

VOGT-KOYANAGI-HARADA-LIKE SYNDROME IN A GERMAN SHEPHERD DOG

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Abstract: A 6-year-old male dog was presented with a one-year history of vision loss, alopecia, and generalized depigmentation of the skin and hair. Ophthalmic signs were the first symptoms, described as conjunctivitis (whites of the eye, and rimgo red) by owners. After that, the skin and hair changes followed within three months. Clinical examination confirmed diffuse generalized depigmentation, hair loss, and blindness. Ophthalmic examination indicated depigmentation of the mucocutaneous junctions of the superior and inferior eyelids, mild conjunctival hyperemia, and congestion of the episcleral vessels. Menace and pupillary light reflexes were decreased. The main aspect was a milky blue surface on the eyes balls and bilateral cataract. No complete ophthalmologic exam was performed. The complete blood count did not show significant changes. Skin scrapings collected from affected areas (alopecic and depigmented) showed an absence of bacteria, fungi or mites. Skin-punch biopsies of depigmented skin from the face and thoracic region were placed in 10% buffered formalin for fixation, sectioned in paraffin, and stained with hematoxylin and eosin (H&E) and Trichrome Masson. The conclusion of histopathology was histiocytic lichenoid interface dermatitis with marked pigmentary incontinence. Such findings, associated with clinical and ophthalmic signs, suggested uveodermatologic or VKH-like syndrome. In addition, epidermal atrophy was noted but are considered a secondary lesion of treatment with anti-inflammatory drugs (SAID). Biochemical and serologic analyzes had elucidated no other cause for the ocular and skin lesions.

A condition known as the Vogt-Koyanagi-Harada (VKH) or uveomeningoencephalitic syndrome is seen in human beings. In 1906, Vogt described a complex of symptoms associated together, as did Koyanagi in 1929. They had inflammation of the front of the uvea (the middle layer of the eye with the richest blood supply, includes the iris, aqueous humor, and choroid); loss of pigment in the skin (vitiligo); hair whitening (poliosis), not only on the head, but eyelashes and brows as well; hair loss (alopecia), and hearing problems (dysacusia). In 1926, Harada had described patients with inflammation of the back of the uvea, retinal detachment, and cerebrospinal involvement (meningitis). Not all patients have all symptoms and the degree of symptomatology differs from patient to patient.¹⁹

In man, the syndrome is described as being of genetic origin, involving multiple hereditary factors.¹² The cause of the disease is still undetermined but a role for the immune system has been suggested, with melanocytes being the target cells. The common link between the ocular, cutaneous and central nervous system signs is a similar embryologic development of pigment containing cells, which are the target of the granulomatous inflammation.²³

The mechanism that triggers the autoimmune reaction is unknown, but sensitization to melanocytic antigens by means of cutaneous injury or possible viral infection has been postulated.^{22, 18}

The tyrosinase family of proteins are enzymes involved in melanin formation and are expressed specifically by melanocytes. Immunization of these peptides into pigmented rats induced ocular and extraocular changes that highly resembled human VKH disease.²⁷

A syndrome similar to this syndrome is recognized in dogs. The disease was first reported in 1977 in two Akita dogs by Asakura *et al.*² Since then, several other affected breeds including the Siberian Husky, Dachshund, Fox Terrier, Shetland Sheepdog, Saint Bernard, Irish Setter, Old English Sheepdog, Golden Retriever, Chow-Chow and Brazilian Fila have been reported.^{4,5,8,12,13,14,16,19,23,25.}

However, the Akita, Siberian husky, Alaskan malamute and Samoyed are most commonly affected. The highest incidence appears among the Akita, suggesting breed predisposition and perhaps genetic transmission.^{3,8,9}

The Akita breed of dog is affected by a number of distinct immune-mediated diseases, including thyroiditis, sebaceous adenitis, pemphigus foliaceus, uveitis, polyarthritis, myasthenia gravis, and uveodermatologic syndrome. The study of Angles *et co.*¹ confirmed loss of DLA genetic diversity in the American Akita dog in common with other pure breeds of dog and suggested a role for certain DLA class II gene alleles in the pathogenesis of UV.

Canine UVD, similarly to human disease, is believed to be due to an immune-mediated reaction against melanocytes, but there is little evidence that demonstrates an underlying trigger factor, although both bacterial and fungal causes have been suggested.^{5,14,10,21}

Because not all human symptoms are expressed in the signs the affected dogs show, the syndrome in dogs should be referred to as Vogt-Koyanagi-Harada-like (VKH-like) or uveodermatologic syndrome (UDS). In dogs, symptoms are depigmentation, hair loss, and blindness. Sometimes there are no warnings, sometimes there are, like the depigmentation and conjunctivitis. The disease is more common in male dogs than female dogs. The age of onset ranges from 13 months to 6 years. Often the first noticeable sign of UDS is uveitis. The skin and hair changes typically follow within three to six months after the eye disease has begun. It's important to note though that while uveitis is always present in VKH-like complex, uveitis alone does not mean the dog has VKH. Ophthalmic signs include diminished or absent pupillary light reflexes, blepharospasm, photophobia, anterior uveitis, involving iris, ciliary body and choroid, keratic precipitates, hyphema, chorioretinitis, and in some cases retinal detachment. Dogs with the Vogt-Koyanagi-Harada-like syndrome have various degrees of uveitis. Conjunctivitis (whites of the eye, and rimgo red) will often be followed by a detached retina, which shows as a milky blue surface on the eye ball. The iris is the main point of attack and as a result the dog suffers a very painful uveitis, which is basically inflammation of the iris and shows itself as a very small pupil with a swollen iris and mainly conjunctivitis, which is often the point of misdiagnosis because it looks like conjunctivitis pure and simple.³ Secondary events include cataracts, iris bombé, secondary glaucoma and loss of vision.^{2,4,9,14}

Depigmentation of the skin at the scrotum, nasal planum and mucocutaneous junctions of the mouth, eyelids and perianal region characterize dermalologic signs. Vitiligo seems to be present in almost every affected dog. Poliosis occurs less frequently, but still is relatively common.^{4,14,17} Neurologic signs in dogs have been reported only twice.^{10,11} Dysacusia has not been recognized in affected dogs.

In common with VKH, the body's antibodies attack melanin-containing cells, shared by the skin, hair, eye, meninges, and ear; whereas, in the dog, the meninges and ear may not be involved because they don't have the same composition. Something happens that causes the melanocytes of the eye and skin begin to express an antigen that the immune system brands as foreign. A recently published study done at UC Davis, details the DLAs (dog

leukocyte antigen) found in dogs affected with UV vs dogs in the control group which were not affected by UV.¹

History, clinical and ophthalmic signs, and complementary laboratory examinations are important for diagnosis. Management of the disease consists of the administration of systemic and topical corticosteroids in high concentrations and, whenever necessary, more potent immunosuppressive drugs. The prognosis is guarded, especially for long-term control and the maintenance of vision. Treatment is as for uveitis in general. Systemic corticosteroids seem especially important. The treatment must be continued for months beyond the point at which the signs subside.

Prognosis is poor overall. The uveitis tends to recur and may result in permanent blindness due to cataract and retinal degeneration after long term separation or inflammation. Even vigorous therapy may not control the situation. In patients in whom inflammation is controlled, useful vision may be retained and melanosis of the skin may recur.

We present a case of uveodermatologic syndrome in a German shepherd, which is the first report of this disease in this breed.

Case history. A 6-year-old male German Shepherd was referred with a one-year history of gradual vision loss associated with alopecia and cutaneous depigmentation. According owners anamnesis the dog showed ocular pain and blind before seeking veterinary advice. . Ophthalmic signs were the first symptoms, described as conjunctivitis (whites of the eye, and rimgo red) by owners. The alopecia and cutaneous depigmentation were developed after ocular manifestation. The debut of the alopecia and depigmentation was to the scrotum, nose and mucocutaneous junctions of the mouth and eyelids but in a year tend to be generalized. The dog was treated in many clinics with some positive but transitory effects.

A **general examination** revealed diffuse generalized depigmentation. The hair was also diminished in several parts of the derma, with some alopecic areas and secondary pyodermitis.

Ophthalmic examination indicated depigmentation of the mucocutaneous junctions of the superior and inferior eyelids, mild conjunctival hyperemia, and congestion of the episcleral vessels. Menace and pupillary light reflexes were decreased. The main aspect was a milky blue surface on the eyes balls and bilateral cataract. No complete ophthalmologic exam was performed.

Biochemical and serologic analyzes had elucidated no other cause for the ocular and skin lesions. The complete blood count did not show significant changes. Skin scrapings collected from affected areas (alopecic and depigmented) showed an absence of bacteria, fungi or mites.

Histopathologic findings. Biopsy samples of depigmented skin from the face and thoracic region were taken. The cutaneous sites were selected on the basis of clinical evidence of depigmentation and on a predilection for this disease already documented. The skin biopsy of the affected areas was performed under general anesthesia. Skin-punch biopsies were placed in 10% buffered formalin for fixation, sectioned in paraffin, and stained with hematoxylin and eosin (H&E) and Trichrome Masson.

Examination revealed a diffuse granulomatous infiltration of the superficial dermis, extending focally in places to involve the superficial adnexal structures, especially hair follicles. Although the dominant cell type in the infiltrate was the macrophage, neutrophils, small lymphocytes and plasma cells were also present. Moderate multifocal to coalescing subepidermal infiltration of mononuclear leukocytes and large macrophages, some of which contain granular, phagocytosed melanin. The infiltrate was below the level of the epidermal basement membrane zone, with accompanying focal minimal spongiosis. There was

prominent pigmentary incontinence, with melanophages clustered within the superficial dermis and around hair follicles. Additionally, there was evidence of fibrosis in the superficial dermal and perifollicular regions. The conclusion of histopathology was histiocytic lichenoid interface dermatitis with marked pigmentary incontinence. Such findings, associated with clinical and ophthalmic signs, suggested uveodermatologic or VKH-like syndrome. In addition, epidermal atrophy was noted but are considered a secondary lesion of treatment with anti-inflammatory drugs (SAID).

DISCUSSION

In case reported here, there was depigmentation of the mucocutaneous junctions of the superior and inferior eyelids, nostrils and scrotal skin, as well as generalized dermatitis and alopecia. A skin biopsy confirmed uveodermatologic syndrome. Histiocyte lichenoid dermatitis, with an absence of pigment within the keratinocytes is the most suggestive sign, as reported previously.²⁶

Clinical examination associated the bilateral uveitis with the generalized depigmentation of skin and hair. Toxic and infectious agents, trauma, neoplasia and immune-mediated diseases, as well as idiopathic causes, are recognized as common causes of bilateral uveitis⁹ but the association of uveitis followed by characteristic dermatitis with depigmentation are specific for uveodermatologic syndrome.

After the first report of uveodermatologic syndrome in two dogs by Asakura in 1977, many other breeds have been shown to be affected.^{4,5,8,12,13,14,16,19,23,25.}

However, uveodermatologic syndrome had not been noted previously in the German Shepherd.

The cause(s) and pathogenesis of this disorder are not fully known. The immune system plays a role, targeting the melanocytes. Viral infections may also be involved.¹³ To date, some alleles, such as *HLA-DR1*, *HLA-DR2* and *HLA-DR4*, have been reported in humans with uveodermatologic syndrome, suggesting that genetic factors are involved. 11 Such alleles have not been identified in affected dogs. However, the high incidence, particularly in Akitas, suggests certain a breed predisposition.^{3,4,8}

The skin lesions of these two Japanese Akita dogs with UVD syndrome were mediated by T cells and macrophages (Th1 immunity), whereas the ocular lesions were more consistent with a B cell and macrophage response (Th2 immunity). These features may not be the same for all cases of UVD syndrome.⁷

Treatment to control the inflammation with rapid and aggressive topical and systemic administration of immunosuppressors resulted in marked clinical improvement of both the ocular and skin lesions. Uveitis can be controlled using topical and subconjunctival corticosteroids, associated with mydriatics and cycloplegics.¹³

The veterinary practitioner should maintain a suspicion for this uveodermatological syndrome not only in the Akita dog, but in any dog displaying signals that remind those of this particular disease.

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