A 13-year-old castrated domestic shorthair cat was referred to the Cornell University Hospital for Animals for evaluation of fever, anorexia, and dermatologic lesions. Twelve days earlier at the referring veterinarian's clinic, erythema and crusting of the pinnal margins were noticed. The dermatologic lesions worsened despite treatment with methylprednisolone acetate (3 mg/kg [1.4 mg/lb] of body weight, once, SC), and the cat developed anorexia and a fever and began vomiting. Hematologic tests revealed thrombocytopenia (111 × 10^9/L; reference range, 175 to 500 × 10^9/L), leukopenia (3.4 × 10^9/L; reference range, 5.0 to 18.9 × 10^9/L), hypercalcemia (13.9 mg/dl; reference range, 7.8 to 11.3 mg/dl), and high alanine aminotransferase (ALT) activity (1,957 U/L; reference range, 12 to 130 U/L). No abnormalities were evident on lateral abdominal and thoracic radiograph views. The cat was treated with lactated Ringer's solution, IV (volume was not reported), cefazolin (20 mg/kg [9.1 mg/lb], IV, q 8 h), and cimetidine (4.5 mg/kg [2.0 mg/lb], IV, q 8 h) but did not improve and was referred for further evaluation.

On physical examination, the cat was lethargic, febrile (rectal temperature, 39.9 C [103.8 F]), and reluctant to stand. The nasal planum was erythematous, swollen, and crusted, and a serosanguineous nasal discharge was evident. Crusting and well-demarcated purple lesions were seen on the tips of the pinnae and tail (Fig 1). Signs of pain were evident during palpation of the foot pads, and the foot pads were erythematous with ecchymotic hemorrhages. Hepatomegaly and renomegaly were detected on abdominal palpation, and the popliteal lymph nodes were slightly larger than normal. The distribution and appearance of the skin lesions were consistent with vascular disease. Differential diagnoses for these lesions included cold agglutinin disease, vasculitis, hypercoagulopathy, systemic lupus erythematosus, a drug reaction, and frostbite.

A CBC, serum biochemical analyses, coagulation tests, urinalysis, tests for FeLV antigen and feline immunodeficiency virus (FIV) antibodies, a slide agglutination test at 37.2 C (99 F) and 3.9 C (39 F), and a serum antinuclear antibody (ANA) test were performed. Hematologic abnormalities included lymphopenia (0.7 × 10^9/L; reference range, 1.3 to 9.1 × 10^9/L), eosinopenia (0.1 × 10^9/L; reference range, 0.2 to 4.3 × 10^9/L), and thrombocytopenia (100 × 10^9/L; reference range, 215 to 760 × 10^9/L). Evaluation of a Wright's stained blood smear revealed rouleaux and a large amount of light-purple smooth globular precipitate interspersed among and displacing hematopoietic cells (Fig 2). A large Buffy coat layer, composed of a flocculent white opaque material, was evident in a centrifuged microhematocrit tube, and a stained smear of the Buffy coat consisted of the same precipitate seen in direct blood smears. The precipitate dissolved when the blood was warmed to 37 C (99 F) and was no

**Monoclonal immunoglobulin G cryoglobulinemia and multiple myeloma in a domestic shorthair cat**

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Cryoglobulins are proteins, usually immunoglobulins, that precipitate when serum is cooled to temperatures less than body temperature and dissolve upon rewarming. Clinical signs of monoclonal cryoglobulinemia are a result of vascular obstruction and tissue ischemia and include erythema, hemorrhage, and necrosis of the extremities. Monoclonal cryoglobulinemia is rare in cats and, when detected, should prompt a search for underlying lymphoproliferative or immune-mediated disease.

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bocytopenia included vasculitis, and pyuria was not evident. Possible causes of thrombocytopenia because the sample was collected from a table surface, voided urine sample were considered contaminants, suggestive of concurrent renal disease. Bacteria in the blood smear from blood held at room temperature (A). This precipitate was not evident in the smear from blood held at the higher temperature (B). Platelets are distinguished from the precipitated cryoglobulin by their darkly stained granular content. Wright's stain; bar = 25 μm.

longer evident in blood smears made from warmed blood. These features were diagnostic for a cryoglobulin.

Results of the FeLV, FIV, ANA, and slide agglutination tests were negative. Pertinent biochemical abnormalities included hypoproteinemia (6.3 g/dl; reference range, 6.5 to 8.9 g/dl) secondary to hypoglycopeninemia (2.5 g/dl; reference range, 2.8 to 4.6 g/dl), high urea nitrogen concentration (38 mg/dl; reference range, 17 to 35 mg/dl), hypercalcemia (13.0 mg/dl; reference range, 8.2 to 11.3 mg/dl), high ALT (288 U/L; reference range, 35 to 134 U/L), and aspartate aminotransferase (105 U/L; reference range, 13 to 46 U/L) activities, and hypocholesterolemia (63 mg/dl; reference range, 73 to 256 mg/dl). Urinalysis of a voided urine sample revealed isosthenuria (specific gravity, 1.012), 1+ proteinuria (sulfosalicylic acid precipitation method), marked bacteriuria, many epithelial cells, and cylindruria (< 1 hyaline and waxy-casts/low-power field). Coagulation testing revealed a prolonged activated partial thromboplastin time (APTT; 34 seconds; reference range, 11 to 23 seconds).

The hypoproteinemia and hypoglycopeninemia were discrepant findings, considering the rouleaux seen in the blood smear and the presence of a cryoglobulin. These values were most likely artifactual low because of precipitation of the cryoglobulin during centrifugation of the sample for plasma preparation. The high ALT and aspartate aminotransferase activities and hypocholesterolemia were suggestive of hepatic disease, and the slightly high urea nitrogen concentration in combination with isosthenuria and cylindruria was suggestive of concurrent renal disease. Bacteria in the voided urine sample were considered contaminants, because the sample was collected from a table surface, and pyuria was not evident. Possible causes of thrombocytopenia included vasculitis, disseminated intravascular coagulation (DIC), and decreased bone marrow production, and the prolonged APTT may have been attributable to hepatic disease, factor XII deficiency, or DIC. Neoplastic disease such as multiple myeloma or lymphoma was the most likely cause of the hypercalcemia, with other conditions such as primary hyperparathyroidism, granulomatous disease, and osteolytic bone disease considered less likely.

Treatment with cefazolin (20 mg/kg [9.1 mg/lb], IV, q 8 h) and fluids (0.9% NaCl to which 20 mEq of K+ had been added/l; 5.5 ml/kg/h [2.5 ml/lb/h]) was begun. Furosemide (1 mg/kg [0.46 ml/lb], IV, q 12 h) was administered to promote calcium resis. Because more invasive procedures were planned, vitamin K1 (5 mg, SC, q 12 h for 3 doses) was given to counteract a possible coagulopathy secondary to deficiency of vitamin K-dependent coagulation factors, which could develop secondary to hepatic disease.

The following day, physical examination revealed mild dyspnea and slightly harsh lung sounds. Further diagnostic investigations were undertaken to determine the amount and nature of the cryoglobulin and the underlying cause. The buffy coat layer produced by the cryoglobulin (cryocrit) was measured as an indirect indicator of the amount of cryoglobulin and was 21%. Blood was collected into a prewarmed syringe and placed into a prewarmed plain glass tube. Serum was obtained after centrifugation at 37.2 C (99 F) and was maintained at this temperature until analysis. An aliquot of serum was allowed to cool at room temperature, then centrifuged to remove the cryoglobulin, and total protein and globulin concentrations in this and in a warmed serum sample were measured. Total protein and globulin concentrations of the cooled sample were 6.1 and 2.5 g/dl, respectively, whereas concentrations of the warmed sample were 8.7 and 5.5 g/dl, respectively, indicating a cryoglobulin concentration of 3 g/dl. Agarose gel serum protein electrophoresis revealed a monoclonal protein that migrated in the γ region of the electrophoreogram. A similar monoclonal protein was evident in the electrophoreogram of a concentrated sample of urine (total protein concentration, 44 mg/dl) and was consistent with light chain proteinuria. Concentration of the monoclonal protein in serum, determined by means of electrophoresis, was 3.0 g/dl, which was identical to the concentration calculated on the basis of total protein and globulin concentrations in warmed and cooled serum samples. Immunoelectrophoresis of the serum sample revealed that the monoclonal cryoglobulin was IgG, and concentrations of IgM and IgA were low.

Abdominal ultrasonography revealed multiple, small, hypechoic hepatic nodules, hepatomegaly, and bilateral renomegaly with reduced corticomedullary definition. The spleen appeared normal. Thoracic radiography revealed mild pleural effusion and a mild alveolar lung pattern in the hilar region but no evidence of osteolysis. Ultrasound-guided aspirates of the liver, spleen, and kidney were obtained, and smears were prepared and stained with Wright's stain. Examination of the smear from the liver revealed large numbers of plasma cells, with a few plasmacytoid lymphocytes and rare lymphoblasts interspersed with cytologically normal hepatocytes (Fig 3). The plasma cells displayed moderate anisokaryosis, and several binucleate cells were observed. A similar population of plasma cells was observed in smears of the splenic aspirate. The smears of the aspirate from the kidney contained low numbers of small mature lymphocytes and renal tubular epithelial cells.

The cytologic results, together with results of immunoelectrophoresis, were diagnostic for multiple myeloma with a monoclonal IgG cryoglobulinemia. The lung pattern was most consistent with pulmonary edema, although pulmonary hemorrhage or pneumo-
nia could not be excluded. Possible causes of the pulmonary edema and pleural effusion were congestive heart failure, iatrogenic volume overload, vasculitis, DIC, and pulmonary thromboembolism. Fluid therapy was temporarily discontinued, and the dosage of furosemide was increased to 2 mg/kg (0.9 mg/lb), IV, every 12 hours. Plasmapheresis to reduce the concentration of cryoglobulin and chemotherapy for multiple myeloma were discussed with the owners, but because of the worsening dyspnea, expense of treatment, and poor prognosis, the cat was euthanatized.

Bone marrow was aspirated from the left femur immediately after euthanasia. Marrow cellularity was increased, compared with normal, with a myeloid-to-erythroid ratio of 5.25:1. Overall, plasma cells comprised 11% of the cells in the bone marrow smears; however, in some areas of the smears, especially areas close to bone marrow spicules, >30 to 40% of the cells were plasma cells. Results of the bone marrow evaluation were compatible with erythroid hypoplasia, megakaryocytic hypoplasia, and multiple myeloma.

At necropsy examination, the skin lesions were as previously described. The liver contained hundreds of dark red gelatinous nodules scattered over the surface and throughout the parenchyma. These were sharply demarcated from the normal hepatic parenchyma and varied in size from <1 mm to 1 cm in diameter. The spleen was moderately enlarged, with hundreds of white loci <1 mm in diameter scattered over the serosal surface and throughout the parenchyma. A small amount of serosanguineous fluid containing flecks of flocculent material was present in the pleural cavity and pericardial sac, and the lungs appeared congested. The long bones were split longitudinally, and the bone marrow was diffusely red.

Sections of skin, liver, spleen, kidney, lung, heart, mesenteric and peripheral lymph nodes, adrenal gland, stomach, small and large intestine, pancreas, brain, peripheral nerve, and bone marrow were routinely prepared and examined histologically. On H&E-stained sections, coagulation necrosis of the distal portions of the ears, tail, and footpads was evident, with a band of neutrophilic infiltrate and early granulation tissue separating viable and nonviable tissue (Fig 4). Coalescing eosinophilic globules mixed with neutrophilic debris occluded most vessels in the sections. Inflammatory cells disrupted the walls of several vessels (especially in the footpads), which also had hypertrophied endothelium indicative of vasculitis. In the liver, aggregates of neoplastic plasmacytoid round cells distended the sinusoids, compressed and destroyed adjacent entrapped hepatic cords, and formed large nodules with extensive hemorrhage and necrosis. Rare mitoses were seen (<1/5 high-power fields), and a few binucleate cells were present. Similar nodules of plasmacytoid round cells were present in the spleen, as were scattered foci of extramedullary hematopoiesis. The femoral bone marrow was mildly hyperplastic and free of neoplastic infiltrate. Lymph nodes adjacent to areas of cutaneous necrosis had marked sinus histiocytosis and hemosiderosis. All lymph nodes examined were free of neoplastic infiltrate. There was moderate pulmonary hemorrhage and edema with scattered fibrin thrombi, globular precipitates, and megakaryocytes in septal capillaries. Lymphocytic, eosinophilic interstitial nephritis was present in both kidneys.

Immunohistochemical staining of sections of liver and spleen was performed, using a streptavidin-horseradish peroxidase technique per the manufacturer’s instructions. Most plasmacytoid cells stained lightly...
for IgG and lambda light chain; a few cells stained for IgM and kappa light chain. None stained for IgA.

Cryoglobulins are proteins, usually immunoglobulins, that precipitate as serum is cooled to temperatures less than body temperature and dissolve upon rewarming. They are most commonly evident as a white gelatinous material but may sometimes appear crystalline or flocculent. Cryoglobulinemia is rare in animals, and to the authors’ knowledge, published reports of cryoglobulinemia in animals are limited to descriptions of 2 dogs with multiple myeloma, a dog with Waldenström’s macroglobulinemia, a horse with lymphoma, and several horses with glomerulonephritis. Recently, Nagata et al described a dog with idiopathic cryoglobulinemia and cryofibrinogenemia. To the authors’ knowledge, cryoglobulinemia has not been previously reported in a cat.

In human patients, cryoglobulins are classified into 3 subgroups on the basis of their immunoglobulin composition. In type-I cryoglobulinemia, a single monoclonal immunoglobulin (usually IgM) is present. This is most commonly associated with lymphoproliferative diseases such as multiple myeloma, Waldenström’s macroglobulinemia, lymphoma, and lymphocytic leukemia, but occasionally can develop in conjunction with immune-mediated diseases. In type-II cryoglobulinemia, a monoclonal immunoglobulin (usually IgM) complexes with polyclonal IgG, whereas in type-III cryoglobulinemia, polyclonal immunoglobulins (usually IgM) complex with polyclonal IgG. Type-II and -III cryoglobulinemia are also known as mixed cryoglobulinemias and may develop secondary to infection (especially with hepatitis C virus), immune-mediated diseases or, very rarely, lymphoproliferative disease. In some circumstances, an underlying disease is not found, and the cryoglobulinemia is described as essential. Using this classification system, type-I and mixed cryoglobulinemia in dogs and horses have been described. Two dogs with multiple myeloma had type-I IgA cryoglobulinemia, and the dog with Waldenström’s macroglobulinemia had type-I IgM cryoglobulinemia. Another dog had an essential mixed IgG-IgM cryoglobulinemia and cryofibrinogenemia, and although a thorough investigation for underlying disease was not performed, the diagnosis was supported by resolution and lack of recurrence of clinical signs when the dog was maintained in a warm environment. A horse with lymphoma had a type-I IgB cryoglobulinemia, and IgG-IgG mixed cryoglobulinemia in another horse with glomerulonephritis has been described. The cat described in the present report had type-I IgG cryoglobulinemia.

The typical clinical signs of cryoglobulinemia are purpura, cold intolerance, acrocyanosis, and ulceration, necrosis, and gangrene of the skin of the distal portions of the extremities. Similar lesions were observed in the cat described in the present report; however, these clinical signs are not present in all patients with cryoglobulinemia. Of the cases of cryoglobulinemia reported in the veterinary literature, only 1 dog and 2 horses had typical lesions. Necrosis of the pinnae occurred in the dog and in 1 of the horses, and distal limb swelling and ulceration occurred in the other horse. Similarly, < 50% of human patients with cryoglobulinemia have typical clinical signs even in cold conditions. The lesions develop as a result of precipitation of cryoglobulin in small-diameter blood vessels, which causes vascular occlusion and tissue ischemia. Subsequently, inflammation may develop at the site of precipitation secondary to complement fixation by IgG. Despite extensive investigation, the physical and chemical characteristics accounting for the temperature-dependent solubility of cryoglobulins have not been determined. Proposed mechanisms include altered amino acid or carbohydrate content of the cryoglobulin, leading to abnormal interactions between water and the protein.

Hyperviscosity syndrome in dogs and people with cryoglobulinemia has been reported. High blood viscosity causes sludging of blood and ischemia and increases cardiac workload. This manifests as retinal vessel dilatation and hemorrhage, retinal detachment, epistaxis or bleeding from other mucous membranes, neurologic abnormalities, and renal and cardiovascular disease. Hyperviscosity may have been responsible for development of signs of congestive heart failure and interstitial nephritis in the cat described in the present report. Additionally, renal tubular damage associated with filtered immunoglobulin light chains and hypercalcemic nephropathy may have played a role in the development of renal disease.

Immune-mediated membranoproliferative glomerulonephritis is common in human patients, particularly those with mixed cryoglobulinemia, and may develop in horses. Arthralgia, peripheral neuropathies, periporal hepatitis, and cirrhosis in people with cryoglobulinemia have also been described. These may develop secondary to immune-mediated, hypoxic, or inflammatory mechanisms. None of these lesions were found in the cat described in the present report.

Cryoglobulinemia should be suspected if a white gelatinous or flocculent material is seen in blood smears, centrifuged hematocrit tubes, or cooled serum; if blood gels during venipuncture; or if technical difficulties are experienced when using automated blood counting machines because of precipitation within the equipment tubing. In this cat, the cryoglobulin was obvious in blood smears, centrifuged hematocrit tubes, and separated serum immediately after processing.

Monoclonal cryoglobulins are usually present in high concentrations and precipitate rapidly; however, polyclonal cryoglobulins are often present in low concentrations and may take several days to precipitate. Therefore, in human patients, it is recommended that serum be stored at 3.9 C (39 F) and examined daily for at least 7 days before the presence of a cryoglobulin is excluded. The method of blood collection and handling is vital when isolating a cryoglobulin for further investigation. Blood should be collected into warmed syringes or evacuated tubes, allowed to clot at 37.2 C (99 F), and separated before cooling to prevent precipitation of cryoglobulin during centrifugation. Cryoglobulinemia in animals may go undetected if serum is not handled in this manner. Once isolated, the cryoglobulin should be washed, redissolved, analyzed by means of electrophoresis or immunoelectrophoresis at 37.2 C (99 F), and classified as a type-I, -II, or -III cryoglobulin.
Treatment of cryoglobulinemia is directed at controlling the underlying disease and minimizing exposure to cold. In human patients with cryoglobulinemia, corticosteroid or nonsteroidal anti-inflammatory treatment is often effective at controlling mild clinical signs. Corticosteroids and alkylating agents such as melphalan, cyclophosphamide, and chlorambucil have been used to treat cats with multiple myeloma with varying results. Most cats respond transiently for 2 to 3 months, although longer remission times have been reported. In the cat described in the present report, the worsening clinical signs, expense of treatment, and poor prognosis prompted the owner to elect euthanasia.

In conclusion, observation of a white gelatinous or flocculent material in blood smears or cooled serum or a large buffy coat layer composed of protein should make veterinary clinicians suspicious of cryoglobulinemia. Cryoglobulinemia is rare in animals, and detection of monoclonal cryoglobulinemia should prompt a search for an underlying lymphoproliferative disease such as multiple myeloma, lymphoma, lymphocytic leukemia, or Waldenström's macroglobulinemia.

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