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A case of maxillary sarcoma in a chimpanzee (*Pan troglodytes*)

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Running Title

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ape, malignant neoplasm, aging, care

Abstract

Oral malignancy is rare in chimpanzees. A 34-year-old female chimpanzee (Pan troglodytes) at Kumamoto Sanctuary, Japan had had developed it. Treatment is technically difficult for chimpanzees while malignant neoplasm is seemingly rising in captive populations. Widespread expert discussion, guidelines for treatment, especially for great apes in terminal stages is urgently needed.

39

40 Case Report

41 Genetically chimpanzees are the closest living relatives of human. We were diverged almost 7 millions
42 years ago, and the changes in disease conditions could have occurred in conjunction with evolutionary
43 changes. As our life expectancies increased, the later-onset diseases such as malignant neoplasm,
44 arteriosclerotic diseases, and dementia have also increased, thus, becoming a serious issue. These diseases
45 are dependent on the lifestyle and aging; they could be referred to as age-dependent diseases.

46 In contrast, very little is known about the nature of age-dependent diseases in chimpanzees. The
47 question remains whether the age-dependent diseases are exclusively human, or simply undiagnosed in
48 chimpanzees. For example, malignancy is extremely rare in chimpanzees [4]. Previous studies have shown
49 only few examples of such diseases in chimpanzees [2, 5].

50 This is the first report of oral sarcoma in a chimpanzee. The case occurred in an estimated 34-year-old
51 wild born female. She was utilized in hepatitis C virus (HCV) infection research at another facility
52 between 1979 and 1987. Persistent HCV infection was observed without other specific notations.

53 The subject's right cheek had started swelling in February 2011. We suspected bacterial infection of the
54 dental root. Antibiotics were administered; however, no improvement was observed (Figure 1). Blood
55 analysis showed slight increases in white-blood-cell, C-reactive protein, and γ-glutamyl
56 transpeptidase levels and decrease in albumin level. No other noteworthy observations were made. Her
57 weight was 43 kg.

Figure 2 shows histopathological image of the lesion. Abnormal undifferentiated cells including spindle cells and adipose-like cells proliferated papillary or focally. Increased N/C ratio and multiple images of mitosis showed this tumor was highly malignant. By immunohistological stain, vimantin was positive, cytokeratine was partially slightly positive. On X-ray examination maxilla invasion was identified, however, no pulmonary metastasis could be observed. Cervical lymph nodes were not swollen.

The common treatment for sarcoma in humans is mainly surgical resection with radiation or chemotherapy. In this case, because extensive resection was required, the reconstruction of the oral cavity must be considered. Surgical resection and radiation could not be options due to technical difficulties. Chemotherapy was avoided as the side effects were thought to be too severe in proportion to the potential results. It was also difficult to give her injection due to risking anesthesia on a daily basis. A conservative palliative treatment was chosen instead during the remaining progression of the disease.

The tumor reached the end of hard palate, began to construct the pharynx. However, food intake was still achieved by altering the texture of food. A timetable was created incorporating contact time with other chimpanzees, with staffs, and time spent alone. Gradually, the time spent being recumbent increased, however, she would still rise to interact with staff. Breathing difficulty appeared except when lying on her right side. On August 15, she had eventually attempted to roll over and reached with her arms and legs out to staff. She died at 9:30 am on August 17. Euthanasia was debated during the course, but was not performed because she was still able to ingest food and did not appear to be in great distress.

When she died her weight was 26 kg. Pathological autopsy showed that the tumor had already invaded

her maxilla. The mass had protruded into the oral cavity, and it was largely necrotic and ulcerated but the tumor had not yet progressed into the orbital cavity. Despite the tumor extended almost to cover the entire palate it did not reach the pharynx. The mandible and cervical lymph nodes were largely swollen and the right cervical lymph nodes entwined the carotid artery. Multiple metastatic lesions were identified in lymph nodes of the pulmonary hilum and of posterior mediastinum, in lungs, and in diaphragm. The right lung showed poor aeration with the lower lung atelectasis. No pleural effusion was observed. No intraperitoneal spread was detected.

Pathological diagnosis: (1) maxillary sarcoma with multiple metastases, (2) respiratory failure due to metastases.

There are very few reports of malignant tumors in chimpanzees. Till recently, a number of hypotheses have been raised, including claims that malignant tumors are simply remain undiagnosed [5] or that because apoptosis suppression difference between human and chimpanzees, there is a known relationship between suppression of apoptosis and increased risk of the onset of malignancy [3][12]. Recent studies also have shown multiple genetic differences associated with malignancies [1, 8, 14, 15]. From these findings, it is now understood that currently, there are very few identified genetic predispositions for malignant neoplasm in chimpanzees.

The ratio that of chimpanzees actually reaches an advanced age is low [9]. Although the frequency of occurrence of malignancy because of gene restoration anomalies increases with aging, the frequency of malignancy remains low in chimpanzees due to the shorter lifespan. This can be a possible explanation for

96 the minimal number of age-related diseases that are observed in chimpanzees.

97 The case subject had persistent HCV infection. In humans, oral squamous-cell carcinoma is considered
98 as a complication of HCV infection [7, 10, 11, 13]. Chimpanzees with a history of being utilized in
99 hepatitis research are numerous in Japan and in several countries, including USA. Although cases of
100 hepatic carcinoma have been reported, thus far there have been no reports of oral malignancy.

101 As outlined above, the possibility is that HCV infection is partially responsible for the oral sarcoma.
102 Since the subject was not young, the potential for gene restoration mistakes to occur at a higher rate along
103 with advancement in age must also be taken into consideration.

104 Noteworthy, that the subject was able to ingest food orally till the end; further, pain did not seem to
105 appear. The subject was able to live out the remainder of her life in relative comfort during the terminal
106 phase of the disease due to devoted staff until her very last day. The actual treatment of a chimpanzee
107 during the terminal phase of disease may be decided on a case-to-case basis. The number of aging
108 chimpanzees in captivity is increasing, and so we have to consider the need for terminal care cases will
109 also increase. Therefore, we think the necessity for a widespread discussion, regarding these issues is
110 inevitable among other chimpanzee holding facilities.

111

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Figure 1

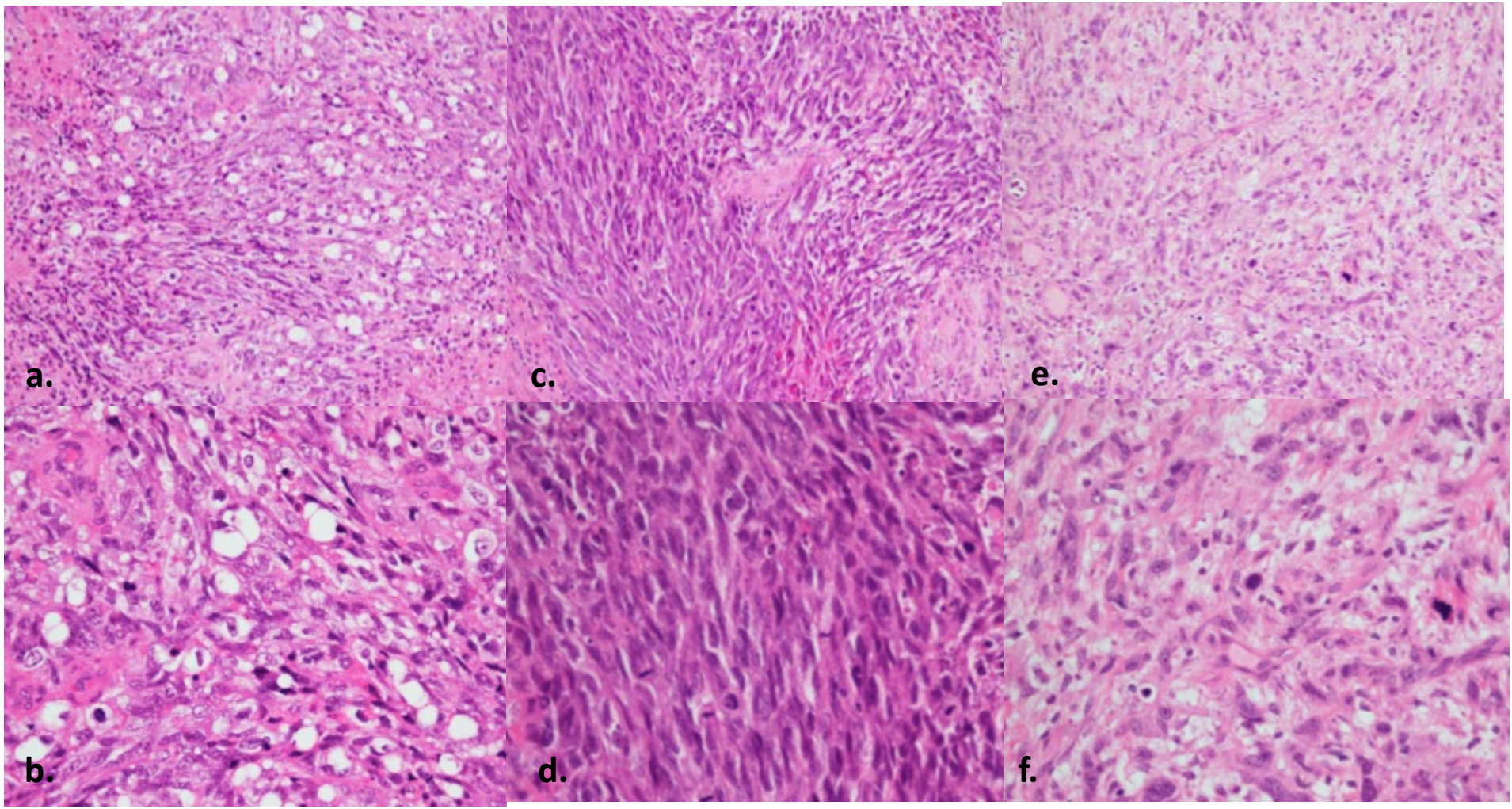

Figure 2