The clinical challenges of the equine periorbital sarcoid

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The equine sarcoid affects horses of all ages, types, and colours without obvious sex predilection and is commonly encountered worldwide. It is by far the commonest equine skin neoplasm (Jackson, 1936; Thomsett, 1979; Pascoe and Summers, 1981; Genetzky, Biwer and Myers, 1983; Marti, Lazary and Gerber, 1993; Broström, 1995). Although the sarcoid has been recognised for centuries (Erk, 1976), it was first characterised by Jackson in 1936. He defined the sarcoid as *"a unique locally invasive, benign neoplastic like tumour of the skin with a variable epidermal component which has a high propensity for recurrence."* The name sarcoid (meaning flesh-like) was used to emphasise the clinical and pathological differences from papilloma, fibroma, and fibrosarcoma and to suggest the malignant sarcomatous appearance of the lesions. Pathologically the equine sarcoid has been categorised as a benign tumour of fibrous tissue (Hendrick and others, 1998). The periocular skin is a recognised predilection site (Knottenbelt, 2009) (Figure 1).

Whilst the pathological features of the equine sarcoid are generally well recognised there is still debate over the possible aetiology. The epidemiology and clinical behaviour of the equine sarcoid are strongly suggestive of an infectious / contagious origin (Lory and others, 1993; Otten et al, 1993; Reid, Smith and Jarrett, 1994; Bloch, Breen and Spradbrow, 1994). Specifically, the Bovine Papillomavirus 1 (BPV1) has been implicated by the finding of a genome that resembles that of the bovine virus in sarcoids (Reid, Smith and Jarrett, 1994; Nasir and Reid, 1999). A retrovirus aetiology has also been proposed (England, Watson and Larson, 1973; Cheevers, Faemi-Nainie and Anderson, 1986). The role of viruses in the aetiology of neoplastic disease has been summarised by Baldwin (1981) and the putative specific features associated with papilloma virus and neoplasia is summarised by Arbeit (1993) and Cotran, Kumar and Robbins (1994).

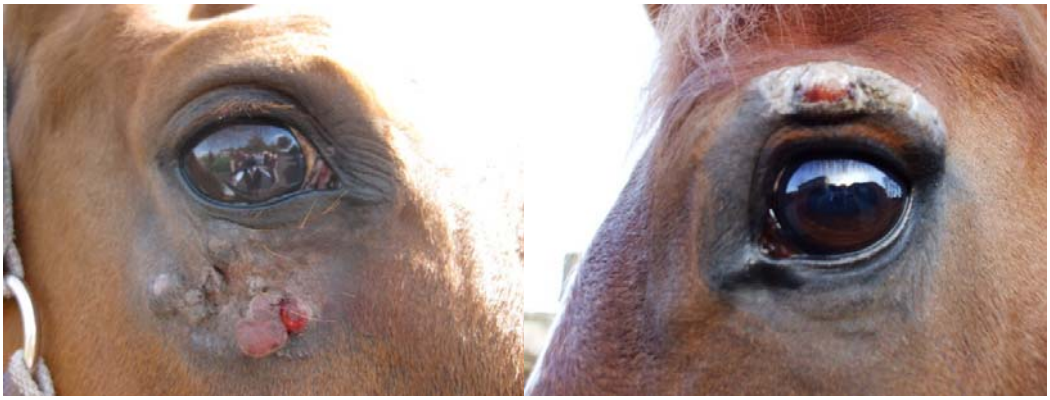


Figure 1: Typical examples of the equine sarcoid affecting the periorbital skin. The major challenges centre on the invasive nature of almost all sarcoids in this site and treatments that involve scarring and deformity can have a profound effect on eyelid function.

A strong genetic predisposition has been identified with over 80% of affected horses being MHC class II alleles (Lazary and others, 1985; Meredith and others, 1986). Strong familial tendencies to sarcoid have been described (James, 1968; Marti and others, 1993).

The distribution of sarcoids and their tendency to proliferate on an individual horse is consistent with an infectious agent. However, the rapid and predictable expansion that is characteristic of sarcoids developing in wounds in particular, introduces the possibility that the vector (assumed to be flies) is possibly transmitting transformed fibroblast cells rather than the virus itself. Most lesions are found in the upper eyelid and the medial canthus is far more often involved than the lateral canthus. This might reflect where flies prefer to feed. Observation of the behaviour of flies on sarcoid affected horses shows the preference that surface-feeding flies have for sarcoid. Laursen (1987) suggested that flies may be significant in the epidemiology of the equine

sarcoid. The clinical distribution and epidemiology of sarcoids suggests that an infectious agent may be involved and that a vector may be responsible for its development at particular sites. Periorbital sarcoids most often develop at the eyelid margins where the skin is thin and hair cover is sparse.

Sarcoids are recognised as having 6 different clinical manifestations (Knottenbelt**,** 2005; Knottenbelt, 2009) and can occur at any cutaneous site but the clinical management of periorbital tumours is known to have serious difficulties (Lavach, 1989). The notorious difficulties with treatment of sarcoids in particular make the prognosis for periorbital sarcoid very guarded (Ragland, Keown and Spencer, 1970; Raphel, 1982; Madewell and Theilen, 1987; McConaghy, Davis and Hodgson, 1994). The function of the eyelid is critical to the health of the eye and the thin elastic nature of the eyelid skin introduces further difficulties. Complications can arise directly or indirectly from the treatment but failure to treat the tumours at this site can also have severe consequences for vision and use for riding Knottenbelt, Edwards and Daniel, 1995).

Diagnosis of sarcoid usually depends on a combination of clinical suspicion and biopsy. Although the histological appearance of the sarcoid fibroblast is not recognisably different from that of normal fibroblasts, Cochrane (1996) has identified that *in vitro* cultures are notably different in both physical appearance and in growth characteristics. The invasive nature of the periocular sarcoid is major constraint upon treatment. Where treatment results in scarring and contraction of the eyelid or a loss of eyelid function, there is an inevitable penalty to pay. Clearly upper eyelid problems are more severe and indeed the histological features of a deep invasive nature may go some way towards explaining why treatment of these lesions (no matter how small they are) is so difficult.

Figure 2: Figure 3: Attempts to remove sarcoids from the eyelids surgically carry a poor prognosis since it is hard to reconcile the need to remove all the sarcoid tissue with preservation of the tissue and its function. Inadequate tissue removal results in recurrence (top left and right) and complete removal can result in unacceptable cicatrisation and loss of function (bottom left and right).

Individual lesions can be clinically classified according to their visual gross appearance (Knottenbelt 2005). The variable nature of the equine sarcoid makes specific classification difficult in some cases but where multiple lesions occur in an individual horse or when more than one of the recognised types is located within one affected area, the diagnosis can justifiably be assumed in almost every circumstance. The challenges of biopsy for confirmation are well recognised but up to the present time the risks of exacerbation have not been

quantified. Interference with a sarcoid (at any site, but particularly in the periorbital region) by trauma, biopsy or partial treatment can result in dramatic deterioration with extensive subcutaneous involvement and frequently conversion to an aggressive fibroblastic lesion (Roberts, 1970; Knottenbelt and Walker, 1994)). Unless appropriate therapy is instituted immediately after the results of the biopsy the process of biopsy appears to have the same effect on overall prognosis as unsuccessful attempts at treatment. Over the last 40 years the author has recorded the effects of biopsy (admittedly not exclusively however on eyelid sarcoids) and from 549 cases in which biopsy of one lesion was performed but not followed up by treatment, exacerbation was present in 86% of cases. This study used each animal as its own control since only horses with another broadly similar sarcoid on its body that was not biopsied, were included. It can probably be justifiably stated that if biopsy is to be performed a plan for treatment should be available immediately after diagnosis is confirmed.

1. **Occult sarcoid**: The affected skin area was hairless or the hair was altered (quantity / density, colour altered and reduced length). Careful palpation commonly revealed small, sub-epidermal, miliary nodules or plaques within the affected regions. Figure 2 shows typical examples of the occult periorbital sarcoid. Alternative diagnoses to be considered for these lesions include dermatophytosis (ringworm), alopecia areata, idiopathic periorbital vitiligo, rub marks, and traumatic superficial abrasive dermatitis (abrasions and scratches).

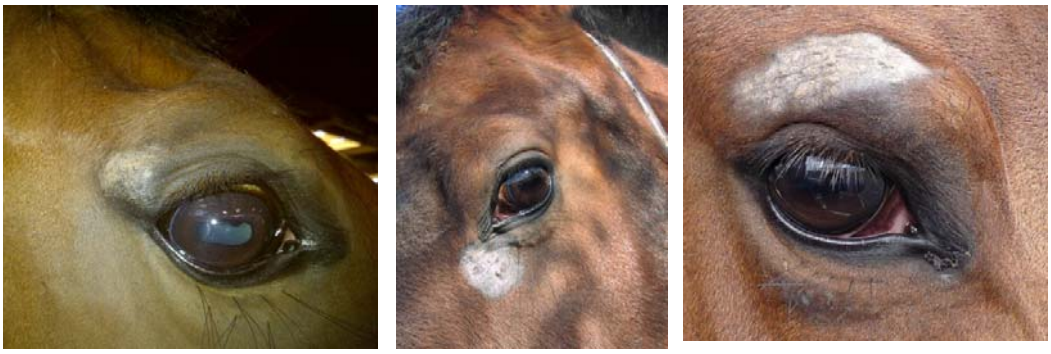


Figure 4: Typical occult sarcoid in the peri-ocular skin. Note the alopecia and prominent hyperkeratosis / scaling. Careful palpation will usually reveal minute (or larger) papules within the skin itself.

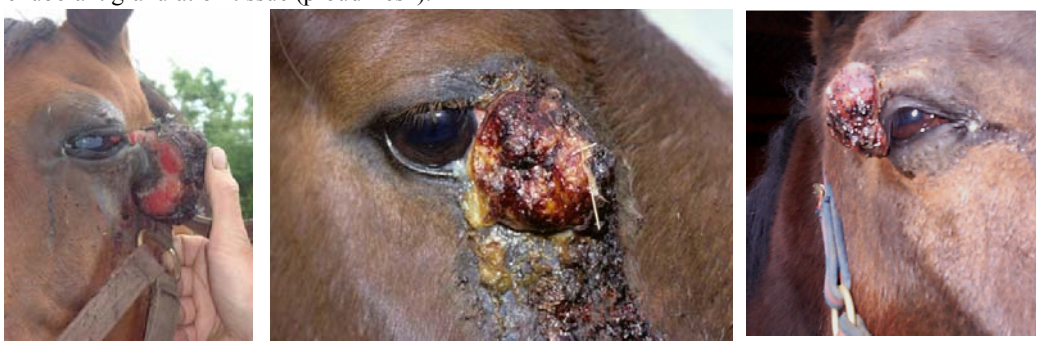
2. **Verrucose sarcoid**: The skin is characteristically alopecic, thickened and has a hyperkeratotic appearance with extensive flaking of the surface of the epidermis. Small or more extensive areas of ulceration are present in many cases. Miliary nodules can often be palpated within the affected skin. Typical examples of periorbital verrucose sarcoid are shown in Figure 4. The differential diagnoses included dermatophytosis, dermatophilosis, viral papilloma and superficial abrasions (recurrent) although the appearance is really very characteristic.

Figure 5: Verrucous sarcoids have a warty appearance that explains the name! They can be large and extensive or more focal. They can also ulcerate.

3. Nodular Sarcoid: Two types of nodular sarcoid are recognisable. Both are solid, spherical or ovoid and have a well-defined palpable outline. Nodular Type A are entirely subcutaneous with no apparent epidermal component detectable by palpation (Figure 4). Nodular Type B have varying involvement of overlying skin. Sometimes there is little involvement (Figure 4) and in others this is much more extensive (Figure 4). The overlying or adjacent skin often shows typical verrucose or occult changes. Foreign body reactions, abscesses, scarring and cutaneous, sebaceous cysts and other non-sarcoid neoplasia were considered in the differential diagnosis of this type.

Figure 6: Nodular sarcoids can be single or multiple and can involve the skin - usually with obvious attachment to a verrucose or occult lesion overlying it. These cases show some typical examples. Note the Type B nodules in to left and Type A in top right. The large Type A nodule in the lower left picture is part of amuch wider verrucose problem.

4. Fibroblastic sarcoid: These have a fleshy, ulcerated appearance and can b divided into two types. Fibroblastic Type 1 sarcoids are pedunculated with a limited, or faint base palpable within the skin (Figure 5). Fibroblastic Type 2 are broader based (sessile) without a recognisable pedicle and often have a diffuse, ill-defined margin with significant thickening palpable beyond the obvious margins of the lesion (Figure 5). The differential diagnosis included squamous cell carcinoma, habronemiasis and exuberant granulation tissue (proud flesh).



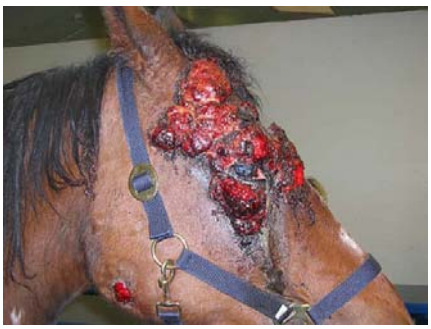


Figure 7: The cardinal features of the fibroblastic sarcoid include an ulcerated surface and a fleshy aggressive appearance. The can be pedunculated (Type1) or sessile (Type 2). They can be very aggressive as shown here – the bottom left picture could be justifiably termed malignant.

5. Mixed sarcoid: In this category individual lesions have the characteristics of two or more of the other more defined types (Figure 6). Various mixed lesions are encountered but most involve both nodular and verrucose components. Diagnosis of these lesions is usually relatively straightforward and there are no other common diseases that have this appearance.

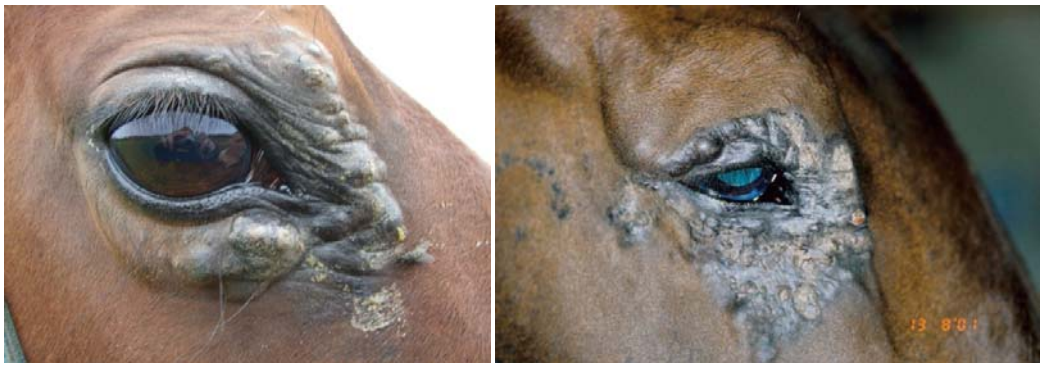


Figure 8: Mixed sarcoids have aspects of more than one of the recognised type but no predominate type.

6. Malignant (aggressive) sarcoid: This unusual form is even rarer around the eye than at other sites but it can occur. It is characterised by aggressive nodules and cords of palpable tumour or highly invasive and destructive (see figure 5). The growth of these masses is usually faster than other types but in a few cases progression is slow (over some years).

Even in severe cases, sarcoids appear to cause little inconvenience but some can be sufficiently large or so situated as to cause some difficulty with eyelid function. Secondary corneal ulceration can develop and obstruction of the naso-lachrymal duct is encountered relatively frequently. The lesions themselves are rarely pruritic and seldom painful on palpation. Ulcerated lesions may become secondarily infected but this is seldom a significant problem. The large majority of periorbital sarcoids start as occult, verrucose or nodular lesions. In many cases owners are unable to define the onset of the disease but typically most report that the growth was slow or sometimes static for many years. In general, nodular, occult or verrucose forms cause little concern to owners until expansion is noticeable. Where the fibroblastic type develops it is usually highly aggressive with faster growth so that treatment is usually sought within a short time.

Murray, Ladds and Campbell, (1978) demonstrated that even the most benign sarcoid lesions at other body sites may have delicate sinuous cords of tumour tissue extending away from the obvious microscopic boundaries of the lesion. In their cases they described only verrucose and fibroblastic lesions and noted that underlying muscle was seldom invaded. Knottenbelt and Kelly (2000) however, found that periorbital sarcoids have a quite different nature. Extension into adjacent muscles is common if not invariable and so treatment is bound to be problematical. The relatively poor results following surgical excision or cryosurgery are entirely understandable when the pathological characteristics of the lesion at this site are appreciated. Effective treatment probably requires removal of most tumour cells either physically or immunologically. Furthermore, when periorbital tissue is diffusely infiltrated by sarcoid, resolution might not be feasible without compromising the muscles and other tissues of the eyelid. Secondary effects from distortion or cicatrization of the eyelid can be very serious and no case should be subjected to these approaches without full consideration and explanation of the possible consequences.

The histological components of the equine sarcoid can include, in variable proportions, fibroblasts, epidermis, and capillaries. In periorbital sarcoids the fibroblastic component is marked, with anisocytosis, and there is local invasion of this tissue into adjacent muscle, connective tissue and nerves. The periorbital sarcoids have variable density of the proliferating connective tissue: some are relatively dense, others are looser, with plentiful intercellular glycosaminoglycan, giving a myxomatous appearance. These variable histological features may result in periorbital sarcoids being given a variety of other histological designations such as neurofibroma, neurofibrosarcoma, myxosarcoma, and fibromyxosarcoma.

The clinically important consideration is that periorbital sarcoids, regardless of histological variation, behave as locally aggressive connective tissue tumours and current diagnostic practice here is to designate all as sarcoid. The use of alternative synonymous histological designations can cause confusion, for both clinicians and owners. These low-grade malignancies at this anatomical site consequently provide particular difficulties in diagnosis and treatment. Although Ivascu and others (1974) used the term sarcoidosis, it is important to recognise that the equine sarcoid is not similar (or probably related) to the disease recognised as Equine Sarcoidosis (Knottenbelt, 2009). The latter is a generalised systemic granulomatous disorder that does have some cutaneous manifestations in some horses. An additional complication with the diagnosis of equine sarcoid is the clinical (visual) similarity between granulation tissue and the fibroblastic form of sarcoid. Differentiation of the two can be difficult because of the common admixture that can develops (Pascoe and Knottenbelt, 1998). However, this is neither a particular nor a common feature of the periorbital sarcoid.

As can be readily recognised from the histological appearance described above, surgical excision of periorbital sarcoids may be fraught with danger. Failure to completely remove the lesion at the first attempt results in deterioration in the clinical behaviour of the regrowth and furthermore worsens the prognosis significantly. Many of the early cases encountered in te series of cases descried by Knottenbelt and Kelly (2000) had been subjected to previous treatment either by the owner (usually involving homeopathic or natural remedies, steroid or keratolytic creams and lotions) or by the attending veterinarian (usually involving surgical excision or cryosurgery or BCG immunomodulation therapy). The cases with the worst prognosis are those that had been unsuccessfully treated several times previously (by whatever method). Even serious cases respond better to the first treatment than the histologically more benign lesions that have received previous unsuccessful therapy.

Diagnostic confirmation by means of biopsy may be specifically contraindicated (Pascoe, 1973, Knottenbelt, 2009). While diagnoses such as fibroma, fibrosarcoma and neurofibroma are possible on histological grounds **most** of these are best regarded as variants of the equine sarcoid. It is possible that the name sarcoid causes more problems with diagnosis than a more definite pathological description and there have been suggestions that the name should therefore be abandoned (Broström, 1995). True fibrosarcoma is extremely rare in horses and the nerve sheath tumours may have similarities with the equine sarcoid. Interestingly, the described history of cases involving previous biopsy of nodular, fibroblastic and verrucose lesions at which various other neoplastic diagnoses were made but which when presented some months later were clearly sarcoid (Knottenbelt and Kelly, 2000) It may be therefore that the diagnosis of these disorders reflects different histological patterns of the equine sarcoid either as result of the characteristics of the sarcoid itself, or of the genetic phenotype of the host or of the specific host-tumour relationship. Although the diagnosis of single lesions can be problematical, the large majority of the horses have more than one periorbital sarcoid and many have lesions fulfilling the clinical criteria for sarcoid at other sites on the body. Single palpebral or periorbital lesions do occur with some frequency with an average of per case over 6 periorbital sarcoids being common in the study by Knottenbelt and Kelly 2000).

Each type of sarcoid has some recognisable clinical behaviour patterns but there are notable exceptions in individual cases. Although for the most part, occult and verrucose lesions around the eye are inclined to remain static (often for many years), some will deteriorate rapidly for no apparent reason. Nodular lesions around the eye generally enlarge progressively over some years but some deteriorate quickly and many of these became ulcerated and patently fibroblastic, emphasising the unpredictability of this lesion!

Although Broström (1995) reported that sarcoids were inclined to develop more aggressively in younger horses and then regress over the life of the horse, Knottenbelt and Kelly (2000) found no similar experience. Spontaneous regression of sarcoids has been recognised in occasional cases for many years (Roberts, 1970; Lane, 1977; Stannard and Pulley, 1978; Brostrom 1995) but this is neither common nor a reliable reason to delay treatment interventions. The reasons for spontaneous regression encountered at other sites are cited as being immunologically based (Broström, 1995) but are probably not a simple matter of primary humoral immunity. By contrast to the viral papilloma and the bovine papilloma virus-induced fibroma (Lancaster and Olson, 1980), no seroconversion to papillomavirus has yet been identified in horses with naturally occurring sarcoid (Broström; 1995). There are clearly some very interesting, poorly understood, aspects of the growth and regression of lesions: environmental factors, iatrogenic or accidental trauma / interference, histocompatibility antigens and genetic factors may be important. The significance of spontaneous, total remission is easy to appreciate but the reasons for it are uncertain. Genuine, total resolution developing simultaneously in different sarcoid types at disparate sites on the body could suggest that there may be an exploitable immunological response. No matter how it is triggered at other sites, periorbital sarcoids appear to be more resistant to the natural spontaneous regression that is occasionally seen at other sites. Lane (1977) notes a remote benefit when a single (or multiple) sarcoids was subjected to cryosurgical necrosis. This was attributed to the "release" of cryoantigens but again this is not a reliable expectation. The current widespread use of autologous subcutaneous implantation of frozen blocks of sarcoid is reported to carry high rates of success but it is hard to visualise why the method should suddenly be "effective" in 2011 when the same method has been found on 3 previous occasions to be ineffective at best and dangerous at worst.

Typically, clinicians in practice aren't very concerned with the classification of sarcoid – they are usually much more interested in what treatment is available. However, since there are well over 40 different treatments published, each with its advantages and disadvantages, it is important to recognise the significant relationships between successful (and unsuccessful) treatment and the sarcoid type present. The fact that there are so many different treatments implies that no one is universally effective and that even with very strict selection criteria there are likely to be failures. Any treatment that purports to be 100% effective is probably suspicious!

Each method has its specific constraints – usually relating to the type of tissue destruction and the lack of specificity for sarcoid. Constraints of Treatment selection was based upon the character, size, exact location, and any complicating factors such as diffuse eyelid involvement or involvement of the nasolacrimal duct or palpebral punctae. The choice of treatment was inevitably directed towards the method currently considered to be most likely to be successful (based on the authors' experience, literature reports and availability). Treatment was selected to provide the best possible prognosis for the case within the financial and technical constraints. In some cases financial considerations proved to be a major limiting factor while in others logistic and technical limitations significantly affected the choice. For these reasons it was not possible to randomise the treatment methods.

The methods available include:

- **Benign Neglect**
- **Surgical excision** (including sharp surgery / laser / ligation / diathermy)
- **Cryosurgery**
- **Radiofrequency hyperthermia**
- **BCG immunomodulation**
- **Radiation brachytherapy** (gamma radiation) / **Radiation** (beta radiation):
- **Photodynamic Therapy**
- **Cisplatin (Intralesional emulsion injection or slow release cisplatin beads)**:
- **Intra-lesional 5 fluorouracil**
- **AW 4 topical treatment**
- **Topical 5% 5 fluorouracil cream**[1] (Efudix®, Roche)
- **Tazarotene** (0.1% gel) (Zorac®)
- **Imiquimod** (Aldara®)
- **Autologous grafting**

Many different therapeutic approaches to sarcoid treatment have been tried and, while at most other sites some flexibility can be tolerated, this is not the case for the periorbital skin – indeed even successful removal of the lesion often leaves a legacy of disability and secondary complications. The fact that many treatment methods have been suggested for the equine sarcoid probably suggests that no single one is universally effective; certainly most practitioners will recognise the frustrations of dealing with this disease. Treatment of periorbital sarcoids in particular has been viewed with considerable trepidation (Ragland, Keown and Spencer, 1970; Raphel, 1982; Madewell and Theilen, 1987; Lavach, 1989; McConaghy, Davis and Hodgson, 1994). The treatment method selected for each case in this series was based on clinical features of the lesion(s) and upon a combination of the owners' resources and the author's experience with the disease. This inevitably resulted in a bias in the treatment selection towards success rather than randomised treatments that might have provided a better overall critical comparison of the methods. Nevertheless, clinicians will inevitably find themselves in the position of having to employ treatment modalities that are known or suspected as being less than ideal for financial or other reasons. This may explain some cases of lesion exacerbation or recurrence.

[1] (*Efudix*, Roche Ltd, UK)

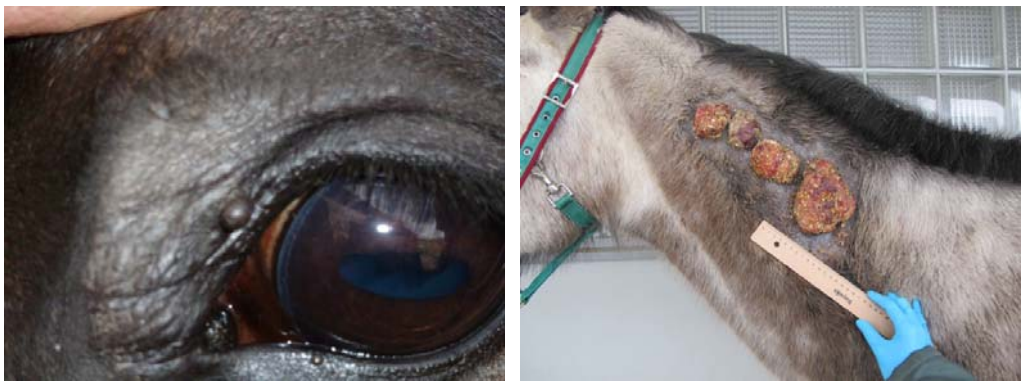


Figure 9: This horse had multiple sarcoids including a diffuse verrucose sarcoid in its left upper eyelid. It was subjected to autologous implantation with disastrous results at the site of the grafting and a complete lack of any detectable efficacy.

Broström, (1995) and Raphel (1982) noted that the periorbital sarcoid (and those at the coronet) presented special problems requiring treatment modalities other than surgical excision. The periorbital sarcoid has reputation for being difficult to manage; many are subjected to a variety of ill-advised interference. Sarcoids of all types have a reputation for more aggressive recurrence after surgical excision (Jackson, 1936) that is likely to require more aggressive surgery (Pascoe and Summers, 1981). The reason for this can be appreciated by reference to the histological appearance (Figure Path6). Broström (1995) reported that, in the general surgical treatment of equine sarcoids, wide excision under general anaesthesia significantly reduced the rate of recurrence and concluded that repeated surgical excision would eventually resolve sarcoid tumours in over 90% of cases. However, such an approach around the eye is probably impossible unless they are Nodular Type 1. Failure to resolve the lesion will inevitably lead to a more extensive and more aggressive lesion requiring more intrusive surgery. Even then, for surgery to be successful it is almost inevitable that some muscular compromise will occur and while this may not be limiting in carefully selected individual lesions in most cases the function of the eyelid will be impaired to some extent. Lesions on the upper lid are most liable to have serious secondary complications because the upper lid has a more prominent role in the blink reflexes and infiltration of the deeper tissues seems to be more aggressive in the upper lid.

Figure 10: Left: This horse had a severe palpebral fibroblastic sarcoid. Enucleation was carried out in an ill-advised approach to treatment and in spite of that (hardly uprising!) the sarcoid recurred. Right: A diffuse verrucose sarcoid was surgically removed from the upper eyelid but recurrence of a n aggressive fibroblastic sarcoid occurred at 2 sites (plus a small central one!) s at around 9 weeks post surgery. It is fair to say that surgical excision can work however!

Failure to resolve the lesion at the first attempt is therefore likely to have a significant worsening of the prognosis for any subsequent attempt (using any method of treatment). This unhappy combination of

circumstances makes surgery dangerous at best. Knottenbelt and Kelly (2000) suggests that, for the most part, periorbital sarcoids should not be subjected to surgical interference. When surgery is being performed the basic principle of minimal contamination techniques (SMART SURGERY) is paramount. This means that the sarcoid needs to be "isolated" from the surgical site by whatever means is convenient. Swabs an, instruments and surgical gloves can be means of transfer of cells from ukcerated (or even non-ulcerated) lesions into the operative site (see Figure 10).

The value of the experimental material AW4-LUDES is very limited in the treatment of periorbital sarcoid. At other sites this preparation appears to have some promise (Knottenbelt and Walker 1994). However, the invasive and destructive nature of the material makes its use generally inappropriate around the eye. The secondary consequences of treatment on the eyelids and the eye itself can be very serious.

Intralesional cisplatin has been used widely and very successfully in cases referred to the University of Davis California. Theon (1997) and Theon et al. (2007) have reported s long term non-recurrence rates well over 90% using a stable emulsion of cisplatin. The method is critical to success and typically of any neoplastic treatment surgical debulking is a good adjunct where that is possible.

Recent studies have confirmed the benefits of imiquimod (Nogueira et al., 2006). This material (marketed as *Aldara*) has antiviral and antitumour effects and is used for treatment of genital warts in humans. The author has used this material on around 80 cases so far with some good successes and some failures it has to be said. The material is owner applied and so is an economic option compared to many others but it use requires particular methods. The previous application has to be removed before the next one is applied – this can be very painful and is resented by most horses. The course of treatment is the other major problem – courses of over 3 months with twice weekly applications is usually required.

The remarkably effective immunotherapy associated with BCG cell wall fraction or live BCG bacillus intradermal vaccine (BCG Intradermal Vaccine, Evans, UK) is particularly interesting. Intra-tumoral injection of periorbital nodular and (some) fibroblastic lesions with BCG (and similar protein materials) has been found to resolve a significant number of cases (Wyman and others, 1977; Winston, Rings and Wyman, 1979; Webster and Webster, 1985; Theilen and Madewell, 1987; Rebhun, 1987; Lavach and others, 1985; Houlton, 1983; Gelatt, 1982; Flemming, 1983; Broström, 1995; Knottenbelt and Kelly, 2000). Owen and Jagger (1987) treated a series of periorbital sarcoids with BCG cell wall fraction and obtained a cure rate of 100%. The cosmetic effects are invariably relatively pleasing in spite of the presence in some cases of a chronic discharging sinus tract. The more superficial types of sarcoid respond less well – probably because intralesional injection, which appears to be a prerequisite for success, is more problematic. Indeed it seems that this method may be contraindicated for these lesions. The BCG acts locally as a non-specific immune stimulant, strongly attracting macrophages to the site where it induces significant protective changes in macrophage activity and in T lymphocyte function in particular (including killer and natural killer cells) (1981; Davies, 1982; Lavach and others, 1985; Misdorp and others, 1985; Theilen and Madewell, 1987; Audibert and Lise, 1993; Cotran, Kumar and Robbins, 1994, Broström, 1995). Ensuring that the material is injected truly intralesionally further enhances the results. Knottenbelt and Kelly (2000) suggest that the volume of injected solution made from the BCG vaccine affects prognosis rather than the actual weight of antigen used although clearly there are dose related effects – big tumours will inevitably need more BCG and excessive dilution with small amounts is probably inevitably going to fail. The basic principle appears to be that the material must be injected intralesionally and that the more careful this is the better the outcome and the fewer the number of injections that need to be given. There are anecdotal reports of successful treatment following a single or two injections given 1 – 4 weeks apart but over the large series reported by Knottenbelt and Kelly, 5 doses was average. Furthermore, the costs and the risks of complications may be reduced by the use of lesser amounts of the antigen and ensuring that it is injected truly intralesionally. This might also explain why the verrucose or occult lesion are far less responsive to the method – it is virtually impossible to define the margins of such lesions and to ensure that the material is injected into sarcoid tissue when the lesion is very superficial. Complications included swelling of the lesion over 2 – 14 days following injection and a few cases developed a chronic

discharging sinus tract that required some surgical interference before total resolution. Also, there are low but real risks of anaphylactic responses unless suitable precautions are taken in advance of the injection. In previously untreated cases it is unlikely that a reaction will occur with the first 2 injections but it seems wise to premedicate in any case with dexamethasone and flunixin (and possibly an antihistamine such as tripelennamine). Adequate emergency anaphylactic drugs should be available whenever this method is used.

Careful consideration and selection of cases is required before performing cryosurgery on periorbital sarcoids. Cryosurgery has limited success in the treatment of periorbital sarcoids in most circumstances but again the operator experience and the concurrent use of an effective chemotherapeutic agent such as cisplatin or 5-fluorouracil will improve the outcome significantly. Typically, failure to resolve the lesions appears to result in deterioration with transformation towards the fibroblastic type of sarcoid. Cases subjected to cryosurgery seem to take an inordinate time to heal sometimes taking nearly 12 months. Biopsy of the wound sites in these cases may revealed granulation tissue interspersed with sarcoid tissue. Resolution will then require other treatment methods.

CO_2 YAG / diode laser surgery, such as that described by Diel and others (1987) and Vingerhoets and others, 1988) can be very effective treatment – the method has singular advantage in limiting seeding of the operative site with cells desquamated from the surface of the lesion or released from cut "roots" of the main mass. From published descriptions it would seem that it may be useful. However, it is also bound to suffer from the same limitations as conventional and cryosurgery when applied to periorbital lesions. The method clearly has promise and we await further reports with interest.

Figure 11: This fibroblastic sarcoid was removed by laser surgical excision. Total resolution was achieved with no recurrence after 12 years.

Hoffman and other (1983) achieved good results with radiofrequency current induced hyperthermia but the author has very limited experience with this method.

Photodynamic therapy is becoming more readily available and the method has singular advantages when it is performed by an experienced operator. It is easy to do irreparable harm also! The same can be said for electrochemotherapy – a method that has been recently described for the treatment of sarcoid (Tamzali et al., 2012); there is no reports of its use specifically around the eye.

Gamma radiation interstitial brachytherapy delivered via radio-gold seeds (Au^{198}) (Wyn-Jones 1979) and $iridium^{192}$ linear sources (Wyn-Jones 1983) has been used in a series of cases of periorbital neoplasia including a number of sarcoids. Remission rates in excess of 90% for the sarcoid lesions, were reported in both methods with a prolonged follow-up period of over 12 months. Other reports have likewise generally reported success rates over 90% (Turrel and Koblik, 1983; Turrel and Stover, 1985; Then and Pascoe 1995; Knottenbelt 2000; Byam Cook, Hanson and Slater, 2006), but some longer-term remission rates are lower (Frauenfelder, Blevins and Page, 1982). It is not clear whether the lower rates are associated with regrowth or the occurrence of new lesions at the same or adjacent sites. The high success rate is not surprising; radiation is probably the best treatment for periorbital sarcoid. The cosmetic effect of the slower delivery isotopes is generally superior to the other methods. However, there are potential (theoretical) complications including (transient) corneal opacity, cataract formation, or necrosis of the underlying orbital bone (with possible sequestration).

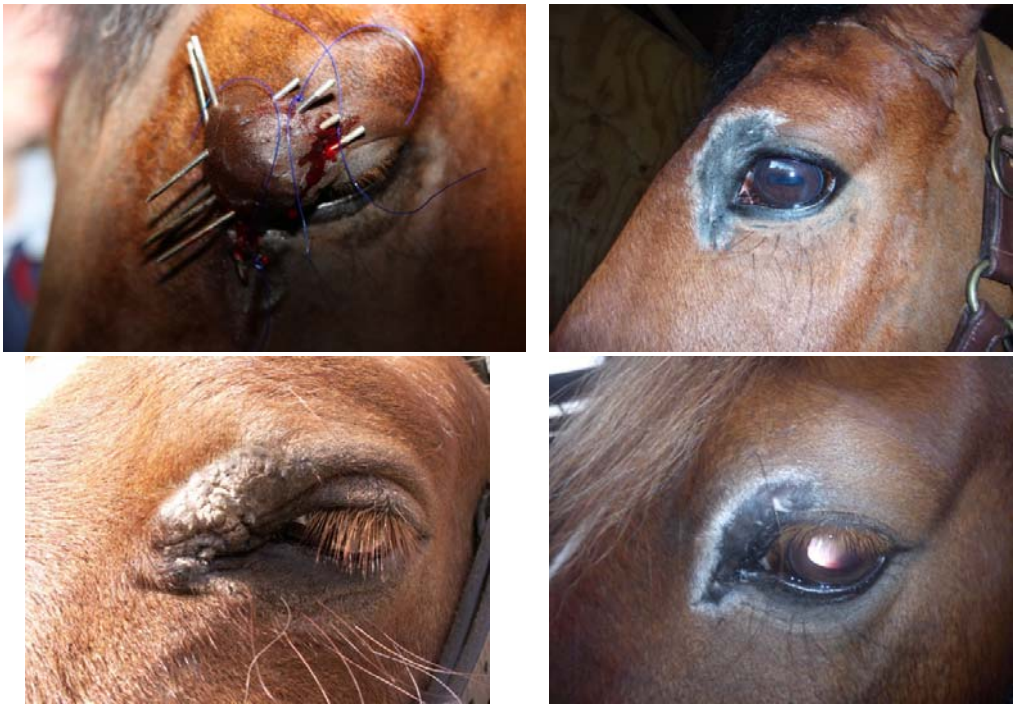


Figure 12: Radiation brachytherapy that delivers 60 – 70 Gy of radiation results in a very acceptable cosmetic effect and almost over 90% success.

When considering radiation personal safety of the veterinarian must be paramount. The half-life of radio gold (Au^{198}) is about 48 hours and so, in order to deliver effective radiation, the initial dose must be very high. Thus, the operator faces significant personal hazard when dealing with this isotope. Iridium, by contrast, has a half-life of 72 days and so the implants can be inserted with relative safety but the sources require to be removed and this necessitates a second potential exposure. Isolation in a radiation protection loose box for 10 – 14 days is required and can be logistically difficult. Methods involving remote after loading using very high dose iridium are far safer but logistically more demanding of facility and technique.

A wide range of homeopathic or other alternative approaches such as acupuncture and herbal remedies are reported in the "appropriately banal" literature. Many owners have tried these – invariably without success prior to referral. There are reported successes admittedly but it is not clear whether these are either genuine or that the treated lesion was sarcoid! There are many anecdotal reports of success but so far no substantial clinical trial has been published to my knowledge. The anecdotal reports of previous attempts by owners and by "homeopathic veterinary surgeons" (and others) suggest that such treatments are not, at present, useful options.

Management of periorbital sarcoids continues to provide clinicians in primary practice and referral centres with significant challenges. Individual veterinary surgeons will undoubtedly have their own "best" treatment and it would seem unwise to interfere with any protocol that results in consistently good results. An early decision to treat periorbital sarcoids needs to be made if the risk of complications is to be minimised. There is some merit in the benign neglect approach but almost invariably, sooner or later, they will erupt into a much more aggressive lesion possibly even warranting the destruction of the horse. Opinions based on retrospective cases are not helpful in identifying the likely "dangerous" cases from those that may remain benign and insignificant for many years. In my experience there are no clinical or pathological features that allow those lesions that will not progress to be identified and therefore left without treatment. However, as with any clinically challenging clinicians need to take extra precautions to warn owners of the particular problems inherent in treatment of the sarcoid at this anatomical site.

SUMMARY: Most conventional treatment methods for sarcoids at other skin sites are not applicable to the periorbital region. Adequate surgical removal, cryosurgery or laser excision is almost impossible and concurrent chemotherapy is to be encouraged since that will significantly improve the results. The unpredictable extent of local invasion of the eyelids and periorbital skin suggest that treatment by these methods should be considered very cautiously, since treatment may make the clinical problem worse. Application of creams such as 5% fluorouracil and AW4-LUDES is problematical because of the possible contact with the eye itself and only superficial lesions well away from the eyelid and those without deep involvement are amenable to these methods. More aggressive topical therapy is clearly impossible at this site because of cicatrisation and secondary severe consequences. Radiation brachytherapy is the best approach to periorbital sarcoid of all types. It is effective in nearly 100% of cases and has very acceptable cosmetic results with little or no side effects. Nodular, and some localised, fibroblastic sarcoids may respond well to intralesional BCG injections and this may be an effective first line approach. Intralesional cisplatin injections has some value but there are logistic problems with its use and currently several different regimens are being explored.

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