Case Report

Delayed metastasis of ocular squamous cell carcinoma following treatment in five horses

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Summary

Identification of regional and/or distant metastasis following treatment and local resolution of primary ocular squamous cell carcinoma (SCC) was observed in 5 horses. In all cases, identification of metastasis occurred at least 18 months following treatment of the primary ocular lesions. In 3 cases, invasion of blood or lymphatic vessels by neoplastic cells was identified in the excisional biopsies of the primary tumour. Two horses developed SCC at 2 or more separate sites. At the time metastases were identified, there was no evidence of local recurrence of the ocular tumour in any of the horses. These cases confirm the importance of long-term monitoring of horses for metastatic disease following treatment of ocular SCC even in the absence of local recurrence.

Introduction

Squamous cell carcinoma (SCC) is a common neoplasm with malignant characteristics including anaplasia, local invasion and metastatic potential (Thomas et al. 2008). Squamous cell carcinoma is generally locally invasive and slow to metastasise (Giuliano 2010) and local recurrence is more commonly reported than metastasis. In the horse, SCC is reported to be the most common neoplasm of the eye and ocular adnexa and the second most commonly diagnosed tumour overall (Strauss 1976; Lavach and Severin 1977; Sundberg et al. 1977; Junge et al. 1984; Giuliano 2010). Equine ocular and periorcular SCC is typically invasive, resulting in discomfort and blindness if untreated (Fischer et al. 2002). The tumour may affect one or more of the cornea; bulbar or palpebral conjunctiva; limbus; third eyelid and eyelids. Treatment generally involves surgical excision of the affected area or laser ablation, with or without adjunctive treatments such as chemotherapy, irradiation, cryotherapy, immunotherapy or photodynamic therapy (Giuliano 2010).

A better prognosis (with lower recurrence rates) has been reported for SCC originating at the third eyelid, nasal canthus or limbus compared to the eyelids (Dugan et al. 1991; King et al. 1991). Reported recurrence rates vary widely but within one year after treatment they are generally lower in cases where adjunctive therapy is used compared to surgery alone (Schwink 1987; Dugan et al. 1991; King et al. 1991; Mosunic et al. 2004; Payne et al. 2009; Giuliano 2010).

Local extension and subsequent tissue destruction can arise secondary to ocular SCC and may affect one or more of the orbit, gullet or pharynx, nasal cavity, paranasal sinuses, nasolacrimal duct, temporomandibular joint and calvarium (Gelatt et al. 1974; Eversole and Lavach 1978; Ellis 2006; D’Angelo et al. 2007; Perrier et al. 2010; Elce et al. 2011). Metastasis of equine ocular SCC to the regional lymph nodes, salivary glands, thorax or elsewhere can also occur, with reported rates of metastasis up to 18.6% (Gelatt et al. 1974; Schwink 1987; King et al. 1991). However, there are few detailed descriptions of metastasis following treatment of primary ocular SCC in the horse and, in most recorded cases, metastases have been identified in association with ocular recurrence or local extension of the tumour (Gelatt et al. 1974; Lavach and Severin 1977; Eversole and Lavach 1978; Schwink 1987; King et al. 1991).

Since SCC can be slow to both recur and metastasise, reappearance of the tumour, months to years after the initial presentation and treatment, is recognised (Ellis 2006; Plummer et al. 2007). Recently, the delayed (occurring at least one year after the initial presentation and treatment) local extension of ocular SCC to the maxillary sinus or periorbital area and regional metastasis to the parotid lymph nodes have been reported in 4 horses (Elce et al. 2011). Recognition of such delayed extension or metastasis would be helful in clinical practice. 

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of SCC has important implications for clinicians treating this tumour. The purpose of this report is to describe 5 further cases of delayed metastasis (including distant metastasis) of SCC following treatment of ocular neoplasia. Local recurrence at the ocular site was not identified in any of the cases at the time that the metastases were diagnosed.

Clinical histories

The medical records of 5 horses identified with delayed metastasis of ocular SCC were reviewed. Relevant clinicopathological details are summarised in the following paragraphs and Table 1. Tissue samples were fixed in 10% neutral buffered formalin, processed routinely to paraffin wax, sectioned at 4 μm and stained with haematoxylin and eosin (H&E) before histopathological examination. Representative slides from each case were reviewed by one author (GRP).

Case 1 was examined in 2002 with a purulent ocular discharge and a soft tissue mass involving the left third eyelid (Fig 1). The entire third eyelid was excised with the horse standing and histopathological examination revealed the presence of foci of SCC in situ and invasive SCC at the free margin. Tumour emboli were noted in a submucosal lymphatic vessel (Fig 2). The horse made an uneventful recovery.

Eighteen months later the animal developed signs of inappetence, weight loss, lethargy and dyspnoea. Clinical examination, thoracic radiography and ultrasonography revealed the presence of a cranial mediastinal mass and the horse was subjected to euthanasia on humane grounds. On post mortem examination, a multinodular, cranial mediastinal mass was identified, along with enlarged tracheobronchial lymph nodes and multiple soft tissue masses (1–3 cm in diameter) scattered through the lungs. Ocular lesions were not identified and parotid, retropharyngeal and submandibular lymph nodes appeared grossly normal. Remaining organs also appeared normal. Histopathological examination of a section of the mediastinal mass, an enlarged bronchial lymph node and a pulmonary nodule confirmed the presence of SCC, with sheets of densely packed pleomorphic neoplastic cells, many with bizarre nuclei and frequent mitotic figures (Fig 3).

Case 2 presented in 2002 with a pale pink, proliferative, soft tissue mass of the right third eyelid. The third eyelid was excised with the horse standing. Histological examination of the excised tissues confirmed the presence of SCC with early invasion of the sub-epithelial connective tissue (Fig 4).

Recurrence of the ocular tumour was not observed during the follow-up period. However, 3 years later, a slow-growing mass of the right submandibular area was identified. The swelling did not improve with 3 courses of i.m. procaine penicillin and, over the next 4 weeks, the horse became dull and inappetent with some weight loss. A malodorous, blood-stained discharge was noted from the mouth. Oral examination revealed ulceration and swelling of the buccal mucosa adjacent to the right mandibular cheek teeth. A firm subcutaneous swelling surrounded by pitting oedema was present in the right submandibular region. In view of the probability of neoplasia and the horse’s age, the owner elected to subject the horse to euthanasia without any further diagnostic work-up. Post mortem examination revealed a cream soft tissue mass in the submandibular tissues (including the submandibular lymph nodes), the parotid lymph nodes, oral cavity and oropharynx. Lesions were not identified in the eyes or periocular tissues. Histological examination of the submandibular, oral and pharyngeal tissues (including the submandibular and parotid lymph nodes) confirmed the presence of SCC. Remaining organs appeared normal.

Case 3 presented initially in 2007 with a small, white, soft tissue mass of the left third eyelid. A presumptive diagnosis of SCC was made and the entire third eyelid was excised with the horse standing. Histological examination confirmed SCC that had invaded the underlying dermis.

The horse remained fit and well, with no recurrence of ocular signs for 2 years. However, in 2009, the horse

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age at initial presentation</th>
<th>Breed</th>
<th>Sex</th>
<th>Colour</th>
<th>Location of primary SCC</th>
<th>Location of metastasis</th>
<th>Presentation to metastasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9 years</td>
<td>Cob</td>
<td>G</td>
<td>Bay</td>
<td>Third eyelid left eye</td>
<td>Mediatinum, lungs and bronchial lymph node</td>
<td>1.5 years</td>
</tr>
<tr>
<td>2</td>
<td>20 years</td>
<td>Anglo-Arab</td>
<td>G</td>
<td>Chestnut</td>
<td>Third eyelid right eye</td>
<td>Submandibular lymph nodes, oral cavity, oropharynx</td>
<td>3 years</td>
</tr>
<tr>
<td>3</td>
<td>16 years</td>
<td>Thoroughbred cross</td>
<td>G</td>
<td>Bay</td>
<td>Third eyelid left eye</td>
<td>Parotid and retropharyngeal gland Right thyroid gland</td>
<td>2 years</td>
</tr>
<tr>
<td>4</td>
<td>9 years</td>
<td>Paint horse</td>
<td>G</td>
<td>Tan and white</td>
<td>Third eyelid and upper eyelid of both eyes</td>
<td>Submandibular, parotid, retropharyngeal and cervical lymph nodes; mediastinum; lungs</td>
<td>3 years</td>
</tr>
<tr>
<td>5</td>
<td>5 years</td>
<td>Cob</td>
<td>F</td>
<td>Skewbald</td>
<td>Bulbar conjunctiva left eye Right nostril</td>
<td>Right parotid and retropharyngeal glands</td>
<td>11 years</td>
</tr>
</tbody>
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F, female; G, gelding.

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presented with signs of weight loss, depression, coughing and dysphagia. Diffuse bilateral swelling of the parotid and retropharyngeal regions, and a bilateral nasal discharge containing food was observed (Figs 5a and b). On endoscopic examination, the walls of the nasopharynx appeared congested and oedematous and the guttural pouches constricted. A transcutaneous wedge biopsy of the enlarged left parotid gland was obtained with the horse standing. Histopathological examination of the biopsy revealed salivary gland tissue, within which were vessels containing neoplastic epithelial cells (Fig 6). A diagnosis of vascular metastases of SCC was made and the horse was subjected to euthanasia at the owner’s request.

Post mortem examination confirmed the presence of extensive infiltration of the parotid and retropharyngeal tissues (including the parotid and retropharyngeal lymph nodes), by firm, cream tissue (Fig 7) which was confirmed to be SCC on histological examination. Histological examination also revealed deposits of SCC in the right thyroid gland with obvious vascular invasion. The eyes, periocular tissues and remaining organs were normal.

Case 4 was first examined in 2006 for evaluation of masses of the right third eyelid and medial, right, upper eyelid margin and the left third eyelid and upper eyelid. The horse was anaesthetised and the right third eyelid resected followed by the application of 4 radiation fields of strontium-90 beta irradiation to the remaining stump. The medial, upper, eyelid margin lesion was also resected and the eyelid received 2 more radiation fields of strontium-90 beta irradiation. Routine transpalpebral enucleation of the left eye was performed, leaving 1 cm margins around the nodular mass. Histological examination confirmed all excised masses as SCC. In the right third eyelid there was invasion of neoplastic cells into the underlying stroma and invasion of blood vessels. Excellent healing of the area occurred and a re-check examination of the ocular region, 8 months post operatively, appeared normal.
Three years later, the horse re-presented with a one month history of intermittent fever, pectoral oedema and progressive forelimb oedema. Several large, circumscribed masses were palpable in the submandibular and retropharyngeal region with the largest located in the left, lateral, cervical area just caudal to the ramus of the mandible. The horse also demonstrated bilateral jugular vein distension. Radiography of the pharynx and thorax revealed a large, well circumscribed mass in the cranial mediastinum; irregular, nodular thickening of the floor of both guttural pouches and poorly circumscribed masses in the pharyngeal region just caudal to the ramus of the mandible. Ultrasonography revealed several areas of well circumscribed, mixed echogenic masses in the submandibular and retropharyngeal regions. Mild pleural roughening and a small volume of pleural effusion were also identified bilaterally in the cranioventral thorax. Upper airway endoscopy revealed bilateral swellings along the ventral floor of the medial compartment of the guttural pouches, consistent with retropharyngeal lymphadenopathy. Differential diagnoses included disseminated bacterial abscessation or metastatic neoplasia. The owners elected not to pursue further diagnostic tests but to attempt long-term antibiotic treatment.

The horse deteriorated rapidly over the following month with worsening cranioventral oedema and the owners elected for euthanasia.

Post mortem examination revealed:

- Post mortem appearance of parotid region showing pale cream tissue (arrow) infiltrating between lobules of parotid gland (P).

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revealed a large mass adherent to the left mandible that compressed the oropharynx and infiltrated and effaced the submandibular, parotid and retropharyngeal lymph nodes. Numerous small, irregular, nodules were observed externally along the tracheal and oesophageal adventitia extending though the thoracic inlet, cranial to the base of the heart and involving the mediastinum. In addition, multiple nodules were present within the lung parenchyma. Histopathological examination of representative samples of the masses revealed a poorly differentiated metastatic SCC.

Case 5 was first examined in 1993 for a mass of the left bulbar conjunctiva close to the lateral canthus, which was excised with the mare standing. Histological examination confirmed the diagnosis of SCC. Six weeks later, local recurrence of the mass was noted and surgical excision was repeated with the horse under general anaesthesia, followed by 2 radiation fields of strontium-90 beta irradiation. Healing of the area occurred and tumour recurrence was not identified over the next 8 months.

Nine months after initial presentation, a 1 cm diameter, ulcerated area of the skin of the right external nostril was noted. A biopsy revealed a SCC in situ. The ulcerated area with a 1 cm margin of normal skin was treated by a triple freeze-thaw cycle of cryotherapy followed by topical application of 5-fluorouracil ointment. The affected area healed uneventfully over the next 3–4 weeks and no further recurrence was noted at the site.

In 2002, 9 years after the appearance of the first SCC lesion in the left eye, a soft tissue mass was identified on the bulbar conjunctiva close to the lateral canthus of the contralateral (right) eye. The mass was excised with the horse under general anaesthesia; histological examination confirmed SCC and the presence of neoplastic cells within blood vessels was noted. The owner declined further adjunctive treatments.

Recurrence of ocular lesions was not observed over the next 2 years. The mare was subjected to euthanasia in 2004 for severe laminitis. At this time, mild enlargement of the right parotid region was present. Post mortem examination revealed enlargement of the parotid gland and retropharyngeal lymph nodes on the right side and histological examination revealed the presence of SCC in both organs. The remaining organs were normal on gross examination.

Discussion

The 5 cases reported herein demonstrate the potential for ocular SCC to metastasise to local lymph nodes or to distant sites following successful resolution of the primary tumour (i.e. without concurrent recurrence of ocular lesions). In 3 cases the metastasis was local to the parotid and/or retropharyngeal lymph nodes (one of these cases also had metastasis to the thyroid glands); one case had local and distant (thoracic) metastases and one case had only distant (thoracic) metastases. Although local extension into adjacent and regional tissues (Elce et al. 2011) and distant metastasis (Gelatt et al. 1974; Lavach and Severin 1977; Eversole and Lavach 1978; Schwink 1987; King et al. 1991) have been reported previously, local recurrence of ocular SCC has been reported most frequently (Schwink 1987; Dugan et al. 1991; King et al. 1991; Mosunic et al. 2004; Plummer et al. 2007). In the horse, ocular lymphatic drainage is thought to involve the parotid, then retropharyngeal lymph nodes (Elce et al. 2011). However, as noted in other species, there may be some individual variation in the order, as determined by lymphoscintigraphy (Nijhawan et al. 2010). It was notable that the regional lymph nodes of the head (parotid, retropharyngeal and submandibular lymph nodes) were affected by metastasis in 4 of the 5 horses described in the present study. However, in one horse, (Case 1), metastasis to the thorax occurred in the absence of any detectable involvement of the regional lymph nodes of the head. There was no evidence of local recurrence of tumour in the ocular tissues in any of these cases when the metastases were diagnosed. This suggests that the original treatment was effective at removing the primary tumour in its entirety but that metastasis of tumour cells to a distant site had already occurred.

These 5 cases also highlight the fact that clinical manifestations of metastatic spread may occur a long time after apparent resolution of the original tumour. In the 5 cases reported here, identification of metastatic spread of SCC occurred between 18 months and 9 years after the initial treatment of the ocular tumours. However, it is acknowledged that the first lesion on the left side of Case 5 (ocular) and the uncommon right nasal SCC may not have been associated with the right parotid and retropharyngeal metastases. The right ocular SCC may have been the primary lesion for these metastases yielding an interval of 2 years between resolution of ocular lesions to detection of lymphadenopathy. The prolonged clinical manifestation of metastases in these cases warrants repeated regular re-examination of horses treated for ocular SCC for several years (Plummer et al. 2007). In human medicine, if the clinical, histopathological or cytological diagnosis is made >2 years after finishing the primary treatment, metastases have been described as delayed (Spector et al. 2001). It is unclear if the metastatic process itself is delayed or if clinical identification of the metastasis is delayed. It seems likely that the slow growth of SCC and the difficulties in identification of subtle lymph node enlargement in horses may permit subclinical existence of the tumours for a prolonged period of time, resulting in delayed identification of lymph node metastases.

There is currently no information available that could be used to predict the risk of recurrence or metastasis of ocular SCC following treatment in horses. It has been noted previously that eyelid SCC metastasises more frequently than limbal SCC (Hendrix 2005). This increased risk of
metastasis has been hypothesised to be due to the ease that cords of tumour cells can spread from the eyelids into the soft tissue, compared to the sclera and cornea where the sharp demarcation between normal, dense, fibrous tissue and neoplastic tissue may act as a barrier to the penetration of neoplastic cells (Hendrix 2005). In 3 horses (Cases 1, 4 and 5), there was histological evidence of neoplastic cell infiltration of blood or lymphatic vessels in the primary ocular tumours, which may have indicated a potential for more widespread dissemination of the tumour. This form of metastasis is believed to occur in 5–10% of human cases of SCC metastasising from the skin (Thomas et al. 2008). It was of interest that in 2 of the 3 cases where vascular or lymphatic emboli were observed, more distant metastasis occurred (Cases 1 and 4). Apart from the possible significance of this neoplastic invasion of blood/lymphatic vessels, no specific histopathological features (such as the mitotic rate or cytological appearance of neoplastic cells) were detected in these 5 horses or in the 4 horses described by Elce et al. (2011) to suggest an increased risk of recurrence or metastasis. Whilst in people, microscopically controlled excision, or excision with frozen section analysis (Thosani et al. 2008), along with evaluation of the sentinel lymph nodes (Faustina et al. 2004), is performed, such an approach would be hampered in the horse by the surgical inaccessibility of the parotid and retropharyngeal lymph nodes in the absence of gross lymphadenopathy.

There are numerous different treatments that can be used for SCC in horses including surgery, cryotherapy, radiotherapy, immunotherapy, photodynamic therapy, radiofrequency hyperthermia, laser surgery and chemotherapy (Giuliano 2010). The use of combination therapies is common practice. Comparisons of recurrence rates between different combinations of therapies are difficult to establish and studies documenting long-term and distant recurrence rates of ocular SCC are currently lacking.

This case series has highlighted the importance of regular monitoring of cases treated for ocular SCC even after resolution of the primary tumour. As a minimum, the authors would recommend prompt investigation of submandibular, retropharyngeal or parotid lymphadenopathy in horses treated for ocular SCC and long-term case follow-up. Additionally, multicentre prospective studies with regular follow-up and particular attention to histopathological features of excised SCC are warranted with the aim to recognise horses at risk for disease progression as well as identify disease progression promptly.

In conclusion, the delayed identification of metastasis of neoplasia described by Elce et al. (2011), and the 5 horses in the present study, illustrates the need for counselling owners of affected horses and for long term careful re-examination after treatment of ocular SCC not only for local (ocular) recurrence of tumour but also for metastatic spread, both locally in sentinel lymph nodes and at distant sites. The identification of neoplastic invasion of blood or lymphatic vessels in tissue samples of the primary tumour may be considered as a marker for increased risk of subsequent metastatic disease.

Authors’ declaration of interests

No conflicts of interest have been declared.

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References


