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VETERINARY PROFESSIONAL DEVELOPMENT SERIES

IMMUNE-MEDIATED DISEASES OF THE DOG AND CAT III. IMMUNE-MEDIATED DISEASES OF THE INTEGUMENTARY, UROGENITAL, ENDOCRINE AND VASCULAR SYSTEMS

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SUMMARY

The first two articles in this series have covered the basis of the immune mediated diseases, systemic immune-mediated diseases and those that involve the haemolymphatic and musculoskeletal system. The purpose of this article is to cover the immune-mediated diseases that involve the integumentary, urogenital, endocrine and vascular systems.

INTEGUMENTARY SYSTEM

Autoimmune skin disorders are being diagnosed with increasing frequency in the dog, and to a lesser extent, the cat. This group of dermatoses can be divided into those which cause vesiculobullous lesions (pemphigus and bullous pemphigoid) and those which tend to cause ulceration and scarring (discoid lupus erythematosus and systemic lupus dermatosis). It is important to note that the intraepidermal bullae of the pemphigus type disorders are often transient and difficult to find. Thus, exudation and crusting are more typical lesions as the thin bullae rupture easily in the dog and cat.

There are many skin diseases with clinical or histological similarities to the autoimmune disorders discussed below. Differential diagnoses include the pustular eruptions of superficial pyoderma and subcorneal pustular dermatosis, toxic epidermal necrolysis, drug eruptions, the cutaneous lesions of dermatomyositis, and mucocutaneous mycoses such as candidiasis. Definitive histologic or immunologic diagnosis is often difficult to achieve due to improper selection of lesions for biopsy, chronic secondary lesions, or secondary bacterial infection. The most satisfactory diagnostic approach is a combination of criteria that include clinical appearance, histologic findings and results of immunologic tests. These criteria are discussed briefly below.

Pemphigus complex

Pemphigus disease is the result of the production of an autoantibody that is directed against the intercellular substance within the epidermis. This interaction can be associated with complement activation which results in the separation of epidermal cells and the formation of intra-epidermal bullae. The presence of complement however, is not mandatory for the development of the typical lesions. Deposition of antibody alone causes a physical separation of the cells, it is thought that this is associated with the release of proteases from the affected epidermal cells. The proteases further exacerbate the situation by digesting the intercellular substance. The deposition of the autoantibody in the epidermis varies, and in so doing gives rise to a number of Pemphigus diseases. Though the distribution of the lesions are quite different, they do appear to be caused by the same autoantibody. The mechanisms that influence both the variable deposition of the autoantibody and the distribution of the lesions are as yet unknown.

Pemphigus foliaceus. This disorder is the most common of the autoimmune skin diseases in the dog and cat. The disease usually has a gradual onset with lesions characterized by alopecia, a pustular eruption, crusting and erythema involving the nose, ears, and periorbita. Lesions frequently become generalized. Typically, there is no mucocutaneous or mucosal involvement. Affected individuals rarely exhibit systemic illness. Histologically the bullae of pemphigus foliaceus are subcorneal in location, and are characterized by the presence of acanthocytes, neutrophils and occasional eosinophils. Direct immunofluorescent techniques reveal an intercellular distribution of IgG, and occasionally, deposits of IgA, IgM or C3. The intercellular immunoglobulin deposits found in the pemphigus group of skin diseases are autoantibodies against some antigenic components of the intercellular cement substance.

Pemphigus erythematosus. Also known as Senear-Usher Syndrome, P. erythematosus is a mild disease of gradual onset with cutaneous lesions similar to both localized pemphigus foliaceus and systemic or discoid lupus erythematosus. Areas of depigmentation, exudation and crusting are present over the nose, ears and periorbita. The lesions may be exacerbated by exposure to sunlight. A subcorneal cleft containing acantholytic cells and neutrophils is seen histologically, and immunoglobulin or C3 can be demonstrated both intraepidermally and along the basement membrane using direct immunofluorescence. Occasionally a positive antinuclear antibody (ANA) test is also found in pemphigus erythematosus.

Pemphigus vulgaris. This disorder is the prototype of the autoimmune vesiculobullous diseases. It is less common in the dog and cat than pemphigus foliaceus. Affected animals are often acutely and severely ill, exhibiting ulcerations and erosions of the oral mucosa, mucocutaneous junctions and occasionally the nail beds. Fever, depression and secondary bacterial infections are not uncommon. Histopathology of the intact bullae reveals acanthocytes in a suprabasilar cleft. Direct immunofluorescence may detect deposits of IgG, IgA, or IgM in the intercellular spaces of the epidermis.

Pemphigus vegetans. This rare disorder is characterized by a generalized crusting, proliferative and exudative dermatitis with alopecia and ulceration. There are no mucosal lesions. Severely affected dogs may be systemically ill. Histopathology of the lesion reveals a suprabasilar cleft containing acanthocytes, inflammatory cells (predominantly neutrophils) and a hyperkeratotic epidermis. Intraepidermal immunoglobulin deposits are demonstrable by direct immunofluorescence.

Bullous pemphigoid

Bullous pemphigoid is the result of an autoantibody that is directed against a component of the epidermal basement membrane. The deposition of the autoantibody is associated with complement activation and disruption of the dermo-epidermal junction. The result of this is the formation of many subepidermal bullae which can cause a significant loss of epidermis in the patient. The autoantibody can be found on all the epidermal basement membrane although the entire skin surface need not be affected clinically.

Bullous pemphigoid. Both acute and chronic forms of this disease have been recognised in dogs. Many cases are intermediate in their clinical course. Acute bullous pemphigoid exhibits many of the clinical features of pemphigus vulgaris, including erythema, bullae formation and ulceration involving the mucocutaneous junctions, oral mucosa, and occasionally the head and ears. Acutely affected animals are often febrile and systemically ill. The chronic form is relatively benign and rarely results in systemic illness but the lesions can occasionally become generalized. Histopathology reveals subepidermal bullae containing eosinophils and neutrophils, but no acanthocytes. Due to the subepidermal location of the cleft, the bullae of bullous pemphigoid are more likely to be found intact in contrast to the intraepidermal bullae of the pemphigus group. Direct immunofluorescence usually reveals linear deposits of immunoglobulin and C3 along the dermo-epidermal junction. IgA, IgM and IgG are found with approximately equal frequency. Indirect immunofluorescence occasionally demonstrates circulating antibasement membrane antibodies, but the incidence and titers are considerably lower in the dog than in man.

Systemic lupus and discoid lupus erythematosus

The lupus diseases differ from one another in that SLE is a multisystemic disease whereas discoid lupus is a relatively benign cutaneous disease lacking systemic manifestations. The cutaneous forms of these diseases results from the deposition of immune complexes (DNA anti-DNA) at the basement membrane. In SLE, complexes can be found uniformly in affected and non-affected skin and as previously discussed is associated with a multisystemic disease. In contrast the deposition of immune complexes in discoid lupus is restricted to the lesions which have a typical distribution and is not associated with a multisystemic disease. Patients with discoid lupus do not have positive ANA and LE tests.

The lesions in both conditions typically include erythema, depigmentation, crusting and scarring affecting the nose, ears and head. As with pemphigus erythematosus, these lesions can be exacerbated by sunlight. Histologically, both of these lupus dermatoses exhibit liquefaction degeneration of the epidermal basal cells, dermo-epidermal separation, dermal edema, and deposition of fibrin and lymphocytes adjacent to the dermo-epidermal junction. Direct immunofluorescence shows granular deposits of immunoglobulin or C3 at the dermo-epidermal junction. In man, these deposits have been shown to represent DNA and anti-DNA complexes.

Therapy of autoimmune skin disorders includes immunosuppressive doses of prednisone or prednisolone in the range of 2–4 mg per kg divided twice daily. Severe refractory cases may respond to the addition of azathioprine or cyclophosphamide to the treatment regime. The success of gold salts (chrysotherapy) in refractory cases of canine pemphigus foliaceus and vulgaris has led to its more routine use in the past few years. Further details on cytotoxic and chrysotherapy are provided in Part IV of this series.

UROGENITAL SYSTEM

Glomerulonephritis. Circulating immune complexes are the most common cause of this disorder. The two most common forms in the dog are idiopathic and the glomerulonephritis of SLE. Other diseases which have been associated with glomerulonephritis (GN) include dirofilariasis, bacterial infections *(pyometra),* drug hypersensitivity (sulphadiazene), and neoplasia. In cats, the disorder is associated with feline leukaemia virus infection, or feline infectious peritonitis.

The hallmark of immune complex glomerulonephritis is proteinuria leading to hypoalbuminaemia. As the disease progresses, protein loss increases and emaciation, oedema, and uraemia become evident, heralding the nephrotic syndrome. Haematologic findings vary, but towards the end stage, non-regenerative anaemia, hypoproteinaemia, and hyperfibrinogenaemia prevail. The abnormal findings on serum biochemistries can include azotaemia, hypoalbuminaemia, hyperglobulinaemia, hypercholesterolaemia, and electrolyte disturbances reflective of end-stage renal failure. A urinalysis usually reveals proteinaceous or cellular cast formation, isosthenuria (late stages), and proteinuria.

Histologically, lesions vary but are characterized most often as membranous glomerulonephritis, with fibrous thickening of glomerular capillary loops and Bowman's capsule. Proliferative change may or may not be present. Deposits of IgG and/or C3 are detected along the glomerular basement membrane (GBM) in a granular pattern using direct immunofluorescent techniques. Methenamine-silver stains of kidney sections show a spiked appearance of the GBM, whereas electron microscopy shows the presence of subepithelial and intramembranous electron-dense deposits. In milder cases, light microscopic findings may be normal, or show only slight mesangial cell proliferation.

The diagnosis of glomerulonephritis of immune-complex origin is based upon the finding of persistent proteinuria and ultimately upon renal biopsy. Treatment consists largely of supportive nutritional, fluid, and electrolyte therapy. The benefit of anti-inflammatory or immunosuppressive therapy of glomerulonephritis has not been evaluated in animals. Presumably, therapeutic measures aimed at either the prevention of immune complex formation or their removal would be of benefit; however, no practical procedures are in routine use. The prognosis is grave in all cases for which no treatable underlying cause can be found.

Male infertility. The finding of high titers of autoantibody to sperm has been associated with testicular atrophy and infertility in dogs experimentally infected with *Brucella canis.* This mechanism is a proposed, but unproven, cause of infertility in naturally infected males.

ENDOCRINE SYSTEM

Autoimmune thyroiditis. There is mounting evidence that autoimmune thyroiditis, similar to Hashimoto's disease in man, is a major cause of hypothyroidism in the dog. Lymphocytic infiltration of the thyroid gland dominates the histologic picture in active cases. However, destruction of thyroidal architecture and fibrous replacement is often the sequellae in *clinically* thyroid-deficient dogs. Antibodies to thyroglobulin are detected in the majority of cases of lymphocytic thyroiditis.

Diabetes mellitus. Antibodies to insulin, insulin receptors, or pancreatic beta (islet) cells are a well documented cause of diabetes mellitus (Type I) in man. A similar cause for diabetes mellitus in dogs has recently been shown for insulin dependent diabetes.

MISCELLANEOUS DISORDERS WITH A SUSPECTED AUTOIMMUNE ETIOLOGY

Vasculitis

Vasculitis is characterised by inflammation and damage to a blood vessel. It can present as either a primary lesion, or as secondary to an underlying disease. It is generally assumed that the majority of these diseases are the result of an underlying immunopathology. There is great confusion concerning this in human medicine and attempts have been made to rationalize the situation. There is no evidence that there is a specific immune mediated disease underlying the observed pathology. There are two broad groups of vasculitis in the dog and cat: Systemic necrotising vasculitis, and Hypersensitivity vasculitis, examples of these are given below.

Polyarteritis nodosa

Polyarteritis nodosa (PAN) is a rare polysystemic necrotizing vasculopathy of uncertain etiology. It is classified among the systemic vasculitis and appears unique from the vasculitis of SLE in that it tends to affect large and medium-sized arterioles and venules. PAN is also devoid of any consistent association with autoantibodies. Several cases of canine and feline PAN are reported in the veterinary literature. Anorexia, lethargy, muscle and joint pain, fever, leukocytosis, ulcerative gingivitis and glossitis, and gastrointestinal, renal or hepatic involvement are common findings. Necropsy lesions are often widespread, with gross thickening and nodular swellings of major arteries such as the aorta, carotid, and pulmonary arteries. Microscopic arterial lesions consist of fibrinous necrosis of the tunica media and panarteritis, characterized by fibrinoid necrosis, neutrophilic infiltrates, and a surrounding admixture of mononuclear cells, particularly in older lesions. Thrombosis and infarction can be seen both in affected, and in normal vessels, including veins and lymphatics. Lesions are found in kidney, pancreas, liver, meninges, muscles, lungs, lymphoid tissue, and connective tissue. The disease is poorly responsive to immunosuppressive therapy.

Necrotizing vasculitis

The term necrotizing vasculitis encompasses a broad spectrum of clinical variants determined by affected vessel size, the distribution of organ lesions, and the mechanism of vessel damage. Some viruses, *e.g.* equine viral arteritis, chemicals and endotoxins can cause *direct* vessel damage. More commonly, drugs or infectious agents cause vessel damage indirectly *via* immunologic mechanisms that incorporate immune complexes, complement activation at the vessel wall, sensitized lymphocytes, and generation of phlogistic and anaphylatoxic mediators. There are several examples of infectious diseases in domestic animals which can produce either an acute or chronic necrotizing vasculitis in conjunction with the immunologic response that they invoke. The best documented example is feline infectious peritonitis. Other suspected, but not well-documented,

agents which can provoke immune complex vasculitis include streptococcal infection, herpes virus infection, equine infectious anaemia virus, and canine corona virus.

The hypersensitivity vasculitis caused by circulating immune complexes often have a characteristic histological appearance that is best described as leukocytoclastic vasculitis. The cardinal features include transmural necrosis of small vessels, *i.e.* arterioles and venules, neutrophilic invasion of the vessel walls, lumenal thrombosis and infarction.

The best approach to establishing a diagnosis of necrotizing vasculitis is by biopsy. Direct immunofluorescence and other methods of identifying immune complex or complement deposition in vessel walls are useful in substantiating an immune complex etiology. However, experience in man and laboratory animal models provides that immune complexes survive only transiently in vessel lesions, often less than 24 hours. Assays for measuring levels of circulating immune complexes are not widely available but are often used to substantiate the diagnosis in man. Demonstration of hypocomplementemia during acute exacerbation of clinical signs is also taken as indirect evidence that immune complexes are a contributing cause of observed vascular lesions.

Treatment of necrotizing vasculitis involves the elimination of suspect drugs or toxins, and any bacterial, rickettsial, or parasitic (filarial diseases) agents which might be involved in the disease process. Anti-inflammatory and immunosuppressive drugs are used to suppress the hypersensitivity reaction. The prognosis is extremely variable. Some cases respond well to therapy and never recur. Others are more chronic and poorly responsive to therapy.

Canine distemper encephalitis. The demyelinating (chronic) form of distemper encephalitis has been associated with autoantibodies to myelin that are known to be pathogenic *in vitro*. In addition, there is increasing evidence that in demyelinating lesions there is inappropriate expression of class II MHC antigens. This finding may in part explain the immunopathologic basis of the lesion.

Uveitis. A combination of recurrent uveitis and cutaneous depigmentation similar to Vogt-Koyanaghi-Harada syndrome in man has been described in Akitas and Huskies. Autoantibodies against melanocytes are the proposed cause. Steroid therapy is suggested for this rare disorder in dogs.

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