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Derek C. Knottenbelt

BVM&S, DVM&S, MRCVS
Philip Leverhulme Hospital
University of Liverpool, UK



**Tumori della cute:
il carcinoma squamocellulare**
Skin neoplasia: squamous cell carcinoma

Domenica, 2 Febbraio 2003, 11.30
Sunday, February 2nd 2003, 11.30

SALA PACINOTTI

MEDICINA INTERNA

Chairperson: Francesca Abramo

Riassunto

Il carcinoma squamocellulare è al terzo posto in ordine di prevalenza fra i tumori cutanei degli equini (dopo il sarcoide ed il melanoma). Nella maggior parte dei casi, la condizione si riscontra a livello della cute delle palpebre, del muso e del perineo, ma formazioni importanti si osservano anche a livello del pene dei maschi castrati (di solito risultano colpiti con maggiore frequenza gli animali più anziani). La razza Clydesdale sembra essere predisposta all'insorgenza della malattia in tutti i siti.

Esiste una stretta relazione fra carcinoma squamocellulare e cute non pigmentata e, più in particolare, nella zone in cui la cute è esposta alla luce solare. Tuttavia, in alcune sedi possono essere coinvolti altri agenti cancerogeni (ad es., lo smegma causa formazioni peniene e clitoridee, rispettivamente, nei maschi castrati anziani e nelle fattrici). Le neoformazioni perianali e quelle delle labbra vulvari sono relativamente comuni, ma risulta difficile ipotizzare che in questa sede il problema sia causato dallo smegma o dalla luce solare.

La localizzazione più comune è indubbiamente rappresentata dall'occhio e dalla cute periorbitale. Le palpebre sono spesso colpite nei cavalli con occhi azzurri o colorati o Cremello e la terza palpebra non pigmentata e la congiuntiva bulbare limbare laterale costituiscono una sede comune in tutti i tipi di equini. Il carcinoma in situ è un carcinoma squamocellulare ristretto all'epitelio corneale superficiale.

Alterazioni precarcinomatose si possono spesso riconoscere sulla cute del pene e delle palpebre (dove è utile un test di ricerca del sangue occulto nelle lacrime); in questi casi l'adozione di semplici misure come l'igiene prepuziale o l'applicazione di un paraocchi può prevenire del tutto la comparsa del tumore.

Si riconoscono due forme principali, una ulcerativa o distruttiva ed una proliferativa superficiale, che esita in una massa tumorale in espansione. La prima può essere molto distruttiva per i tessuti e sono comuni i sanguinamenti e le infezioni secondarie. Questo tipo è più frequente a livello di palpebre e muso. Le forme proliferative sono comuni sulla terza palpebra, sul pene e sulle labbra vulvari e sul clitoride.

La malignità non è una caratteristica comune delle forme cutanee, mentre è molto più probabile in quelle gastriche ed in quelle che si localizzano a livello di bocca, faringe e cavità nasale. I carcinomi squamocellulari del pene nei cavalli castrati più giovani (< 10 anni di età) sono di gran lunga più frequentemente maligni di quelli che si verificano nei cavalli castrati più anziani nella stessa sede. Sono state descritte forme polmonari secondarie e generalizzate in cui erano presenti gravi effetti secondari sia locali che sistemici. In un caso relativo ad un pony anziano portato alla visita perché presentava atassia/paraplegia dei quarti posteriori è stata descritta una diffusione metastatica ai corpi vertebrali. La forma gastrica è di solito altamente aggressiva e si ha una disseminazione secondaria direttamente attraverso ed all'interno del peritoneo e del fegato ed ematogena a fegato, polmoni e, da qui, ad altri organi principali.

Le localizzazioni sono rappresentate da:

1. Cute
 - a. Muso
 - b. Perineo
 - c. Pene
 - d. Vulva
 - e. Clitoride
2. Palpebre/occhi
 - a. Congiuntiva
 - b. Cornea

3. Forme interne

- a. Faringee
- b. Nasali
- c. Orali
- d. Gastriche

Il trattamento è sempre difficile, ma almeno la maggior parte delle forme che risultano accessibili ha una natura più benigna e può essere più suscettibile di escissione chirurgica. Il carcinoma squamocellulare è sempre molto sensibile alle radiazioni gamma e beta e, quando risulta fattibile e disponibile, questa terapia può essere utilizzata come protocollo di trattamento efficace. Spesso, tuttavia, la chirurgia rappresenta l'unica opzione e l'escissione meticolosa risulta frequentemente curativa. Recentemente, l'uso di cisplatino e 5-fluorouracile ha offerto una nuova possibilità ma, anche così, esistono molti casi in cui le difficoltà di accesso o di realizzazione pratica precludono il trattamento.

Le forme palpebrali e peniene/clitoridee e vulvari rappresentano i migliori candidati al trattamento chirurgico. In alcune localizzazioni, è anche attuabile la criochirurgia, ma risulta difficile trattare totalmente l'area coinvolta.

La prognosi per la maggior parte delle forme è buona, ma di solito si consiglia di adottare un approccio riservato, data la difficoltà di garantire l'ablazione totale del tumore. Le associazioni di chirurgia e radioterapia o farmaci antimitotici topici di solito rappresentano la migliore soluzione. L'amputazione completa o parziale del pene è un trattamento molto efficace, a condizione che non vi sia alcun coinvolgimento dell'anello prepuziale o dei linfonodi iliaci.

Summary

Squamous cell carcinoma is the third most prevalent skin tumour of horses (behind sarcoid and melanoma). The condition is most often found in the skin of the eyelids, face and perineum but important forms occur on the penis of geldings (usually older aged animals are more often affected). The Clydesdale bred seems to be predisposed to the disease at all sites.

There is a close relationship between SCC and non-pigmented skin and more particularly where the skin is exposed to sunlight. However in some locations other carcinogens may be involved (e.g. smegma causes penile and clitoral forms in older geldings and mares respectively). Perianal forms and vulvar labial forms are relatively common but it is hard to visualise smegma or sunshine causing the problem here.

The commonest site is undoubtedly the eye and periorbital skin. The eyelids are often affected in wall eyed or coloured or Cremello horses and non-pigmented third eyelid and lateral limbal bulbar conjunctiva is a common site in all types of horses. Carcinoma in situ is a SCC that is restricted to the superficial corneal epithelium.

Pre-carcinomatous changes can often be recognised on penile skin and the eyelids (in the latter cases a lacrimal occult blood test is helpful) and in these cases simple measures including preputial hygiene or blinkers may prevent the tumour appearing at all.

Two major forms are recognised. These include an ulcerative or destructive form and a superficial proliferative form that results in an expanding tumour mass. The former can be very destructive of tissue and bleeding and secondary infection is common. This type is commonest on the eyelids and the face. The proliferative forms are common on the third eyelid, the penis and the vulvar lips and clitoris.

Malignancy is not common in the cutaneous forms but the gastric form and those forms that occur in the mouth, pharynx and nasal cavity are much more likely to be malignant. Penile SCC in younger geldings (<10 years of age) are far more often malignant than those that occur in older geldings at the same site. Secondary pulmonary and generalised forms have been described in which there have been serious secondary effects both locally and systemically. Metastatic spread to the vertebral bodies have been reported in a case of an old pony that was presented for hindquarter ataxia/paraplegia. The gastric form is usually highly aggressive and secondary dissemination occurs directly across and into the peritoneum and liver and haematogenously to the liver, lungs and thence to other major organs.

Locations include:

- 1. Skin*
 - a. Face / Muzzle*
 - b. Perineum*
 - c. Penis*
 - d. Vulva*
 - e. Clitoris*
- 2. Eyelids / Eyes*
 - a. Conjunctiva*
 - b. Cornea*
- 3. Internal forms*
 - a. Pharyngeal*
 - b. Nasal*
 - c. Oral*
 - d. Gastric*

Treatment is always difficult but at least most forms that are accessible have a more benign nature and may be amenable to surgical excision. SCC is always very sensitive to gamma and beta radiations and so where these are feasible and available this is an effective treatment protocol. Often however, surgery is the only option and then meticulous excision is often curative. Recently the use of cisplatin and 5-fluorouracil have provided a new possibility but again there are many cases in which access or practicality preclude treatment.

Eyelid forms and penile / clitoral and vulvar forms are the best candidates for surgical treatment. Cryosurgery is also feasible in some locations but it is difficult to treat the total area involved.

The prognosis for most forms is good but a guarded approach is usually advised because of the difficulty of ensuring total ablation of the tumour. Combinations of surgery and radiation or topical antimetabolic drugs usually provide the best outlook. Complete or partial amputation of the penis is a very effective treatment provided that there is no involvement of the preputial ring or the iliac lymph nodes.

Primary squamous cell carcinoma is a common tumour of horses that is restricted to squamous epithelium. Within the broad pathological group there is wide variation in the prevalence of each type. The histological characteristics are typical and easily recognised and the extent of malignancy is likewise easily recognised by the extent of differentiation and the character / normality (or otherwise) of the keratin production. The less aggressive the tumour, the greater the normality and the greater the extent of production of keratin. Highly malignant forms produce virtually no keratin and have a particularly aggressive nature with rapid metastatic spread via blood and lymphatics to either remote or organs or to the local draining lymph node.

Solar radiation, geographical location, and individual susceptibility (which may relate to breed, age and lack of adnexal pigment) are probably the most important risk factors associated with SCC. Predispositions to squamous cell carcinoma occur within breeds (the Clydesdale Horse is probably predisposed) and within colour variations.

There is little doubt amongst clinicians that depigmented skin exposed to carcinogens such as smegma (in the case of penile and clitoral forms) and sunlight (in cutaneous and

ocular forms) are implicated but there are no scientific studies that confirm this widely held belief. Certainly most clinicians will recognise that certain animals including coloured and cream ponies are predisposed. Furthermore smegma is a likely carcinogen in geldings because breeding stallions appear to be much less likely to succumb to the penile forms than aged geldings.

Sites:

Integumentary

1. Facio-nasal
2. Palpebral
3. Conjunctival
4. Corneal
5. (Perineal)

Alimentary Tract

1. Oro-palatine
2. Oro-Pharyngeal
3. Gastric
4. Anal

Respiratory Tract

1. Nasal
2. Paranasal sinuses
3. Nasopharynx

Reproductive tract

1. Penile
2. Vulval
3. Clitoral

Forms: From a purely clinical perspective three major forms of the disease are recognised.

1. Proliferative forms in which the tumour develops in a proliferative fashion. A common site for this type is the penile form in older geldings and the carcinoma in situ on the cornea.
2. Ulcerative / Destructive forms that result in tissue loss and erosions and ulcerations. These are commonly found for example on the non-pigmented eyelids and third eyelids. It is also the predominate form in perianal or perineal forms of the disease (as opposed to the vulvar form in mares)



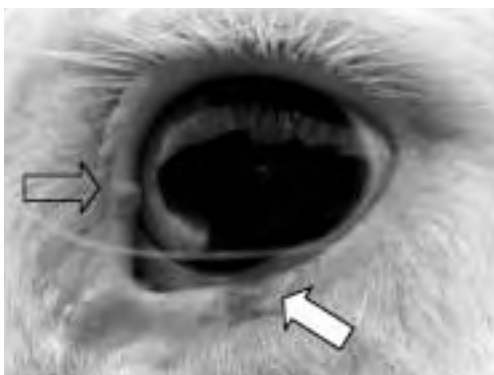
Perianal squamous cell carcinoma. Note the non-pigmented skin.

3. Combined ulcerative / Destructive forms are actually quite common and are typified by the vulvar or clitoral forms. Younger geldings are liable to this form and where it occurs in horses under 10 years of age there is a very high degree of malignancy associated with it.

OCULAR AND PERIOcular SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma (SCC) occurs in the eyelids, the conjunctiva (particularly of the third eyelid and the lateral limbus of the eye) and on the surface of the cornea (carcinoma in situ). Palpebral SCC (pSCC) is often extensive, highly destructive, and invasive. However, a milder proliferative, slower growing form is sometimes encountered. Non-pigmented eyelids are much more liable to develop the destructive and ulcerative form and certain breeds seem more liable to its development. Although for the most part SCC of the eyelids and orbital structures are very seldom malignant they can cause extensive destruction or infiltration and so treatment becomes progressively more problematical.

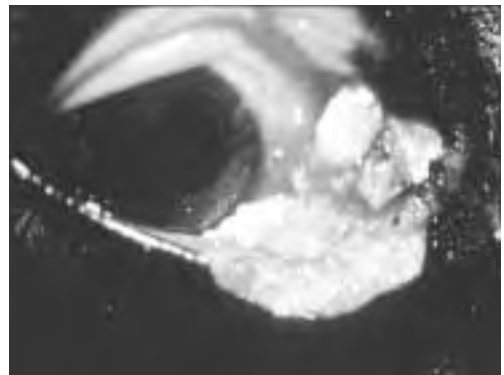
The least common ocular forms include a lateral limbal form that is invariably proliferative (at least until the condition is advanced) and a carcinoma in situ where the corneal epithelium is involved. The latter are sometimes difficult to diagnose. Usually cases are pre-



Early ulcerative (white arrow) and proliferative palpebral carcinoma (open arrow).

sented for investigation of ocular discharges (usually with a characteristic purulent appearance).

Clinical diagnosis of the condition is usually simple when the changes are advanced but in the early stages lacrimation is a feature and testing the tears with a urine blood dipstick usually reveals blood. Sometimes the lacrimation is plainly haemorrhagic. Pathological diagnosis of all the forms is easily achieved by biopsy but some sites are not amenable to excision of large pieces of tissue so pathologists need to be informed of the nature of the lesion and the location of the biopsy within it.



Severe ulcerative (destructive) carcinoma of the lower lid and caruncle. The tumour also involved the third eyelid and was treated successfully with gamma radiation.



A typical proliferative carcinoma on the nictitans. This was treated successfully by surgical excision of the affected area leaving a distorted but functional nictitans.



A severe highly destructive carcinoma on the muzzle. This is only treatable by radiation and even then there is likely to be gross deformity. (Slide courtesy of E.R Singer)

CUTANEOUS SQUAMOUS CELL CARCINOMA

Cutaneous forms of squamous cell carcinoma occur in the facial region, the ears and the perineal skin (see Figure above). The large majority of these are ulcerative / destructive forms and the site and extent of tissue loss at the time of initial presentation dictate the prognosis.

PENILE SQUAMOUS CELL CARCINOMA

A pre-cancerous change in the skin of the penis and the glans may be detectable – usually such cases are presented for investigation of a preputial discharge [often containing some (stale) blood]. Penile squamous cell carcinoma is recognised in two major forms that have different implications for prognosis and treatment.

The common form occurs in old geldings – stallions are very rarely affected and this suggests that smegma may be a significant carcinogen. The lesions may be proliferative or ulcerative / destructive or there may be a combination of the two. The glans is most often affected while the preputial reflection and the skin of the shaft of the penis may sometimes be involved. Lesions may be multiple and may be ulcerated or proliferative.



Pre-carcinomatous changes on the penile skin of an aged gelding (left) and a single smaller, haemorrhagic carcinoma on the penile skin of a younger horse. Both were successfully treated. Hygiene forms a major part of the management of these forms.



Malignant squamous cell carcinoma of the glans in a 9 year old gelding. There was iliac lymph node involvement and the shaft of the penis felt “wooden”. Treatment was not attempted.

In younger horses (< 10 – 14 years of age) there is a much higher malignancy rate and these cases are often beyond treatment on presentation. The lesions are often highly malignant in appearance and often the glans is the primary lesion.

The more malignant forms and those that have a very chronic course may sometimes “seed” into the skin at the preputial ring or preputial orifice. These lesions are also very aggressive and they may occur independently of the penile forms. The prognosis for these cases is extremely poor and en bloc resection of the penis and the prepuce with perineal ure-

throstomy is the only therapeutic course of action to take. The site may become strictured by a combination of fibrous tissue scarring and tumour expansion and so the first signs of this complication may be difficulty with urination.

VULVAR / CLITORAL SQUAMOUS CELL CARCINOMA

Vulvar or clitoral forms occur almost exclusively in older mares. It is suggested that the carcinogenic properties of smegma may be involved in the development of the clitoral form and at this site carcinomas can develop on pigmented skin. The vulvar forms are usually proliferative when they develop within the vestibule and ulcerative when they involve the lips of the vulva. The clitoral form is invariably proliferative. Treatment is usually a combination of radiation (where feasible and available) and surgical excision. Topical 5-fluorouracil (5% cream) has been used successfully but it is very slow and can be an uncomfortable and therefore difficult treatment to complete. Intralesional cisplatin has also recently gained some favour but the logistics of this material are difficult and a stable emulsion must be used. The aqueous solutions or other solutions are not likely to be effective and in any case require to be repeated frequently over some weeks or months.

MUCOSAL SQUAMOUS CELL CARCINOMA

Squamous cell carcinoma can occur in any squamous epithelium. The commonest sites for these forms are in the oral and nasal cavities (including the paranasal sinuses) and the in the pharynx. The main presenting signs include chronic serosanguinous / fetid nasal discharge or oral bleeding with the possibility of secondary signs including nasal obstruction in the nasal forms and dysphagia in the oral forms. However, in spite of an aggressive tumour the clinical signs may not be obvious. Because these forms are usually prolif-

erative (at least to some degree) facial distortions and swellings may be detected. These forms often have an aggressive destructive nature and so it is possible to have a large proliferative lesion with extensive surrounding destruction.

GASTRIC CARCINOMA

Gastric squamous cell carcinoma by definition can only occur in the oesophageal (squamous) portion of the stomach. The suggested carcinogens include recurrent gastric infestation with *Habronema* and *Draschia* spp. worms or *Gastrophilus* spp (Bots) but there are many horses with high infestations of all these that never develop any pathology let alone carcinoma. There is no evidence in horses of a bacterial carcinogen. Usually the lesions are a combination of proliferation and destruction and this is probably the most aggressive for of the condition in horses. There is a high rate of direct spread to the liver and secondary metastatic spread to the lungs. The initial signs are not usually obvious and so on presentation these cases are usually clinically ill with weight loss, recurrent anterior abdominal pain and inappetance. They may be marginally anaemic but usually recurrent colic, weight loss and a harsh dry coat are the main signs. Because these signs are often attributed to other conditions and because a long endoscope is required for diagnosis cases are often presented late in the course. It is sometimes possible to obtain a tentative diagnosis from gastric washings (containing both blood and abnormal squamous cells) or from peritoneal fluid (containing blood, protein and abnormal squamous cells that should definitively never appear in peritoneal fluid) usually in the latter cases there are reactive mesothelial cells also and so the diagnosis may be confused with mesothelioma or simply a reactive peritoneal cavity.

Management:

Established SCC is usually locally aggressive and the prognosis is poor if pericocular and/or orbital tissues have been invaded. Squa-

mous cell carcinoma of the upper and lower eyelids can be treated by surgical excision/debulking combined with cryotherapy (usually a double freeze-thaw cycle with liquid nitrogen) or brachytherapy (usually via a strontium-90 applicator).

Note:

Laser therapy has been used to treat a variety of equine eyelid tumours, but that it is too early to assess the overall long-term success rate.

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Interestingly a particularly invasive form of SCC occurs in the nasal chambers, the paranasal sinuses and the hard palate. The former are characterised by a combined form of proliferation and expanding destruction. This is a common cause of exophthalmos in aged horses and of oral and dental difficulties in all ages of horse.

The management of squamous cell carcinoma relies upon surgical removal or cryonecrosis, where these are feasible or to the application of various antimetabolic and cytotoxic chemicals. Radiation is the gold standard of therapy in suitable sites where surgical removal cannot be contemplated or where the tumour margins cannot be defined sufficiently to allow total removal. There are no immunological methods for the management of this tumour type.

a) Benign neglect is ill advised for this condition. Those tumours that are small and benign may however be observed carefully at regular intervals. Extension into the orbit from the paranasal sinuses or nasal chambers is usually a bad prognostic sign and surgery becomes increasingly more difficult.

b) Surgical excision: This is a realistic proposition for nictitans and conjunctival forms and for most cases of early penile carcinoma; indeed it is the treatment of choice for all defined types of carcinoma at all sites but the criteria for selection of this method are strict. Surgical removal of corneal *carcinoma in situ* is extremely difficult requiring microsurgical techniques involving a superficial keratectomy of the affected area and a margin of 1 – 2 mm. Eyelid tumours are seldom amenable to this option. But very small, localised proliferative lesions can be excised if the margin of the lid can be preserved or can be reconstructed satisfactorily to preclude the complications arising from poor eyelid function. Surgical ablation should not be contemplated if the tumour has already invaded the local lymph node or there are difficulties with margin definition. Surgical amputation of the penis in suitable cases is curative and recurrences are rare provided that the surgery is properly performed and that all the tumour tissue is removed. Attempts at en bloc resection for cases of aggressive carcinoma carry a correspondingly poor prognosis because the surgery is a temporary salvage procedure in most cases. Some sites of course totally preclude surgical removal. Clitoral and some vulvar forms can be surgically removed with a reasonable prognosis.

c) Cryosurgery: Cryonecrosis is a fast but rarely effective method of treatment for eyelid lesions and small lesions elsewhere. Nasal lesions and some oral lesions may be managed in this way but the results are dependent upon the surgical efficiency of total tumour ablation. Thermocouple assistance is obligatory. Lesions that are ulcerated and which bleed significantly can be managed by careful cryosurgery. Nictitans, limbal SCC, and carcinoma in situ have all

been treated by cryosurgery with variable successes. The secondary effects of the freeze may be very serious and so its use should be strictly restricted to small eyelid lesions and to limbal superficial lesions. There are areas of course where this is totally impossible.

d) 5-Fluoro-uracil: The value of this chemical in ointment formulation has been described for oral SCC (Patterson, 1997) but there are no reports of its use in the eyelids or for ocular lesions. It would seem that this is an area that could have some prospect. A 5% solution of 5-F-U has been used by the author to treat a small limbal carcinoma that regrew at the site of a previous surgical excision but the true nature of the lesion (carcinoma v granuloma) was never established pathologically. Topical 5-FU requires persistent application over some weeks or even longer and highly invasive or aggressive lesions do not seem to respond effectively in the time available. The commercial ointment is 5% but it may be that this is plainly too weak to control a large or difficult lesion.

e) Cisplatin: Intralesional infiltration of an emulsion of cisplatin in almond (or sesame) oil or a stable emulsion containing a higher concentration of cisplatin can be used. It is effective in some cases although there are few reports of efficacy compared to other standard methods. The method is difficult logistically because the material needs to be injected intralesionally in a stable form and 1 mg cisplatin needs to be delivered to 1 ml of tumour and so the volume and concentration of the chemical are critical. A stable emulsion is difficult to obtain in some cases because of the lack of water solubility of the chemical and the need to use an aqueous solution.

f) Immunomodulation using BCG: The author has had little success with this approach, in stark contrast to its value in the treatment of bovine ocular and periocular SCC. The reasons for this are not clear. In any case it is not of any value in sites away from the eye.

g) Radiation: Radiation treatment is probably the best available option for all forms of

SCC in the horse but in the periorbital region there are logistic complications that significantly reduce its value much less. SCC is very susceptible to both gamma and beta radiation. Gamma radiation is used extensively (via linear iridium¹⁹² sources) in Liverpool for the treatment of palpebral forms of SCC. Beta radiation delivered via a Strontium⁹⁰ plaque has also had considerable benefit on limbal. Nictitans and carcinoma in situ lesions. The cosmetic effects of the treatment are remarkably good with a relatively rapid resolution and minimal secondary complications even in severely destructive eyelid cases. The relatively poor penetration of beta radiation (limited to 1 – 2 mm deep) means that surgical treatment may need to be applied before application of radiation. As is always the case every piece of tissue removed from a surgical site should be submitted for histopathology so that rational treatment/dose calculations can be made. Where ever possible this option should be considered to be the definitive method and is a useful fall back method when others are either not feasible or fail to resolve the problem.

Prognosis:

The prognosis for squamous cell carcinoma is dependent on:

1. The site of the lesion and its suitability for any effective therapy
2. The malignancy of the tumour itself
3. The duration of the lesion and failed attempts to treat it
4. The extent of secondary consequences arising from the tumour.

For the most part SCC in the horse has less malignancy than in most other species but gastric carcinoma, oropharyngeal carcinoma and penile carcinoma in younger geldings are usually (but not invariably!) far more malignant than the others. The tumour may metastasise by haematogenous or lymphatic extension but at some sites (especially the stomach forms) spread may be by contiguous expansion into adjacent organs. Thus the gastric form may extend into the liver and cause severe liver damage.



Conjunctival SCC of the nictitans tested by urine dipstick showing heavy blood contamination.

Secondary squamous cell carcinoma lesions have been described in the lumbar vertebral body in an aged pony with senile carcinoma (Harrison et al., 1994) and in the lungs from most forms where these have become highly aggressive.

Typically of any neoplastic disease the prognosis is heavily dependent on the time interval between onset and diagnosis. An early diagnosis is critical but the clinical signs are usually not distinctive and could easily be missed. For example the earliest signs of SCC of the conjunctiva or cornea is haemorrhagic lacrimation. This rather non-specific sign can be detected by the simple expedient of inserting a urine dipstick into the conjunctival sac and reading the "blood" square. However, there are other causes of this also! There is certainly no justification for routine gastroscopy or peritoneal tap on the off chance that the horse may have a gastric carcinoma!

Tumour markers would seem to be the future hope for early diagnosis but as yet no specific (or non-specific) marker has yet been identified for horses. Until we have methods for early diagnosis and better treatments (with radiation teletherapy being the best overall option) the SCC is likely to provide both a diagnostic challenge and a therapeutic problem.

References

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 Harrison LD, May *** (199*) Penile carcinoma with secondary metastasis to the lumbar vertebrae. Vet Rec.