Xanthine Crystaluria and Nephropathy in a young DSH Cat

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Interpretation and Diagnosis

Figure 1 and Figure 2 show wet mounts of the urinary sediment. Yellowish amorphous structures and large numbers of about 4 µm long needle-like crystals were detected using HPF (40x). The crystals could not be identified by microscopy, but urates or uric acid were suspected initially. This suspicion was supported by dissolution of the crystals in 10% KOH.

A small amount of micro-concrements which could be collected from a urethral plug were submitted to the Urolith Analysis Center (Bonn, Germany) for analysis by infrared spectroscopy. The result was 100% xanthine.

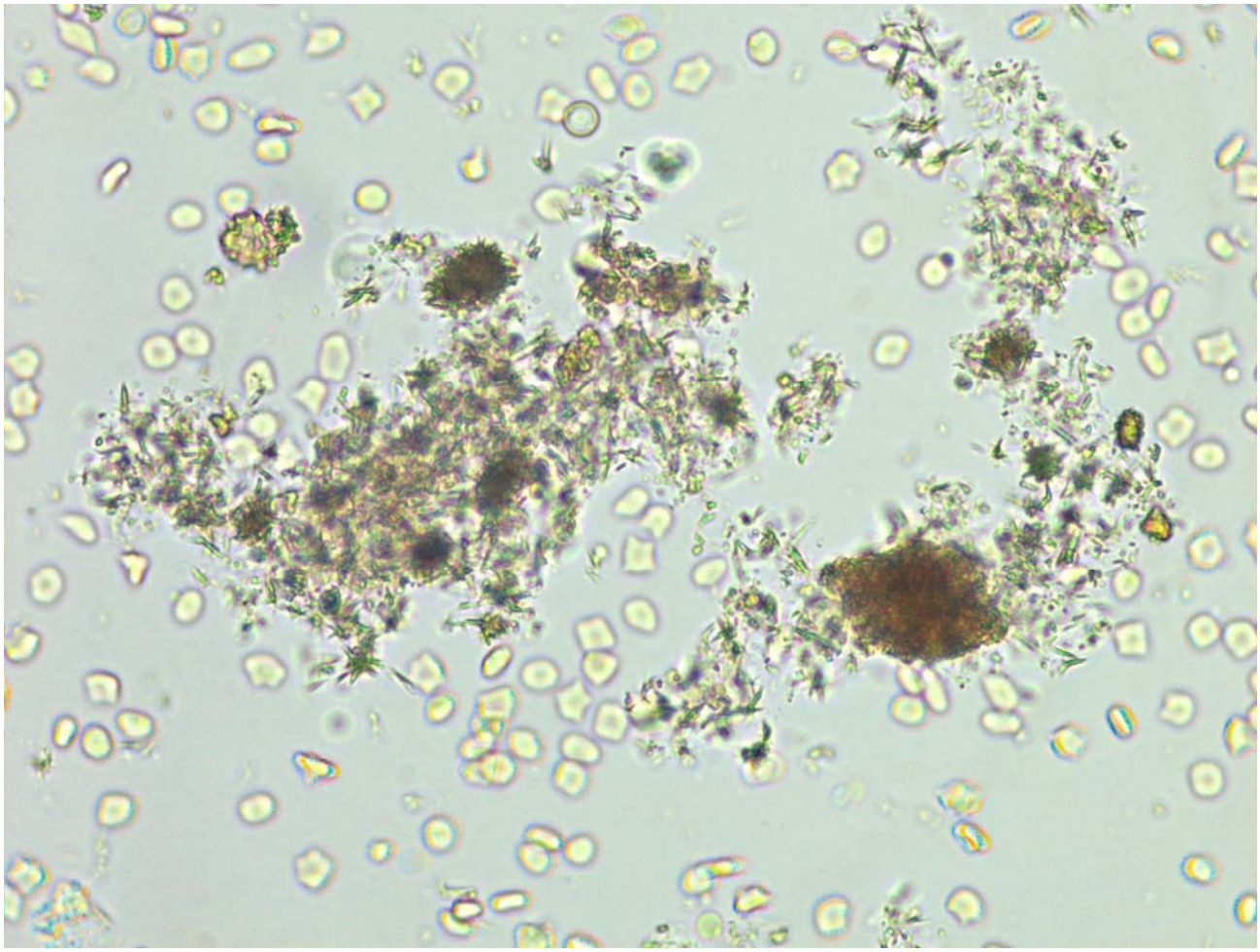

Figure 1: Photo of first sample submission with crystals and haematuria (40x, unstained sediment)

Other findings in the urinary sediment were a persistent bacteriuria together with moderate pyuria and a marked haematuria. The later two findings were attributed to the persistent urinary tract infection which could be verified by bacterial culture of one or two bacterial species (Figure 2).

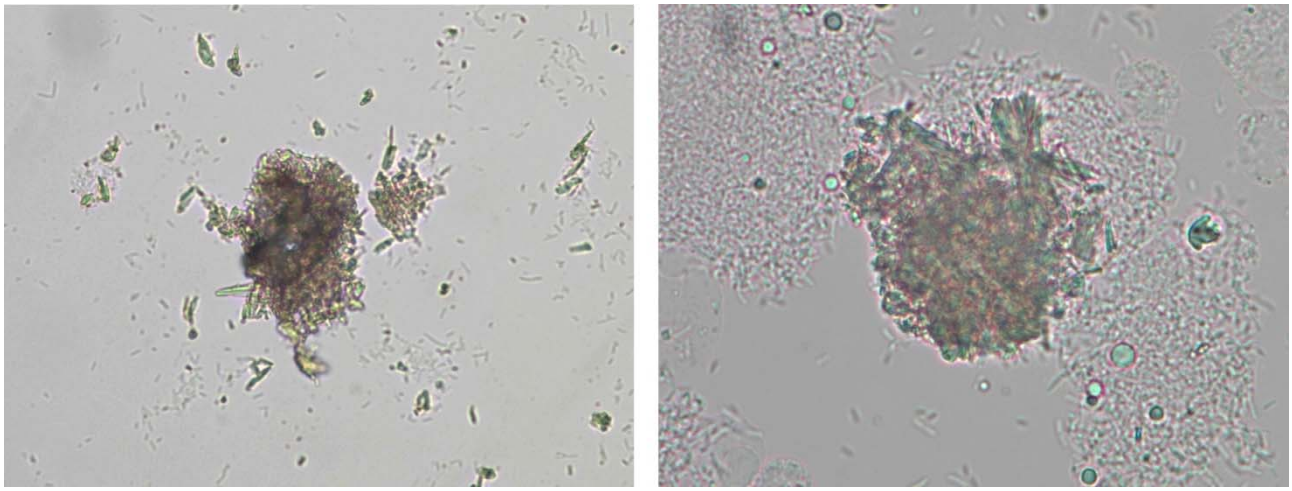

Figure 2: Photo of a successive sample submission with crystals and bacteriuria (40x, unstained sediment)

The serum biochemistry panel revealed a marked azotaemia while uric acid was within reference intervals (WRI) (Table 2). The azotaemia became more pronounced when another blood sample was analyzed in week 48. Interestingly no anemia was detected.
The uric acid concentration was WRI in both samples but was higher in the second blood sample.

Table 2: Serum and urinary biochemistry

SERUM	**Week 14**	**Week 28**	**Reference range**
Urea (mmol/l)	28.9	37.6	3.3 – 13.7
Creatinine (µmol/l)	335.9	459.7	< 141.4
Phosphorus (mmol/l)	1.2	3.1	0.8-1.6
Uric acid (µmol/l)	11.9	35.7	< 59.5
Plasma UA/crea (µmol/µmol)	0.035	0.077	0.400
URINE			**Control group***
Urine uric acid (µmol/l)	690.2	315.4	-
Urine creatinine (µmol/l)	6586	4959	-
Urine UA/crea (µmol/µmol)	0.100	0.060	0.033

*3 healthy cats

Discussion

Xanthine is a metabolite produced by the degradation of the purines adenine and guanine into allantoin in the liver which is then excreted in the urine. High concentrations of purines are found in meat and meat products, especially in internal organs such as liver and kidney. Xanthine is the most insoluble of all purine metabolites in urine at any pH and is physiologically converted into uric acid and in a second reaction step into highly soluble allantoin by the enzyme xanthine oxidase (XO, EC: 1.17.3.2), a metalo-enzyme requiring FAD, a molybdenum cofactor and an FeS-cluster. In human beings hereditary xanthinuria is classified into subtype I, caused by a mutation of XO; subtype II, a defect in the aldehyde oxydase and subtype III, caused by a loss-of-function mutation of the molybdenum cofactor synthetase. Subtype III is associated with severe neurologic disorders with a neonatal onset.

Xanthine crystaluria and urolithiasis can develop from an excess of xanthine in the urine. This condition can occur during treatment with the XO inhibitor allopurinol. A hereditary functional XO

defect has been described in a family of Cavalier King Charles Spaniels and some unrelated Dachshunds.

In the cat xanthine crystaluria or xanthine urolithiasis seems to be an extremely rare condition. From the analysis of urinary calculi it was concluded that the frequency was 0.16%. In one report a congenital defect was suspected, because 2 cats from the same litter developed a xanthine urolithiasis.

The cat in our case did not receive any medication before the first sample of urine was submitted and was fed a standard commercial food. The onset of urinary problems was at the age of 2 years and the excretion of xanthine crystals continued for a period of at least 6 months.

The crystals found in the urine sediment could not be positively identified as xanthine by microscopy, and to our knowledge the visual differentiation between xanthine, (ammonium) urates, or some conformations of uric acid crystals is impossible. Correct identification can be achieved by infrared spectroscopy.

Figure 3 shows the urine sediment collected from the same cat during a control check-up. These crystals have a different morphology to the ones found previously. The rhomboid structure displayed in the inset shows the morphology of the flower-like crystals in greater detail, which could be consistent with uric acid crystals. However, we could not find evidence as to whether the chemically closely related xanthine could form such crystals in urine as well.

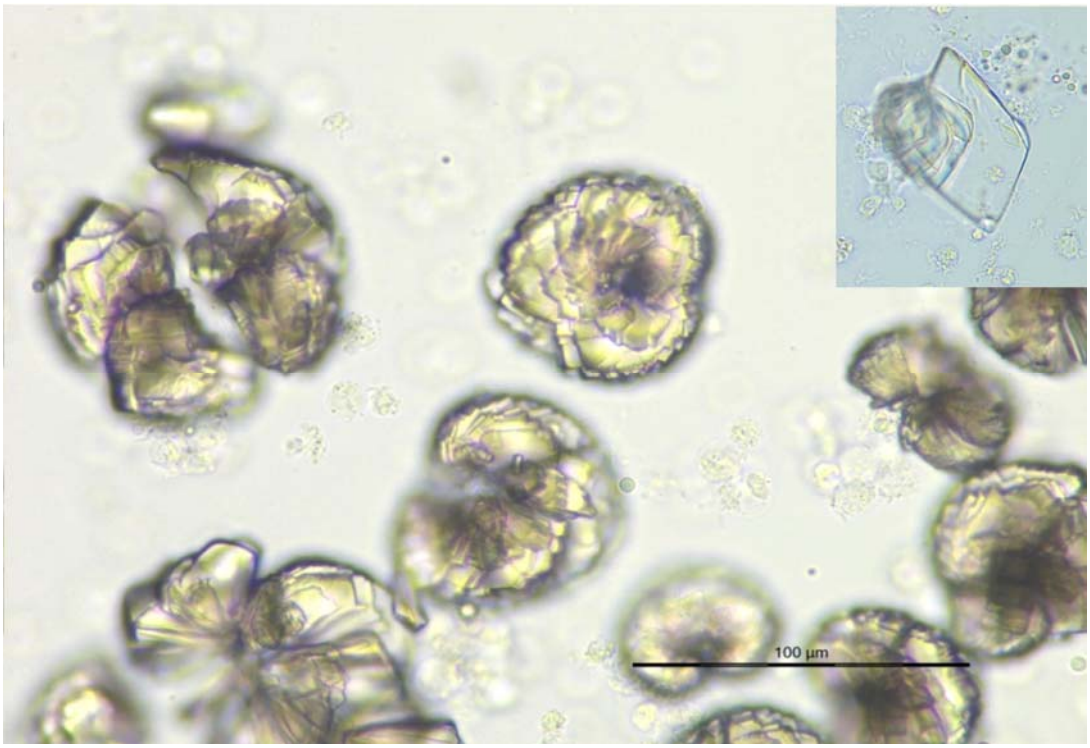

Figure 3: Other crystalline structures found in the urinary sediment. The insert shows a detail which microscopically resembles the rhombus-like structure of uric acid (both 60x, unstained).

The cat developed renal disease at the age of 2 years. The cause for this condition could not be detected, but it has been reported that a cat with xanthinuria developed chronic renal insufficiency at the age of 10 months. Those authors speculated that this could have been caused by direct tubular damage. In the cat presented here the low specific gravity (1.014 to 1.018 on several urine samples) could be consistent with tubular damage. However, casts were not found and a post-renal

component – caused by concrement seen with ultrasound in the renal pelvis cannot be excluded.

One report states that uric acid was reduced in serum and urine compared to a control group as would be expected in XO deficiency. In another report however, the uric acid concentration was WRI. The cat presented here had a plasma uric acid WRI at the first referral. The moderate increase at week 48 (but still WRI) could have been caused by the accumulation of nitrogenous substances due to the renal insufficiency. As uric acid could be detected it is possible that the XO activity in this cat was reduced, but not completely absent. In a study it was found that feline xanthine uroliths frequently did not consist of 100% xanthine but also contained variable amounts of uric acid.

The reason for the xanthine crystaluria, i.e., the location of the enzyme defect in the purine metabolic pathway has not yet been detected in this cat. However, there is some evidence of a congenital disease: the early onset, the early development of concurrent kidney disease and the lack of allopurinol medication. There was no evidence of a neurological disorder; therefore a xanthinuria of subtype III is unlikely. The determination of the purine metabolites hypoxanthine and xanthine in plasma and urine, as well as the detection of a mutation could help to clarify the cause of the xanthine crystaluria presented here.

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