Cutaneous vasculopathy and pulmonary thromboembolism in an unstable diabetic cat

Topics in Companion Animal Medicine

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--Manuscript Draft--

Manuscript Number:	TCAM-D-20-00014R2
Article Type:	Case Report
Keywords:	Critical care-small animal; Internal medicine-feline; Pathology-skin; Diabetes mellitus; Coagulopathies
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Manuscript Region of Origin:	Europe
Abstract:	A six-year-old, male-neutered, domestic short-haired cat was referred for further management of a three-month history of uncontrolled diabetes mellitus. The cat visited the hospital on three occasions during a three-week time period. Hyperglycemia was documented at all visits. The cat initially presented with evidence of hypovolemia, cranial abdominal pain and dehydration. Moderate hyperglycemia, mild ketonemia and severe hypokalemia were documented. A 3 x 2 cm skin lesion with associated alopecia and erythema was first noticed at a routine follow-up examination (visit two) one week later. A diagnosis of diabetic ketoacidosis was made six days later. The previously identified skin lesion now measured 6 x 2.5 cm. Two episodes of respiratory distress were identified at this visit, with no evidence of cardiac or pulmonary pathology. The cat developed a moderate anemia (packed cell volume 16 %, total solids 7.9 g/dL) on the fifth day of hospitalization. Fluid therapy, electrolyte supplementation, regular insulin, anti-emetic and analgesia medications were administered during visits one and three. Due to development of anemia, suspected pulmonary thromboembolism events and progression of skin lesions, euthanasia was elected. A diagnosis of cutaneous vasculopathy with secondary ischemic necrosis was made post-mortem and pulmonary thromboembolism was confirmed. To the authors' knowledge, this is the first report of cutaneous vasculopathy and pulmonary thromboembolism in a cat with confirmed diabetes mellitus, warranting further research to assess if hypercoagulability is common in this patient population, as routine thromboprophylaxis and anti-coagulation may be potentially indicated.
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Response to Reviewers:	

Dear Dr Moore and Reviewers,

On behalf of all authors, I would like to thank you for your further review of this manuscript. An unstructured abstract has been added to the manuscript.

We look forward to hearing from you in due course.

Best wishes,

Dr Katrina Manson

Title page

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Abstract

A six-year-old, male-neutered, domestic short-haired cat was referred for further management of a three-month history of uncontrolled diabetes mellitus. The cat visited the hospital on three occasions during a three-week time period. Hyperglycemia was documented at all visits.

The cat initially presented with evidence of hypovolemia, cranial abdominal pain and dehydration. Moderate hyperglycemia, mild ketonemia and severe hypokalemia were documented. A 3 x 2 cm skin lesion with associated alopecia and erythema was first noticed at a routine follow-up examination (visit two) one week later. A diagnosis of diabetic ketoacidosis was made six days later. The previously identified skin lesion now measured 6 x 2.5 cm. Two episodes of respiratory distress were identified at this visit, with no evidence of cardiac or pulmonary pathology. The cat developed a moderate anemia (packed cell volume 16 %, total solids 7.9 g/dL) on the fifth day of hospitalization.

Fluid therapy, electrolyte supplementation, regular insulin, anti-emetic and analgesia medications were administered during visits one and three. Due to development of anemia, suspected pulmonary thromboembolism events and progression of skin lesions, euthanasia was elected. A diagnosis of cutaneous vasculopathy with secondary ischemic necrosis was made *post-mortem* and pulmonary thromboembolism was confirmed.

To the authors' knowledge, this is the first report of cutaneous vasculopathy and pulmonary thromboembolism in a cat with confirmed diabetes mellitus, warranting further research to assess if hypercoagulability is common in this patient population, as routine thromboprophylaxis and anti-coagulation may be potentially indicated.

Abbreviations list

aPTT	activated thromboplastin time
bpm	beats per minute/ breaths per minute
CRI	constant rate infusion
h	hours
IV	intravenous
PT	prothrombin time
NaCl	sodium chloride
NAD	nicotinamide adenine dinucleotide
PTE	pulmonary thromboembolism
q	every
RI	reference interval
RR	respiratory rate
SQ	subcutaneously

Clinical Report

A six-year-old, male-neutered, domestic short-haired cat, weighing 5.7 kg (12.54 lbs) with a body condition score of 6 out of 9, was referred to the Royal (Dick) School of Veterinary Studies' Hospital for Small Animals, for further management and investigation of a three-month history of uncontrolled diabetes mellitus. At time of referral, the patient was receiving 9 IU (1.6 IU/kg) Caninsulin[1] lente insulin SQ every 12 hours.

On examination, the cat was determined to have evidence of hypovolemia (dull mentation, heart rate 160 bpm, hypodynamic femoral pulses, RR 44 bpm and temperature 37.7 °C [99.9 °F]), with other pertinent clinical examination findings including cranial abdominal pain and dehydration (estimated at 8-10%). Stabilization was achieved with one 5 ml/kg isotonic crystalloid IV fluid[b] bolus. Initial investigations included an emergency blood panel (venous blood gas and electrolyte measurement, PCV, total solids, blood glucose, lactate, creatinine and serum ketone concentrations), CBC, serum biochemistry, urine analysis and culture, abdominal ultrasound, thoracic radiography and submission of serum for insulin-like growth factor-1 measurement. Moderate hyperglycemia, mild ketosis with no acidemia and severe hypokalemia were identified (**Table 1**). Other pertinent blood abnormalities included an increased alanine transaminase (773 U/L; RI 6 - 81 U/L) and increased total bilirubin (1.6 mg/dL; RI 0 - 0.4mg/dL) Urine culture was negative. Thoracic radiographs were unremarkable, while significant findings from the abdominal ultrasound included generalized hepatomegaly with hyperechoic parenchyma. There was no ultrasonographic evidence of pancreatitis. After initially assessing blood clotting times (PT 16 seconds; RI 15-22 seconds and aPTT 111 seconds; RI 65-119 seconds), ultrasound-guided fine needle aspirates of the liver were performed. The aspirates were consistent with moderate hepatic lipidosis.

Hypersomatotropism was excluded with a normal serum insulin-like growth factor-1 result (217 ng/mL; RI 50 – 1000ng/mL).

The patient's dehydration was corrected over 12 hours using an IV isotonic crystalloid solution[2] with potassium chloride supplementation (40 mEq/L) at 5.3 mL/kg/h. Additional medications included maropitant (1 mg/kg IV q24h) and methadone (0.2 mg/kg IV q6h) for management of any potential nausea and abdominal discomfort secondary to potential pancreatitis, respectively. By the following day, the cat was comfortable and eating 50% of his calculated resting energy requirements voluntarily, as well as adequately hydrated and with improved electrolyte disturbances (**Table 1**). Analgesia was deescalated to buprenorphine (0.02 mg/kg IV q8h) and a CRI of both potassium phosphate (0.05 mmol/kg/h) and magnesium sulfate (0.02 mEq/kg/h) were started for correction of the previously documented hypophosphatemia and hypomagnesemia. A singular 1 IU intramuscular injection of regular insulin[3] was administered before starting Prozinc[4] insulin (0.26 IU/kg [1.5 IU] SQ q12h). Over the following 12 hours, buprenorphine was stopped due to patient comfort and lack of ultrasonographic evidence of pancreatitis, and the CRIs were titrated down.

Over the course of days three and four of hospitalization, the cat was eating his full resting energy requirements, as well as drinking and urinating independently. The patient was discharged on the fourth day with Prozinc[4] insulin (0.26 IU/kg [1.5 IU] SQ q12h) and oral potassium supplementation[5] (2 mEq in food q12h).

Persistent hyperglycemia was identified at a revisit appointment (visit two) one week later (**Table 1**). The dose of insulin[4] was increased to 2 IU SQ q12h and the cat was discharged the

following day. At this visit, a 3 x 2 cm skin lesion with associated alopecia and erythema was identified over the right scapula, partly raised and with a scab. This lesion had been treated empirically with cefovecin with the referring veterinarian three days following discharge from visit one due to the suspicion of a cat bite abscess.

The patient represented as an out-of-hours emergency six days later (visit three) with a presenting complaint of anorexia, vomiting and collapse. On presentation, the cat was in shock, obtunded, estimated to be 8% dehydrated and had a body temperature of 39.7 °C (103.5 °F). His heart rate was 174 bpm and RR 20 bpm with no abnormalities noted on auscultation or abdominal palpation. The cat weighed 4.97 kg (10.96 lbs), representing a 0.73 kg (1.61 lbs) weight loss, with a body condition score of 4 out of 9. Systolic blood pressure via Doppler was 130 mmHg. There was no peripheral lymphadenopathy. The previously identified scapular skin lesion was still present and had increased in size (now measuring 6 x 2.5 cm).

An emergency blood panel (parameters as above) was performed. Significant findings included a severe metabolic acidosis and respiratory alkalosis, marked hypokalemia, moderate hypomagnesemia, moderate hyperglycemia and severe ketonemia (**Table 1**). Point of care ultrasound was negative for free thoracic or abdominal fluid, and urine culture revealed no bacterial growth. A diagnosis of diabetic ketoacidosis was made. The patient received two 10 mL/kg IV isotonic crystalloid fluid[2] boluses and then started on IV isotonic crystalloid fluids[b] at a rate of 5 mL/kg/h supplemented with potassium chloride (80 mEq/L) to correct dehydration and hypokalemia, respectively. Additional medications included amoxicillin-clavulanic acid (20 mg/kg IV q8h) due to the potential of a bacterial aetiology

causing the skin lesion, maropitant (1 mg/kg IV q24h) due to the recent history of vomiting and buprenorphine (0.015 mg/kg IV q8h) for potential pain associated with the skin lesion.

Approximately four hours after presentation, the cat developed a sudden increase in RR (100 bpm) and effort, with no abnormalities noted on auscultation. Pulse oximetry measured a saturation of 91 – 93 %, which increased to 100 % with supplemental flow-by oxygen. One dorsoventral thoracic radiograph was subsequently performed with no abnormalities identified on review by a board-certified radiologist. Therefore, PTE was considered the most likely differential diagnosis and the patient was moved to an oxygen kennel. Further orthogonal radiographic views were precluded by patient instability.

Venous blood gas and electrolytes were repeated approximately four and a half hours after presentation. There was still a severe metabolic acidosis and respiratory alkalosis (pH 7.20, venous partial pressure of carbon dioxide 17 mmHg and bicarbonate 6.4 mmol/L), but the hypokalemia had improved (3.7 mmol/L). Sodium bicarbonate diluted in 0.9% NaCl[6] (1.2 mEq/kg IV over 6 hours) was administered and a regular insulin[3] CRI was started six hours following presentation (1.1 IU/kg in 250ml 0.9 % NaCl) with frequent blood glucose monitoring and glucose supplementation initiated as previously described. [1]

The following morning, the cat was clinically brighter and no longer oxygen dependent with a normal RR (32 bpm) and pattern. Hyperthermia was noted (39.9 ° C [103.8 ° F]), thought to be secondary to a raised environmental temperature within the oxygen kennel (the initial pyrexia had normalized by ten hours after admission) and subsequently resolved without intervention. A triple lumen central venous catheter was placed under sedation (butorphanol 0.3 mg/kg IV, midazolam 0.3 mg/kg IV, ketamine 1 mg/kg IV and alfaxalone 2 mg/kg IV)

into the left jugular vein using the Seldinger technique and blood samples were taken for CBC and serum biochemistry. Mild lymphopenia (0.749 x10e9/L; RI 1.5 - 7 x10e9/L) was present and blood smear assessment by a board-certified clinical pathologist revealed moderate red blood cell anisocytosis along with mild neutrophilic toxic changes. Serum biochemistry showed moderate increase in alanine transaminase (151 U/L; RI 6 – 83 U/L]) and mild hypophosphatemia (1.0 mmol/L; RI 1.4 - 2.5 mmol/L]) but was otherwise unremarkable.

The cat was continued on IV isotonic crystalloid fluids[2] with supplementation of potassium phosphate (0.02 mmol/kg/h), magnesium sulfate (0.5 mEq/kg/day) and potassium chloride (0.17 mEq/kg/h to 0.25 mEq/kg/h) to a total fluid rate of 6 mL/kg/h. The previously described medications and management of diabetic ketoacidosis were continued.

During days three and four of hospitalization, the patient's serum ketones decreased (**Table 1**) and supplementation of potassium phosphate, potassium chloride and magnesium sulfate were gradually reduced, with reintroduction of oral potassium supplementation[5] (2mL PO q12h). The blood glucose stabilized with a nadir of 7.9mmol/L, hence Prozinc[4] insulin (2 IU SQ q12h) was restarted and the regular insulin[3] CRI was discontinued.

On the fifth day of hospitalization, the cat developed a moderate anemia (**Table 1**). In-saline agglutination was negative both macroscopically and microscopically. In-house blood smear analysis performed by a board-certified internal medicine specialist, demonstrated anisocytosis and polychromasia, with possible spherocytes present. No complete blood count was submitted at this time due to financial limitation. The patient became tachypneic (60bpm) and hypoxemic (SPO2 91%) again, both responsive to supplemental oxygen. Point

of care ultrasound found no free thoracic fluid, there was no chamber enlargement or septal flattening noted and the left atrial to aortic ratio was within normal limits. Development of left sided congestive heart failure was therefore deemed unlikely. [2] Thoracic radiography or CT were not performed at this time after discussion with the owner due to financial limitations.

Due to progression of the skin lesion, a dermatology consultation was performed by a board-eligible dermatologist. On dermatological examination, a large oval-shaped, non-exudative eschar was present at the right caudal scapula measuring 6 x 2 cm, with slightly raised and thickened edges bordered by a ring of alopecia (**Figure 1A**). Pain was elicited when trying to palpate and lift this lesion, so it was unable to determine if there was attachment to the underlying subcutaneous tissue. After shaving the fur, a smaller lesion, with ring of thickened epidermis and smaller eschar in center, was noted over the left scapula, measuring 4 x 1 cm, symmetrical in location to the contralateral lesion (**Figure 1B**). The remaining skin was considered unremarkable. Fine needle aspirates and samples for cytology were taken from both lesions. These were reported by a board-certified clinical pathologist as moderate neutrophilic inflammation with possible involvement of adipose tissue and no underlying bacteria or other etiological agents noted. Hair plucks were negative for evidence of parasites or fungal hyphae.

Despite initial stabilization of diabetic ketoacidosis, in light of the patient's concurrent progressive anemia, tachypnea, dermatological lesions and financial implications, euthanasia was performed.

Necropsy examination was undertaken and notable findings from gross necropsy included: bilateral, regionally extensive, chronic, ulcerative dermatitis and panniculitis of the right and left thorax (**Figure 2A**); mild, multifocal pancreatic nodules; and focal pulmonary artery thrombosis with a 4.5cm firm, linear present, extending within the blood vessel lumen into the right caudal lung lobe. The heart weighed 24 g and at the time of necropsy examination the cat weighed 5.2 kg; heart weight to body weight ratio = 4.6 g/kg body weight. [Normal is 3.83+/-0.2g/kg]. [3] Histopathological findings included bilateral, marked, regionally extensive, ischemic necrosis extending from the epidermis to the subcutis and skeletal muscle with associated vascular fibrinoid necrosis and thrombosis and moderate mixed inflammation. A thrombus was identified in the pulmonary artery. (**Figure 2B**). Additionally, vacuolation of the cells within the pancreatic islets (**Figure 2C**), hepatic lipidosis and mild, left ventricular endomyocardial fibrosis were noted. These findings led to final diagnoses of cutaneous vasculopathy with secondary ischemic necrosis, pulmonary artery thrombosis, diabetes-associated pancreatic islet vacuolation and hepatic lipidosis; and concurrent mild, left ventricular endomyocardial fibrosis.

Discussion

To the authors' knowledge, the present clinical report is the first documentation of a cutaneous vasculopathy with thrombosis and pulmonary thrombosis in a cat with confirmed diabetes mellitus. Advanced coagulation testing was unfortunately not performed in this cat but this case suggests that the thrombosis identified at necropsy may be associated with hyperglycemia and development of a vasculopathy.

Vascular complications of both the macro- and micro-circulation are well described in people with hyperglycemia. [4-6] In these patients, hyperglycemia may result in the development of

an angiopathy and limb necrosis, along with a myriad of other skin conditions. [7] A prolonged state of hyperglycemia is a potential cause of this patient's vasculopathy. In both experimental models and human patients, hyperglycemia may lead to the development of vascular injury, oxidative stress, [8,9] and release of pro-inflammatory cytokines. [10] By passive diffusion, glucose can accumulate within endothelial cells, resulting in the activation of the aldose reductase and sorbitol dehydrogenase metabolic pathways, thus altering the cell redox potential and increasing the risk of oxidative injury. [5] Additional mechanisms associated with the development of oxidative stress as a consequence of hyperglycemia include activation of nitric oxide due to increased expression of endothelial and inducible nitric oxide synthase genes [1,12] and development of advanced glycation end-proteins. [13] Together, these mechanisms may predispose to development of tissue ischemia and secondary necrosis, with development of histopathological changes consistent with those documented in this patient. In support, a relationship between glycemic index and tissue necrosis has previously been assessed in an experimental rat model, where the same degree of limb ischemia was induced to both euglycemic and hyperglycemic rat populations, and a significantly higher rate of limb necrosis was identified in the hyperglycemic population. [14]

Differential diagnoses for the cutaneous lesions included a drug-induced, heat- or solar-induced necrosis, neoplasia, or trauma. A local reaction to insulin injection was thought possible as the lesion developed close to an area the owner had been injecting the insulin. However, the owner confirmed that the insulin was being administered in the interscapular region and not over the scapulae, suggesting an adverse reaction was unlikely. Many drugs can cause vasculitis including antibiotics. [15] However, the lesion appeared before the administration of any antibiotics or any other medications, with no history of a recent vaccination. Lesions of this nature would be thought to cause pain, as although the tissue

underneath was devitalized, the dark, leathery eschar was firmly attached at the edge to healthy skin. A culture from the lesion was not submitted but had been planned if treatment were to have continued as secondary infection may have been present, even if the lesion itself was not thought to be of infectious origin.

The inflammatory response and oxidative injury associated with hyperglycemia, resulting in development of a vasculopathy may also have contributed to development of a hypercoagulable state. [5] This is suggested in the current clinical report by the presence of both vascular thrombosis in the skin and a pulmonary artery thrombus on necropsy evaluation. Human diabetic patients are at increased risk for an ischemic cardiovascular event due to an increased thrombin and fibrin generation rate, and delayed clot lysis. [4] A combination of increased platelet activity and turnover, increased thromboxane A2 generation from arachidonic acid metabolism, increased expression of both pro-coagulant, surface glycoproteins and adhesion molecules, and decreased expression of anti-coagulant molecules, are the likely mechanisms associated with hypercoagulability. [16-18] At present, the incidence of hypercoagulability in feline diabetic patients is not known, but a relationship with thrombosis has been previously documented in canine diabetic patients. [19] The direct impact of hyperglycemia on coagulation status has largely been assessed in experimental studies utilizing healthy patient populations in veterinary medicine. A study evaluating the impact of intravenous dextrose administration on thromboelastography and standard coagulation parameters in a group of healthy dogs, was not able to induce a hypercoagulable state. [20] Despite dextrose supplementation, no dog developed hyperglycemia in that study. Another study was undertaken to assess how dextrose administration in a population of healthy horses impacted coagulation. Despite the development of hyperglycemia in all horses, there was no evidence of hypercoagulability as determined by rotational

thromboelastometry, measurement of PT and aPTT or thombin-antithrombin complex level. [21] The absence of a hypercoagulable state in that study may have been the consequence of an insufficient duration and/or magnitude of hyperglycemia or inappropriate methodology to determine presence of hypercoagulability. Therefore, although there is limited veterinary literature evaluating the effect of hyperglycemia on coagulation status, especially in a clinical population, this case suggests that diabetes mellitus may be a disease process associated with an increased risk of pulmonary thrombus formation in cats.

Pulmonary thromboembolism can result from a hypercoagulable state, either directly due to formation of a thrombus within the pulmonary vasculature or as a consequence of embolization from thrombi elsewhere. [22] Pulmonary thromboembolism in human diabetic patients is a well-recognized complication, [23] but to the authors' knowledge, not reported in feline diabetic patients. Other possible risk factors and disease processes with a known association with thromboembolic disease in cats include, but not are limited to, corticosteroid administration, [24] feline infectious peritonitis, [25] immune-mediated hemolytic anemia, [24] neoplasia, pancreatitis, hepatic lipidosis and myocardial disease. [26] At necropsy, there was no histopathological evidence of neoplasia or pancreatitis. However, there was minor increase in heart weight to body weight ratio grossly and mild endomyocardial fibrosis was noted on histology of the left ventricle, therefore cardiac disease cannot be excluded as an underlying contributing factor. This was thought less likely given the normal *antemortem* point of care echocardiography, although these findings were not confirmed by a board-certified cardiologist. [3,4] The significance of hepatic lipidosis which was identified at necropsy in this cat is also not known given the prior association of hepatic lipidosis and pulmonary thromboembolism in cats. [26]

Despite concern for the presence of a pulmonary thrombus, this was not definitively diagnosed until necropsy examination and, unfortunately, no specific treatment was initiated in this patient. There was no evidence of underlying pathology on the one radiographic view obtained during the initial episode of tachypnea; however, this does not rule out PTE. At present, there is no gold standard diagnostic test to diagnose PTE in feline patients. Nonetheless, diagnostics including arterial blood gas assessment, thromboelastography, D-dimers, echocardiography, and CT pulmonary angiography have been described for diagnosis of PTE, with CT pulmonary angiography thought to be the gold standard. [25]

Previous studies investigating hypercoagulability in feline patients have utilized multiple assays to assess coagulation, with a requirement to have two of the following: hyperfibrinogenemia, increased Factor VIII activity, antithrombin deficiency, and markers of systemic or dysregulated thrombin formation (e.g. high thrombin-antithrombin complex or D-dimer concentration); as well as assessment of traditional assays of PT and aPTT. [26] The current clinical report suggests potential utility for assessing for hypercoagulability in feline patients with persistent hyperglycemia, however, the most optimal method for hypercoagulability assessment in cats is not known. Viscoelastic testing has gained popularity over the years with hypercoagulable profiles being identified in dogs with disease processes such as immune mediated hemolytic anemia, [27-30] pancreatitis, [31] and protein losing nephropathy, [32-34] amongst others. Currently, limited literature exists assessing utility of viscoelastic testing in feline clinical cases [35] and at present there is insufficient evidence to recommend how hypercoagulability should be defined in companion animals based on viscoelastic parameters. [36] More direct tests for hypercoagulability, such as thrombin generation assays, are rarely available in a clinical setting and there is currently only limited evidence assessing the utility of such assays in cats. [37] Had we assessed for

hypercoagulability in this cat, even with measurement of the more routinely available fibrinogen and D-dimers concentrations, this would have strengthened our suspicion for the presence of thromboembolic disease and likely led to the institution of an antithrombotic.

Empirical treatment based on clinical signs and individual risk factors, including an indwelling central venous catheter, could however have been considered. When implementing an antithrombotic medication, thrombus location in clinical patients is traditionally cited to influence prescribing habits. Arterial clots are formed under high shear states and are platelet rich; compared to venous clots formed under low shear conditions and consisting mostly of fibrin and red blood cells. [38] A CT pulmonary angiography would have been beneficial for assessment of both the presence and location of pulmonary thrombosis in this cat. It could be argued that CT pulmonary angiography to assess for the location of a thrombus would be of greater benefit compared to hypercoagulability testing when clinical signs suspected to be a consequence of a hypercoagulable state (e.g. PTE) are present. Current veterinary guidelines state that anticoagulant agents, such as low molecular weight heparins or factor Xa inhibitors, should be used for prevention of venous thromboembolism in cats, compared to an antiplatelet agent, specifically clopidogrel, for prevention of arterial thromboembolism in cats. [39] However, institution of dual therapy with both an anticoagulant and antiplatelet drug should be considered when there is high risk of thrombosis. Therefore, based on these guidelines dual therapy would have been reasonable in this patient regardless of the location of the thrombus in the pulmonary vasculature, however, CT pulmonary angiography would have allowed for justification for the increased potential risk of hemorrhage associated with administration of both an anticoagulant and antiplatelet drug. There are no studies to the author's knowledge of risk of bleeding with dual therapy in cats, in limited canine studies no increased risk of bleeding was encountered,

however increased risk of bleeding has been described with combination therapy in people. [40, 41]

Recent literature has identified conditions where veterinary patients might be at higher risk of thrombosis and makes recommendations for potential pharmacological interventions with either anticoagulant or anti-thrombotic medications. [42] However, at present, there is limited evidence to recommend routine, preventative anti-thrombotic treatment in human diabetic patients unless there is an active or prior history of a thrombotic event. [42, 43] There are no recommendations regarding the use of anticoagulants and/or antiplatelet drugs in veterinary medicine for either canine or feline diabetic patients.

In this clinical report, moderate anemia was documented prior to euthanasia. Potential causes of the anemia include hyperglycemia, anemia of chronic disease and hemolysis. Hyperglycemia has the potential to result in anemia due to plasma volume expansion secondary to an osmotic effect and consequent reduction in hematocrit due to hemodilution. Anemia of chronic disease and iatrogenic causes associated with blood sampling offer further explanations, as well as immune-mediated or non-immune-mediated hemolysis. Interestingly, anemia in type II diabetic human patients may be the consequence of renal insufficiency, [44] erythropoietin deficiency, [44] chronic inflammatory status associated with oxidative injury and formation of advanced glycation end-proteins, [45] as well as hemolysis associated with glucose-6-phosphate dehydrogenase deficiency and/or microangiopathic hemolytic anemia, due to increased fragility of erythrocytes and subsequent fragmentation secondary to small vessel disease such as vasculitis. [46-48] Microangiopathic hemolytic anemias may be non-regenerative due to cytokine mediated suppression of the bone marrow (from the primary disease process) and spherocyte-like cells can be seen as fragmentation products, despite no

immune-mediated component. [48] Therefore, microangiopathic hemolysis may have explained the cause for the anemia documented in the current clinical report, as the in-house blood film analysis prior to euthanasia was suggestive for the presence of spherocytes, despite a negative macroscopic and microscopic in-saline agglutination test, although this was not reviewed by a board-certified clinical pathologist.

In conclusion, this case suggests that vascular complications, such as those noted in human diabetics, may also be seen in cats with diabetes mellitus. Prospective clinical research studies are warranted to further understand if routine assessment of coagulation status in feline patients exhibiting persistent hyperglycemia should be recommended and if thromboprophylaxis and/or anti-coagulation should be considered.

Acknowledgements

The authors declare that there were no conflicts of interest. Katrina C. Manson and Glynn A. Woods were involved with obtaining data to describe the case and all authors were involved with manuscript preparation.

No third-party funding or support was received in connection with this case management or the writing or publication of the manuscript.

Footnotes

1. Caninsulin, MSD Animal Health, Milton Keynes, UK
2. Aquapharm 11 (Hartmann's) solution for infusion, Animal Care Ltd, York, England
3. Hypurin Bovine Neutral Insulin injection 100 IU/mL, Wockhardt UK Ltd., Wrexham, UK
4. Prozinc 40 IU/mL, Boehringer Ingelheim, Ingelheim am Rhein, Germany
5. Kaminox, VetPlus, Lytham, UK
6. Sodium chloride injection 0.9 % w/v, Hameln Pharmaceuticals Ltd., Gloucester, UK
7. VetStat Electrolyte Blood Gas Analyser, Idexx Laboratories, Inc., Maine, USA
8. Statstrip Lactate Xpress Meter, Nova Biomedical, Waltham, MA, USA
9. Catalyst Dx Chemistry Analyzer, Idexx Laboratories, Inc., Maine, USA

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Figure legends

Figure 1: Clinical photographs of skin lesions taken from a six-year-old, male-neutered, domestic short-haired cat with uncontrolled diabetes mellitus, on day 5 of visit 3. (A) demonstrates an initial primary lesion on the right caudal scapular region, showing a large oval eschar with the edges slightly lifting away from the underlying tissue. (B) Smaller, newer lesion on the left caudal scapular region, with a smaller eschar developing in the center of the area of alopecia. The lesions were symmetrical in location.

COLOUR REPRODUCTION

Figure 2: Histopathological images of skin lesions from a six-year old, male-neutered, domestic short-haired cat with uncontrolled diabetes mellitus; samples taken at necropsy. (A) documents a section of initial skin lesion with regionally extensive epidermal and dermal necrosis extending into the subcutis. Hematoxylin & eosin X4, Bar = 500 microns. (B) and (C) Vessels in the subcutis below and alongside the lesion have vascular fibrinoid necrosis and occasional thrombosis. Hematoxylin & eosin X20, Bar = 100 microns.

COLOUR REPRODUCTION

Tables

Table 1: Blood parameters obtained from the patient during hospitalization for each visit. The range (minimum to maximum) of blood values is given when more than one value was obtained each day. Absence of a value indicates that the blood parameter was not measured on that day. Blood gas parameters were measured using a VetStat Analyzer[7], point of care meters were used to measure blood lactate and ketone concentrations[8], and an in-house analyzer[9] was used to measure both magnesium and phosphorous concentrations. Sodium values were not corrected

Figure

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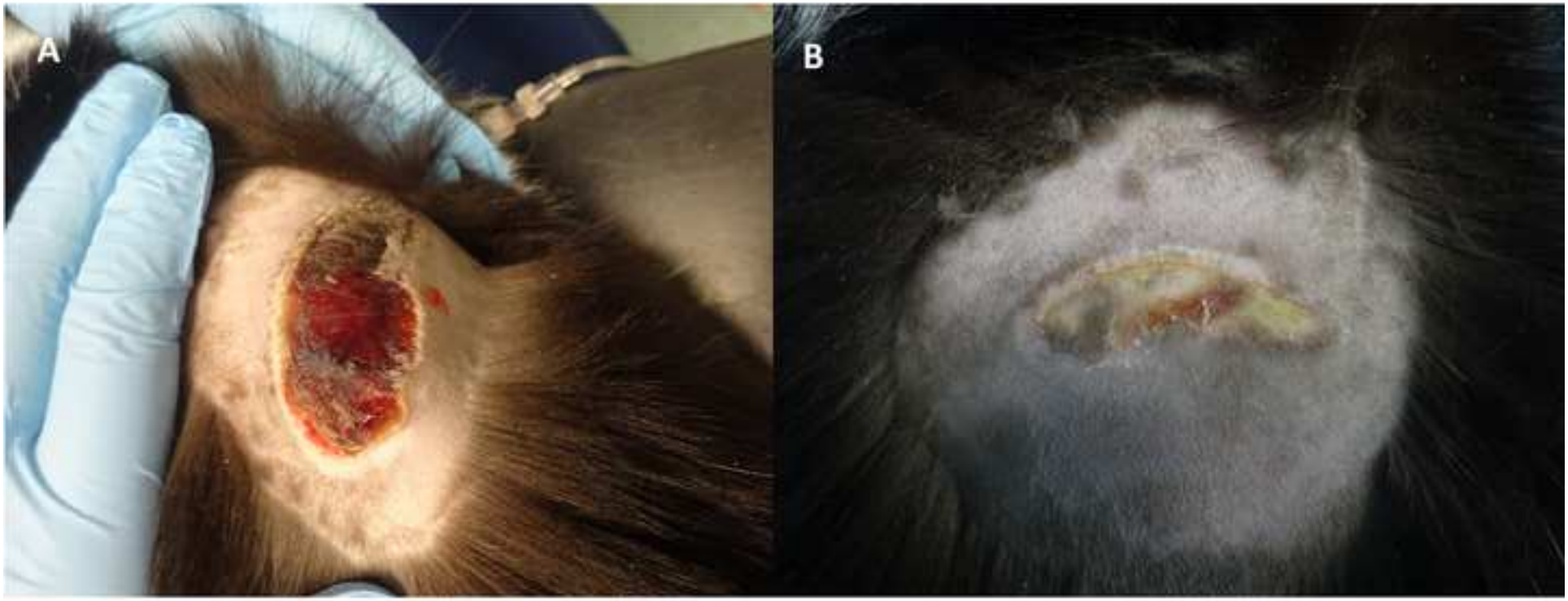

Figure

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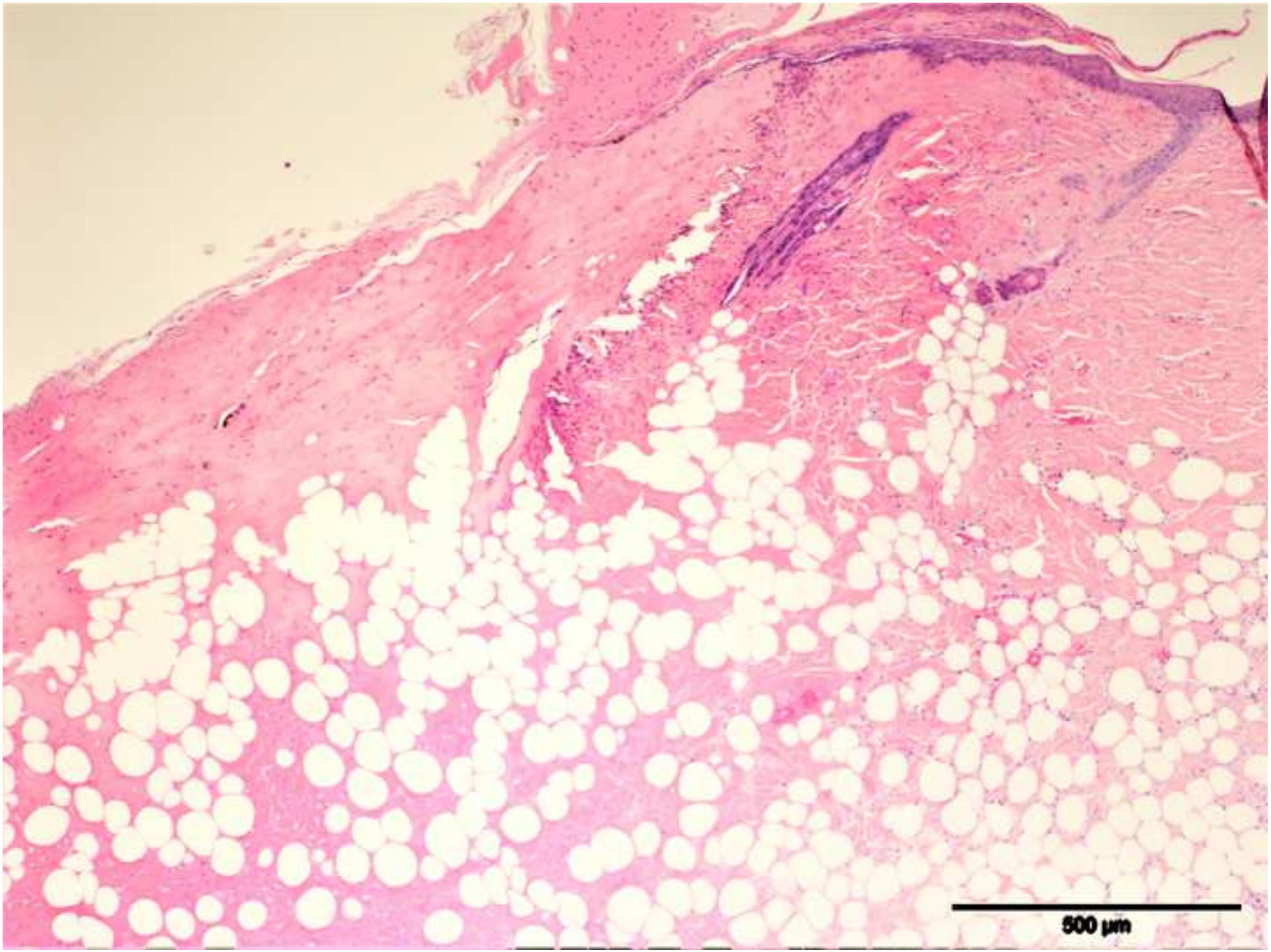

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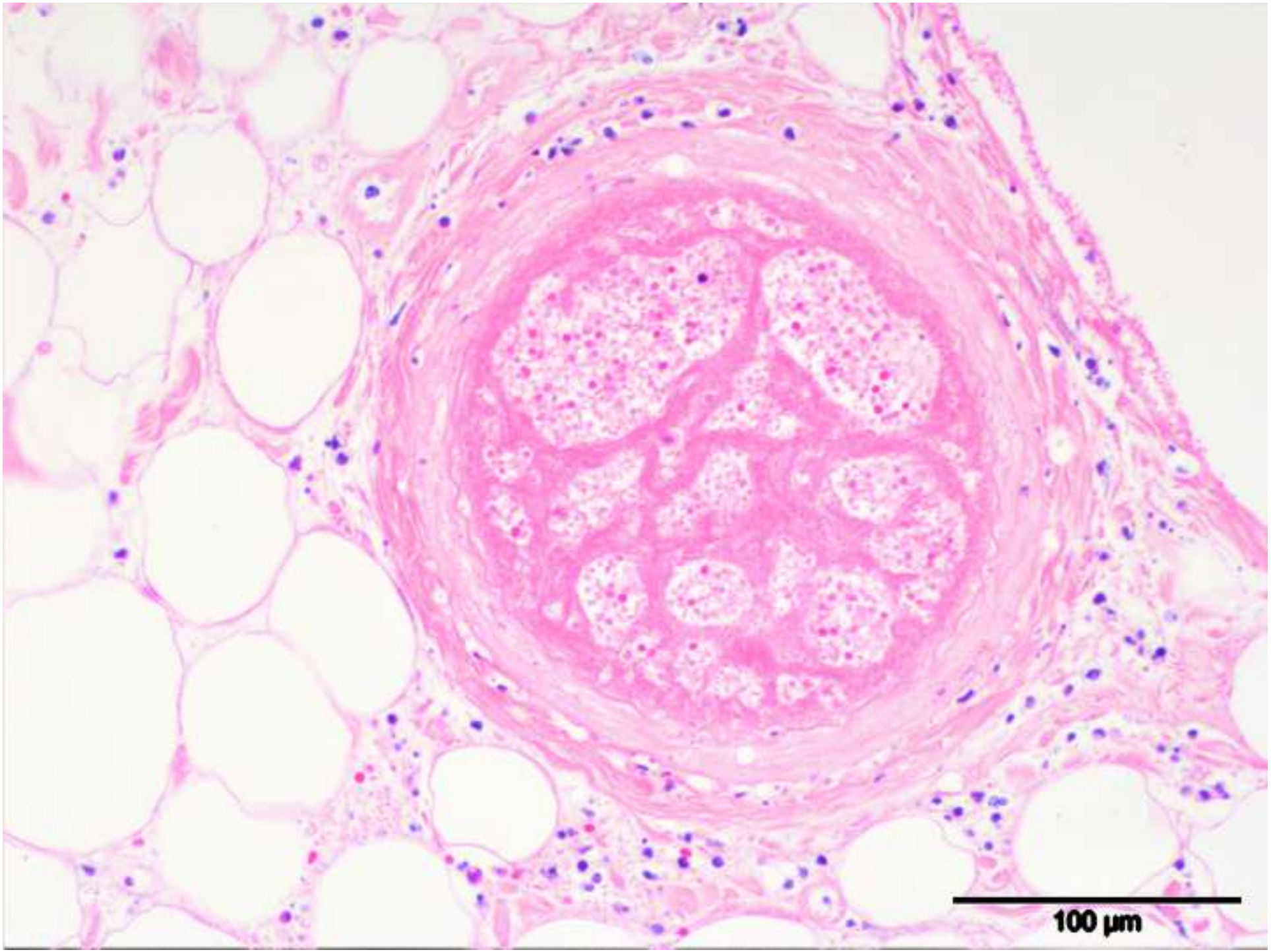

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