Case Report Rapport de cas

Combination of cyclosporin A and prednisolone for juvenile cellulitis concurrent with hindlimb paresis in 3 English cocker spaniel puppies

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Abstract — Three 7-week-old, English cocker spaniel littermates were diagnosed as having juvenile cellulitis with concurrent neurologic signs based on history, histopathology, and therapeutic response. The puppies were treated with cyclosporin A and prednisolone. Skin lesions and hindlimb paresis improved following treatment.

Résumé — Combinaison de cyclosporin A et de prednisolone pour la cellulite juvénile concomitante à une parésie des membres postérieurs chez 3 chiots épagneuls cocker anglais. Trois compagnons de portée épagneuls cocker anglais âgés de 7 semaines ont été diagnostiqués comme étant atteints de la cellulite juvénile avec des signes neurologiques concomitants en se fondant sur l’anamnèse, l’histopathologie et la réponse thérapeutique. Les chiots ont été traités avec de la cyclosporin A et de la prednisolone. Les lésions cutanées et la parésie des membres postérieurs se sont améliorées après le traitement.

Can Vet J 2010;51:1265–1268

Juvenile cellulitis, also called juvenile pyoderma, juvenile sterile granulomatous dermatitis and lymphadenitis, or puppy strangles, is an uncommon granulomatous and pustular sterile dermatitis of the face, pinnae, and submandibular lymph nodes and is seen typically in puppies (1). On occasion, lesions may appear on the feet, abdomen and thorax, vulva, prepuce, or perianal area (2,3). Age of onset usually ranges from 3 wk up to 8 mo and 1 or more puppies in a litter may be affected (3–6). Although the cause of the disease is uncertain, an underlying immune dysfunction is strongly suspected because the response of the lesions to glucocorticoid therapy is excellent. A hereditary predisposition has been proposed, but the pathophysiology of this disease has not been determined (2).

Early clinical signs consist of an acutely swollen face, especially the eyelids, lips, and muzzle. Within 24 to 48 h, papules and pustules spread rapidly on the lips, muzzle, chin, bridge of the nose, and perioral area. Lesions are characterized by fistulation or drainage with copious purulent discharge, swelling, ulcerated crust formation and lymphadenopathy. There are 2 previous reports of concurrent neurological symptoms in juvenile cellulitis patients. In the first, 2 Shetland sheepdog puppies with panniculitis had neurologic signs consistent with spinal cord lesions (3). Recently, Hutchings (7) reported a case of juvenile cellulitis with acute onset unilateral hindlimb lameness related to a joint problem.

This case report describes juvenile cellulitis associated with hindlimb paresis in 3 littermates, and the subsequent treatment with immunosuppressive drugs. To the authors’ knowledge, this is the first report of cyclosporin A (CsA) therapy and cerebrospinal fluid (CSF) analysis in dogs with juvenile cellulitis and neurologic signs.

Case description

Three 7-week-old, English cocker spaniel littermates (1 female and 2 males) were presented with facial dermatitis, pustular otitis externa, back pain, hindlimb paresis, and poor growth. The female puppy showed the most severe neurologic sign and a state of poor growth; however, the general condition and appetite of the 3 puppies were normal. The 5 littermates were normal and all puppies had been kept indoors and fed a commercial diet for puppies. The owners reported that the skin lesions appeared 2 wk after birth and the puppies were taken to the local veterinarian at 3 wk of age. The veterinarian had prescribed cephalexin (30 mg/kg, PO, TID) for 4 wk but there was no response. Sporadic hindlimb weakness began 1 wk after the initial presentation to the local veterinarian. The 3 puppies had not been vaccinated due to their illness. The 5 littermates remained normal and healthy.

Upon initial presentation, the same diagnostic procedures were performed on the 3 affected puppies. The patients had...
swollen faces, with crusting and painful fistulae on the dorsal muzzle and lower eye lids. On physical and neurologic examination, bilateral mild swelling of the submandibular lymph nodes and signs of lower motor neuron (LMN) involvement, including decreased muscle tone, knuckled toes, and back pain through the second to fourth lumbar area (L2-L4) were observed. The puppies tried to carry most of their weight on the thoracic limbs. The mental status of the 3 puppies was normal. Both hindlimbs barely sustained their body weight and hindlimb muscle tone and spinal reflexes were decreased in all 3 patients. The female puppy showed more severe hindlimb paresis compared to the 2 male puppies. The cranial nerves were intact.

On the initial dermatological examination of the face, all lesions were nonpruritic, crusted, and pustular. Swellings on the lower eye lids, the bridge of muzzle, and perioral region were evident (Figure 1A). There were decubital ulcers owing to the hindlimb paresis (Figures 1B and 1C). Multiple deep skin scrapings were negative for demodex mites and dermatophyte culture of hair was negative. Three different lesions on each puppy were scraped until blood was visible. When the skin lesions were squeezed for the deep skin scraping, yellowish fresh exudates came from the crusted skin lesions. Then, specimens for bacterial culture were sampled. Impression smears of the exudate showed numerous degenerative neutrophils and some macrophages without bacteria on Diff-Quik stain (Merck, Darmstadt, Germany). Bacterial cultures (both aerobic and anaerobic culture) of fresh exudates were negative. Punch biopsy specimens (4 mm in diameter) were taken from the dorsal muzzle in all puppies. The margins of skin lesions were biopsied and the specimens were fixed with 10% phosphate buffered formalin.

Histopathological lesions were severely pyogranulomatous, targeting the adnexa, in particular the sebaceous glands (sebaceous adenitis), which is an early lesion in canine juvenile cellulitis and as the lesions progressed, folliculitis became dominant (Figure 2). The differential diagnosis for the skin lesions included bacterial pyoderma, demodicosis, angioedema, and dermatophytosis which were all ruled out based on the diagnostic tests. The differential diagnosis for hindlimb paresis included soft tissue injuries, orthopedic injuries, distemper, toxoplasmosis, neosporosis, Rocky Mountain spotted fever, septic arthritis, and ehrlichiosis. In all 3 puppies, canine distemper was ruled out by reverse transcriptase polymerase chain reaction (RT-PCR) on nasal and ocular discharge and serum conducted by a commercial laboratory (Neodin Vetlab, Seoul, Korea).

Cerebral spinal fluid (CSF) was taken through an atlanto-occipital puncture of the female puppy. Intubation was performed after injection of propofol (Anepol; Hana Pharm, Seoul,
Korea), 6.6 mg/kg, IV, for induction. Then, isoflurane (Rhodia, Organique Fine, Seoul, Korea, 1.0%–3.0%) was used for general anesthesia. The CSF sample was submitted for cytology, protein determination, and bacterial and fungal culture. Analysis revealed mononuclear pleocytosis (lymphocytes and predominant monocytes) (Figure 3), which indicates central nervous system inflammation. Total protein in the CSF was increased (0.97 g/L; reference range: < 0.25 to 0.35 g/L). The bacterial (both aerobic and anaerobic) and fungal cultures of CSF were negative. All the tests indicated that the neurological signs could be related to CNS inflammation. Tests for toxoplasma IgG/IgM (Neodin Vetlab, Seoul, Korea) in serum samples of all puppies were negative. Polymerase chain reaction for Anaplasma platys was negative. Examination for neosporosis, Rocky Mountain spotted fever, and Ehrlichia canis was not performed because these afflictions have not been reported in dogs in Korea. Radiographic examinations of the spinal cord and skull were performed to rule out any other neurological diseases, including spinal cord abnormalities and intervertebral disk disease, but the films showed no remarkable findings.

Initial treatment of the 3 puppies consisted of prednisolone (Korea Pharma, Seoul, Korea), 2 mg/kg, PO, BID, and cephalixin (Cephalexin, Newgenpharm, Seoul, Korea), 30 mg/kg, PO, TID. The skin lesions improved (Figure 1D), but the neurologic signs did not show any improvement. Eight weeks after the initial presentation, only minor pustular dermatitis of the face and otitis externa was present and complete remission of the skin lesions was achieved by the 10th wk. Cephalexin was then discontinued. The neurological signs, however, remained and prednisolone, 2 mg/kg, PO, BID, was administered for 8 wk until the 3 puppies showed side effects to the drug such as hepatomegaly, polyuria, and polydipsia. The female puppy died; therefore, prednisolone was tapered for the other puppies to a dose of 1 mg/kg, PO, q12h, for 3 wk and maintained at this dose. Cyclosporin A (Hanmi Pharma), CsA; 5 mg/kg, PO, SID, was added to the prescription for continuing immunosuppression. With the combination of CsA and prednisolone, hindlimb paresis became mildly improved, which was evidenced by the puppies supporting their weight with their hindlimbs and walking for 5 to 10 s periods. Fourteen weeks after the initial presentation, the 2 puppies had progressively recovered from their neurologic signs. The combination therapy of CsA and prednisolone was maintained for another 4 wk. Complete blood (cell) counts and serum biochemical tests were performed during this combination therapy to identify possible side effects such as bone marrow suppression and hepatotoxicity. However, the results showed only mildly elevated hepatic enzymes. We continued to taper the dose of prednisolone and maintained CsA administration at the starting dose for another 4 wk.

**Discussion**

Although the causative agent of juvenile cellulitis remains unclear, several theories have been proposed. Immunologic pathoetiology and heritability may be the causes, based on response to glucocorticoids and family history (8). Even though euthanasia is necessary in some individuals, most patients recover with steroidal and antibiotic therapy.

In this case, the skin lesions improved dramatically, but the neurological signs were not resolved with prednisolone therapy. An immunological basis may be hypothesized for the etiology of hindlimb paresis based on the CSF analysis with elevated total protein and predominant monocytes and lymphocytes and the responsiveness to the immunosuppressive drug CsA. However, this was not confirmed because histopathological examination of the spinal cord was not performed.

Recently, a report suggested a critical role for interleukin-6 (IL-6) in autoimmune spinal cord disorders (9). IL-6 is a glycoprotein cytokine that mediates signal transduction between immune cells, induces acute-phage protein synthesis, and controls growth and differentiation of cells of the immune and
hematopoietic systems (10). In addition, the presence of IL-6 and its colocalization with neuropeptide in peripheral nerve fibers has been demonstrated in normal and inflamed human skin (11) and several neuropeptides, including vasoactive intestinal polypeptide (VIP), substance P (S), calcitonin gene-related peptide (CGRP), are involved in neurogenic inflammation in allergic dermatitis in humans (12,13). Thus, studies on these neuropeptides in dogs with juvenile cellulitis may aid in understanding the immunologic relationship between skin disease and neurogenic inflammation.

CsA is a cyclic oligopeptide macrolide that is extensively used in organ transplantation and autoimmune disorders to control neurologic signs due to its immunosuppressive properties. It is a lipophilic peptide with poor blood-brain barrier permeability that may be effectively trapped in the cerebral endothelial cells and the choroid plexuses (14). In immune-mediated neurologic disease, such as granulomatous meningoencephalomyelitis (GME), in which the lesions are related to perivascular processes, a therapeutic cyclosporine concentration is more likely to be present in affected areas of the neurologic system (15). Unfortunately, the female puppy which showed the most severe hindlimb paresis and impairment of growth died before she was evaluated for the therapeutic effect of CsA on the neurologic signs. The neurologic signs of the 2 male puppies, however, gradually improved with CsA treatment.

There are several reports with regard to the beneficial effect of cyclosporine on inflammatory spinal injury in animal models (6,16,17). In a recent study of CsA treatment for experimental autoimmune encephalomyelitis in rats, high doses of CsA improved clinical signs, but disease relapsed at the cessation of treatment whereas administration of low doses of CsA induce a chronic relapsing course (18).

It is believed that dogs are less susceptible to the toxicity of CsA than are other animals based on the study in rats, mice, rabbits, and dogs (19). Dogs, however, may also uncommonly experience gingival hyperplasia and papillomatosis, vomiting, diarrhea, bacteriuria, bacterial skin infections, anorexia, hirsutism, involuntary shaking, nephropathy, bone marrow suppression, and lymphoplasmoid dermatosis at daily doses of 20 to 30 mg/kg (20). In the present cases, there were no abnormalities indicating drug toxicity. It is thought that close monitoring for bone marrow suppression is needed because both CsA and prednisolone have immunosuppressive effects. But there was no remarkable finding in blood profiles after combination therapy (CsA and prednisolone) in this case.

In conclusion, this case demonstrates that, in addition to the skin lesions, juvenile cellulitis is likely related to inflammation of the spinal cord and that management with immunosuppressive therapy using the combination of CsA and prednisolone may be beneficial.

References