

# Satellite Article

## Vasculitis: just what does it mean?

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### Introduction

**Vasculitis** (syn. **arteritis**, **angiitis**) is a descriptive term applied to inflammation of arteries, veins and capillaries in variable proportions. The pathology is associated with a wide range of diseases; **it is not itself a diagnosis**. A number of specific and nonspecific vasculitis disorders are recognised in all species but it is a comparatively rare event in horses. Although in human medicine and, to a somewhat lesser extent, small animal medicine, a wide range of different syndromes are recognised, relatively few occur in horses and these are poorly categorised broad clinical descriptions are therefore usually used. The names applied to other species are used for horses, but often there are significant differences and this may not, therefore, be justified and may result in misleading interpretations, treatments and prognosis.

### Clinical considerations

Cases in which vasculitis is a feature offer considerable diagnostic and therapeutic challenges. It can occur in any vessel at any site and may therefore affect a limited area or a single organ, such as the skin, or multiple organ systems. The wide range of vessels means that almost any organ system can be moderately or severely compromised, leading to an **almost infinite range of clinical signs with a corresponding array of differential diagnoses**. It is not clear why, in some cases, the condition remains localised while, in others, a more general pathology is present.

**Clearly, the resulting clinical signs and prognosis depend on the organ system and the extent of the problem.** In the horse, it seems that the **postcapillary venules** are the most affected vessels, but some specific diseases affect other blood vessels, e.g. equine **viral arteritis**. Most of the significant sporadic diseases result in at least some dermatological signs, but their nonspecific nature may make a definitive diagnosis problematical. Remarkably, the lesions are more often found on the distal limbs but the upper limb regions, pinnae, muzzle, periocular area, and ventral abdomen may be affected. **Lesions are not usually symmetrical.** There are histological features that help the diagnosis, and skin

biopsy can therefore be helpful. **Without cutaneous signs, the diagnosis is usually restricted to clinical inference alone and the presence of oedema is a helpful sign but should not be overinterpreted.** Systemic signs may be associated specifically with the oedema (including respiratory stridor, central nervous signs and cardiac dysfunction).

### Pathological considerations

Vasculitis can be **primary** or **secondary** to another underlying disease. Some of the more common forms of vasculitis are shown in **Table 1**.

- **Primary vasculitis** is often directly associated with infectious disease. **African horse sickness (AHS)**, **equine viral arteritis (EVA)**; Timoney and McCollum 1993), **equine infectious anaemia (EIA)** and **equine ehrlichiosis** are characterised by primary vasculitis. In these diseases, the inflammatory responses result primarily from nonimmunological stimuli released by the injured vascular endothelial and intimal cells. Apart from the direct effects of the pathogen (nonimmunological stimuli), immune complexes are probably laid down within the damaged area and these may cause an exaggerated inflammatory response.

**TABLE 1: The recognised syndromes characterised by vasculitis in horses**

#### Infectious conditions

- i) African horse sickness (AHS)
- ii) Equine viral arteritis (EVA)
- iii) Equine infectious anaemia
- iv) Equine ehrlichiosis

#### Immune-mediated conditions

- i) *Purpura haemorrhagica*
- ii) Systemic lupus erythematosus-like syndrome of horses
- iii) Drug eruptions
- iv) Paraneoplastic vasculitis
- v) Idiopathic immune-mediated vasculitis

#### Physical conditions

- i) Trauma-induced (focal or regional) vasculitis
- ii) Photo-activated vasculitis (of nonpigmented skin)
- iii) Pastern and cannon leucocytoclastic vasculitis



**Fig 1: A horse with toxic vasculitis showing prominent circular cutaneous necrosis primarily affecting the distal limbs. There were no significant petechial haemorrhages and little oedema. This case was found to have arterial occlusion.**

- **Secondary vasculitis:** The large majority of noninfectious vasculitides, and indeed some of the infectious ones too, have an immunological basis. Immune responses may be initiated by heterologous antigens, such as viruses and injected proteins (and some drugs), and by auto-antigens (such as immunoglobulins) and other endogenous proteins.

**The evidence for an immunological aetiopathogenesis includes** the pathological similarity to hypersensitivity responses typical of the Arthus Reaction. Rich (1942) noted that hypersensitivity (immune) responses caused vasculitis in human patients following injection with virus carrying horse serum, in sulphonamide-treated patients and in rabbits. Subsequently, vasculitis (of this specific type) was found to be the result of the deposition of circulating immune complexes in small vessel walls (Dixon *et al.* 1958). This deposition results in activation of inflammatory effector cells (such as neutrophils, plasma cells, platelets and endothelial cells) and precipitates an acute inflammatory response. Furthermore, DNA and anti-DNA immune complexes can often be found associated with some of the conditions, such as systemic erythematosus-like syndrome of horses (SLE). It is usually suggested that the response is a combination of *Types I and III* hypersensitivity reactions (Manning and Sweeney 1986). The process also promotes coagulation and thrombotic occlusion of small vessels. The combination of vascular thrombosis and a prominent inflammatory response results in vascular necrosis, haemorrhage and continuing thrombosis.

### **Diagnostic considerations**

The importance of vasculitis in the equine species is undisputed and it is a considerable therapeutic handicap that we do not have the full gamut of diagnostic procedures to confirm the primary problem. The most common pathological response is leucocytoclastosis, in which neutrophilic nuclear



**Fig 2: This series of pictures illustrates a generalised vasculitis in a case of systemic lupus erythematosus-like syndrome of horses. There was involvement of joints, eye and skin and general signs of major organ damage. The signs resolved rapidly with high-dose prednisolone therapy, but recurred when it was reduced.**

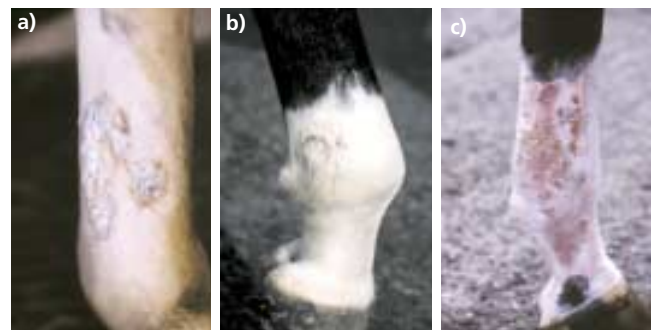


**Fig 3:** Cutaneous petechial and echymosomal haemorrhages and severe ventral and limb oedema in a coloured mare with an jejuno-jejunal intussusception. The vasculitis in this case was probably due to endotoxaemia.

debris is deposited in and around the vessels (Morris 1998). Vasculitis is often accompanied by necrosis of blood vessels and thrombotic occlusion of the affected vessels. The relative locations of the inflammatory response and the thrombosis may significantly alter the overt clinical signs; oedema and petechial haemorrhages on stressed mucosae may be present or absent. Thrombosis of arterioles in the absence of capillary damage may result in necrosis rather than oedema or petechiation, while occlusion of venules with capillary endothelial damage probably results in both. It is difficult, however, to visualise a circumstance where petechiation occurs in the absence of protein leakage into the interstitial space, such as is reported in the present interesting case



**Fig 4:** Prominent limb oedema in a characteristic form typical of purpura haemorrhagica. The gelding had recovered from an upper respiratory tract virus with a secondary streptococcal infection some weeks previously. It is also possible that the vasculitis was at least partially related to prolonged penicillin treatment. In spite of aggressive steroid treatment, this horse developed severe cerebral oedema and was destroyed.



**Fig 5:** The characteristic features of pastern and cannon leucocytoclastic vasculitis showing skin necrosis restricted to the lateral aspect of the white limbs. Figure 5c shows the appearance of the skin after close clipping. The case was diagnosed with vasculitis from skin biopsy and responded simply to avoidance of sunlight.

by Garcia *et al.* (2002). In severe cases, there may be a more extensive sloughing and exudation of the skin.

## Discussion

The fact that the skin is commonly involved with petechiation and/or oedema and/or overt skin necrosis (Morris 1987; **Fig 1**) means that clinicians usually have some visible evidence of disease and will have the opportunity to obtain biopsy material to help the diagnostic process. In some cases, such as EVA and AHS, cutaneous vessels may not obviously be involved. No matter how the initial immune complex deposition occurs, the final common pathway is largely similar.

Vascular inflammation, with adhesion of leucocytes to endothelial cells, the invasion of the vascular wall by inflammatory cells and necrotising injury, lead to haemorrhage, plasma leakage and thrombosis (**Fig 2**). Therefore, the histological appearance would be expected to be similar and a pathological diagnosis is therefore reliant upon supportive clinical, serological and/or

immunohistochemical tests. For example, **immune complexes** on vascular endothelium might indicate an immune complex pathogenesis, while detection of **anti-basement membrane antibody** might suggest antibody-mediated vascular injury. A primary cause may be identifiable. Conditions such as systemic lupus erythematosus-like syndrome of horses, **purpura haemorrhagica** (Fig 2) and drug eruptions usually have an immunological basis, although the actual pathogenesis is not always apparent or understood.

While many of the immunological conditions resulting in vasculitis have an infectious origin, some do not; and it may then be difficult to establish the true aetiology. In the case described by Garcia *et al.*, evidence for the infectious origin of the problem was circumstantial but convincing. In the horse, vasculitis may be a feature of endotoxaemia (Fig 3), radiation exposure (including primary and secondary actinic dermatitis and photosensitisation), physical and chemical injury and some specific poisonings. A significant number of cases may be a result of drug administration and it is essential, therefore, to obtain a complete history before making a diagnosis. **Common things occur commonly, and the case reminds us of the need to consider the history of the case and its contact animals.**

Primary cases usually show other signs that are more or less pathognomonic, and the presence or absence of vasculitis is simply a component of the underlying disease. **The case described by Garcia and colleagues is interesting because of the absence of oedema.** By far the majority of cases develop oedema because the venules are the vascular structure most often affected in horses (Morris 1986). Furthermore, damage to the capillary walls causes an increased permeability and leakage of protein and possibly cells.

**The oedema resulting from vasculitis has some significant differences from other causes of abnormal extracellular fluid accumulation.** Because of the protein leakage and persisting vascular damage, it is difficult for the fluid to be removed by normal osmotic means or by the lymphatic vessels. Therefore, the oedema is generally more persistent and may not subside simply with gentle exercise. In this respect, of course, it can be similar to the oedema that occurs with lymphangitis, but again this form is seldom severe unless there is concurrent vasculitis/cellulitis and lymphangitis (Fig 4).

In many cases of vasculitis (however caused), leakage of red cells into the extracellular fluid results in the typical purpuric appearance with petechial and sometimes ecchymotic haemorrhages in stressed mucosae throughout the body, such as the nasal and oral mucosa and the vulva (Fig 3). The presence or absence of petechial haemorrhages is often used to confirm or refute a diagnosis of vasculitis, implying that leakage and purpuric or petechial haemorrhages need to be present for the diagnosis to be made. This again is probably too simplistic; **when haemorrhages are present the diagnosis may be supported** (so long as there are no other reasons for the sign to be present).

**Purpura haemorrhagica** is probably the most widely recognised clinically significant immune-mediated vasculitis of horses. This condition illustrates many of the classical general

signs of an acute, noncontagious neutrophilic necrotising vasculitis with 'typical' clinical signs and history. It is generally accepted that streptococcal infections are involved in the pathogenesis of most cases (Scott 1988; Timoney 1993), but it can also be a sequel to equine Influenza. Prominent limb and head and neck oedema, and petechial haemorrhages in the oral and respiratory mucosae, are the major presenting signs in most cases. These signs are typical of a necrotising vasculitis in which there is variable leakage of plasma proteins and fluid into the tissues. Oedema is a significant feature of almost every case (Fig 4).

**In the case described in the accompanying paper,** the possible causes of absence of oedema include occlusion of end-arteries (possibly independently or concurrently with capillaries and venules) and an absence of capillary wall permeability (possibly resulting from deposition of immune complexes without destruction). In the former case, the dynamics of oedema formation are not met; arterial blood is simply shunted away or becomes static behind a plug of coagulated blood. Oedema may not form under these conditions. In cases where damage to the capillaries results in nonpermeable vessel walls, there may be no net movement of fluid into the extracellular space either; furthermore, under these conditions large protein molecules may still be retained in the circulation. Again, clinically significant oedema may not be present. However, the presence of petechiation is difficult to explain under these conditions.

**Photo-activated vasculitis** and pastern and cannon **leucocytoclastic vasculitis** (PCLCCV) (Fig 5) are two very interesting forms of secondary vasculitis in which actinic radiation is probably the trigger factor (Stannard 1987). The former condition is encountered when photodynamic agents (including some plant toxins or phylloerythrin) accumulate in the skin. Activation causes release of inflammatory mediators and a prominent vasculitis is a feature of this. PCLCCV is a recently described condition in which there is a localised vasculitis affecting primarily the distal lateral aspect of nonpigmented limbs. **There are many enigmatic features of this disease.** Oedema and haemorrhages are not a feature; superficial necrosis of the skin is the main presenting sign. The condition is restricted to white limbs and, more often, the lateral aspect of white hindlimbs. The correlation with sunlight is strongly suggestive of a photo-activated condition.

**Auto-antibodies can also be responsible for the development of immune-mediated vasculitis** and this is given as the reason for the development of systemic lupus erythematosus-like syndrome (Stannard 1996). However, true Lupus cells may not be a common occurrence in horses and antinuclear antibodies may be difficult to detect. Paraneoplastic vasculitis arising from tumour antigens is rare in horses; probably because the systemic neoplastic diseases are themselves rare.

The management of cases of vasculitis depends on both the cause and the target organs. Multiple organ involvement such as occurs in systemic erythematosus-like syndrome of horses (Pascoe and Knottenbelt 1999) usually has a much more problematic disease course than single organ vasculitis.

Management requires that the primary cause is treated and that the resulting inflammatory responses are suppressed, usually with corticosteroids at high doses for prolonged periods. However, such steroid therapy might specifically be contraindicated in infectious vasculitis conditions.

**The immune-mediated vasculitides have attracted little research enthusiasm, but they deserve far greater attention because they are important and the effects can be far reaching with multi-organ involvement.**

## References

- Dixon, F.J., Vasquez, J.J. and Weigle, W.O. (1958) Pathogenesis of serum sickness. *Arch. Pathol.* **65**, 18-22.
- Garcia, E., Costa, L.R.R., McClure-Blackmer, J.M. and Foil, C.S. (2002) Necrotising vasculitis without subcutaneous oedema in a miniature horse. *Equine vet. Educ.* **14**, 243-246.
- Manning, T.O. and Sweeney, C. (1986) Immune mediated equine skin diseases. *Comp. cont. Educ. pract. Vet.* **12**, 979-987.
- Morris, D.D. (1986) Vasculitis in horses. In: *Proceedings of the American Veterinary Medical Association*. pp 3-8.
- Morris, D.D. (1987) Cutaneous vasculitis in horses: 19 cases (1978-1985). *J. Am. vet. med. Ass.* **191**, 460-464.
- Morris, D.D. (1998) Diseases of the hemolymphatic system In: *Equine Medicine*, Eds: S.M. Reed and W.R. Bayly, W.B. Saunders Co., Philadelphia. pp 579-582.
- Pascoe, R.R. and Knottenbelt, D.C. (1999) Immune mediated and allergic diseases. In: *Manual of Equine Dermatology*, W.B. Saunders Co., London. pp 164-168.
- Rich, A.R. (1942) The role of hypersensitivity in periarteritis nodosa as indicated by 7 cases developing during serum sickness and sulphonamide therapy. *Bull. John Hoskins Hosp.* **71**, 123.
- Scott, D.W. (1988) Vasculitis. In: *Large Animal Dermatology*, W.B. Saunders Co., Philadelphia. pp 321-324.
- Stannard, A.A. (1987) Photoactivated vasculitis. In: *Current Therapy in Equine Medicine*, 2nd edn., Ed: N.E. Robinson, W.B. Saunders Co., Philadelphia. pp 646-647.
- Stannard, A.A. (1996) Pastern and cannon leucocytoclastic vasculitis. In: *Proceedings of The International Workshop on Equine Dermatology*, British Equine Veterinary Association, Newmarket. pp 56-59.
- Timoney, J.F. (1993) Strangles. *Vet. Clin. N. Am.* **9**, 295-309.
- Timoney, P.J. and McCollum, W.H. (1993) Equine viral arteritis. *Vet. Clin. N. Am.* **9**, 295-309.