AUTOIMMUNE SKIN DISEASES

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Bullous autoimmune skin diseases, characterized by the formation of bullae or vesicles, are divided into two groups dependent on the location of clefts and the formation of bullae within the skin. In the pemphigus group of diseases the vesicles form intradermally; in pemphigoid the clefts occur at the dermal epidermal junction.

The primary lesion of pemphigus is acantholysis in which the epidermal cells lose their adhesion, separate from one another and become rounded. The loss of cellular adhesion is due to autoantibody directed to one or more of the cell adhesion proteins, particularly the desmosomal antigens of the keratinocytes of stratified squamous epithelium. Marked heterogeneity of desmosomal antigens of squamous epithelium occurs dependent on the degree of maturation and differentiation of the keratinocytes within the epithelium. In vitro studies of cultured keratinocytes have shown differences in antigenic expression dependent on culture conditions. Thus antigen expression in vivo, may also depend on the location and function of squamous epithelium in different areas of the body.1,2

The two distinct disease entities of pemphigus are distinguished by the site of epidermal clefting. Antibody in pemphigus foliaceous is bound primarily to desmoglein 1 of more mature cells in the subcorneal or granular layer resulting in superficial vesicles. Antibody in pemphigus vulgaris binds to desmoglein 3 of basal cells and sometimes one or two suprabasal cell layers forming suprabasilar clefts. Additionally, pemphigus may be drug induced or occur secondarily to primary neoplasia (paraneoplastic pemphigus). Pemphigus foliaceous is the most common form of pemphigus in the horse. It affects horses of all ages, breeds and sex. Because of the superficial nature the primary lesions of vesicles and pustules are often not clinically recognized and the presenting signs are of an exfoliative dermatitis with crusts, scales, erosions, epidermal collarettes and alopecia.1,3,4 Many horses are painful and approximately 50% are pruritic, especially in hot, humid weather and/or when exposed to intense solar radiation.5 Pain and pruritis often cause self inflicted trauma which result in numerous secondary lesions.

Lesion distribution varies considerably. Lesions may initially occur in a generalized distribution. Lesions may begin on the dorsal body surface of the neck and back and spread ventrally or they may begin ventrally and spread dorsally. Horses with lesions that begin on the limbs generally have lesions associated with the coronary bands, pasterns and fetlocks which are often confluent. In other cases that begin with a dorsal distribution, lesions may be found over the entire dorsum, sparing the limbs and head, on the head only or regionally on the neck. Lesions may be confined to the axillary and perineal areas and the head. Lesions may rapidly generalize in 2 to 4 weeks or remain localized for months. In general, lesion distribution is symmetric, chronic and progressive.1,3-6

Horses may have concurrent clinical and laboratory signs of systemic illness. Clinical signs include depression, decreased appetite, weight loss, ventral and limb edema, and pyrexia. Abnormal laboratory findings include a mild normocytic normochromic anemia, neutrophilia, mild hypoalbuminemia and hypergammaglobulinemia.1,3,5 In our clinic it is common for the client to report some degree of depression (mild behavior change) and slight decrease in appetite. The number and severity of other systemic signs generally correlate with the severity of the skin lesions (generalized vs. localized) and their duration.

Differential diagnosis includes dermatophytosis, dermatophilosis, parasitic dermatitis
including onchocerciasis, culicoides hypersensitivity and ventral midline dermatitis, seborrhea complex, bacterial folliculitis, contact dermatitis, drug eruptions, equine exfoliative dermatitis and sarcoidosis. Definitive diagnosis is made from the history, physical examination, cytologic evaluation of direct smears, and skin biopsies for histologic evaluation.

Laboratory evaluation of direct smears and skin biopsies is dependent on proper sampling of primary lesions. Because of the transient nature of vesicles and pustules the horse may have to be carefully examined for several days to ensure sampling of newly formed lesions. Microscopic examination of cytologic preparations of lesions usually reveal numerous acanthocytes (large, rounded darkly staining epithelial cells), nondegenerate neutrophils and/or eosinophils with no intracellular bacteria. Skin biopsies for histological evaluation are generally most successfully obtained by a wedge biopsy across an intact lesion that is pinned prior to fixation in 10% buffered neutral formalin. Because of the superficial nature of the bullae and associated crusts, surgical preparation of the biopsy site should not be done. Histopathologic changes include acantholysis within the stratum corneum or a granulosum with clefts, vesicles or pustules. Hair follicles may be similarly affected. Acantholytic cells may be found singularly or in clusters with neutrophils and/or eosinophils within the lesions or on the surface of erosions. Trichophyton equinum infections may have crusts and acantholytic cells and mimic the cytologic and histologic findings of pemphigus, thus fungal stains should be performed on all biopsies taken to rule out pemphigus.

The importance of correlating historical, physical and laboratory findings to diagnose pemphigus is emphasized by a group of horses seen in our clinic that suffered from Culicoides spp. and other insect hypersensitivities for 1-3 years prior to the onset of pemphigus foliaceous. The history typically reveals a seasonal pruritic dermatitis that responds to insect avoidance management that becomes progressively worse each season. Clinical presentation at the time of positive direct immunofluorescent testing and characteristic histopathologic changes of the skin usually occurs in the winter. Recent history from the client complaint notes that the pruritis and/or lesion development do not subside with cooler temperatures and decrease in the insect population. Careful examination of the horse will usually reveal characteristic new lesions often in locations not typical of insect hypersensitivity. The pathogenesis of pemphigus foliaceous subsequent to insect hypersensitivity is unknown. A human variant of pemphigus foliaceous, Brazilian pemphigus, occurs in well defined areas of unimproved jungle of South America and is associated with a particular species of Simulian flies. Passive antibody studies have shown Brazilian pemphigus to be a true autoimmune disease. The incidence is higher in certain families of genetically related people and is not contagious. Although controversy exists on the presence or absence of a viral agent the current hypothesis is against an infectious agent. Chronic inflammation may result in transformation of epidermal cell antigens or antibodies to components of insect saliva may cross react with epidermal cell antigens.

Although some cases of pemphigus resolve spontaneously most require substantial doses of systemic corticosteroids with or without the use of other immunosuppressive drugs. Since treatment may result in severe adverse side effects it is important to fully evaluate the patient prior to treatment. Supportive care, particularly in hot humid climates, will help speed the response to therapy. Affected horses should be protected from sunlight as ultraviolet light is known to aggravate lesions and often produces an intense burning sensation in humans. Gentle cleansing of the skin, particularly in hot weather when sweating occurs, will minimize pruritis. Minimal topical agents such as commercial horse shampoos and fly repellents should be used as these compounds often aggravate skin lesions. Fly control is best provided by strategically
placed fans to prevent insects from landing.

Initial treatment with 1.5 – 2.5 mg/kg of prednisone or prednisolone per os once daily will usually result in a cessation of new lesions and improvement in skin condition in 10-20 days. Because of the limited and variable bioavailability of prednisone, some horses may not respond to this drug. Once remission has occurred, the total dose of prednisone may be decreased by 50 mg every 5-7 days until a maintenance level is reached. Alternate day therapy can then be initiated with the lowest effective dose. Horses not controlled by prednisone may be controlled with 0.02 – 0.1 mg/kg of dexamethasone given in a similar regimen. Many horses do not respond to corticosteroid treatment alone. Multimodal treatment with one or a combination of therapies will often give more favorable results. Adjunctive therapy with essential fatty acids (Omega Horse Shine®, Omega Fields, info@omegafields.com or Omega Max®, Triple Crown Nutrition, Inc. www.triplecrownfeed.com) and vitamin E (13 IU/kg/day PO) often work well with steroid therapy. Pentoxyfylline (8-10 mg/kg PO 2-3 times/day) may decrease the production of inflammatory cytokines and modulate the immune response. Azothioprine (2-3 mg/kg PO q 24 hrs for 3-4 weeks and then every other day) is an immune suppressive drug and can be used as a “steroid sparing” drug when adverse effects of steroids are anticipated or occur. Alternatively gold salt therapy (aurothiomalate) may be used. Patients are given 2 test doses of 20 mg and 40 mg/IM one week apart and then 1 mg/kg weekly until remission. Concurrent use of corticosteroids during the first 3 to 6 weeks of gold salt therapy may help resolution of lesions. Once remission occurs maintenance therapy consists of injections of 1 mg/kg every 3-6 weeks. Although side effects of gold therapy are common in other species (dermatitis, stomatitis, proteinuria, blood dyscrasias) adverse reactions have not been reported in the horse. It is advisable, however, to monitor patients with biweekly CBC’s and weekly urinalysis during initial therapy and then every 2-3 months during maintenance therapy. (Note: Currently aurothiomalate and other gold compounds are only available in Canada.)

Many cases treated for 3-6 months and then removed from therapy remain in remission for weeks to years. Reoccurrence has occurred as long as 21/2 years after cessation of therapy. In general the sooner reoccurrence occurs or if reoccurrence occurs on maintenance therapy the harder it is to control the disease in the future. Many horses with pemphigus foliaceous are not alive one year after diagnosis. Although successful medical management the majority of cases is probably possible, many owners become discouraged and frustrated at the expense and “inexact science” of managing chronically affected cases.

**Pemphigus vulgaris** with suprabasilar vesicle formation, although common in the dog and man, is not common in the horse. Two cases have been diagnosed in our clinic in the last 25 years. Recently a case has been reported in the literature. **Bullous pemphigoid**, characterized by clefting at the dermal epidermal junction and the deposition of immunoglobulins and complement in the basement membrane of the basal epithelial cells, is also rare. Antibodies in pemphigoid are directed against the basilar surface of the epithelial cells and, on direct immunofluorescent testing, are found in a linear deposit along the basal cell basement membrane. Complement deposition is heavy and may obscure immunoglobulin deposition on direct immunofluorescent testing. The 4 cases documented in the literature and the 3 cases diagnosed in our clinic have been characterized by large lesions and prominent Nikolsky’s sign, in which new clefts are easily formed by the application of digital shearing force to the skin. All of the horses were severely systemically ill and were nonresponsive to therapy. Two cases had corneal lesions and one case at the University of Georgia had immunoglobulin deposits within the kidney.
No single concept has emerged concerning the cause of bullous autoimmune skin diseases. Experimental animal studies infer that the diseases result from a range of genetic and immunological abnormalities which may be influenced by environment that differ from one individual to the next. Because some cases remain in remission without continuous therapy and others do not, there are likely many predisposing causes. Drug-induced and paraneoplastic pemphigus resolve (with therapy) once the inciting cause is removed. Other predisposing factors may include systemic diseases, stress and allergies.

**Alopecia areata**

Alopecia areata is a rare autoimmune disease that can have a variety of presentations and clinical progression that occurs in humans, dogs and equids. T lymphocytes directed against antigens of the hair matrix and root sheath epithelium result in hair loss. Autoantibodies directed against hair follicle antigens have also been demonstrated in cases of alopecia areata in the horse, however their significance is not yet known. Hereditary factors may be important in pathogenesis. Diffuse thinning of the mane and tail, formerly known as idiopathic dystrophy of the mane and tail, frequently found in Appaloosas, is now considered a form of alopecia areata. Alopecia areata also occurs as one or more circumscribed to patchy areas of alopecia on the body. The onset of alopecia may be gradual or rapid. Clinical signs may wax and wane in a synchronous (i.e. be more severe in summer or winter) or asynchronuom fashion. Periods of spontaneous remission may occur or affected areas of the skin may recover while other areas become affected. In most cases visual examination of the skin appears normal and the horse is not pruritic, although some cases with pathohistologic findings consistent with alopecia areata may have crusts, pruritus and/or pain. Alopecia areata should be considered as a rule out in cases where patchy, nonpruític, apparently noninflammatory alopecia occurs.

Diagnosis is confirmed by biopsy and histologic evaluation of newly affected areas of skin. Lymphocytic bulbitis is the pathognomonic finding with accumulations of lymphocytes in a "swarm of bees" pattern around hair bulbs in the anagen phase. Lymphocyte invasion of the of the matrix of the bulb and outer root sheath may also be seen, however these lesions often difficult to demonstrate and multiple biopsies may be needed.

Treatment is most effective with either topical or systemic corticosteroids. However, many cases respond poorly or not at all and long term immunosuppressive doses are needed. Thus, treatment may not be justified in every case, particularly if a prospective treatment trial is not effective.

Suggested Reading


References

8. Scott DW. Marked acantholysis associated with dermatophytosis due to Trichophyton equinum in two horses. Vet Dermatol 1194. 5: 105-110