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Pauci-immune glomerulonephritis in a captive chimpanzee (*Pan troglodytes*), and a review of spontaneous cases in animals

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Abstract

Background—Crescentic glomeruli are the hallmark finding in rapidly progressive glomerulonephritis (RPGN) and are characterized by disruption and proliferation of the glomerular capsule and an influx of cells into Bowman's space. Pauci-immune type RPGN is identified by a lack of immunoglobulins and immune complexes in the glomerular basement membrane.

Methods—Complete necropsy and histology were performed on the affected chimpanzee. Electron microscopy was performed on kidney sections. A search of the literature was performed to identify spontaneous RPGN in animals.

Results—We report a case of crescentic glomerulonephritis of the pauci-immune type in a Hepatitis C Virus infected 28 year-old male chimpanzee (*Pan troglodytes*) who was humanely euthanized for a cardiac related decline in health.

Conclusion—To our knowledge, this is the first report describing pauci-immune crescentic glomerulonephritis in a non-human primate.

Keywords

Crescentic Glomerulonephritis; Rapidly Progressive Glomerulonephritis; Pauci-immune; Nonhuman primate; Chimpanzee

Introduction

Glomerulonephritis is a major cause of kidney disease leading to renal failure in both animals and humans. Compromise of the basement membrane leading to glomerular epithelial crescents is a common finding in severe forms of diffuse glomerulonephritis, and often prefaces end stage renal failure within days to weeks of presentation [1, 8, 31]. Glomerular crescents are characterized by hyperplasia of the parietal epithelial cells lining

Bowman's capsule, along with an infiltrate of inflammatory cells, including macrophages and lymphocytes, and plasma proteins into Bowman's space [3, 31, 35]. Together, these cells form a classical crescent shape surrounding the renal corpuscle. When 50% or greater of glomeruli are affected the disease is termed crescentic glomerulonephritis or rapidly progressive glomerulonephritis (RPGN) with the latter term being more common in human medicine [35].

We report a case of pauci-immune RPGN in a 28 year old, male chimpanzee (*Pan troglodytes*), that was identified as an incidental finding. To our knowledge, this is the first description of crescentic glomerulonephritis in a chimpanzee, and the only account of pauci-immune RPGN in any animal. Following the case report, we present a review of the veterinary literature of spontaneous RPGN.

Materials and Methods

Animals

All animal care and procedures were approved by the Texas Biomedical Research Institute Institutional Animal Care and Use Committee. The chimpanzee was housed in an indoor-outdoor, metal and concrete cage and fed a standard commercial monkey chow (Teklad®, PMI Nutrition International, LLC, Brentwood, MO 63144). Water was available *ad libitum*, and fresh fruits and vegetables were fed daily.

Pathology

A complete necropsy was performed, and appropriate tissue samples were taken for histologic evaluation. All tissues were fixed in 10% neutral buffered formalin, processed conventionally, embedded in paraffin, cut at 5 microns, stained with hematoxylin and eosin, and evaluated by light microscopy by at least one board-certified veterinary pathologist. Histochemical staining for periodic acid-Schiff (PAS) and periodic acid methenamine silver (PAMS), were performed according to standard protocol.

A representative sample of kidney was removed from the formalin fixed paraffin embedded block, reverse processed through xylenes and graded alcohols and then rehydrated. The sample was then post fixed in 2% phosphate buffered glutaraldehyde overnight at 4 degrees Celsius, followed by 2 hours in Dalton's chrome osmium, processed through graded alcohols and propylene oxide, infiltrated and embedded in freshly prepared polybed resin, oriented in BEEM™ capsules and cured overnight at 64 degrees Celsius. Blocks were sectioned using a Leica Ultracut 6 for thick (0.5 um) sections and placed on glass slides and stained with 1% Toluidine blue. Thin sections (50 angstroms) were placed on 200 mesh copper grids and stained with 35% alcoholic uranyl acetate, followed by 0.1% aqueous lead citrate. Sections were viewed on the JEOL™ 1400 transmission electron microscope. Digital images were captured using a Gatan Orius™ camera.

Testing for anti-neutrophilic cytoplasmic antibodies (ANCA) was performed at a reference laboratory according to standard protocols.

For immunohistochemical labeling, reagents were procured from Ventana Medical Systems, Tucson, AZ. All stains were completed using the Ventana BenchMark Ultra automatic stainer with the UltraView DAB detection kit. IgA, IgD & IgM were polyclonal rabbit antibodies (Ventana catalog number 760-2652, 760-4444 and 760-2654 respectively) which were treated with Hier in CC1 at 99 degrees Celsius for 36 minutes, then incubated at 37 degrees Celsius for 48 minutes and counterstained with Haematoxylin (Ventana catalog number 760-2021)/Bluing (Ventana catalog number 760-2037) for 4 minutes each. IgG was a polyclonal rabbit antibody (Ventana catalog number 760-2653) which was treated with a Protease 1 digest for 4 minutes, then incubated at 37 degrees Celsius for 16 minutes and counterstained with Haematoxylin (Ventana catalog number 760-2021)/Bluing (Ventana catalog number 760-2037) for 4 minutes each. Note: These stains are optimized for humans.

Literature review

We performed a literature search for all published cases of spontaneous crescentic glomerulonephritis/RPGN in animals. Mouse models and experimentally induced RPGN were excluded.

Case Report

History

The 28 year old, male chimpanzee was euthanized after experiencing increased respiratory distress and poor recovery from anesthesia following a routine annual physical examination. ECG during the sedated physical exam revealed atrial fibrillation and right bundle branch block.

The animal had a history of mild iron-responsive anemia, hypoproteinemia, hypoalbuminemia, mildly elevated ALT, mildly elevated cholesterol, and markedly elevated GGT and triglycerides in the three years prior to euthanasia. Triglycerides were normal on the day of euthanasia. Urinalysis was not performed. An ultrasound guided biopsy of the liver two years prior to euthanasia revealed diffuse moderate to severe hepatopathy, attributed to the animal's status as positive for Hepatitis C Virus (HCV) from experimental inoculation.

Gross pathology

At necropsy, the kidneys were grossly normal in terms of shape, color and consistency with the exception of a 4 cm diameter area of pallor and firmness in the right kidney. The animal had subcutaneous scrotal, preputial and periocular edema, with approximately 200 ml of straw colored fluid in the pleural cavity, an additional 100ml of similar fluid in the pericardial sac, and 150 ml of blood tinged fluid in the abdominal cavity. The heart was enlarged and the right ventricle was mildly distended. The left lung lobes were red-pink, pale and firm. The liver was rough, nodular and slightly firm with several 1–4 mm diameter irregular areas of dark red parenchyma. A 10cm diameter cyst filled with clear fluid was attached to the surface of the liver and gallbladder.

Histology

The area of pallor in the kidney was characterized by diffuse moderate to marked periglomerular and interstitial fibrosis with moderate lymphoplasmacytic interstitial nephritis. Occasional proteinaceous debris was present in the tubules. Diffusely, the glomeruli had marked expansion of the Bowman's capsule and concurrent filling of Bowman's space by increased numbers of parietal epithelial cells and spindle cells often compressing the glomerular tuft (Fig. 1). Affected glomeruli displayed segmental hyperplasia with basement membrane thickening and hypertrophy. A sample of grossly normal tissue from the same kidney had similar changes, though the crescents were less pronounced than in the infarct-like area of tissue. There was also a difference in the frequency of crescents with 98% of the glomeruli affected in the infarct-like area and 78% of glomeruli affected in the grossly normal kidney. Histochemical staining of affected renal tissue with PAS (Fig. 2) and PAMS highlighted the thickened, undulating glomerular basement membranes, increased mesangial matrix, and glomerular crescents. Masson's trichrome stain (Fig. 3) revealed moderate to severe interstitial, periglomerular and arteriolar fibrosis.

Microscopic examination of the heart revealed that approximately 25% of the left ventricle and septum had been replaced with irregular areas of fibrosis, separating and replacing myocardial fibers. Adjacent myofibers were irregularly shaped, shrunken, vacuolated and had loss of cellular detail. There were multifocal mild accumulations of lymphocytes within the myocardial interstitium. Similar, but minimal, findings were observed in the right ventricle. The pulmonary alveoli contained numerous intraluminal macrophages with brown cytoplasm consistent with heart failure. The liver contained areas of telangiectasia and nodular regeneration, with scattered hepatocyte degeneration, hemosiderin deposition, and extramedullary hematopoiesis. The fluid filled structure was a biliary cyst.

Electron Microscopy

Electron microscopic examination revealed patchy, mild fusion of podocyte foot processes, periglomerular fibrosis and moderate expansion of the mesangial matrix (Fig. 4). There were no subepithelial, membranous, subendothelial or extraglomerular deposits.

Immunostaining

Immunohistochemical staining using CD68 and Ki67 demonstrated the presence of intermittent, sparse macrophages and proliferation of cells, respectively, within crescents. Immunohistochemistry for IgA, IgD, IgM and IgG was unsuccessful as noted by abundant background staining in all samples, including positive (human tonsil with plasma cell cytoplasmic immunoreactivity) and negative control (normal chimpanzee renal tissue); this data was not contributory and therefore not published.

Fresh tissue was not collected at the time of necropsy to submit for immunofluorescence.

Immunology

Serum from this animal was submitted to a reference laboratory (Scott & White Reference Laboratory, Temple, TX) and determined to be negative for the presence of ANCA.

Review

Three major types of RPGN have been classified in humans. Type I, anti-glomerular basement membrane (GBM) glomerulonephritis, is the most aggressive form of RPGN with the highest frequency of renal insufficiency at the time of diagnosis [13] and often accompanies systemic vasculitis and pulmonary hemorrhage as the manifestation of Goodpasture's Syndrome [7, 13]. Classification relies upon the detection of linear deposits of anti-GBM antibodies by immunofluorescence [13]. Type II, immune-complex glomerulonephritis, is less frequently associated with crescent formation compared to the other forms of RPGN and is attributed to antibody-antigen complexes embedded in the GBM and glomerular tuft. This form of RPGN is most often diagnosed post staphylococci/streptococci infection but can be associated with lupus nephritis as well as membranoproliferative glomerulonephritis (MPGN) and other immune-complex diseases [13, 20]. Type III, pauci-immune glomerulonephritis is the most common form of crescentic glomerulonephritis [7, 13] and is characterized by a lack of immune deposits in the GMB and anti GBM antibodies [13, 25]. Pauci-immune glomerulonephritis is usually accompanied by anti-neutrophilic cytoplasmic antibodies (ANCA) in serum and is therefore also referred to as ANCA glomerulonephritis [1, 7, 13, 20, 31]. This form of RPGN is most often linked with systemic vasculitis and autoimmune inflammatory diseases such as granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) or Churg-Strauss syndrome [13, 20]. However, idiopathic and renal limited vasculitis forms of type III RPGN have been identified in patients lacking systemic vasculitis [35].

A recent consensus report on glomerulonephritis by Sethi et al (2015) includes two additional glomerulonephritis types; monoclonal Ig glomerulonephritis and C3 glomerulopathy, which can both result in the formation of glomerular crescents. Monoclonal Ig glomerulonephritis is identified by the presence of Ig deposits and most commonly, a membranoproliferative pattern, although alternative patterns of injury such as crescentic or sclerotic may be present. C3 glomerulopathy is characterized by C3 deposition in the glomeruli due to abnormal regulation of the complement pathway. This form usually does not involve heavy deposits of Ig and in the past has been described as a finding in type II or III glomerulonephritis depending on the pathogenesis [20,28].

Despite the above classifications, it is not rare to see patients with an overlap of immunopathological phenotypes [13] and determining the type of RPGN usually requires immunohistochemical staining, electron microscopy and serology for immunoglobulin classification.

Regardless of the type, RPGN is considered to result from a primary inciting cause triggering a pro-inflammatory state with the activation of complement and compromise of the glomerular basement membrane; this acute, necrotizing lesion is then followed by proliferation of cells forming the crescent [11, 13]. RPGN carries a poor prognosis and is clinically characterized by rapid loss of renal function including oliguria, weight loss, and extra-renal symptoms depending on the primary cause [3, 20].

Although RPGN has been well studied and documented in humans, the disease is far less common and researched in animals; few naturally occurring cases have been documented, and crescentic glomerulonephritis is generally not included as a classification of glomerulonephritis in animals [5]. Naturally occurring cases have been described in dogs, sheep, a macaque and most recently a polar bear [1, 3, 9, 18, 34]. However, the pauci-immune type of RPGN has not been reported in animals.

RPGN has been documented in dogs although details of the type of crescentic glomerulonephritis are not usually described. Young Rottweiler dogs affected with juvenile onset renal disease have demonstrated histologic changes consisting of glomerular crescents and thickened GBM associated with familial renal disease resulting from type IV collagen defects similar to Alports disease in humans [36]. Crescentic glomerulonephritis, associated with leishmania antigen, has been documented in a single case of canine leishmaniasis [6]. In a prospective study of 76 dogs previously diagnosed with chronic interstitial nephritis, one was identified to have naturally occurring diffuse crescentic glomerulonephritis with granular capillary wall IgA deposits [18]. Another study identified 1 of 115 dogs with glomerular disease as crescentic focal glomerulonephritis based on fibrocellular proliferation of parietal glomerular epithelial cells filling parts of Bowman's space [34]. These cases have sparked debate over whether crescentic glomerulonephritis occurs in a diffuse or focal form in dogs, as there have been multiple reports of focal [21, 37] and diffuse [16, 18, 22] presentations.

Finnish Landrace sheep have a spontaneous, naturally occurring, inherited, RPGN thought to be caused by a fault in the complement system. The disease leads to the build-up of antibodies in the GBM and the interposition of mesangial cells and matrix between the endothelium and GBM, similar to type II anti-GBM type glomerulonephritis [9]. An unusual finding in these sheep is the presence of discontinuities (gaps) in the GBM [9].

Crescentic glomerulitis was reported in a 4-year-old female pigtailed macaque (*Macaca nemestrina*) experimentally infected with simian immunodeficiency virus and *Mycobacterium bovis*; the macaque was found to have type IgA immune complex deposition in the GBM and mesangium [3].

A 17-year-old male, zoo born, polar bear with clinical signs of liver and renal failure was diagnosed with crescentic glomerulonephritis of the immune complex type, based on the presence of electron-dense deposits in the GBM. This is most consistent with type I or II RPGN, although without immunostaining it is difficult to definitely determine the type [1].

Discussion

We report a case of pauci-immune RPGN in a chimpanzee (*Pan troglodytes*). To our knowledge, this is the first description of crescentic glomerulonephritis in a chimpanzee, and the only account of pauci-immune RPGN in any animal. The glomerular crescents were primarily composed of basement membrane, parietal epithelial cells, spindle cells, fibrosis, and proteinaceous material.

The lack of glomerular immune complex deposits and immunoglobulins as noted on electron microscopy is most consistent with pauci-immune crescentic glomerulonephritis. Although RPGN has been well studied and documented in humans, only a few naturally occurring cases of crescentic glomerulonephritis have been identified in animals [1, 3, 9, 18, 34]. This lesions in chimpanzee vary from the other naturally occurring reports in animals based on a lack of immune deposits in the glomeruli. The history of ECG arrhythmias, myocardial fibrosis, generalized subcutaneous edema, pleural edema, ascites, and microscopic pulmonary changes consistent with heart failure indicate the cause of poor recovery from anesthesia was a result of cardiomyopathy. This is not unusual, as interstitial myocardial fibrosis has an approximately 80% incidence, and may account for up to 68% of deaths, in aged chimpanzees [2, 17, 23, 27].

Glomerulonephritis has been well documented in chimpanzees and other non-human primates [4, 10, 26, 29], however, this is the first report of pauci-immune type RPGN in a non-human species. After identifying the renal lesions in this case, all deceased chimpanzees with any form of renal pathology were identified for microscopic reevaluation for the presence of crescents. Of 191 chimpanzees necropsied at this institute, 59 were identified to have renal pathology (nephritis, nephrosis, glomerulonephritis or glomerulosclerosis). Of these 59, two additional animals, other than this case, had glomerular crescents present in their tissue samples. Both were diagnosed as glomerulonephritis, and as they had less than 5 crescents present in the entire tissue sample (1–2%) would therefore not be considered RPGN.

Renal disease in chimpanzees is not rare, particularly as an age-related disease; however, it is necessary to consider that this animals positive HCV status may have played a role in the pathogenesis of RPGN [17]. The incidence of HCV infection related immune-complex glomerulonephritis in humans has been well documented, with the primary glomerular lesions of membranoproliferative glomerulonephritis [14, 30, 33]. However, to our knowledge, only two documented cases of RPGN have been speculated to be associated with concurrent HCV infection [12, 33]. Clinical and pathologic evidence supports that a deposition of immune complexes containing anti-HCV antibodies and antigens in the glomerular capillary walls leads to inflammation and subsequent deterioration of the glomerular filtration system [29, 32]. The lack of immunoglobulin deposits argues against a role of HCV in the pathogenesis of this case, although, there has been speculation that small amounts of HCV antigen will prevent formation of detectable complexes [14, 33].

The increase in severity and number of crescents in the glomeruli of the infarct-like area compared to the rest of the kidney suggests a possible relationship between RPGN and ischemia. Currently, there are no publications of renal infarction related crescentic glomerulonephritis; however, there has been one report of RPGN development post renal ischemia-reperfusion [32], and another report of a woman with a cerebral ischemic infarct and RPGN associated with chronic use of the drug propylthiouracil [15].

Pauci-immune type glomerulonephritis has been associated with systemic autoimmune diseases such as, granulomatosis with polyangiitis (GPA, Wegener's granulomatosis), microscopic polyarteritis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA,

Churg-Strauss syndrome) [15, 24, 31]. The lack of evidence of systemic disease in the animal's history, and findings on gross and microscopic examination, decrease the likelihood that this case of pauci-immune glomerulonephritis was associated with any of these systemic autoimmune diseases. While the majority of patients with pauci-immune glomerulonephritis are ANCA positive, there is significant variability depending on the underlying syndrome. For example, only 5% of patients with GPA are negative for ANCA, while over 30% of patients with EGPA are negative for antibodies [19]. This animal was negative for ANCA antibodies, however, it is of importance to note that the ANCA antibody test has not been validated on non-human species making this negative result not entirely reliable. Additionally, pauci-immune type RPGN has been associated with certain drugs revealed to induce autoantibodies: propylthiouracil, methimazole, penicillamine, and allopurinol [15, 20]. To our knowledge, this chimpanzee was not exposed to any of these drugs.

Pauci-immune RPGN remains a rare finding in non-human primates and other animals. The pathogenesis is generally uncertain when it is encountered. We propose three possible scenarios in this chimpanzee: (1) this is an idiopathic, renal limited case, well documented to occur [20, 31, 35]; (2) the chronic HCV infection state of this animal is somehow related to crescentic glomerulonephritis formation as seen in rare human cases, [12, 33], and (3) a renal ischemic event may have been the inciting factor.

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Figure 1. Pauci-immune RPGN in a Chimpanzee. Kidney. (A) Less affected area. (B) Infarct-like area. Note crescents (arrow), characterized by marked expansion of the Bowman's capsule and concurrent filling of Bowman's space by increased numbers of parietal epithelial cells and spindle cells compressing the glomerular tuft. Note lymphoplasmacytic interstitial nephritis. H&E.

Figure 2. Pauci-immune RPGN in a Chimpanzee. Kidney. Note the thickened, undulating glomerular (black arrow) and tubular basement membranes (yellow arrow), increased mesangial matrix, and glomerular crescents. PAS procedure.

Figure 3.
Pauci-immune RPGN in a Chimpanzee. Kidney. Note the moderate to severe interstitial and periglomerular fibrosis (blue stain). Masson's trichrome stain.

Figure 4. Pauci-immune RPGN in a Chimpanzee. Kidney. Electron micrograph of glomerular tuft. Note patchy mild fusion of podocyte foot processes (red arrow) and moderate expansion of the mesangial matrix (yellow star).