The Curious Case of Koda's Colorlessness

Uveodermatologic Syndrome

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Introduction

The distinct color of an individual's hair and skin is made possible by one particular cell type: the melanocyte. Melanocytes synthesize melanosomes, or melanin granules, that aggregate in the hair, skin, uvea, oral mucosa, cochlea, and to a lesser extent the meninges. Autoimmune diseases that affect melanocytes therefore cause a lack of pigmentation in the associated tissues. One specific disease noted in veterinary medicine is that of the uveodermatologic syndrome. Uveodermatologic syndrome was discovered following comparisons between canine patients and human patients with the disease in human medicine known as Vogt-Koyanagi-Harada (VKH). While VKH affects skin and eyes like uveodermatologic syndrome, it also affects the central nervous system and auditory function; these signs are not often observed in uveodermatologic syndrome. Despite the differences, the mainstay for treatment in canine and human patients is that of immunosuppression aimed at lessening the individual's own attack on its melanocytes.[3,4,5]

History and Presentation

Canines are the veterinary species implicated in uveodermatologic syndrome. Akitas, Siberian Huskies, and Samoyeds are suspected to be predisposed to uveodermatologic syndrome. While the age of onset is variable, mean and median values hint to 3-4 years of age being the most common. Males are at twice the risk of females to develop uveodermatologic syndrome; the reason for this discrepancy is not yet clear.[4,5]

Dogs will often present with ocular signs prior to onset of dermatologic signs. However, reverse and simultaneous presentations have been documented. Patients presenting clinical signs are likely to be poor or decreased vision with complete blindness not uncommon. Other commonly seen signs at presentation include uveitis and conjunctivitis.[4] Aqueous flare, iris abnormalities

(iridal edema, posterior synechiae, rubeosis iridis, and pigment on anterior lens capsule), retinal detachment and/or degeneration, and choroidal depigmentation or chorioretinal infiltrate have also been reported as intraocular abnormalities seen with uveodermatologic syndrome.[5]

Although dermatologic lesions may vary in severity, most lesions are found on the head and face with the most affected areas being the nasal planum, periorbital skin, and lips. The lesions reported the most are leukoderma and/or leukotrichia (the term vitiligo may be used), followed closely by erosions, ulcerations, alopecia, crusts, and erythema. Other cases have reported pruritus, hyperkeratosis of paw pads, onychomadesis, and swelling of the nose. Lesions are bilaterally symmetric in almost all cases.[4.5]

Auditory and central nervous disease is noteworthy. However, this is most commonly seen with VKH in humans. While it is plausible that auditory and central nervous system disease exists in our canine patients, it may go undetected. This may be due to canines having a shorter lifespan, the lack of strong diagnostics for hearing impairment in veterinary medicine, and the inaccessibility of diagnostics such as MRIs to look for underlying meningitis in canine patients.[4]

Pathophysiology

The etiopathogenesis of uveodermatologic syndrome is not fully understood. It meets the criteria for an autoimmune disease; the mechanism hasn't been completely revealed, though. There is general agreement that the disease targets melanocytes or melanocyte-associated antigens (tyrosinase), and via an unknown mechanism triggers a granulomatous inflammatory response.[2,3,5] With VKH in humans, it has been experimentally shown that lymphocytes exposed to peptides derived from the tyrosinase family induces marked lymphocytic proliferation. It is suspected that ocular lesions involve a B cell and macrophage response (Th2 immunity) and skin

lesions involve T cell and macrophage response (Th1 immunity).[2,3] An increased risk to developing the disease has been linked to canines with the dog leukocyte haplotype (DLA)-DQA1*00201. Other alleles of the DLA class II have not been shown to have an increased risk. Antiretinal antibody (ARA) involvement is up for debate in human VKH syndrome, and one dog in veterinary medicine has been shown to have ARA activity. The discrepancy of ARA titers comes with not knowing whether they are the cause or a sequela or a previous disease process such as cancer retinopathies, toxoplasmosis, or age-related change.[4]

Considering the locations affected the most in the body by the uveodermatologic granulomatous response, it is important to understand that the uvea (ciliary body, iris, and choroid), retina, oral mucosa, nasal planum, and skin contain the highest concentrations of melanocytes in the body. When the autoimmune response is triggered, macrophages target and destroy the melanocyte cell population. The granulomatous and lymphocytic infiltrate leads to the tissue damage observed as clinical signs. The destruction of the melanocytes and subsequent leakage of melanosomes into tissues is the cause of the leukoderma and/leukotrichia.[2,3,4,5]

Differential Diagnoses

When presented with a dog with panuveitis, differentials such as idiopathic/immune mediated disease (uveodermatologic syndrome), systemic blastomycosis, and tickborne diseases (*Ehrlichia* and *Rickettsia*), and lymphoma should be considered. Other infectious diseases such as histoplasmosis, leptospirosis, and aspergillus can be considered with a lesser extent. For the dermatologic signs of leukotrichia and/or leukoderma, erosions to ulcerations, and crusts, differentials include discoid lupus erythematosus, systemic lupus erythematosus, pemphigus foliaceus, pemphigus erythematosus, and epitheliotropic lymphoma. The presence of signs in

both the ocular and dermatologic locations should yield high suspicion for uveodermatologic syndrome regardless of breed.[3]

Diagnostic Approach/Considerations

Diagnosis of uveodermatologic syndrome is based primarily on signalment and pathognomonic clinical signs. For a dog presenting with primarily ocular signs, performing a thorough physical and ophthalmic exam will provide clues for diagnosis and degree of severity. Fully evaluating the anterior and posterior chambers of the eye is important for assessment of aqueous flare and chorioretinitis. Measuring intraocular pressures is recommended as glaucoma is a common sequela to the inflammatory response brought on by uveodermatologic syndrome and is often the cause of blindness. In human VKH, it has been shown that those suffering from the disease are at a higher likelihood of developing keratoconjunctivitis sicca (KCS). Fluorescein staining of the cornea should be performed to rule out corneal ulcerations as potential irritants. Fundic examination should be performed to assess retinal depigmentation, optic nerve cupping and/or edema, and retinal detachment.[5] When considering dermatologic differentials, characteristic lesions such as facial vitiligo, erosions, and crusts are highly suspect for uveodermatologic syndrome.[3,4]

Additional diagnostic testing should be aimed at ruling out infectious or neoplastic causes. Tickborne disease serum titers, fungal urine/serum titers, and leptospirosis titers are recommended. Diagnostic imaging is useful for detecting pulmonary fungal disease, lymphadenopathy, and organomegaly. Impression smears of skin lesions or aspirates of lymph nodes, bone marrow, or other organs/masses may be beneficial at diagnosing infectious or neoplastic etiologies as well. While the likelihood of obtaining a diagnosis from a minimum database (CBC, chemistry, urinalysis) is very low, it may provide an understanding of the extent

of systemic involvement in addition to acting as a baseline for comparison once treatment is initiated.[1] Thorough steps to rule out infectious and neoplastic causes are necessary due to the vastly different treatment courses (i.e. immunosuppressives vs antifungals) that could result in worsening of the disease state.

Histopathology is often utilized for confirmation purposes. Biopsies of the skin should be collected from lesion margins or from areas of recent depigmentation.[4] If antemortem enucleation or post-mortem examination is pursued, submitting the globe for histopathology is a viable option for confirmatory diagnosis as well.[2] The characteristic histopathologic feature of uveodermatologic syndrome is lichenoid dermatosis of predominately histiocytic inflammation with macrophages containing melanin pigment dispersed among other lymphocytes, neutrophils, and plasma cells.[3] Other findings may include epidermal hyperplasia which is often accompanied by erosions, ulcers, and crust formation. Loss of melanocytes leads to epidermal depigmentation. Histopathology should be pursued sooner in the disease process rather than later as compensation occurs with chronicity, and characteristic changes may not be present if biopsies have been delayed.[2,4]

Treatment and Management Options

The mainstay for treatment in both uveodermatologic syndrome in dogs and VKH in humans is glucocorticoid therapy. A recent retrospective study demonstrated that early and high-dose immunosuppressive doses in dogs yields a stronger response to therapy as seen in humans with VKH. Utilization of multimodal immunosuppressive therapy with such agents as azathioprine, cyclosporine, chlorambucil, cyclophosphamide, and mycophenolate mofetil has previously been reserved for chronic or recurrent cases; however, it has been demonstrated that an initial multimodal implementation results in a better visual outcome. Topical steroids and cycloplegic

agents are often utilized for a local reduction in inflammation and pain as well as preventive measures for the development of synechiae.[3.4.5]

As with any patient on long term glucocorticoids and immunosuppressives, continual monitoring of liver and kidney function in addition to close watch for any gastrointestinal upset is recommended.[5] Regular re-evaluation by an ophthalmologist for development or worsening of secondary sequelae (glaucoma, posterior synechiae, cataracts, optic nerve cupping, retinal atrophy or detachment) should be a mainstay of therapeutic monitoring even if only dermatologic signs are all that are present.[4]

Expected Outcome and Prognosis

Clinical remission can be achieved in cases of uveodermatologic syndrome in dogs. It is judged based on improvement or re-establishment of vision in dogs that originally presented with blindness, the prevention of new signs developing, and the lack of progression or resolution of pre-existing ocular and/or skin lesions. In contrast to humans with VKH, dogs with uveodermatologic syndrome are likely to relapse following discontinuation of immunosuppressive therapy. If lesions are progressive and sequela are unable to be controlled, therapy is deemed to have failed.[4]

In general, the prognosis for life with a diagnosis of uveodermatologic syndrome is good. Lifelong treatment should be discussed with owners with potential for eventual failure of therapy. The prognosis for vision is guarded.[4,5] Even with aggressive therapy, ocular damage is often irreversible. Enucleation for the sake of comfort should be considered in patients with complete loss of sight. Dogs can live a good quality of life without vision. However, the quality

of life of the owner is worthy of consideration as well. Humane euthanasia is an acceptable option, especially in the face of chronic, recurrent disease and a lack of response to therapy.[5]

Other Pertinent Information

Most of the research done in veterinary medicine is either in the form of retrospective studies or prospective studies including very few participants.[5] Because of this, a standardized treatment protocol has not been established for cases determined to be uveodermatologic syndrome. Considering the autoimmune etiology, most veterinarians appropriately begin immunosuppressive doses of glucocorticoids.[4.5] Determining the ideal course of therapy, however, would be beneficial. Further research is needed to provide a known treatment protocol that achieves clinical remission and keeps vision loss at bay.[5]

Conclusion

Uveodermatologic syndrome is an autoimmune disease that targets melanocytes through an unknown mechanism of action. Clinical signs are most commonly seen in ocular and dermal tissues with the most characteristic being bilateral panuveitis and leukoderma/leukotrichia. Akitas, Siberian Huskies, and Samoyeds are breeds suspected to be predisposed to the condition and the average age of onset is roughly 3 years of age.[2,3,4,5] While lifelong immunosuppressive therapy provides a good prognosis, the prognosis for vision long-term is guarded. Should a patient present with signs suspicious for uveodermatologic syndrome, referral for care under an ophthalmologist and dermatologist is recommended.[4]

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