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TITLE: Occurrence, management and outcome of immune-complex glomerulonephritis in dogs with suspected glomerulopathy in the UK

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Summary

Objective: The objective of the study was to investigate the percentage of dogs diagnosed with immune-complex glomerulonephritis in the United Kingdom (UK), in a large cohort of dogs with clinical suspicion of glomerular disease where renal histopathology including routine light microscopy, transmission electron microscopy and immunofluorescence had been performed. The second objective of the study was to describe prescribed treatment and long-term clinical outcome of dogs diagnosed with immune-complex glomerulonephritis.

Methods: Sixty-two dogs originating from the UK who underwent renal biopsies for investigation of suspected glomerulopathy (urine protein-to-creatinine ratio persistently >0.5) were included in this retrospective multicentre study. Signalment, clinico-pathological abnormalities, histopathological diagnosis, treatment following diagnosis and survival were recorded.

Results: Twenty-seven percent (17/62) of the population of dogs with suspected glomerular disease were diagnosed with immune-complex glomerulonephritis. Fifty-three percent (9/17) of dogs diagnosed with immune-complex glomerulonephritis were still alive at the study end point, with a median follow-up time of 366 days (range 52-1299). Six dogs diagnosed with immune-complex glomerulonephritis were treated with mycophenolate. Four received solely mycophenolate for immunosuppression and two received mycophenolate and chlorambucil, and all six were alive at data collection (median follow-up time 712.5 days (range 73-1299)). Seven dogs diagnosed with immune-complex glomerulonephritis did not receive immunosuppressive treatment, only one of these dogs was alive at study end point (median survival time 302 days (range 52-723)).

Clinical relevance: Immune-complex glomerulonephritis may be less frequent in the UK than previously reported in North America and mainland Europe, reducing the likelihood of treatment modification following renal biopsy. Mycophenolate was the most commonly used immunosuppressant for cases of immune-complex glomerulonephritis.

Key-words: immune-complex glomerulonephritis; dog; UK; mycophenolate; outcome; renal biopsy; kidney

Word count (excluding summary and references): 3992

Introduction

Glomerular disease is suspected in cases of persistent renal proteinuria (Urine Protein-to-Creatinine ratio (UPC) ≥ 0.5 in dogs) (Lees *et al.*, 2005). Immune-complex glomerulonephritis (ICGN) is reported as the most common cause of proteinuria in dogs undergoing renal biopsy for suspected glomerular disease, with a prevalence of 48% in North America (Schneider *et al.*, 2013) and 50% in European countries (Mainland Europe and UK altogether) (Aresu *et al.*, 2017). Other common diagnoses include primary glomerulosclerosis (21%), amyloidosis (15%), other non-immune complex mediated glomerulopathies (9%), non-immune complex mediated nephropathies (5%) and primary tubulointerstitial disease (2%) (Schneider *et al.*, 2013).

The International Renal Interest Society (IRIS) proteinuria consensus statements recommend that dogs with ICGN should not only receive standard anti-proteinuric therapy (Brown *et al.*, 2013), but should also receive immunosuppressive therapy comprised of one or more immunosuppressive drugs, once medical investigations have been performed to exclude possible underlying systemic disease (Segev *et al.*, 2013). According to the IRIS proteinuria consensus statements, "Dogs with peracute or rapidly progressive glomerular disease should receive [...] mycophenolate alone or in combination with prednisolone, or cyclophosphamide (continuous or pulse therapy) alone or in combination with prednisolone", and "Dogs with active but stable or slowly progressive glomerular diseases with an immune-mediated foundation [...] may receive [...] mycophenolate, chlorambucil alone or in combination with azathioprine on alternating days, cyclophosphamide and glucocorticoids or cyclosporine" (Segev *et al.*, 2013).

The diagnosis of ICGN requires renal biopsy with evaluation by light microscopy (LM), transmission electron microscopy (TEM) and immunofluorescence (IF) (Cianciolo *et al.*, 2013). Although renal biopsy procedures in dogs (by ultrasound-guided percutaneous approach, laparotomy or laparoscopy) are considered relatively safe, historically, complications are reported in up to 13% of cases with the most common complication being severe haemorrhage and death in 2.5% of cases (Vaden *et al.*, 2005). The cost of taking and interpreting renal biopsies can be prohibitive for owners, as this procedure should be performed under general anaesthesia and samples should be collected, prepared and interpreted by specialised veterinary nephropathologists.

Considering the percentage of dogs diagnosed with ICGN in North America and in Europe, and the specific treatment recommendations made for ICGN management, it appears that performing kidney

58 biopsies in appropriately chosen cases may change the treatment approach and therefore be clinically
59 relevant in half of the cases with suspected glomerular disease.

60 To the authors' knowledge there is currently no published data in the veterinary literature describing the
61 occurrence of ICGN or primary glomerular disease in the United Kingdom (UK); however, in the authors'
62 experience ICGN are not commonly diagnosed in the UK.

63 The first objective of this study was therefore to investigate the prevalence of ICGN from a large cohort
64 of dogs originating from the UK where there was clinical suspicion of glomerular disease and where
65 renal histopathology including routine light microscopy (LM), transmission electron microscopy (TEM)
66 and immunofluorescence (IF) had been performed. The aim was to be able to better inform clinicians
67 and owners about the likelihood of a treatment modification (i.e. immunosuppressive therapy) following
68 renal biopsy.

69 To date, long-term clinical outcome data in dogs diagnosed with ICGN have not been reported and
70 despite the logic of immunosuppressive strategies for this disease, there is a lack of published literature
71 supporting this therapeutic approach.

72 The second objective of the study was therefore to report prescribed treatment and long-term clinical
73 outcome of dogs diagnosed with ICGN in the UK.

74 The third objective of the study was to describe the prevalence, prescribed treatment and survival for
75 dogs included in the study and not diagnosed with ICGN.

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Materials and Methods

The study was approved by the Royal Veterinary College Ethical Committee (*Social Science Research Ethical Review Board URN SR2017-1139*).

Case selection

The computer database of the International Veterinary Renal Pathology Service (IVRPS; The Ohio State University – Columbus, Ohio, USA) and European Veterinary Renal Pathology Service (EVRPS; University of Turin, Italy) were retrospectively searched for canine renal biopsies (including wedge and needle core biopsy) originating from the UK and submitted from the 1st of January 2010 to the 1st of September 2017 by a diploma holder in the field of small animal internal medicine (Royal College of Veterinary Surgeon, American College of Veterinary Internal Medicine or European College of Veterinary Internal Medicine diploma holder) or by a veterinarian working under the supervision of a diploma holder in small animal internal medicine.

Inclusion criteria were the presence of persistent and/or severe proteinuria, characterised by a UPC \geq 0.5 on more than one occasion (Lees *et al.*, 2005) together with a definitive histopathological diagnosis obtained on the basis of LM, TEM and IF, and the presence of complete signalment, UPC and serum albumin and creatinine concentrations at the time of diagnosis as well as clinical follow-up until time of death or until data collection (1st September 2017). Samples obtained post-mortem were excluded.

Due to wide variation in the data reported on submission forms, treatments administered prior to biopsy, and diet used prior to and following sampling were not recorded. Causes of death were not recorded, as they were often speculative. Treatment prescribed following renal biopsies and concurrent illnesses were recorded.

Case follow-up, survival and outcome

The primary veterinarian of each case was contacted by one of the authors to obtain the most recent follow-up information. Cases were included only if clinical follow-up was available until time of death or until data collection (1st September 2017) if still alive. There was no minimal follow-up time for the study. Survival was calculated as the time in days from the date of renal biopsy until the exact date of death or the study end point (1st September 2017) if still alive.

The number of dogs alive at the study end point, median follow-up time and median survival time of dogs that died prior to data collection were evaluated and survival times compared between groups .

Follow-up UPC was recorded at variable time points due to non-standardised retrospective data

collection. For the purposes of this study, therapeutic success in management of ICGN was defined as a reduction in the UPC by 50% or by achieving a UPC<0.5 (Brown *et al.*, 2013; Segev *et al.*, 2013) at some point following biopsy. Dogs were considered not to have reached therapeutic success if they failed to fulfil at least one of these criteria.

Renal biopsy processing, evaluation and classification

All renal biopsies were routinely processed and evaluated by LM, TEM and IF examination as previously described (Cianciolo *et al.*, 2013) (Cianciolo *et al.*, 2015), by board-certified veterinary histopathologists working at the IVRPS or at the EVRPS. Classification of renal lesions was based on diagnostic criteria developed by the World Small Animal Veterinary Association renal biopsy panel (Cianciolo *et al.*, 2015). Transmission electron microscopy was used as the gold standard method for immune - complex detection. Renal biopsies were analysed individually and then grouped into the following disease categories: immune - complex - mediated glomerulonephritis (ICGN), GS, AM, not otherwise specified glomerulopathies (NOS GP) and other unspecified renal lesions (URL). Not otherwise specified glomerulopathies (NOS GP) included minimal change disease, podocytopathies and other glomerular basement membrane abnormalities. Other unspecified renal lesions (URL) included cases for which a definitive histopathological diagnosis had been reached but did not belong to any of the categories mentioned earlier, including primary tubulointerstitial disease and non-immune complex mediated nephropathy..

Statistical analysis

Descriptive statistics are reported. Clinical parameters, survival and duration of follow up are reported as median (range) (SPSS Statistics®, IBM Corp.). Survival times for dogs grouped according to glomerular pathology were evaluated using Kaplan-Meier survival curves (SPSS Statistics ®, IBM Corp.).

Results

A total of 95 UK cases were identified from the databases. For all cases baseline creatinine, albumin and UPC were available. Twenty-three cases were excluded because clinical follow-up could not be obtained. Three cases were excluded because renal biopsies had been obtained post-mortem. These three cases were diagnosed with thrombotic microangiopathy, a lesion pathognomonic of Cutaneous and Renal Glomerular Vasculopathy (CRGV) (Holm *et al.*, 2015). Seven additional cases were excluded as the biopsies obtained were of non-diagnostic quality. Sixty-two dogs were therefore included in the study.

Signalment

The median age was 8 years (range, 7 months to 15 years). There were 37 males (29 neutered) and 25 spayed females. Twenty-two breeds were represented (Table 1) with Golden Retriever and Labrador retriever being the most common purebreds (21% total).

Histopathological diagnosis

The most common histopathological diagnosis obtained was GS (35%, 22/62), followed by ICGN (27%, 17/62) (Table 2). Most of the dogs diagnosed with GS were female (68%, 15/22) whereas most of the dogs diagnosed with ICGN were male (88%, 15/17). Unspecified renal lesions (URL) represented 13% of the population, with 5 dogs being diagnosed with primary tubulointerstitial disease and 3 dogs with non-immune complex mediated nephropathy. Clinical data for dogs divided according to renal pathology diagnosis are presented in Table 2.

Biochemical and urinary abnormalities associated with histopathological diagnosis

In our population, AM was the renal pathology diagnosis associated with the lowest median serum albumin concentration (15g/L) and the highest magnitude of proteinuria (median UPC 16.6), followed by ICGN with a median albumin concentration of 20g/L and median UPC of 6.9. The distribution of UPC, creatinine and albumin are represented for each disease group in Figures 1 a, b, c.

Standard medical management for all dogs undergoing renal biopsy

Following renal biopsy sampling, 52 dogs (84%) were treated with angiotensin-converting enzyme inhibitors (ACEi), 37 (60%) with antiplatelet agents (19 with clopidogrel, 17 with aspirin, 1 with both), 14 (23%) with amlodipine, 14 (26%) with polyunsaturated fatty acids and 5 (8%) with angiotensin receptor blockers. Fifteen dogs (24%) received immunosuppressive therapy following sampling (6 prednisolone only, 4 mycophenolate only, 1 cyclosporine only, 1 azathioprine only, 3 received a combination of

immune-suppressive drugs). Five of the fifteen dogs treated with immunosuppressive medication did not belong to the ICGN group and received this medication for another condition (including concurrent inflammatory bowel disease and non-renal lymphoma).

Treatment for the ICGN group

Seventeen dogs (27%) were diagnosed with ICGN (Table 4) with all but one dog receiving ACEi treatment following diagnosis. Ten dogs (59%) with ICGN received either single or combined immunosuppressive therapy (Table 4). All dogs treated with mycophenolate (n=6, including 4 dogs having received mycophenolate only and 2 dogs having received mycophenolate and chlorambucil) were alive at the study end point (median follow-up time 712.5 days (range 73-1299), with treatment success (defined as UPC decreased by 50% or UPC < 0.5) reached in four out of these six dogs (66%). Mycophenolate dose and treatment duration were not available. No relapse in proteinuria (i.e. increase to UPC >0.5 or failure to achieve 50% reduction) was documented during the follow-up period for these 4 cases (median follow-up time 734 days, range 73-875 days). Figure 3 shows the progression of UPC for these four dogs during the first year following diagnosis and treatment. Two of the dogs in the mycophenolate group also received concurrent chlorambucil therapy, one of which did not achieve treatment success. The one dog treated with chlorambucil alone reached treatment success and was still alive at data collection. The one dog treated with azathioprine died 4.5 months following diagnosis. Seven dogs (41%) with ICGN did not receive any immune-suppressive therapy and only one of them was alive at the study end point (median survival 302 days (range 52-723)). Three of the seven dogs (43%) with ICGN that did not receive immunosuppressive therapy achieved a reduction of their UPC by more than 50% or UPC <0.5 during follow up. All of these dogs were treated with ACEi.

Survival for all dogs undergoing renal biopsy

Survival times are reported in Table 3, and compared between groups in Figure 2.

In our population, renal amyloidosis was associated with the smallest percentage of animals still alive at data collection (29%) and the shortest median survival time (statistical analyses not performed). One dog diagnosed with AM, however, was still alive more than 3 years following diagnosis. This dog had a UPC of 3.9 at the time of diagnosis.

Survival for the ICGN group

In the ICGN group, nine dogs (53%) were still alive at the study end point with a median follow-up time of 652 days (range, 73-1299), and the median survival time of the eight dogs with ICGN that died prior

192 to data collection was 164 days (range, 52-723). Nine of the seventeen dogs (53%) with ICGN had a
193 reduction of their UPC by more than 50% or reached a UPC <0.5 during the follow-up period.

Discussion

This is the first study to explore the occurrence of ICGN specifically in dogs in the UK using the combination of LM, TEM and IF for accurate diagnosis.

Similar to the two studies previously published evaluating the prevalence of glomerular disease in the USA and Europe (Schneider *et al.*, 2013) (Aresu *et al.*, 2017), the Golden Retriever and Labrador Retriever were the most common breeds represented although both also represent popular breeds in the UK.

Glomerulosclerosis was the most common diagnosis in dogs undergoing renal biopsy in the UK (35%), with an occurrence similar to that reported in previous studies (Schneider *et al.*, 2013), (Aresu *et al.*, 2017) and with most dogs being female (68% in this study, 72% in the North American study (Schneider *et al.*, 2013)). The occurrence of NOS GP and amyloidosis was 13% and 11% respectively, being similar to previous reports (Schneider *et al.*, 2013), (Aresu *et al.*, 2017).

The study revealed the occurrence of ICGN in dogs undergoing renal biopsy to be lower in the UK population (27%) when compared to North America (48%) (Schneider *et al.*, 2013) or Europe (including Mainland Europe and UK altogether ; 50%) (Aresu *et al.*, 2017). Fifty-three percent of dogs diagnosed with ICGN in the UK were alive at the study end point with a median follow-up time of 652 days (range 73-1299). Median survival time of dogs that died was 162 days (range 52-723). All dogs treated with mycophenolate were alive at data collection (median follow-up time 712.5 days (range 73-1299), with treatment success reached in 4/6 of them.

In this study, most of the dogs diagnosed with ICGN were male (88%). This seems to differ from previous results, as only 45% of dogs diagnosed with ICGN in North America were males (Schneider *et al.*, 2013).

The seemingly lower percentage of ICGN diagnosed in dogs undergoing renal biopsy for possible glomerular disease in the UK may be due to a lower prevalence of ICGN in the general UK canine population. This may be explained by a lower prevalence of infectious diseases in this country compared to North America and Mainland Europe. Membranoproliferative glomerulonephritis (MPGN) is considered one of the most common causes of ICGN in dogs with a reported prevalence of 26-60% (Macdougall *et al.*, 1986) (Koeman *et al.*, 1987) (Cianciolo *et al.*, 2015) and is mainly induced by infectious diseases with immune complex accumulation on the sub-endothelial side of the glomerular basement membrane (Vaden, 2017). *Dirofilaria immitis* (Nakagaki *et al.*, 1993), *Leishmania infantum* (Aresu *et al.*, 2013) (Zatelli *et al.*, 2003), *Babesia* spp. (Wozniak *et al.*, 1997) (Máthé *et al.*, 2007) and

other tick borne diseases (IRIS Glomerular Study Group *et al.*, 2013) and systemic fungal diseases such as *Coccidioides* spp. (Mehrkens *et al.*, 2016) have been associated with the development of ICGN and are non-existent to rare in the UK unless the patient has a travel history (Johnson, 2016) (Crawford *et al.*, 2013) (Genchi *et al.*, 2014) (Silvestrini *et al.*, 2016). However, *Borrelia burgdorferi* is present in the UK (Shaw *et al.*, 2005) and has also been reported as an inciting cause for ICGN, although its importance remains controversial (Hutton *et al.*, 2008). Due to the retrospective nature of this study, infectious disease screening was not standardised and the travel history and infectious disease status of many cases in the current study was unknown. However, it is possible that dogs from the UK will less commonly develop infection-induced ICGN.

The different percentage of ICGN diagnosed in dogs undergoing renal biopsy for possible glomerular disease in the UK may also be explained by the low number of cases included in this study, or by a difference in inclusion criteria between studies. Inclusion criteria for the study performed in North America were the following: dogs with a history of nephritic syndrome, nephrotic syndrome, or glomerulonephritis, or a UPC>2, or persistent renal proteinuria (proteinuria identified on routine urinalysis with or without UPC >0.5 on multiple occasions in the absence of prerenal or postrenal causes for proteinuria) (Schneider *et al.*, 2013). Inclusion criteria for the study performed in Europe was any renal biopsy specimen interpreted by LM and TEM (Aresu *et al.*, 2017). One of the inclusion criteria for the current study was UPC≥0.5 on more than one occasion (Lees *et al.*, 2005). Although 0.5 is considered as the upper reference for canine UPC, this criteria may represent a selection bias, because some clinicians would consider kidney biopsies only when UPC>2 or above. The current study only included cases with available follow-up, which once again was not the case for previously reported studies. These disparities between inclusion criteria represent a limitation to ICGN occurrence comparison.

Finally, cases for the North American study were retrospectively collected between 2007 and 2012 (Schneider *et al.*, 2013). It is possible that recommendations issued in the 2013 IRIS proteinuria consensus statement (Littman *et al.*, 2013) raised awareness around ICGN and increased the number of kidney biopsies performed, modifying the population of dogs undergoing renal biopsies. Although statistical analyses were not performed, there was an overlap in the UPC, albumin and creatinine concentrations between different histopathological diagnoses in this study, such that none of these parameters appeared to be possibly used to discriminate between underlying glomerular disease

conditions. This confirms, as previously documented by Schneider and colleagues (2013), the requirement to obtain renal biopsies in order to determine whether immune complex deposits are present prior to potentially pursuing immunosuppressive therapy in these dogs.

To the author's knowledge, this is the first study reporting the long-term outcome of a group of dogs diagnosed with ICGN. Out of the 17 cases diagnosed with ICGN, more than half were still alive at data collection with a median follow-up time of 652 days (range 73-1299). When long-term outcome was compared between disease groups in our population, NOS GP was the group with the longest median survival time and median follow-up time, followed by ICGN and GS. In our study, renal AM was associated with the worst prognosis, with only 29% of animals alive at time of data collection and a median survival time of less than 5 months. A previous study comparing dogs diagnosed with glomerular disease and nephrotic syndrome (NS) versus dogs diagnosed with non-nephrotic glomerular disease (NNGD) reported a median survival time of 12.5 days for dogs with NS versus 104.5 days for dogs with NNGD dogs (Klosterman *et al.*, 2011). Less than half of the dogs described in that study underwent renal biopsies, therefore definitive histopathological diagnosis was not reached and direct comparison with our results is difficult. Overall, it would appear that survival times were longer in our study compared to that study.

IRIS current recommendation for histopathologically diagnosed ICGN in dogs states the following (Segev *et al.*, 2013) : "for diseases associated with profound proteinuria, attendant hypoalbuminaemia, nephrotic syndrome, or rapidly progressive azotaemia, single drug or combination therapy consisting of rapidly acting immunosuppressive drugs is recommended. The Study Group recommends mycophenolate alone or in combination with prednisolone. For stable or slowly progressive glomerular diseases, the Study Group recommends mycophenolate or chlorambucil alone or in combination with azathioprine on alternating days". In this study, seven dogs in the ICGN group (42%) did not receive any immune-suppressive therapy, and only one of these was alive at the time of data collection. It is interesting to note that 43% of dogs diagnosed with ICGN that did not receive immunosuppressive therapy achieved a UPC<0.5 or a reduction of their UPC by more than 50% following biopsy, highlighting that in some cases, ICGN (or ICGN-induced proteinuria) may be self-resolving and/or controlled by blockade of the renin angiotensin aldosterone system and nutrition adjustment (reduced n6/n3 polyunsaturated fatty acid ratio, protein restriction) as recommended by the IRIS proteinuria consensus statement (Brown *et al.*, 2013). Due to the retrospective nature of the study it is not possible to ascertain

why immunosuppressive therapy was not prescribed in these dogs, for example if there was concurrent concern for an infectious aetiology that required treatment.

Six dogs with ICGN were treated with mycophenolate (n=2 with concurrent chlorambucil), all of which were alive at data collection, with treatment success reached in 4/6 of the dogs within 6 months. The dogs in this study were included retrospectively and also received other medication such as ACEi which may have contributed to the reduction of their UPC. It is therefore impossible to know whether a similar positive response would have occurred with other immunosuppressive agents in these dogs or whether the positive response is specifically related to the use of mycophenolate. Repeated renal biopsies (or post-mortem examination) were not performed for any of the cases in this study but would provide further information regarding disease resolution or progression in response to treatment. Relationship between treatment and survival were not statistically analysed considering the low number of cases per group, therefore it is unknown if mycophenolate improves the outcome of dogs diagnosed with ICGN.

Limitations of the study include its retrospective nature, the low number of dogs included, lack of information regarding travel history of included cases, treatment prior to biopsy, concurrent diseases and unknown cause of death, as well as the lack of standardised protocols for investigations prior to biopsy, treatment and follow-up. As an example, the UPC follow-up over-time was only available and therefore described for dogs diagnosed with ICGN, treated with mycophenolate and that responded to treatment. Clinico-pathological results included in this study were obtained from a number of different diagnostic laboratories, although interpretation of renal pathology was performed by veterinary nephrologists (LA and RC).

Having considered these limitations, the data obtained in this study is informative for clinicians practising within the UK when presented with dogs with proteinuria that is considered likely to be glomerular in origin. Where possible, renal biopsy should be considered in order to document the presence of ICGN prior to considering immunosuppressive therapy, particularly given the apparently lower occurrence of ICGN in the UK population of dogs with glomerular disease. Furthermore, it is important to discuss with owners the fact that renal biopsies would lead to a different therapeutic strategy in approximately a quarter of cases. Nevertheless, for those dogs where ICGN is identified, owners should be counselled that long-term outcomes could be favourable. Further study is warranted to further differentiate the underlying aetiology of ICGN, location of immune-complex deposition and whether different immunosuppressive treatment strategies may be beneficial.

314 **Conclusion**

315 This study revealed that the occurrence of ICGN might be lower in the UK than previously reported in
316 North America and mainland Europe, which may influence clinician's decisions in terms of renal biopsy
317 and/or treatment. The prognosis associated with ICGN appears overall fair, and from this data
318 mycophenolate is the most commonly used immunosuppressive drug.

Figures legend:

Table 1. Breeds of dogs biopsied for evaluation of suspected glomerular disease

Table 2. Histopathological diagnosis, urine and serum biochemical abnormalities of dogs biopsied for evaluation of suspected glomerular disease

GS: glomerulosclerosis, ICGN: immune-complex glomerulonephritis, NOS GP: not otherwise specified glomerulopathies, AM: amyloidosis, URL: unspecified renal lesion, UPC: urinary protein-to-creatinine ratio

Table 3. Median survival time and median follow-up time per disease group

n: number, GS: glomerulosclerosis, ICGN: immune-complex glomerulonephritis, NOS GP: not otherwise specified glomerulopathies, AM: amyloidosis, URL: unspecified renal lesion

Table 4. Signalment, clinico-pathological abnormalities at the time of diagnosis, treatment and outcome of the 17 cases diagnosed with ICGN

UPC: urinary protein-to-creatinine ratio

Figure 1a. UPC ratios for each disease group

Figure 1b. Creatinine concentrations for each disease group

Figure 1c. Albumin concentrations for each disease group

GS: glomerulosclerosis, ICGN: immune-complex glomerulonephritis, NOS GP: not otherwise specified glomerulopathies, AM: amyloidosis, URL: unspecified renal lesion, UPC: urinary protein-to-creatinine ratio

Figure 2. Kaplan Meyer survival curves for dogs that have undergone renal biopsy according to underlying pathology identified

GS: glomerulosclerosis, ICGN: immune-complex glomerulonephritis, NOS GP: not otherwise specified glomerulopathies, AM: amyloidosis, URL: unspecified renal lesion

349 Figure 3. Longitudinal evaluation of UPC values for the four dogs diagnosed with ICGN, treated with
350 mycophenolate and that responded to treatment for the first 12 months period after renal biopsy
351 *UPC: urinary protein-to-creatinine ratio*

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