Brief Report

Four Cases of Spontaneous Neoplasia in the Naked Mole-Rat (Heterocephalus glaber), A Putative Cancer-Resistant Species

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Received December 29, 2015; Accepted February 25, 2016

Decision Editor: Rafael de Cabo, PhD

Abstract

The naked mole-rat (Heterocephalus glaber) is widely acclaimed to be cancer-resistant and of considerable research interest based on a paucity of reports of neoplasia in this species. We have, however, encountered four spontaneous cases of neoplasia and one presumptive case of neoplasia through necropsy and biopsy of individuals in a zoo collection of nonhybrid naked mole-rats bred from a single pair. One case each of metastasizing hepatocellular carcinoma, nephroblastoma (Wilms’ tumor), and multicentric lymphosarcoma, as well as presumptive esophageal adenocarcinoma (Barrett’s esophagus-like) was identified postmortem among 37 nonautolyzed necropsy submissions of naked mole-rats over 1-year-old that were submitted for necropsy between 1998 and August 2015. One incidental case of cutaneous hemangioma was also identified antemortem by skin biopsy from one naked mole-rat examined for trauma.

Keywords: Barrett’s esophagus—Blastemal predominant—Cancer-resistance—Heterocephalus glaber—Naked mole-rat—Neoplasia—Nephroblastoma—Wilms’ tumor

The naked mole-rat (Heterocephalus glaber) is a unique rodent species with a long life span, often reaching over 30 years in captivity (1). There is great interest in research of this species for its eusocial behavior, its mechanisms of longevity, and particularly for its putative resistance to cancer. The claim that naked mole-rats (NMR) are resistant to cancer primarily stems from the research and series of publications by a single research group who have reported an absence of cancer in more than 2,000 NMR necropsies (2–4) and a resistance of NMR fibroblasts to carcinogenesis after transduction with the oncogenes SV40 and RasG12V (5). In support of the claim to cancer resistance, a number of possible mechanisms have been identified that may prevent replication of neoplastic cells in NMR (6–9). The interest in this putative cancer resistance has led to several reviews, a large amount of popular media coverage, and the NMR being named Vertebrate of the Year by Science Magazine in 2013 (1,10–12). The claim to cancer resistance was also initially supported by a retrospective study that examined necropsy findings from 138 adult NMR and found no cases of neoplasia (13).

However, the report did describe a case of renal tubular adenomatous hyperplasia, which in rats is considered to be a preneoplastic lesion, as well as a possible case of splenic lymphosarcoma, which was also reported as a preneoplastic change (13). Furthermore, this study was followed up with the first report of neoplasia in NMR, which described a subcutaneous adenocarcinoma and a gastric neuroendocrine carcinoma (carcinoid) from an NMR of different zoological collections (14).

Despite the paucity of reported cases of neoplasia in NMR, we have identified four spontaneous cases of neoplasia and one presumptive case of neoplasia through biopsy and routine necropsy of individuals in the exhibit collection at Disney’s Animal Kingdom. Metastatic hepatocellular carcinoma, nephroblastoma (Wilms’ tumor), and multicentric lymphosarcoma, as well as presumptive esophageal adenocarcinoma (Barrett’s esophagus-like) were diagnosed at the time of necropsy in a subset of 37 nonautolyzed NMR over 1-year-old from a total of 72 necropsy submissions between 1998 and August 2015. The remaining case of neoplasia—cutaneous...
hemangioma—was diagnosed antemortem through skin biopsy of 1 NMR from a collection of 57 individuals.

All NMR in the collection are zoo-born, nonhybrids acquired from Work As Play (Portal, Arizona) as adults in February 1998, or have since been born at Disney’s Animal Kingdom. The entire population is descended from a single breeding pair. Ages are known for individuals born into the collection; however, for individuals received from Work As Play, an age range was determined by the known number of years at Disney’s Animal Kingdom (the youngest possible age) and the year of first breeding in the colony at Work As...
Play (oldest possible age). NMR are maintained in a Hydro-stone display with a glass front in three separate colonies of 26, 27, and 4 individuals (57 total). Each chamber is illuminated by a fluorescent bulb that is on from 7:00 am to between 5:00 and 8:00 pm every day. The temperature within the exhibit is maintained between 80 and 85°F, and the humidity is maintained between 60% and 80%. Eco Earth Coconut Fiber Substrate (Zoo Med Laboratories Inc., San Luis Obispo, CA) is provided in all living spaces and is replaced approximately every other day. Daily food consists of sweet potato, red grapes, banana, apple, rodent pellets, corn, radish, carrot, kale, turnip, celery, shelled peanuts, and Mazuri Primate Growth & Repro Biscuit (Land O'Lakes Purina Feed LLC, Richmond, IN). Other foods provided 1–4 times a week include unshelled Walnuts, shelled sunflower seeds, green beans, mixed nuts, browse, and bell pepper. All necropsies and histopathological examination were performed by the veterinary pathology service at Disney’s Animal Kingdom. All histologically examined tissues were sectioned at 2–5 µm thickness and stained with hematoxylin and eosin.

Hepatocellular carcinoma with numerous metastases to the lungs and transcoelomic carcinomatosis within the peritoneal cavity was diagnosed in a 17- to 24-year-old female, which was euthanized due to cyanosis and severe dyspnea in conjunction with the presence of a large abdominal mass (Table 1). Grossly, the masses were round to multinodular and yellow, soft, and glistening (Figure 1A and B). Histologically, they were composed of well-differentiated neoplastic hepatocytes with moderate lipid accumulation. Binucleated cells were frequent, yet there was minimal nuclear atypia, and the mitotic index was <1 per 10,400× fields (Figure 1C and D).

Blastemal predominant nephroblastoma (Wilms’ tumor) was diagnosed in a 6- to 13-year-old male, which was euthanized due to the presence of a large, inoperable mass in the abdomen. Zoo staff noticed the mass; however, the NMR exhibited typical behavior and appetite (Table 1). Grossly, the right kidney was largely effaced by a 2 × 1.5 × 1.5 cm, ovoid, soft, tan mass. The mass was 20% of body weight (10 g in a 50-g NMR). Histologically, the mass was composed of poorly differentiated, closely packed and overlapping small blue cells, which formed large sheets occasionally lobulated by loose, paucicellular areas of spindle cells and which exhibited frequent perivascular palisading and occasional ribbons (Figure 2A–C). The neoplastic cells had scant cytoplasm and round nuclei with single prominent centrally located nucleoli. The mitotic index was 8 per 10,400× fields. Remnant renal cortex was severely compressed and atrophied with fibrosis.

Multicentric lymphosarcoma was diagnosed in the spleen, lymph nodes, lungs, kidneys, salivary glands, and intestinal tract of an 8- to 11-year-old male, which was euthanized due to declining quality of life with signs of weight loss, weakness, and ataxia (Table 1).
Grossly, the mandibular, sublumbar, and popliteal lymph nodes were visibly enlarged up to 3 mm in diameter, and ranged from mottled red and tan to diffusely dark gray. The spleen also appeared enlarged and weighed 1.4% of body weight (0.55 g in a 38.5-g NMR). The typical rat spleen is approximately 0.2% of body weight (15). There was loss of normal architecture in the salivary glands, lymph nodes, and spleen, as well as rare extension of large lymphocytes across the capsule of a lymph node (Figure 3A). Histologically, the neoplastic cells exhibited moderate anisocytosis and anisokaryosis. The nuclei were round, occasionally cloven, and infrequently reniform. The cells were occasionally binucleated, and the mitotic index was 9 per 10,400× fields (Figure 3B).

Cutaneous hemangioma was diagnosed antemortem by skin biopsy in a 14-year-old male. The lesion was an incidental finding during examination of trauma (Table 1). Grossly, the tumor was a firm, 2×1 mm, dark brown, oval discoloration of the left flank. Histologically, the lesion was composed of blood-filled, cavernous vascular channels in the dermis, which were lined by quiescent, spindle-shaped endothelial cells (Figure 3C and D). No mitotic figures were seen.

Presumptive esophageal adenocarcinoma was diagnosed in a 16- to 19-year-old male, which was euthanized for weight loss over several years and anorexia over several days leading to an extremely thin body condition combined with a progressive decrease in mobility (Table 1). Grossly, the distal esophagus was markedly thickened by a nodular expansion of the wall (Figure 4A). Histologically, there was circumferential metaplasia of the normally keratinized stratified squamous epithelium to a markedly dysplastic and tortuous columnar epithelium on lamina propria with numerous glands and cystic spaces (Figure 4B). Large portions of the mucosa were ulcerated with diphtheritic membranes and marked mixed inflammation (Figure 4C). The lesion was presumptively considered to be malignant based on suspicion of infiltration into the submucosa and prominent ulceration. The columnar epithelial cells were well differentiated and exhibited basal polarity of the nucleus and apical vesicular clearing of the cytoplasm. The mitotic index was 7 per 10,400× fields.

Nephroblastoma (Wilms’ tumor) is a malignant embryonal neoplasm of the kidney. In humans, it is the most common renal tumor in children and frequently presents in otherwise healthy children as an abdominal mass (16). It is also the second most common renal tumor in pigs, and although the tumors largely develop during fetal life, they are typically asymptomatic and are frequently found in older animals (17). It is worth noting that the male diagnosed with nephroblastoma was the youngest NMR in our study (6–13 years old). It is possible that the NMR nephroblastoma was present from early life, growing for a long time undetected.
Although one publication described a case of suspect lymphosarcoma in a NMR in which the spleen was enlarged (13), the authors conservatively opted to report this as a preneoplastic lesion. We, however, identified a similar cell population in the spleen, as well as multiple other organs with marked enlargement and loss of architecture and rare extension across the capsule of a lymph node, indicative of lymphosarcoma.

Concerning the presumptive esophageal adenocarcinoma, the lesion is similar to that seen in cases of Barrett’s esophagus (dysplastic metaplasia), which in humans is considered a preneoplastic lesion that frequently leads to esophageal adenocarcinoma (18). Although it is not clear whether development in the NMR progressed as reported in humans (19), the history of weight loss over several years is potentially consistent with a slowly progressing change in the esophagus. Moreover, no other lesions that would explain weight loss were identified at necropsy. Although the lesion exhibited high-grade dysplasia, it exhibited minimal tissue invasion, making definitive diagnosis of adenocarcinoma difficult. However, the lesion was extensively ulcerated, which in humans is thought to correlate strongly with malignancy (20,21). It is worth noting that besides surgical and transgenic mouse and rat models, Barrett’s esophagus has rarely been reported in nonhuman species, with a few reported cases in dogs and cats (22–24).

Despite the paucity of reports of cancer in NMR, we have identified neoplasms in approximately 8% (3/37) of necropsied nonautolyzed NMR over 1-year-old (including the presumptive esophageal adenocarcinoma), as well as in approximately 2% (1/57) of the living population by biopsy. Although this prevalence of neoplasia is still low in comparison to rat and mouse species (25–27), given that three of the NMR were euthanized due to severe clinical signs attributed to their neoplasms, cancer appears to be a notable cause of morbidity in this zoo collection.

Compared to previous reports of more than 2,000 NMR without a single case of neoplasia (4), it appears that the NMR population at Disney’s Animal Kingdom may be particularly prone to cancer. Where cancer has been reported, the number of NMR examined was not made clear, rendering comparison of prevalence difficult, yet the only two reported cases were from different zoos (14). Also, most previous publications on NMR pathology have provided little data on age or postmortem condition for necropsies, which further complicates comparison (2–4). Although one study limited case selection to nonautolyzed adults, age was not reported (13). Since the development of cancer is strongly correlated with age (28), it is possible that previous reports have examined too few NMR of advanced age. However, given that the age range of NMR with cancer in this study was 6 years old at the youngest and 24 years old at the oldest

Figure 4. Esophageal adenocarcinoma (presumptive). (A) Near the cardia, the esophagus is markedly widened by a mass. (B) The mass in A composed of tortuous and often cystic columnar epithelium with a lamina propria. (C) Multifocal ulceration of the mucosal epithelium with a diphtheritic membrane containing neutrophils.
(average 12–16 years old), it seems unlikely that there is a notable difference between previous studies and ours.

The NMR population at Disney's Animal Kingdom is entirely descended from a single mating pair. A founder effect and subsequent inbreeding may have led to frequent expression of recessive deleterious mutations. Notably all of the cancers we have seen originate from different organs and cell populations, which may be more suggestive of mutation, such as one affecting p53 or p16 function, which are associated with a wide variety of cancers (29,30), as opposed to environmental risk factors that are frequently associated with specific neoplasms (31). Interestingly, at least one reported mechanism of cancer resistance in NMR, high-molecular-mass hyaluronan, may not apply to the types of neoplasia herein reported (8). It is also worth noting that NMR, even in the wild, have been shown to exhibit a high level of inbreeding as a consequence of their unusual breeding behavior in which one female in the colony breeds with a small number of males—both breeding females and males are frequently recruited from within the colony (32,33).

Our discovery of a line of NMR that may be prone to cancer could be invaluable in further understanding cancer resistance and oncogenesis. Research is underway to identify mutations within the neoplasms and the population.

Acknowledgments

The authors would like to thank Dr. Joao Pedro de Magalhaes for encouragement and advice concerning publication of our findings, as well as Susan Feltman and Emily Mattrox for assistance in retrieving age data. All accession numbers, necropsy reports, and histological slides of naked mole-rats evaluated in this study are archived at Disney's Animal Kingdom. The authors declare no conflicts of interest, and no funding was provided for this retrospective study.

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