Progressive Depigmentation in a Patient with Panuveitis and Meningitis

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Question

A 47-year-old Cuban female presented with a 5-year history of progressive depigmentation on her central face. She also complained of recent-onset hair shedding and white hairs throughout her scalp requiring frequent dyeing. Her past medical history was notable for a hospital admission due to headache, vertigo, and bilateral ocular pain; further workup revealed a lymphocytic meningitis and bilateral panuveitis, necessitating oral steroid therapy. Review of systems was positive for recurrent episodes of bilateral eye pain and photophobia, tinnitus, and diffuse arthralgia. Her family history was positive for autoimmune thyroid disease in both sisters.

Physical examination demonstrated well-demarcated coalescing depigmented patches involving the central face (Fig. 1a, b), depigmented macules on her sacrum (Fig. 2), and scattered depigmented macules on her bilateral legs and back, which were positive on Wood's lamp examination. Poliosis along the frontal hairline and bilateral erythematous conjunctivae were additionally observed. Laboratory examination, including ANA, double-stranded DNA, anti-Smith antibody, SSA/SSB antibody, Scl-70 antibody, RNP antibody, rheumatoid factor, c-ANCA, thyroid peroxidase antibody, and complement levels, was within normal limits.

Given the constellation of physical findings and a history of uveitis and meningitis, what is your diagnosis?

Fig. 1. a, b Sharply demarcated coalescing depigmented patches predominately on the central face.

Fig. 2. Few depigmented macules on the sacrum.

Answer

Vogt-Koyanagi-Harada (VKH) syndrome, also known as uveomeningitis or alopecia-poliosis-uveitis-vitiligo syndrome, is a multisystem autoimmune disorder affecting melanocytes in the integumentary system, eye, inner ears, and meninges, resulting in a distinct clinical phenotype characterized by vitiligo, poliosis, bilateral granulomatous panuveitis, auditory abnormalities, and aseptic meningitis. The disease is exceptionally rare with an incidence of approximately 1.5–6 per 1 million patients in the US [1].

VKH syndrome typically develops during the third to fourth decade of life, and most frequently affects women, with a female to male ratio of 2:1 [2]. VKH is most prevalent in individuals of darker skin, including Asians, Native Americans, Hispanics, Asian Indians, and Middle Easterners [3]. However, individuals of African descent are uncommonly affected [2]. Among all cases of uveitis, VKH accounts for approximately 1–4% of cases in the US [1, 2].

Although the exact etiology and pathogenesis of VKH remain to be elucidated, VKH is thought to be due to a Th₁ autoimmune response directed against antigenic proteins associated with melanocytes, such as tyrosinase, tyrosinase-related protein 1 (TRP1), and tyrosine-related protein 2 (TRP2) [2]. Interleukin (IL)-7, IL-17, and IL-23 are involved in the initiation and maintenance of the inflammatory process [4]. Viruses such as CMV and EBV may play a role as inciting triggers [4]. Failure to mount an effective immune response against viral infections due to poor natural killer cell and cytotoxic T lymphocyte function has been linked to the development of VKH in genetically susceptible individuals; HLA-DRB1*0405 is the main susceptibility allele for VKH [5, 6]. Strong associations with HLA-DR4 and HLA-DR53 have also been demonstrated in Japanese, Chinese, North American, and Hispanic populations [2].

VKH is classified into 4 distinct consecutive stages. (1) *Prodromal stage* characterized by flu-like symptoms of fever, vertigo, meningismus, and nausea lasting 1–2 weeks, in which over 80% of cases have cerebrospinal fluid pleocytosis with lymphocytic predominance. Hypersensitivity to touch of the hair and skin may also be present. (2) *Acute uveitic stage* manifesting with sudden bilateral vision loss, photophobia, and ocular pain lasting several weeks. (3) *Chronic (convalescent) stage* characterized by depigmentation in the skin and uveal tissue, lasting several months to years. (4) *Chronic recurrent stage*, usually due to suboptimal treatment, in which mild pan-

uveitis with recurrent episodes occurs [2]. Dalen-Fuchs nodules, or aggregates of lymphocytes and pigment-laden macrophages, may be visualized at the retinal pigment epithelium during the convalescent stage [2]. Ocular complications, including cataracts, glaucoma, choroidal neovascularization, and subretinal fibrosis, are common during the final stage [2].

Cutaneous manifestations, such as vitiligo, poliosis, and alopecia appear during the convalescent stage [2]. Vitiligo develops in the vast majority of cases, and commonly affects the head, neck, and trunk in a symmetrical distribution. The sacrum is also commonly affected. Poliosis of the eyelashes, eyebrows, and scalp hair tends to last months to years. Diffuse alopecia occurs in up to 70% of patients, and can relapse and remit [7]. Although rare in North American patients, 85% of Japanese patients present with perilimbal vitiligo, known as Sugiura's sign, as the earliest cutaneous manifestation of VKH [2]. Depigmentation of the choroid leads to a bright, orange-red appearing fundus and a pale optic nerve known as the "sunset glow" fundus [2].

The diagnosis of VKH is made by the clinical presence of uveitis as demonstrated by angiography or ultrasonography of the eyes [2]. According to the revised diagnostic criteria established at the First International Workshop on VKH in 2001, the disease must meet 3 requirements: (1) no history of ocular trauma, (2) no evidence suggestive of other ocular diseases, and (3) bilateral ocular involvement. VKH can be categorized into 3 disease categories – complete, incomplete, and probable – based on whether cutaneous and/or neurologic or auditory findings are present. Cutaneous findings must develop after the onset of ocular or neurologic symptoms to properly make the diagnosis [8, 9]. While biopsy is not necessary, histologic examination of the affected skin demonstrates a mononuclear infiltrate consisting of CD4+ lymphocytes, confirming the role for cell-mediated immunity. Histologic examination of the scalp shows peribulbar mononuclear infiltrates as seen in alopecia areata [7].

Based on cutaneous manifestations, differential diagnosis can include vitiligo, piebaldism, Waardenburg syndrome, and Alezzandrini syndrome among others [1]. Vitiligo is caused by an autoimmune destruction of melanocytes, resulting in well-demarcated, mostly symmetrical, depigmented patches. However, it is not preceded by uveitis or aseptic meningitis-like symptoms and is predominantly skin limited. Both VKH and vitiligo have an autoimmune etiology, unlike the other diagnoses described below. Piebaldism is a rare autosomal dominant disorder characterized by congenital poliosis and vitiligo;

extracutaneous manifestations are rare. Presence of a white forelock overlying the amelanotic skin may be the only manifestation in most individuals. Pathogenesis involves a mutation of the c-Kit gene leading to abnormal melanocyte migration during embryogenesis [10, 11]. Waardenburg syndrome also presents with poliosis and vitiligo. Extracutaneous manifestations are frequent, including congenital sensorineural hearing loss, dystopia canthorum, heterochromia irides, and a hypertrophic nasal root [11, 12]. Mutations in genes involved in cell formation and development, such as PAX3, MITF, and SOX10, are responsible for the disease [11]. Alezzandrini syndrome presents with unilateral poliosis and vitiligo and ipsilateral retinal detachment, blindness, and hypacusis. Depigmentation of the skin is classically confined to the face, unlike in VKH where the neck, trunk, legs, and sacrum are known to be involved in a symmetrical manner. Pathogenesis is unknown, but believed to be an interplay of genetics, autoimmunity, neural, biochemical, and oxidative stress, viral infection, and melanocyte detachment mechanisms [13].

Early and aggressive systemic corticosteroids are the mainstay of treatment for acute VKH disease [2]. In patients with chronic recurrent disease or disease refractory to corticosteroids, immunosuppressive agents such as cyclosporine, azathioprine, methotrexate, chlorambucil, or cyclophosphamide can be employed to suppress ocular inflammation. Biologic agents, such as adalimumab, infliximab, and rituximab, as well as anti-vascular endothelial growth factor agents, bevacizumab and ranibizumab, are currently being studied for refractory uveitis [1]. Vitiligo associated with VKH has been treated successfully

with topical calcineurin inhibitors and topical corticosteroids; methotrexate, mycophenolate mofetil, and azathioprine have also been used for progressive disease [8, 9, 14]. Alopecia has been shown to respond to systemic corticosteroid therapy, but additional studies are warranted [14]. Ocular complications require close follow-up with ophthalmology and potential therapy with laser or surgical iridectomy [4]. This case exhibits the imperative diagnosis of VKH made by dermatology to allow for earlier intervention to prevent long-term visual impairment and morbidity associated with the disease.

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Statement of Ethics

Written consent was obtained from the patient. The authors have no ethical conflicts to disclose.

Disclosure Statement

The authors report no conflicts of interest.

Keywords

Vitiligo · Uveitis · Poliosis · Aseptic meningitis · Vertigo · Alopecia

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