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SERIES OF CLINICAL CASES AND MANAGEMENT OF HISTOPATHOLOGICALLY DIAGNOSIS OF SQUAMOUS CELL CARCINOMA IN AFRICAN PYGMY HEDGEHOGS (*Atelerix albiventris*)

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SUMMARY

Squamous cell carcinoma (SCC) is frequently seen as an invasive cutaneous tumour that can be fatal in animals. In this case series, the clinical management of histopathologically diagnosis of SCC in three different individuals of African pygmy hedgehogs is described. In two of the cases presented, the tumours were presented as an oral mass on the gingiva, which were ulcerative and septic. Lumpectomy was performed in both cases and histopathology revealed encapsulated mass composed of neoplastic cells showing squamous differentiation arranged in islands with presence of keratin pearls, intercellular bridges and frequent mitotic figures which are typical features of squamous cell carcinoma. Following lumpectomy, the two hedgehogs were discharged but were later found to developed ocular lesion and anorexia before they were found dead. In the third case, SCC was diagnosed on the phalanges of the 3rd and 4th digits and surgical resection was successfully performed in this case and post-surgical complications were not recorded. Squamous cell carcinoma is one of the most common malignant tumours in African pygmy hedgehogs. In this case series, three cases of SCC were diagnosed using histopathology which two of the cases had predilections in the oral cavity while the third one only involved the digits.

Keywords: African pygmy hedgehog, squamous cell carcinoma, histopathology, management, lumpectomy

INTRODUCTION

The African pygmy hedgehog (*Atelerix albiventris*) is within the order Eulipotyphla and family of Erinaceidae (Cassola, 2016). They are one of the two most common species of pet hedgehogs, the other being the European hedgehog (*Erinaceus europaeus*). African pygmy hedgehog or also known as the central African hedgehog is popularly known as the four-toed hedgehog, the only species of hedgehog with four toes while others have five. This species is native to the savannah and steppe regions of central Africa (Ivey and Carpenter, 2012). They are solitary, nocturnal and very active animals. In captivity, a base diet of commercially available hedgehog diet, reduced calorie cat or dog diet supplemented with small amounts of mixed fruits, vegetables and live insects (Heatley, 2009). Common health problems in hedgehogs include dental disease (periodontitis, gingivitis), urinary disease (urolithiasis, cystitis and pyometra), dermatological diseases (mite infestation, skin abscess) and neoplasia (mammary gland tumour, lymphoma, oral squamous cell carcinoma).

Squamous cell carcinomas (SCC) are malignant tumours of the epidermis in which cells demonstrate differentiation to squamous cells (Hauck, 2015). These tumours are often locally aggressive, invading adjacent tissues. Some tumours contain more differentiated cells, keratin, often in whorls (keratin pearls) and visible desmosomes (intercellular bridges) while others induce a scirrhous, a hard slow-growing malignant tumour having a preponderance of fibrous tissue response (Gelberg, 2012). Oral SCC is the third most common neoplasia in the hedgehogs (Heatley *et al.*, 2005) resulting from a malignant epithelial tumour originating from the oral cavity involving different degrees of squamous cell differentiation with a tendency for early and extensive lymph node metastases. In hedgehogs, SCC has been reported to occur in the oral cavity, skin and oronasal cavity (Rivera and Janovitz, 1992; Couture *et al.*, 2015; Spugnini *et al.*, 2018). In this case series, three different cases of histopathologically diagnosis of SCC in African pygmy hedgehogs are discussed mainly in medical and surgical management.

CASE PRESENTATION

Case 1

A 2 year-old female African pygmy hedgehog weighing 260 gram was an indoor pet managed with wood shaving bedding and fed with dry cat kibble. The owner noticed a growth on her mandible but was not

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certain for how long the mass had been there. The owner also noticed that the hedgehog was eating the wood shavings. The hedgehog was brought to University Veterinary Hospital (UVH), Universiti Putra Malaysia (UPM) for further examination. Upon physical examination, it had a soft mass on the left ventral mandible of approximately 2 cm x 2 cm in diameter (Figure 1A). The left mandibular gingiva was swollen, ulcerated and had purulent discharge. Tooth root abscess and oral neoplasia were the differential diagnoses made upon the clinical examination. Fine needle aspiration was performed from the mandible penetrating the skin towards the mass to collect samples for cytological examination. Cytological analysis revealed numerous intact bacteria and neutrophils, with degenerated neutrophils including phagocytised bacteria. Based on this, tooth root abscess was firstly diagnosed and treated with oral flushing twice daily using a diluted (1:10) chlorhexidine gluconate as an antiseptic mouth wash after every meal. Oral anti-microbial, enrofloxacin (5 mg/kg), twice a day for 7 days and non-steroidal anti-inflammatory, meloxicam (0.2 mg/kg), IM once a day for 5 days was also administered. The owner visited a week after with the hedgehog and felt concerned about the progressive oral mass and weight loss. Physical examination revealed a 30 gram drop in body weight within a week. Reassessment findings revealed, the mass was approximately 4 cm x 3.5 cm in size with purulent discharge. Oral tumour was ruled-in since the condition did not resolved with the initial treatment and indicated with an aggressive progression. Radiograph of the skull revealed no evidence of bone lysis at the cranium and mandible. Hence, lumpectomy was performed and the mass was assessed histopathologically.

For the anaesthetic protocol, the hedgehog was induced with 5% isoflurane using a standard dog-size facemask as an induction chamber. Prior to induction, animal is pre-oxygenated to extend the safe apnoea time due to the irritant nature of the gas that may cause the patient to hold its breath (Longley, 2008). Anaesthetic plane was assessed based on loss of jaw tone, loss of limb tone, loss of corneal and pedal reflex as well as 15-30% drop in respiratory rate and heart rate. A modified 20 ml syringe was attached to her snout acting as a facemask and 1-3% isoflurane was flowed through the syringe as maintenance.

The histopathology results revealed effacement by proliferative epidermoid, pleomorphic cells arranged in islands separated by abundant stroma containing large number of fibroblast and collagen, while keratin pearls and mitotic figures were observed (Figure 2A). The cellular changes observed through the histopathological evidence demonstrates the characteristics of squamous cell carcinoma. The purulent aspirate collected during the surgical resection was tested for bacterial isolation and identification yielded no colony growth. On day 10 post-operative, the patient got anorexic and had to be gavaged with intensive care soft diet (Prescription diet a/d®). On day 24 post-operative, ocular lesion typified by a cloudy ulcerated cornea was observed. The animal was found dead on day 31 post-operative, however post-mortem was not performed as wanted by the owner.

Case 2

A female adult hedgehog with a body weight of 230 gram and body condition score of 2 out 5 was presented to the UVH with a complaint of progressive swelling on the face for a past 4 weeks. Three days before presentation, antibiotic and nonsteroidal anti-inflammatory were prescribed by a private veterinary clinic, however no information was able to retrieve from the client on the prescribed medication. Upon physical examination, the animal was bright, alert and responsive with moderate congestion of mucous membrane. There was marked swelling and ulcerated mass on the right lower gingival region with tooth rot and detachment of the right lower premolar (Figure 1B). At this point, oral mass was highly suspected based on the nature of the mass and non-responsive to the initial treatment. Lumpectomy is decided by taking into consideration of the owner cost constraint and delayed action could provide times for further growth and potential metastasis.

A 2 cm diameter mass was excised and the mass was fixed in 10% formalin for histopathology analysis. Histopathological examination indicate proliferation of squamous cells that were arranged in islands with prominent intercellular bridges and occasional mitotic figures seen in the absence of keratin pearls. Furthermore, there were evidence of ulceration at the epidermis layer with intense infiltration of inflammatory cells which highly suggestive of bacterial infection (Figure 2B-2C). The histopathological diagnosis was poorly differentiated squamous cell carcinoma with secondary bacterial infection. Post-operatively the hedgehog was treated with oral anti-microbial, clindamycin (25 mg/kg), BID for 10 days and non-steroidal anti-inflammatory, meloxicam (0.5 mg/kg), SID for 7 days. The hedgehog was discharged and the appetite improved but a month later the animal became anorexic for three days and died subsequently.

Case 3

The hedgehog was a 3 ½ years old female, weighing 500 gram managed indoor and fed with cat kibbles and mealworms. The patient was presented with a non-healing ulcerative mass on the right hind limb since one month ago. Physical examination revealed an ulcerative wound on the right hind limb 3rd and 4th digits (Figure 1C) and crusty lesions observed on both ear pinna. Incisional biopsy was performed and the mass was histopathologically evaluated. The histopathology examination revealed evidence of infiltrative neoplastic epidermal cells into the dermis with presence of keratin pearls and mitotic figures (Figure 2D). The loss of architectural structure of the epithelia as well as absence of normal tissue further supports the diagnosis of SCC. Surgical resection of the mass on the 3rd and 4th digits was performed with 1 cm from the tumour margin under inhalational anaesthesia. The hedgehog was induced with 5% isoflurane and was maintained with 2% isoflurane vaporised in 100% oxygen. Post-operatively, the hedgehog was treated with meloxicam (0.2 mg/kg) SID for 5 days and clavulanic acid-amoxicillin drops (15



Figure 1. (A) Firm, soft growth at the left ventral mandible about 3.5 cm x 4 cm (circle). (B) Showing ulcerative mass at the right lower gingival margin measuring 2 cm x 2 cm (arrow). (C) Non-healing ulcerative wound of the right hind limb with third and fourth digit has been amputated previously.

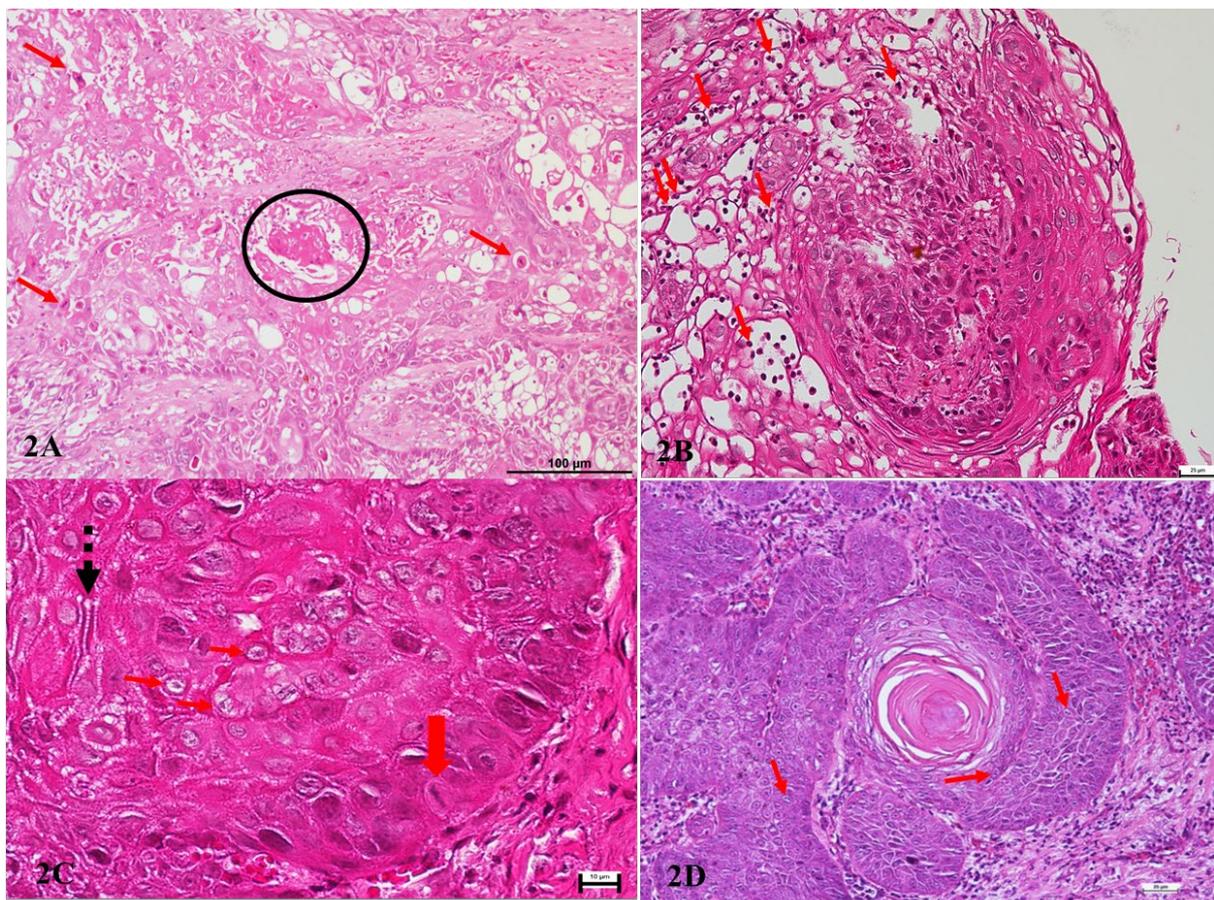


Figure 2. (A) Histopathological changes of mass resection showing keratin pearl that is not well formed (circle) and frequent mitotic figure (small arrows). (B) Showing proliferative cutaneous squamous cells arranged in islands and whorls can be observed at the centre. There is also intense infiltration of inflammatory cells typified by neutrophils indicative of secondary bacterial infection (small arrows). (C) Prominent intercellular bridges (round-dot arrow) and occasional mitotic figures (wide arrow) albeit no obvious keratin pearls were noted, keratinization of single cells were observed (small arrows). (D) Evidence of invasiveness of epidermis cell into the dermis with presence of keratin pearls (centre) and mitotic figures (small arrows).

mg/kg) BID. The patient returned for wound cleaning 5 days post-discharged and the prognosis of the case was good with expecting a delayed wound healing due to poor blood circulation to the distal end of the digit.

DISCUSSIONS

Neoplasia is responsible for higher death rates in African pygmy hedgehogs (Hsieh *et al.*, 2015). An earlier study on hedgehogs at necropsy showed prevalence rates of neoplasia ranging from 29% to 51.5%, out of it 85% were malignant neoplasia (Raymond and Garner, 2001; Heatley *et al.*, 2005). A more recent study showed that the three most common histologic tumour types are mammary gland adenocarcinoma (20%), lymphosarcoma (17%) and oral squamous cell carcinoma (14%) (Hsieh *et al.*, 2015). These tumours typically occur in geriatric animals that are older than 2 years old (Heatley, 2009). These are in agreement with the cases reported where all the hedgehogs presented were 2 years old and above.

It has been suggested that the high occurrence of neoplasia in captive hedgehogs is due to genetic disorders (Mayer and Donnelly, 2015). This may be due to the extensive inbreeding practice among captive African pygmy hedgehogs as exotic pets resulting in the accumulation of oncogenic homozygous genetic mutations (Ujvari *et al.*, 2018). The oral, oro-nasal and cutaneous sites are the most common predilection sites for SCC in hedgehogs (Couture *et al.*, 2015; Spugnini *et al.*, 2018). In this report, two of the animals had SCC in the oral cavity while one had a cutaneous form on the limb that invaded into the digits. A diet of inappropriate consistency causes periodontitis and gingivitis which may be the initial stage to SCC in the oral cavity. The chronic irritation and inflammation may stimulate the proliferation of previously initiated cancer cells, by increasing mutation rates and altering proliferation signals (Rakoff-Nahoum, 2006; Ujvari *et al.*, 2018). This coincides with the findings of this report where both cases of SCC in the oral cavity had underlying suppurative inflammatory condition of tooth rot abscess and gingivitis.

There is limited information available in exotic animals on treatment of neoplasia beyond individual case reports (Zehnder *et al.*, 2018). Treatment of SCC is primarily surgical whenever feasible through wide resection surgical excision for long term control (Hauck, 2015). However, surgical resection should be supplemented with adjuvant therapy such as chemotherapy or radiotherapy if incomplete resection is suspected. In this report, lumpectomy performed in the two cases of oral SCC was not successful in the long term as the animals died most likely due to metastasis. However, the third case of resection on the limb was successful. This is supported with a previous case where surgical resection of SCC done 1 cm to the tumour margin showed no recurrence near the surgical site until 3 months later (Couture *et al.*, 2015). Some of this case, hedgehogs had mass development to the eye and anorexia that causes poor quality of life. In a report by Aguila *et al.* (2019), 29% of SCC in hedgehogs had the mass causing unilateral exophthalmia, and 11% cases had the mass

grew cranial to the ocular globe causing endophthalmia. Anorexia is believed to be the direct effect of mass in the oral cavity that alleviate pain.

Currently, there are no approved cancer chemotherapeutic agents for use in exotic animals except for a few experimental cases (Kent, 2004). In a previous report, bleomycin, subcutaneously administered at 20 U/m² weekly in a ferret with SCC led to a decrease in tumour size without signs of toxicity (Hamilton and Morrison, 1991). However, substantial tumour growth was observed 64 days post treatment commencement and the ferret was euthanized. In this report there was no tumour specific chemotherapeutic intervention administered to the patients post surgically, except for routine antibiotics and non-steroidal anti-inflammatory.

The use of electro-chemotherapy in a hedgehog with SCC where bleomycin was injected intra-tumour and electric pulses were placed on the tumour, however, the animal remained in partial remission for five months until the tumour progressed (Spugnini *et al.*, 2018). Electro-chemotherapy consists of applying short high-intensity pulsed electric fields to cells, in response to which, the plasma membrane's permeability to numerous molecules transiently increases, resulting in facilitation of cellular uptake of cytotoxic agents, thus increasing their cytotoxicity (Miklavčič *et al.*, 2014). The treatment relies on the phenomenon termed electroporation, which occurs when externally delivered electric field induces a sufficiently large transmembrane voltage. Radiotherapy can also be used as adjuvant therapy after lumpectomy or used when surgical removal is not possible. External beam radiotherapy done successfully in a ferret with SCC showed no recrudescence of tumour after 3 months (Graham *et al.*, 2006).

CONCLUSION

In this case series, three cases of SCC were diagnosed using histopathology. Two of the cases had predilection in the oral cavity while the third one involved the digits. Surgical resection was successful in the third case but presented with poor prognosis in two other cases where this could have been attributed to metastasis of the tumour. Hence, wide surgical resection as was done in the third case is recommended in order to prevent squamous cell carcinoma recrudescence.

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