Fatal proteinuric kidney disease in a 30-month-old German Fleckvieh heifer caused by unilateral focal segmental glomerulosclerosis subsequent to a non-functional counterpart kidney

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Summary

A case of secondary focal segmental glomerulosclerosis (FSGS) in a heifer is presented. A 30-month-old female German Fleckvieh heifer showed deterioration of the general condition, a poor nutritional status, proteinuria, hypoalbuminemia, and renal azotemia. Pathologically, it was diagnosed with unilateral hydronephrosis, and contralateral renal fibrosis with numerous cysts. Histologically, the fibrotic kidney showed FSGS, hyaline reabsorption droplets in proximal tubular epithelial cells, interstitial fibrosis, and tubulointerstitial inflammation. Apart from that, thrombotic microangiopathy (TMA) was seen in few renal arteries and meningeal arterioles. Pathogenesis of FSGS secondary to unilateral renal parenchymal loss (hydronephrosis) and TMA is discussed.

Keywords: cattle, kidney, focal segmental glomerulosclerosis, thrombotic microangiopathy

Unilaterale fokale segmentale Glomerulosklerose mit fatalem renalem Proteinverlust-Syndrom als Folge eines kontralateralen chronischen Nierenversagens bei einer 30 Monate alten Deutsches Fleckvieh Färse

Ein Fall von sekundärer fokaler segmentaler Glomerulosklerose (FSGS) bei einer Färse wird vorgestellt. Eine 30 Monate alte weibliche Färse (Deutsches Fleckvieh) zeigte eine Verschlechterung des Allgemeinbefindens, einen schlechten Ernährungszustand, Proteinurie, Hypoalbuminämie und eine renale Azotämie. Pathologisch-anatomisch wurden eine einseitige Hydronephrose sowie eine kontralaterale Nierenfibrose mit zahlreichen Zysten diagnostiziert. Histologisch zeigte die fibrotische Niere eine FSGS, eine hyalintropfige Speicherung in proximalen Tubulusepithelzellen, eine interstitielle Fibrose und eine tubulointerstitielle Entzündung. Darüber hinaus wurde eine thrombotische Mikroangiopathie (TMA) in wenigen renalen Arterien und meningealen Arteriolen gefunden. Die Pathogenese der FSGS als Folge des einseitigen Verlusts von Nierenparenchym (Hydronephrose) und der TMA wird diskutiert.

Schlüsselwörter: Rind, Niere, fokale segmentale Glomerulosklerose, thrombotische Mikroangiopathie

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Introduction

Focal segmental glomerulosclerosis (FSGS) in humans is one of the most common causes of proteinuric kidney disease that eventually progresses to the end-stage renal failure, and accounts for approximately 20% of cases of the nephrotic syndrome in children and 40% of such cases in adults in the United States (Kitiyakara et al., 2003; D'Agati et al., 2011; Tsvetkov et al., 2016). It can be classified into primary (specific cause unknown) and secondary forms (familial/genetic, virus-associated, drug-induced, adaptive) (D'Agati et al., 2011). In human medicine, there is a plethora of scientific reports on FSGS (for review see Sethi et al., 2015). In contrast, in veterinary medicine the number of reports dealing either exclusively or in a broader sense with FSGS in domestic animals is very limited (Wimberly et al., 1981; Vilafranca et al., 1994; Kishnani et al., 2001; Costa et al., 2003; Aresu et al., 2010; Cianciolo et al., 2013; Suguhara et al., 2015).

Hydronephrosis is caused by impairment of urine flow, which can either be the result of urinary calculi, chronic inflammation, ureteral neoplasia, compression of the ureters by surrounding inflammatory or neoplastic tissue, urethral neoplasia, neurogenic functional disorders, ligation, or developmental alterations of the lower urinary tract (Harrison et al., 1983; Newman, 2012; Cianciolo and Mohr, 2016). One or both kidneys may be affected. In unilateral hydronephrosis in domestic animals, the contralateral kidney can compensate if it is normal (Cianciolo and Mohr, 2016). In contrast, there is evidence from the literature that in rats and human patients in cases of various forms of renal parenchymal loss, consecutive sustained glomerular hyperfiltration is ultimately detrimental to structure and function of remaining nephrons (Brenner, 1985; Brenner et al., 1996). In humans, secondary FSGS can develop as hyperfiltration injury in enlarged glomeruli (D'Agati et al., 2004; Schwartz, 2007; Gasim and Falk, 2014; Arias, 2015). Clinically, nephrotic syndrome is a typical sequela to FSGS (Habib, 1973). Whether renal parenchymal loss is not necessarily compensated by the remaining nephrons, in other words, whether hyperfiltration and subsequent damage of remaining glomeruli may also be expected in domestic animals, needs to be clarified (Brown et al., 1997; Newman, 2012).

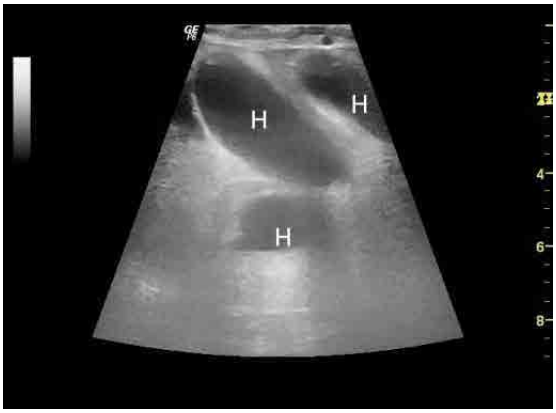

Figure 1: Ultrasonography: left kidney, multiple anechogenic fluid spaces (H).

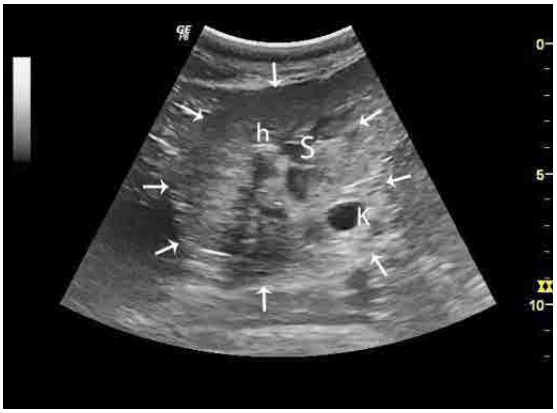

Figure 2: Ultrasonography: right kidney (contour marked by arrows), no differentiation between cortex and medullary pyramids discernible, dilatation of the sinus renalis (S), hyperechogenic structure (h) with distal echogenic deletion.

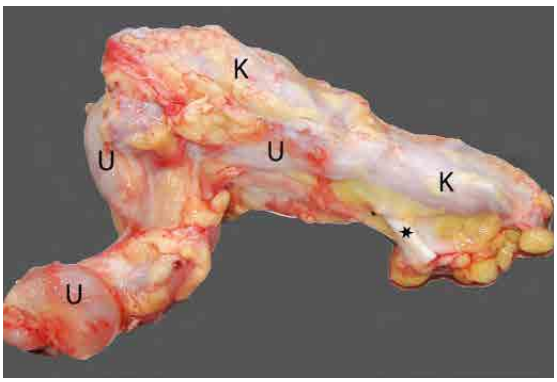

Figure 3: Left kidney, hydronephrosis (K), blind ending ureter (U), arteria renalis (asterisk).

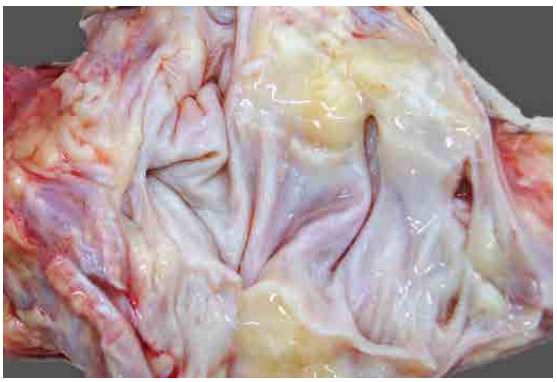

Figure 4: Left kidney, hydronephrosis cut open, extremely dilated calices.

Hydronephrosis in cattle has previously been reported (e.g. Harrison et al., 1992; Chandler et al., 2000). To the authors' knowledge, there are brief reports exclusively dealing with FSGS in dogs, cats and horses, but not in cattle (Wimberly et al., 1981; Aresu et al., 2010; Sugahara et al., 2015).

Case history and clinical examination

A thirty-month-old female German Fleckvieh heifer was referred to the Clinic for Ruminants with Ambulatory and Herd Health Services, Ludwig-Maximilians-University Munich. The heifer was 8 months pregnant. First signs of disease, as noticed by the farmer, were reduction in feed intake since one week before admission, but neither fever was detected nor colic observed.

Clinical examination revealed deterioration of the general condition and poor nutritional status. The urine was clear, yellow, and with a specific gravity of 1.021 g/l and a pH of 6.5. As indicated by a test-strip (Medi-Test Combi 5 S, Machery-Nagel, Germany), there was significant proteinuria (5 g/l), marked hematuria (more than 250 erythrocytes/µl) and trace glucosuria; ketone bodies were not detected. During rectal palpation, the left kidney was attainable only by fingertips. Neither generalized edema nor signs of hemorrhagic diathesis were discernable.

Laboratory results of whole blood and serum (parameter: value units [physiological range or lower and upper limit, respectively]) showed alkalosis (pH: 7.5 [7.35–7.45]), anemia (erythrocytes: 4.4 T/l [5-8], hemoglobin: 4.41 mmol/l [6.2-8.7], hematocrit: 19 % [30-36]), slight leukopenia (leukocytes: 3.4 G/l [4-10]), normothrombocythemia (620 G/l [200-800]), renal azotemia (urea: 49.5 mmol/l [< 5.5], creatinine: 1095 µmol/l [< 110]), hyponatremia (Na^+: 131 mmol/l [135-150]), hypocalcemia (Ca^{2+}: 0.89 mmol/l [1-1.3]), hypoalbuminemia (21 g/l [30-40]), but normoproteinemia (total protein: 59 g/l [60-80]), and a markedly shortened glutaraldehyde test (< 0.5 minutes [> 15]). A QUIKtest was not carried out. Ultrasonographic examination revealed multiple anechogenic fluid spaces in the left kidney (Fig. 1). The right kidney revealed echogenic parenchyma with no clear distinction of the corticomedullary junction, and echogenic 'floating structures' with distal echogenic deletion (Fig. 2). Based on the findings, pyelonephritis was suspected. The heifer was euthanatized because of poor prognosis, and submitted to the Bavarian Health and Food Safety Authority.

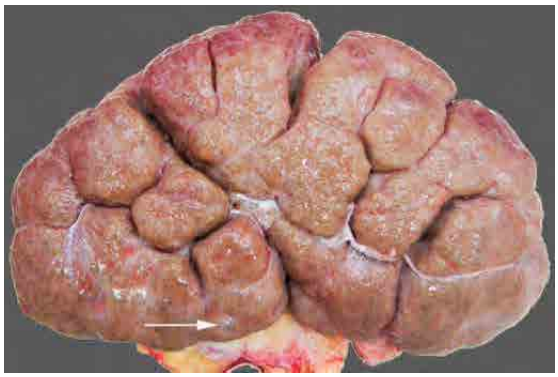

Figure 5: Right kidney, grey, superficially granular, numerous cysts (one of the largest cysts: arrow).

Macroscopic findings

Post-mortem examination revealed subcutaneous edema of the head, hydrothorax, a pale myocardium, extensive meningeal hemorrhage, bilateral hematoma adjacent to jugular veins, blood in the sphenoid sinuses, and petechiae of the mucous membranes of pharynx and trachea. The cecal contents had a faint odour of ammonia. The left kidney was markedly hydronephrotic and presented as a pale fluctuating sac (19 × 6 × 6 cm). The left 10 cm long tortuous ureter ended blindly without connection to the urinary bladder (Fig. 3). When the sac was cut open, clear watery, yellow liquid flowed away from the extremely dilated calices (Fig. 4). In its wall, sparse remnants of cortical renal tissue could be found. The right kidney was normal in size (21 × 11 × 4.5 cm), fibrotic (grey and firm), showed a coarsely granular surface and innumerable cysts with a size up to 5 mm in diameter (Fig. 5). The cut surface was striped grey.

Apart from these findings, the animal proved pregnant (length of the female fetus: 71 cm). Formalin-fixed specimens of brain, heart, and both kidneys were processed routinely for histological investigation (paraffin embedded, cut in 4 µm thick sections, mounted on glass slides and stained with hematoxylin and eosin [HE], Goldner's [Breuer] and Masson's [Nickeleit] trichrome method; periodic acid-Schiff [PAS]-histochemistry).

Histological findings

Histology of the left kidney showed most severe hydronephrosis with marked parenchymal scarring and associated lymphocytic infiltrates. In the right kidney numerous markedly enlarged glomeruli (with a diameter of up to 400 µm; physiologic diameter in cattle: 244 µm) were noted (Fig. 6). Some of them showed focal segmental glomerulosclerosis (FSGS) and hyalinosis with concomitant adhesion to Bowman's capsule as well as focal and segmental marked activation of podocytes (Figs. 7 & 8). Rare glomeruli demonstrated segmental tuft collapse with marked activation of the overlying podocytes,

i.e. collapsing FSGS (Fig. 9). Occasionally, global glomerular sclerosis was seen. Numerous tubules were dilated containing proteinaceous cast material, tubular epithelial cells showed protein reabsorption droplets, likely a sign of the marked proteinuria. Moderate interstitial fibrosis and mild to moderate tubulointerstitial nephritis added to the picture. In very few interlobular small caliber arteries evidence of recent onset thrombotic microangiopathy (TMA) was seen with intimal necrosis, fibrin accumulation, endothelial activation and extravasated red blood cells (Fig. 10). Small fibrin thrombi/fibrin accumulations were also found in isolated meningeal arterioles (Fig. 11). The heart revealed intimal sclerosis of myocardial arteriae and focal myocardial fibrosis.

Discussion

The authors present for the first time morphologic evidence of FSGS in cattle with features resembling hyperfiltration induced injury and secondary FSGS in humans (D'Agati et al., 2004, 2011; Arias, 2015). In the animal described here, unilateral severe hydronephrosis presumably resulted in hypertension followed by renal parenchymal injury, increased glomerular pressure and glomerular hyperfiltration in the right kidney (Brenner, 1985; Carlström et al., 2006; Newman, 2012). Glomeruli of the contralateral kidney then hypertrophied markedly up to a diameter of 400 µm (physiologic diameter in cattle: 244 µm) with presumed podocyte loss and the development of secondary FSGS (Nagata et al., 1992 a, b; Kwoh et al., 2006; Metcalfe, 2007; Yamamoto, 2010).

FSGS in man is clinically characterized by nephrotic syndrome (D'Agati et al., 2011). Both clinically and pathologically, the heifer showed marked proteinuria, hypoalbuminemia, subcutaneous edema, and pleural effusion. Thrombosis in the present case may have resulted from loss of antithrombin III in the setting of the nephrotic syndrome, or possibly from endothelial injury secondary to severe hypertension (Shibagaki and Fujita, 2005; Zhang et al., 2008; Newman, 2012). As a sequela, consumptive coagulopathy associated with hemorrhages (meningeal; mucous membranes, presumably including those of the urinary passages; hematoma adjacent to jugular veins probably caused by venipuncture, aggravated by coagulopathy) is conceivable. How-

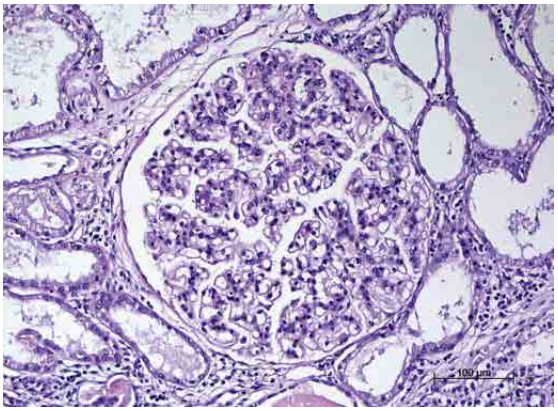

Figure 6: (PAS): Right kidney, hypertrophic glomerulus (~ 400 µm in diameter).

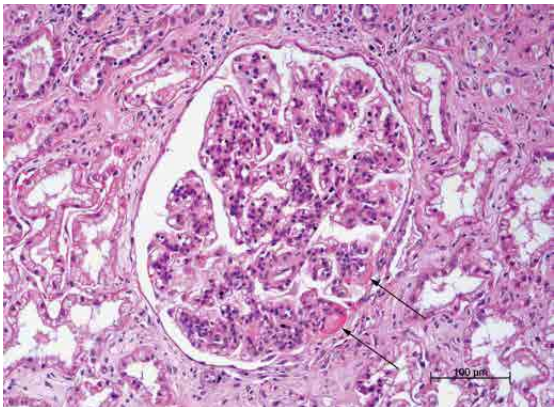

Figure 7: (HE): Right kidney, FSGS with hyalinosis and tuft adhesion to Bowman's capsule (arrows).

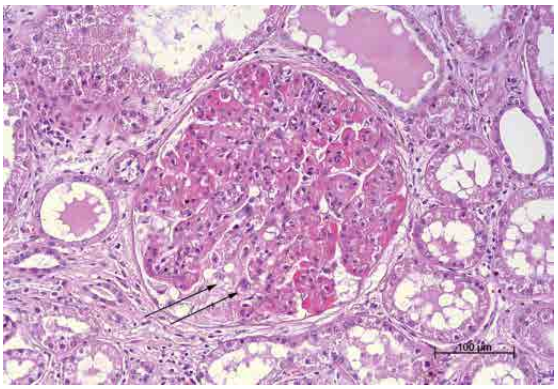

Figure 8: (HE): Right kidney, small segment of tuft collapse with crowding of podocytes (arrows).

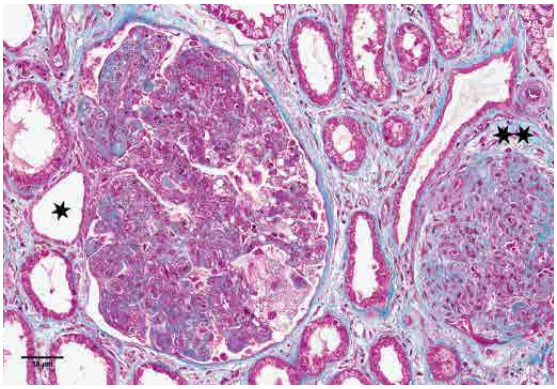

Figure 9: (Masson's trichrome): Right kidney, segmental collagen deposition and tuft collapse in FSGS (asterisk), global glomerular sclerosis (double asterisk).

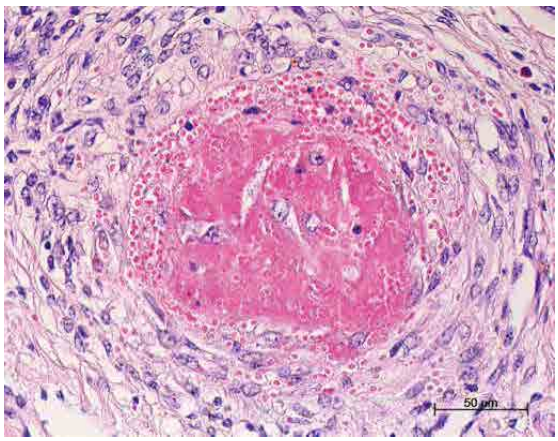

Figure 10: (HE): Right kidney (TMA), occluding arterial thrombus, intimal necrosis, extravasated red blood cells.

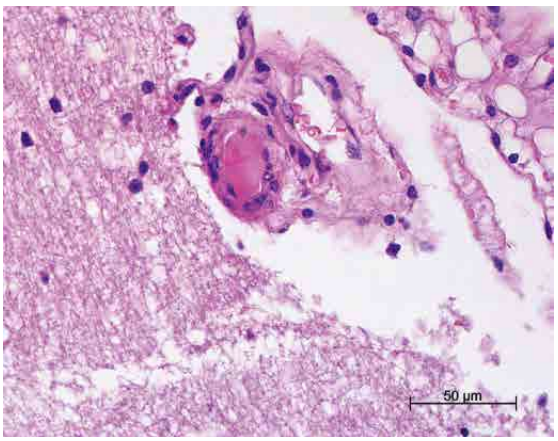

Figure 11: (HE): Brain (TMA), thrombus occluding a meningeal arteriole.

ever, laboratory examination revealed normothrombocythemia (a QUIKtest was not carried out). Myocardial fibrosis (and possibly intimal sclerosis of myocardial arteriae) was a further consequence of systemic hypertension (Weber and Brilla, 1991; Müller et al., 2012). Hypoalbuminemia – probably due to loss via kidneys – accompanied by normoproteinemia may have resulted from increased globulin synthesis.

Conclusions

FSGS should also in veterinary medicine be considered as a distinct disease entity. In this context it will be necessary to apply a classification into primary and secondary forms. The old concept that in case of unilateral hydronephrosis the remaining kidney, if normal, compensates adequately, is questionable.

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