Equine melanoma

Summary

The equine melanoma is a very common nodular skin disease of older (over 7-8 years of age) grey horses. Over 80% of grey horses will have at least some melanoma lesions during their lives.

- Horses can develop melanoma at any age – some can even be present at birth!
- Due to the prevalence in grey horses it is easy to view them as invariably benign, incidental skin tumours.
  - The large majority are benign and even when large can still have very little clinical implication.
  - Over 80% of melanoma lesions will develop aspects of malignancy eventually – some are fast and others are slow to transform to malignancy
  - Size is not the important factor – some big tumours are totally benign and other small ones are very malignant.
- Melanoma can become highly malignant in some cases. And can occur with some frequency in the internal organs

Typical peri-anal and sheath melanomas. All such tumours are progressive and many will develop various degrees of malignancy.
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.

**Which horses are affected?**

Most grey horses over 10-12 years of age will have at least some melanoma lesions. The large majority of affected horses have multiple lesions.

Melanoma also occurs in non-grey horses, and cremello/albino horses are sometimes severely affected. When this condition occurs in non-grey horses it tends to be more dangerous than in grey horses.

The Arabian, Lipizzaner, Andalusian and Percheron breeds are probably more susceptible, whilst the naturally grey Erisakay pony is probably a less affected breed. Breed susceptibility to melanoma may not be totally true and it is the colour grey which is the most significant predisposing factor.

Where the coat colour is flea-bitten grey with chestnut or brown flecks, the susceptibility for melanoma is much reduced. It is still higher in these colours than in chestnut or horses of other colourings.

**What do they look like?**

Melanoma 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. Individual tumours may grow at an alarming rate while those adjacent may remain static.

Characteristically melanomas are small, isolated nodules with a very black colour. As they become more dangerous they can get bigger and merge into larger areas of tumour.

Very seldom, if ever, do melanomas regress spontaneously.

The faster growing lesions, and those which are subjected to
trauma of any type (including biopsy) may ulcerate and expose a black soft rather amorphous tissue. The surface of melanomas may bleed and exude a black tarry jelly like material.

They may also lose their colour, becoming gradually grey/blue then beige and finally red/pink in colour.

Where are they found?

Almost all primary melanoma lesions on horses are found in the skin. Where internal melanomas are found it can reasonably be assumed that these have derived from lesions in the skin and this means necessarily that at least one skin tumour is likely to be malignant.

- There are only two non-cutaneous natural locations for melanocytes – the inner ear and the eye (iris pigmented epithelium and the retinal pigmented epithelium)

Most commonly, melanoma is encountered in the skin of the perineum – around the anus and the base of the tail are the most frequent sites. Over 50% of melanoma tumours are situated in and around the perineum.

Melanoma can also occur in the following areas:

- Eyelids, iris and retina
- Mouth, in particular the lips
- Parotid salivary glands and lymph nodes
- Penile and vulvar skin
- Internal organs, including the intestine, heart and lungs

Post mortem studies of the equine melanoma confirm that almost every organ can be affected, but that there is seldom any major clinical consequence unless the tumour interferes with normal function of that organ. In some sites therefore they can reach large size without problems but in other sites such as the eye and the spinal cord, even small tumours can have a devastating effect.

What causes melanoma?

Apart from a genetic susceptibility that is linked to the grey genes, little is known about this disease. There is no evidence to suggest that the condition is in any way related to exposure to sunshine as it is in humans. The sun does not usually shine around the anus and ventral tail, or the internal areas of the sheath or lips.
Typically melanomas start as small (one cell) changes that result in an expanding clone of abnormal cells. It does seem that the trigger for true cancerous change is an abnormal accumulation of melanin pigment in otherwise normal cells. This means that the early “tumours” are very benign – they are probably not really cancer at all, perhaps being better regarded as a “storage disease”!

Changes to the genetic structure of the cells seems to be triggered by the abnormal and sustained presence of the pigment of the cells.

- This is quite different from the melanoma of non-grey horses, humans and dogs which is much more like the conventional cancer mechanism involving an induced sudden genetic mutation in one cell that follows exposure to UV light or some other cancer inducing factor.

**How can I be sure it’s a melanoma?**

Most melanomas are obvious and easily recognised. They are black, solid and single/multiple nodules in the skin. They can be mistaken for other conditions, and most importantly, they aren’t all black; they can be fleshy and pink in appearance too!

Knowing that a tumour is a melanoma is only half the problem, we need to know what kind of melanoma it is since that has profound implications for the horse.

Conditions that could resemble or be mistaken for melanoma include other cutaneous nodular diseases including sarcoid and carcinoma, as well as other internal neoplasms. The clinical appearance is usually so distinctive that in most cases histological confirmation is probably neither necessary nor wise.

Samples taken from the tumour site, either by a needle or by an excised piece of tumour, will usually confirm the diagnosis however.

There are nevertheless some important issues:

- The majority of tumours are of a benign type
- Some are highly malignant.
  - This can be part of an otherwise very benign mass
- Size is not an indicator of malignancy. Some tumours can be large and benign, whilst others can be small and malignant.
- Some have a largely benign nature with highly malignant parts within it. It depends then what is sampled as to how it can be assessed.

The pathological description of the common form in grey horses is the subject of considerable controversy. Some pathologist 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 horses get older the hair becomes whiter while the skin stays black in colour.

Consequences of melanoma

The main effects are due to their space occupying nature but in some tissue locations can have a serious functional consequence.

- A melanoma within the spinal cord could be extremely benign in its pathological character but the clinical consequences may be catastrophic.
- A melanoma in the sub nodal interventricular septum of the heart may cause severe cardiac dysrhythmia – even resulting in a complete 3rd degree heart block or death.
- Massive perianal melanomas can result in defecation and urination problems. In mares they may create reproductive difficulties with both mating and parturition.

Melanomas can result in an unacceptable distortion of the local anatomy in various organs with perhaps the commonest of these sites being the parotid (throat) region below the ear. In these cases, there may be enormous expansion of the tumour masses. In spite of this they seldom cause significant functional problems. Airway distortions and pressure can however, occasionally arise.

Types of melanoma

Guttural pouch and parotid melanoma

Melanoma masses are commonly found in the throat/parotid region where they may involve the lymph nodes and parotid salivary gland. They can reach massive proportions but do not often create any airway obstructions. These lesions are invariably secondary to other melanomas in the skin.

All cases showing cutaneous melanoma should be examined endoscopically for any guttural melanoma in the parotid region.
pouch involvement prior to any treatment at all. The presence of melanosis or melanoma within the pouches indicates that multiple areas may be affected. Most grey horses will have at least some melanosis visible on the mucosa of the guttural pouch. It can show as tiny black spots – most often on the outer surface, but can be almost anywhere.

Most often melanoma will be found on the mucosa overlying the maxillary artery, and sometimes on the other major arteries and veins within the pouch. In a few cases these major arteries can burst causing a rapid fatal bleed.

Interestingly, repeated endoscopy confirms that these do not always remain static. They may expand slowly or regress and “re-appear” at other sites. The clinical appearances of guttural pouch melanomas are like “splashes of black paint”. There may be larger or smaller areas involved, as well as tiny lesions.

- Since melanoma does not occur naturally in the lining of the guttural pouches, the tumours have to derive from another source. This means that although those lesions within the guttural pouches can be very static, they must indicate the presence of a disseminating source.

Parotid involvement is a relatively common form of melanoma and in some cases the expansion can be massive. There is seldom any major clinical consequence with parotid involvement. Parotid melanomas are rarely ulcerated unless they are interfered with by surgical biopsy.

The more serious and aggressive forms are much more obvious as spherical or unevenly spherical shaped tumours. Sometimes malignant forms are this shape also. Usually they have a shiny surface and 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 may bleed considerably giving a misleading diagnosis of guttural pouch mycosis.

The presence of these lesions can be used as an index of the rate of progression of internal melanoma because they are relatively protected and unlikely to be significantly affected by other factors such as external or self-trauma.
Intraocular melanoma

A few melanomas occur in the eye itself; usually associated with the pigmented epithelium of the iris. Intraocular melanoma seldom becomes malignant, but the space occupying nature does compromise vision and corneal endothelial and iris function.

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 causes contact corneal oedema and non-ulcerative keratopathy.

The most common forms encountered in the eyes of 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. Primary iridal melanomas have no increased tendency to malignancy as far as the authors experience will allow such a statement! They are usually very slow growing and can sometimes remain symptom free for life.

In a few cases, contact between the tumour and the corneal endothelium can cause a significant keratopathy and consequent pain and opacity. A few cases expand into the vitreous and cause serious visual defects, glaucoma or posterior segment haemorrhages. Retinal lesions are very rare but there is no information on the effects these small
Malignant melanoma

The malignant forms of melanoma are usually highly aggressive with rapid widespread dissemination of multiple 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 (again the abnormal 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 Syndrom if the tumours constrict or alter the function of the nerves 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, more likely to be malignant and non-specialist interference should probably 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.

Typically, malignancy carries a very poor prognosis, although some cases survive for reasonable periods of time.

*Veterinary surgeons will always consider the possibility that any clinical sign could be caused by melanoma. This includes colic, ataxia, blindness, weight loss, lameness, muscle wasting and altered brain function.*

**Diagnosis**

Diagnosis of melanoma in the typical sites is relatively straightforward.

It is not usually necessary to biopsy the lesions but a fine needle aspirate will probably not have any dissemination implications from 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 small (2ml max) syringe attached to a fine (21g max) 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 for staining and microscopic examination.

- The cells can be stained specifically, 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 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.

Malignant forms may be recognised clinically if the tumour is visible and ulcerated, but otherwise a pathologist is an important aid to the clinical process.

**Treatment/management options**

Melanoma is probably best regarded as untreatable but manageable 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 development of the condition we are unlikely to be able to either cure or prevent their occurrence.

The most basic concepts relating to this tumour type include the following aspects:

- Melanoma always starts out small, benign and visible (almost all primary tumours are in the skin and should be identifiable!)
  - At this stage they are easy and safe to remove
- Over 80% of melanomas will become malignant in time – some will be sooner and some later. There is little that can be seen in the early stages of that which indicates transition to malignancy; later on they may ulcerate, change from black to grey or even fleshy pink.
  - At this stage there is probably an obligation to remove them to reduce the risk of spreading as much as possible. It is often however too late already to stop the spread since this probably happens very early in the disease progression.
• There is no treatment for disseminated/spread melanoma at present – some improvements can be made with a variety of treatment/management options
• It is far better to deal with tumours when they are small, easy and [relatively] safe
  o Removing small tumours reduces the tumour burden and reduces the risk of transition to malignancy and reduces the threat to important internal organs and structures.

Benign Neglect

Many cases are conventionally managed by benign neglect. This is based on the premise that they may not alter significantly for many years and meantime may have no material effect on the horse. However, if this option is chosen, they 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 not really be taken to indicate the behaviour of all the others; every tumour has its own pathological behaviour!

It may take years before the condition is either cosmetically/socially unacceptable or becomes functionally important. Indeed, the horse may die with the condition rather than because of it. The problem is that this is fine in retrospect but is no help to a seriously affected horse that is going to die because of the condition.

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 breeding stallions by the author without any secondary consequences.
• Tumours that have a functionally limiting effect (such as in the eyelid or iris) are probably best removed surgically.
Cryosurgery

Cryonecrosis of melanoma lesions is a relatively fast but rarely effective method of treatment. Lesions that are ulcerated and which bleed significantly can sometimes be managed by careful and repeated cryosurgery.

- On the eyelids this is probably not advisable because of the consequent scarring.

Cryosurgery can be combined with local chemotherapy to get a better overall effect.

Cimetidine

Oral cimetidine therapy has been reported to be successful in some cases of melanoma, but its value in specific types 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. As it is relatively simple it is at least an option. Cimetidine is administered by mouth at 3.5mg/kg (q 12h) or 7.5mg/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 there is a response then the treatment continue until 3 weeks after there is no further improvement.

The value of long-term treatment is uncertain with no current scientific reports of a significant response. In the very few cases that are reported to respond at all, pulse treatments applied for 4 weeks every 8 weeks may be capable of maintaining an improvement. The results of this protocol are almost impossible to assess without a more detailed trial that badly needs to be done.

Recent research has confirmed that this is not an effective way of managing melanoma and should probably not be used.

Cisplatin

The value of cisplatin is also uncertain but there are reports of successes with a cisplatin/sesame oil emulsion containing 1mg cisplatin per ml. The material can be infiltrated into the lesion at fortnightly intervals. Some improvements are reported.
Melanoma vaccines

Development in the management of human malignant melanoma using X-irradiated autogenous melanoma cells suggested 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. Anti-tyrosinase vaccines are now commercially available for dogs (ONCEPT™, Merial, USA) in which there are reports of successes. There are also reports of significant benefit from these in a few equine cases; as a rule cures are not achieved (that would be very surprising!) but some remission and stabilisation of growth rates seems more commonly reported (Brazil, 2015).

However, there is no consensus on the value and unpredictability of the results which make the method a bit of a lottery that costs a lot of money for a ticket!

Radiation

Radiation treatment has a surprisingly poor effect on melanoma tumours. High doses of gamma radiation delivered via a linear iridium 192 source had no material effect on one case treated at Liverpool University. Similarly, beta radiation also had no effect when applied to lesions on the lower lids of a horse.

Long term outlook

The prognosis for life in an uncomplicated case of cutaneous melanoma in a grey horse is usually good. Many affected horses live normal lives and it is often simply the cosmetic and social appearance of the tumours that result in the animal being destroyed. However, it is wise to point out that the disease is unpredictable. Even small tumours in “inconvenient” sites could 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 dysrrhythmia) 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 tumours or those 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 for owners of grey and cremello horses in particular.

Profound muscle wasting of the right gluteal muscles arising from a spinal cord melanoma

Nicitans prolapse as a result of exphthalamos due to an orbital/retrobulbar melanoma.
If you want to learn more have a look at:

Other interesting reading and reference material:


