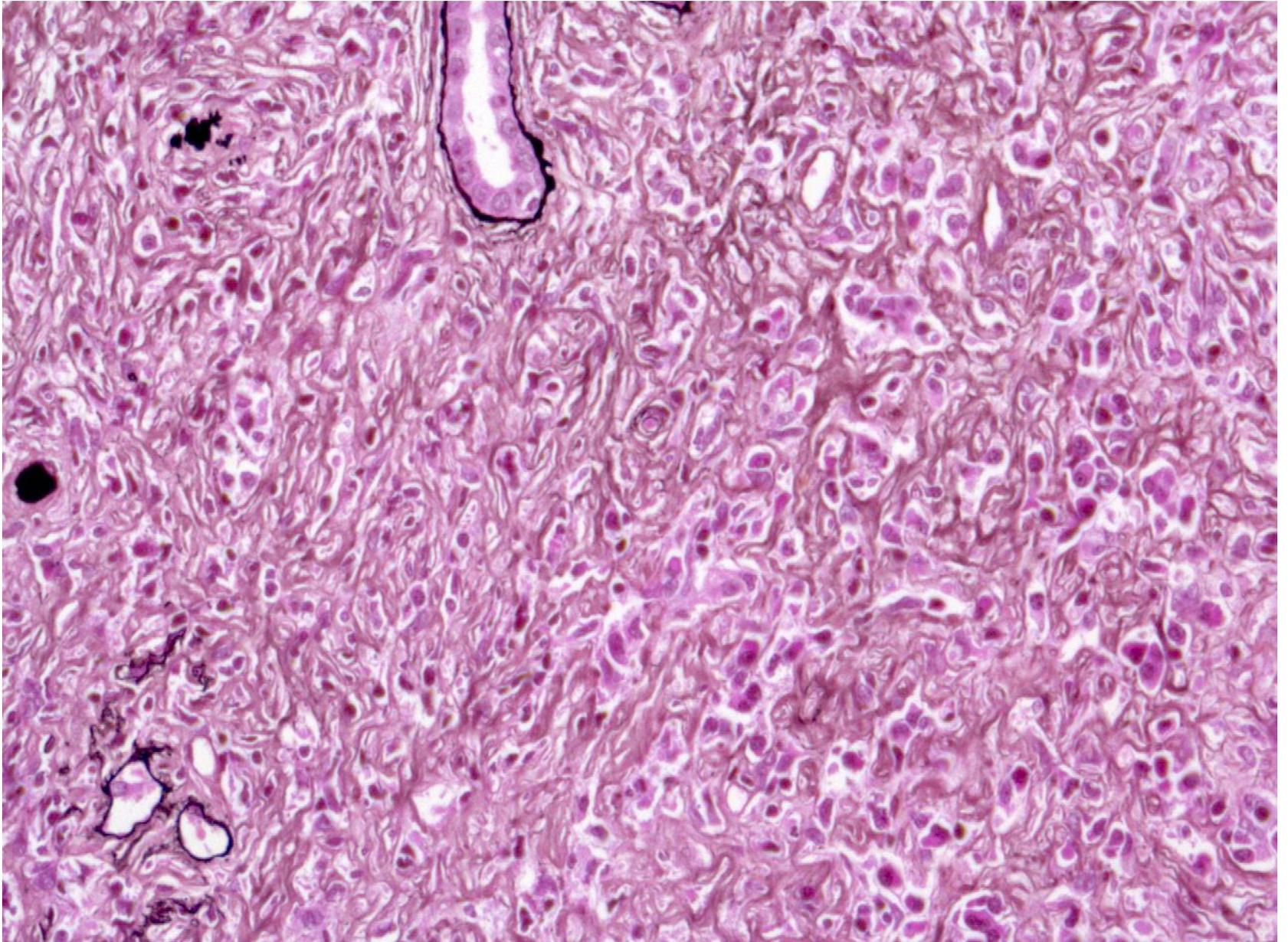


Figure 8

