

Use of topical colchicine to treat squamous cell carcinoma in a Little Corella

KA Fryer BSc, BVSc, MANZCVS
Cannon & Ball Veterinary Surgeons Ltd,
461 Crown St,
West Wollongong, NSW 2500
kafn6539@gmail.com



A 53 year old male Little Corella (*Cacatua sanguinea*) was presented with an infected open wound overlying the pectoral muscles. The bird had a long history (more than 25 years) of intermittent feather picking and poor diet. At the time of presentation the bird was wearing a neck brace to prevent self-mutilation. It was in reasonable body condition, weighing 435g, but feather quality was poor. A wound with purulent discharge was present overlying the keel. The bird was anaesthetised with Isoflurane, the wound debrided and an attempt made to close the wound. An area of abnormal skin was identified near the wound during this process. Biopsy samples were taken from the wound margin and of the abnormal skin. These were submitted for histopathology and a diagnosis of squamous cell carcinoma subsequently made.

Two weeks later the original wound was reviewed and a triangular area of abnormal tissue 33mm at the base and 32mm high was identified. Treatment options were discussed as follows:

1. Surgery to remove the remaining squamous cell carcinoma. As these are usually slow growing neoplasms that rarely metastasise, it was hoped that a cure might be achieved if the abnormal tissue was removed. Due to the size of the lesion, the skin deficit would be too large for primary closure and would require management as an open wound.
2. Strontium 90 radiation has been used for squamous cell carcinomas with limited reports as to its efficacy or side effects (Nemetz and Broome, 2004). This was available at a referral centre 1.5 hours north of our clinic. The owner lived 2.5 hours south of our clinic and felt this would be too far to drive.
3. Cisplatin and carboplatin have both been used for various neoplasms in birds. Although research into the safety of these two products has been published, little data exists as to their effectiveness in treatment of squamous cell carcinomas (Filippich et al., 2000, 2004, 2005). They are more likely to be effective where the mitotic index is high. Neither of these products had been previously used in our clinic, and we were not

equipped to handle such chemotherapeutics. The best options for administration of either of these chemotherapeutics would be referral. As for Strontium 90, the owner declined this option.

Surgery was performed a week later to remove as much of the remaining abnormal tissue as possible. In one small area this appeared to extend into the underlying pectoral muscle. This was removed with a narrow margin. The wound was closed as much as possible leaving a 3cm diameter deficit, which was managed as an open wound.

Histopathology confirmed that the squamous cell carcinoma was now penetrating into the underlying muscle.

The deficit was covered with Kendall AMD® foam dressing (a 0.5% polyhexamethylene biguanide HCl-impregnated foam manufactured by Covidien) sutured to the surrounding skin for the first 24 hours. This was replaced with adhesive hydrocolloid dressings (Comfeel® plus transparent ulcer dressing manufactured by Coloplast) that were changed every five days. Although these dressings seemed to be aiding in contracture and epithelialisation of the wound, the neoplastic areas in the pectoral muscle appeared to be growing rapidly, so after three weeks they were replaced with Atrauman® (a fine paraffin dressing manufactured by Hartmann) and Ag Atrauman® (silver sulfadiazine impregnated fine paraffin dressing manufactured by Hartmann).

During the five weeks of wound healing the owner and the author continued to research alternative options for treatment. The owner wanted to consider treatments that could be managed at home, and since she had difficulty administering medication orally, topical options were favoured.

Topical products such as Imiquimod and Fluorouracil were ruled out as options to treat any remaining neoplasm due to toxicity concerns when applying to muscle. No studies could be found on the use of Fluorouracil in birds.

References to the use of colchicine topically for treatment of actinic keratosis in humans lead us to look into this option further (Akar et al., 2001; Russo, 2005). Actinic kera-

tosis is considered by many to be a form of squamous cell carcinoma *in situ* (Feldman and Fleischer, 2011). Trials with 0.5% and 1% topical colchicine have been successful in treating or slowing down the development of actinic keratosis in 73-77% of human patients treated (Akar et al., 2001).

The effects of Colchicine on mitosis, through binding to tubulin within the cell and interfering with microtubule dynamics, have been known for over 40 years. The primary use of this compound in human medicine is in the treatment of gout. The anti-cancer properties have not been utilised due to potential toxicity. However oral colchicine is used in birds for treatment of liver fibrosis and gout. It was proposed that we might be able to slow down the progression of the neoplasm using colchicine topically. We did not expect to achieve a cure.

As colchicine ointment was not available we applied 0.04mg/ml colchicine in pluronic gel to the affected area twice daily for 10 days. To allow for the possibility that

colchicine might be absorbed systemically the volume applied was calculated to allow no more than 0.04mg / kg delivered daily - the oral dose commonly used by me (VIN, 2015).

The first 10 days of treatment was performed in clinic to allow assessment of response and ensure accurate application. Each day the residual gel was cleaned away with chlorhexidine wash before the new application was made. The wound area was measured using calipers before treatment began and again daily. Photographs were taken at regular intervals. Biopsies were taken on day 10 to assess effect on mitotic index.

At presentation for the treatment trial to start a caseous plaque covered the neoplastic area. The bird had been on intermittent (due to owner compliance) Amoxicillin - clavulanic acid oral drops and meloxicam (0.5 mg/kg PO SID) to control infection and pain respectively. This caseous tissue was removed prior to first application.



Day 1 - before debriding

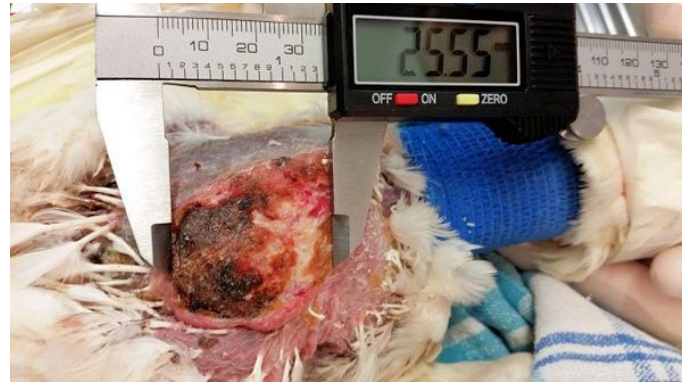


Day 1 - debrided and gel applied - 31.99mm x 24.93mm



Day 3 = 31.35mm x 29.95mm

On day 3 a dark necrotic crust was evident. This was consistent with that seen in human trials with actinic keratosis (Akar et al., 2001).



Day 5 = 25.55mm x 21.42mm



Day 9 = 33.46mm x 22.06mm



Day 10 after debriding

Results of histopathology performed on day 10 reported a mitotic index of 9 (mitotic index on the initial histopathology was 30). Histopathology also showed colonisation of the necrotic areas with pleomorphic bacteria.

From day 10 the bird was discharged and the owner continued treatment. Revisits to the clinic occurred every 5-7 days. The bird was started on amoxicillin-clavulanic acid oral drops (125 mg/kg) in response to the histopathology results. At the first revisit, six days after discharge, a swab was taken for culture and sensitivity. Results indicated an *E.coli* infection. To facilitate administration of antibiotics a pluronic gel containing both 0.04mg/ml of colchicine and 24mg/ml metronidazole was formulated.

Two weeks after discharge the area of visibly abnormal tissue was spreading anteriorly. A biopsy was taken to determine whether this was neoplastic spread or inflammation as a result of the treatment. Histopathology confirmed spread of the neoplasm with a mitotic index of 20. One week later the owner advised that she had been

missing treatments as she felt application was causing irritation to the bird. The bird was euthanased 44 days after Colchicine treatment began, 112 days after initial diagnosis.

Discussion

Squamous cell carcinoma is a potential cause of apparent self-trauma in birds. Although it is unlikely that the squamous cell carcinoma was present for the 20 year duration of feather plucking in this bird it is possible that the chronic inflammation caused by this habitual behaviour may have contributed to development of this neoplasm. Earlier detection may have allowed for a more successful surgical outcome.

Treatment trials with colchicine ointment in humans have been performed on actinic keratosis - a more superficial and less aggressive form of squamous cell carcinoma. In the trial referenced, treatment was applied for 10 days, with an unspecified number of patients re-

ceiving a second application for 10 days. Follow up was performed at 10 days, 1, 2 and 6 months and a significant reduction in the number and size of lesions was reported (Akar et al., 2001).

We used this treatment on a more advanced and aggressive stage of squamous cell carcinoma. We knew we may not achieve a result, but as the owner had declined all other options it was agreed we had nothing to lose. The first 10 days of treatment appeared promising, with an apparent decrease in mitotic index. We interpreted this as a slowing down of the rate of growth of the neoplasm. This interpretation was based on the understanding that mitotic index is an indicator of the potential malignancy of a neoplasm (De Vico et al., 1994; Maiolino et al., 1995).

Ongoing improvement may have been affected by the following factors:

- Treatment resulted in necrotic crusting of the external surface of the wound. This crust may have affected further penetration of the colchicine into the underlying neoplasm. Although it was debrided occasionally, it might have been done more often. There was no way to determine how well the colchicine was absorbed.
- Secondary infection occurred possibly as a result of environmental contamination. Although fitted with a neck brace to prevent feather plucking, this bird had learnt to rub its chest on the furnishings in the cage. Although the wound was bandaged it was difficult to maintain this bandage while applying medication to a bird that was not amenable to handling by strangers
- Infection was poorly controlled with oral antibiotics, possibly due to a combination of owner compliance difficulties and continued contamination of an open wound.
- In the third 10-day period metronidazole was added to the colchicine pluronon. This may have had an effect on absorption or activity of the colchicine.
- It is possible that apparent improvement in the initial phase was despite treatment.
- The human study that provided our reference point for trialing this treatment was aimed at reviewing the effects of two different concentrations of colchicine ointment. It showed that 0.5% colchicine was more effective than 1%. In order to attempt to reduce the risk of toxicity colchicine was applied a much lower concentration.

Routine laboratory tests such as CBC and biochemistry were not performed before or after treatment. No post-mortem was performed to assess the effect of either the neoplasm or treatment on other organs.

This trial involved only one bird and if it were to be considered a scientifically consistent trial there were many errors in its planning and conduction. Our primary aim here however was to provide the owner with an opportunity to “do something”. The bird and owner had been constant companions for over 40 years. It was important to us not only to trial a treatment that may be useful in the future but to recognise and support the human animal bond in doing so.

The treatment may have some merits in earlier phases of the disease. If we had discovered it earlier, perhaps topical colchicine would have been more useful as an alternative to surgery rather than an adjunct.

In the human field, research continues into the use of colchicine and its analogues as chemotherapeutic agents, with studies published as recently as 2014 (Larocque et al., 2014). The main limiting factor appears to be colchicine’s inherent toxicity and a lack of selectivity in the type of cells it targets.

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