

Pseudotumors due to IgG4 Immune-Complex Tubulointerstitial Nephritis Associated With Autoimmune Pancreatocentric Disease

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Abstract: Autoimmune pancreatitis (AIP) is a mass-forming chronic fibroinflammatory condition centered on the pancreaticobiliary system and characterized by predominant immunoglobulin G4 (IgG4)-positive plasma cells. Recent reports have brought to light the multiorgan involvement of this disease. We describe a series of 5 cases of tubulointerstitial nephritis (TIN) associated with AIP and characterize the clinical, pathologic, ultrastructural, and immunopathologic features of TIN. The specimens consisted of 4 biopsies and 1 nephrectomy. The average patient age was 64 years (range 45 to 78) and the male to female ratio was 4:1. All had histologic and/or clinical and radiographic evidence of AIP, mass-forming sclerosing cholangitis, or both. The clinical impression in 4 patients was a renal mass or vasculitis. Two patients had renal insufficiency. Histologic preparations revealed a dense tubulointerstitial lymphoplasmacytic infiltrate. Eosinophils were often numerous. Tubulitis and tubular injury were present, along with tubular atrophy with focally thickened tubular basement membranes (TBMs). The histologic appearance ranged from a cellular, inflammatory pattern without tubular atrophy to a striking expansive interstitial fibrosis with tubular destruction. The nephrectomy specimen demonstrated a masslike nodular pattern of inflammation with normal renal tissue elsewhere. Glomeruli were uninvolved. By immunohistochemistry or immunofluorescence, numerous plasma cells in the infiltrate were positive for IgG4. TBM granular IgG deposits, predominantly of the IgG4 subclass, were detected in 4 of 5 cases by either immunofluorescence or immunohistochemistry. By electron microscopy, corresponding amorphous electron-dense deposits were present in the TBM in these cases. This type of TIN, typically characterized by a masslike lesion consisting of a lymphoplasmacytic infiltrate with eosinophils and prominent IgG4-positive plasma cells and immune-complex deposits in the TBM, may be part of a systemic IgG4-related disease, which we term "IgG4-associated immune complex Multiorgan Autoimmune Disease" (IMAD).

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Autoimmune pancreatitis (AIP), also known as sclerosing pancreatitis, is a rare, mass-forming chronic fibroinflammatory condition characterized by predominant immunoglobulin G4 (IgG4)-positive plasma cells.⁵ Although this inflammatory disease of the pancreas has been speculated upon for over 50 years, this disease was recognized as a distinct entity only recently.^{6,27,38,47}

AIP mimics pancreatic carcinoma both clinically and radiographically; patients are typically older males who present with obstructive jaundice and are found to have a pancreatic mass by imaging studies.²⁷ Indeed, in the United States AIP accounts for approximately one fourth of Whipple procedures for benign conditions.³ As distinct from pancreatic carcinoma, these patients have been reported to show an elevated serum IgG4 concentration.¹⁶ AIP typically shows a dramatic response to steroid treatment.^{23,40,45}

More recently the extrapancreatic manifestations of AIP have been increasingly recognized, with inflammatory lesions reported to involve the salivary gland, liver and biliary system, and inflammatory pseudotumors in the breast, lung, liver, and orbit.^{9,11,18,24–26,32,34,44} AIP has also been associated with inflammatory bowel disease and retroperitoneal fibrosis.^{9,15,24,33,48} Some have proposed the term "IgG4-related Systemic Disease" to refer to the systemic nature of the disease.⁴⁶

Five individual cases of tubulointerstitial nephritis (TIN) associated with AIP have been reported to date, and 3 of these cases describe only the light microscopic appearance.^{32,37,42,43,46} Here we present a series of the clinical, pathologic, ultrastructural, and immunopathologic features of TIN, including a nephrectomy, associated with AIP/hepatobiliary disease.

MATERIALS AND METHODS

Renal biopsy (3) or nephrectomy (1) cases showing TIN were identified from 56 patients with clinical and radiographic, and/or histopathologic, evidence of AIP at the Massachusetts General Hospital from 1981 to 2005

(Among those cases, we identified 21 patients on whom a pancreatoduodenectomy was performed. Upon review the diagnosis of AIP was confirmed by meeting the histologic criteria previously published.). An additional renal biopsy was sent in consultation. Light, immunofluorescent (IF), immunohistochemical (IHC), and electron microscopic features were characterized.

On the 3 cases for which frozen tissue was available, routine IF microscopy was performed using fluorescein isothiocyanate-conjugated polyclonal rabbit antibodies to IgG, IgM, IgA, C3, C1q, κ and λ light chains, fibrinogen, and albumin. Staining for IgG subclasses was performed by indirect IF on frozen sections cut from tissue specimens using mouse monoclonal antibodies to IgG subclasses (Zymed, Carlsbad, CA) diluted 1:25. Specific binding was detected using fluorescein isothiocyanate-conjugated-rabbit antimouse immunoglobulins (Dako-Cytomation, Glostrup, Denmark and Carpinteria, CA) diluted 1:50.

IHC was performed using the avidin-biotin complex-peroxidase method with monoclonal antibody to human IgG4 (Zymed, Carlsbad, CA; dilution 1:50) in the 5 cases with available paraffin-embedded tissue. An automated immunostainer (Ventana Medical Systems, Tucson, AZ) was used. IgG4-positive plasma cells were counted per high power field (hpf, 400 $\times$ magnification, 0.62 mm² field) in the most densely populated area of the slide. The presence of a significant number of IgG4-positive plasma cells was defined as > 30/hpf, a number typical of our cases and greater than what has been suggested in the pancreatic literature.⁴⁹

Electron microscopy (EM) was performed on all 5 cases. In 2 cases, tissue for EM was fixed in Karnovsky II solution and buffered in sodium cacodylate. In the remaining 3 cases, tissue for EM was retrieved from the paraffin block, as previously described.¹⁰

Seven additional renal biopsies showing tubular basement membrane (TBM) immune deposits were included for comparison for IgG4 staining by IF and/or IHC. The diagnoses on these cases were lupus nephritis (n = 4), IgA nephropathy/Henoch Schönlein purpura (n = 1), nephronophthisis (n = 1), and BK polyoma virus nephropathy (n = 1). These patients did not show clinical, radiographic, or histopathologic evidence of AIP.

CASE REPORTS

Fifty-six patients with clinical and radiographic or pathologic evidence of AIP were identified from the Massachusetts General Hospital files between 1981 and 2005. Among these 56 patients, 4 kidney specimens (3 biopsies and one nephrectomy) were identified (7%). One additional renal biopsy was received in consultation. During this time period, there were approximately 4300 native kidney biopsies reviewed at our institution. The mean patient age was 64 years (range, 45 to 78). The male to female ratio was 4:1. The details of all 5 cases are presented below.

Table 1 provides a summary of the clinicopathologic features for these 5 cases and the reported cases in the literature. Table 2 summarizes the multiorgan involvement in these 5 patients with interstitial nephritis.

Case 1

A 71-year-old man came to medical attention because of a persistent dry cough and nasal discharge. The patient's evaluation eventually led to a chest CT scan, which showed multiple bilateral pulmonary nodules. Biopsy of these lesions revealed an unusual lymphohistiocytic vasculitis. An abdominal CT scan showed evidence of obstructive jaundice, with dilated intrahepatic and extrahepatic ducts, and a solid mass within the pancreatic head; multiple scattered masses in both kidneys; and a solid mass surrounding the aorta compatible with lymphadenopathy or retroperitoneal fibrosis. The patient ultimately developed jaundice, which required endoscopic retrograde cholangiopancreatography stenting. Needle biopsy of the pancreas at this time was inconclusive.

The patient had no history of autoimmune disease. He previously had a salivary gland nodule that on pathologic examination showed chronic sclerosing sialadenitis, but he did not have other clinical features of Sjögren syndrome. One renal mass was biopsied because of concern of growth of the mass by CT scan. The creatinine was normal at the time of renal biopsy. Antineutrophil cytoplasmic antibody and antinuclear antibody tests were negative. The total serum IgG level was elevated, at 1990 mg/dL (normal range, 600 to 1500 mg/dL); IgG subset level measurements revealed normal IgG1 and IgG3 levels, slightly elevated IgG2, and markedly elevated IgG4 (1030 mg/dL; normal range, 8 to 140 mg/dL).

The renal biopsy (Fig. 1) revealed a dense destructive tubulointerstitial inflammatory infiltrate in the cortex and medulla, with expansile and dissecting interstitial fibrosis. The infiltrate was composed of mature plasma cells, numerous eosinophils, mononuclear cells, and rare neutrophils. Mononuclear cell tubulitis was present. A small patch of cortex did not show inflammation; otherwise, the entire sample was involved. Many tubules were atrophic, with focal tubules showing thickened basement membranes. Glomeruli and arteries were unremarkable and were not inflamed.

Routine IF microscopy showed finely granular interstitial and peritubular basement membrane deposits that stained for IgG, C3, κ and to a lesser degree IgM and λ . Staining for IgG subclasses showed TBM and interstitial staining for IgG4 (3+), IgG1 (1+), and IgG3 (trace). Staining for IgG2 was negative.

EM showed electron-dense deposits along and within the TBMs, corresponding to the distribution of immunoglobulin and complement deposition seen by IF. The deposits did not show substructure. The glomeruli were normal and were free of deposits.

IHC for IgG4 showed numerous (> 30/hpf) IgG4-positive plasma cells, as well as focal finely granular interstitial staining. TBM deposits were not readily discernible by IHC, possibly because of background staining. Other IHC stains revealed a mixture of CD68⁺ macrophages, CD3⁺ T-cells, few CD20⁺ B-cells, and polytypic (κ -positive and λ -positive) plasma cells. Rare plasma cells stained for IgM. Staining for α -smooth muscle actin (SMA) revealed predominantly interstitial staining of myofibroblasts.

Case 2

A 57-year-old man presented with fatigue, abdominal pain, nausea and vomiting, and weight loss. He was found by

TABLE 1. Clinical and Pathologic Data in Patients With Interstitial Nephritis Associated With Autoimmune Pancreatocentric Disease

Case No.	1	2	3	4	5	6: Uchiyama-Tanaka et al ⁴³	7: Takeda et al ⁴²	8: Watson et al ⁴⁶	9: Rudmik et al ³⁷	10: Nakamura et al ³²
Age (years)	71	57	68	78	45	64	66	67	52	52
Sex	M	M	F	M	M	M	M	M	M	M
Clinical impression	Vasculitis or lymphoma	Renal mass	Lymphoma or multifocal RCC	Renal insufficiency	Renal masses	Renal insufficiency, proteinuria	Renal insufficiency	Renal insufficiency, proteinuria	Pancreatic and renal masses	Renal masses
Creatinine at time of renal specimen (mg/dl)	0.9-1.1	Normal	0.9-1.1	3.0	7.0	4.5	2.3	3.4	0.7	0.8
Immunologic laboratory studies										
ANA	—	NA	+ 1:80	+ 1:160	—	+ 1:160	+	—	—	—
Complement										
C3	NA	NA	Normal	Decreased	NA	Decreased	Decreased	Normal	NA	NA
C4	NA	NA	Decreased	Decreased	NA	Decreased	Decreased	Normal	NA	NA
Serum IgG	Elevated	NA	Elevated	Elevated	NA	Elevated	Elevated	Elevated	Elevated	Elevated
Serum IgG4	Elevated	NA	NA	NA	NA	NA	Elevated	Elevated	Elevated	Elevated
Renal specimen	Biopsy	Nephrectomy	Biopsy	Biopsy	Biopsy	Biopsy	Biopsy	Biopsy	Biopsy	Biopsy
Glomerular disease	—	—	Mesangial hypercellularity	—	Mesangial immune deposits	Membranous glomerulonephritis	Mesangial hypercellularity	Membranous glomerulonephritis	—	—
Light microscopy										
Tubules/interstitium	TIN	TIN	TIN	TIN	TIN	TIN	TIN	TIN	TIN	TIN
IF or IHC immune deposits										
Glomeruli	—	—	—	—	1-2+ mesangial IgG/C3/K/L	Gran GBM IgG/C3	—	Gran GBM IgG	NA	NA
Tubulointerstitial deposits										
IgG	2+ gran, focal	NA	NA	1-2+ gran, focal	2+ gran, focal	—	+ gran, focal	+ gran, widespread	NA	NA
IgM	1+ gran, focal	NA	NA	—	—	—	NA	NA	NA	NA
IgA	—	NA	NA	—	—	—	NA	NA	NA	NA
C3	1+ gran, focal	NA	NA	1+ gran, focal	—	—	+ gran, focal	NA	NA	NA
C1q	—	NA	NA	—	—	—	NA	NA	NA	NA
Kappa	1+ gran, focal	NA	NA	1+ gran, focal	2-3+ gran, focal	—	NA	NA	NA	NA
Lambda	1+ gran, focal	NA	NA	1+ gran, focal	2-3+ gran, focal	—	NA	NA	NA	NA
IgG1	1+ gran, focal	NA	NA	—	NA	NA	—	NA	NA	NA
IgG2	—			2+ gran, focal				NA		
IgG3	1+			—				+		
IgG4	3+ gran, focal			3-4+ gran, focal			+ (IHC)	+		
IF or IHC IgG4+ plasma cells	> 30/hpf	> 30/hpf	> 30/hpf	NA	Numerous	NA	+	+	+	+
EM deposits										
Glomeruli	—	—	—	Not sampled	+ mesangial	+ subepi	—	+ subepi, intramembr	NA	NA
TBM	+	—	+	+	+	—	+	+		
Interstitium	—	—	+	—	—	—	—	+		

ANA indicates antinuclear antibody; gran, granular; RCC, renal cell carcinoma; NA, not available.

TABLE 2. Organ System Involvement in Patients With Interstitial Nephritis

Case No.	1	2	3	4	5
Kidney	+	+	+	+	+
Pancreas	+	+	+	+	—
Liver/biliary system	—	—	+	+	+
Salivary gland	+	+	—	—	—
Lung	+	—	—	—	+
Orbit	—	—	+	—	—
Colon (inflammatory bowel disease)	—	—	+	—	—

CT scan to have a pancreatic tail mass that was suspicious for malignancy. The patient underwent distal pancreatectomy, splenectomy, and left nephrectomy for tumor at an outside institution. He was then seen at this hospital seeking a second opinion. Sections of the pancreas showed lymphoplasmacytic infiltration and fibrosis with acinar atrophy consistent with AIP. In addition, by report a submandibular gland, excised at an outside hospital, showed chronic sclerosing sialadenitis.

The nephrectomy specimen (Fig. 2) showed a mass-forming dense inflammatory cell infiltrate in the cortex and outer medulla. The infiltrate was composed predominantly of plasma cells and mononuclear cells, with rare eosinophils and neutrophils. No lymphocytic or plasma cell atypia was identified. Mononuclear cell tubulitis was present. Tubular injury was present within the inflammatory mass, but there was relatively little tubular atrophy, and TBMs did not appear thickened. Interstitial fibrosis was sparse. The glomeruli were unremarkable. The renal parenchyma away from the inflammatory infiltrate was normal, without tubular atrophy or interstitial fibrosis. Arteries were unremarkable.

IHC for IgG4 revealed numerous (> 30/hpf) IgG4-positive plasma cells. No TBM or interstitial staining for IgG4 was identified, either within or outside the area of dense inflammation. Staining for α -SMA did not stain tubular epithelial cells and did not reveal myofibroblasts within the interstitium. Tissue for EM was retrieved from the paraffin block and showed absence of amorphous immune deposits in TBMs, the interstitium, and glomeruli. There was a very focal accumulation of material with vesicles in rare thickened TBMs; the appearance of this material was not typical of immune deposits and was interpreted as cell debris. Frozen tissue was not available for IF. Additional tissue was not available for κ and λ light chain IHC staining.

Case 3

A 68-year-old woman was found to have bilateral renal lesions, which were discovered on a routine abdominal scan to evaluate a previously detected liver mass. On repeat scans, the renal masses had become larger, prompting repeated biopsies. The patient's creatinine at the time of biopsy was 0.9 mg/dL. The patient had a history of type II diabetes mellitus, Crohn's disease, a liver mass which when biopsied showed sclerosing cholangitis, and bilateral orbital and multiple liver and renal inflammatory lesions. An endoscopic ultrasound done 3 years back showed sclerosing pancreatitis; no pancreatic biopsy was done. Several months after the patient's third renal biopsy, her creatinine increased to 1.6 mg/dL. Laboratory tests performed after the renal biopsy showed elevated IgG in the serum (3650 mg/dL, normal range 614 to 1295).

The third renal biopsy (Fig. 3) showed a destructive tubulointerstitial infiltrate with prominent fibroblasts. The infiltrate was composed of mature plasma cells, prominent eosinophils, and mononuclear cells. In the areas of inflammation, there was also mononuclear and plasma cell tubulitis, tubular injury, and atrophy with markedly thickened TBMs. Some atrophic tubules showed "target lesions" of TBM duplication and rupture. Interstitial fibrosis was expansile and infiltrative between the atrophic tubules. Granular TBM deposits could be identified on trichrome stain. Glomeruli were normal or showed mild mesangial hypercellularity. Arteries were unremarkable or showed mild arteriosclerosis.

Material for EM was retrieved from the paraffin block. TBMs were markedly thickened and showed striking electron-dense deposits. The deposits did not show substructure. In addition, small electron-dense deposits were seen scattered within the fibrotic interstitium. The glomeruli were free of deposits.

An IHC stain for IgG4 showed punctate staining in many thickened TBMs and in the interstitium. In addition, many (> 30/hpf) plasma cells stained for IgG4. κ and λ staining by IHC revealed polytypic plasma cells. Staining for α -SMA revealed numerous myofibroblasts in the interstitium; some tubular epithelial cells stained as well. Frozen tissue was not available for IF.

Of note, the 2 previous renal biopsies done 1 year back showed arteriosclerosis and scant areas of inflammation consisting of mononuclear cells, plasma cells, and rare eosinophils; these specimens were considered nondiagnostic. A retrospective stain for IgG4 on one biopsy revealed rare scattered IgG4-positive plasma cells and no definite TBM or interstitial immune deposits.

Case 4

A 78-year-old man had a 3-month history of fatigue and anemia. He was found to have an increased creatinine from a baseline of 1.2 to 3.0 mg/dL. A renal biopsy was performed because of the patient's renal insufficiency. Approximately 1 year back, the patient underwent an extrahepatic common bile duct resection and cholecystectomy for a suspicion of cholangiocarcinoma. This pathologic specimen showed extensive fibrosis and lymphoplasmacytic inflammation of the common bile duct, with extension into the surrounding soft tissue. Two years later, the patient underwent a Whipple resection for chronic pancreatitis; this specimen revealed features diagnostic of AIP.

The renal biopsy (Fig. 4) showed widespread, severe interstitial fibrosis accompanied by a patchy inflammatory infiltrate consisting of mononuclear cells, plasma cells, and rare eosinophils. Mononuclear cell tubulitis was present. Tubules were atrophic, with focally thickened basement membranes. Glomeruli were normal by light microscopy. Arteries were unremarkable.

By IF, the glomeruli were negative for immunoglobulins and complement. TBMs stained focally in a granular pattern for IgG (1-2+) and C3 (1+). Staining for IgG subclasses showed granular TBM staining for IgG4 (3-4+) and IgG2 (2+). The TBMs were negative for IgG1 and IgG3.

EM showed thickened TBMs with amorphous intramembranous electron-dense deposits. Glomeruli were free of deposits.

IHC for IgG4 was performed but was technically unsatisfactory due to tissue preservation. Additional tissue was not available for κ and λ IHC staining.

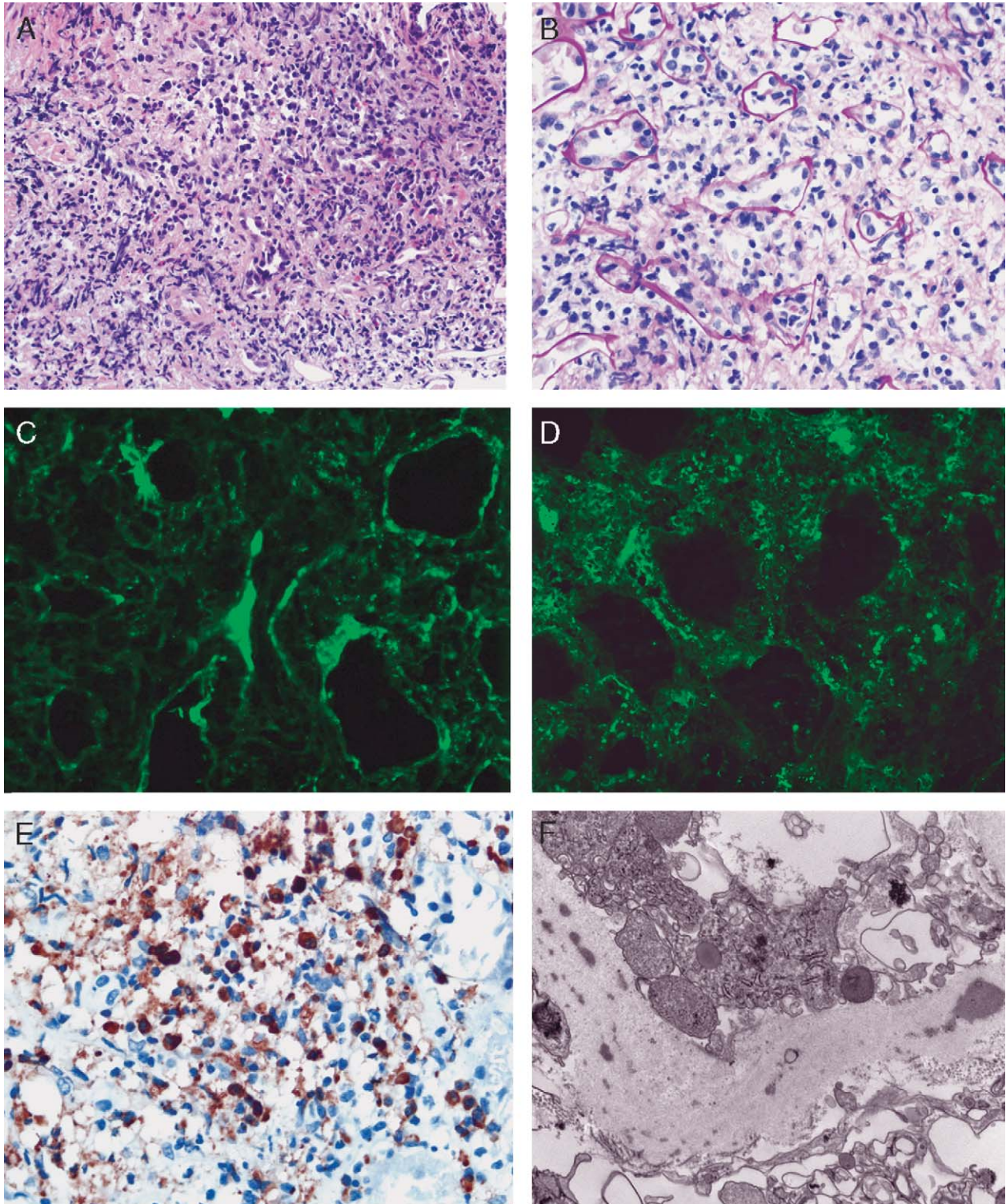


FIGURE 1. Case 1. Dense inflammatory infiltrate with prominent plasma cells and eosinophils (A, hematoxylin and eosin). Tubulitis is present, along with TBM injury and duplication (B, Periodic acid-Schiff (PAS)). Immunofluorescence for IgG (C) and IgG4 (D) shows granular TBM and interstitial immune-complex deposition. Numerous plasma cells stain for IgG4 by IHC (E). TBM electron-dense deposits are apparent in thickened TBMs by EM (F).

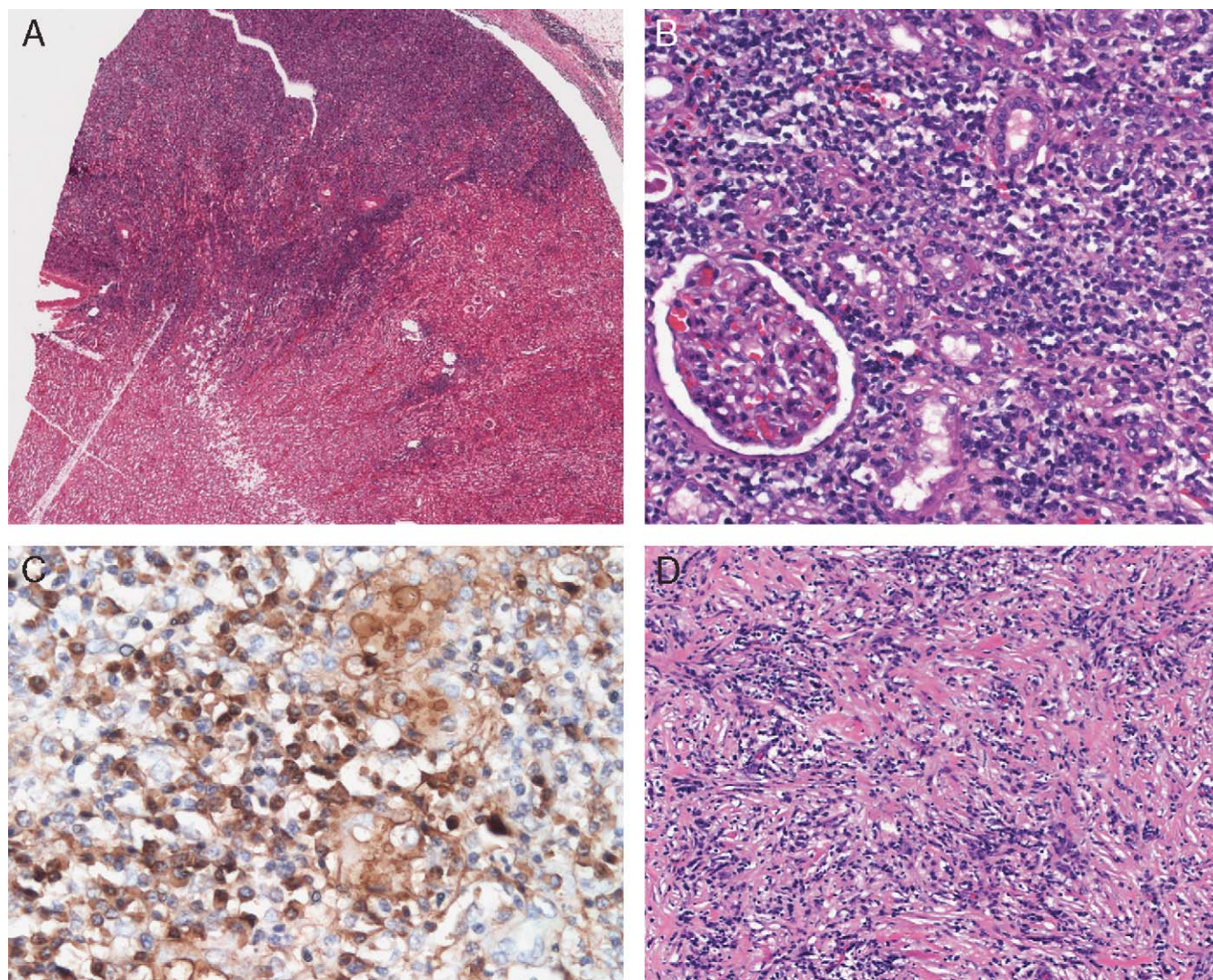


FIGURE 2. Case 2. Section from a nephrectomy specimen showing a mass-forming inflammatory infiltrate predominantly in the renal cortex (A, hematoxylin and eosin). Higher magnification reveals a dense lymphoplasmacytic tubulointerstitial infiltrate and normal glomeruli (B, hematoxylin and eosin). Numerous plasma cells stained for IgG3 by IHC (C). The inflammatory infiltrate also extended outside the kidney into the surrounding fat, with prominent fibrosis (D, hematoxylin and eosin); numerous plasma cells in this extrarenal location also stained for IgG4.

Case 5

A 45-year-old man had chronic renal failure, with a creatinine of 7.0 mg/dL. Laboratory studies revealed mild proteinuria (1 g/d) and microscopic hematuria, as well as peripheral blood eosinophilia. The antinuclear antibody was negative, along with tests for hepatitis B and C. On imaging studies, the patient was found to have enlarged kidneys, at 16 cm each, containing multiple masses. A first renal biopsy was done 2 years before at another institution; that biopsy was reported to show a dense mixed inflammatory infiltrate consisting of T cells, B cells, and polytypic plasma cells, not diagnostic of a lymphoproliferative disorder. During the time of this evaluation, the patient also underwent a liver biopsy for clinically identified subcapsular nodules that were suspicious for a lymphoproliferative disorder. By report, the biopsy showed a chronic fibroinflammatory process, without evidence of lym-

phoma. A first liver biopsy done 5 years back was diagnosed as chronic cholestasis consistent with sclerosing cholangitis. Of note, pulmonary nodules of unknown etiology were also seen on imaging studies. There was no known pancreatic involvement. A second renal biopsy was performed to evaluate for sarcoidosis or a lymphoproliferative disorder.

The second kidney biopsy, performed at an outside institution, showed severe interstitial nephritis, with patchy involvement by a dense inflammatory cell infiltrate in the cortex and medulla (Fig. 5). Widespread interstitial fibrosis and tubular atrophy was present, particularly in the inflamed areas. The infiltrate was composed of plasma cells, mononuclear cells, and eosinophils. TBMs were thickened. Arteries showed intimal fibrosis but were otherwise unremarkable. Glomeruli were unremarkable by light microscopy. Routine IF microscopy showed diffusely positive granular interstitial and TBM staining

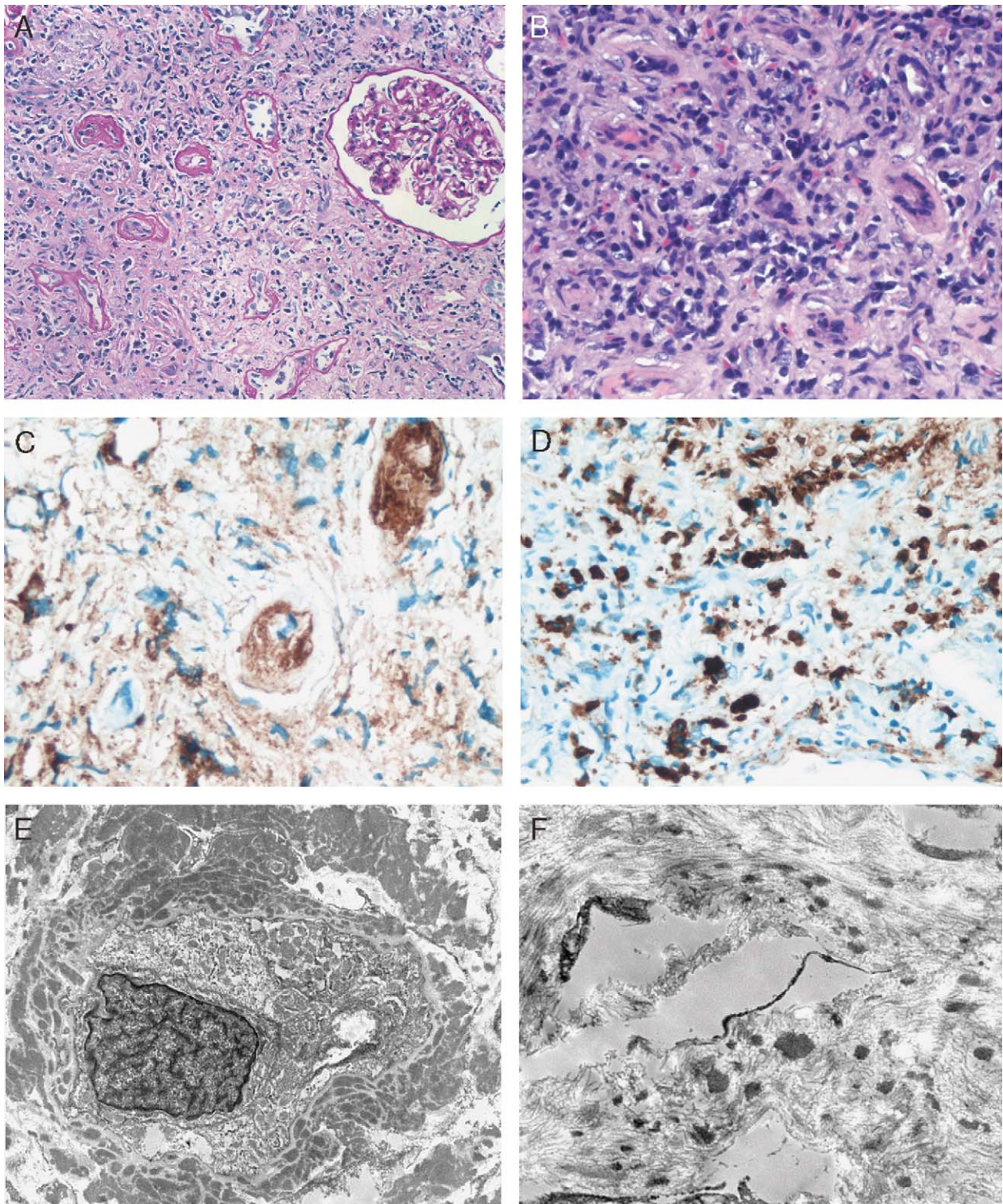


FIGURE 3. Case 3. Destructive and expansile inflammatory cell infiltrate with atrophic tubules; the glomeruli are unaffected (A, PAS). On higher magnification, prominent plasma cells and eosinophils are apparent, as well as TBM thickening (B, hematoxylin and eosin). IHC for IgG4 stains granular TBM deposits (C) and numerous plasma cells (D). By EM, massive TBM electron-dense deposits (E) and interstitial deposits (F) are seen.

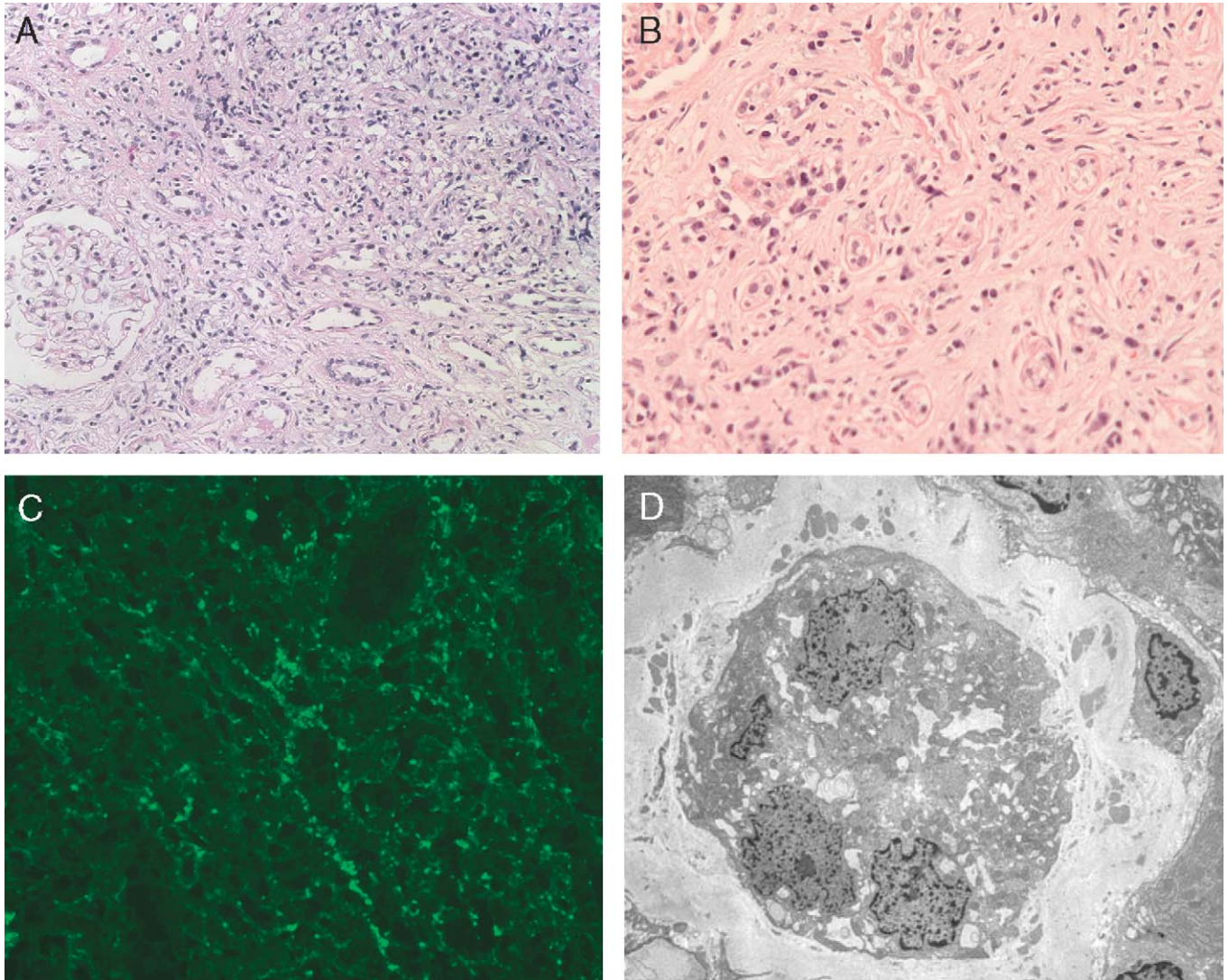


FIGURE 4. Case 4 shows a less inflammatory, more sclerotic pattern (A, PAS) with infiltrating plasma cells and eosinophils (B, hematoxylin and eosin). IF shows granular TBM and interstitial deposition of IgG4 (C). Corresponding amorphous electron-dense deposits are present within thickened TBMs by EM (D).

for IgG (2+) and κ and λ immunoglobulin light chains (2-3+). In addition, there was granular mesangial staining for IgG (1-2+), C3 (1+), and κ (1+) and λ (1+) light chains. IF staining for IgG subclasses, performed at our institution, revealed numerous IgG4-positive plasma cells and rare plasma cells that stained for IgG1, IgG2, or IgG3. No TBM staining for IgG subclasses, however, were identified by our technique, probably the result of a technical artifact. IHC revealed polytypic (κ -positive and λ -positive) plasma cells.

EM showed scattered amorphous electron-dense deposits within the TBM. In addition, there were few scattered small mesangial deposits and rare subendothelial deposits. No tubuloreticular structures were identified.

CONTROLS

The 7 reference renal biopsies with TBM deposits showed granular staining predominantly for IgG1 alone

or with IgG2 or IgG3 by IF. None showed TBM staining for IgG4.

DISCUSSION

We describe 5 cases of a newly recognized type of TIN associated with pancreatocentric systemic autoimmune disease. These cases may exemplify a distinct subset of immunologically mediated interstitial nephritis with immune-complex deposition.

Four of five patients in this series presented with a suspicion of renal masses; 2 had renal insufficiency at presentation. All 5 cases showed a plasma cell-rich TIN with eosinophils, and 4 showed TBM immune deposits. Some histopathologic heterogeneity was present. Some cases showed a more densely cellular, inflammatory pattern, whereas the other cases showed a striking

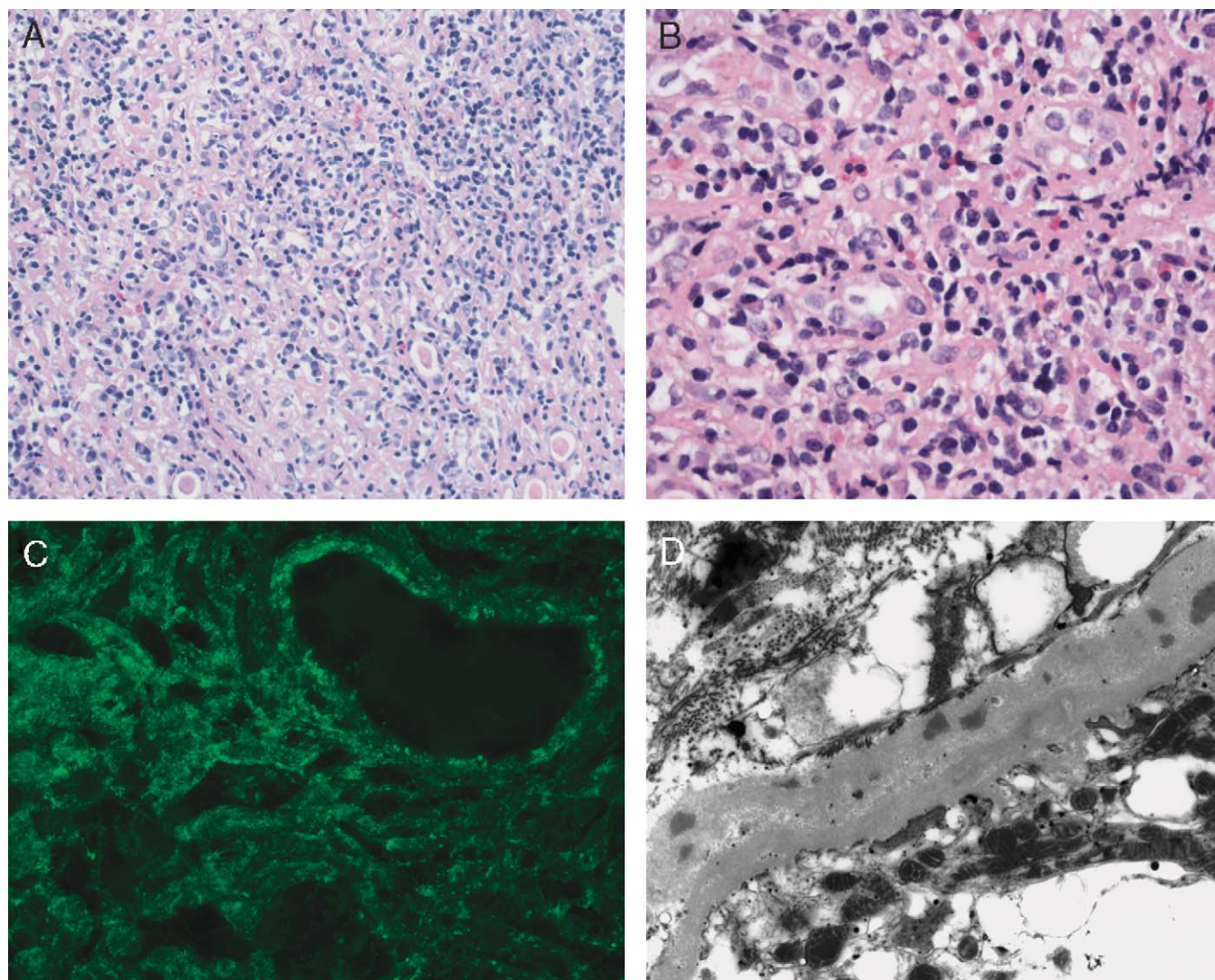


FIGURE 5. Case 5. Dense lymphoplasmacytic infiltrate in a kidney with many atrophic tubules (A, hematoxylin and eosin); eosinophils are prominent (B, hematoxylin and eosin). IF shows granular TBM and interstitial staining for IgG (C). EM reveals corresponding amorphous electron-dense deposits within TBMs (D).

expansile interstitial fibrosis with tubular destruction (case 4 in particular), along with a patchy lymphoplasmacytic infiltrate. In addition, one of the 5 cases did not have TBM deposits (case 2). This case showed marked inflammatory features with localized mass formation, but without the more chronic changes of interstitial fibrosis, tubular atrophy, and TBM thickening. This finding implies that the immune complexes are a late manifestation and not the primary process. We speculate that the heterogeneity in the pathologic features are due to different stages in the kidney disease: first, an early disease showing severe inflammation, without tubular atrophy, interstitial fibrosis, or immune deposits (eg, case 2); second, a cellular phase with immune deposits and evolving tubular atrophy and interstitial fibrosis; and third, a dense, destructive pattern of fibrosis with accumulated immune complexes. Staining for α -SMA

correlated with stages of interstitial fibrosis and presence of myofibroblasts. One case showed few scattered SMA-positive tubular epithelial cells, possibly representing tubular epithelial-to-mesenchymal transition as contributing to the interstitial fibrosis.²⁹

Most of the lesions in this series were biopsied for a clinical suspicion of a neoplasm. Not uncommonly in clinical practice a patient undergoes biopsy for a renal mass, only to result in a nondiagnostic specimen consisting of renal parenchyma with fibrosis and an inflammatory cell infiltrate reactive to an adjacent tumor. Indeed, 2 patients in this series underwent repeated renal biopsies for continued concern for malignancy. In the cases presented here, the inflammatory lesion itself accounted for a mass. An inflammatory mass can be distinguished from reactive inflammation by the presence of a destructive, expansile interstitial fibrosis with prominent fibro-

blasts, a mixed inflammatory cell infiltrate that includes many plasma cells and eosinophils, tubulitis, and, in particular, TBM immune deposits. A history of AIP, another inflammatory disorder, or evidence of masses in other organs is helpful, although not essential. In this series, 4 of 5 patients presented with extrarenal manifestations, whereas 1 patient (case 2) showed renal involvement at the same time as the clinically identified pancreatic disease. The renal biopsy and nephrectomy cases in this series were identified and selected, however, from a group of patients who showed evidence of autoimmune pancreatobiliary disease. Still, renal involvement may be quite common among patients with AIP, with one study showing radiographic evidence of renal lesions in 35% of patients undergoing evaluation for AIP.⁴¹

The clinical and histopathologic findings in the kidney closely resemble the reported extrarenal manifestations of this disease.⁹ Clinically, these patients often present with an ill-defined mass or multiple masses that simulate lymphoma. The tissue samples show a destructive lymphoplasmacytic infiltrate with eosinophils, similar to what is described in the pancreas. In addition, we have shown by EM amorphous electron-dense immune deposits in the ductal basement membranes in the pancreas and the salivary glands, analogous to the TBM deposits seen in the kidney.¹⁰ The immunopathologic characteristics correspond as well, *vis-à-vis* IgG4 in plasma cells and in deposits.

Granular TBM immune deposits are an unusual finding in the kidney, except in cases of lupus nephritis, and they are usually associated with glomerular deposits.²⁸ Granular TBM deposits have been described in association with several other systemic immune diseases (Sjögren syndrome, familial immune-complex interstitial nephritis, IgE immune-complex disease, and graft-versus-host disease), glomerulonephritis [membranous glomerulonephritis (MGN), IgA nephropathy], and infections (bacterial endocarditis, infectious mononucleosis, mycoplasma pneumonia, and polyoma virus interstitial nephritis).^{7,8,12,17,19,35,39} The renal disease we describe here combines a clinical syndrome of mass-forming inflammatory lesions in various organs with immunologic features of immune-complex deposits and IgG4 subclass predominance. None of the patients in this series had evidence of infection; nor did they meet criteria for systemic autoimmune disease other than AIP. It may be argued that these cases represent a form of systemic Sjögren syndrome, in particular in our 2 cases with salivary gland involvement. Indeed, some patients with AIP have been reported to have Sjögren syndrome, and Sjögren syndrome has been described as producing "pseudolymphoma" lesions in various organs.^{13,14,30,34,36} A systemic IgG4-associated disease may indeed account for some cases of Sjögren syndrome.

Rarely, TBM immune deposits are seen in idiopathic interstitial nephritis. One report of 8 cases has shown a subset of TIN with TBM immune-complex deposits to be associated with hypocomplementemia.²² IgG subclass predominance was not studied in these

cases. However, 80% of the reported AIP-associated interstitial nephritis cases of in which complement levels were measured (Table 1) showed decreased levels of at least one complement component. Another observation is the occasional association of immune-complex TIN with MGN, another IgG4-predominant immune-complex disease. Although not present in the current 5 cases, MGN has been seen in 2 of the 5 literature cases of AIP-associated TIN (Table 1). These coexisting renal findings may represent a sampling bias as patients with proteinuria may be more likely to undergo biopsy, or the findings may represent a true pathogenic relationship.

In the past several years, investigators have found AIP to be associated with elevated serum IgG4 and with IgG4-positive plasma cells in tissue samples.^{4,5} Similarly, the cases in the current series show elevated serum IgG4 levels (in 2 patients tested), numerous IgG4-positive plasma cells in the tissue, and/or predominant IgG4 in immune-complex deposits. In addition to IgG4, we also describe presence of other IgG subclasses in the immune-complex deposits, as has not been studied previously. It is unclear whether IgG4 staining of plasma cells or TBMs is specific for this disease. The glomerular deposits in MGN and fibrillary glomerulonephritis are known to stain for IgG4,^{20,21} although to our knowledge TBM staining for IgG4 has not been reported. Although we had a small number of other diseases with TBM deposits with which to compare our IgG4 staining, the TBMs of none of these other diseases showed staining for IgG4.

IgG4 is an unusual antibody, the rarest IgG subclass in the circulation of normal individuals.³¹ Elevated titers of IgG4 are found in conditions of chronic antigen exposure; for example, beekeepers show elevated IgG4 directed against bee venom.² IgG4 is "functionally monovalent," meaning that it behaves as though it has a single antigen-binding site, unlike other IgG subclass molecules. The monovalency is explained by weak inter-heavy chain disulfide bridges, such that IgG4 half-molecules with different antigen specificities are exchanged among themselves.¹ In this way, IgG4 is thought to act as an anti-inflammatory antibody, unable to fix complement or otherwise activate an immune response. In its relation to disease, we may speculate that IgG4 is deposited in basement membranes as a result of chronic immunologic attack on a common autoantigen in the tubular epithelial cells in the kidney as well as in epithelial cells in other affected organs. The IgG4 itself may serve as a "blocking antibody" to quench this attack. What the exact autoantigen is, or why this disease tends to form discrete inflammatory masses, is unclear. In a study using AIP patients' sera, Aoki et al⁵ found IgG4 autoantibody reactivity directed toward pancreatic duct epithelium, bile duct epithelium, and salivary gland duct epithelium. Tissue from the kidney was not included in this study, but given the patterns seen in other organs, we suspect the presence of autoantibody reactivity to renal tubular epithelial cells.

In summary, we present the features of 5 cases of an unusual subset of autoimmune TIN. The disease typically presents in older men as masses or renal failure; the patients may have a history of other inflammatory or autoimmune disease. The disease has an immunologic feature of IgG4 subclass predominance. This type of TIN may be part of a systemic IgG4-related disease, which we term "IgG4-associated immune complex Multiorgan Autoimmune Disease" (IMAD).

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