Pemphigus Foliaceus in a Dog Following Ingestion of *Echinacea Purpurea* Plants

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ABSTRACT

This report describes a case of pemphigus foliaceus (PF), an autoimmune skin disease diagnosed in a 5-year old female American Pit Bull Terrier dog, several days after ingesting *Echinacea purpurea* plants. In human alternative medicine, *Echinacea purpurea* **i**s used to enhance the immune system. The dog showed oozing pustules, crusts, papules, alopecia and fever. Pemphigus foliaceus was confirmed by histopathology. Treatment for over a 1-year period consisted of prednisone, mycophenolate-mofetil, antibiotics and medical shampoos. After one year of remission, all treatments were tapered and eventually stopped. The dog has been in remission for over five years.

Keywords: Canine; Dermatology; Immune-Mediated Skin Disease; Mycophenolate-Mofetil; Hyperkeratosis; Pustules.

INTRODUCTION

Pemphigus foliaceus (PF) is the most common autoimmune skin disease in dogs (1). It is an autoimmune vesicobullous to pustular skin disease that is characterized by acantholysis or loss of adhesion between keratinocytes (2). The development of autoantibodies against keratinocytes may result from an abnormal immune regulation or abnormal antigen stimulation. The desmosomal antigens reportedly targeted are desmoglein 1 (2). In PF, the initial signs may present as papules, rapidly developing to pustules, leading to widespread areas of erosion and yellow crusting. The footpads are often affected with fissures and hyperkeratosis. The head, face, and ears are involved in 80% of the cases (1). Nasal depigmentation may develop later in the course of the disease.

Data on breed incidence is not always compared to a relevant base population, but Akitas and chow chows appear to be overrepresented, with cocker spaniels, dachshunds, and Labrador retrievers prominently featured in most studies (1). PF appears to be idiopathic in nature, without any apparent predisposing causes (1). However, some evidence suggests that that PF might be triggered or induced by systemic or topical drugs like cimetidine, Itraconazole, Metaflumizone and lime sulfur (1-7).

Treatment of PF includes immunosuppressive doses of glucocorticoids (GC), usually prednisone or prednisolone, azathioprine, chlorambucil, mycophenolate-mofetil or their combinations (1). With control of the disease, drugs are carefully tapered, with periodical monitoring (1). The prognosis of PF is fair to good (1). Although some dogs remain in remission after immunosuppressive therapy is tapered and eventually discontinued, most require lifelong therapy to maintain remission (1).

CASE REPORT

A 5-year old neutered female American Pit Bull Terrier was presented to the Dermatology Department, Hebrew University Veterinary Teaching Hospital with clinical signs of oozing pustules over a prior 6-month period. The dog

was fully vaccinated and its past medical history was unremarkable. The dog has been treated by a private practitioner several times with prednisone (brand unknown; 1mg/kg PO, q24h for 2-3 weeks) during that period, with some improvement following each treatment course, although the lesions relapsed each time when prednisone dose was tapered.

According to the owners, the dog ingested *Echinacea* plants in the garden over a period of several days prior to the appearance of the initial skin lesions. These first appeared on the back and then spread quickly to the abdomen, groins, chin, and head.

On physical examination, the dog was alert, with a rectal temperature of 39.7°C, unremarkable heart rate and respiratory rate, however a weak systolic heart murmur was auscultated. Dermatological examination showed epidermal collarettes, crusted papules, and oozing pustules, on the skin of the face, neck, abdomen, and legs. Hyperkeratosis on one right front leg footpad and one left hind leg footpad was noted. The pustular oozing was bloody and was evident mostly in lesions assessed as being new. Old lesions were covered with yellow-gray crusts. Pruritus was mild.

Complete blood count showed mild leukocytosis (white blood cell count, 14.36x10^3/μL; reference interval [RI], 5.2-13.9 x10^3/μL), Neutrophilia (Neutrophils count, 11.13x10^3/μL reference interval [RI], 3.9-8 x10^3/μL), and mild anemia (red blood cell count 5.14x10^6/μL; RI, 5.7-8.8 x10^6/μL) and the packed cell volume were mildly decreased (35%; RI, 37.1-57.0%).

Skin scrapes from several areas of the lesions were negative for *Demodex* spp. and *Sarcoptes* spp. mites. Impression smears were obtained from several areas and stained with a Romanowsky staining solution. Cytology revealed cocci, numerous macrophages, neutrophils and eosinophils, and few acantholytic cells.

Five skin punch biopsies were obtained from skin lesions from the head, abdomen, back, and legs. The histopathology findings showed epidermal hyperplasia, spongiosis and severe exocytosis, intra-epidermal pustules with numerous acantholytic cells and neutrophils, compatible with a diagnosis of PF.

Immunosuppressive treatment was initiated, with prednisone (Prednisone, Rekah, Holon, Israel; 1.8 mg/kg PO q12h), and additional medications included famotidine (Gastro 10, Unipharm, Tel Aviv, Israel; 10 mg PO q24h) and antibacterial/antifungal shampoo (Malaseb shampoo, 2% miconazole nitrate and 2% chlorhexidine gluconate, Bayer Animal Health, Shawnee Mission, KS, USA) once a week.

The dog was reexamined three weeks later and showed marked improvement. The amount of crusts decreased with only a few remaining oozing pustules left and the hyperkeratotic footpads becoming thinner. Impression smear cytology from the remaining pustules showed few cocci, *Malassezia* sp. yeasts and numerous degenerated neutrophils, and no acantholytic cells. Over the next three months, prednisone was continued (initially 1.8 mg/kg PO q12h for 45 days, and then tapered up to 0.9 mg/kg PO q12h), with cephalexin (21-25 mg/kg PO q12h) and antibacterial/antifungal shampoo. At reexamination, three months later, the owners reported polyuria and polydipsia, and the dog lost weight and showing thinning of the skin and temporal muscles atrophy. Serum chemistry showed increased activity of hepatobiliary enzymes (alanine transaminase 286 U/L; RI 19-67; alkaline phosphatase, 427 U/L; RI 21-170; γ-glutamyl-transpeptidase, 42.3 U/L; RI, 0-6.0). The dog was then tentatively diagnosed with iatrogenic Cushing's syndrome. Therefore, mycophenolate-mofetil (Cellcept, Hoffmann-La Roche, Basel, Switzerland; 21.5 mg/kg PO q12h) was added, while prednisone dose was gradually tapered over eight months (from 0.9 mg/kg PO q12h to 0.2 mg/kg PO q7d). Over this 8-month period, mycophenolate-mofetil was also tapped gradually (21.5mg/kg PO q12h to 10.5 mg/kg PO q7d) while antibacterial/antifungal shampoo once a week bath is continued.

At recheck, 11 months from initiation of therapy, only few skin lesions remained. Prednisone and mycophenolate-mofetil were both discontinued. The dog was then prescribed a topical antibiotic-GC ointment (to be applied q12h for two months; Threolone; Abic, Netanya, Israel; the ointment contains chloramphenicol 3.0% and prednisolone 0.5%).

At reexamination, two months later (13 months from initiation of therapy), the dog had fully recovered, and all medication was discontinued. Over the next five years, at all follow-up examinations, the dog was still completely recovered, with no signs of PF.

DISCUSSION

In this case, the suspected cause for the eruption of PF was the ingestion of *Echinacea purpurea* plants. Treatment for over a period of one year had led to a long-term sustained remission. The putative role of the *Echinacea* in the pathogenesis

of the PF, in this case, could not be proven. Challenging the dog with *Echinacea* after remission might have provided a definite evidence had the signs recurred, but this avenue was not pursued as it is was considered unethical.

In human alternative medicine, *Echinacea* is used to enhance immune function, however, it has been reported to trigger the onset of autoimmune diseases or exacerbate pre-existing autoimmune disease (8). Human patients suffereing from autoimmune diseases are instructed to avoid immune stimulatory herbal supplements such as *Echinacea* spp. A review of cytokine activity in patients treated frequently with used plants and herbs in alternative medicine, *Echinacea* spp. were reported to enhance production of interleukin (IL)-1, IL-1α, IL-1β, IL-6, IL-10, IL-12 and tumor necrosis factor α (9). It has been shown that *Echinacea* spp. can stimulate natural killer (NK) cells; Herbal *Echinacea purpurea* extract applied *in vitro* to human cells had led to increased NK function as well as antibody-dependent cell cytotoxicity (9). In one reported case, a man with well-controlled pemphigus vulgaris developed blisters on his trunk, head, and oral mucosa within one week of initiating *Echinacea* supplementation, and also developed upper respiratory tract infection (9). Another case report described an *Echinacea*-induced acute cholestatic autoimmune hepatitis (ACAH). The authors hypothesized that given its effect on increasing the number and activity of immune system cells, the use of *Echinacea* spp. may result in a breakdown of the hepatic self-control of autoimmunity in susceptible patients, who may therefore present with ACAH (10).

In the veterinary literature published in English, there is only a single published study examining the effect of *Echinacea* spp. in dogs (11). In that study, oral administration of a hydroethanolic extract of *Echinacea* (1 mL of 5% q12h for two months) to a group of dogs led to significant increases over time in the hematocrit, red blood cell count and hemoglobin concentration, as well as phagocytotic activity and IgM production compared to a control group that received only water. Few studies on the influence of *Echinacea* in other veterinary species are available. In one study, *Echinacea purpurea* led to cellular immunity defense stimulation in mice through stimulating granulocyte chemiluminescent (Chemiluminescence is the emission of cold light as a result of a chemical reaction) and inducing lymphocyte proliferation (12). Another study has investigated the influence of consumption of *Echinacea* in horses and concluded that it increased the neutrophil phagocytic ability and stimulated the immune system (13). A further study examined the effects of *Echinacea* compound on the immune function of weaned piglets and reported that it led to an increase in neutrophil counts and an improvement in the level of antibodies against swine diseases (14). These studies in veterinary medicine imply that *Echinacea* spp. affects immune functions in animals.

In this case, the dog was perfectly healthy and only after the owner brought the *Echinacea* plants and the dog ate them he began to suffer from PF. Our hypothesis is that the *Echinacea* plants that the dog ate may have induced an immune system simulation that resulted in this autoimmune disease.

Recently, a study was conducted to examine the efficacy of the treatment of autoimmune diseases in dogs (15). The researchers concluded that mycophenolate-mofetil could be used as a second-line immunotherapeutic in immune-mediated skin disease in dogs and that the side effects seen were minimal. Our case is consistent with the study results, the dog completely recovered after using the mycophenolate-mofetil and although the dog was treated initially with high dose, no adverse effect was seen and the drug was well tolerated. In light of the results, in similar cases, it is advisable to consider using mycophenolate-mofetil and prevent the side effects of steroids.

In summary, this case, we described a dog suffering from PF after eating *Echinacea purpurea* plants. Echinacea has immune modulatory properties and several studies linked to *Echinacea* and autoimmune diseases. Furthermore, the effect of the herb on the immune system has been described. We hypothese in this case that there was an association between eating *Echinacea* plants and the outbreak of PF and that the plants may have triggered an immunological response that caused autoimmune skin disease. The role *Echinacea* on autoimmune diseases requires further investigation.

NOTE FROM THE EDITOR

Dr. Gila Zur passed away before completing this article. The journal is honored to publish this item and the members of the editorial board of the IJVM send her family and friends their condolences. Gila contributed greatly to the veterinary world though her compassion and knowedge. We all miss her!

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