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Proliferative, necrotizing and crescentic immune complex-mediated glomerulonephritis in a cat

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Abstract

Case Summary A 5-year-old cat was examined for vomiting and anorexia of 2 days' duration. Azotemia, hyperphosphatemia and hypoalbuminemia were the main biochemical findings. Serial analyses of the urine revealed isosthenuria, proteinuria and eventual glucosuria. Hyperechoic perirenal fat was detected surrounding the right kidney by ultrasonography. Histopathologic evaluation of ante-mortem ultrasound-guided needle biopsies of the right kidney was consistent with proliferative, necrotizing and crescentic glomerulonephritis with fibrin thrombi, proteinaceous and red blood cell casts, and moderate multifocal chronic-active interstitial nephritis. Owing to a lack of clinical improvement, the cat was eventually euthanized. Post-mortem renal biopsies were processed for light microscopy, transmission electron microscopy and immunofluorescence. This revealed severe focal proliferative and necrotizing glomerulonephritis with cellular crescent formation, podocyte injury and secondary segmental sclerosis. Ultrastructural analysis revealed scattered electron-dense deposits in the mesangium, and immunofluorescence demonstrated positive granular staining for λ light chains, consistent with immune complex-mediated glomerulonephritis. Severe diffuse acute tubular epithelial injury and numerous red blood cell casts were also seen.

Relevance and novel information To our knowledge, this is the first report of naturally occurring proliferative, necrotizing and crescentic immune complex glomerulonephritis in a cat.

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Case description

A 5-year-old spayed female domestic shorthair cat was evaluated for vomiting and anorexia of 2 days' duration. The cat was housed indoors with 10 other cats, had no previous relevant medical problems and only received monthly topical selamectin. Physical examination revealed bilateral renal pain. The remainder of the physical examination was unremarkable.

Initial blood chemistry tests revealed markedly elevated concentrations of blood urea nitrogen (162 mg/dl; reference interval [RI] 15–32 mg/dl), creatinine (13.7 mg/dl; RI 1.0–2.0 mg/dl) and phosphorous (14.5 mg/dl; RI 3.0–6.6 mg/dl). At that time, the albumin concentration was within the RI (2.5 g/dl; RI 2.4–3.8 g/dl) with a mild elevation in aspartate aminotransferase (53 U/l; RI 1–37 U/l). The remaining chemistry values were within their respective RIs. A complete blood count revealed a moderate non-regenerative anemia with a packed cell volume of 23% (RI 31.7–48.0%) with no reticulocytes observed.

Urine obtained via cystocentesis on the day of initial evaluation demonstrated minimal concentration (urine specific gravity 1.013) with 3+ protein and rare cocci and

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rods observed in the sediment; no casts were observed. Urine culture obtained from the same sample did not yield any growth of bacteria. A urine protein:creatinine ratio was elevated at 1.81 (normal <0.20).

Abdominal radiographs did not reveal abnormalities. Ultrasound showed that the right kidney was 4.5 cm long and the left kidney was 4.2 cm long. Both had normal corticomedullary definition, and no ureteral dilation or uroliths were seen.

Testing for feline leukemia virus and feline immunodeficiency virus (ELISA SNAP FIV/FeLV Combo Test; IDEXX Laboratories), *Dirofilaria* antigen and *Ehrlichia canis, Anaplasma phagocytophilum* and *Borrelia burgdorferi* (SNAP 4Dx Plus Test; IDEXX Laboratories) antibodies was negative.

The cat received supportive care and antibiotic therapy consisting of intravenous fluids, ampicillin (22 mg/kg IV q8h, ampicillin sodium injection, powder, for solution; Sandoz), enrofloxacin (5 mg/kg IV q24h, Baytril; Bayer), buprenorphine (0.0125 mg/kg IV q6h, Buprenex [buprenorphine hydrochloride] Injectable; Reckitt Benckiser Pharmaceuticals) and ondansetron (0.2 mg/kg IV q8h, NOVAPlus Ondansetron Injectable; Fresenius Kabi USA). Aluminum hydroxide (aluminum hydroxide liquid; Rugby Laboratories) was administered with food (11 mg/kg q8h). Maropitant (1 mg/kg IV q24h, Cerenia [maropitant citrate] Injectable; Zoetis) and mirtazapine (1.875 mg PO q72h, Mirtazapine tablet, film coated; Aurobindo Pharma) were later added to the treatment regimen in the face of persistent nausea and anorexia.

Throughout hospitalization the cat developed glucosuria (2+) despite a normal plasma glucose measurement (123 mg/dl; RI 67–168) and hypoalbuminemia (albumin 2.2 g/dl; RI 2.4–3.8 g/dl).

To rule out renal lymphoma as the cause of azotemia, a fine-needle aspirate of the right kidney was obtained 2 days after presentation. Cytology revealed no cellular abnormalities. Ultrasound-guided needle biopsies of the left kidney were obtained on day 4 of hospitalization. Samples were evaluated with light microscopy using only hematoxylin and eosin staining. Results were consistent with a necrotizing and proliferative glomerulonephritis (GN) of unknown etiology. Erythrocytic casts were observed.

Owing to lack of improvement in azotemia, the cat was euthanized. Full necropsy was declined but the owner consented to the collection of renal tissue; wedge samples of the right kidney were obtained immediately post mortem and submitted to the International Veterinary Renal Pathology Service. Samples were serially sectioned at a thickness of 3 µm and stained with hematoxylin and eosin, Periodic acid–Schiff and Masson's trichrome stains, and Congo red and Jones' methenamine silver methods. Histopathology revealed diffuse segmental endocapillary hypercellularity with fibrinoid necrosis of glomerular tufts (Figure 1). Approximately 10% of glomeruli had cellular crescents within Bowman's space. The glomerular basement membrane (GBM) had double contours. Segmental sclerosis and synechiae were present in some glomeruli. Diffusely, tubules were at various stages of injury and regeneration. Numerous erythrocytic casts were present in distal nephrons. Interstitial fibrosis and inflammation was mild and patchy.

On transmission electron microscopy (TEM) (Figure 2a), glomerular capillary loops were lined by swollen endothelial cells and contained inflammatory cells, fibrin and cell debris. Mesangium contained scattered electron-dense deposits, consistent with immune complexes. There were irregular intramembranous and rare subendothelial electron-dense deposits associated with interposed mesangial cells. Podocytes had multifocal podocyte foot process effacement. There was severe tubular injury characterized by epithelial cell necrosis with loss of nuclei, degenerative changes with surface blebbing, brush border loss and regeneration with anisokaryosis.

Renal tissue was kept in Michel's buffer for 10 days prior to submission to the International Veterinary Renal Pathology Service. Once received, these samples were embedded in Optimal Cutting Temperature (OCT compound; Tissue-Tek) and frozen. Serial sections of tissue were stained with polyclonal caprine antibodies against feline IgG, IgM and IgA (Caprine anti-cat IgG, IgM and IgA polyclonal antibodies; Bethyl Laboratories), as well as polyclonal rabbit antibodies against human kappa and λ light chains (LLC) and complement (C)1q (rabbit anti-human λ light chain, kappa light chain and C1q polyclonal antibodies; Dako North America), which are known to cross-react with the feline proteins. Evaluation of these samples revealed weak positive granular staining for IgA, IgM and LLC within the mesangium (Figure 2b–d). Staining for IgG was equivocal; staining for C1q and kappa light chains were negative. Taken together, the pathologic evaluation demonstrated an immune complex-mediated, proliferative, necrotizing and crescentic GN with IgA- and IgM-dominant immune complexes.

GN is a common cause of kidney disease in dogs and humans; however, it is uncommonly documented in cats. Glomerular injury disturbs the glomerular filtration barrier, resulting in proteinuria and subsequent tubulointerstitial damage.

Discussion

Many different types of glomerulopathies have been reported in dogs, including amyloidosis, membranoproliferative glomerulonephridites and viral-associated glomerulopathies. Many are hypothesized to be secondary to systemic diseases, including neoplastic, infectious and non-infectious inflammatory disorders.[1,2] Recently, a large retrospective study reported the pathologic lesions of 501 dogs were biopsied for the clinical indication of

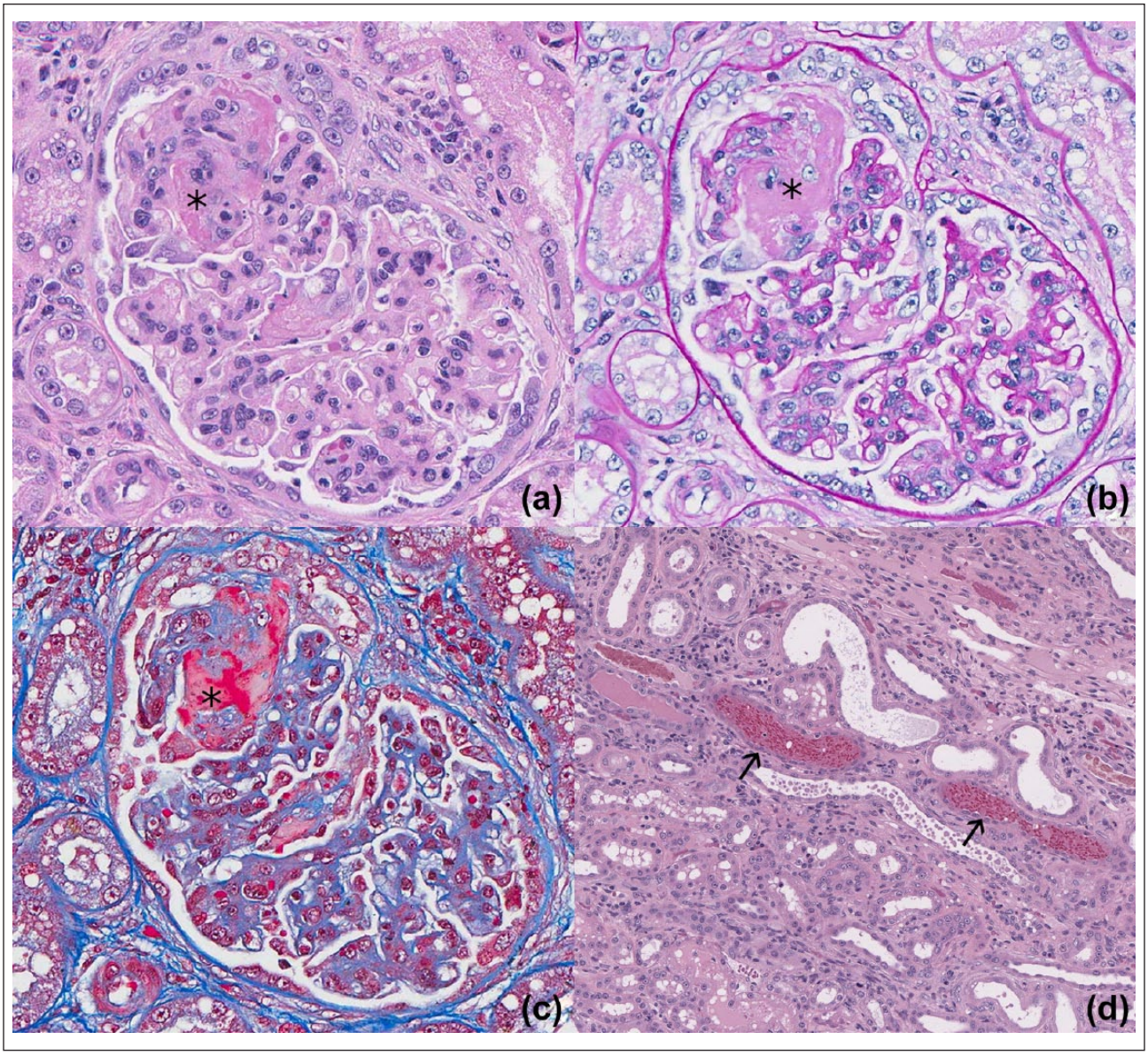

Figure 1 Serial sections of a glomerulus stained with (a) hematoxylin and eosin, (b) Periodic acid–Schiff method and (c) Masson's trichrome. There is a segmental fibrinocellular crescent (*) and moderate hypercellularity in the mesangial and endocapillary compartments. Magnification × 400 for all photomicrographs. (d) Red blood cell casts (arrows) in collecting ducts of the renal medulla (hematoxylin and eosin; magnification ×200)

proteinuria.[3] Approximately half of all dogs evaluated in that study had immune complex GN (ICGN).

Less is known regarding the types and prevalence of glomerular disease in cats. Histologic lesions consistent with ICGN and confirmed with TEM were observed in only one animal in one study of chronic kidney disease in 60 cats.[4]

In humans, crescentic GN is well documented. Crescents develop when glomerular capillaries rupture and blood, fibrin and inflammatory cells are released into Bowman's space. Human crescentic GN can have many causes, including types of ICGN, pauci-immune GN and anti- GBM disease. Human ICGNs that often cause crescents are lupus nephritis and IgA nephropathy (IgAN). No matter what the underlying disease process is, if more than half of the sampled glomeruli have crescents, the prognosis is worse.[5] Advanced diagnostics such as TEM and immunofluorescence (IF) are required in human nephropathology to distinguish between the possible causes of crescentic GN. Crescentic GN in animals has been rarely reported and the most commonly affected animals are pigs and sheep with abnormalities in complement pathways.[6,7]

Red cell cylindruria is rare in veterinary species but common in humans with active crescentic GN. In humans, erythrocytic casts or dysmorphic red blood

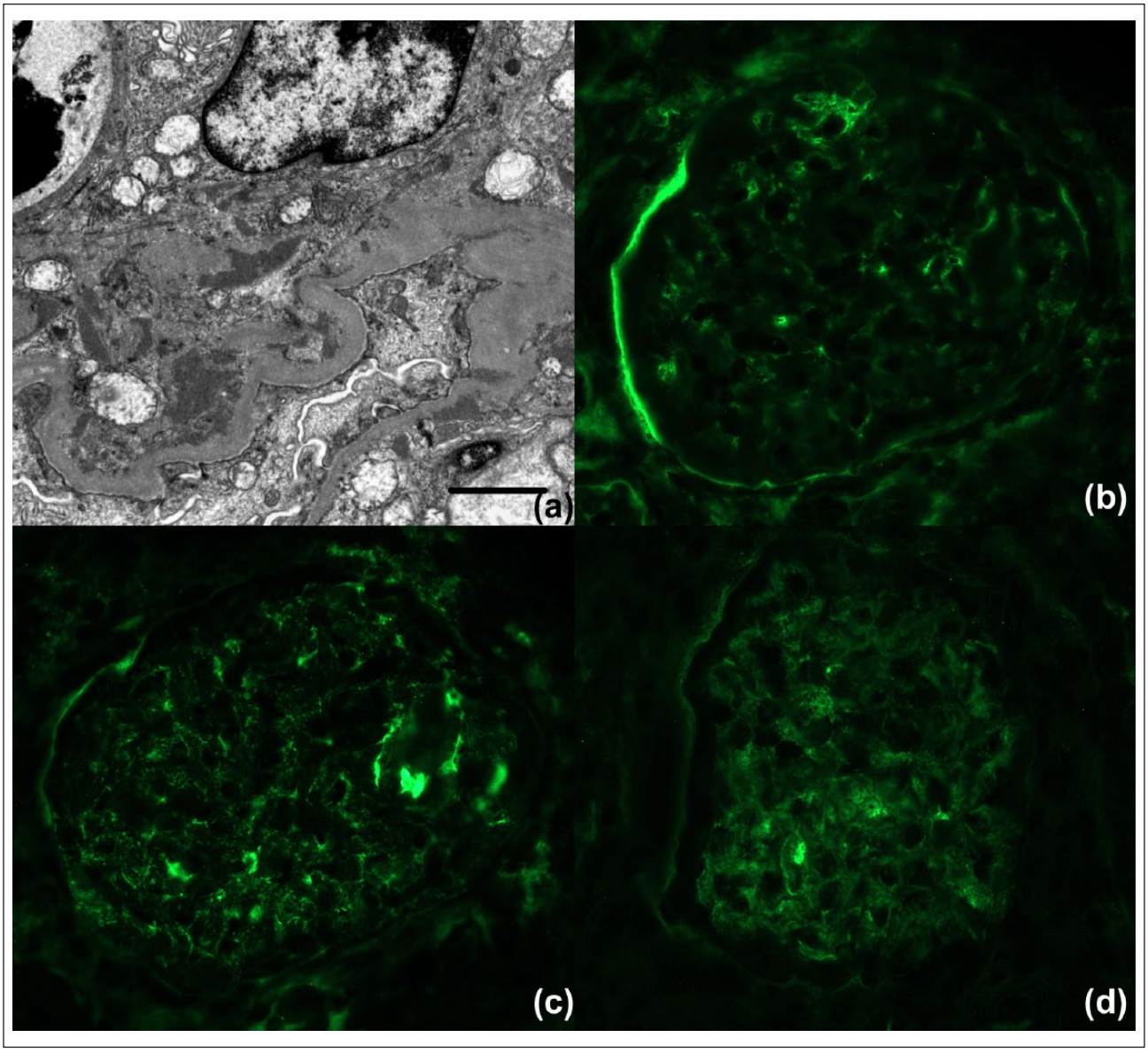

Figure 2 Transmission electron microscopy of (a) a glomerulus reveals scattered electron-dense deposits in mesangial and subendothelial zones. Podocyte foot processes are effaced. Bar = 2 µm. Direct immunofluorescence using antibodies against (b) immunoglobulin (Ig)G, (c) IgM and (d) IgA. Staining for IgG was equivocal whereas there was distinct granular staining with antibodies against IgM and IgA

cells warrant renal biopsy.[8] One study that evaluated renal pathology in humans with isolated microscopic hematuria demonstrated IgAN to be the most common diagnosis; only 6.4% of humans had normal kidney structure.[9] Other differential diagnoses for red blood cell casts include systemic lupus erythematosus and membranous GN.[10]

In cats, membranous GN, characterized by deposition of immune complexes along the subepithelial aspect of the GBM, is the most common form of GN; other forms appear to be less common.[11–13] The prevalence, historical and diagnostic findings, as well as the clinical course of other forms of feline glomerulopathy are poorly characterized.

Histopathology in this case revealed segmental necrosis of glomerular tufts with crescent formation. In humans, these features can be observed in pauci-immune GN, anti-GBM GN and ICGN. Differentiation requires TEM and IF; serologic assays can further support the diagnosis. Pauci-immune GN has neither electron-dense deposits nor positive IF staining. Anti-GBM GN has strong linear staining with IgG, LLC and C3 along capillary walls, and does not involve immune complex formation; therefore, TEM does not reveal electron-dense

deposits. Neither pauci-immune GN nor anti-GBM GN has significant glomerular hypercellularity. Lastly, ICGN will result in positive IF staining and electron-dense deposits. Notably, immune complexes are comprised of one or multiple immunoglobulin types together with an antigen. In humans, ICGN can be further subdivided by the type of immunoglobulins present. Lupus nephritis is IgG dominant but there is often concomitant IgA, IgM and complement components C3 and C1q. IgA is dominant or co-dominant in IgAN.

Using the diagnostic algorithms for humans, this case falls into the category of ICGN. The IF revealed granular labeling with IgA, IgM and LLC in mesangial zones, which agrees with where most of the electron-dense deposits were identified ultrastructurally. In our experience and that of others, IgM labeling is often non-specific. Furthermore, there is no association between IgM deposition and crescentic or necrotizing GN in humans, dogs or cats, whereas there is an association between IgA deposition and crescentic GN in humans. Unfortunately, the IF sample was held in Michel's buffer for 10 days – the suggested maximum time is 5 days. It is possible that negative IgG staining was due to the prolonged storage in this medium. Therefore, this is a case of proliferative and crescentic ICGN with IgA dominant deposits, with the caveat that the IgG staining might have been negatively affected by the prolonged storage in Michel's buffer. Of note, the histopathologic phenotype of necrotizing and crescentic lesions can be seen in human IgAN.

To our knowledge, this is the first report of naturally occurring proliferative, necrotizing and crescentic GN with mesangial immune complex deposits observed in the cat. Focal mesangioproliferative glomerulopathy has been previously diagnosed by light microscopy in an Abyssinian cat.[11] This cat was one of a number of related cats that all demonstrated proteinuria and hematuria. Other affected cats in that report lacked glomerular abnormalities on light microscopy. IF and TEM were not performed in any of these cats; therefore, whether any of these cats had ICGN is unknown.

Proliferative GN has been induced in experimental models of feline GN.[14] This model, known as 'serum sickness', utilized intravenous administration of human serum albumin to cats to induce ICGN. Information extrapolated from the 'serum sickness' model of PGN would suggest that the cat in this report likely developed an immune response to an unknown circulating antigen. The mesangial immune complex deposits and positive IgA IF support the hypothesis that this cat had naturally occurring ICGN. Infectious disease screening and urine culture were negative; however, owing to the acute nature of the disease it is possible that convalescent antibody titers or a necropsy might have confirmed infection.

The diffuse tubular injury present in this case was secondary to active GN. Erythrocytic casts are rarely reported in veterinary species but can be common in humans with GN, depending on the type of glomerulopathy.[10] In humans, erythrocytic casts have a sensitivity and specificity of 12.2% and 100.0%, respectively, in diagnosing glomerular source of hematuria.[15] The lack of red blood cell casts in the urinalysis of this cat, but presence on biopsy, might suggest that this phenomenon is underdiagnosed in this species. Possible explanations for the disparity between the urinalysis and biopsy findings might include tubular obstruction, as well as decreased glomerular filtration rate and urine output yielding lower excretion of casts. The urine was analyzed promptly in this cat, suggesting that cast dissolution due to prolonged storage is unlikely.

Conclusions

Overall, the injury present in both the glomeruli and tubules made this cat's disease difficult to manage medically with traditional supportive care. Extracorporeal renal replacement therapy would have helped correct this cat's uremia; however, it was declined. Immunosuppressive therapy appears warranted based on the histopathology results; however, a predictable response is unknown. Because interstitial fibrosis was mild and tubular regeneration was observed, it is possible that dialytic support and immunosuppressive therapy might have led to improvement in renal function in this case.

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