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Clinical Manifestation of A Cat With Acute Acetaminophen Toxicity

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Abstract
This case report presents diagnostic methods used for a 2.5 kg, 1-year-old female British Shorthair cat admitted to the veterinary hospital with non-specific symptoms, including anorexia, lethargy, jaundice and dehydration. After a comprehensive evaluation of the anamnesis, clinical findings, laboratory results, imaging and the exclusion of similar diseases, a diagnosis of iatrogenic acetaminophen toxicity was established. While numerous case reports and studies address acetaminophen toxicity, this report emphasizes how the employed diagnostic methods contribute to accurate diagnosis. Ultimately, thorough evaluation of anamnesis data, combined with these examination techniques, can facilitate precise disease identification and enhance awareness of its characteristics. Moreover, case reports like this one can increase awareness and help reduce fatalities associated with acetaminophen intoxication.
Keywords: Acetaminophen, Cat, Toxicity.

Akut Asetaminofen Toksikasyonlu Bir Kedinin Klinik Görünümü

Öz
Bu vaka raporu, anoreksi, letharji, ikterus ve dehidrasyon gibi spesifik olmayan semptomlarla hayvan hastanesine başvuran 2.5 kg, 1 yaşında dişi bir British Shorthair kedisi için kullanılan tanı yöntemlerini sunmaktadır. Anamnez, klinik bulgular, laboratuvar sonuçları, görüntüleme ve benzer hastalıkların dışlanmasının kapsamlı bir değerlendirilmesinin ardından, iatrojenik asetaminofen toksisitesi tanısı konulmuştur. Asetaminofen toksisitesini ele alan çok sayıda vaka raporu ve çalışma bulunmasına rağmen, bu rapor kullanılan tanı yöntemlerinin doğru tanıya nasıl katkıda bulunduğunu vurgulamaktadır. Nihayetinde, anamnez verilerinin detaylı değerlendirilmesi ve bu muayene tekniklerinin bir araya getirilmesi, doğru hastalık tanısını kolaylaştırabilir ve hastalığın özellikleri hakkında farkındalığı artırabilir. Ayrıca, bu gibi vaka raporları, asetaminofen zehirlenmesi ile ilişkili ölümleri azaltmaya yardımcı olmak ve farkındalığı artırmak için önemlidir.
Anahtar kelimeler: Asetominofen, Kedi, Toksikasyon.

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Introduction

A wide range of over-the-counter (OTC) medications is available in veterinary practice, many of which carry risks of toxicity, and their use is becoming more widespread. These OTC drugs are easily obtained from the market, are often inexpensive, and can be purchased without a prescription or professional guidance. Presently, the deliberate misuse of OTC medications is a significant issue in both veterinary and human healthcare (Gülersoy et al., 2021). For example, acetaminophen, also called paracetamol, is a widely used and effective analgesic and antipyretic in humans. However, it is closely linked to severe complications in companion animals, with toxicity cases frequently reported. (Özkan, 2017). The primary cause of acetaminophen intoxication is the owner's improper administration of the drug without first consulting a veterinarian (Denzoin Vulcano et al., 2013). In mammals acetaminophen is biotransformed to nontoxic products in the liver via conjugation with glucuronic acid and excreted by the kidneys. A small portion of acetaminophen is metabolized through the cytochrome P-450 enzyme pathway producing a metabolite, N-acetyl-para-benzoquinoneimine (NAPQI) which is highly toxic. Acetaminophen exposure becomes toxic, when glucuronidation and sulfation pathways become saturated. NAPQI binds to cellular proteins and membranes and leads to cellular injury and death, particularly hepatocytes. Cats are extremely sensitive to the toxic effects of acetaminophen, since the conjugation of glucuronides with many toxic compounds occurs slowly in cats. This is due to little possession of glucuronyl transferases. Deficiency of the glucuronide conjugation pathway results in more drug being conjugated to sulfates; however, the sulfation pathway is also lower in cats than other species (Allen, 2003; Sidhu et al., 2021). Acetaminophen poisoning is commonly presented with clinical signs of anorexia, dullness, facial and paw edema, muddy mucous membranes, respiratory distress and hematuria (Sidhu et al., 2021). There is no safe dose of acetaminophen for cats, making its toxicity more prevalent in felines than in canines. The toxic dose is reported to be between 50-100 mg/kg body weight; however, signs of toxicity and even death can occur at doses as low as 10 mg/kg body weight (Aronson & Drobatz, 1996; Sidhu et al., 2021). This case presentation aims to raise awareness of the clinical signs and symptoms associated with acetaminophen toxicity, a condition with a high mortality rate due to misuse. It focuses specifically on the clinical manifestations of acetaminophen overdose in cats.

Case Description

A 2.5 kg, 1-year-old female British Shorthair cat was brought to Harran University Veterinary Faculty Animal Hospital showing anorexia, lethargy, severe jaundice, and hematemesis. The owner reported administering 120 mg of acetaminophen (Calpol®, Abdi Ibrahim, Türkiye) orally to the cat once daily for two consecutive days, without prior consultation. During this time, the patient started vomiting, showed persistent anorexia, and exhibited symptoms such as hematemesis and abdominal swelling. Before the onset of illness, the cat was fed a commercial dry cat food and was an intact indoor cat with no previous medical history. It was noted that antiparasitic treatments and vaccinations were administered regularly. After evaluating the anamnestic data, physical and laboratory examinations were conducted. The physical examination included measurements of respiratory rate (RR), heart rate (HR), an assessment of palpable lymph nodes, auscultation of the lungs and heart, and a rectal temperature check. At this time, a fecal sample was collected directly from the rectum using a sterile swab for examination. The physical assessment revealed a

skin turgor of 4 seconds, indicating an 8% dehydration level, accompanied by enophthalmos and prolonged skin elasticity. Additionally, the gingival and conjunctival mucosa appeared anemic, with the gingival capillary refill time exceeding 2 seconds. HR and RR were measured at 45 beats per minute (reference range: 16-40/min) and 60 breaths per minute (reference range: 120-140/min), respectively. The rectal temperature was recorded at 39.8 °C (reference range: 37.5-39.1 °C) (Klaasen, 1999). Lung auscultation indicated bradypnea, with mild crackles noted in the cranial lobes (16 breaths per minute). The fecal sample (2 to 3 g) was mixed with 15 mL of pre-made zinc sulfate solution ($ZnSO_4$, specific gravity 1.18) in a 15 mL conical tube. If necessary, more $ZnSO_4$ was added to maintain the volume at 15 mL, and the mixture was centrifuged at 500 to 600 × g for 5 minutes. After centrifugation, additional $ZnSO_4$ was added to create a positive meniscus, onto which a coverslip (22 mm × 22 mm) was placed for 5 minutes. The coverslip was then removed and examined under a light microscope (×40 magnification, Olympus, Japan). The fecal analysis revealed no parasites or parasite eggs. After the physical examination, venous blood samples (3-5 mL) were collected via venipuncture of the cephalic vein for a complete blood count (CBC, using K_3EDTA tubes) and serum biochemistry (using tubes without anticoagulant), following proper aseptic protocols. Imaging studies, including radiographic and ultrasonographic examinations, were then performed for further investigation

Table 1. Haematological findings

Parameters	Result	Reference values*
WBC (/µL)	13.4	3.0- 14.8
Lymp (x10^9/L)	4.06	1.2 – 8.0
Mono (x10^9/L)	0.99	0- 600
Neu (x10^9/L)	8.00	2.5- 8.5
RBC (x10^6/µL)	2.18	5.92- 9.93
HGB (g/dL)	6.30	9.3- 15.9
HCT (%)	22.4	29- 48
MCV (fL)	102.7	37- 61
MCH (pg)	28.7	11- 21
MCHC (%)	47	30- 38
PLT (x10^3/µL)	350	200- 500

WBC; Leukocyte, Lymp; Lymphocyte, Mono; Monocyte, Neu; Neutrophil, RBC; Red blood cells, HGB; Hemoglobin, HCT; Hematocrit, MCV; Mean cellular volume, MCH; Mean corpuscular hemoglobin, MCHC; Mean corpuscular hemoglobin concentration, PLT; Platelet, *(Klaasen, 1999).

The CBC analysis showed elevated mean cellular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) compared to reference values, while erythrocyte (RBC), hematocrit (HCT), and hemoglobin (HGB) levels were below normal (Table 1). Comparison of the serum biochemical analysis results with reference values revealed increased mean levels of cholesterol (CHOL), total protein (TP), gamma-glutamyl transpeptidase (GGT), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (TBIL) along with decreased albumin (ALB). (Table 2). Imaging investigations comprised radiographic examinations (in lateral and ventrodorsal positions, DR, Fujifilm, Japan) and ultrasonography (using a 7.5-11 MHz microconvex probe, Mindray Z60, China) of the thorax and abdomen. The radiographic examination revealed renomegaly and a loss of visceral detail, while the ultrasound showed renal cortical hyperechogenicity, free fluid, decreased corticomedullary separation, structural deterioration, and hyperechogenicity in the liver.

Table 2. Biochemical findings

Parameters	Result	Reference values*
TP (g/dL)	8.5	6.0- 7.9
ALB (g/dL)	2.1	2.5- 3.9
ALP (U/L)	65	10- 50
GLU (mg/dL)	100	50- 170
TBIL (mg/dL)	1.2	0.1- 0.4
CHOL (mg/dL)	250	75- 220
GGT (U/L)	20	1-10
ALT (U/L)	131	10- 100
Ca (mg/dL)	10.8	8.2- 10.8
CRE (mg/dL)	1.11	0.6- 2.4
BUN (mg/dL)	29.2	14- 36
AST (U/L)	33	10- 100

TP; Total protein, ALB; Albumin, ALP; Alkaline phosphatase, GLU; Glucose TBIL; Total bilirubin, CHOL; Cholesterol GGT; Gamma glutamyl transferase ALT; Alanine aminotransferase, Ca; Calcium, CRE; Creatinine, BUN; Blood urea nitrogen AST; Aspartate aminotransferase, *(Klaasen, 1999).

Based on the clinical, laboratory, and imaging abnormalities, the differential diagnosis included Feline Cholangitis/Cholangiohepatitis Syndrome, Feline Calicivirus (FCV), Feline Herpesvirus (FHV), Feline Immunodeficiency Virus (FIV), Feline Leukemia Virus (FeLV), Feline Parvovirus (FPV), and Toxoplasmosis. To rule out diseases with similar clinical manifestations, the following diagnostic assays were performed: FCV antigen (Asan Pharm®, Korea; sensitivity 96%, specificity 98%), FHV antigen (Asan Pharm®, Korea; sensitivity 96.5%, specificity 98%), FIV antibodies/FeLV antigen (Asan Pharm®, Korea; sensitivity 98%, specificity 98.7%), FPV antigen (Asan Pharm®, Korea; sensitivity 97.8%, specificity 98.8%), and Toxoplasma antibodies (Anigen, China; sensitivity 100%, specificity 99%). Following negative results, the Biopanda Feline Coronavirus Antigen Rapid Test (relative sensitivity 92.54%, relative specificity 97.09%) was conducted for FIP diagnosis to detect Feline Coronavirus (FCoV) antigen, and all tests returned negative. In conclusion, the diagnosis of iatrogenic acute acetaminophen toxicity was confirmed through anamnesis, physical examination, and laboratory and imaging findings.

Discussion

Acetaminophen toxicity is relatively common due to oral administration by owners or accidental ingestion by animals. Acetaminophen has no safe dose for cats, which leads to its toxicity being more common in felines than in canines. The toxic dose is reported to range between 50 and 100 mg/kg of body weight; however, toxicity and even death can occur at doses as low as 10 mg/kg of body weight (Aronson & Drobatz, 1996; Sidhu et al., 2021). In this case, the administration of 120 mg of acetaminophen once daily for two days resulted in findings in the cat, including hemolytic anemia, pigmenturia, depression, and icterus. Since symptoms such as bradycardia, respiratory depression, and dehydration are non-specific, they must be assessed alongside anamnestic data consistent with acetaminophen intoxication. Recognizing the clinical manifestations aids in diagnosing acetaminophen toxicity and helps alert pet owners to this serious condition. Also, case reports like the present one can help raise awareness and reduce fatalities related to this condition.

The CBC is one of the most frequently conducted laboratory tests in medicine, offering insights into the size and quantity of circulating blood cells. Within the CBC, the red cell indices are

calculated parameters that include RDW, MCV, MCH, and MCHC. These indices are derived from measured HGB, HCT, and RBC counts, and they aid in identifying the etiology of anemia (El Brihi & Pathak, 2024). A previous study reported changes in hematological values, including WBC, MCV, MCH, PCV, and MCHC, as a result of acetaminophen toxicity, which were associated with induced liver injury. Given that hemolytic anemia is a key clinical symptom of acetaminophen intoxication, the low levels of RBC and HGB observed in this case are likely due to excessive accumulation of methemoglobin. This accumulation may cause hemoglobin denaturation, Heinz body formation, increased osmotic fragility of RBCs, and subsequent hemolytic anemia, leading to icterus, hemoglobinemia, tissue anoxia, and cyanosis (Juma et al., 2015). Thus, the low RBC, HGB, and HCT levels observed in this case may be explained by increased osmotic fragility of RBCs and induced hepatotoxicity (Juma et al., 2015; Özkan, 2017). Therefore, although serum biochemistry is more useful for assessing the degree of hepatotoxicity, the evaluation of hematological values can also provide important information for prognosis and treatment planning (Juma et al., 2015).

In all species, acetaminophen is metabolized in the liver through glucuronidation, oxidation, and sulfation. The resulting glucuronide and sulfate conjugates are non-toxic and are excreted in urine and bile. In most species, the oxidation pathway plays a minor role, while glucuronidation is the primary route of acetaminophen metabolism. However, cats have a limited capacity to conjugate with glucuronic acid due to low levels of glucuronyl transferase, the enzyme responsible for the final step of the glucuronidation pathway. As a result, cats have a restricted ability to metabolize acetaminophen into non-toxic metabolites. These inactive metabolites are eliminated by the kidneys (Bates, 2013). When the glucuronidation and sulfation pathways become saturated, acetaminophen is alternatively metabolized through the cytochrome P-450 enzyme pathway, leading to the formation of a toxic metabolite known as N-acetyl-p-benzoquinone imine (NAPQI). Normally, the toxic effects of NAPQI are mitigated by its conjugation with glutathione. However, when exposure to acetaminophen exceeds the capacity of these pathways, NAPQI can bind to cellular proteins and membranes, resulting in cellular injury and death, primarily in hepatocytes (Allen, 2003). Thus, laboratory findings of hepatotoxicity generally develops 24-36 hours post-ingestion. It was highlighted that in cases of acetaminophen intoxication, hepatic enzymes should be monitored carefully (Richardson, 2000). In this case, notable serum biochemistry abnormalities included elevated levels of ALT, TP, ALP, GGT, CHOL and TBIL along with decreased ALB. The increased liver enzymes observed align with findings from previous reports (Sidhu et al., 2021). The elevated hepatic enzymes such as ALT, ALP, GGT were likely due to liver damage. ALT activity is the most frequently used biomarker for hepatotoxicity. Elevated levels of this enzyme are released during liver damage. Its measurement is a more specific test for detecting liver abnormalities, as it is primarily found in the liver. ALT is considered a more specific and sensitive indicator of hepatocellular injury than AST. ALP is predominantly found in the cells lining the biliary ducts of the liver. Its levels may be elevated if bile excretion is inhibited due to liver damage. GGT is an enzyme found in the liver, kidneys, and pancreatic tissues, with its concentration being lower in the liver compared to the kidneys. It is more clinically useful than ALP. While ALP is more sensitive, GGT is much more specific. The elevation of either of the two enzymes helps determine the occurrence of liver injury (Singh et al., 2011). Liver cells are involved in many pathways of lipid metabolism, such as oxidizing triglycerides to produce energy,

lipoprotein production, conversion of excess carbohydrates and proteins into fatty acids and triglyceride, or synthesis of cholesterol and phospholipids. Acetaminophen has been demonstrated to irreversibly inhibit fatty acid β-oxidation, disrupt lipid metabolism and increase triglyceride levels in the serum and liver (Suciu et al., 2015). The increase in bilirubin was attributed to accelerated RBC destruction. Additionally, the elevated bilirubin levels may be linked to reduced hepatic clearance and liver dysfunction (Ettinger & Feldman, 2010). Serum TP levels generally do not increase in acetaminophen toxicity and often remain within normal ranges. However, in rare cases, conditions such as hemoconcentration (e.g., dehydration caused by vomiting) or an acute-phase inflammatory response can lead to slight increases in specific protein fractions, particularly globulins. In the present case, the low ALB level, coupled with elevated TP, may suggest an increase in globulin levels. While elevated TP is not a hallmark of acetaminophen toxicity, serum biochemical parameters can provide valuable insight into concurrent hemoconcentration or inflammatory processes (Juma et al., 2015; Sidhu et al., 2021).

Ultrasonography is a key and sustainable imaging method for monitoring hepatic diseases. It is an inexpensive, real-time, and noninvasive technique for detection (Tanaka, 2020). As previously noted, the primary toxic effect of acetaminophen is hepatotoxicity, leading to damage to hepatic cells. In the acute stages of acetaminophen toxicity, liver tissue may appear less dense or more radiolucent on radiographs due to necrosis, edema, or fatty infiltration. However, these changes are often subtle and may not be as obvious as on ultrasound or computed tomography scan (Ettinger & Feldman, 2010; Tanaka, 2020). Consequently, ultrasonography is recommended, with the most significant ultrasonographic finding being perirenal fluid leakage, which is thought to be caused by anoxia induced by methemoglobin, leading to increased capillary wall permeability (Juma et al., 2015). Therefore, the abnormal ultrasonographic findings in this case were associated with elevated capillary permeability. Radiographic imaging findings in this case, including altered liver density, were consistent with the loss of visceral detail typically observed in visceral vascular emergencies (Figure 1). Also, previous reports have documented subcutaneous edema related to hypoalbuminemia (Soeters et al., 2019). In this case presentation, free fluid was observed in Morison's pouch probably due to low ALB level (Figure 2). Assessing free fluid in Morison's pouch during acetaminophen toxicity can offer valuable insights into the severity of the condition and aid in prognostic estimation.

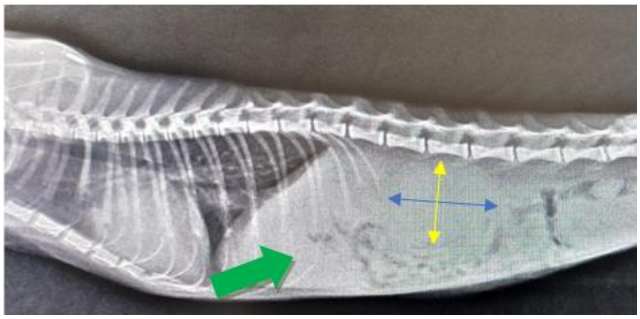

Figure 1. Loss of visceral detail (green arrow), Renomegaly (indicated by blue arrow; 6.68 cm, yellow arrow; 6.39 cm)

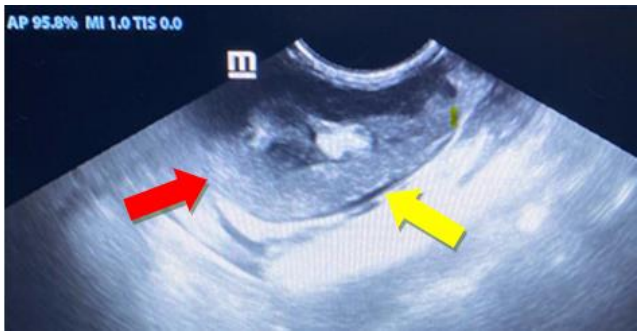

Figure 2. Free fluid in Morison's pouch (yellow arrow) and renal cortical hyperechogenity (red arrow)

Conclusion

In conclusion, the identified toxicity is commonly encountered in clinical practice. Assessing the mentioned parameters is crucial for early suspicion of toxicity and prompt initiation of

treatment protocols. Alongside CBC and serum biochemistry, imaging techniques particularly ultrasonography play a vital role in detecting complications and predicting prognosis. A thorough evaluation of anamnesis data, combined with these examination methods, can aid in accurate disease diagnosis and enhance awareness of its characteristics. Additionally, case reports like the present one can enhance awareness and help reduce fatalities associated with acetaminophen intoxication.

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Ethical Statement

This study does not present any ethical concerns.

Conflict of Interest

The authors declared that there is no conflict of interest.

Data Availabilty Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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