Pemphigus Foliaceus in a Cat

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Abstract

"Duane," a 6-year-old castrated male Himalayan cat presented to the Dermatology Service at the Cornell University Hospital for Animals for evaluation of a progressively worsening, widespread crusting dermatopathy of approximately three months duration. On presentation, Duane had extensive areas of alopecia and crusting on his face, nasal planum, external pinnae, dorsum, and clawbeds. Thoracic radiographs ruled out the presence of a thymoma as a possible cause for the exfoliative dermatosis. Cytology of the crusting lesions revealed the presence of acantholytic keratinocytes and supported a diagnosis of pemphigus foliaceus. Histopathology of biopsies taken of affected skin verified the presence acantholytic keratinocytes and confirmed the diagnosis of pemphigus foliaceus. Immunosuppressive therapy using oral dexamethasone was started. Various adjustments to the treatment regimen were made as complications were encountered. This case illustrates the importance of accurately diagnosing pemphigus foliaceus and the challenges of effective treatment.

Introduction

Pemphigus foliaceus is one variant within the pemphigus disease complex. There are at least five recognized forms of pemphigus including pemphigus foliaceus, pemphigus erythematosus, pemphigus vulgaris, pemphigus vegetans, and paraneoplastic pemphigus.[1] All the pemphigus variants are autoimmune diseases in which autoantibodies are produced against the adhesion molecules that hold cells of the epidermal layers together. The diseases differ in their target antigen, the depth of the target antigen within the epidermis, and the resulting distribution and severity of clinical signs.

Pemphigus foliaceus is the most common of the pemphigus diseases and is also considered the most common autoimmune dermatosis in dogs and cats.[1-3] It has been reported in humans, dogs, cats, horses and goats, the dog being the most thoroughly studied of non-human patients.[4] A genetic predisposition has been reported in dogs. Cats do not appear to have a breed or sex predilection for the disease. The median age of onset in the cat is approximately 5 years old, but all ages can be affected.[3, 4] Various etiologies for pemphigus foliaceus have been proposed including spontaneous idiopathic, drug-induced, secondary to chronic disease (especially chronic skin disease), environmental, genetic, and possibly diet-related. Additional factors such as ultraviolet light exposure and stress have been suggested to exacerbate the disease in some situations.[1, 5]

In humans with pemphigus foliaceus, desmoglein I has been identified as the target antigen. A recent study in dogs has indicated that desmoglein I appears to be only a minor autoantigen for canine pemphigus foliaceus.[4] The target antigen has not yet been proven in cats.[2] Desmoglein I is a glycoprotein of the cadherin group of intercellular adhesion molecules that hold cells of the epidermis together. Binding of antibodies, usually IgG autoantibodies, to desmoglein molecules stimulates a pathway that eventually results in breakdown of these adhesion molecules. The exact mechanism of action of this breakdown is not currently known. The end result is loss of cohesion between epidermal cells and the formation of acantholytic keratinocytes, the hallmark feature of pemphigus. In pemphigus foliaceus, this process usually occurs within the stratum granulosum resulting in intragranular or sub-corneal acantholysis.

Clinically, acantholysis manifests itself as varying degrees of pustules, vesicles, erosions or ulcerations, and crusting. Pustules are very transient and therefore rarely seen in dogs and cats due to their thin epidermis.[1] The distribution of lesions in cats is usually localized early in the course of the disease, typically affecting the ears, face and feet, but can become more generalized with

time.[1, 2] There are a large number of differential diagnoses for pemphigus foliaceus, therefore accurate diagnosis of the disease is crucial if appropriate therapy is to be initiated.

Case History

"Duane," a 6-year-old castrated male Himalayan cat presented to the Dermatology Service at the Cornell University Hospital for Animals on October 10, 2007 as a referral for evaluation of a progressively worsening, widespread crusting dermatopathy of approximately three months duration. Back in July of 2007, Duane was diagnosed by the referring veterinarian with bilateral otitis and chronic bilateral conjunctivitis. The otitis was treated with a course of Baytril®, Cerumene®, and Panalog® ointment. The conjunctivitis was thought to be due to a herpes viral infection and was treated with Idoxuridine® drops, L-lysine, and NeoPolyDex® ophthalmic solution. At a recheck examination two weeks later, Duane's conjunctivitis appeared to be resolving, but a new dermatitis on the caudal pinnae had developed. Synotic® with Baytril® was prescribed for the dermatitis. On August 9th, Duane returned again to the referring veterinarian for further evaluation of the dermatitis on his ears that had worsened and spread to include his face, nose, and chin. The lesions were reported to be inflamed and crusty, but non-pruritic. Duane was treated with ketoconazole and amoxicillin for a presumptive dermatophytosis and secondary superficial pyoderma. On August 17th, Duane was examined after a possible cat fight. The otitis and dermatitis persisted. An injection of penicillin was given and Duane was sent home on a course of Clindamycin® drops to treat the puncture wounds from the fight. On October 2nd, a new veterinarian prescribed a lyme sulfur dip and Tresaderm® to treat the presumed fungal skin infection. Shortly thereafter on October 8th, Duane returned to his regular veterinarian as his skin condition had worsened and he was no longer eating. He was in very poor body condition,

dehydrated, had significant amounts of flea dirt on his skin, and had advanced dental disease. A free T4 test was performed and was within normal limits. A chemistry panel showed mildly elevated glucose (181 mg/dL) and hyperglobulinemia (5.4 g/dL). Complete blood cell count revealed a leukocytosis (21.57 K/uL) with neutrophilia (18.93 K/uL) and basophilia (0.11 K/uL), and a very mild anemia (29.6%). Duane was referred to the Cornell Dermatology Service for further diagnostics. During this course of treatment prior to coming to Cornell, the owner reported that the only medication that seemed to improve Duane's lesions was a human preparation ointment of clotrimazole and betamethasone.

Clinical Findings

On October 10, 2007, Duane was seen by the Cornell Dermatology Service. On presentation, Duane was lethargic and in poor body condition, weighing 5.2 pounds. Heart rate, respiratory rate and temperature were within normal limits. His coat was poorly-groomed and he had numerous areas of alopecia and crusting of the skin including the face, margins of the pinnae, nasal planum, fore- and hindlimbs, clawbeds, rump, chest and dorsum. Certain alopecic areas, specifically the dorsum, were hyperpigmented. In other areas, the skin was scaly and covered with honey-colored crusts. The pawpads and periareolar regions were spared and appeared to be normal. Duane also had very hypotonic skin, especially on his ventrum. Flea dirt was noticed on his dorsum. Additionally, Duane had moderate periodontal disease and was missing numerous teeth. His eyes appeared to be normal. A moderate amount of waxy brown discharge was noted in the ears. A mild I-II/VI apical left-sided systolic heart murmur was ausculted. A bilateral thyroid slip was palpated in the neck. There were no other obvious abnormalities on the remainder of the physical exam.

Problem List and Differential Diagnoses

Based on Duane's history and physical exam, his problem list consisted of: a history of bilateral conjunctivitis, bouts of anorexia, depression, poor body condition, evidence of flea infestation, chronic widespread crusting dermatopathy, mild left-sided systolic heart murmur, bilateral thyroid slip, and moderate-to-severe dental disease and tooth loss. Anorexia and depression are both non-specific signs that can be seen with a wide range of diseases. Poor body condition and weight loss can also result from numerous diseases, including any chronic disease leading to anorexia, systemic diseases, neoplasia, hyperthyroidism, malabsorption diseases and dental disease. Differentials for a left-sided systolic heart murmur include anemia, hypertrophic cardiomyopathy, dilated cardiomyopathy, hyperthyroidism, valvular disease, and induced (in the case of thin cats). Differentials for a palpable thyroid slip include hyperthyroidism and thyroid neoplasia.

While the above problems and their differentials were important to consider, the main focus of the Dermatology Service was the chronic crusting dermatopathy. There are a large number of differential diagnoses for a crusting dermatopathy, often resulting in a very difficult and lengthy process of diagnostic tests. Infectious causes include bacterial folliculitis, dermatophilosis, dermatophytosis, *Malassezia,* and viral dermatoses. Various ectoparasites such as *Demodex*, *Otodectes*, *Notodres*, *Sarcoptes*, *Cheyletiella*, and lice can produce crusting skin disease. Immune-mediated diseases including diseases of the pemphigus complex, discoid and systemic lupus erythematosus, cold agglutinin disease and vasculitis are also possible causes. Crusting lesions can result from allergies to fleas and specific foods. Miscellaneous causes for a crusting dermatosis include cutaneous adverse drug reactions, cutaneous lymphoma, Bowen's Disease, and thymomas.[4]

Diagnostics

A complete blood cell count and chemistry panel had been performed at the referring veterinarian just two days prior to presentation at Cornell, so it was decided not to repeat those diagnostics. A thyroid panel was performed to check for hyperthyroidism as a thyroid slip had been palpated on physical exam. Both Total T4 and Free T4 were below the reference range, indicating that Duane was clearly not hyperthyroid. As hypothyroidism is very rare in cats and Duane was not exhibiting clinical signs consistent with hypothyroidism, it is also unlikely that Duane was hypothyroid. Low thyroid hormone levels have been reported in systemically ill cats.[1]

Orthogonal radiographs were performed to evaluate Duane's heart and to look for evidence of a thymoma. Duane became fractious during the procedure, so patient positioning was not ideal. Except for a chronic malunion fracture of the right 10th rib, there were no obvious abnormalities within the thorax. Radiographic signs of a thymoma, which might include a soft tissue opacity in the cranial mediastinum and widening of the cranial mediastinum, were not detected. Thymomas have been reported to produce paraneoplastic syndromes including exfoliative dermatitis in cats. The patient typically initially develops a non-pruritic, scaling dermatitis on the head and pinnae. The dermatitis can later become more generalized and results in alopecia. If caught early in the course of disease, surgical removal of the thymoma can reverse the dermatitis.[1]

Impression cytology of a representative crusty area of Duane's skin was performed and revealed large clusters of acantholytic keratinocytes in rafts, large numbers of neutrophils, and nuclear streaming. This cytologic evidence in combination with Duane's history, clinical signs, and distribution of lesions, led to a tentative diagnosis of pemphigus foliaceus.

Skin biopsies of the lesions were taken and submitted for histopathology. Histopathology results later confirmed the diagnosis of pemphigus foliaceus. The skin sections showed moderate

epidermal hyperplasia and mild epidermal spongiosis. Multiple sections of skin were covered in crusts that were composed of large numbers of acantholytic keratinocytes, non-degenerate and degenerate neutrophils, and a proteinaceous background. A morphologic diagnosis of pustular dermatitis was made with a specific diagnosis of superficial pemphigus.

Treatment and Outcome

Based on a high suspicion of pemphigus foliaceus (histopathology results were not immediately available for definitive diagnosis), Duane was started on immunosuppressive therapy using oral dexamethasone at 0.4 mg/kg/day. At a recheck examination two weeks later on 10/25/07, Duane's condition appeared to be improving. His appetite was excellent, the lesions were healing, hair was regrowing, and no new lesions were seen. The plan was to continue the oral dexamethasone at the 0.4 mg/kg/day dose until the active lesions had resolved, and then start tapering the dose, with another recheck appointment in 10 days.

Duane did not return until three weeks later on 11/15. At that visit, there were no new skin lesions and hair had continued to regrow. The owner reported that Duane's appetite was good, his weight had increased, and he appeared to be urinating more than normal (likely a side effect of the steroid administration). Duane was pruritic and flea dirt was noticed on his skin. His bilateral conjunctivitis had also returned. As there were no currently active skin lesions present, Duane was tapered to every-other-day steroid therapy. His owner was also instructed to apply Advantage® topically to treat the flea infestation.

Approximately 1 month later, Duane returned on 12/21 to Cornell. Prior to presentation for this visit, Duane had been seen by his regular veterinarian where he was diagnosed and treated for a presumptive ear infection and watery eyes with Clavamox®, Panalog®, and Cerumene®. Soon

after starting those medications, crusting lesions redeveloped on the face, chin and tail. On physical exam at Cornell, Duane had crusting lesions on his nose, ears, around his eyes, and on his tail. He was also wheezing and had mucopurulent discharge from his left nostril. Cytology of a crusty lesion revealed the presence of many neutrophils, nuclear streaming, a few cocci, but no acantholytic cells. Ear cytology showed neutrophils and debris. Given the bacterial folliculitis and the possibility of a drug-induced skin reaction (possibly due to amoxicillin) or recrudescence of the pemphigus, Duane was placed on 14 day course of oral Baytril® and his dexamethasone was increased to daily administration. The owner was instructed to discontinue all other medications and return for a recheck in 10 days.

Phone communication with the owner revealed that Duane was becoming progressively worse on the Baytril®, so after a couple of days of treatment, the owner discontinued the Baytril®. On 1/2/08, treatment with doxycycline was started in an attempt to control the secondary skin infection and to provide some immunomodulating effects. Duane's lesions continued to worsen. Intermittently throughout the course of all treatments, the owner applied a human topical of clotrimazole and betamethasone on Duane's lesions. On 1/6, the doxycycline was discontinued and the owner was instructed to continue the dexamethasone alone. Since that time, Duane's disease has followed a waxing and waning course.

At the time of his last visit on 2/5, Duane was depressed, febrile (105.3 degrees Fahrenheit), and had severe crusting on his pinnae, face, chin, paws, perineum, and clawbeds. Mucopurulent discharge was present around his eyes. Cytology of a crusty lesion showed numerous cocci, neutrophils, and acantholytic keratinocytes (free and in rafts). Additional immunosuppressive therapy was warranted to treat the pemphigus. Complete blood count showed an inflammatory leukogram (WBC 32.3 thou/uL). ALT and AST were mildly elevated on the chemistry panel,

likely due to steroid administration. Testing for *Toxoplasma gondii* was performed to verify a negative titer prior to starting another immunosuppressive drug. Duane was negative for *Toxoplasma* and treatment with oral cyclosporine (20 mg/day) was initiated. Oral dexamethasone administration was continued every other day. Simplicef® (25 mg/day for 30 days) was also prescribed to treat the secondary bacterial folliculitis. The owner was additionally instructed to apply Synotic® topically on the lesions. The possibility of a food allergy contributing to or complicating the pemphigus foliaceus was discussed with the owner and a novel protein diet was suggested as a future course of action.

Discussion

Much of the research that has been done on non-human pemphigus foliaceus has been canine-based. More recently studies have attempted to better define the disease in the cat. While much of the disease process of pemphigus foliaceus is the same in cats and dogs, some variability between the species exists.

Clinical Signs

The clinical signs of pemphigus foliaceus in the cat are typically localized to begin with and then can become generalized with time. Crusting lesions and subsequent hair loss usually start on the face, nasal planum, periocular skin, and ears and are bilaterally symmetrical.[3, 4] A study involving 57 cats with pemphigus foliaceus reported that approximately 78% of the patients had lesions involving the head or face.[3] The crusts are often a distinct honey color. The paws, clawbeds, and pawpads can become involved.[4] In cats, paronychia (affected clawbeds) and nipple involvement (periareolar lesions) are common and highly suggestive of pemphigus foliaceus.[1, 6] Mucocutaneous involvement is rare. Clinical signs may follow a waxing and waning course. Pruritus and pain are

variable. If the patient is pruritic, the lesions typically proceed the itching.[7] Anorexia, depression and fever are also variable but highly non-specific.[1, 3, 6] The exact progression of the distribution of lesions in Duane is difficult to tell from the history, but he did appear to initially have lesions specifically on his ears that later became more generalized. Duane exhibited paronychia but no periareolar involvement.

Diagnosis

The combination of history, clinical signs, elimination of other differential diagnoses, and cytology results can be highly suggestive of pemphigus foliaceus, but the definitive diagnosis is made based on histopathology.[3, 8] Ideally, multiple skin biopsies should be taken of pustular areas. However, because pustules are so transient in dogs and cats, this is often not possible and a representative crusty lesion can be sampled instead and may be sufficient to make a diagnosis. Corticosteroid therapy prior to or at the time of biopsy can decrease the chances of obtaining a diagnostic sample, therefore steroids should be avoided before biopsies are performed.[3] Diagnosis of pemphigus foliaceus is made when numerous acantholytic keratinocytes (often in rafts)[4] are seen in either crusts or intraepidermal pustules along with intragranular or subcorneal acantholysis with resultant cleft and vesicle or pustule formation.[1] The acantholytic keratinocytes (acanthocytes) are rounded epithelial cells that have a morphologically normal nucleus and either a normally-stained or basophilic cytoplasm. Degenerate and non-degenerate neutrophils usually predominate in the pustules, but occasional eosinophils can be seen.[3, 4] Cats can often have mast cells present.[3] Acanthocytes can be seen with other inflammatory skin conditions including bacterial folliculitis and dermatophytosis.[4] In pemphigus foliaceus, the number of acanthocytes is usually significantly higher and this allows some degree of differentiation from the other diseases. The presence

acanthocytes in rafts is also more indicative of pemphigus foliaceus.[4] When in doubt, special stains and a fungal culture can be performed to rule out dermatophytosis.

Immunofluorescence testing for antidesmoglein I autoantibodies is another method of diagnosing pemphigus foliaceus. Both direct and indirect forms of the test exist. The direct test which looks for skin-fixed intercellular epidermal IgG, has some validity, but the indirect test (detection of circulating autoantibodies) has proven highly unreliable. Immunofluorescence testing has played a role in research but is not routinely used in practice.[1] Glucocorticoid therapy prior to or concurrent with immunofluorescence testing has been shown to affect test results.[4, 9]

Complete blood count and chemistry panel usually show non-specific changes that do not typically aid in the diagnosis of pemphigus foliaceus. Mild-to-moderate leukocytosis and neutrophilia, and mild non-regenerative anemia (of chronic disease) can be present. Mild hypoalbuminemia and/or hyperglobulinemia can also sometimes be seen.[1, 2, 5]

Treatment

Immunosuppressive therapy is the mainstay of treatment for pemphigus foliaceus. The goal is to curb the body's production and binding of autoantibodies to desmoglein and thereby prevent the loss of cohesion between epidermal cells. Various drug combinations can be used to try and manage the disease. Patient response is very individual and it can require many changes to the drug regimen to achieve a satisfactory response to medical therapy. In cats, prednisolone (4-8 mg/kg/day), triamcinolone (0.6-2 mg/kg/day), or dexamethasone (0.2-0.4 mg/kg/day) alone are the first approach drugs for treating pemphigus foliaceus. A recent retrospective study in cats has indicated that triamcinolone may be more likely to induce remission and have fewer side effects than other steroids and steroid combinations.[3] Duane was started on oral dexamethasone as the Cornell Dermatology Service has historically used this as the induction steroid in cats.

Once the disease has become inactive (meaning no new lesions have appeared and old lesions appear to be resolving), glucocorticoid administration is tapered to every other day therapy to minimize side effects.[1] While complete resolution of the disease is the ideal goal, this is often not possible and a good level of control of the disease can be considered adequate. In approximately 50% of patients, oral glucocorticoids alone produce unsatisfactory results.[1]

If there is lack of or incomplete response to a glucocorticoid, an alternate glucocorticoid can be tried or a second line of immunomodulating agents can be used in combination with the glucocorticoid. In cats, chlorambucil (0.1-0.2 mg/kg/day) is considered the alternative drug of choice and functions as a cell-cycle non-specific alkylating agent. Side effects of chlorambucil include myelosuppresion and gastrointestinal toxicity.[5] In dogs, azathioprine is typically used as the alternative drug. Azathioprine is not usually used in cats as it has been shown to cause serious leukopenia and thrombocytopenia.[1] Cyclosporine (5-10 mg/kg/day) is another alternative, but an expensive one. It functions by suppressing helper T cells and other components of the cell-mediated immune response. Variable responses to cyclosporine have been recorded and more studies need to be performed to assess its possible glucocorticoid-sparing and sole agent effects.[4, 5, 10] Side effects of cyclosporine are commonly GI-related, but are rarely seen at usual dosages. Cyclosporine, instead of chlorambucil, was used in addition to the dexamethasone in Duane because it requires less frequent recheck examinations and bloodwork (i.e. has fewer side effects), which was financially a more feasible option for the owner. Cyclosporine takes approximately 3 weeks to show effects.

One other alternative treatment, more effective in cats than in dogs, is gold salt therapy. Gold salt therapy, also known as chrysotherapy, is believed to have immunomodulating, anti-inflammatory, antirheumatic, and antimicrobial effects. The exact mechanism of action is not

currently known but involves suppression of helper T-cells. Gold salts exist in oral (auranofin) and parenteral (aurothioglucose) forms. Auranofin is supposedly less toxic but also less efficacious than the intramuscularly administered aurothioglucose. Only the injectible form has been used in cats. Gold salt therapy is expensive and side effects include possible immune-mediated thrombocytopenia, hemolytic anemia, leukopenia, GI disturbances, muscle pain at the injection site, and renal and hepatic toxicity. It usually takes 6-12 weeks for beneficial effects to be seen.[5, 11] In a severe case of pemphigus, this time to effect may be too long to warrant treatment with gold salts. Other treatment options should be exhausted before trying chrysotherapy.

When the disease is localized, topical steroid ointments are a possible treatment option. Topical treatment should be started with a more potent glucocorticoid such as triamcinolone, betamethasone, or fluocinolone. Once improvement is noted, maintenance therapy should be continued with 1-2% hydrocortisone. Topically applied tacrolimus has also shown some promise, but more studies need to be performed.[5, 7] For severe cases of pemphigus, one author has proposed shock doses of intravenous prednisolone or dexamethasone followed by oral glucocorticoid therapy to bring the disease under control. However, this method of treatment comes with increased risk of side effects.[5]

If concurrent bacterial skin infection exists, antibiotics should be prescribed to eliminate the infection. Some authors advocate antibiotic administration even without signs of current bacterial infection to preempt infection possibly acquired during the immune-suppressed state of treatment.[4] However, antibiotic administration is not without risks if the pemphigus is drug-induced. In Duane's case, exposure to numerous medications may have played a role in the development and/or recrudescence of his disease. Cutaneous adverse drug reactions resembling pemphigus foliaceus have been reported in cats following the administration of such drugs as ampicillin,

sulfonamides, and cephalexin.[2, 12] In the few case reports indicating a possible link between drug therapy and pemphigus foliaceus, lesions usually developed within three weeks of starting the drug and then started to resolve within two weeks of discontinuing the drug, although a period of steroid therapy may be necessary to induce remission.[2]

Based on the theory of a diet-induced pemphigus foliaceus, one approach to treating the disease may include a novel protein diet. In humans, certain chemical components of foods are hypothesized to contribute to the development of pemphigus. Such chemicals include thiols, isothiocyanates, phenols and tannins. Introducing a novel, restricted diet in dogs and cats may play a role in alleviating the disease.[1]

Prognosis

Pemphigus foliaceus carries a guarded prognosis. While not as grave a disease as pemphigus vulgaris, death is a possible outcome and becomes more likely if the patient fails to receive treatment for the disease. Even with treatment, control or resolution of the disease is not guaranteed as patient response to therapy is extremely variable. Some patients need to be treated for life. As previously mentioned, about 50% of patients require additional therapy beyond glucocorticoids alone. Typically if steroids are going to help the patient, improvement of clinical signs will be seen in approximately 2 weeks. The time and expense required to find an effective drug combination can limit treatment. Side effects of the drugs can also decrease the pet's quality of life to a point where further treatment becomes intolerable for the patient and owner. While the percentage of patients that actually die from the direct effects of pemphigus is probably low, the percentage euthanized for the above reasons is higher. It has been estimated that 10% of patients with canine and feline pemphigus foliaceus fail to respond to any treatment and are euthanized.[1] Cats tend to respond better to treatment than dogs do. Whether this is because cats have a superior

ability to tolerate medical therapy or the form of pemphigus foliaceus they develop is less severe, is unknown.[3]

Regular monitoring with physical exams and blood work (complete blood count and chemistry panel) is essential in these patients, especially when combination immunosuppressive therapy is being used. The suggested interval between rechecks at the start of therapy is two weeks.[6] Once steroids have been tapered and an effective degree of control has been achieved, rechecks can become less frequent. Urinalysis and urine culture and sensitivity should be performed regularly to monitor for opportunistic bacterial infections. However urinary tract infections appear to be more of a problem in dogs than in cats. Unfortunately, these frequent veterinary visits for monitoring and diagnostics are an added and often prohibitive expense to treating this disease.

The end result of Duane's case remains to be seen. As treatment with cyclosporine was just recently started, it is too soon to tell if this will improve his condition. However, as he has failed to respond adequately to previous treatments, his prognosis is guarded. Secondary bacterial skin infections, recurrent conjunctivitis, side effects of the dexamethasone, and the owner's financial constraints may significantly limit future treatment options. Inconsistent owner compliance with treatments may also play a role in Duane's lack of improvement. Duane's case illustrates the potential challenges of diagnosing pemphigus foliaceus, the variability in patient response to therapy, and the extreme difficulty of finding the right combination of medications. His situation also demonstrates the complex etiology of pemphigus foliaceus, in which additional factors such as drug-induced reactions and food allergies may play a role in either the development or exacerbation of the disease.

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