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Tumori della cute: il melanoma

Skin neoplasia: melanoma

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SALA PACINOTTI

MEDICINA INTERNA

Chairperson: Francesca Abramo

Riassunto

Il melanoma equino è un tumore molto comune che colpisce principalmente (ma non esclusivamente) i cavalli grigi di età superiore ad 8 anni. La maggior parte delle neoplasie si localizza a livello della cute, ma risultano comunemente colpiti in una certa misura gli organi interni. La grande maggioranza dei melanomi che si riscontrano nei cavalli grigi è di natura benigna ed esistono alcuni dubbi circa il fatto che si tratti di un'autentica malattia neoplastica piuttosto che di una malattia da accumulo correlata al progressivo incanutimento dei peli via via che i cavalli grigi invecchiano. I tumori che si verificano nei cavalli di colore diverso dal grigio hanno una maggiore tendenza alla malignità e solo in pochi cavalli grigi si riscontrano forme altamente maligne.

Il perineo è la sede più comune, ma accumuli melanotici ed autentici melanomi si possono avere anche nella parete delle tasche gutturali. Questa è una sede utile per esaminare la natura dei tumori che colpiscono un cavallo e l'esame va effettuato di routine nell'ambito della valutazione clinica di tutti i soggetti grigi di età superiore a 10 anni, indipendentemente dal fatto che mostrino o meno melanomi cutanei.

Gli effetti comuni dei tumori sono correlati alla loro natura occupante spazio, ma alcuni possono essere funzionalmente limitanti per altre ragioni. Le lesioni all'interno delle tasche gutturali possono sanguinare abbondantemente o interferire con i nervi che attraversano la tasca stessa. Le lesioni della regione parotideale sono comuni e molto difficili da trattare. Tumori singoli isolati (ulcerati o meno) possono essere rimossi chirurgicamente con una certa sicurezza, ma il chirurgo DEVE essere consapevole del fatto che, occasionalmente, si può avere un'elevata malignità. È improbabile che un singolo intervento chirurgico esiti in una disseminazione tumorale catastrofica – di solito le neoplasie sono già ampiamente disseminate prima che venga richiesto qualsiasi intervento per qualunque singola lesione preoccupante. I segni dell'elevata malignità possono essere raccolti attraverso un semplice esame di una lesione ulcerata. La presenza di noduli rosa, crema o grigi all'interno di una neoplasia in gran parte nera è un cattivo segno prognostico. Istologicamente, il tumore non è ancora stato definito con precisione. L'aspetto istologico di un tumore decisamente benigno può far pensare ad un'elevata malignità e viceversa, per cui probabilmente non è il caso di presumere che si tratti di formazioni di natura maligna o benigna.

Le opzioni terapeutiche sono scarse. Recentemente è stata utilizzata la cimetidina con alcuni risultati incoraggianti, ma l'autore ha riscontrato nella grande maggioranza dei casi un beneficio molto scarso. Tuttavia, il trattamento talvolta funziona ed alla dose di 3,5 mg/kg ogni 12 ore non risulta pericoloso anche se non ottiene l'effetto sperato. Di solito si osserva una risposta (attraverso la misurazione di un particolare tumore) entro tre settimane, che si può protrarre fino a tre-quattro mesi. È possibile sottoporre ad un trattamento pulsante i casi che mostrano un miglioramento rilevabile, al fine di limitare i costi correlati alla terapia persistente. Di solito, è possibile ottenere risultati di questo tipo effettuando la somministrazione del farmaco per due settimane e poi cessandola per una settimana. In ultima analisi, può essere fattibile ricorrere ad un trattamento intermittente 50:50 per dimezzare il costo.

Summary

The equine melanoma is a very common tumour that predominately (but not exclusively) affects grey horses over the age of 8 years. Most tumours occur in the skin but internal organs are commonly affected to some degree. The large majority of melanomas occurring in grey horses are benign and there is some questions as to whether it is a true neoplastic disease or is a storage disease related to the progressive whitening of the hairs as grey horses get older. Tumours that occur in horses other than grey in colour have a higher tendency to be malignant and in a few grey horses a highly malignant form occurs.

The perineum is the commonest site but melanotic accumulations and genuine melanomas can occur in the wall of the guttural pouches also. This is a useful place to examine the nature of the tumours that a horse has and examination should be included routinely in the clinical examination of all grey horses over the age of 10 years regardless of whether they have melanomas in the skin or not.

The common effects of the tumours relate to their space occupying nature but some can be functionally limiting for other reasons. Lesions within the guttural pouch can bleed heavily or can interfere with the nerves that traverse the pouch. Lesions in the parotid region are common and are very difficult to manage. Individual isolated tumours (whether ulcerated or not) can be removed surgically with confidence but surgeons MUST be aware of the occasionally high malignancy that can occur. It is unlikely that a single surgical interference will result in catastrophic dissemination of tumours – usually the tumours are already widely disseminated before any interference is warranted for any troublesome individual lesion. Signs of high malignancy can be gleaned from a simple examination of an ulcerated lesion. The presence of pink, cream or grey nodules within the largely black neoplasm is a bad prognostic sign. Histologically the tumour has not been defined with any confidence as yet. High malignancy can be implied from histological examination in a very benign tumour and vice versa and so it is probably unwise to assume either a malignant or benign nature.

The treatment options are few. Recently cimetidine has been used with some encouraging results but the author had found very little benefit in the large majority of cases. However, the treatment does sometimes work and at the dose rate of 3.5 mg / kg q 12h it does no harm if it does no good. Usually a response will be evident (by measurement of a particular tumour) within 3 weeks and this can be sustained for up to 3 – 4 months. It may be possible to pulse treat cases that have a detectable improvement in order to limit the costs involved of persistent medication. Administering the drug for 2 weeks and then stopping for one week usually performs pulse treatment. Ultimately it may be feasible to use a 50 : 50 pulse treatment to halve the cost.

Acknowledgements:

I am grateful to Professor Donald F Kelly for help with the photomicrographs and histological descriptions of the melanomas described in this paper.

The equine melanoma is a very common nodular skin disease of horses and because of the frequency they are encountered in the skin of grey horses it is easy to view them as invariably benign, incidental skin tumours. This is indeed far from the case as they occur with some frequency in the internal organs and they can become highly malignant in some cases. There is no evidence to suggest that the condition is in any way related to exposure to sunshine (as in humans). The Arabian bred is said to be more susceptible than others but this may not be totally true.

The common forms of melanoma are encountered in the skin of the perineum; over 60% of melanomas occur in the skin and over 50% of these are situated in and around the perineum. Here they are an almost invariable finding in grey horses over 10 – 12 years of age. Indeed there are almost no grey horses over this age that will not have at least some melanomas and



Multiple melanomas in the perineum of a mare. Note that some are ulcerated.

the large majority have perineal lesions. The tumours are easily recognised. Usually they start as small solid spherical lumps in and under the skin. They may form chains and can vary in size quite dramatically.

Similarly individual tumours may grow at an alarming rate while those adjacent may remain static. They seldom, if ever, regress spontaneously. The faster growing lesions and those that are subjected to trauma of any type (including biopsy) may ulcerate and expose a black, tarry soft rather amorphous tissue. The surface may bleed and exude a black tarry jelly like material.

Rarer forms of melanoma occur in the eyelids, iris, retina, mouth, parotid salivary glands and lymph nodes, penile skin and in internal organs, including the intestine, heart and lungs. Post mortem studies of the equine melanoma confirm however that almost every organ can be affected but that there is seldom any major clinical consequence. Melanomas occurring in non-grey horses tend to be more dangerous than the more common form in grey horses. Usually the former are single and isolated while in grey horses they are usually present in large numbers (although single lesions can be encountered) and may occur in clusters. The condition in non-grey horses can be highly malignant.

The pathological description of the common form in grey horses is the subject of considerable controversy. Some pathologists consider that the common benign form is best viewed as a melanosis (or melanotic hamartoma) rather than a tumour. It is sometimes thought of as a storage disease because as grey



A palpebral melanoma.

horses get older the skin becomes whiter and whiter – but melanomas become more common in older horses. This implies that at least in some cases the melanin may not be being incorporated into the hair shafts and so accumulations of melanin may be reasonably expected to occur. However, the difficulty with this theory is that melanomas are far more common where there is no hair at all and so it may simply be that the melanocyte cells are naturally dividing in an abnormal fashion but that the cells themselves are normal (this is the definition of a hamartoma¹).

From a histopathological perspective melanoma in horses is a major problem. There are few distinctive features that suggest malignancy in the horse.

The main effects from the tumours are due to their space occupying nature but in some tissues locations they can have a serious functional consequence. Thus a melanoma within the spinal cord could be extremely benign in its pathological character but the clinical consequences may be disastrous. Similarly a melanoma in the sub nodal inter-ventricular septum of the heart may cause severe cardiac dysrhythmia – even resulting a complete 3rd degree heart block or death. Melanomas can result in an unacceptable distortion of the local anatomy in various organs with perhaps the commonest of these sites being the parotid region. In these cases there may be enormous expansion of the tumour masses but in spite of this they seldom cause and significant functional problems. Tumours that develop in the spinal cord may be devastating while massive perineal melanomas can result in defaecation and urination problems or in mares there may create reproductive difficulties both with mating and with parturition.

¹ A hamartoma is defined as an abnormal accumulation of a normal tissue type in a normal or abnormal location.



Parotid melanoma. The guttural pouch was extensively involved with melanosis and melanoma.

LESS USUAL MELANOMAS

a) Guttural pouch and Parotid melanoma.

Parotid involvement is a relatively common form of melanoma and in some cases the expansion can be massive. However, there is seldom any major clinical consequence. However, morbid examination of the masses will usually reveal that the tumour has spread from the parotid lymph node to the parotid salivary gland by direct extension. The original condition may be within the ipsilateral guttural pouch. Parotid melanomas seldom ulcerated unless they are interfered with by surgical biopsy.

Melanosis and melanoma (as well as malignant melanoma) occur within the guttural pouch. Most grey horses will have at least some melanosis visible on the mucosa of the guttural pouch. Most often this will be found on the mucosa overlying the maxillary artery or sometimes the other major arteries and veins in the pouch. Interestingly repeated endoscopy will confirm that these do not remain static but may expand slowly or may regress and appear at other sites. The clinical appearances of these are like “splashes of black paint”. There may be larger or smaller military areas involved. In any case they have a benign appearance and a singularly benign nature. The more serious aggressive and sometimes malignant forms are much more obvi-

ous as spherical or unevenly spherical shaped tumours. They usually have a shiny surface and again are most often found on the walls of blood vessels. In spite of their size and apparent aggression they seldom ulcerate but when they do they may bleed considerably giving a misleading diagnosis of guttural pouch mycosis.

The author commonly uses these lesions as an index of the rate of progression of the condition because they are relatively protected and unlikely to be significantly affected by any other factors such as external or self-trauma.

b) Intraocular melanoma.

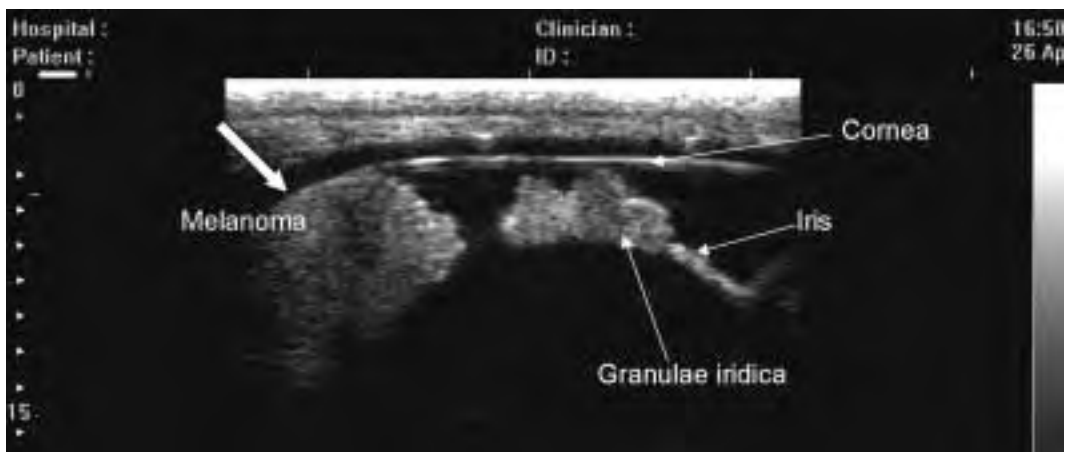
A few melanomas occur in the eye itself. Tumours developing in the eye can be serious in that the expanding tumour (usually within the ciliary body or the iris itself) has effects on vision and ultimately cause contact corneal oedema and non-ulcerative keratopathy.

The commonest forms encountered in the horse are ciliary or iridal melanomas. They are most often located in the nasal quadrants at the base of the iris – often they have a blue-black appearance rather than pure black (this may distinguish them from iris cysts and *granulae iridica* that characteristically have a very black or dark brown appearance).

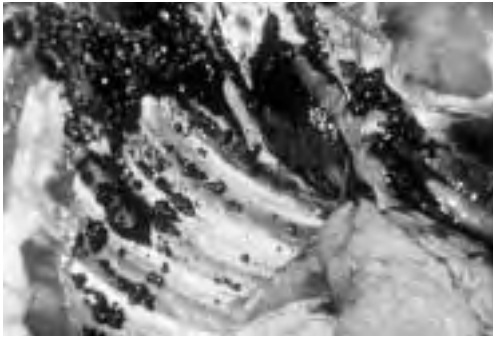
The clinical effects are related to their space occupying nature rather than any malignancy. Indeed primary iridal melanomas have no increased tendency to malignancy as far as the authors experience will allow such a statement! Retinal lesions are very rare but there is no information of the effects these small aggregations might have on visual acuity.

MALIGNANT MELANOMA

The malignant forms are usually highly aggressive with rapid widespread dissemination of military tumours in all major organs and body cavities. Malignant abdominal melanoma has, in the authors experience resulted in strangulating and non-strangulating surgical colic. Massive peritoneal and pleural effusions (often tainted with blood and containing obvious melanocytic cells) may be encountered. Usually the abdominal dissemination results in involvement of the major organs including the spleen, kidney and liver in particular. Each of these may cause individual clinical signs. For example renal involvement may cause haematuria (usually melanocytic cells are obviously present in the cellular deposit from a urine sample). Involvement of the spleen may cause peritoneal bleeding (but again the abnormal



High frequency ultrasonogram of an iridal melanoma that caused contact corneal oedema on the inferior hemisphere of the cornea (arrow). The eye was non-painful for some months but a partial iridectomy was performed when the pain the eye became uncomfortable. There was no material complication from the surgery and the condition did not recur.



Malignant melanoma in the chest of a horse presented for Bilateral Horner's Syndrome.

melanin producing cells will be present). Within the chest cavity malignant melanoma can have both space occupying and functionally limiting effects. In the authors experience massive accumulations can cause bilateral Horner's Syndrome if the tumours constrict or alter the function of the cranial sympathetic trunk at the thoracic inlet in particular.

Recognition of the rare malignant form of melanoma is important because of the implications of interference or attempts to surgically remove individual tumours. Ulcerated malignant tumours can be differentiated from their benign counterparts by the inclusion of yellow, pink or grey areas of tissue. These probably represent areas of amelanotic melanoma and these are in the authors experience always malignant and interference should be avoided. Otherwise diagnosis of malignancy relies on the help of a skilled pathologist. The reality is that we know little about the disease and so much of the advice that is given is based simply on experience.

Differential Diagnosis:

The differential diagnoses of melanoma include other cutaneous nodular diseases and other internal neoplasia. The clinical appearance is so distinctive that in most cases confirmation is probably neither necessary nor wise.

Diagnosis:

Diagnosis of melanoma in the typical site is relatively straightforward when they are found

in the skin in typical sites. It is not usually necessary to biopsy the lesions but a fine needle aspirate will probably not have any dissemination implications in the benign form at least. During this procedure it is important that the fine needle is placed centrally into the tumour and that it is not moved around within the tumour more than absolutely necessary. A large syringe attached to the needle is used to aspirate a few cells into the needle and these are then forcibly expelled from the needle onto a glass microscope slide (or into a formal saline solution) for staining and microscopic examination. The cells can be stained specifically of course but direct examination will usually identify the dark brown - black melanin containing cells. Specific examination of the cells themselves is best left to an experienced pathologist because identification of malignancy from these specimens is very difficult. It is equally easy to confirm the diagnosis from a biopsy of a portion of the tumour or excisional biopsy of whole lesion. Simply cutting the section or direct observation of the biopsy specimen will confirm that the tumour is a melanoma. Again the classification is a matter for a pathologist. Malignant forms may be recognised clinically if the tumour is visible and ulcerated but otherwise a pathologist is an important aid.

TREATMENT

Melanoma is probably best regarded as untreatable at the present time. Many cases are manageable by a variety of methods but until we have a much better understanding of the mechanisms that are involved in the conditions development we are unlikely to be able to either cure them or prevent their occurrence.

a) Many cases are best treated by benign neglect – they may not alter significantly for many years but should be checked at regular intervals. Checking such cases should involve careful assessment of the parotid salivary gland and parotid and retropharyngeal lymph nodes (often best checked by endoscopic examination of the guttural pouches). It is also

useful to monitor the size by accurate measurement of one or more positively identifiable lesions. Nonetheless a few static tumours or a few expanding ones should be not really be taken to indicate the behaviour of all the others. Benign neglect is the common and sensible approach in most cases. It may take many years before the condition is either cosmetically / socially unacceptable or becomes functionally important.

b) Surgical excision: This is a realistic proposition provided that the tumour can be removed without significant skin damage or consequent scarring. In some sites such as the eyelid or mouth, scrupulous reconstructive surgery to preclude the complications arising from functional deficits. Individual ulcerated or pedunculated tumours are a good surgical proposition. Extensive penile melanomas have been successfully removed from an aged breeding stallion by the author without any secondary consequences. Surgical removal of tumours that have a functionally limiting effect (such as in the eyelid or iris) are probably best removed surgically although there remains an inherent (if minute) risk of dramatic exacerbation.

c) Cryosurgery: Cryonecrosis of melanoma lesions is a fast but rarely effective method of treatment. Lesions that are ulcerated and which bleed significantly can be managed by careful cryosurgery. On the eyelids however, this is probably not advisable because of the consequent scarring.

d) Cimetidine: Oral cimetidine therapy has been reported to be successful in some cases of melanoma but its value in specific types of melanoma such as palpebral and ocular melanoma is not reported independently. Furthermore there are no reports of its efficacy in malignant forms of the disease (although this is hardly surprising!). Cimetidine acts through its effects on T Killer cells and so may be expected to have some effect. However, the results are very variable with some reports finding no benefit but as it is relatively simple it is at least an option. Cimetidine is administered by mouth at 3.5 mg/kg (q 12h) or 7.5 mg / kg (q 24h). Treatment is continued for up to 6 weeks but if no change is detected by 3 weeks

there is probably little point in continuing. If however, there is a response then the treatment should continue until 3 weeks after there is no further improvement. The value of long-term treatment is uncertain but we have found that pulse treatments applied for 4 weeks every 8 weeks is capable of maintaining the improvement. The results of this protocol are almost impossible to assess without a more detailed trial that badly needs to be done!

e) Cisplatin: The value of cisplatin is also uncertain but we have had considerable success with treatment of melanomas using a cisplatin / almond oil emulsion containing 1 mg cisplatin per ml. The material can be infiltrated into the lesion at fortnightly intervals. We have no specific experience of its use on eyelid melanoma but it would seem likely to be worth a try. The emulsion appears to have no harmful or painful effects on the eye (when we have used it for other palpebral tumours).

f) Melanoma vaccines: Recent developments in the management of human malignant melanoma using X-irradiated autogenous melanoma cells suggest that there may be some expectation of an immunological method of treatment. The reports of the use of this method in horses are preliminary at present (Jeglum 1997) but there does appear to be some value in the process.

g) Radiation: Radiation treatment has a surprisingly poor effect on melanoma tumours. High doses of gamma radiation delivered via a linear iridium¹⁹² source had no material effect on one case treated at Liverpool University. Similarly beta radiation also had no effect when applied to two individual lesions on the lower lids of a horse.

Prognosis:

The prognosis for life in an uncomplicated case of cutaneous melanoma in a grey horse is good. Many affected horses live normal lives and it is often simply the cosmetic and social appearance of the tumours that resulting the animal being destroyed. However, when talking to clients it is wise to point out that the disease is unpredictable. Even small tumours in 'inconvenient' sites will have a profound effect on the animal; for example a large melanoma in

the thoracic inlet could cause recurrent choke or have neurological effects (or both). Spinal, ocular, cardiac, or brain tumours may be catastrophic while others may cause clinical disease (colic or cardiac dysrhythmia and reduced athletic performance for example) that is not immediately attributable to the melanoma. Not all these are treatable and so may threaten the life of the horse. A few cases are highly malignant and it is currently impossible to predict which ones they will be. Generally however, rapid growing or those tumours with non-pigmented components are dangerous. In these cases, which probably represent less than 1% of affected horses have a short rapidly progressive course and this can usually be identified clinically during repeated examinations over some weeks; the course may however be fulminating and lead to death within days.

The condition should not be belittled and treated as invariably benign; regular checks and careful sensible advice to the owner.

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