

SMALL ANIMAL

Cycads – Sago 'palm' toxicity

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Figure 1. Cycad plant.

Over the last 6 months, we have had increasing reports of dogs with acute liver failure. Many of these dogs are later identified to have ingested a known hepatotoxin – 'Sago 'Palm'(which is actually a cycad). The liver failure is usually acute and severe. Some dogs have died regardless of the amount of the toxin they have ingested. The seed is highly toxic, and other parts of the plant also have toxic capacities. The seed appears to be attractive to dogs – and they subsequently ingest them.

Cycad palms are common in many parts of the world. Species include: *Cycas revolute*, *Cycas circinalis* and *Zamia floridana*. They prefer tropical and subtropical regions, and are becoming popular ornamental plants and bonsai. The climate of Sydney extending up the central-north coast of NSW and QLD is perfect for growth. The toxicity of the plant is **well known** for both humans and animals. Toxins include: cycasin, b-methyloamino-L-alanine, and another unidentified toxin. The toxins are in all parts of the plant, but are concentrated in the seeds and roots. Metabolites of ingested toxins are also highly toxic. Toxic effects include: neurotoxicity, carcinogenicity, mutagenicity, teratogenicity and hepatotoxicity. The seeds and nut contain large amounts of cycasin, and ingestion of as few as 2 seeds has been reported to result in clinical signs in dogs (Albretsen, 2004).

The plant appears to be a popular and pretty small palm tree; the increase in toxicity is likely to reflect

an increase in popularity of the tree rather than an increase in the cycad seed's toxicity. At the Small Animal Specialist Hospital (SASH), we have seen or been advising other hospitals on the management of at least 10 cases in the last 6 months.

How can you recognise these dogs?

The dogs typically present with non-specific signs including vomiting and lethargy. Some dogs will have unusually yellow urine, and others will already be icteric and showing more obvious signs of liver failure. These signs are obviously non-specific to Sago seed ingestion.

Clinical signs seen with Sago Cycad-Palm toxicosis can occur within 15mins to several hours after ingestion. The three main organ systems affected are:

1. Gastrointestinal
2. Liver
3. Central Nervous System.

In your consultation you may ask the client further questions about **general toxin access**. Typically we try to ensure we ask the following questions:

- Is there any access to typical liver toxins (NSAIDs, xylitol [NB: this is recently reported to be found in peanut butter in the UK and causes severe hypoglycaemia, liver failure, and can be fatal], sago palm, heavy metals, drugs)?
- Is there any access to typical renal toxins (NSAIDs, lilies [cat], raisins and grapes, heavy metals, chemotherapy agents, ACEis etc)?
- Have you seen your pet chew on any plants (i.e. Brunfelsia, Sago, Lilies)? If unsure get them to take a photo of any flowering plants or plants the animal may have been seen chewing.
- Does your pet chew on anything strange?



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Figure 2. Inguinal petechiation.

- › Does your pet enjoy chews? (for example – Chinese jerky has been associated with glucosuria which is associated with acquired fanconi, and many other jerkies are ‘moistened’ with glycerol/ glycerine that is a mild gastrointestinal irritant)

Most clients will be able to confirm access to the plant. Most dogs will present within 36 hours of ingestion. Any age or breed of dog can be affected.

On examination you may notice signs of gastrointestinal disease, liver disease (acute hepatic necrosis), and/or central nervous system abnormalities

Gastrointestinal:

- › Vomiting (check for cycad seeds)
- › Diarrhoea (check for cycad seeds)
- › Excessive salivation
- › Anorexia

Hepatic:

- › Icterus – Jaundice
- › Pain on cranial abdominal palpation +/- mild hepatomegaly
- › Ascites
- › Bruising – petichiation, echymoses
- › Melaena

Neurological:

- › Weakness
- › Seizures
- › Encephalopathy
- › Ataxia
- › Tremors
- › Coma

Blood work:

- › Increased liver enzyme activities
 - › ALT and AST is usually very high
 - › Severe elevations in ALT and AST are negative prognostic indicators
 - › ALKP may be mildly – moderately increased

- › Bilirubin is often elevated and is a negative prognostic indicator
 - › If the bilirubin is not increased, a fasting bile acid +/- bile acid stimulation test may be performed, that may reveal abnormal liver function. This is not specific to liver toxin ingestion.
- › Ammonia may be increased – especially after a tolerance test in dogs with liver failure
 - › Care must be taken when performing the ammonia tolerance test, as the assay is liable to error if the rigid procedural protocol is not performed.
 - › Ammonia tolerance tests should not be performed in patients with encephalopathy
- › Signs of hepatic synthetic failure may include
 - › Hypocholesterolaemia
 - › Hypoalbuminaemia (negative prognostic indicator)
 - › Hypoglycaemia
 - › Decreased urea / BUN
 - › Increased post prandial +/- resting bile acids
- › In advanced disease, there may be:
 - › Coagulopathy
 - Increased activated partial thromboplastin time (APTT)
 - Increased prothrombin time (PT)
 - Alterations in FDPs, D-Dimers etc may occur with DIC / complicated coagulopathies from liver failure. These are not routinely tested.
 - › Thrombocytopenia
 - Prolonged buccal mucosal bleeding time (use standardized device)
 - › Thrombocytopaenia
 - Confirm with blood smear examination, and perform mean platelet volume in Cavalier King Charles Spaniels that are prone to macrothrombocytopathias
 - › Hypoglycaemia
 - This may be an indication of severe liver failure, and result in seizures. This is uncommon. The client should be questioned on access to xylitol, and exclusion of sepsis and other causes of hypoglycaemia should be considered in a patient without known access



Figure 3. Melena on thermometer.

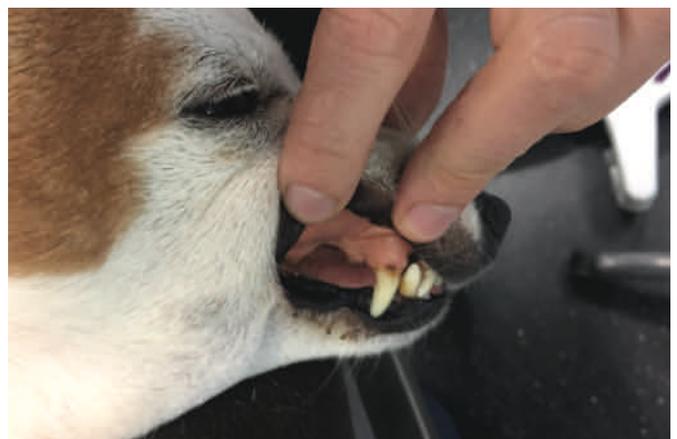


Figure 4. Jaundiced pink – yellow mucous membranes.

- to Sago seeds. Hypoglycaemia from liver failure is a negative prognostic indicator.
- › Encephalopathy
 - This may or may not be related to increase in ammonia – other toxins may also cross the blood brain barrier and cause astrocyte dysfunction in liver failure including endogenous and exogenous benzodiazepines.

There is no blood test to detect the toxin in the blood stream or faeces.

How do I treat these dogs?

If a dog is known to have ingested sago seeds – decontamination is essential. Once this toxin has caused liver failure, the prognosis is GRAVE.

- › Induce emesis (if safe to do so)
- › Gastric lavage
- › Enema (may also help you to identify the seeds, if ingested)
- › Activated charcoal (administration is a **positive prognostic indicator** in some studies, this may be as patients are less severely affected on presentation, but nevertheless, it gives us hope that we can treat these dogs if identified and managed aggressively early!)

If the dog has hepatotoxicity – without hyperbilirubinaemia:

- › Admit for supportive care. Induce emesis and decontaminate
- › Start supportive care for hepatotoxicity:
 - › N-Acetylcystine (orally or IV if the dog is not eating)
 - › Denmarin® orally (small, medium, large dog PO SID)
 - Silymarin
 - S-AdenylMethionine (SAMe) (90mg/kg PO SID)
 - › Ursodeoxycholic acid 15mg/kg PO SID

If the dog has hepatotoxicity – without hyperbilirubinaemia:

- › Admit for supportive care. Induce emesis and decontaminate
- › Supportive care:
 - › Intravenous fluid therapy
 - › Pain relief (if indicated)
 - › Proton pump inhibitors: if signs of GI ulceration (haematemesis / melena)
 - Esomeprazole / Omeprazole 2mg/kg/day
- › Anti-nausea:
 - › Maropitant 1mg/kg SQ (IV – not registered) SID
 - › Ondansetron 0.5mg/kg IV SID – BID (higher doses may sedate the patient if severe hepatic failure)

- › Start supportive care for hepatotoxicity:
 - › N-Acetylcystine (orally or IV if the dog is not eating)
 - › Denmarin (branded as small dog, medium dog, large breed dog)
 - Silmarin / Silybinin
 - S-AdenylMethionine (SAMe) – if use alone – 90mg/kg PO SID
 - › Ursodeoxycholic acid 15mg/kg PO SID
 - › Vitamin E 10IU/kg PO SID
 - › Omega III Fatty acids – Quality fish oils (100IU/kg PO SID)

Helpful tip: if there is no coagulopathy and the patient is difficult to give oral medications to – consider placing an Oesophageal Feeding Tube EARLY – to facilitate administration of medications (and nutrition), as many of these are not available IV.

Monitoring Patients

In a patient with hepatotoxicity – whilst the patient is hospitalized:

- › Daily blood work:
 - › PCV TP Albumin
 - Anaemia or haemoconcentration
 - Total proteins may decline from GI blood loss – panhypoproteinaemia
 - **Mild** Hypoalbuminaemia may occur due to decreased acute phase protein production, marked hypoalbuminaemia may reflect reduced production from the liver
 - › Blood glucose
 - Hypoglycaemia may be due to sepsis, or reduced hepatic production
 - Severe hypoglycaemia is a negative prognostic indicator
 - › ALT
 - Increasing ALT without bilirubin is an indicator of ongoing hepatocellular injury – intensify treatment if possible!
 - › TBil
 - Bilirubin: If the bilirubin is increasing – this is a negative prognostic indicator. This is likely to be due to obstructive cholestasis
 - › Monitor electrolytes
 - Slow correction of hyper or hyponatraemia required
 - Avoid metabolic alkalosis
 - Avoid hypokalaemia (both will increase ammonia trapping in astrocytes in the brain)
- › TPRs including body weight at least every 12 hours
- › Neurological status
 - › Hepatic encephalopathy is not uncommon in acute liver failure. Ammonia is not the only toxin that may contribute to HE – avoid benzodiazepine administration, if they have been administered – consider reversal with flumazenil

- › Stool
 - › Melena / haematechezia may reflect a coagulopathy / platelet disorder
- › Urine
 - › Hyperbilirubinaemia may manifest initially as dark urine – do a dipstick if this is the case. Bilirubinuria of $\leq 2+$ is only seen in male dogs.
 - › Inadequate urine production may reflect dehydration, but also may develop as a consequence of DIC – MODS. If the patient isn't voiding adequate volumes of urine – record the urinary bladder size by ultrasound. Give a fluid bolus (10mL/kg 0.45% NaCl + 2.5% glucose – Hartmann's or NaCl not recommended in liver failure). Reassess the urinary bladder size. If the size of the bladder has increased it is likely the patient is producing urine. If the bladder size has not increased, attempt frusemide 2mg/kg (take care – as may lead to hypokalaemia if repeated administration).
- › Stromal collapse - early periportal fibrosis and bile duct proliferation
- › Variable inflammatory cell infiltration
- › **Chronic (>40 days after ingestion)**
 - › Diffuse hepatocellular necrosis, degeneration and regeneration with extensive stromal collapse, bridging fibrosis with nodular regeneration, biliary hyperplasia, distended bile canaliculi, bile plus, lymphocytic and plasmacytic infiltration.
 - › Multiple acquired shunts may also be seen
 - › Mitotic figures, megalocytosis, and multinucleated hepatocytes may also be seen.

Conclusion

Sago palm is a cycad. It is highly toxic. If ingestion is known, decontamination is the best strategy, as prognosis is guarded in patients that develop advanced liver failure.

References

- Albretsen JC. Cycasin. In: Plumlee KH, ed. *Clinical Veterinary Toxicology*. St. Louis, MO: Elsevier Mosby; 2004:392-394.
- Survival and Prognostic Indicators for Cycad Intoxication in Dogs (2011) D. Ferguson, M. Crowe, L. McLaughlin, and F. Gaschen, *Journal of Veterinary Internal Medicine* 2011;25:831–837

If signs of a coagulopathy / liver failure have been or are present: additional tests would include:

- › Coagulation parameters
 - › PT, APTT, Platelet count
- › Abdominal ultrasound can be used to confirm the presence of ascites, and abdominal girth size can help if there are signs of ascites.
- › Resting bile acids and / or ammonia can be used also to assess hepatic function

Further Diagnostics

- › Abdominal Ultrasound
 - › There are no specific ultrasonographic changes that occur in the liver with this toxicity.
- › Liver biopsies may be indicated (or be performed) if the toxin has unknowingly been ingested. Liver biopsies can be performed in patients without coagulopathies (normal APTT, PT, platelet count, Buccal mucosal bleeding time). Ultrasound guided sample collection is recommended.

Histopathology Liver Biopsies

Few samples have been collected from dogs affected by the toxin. Changes may include the following:

- › **Acute (0-2 days)**
 - › Centrilobular haemorrhage and congestion with moderate to marked centrilobular hepatocellular necrosis and neutrophilic infiltration
- › **Subacute (5-28 days after ingestion)**
 - › Severe centrilobular coagulative necrosis
 - › Hepatocellular degeneration with scattered attempts at regeneration
 - › Swollen hepatocytes (hydropic degeneration)



Figure 5. Bruising after venipuncture in a coagulopathic patient.



Figure 6. Sago seeds retrieved from the rectum of a dog that died from sago toxicity.

Comment courtesy of:

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Thank you Amy for contributing this very impressive C&T.
 We see these cases sporadically, not as many as a spate of them we had 5-10 years ago. They produce horrible toxicity – patients often present satisfying all the criteria of Fulminant Liver Failure (Jaundice, Hypoglycaemia, Coagulopathy, Encephalopathy).

Huge ICU cases with 50% mortality if present jaundiced and coagulopathic; and chronic liver disease often ensues in the survivors. I only know of 1 survivor who remains normal liver enzymology and TBA study after 12 or so months of presentation; this dog's housemate (both Labradors of different ages, remains happy and well but with liver enzymology persistently increased with poor bile acid results (on SAME, Silybin, and UDCA). We've had a couple that survived the initial AHF but developed low albumin ascites with 'scrunched' up fibrotic liver within 3-6 months of the acute episode.

1. A point of trivia: Botanists are quick to declare that Cycads are NOT palms. They are from the family Cycadaceae and are gymnosperms which means they are naked seeded (unfertilised seeds are open to the air to be directly fertilised by pollen). They are not closely related to the true palms (family Arecaceae) which are angiosperms (enclosed seeds with more complex fertilisation arrangements)
2. The use of N-acetylcysteine to mitigate hepatotoxicity from toxins is well researched in people and we tend to follow the recommendations made by our human counterparts. Traditionally, the suggested dose regime (Prescott LF *et al* in *Lancet* 1977; 2: 432-434) has been a loading dose of 150mg/kg over the first hour, then 50mg/kg over 4 hours, then 100mg/kg over 16 hours. This attempts to allow for the long half-life of many toxins, including Cycasin. Recently, a few papers have shown less adverse reactions in people and laboratory animals using lower loading doses (Bateman DN *et al* in *Lancet* 2014; 383: 697-704 / Wong A & Graudins A in *Clinical Toxicology* 2016; 54: 115-119 / Isbister GK *et al* in *Clinical Toxicology* 2016; 54: 120-126), resulting in the newer recommendation of 50mg/kg/hr for the first 4 hours, then 100mg/kg over the next 16 hours. 🌀



Read a manuscript Terry produced in 2005 for Science Week available in the eBook.