Case Report

Primary Myxoid Liposarcoma of the Greater Omentum in a Rhesus Macaque (*Macaca mulatta*)

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We here report a spontaneous case of primary myxoid liposarcoma of the greater omentum with subsequent transperitoneal recurrence. The primary mass was incidentally found during an exploratory laparotomy for a presumed diagnosis of trichobezoar or phytobezoar and was removed surgically. Histopathologic examination of the mass revealed the presence of a myxoid liposarcoma. Eleven months later, recurrence with severe transperitoneal sarcomatosis of the myxoid liposarcoma was noted and confirmed by necropsy and histopathology. A review of the literature revealed that liposarcoma in NHP conforms to the behavior and prognosis of this neoplasm in humans.

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Liposarcoma is a mesenchymal tumor that originates from primitive cells that undergo adipose differentiation.²¹ Liposarcoma has been reported in humans and several species of animals, such as dogs, cats, cattle, birds, rats, horses, seals, pigs, guinea pigs, and NHP, including Japanese macaques (*Macaca fuscata*), bonnet macaque (*M. radiata*), and potto (*Perodicticus potto*).^{8–10,16,17,26,27,30} In humans, liposarcomas commonly arise in the deep soft tissue of an extremity or within the retroperitoneum.¹³ Dogs and cats develop liposarcoma in almost any tissue of the body, although commonly in the extremities.^{26,27} The etiology of liposarcoma is undetermined, although in dogs the lesion has been associated with foreign bodies, whereas in cats, liposarcoma has been associated with vaccination sites and retroviral infection.²⁶ Conversely, it is well established that liposarcoma does not emanate from malignant conversion of a preexisting lipoma.²⁶

Liposarcoma is a broad term that refers to a soft-tissue sarcoma of adipose origin ranging from essentially innocuous with local recurrence to aggressive, malignant tumors with metastasis, for this reason, liposarcoma is further cataloged into different categories. In humans, the World Health Organization recognizes 4 categories of liposarcoma: 1) well-differentiated, 2) dedifferentiated, 3) pleomorphic, and 4) myxoid.^{11,13,24} In veterinary medicine, there is no defined classification system, although liposarcoma is typically placed into 3 categories: 1) well-differentiated, 2) pleomorphic, or 3) myxoid.²⁶ Well-differentiated liposarcoma is the most common type in people and animals,^{15,26} and is slow-growing and locally aggressive with uncommon recurrence after complete surgical excision.¹² In humans, approximately 10% of well-differentiated lesions dedifferentiate into nonlipogenic sarcomas with a 15% to 20% chance of metastasis.^{9,13} Dedifferentiated liposarcoma most commonly arises in the retroperitoneum.²² Pleomorphic liposarcoma is more clinically aggressive and rare in humans,²² although it is much more common in animals.²⁶ In all species, liposarcoma tends to be a

high-grade sarcoma with high potential for metastasis to the lungs (30% to 50%) and a high mortality rate (40% to 50%).^{13,26}

Myxoid liposarcomas are predominantly composed of stellate to spindle to round mesenchymal cells within a mucinous to myxoid matrix^{13,22} and can be differentiated from a myxosarcoma by identification of cytoplasmic lipid vacuoles within the liposarcoma cells. In people, this tumor typically develops in young patients, has a predilection for the extremities,¹³ and rarely develops in the retroperitoneum or subcutaneous tissues.²⁵ In animals, liposarcoma is often found in body cavities, including the omentum and retroperitoneum.²⁶ Tumors with a high histologic grade are prone to recur locally and to develop distant metastases,¹³ and the metastatic rate can reach 60%.²⁶ The prognosis is guarded and contingent on the histologic grade, presence of necrosis, and TP53 overexpression.¹³

In NHP, liposarcoma appears to be rare, and only 3 cases have been reported: a well-differentiated tumor in a bonnet macaque (*M. radiata*), a round-cell variant of myxoid liposarcoma in a Japanese macaque (*M. fuscata*), and a myeloliposarcoma in a potto (*P. potto*). Here we present a case of myxoid liposarcoma that originated within the omentum of the greater curvature of the stomach with aggressive abdominal recurrence after surgical excision in a rhesus macaque (*M. mulatta*).

Clinical case. A 9-y old, high-ranking, male rhesus macaque (*M. mulatta*) housed in an outdoor, multimale, multifemale SPF breeding colony at the California National Primate Research Center (Davis, CA) was found during routine, sedated (ketamine 10 mg/kg IM; Mylan Institutional, Rockford, IL) semiannual physical exam to have a slightly firm, irregular, central cranial abdominal mass (approximate dimensions, 9 × 5 cm) and a right inguinal hernia (4 × 4 × 3 cm). The macaque weighed 11.45 kg at presentation, which represented an approximate loss of 1 kg (approximately 8%) during the previous 6 mo, although he had an acceptable body condition score of 2.5 (maximum, 5).^{7,31} Body temperature, heart rate, and respiration rate were within normal limits; no other abnormalities were found on physical examination. The presurgical hematology, differential analysis, and blood smear evaluation all were within normal limits. At this time, the presumptive diagnosis was a gastric trichobezoar

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and a right-sided, nonreducible inguinal hernia. Exploratory laparotomy and right inguinal hernia repair were scheduled.

This colony-bred animal had no pertinent previous medical history except for routine management. The colony is SPF for *Macacine herpesvirus 1* (herpes B virus), SIV, simian retrovirus, simian T-cell leukemia virus, and tuberculosis. All animals in this enclosure were maintained according to the USDA Animal Welfare Act and Regulations^{1,2} and the *Guide for the Care and Use of Laboratory Animals*.¹⁴ The animal care and use program, including protocols for the maintenance and breeding of rhesus macaque colonies of the University of California, Davis, is approved by the University of California–Davis IACUC, fully accredited by AAALAC, USDA-registered, and maintains a Public Health Services Assurance.²³

Preoperatively, the macaque was fasted, sedated with ketamine (10 mg/kg IM), and maintained on isoflurane (1.5% to 2%; Piramal Critical Care, Bethlehem, PA). The abdomen was routinely surgically prepared. A skin and abdominal incision was made from the xiphoid process to the umbilicus. Exploration of the cranial abdominal cavity revealed a large (10 × 15 × 4 cm), multiloculated mass arising from the mesentery in close approximation to the greater curvature of the stomach (Figure 1 A). However, the mass was not in direct contact with the gastric serosa. Approximately 1/4 of the mass was composed of a moderately firm, white nodule adjacent to the greater curvature of the stomach. The remainder of the mass was composed of predominantly tan, soft, and gelatinous nodules with irregular dark-red and brown hemorrhagic regions and exuded viscous, mucinous material on sectioning (Figure 1 A and B). The mass was excised by using dissection and ligation (4-0 polyglycolic acid suture, Ethicon, Somerville, NJ). The greater curvature of the stomach was inspected for bleeding and post resection trauma. Minor serosal bruising was noted where the mesenteric vessels were ligated, but the perfusion and integrity of the stomach were adequate. The mass was placed in 10% buffered formalin and submitted for histopathologic analysis and further characterization. No additional masses or metastases were found on further exploration. The abdominal wall and skin were then closed in a standard continuous pattern by using polyglycolic acid suture (Ethicon). The right inguinal hernia was repaired by incising the skin over the right inguinal ring to expose the herniated sac, which was incised, and the herniated omentum inside the sac was removed. The right inguinal ring was reduced in size according to standard technique by using polypropylene (Prolene, Ethicon). The skin was then closed by using a standard continuous pattern of polyglycolic acid suture (Ethicon).

Postoperatively, the macaque received oxymorphone (0.15 mg/kg IM every 8 h for 3 d; Endo Pharmaceuticals, Chadds Ford, PA), ketoprofen (5 mg/kg IM daily for 3 d; Fort Dodge Animal Health, Fort Dodge, IA), and cefazolin (25 mg/kg IM every 12 h for 5 d; Steri-Pharma, Syracuse, NY). The animal was assessed daily for 7 d postoperatively for adequate analgesia and potential postoperative complications. Postoperatively, he was stable with a good appetite, good hydration, and normal stool. The incision healed well. The animal was discharged 10 d after surgery and returned to his outdoor enclosure.

Histopathologically, the mass was composed of poorly demarcated nodules and sheets of oval to stellate neoplastic cells embedded in a variably abundant loose mucinous stroma. The cells had round to oval nuclei with finely granular chromatin (Figure 1 C and D). The finely vacuolated amphophilic cytoplasm contained variable numbers of small lipid droplets which were highlighted by using oil red O (Figure 1 E). The mitotic index was less than 1 per 400× field. In addition, irregular regions of hemorrhage and necrosis were scattered throughout

the mass. On the basis of histology, the mass was determined to be a myxoid liposarcoma.

Approximately 11 mo after excision of the abdominal mass, the macaque presented for minor left leg trauma and severe abdominal distension that impeded thorough abdominal palpation. The animal was sedated with ketamine (10 mg/kg IM) and dexmedetomidine (11 µg/kg IM). His weight had increased to 13.4 kg although his body condition score had decreased to 2.0. His temperature and heart rate were within normal limits, but he was tachypneic, with a respiratory rate of 60 breaths per minute.

Abdominal radiography (Figure 2) revealed a complete loss of serosal detail within the abdomen. On the lateral view, few gas-filled intestines were visible. Displacement of intestinal loops cranial just under the shape of the liver created a large mass effect from cranial to midabdomen caudad.

Abdominal ultrasonography was difficult to interpret. A small amount of hypoechoic free fluid around the liver was present and suspected to be ascites. However, normal anatomic structures, such as kidneys, spleen, and intestine, were difficult to identify, because the borders of these organs were poorly defined, and the whole abdomen was of mixed echogenicity. An ultrasound-guided fine-needle aspirate of the presumed mass in the caudal abdomen was obtained and submitted for cytology. The cytologic results revealed a moderate number of RBC, with a moderate number of epithelial cells, and no evidence of inflammation; the sample was nondiagnostic.

Due to our suspicion of a large, invasive abdominal mass and given the previous history of abdominal liposarcoma, euthanasia followed by full necropsy and histopathologic examination was elected.

On gross necropsy, the abdomen was markedly distended and contained only a small amount of red, viscous fluid. The majority of the abdominal space was filled with a multilobular, pale, tan to red to brown, firm to soft, 3.98-kg mass that compressed the abdominal viscera and appeared to efface the omentum (Figure 3 A). The nodules varied in size from a few millimeters to 16 × 18 × 10 cm and multifocally adhered to most abdominal viscera. Small nodules were present within the tunics surrounding the testicles and multifocally penetrated through the diaphragm into the thoracic cavity. On further dissection, we found multiple adhesions of the mass to the liver capsule and large nodules between the liver and diaphragm with secondary compression of the right lateral liver lobe.

On histopathology, the abdominal masses were extremely variable in cell density and myxoid stromal content. Some areas (Figure 3 B) had abundant myxoid stroma and wide-spaced, well-differentiated spindle cells, similar to the original biopsy. Other regions (Figure 3 C and D) had scant myxoid stroma with densely packed spindle to polygonal cells, moderate anisocytosis and anisokaryosis, a high mitotic index (maximum, 15 per 400× field), and bizarre mitotic figures (Figure 3 D). In all regions, many of the neoplastic cells had distinct cytoplasmic vacuoles, confirmed to contain lipid according to positive staining with oil red O (data not shown). Histology also confirmed the presence of transperitoneal sarcomatosis, with adherent and invading myxoid liposarcoma nodules on various organs including the liver, spleen (Figure 3 E), gastrointestinal tract, testis, and abdominal wall.

The final diagnosis was myxoid liposarcoma of the greater omentum, with recurrence as transperitoneal sarcomatosis.

Discussion

There have been 3 reports of liposarcoma in NHP in the literature.^{8,9,17} The most recent report featured a female geriatric

Figure 1. (A) Surgical resection of mass. Large multinodular mass (asterisks) within the greater omentum closely associated with the greater curvature of the stomach (arrows). (B) Nodules within the mass are variably white, tan, and dark red (hemorrhage). Scale bar, 1 cm. (C through E) Histopathology of the myxoid liposarcoma biopsy. (C) The mass is sparsely cellular with abundant loose mucinous stroma. Hematoxylin and eosin; magnification, 200x. (D) The neoplastic cells are stellate and angular, with oval to round nuclei; mitotic figures are rare. Hematoxylin and eosin; magnification, 400x. (E) Clusters of lipid droplets within the neoplastic cells stain bright red. Oil red O; magnification, 400x.

Figure 2. Left lateral abdominal radiography shows a loss of serosal detail within the abdomen. Few gas-filled intestinal loops are displaced craniad, creating a large mass effect from cranial to midabdomen caudad.

bonnet macaque (*M. radiata*), in which a well-differentiated liposarcoma presented as an ulcerated, rapidly growing subcutaneous mass in the umbilical area. The mass was surgically

removed, and no recurrence was found 18 mo after excision.⁹ In 2007, a second case of liposarcoma was reported: a 5-y old female Japanese macaque (*M. fuscata*) was diagnosed with a round-cell variant of myxoid liposarcoma at necropsy. The authors suspected that the primary mass originated from the right retroperitoneum, and, at the time of necropsy, the tumor had spread to the abdominal cavity and omentum.¹⁷ The third previously reported case of liposarcoma was in a geriatric female potto (*Perodicticus potto*), a primitive NHP of the suborder Strepsirrhini. In that case, the liposarcoma was reported to be a myeloliposarcoma because, the mass originated from the medial aspect of the thigh and caudal abdomen. The mass was removed surgically, and no recurrence was noted 14 mo after resection.⁸ As we can appreciate from these different cases, the clinical behavior of liposarcoma in NHP varies from locally aggressive with no recurrence after excision in the case of well-differentiated liposarcoma to recurrence with severe spreading to adjacent structures and possible metastasis in the case of myxoid liposarcoma. In the human medical literature, the histologic classification and location of liposarcoma are predictive of the biologic behavior of the lesion and its prognosis. For example, in well-differentiated liposarcoma, prognosis is contingent on tumor location. Well-differentiated liposarcoma localized in

Figure 3. (A). Gross necropsy of the abdomen. The majority of the abdominal space was filled with a multilobular, mass that compressed the abdominal viscera. (B). Histopathology of the myxoid liposarcoma, well-differentiated area. Well-differentiated spindle cells are loosely arranged within abundant myxoid stroma. Hematoxylin and eosin; magnification, 200×. (C and D). Histopathology of the myxoid liposarcoma, poorly differentiated area. (C) Pleomorphic spindle to polygonal cells are closely packed within scant myxoid stroma. Hematoxylin and eosin; magnification, 200×. (D) Cellular and nuclear pleomorphism and numerous mitotic figures (arrow heads) are observed. Hematoxylin and eosin; magnification, 400×. (E) Histopathology of the spleen. Well-differentiated neoplastic cells are adhered to and multifocally invading the splenic capsule. Hematoxylin and eosin; magnification, 40×.

surgically accessible soft tissue in which wide-margin excision is performed has a mortality rate of 0%, whereas a tumor arising from the retroperitoneum can have local recurrence with a mortality rate up to 80%.¹³ In contrast, myxoid liposarcoma is inclined to reappear locally even when wide-margin excision is performed, and at least 1/3 of these masses metastasize, depending on histologic grade.¹³ Alternatively, a study of 56 cases of liposarcoma in dogs did not show a direct relationship between tumor behavior or prognosis and histologic classification.³ According to the NHP cases we reviewed, liposarcoma in NHP follows the behavior and prognosis found in the human literature.

On histologic examination, our differential diagnoses for the macaque we present included myxosarcoma and myxoid liposarcoma because the predominant pattern was a proliferation of spindle cells within abundant myxoid stroma. In accordance with the human histologic classification of liposarcoma, definitive diagnosis of this myxoid liposarcoma was achieved by noting the abundant myxoid stroma and the lipid droplets within the neoplastic cells, confirmed by oil red O staining.^{19,20} Although increased polymorphism and invasion are present in the recurrent tumor, the majority of the sections have a histologic appearance similar to the original biopsy (compare Figures 1 C and 3 B). The histologic variation of the stroma and mitotic index between the original and recurrent tumors—and even between nodules in the same tumor—is striking (compare Figure 3 B and C). This finding demonstrates that thorough and widespread sampling of these tumors is required to best predict clinical behavior.

Clinical differential diagnosis for a cranial central abdominal mass in NHP should include gastric foreign body, abscess, cyst, and neoplasia of the surrounding organs, including the liver, pancreas, and gastrointestinal system. Spontaneous abdominal neoplasia in nongeriatric, adult NHP is rare; most spontaneous neoplasms in NHP arise in the geriatric (older than 20 y) population, with adenocarcinoma of the large intestine being the most prevalent tumor.²⁹ A 2011 review of spontaneous neoplasia in captive rhesus macaques did not report liposarcoma.²⁹ In our case, a presumed diagnosis of a gastric foreign body (trichobezoar or phytobezoar) was reached in light of the location, texture, and size of the abdominal mass. In our colony, incidental palpation of a cranial abdominal mass with no associated clinical signs in a young adult animal is commonly associated with the presence of a trichobezoar. Because of the low incidence of spontaneous tumors in adult NHP and the high prevalence of trichobezoars and phytobezoars in our outdoor colony, no further diagnostics were performed before the exploratory laparotomy.

At the second presentation, the general appearance and clinical history of the animal was highly suggestive of a relapse of the primary neoplasia, because he had gained almost 2 kg but his body condition score decreased from 2.5 to 2.0 despite severe abdominal distension. At that time, several diagnostic modalities were performed and yielded equivocal diagnostic success. Abdominal radiography confirmed the presence of a large abdominal mass, but ultrasonography and cytology

were nondiagnostic. According to the literature, fine-needle aspiration and cytology can be used to diagnose liposarcoma. Cytologic findings compatible with liposarcoma included the presence of dense aggregates of mesenchymal cells containing variable numbers of lipid vacuoles with or without multinucleated cells; some authors even recommend staining with oil red O, which has been shown to be an economical diagnostic tool to confirm and differentiate canine liposarcoma from other soft tissue sarcomas.^{4,10,19,28}

Aggressive surgical mass excision with wide margins remains the most effective treatment for liposarcoma.^{3,6,10,15,18,21,22,25,30,32} Liposarcoma in the extremities can necessitate extensive surgical resection, depending on the invasiveness of the mass, but adequate margins usually can be obtained. However, abdominal liposarcoma resection with wide, clean margins can be surgically challenging.²² In our case, the close proximity of the mass to the stomach and its vascularization prevented wide-margin excision. In human medicine, some tertiary sarcoma centers promote the excision of bordering viscera or structures to prevent local recurrence.⁵ However, in our case, in view of the lack of definitive diagnosis of the primary mass at the time of surgery and the morbidity associated with partial gastric resection, we chose to conserve the vasculature and integrity of the stomach as much as possible. In addition, it is common practice in human medicine to perform several surgeries to remove recurrent liposarcoma,¹⁸ but this practice is associated with increased surgical risk because of the formation of adhesions, fibrosis, and other postoperative complications, including infection, effusion, and leakage from intestinal anastomoses.¹⁸ The utility of radiotherapy of well-differentiated liposarcoma is still debated, but myxoid liposarcomas are highly radiosensitive, and radiotherapy has been used for local control of tumors as well as to debulk tumors prior to surgery.²² In the case we present here, radiotherapy of the abdomen was not an option. It is important to note that, depending of the location of the mass, radiotherapy of the abdomen may cause toxicity to essential abdominal organs.²² Systemic standard chemotherapy effectiveness is still being evaluated, because different subtypes of liposarcoma have variable chemosensitivities.²²

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