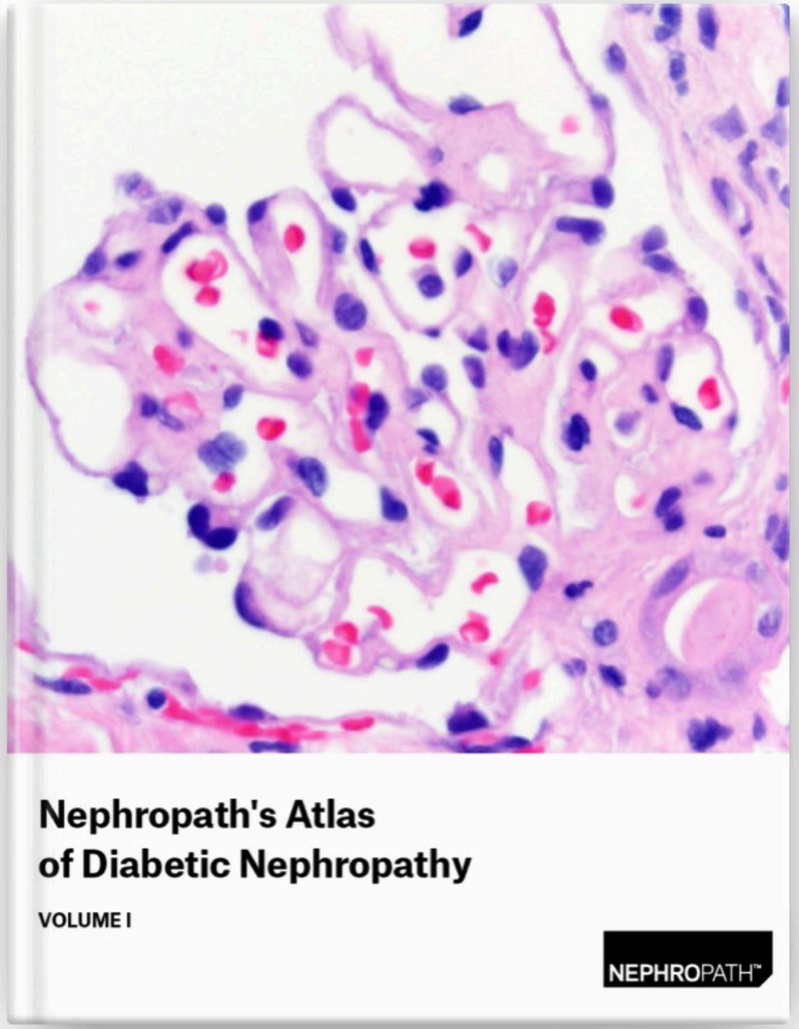
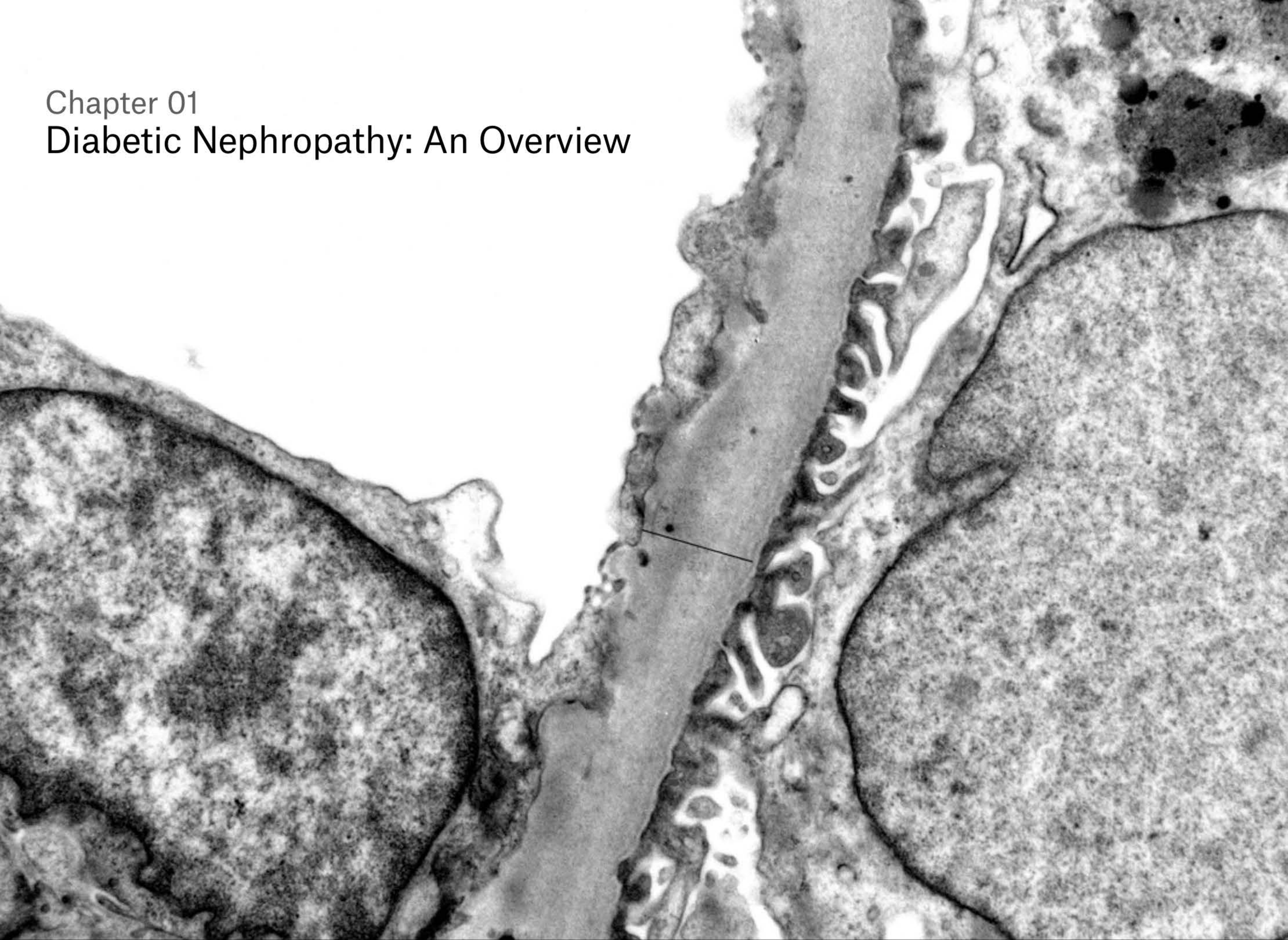


Nephropath's Atlas of Diabetic Nephropathy

Fred Silva, M.D. and Others

Chapter 01

Diabetic Nephropathy: An Overview



Diabetic Nephropathy: An Overview

Definition and Importance

The term “diabetic nephropathy” (DN) describes a number of renal functional and morphologic changes caused by Diabetes Mellitus (DM), as observed in type I and type II DM. It is estimated that approximately 25-35% of patients with long-standing diabetes mellitus develop diabetic nephropathy and renal failure. As a result of these changes, diabetes is the most common cause of end-stage kidney disease in the United States, accounting for 1/3 to ½ of patients on dialysis. Furthermore, patients with diabetic nephropathy have a higher frequency of co-morbid complications, such as cardiovascular disease and retinopathy.

Clinical Features

Renal involvement occurs early in the course of diabetes, although it may be initially undetected. Microalbuminuria (urinary albumin excretion between 30 and 300 mg/24 hrs) is the earliest finding, present soon after the clinical onset of diabetes, and it predicts an increased likelihood of developing progressive diabetic nephropathy. Elevation of the glomerular filtration rate (GFR), seen early in the course of the disease, may be a harbinger of future progressive diabetic nephropathy. Proteinuria, as detected by the standard dipstick analysis (about 500 mg/24 hrs of protein), typically occurs more than 15-20 years after the clinical onset of diabetes mellitus. However, a shorter onset (of less than 5 years) is not uncommon in type II diabetics. Microhematuria may be present in

as many as one-half of patients with pure diabetic nephropathy. Over time, serum urea nitrogen and creatinine become progressively elevated and complications of renal insufficiency, such as hyperkalemia or acidosis, may occur.

Noteworthy systemic findings with renal implications include diabetic retinopathy and systemic hypertension. The occurrence of diabetic retinopathy correlates well with the advance of renal disease. Systemic hypertension is often associated and may precede the development of proteinuria and progressive diabetic nephropathy.

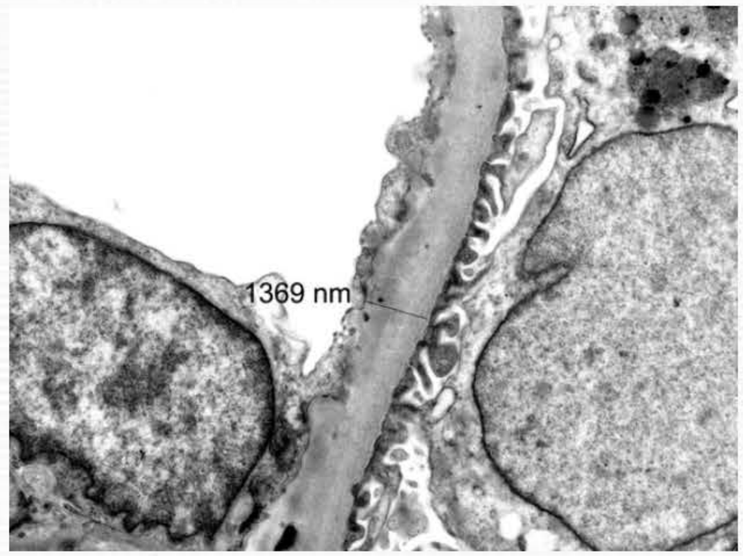


Fig 1-1 Thick GBMs 1369 nm (label), Electron photomicrograph.

Pathology Findings

Diabetic nephropathy affects all four components of the kidney: the glomeruli, tubules, interstitium, and the blood vessels.

Glomerular Changes

Early in the clinical course of diabetes mellitus, there is glomerulomegaly probably corresponding to the supernormal GFR. Another significant early change is thickening/widening of the GBM, which may occur as early as one and a half to two years after the clinical onset of diabetes (Fig 1-1). It occurs in virtually all diabetic individuals, even in those without significant proteinuria.

As the disease advances, diffuse mesangial expansion (Fig 1-2) increases, and it is found in varying degrees of severity in virtually all cases of advancing diabetic nephropathy.

Nodular diabetic glomerulosclerosis is usually superimposed upon diffuse mesangial expansion and is manifested by the occurrence of the characteristic

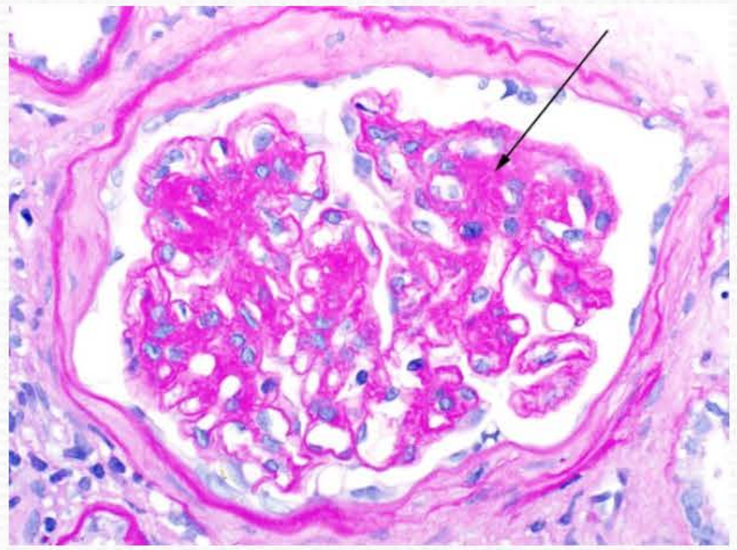


Fig 1-2 Mild mesangial expansion (arrow), PAS stain.

(and formerly pathognomonic) lesion - the Kimmelstiel-Wilson (KW) nodule, encountered in approximately 25% of biopsies in advanced diabetic nephropathy (Fig 1-3). The nodules are rounded or ovoid, composed of increased mesangial matrix, and have varying sizes and irregular distribution within individual glomeruli. They generally occur at 15-20 years after the clinical onset of type 1 DM, but may be encountered with only a short history of DM. KW nodules have also been seen inpatients without known DM. However, these patients usually are found to have diabetes mellitus or glucose intolerance when a detailed search takes place due to the biopsy findings.

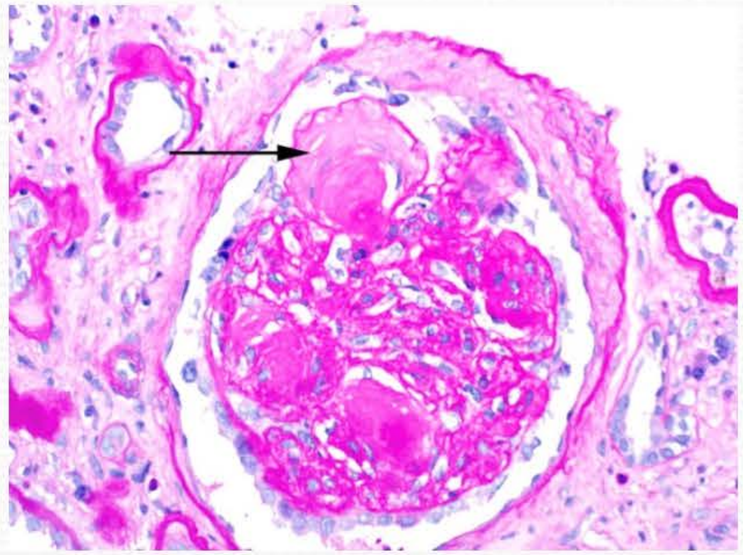


Fig 1-3 KW nodule (arrow) superimposed on mesangial matrix expansion, PAS stain.

Mesangiolysis is manifested by dissolution/attenuation and occasional lamellation of the mesangial matrix (Fig 1-4). It is thought that this causes the glomerular capillary loops to lose their anchor to the mesangial matrix leading to microaneursyms. Another characteristic and advancing lesion seen in diabetic nephropathy is the "exudative" or the more appropriately-termed "insudative" lesion. These lesions result from insudation of plasma proteins into the glomerular capillary wall (fibrin cap or hyaline cap) (Fig 1-5), between the parietal epithelium and Bowman's capsule (“capsular drop”), and arteriolar walls (hyaline arterioslosclerosis), with accumulation of hyaline material into these locations.

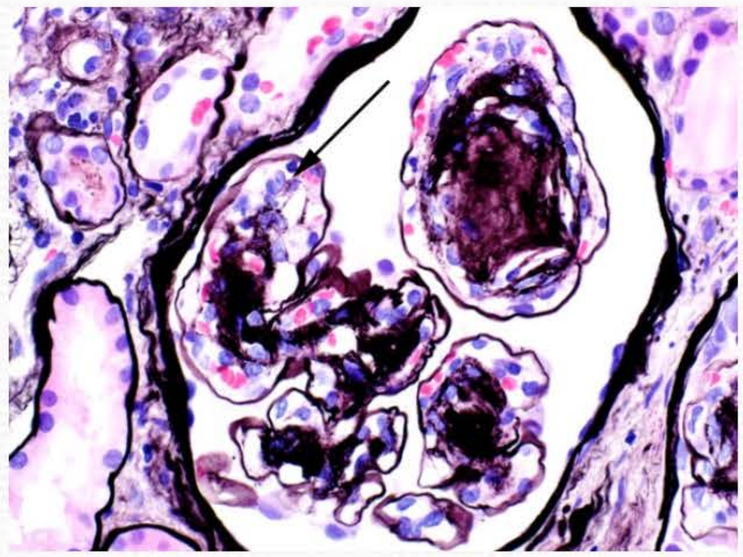


Fig 1-4 Loss of mesangial integrity with early microaneurysm formation (arrow), Silver stain.

Eventually, the progressive glomerulosclerosis and vascular changes lead to global glomerulosclerosis. Sclerotic glomeruli in diabetes tend to be large, and often times remnants of KW nodules can be detected.

Tubulointerstitial Changes

Tubular changes are secondary to the glomerular disease, and include hyaline protein resorption droplets (hyaline change) and lipid droplets within the tubular epithelium. As the renal disease progresses, there may be tubular atrophy with progressively thickened tubular basement membranes.

Interstitial fibrosis is likely the principal determinant of long-term renal function, and it is often proportional to the vascular and glomerular changes. Interstitial inflammation may be present and composed predominantly of lymphocytes with occasional neutrophils and eosinophils. Interstitial inflammation may be severe even in the absence of infection or allergic reaction.

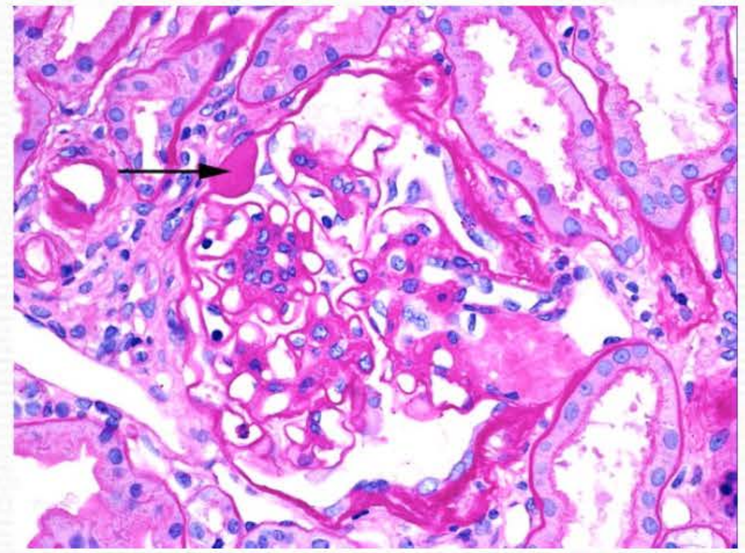


Fig 1-5 Glomerulus with capsular drop (arrow), Silver stain.

Vascular Changes

Vascular changes include intimal fibroplasia in larger arteries and hyaline arteriolosclerosis in small renal arterioles. Hyaline arteriolosclerosis is commonly noted in the afferent arterioles. If both afferent and efferent arterioles are recognized entering and exiting the glomeruli, then hyalinization of the efferent arteriole can be recognized. This finding is considered quite specific for DM, but has been described in non-diabetic conditions.

Immunofluorescence Findings

The hallmark of advanced diabetic nephropathy by IF is the nonspecific diffuse linear staining of the tubular basement membranes and glomerular basement membranes with albumin and IgG, often accompanied by Kappa and Lambda light chains staining of the same intensity. The insudative lesions often show nonspecific, non-immunologic staining for IgM and C3.

Electron Microscopy Findings

The most characteristic ultrastructural changes are diffuse thickening of the glomerular basement membranes (GBM), and the increase in the amount of mesangial matrix (mesangial sclerosis). Some investigators have suggested that the finding of moderately thickened GBMs in a patient without known diabetes mellitus should be investigated for the presence of diabetes mellitus. The glomerular visceral epithelial cells often show extensive effacement of the foot processes.

Pathological Differential Diagnosis

A number of glomerular lesions can resemble diabetic nephropathy by light microscopy and a list of common differential diagnoses include hypertensive renal disease, light chain deposition disease, membranoproliferative glomerulonephritis, amyloidosis, fibrillary glomerulopathy and idiopathic nodular glomerulosclerosis, among others.

Other Renal Diseases In Patients With Diabetes

Virtually all of the common renal diseases have been documented to occur in diabetic patients. The most common are membranous glomerulonephropathy and infection-associated GN, followed closely by IgA nephropathy, and then various other glomerulonephritides. Papillary necrosis, acute pyelonephritis, and advanced arterial/arteriolar nephrosclerosis are common and severe complications of advancing diabetic kidney disease.

Etiology/Pathogenesis

The pathogenesis of diabetic nephropathy is not completely understood. Most evidence suggests that the diabetic renal changes are caused in large part by the underlying diabetic metabolic defects of the hyperglycemia, insulin deficiency or other aspects of the glucose intolerance. Genetic components play a role, and more than 90 genes have been implicated in diabetes type 1, and at least 36 genes in type 2. Other contributing factors include hemodynamic alterations (hyperfiltration) and systemic hypertension. An extensive review on the etiology and pathogenesis of diabetes is beyond the scope of this book, and can be found elsewhere in the literature.

Treatment/Prognosis

Although the majority of patients with diabetes mellitus do not develop significant clinical renal damage, those with proteinuria usually develop progressive diabetic nephropathy. The time interval from the clinical onset of diabetes to clinical proteinuria is usually from 10-15 years, and end-stage renal disease follows that in about 5-10 years.

The cornerstone of the therapy is control of hyperglycemia and hypertension which may delay or prevent the development of nephropathy, but does not appear to have significant effect on disease progression once the diabetic nephropathy is overt. ACE inhibitors may reduce proteinuria and slow the progression to renal failure.

Dialysis, renal transplantation, and combined pancreas-renal transplantation are the final therapeutic modalities for advancing diabetic nephropathy. Survival rates for diabetic patients undergoing transplantation are better than those on

dialysis, however features of recurrent diabetic disease can be noted as early as two years after transplantation. Cardiovascular disease is the most common cause of death in ESRD patients with diabetes mellitus.

Modified from "Non-Neoplastic Kidney Diseases" (in the AFIP/ARP Atlas of Nontumor Pathology Series) by Vivette D'Agati, J. Charles Jennette, and Fred G. Silva. 2005. Chapter 17: Diabetic Nephropathy. Pp 457-480. With permission.

Figure 1-1 Thick GBMs 1369 nm (label), Electron photomicrograph.

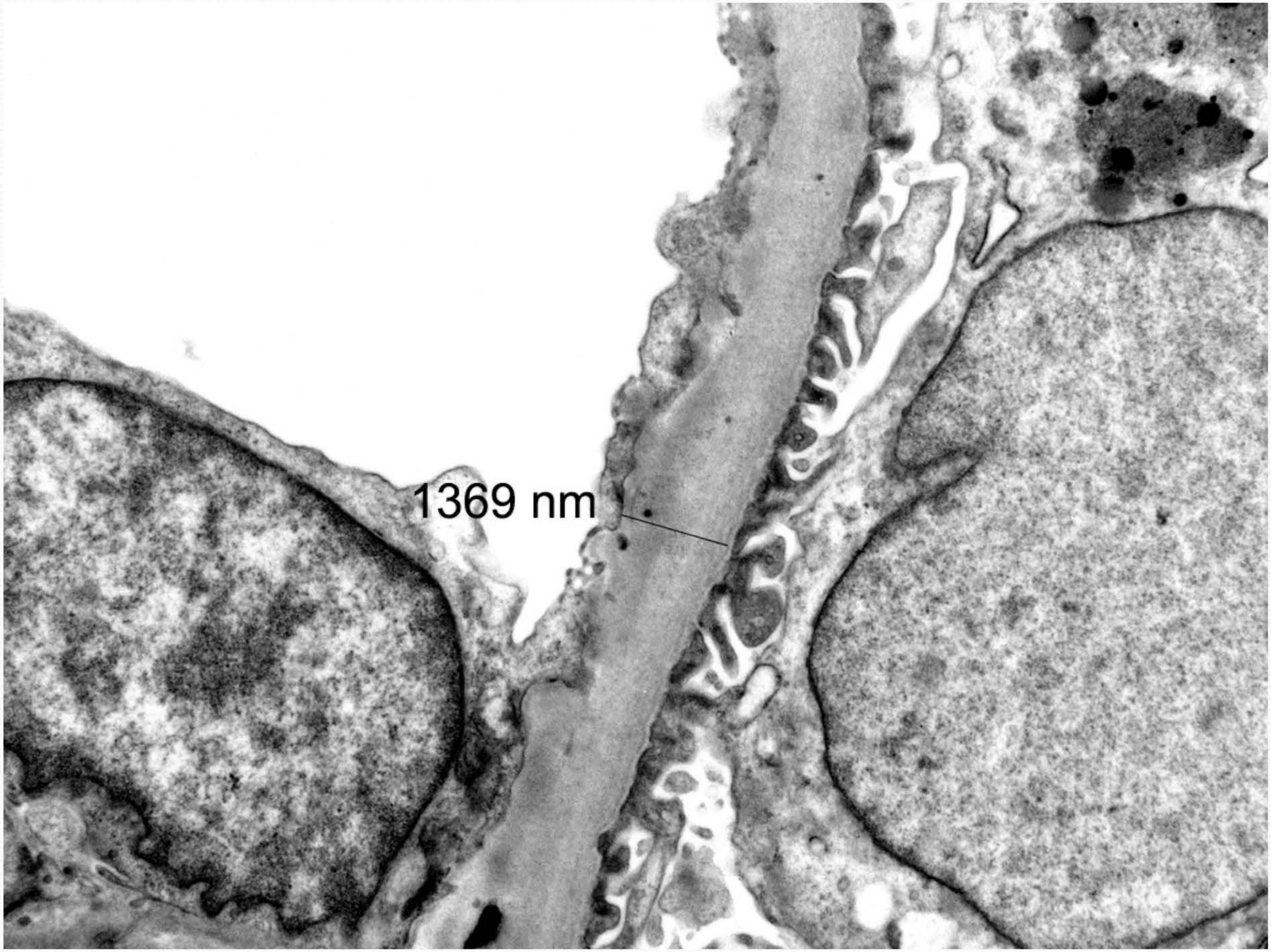


Figure 1-2 Mild mesangial expansion (arrow), PAS stain.

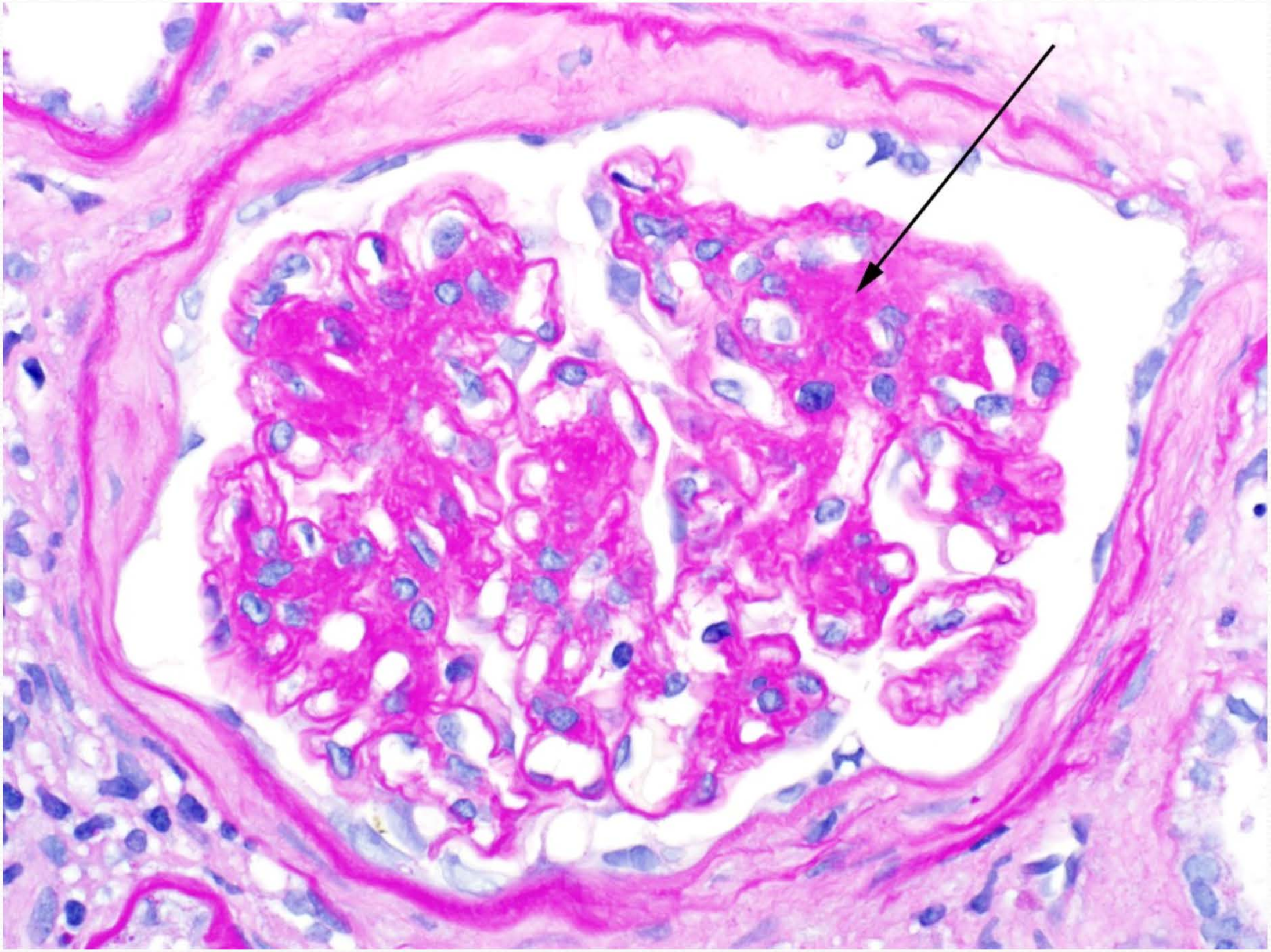


Figure 1-3 KW nodule (arrow) superimposed on mesangial matrix expansion, PAS stain.

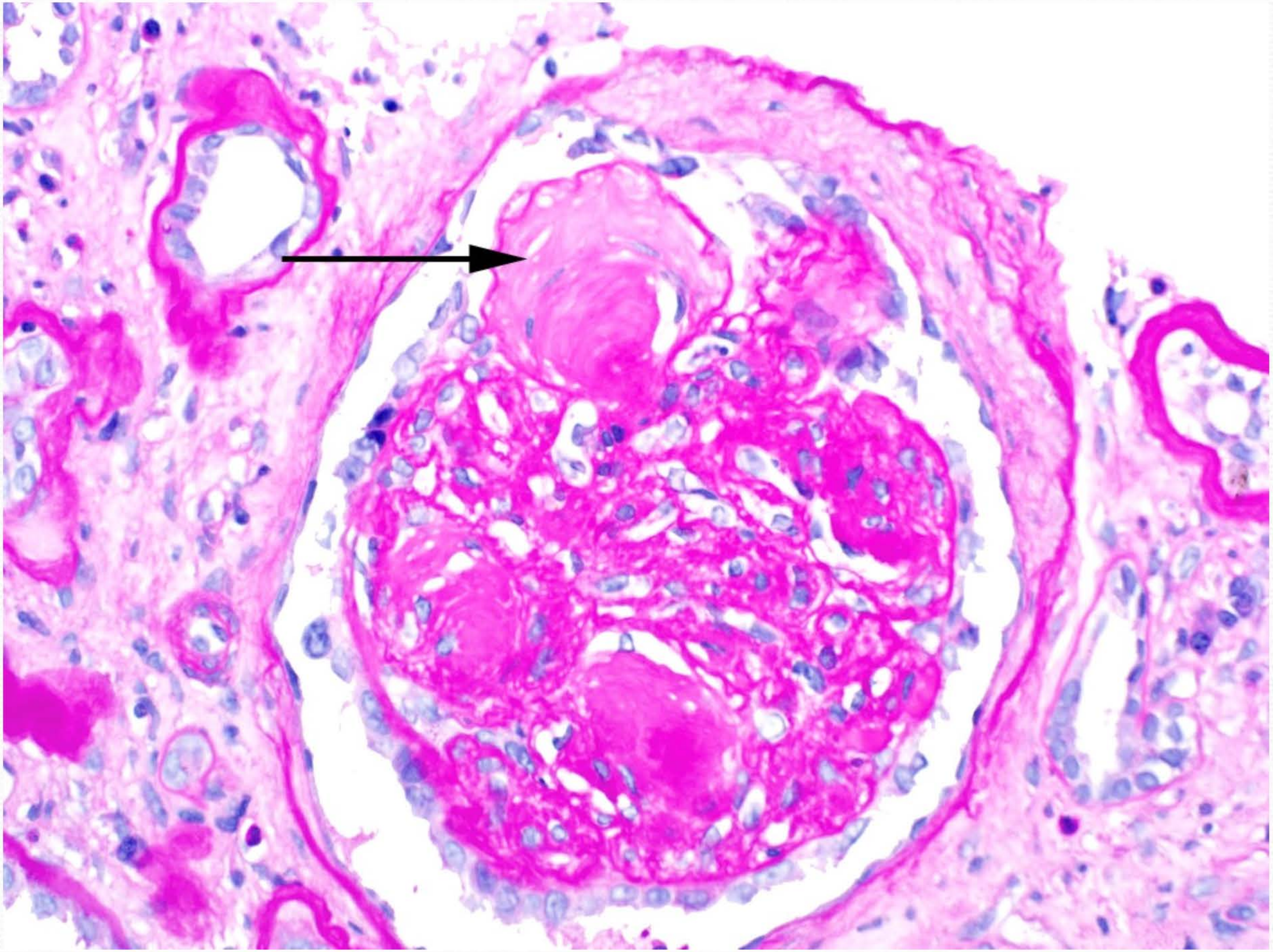


Figure 1-4 Loss of mesangial integrity with early microaneurysm formation (arrow), Silver stain.

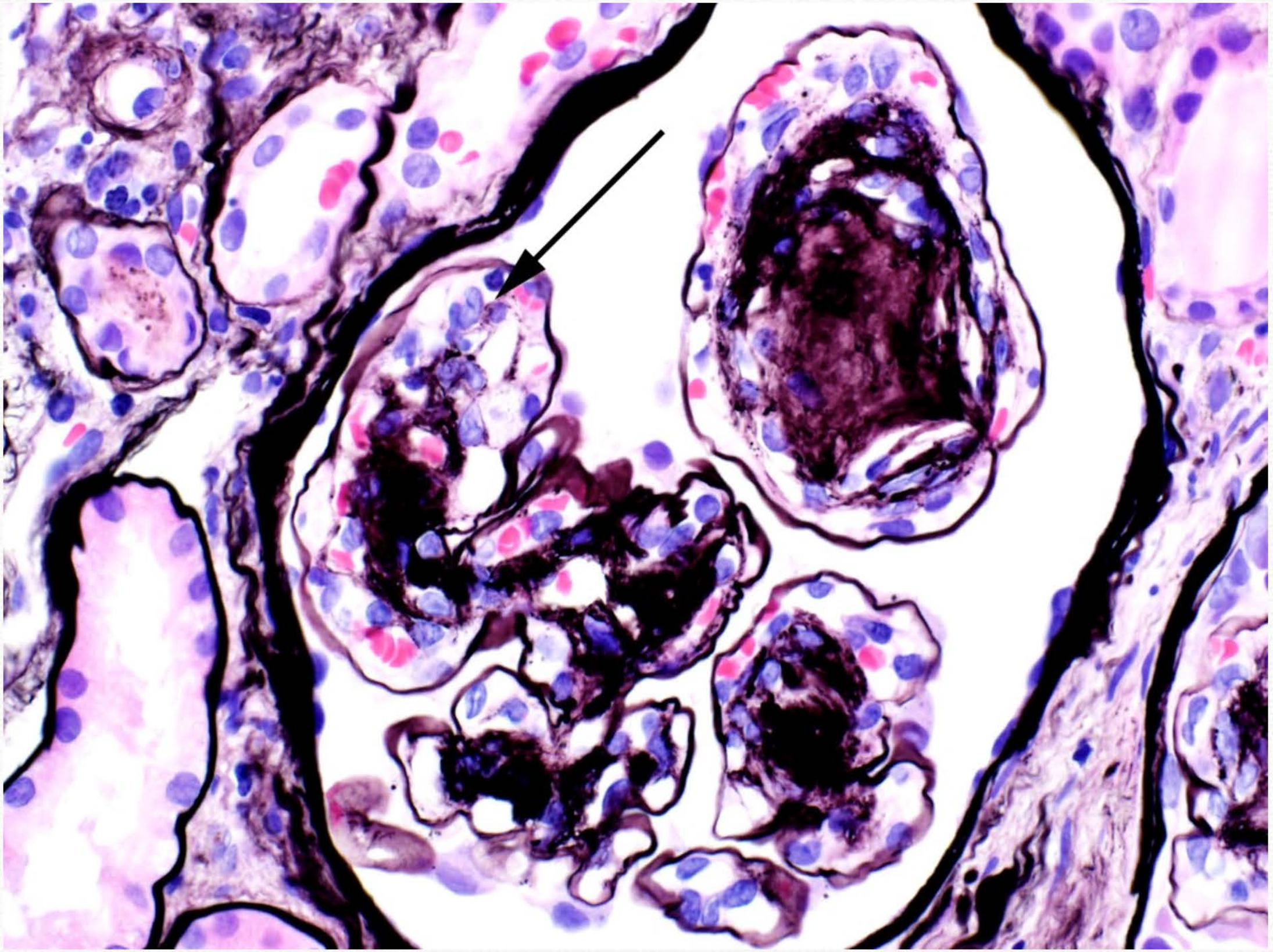


Figure 1-5 Glomerulus with capsular drop (arrow), Silver stain.

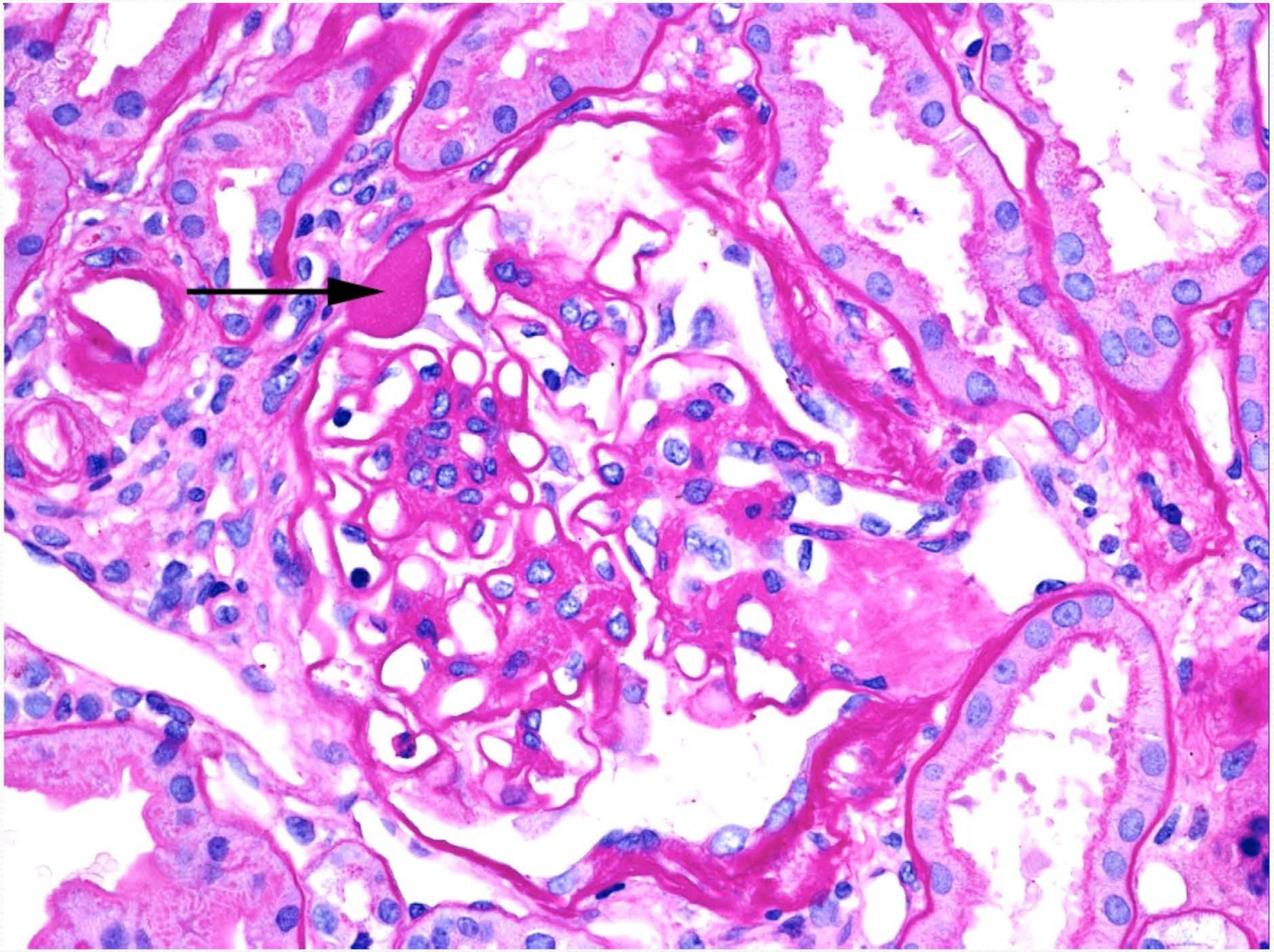


Figure 1-6 Interstitial fibrosis and thick TBMs (arrow), Trichrome stain.

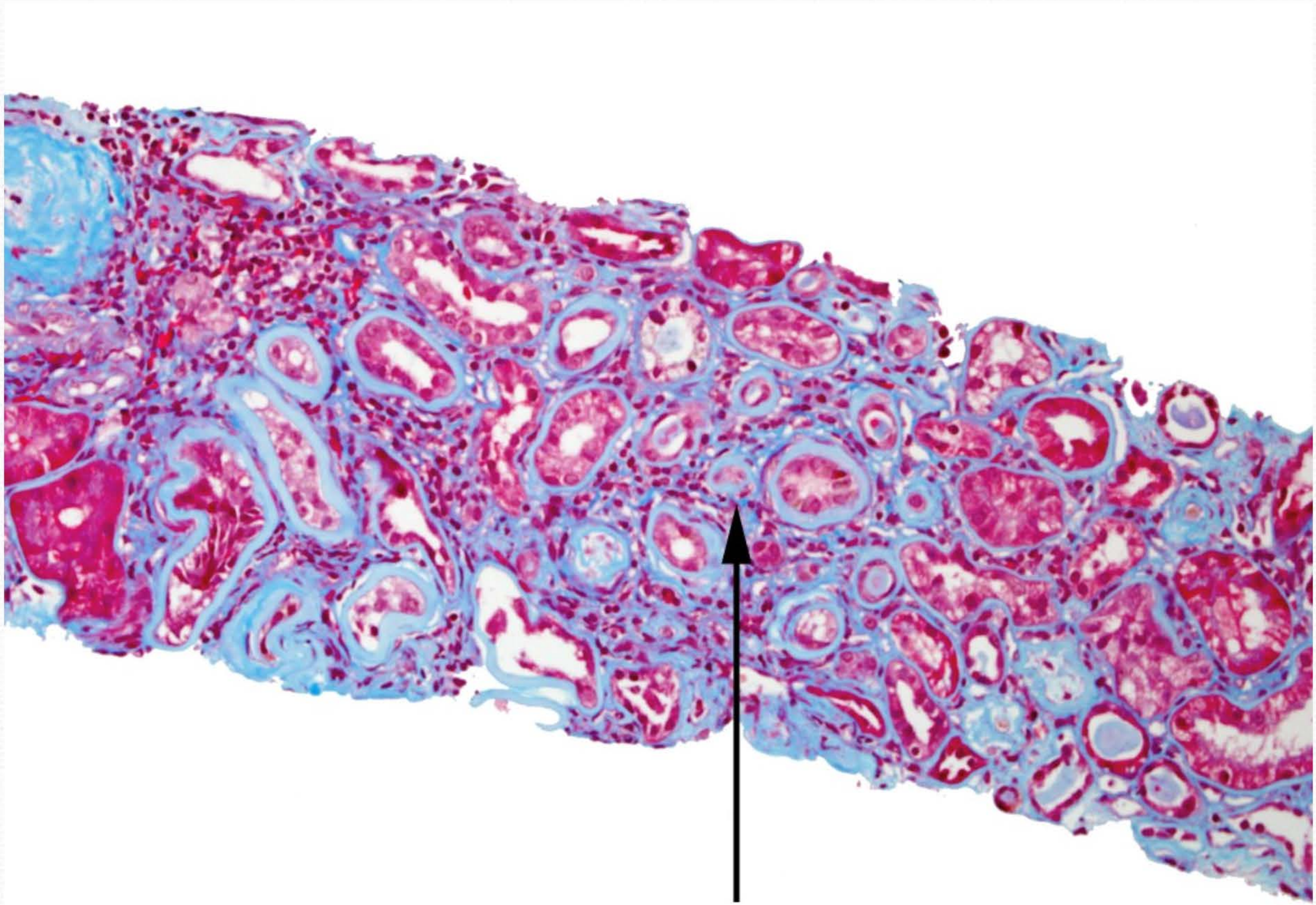


Figure 1-7 Hyalinization of afferent (single arrow) and efferent (double arrows) arterioles, PAS stain.

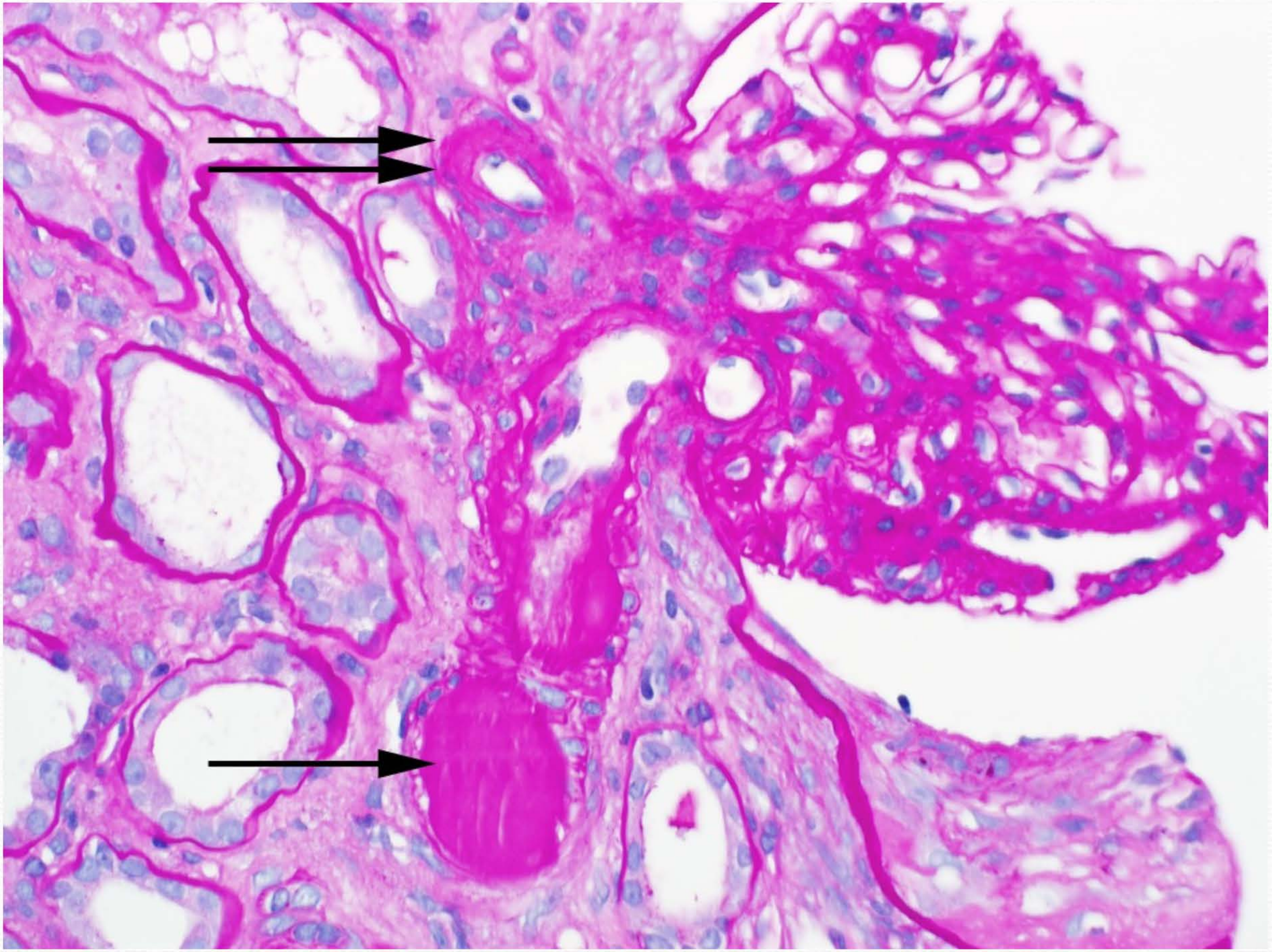


Figure 1-8 Linear tubular basement membrane staining for IgG (arrow), Fluorescence.

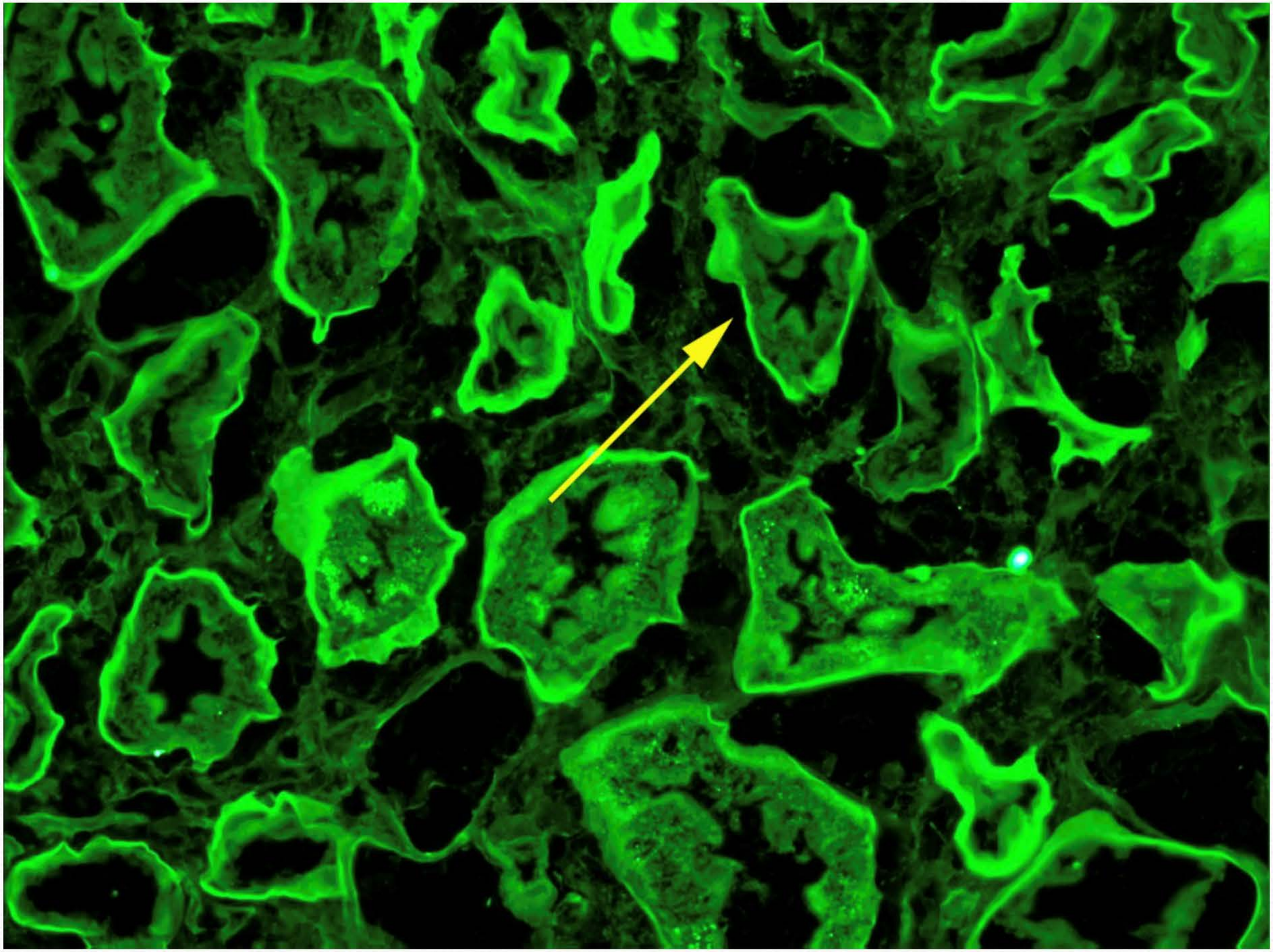


Figure 1-9 Linear tubular basement membrane staining for Albumin (arrow), Fluorescence.

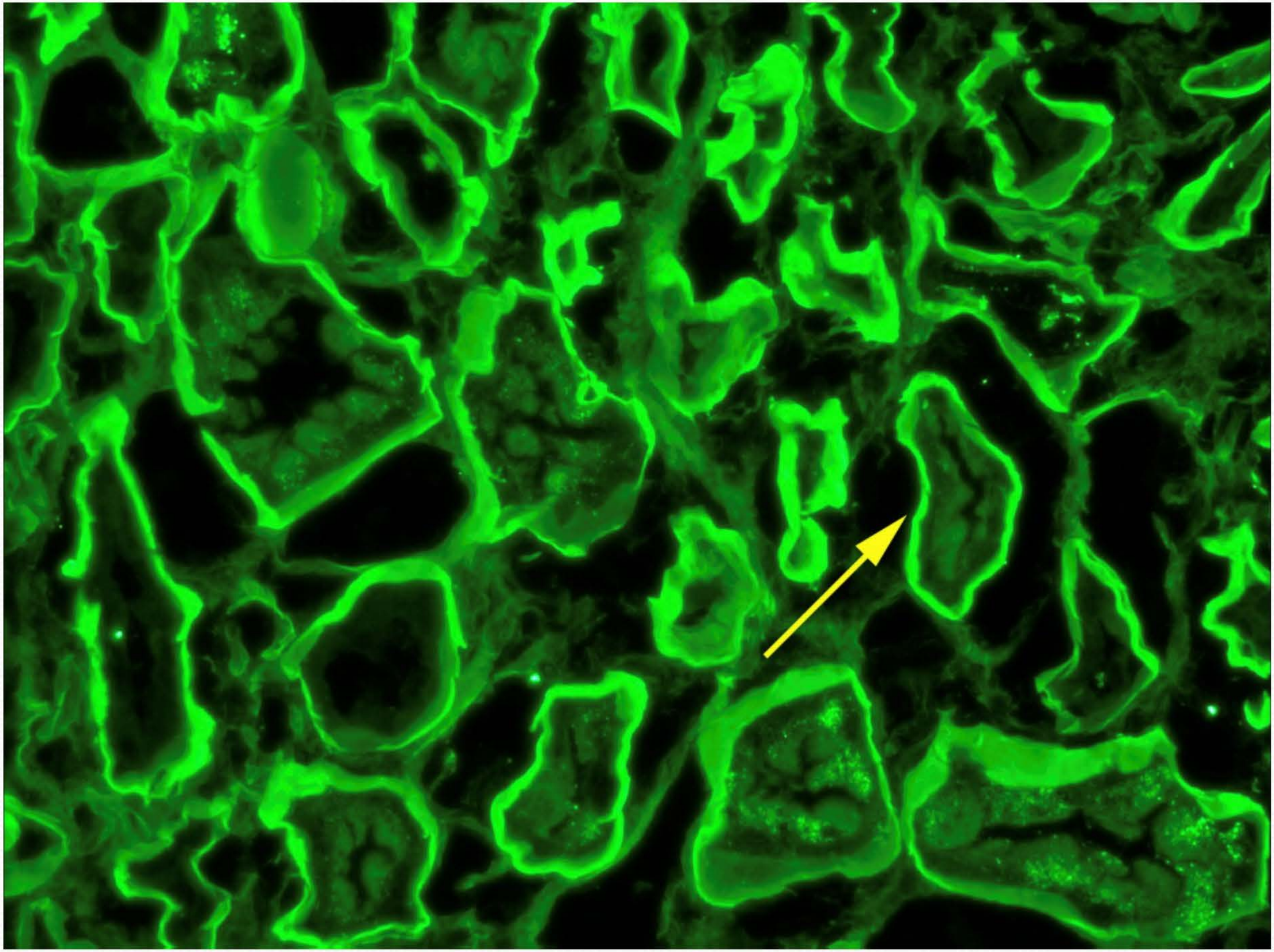
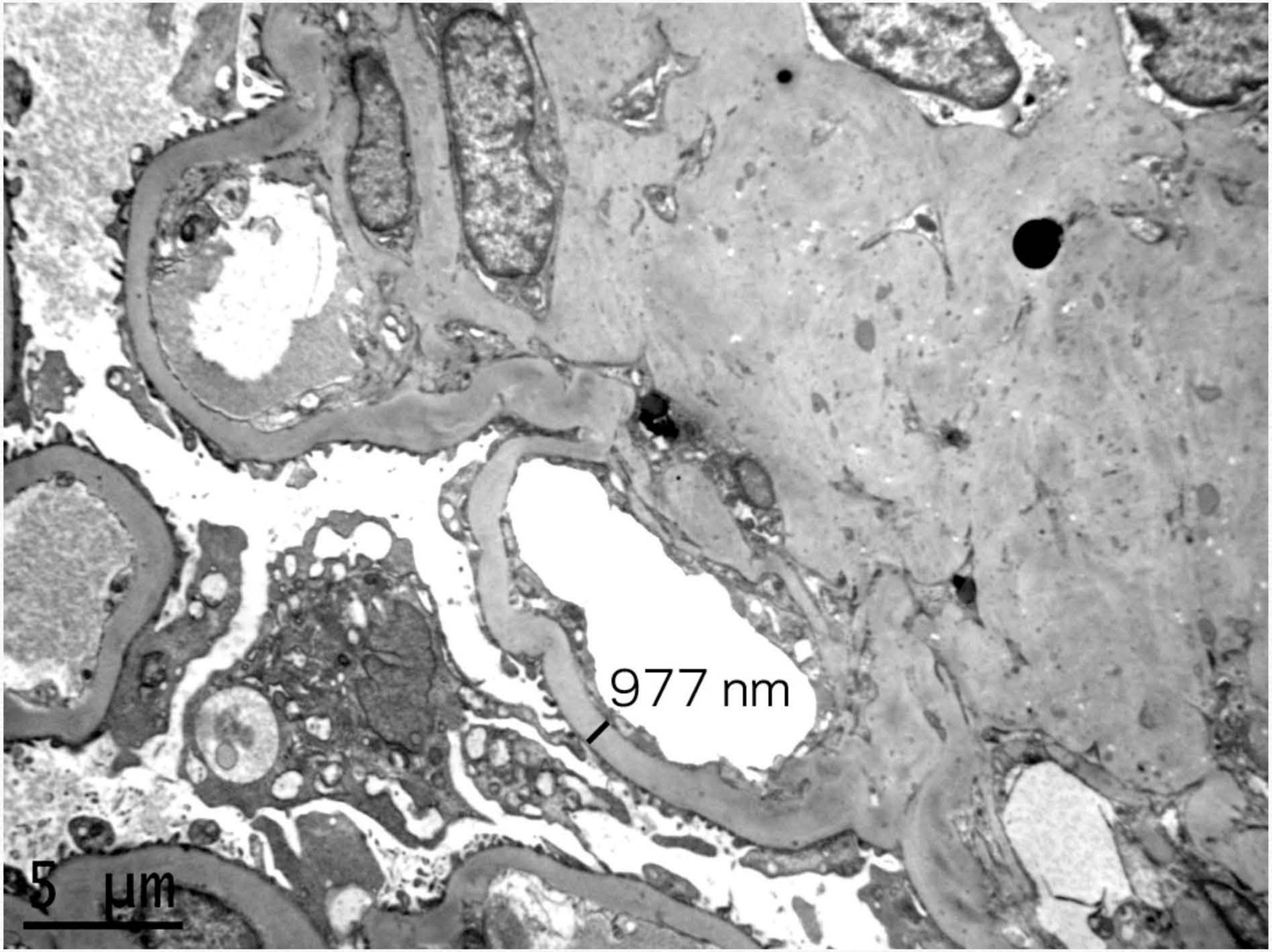
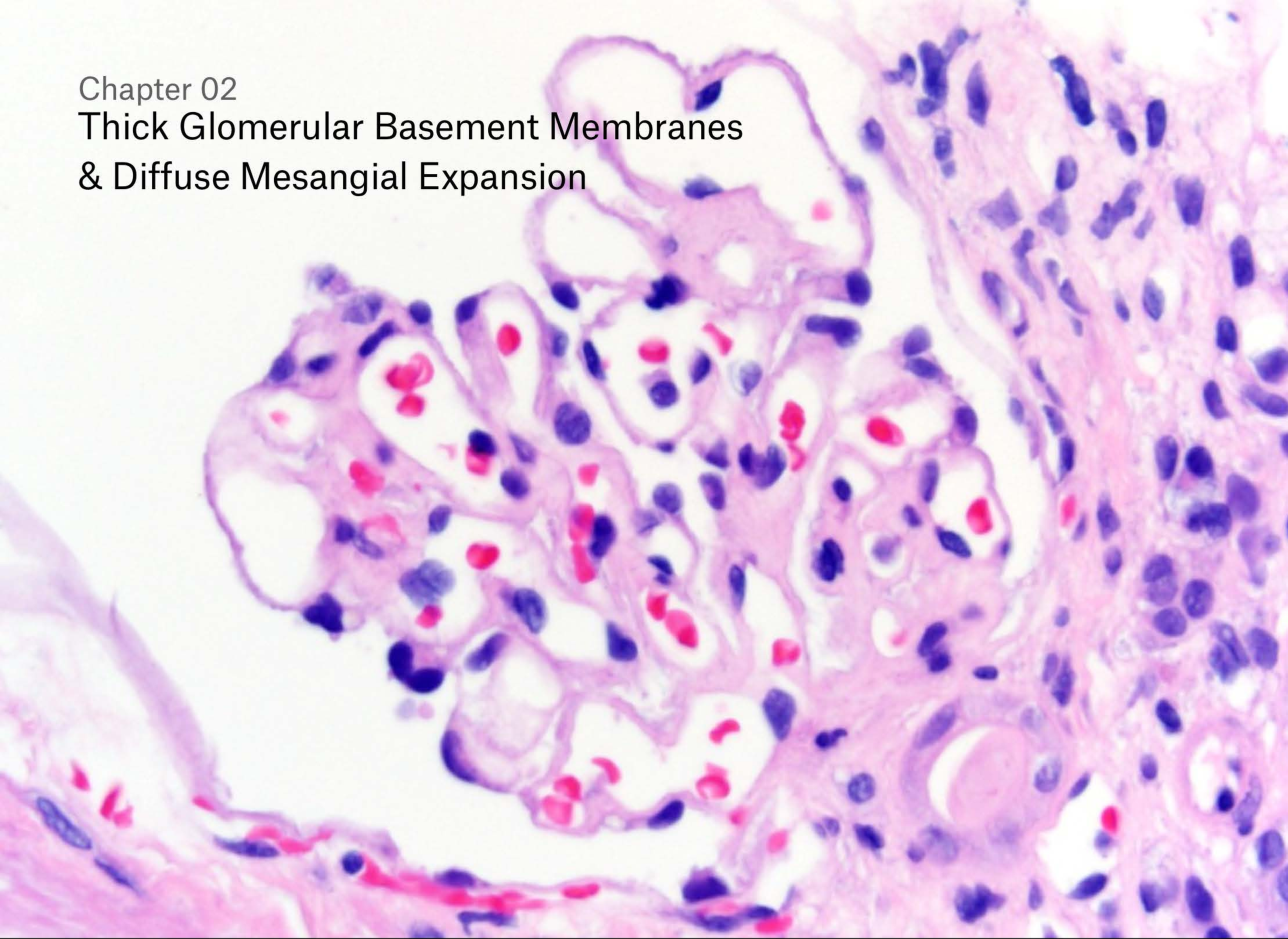


Figure 1-10 Thick GBMs (977 nm) and mesangial expansion, Electron photomicrograph.



Chapter 02

Thick Glomerular Basement Membranes & Diffuse Mesangial Expansion



Thick Glomerular Basement Membranes & Diffuse Mesangial Expansion

Thickening of the glomerular basement membranes (GBM) is a characteristic sign of diabetic nephropathy (DN) (Fig 2-1–Fig 2-3). This change is not pathognomonic, since it has also been reported in vascular disease, hypertension and aging. GBM thickening is accompanied by an increase in mesangial matrix (so-called "diffuse diabetic glomerulosclerosis" discussed in detail below). Together these two morphologic features lead to a progressive reduction in the glomerular filtration surface area. However, both of these changes are difficult/impossible to identify in the early stages because DN begins in clinical and laboratory silence. In addition, these changes are only recognizable by ultrastructural examination and recognition of early mesangial volume increase requires morphometric analysis. As DN advances, GBM thickening and mesangial expansion are found in varying degrees of severity. GBM thickening is the result of an increase of extracellular matrix accumulation and diminished removal.

In the mid-20th century there was a controversy as to which came first, the GBM thickening or the increase in mesangial volume, though some investigators believed that the two lesions occurred together. Part of the problem was that pathologists were examining kidney tissue from autopsies using only H&E stained light microscopy sections. Thus they rarely saw kidneys in the early

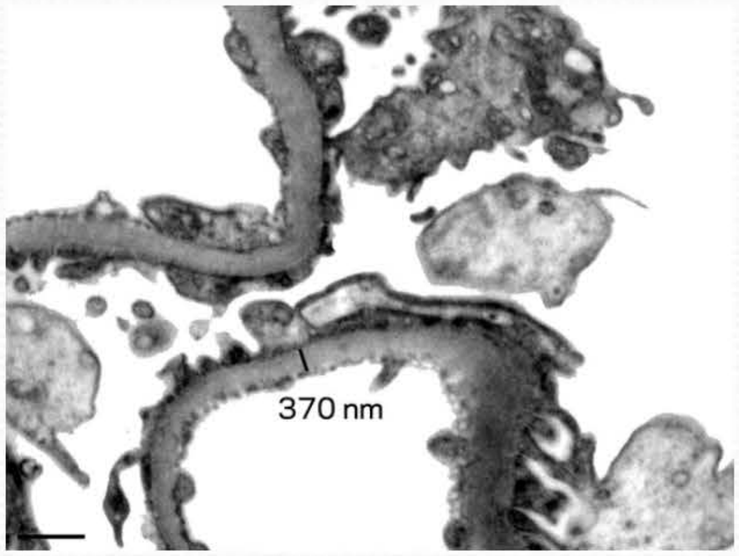


Fig 2-1 Normal GBM 370 nm (label), Electron photomicrograph.

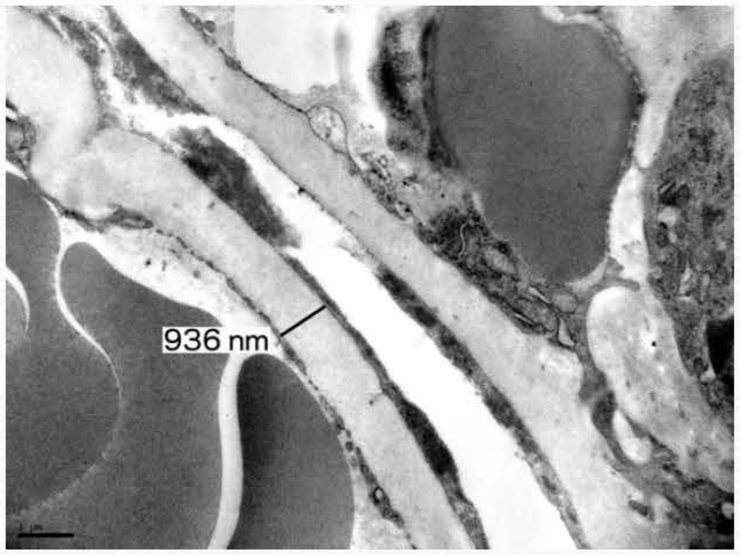


Fig 2-2 Thick GBMs 936 nm (label), Electron photomicrograph.

stages of diabetic nephropathy and if they did, they would not have recognized the earliest changes by light microscopy alone. The availability of the renal biopsy beginning in the 1950s and rapidly expanding in the 1960s–1970s changed our understanding of DN. In 1975, Osterby et al showed that GBM thickening is the first measureable change in DN, occurring within 1 1/2–2 years of the "onset" of DM. GBM thickening continues such that at five years, the thickness of the GBM is increased by 30%. Though the GBM thickening does come first, it appears to be a distinction without a difference since mesangial expansion occurs almost at the same time and it is the mesangial matrix increase that is best related to the decline in renal function.

The GBM can be measured in a number of ways. The simplest is the use of the line measurement tool on digitized samples. This is all that is needed in routine diagnostic evaluation (though research techniques include a variety of morphometric techniques such as the orthogonal intercept method). A variety of "normal" ranges have been reported. But each renal biopsy laboratory has to develop their own normal range of GBM thickness by gender and age as there are differences in fixation, processing and electron microscopes between labs. The thickness of the GBMs increases gradually reaching adult thickness by about nine years of age. The number of needed measurements from different locations has been noted by Steffes et al, and recently updated by Haas. It is also important to know that GBM measurements from retrieval of material for ultrastructural studies from formalin-fixed paraffin embedded material may lead to artifactual GBM thinning. There are also descriptions of segmental thinning of GBMs in patients with DN, as in many other glomerular diseases.

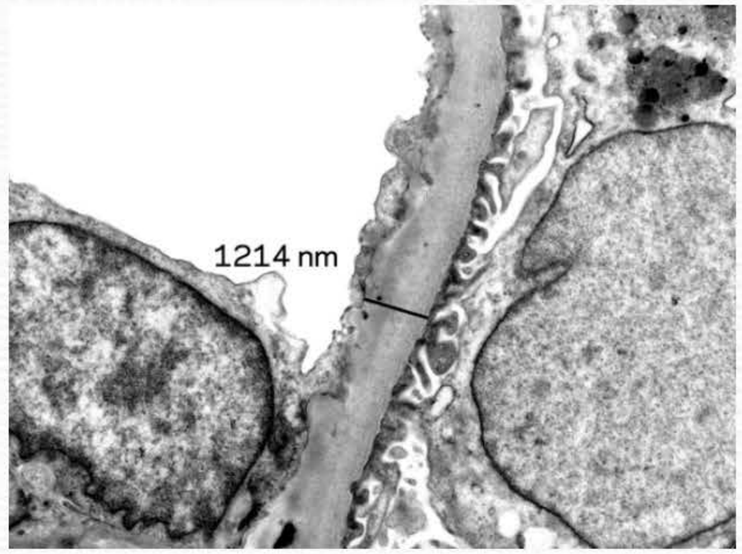


Fig 2-3 Thick GBMs 1214 nm (label), Electron photomicrograph.

The GBM width is highly correlated with albuminuria. According to Mauer, GBM thickness is "... a closer surrogate to the pathogenesis of albuminuria" than other glomerular findings. Interestingly, in experimental animals, the thickening of the GBMs may still be present in spite of a marked decrease in proteinuria following treatment with islet cell transplant. Lai et al has suggested that when one encounters a renal biopsy showing a moderate to severe increase in the GBM width, one should always check to see if the patient has DM and DN. A mild increase in GBM width is not necessarily specific to DN (even in patients with proteinuria) and may be due to such things as vascular disease, hypertension, and aging. In a patient with DN it is usually difficult to discern how much of the thickening of the GBM is secondary to DM and how much to hypertension and vascular disease, since these processes are usually present in the patient with DM.

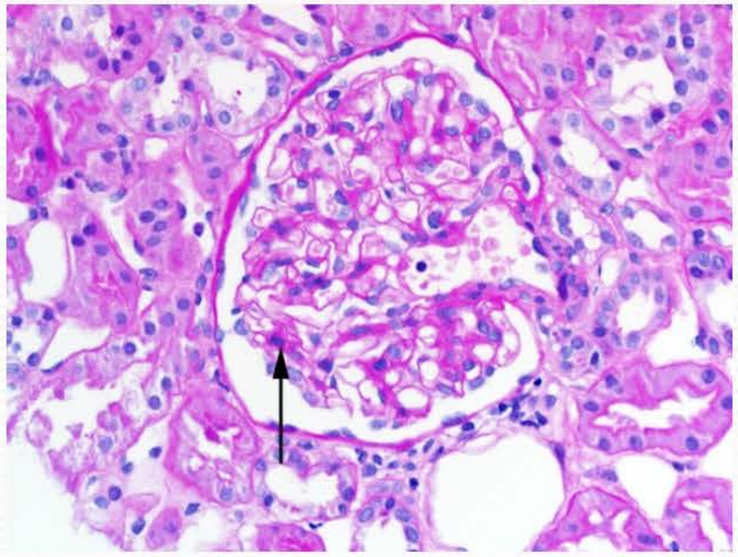


Fig 2-4 Normal mesangial area (arrow), PAS stain.

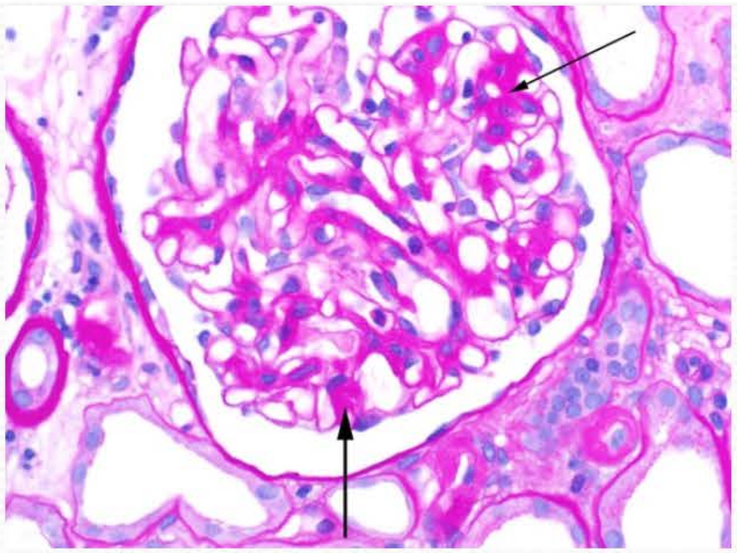


Fig 2-5 Mild mesangial expansion (arrow), PAS stain.

Diffuse Diabetic Glomerulosclerosis

Though the earliest morphologic change in DN is GBM thickening, it is only recognizable by ultrastructural examination. The first change noted by light microscopy in diabetic nephropathy is diffuse glomerulosclerosis (Fig 2-4–Fig 2-6). This is best demonstrated using the PAS reaction and is manifested by widening of the mesangial regions secondary to increased mesangial matrix. This varies from mild and segmental to global and diffuse. These changes are seen throughout the cortex with no predisposition to either juxtamedullary or subcapsular glomeruli.

The term “sclerosis” in the kidney is somewhat analogous to the term “scarring” in other organs and is the result of imperfect resolution of injury/ disease. In the glomerulus however, it is collagen type IV that is found in sclerotic areas, rather than the interstitial collagens types 1 and 3 typical of scarring elsewhere throughout the body.

Determining mesangial hypercellularity is straightforward (counting cells in the mesangial regions, away from the vascular pole, using 2–3 micron sections as in the Oxford Classifications for IgA nephropathy). However defining increased mesangial matrix is more difficult. Tervaert et al, in their classification scheme for diabetic nephropathy, provide a clearly stated definition of mesangial expansion. Increased mesangial matrix is defined by matrix regions that are “increased” compared to comparable mesangial regions in “normal glomeruli” and those that have somewhat convex or slightly rounded contours. Still, accurate and reproducible determination of increased mesangial matrix remains a challenge.

Finally, mesangial hypercellularity does occur in the early phase of mesangial expansion. Over time, the cellularity decreases though matrix increase continues.

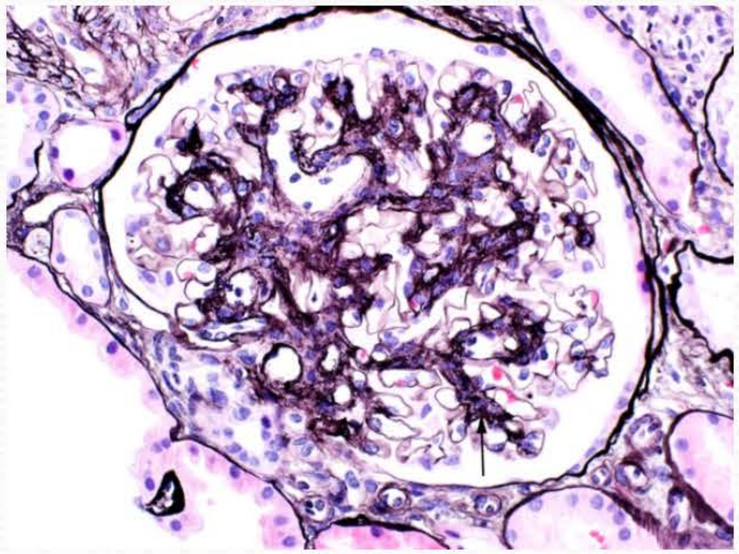


Fig 2-6 Mild mesangial expansion (arrow), Silver stain.

Figure 2-1 Normal GBM 370 nm (label), Electron photomicrograph.

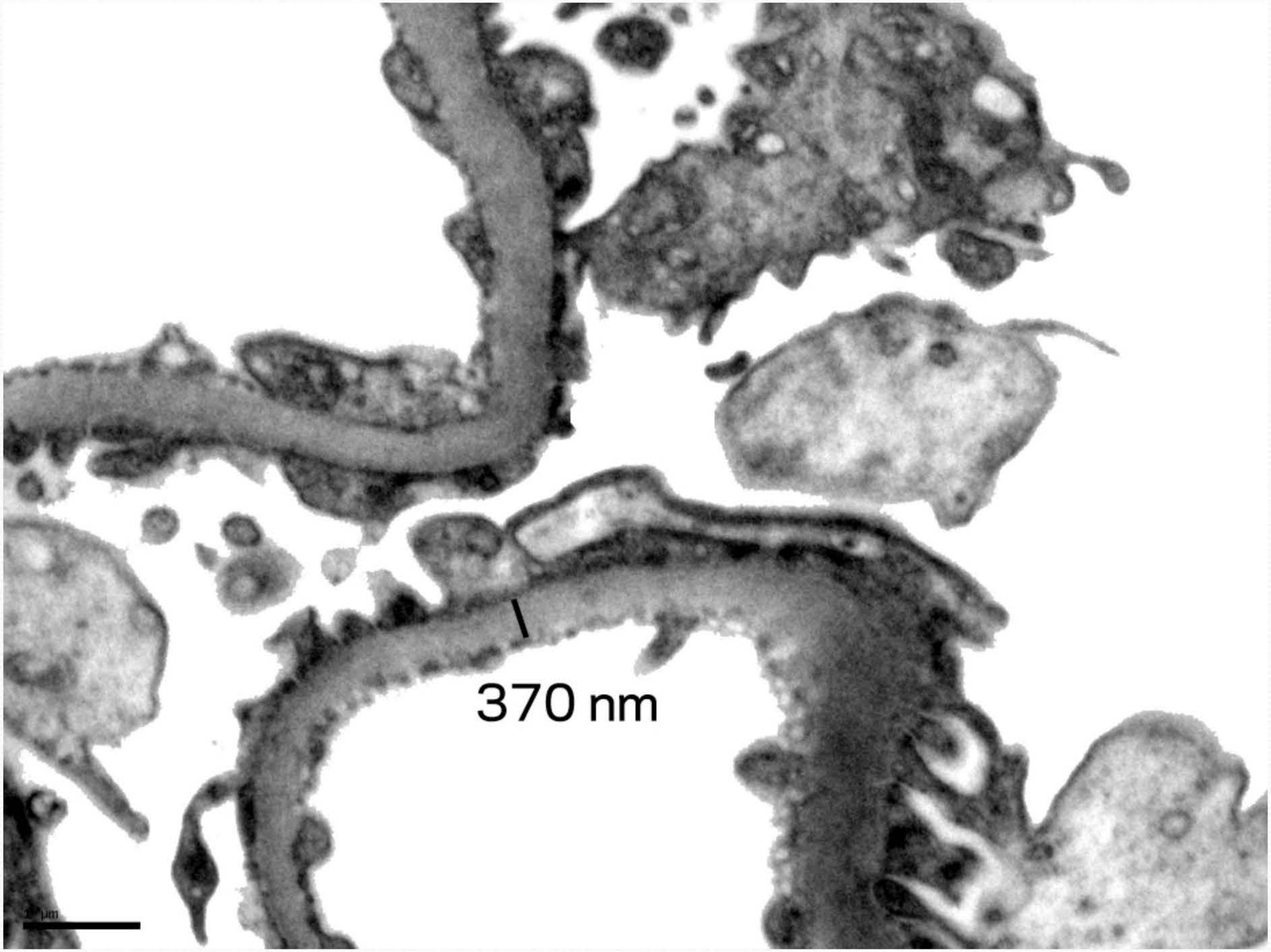


Figure 2-2 Thick GBMs 936 nm (label), Electron photomicrograph.

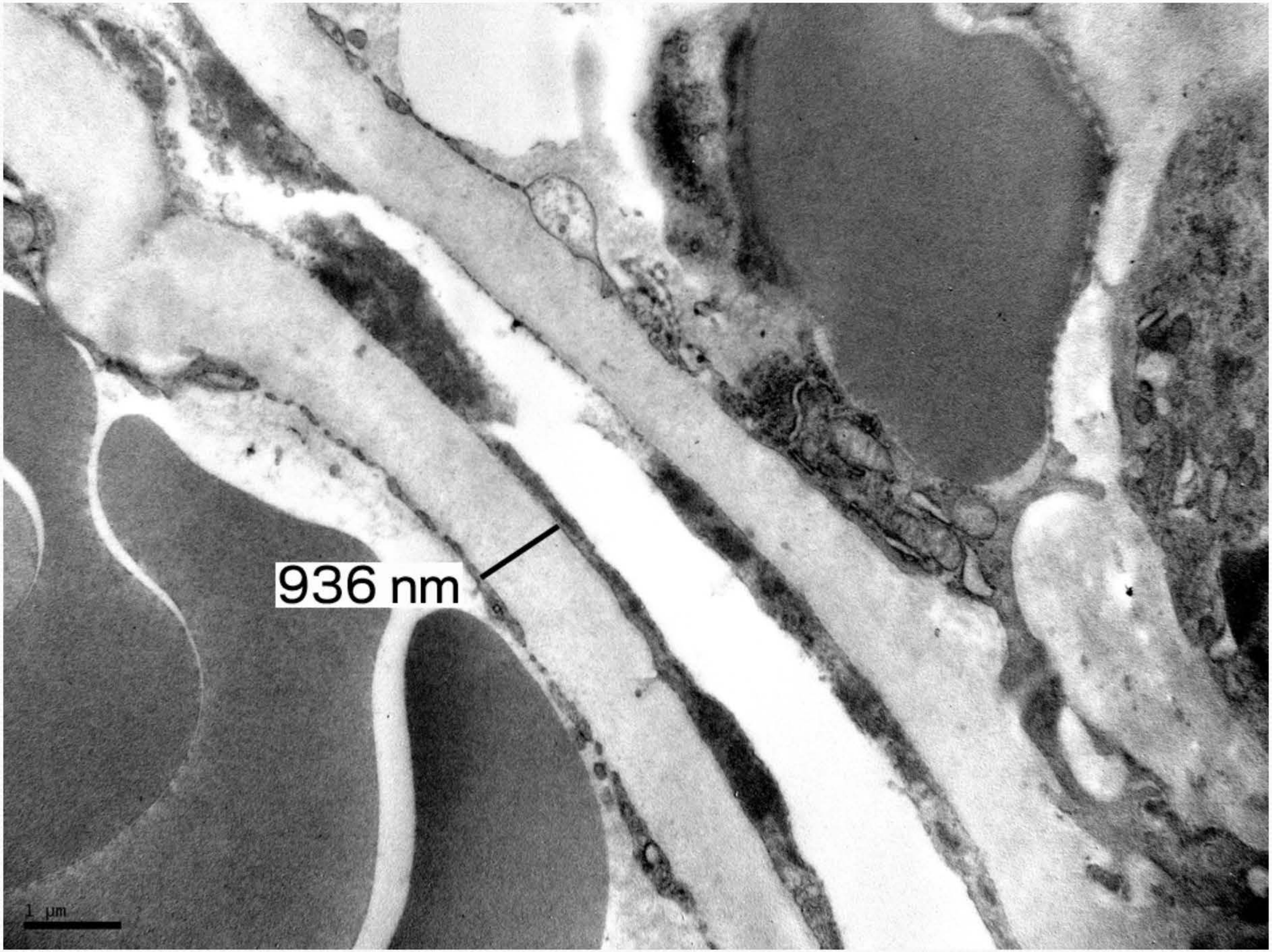


Figure 2-3 Thick GBMs 1214 nm (label), Electron photomicrograph.

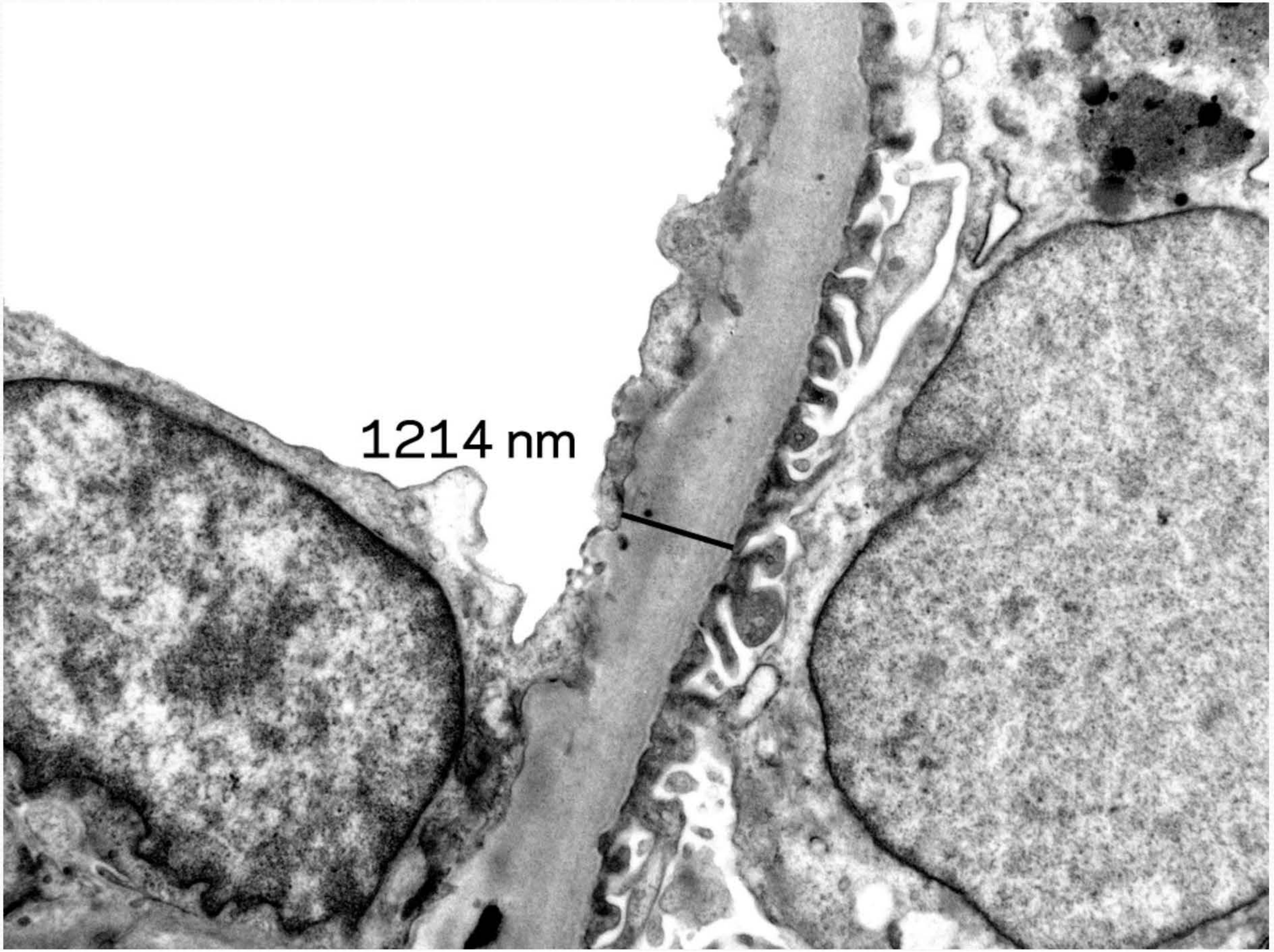


Figure 2-4 Normal mesangial area (arrow), PAS stain.

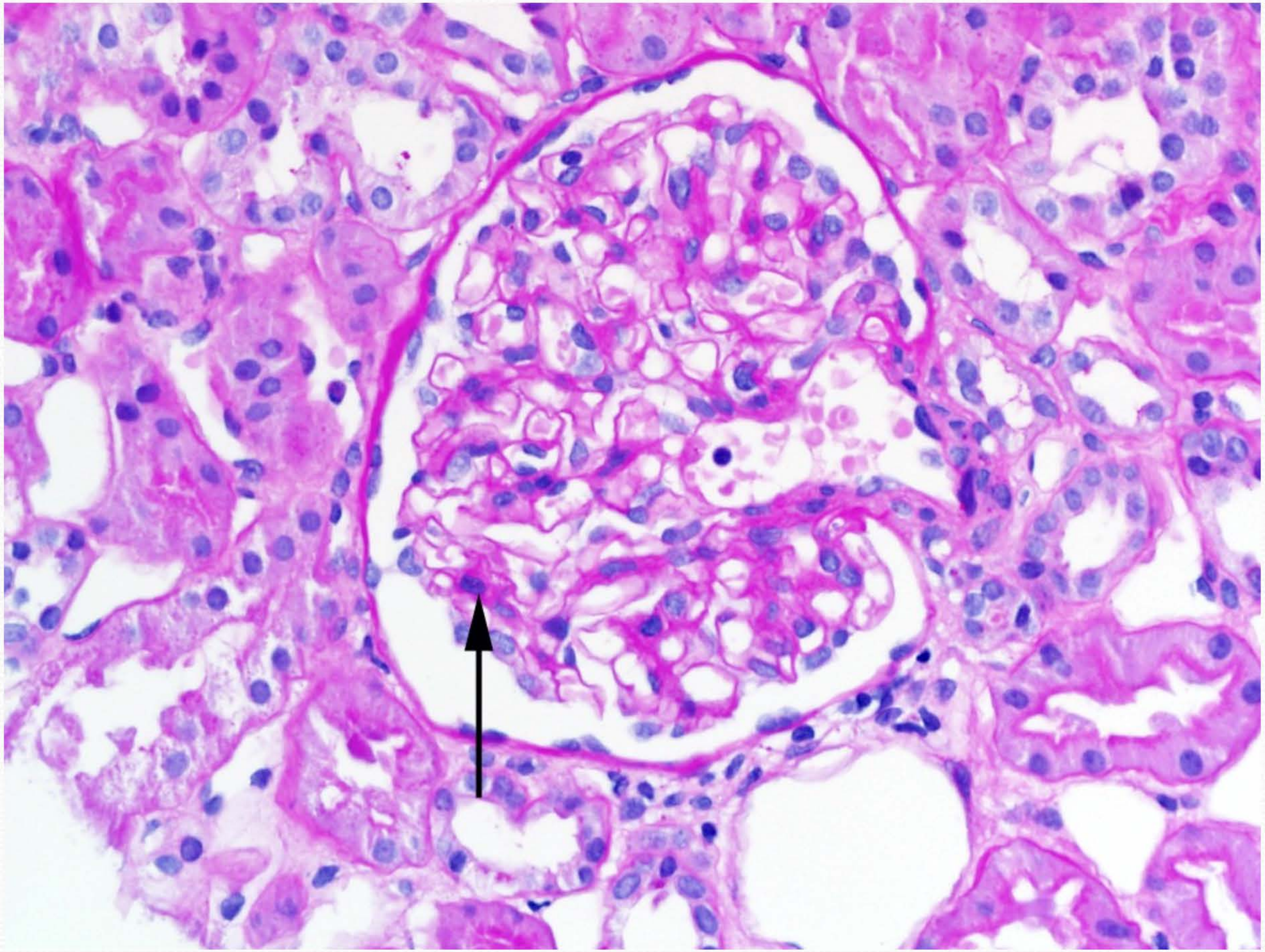


Figure 2-5 Mild mesangial expansion (arrow), PAS stain.

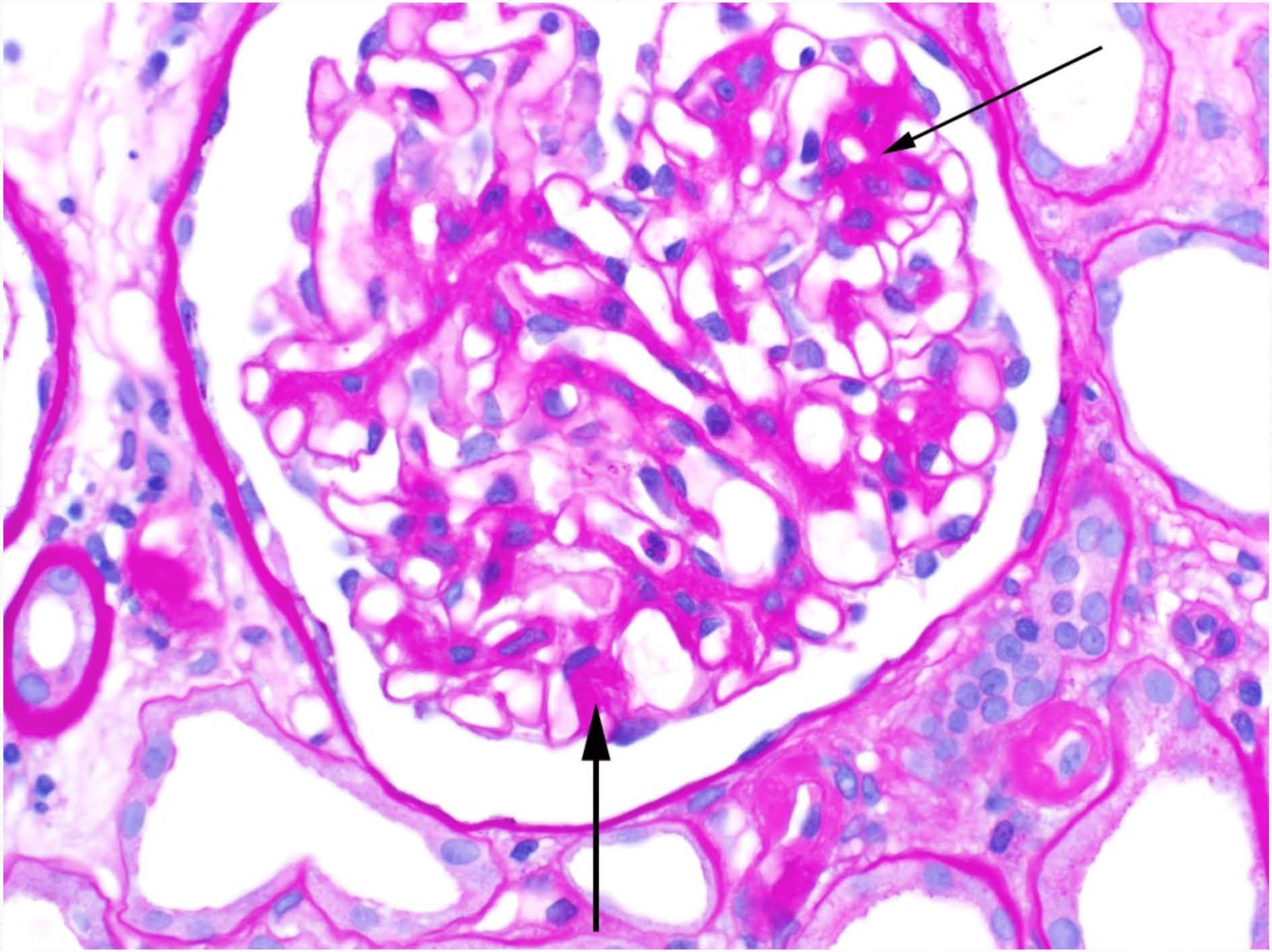


Figure 2-6 Mild mesangial expansion (arrow), Silver stain.

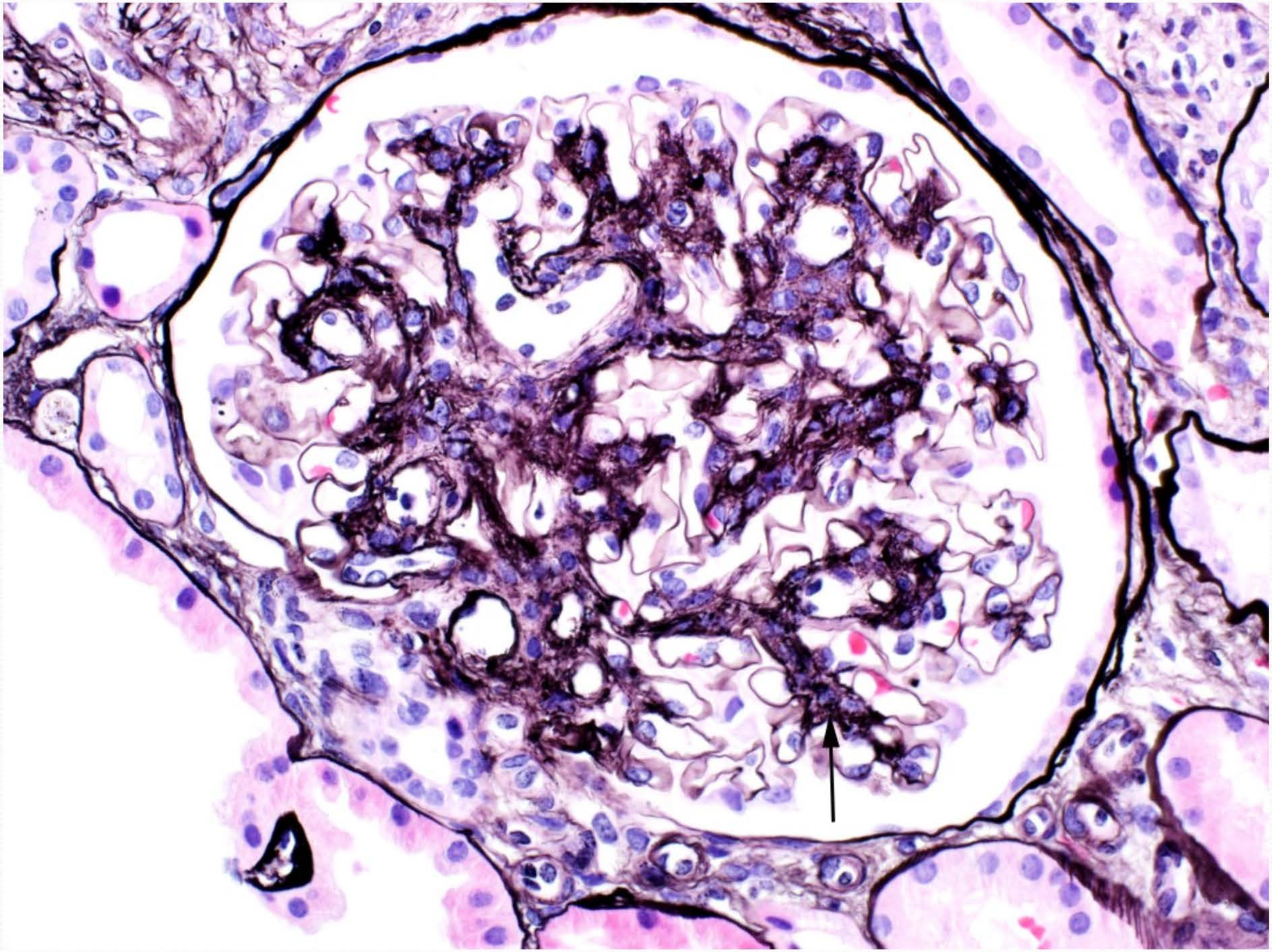


Figure 2-7 Thick GBMs 955 nm (label), Electron photomicrograph.

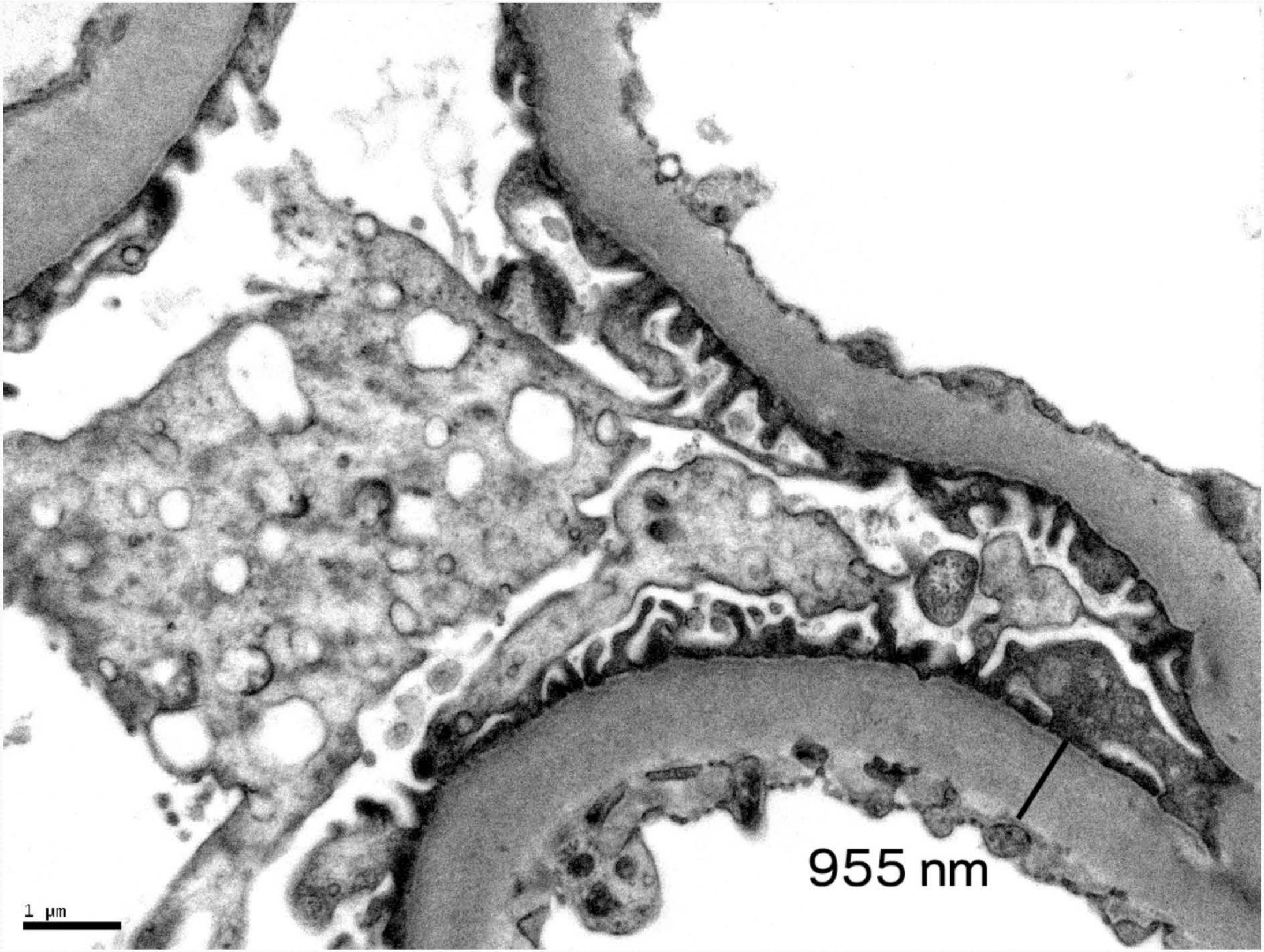


Figure 2-8 Mild mesangial expansion (arrow), PAS stain.

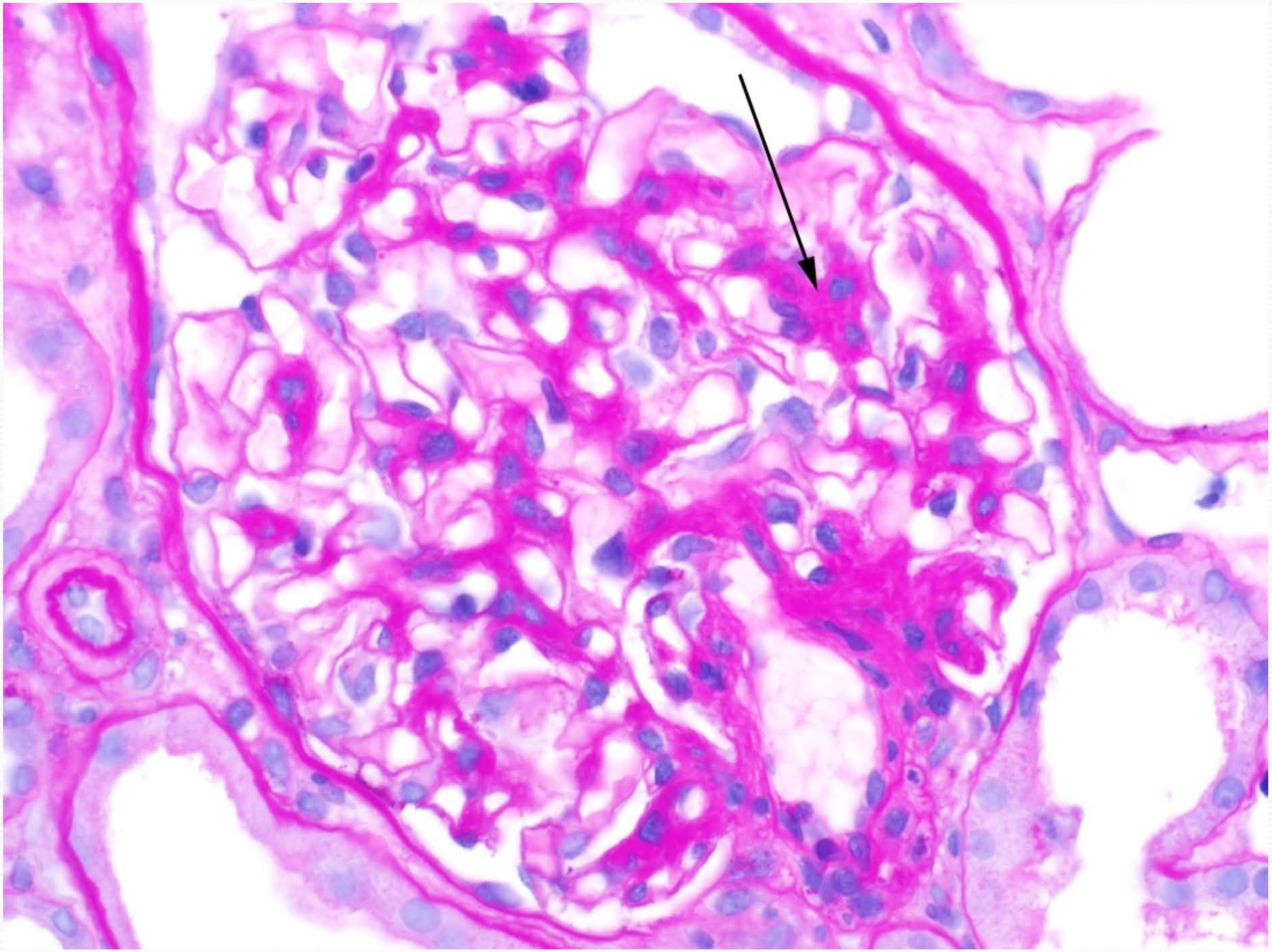


Figure 2-9 Mild mesangial expansion (arrow), PAS stain.

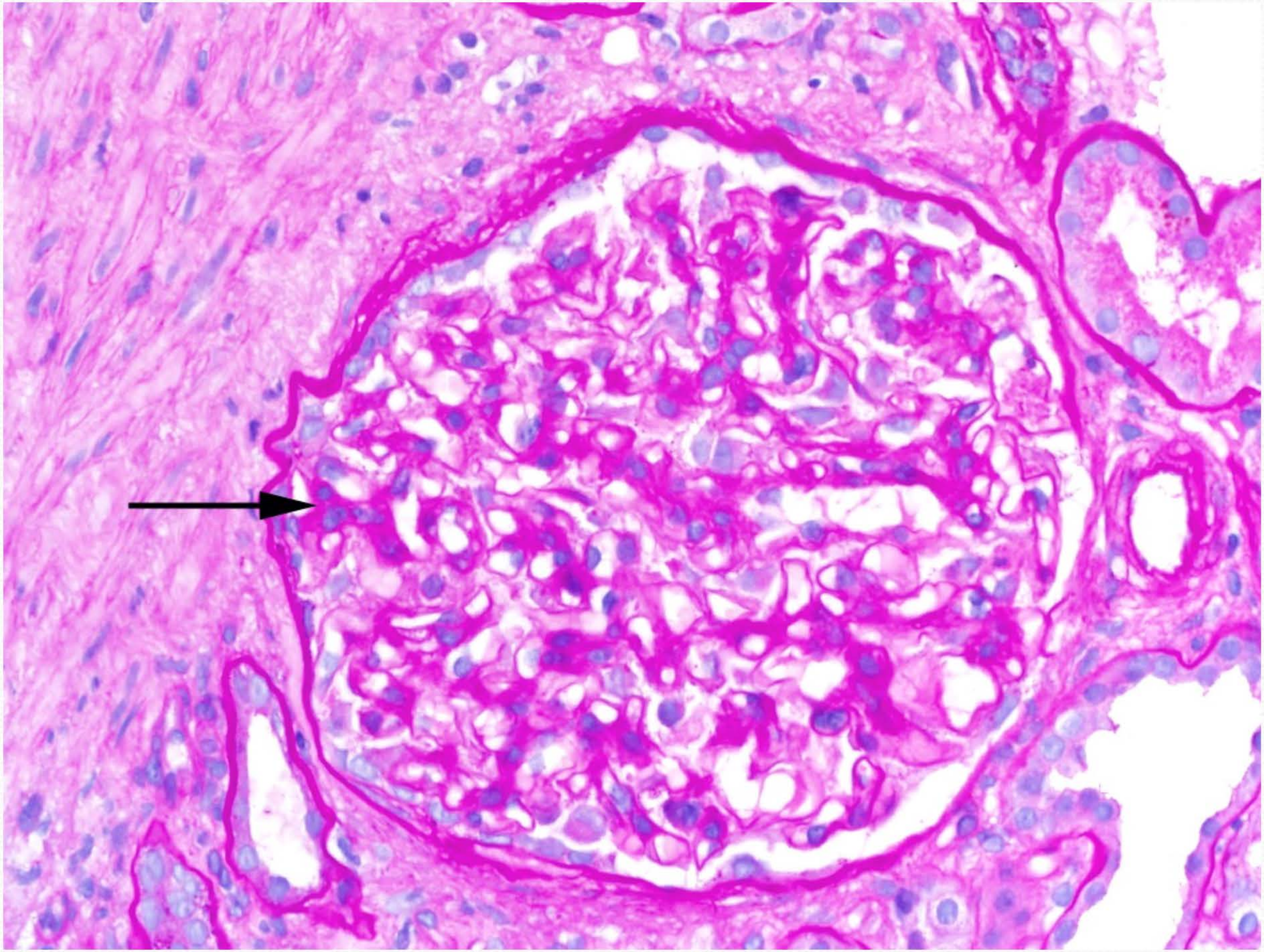


Figure 2-10 Mild mesangial expansion (arrow), Silver stain.

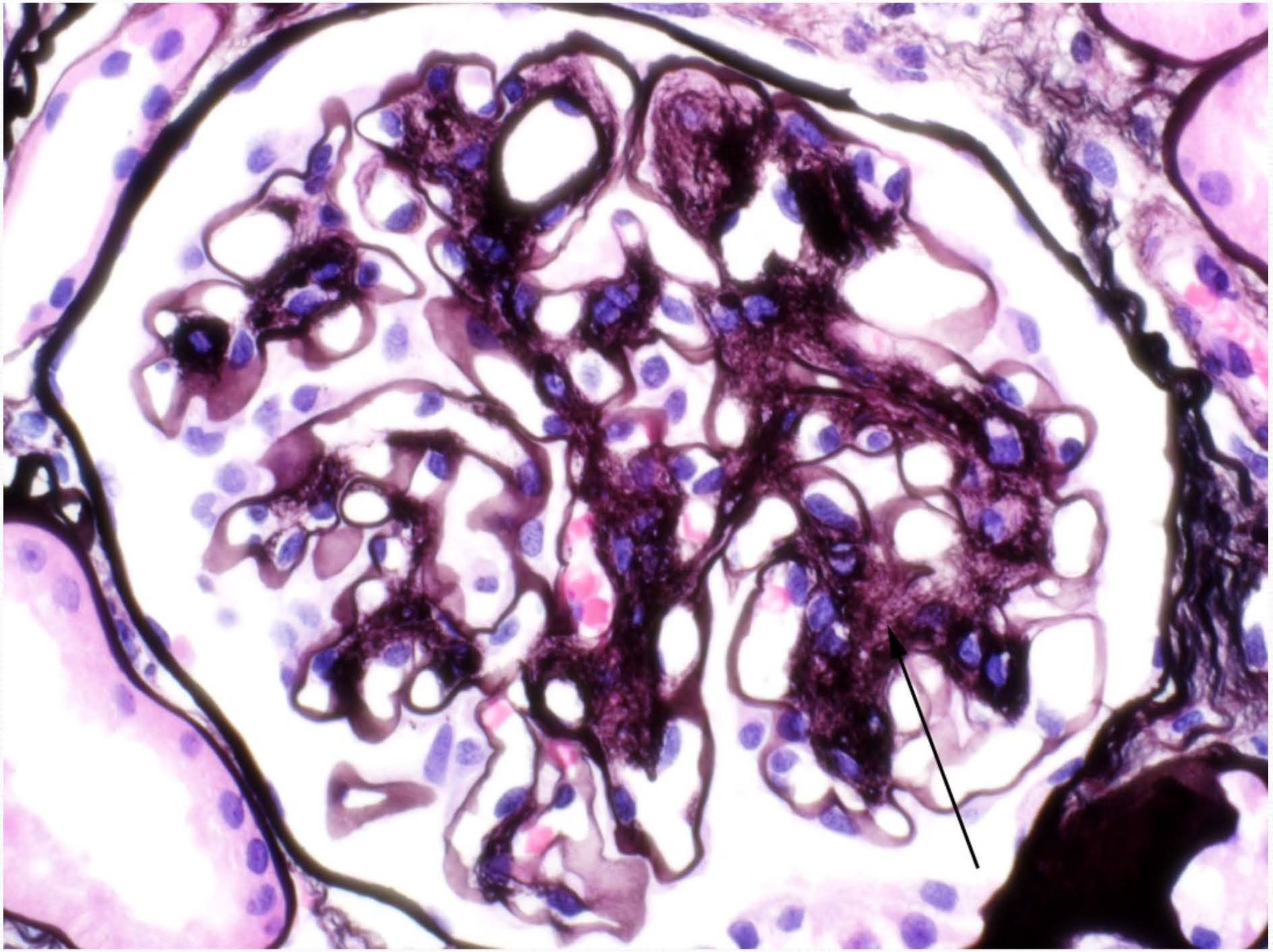


Figure 2-11 Mild mesangial expansion (arrow), H&E stain.

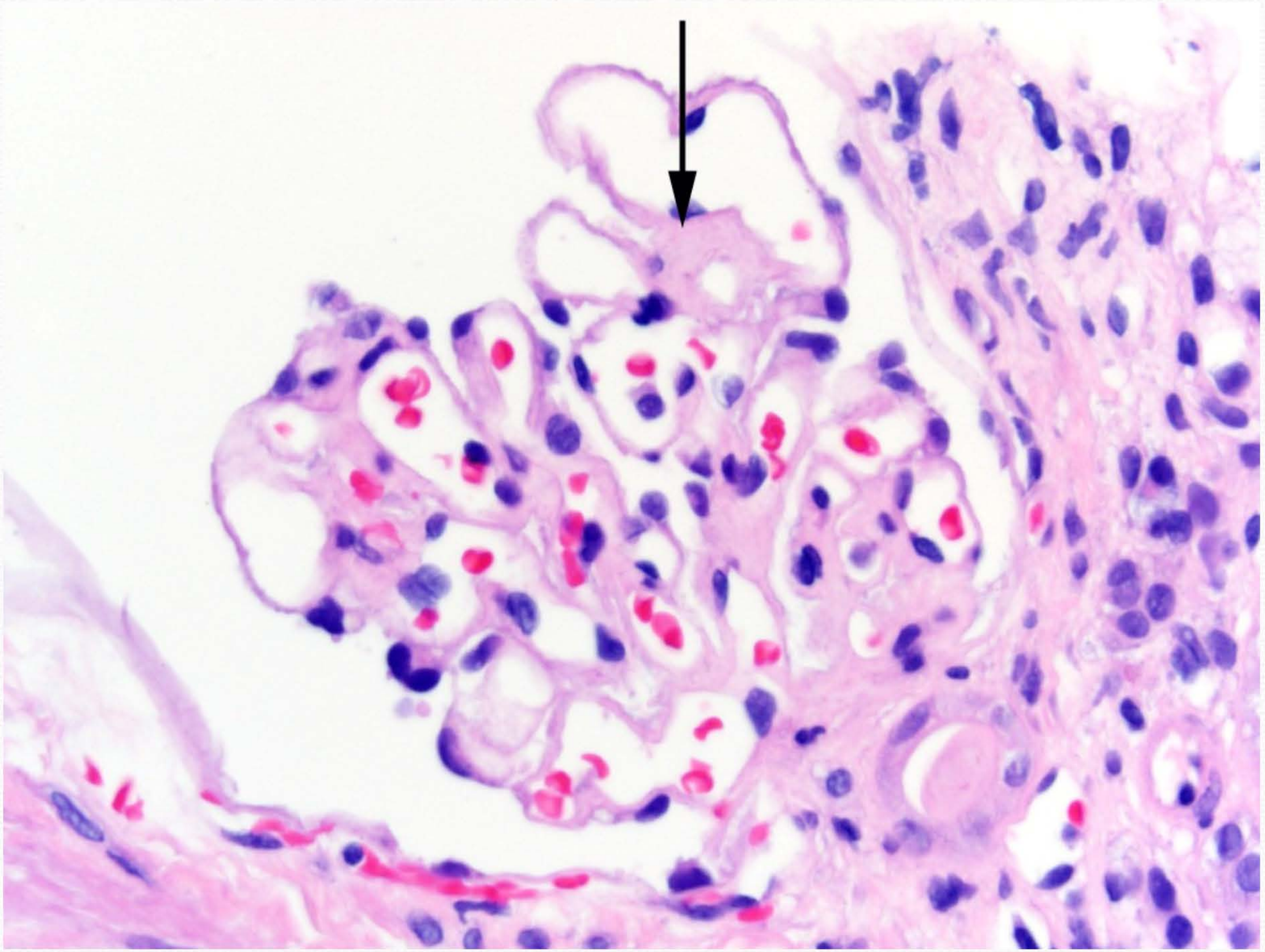
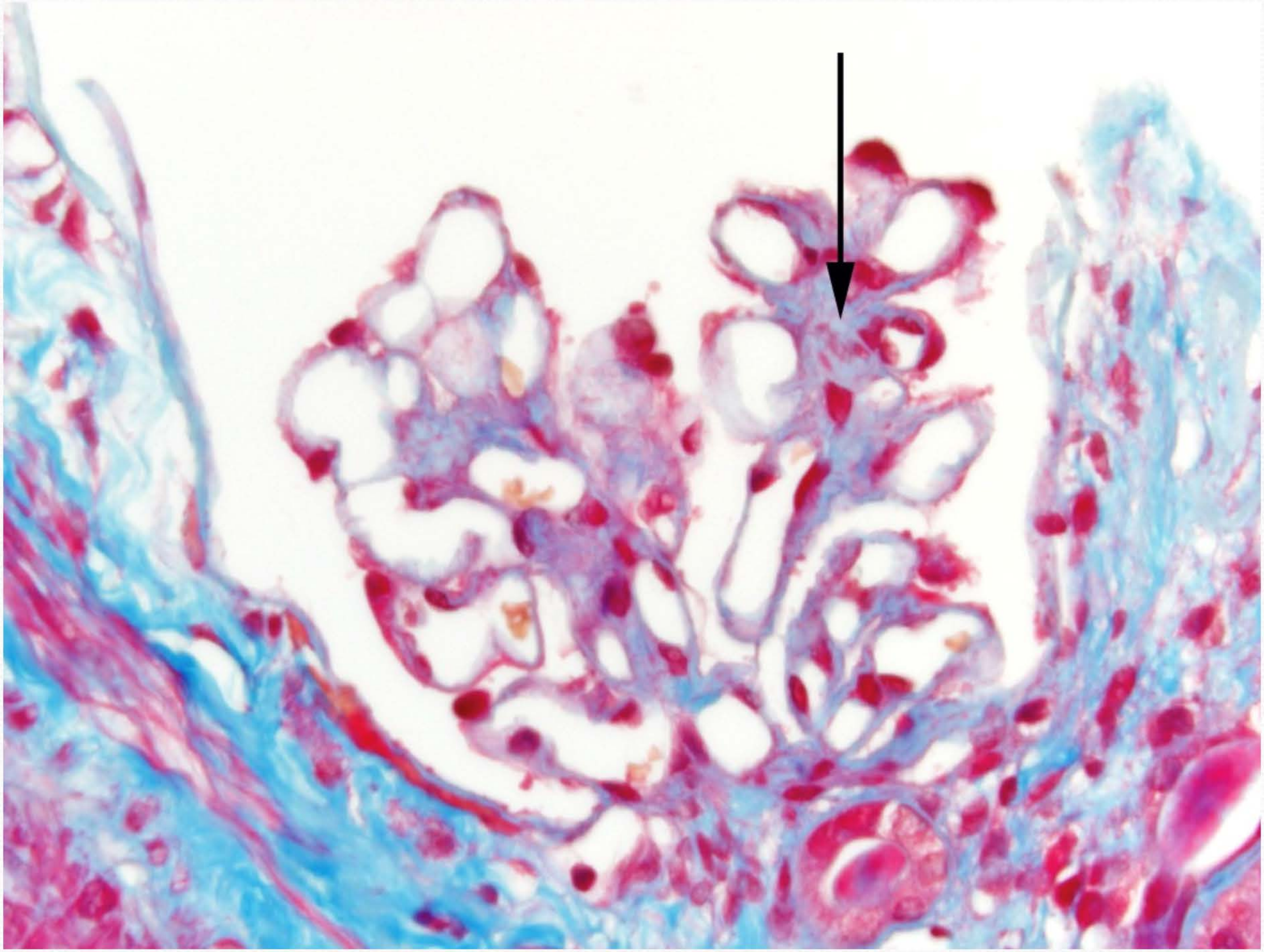
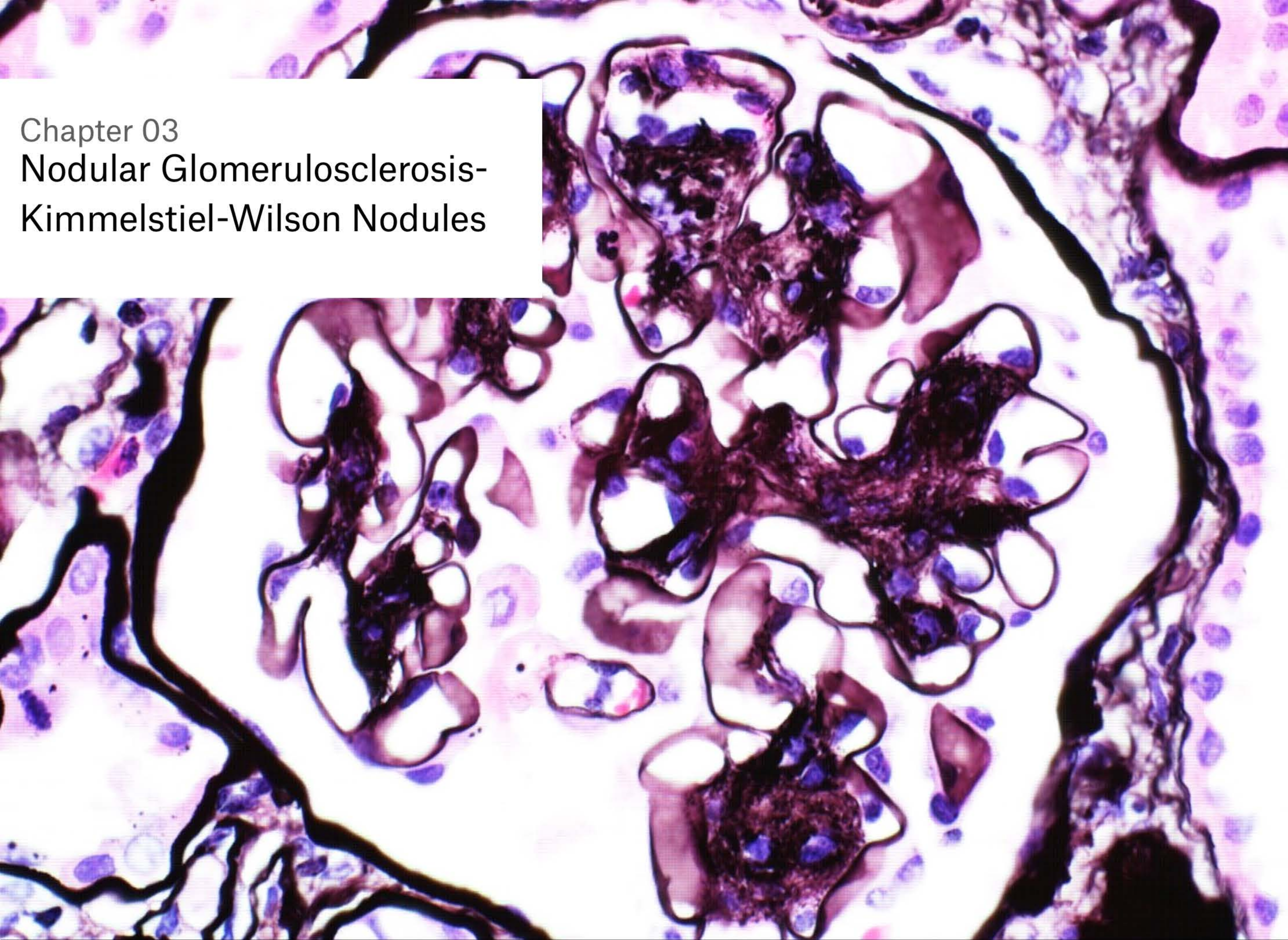


Figure 2-12 Mild mesangial expansion (arrow) same glomerulus as Fig 2-11, Trichrome stain.



Chapter 03

Nodular Glomerulosclerosis-Kimmelstiel-Wilson Nodules



Nodular Glomerulosclerosis-Kimmelstiel-Wilson Nodules

In 1936 Kimmelstiel and Wilson described the autopsy findings of 8 patients (7 known to have diabetes mellitus, probably adult onset), which was arguably the first clear morphologic description of diabetic nephropathy. As an aside, the 8th patient was not a known diabetic, and it remains unclear what the patient had for certain. To quote Kimmelstiel and Wilson (KW) from this seminal article:

"Cases are described which show a striking hyaline thickening of the intercapillary connective tissue of the glomerulus. Evidence is presented that the change is degenerative in nature and suggests that arteriosclerosis and diabetes may play a part in its causation. The lesion is therefore termed intercapillary glomerulosclerosis. The characteristic clinical features are a previous history of diabetes, widespread oedema of the nephrotic type and gross albuminuria. Hypertension is frequently found, and in many cases associated with renal decompensation."

In "nodular diabetic glomerulosclerosis," the KW nodules are usually, but not always, superimposed upon diffuse diabetic glomerulosclerosis (increased mesangial matrix/thickened GBMs) (Fig 3-1). These KW nodule formations have been thought to occur in more than 25% of renal biopsies in patients with advancing diabetic nephropathy, although the true prevalence of this important lesion is uncertain.

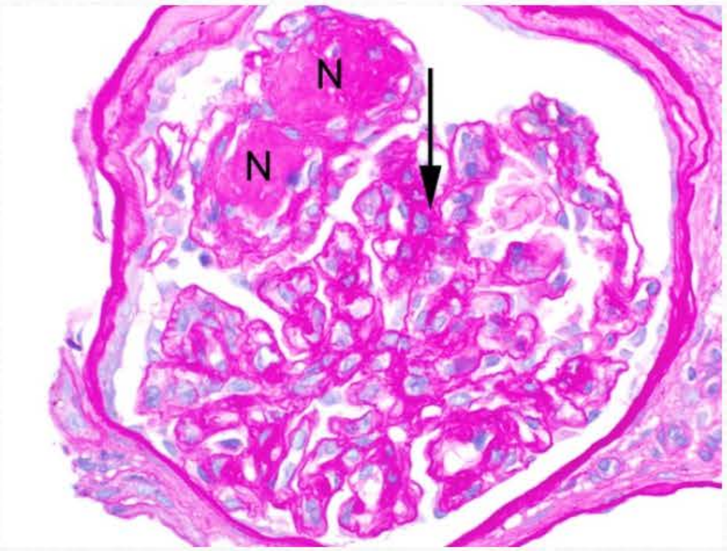


Fig 3-1 KW nodules (N) superimposed on mesangial matrix expansion (arrow), PAS stain.

The glomeruli most often contain only one or two KW nodules, but sometimes many are seen within the glomerulus producing a lobular glomerular formation (Fig 3-2). If multiple KW nodules are present within a glomerulus, they often tend to vary in size. Although they may vary considerably in shape, they usually are rounded, ovoid or spherical and composed of increased mesangial matrix material. Usually, there are only a few mesangial cells noted at the periphery of the nodule, although the cellularity may vary and a few KW nodules may be somewhat replete with cells (Fig 3-3). The size varies, and early ones may be difficult to identify with their slightly rounded mesangial regions just beginning to impinge in a convex nature into the adjacent glomerular capillary lumen (Fig 3-4), to huge KW nodules occupying most of the glomerulus. These mesangial nodules may appear multilayered or laminated/lamellated (like growth rings in a tree) with the Jones methenamine silver stain (Fig 3-5). These nodules composed of increased mesangial matrix materials have the same H&E eosinophilic staining characteristics of the normal or slightly expanded mesangium (as in "diffuse diabetic glomerulosclerosis"). Trichrome and PAS reactions in these KW nodules are the same as in the more normal mesangial regions just noted.

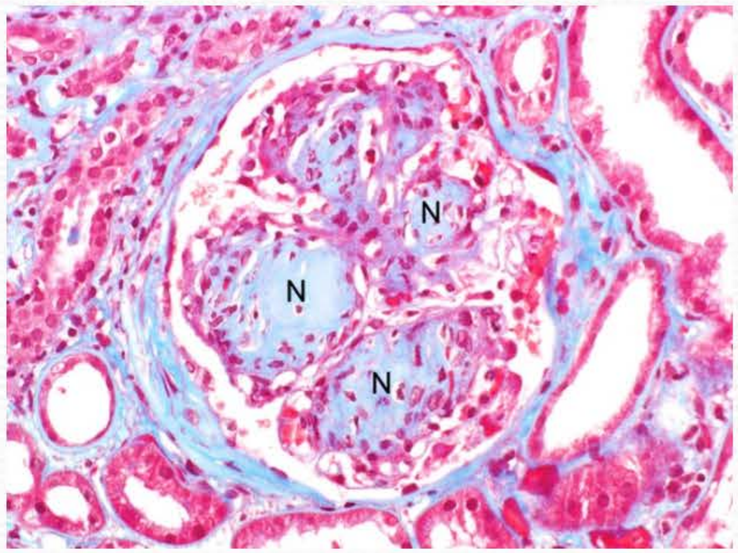


Fig 3-2 Many KW nodules (N), Trichrome stain.

Although these KW nodules are generally said to occur at time periods of 15–20 years after the clinical onset of type 1 diabetes, they may be encountered in a patient with a short documented history of DM. It should be noted that much of the natural history of DM and DN lesions can develop in complete clinical silence, and it is not unusual to find diffuse and nodular diabetic glomerulosclerosis in patients not known to have DM, or to have only been clinically aware of it for a few years.

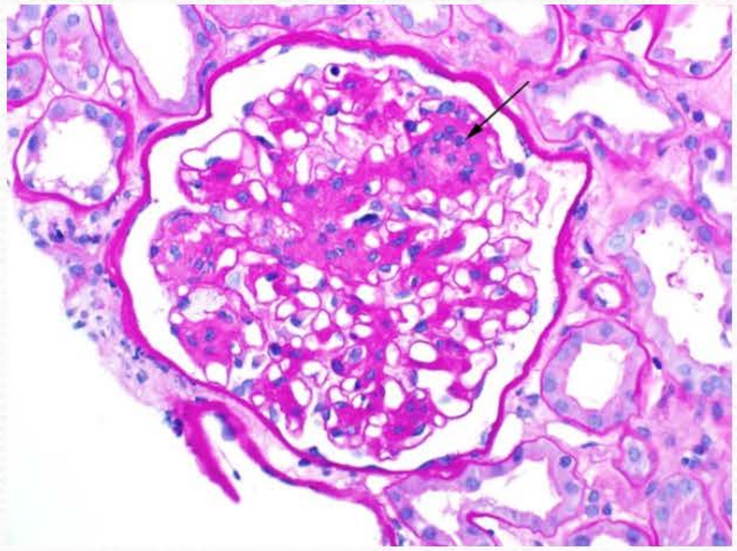


Fig 3-3 Some KW nodules may be hypercellular (arrow), PAS stain.

As noted by Mauer et al "the critical lesion in type I diabetes mellitus (TIDM) is mesangial expansion morphometrically termed mesangial fractional volume..."

They found a significant inverse correlation between the mesangial fractional volume and the GFR when the glomerular mesangial region expands and restricts/distorts the glomerular capillaries thereby diminishing the glomerular capillary filtration surface. Mesangial volume is also related to increased hyperalbuminuria and hypertension.

These KW nodules may persist in glomeruli showing virtually complete global glomerulosclerosis ("tombstones" according to Dr. Gloria Gallo), and should be searched for in advanced renal disease approaching end stage renal disease.

The etiology(ies) of KW nodule formation is/are obviously related to either increased mesangial matrix production and/or decreased mesangial matrix removal/destruction. Recent studies suggest that both mechanisms apply. Pancreas transplantation has shown the total disappearance of KW lesions at 10 years after transplantation. Thus they are potentially reversible under the right conditions (for now in the human, just pancreatic transplantation).

The role of mesangiolysis and glomerular microaneurysm formation in the production of these mesangial nodules will be covered in that section (see "Mesangiolysis and Microaneurysms").

Of importance, these nodular mesangial nodules are not pathognomonic for a diabetic nephropathy, and can be seen from patients with a number of other non-diabetic renal disease including amyloidosis, light chain deposition disease, membranoproliferative glomerular patterns, patients with a heavy cigarette smoking history, fibrillary glomerulopathy, and sometimes even patients in whom the underlying disease cannot be discerned, so-called pseudo-diabetic nodular glomerulosclerosis.

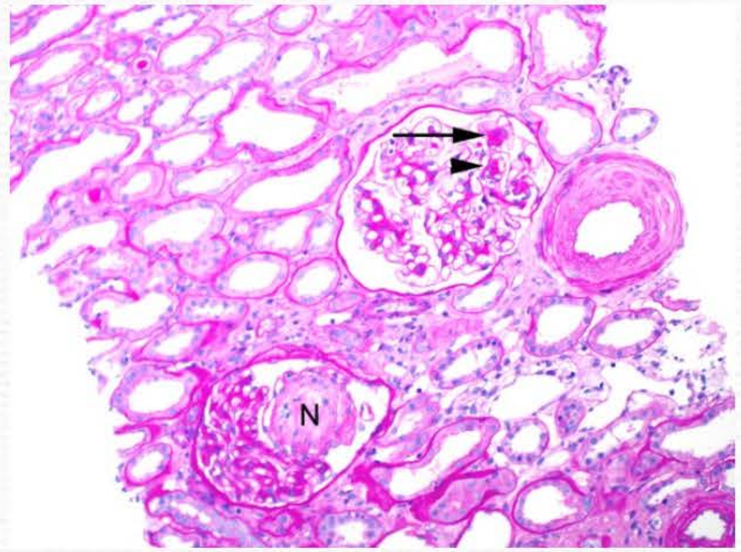


Fig 3-4 KW nodules with size variation, one huge nodule (N), very small KW nodules (arrow) and incipient KW nodule (arrowhead), PAS stain.

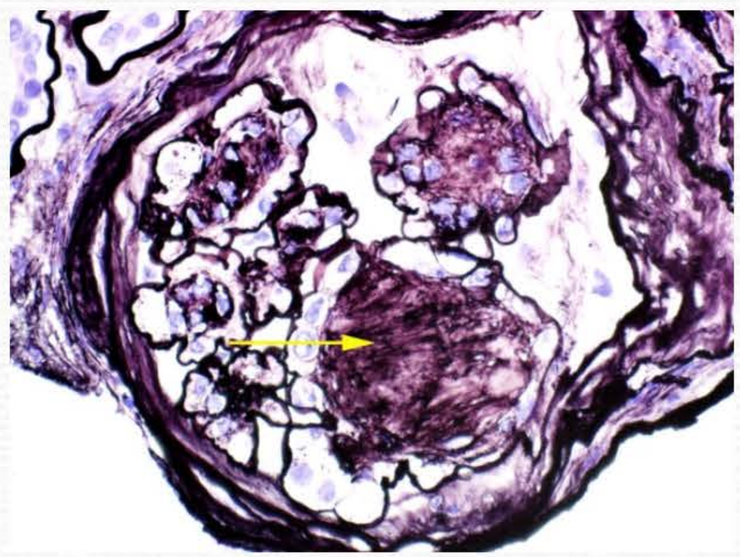


Fig 3-5 KW nodules show a laminated appearance (arrow), Silver stain.

Figure 3-1 KW nodules (N) superimposed on mesangial matrix expansion (arrow), PAS stain.

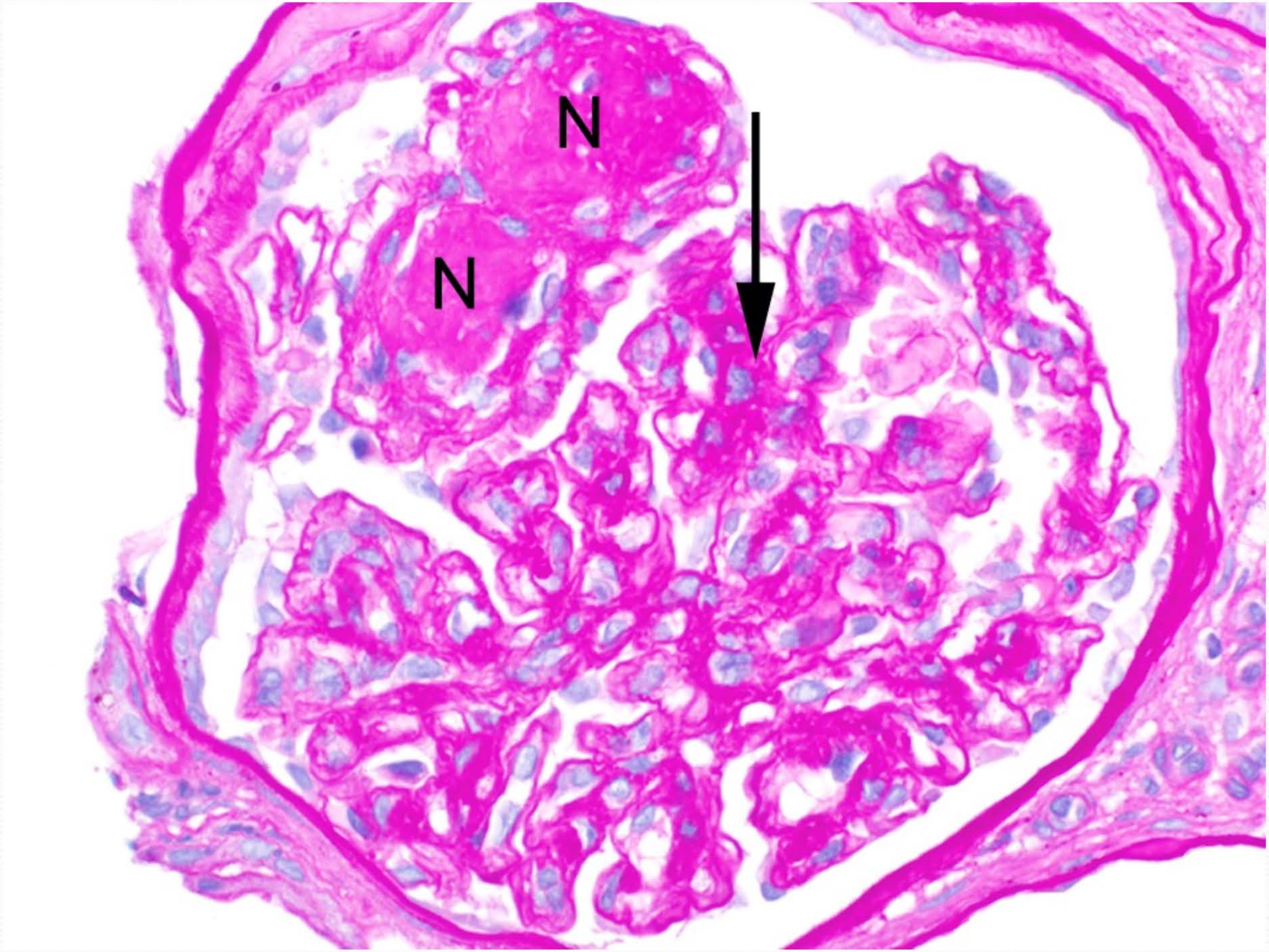


Figure 3-2 Many KW nodules (N), Trichrome stain.

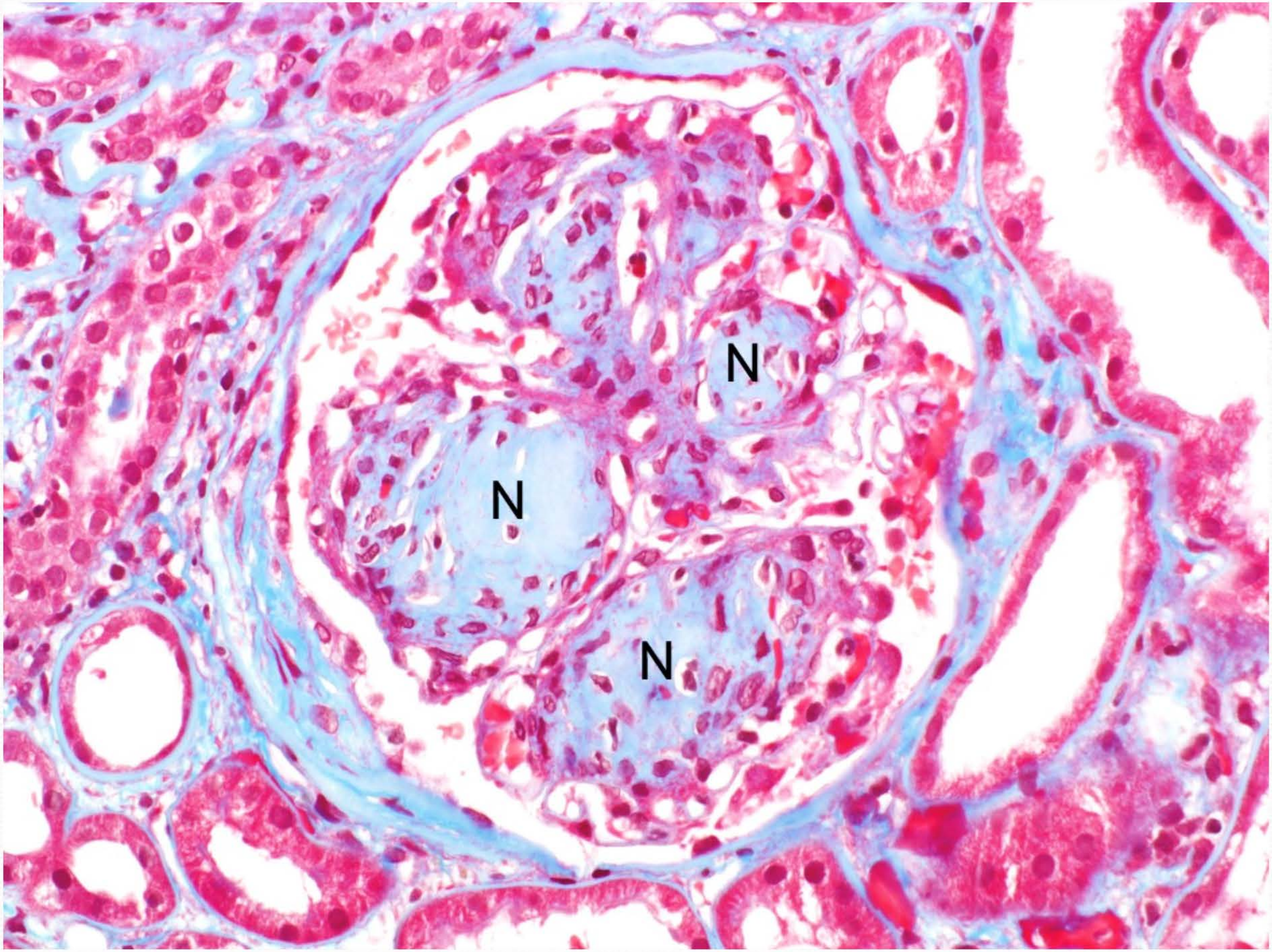


Figure 3-3 Some KW nodules may be hypercellular (arrow), PAS stain.

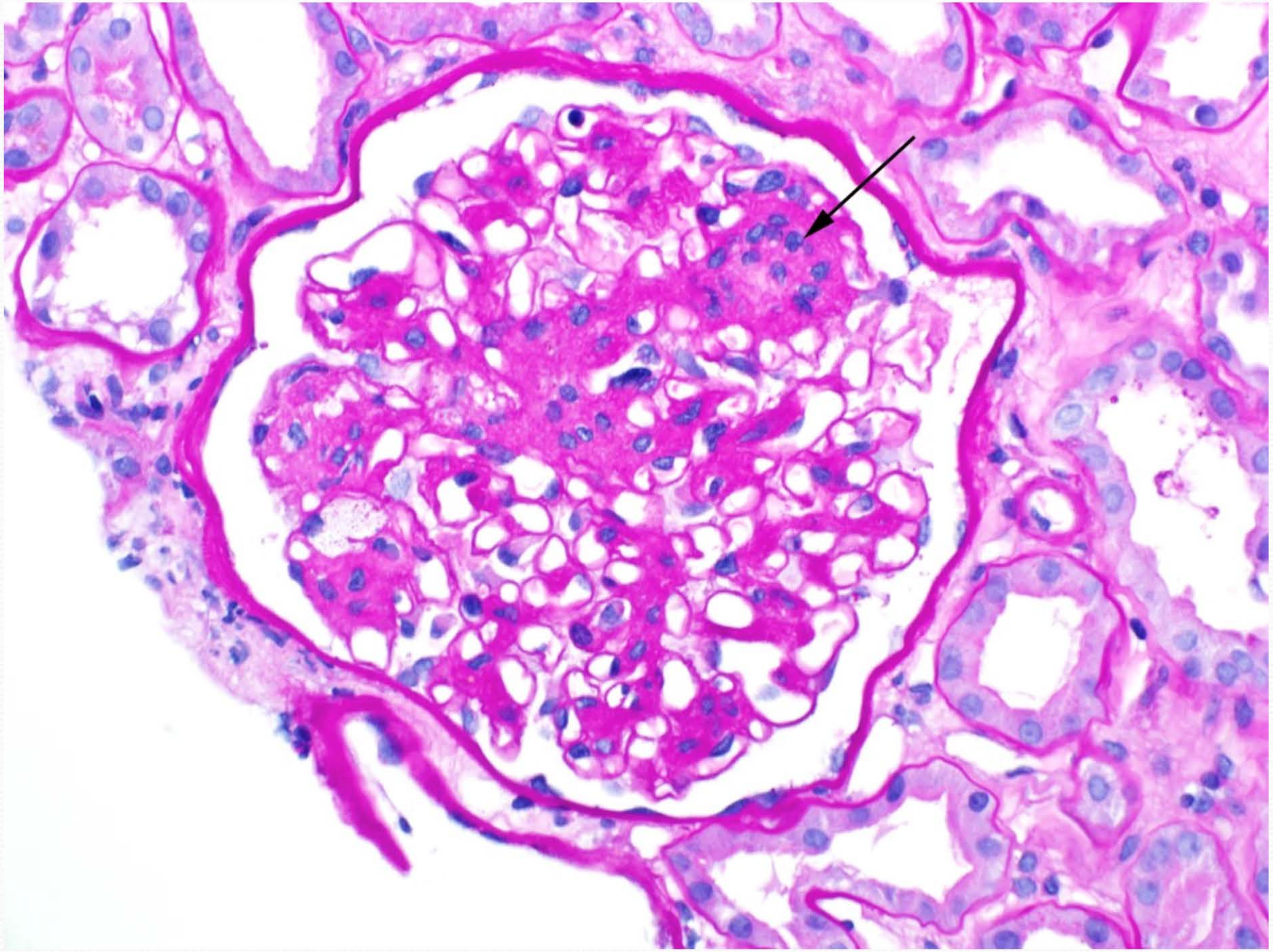


Figure 3-4 KW nodules with size variation, one huge nodule (N), very small KW nodules (arrow) and incipient KW nodule (arrowhead), PAS stain.

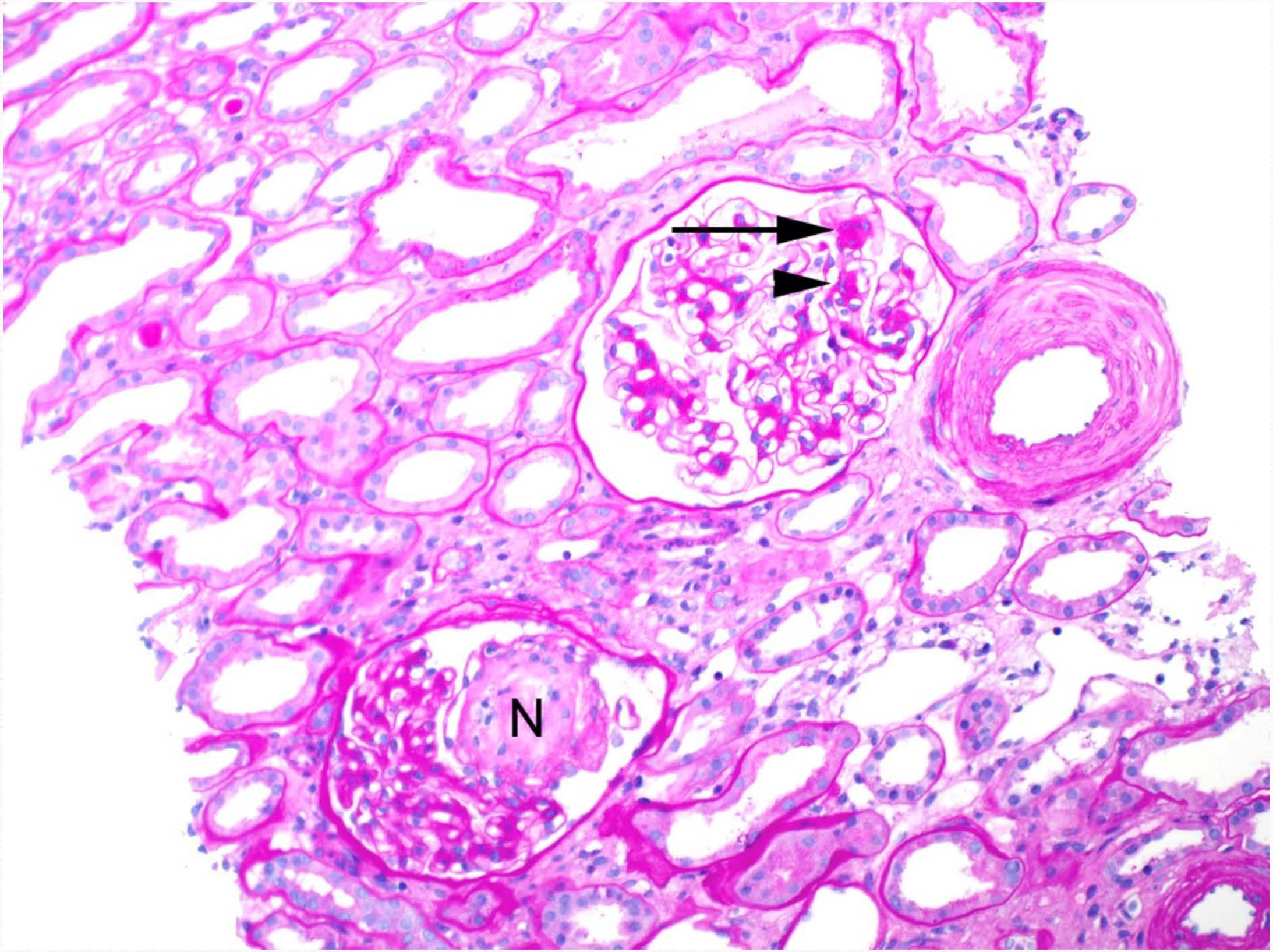


Figure 3-5 KW nodules show a laminated appearance (arrow), Silver stain.

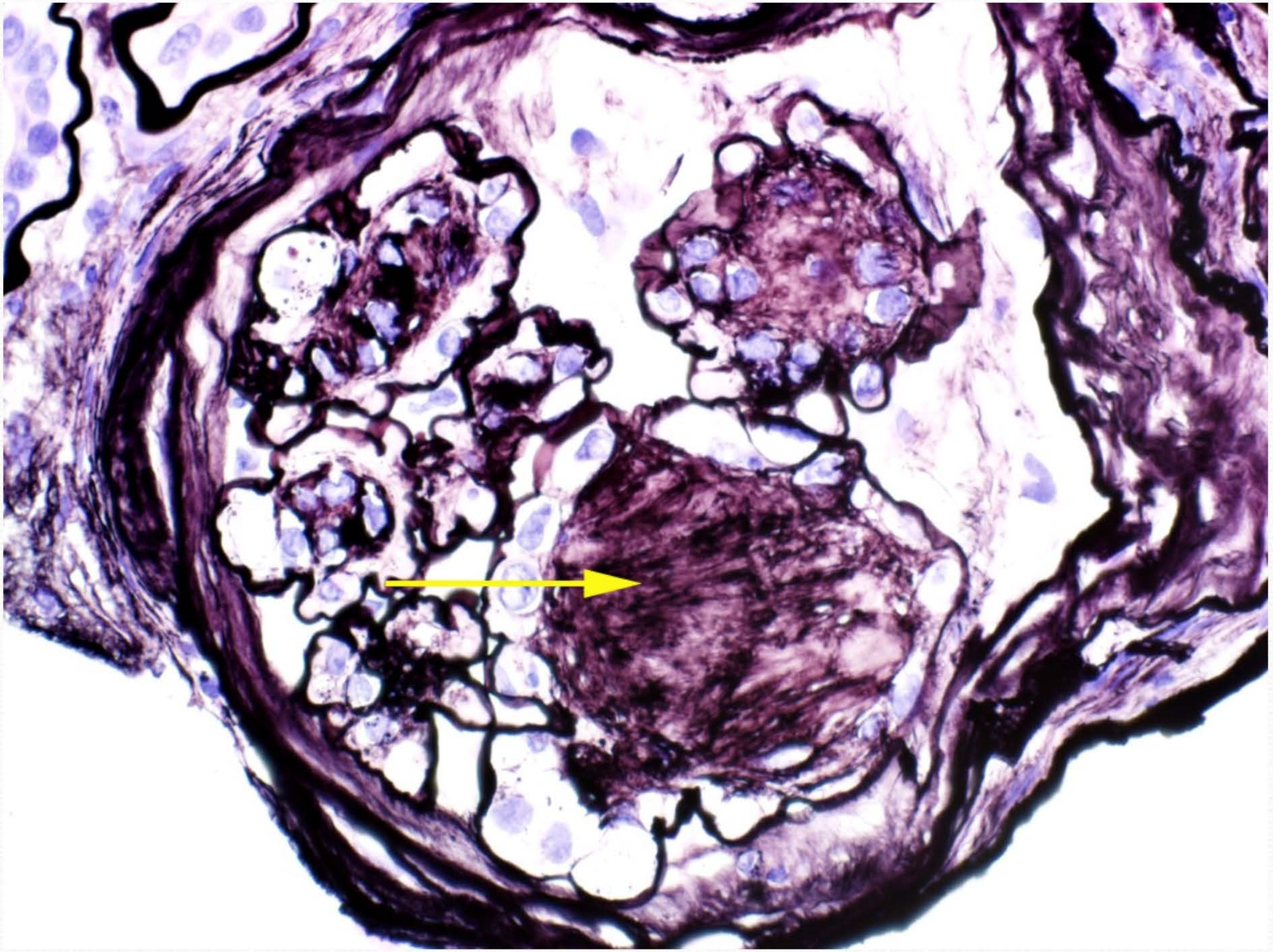


Figure 3-6 Small KW nodule with incipient KW nodule (arrow), PAS stain.

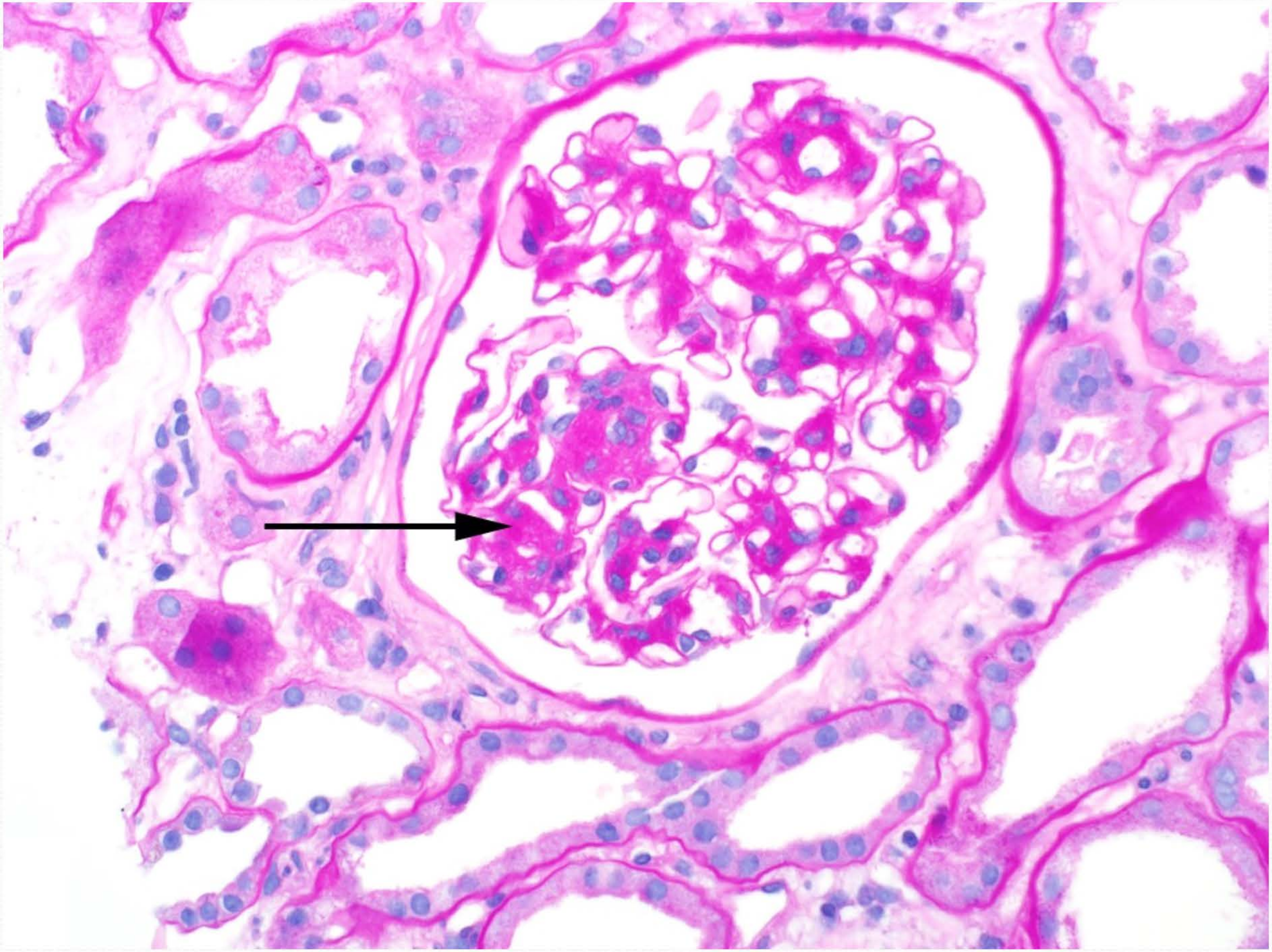


Figure 3-7 Large KW nodule (N), PAS stain.

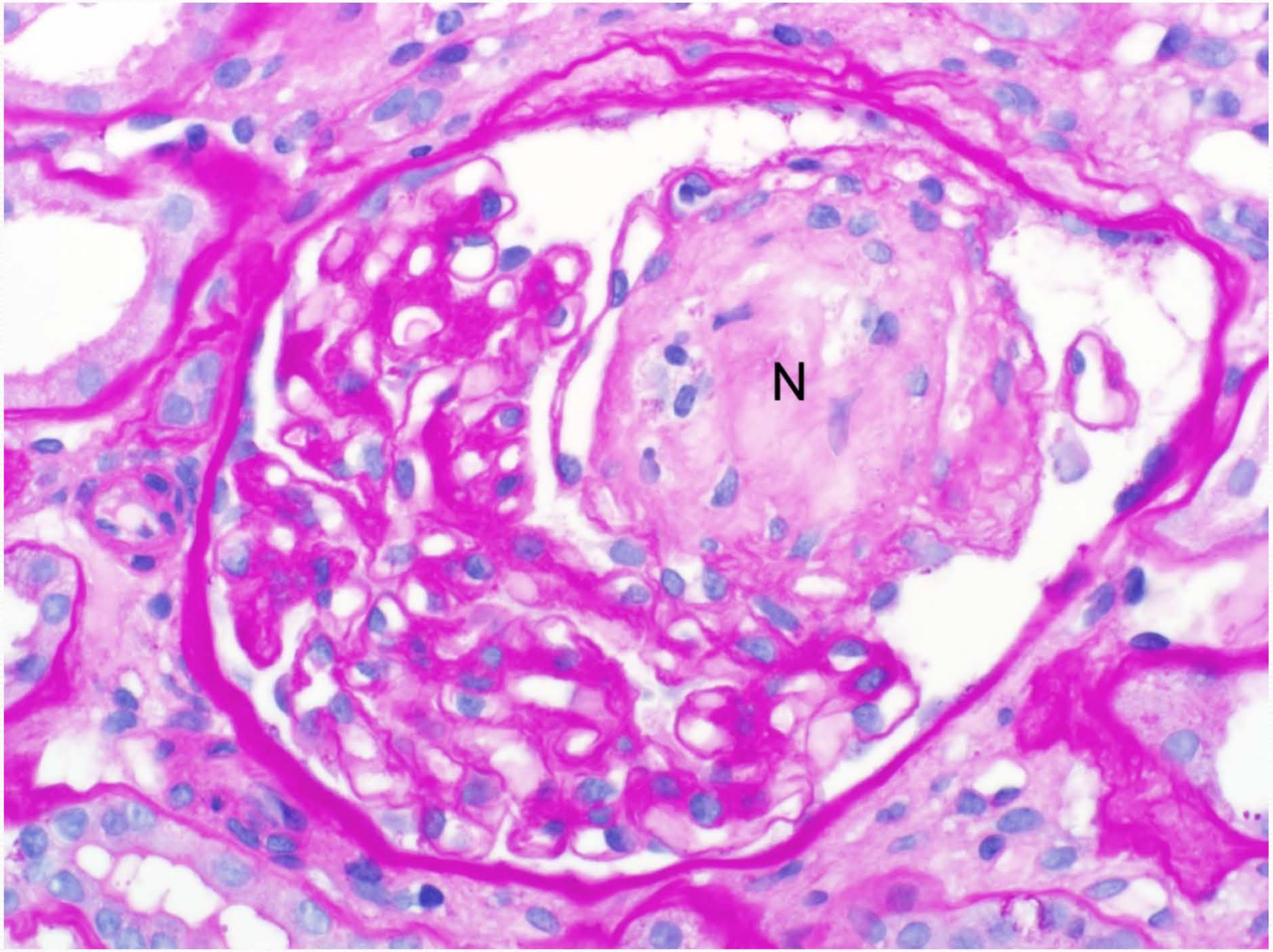


Figure 3-8 One KW nodule (arrow) superimposed on mesangial matrix expansion, PAS stain.

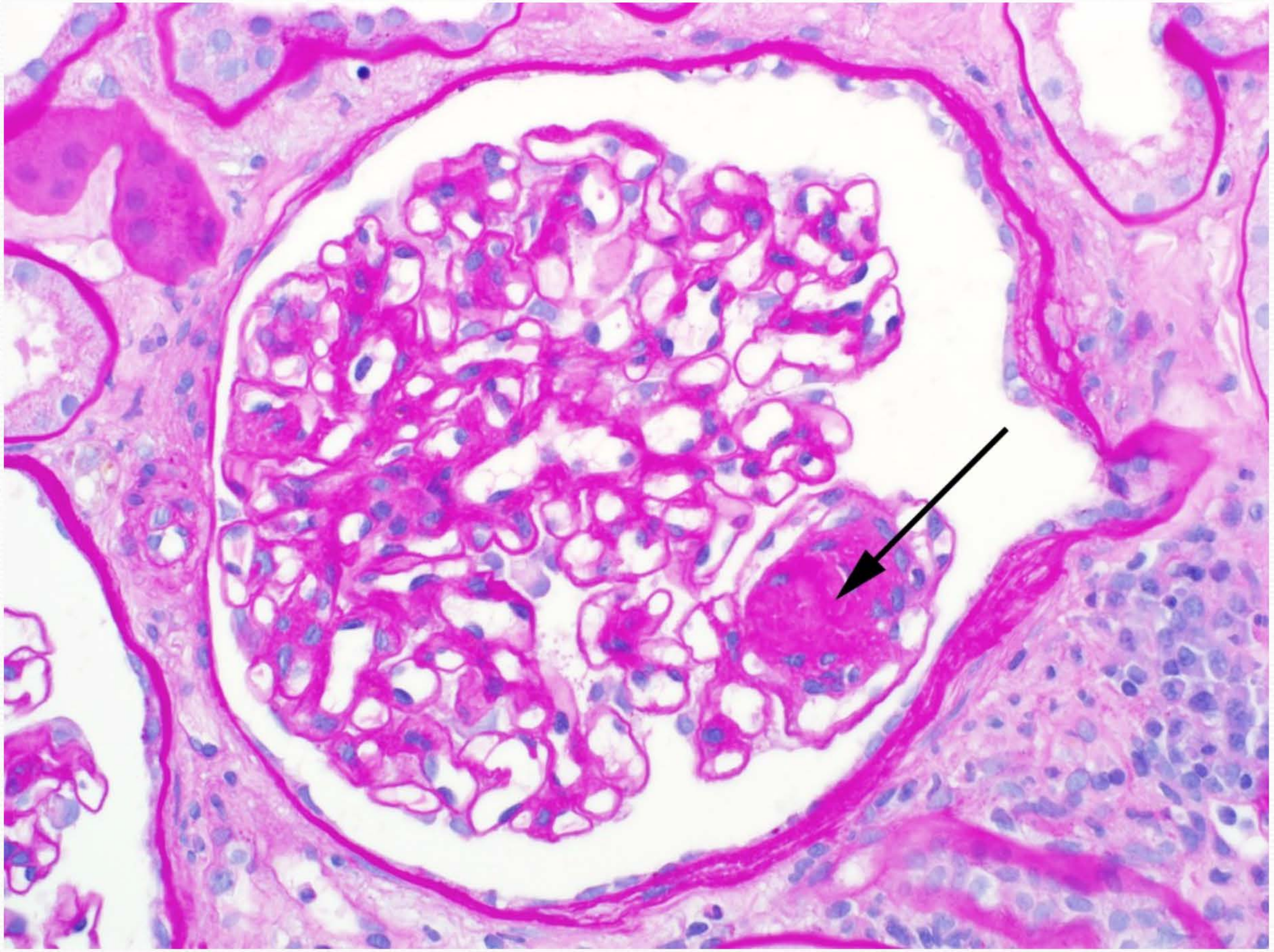


Figure 3-9 Multiple KW nodules (N) of varying size, PAS stain.

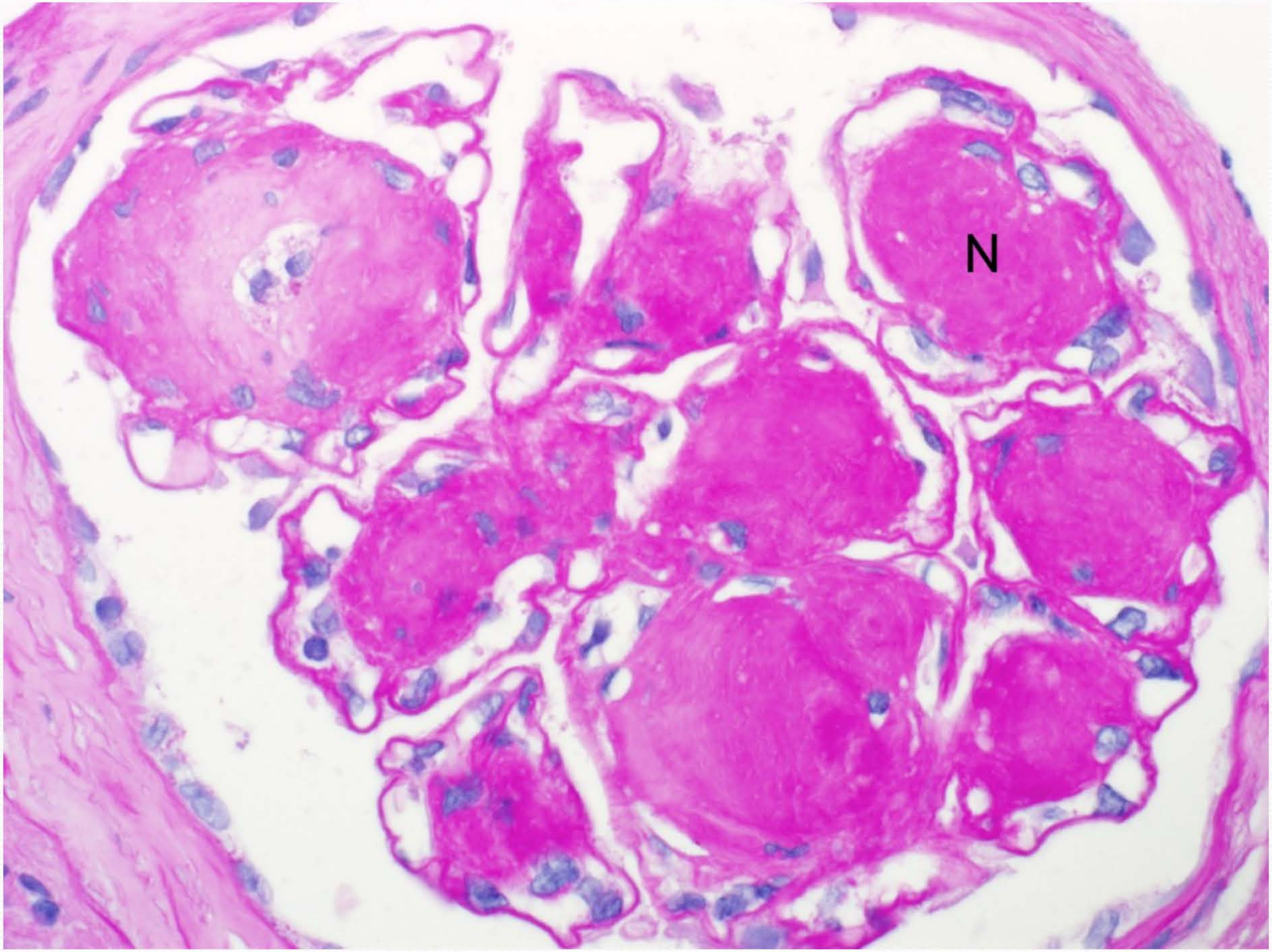
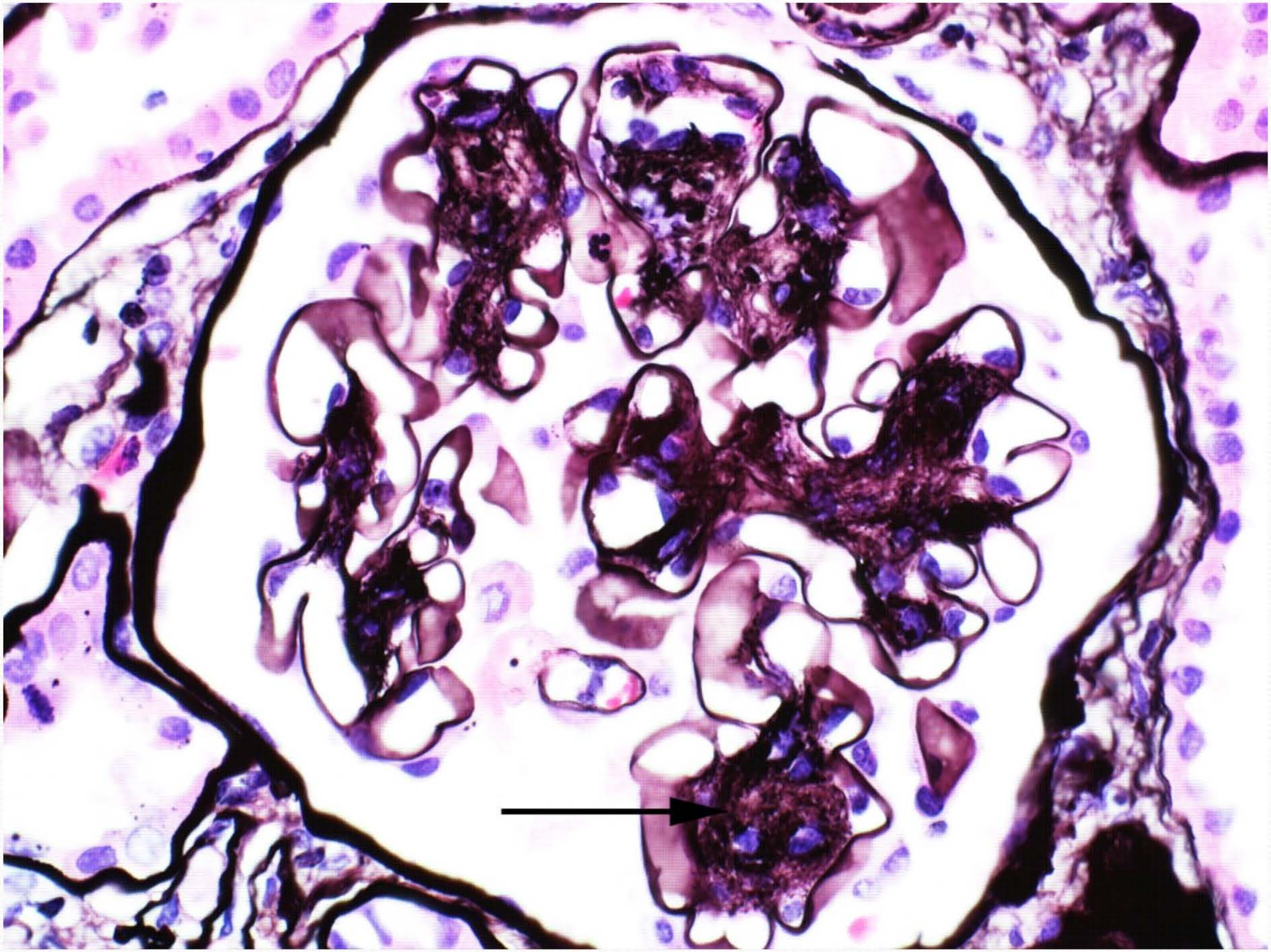


Figure 3-10 Early, silver positive KW nodule (arrow), Silver stain.



Chapter 04

Mesangiolysis and Microaneurysms

Mesangiolysis and Microaneurysms

Mesangiolysis is the dissolution of the mesangial matrix which can be brought on by a number of different disorders (and probably mechanisms). Mesangiolysis can be difficult to identify histologically. It is manifested by attenuation, fraying, and focal dissolution of the mesangial matrix. Although pathologists are attuned to seeing what IS there (a disease process or morphologic change), it is often more difficult to determine what is NOT there (e.g., loss of mesangial matrix). This fraying and focal dissolution of the mesangial matrix may be identified by light or electron microscopy (Fig 4-1–Fig 4-4). By light microscopy, mesangiolysis is best seen on Jones silver methenamine stained sections. Mesangiolysis can also be identified on PAS stained sections by a pale, moth-eaten appearance of the mesangial areas and nodules.

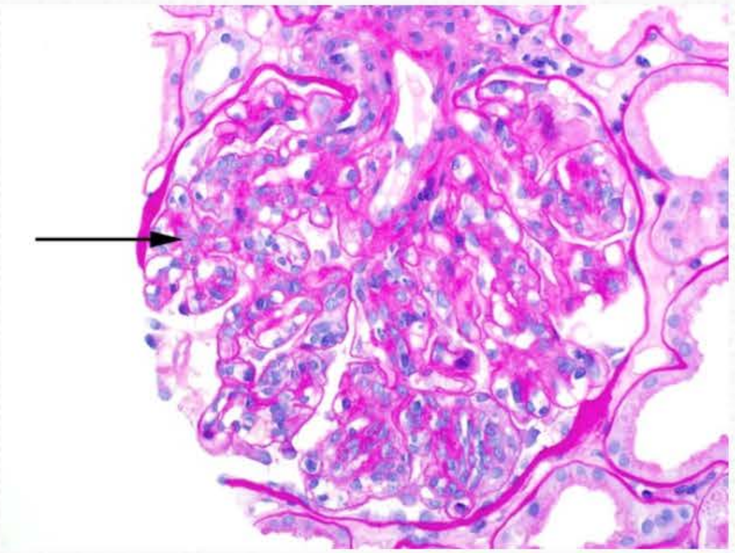


Fig 4-1 Dissolution of mesangium in several segments of glomerulus (arrow), PAS stain.

Kriz et al have shown that the mesangial matrix contains microfibrils which anchor the adjacent glomerular capillaries and afford stability in the face of intracapillary hemodynamic forces. Dissolution or destruction of the mesangial matrix (i.e., mesangiolysis) can lead to loss of these anchoring fibrils. Without this anchoring mechanism, the pressure of hemodynamic forces may cause ballooning or ectasia of the glomerular capillaries into Bowman's space, leading to microaneurysm formation. Microaneurysms are very characteristic of advanced/advancing diabetic nephropathy, but may also be seen in other conditions such as light chain deposition disease, thrombotic microangiopathy, membranoglomerulonephritis, and even amyloidosis on rare occasions.

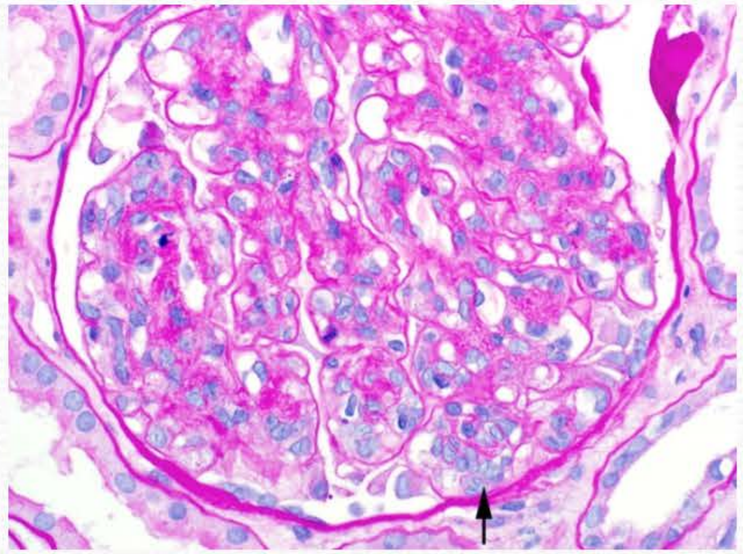


Fig 4-2 Loss of mesangial integrity with early microaneurysm formation (arrow), PAS stain.

Microaneurysms may lead to additional histologic lesions. Rupture of the dilated capillaries may occur, causing synechiae/adhesions to Bowman's capsule (Fig 4-6) and fibrotic and other changes to the widened, abnormal Bowman's space (Fig 4-7).

Kimmelstiel-Wilson mesangial nodules are often seen associated with microaneurysms (Fig 4-8). Bloodworth et al. have suggested that the microaneurysms are not only related to the mesangial nodules, but are central to the process of KW nodule formation. Exuberant mesangial repair following mesangiolysis leads to expansion of mesangial matrix and mesangial sclerosis, as noted in various experimental models. The ectatic glomerular capillaries of microaneurysms adjacent to mesangial nodules often contain accumulations of erythrocytes, cellular debris, hyaline, and fibrinoid material (Figs 4-9 – 4-11). Some investigators have thus suggested a sequence of repeated bouts of mesangiolysis, microaneurysm formation, and exuberant repair attempts, leading to accumulation of this cellular and noncellular material in the dilated capillaries. Subsequent glomerular capillary collapse and/or accretion, then leads to the formation of the KW nodules. On silver stain, the KW nodules often show lamination similar to growth rings in a tree, suggesting successive layering and growth of matrix on the outer, convex surface of the initial nodule (see Chapter 3).

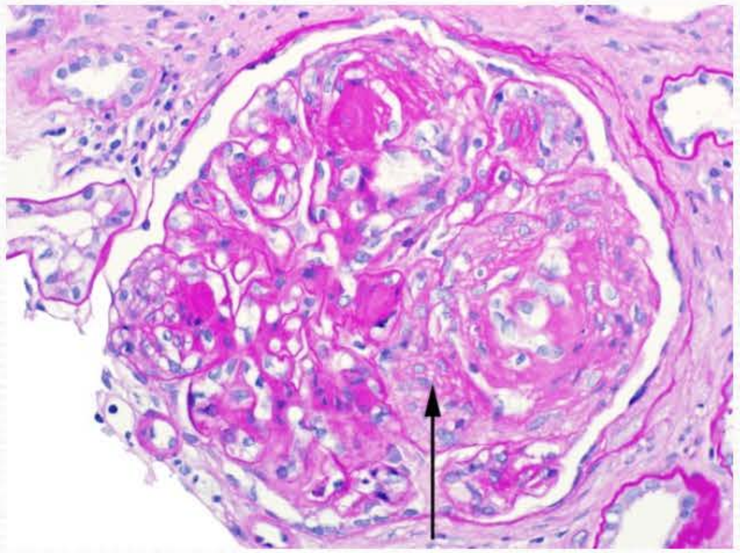


Fig 4-3 Pale, moth-eaten appearance of mesangial nodules (arrow) due to Mesangiolysis, PAS stain.

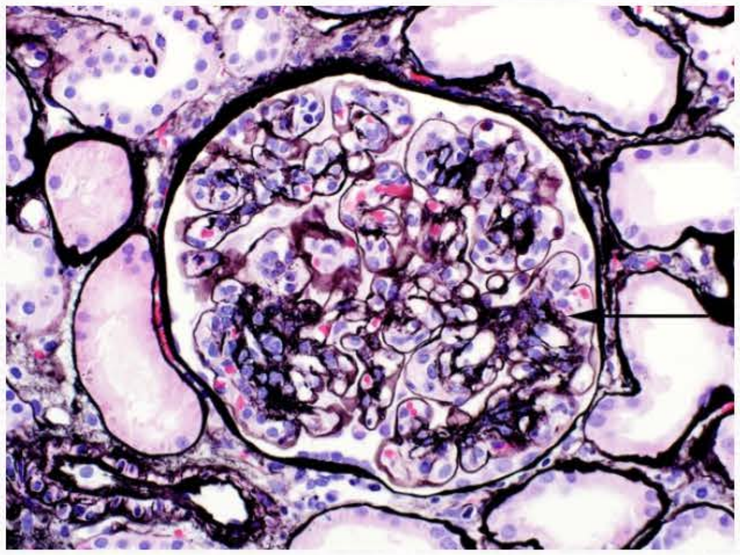


Fig 4-4 Fraying of mesangium (arrow), Silver stain.

Figure 4-1 Dissolution of mesangium in several segments of glomerulus (arrow), PAS stain.

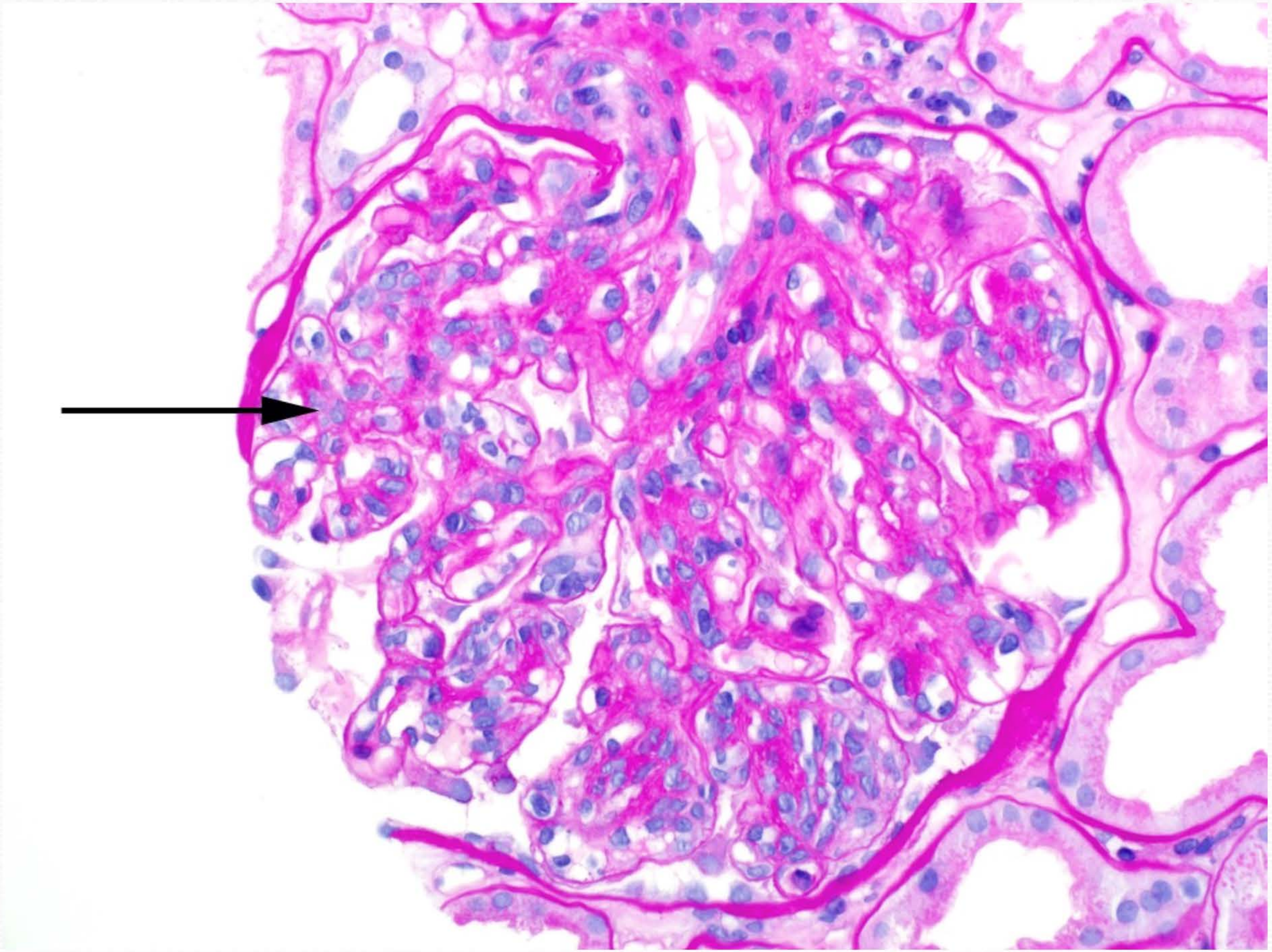


Figure 4-2 Loss of mesangial integrity with early microaneurysm formation (arrow), PAS stain.

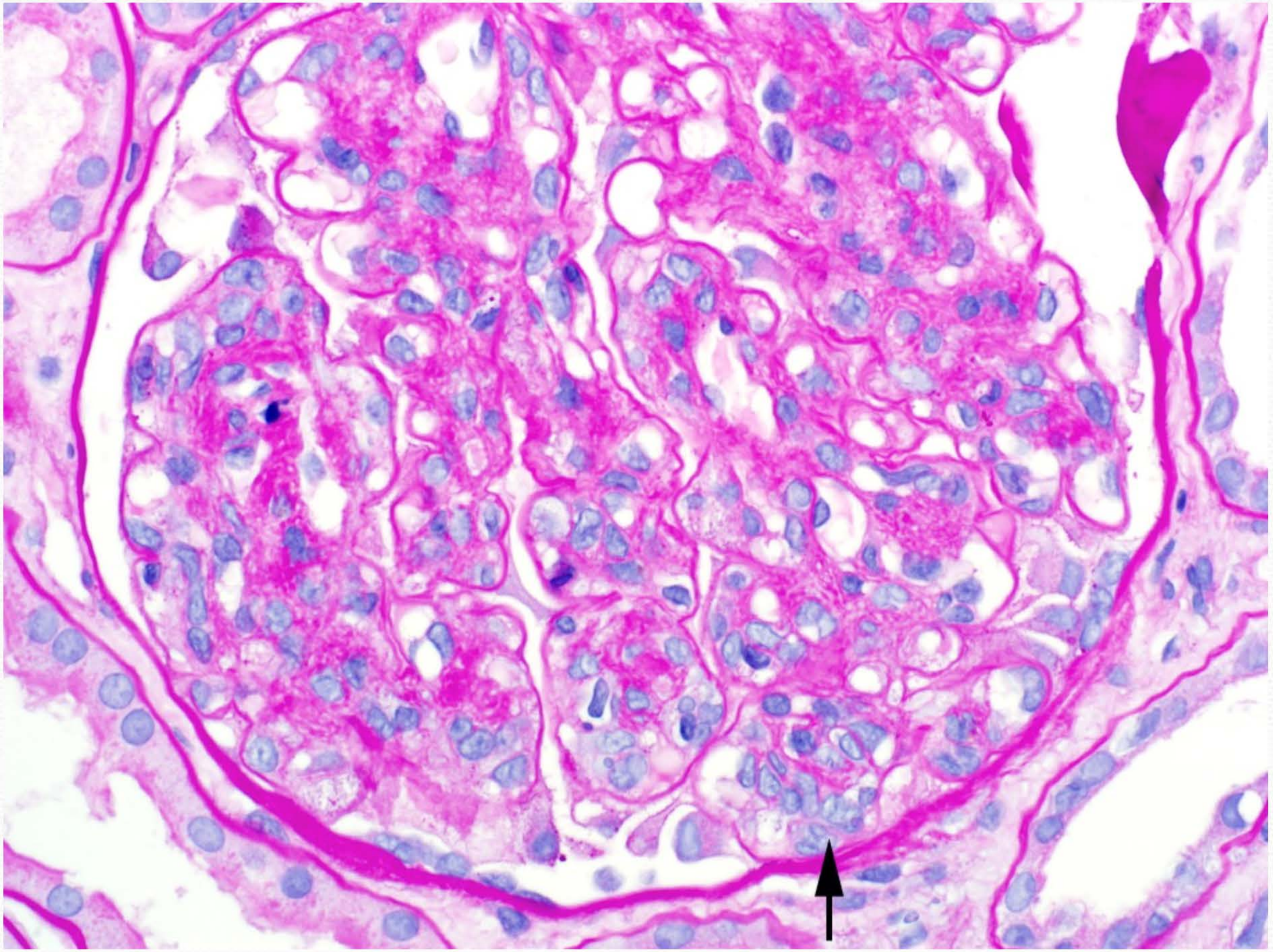


Figure 4-3 Pale, moth-eaten appearance of mesangial nodules (arrow) due to Mesangiolysis, PAS stain.

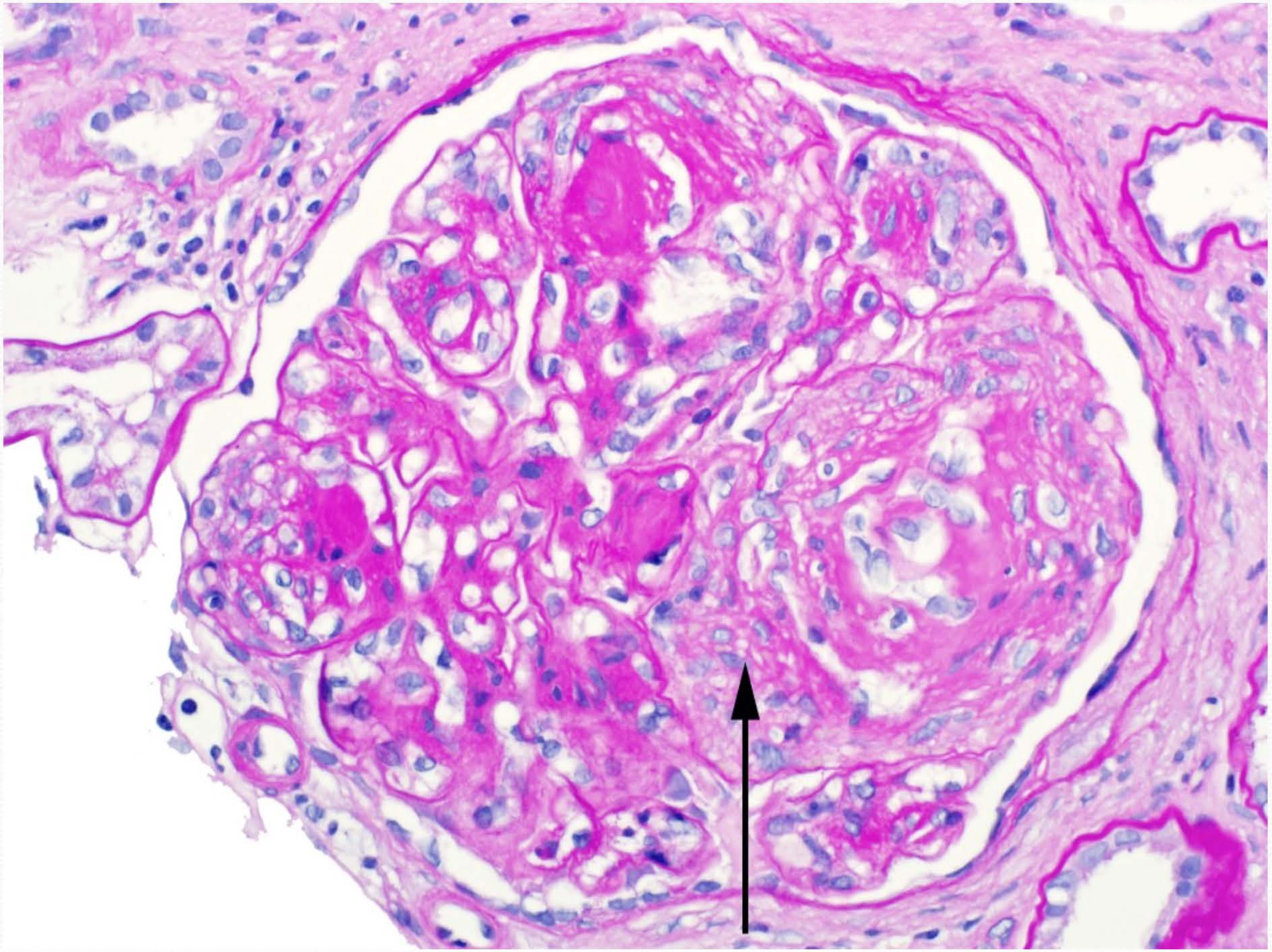


Figure 4-4 Fraying of mesangium (arrow), Silver stain.

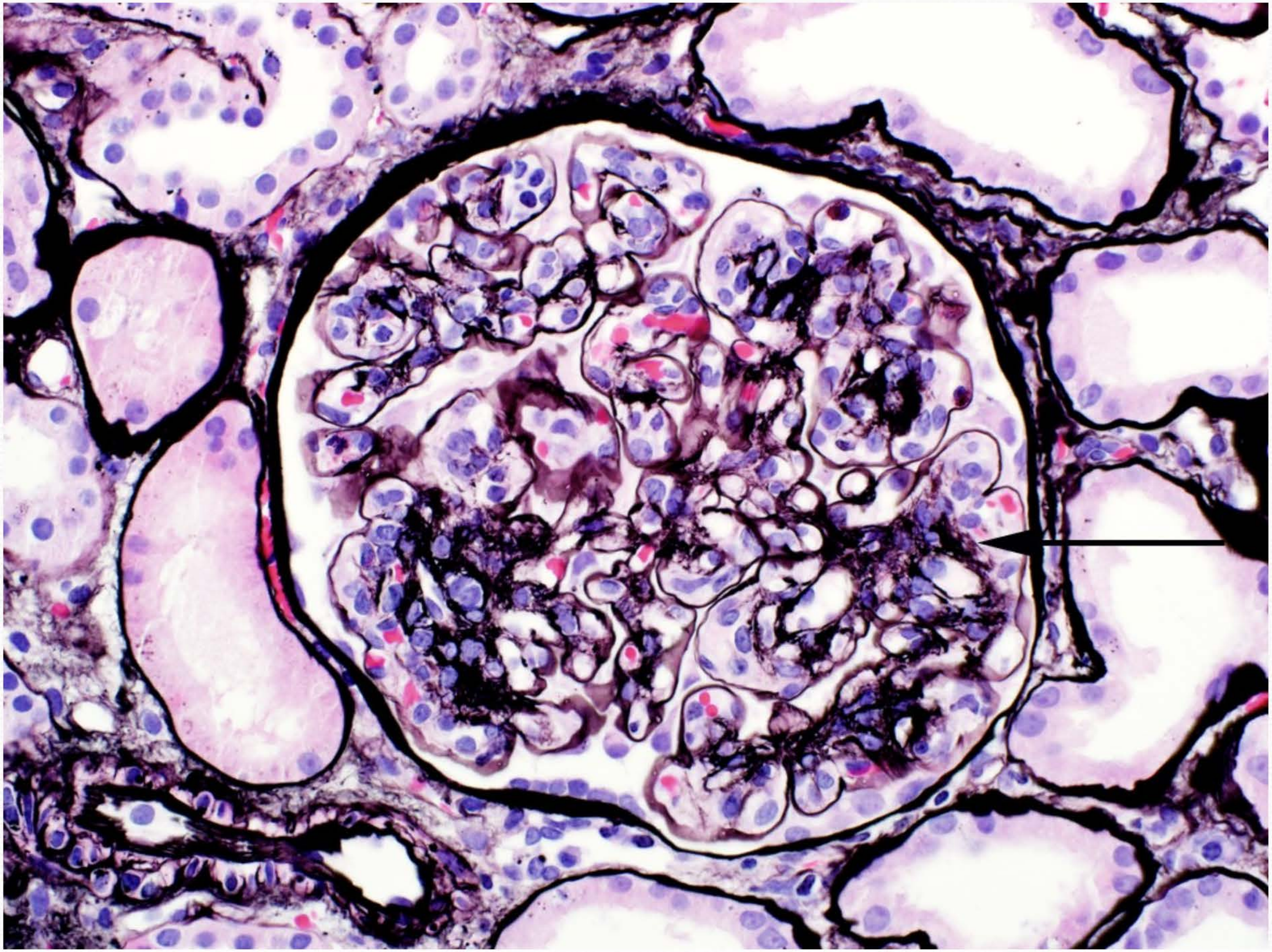


Figure 4-5 Mesangiolysis and microaneurysm formation (arrows), Electron photomicrograph.

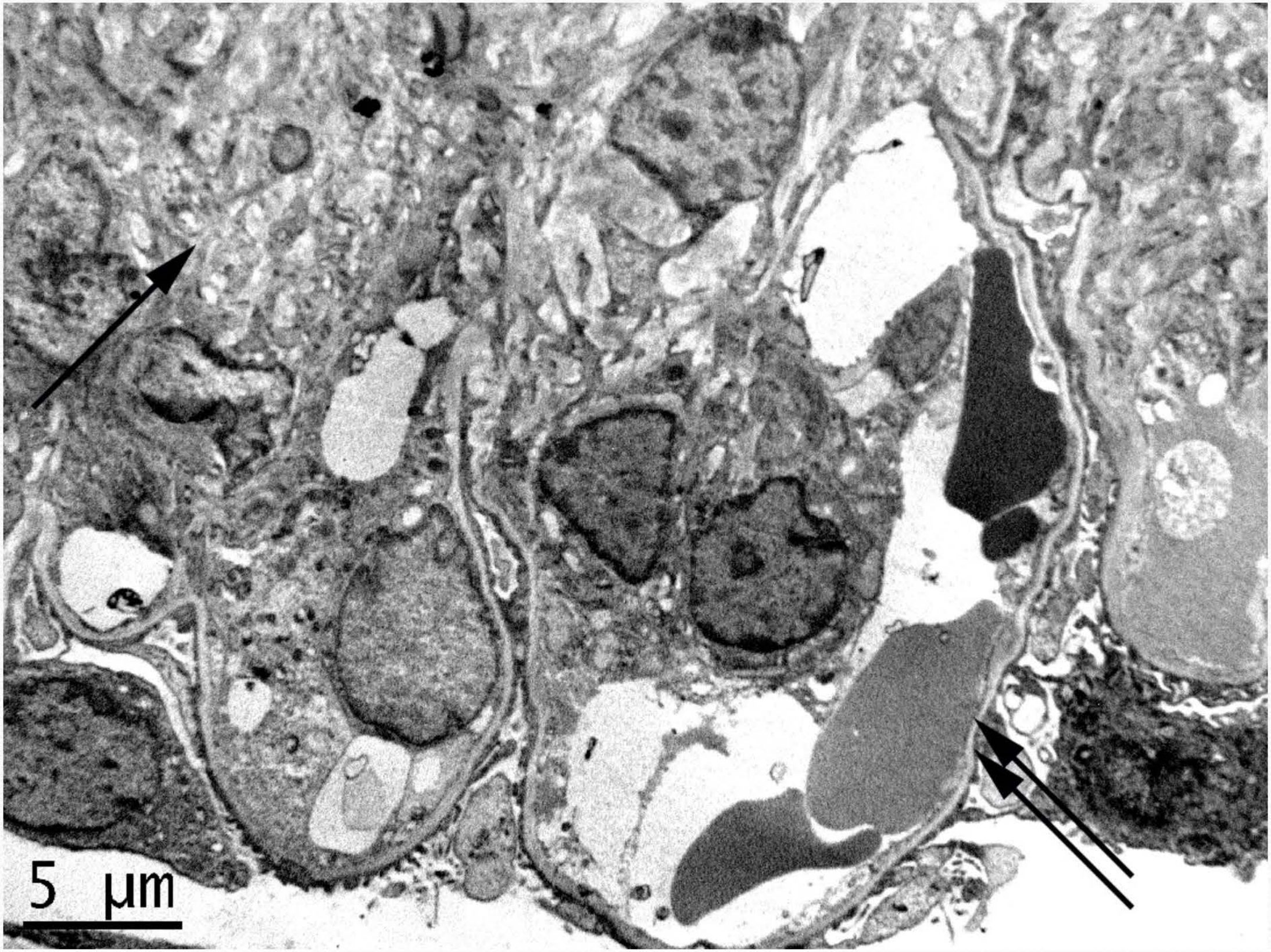


Figure 4-6 Small area of adhesion to Bowman's capsule (arrow), Trichrome stain.

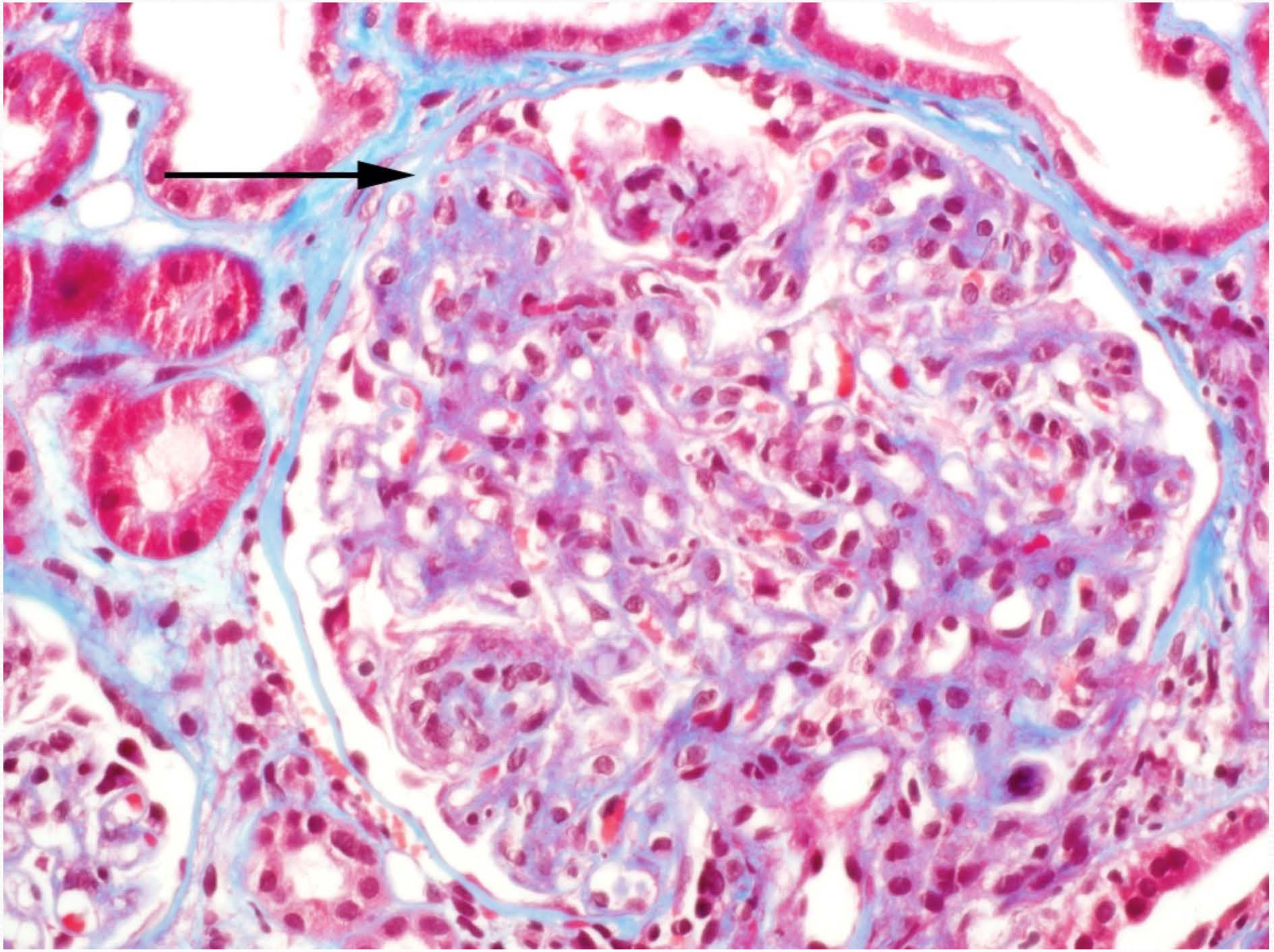


Figure 4-7 Epithelial proliferation in Bowman's space (arrow), PAS stain.

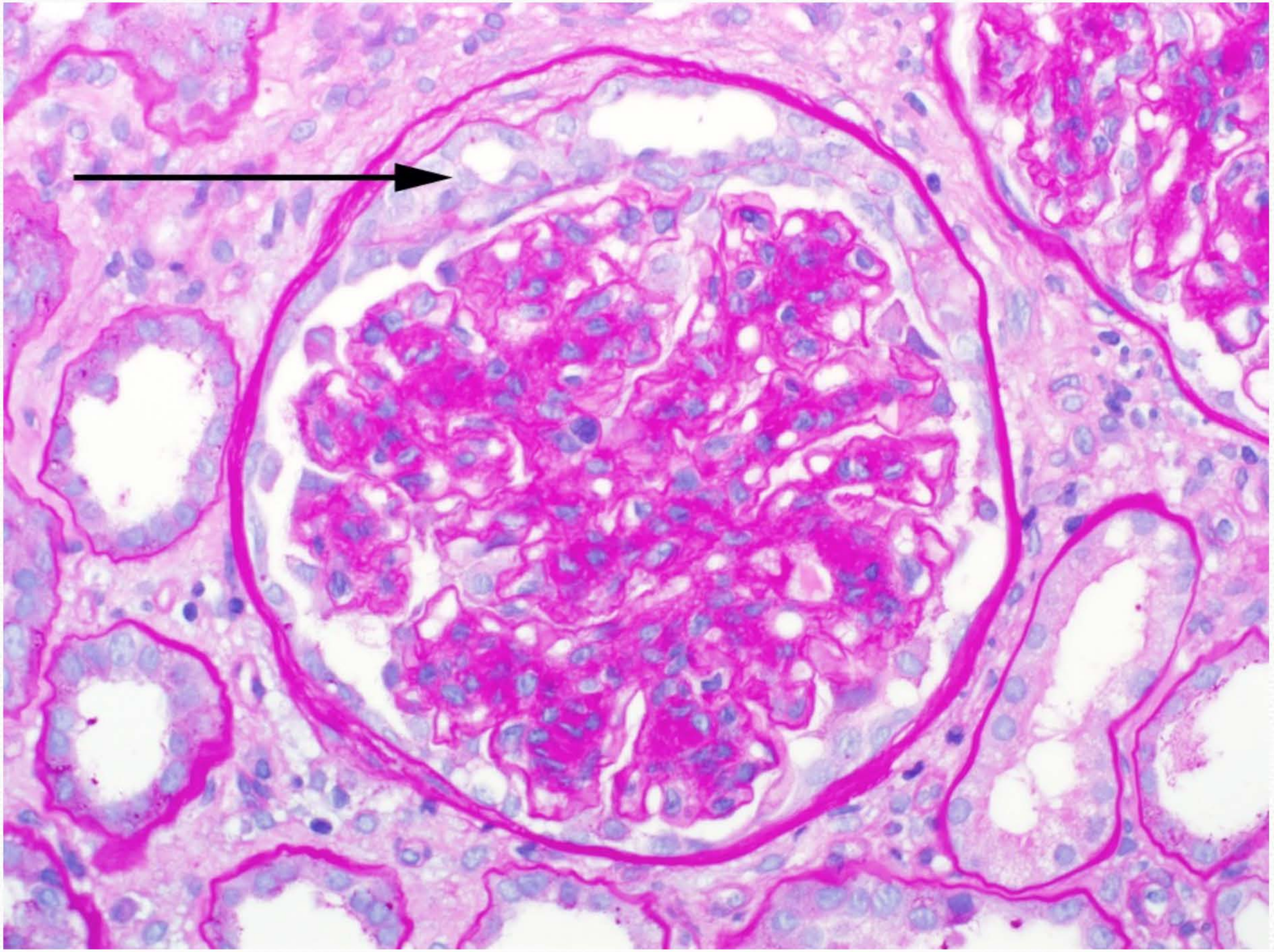


Figure 4-8 KW nodule with microaneurysm (arrow), Trichrome stain.

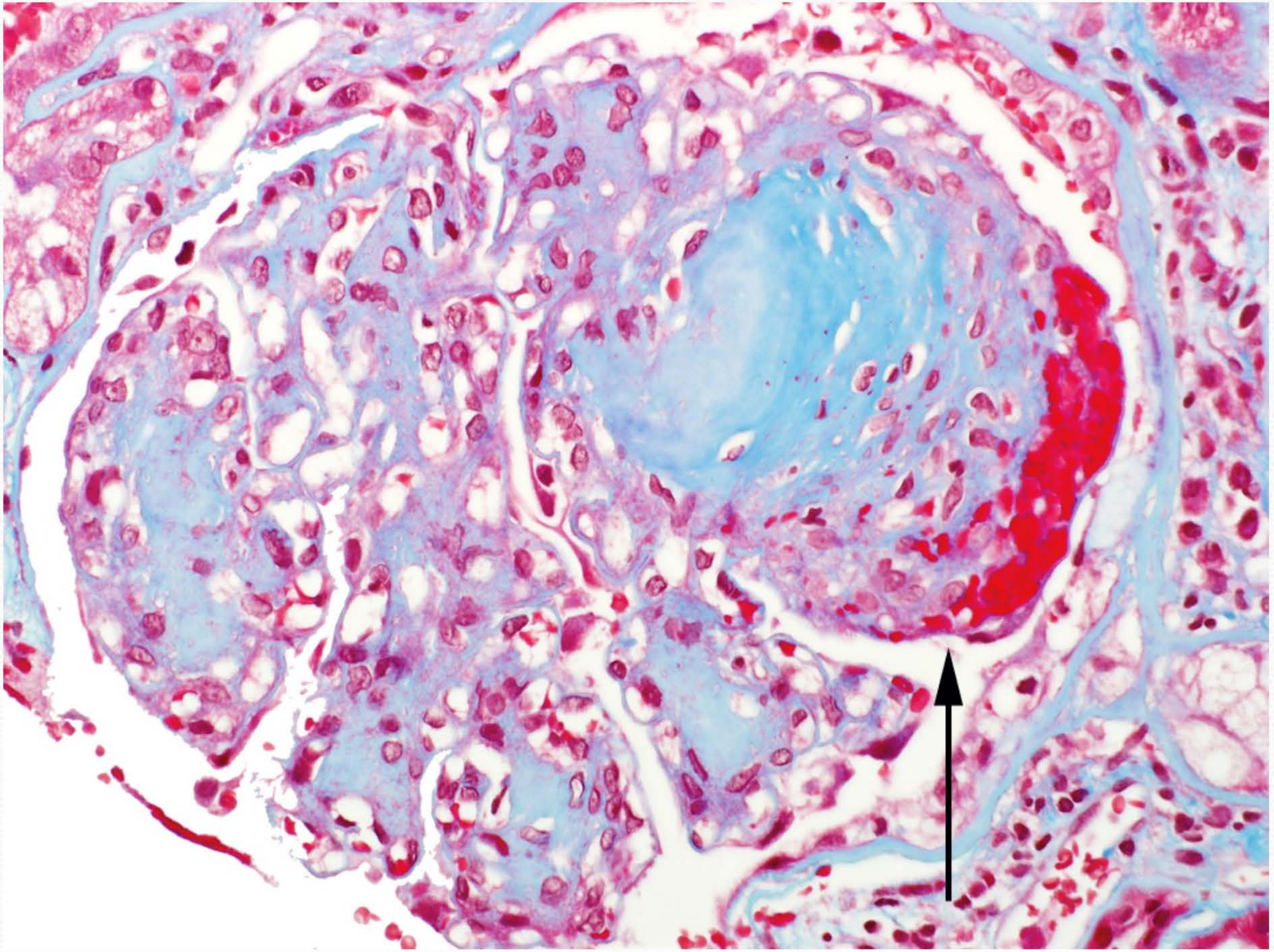


Figure 4-9 Microaneurysm with RBC fragments and fibrinoid material (arrow), Silver stain.

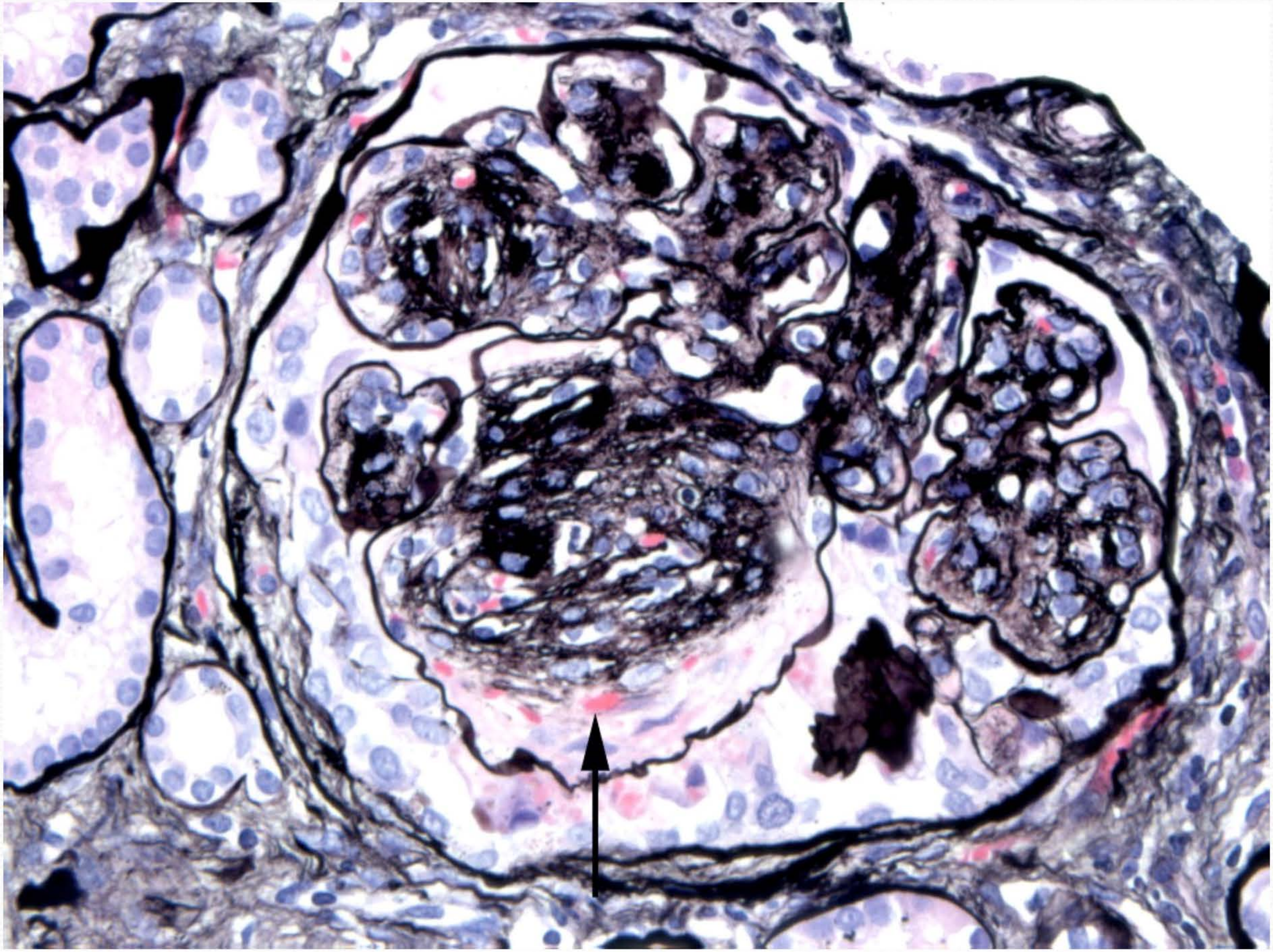


Figure 4-10 Microaneurysm containing numerous RBCs (arrow), Silver stain.

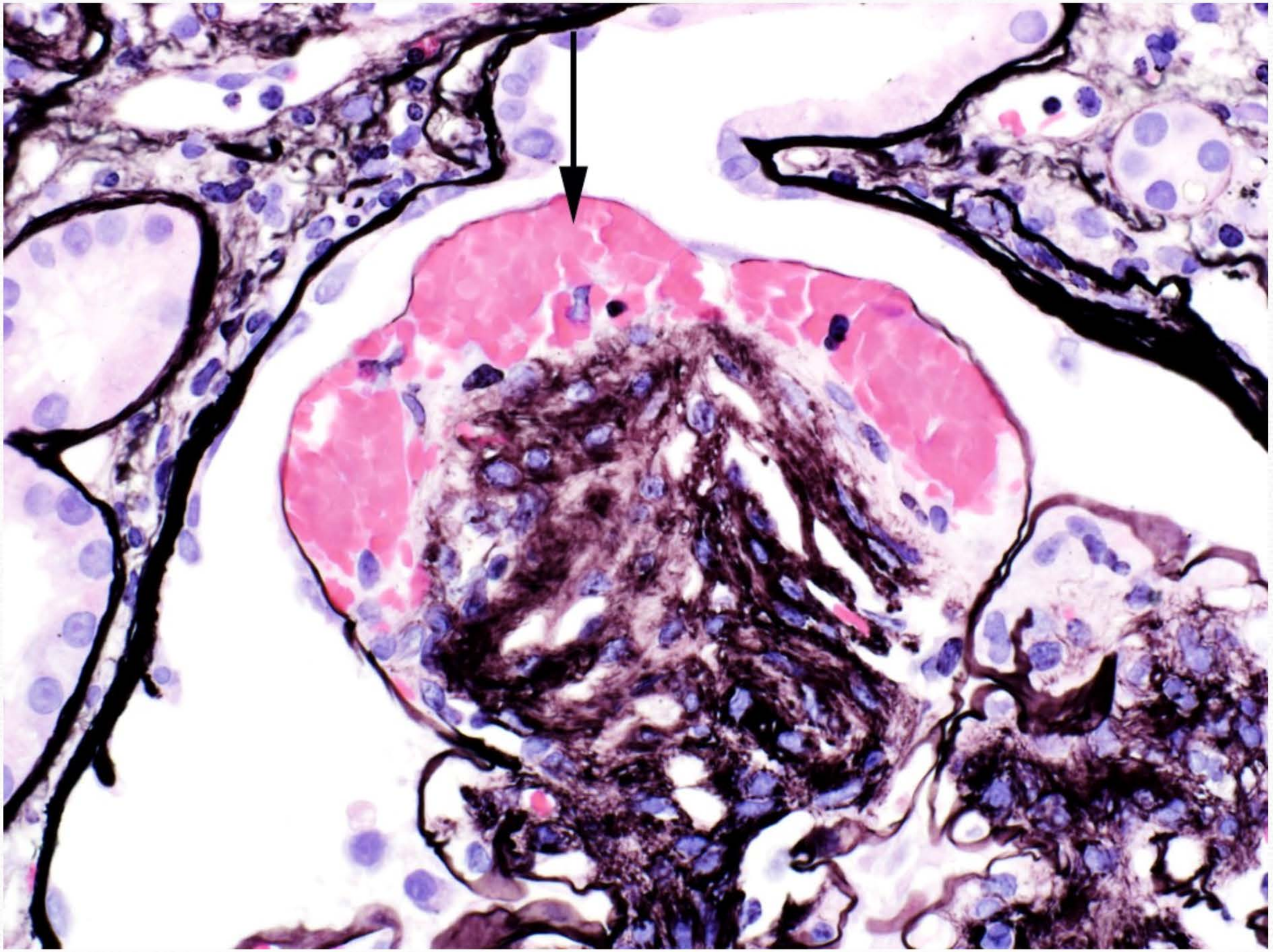
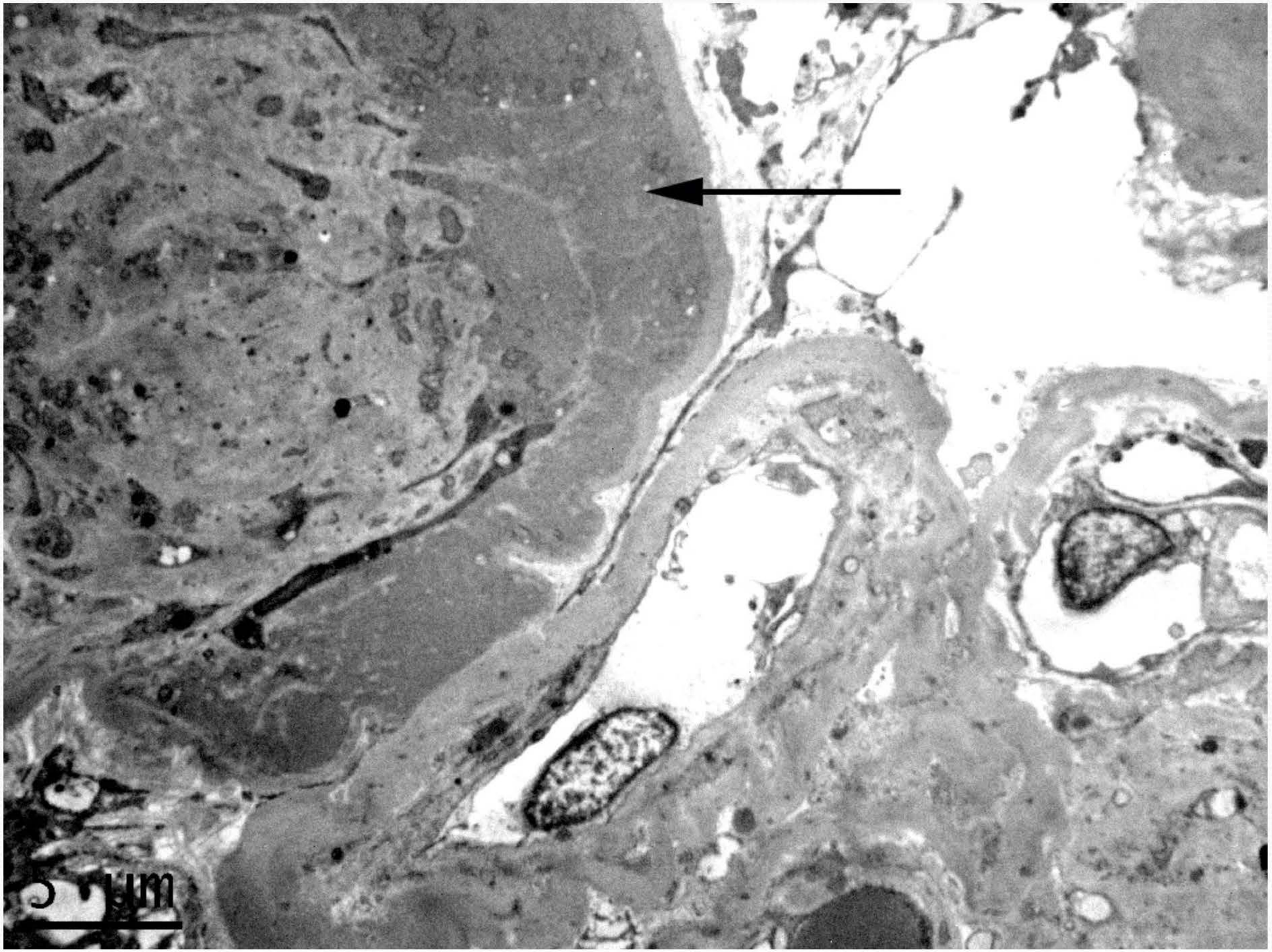
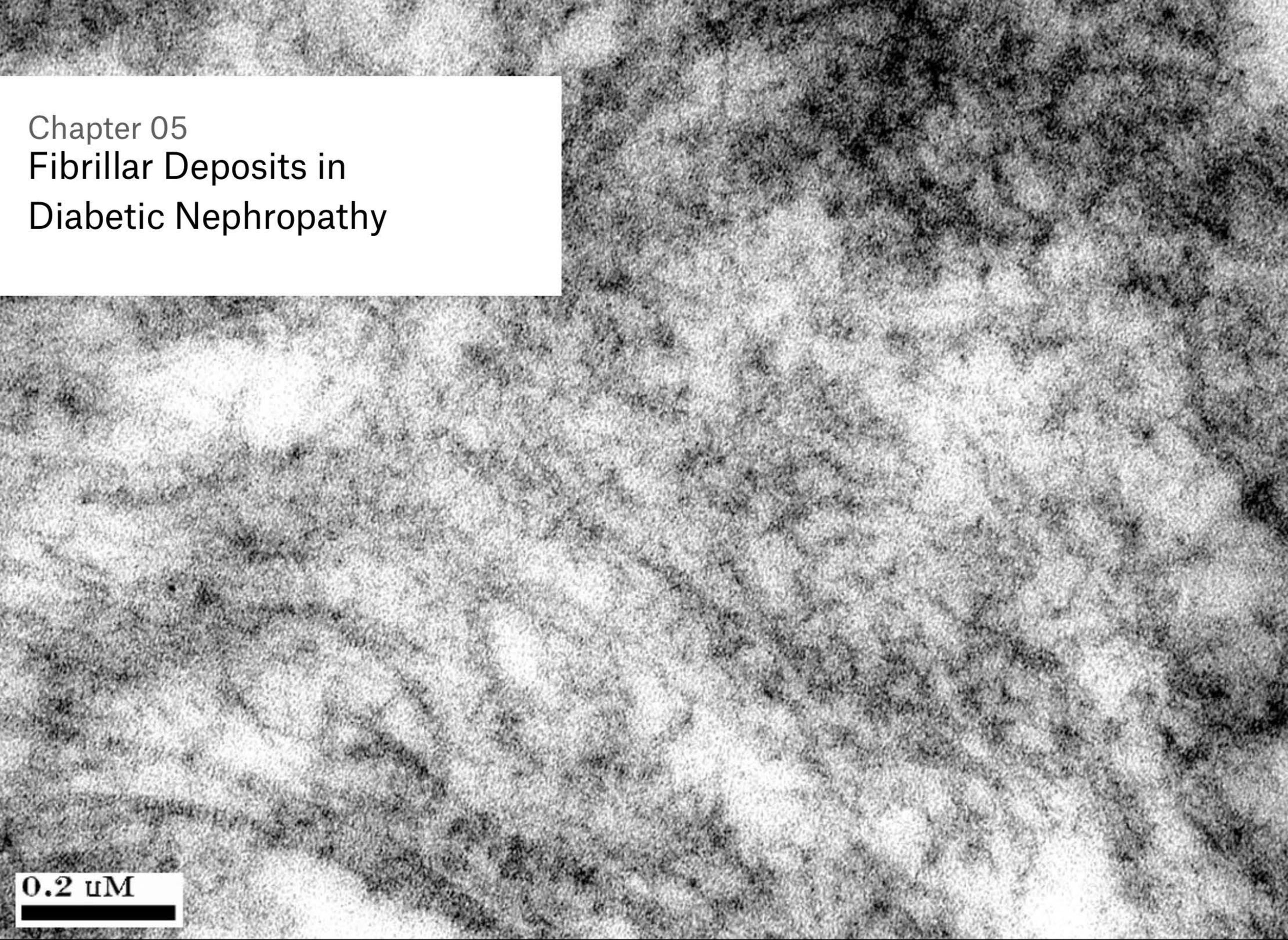


Figure 4-11 Hyaline material in microaneurysm (arrow), Electron photomicrograph.



Chapter 05

Fibrillar Deposits in Diabetic Nephropathy



Fibrillar Deposits in Diabetic Nephropathy

Early electron microscopy descriptions of glomerular mesangium in diabetes revealed the presence of fibrils, particularly in cases of nodular glomerulosclerosis (Fig 5-1–Fig 5-5). These were present in addition to hyaline material, granular and proteinaceous material, and electron dense or vacuolated lipid droplets. Transmission electron microscopy studies showed that mesangial nodules included a meshwork of very fine (20 Å) fibrils surrounding a variety of structures including collagenous fibrils and non-collagenous circular fibrils (30 nm).

Antibodies against type I collagen were found in the mesangium and in the fibrotic interstitium in DN. Immunohistochemical (IHC) studies showed the presence of collagen V and collagen VI in nodular lesions. These collagens were not observed in cases of diffuse glomerulosclerosis. These latter findings suggested that the accumulation of these fibrils in the mesangium could be a factor in the formation of Kimmelstiel-Wilson nodules. Another possible hypothesis for the formation of fibrils is that they might represent advanced glycation end products (AGE) cross-linked to other proteins. IHC studies revealed positive AGE staining in mesangial areas in advanced diabetic nephropathy, and strong AGE staining in nodular lesions, as opposed to lack of staining in control kidneys and in patients without DN.

Although the presence of glomerular microfibrils appears to be of no prognostic significance, this finding raises a number of important differential

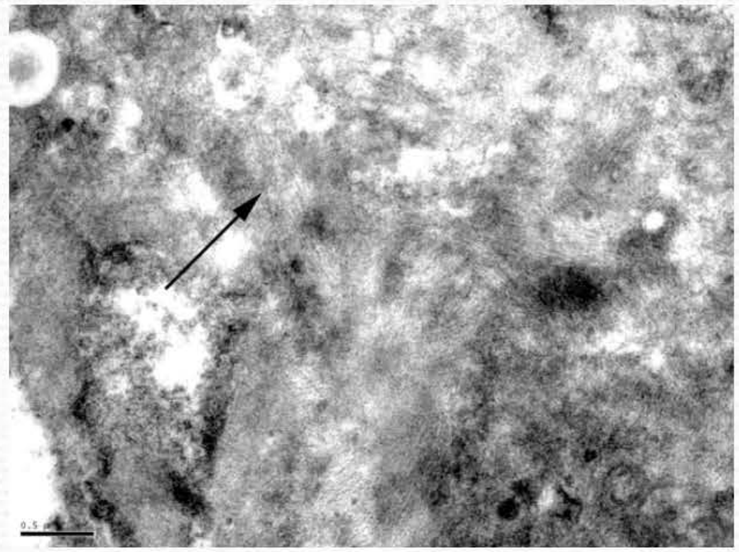


Fig 5-1 Rare irregularly distributed fibrils (arrow) in mesangial nodule, Electron photomicrograph.

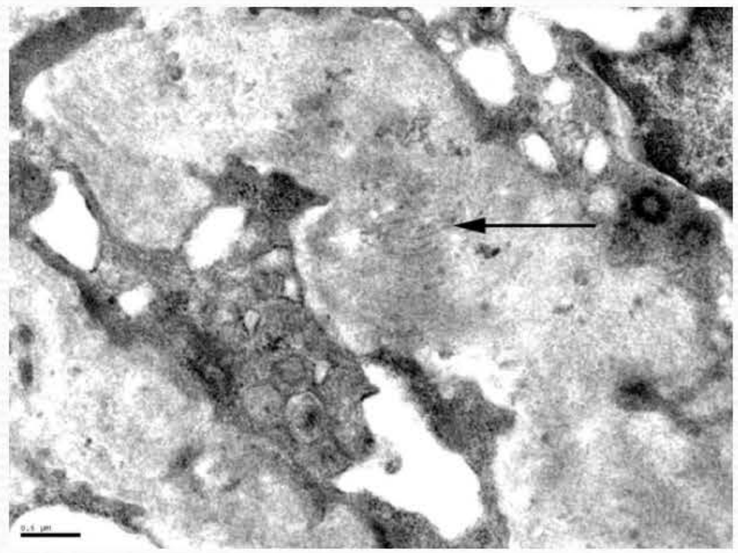


Fig 5-2 Rare irregularly distributed fibrils (arrow) in mesangial nodule, Electron photomicrograph.

diagnoses. Since early reports, the resemblance of these fibrils to amyloid and the importance in making such distinction were emphasized. Fibrillary material in diabetes is Congo red and Thioflavin T and S negative, as opposed to characteristic positive staining in amyloid. There is also no predominance of kappa or lambda light chains, and IHC stains for serum amyloid P protein and subtypes of amyloid are also negative. Cases of fibrillary glomerulopathy also enter in the differential diagnosis, but these should also have IgG, C3, kappa and lambda light chains by immunohistochemical studies. The fibrils in fibrillary glomerulopathy are also present in the subendothelial space.

Finally cell debris, apparently remnants of cellular organelles, can be also seen enmeshed in the mesangial matrix and has been noted by Najafian et al as well as Bariety et al (Fig 5-6).

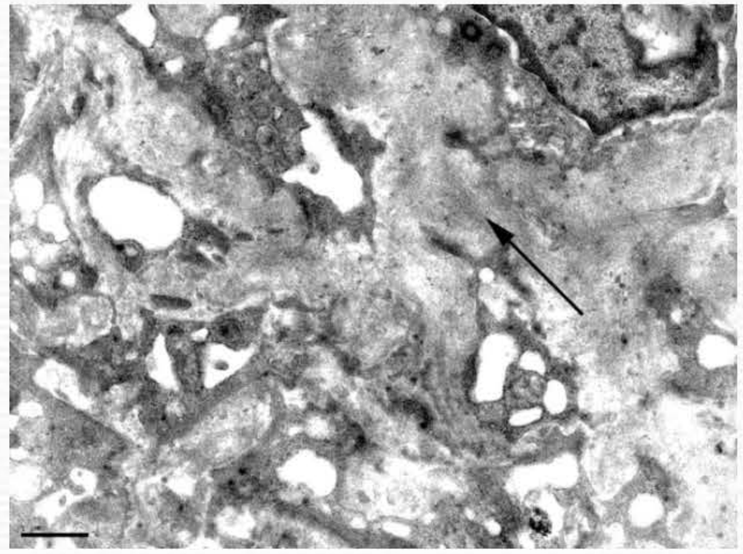


Fig 5-3 Occasional irregularly distributed fibrils (arrow) in mesangial nodule, Electron photomicrograph.

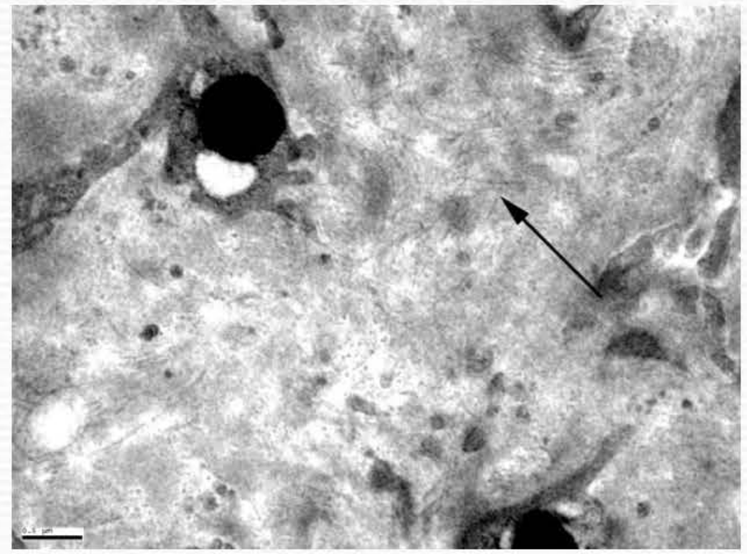


Fig 5-4 Occasional irregularly distributed fibrils (arrow) in mesangial nodule, Electron photomicrograph.

Figure 5-1 Rare irregularly distributed fibrils (arrow) in mesangial nodule, Electron photomicrograph.

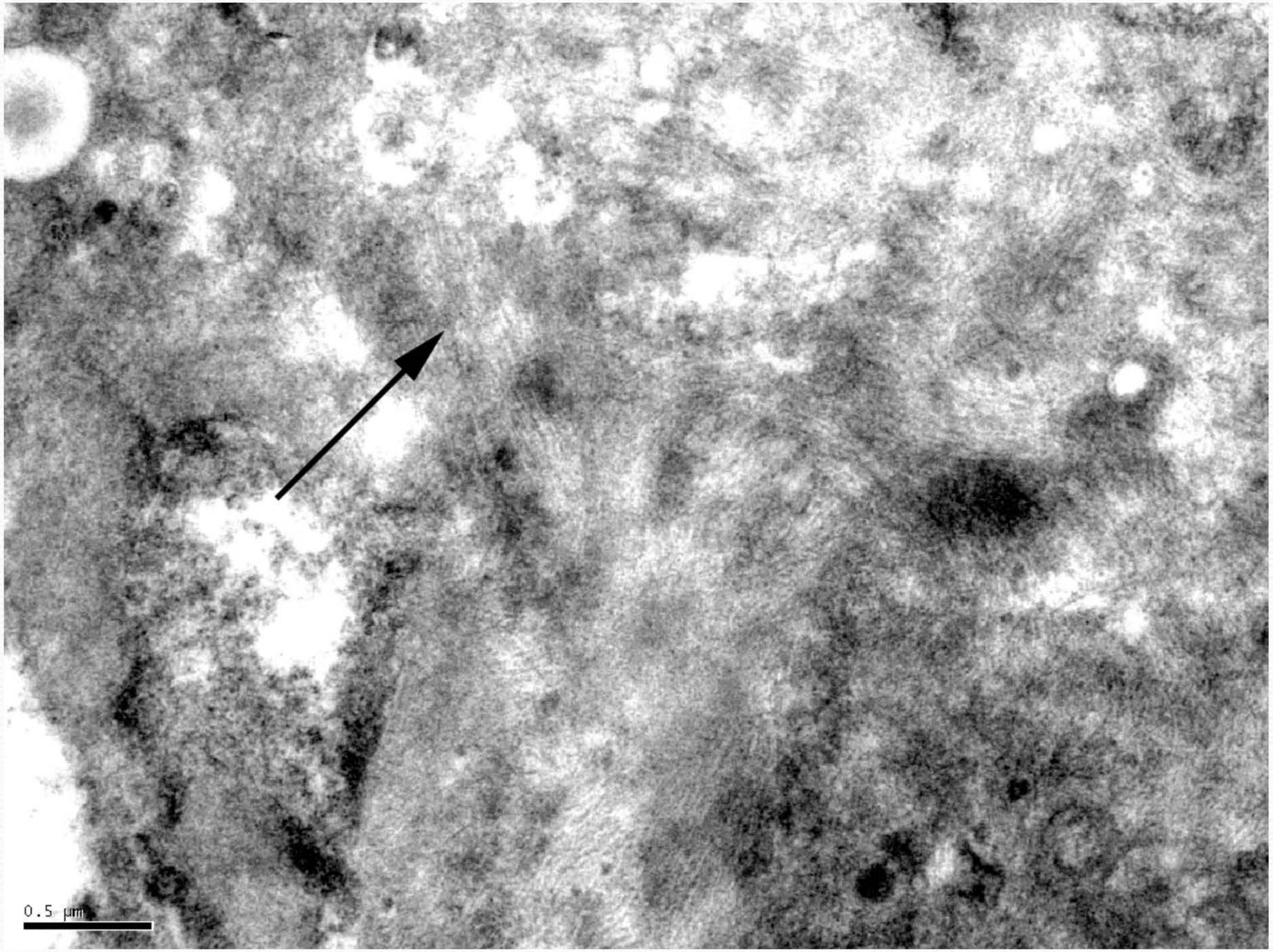


Figure 5-2 Rare irregularly distributed fibrils (arrow) in mesangial nodule, Electron photomicrograph.

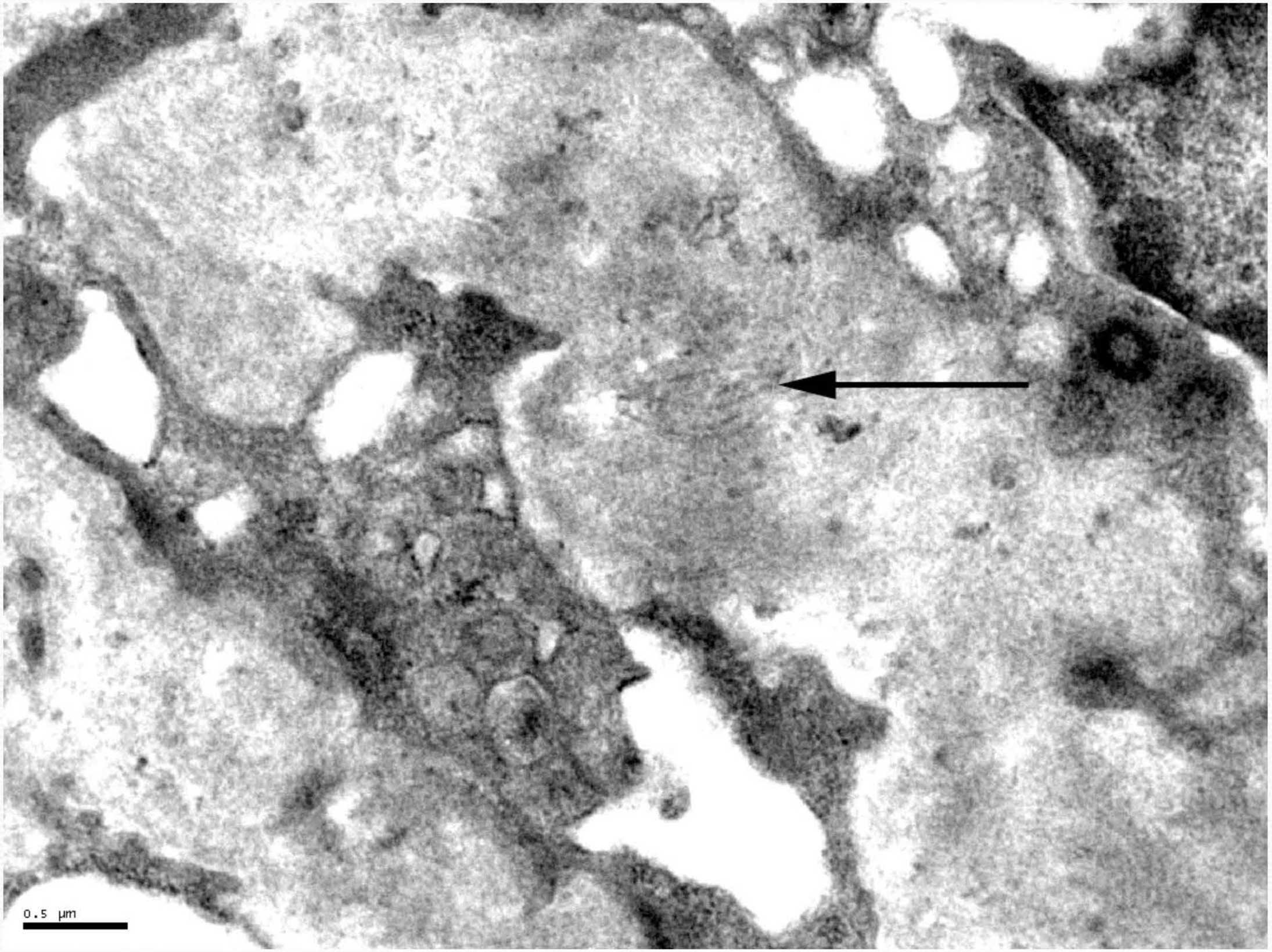


Figure 5-3 Occasional irregularly distributed fibrils (arrow) in mesangial nodule, Electron photomicrograph.

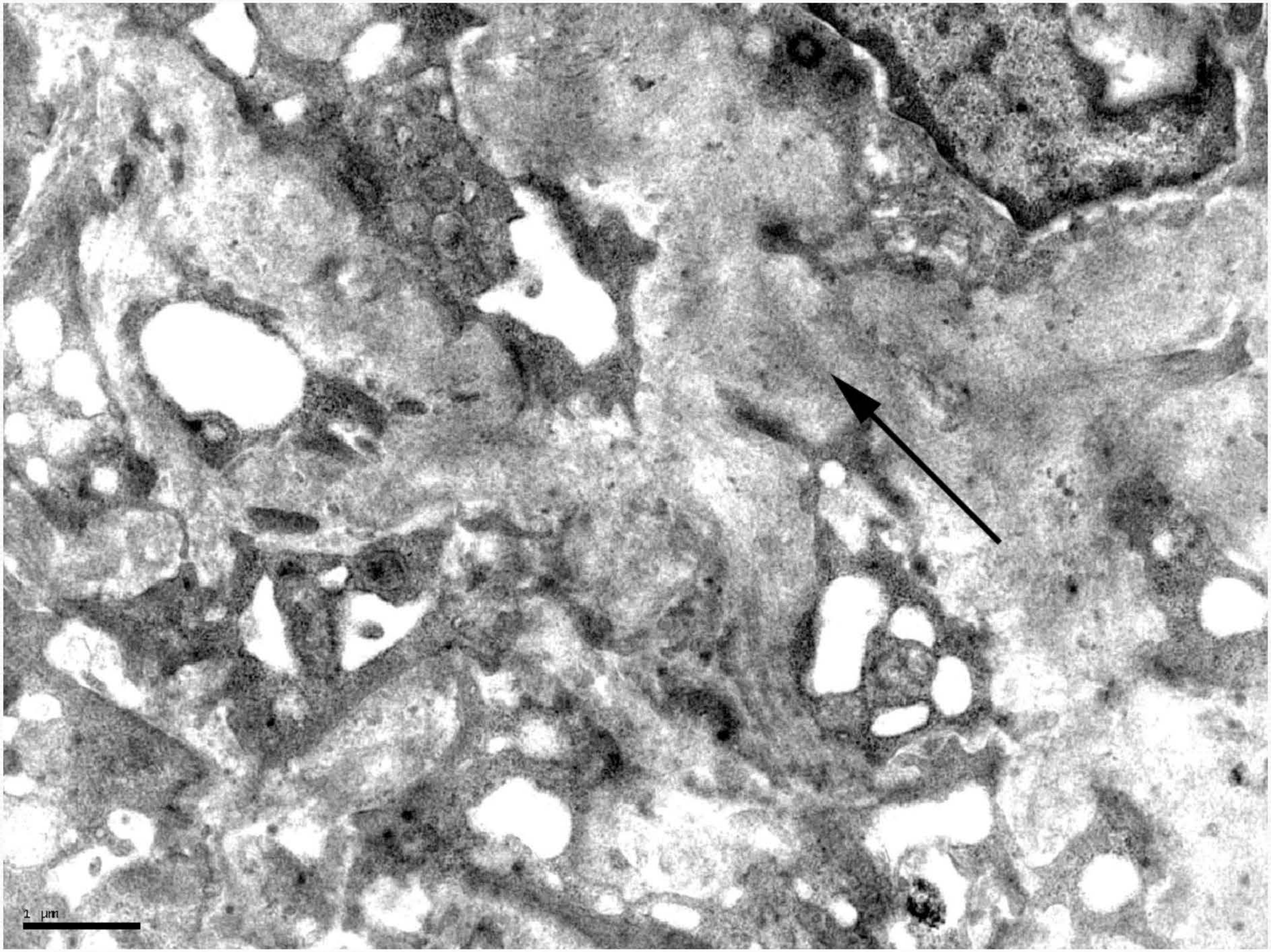


Figure 5-4 Occasional irregularly distributed fibrils (arrow) in mesangial nodule, Electron photomicrograph.

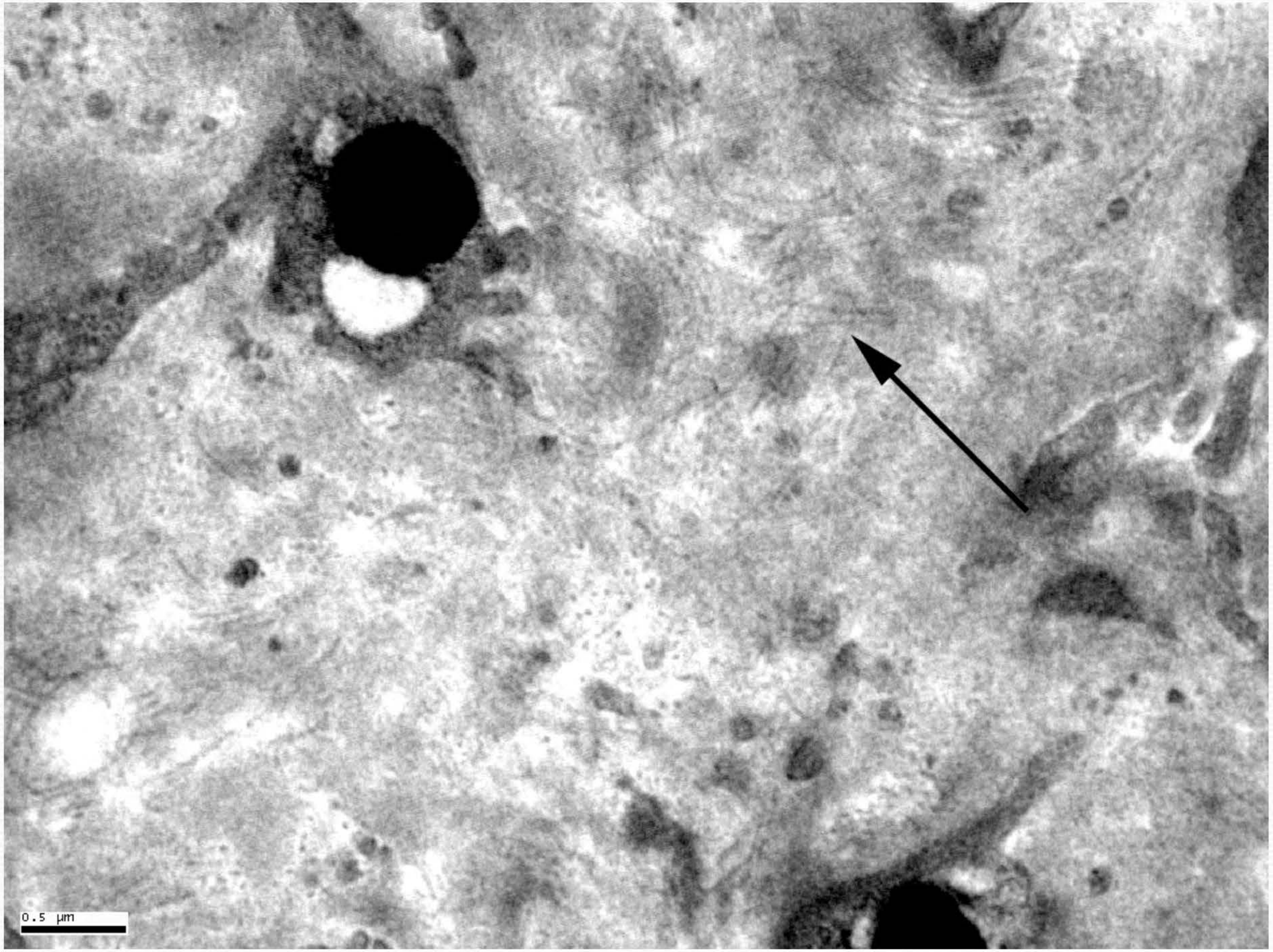


Figure 5-5 Irregularly distributed fibrils (arrow) in mesangial nodule, Electron photomicrograph.

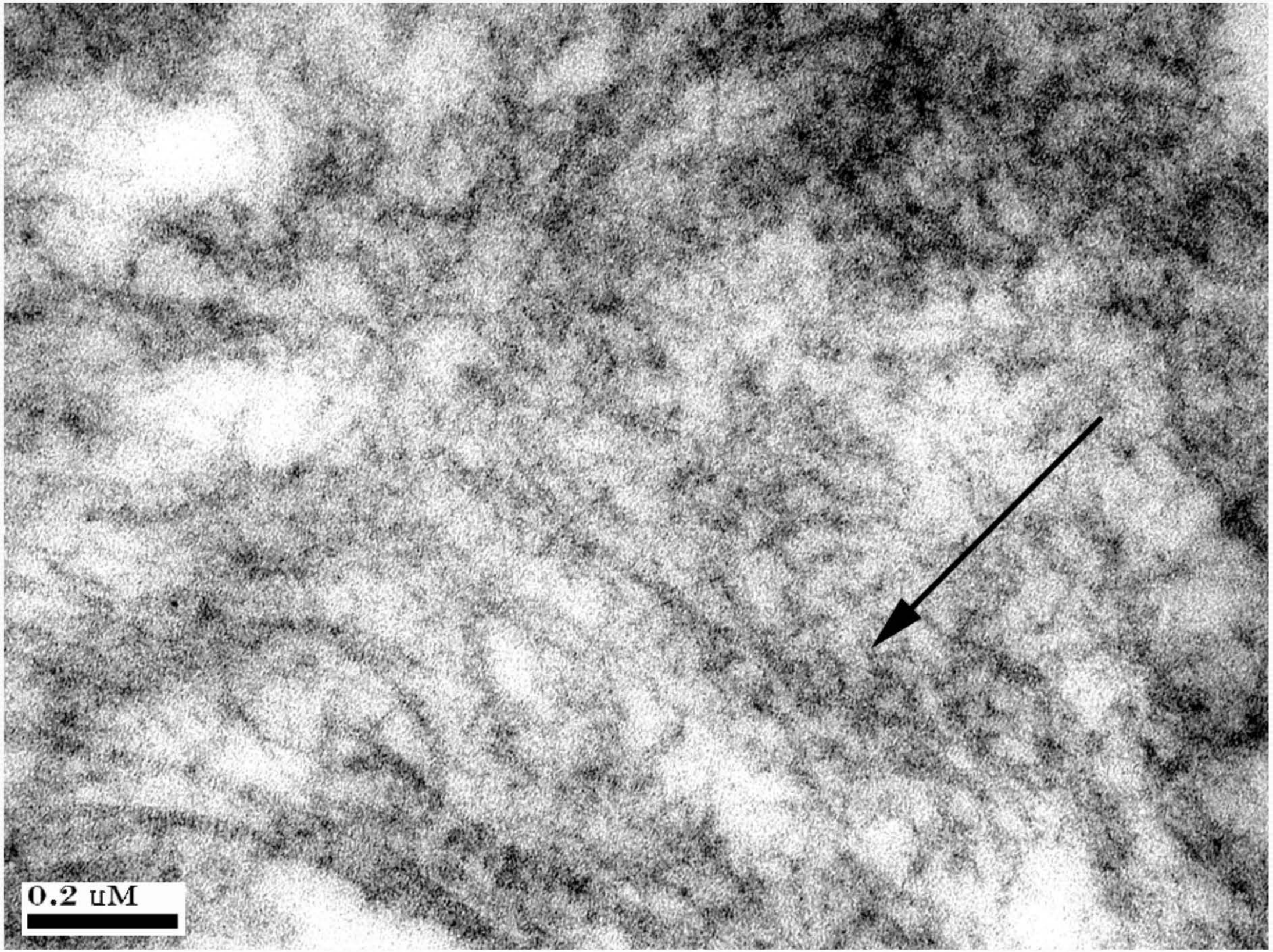
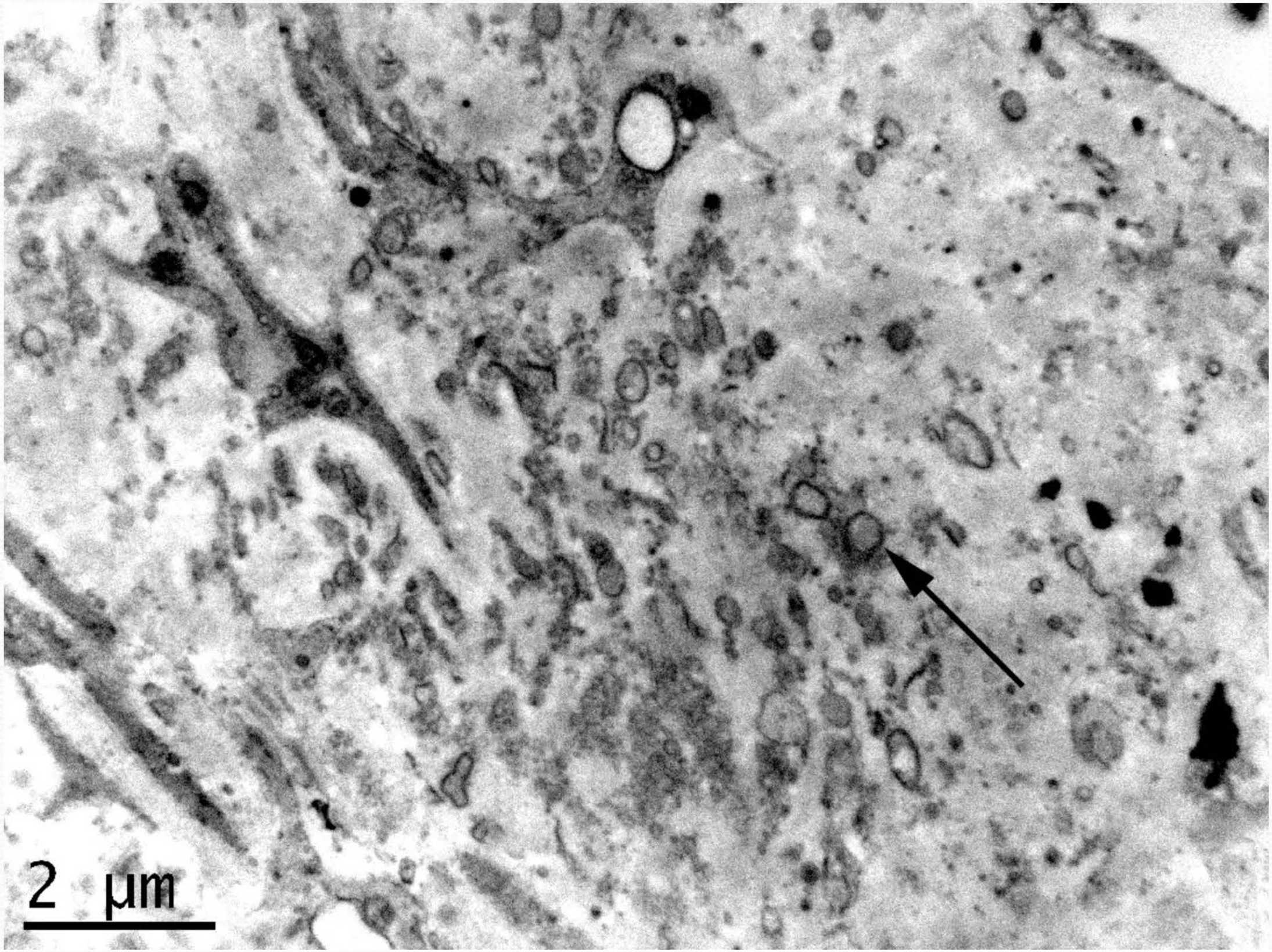


Figure 5-6 Mesangial expansion with cellular debris (arrow), Electron photomicrograph.



Chapter 06

Capsular Drops and Hyaline Caps

Capsular Drops and Hyaline Caps

There are two glomerular "hyaline lesions" seen in diabetic glomerulosclerosis, capsular drops and hyaline (aka fibrin) caps. These lesions are distinguished based on location with the capsular drop being present in Bowman's capsule and the hyaline cap located within the glomerular tuft. Hyaline consists of an amorphous, acellular, glassy, homogeneous material which stains eosinophilic on H&E stain and is PAS positive while silver negative. Hyaline lesions will occasionally show nonspecific staining on immunofluorescence, particularly with IgM and C3.

The capsular drop is characterized by small accumulations of hyaline within Bowman's capsule (Fig 6-1–Fig 6-3). The material is typically located between the basement membrane of Bowman's capsule and the adjacent parietal epithelium of the glomerulus. It can occur along any segment of Bowman's capsule (e.g., vascular or peripheral). The mechanism of capsular drop formation has been enigmatic. Many believe that these lesions derive from plasma proteins tracking from the vascular pole to Bowman's capsule (i.e., the arteriolar deposits exit the wall of the arteriole and penetrate the GBM near the hilar reflection and basement membrane of Bowman's capsule). EM studies by Stout show hyaline deposits on either side of and within the capsule suggestive of penetration.

The hyaline cap has traditionally been known as a "fibrin" cap, however this term is a bit of a misnomer as the lesions are not actually composed of fibrin. These lesions are characterized by accumulations of hyaline between the endothelium and the glomerular basement membrane (Fig 6-4–Fig 6-5). The

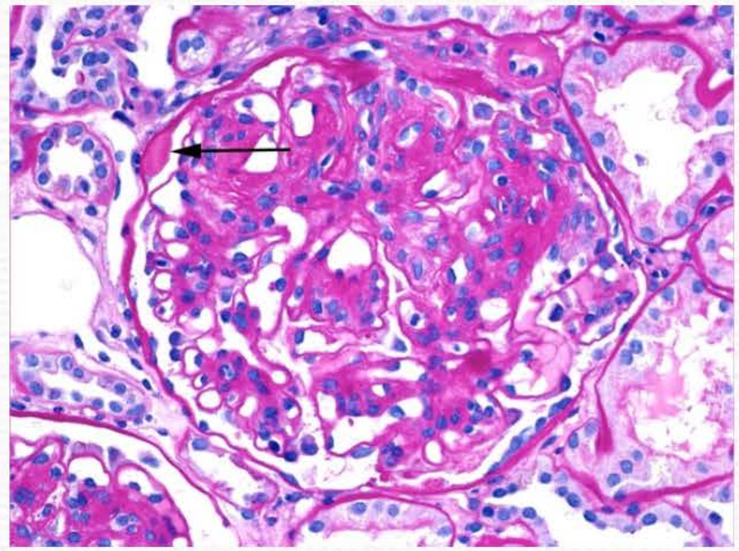


Fig 6-1 Diabetic glomerulosclerosis with capsular drop (arrow), PAS stain.

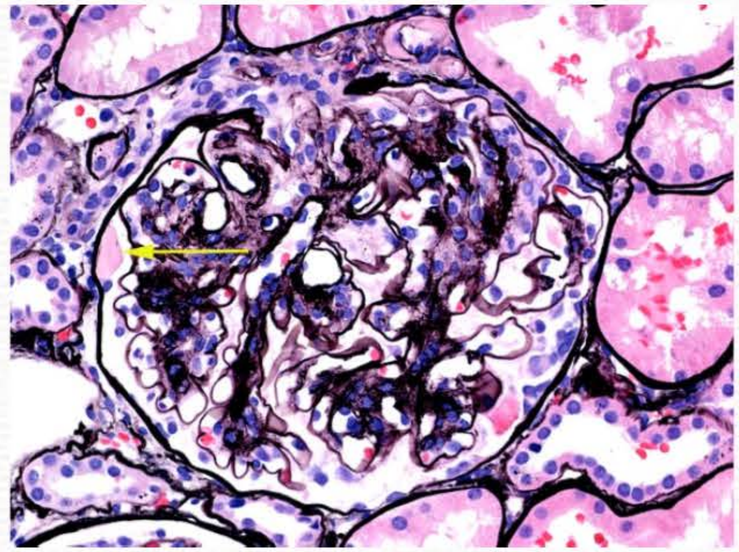


Fig 6-2 Silver negative capsular drop (arrow), Silver stain.

pathogenesis is uncertain, though it is believed to be secondary to “pushing of plasma proteins” into the glomerular capillary wall. These lesions may vary in size and may be small, or large enough to occlude the glomerular capillary lumen.

Ultrastructurally, hyaline lesions have a granular electron dense appearance and are usually found in areas of glomerular sclerosis just under the glomerular basement membrane (Fig 6-6). These hyaline lesions can mimic and be difficult to distinguish from more discrete immune type deposits. Higher power examination frequently reveals a “mottled” appearance to the electron dense deposits of hyaline.

Capsular drops and hyaline caps are most commonly seen in the setting of diabetic nephropathy. However, they can be found in numerous other disorders and are not pathognomonic for diabetes. Capsular drops can also be seen in patients with advanced glomerular disease showing sclerosis and hyalinosis. In total, Stout found them in approximately 5% of non-diabetic cases and 37% of cases of diabetic nephropathy. Thus, although the capsular drop is not very common in patients with diabetic nephropathy, it is even less common in other renal diseases. Hyaline caps can be present in patients with segmental glomerulosclerosis related to systemic hypertension as well as primary focal segmental glomerulosclerosis.

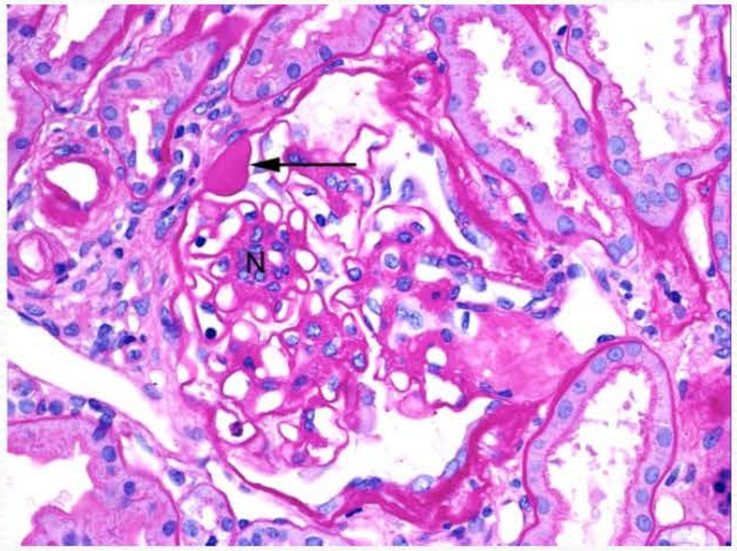


Fig 6-3 Glomerulus with hypercellular nodule (N) and capsular drop (arrow), PAS stain.

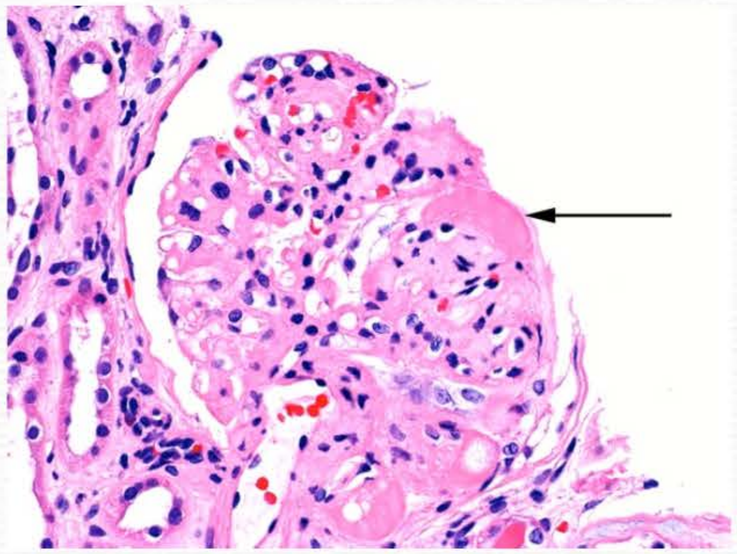


Fig 6-4 Glomerulus with hyaline cap (arrow), H&E stain.

Figure 6-1 Diabetic glomerulosclerosis with capsular drop (arrow), PAS stain.

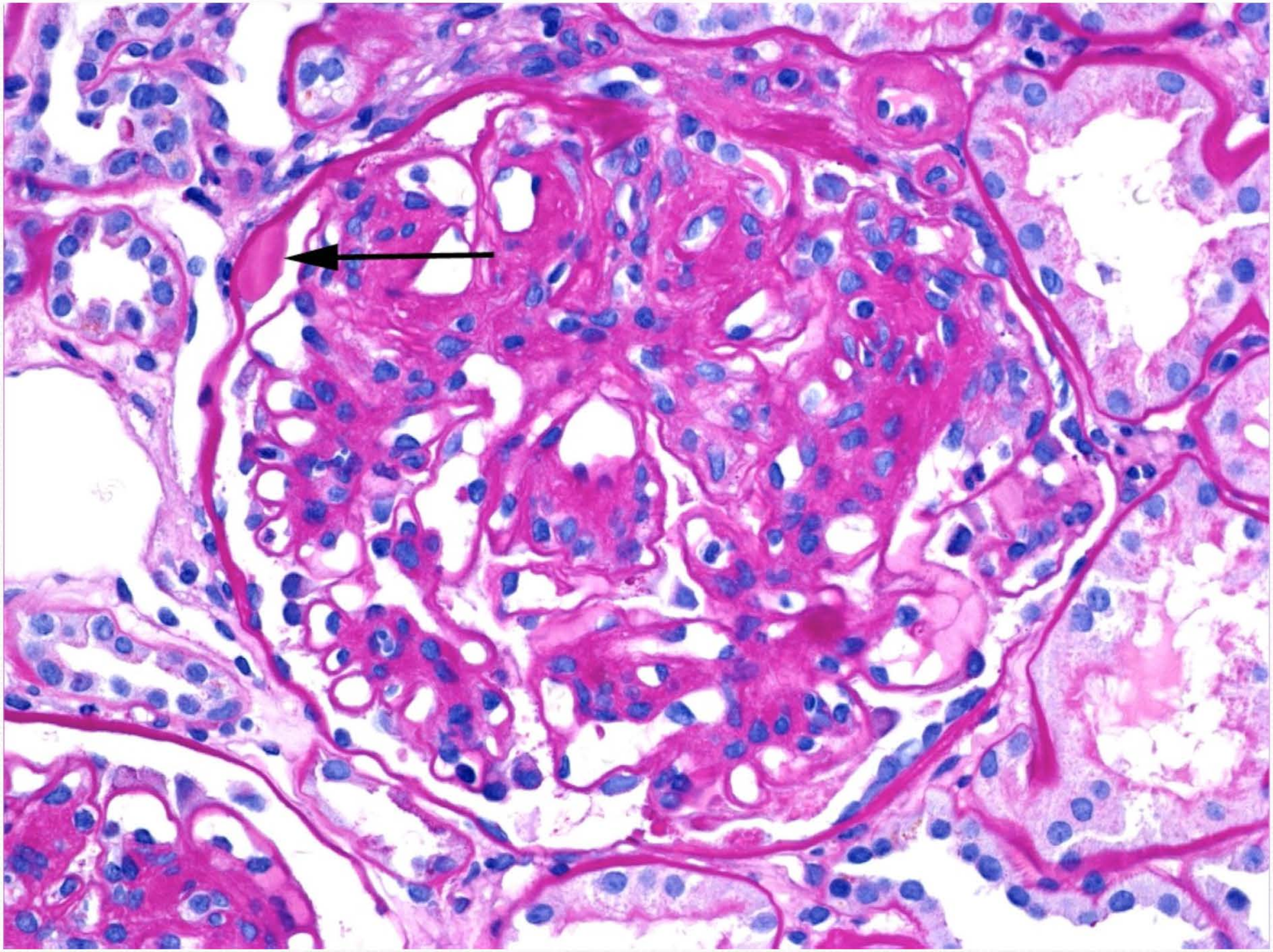


Figure 6-2 Silver negative capsular drop (arrow), Silver stain.

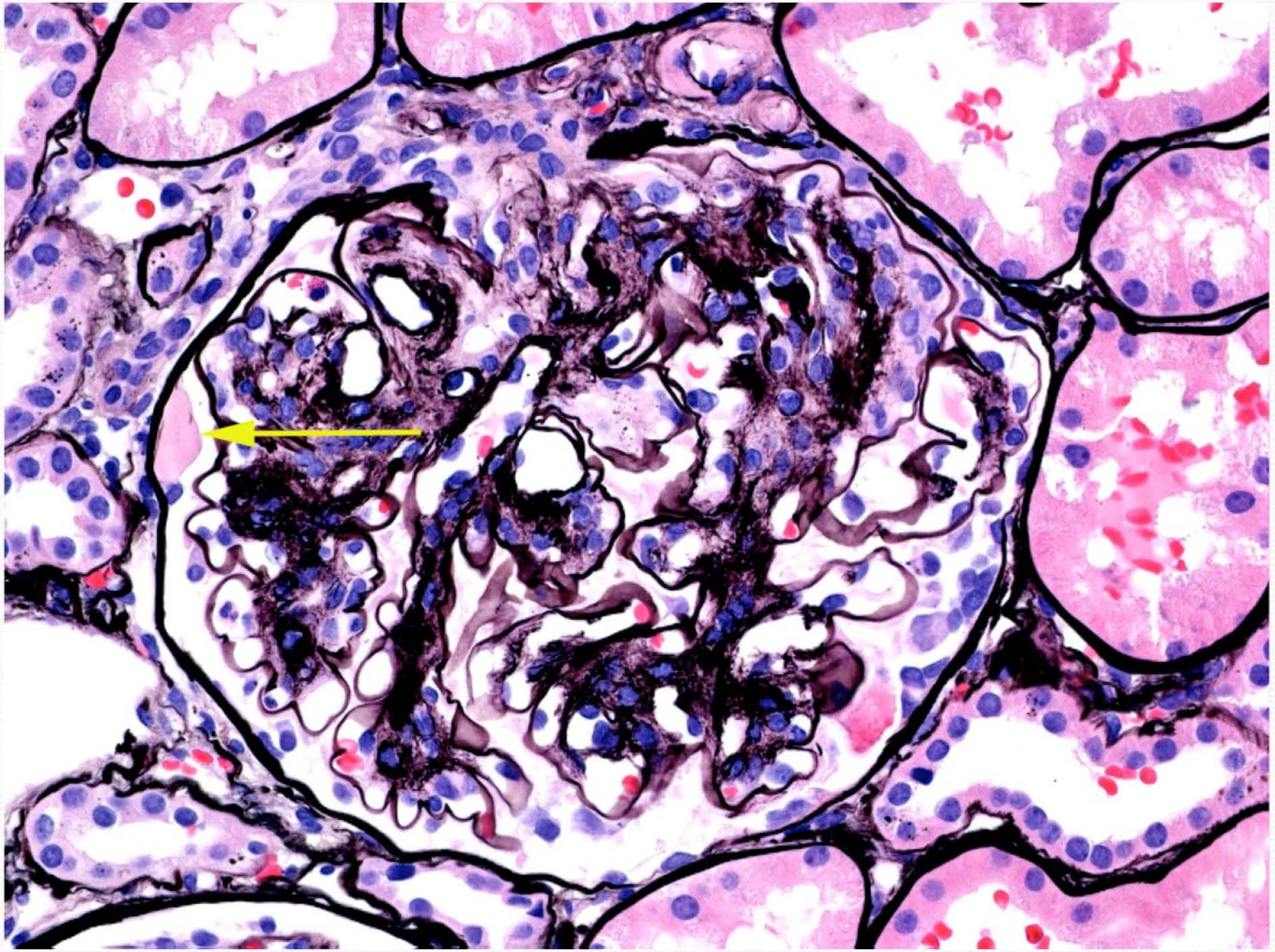


Figure 6-3 Glomerulus with hypercellular nodule (N) and capsular drop (arrow), PAS stain.

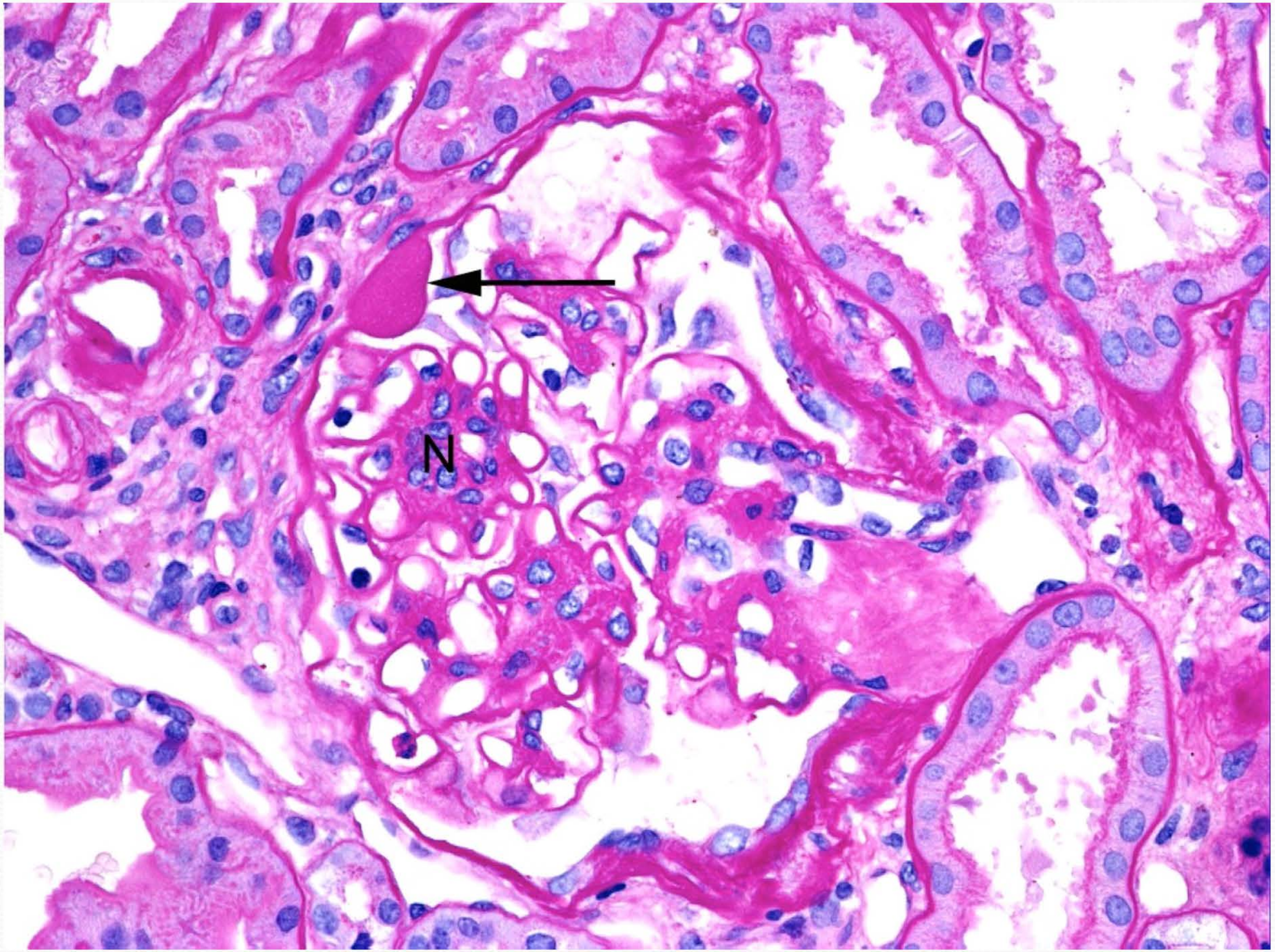


Figure 6-4 Glomerulus with hyaline cap (arrow), H&E stain.

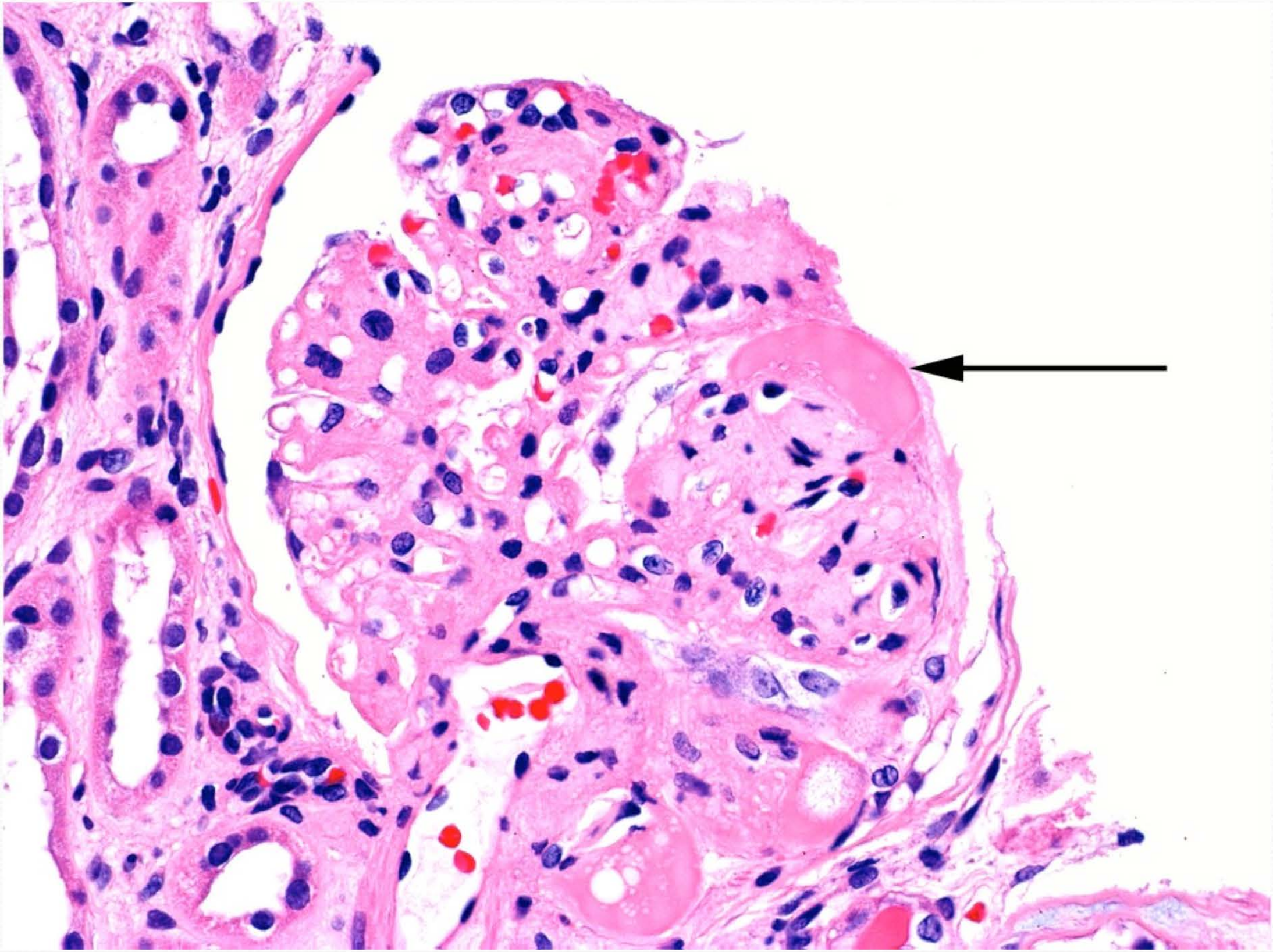


Figure 6-5 Glomerulus with hyaline cap (arrow), PAS stain.

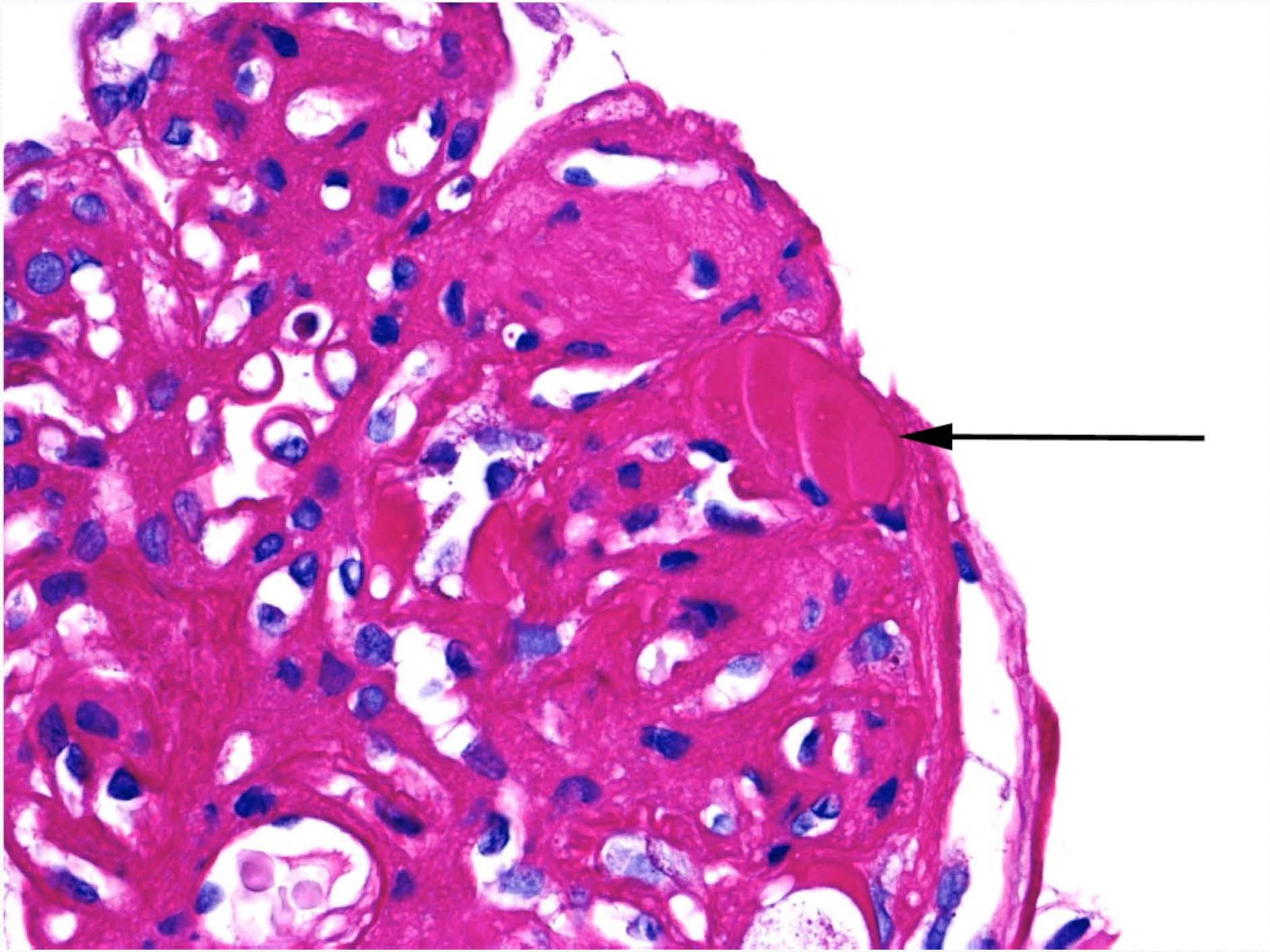


Figure 6-6 Hyaline cap appears as electron dense material ultrastructurally (arrows), Electron photomicrograph.

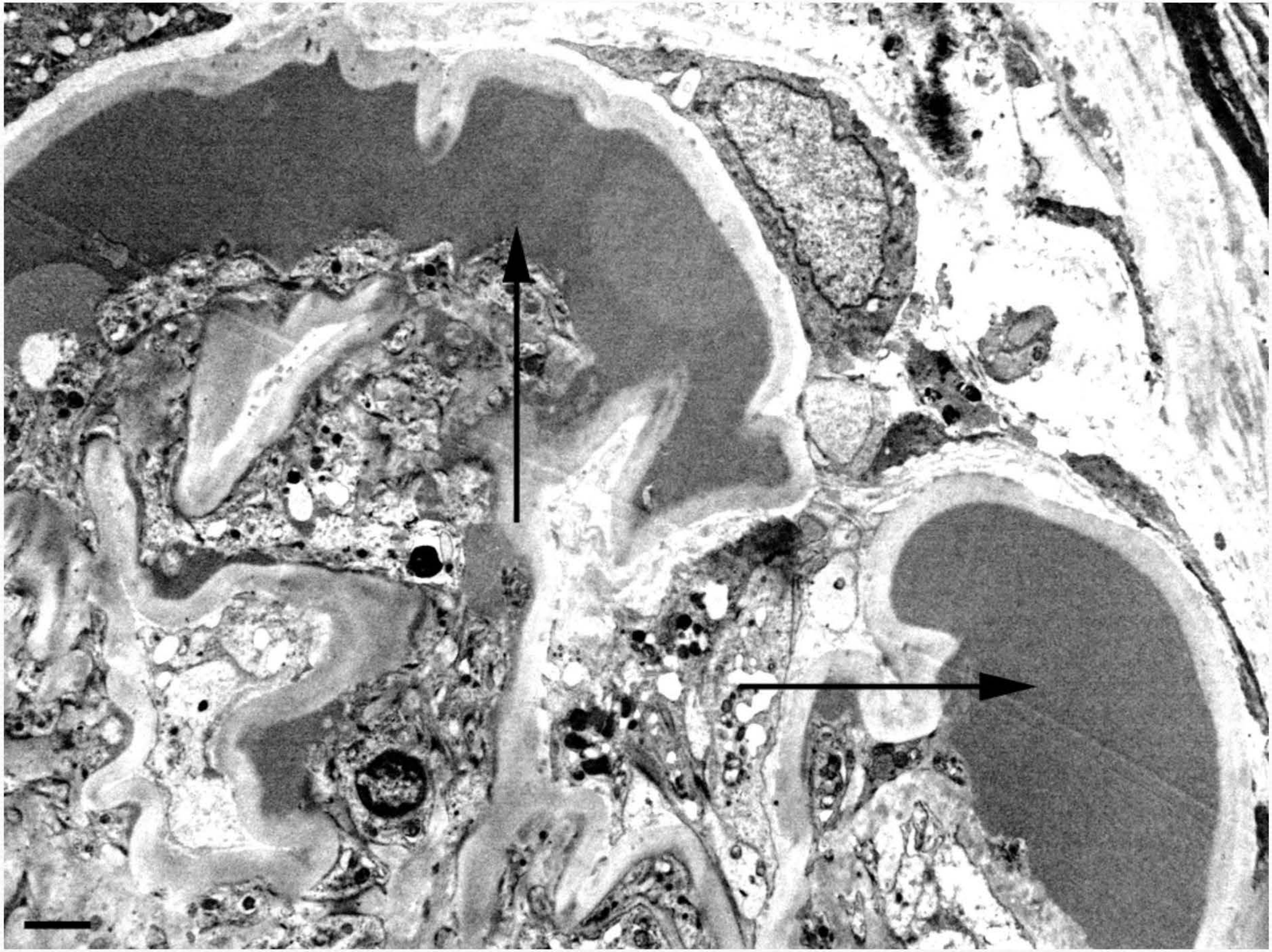


Figure 6-7 Glomerulus with large capsular drop (arrow), Jones methenamine silver stain.

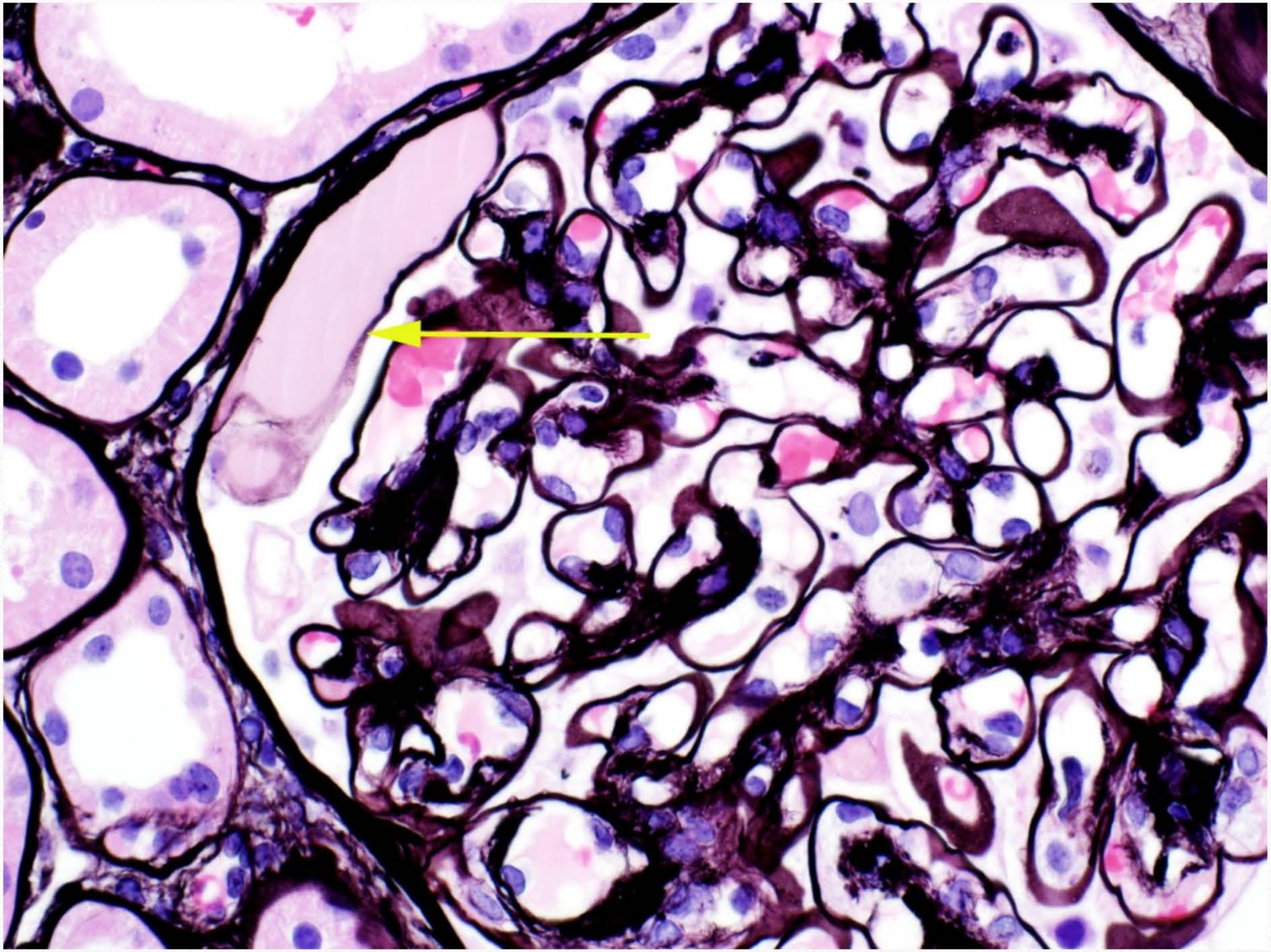


Figure 6-8 Glomerulus with nodular glomerulosclerosis and capsular drop (arrow), H&E stain.

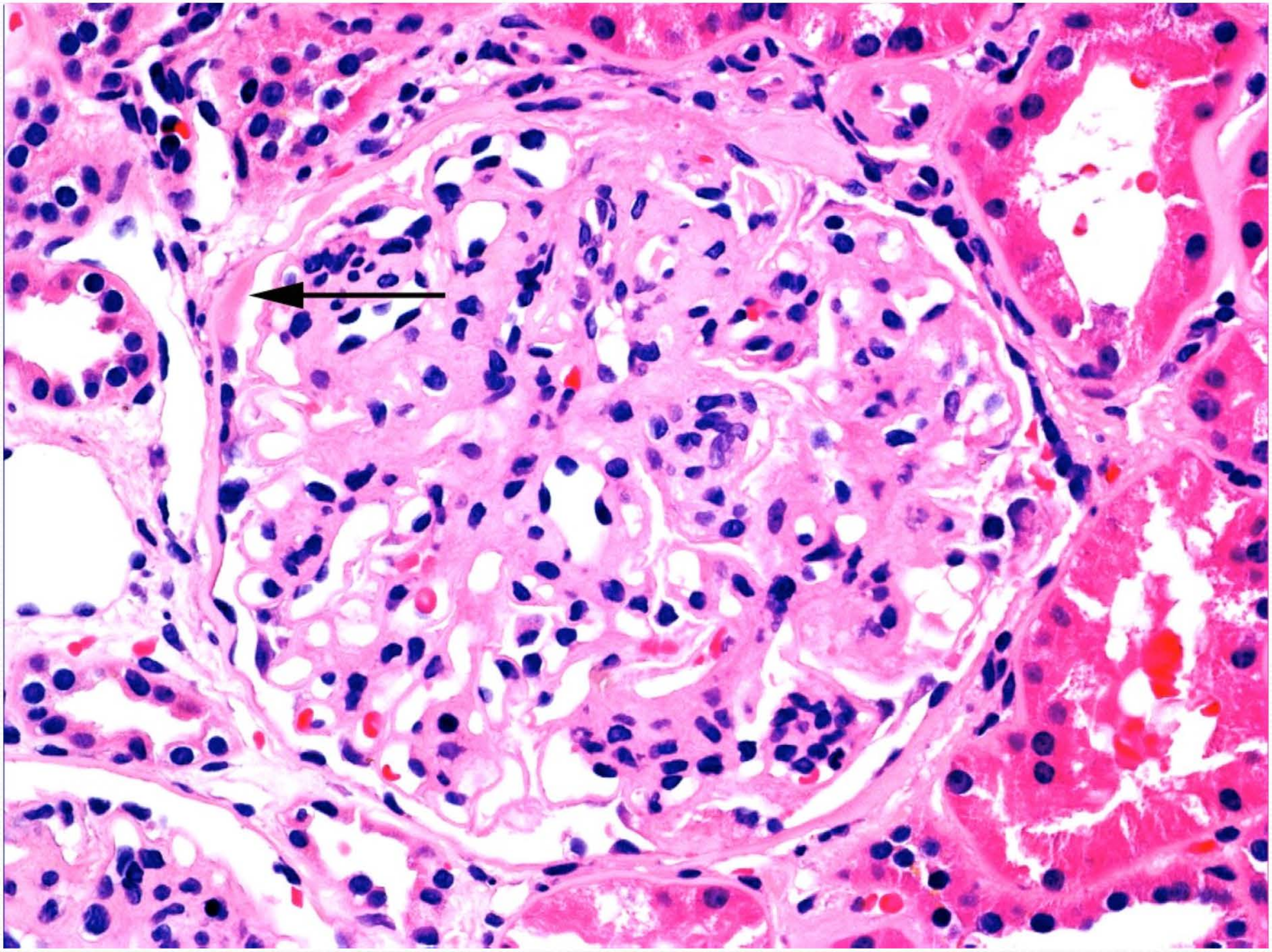


Figure 6-9 Hyaline cap (arrow) stains negative on Jones methenamine silver stain.

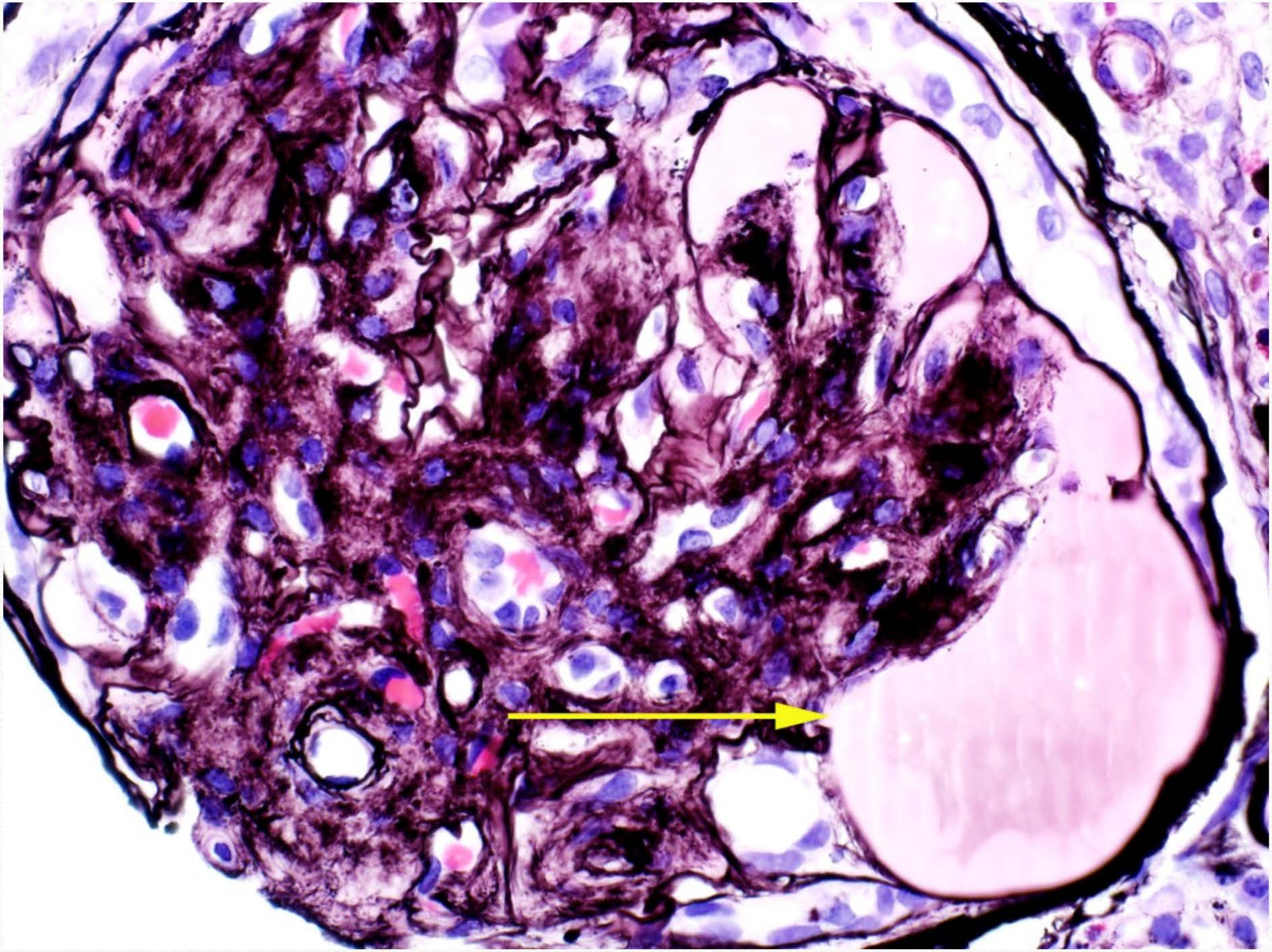


Figure 6-10 Glomerulus with hyaline cap (arrow), trichrome stain.

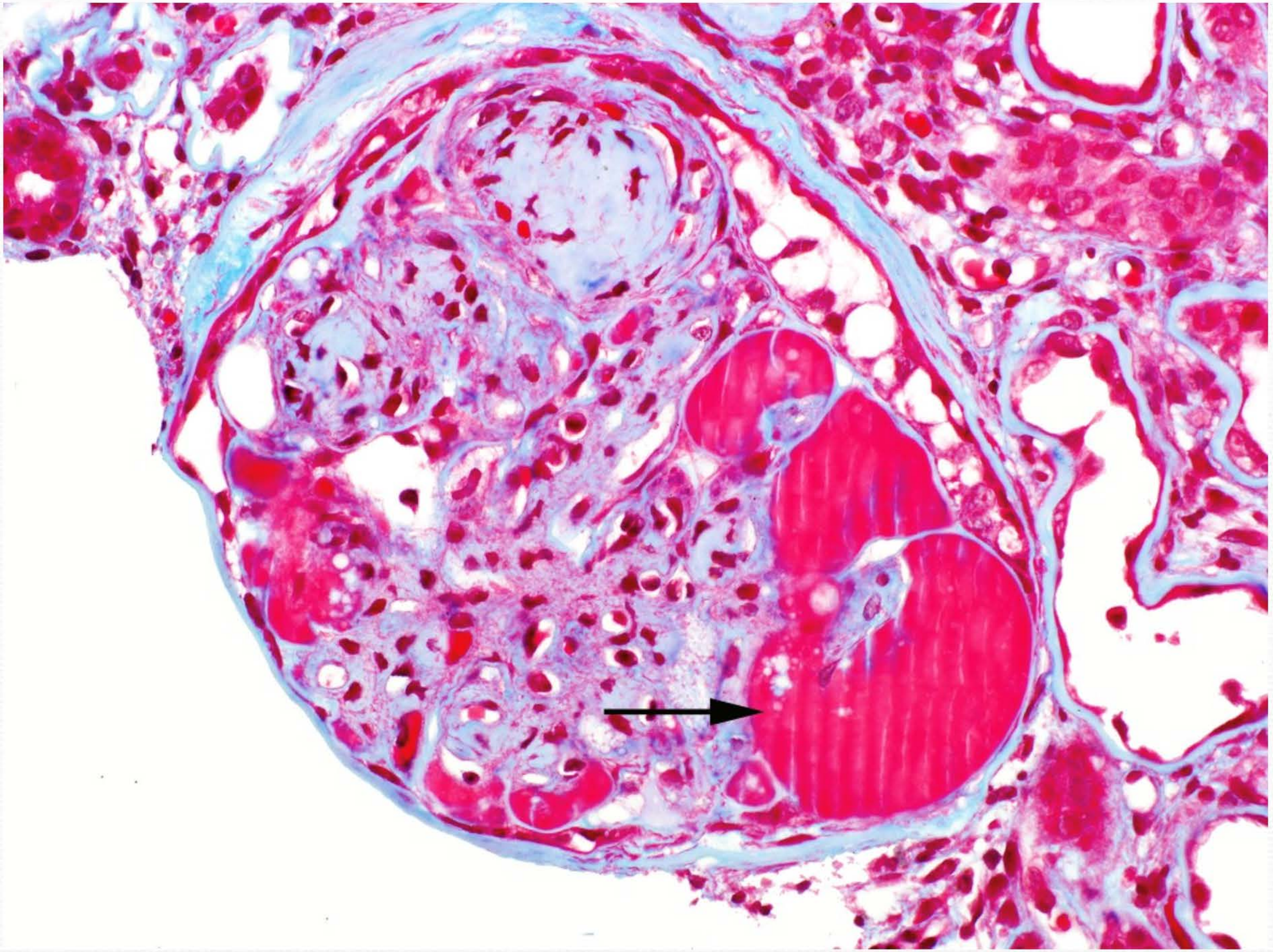
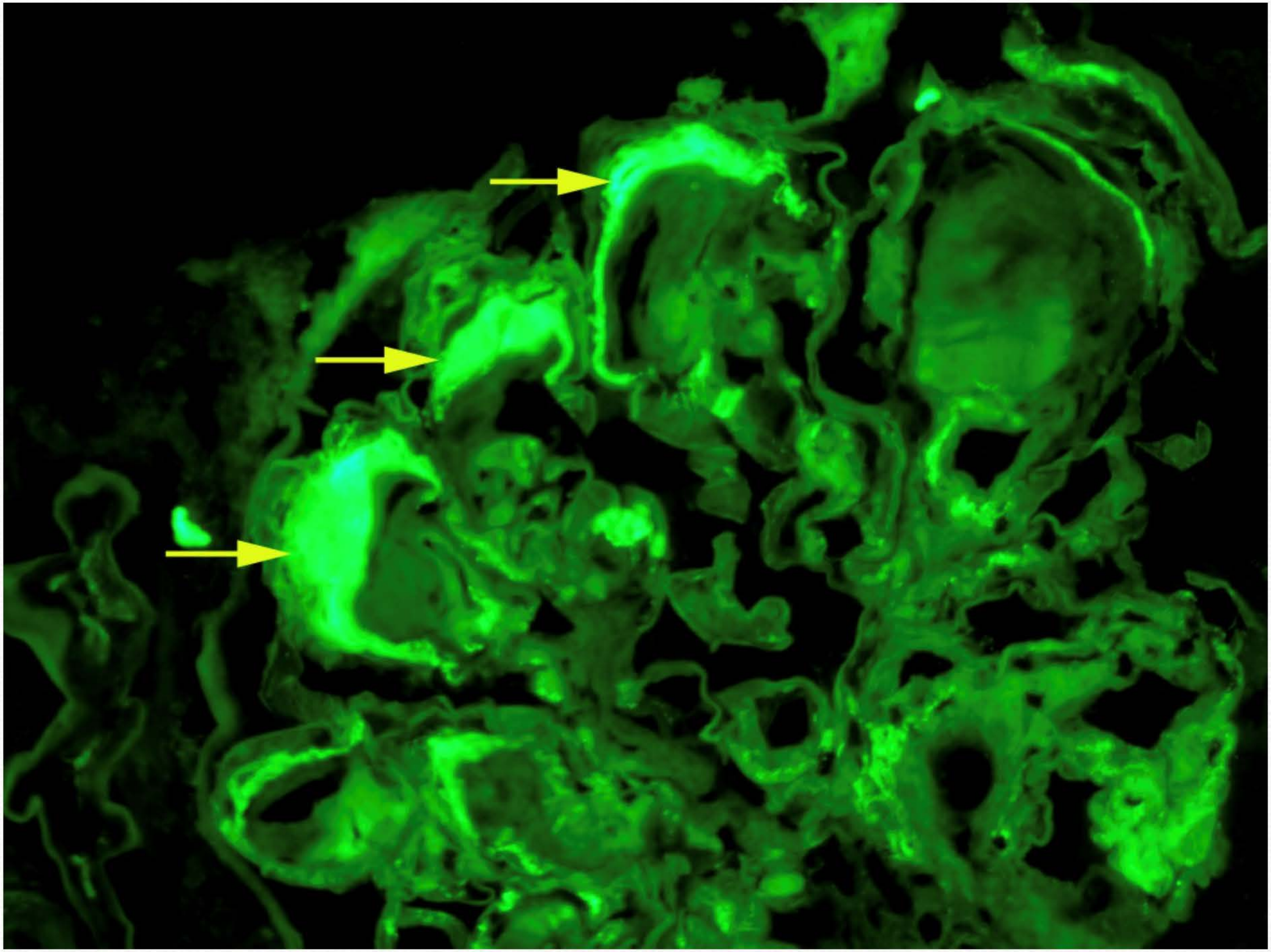
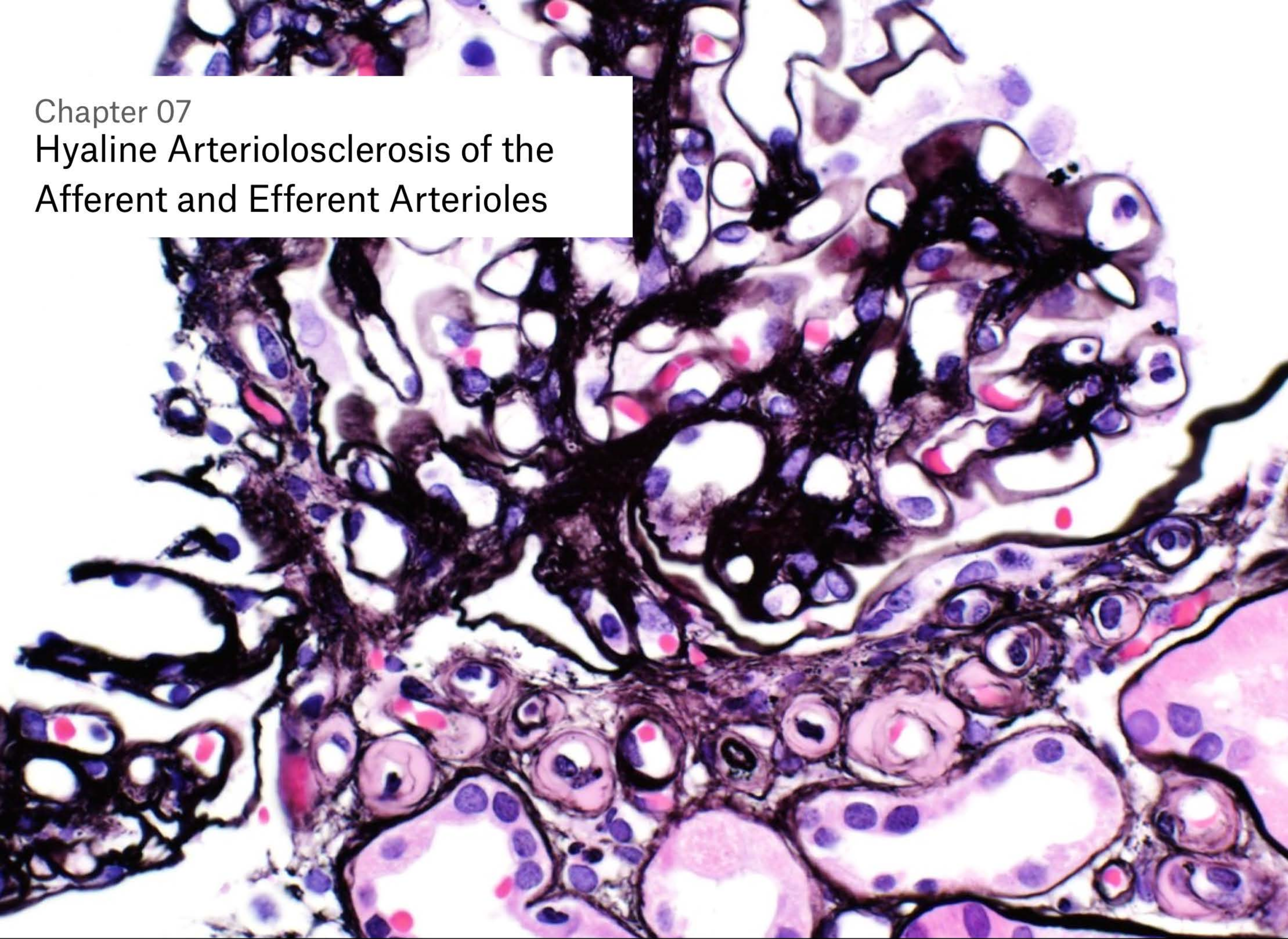


Figure 6-11 Hyaline cap with nonspecific staining for immunoglobulin (arrows), IgM by direct immunofluorescence.



Chapter 07

Hyaline Arteriolosclerosis of the Afferent and Efferent Arterioles



Hyaline Arteriolosclerosis of the Afferent and Efferent Arterioles

Hyaline arteriolosclerosis refers to the glassy somewhat refractile nature of the deposition of acellular material in arterioles with apparent narrowing or even complete closure of the arteriole lumens (Fig 7-1). Hyaline deposition is the result of an insudative process; that is, a lesion in which plasma proteins are "pushed" into the vessel wall by hydrostatic pressure. Insudative deposits are homogenous, eosinophilic, and often fill the entire circumference of the vascular wall. By electron microscopy these arterioles contain very dense homogenous deposits with occasional scattered membrane profiles and small vacuoles (Fig 7-2).

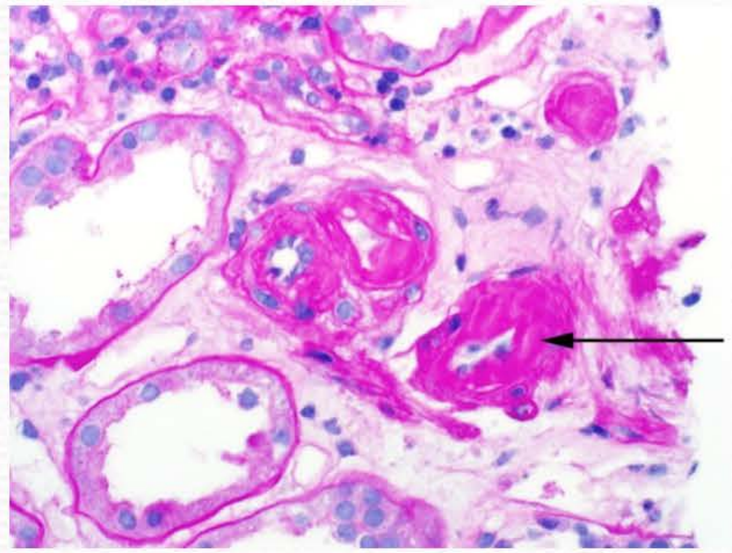


Fig 7-1 Glassy hyaline in an arteriole (arrow), PAS stain

Although hyalinization of the afferent arteriole is most severely and most commonly seen in patients with advanced diabetic nephropathy, it can be seen in patients with hypertension, aging, and other conditions (gout, etc). Thus, though not specific, in the setting of glomerular changes such as increased mesangial matrix and/or thickened GBMs, the hyalinosis is most likely associated with the diabetic condition.

Interestingly, though the hyalinization appears to compromise the arteriole lumen when the tissue is immersion fixed (standard practice) (Fig 7-3), perfusion-fixed kidneys reveal the opposite story. In fact, the lumen is not narrowed and the hyaline material is compressed against the vascular wall. Indeed it has been suggested that the plasmatic hyaline insudate is a response

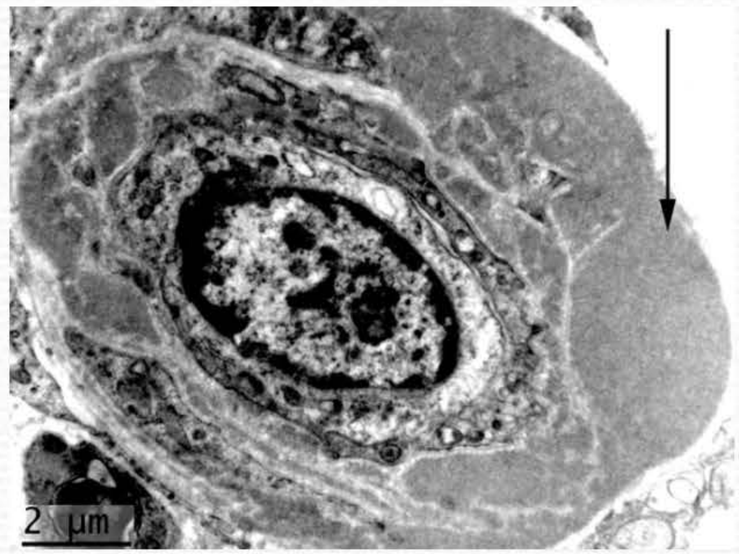


Fig 7-2 Electron dense hyaline (arrow), Electron photomicrograph.

to the loss of the medial muscle layer of the arteriole, and secondarily serves as a tamponade to fill in the missing muscle cells in the media.

It is important to search in a renal biopsy for glomeruli that have both an afferent and an efferent arteriole at the vascular pole because afferent and efferent hyalinization of these arterioles is a characteristic finding in diabetic renal disease (Fig 7-4). Typically, the afferent arteriole enters the glomerulus in a perpendicular fashion (Fig 7-5) and the efferent arteriole exits and loops around a portion of the glomerular tuft adjacent to Bowman's capsule (Fig 7-6). However, to correctly identify the afferent and efferent arterioles requires a section with both arterioles visible at the vascular pole. Alternatively, if one arteriole is seen arising from an interlobular vessel, then it can be identified an afferent arteriole.

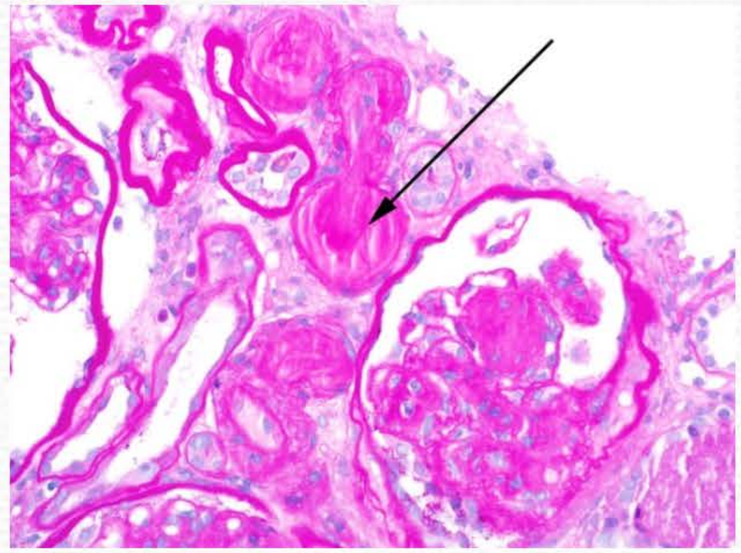


Fig 7-3 Arteriole with apparent occlusion by hyaline (arrow), PAS stain.

It was once thought that hyaline arteriolosclerosis of both the afferent and efferent arterioles was pathognomonic of diabetic nephropathy. However, this change in both arterioles has been noted described in non-diabetic conditions including cyanotic congenital heart disease, gout, aging, and in calcineurin inhibitor toxicity.

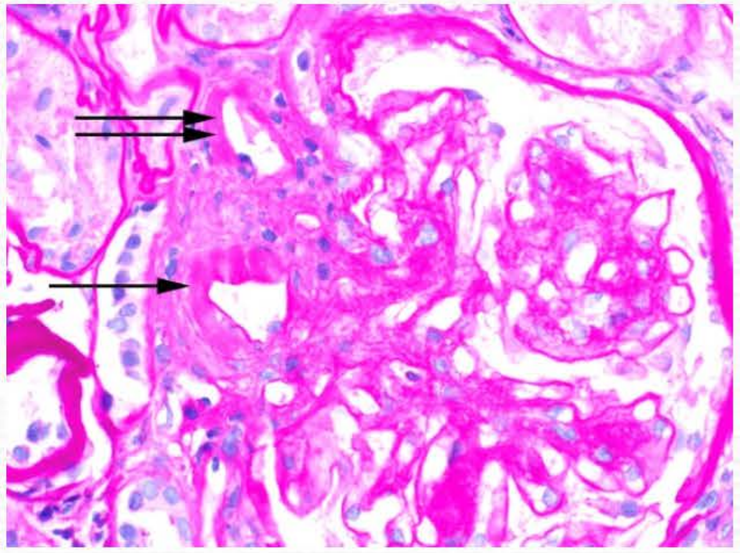


Fig 7-4 Hyaline in both afferent (arrow) and efferent arterioles (double arrows), PAS stain.

The pathogenetic mechanism(s) leading to the hyalinization of the efferent arterioles (downstream from the afferent arteriole and glomerular capillaries and under diminished pressures) is uncertain. This may speak to the volume of intramural and/or mesangial vascular flow. Alternatively, this may reflect the changes seen in the small arterioles throughout the body in patients with diabetes.

There is often increased vascularity at the hilum of the diabetic glomerulus in addition to the usual afferent and efferent arterioles (Fig 7-7). It is thought that

these represent extra efferent arterioles (EEAs). Many extra efferent vessels have been noted per glomerulus, apparently each draining a separate glomerular lobule. Several studies (including three-dimensional analysis) have shown a complex arborization of the arterioles and that most of these EEAs appear to be connected to the second- and third-order branches of the periglomerulur arterioles (afferent and/or efferent) and could represent shunts into the peritubular capillaries. Vascular remodeling and shunt formation of various types have been described in diabetic nephropathy, and this is sometimes thought to be associated with increased glomerular inflow and facilitates efferent blood flow from the glomerulus. This neovascularization/ neoangiogenesis was first observed in type I diabetics with microalbuminuria, but is more frequently seen in patients with elevated albumin-secretion.

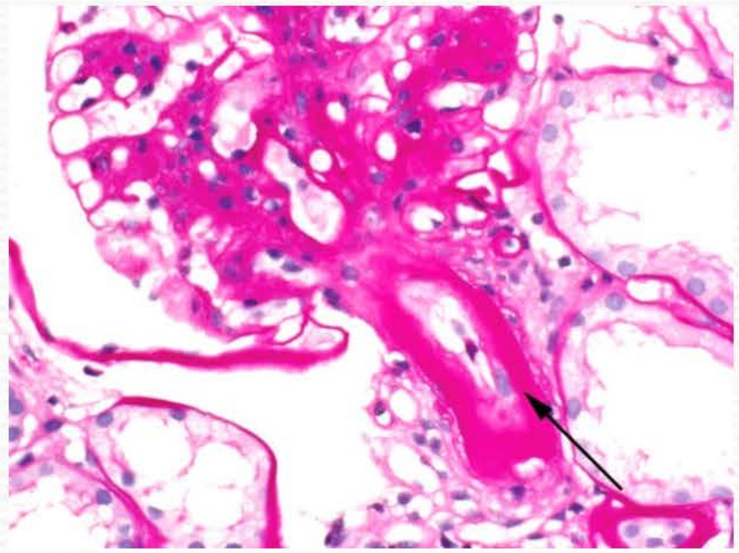


Fig 7-5 Hyalinized afferent arteriole entering the glomerulus at a right angle (arrow), PAS stain.

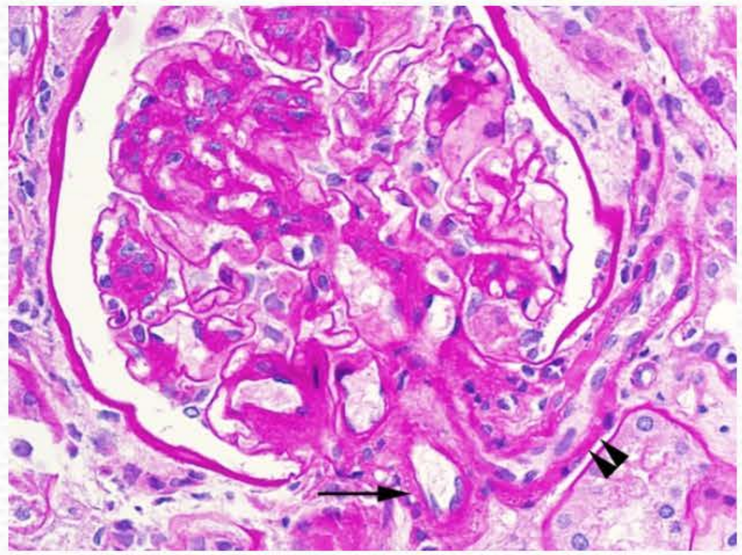


Fig 7-6 Hyalinized efferent arteriole leaving the glomerulus curving around Bowman's capsule (arrowheads), hyalinized afferent arteriole (arrow), PAS stain.

Figure 7-1 Glassy hyaline in an arteriole (arrow), PAS stain.

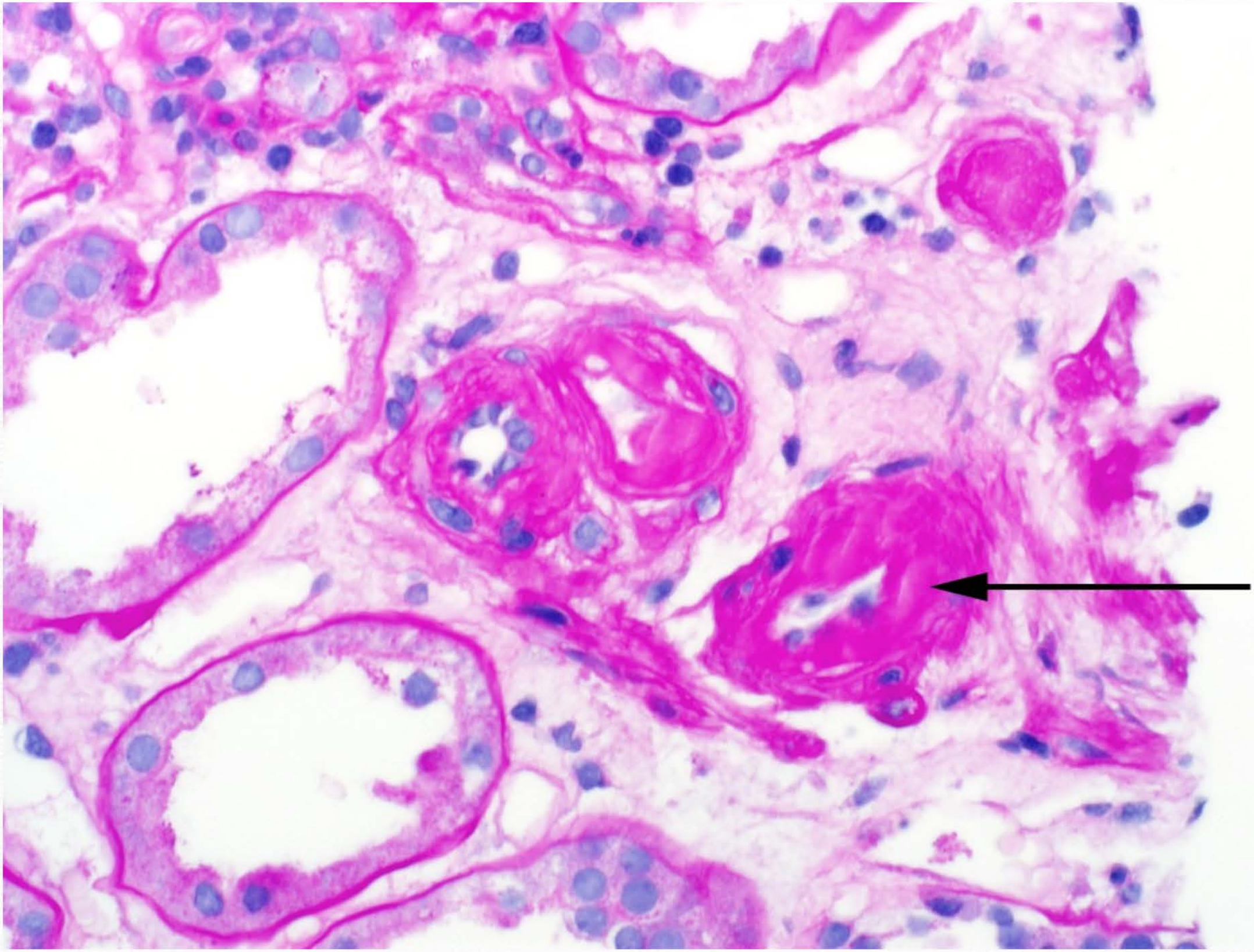


Figure 7-2 Electron dense hyaline (arrow), Electron photomicrograph.

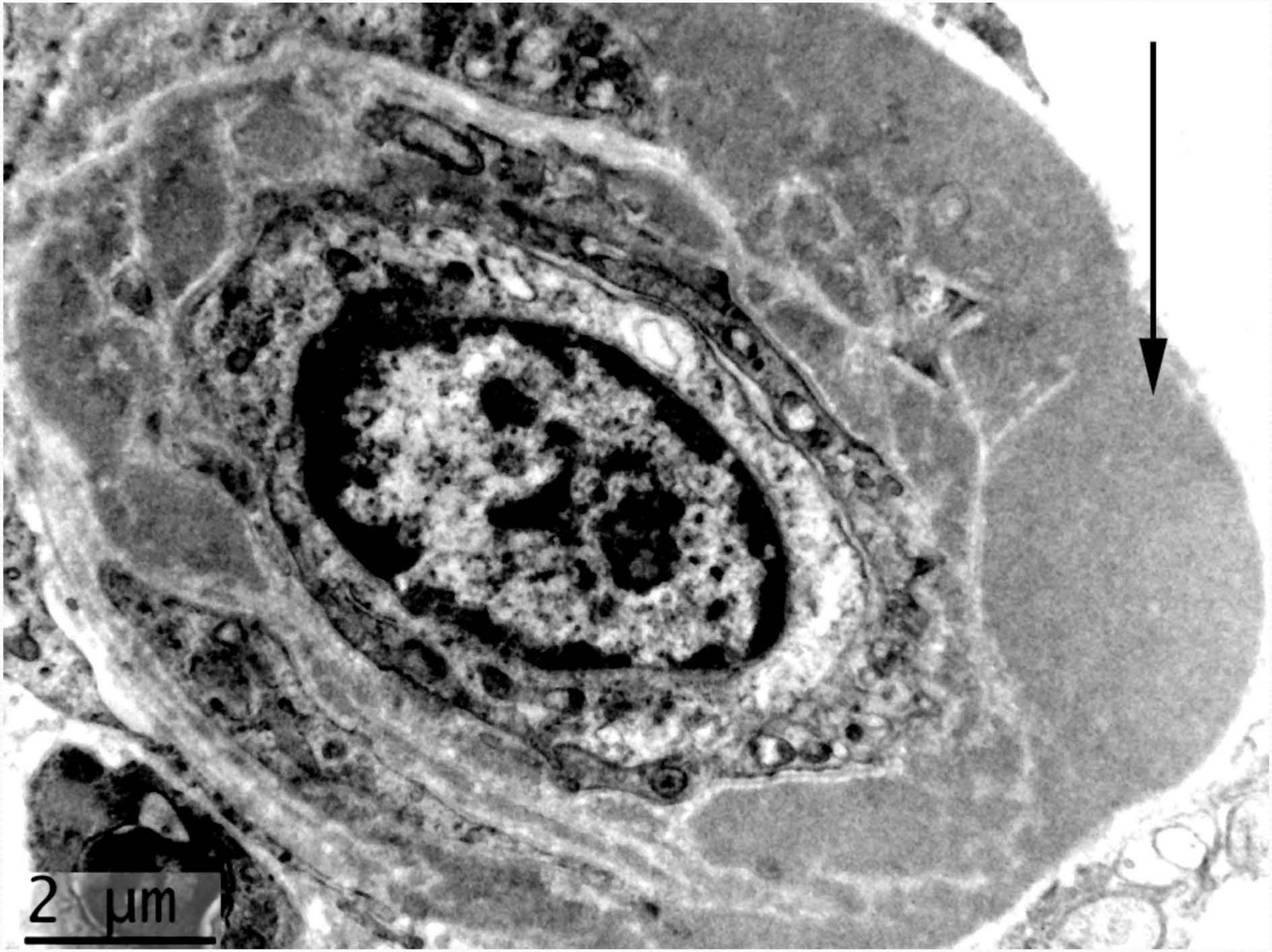


Figure 7-3 Arteriole with apparent occlusion by hyaline (arrow), PAS stain.

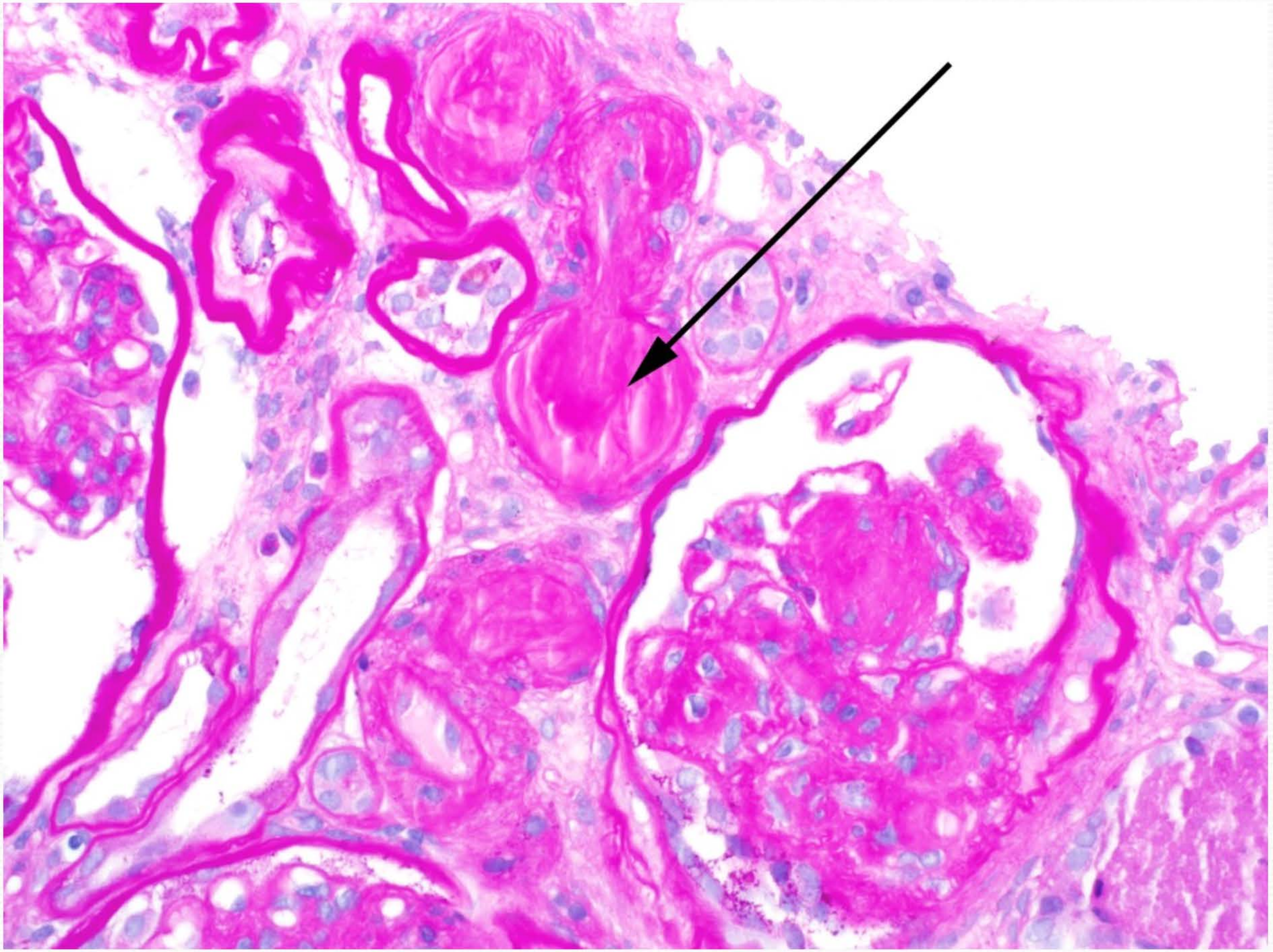


Figure 7-4 Hyaline in both afferent (arrow) and efferent arterioles (double arrows), PAS stain.

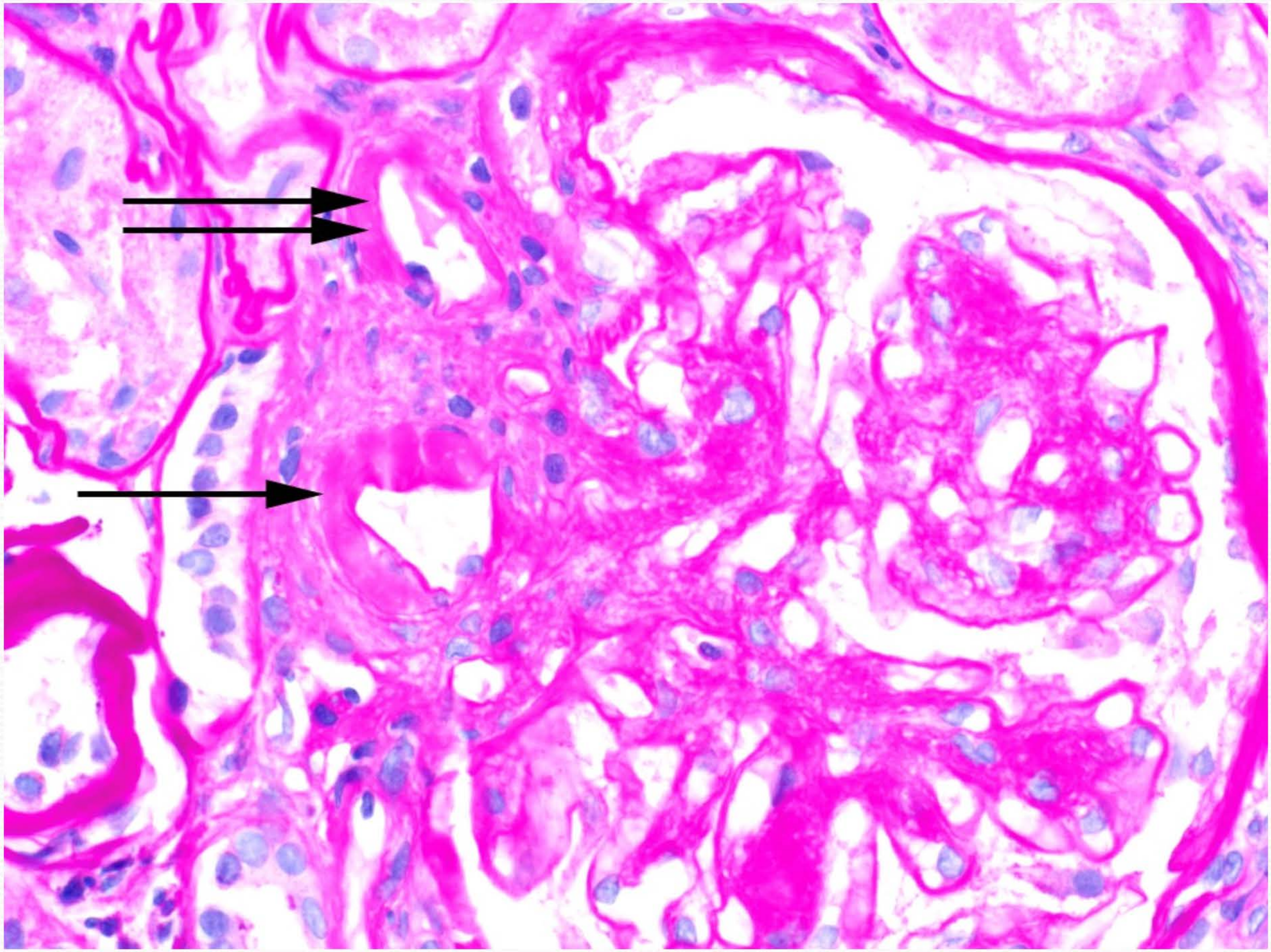


Figure 7-5 Hyalinized afferent arteriole entering the glomerulus at a right angle (arrow), PAS stain.

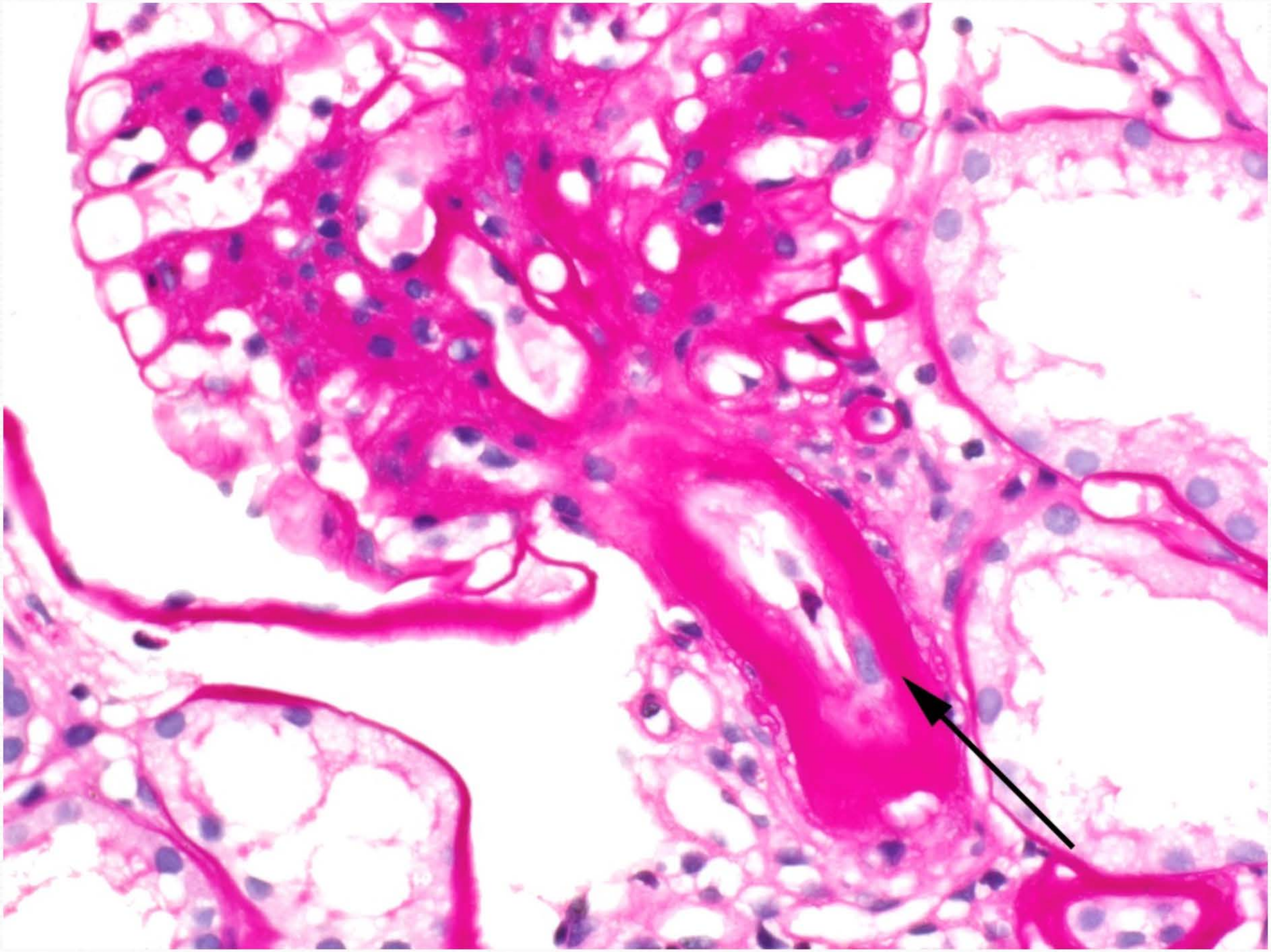


Figure 7-6 Hyalinized efferent arteriole leaving the glomerulus curving around Bowman's capsule (arrowheads), hyalinized afferent arteriole (arrow), PAS stain.

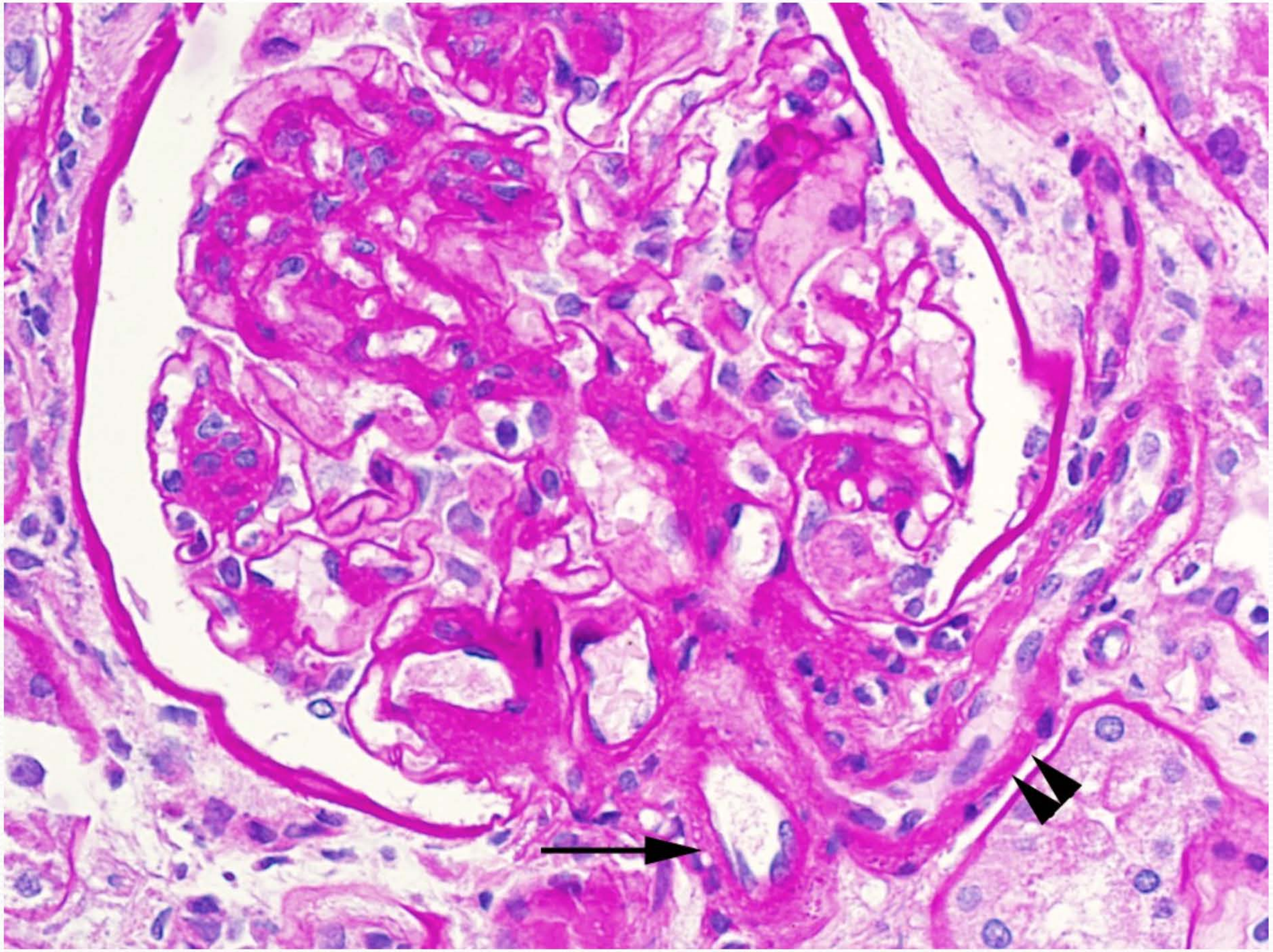


Figure 7-7 Hyalinized neovascularization at the glomerulus hilus (arrow), Silver stain.

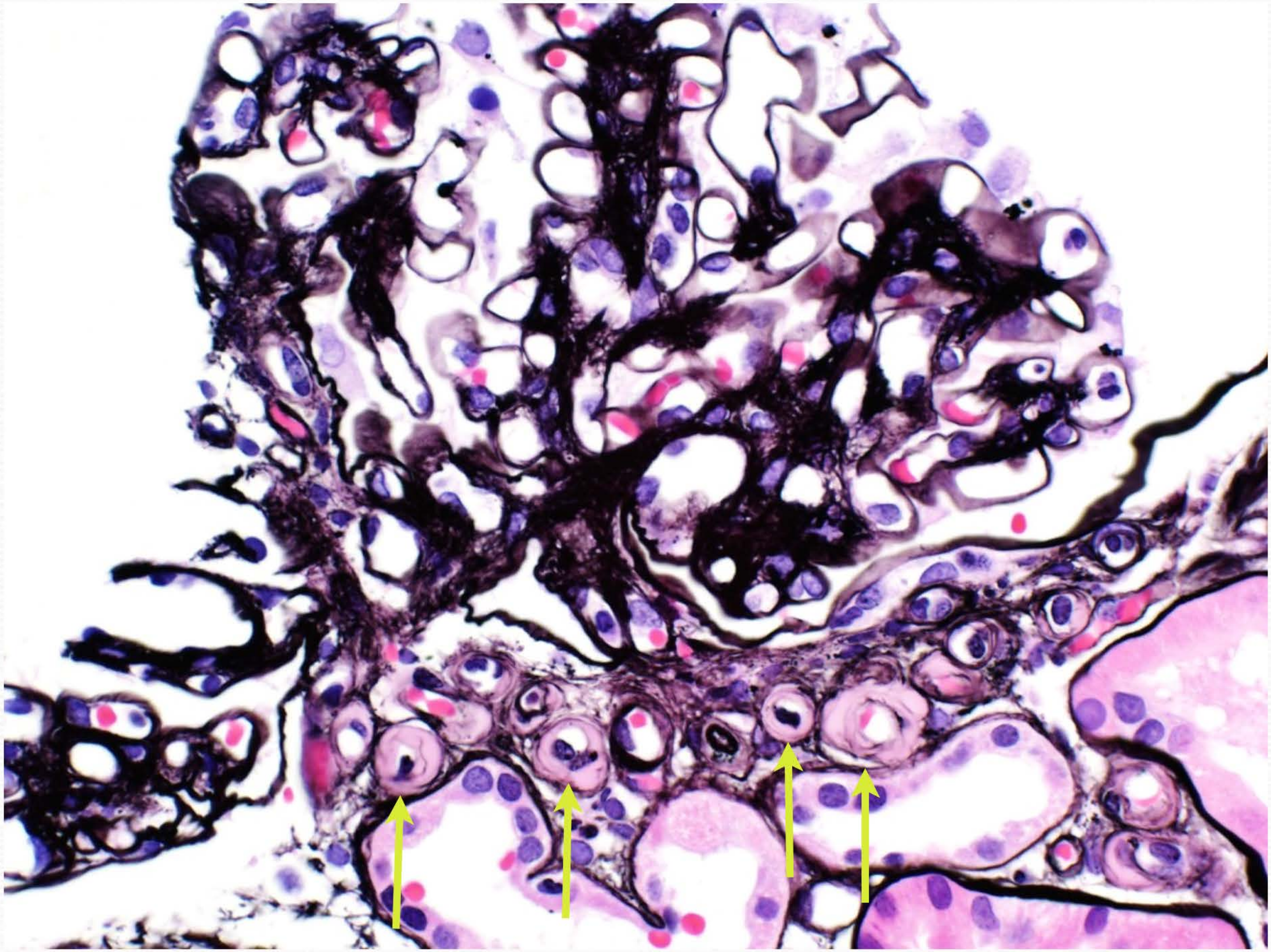


Figure 7-8 Arteriolar hyaline stains red on trichrome stain (arrow), Trichrome stain.

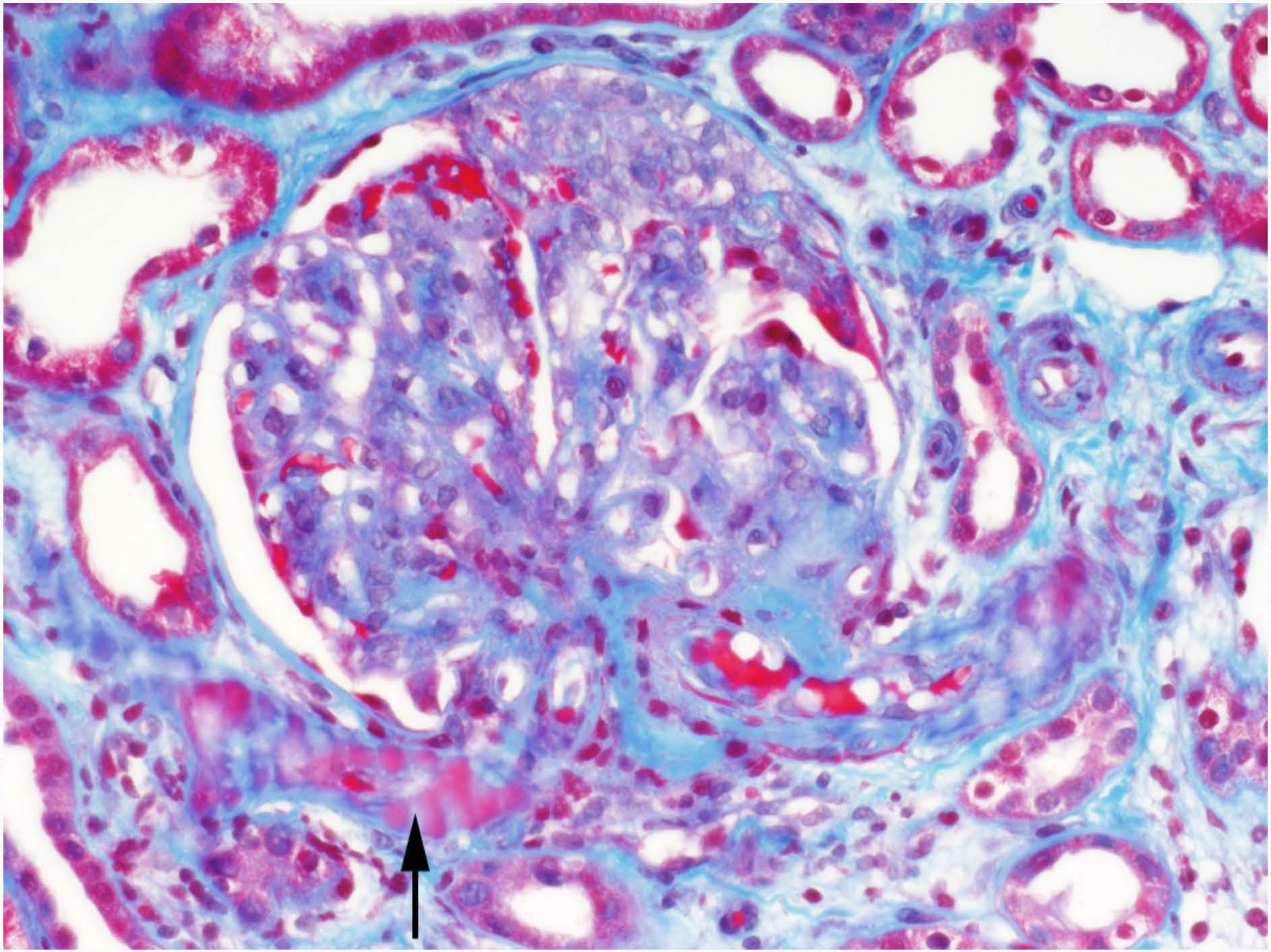


Figure 7-9 Arteriolar hyaline is silver negative (arrow), Silver stain.

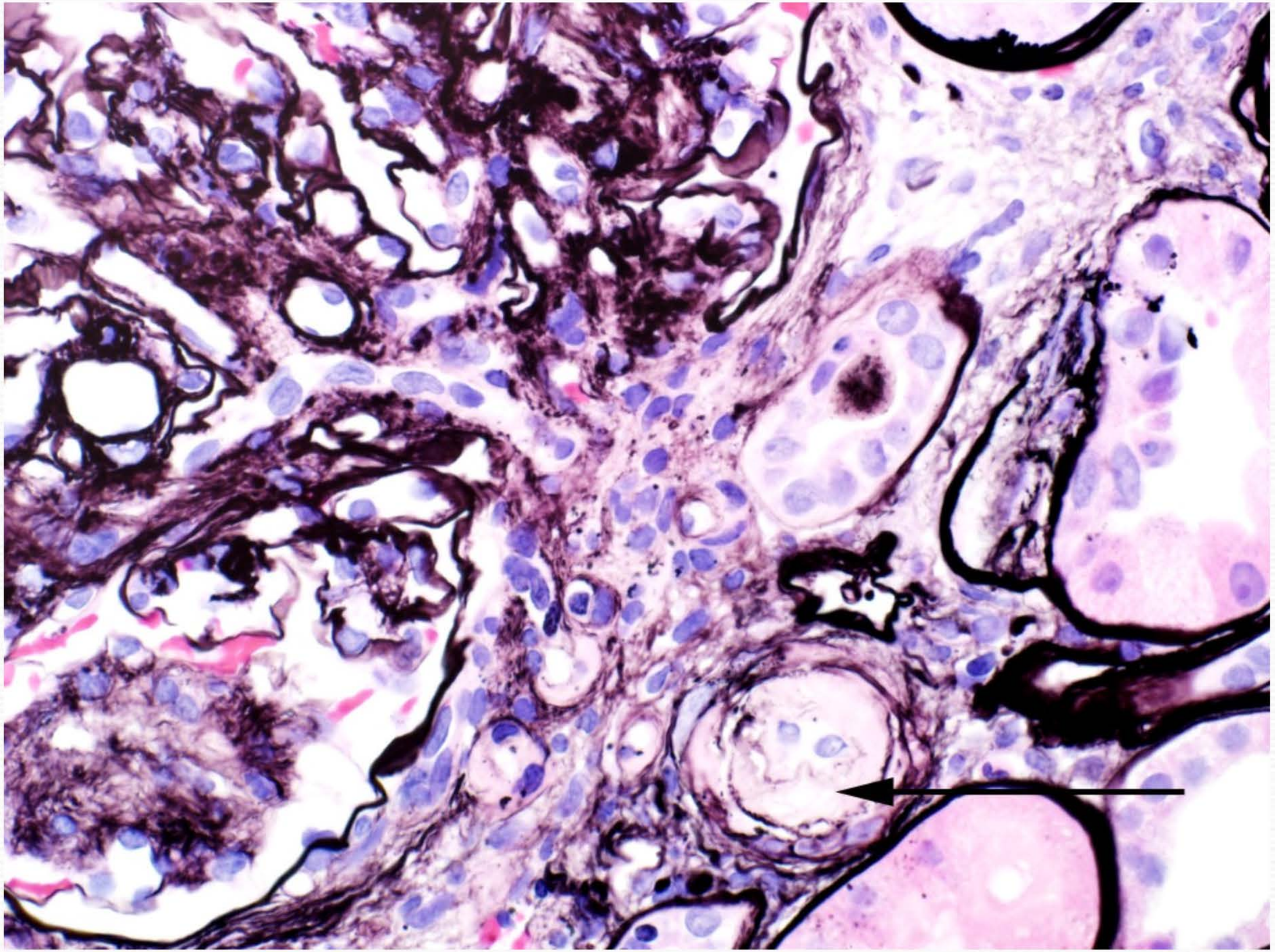


Figure 7-10 Hyaline in an arteriole (arrow), PAS stain.

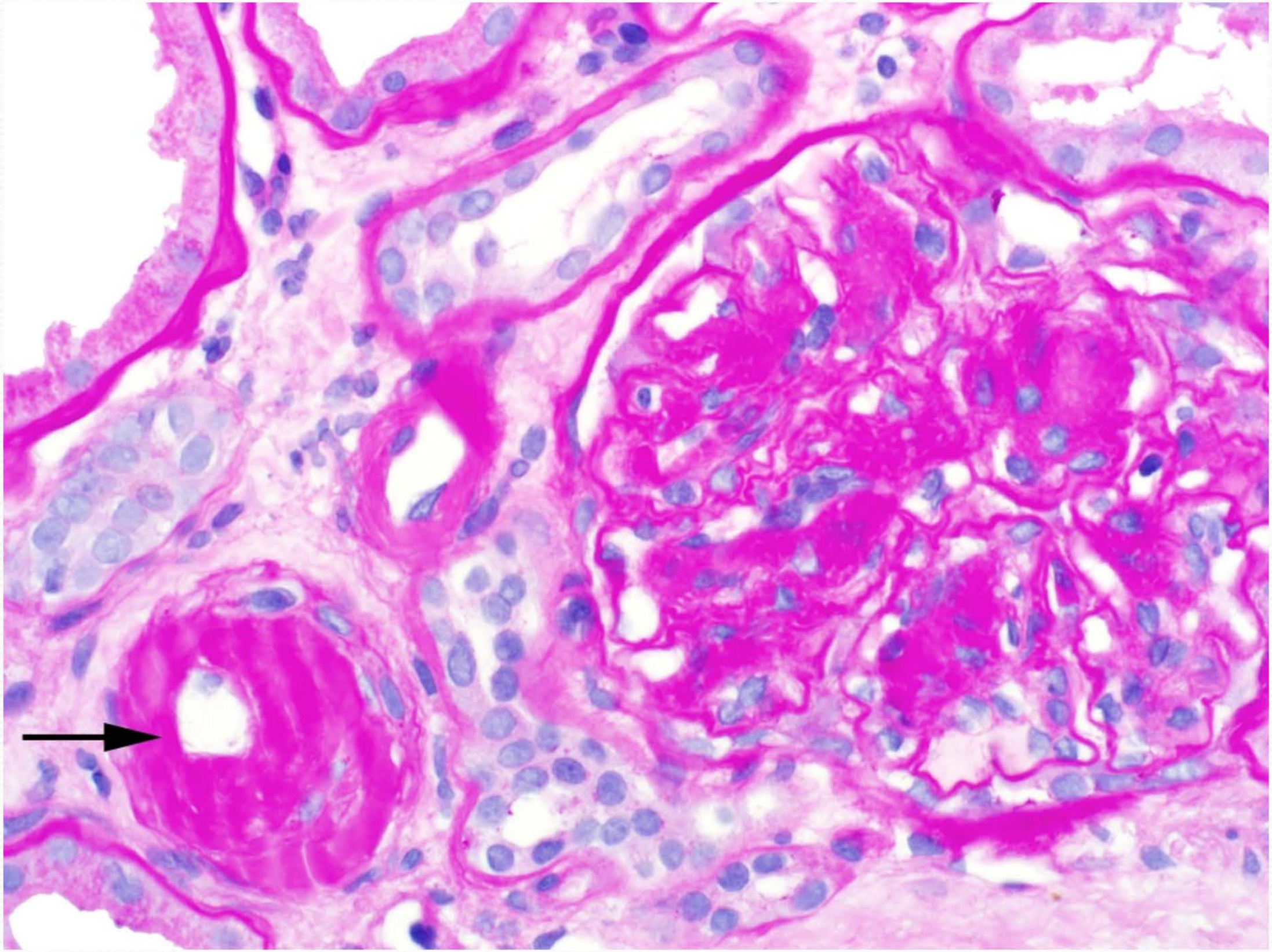
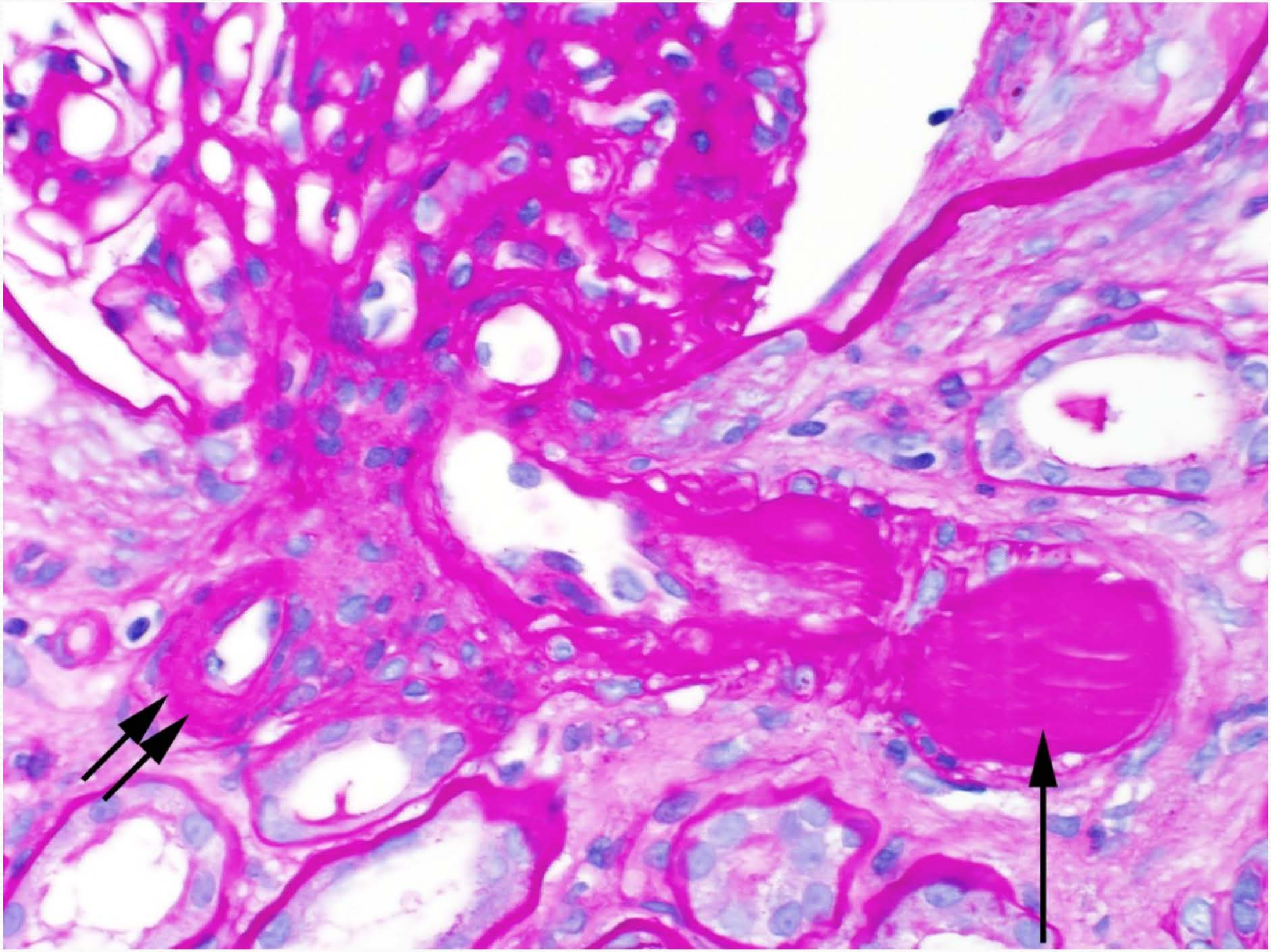
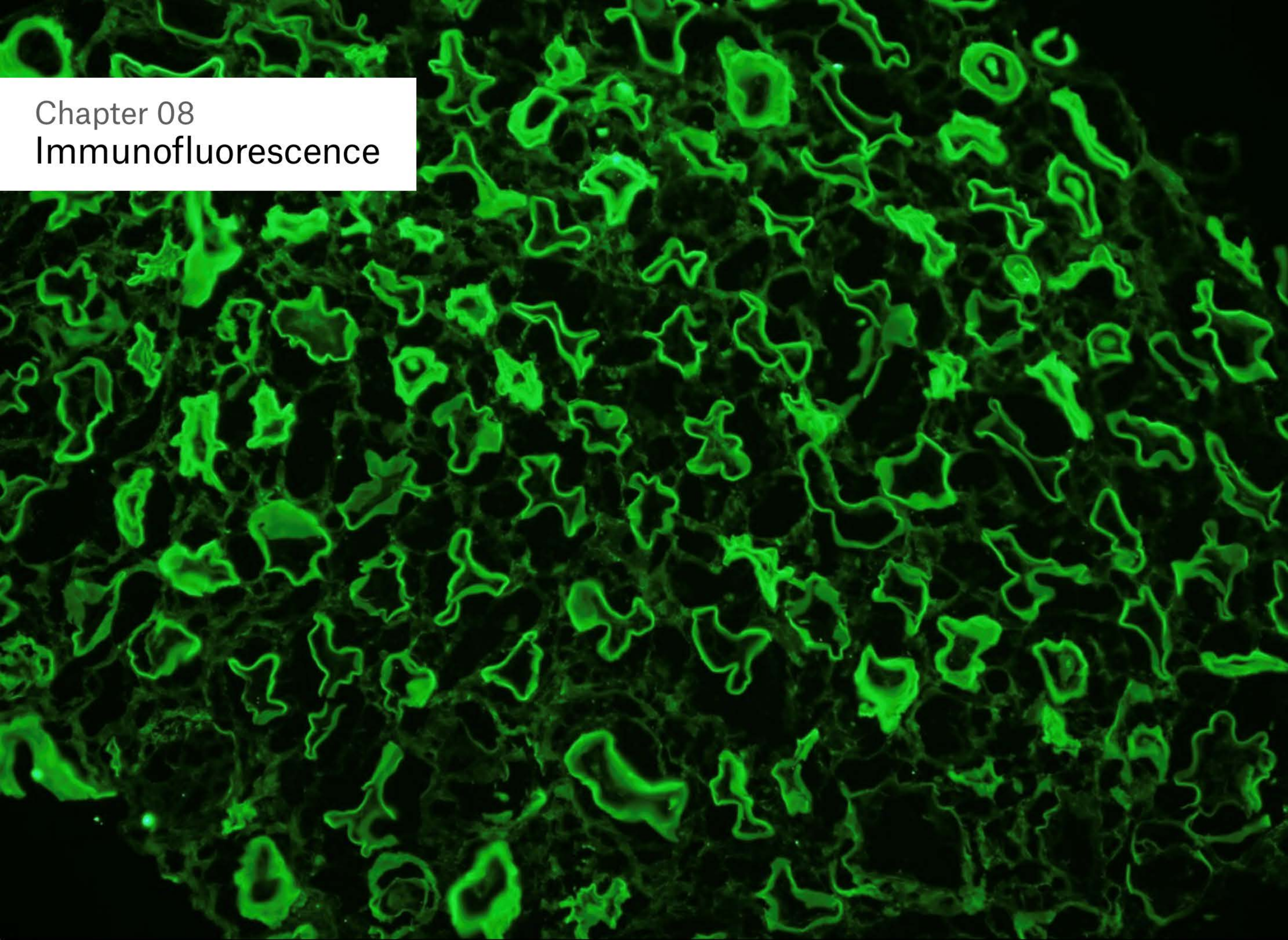


Figure 7-11 Glassy pink hyaline in both afferent (arrow) and efferent arterioles (double arrows), PAS stain.



Chapter 08

Immunofluorescence



Immunofluorescence

Routine immunofluorescence microscopy (IF) study of the diabetic kidney is critically important to exclude an accompanying immune-mediated disease (e.g. infection-associated glomerulonephritis, membranous glomerulopathy, IgA nephropathy, etc). However, diabetic nephropathy has characteristic (though not specific) findings by IF including an intense linear staining along the glomerular and tubular basement membranes for albumin and IgG, and thus also kappa and lambda light chains (Fig 8-1– Fig 8-2). This does not represent an anti-GBM or anti-TBM antibody phenomenon because, when eluted from the biopsy material, the IgG fails to show specific binding to renal parenchymal structures. Complement is usually not detected in this scenario. If there is a superimposed immune complex-mediated renal disease in a diabetic patient then the tubular (and glomerular) basement membrane staining should be granular and generally includes both immunoglobulin(s) and complement.

The mechanism of the linear deposition of IgG is uncertain but may be related to the abnormal and thickened (and possibly "sticky") GBMs and TBMs in diabetic nephropathy. Some have suggested that it is charge related, but the difficulty in eluting these proteins is against a charge-related mechanism.

This linear staining is usually of only passing interest in the patient with otherwise unremarkable diabetic nephropathy. However, recognition of light chain deposition disease (LCDD, which also stains the GBMs and TBMs for one of the two light chains) on a background of diabetic nephropathy is difficult. The key to recognition is the light chain restriction. Confirmation requires electron microscopy demonstrating the presence of very finely granular (powdery) deposits on the outer third of the TBMs and in the subendothelial area of the GBMs. Thus even this non-specific, non-immunologic, bright, linear staining in a diabetic for IgG and albumin needs to be studied carefully through the entire series of IF stains.

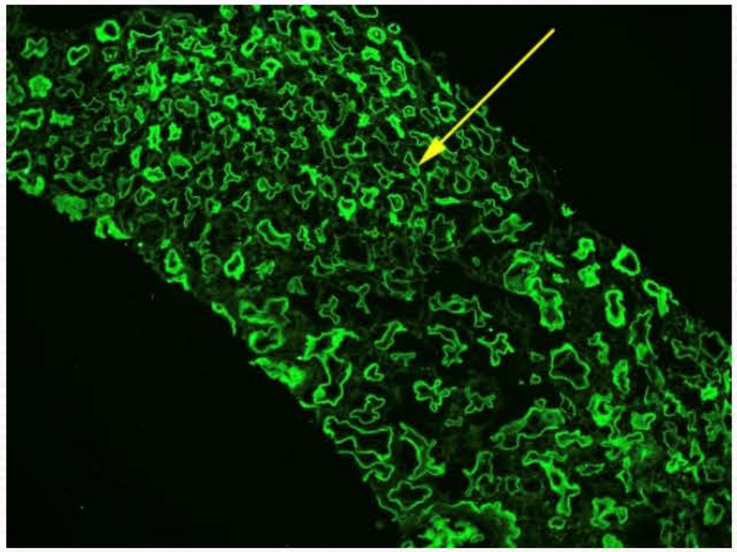


Fig 8-1 Linear tubular basement membrane staining for IgG (arrow), Fluorescence stain.

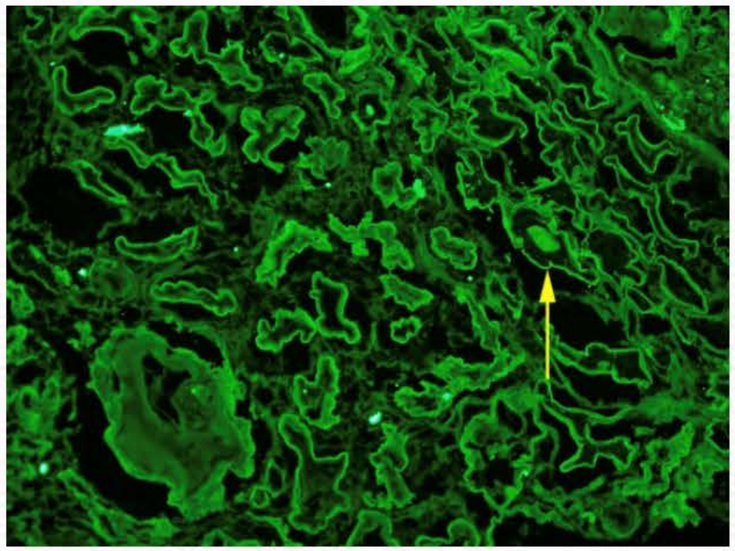


Fig 8-2 Linear tubular basement membrane staining for albumin (arrow), Fluorescence stain.

Granular IF patterns for the immunoglobulins and complement raises the possibility of either an alternate diagnosis or a superimposed glomerular and/or tubular disease. For example, there may be granular glomerular staining for IgA and/or IgG and C3 in the diabetic in the setting of infection (Nasr et al). If there is doubt as to whether the IF staining is linear or granular, the final interpretation should depend on electron microscopy study.

Non-specific, non-immunologic deposition of complement (usually C3) and IgM, can be found in areas of glomerulosclerosis and this is not specific for diabetic nephropathy (Fig 8-3). This may result from trapping of large molecules in injured components. IgA is often seen in tubular casts as IgA is secreted by the renal tubular epithelium. C3 is often nonspecifically noted in vascular components and at the hilar portion of glomeruli (Fig 8-4). Lastly, the segmental absence of immunofluorescence staining can be seen in glomeruli with mesangiolysis (Fig 8-5).

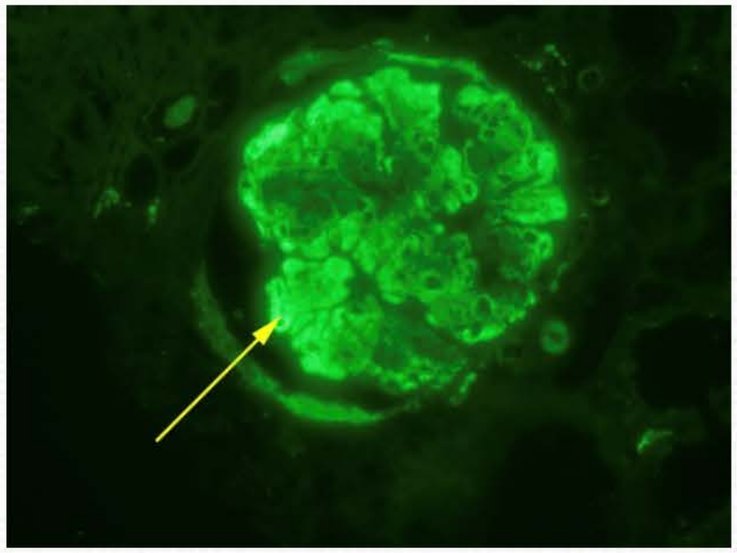


Fig 8-3 Nonspecific glomerular staining for IgM (arrow), Fluorescence stain.

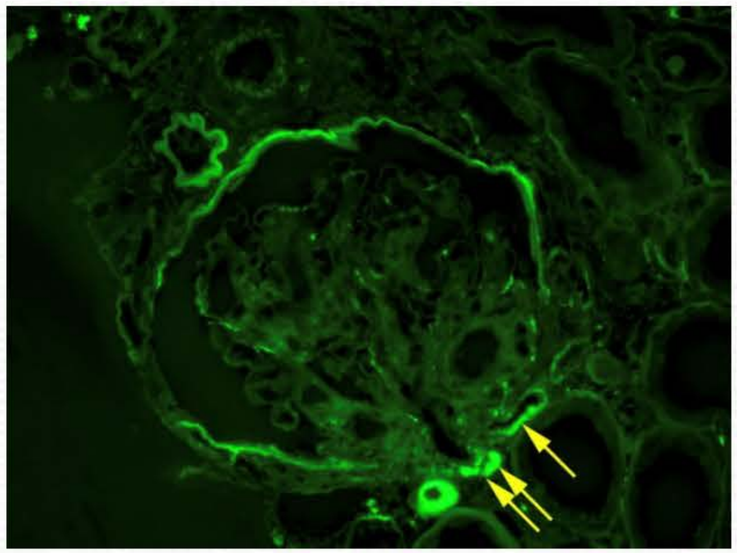


Fig 8-4 C3 staining of (double arrows) afferent and efferent arterioles (arrow), Fluorescence stain.

Figure 8-1 Linear tubular basement membrane staining for IgG (arrow), Fluorescence stain.

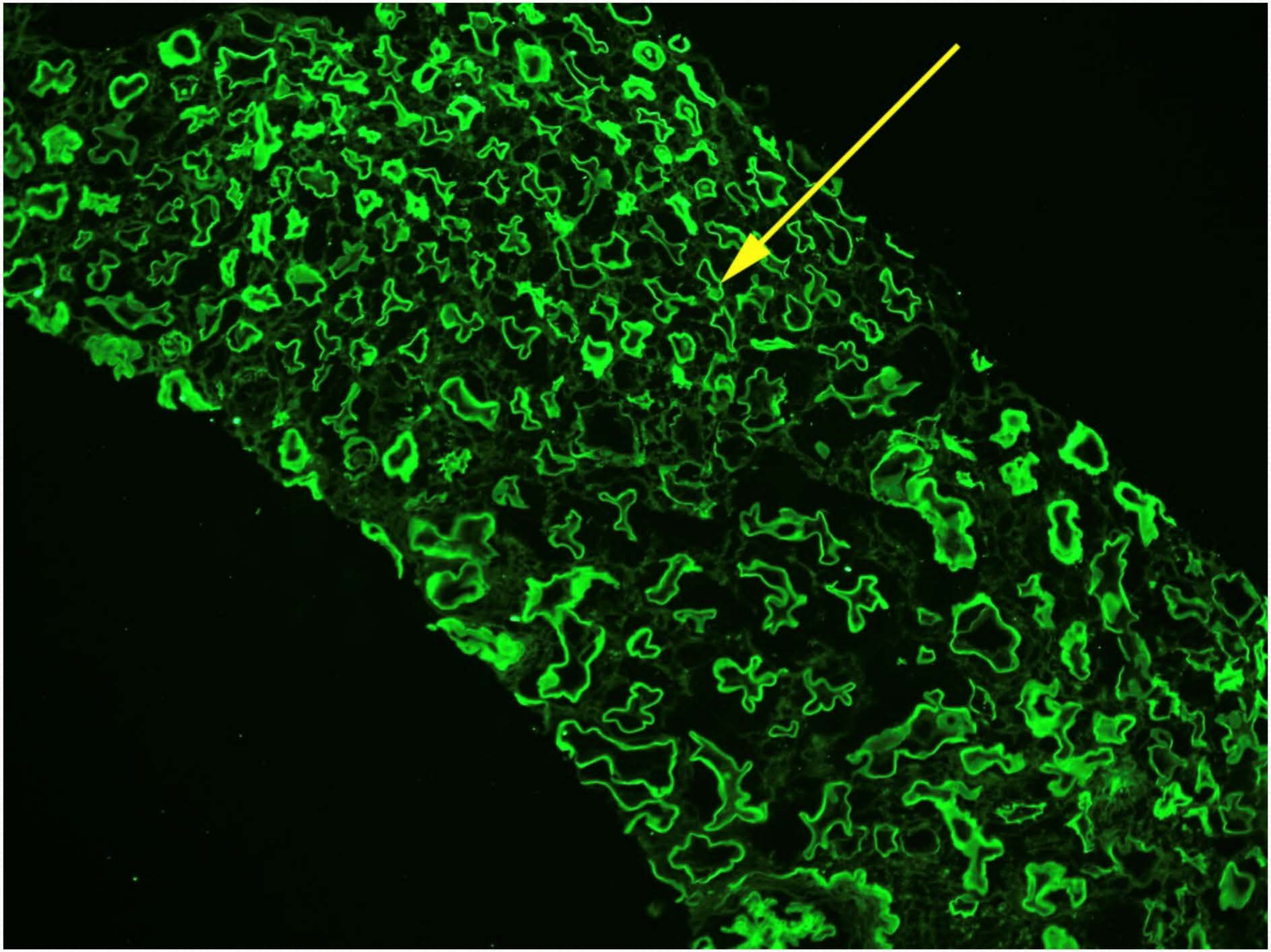


Figure 8-2 Linear tubular basement membrane staining for albumin (arrow), Fluorescence stain.

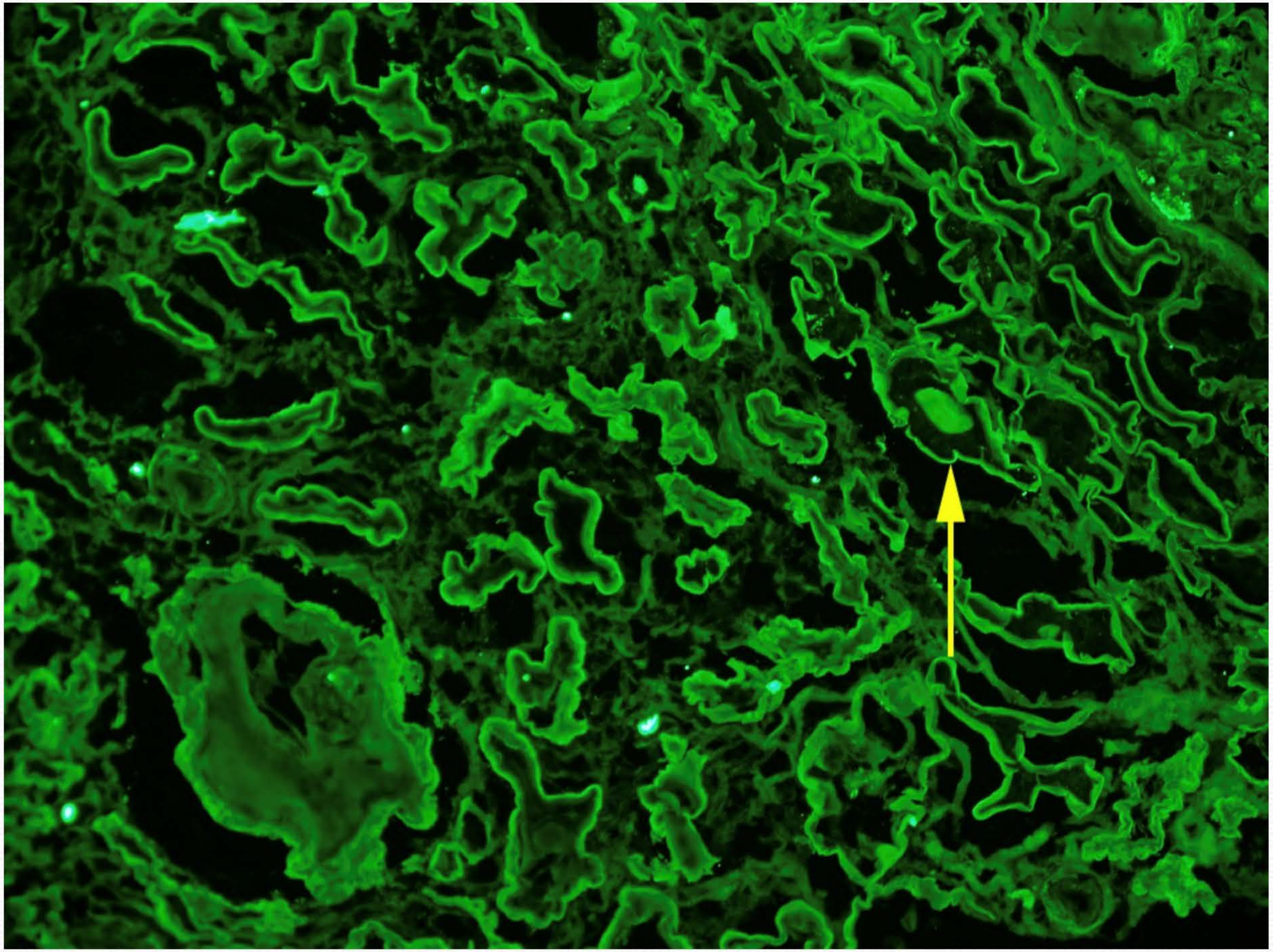


Figure 8-3 Nonspecific glomerular staining for IgM (arrow), Fluorescence stain.

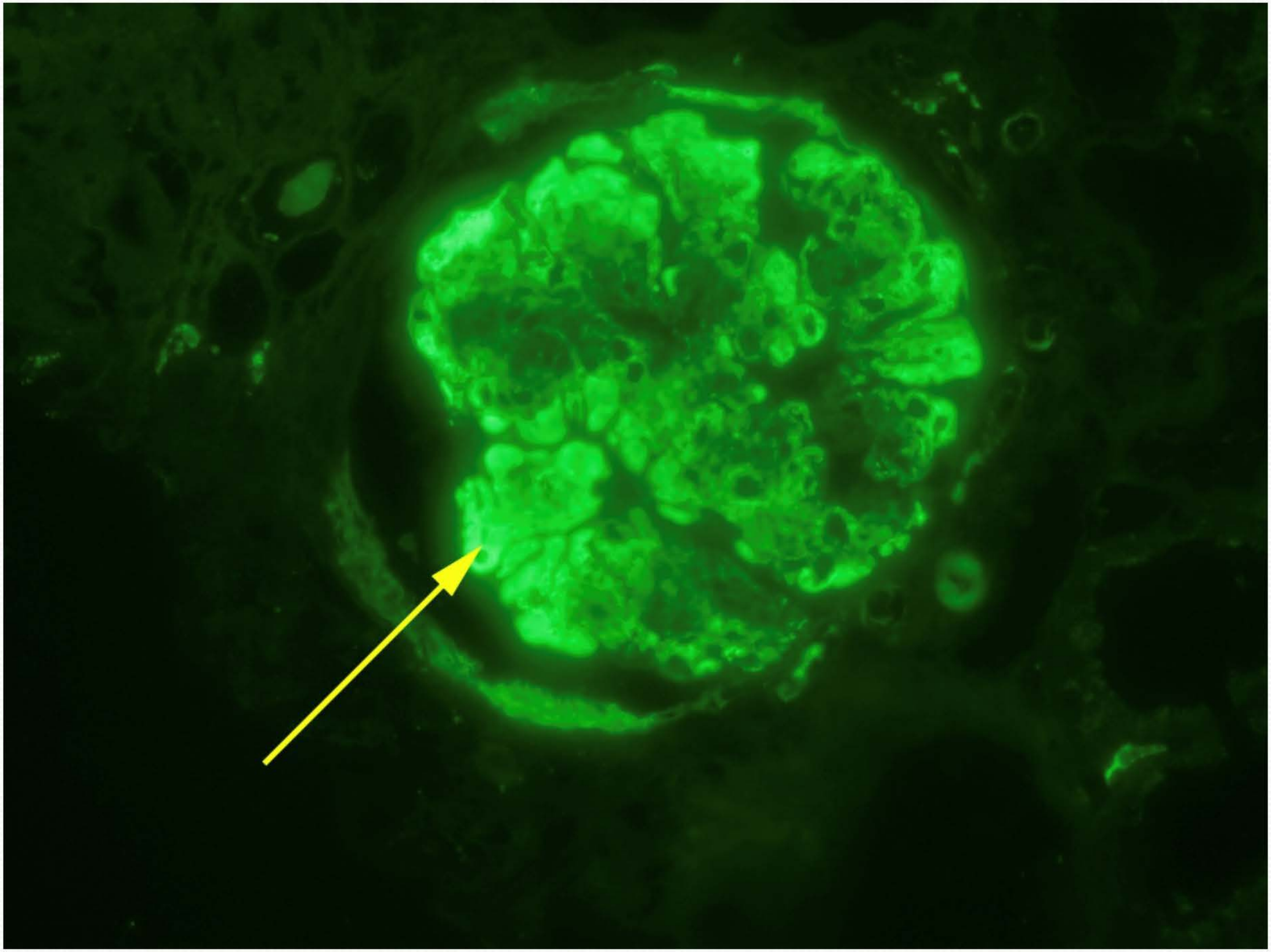


Figure 8-4 C3 staining of (double arrows) afferent and efferent arterioles (arrow), Fluorescence stain.

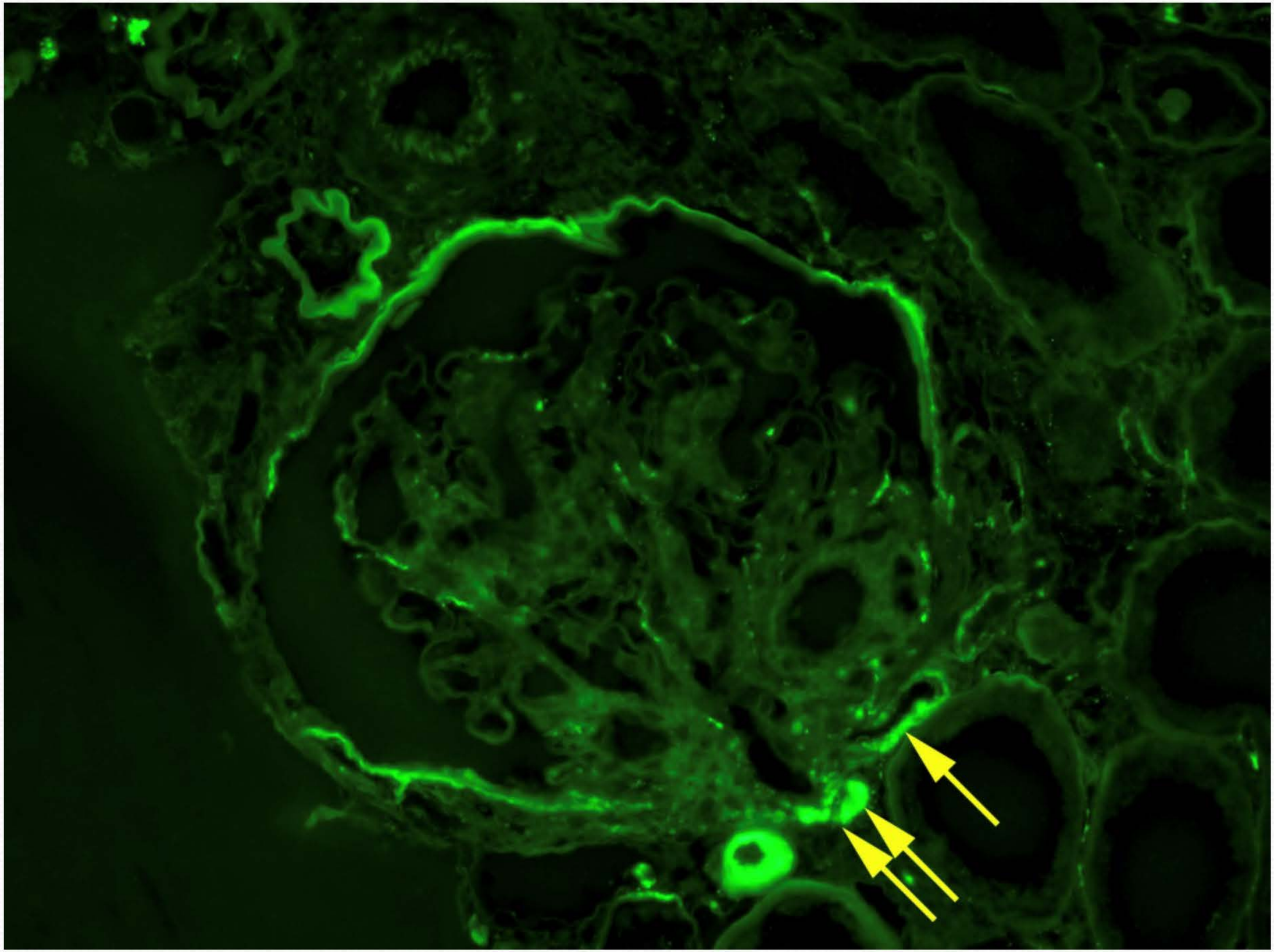


Figure 8-5 Glomerulus with absence of non-specific C3 staining in area of mesangiolysis (arrow), Fluorescence stain.

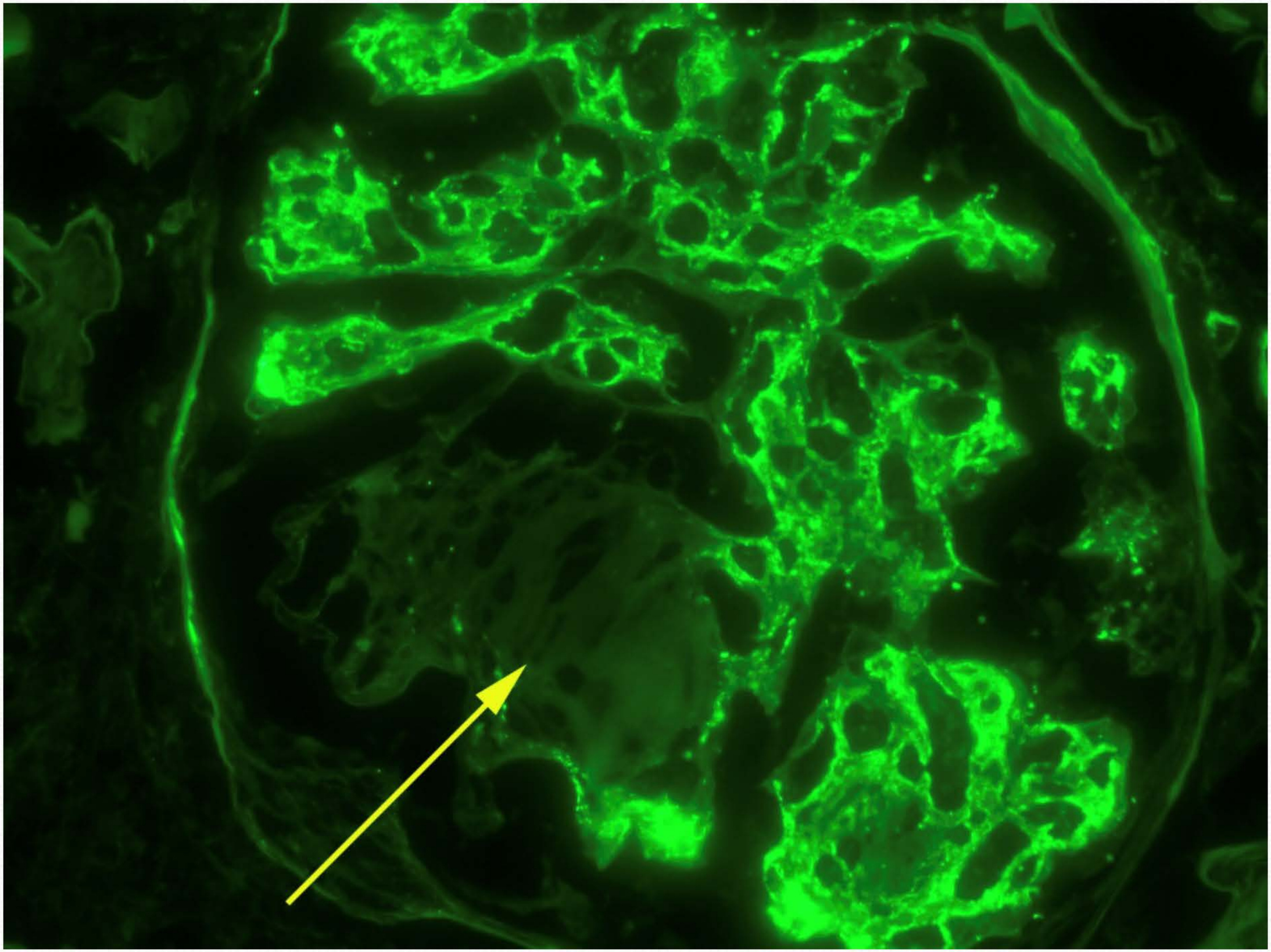


Figure 8-6 Linear tubular basement membrane staining for IgG (arrow), Fluorescence stain.

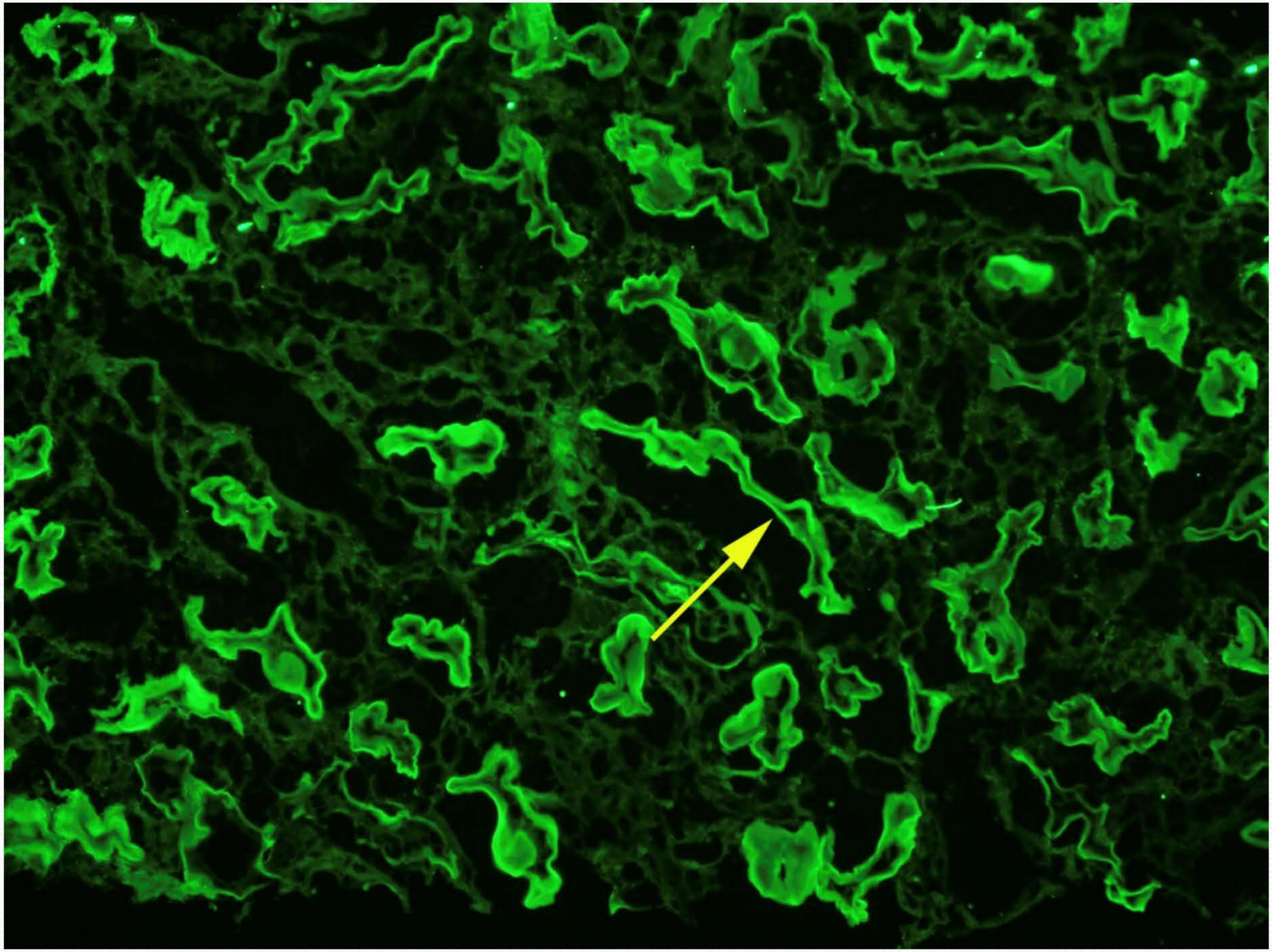


Figure 8-7 Linear tubular basement membrane staining for IgG (arrow), Fluorescence stain.

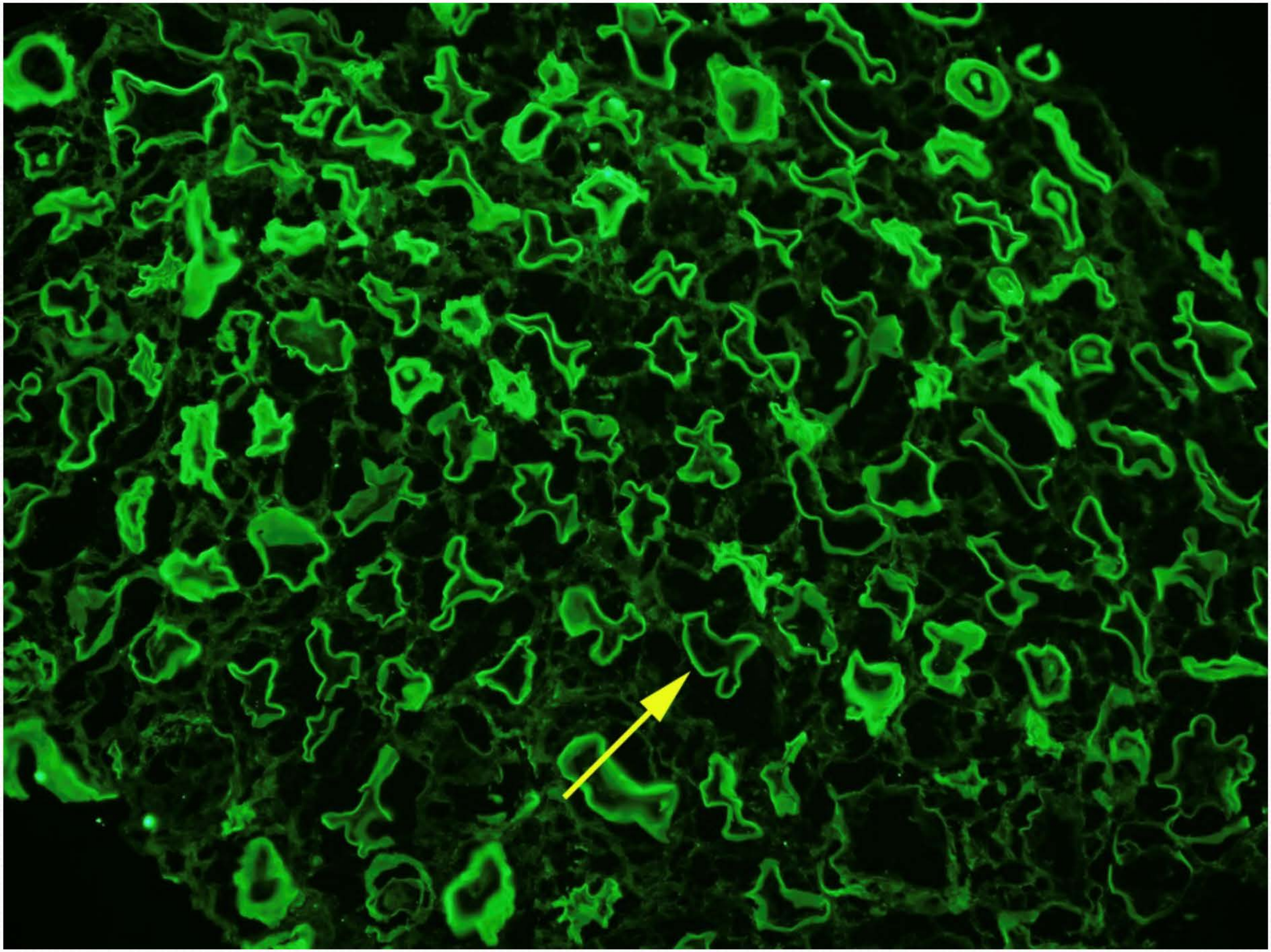


Figure 8-8 Linear tubular basement membrane staining for IgG (arrow), Fluorescence stain.

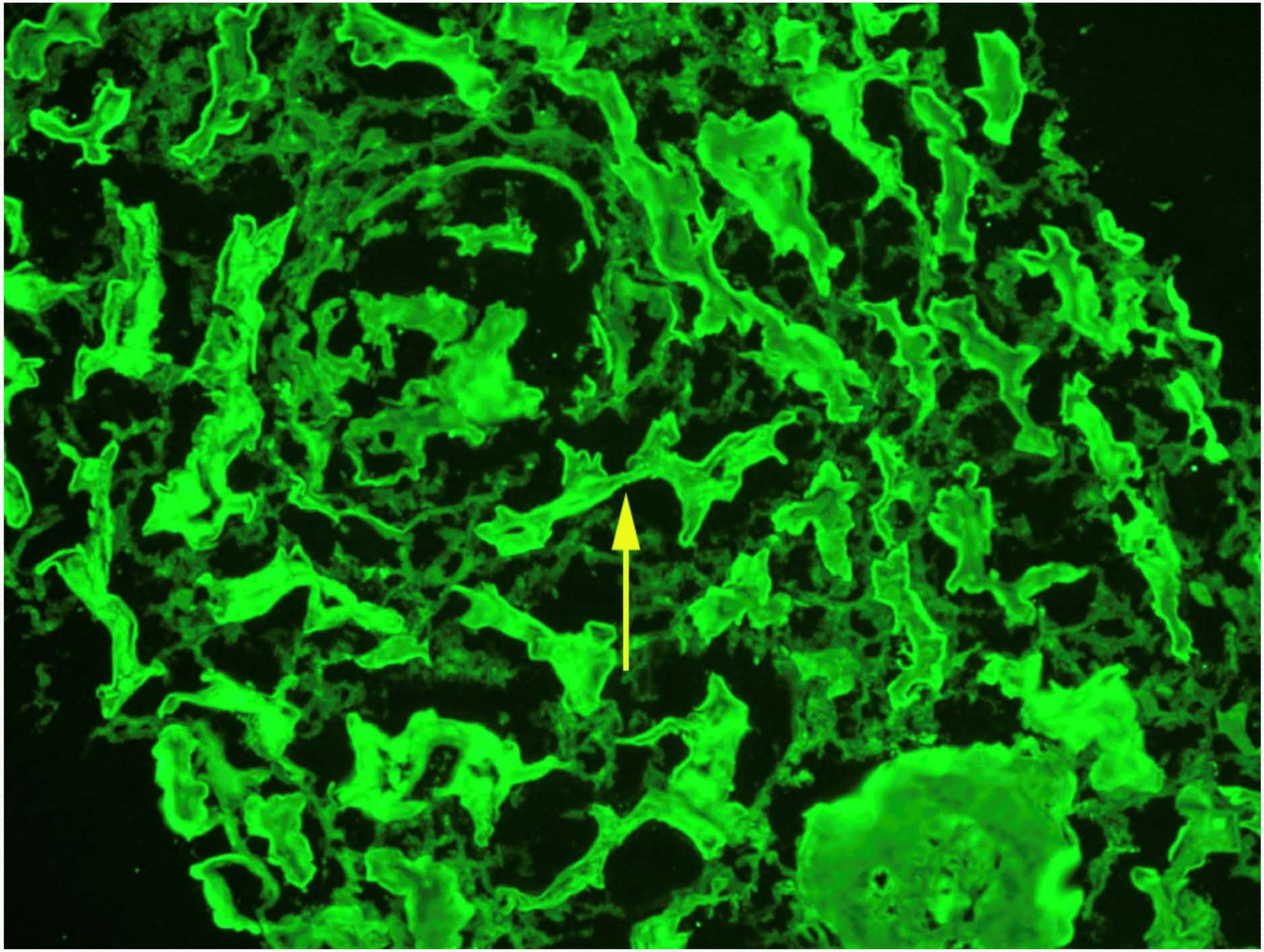


Figure 8-9 Linear tubular basement membrane staining for Albumin (arrow), Fluorescence stain.

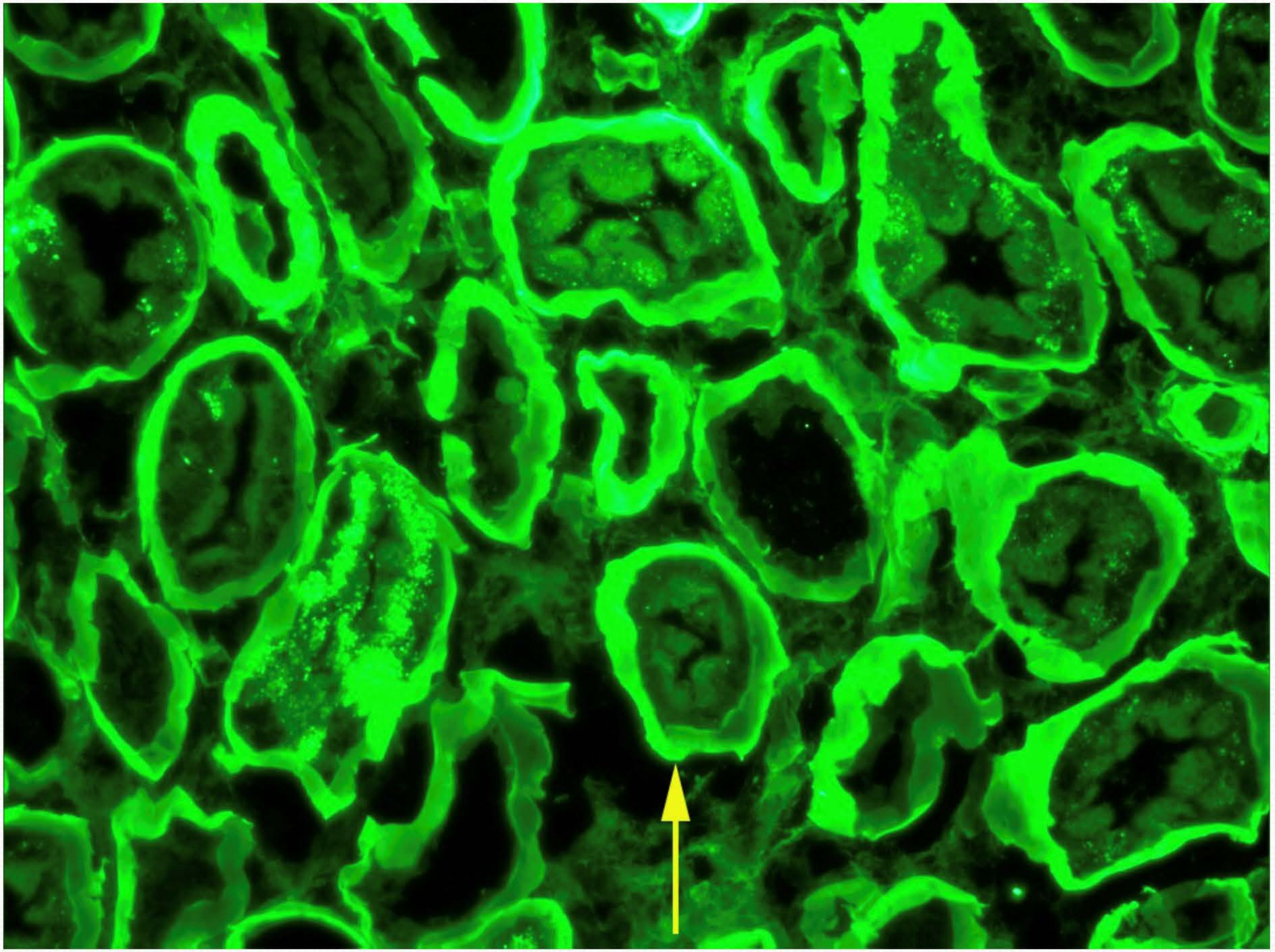
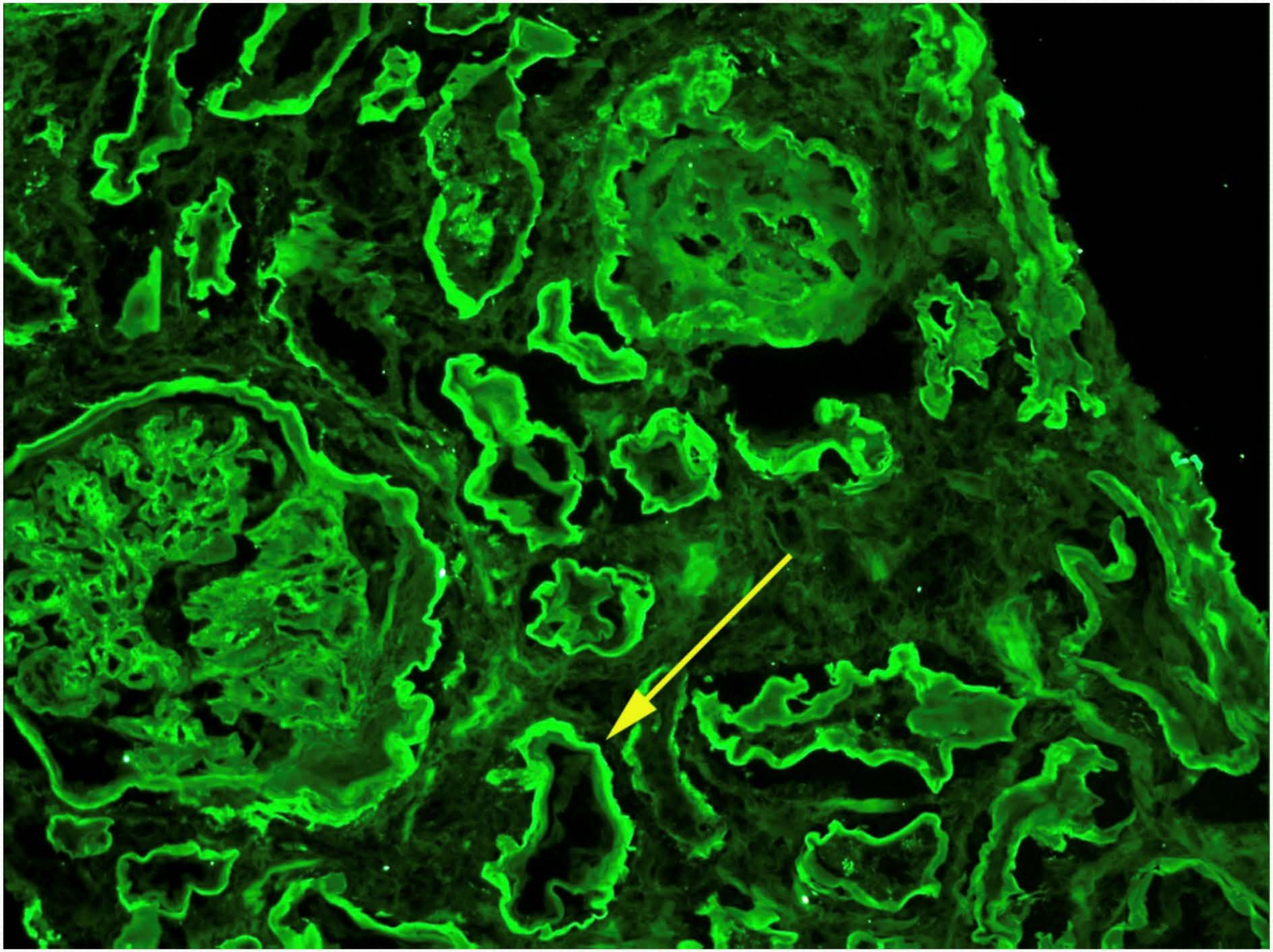


Figure 8-10 Linear tubular basement membrane staining for Albumin (arrow), Fluorescence stain.



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