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Effect of vincristine on oral cavity carcinoma in rhesus monkey *(macaca mulatta)*

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Abstract

An adult male rhesus monkey (*Macaca mulatta*) presented a malocclusion of teeth/ jaw with slight swelling in the upper mandible in particular on right upper canine with diffused growth in the lower incisor and was showing progressive loss in the weight of the animal. Histopathology of the biopsied tissue confirmed the lesion as Squamous Cell Carcinoma (SCC). The animal was treated with Vincristine sulphate for three consecutive days two weeks apart. During and after treatment, there was gradual reduction in the growth with some changes in hematological parameters and weight. Squamous cell carcinoma is one of the most common oral neoplasia in many species including macaques. Treatment with Vincristine sulphate has a good response to prolong the life of the animal.

Key words: Macaque, Squamous cell carcinoma, Vincristine

Abbreviations: WBC: White Blood Cells, LYM : Lymphocyte Percentage, GRA: Granulocyte Percentage, RBC: Red Blood Cells, MCV : Mean Corpuscular Volume, Hct: Hematocrit , MCH: Mean Corpuscular Hemoglobin, Hb: Hemoglobin

Introduction

Squamous cell carcinomas (SCC) are one of the most commonly reported oral cavity tumors. They are characterized as firm, nodular to irregular, soft-tissue masses that are often ulcerated (Ettinger and Feldman, 2004). These tumors are frequently and highly invasive to local bone and muscle and occasionally metastasize to local and regional lymph nodes (Ettinger and Feldman, 2004). In general, neoplastic conditions are rare in nonhuman primates, however SCC and lymphoma are the most commonly reported oral cavity neoplasms in these species (Bennett et al., 1998). SCC has most commonly been reported in rhesus macaques (*Macaca mulatta*) and baboons (Papio spp.). Among, nonhuman primate species, SCC has occurred in the oral cavity integument, esophagus, stomach, lung, prepuce–penis, cervix, uterus, and eye (Haddad et al., 2009). These neoplasms have also been reported to occur in cynomolgus macaques, marmosets, squirrel monkeys, tree shrews, capuchins, tamarins, black spider monkeys, sooty mangabeys, a spectacled langur, and orangutan (Haddad et al., 2009). The oral cavity is the most common site of SCC in nonhuman primates, and metastasis occurs in approximately 23% of cases (Haddad et al., 2009). The average age at diagnosis of oral SCC in rhesus macaques is 17.6 years (Simmons and Mattison, 2011). In baboons, SCC is the third most common neoplasm, after intestinal adenocarcinoma and lymphosarcoma (Cianciolo and Hubbard, 2005). The following case report describes an oral cavity SCC in rhesus monkey and their treatment effects.

Case Presentation

One of the adult Rhesus monkey was noticed with low body weight, weak body condition and malocclusion of jaws and teeth. The animal had a jaw deformity since birth, otherwise apparently the animal was normal. The animal was salivating very often, and saliva was observed running around the mandibles. On cage side examination, the macaque was active, alert, responsive, with normal stools, urine and showing normal food habits. The salivation continued for many years without any growth or any abnormality. The animal was regularly screened for tuberculosis, Herpes, and Hepatitis B virus and was tested negative for these diseases.

At the age of 19 year, the animal was noticed with a progressive growth in upper mandible in gums especially at around right upper canine. There was also a diffused growth on lower canine region. It appears as if it has originated from buccal serous and mucus layers and had extended in between the incisors and molar teeth to make the teeth embedded in the growth. This was making increasing gap between the teeth. Within two to three months, the growth was very progressive and proliferative. Finally, it was planned for a biopsy of the proliferative tissue. The macaque was anesthetized with ketamine hydrochloride 10mg/kg b.w. by i.m. route and a small tissue was collected from the upper mandible. A radiography examination and blood samples were collected for further investigations.

On histopathology examination, we could observe nests of neoplastic squamous epithelial cells arising from the epidermis and then invading into the dermis. The neoplastic cells were well differentiated and had eosinophilic cytoplasm with vesicular nucleus. There was also variation in size, shape of the cells along with variation in cytoplasm to nucleus ratio of the neoplastic cells. The mitotic figures distribution was seen in more number near the invasive dermal region. Also, angiogenesis was observed near dermal invasion region. There was also invasion of neoplastic epithelial cells in the blood vessels. The above histopathological results confirmed the growth as Grade-1 Squamous cell carcinoma (Figure 3).

Considering the pathological findings, radiology, gross appearance and health of this monkey, we planned to go for a chemotherapy treatment. The monkey was injected with three doses of Vincristine sulphate (0.4 ml of Vincristine mixed with 4.5 ml of normal saline and given intravenously) two weeks apart. The animal was supplemented with liver tonic and B-complex injections three days i/m and orally, with additional soft food supplements daily. Routine blood samples were taken every month to check hematology parameters and daily careful observation was done for any abnormal changes in food habit or any physiological changes. The monkey was little dull after every dose for two to three days and appetite was also reduced. Later, the appetite was improved and no further progression in the growth was seen. The ulcerations and proliferative lesions improved gradually (Figure 1). Reduction in RBC, Hemoglobin, Hematocrit parameters was observed during the treatment period but recovered gradually afterwards. There was no significant change in other blood parameters (Figure 2).

SCC has been reported in other macaque species and in particular tongue, gingiva, esophagus, gastric cardia, eye, lungs, penis, mammary areas, and cervix. However, the oral cavity is the most common site in macaques (Kaspareit et al., 2007). The shape of SCC oral can be flat and can be proliferative. These lesions also vary from well-differentiated cells that include whorls of keratin (keratin pearls) and desmosomes (intercellular bridges) to undifferentiated cells with high mitotic activity (McGavin and Zachary, 2007). The average age of affected nonhuman primates is 11.9 ± 1.2 years as reported earlier (Kaspareit et al., 2007). Metastasis occurs in approximately 23% of all cases in nonhuman primates (Kaspareit et al., 2007) but in this case, there was no metastasis apparently. Surgery is the treatment of choice for most of the squamous cell carcinomas in animals. However, surgical excision of SCC in baboons and common marmosets resulted in survival less than 7 month after diagnosis (Haddad et al., 2009; McIntosh et al., 1985). Other treatment modalities include treatment with chemotherapeutic agent and photodynamic therapy. Cisplatin is the best chemotherapeutic agent for nasal squamous cell carcinoma treatment (Slatter, 2003). In the present case, we administered Vincristine sulphate. A variety of single or combination protocols have been employed (cyclophosphamide, vinblastine, methotrexate and prednisolone) for the SCC treatment, but none has demonstrated superiority to intravenous chemotherapy with vincristine alone (Murchison, 2008). Weekly intravenous administration of Vincristine is presently the most effective and practical chemotherapy however, the side effects of Vincristine therapy includes occurrence of local tissue lesions due to extravasation of the drug during intravenous injections, resulting in the development of necrotic lesions with crusts in non-tumorous tissue. Considering the above, Vincristine was adopted and it has potentially reduced the tumor and soft tissue swelling with improvement in clinical signs. Hence, Vincristine sulphate at the earlier stage of treatment could extend the life of the macaques with oral squamous cell carcinoma.

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Figure 1 : Gross pathology of the oral cavity lesions before, during and after treatment. X-ray shows growth on the mandibular region.

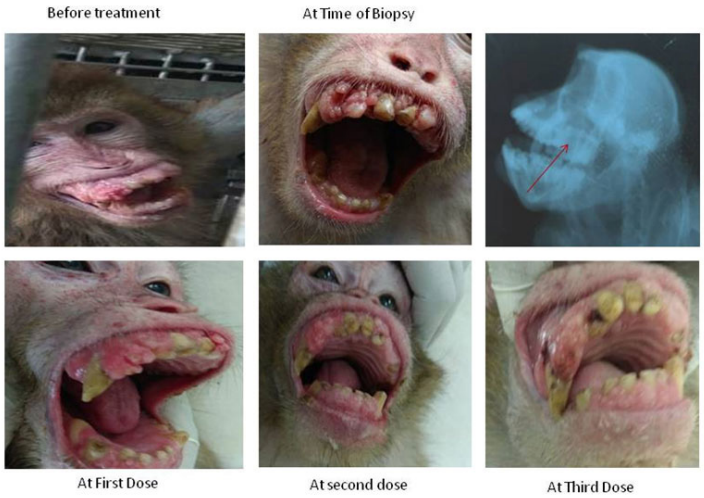

Figure 2 : Hematological changes before, during and after the treatment. There was marked reduction in Hemoglobin and RBC and Hemotocrit during Vincristine treatment.

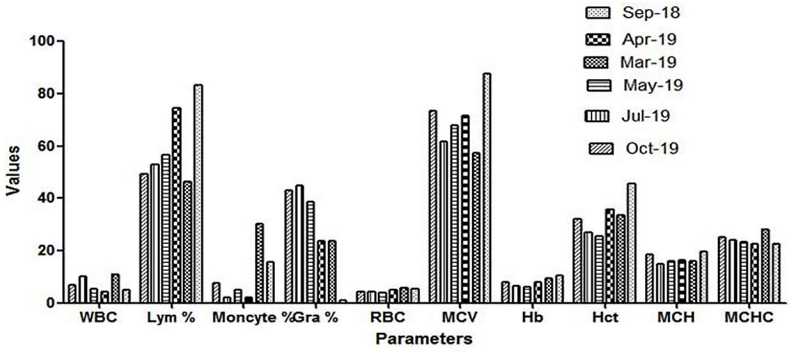

Figure 3 : Grade-1 well differentiated invasive Squamous cell carcinoma.

Nests of neoplastic squamous epithelial cells arising from the epidermis and invading into the dermis [red arrow]. Neoplastic cells are well differentiated [Grade 1], eosinophilic cytoplasm and vesicular nucleus. Variation in size, shape of the cells along with variation in cytoplasm to nucleus ratio of neoplastic cells. Distribution of mitotic figures were seen in more number near the invasive dermal region [green arrow]. Also, angiogenesis was observed near dermal invasion region [black arrow]. Also we have observed the invasion of neoplastic epithelial cells in the blood vessels.