Review Article

A review of equine mucocutaneous squamous cell carcinoma

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Summary

Squamous cell carcinoma (SCC) accounts for approximately 20% of all equine mucocutaneous (MC) tumours and continues to present a therapeutic challenge to practitioners. Most MC-SCC are locally invasive and slow to metastasise, but metastasis to local lymph nodes is not uncommon. The most common location for MC-SCC is the periorbital region, with the eyelid most commonly affected. Although only 13% of MC-SCC involves the external genitalia, MC-SCC is the most common neoplasm of male genitalia. Equine caballus papillomavirus-2 has recently been linked to MC-SCC and may prove to be necessary for tumour development. Risk factors may include chronic exposure to ultraviolet light and chronic skin irritation. Horses developing genital MC-SCC tend to be older compared to those with periorbital MC-SCC. Histopathology is required for definitive diagnosis of MC-SCC, although horse phenotype and lesion location may suggest MC-SCC. Several treatment modalities have been successful in eliminating or managing MC-SCC, with surgical excision and intratumoural chemotherapy yielding the best results. Other treatment options including cryotherapy, hyperthermia, radiotherapy and photodynamic therapy are often used as adjunctive therapies. Early recognition of tumours and prompt intervention are associated with a positive outcome.

Introduction

Mucocutaneous squamous cell carcinoma (MC-SCC) is the second most common skin tumour of the horse (Valentine 2006; Theon *et al*. 2007), as well as the second most common equine tumour overall (Sundberg *et al*. 1977). Chronic high ultraviolet light challenge is considered a significant aetiological factor in squamous cell transformation and subsequent tumour development (Pazzi *et al*. 1996; Teifke and Lohr 1996). The nature of MC-SCC varies widely and ranges from slow growing, benign tumours to rapidly growing, highly malignant and invasive tumours. MC-SCC is locally invasive and typically slow to metastasise to local lymph nodes, but the frequency of metastasis for MC-SCC is reported to be as high as 19% (Lavach and Severin 1977; King *et al*. 1991; van den Top *et al*. 2008a). Delayed local metastasis without recurrence of primary tumour has been reported following treatment (Elce *et al*. 2011). Early MC-SCC lesions are often small superficial nodules that may be covered with normal skin. As the epidermal layers are disrupted by the developing tumour, ulceration and malodorous necrosis may be observed. The superficial aspects of these proliferative tumours may become traumatised and infected with opportunistic pathogens. In contrast to slow growing, locally invasive MC tumours, penile forms in younger horses (age <8 years) tend to be aggressive and commonly metastasise to regional lymph nodes. Similarly, gastric SCC is highly malignant with a 68% rate of metastasis and a median survival time of 4 weeks from onset of clinical signs (Taylor *et al*. 2009).

Clinical description

The most common location of MC-SCC is the periorbital (ocular and adnexal) region, which constitutes up to 72% of all equine MC-SCC cases (Theon *et al*. 2007) (**Fig 1**). The most prevalent periorbital tumour location is the eyelid, followed by the third eyelid, cornea, limbus (corneo-scleral junction), conjunctiva and orbit (Cotchin 1977; Lavach and Severin 1977; Junge *et al*. 1984; Dugan *et al*. 1991; King *et al*. 1991; Mosunic *et al*. 2004) (**Fig 2**). Tumour location may also include the genitalia (13%), face and ear pinnae (5%) (**Fig 3**), perianal region (5%) and extremities (3%) (Theon *et al*. 2007). An increased prevalence of periorbital MC-SCC is reported in Paint Horses, Quarter Horses, Appaloosas and draught horses (Schwink 1987; King *et al*. 1991; Mosunic *et al*. 2004; Valentine 2006), while penile/preputial MC-SCC is most common in Quarter Horses and Appaloosas (Valentine 2006). Although the overall prevalence is low, the most common neoplasm of the male genitalia is MC-SCC (Brinsko 1998; van den Top *et al*. 2008a), and is thought to result, in part, from chronic keratosis due to chronic irritation (such as that afforded by smegma), although this is controversial (Plaut and Kohn-Speyer 1947; Van Howe and Hodges 2006). The incidence of equine MC-SCC in the male external genitalia has been reported to be higher than that associated with the female external genitalia (Valentine 2006). The mean age of horses with periorbital MC-SCC is 13 years (Mosunic *et al*. 2004; Valentine 2006), while older horses tend to develop genital MC-SCC (mean age 20 years) (Valentine 2006; van den Top *et al*. 2008b).

Aetiology

Although risk factors such as chronic ultraviolet radiation exposure and chronic keratosis probably contribute to equine MC-SCC development, a novel equine papillomavirus, termed equine caballus papillomavirus-2 (EcPV-2) has been recently identified as a likely aetiological agent for the development of equine MC-SCC (Scase 2007; Vanderstraeten *et al*. 2011). EcPV2 DNA was detected in 100% of ocular and genital MC-SCC lesions and genital papillomas, and ~50% each of ocular, penile and vulvovaginal swabs from healthy horses (Vanderstraeten *et al*. 2011). This suggests that EcPV2 infection is necessary but not sufficient to induce tumoural transformation, which is consistent with bovine papillomavirus infection in equine sarcoids and human papillomavirus (HPV)

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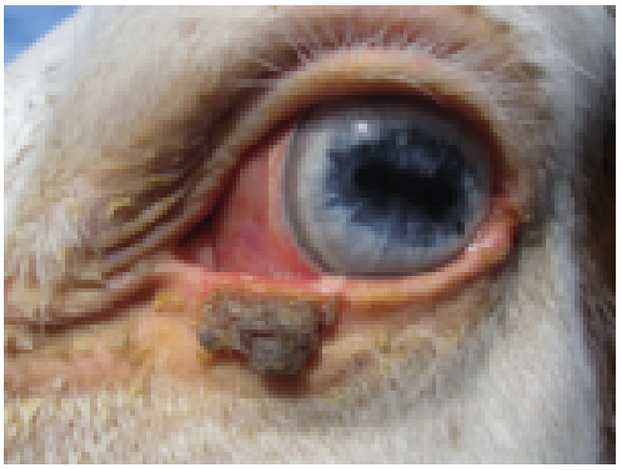

Fig 1: Periorbital mucocutaneous squamous cell carcinoma in a 28-year-old Paint mare.

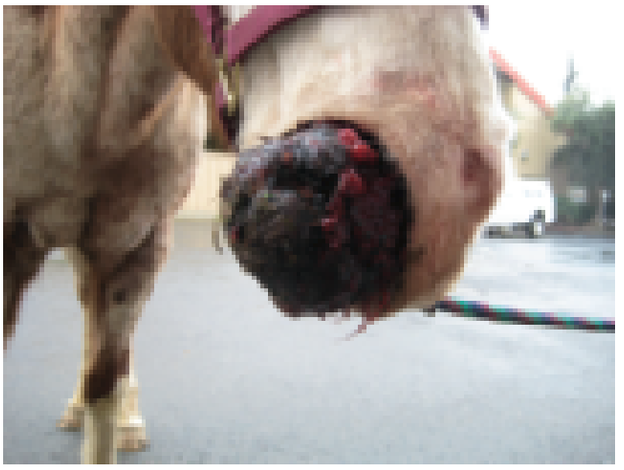

Fig 3: Squamous cell carcinoma of nasal mucocutaneous junction in a 26-year-old Appaloosa gelding.

Fig 2: Third eyelid mucocutaneous squamous cell carcinoma in a 21-year-old Thoroughbred gelding.

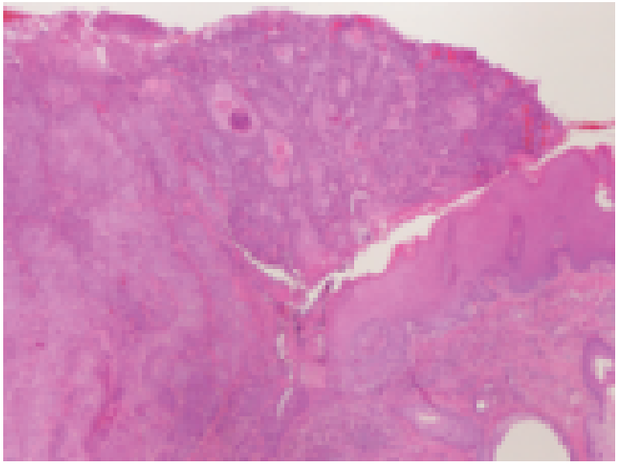

Fig 4: Haematoxylin and eosin stained photomicrograph of mucocutaneous squamous cell carcinoma characterised by disorganised nests and trabeculae of squamous epithelial cells proliferating from the surface and invading the underlying dermis. Note the normal stratified squamous epithelium on the right side of the image (100× magnification).

infection in cervical and anogenital cancer (Carr *et al*. 2001; Bogaert *et al*. 2007). Furthermore, identification of EcPV2 DNA in healthy equine tissue indicates the existence of latent infection that will not progress to clinical lesions in most horses, which is comparable to that in man where the majority of the population undergoes subclinical HPV infection without progression to clinical disease (Koutsky *et al*. 1988).

Diagnosis

Differential diagnoses for equine MC-SCC include equine sarcoid, papilloma (especially of the genitalia and third eyelid), mast cell tumour, exuberant granulation tissue, habronemiasis, phycomycosis, cutaneous lymphoma and melanoma. Definitive diagnosis requires submission of affected skin/mucosa for histopathological examination in the form of a biopsy, although radiography and computed tomography may help differentiate paranasal sinus SCC from sinusitis (Kowalczyk *et al*. 2011). If possible, a biopsy should include both the neoplastic tissue and its interface with normal appearing skin (**Fig 4**). Local lymph nodes should be assessed clinically (including iliac lymph nodes, which can be palpated *per rectum*) and if lymph node involvement is suspected, fine needle aspirates and/or biopsies should be performed when possible to assess metastasis. Secondary spread to regional lymph nodes may support a poor prognosis and may influence the decision to initiate treatment.

In man, several variations of SCC grading have been described (Chaux *et al*. 2009; Sobin *et al*. 2010). Equine MC-SCC have been evaluated and grouped by differentiation grade, following histopathological characteristics used in human medicine (Chaux *et al*. 2009). This criteria defines G1 (*grade 1*) lesions as well-differentiated tumours, with neoplastic cells nearly identical to normal or hyperplastic squamous cells. In contrast, G3 (*grade 3*) lesions are considered poorly differentiated with anaplastic squamous cells that contain high nuclear : cytoplasmic ratio, numerous mitotic figures, clumped chromatin and prominent nucleoli. *Grade 2* (G2) tumours

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describe moderately differentiated squamous cells and do not fit into criteria described for either G1 or G3 lesions. In a recent study, 81 equine MC-SCC were grouped by differentiation grade based on histopathology; metastasis was confirmed in 44% of tumours graded as G3, compared to 25% for G2 and only 3% for G1. Eighty percent of the G3 tumours had an unsuccessful outcome (i.e. tumour recurrence or euthanasia; van den Top *et al*. 2011). Taken together, these data suggest that the G1–G3 grading scale may be beneficial in characterising equine MC-SCC and predicting outcome in affected horses.

Treatment

Several modalities have been recommended for treatment of equine MC-SCC; these are most successful when treatment is initiated early in the course of disease. Surgical management, cryotherapy, hyperthermia, radiotherapy, chemotherapy and photodynamic therapy are used with degrees of success relative to the accessibility and invasiveness of the tumour.

Conventional excision

Surgical excision is typically performed on tumours in which a satisfactory surgical margin of 0.5–1.0 cm can be achieved; however, higher rates of recurrence have been reported with excision of ocular MC-SCC without concomitant use of adjunctive therapy (King *et al*. 1991; Mosunic *et al*. 2004). Therefore, adjunctive treatments are often used following surgical debulking of MC-SCC. Depending on size and location of male genital MC-SCC, surgical techniques may include local excision, segmental posthioplasty ('reefing'), partial phallectomy, and *en bloc* penile and preputial resection with penile retroversion (Scott 1976; Markel *et al*. 1988; Doles *et al*. 2001; Archer and Edwards 2004). Use of CO_2 laser for surgical management of MC-SCC resulted in complete resection without recurrence in 78% of cases (McCauley *et al*. 2002), suggesting a viable method for MC-SCC removal. When MC-SCC metastasis to regional lymph nodes is detected, those nodes should also be excised.

Cryotherapy

Cryotherapy has been used successfully in the management of MC-SCC, often after surgical debulking (Joyce 1976; Hilbert *et al*. 1977; Harling *et al*. 1983). This involves application of liquid nitrogen at -196°C (by spray or probe) to lyse tumour cells through intracellular ice formation. The best results are often for treatment of early or precancerous MC-SCC, especially on the penis and prepuce (Bosch and Klein 2005; Stick 2006).

Hyperthermia

Hyperthermia has been used as an adjunctive therapy following surgical debulking for equine MC-SCC (Grier *et al*. 1980; King *et al*. 1991; Moore 1992). In one study, 8 horses with ocular MC-SCC were treated with hyperthermia, half of which had been treated previously with surgery, cryotherapy, radiotherapy or immunotherapy; 75% of these tumours regressed and, of the 25% that required additional hyperthermia, 66% regressed (Grier *et al*. 1980).

Radiotherapy

Radiotherapy uses ionising radiation to kill tumour cells by damaging nucleic acids and protein through free radical formation. Two forms of radiotherapy include teletherapy and brachytherapy. Teletherapy is high energy x-ray or γ-ray radiation that is applied 80–100 cm from the tumour by a linear accelerator or cobalt-60 unit and thus requires multiple treatments under general anaesthesia. Teletherapy is used for advanced tumours that cannot be completely excised and, although it is often used palliatively, it has been curative for periorbital MC-SCC in ~50% of cases (Theon 1998). With respect to brachytherapy, success rates for treatment of periorbital MC-SCC using iridium-192 were 82% at one year post treatment and 64% at 5 years (Theon and Pascoe 1995). Strontium-90 is β radiation and is directly applied with a probe to the neoplastic tissue. Because the radiation only penetrates ~2 mm, strontium-90 should only be used for superficial lesions. In one study, 83% of limbus, cornea or third eyelid MC-SCC were successfully treated with strontium-90 radiation when combined with superficial keratectomy and permanent bulbar conjunctival grafts (Plummer *et al*. 2007). Periorbital MC-SCC treated with several adjunctive forms of radiation therapy had a significantly lower recurrence rate (12%) than those treated without adjunctive radiation therapy (44%; Mosunic *et al*. 2004), supporting its use as an effective treatment modality. To summarise, brachytherapy is often used as an adjunctive therapy following surgical debulking of MC-SCC but may also be used alone for small lesions that cannot be completely excised. Complications include loss of hair pigment, permanent epilation, palpebral fibrosis, and cataract and corneal ulceration (Theon and Pascoe 1995; Theon 1998). Some cutaneous tumours suitable for brachytherapy are also good candidates for intratumoural chemotherapy, and the choice between the 2 modalities is based on tumour type, size, degree of invasiveness, predicted cosmetic and functional outcome, access to a radiation therapy facility, and cost.

Chemotherapy

Intralesional and topical chemotherapy have been used with some success for equine MC-SCC. Intratumoural cisplatin, 5-fluorouracil (5-FU), mitomycin-C and bleomycin have been used to treat equine MC-SCC. Cisplatin (cis-diammine dichloroplatinum) inhibits DNA synthesis by binding to DNA. Two different approaches allow controlled-release administration: intralesional injection of a viscous fluid and implantation of biodegradable beads. The first method involves reconstitution of cisplatin powder with sterile water at a concentration of 10 mg/ml, followed by mixing with sesame seed oil (60%) and sorbitan monooleate (7%) by use of the pumping method (Theon *et al*. 1997). This results in 3.3 mg cisplatin/ml, and the dosage is 1 mg cisplatin/cm^3 of tissue. The treatment recommendation includes 4 intratumoural injections given at 2-week intervals (Theon *et al*. 2007) and is often initiated immediately following surgery (Theon *et al*. 1993, 1999, 2007). Cisplatin beads are typically implanted through stab incisions at 1.5 cm intervals in the tumour bed and surrounding skin. It is recommended that tumours >1.5 cm be debulked prior to implantation, while tumours <1.5 cm be treated with bead implantation alone (Hewes and Sullins 2006). Intratumoural cisplatin, in the injectable or bead formulation, yields similar success rates for the treatment of MC-SCC (Hewes and Sullins 2006; Theon *et al*. 2007). In horses with MC-SCC that were treated with cisplatin injections, one study reported a relapse-free rate of 65% (Theon *et al*. 1993), while a second study reported an 88% success rate (Theon *et al*. 2007). Similarly, approximately 85% of horses with MC-SCC treated with

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perioperative or post operative cisplatin injections were tumour-free after 4 years (Theon *et al*. 1999). For horses that were treated with cisplatin beads, 60% of animals with MC-SCC were cured after 2 years (Hewes and Sullins 2006). In general, 3 applications of cisplatin beads at one month intervals are recommended for treatment of MC-SCC (Hewes and Sullins 2009). These data suggest that both forms of cisplatin are effective adjunctive therapies for treatment of MC-SCC, with most treatments performed after surgical debulking. Overall, cisplatin success rates are slightly lower for treatment of MC-SCC compared to equine sarcoid.

Five-fluorouracil is available as a topical cream and as a sterile, injectable solution. It is an anti-metabolite drug that promotes DNA mutation during cell replication, which results in cell death. It is an alternative to other chemotherapy drugs that does not require special preparation or equipment to deliver, and is relatively inexpensive. Treatment recommendations vary from daily application for 10–14 days, to twice monthly application for up to 8 months (Fortier and MacHarg 1994). A success rate of 90% was found in horses with MC-SCC of the external genitalia that received combination therapy in the form of surgical excision and 5-FU application (Fortier and MacHarg 1994). In a small study of horses with early MC-SCC of the external genitalia, 2 of 3 horses remained tumour-free after a single course of topical treatment while one was controlled by application of 5-FU for 7 days every 6 weeks (Paterson 1997). In addition, intralesional injection of 5-FU has been successful in markedly reducing the size of periorbital MC-SCC that could not be resected (Pucket and Gilmour 2011). Because 5-FU is most effective in active, replicating tumour tissue, debulking or laser surgery is typically recommended before use for larger neoplasms.

Mitomycin-C is an antimicrobial that has antitumour properties, and has been used as an adjunctive therapy immediately following CO_2 laser treatment of equine ocular MC-SCC (Rayner and Van Zyl 2006). In this study, mitomycin-C-soaked sponges were applied to the lasered area for 1–5 min during anaesthesia. Of 10 affected eyes, 7 remained free of tumour up to 17 months post treatment, while 3 required additional treatment, resulting in an overall success rate of 70% (Rayner and Van Zyl 2006). Similarly, clinical resolution of ocular MC-SCC occurred in 75% of treated eyes with mitomycin-C administration alone (Malalana *et al*. 2010).

Bleomycin is an effective anticancer agent for MC-SCC, but when compared to cisplatin for intratumoural treatment of eyelid MC-SCC, cisplatin was found to be a better choice based on therapeutic benefit and treatment cost (Theon *et al*. 1997).

Although unproven as an efficacious treatment modality, oral administration of piroxicam has been used as adjunctive treatment for MC-SCC and may be useful in preventing recurrence. This anti-inflammatory drug is thought to exert chemotherapeutic effects by inhibiting tumour cell growth (Moore *et al*. 2003; Elce *et al*. 2007; Smith *et al*. 2008).

Photodynamic therapy

Photodynamic therapy involves a photosensitiser drug (porphyrin compound) that, upon activation by light, reacts with tissue to produce free radicals and cause irreversible oxidation of critical cellular components (Giuliano *et al*. 2007). Photosensitisers are preferentially absorbed by proliferating tissue, which allows for selective uptake by tumour cells that are then destroyed when light is delivered to a highly specific area. Local photodynamic therapy for the treatment of equine periorbital MC-SCC has shown promising results in a small number of horses. Surgical resection followed by one-time, local photodynamic therapy was curative for at least 2 years post treatment in 7 of 9 horses (Giuliano *et al*. 2008). More research is needed before photodynamic therapy can be compared with other treatment modalities for management of equine MC-SCC.

Conclusion

In summary, there are several treatment options available for MC-SCC, and the choice depends highly on tumour location, size, invasiveness and cost. Unfortunately, comparison of studies is difficult due to varying definitions of a successful outcome and differing follow-up time to recurrence. However, general conclusions may be drawn. Topical application of 5-FU is the treatment of choice for superficial skin tumours or precancerous lesions that are confined to the epidermis. Small but more invasive tumours may be cured with radiotherapy or intratumoural cisplatin, but larger tumours require surgical management and adjunctive therapy with cryotherapy, hyperthermia, radiotherapy or cisplatin. Similar to other forms of neoplasia, early recognition of MC-SCC and subsequent intervention results in a more favourable prognosis.

Authors' declaration of interests

No conflicts of interest have been declared.

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