

Rare simultaneous occurrence of two supposedly antagonistic diseases: Vogt-Koyanagi-Harada disease and allergic conjunctivitis

Mariana Couto, MD^{a,b}, and Mário Miranda, MD^b

Clinical Implication

- Vogt-Koyanagi-Harada disease and allergic conjunctivitis (classically Th1 and Th2 diseases, respectively) might coexist in one patient. It is important to also bear in mind allergic diseases as a cause of ocular symptoms in patients with diagnosed autoimmune disorders.

TO THE EDITOR:

Vogt-Koyanagi-Harada disease (VKHD) is an autoimmune disorder that affects melanocyte-rich tissues (eye, inner ear, meninges, and skin). Genetically susceptible individuals, possibly under the effect of an infectious trigger, produce CD4⁺ and CD8⁺ T lymphocytes against melanoma cells and/or melanocyte-related antigens.¹ A Th1 cytokine profile was described in patients with VKHD after exposure to melanocyte-derived antigens. It was observed that their mononuclear cells (MNC) produced larger amounts of IL6, IL8, and IFN- γ , and recognized melanocyte-derived peptides with higher affinity than control subjects; conversely, it also was shown that the MNCs of these patients did not secrete IL4, a Th2-cytokine.² This verdict might lead clinicians to suppose that patients with VKHD would not be prone to develop Th2-cytokine-dependent disorders, such as allergic diseases.

We describe the clinical case of a 46-year-old woman who was referred to our allergy division for recurrent episodes of ocular itching and tearing, accompanied by aqueous rhinorrhea, sneezing, and nasal itching, mainly during spring and summer, in the past 2 years. She had no bronchial symptoms. Results of a clinical examination revealed inferior turbinate hypertrophy and skin depigmentation in her legs. Her medical history was remarkable for the diagnosis 7 years before of VKHD made by her ophthalmologist, after an acute episode of bilateral red eye. She had already presented at that time with small areas of skin depigmentation on her legs. The audiogram was normal and so were the cerebrospinal fluid analysis. She was medicated with systemic methylprednisolone for 6 months, and her visual acuity has been stable for the past 5 years.

The allergy workup performed included skin prick tests, which were positive (the mean of the largest and perpendicular diameter of the wheal ≥ 3 mm for each allergen, and controls showed adequate reactions) to cat, *Platanus acerifolia*, *Betula alba*, *Olea europaea*, *Parietaria judaica*, *Plantago lanceolata*, *Artemisia vulgaris*, grass, and cereal pollens. Immunologic evaluation revealed normal IgG (1250 mg/dL), IgA (300 mg/dL), and IgM (121 mg/dL); IgD was <1 mg/dL and autoantibodies were negative, except for anti- β 2glycoprotein-I IgM (47.1 SMU) and IgG (31.2 SMU); total and specific IgE results are presented in Table I. Hemogram; ionogram; renal, liver, and thyroid

functions; complement system; erythrocyte sedimentation rate; and angiotensin converting enzyme levels were within normal ranges.

She started oral antihistamines and nasal mometasone furoate, with improvement. Later, she started having oropharyngeal pruritus when eating peach, plum, and melon. Skin prick tests with commercial extracts of fruits, profilins, and lipid transfer proteins were positive only to profilins. A few months later, the patient decided to start specific immunotherapy to avoid daily medication during the spring months, especially topical. Subcutaneous immunotherapy to grass pollens then was started; she currently has improved without needing regular drugs.

This is the first time to our knowledge that the coexistence of VKHD and allergic conjunctivitis and rhinitis in one patient is described. It proves that these 2 conditions (classically Th1- and Th2-mediated diseases and, therefore, supposedly antagonistic) that involve the same target organ might occur simultaneous in the same patient. Patients with VKHD are probably able to produce IL4 in relation to a Th2-mediated process under determinate circumstances.

Although the exact etiology of VKHS remains unclear, there are currently 3 main hypotheses proposed to explain it: the genetic, the infectious, and the immunologic hypothesis.³ It has been postulated that the autoimmune response against melanocytes that occurs in VKHD might be triggered by an infectious agent in a genetically susceptible individual. This case report could possibly support the previous hypothesis that atopic and autoimmune diseases could share some risk factors, such as infections,⁴ which increase the immune system propensity to generate both Th1- and Th2-mediated inappropriate responses to otherwise benign antigens.⁵ However, although VKHS classically begins with vague systemic symptoms suggestive of a viral infection, a clear association between a specific viral agent and the disease has not been established.³ Therefore, the immunologic hypothesis seems more plausible, due to the great progress that has been made during recent decades because of the rapid development in immunology and related techniques.³ Recently, 2 new T helper subsets were described in patients with VKHD: T helper 17 (Th17) and regulatory T cells.^{6,7} Th17 cells are implicated in clearing pathogens during host defense reactions and in inducing tissue inflammation in autoimmune diseases⁸ as well as in some forms of asthma and atopic eczema with neutrophilic infiltration. Regulatory T cells have been clearly implicated as potent inducers of a nonresponsive state in several immune-mediated pathologies such as autoimmunity and allergy.⁹ In addition to the important role of natural Foxp3⁺ Treg cells in preventing autoimmunity, it has become established that Foxp3 expression can be peripherally induced after T-cell activation in the presence of TGF- β .⁹ These peripherally induced Treg cells are also believed to be important for tolerance induction to nonselfantigens, including allergens. Besides, Th17 cells, which have been implicated in autoimmunity and allergy, share with induced Treg cells the need for TGF- β to differentiate.⁹

Further studies are needed, namely, by investigating the T-cell profile of patients with both of these condition or possibly by searching for atopy in patients with VKHD and eventually

TABLE I. Laboratory allergy workup

	Results (kU/L)
Total IgE	49.9
Specific IgEs	
Grass mixture	51
Weeds mixture	0.55
Trees mixture	0.49
Cat	<0.10
<i>Triticum</i>	3.55
<i>Platanus acerifolia</i>	0.60
<i>Betula alba</i>	0.32
<i>Olea europaea</i>	0.52
<i>Parietaria judaica</i>	0.46
<i>Plantago lanceolata</i>	0.64
<i>Artemisia vulgaris</i>	0.33

challenging their MNCs with allergens instead of only melanocyte-derived peptides. The significant cumulative quality of life impact of both conditions led us to assign allergen-specific immunotherapy, which was a useful therapeutic option in this patient. It is important to reveal these clinical cases for clinicians to bear in mind allergic diseases as a cause of ocular symptoms also in patients with autoimmune ocular diseases.

^aImmunology Lab, Faculty of Medicine, University of Porto, Porto, Portugal

^bImmunology Department, Hospital of São João EPE, Porto, Portugal

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication September 5, 2013; revised November 9, 2013; accepted for publication December 16, 2013.

Corresponding author: Mariana Couto, MD, Immunology Department, Hospital of São João EPE, Alameda Prof Hernâni Monteiro, 4200 – 319 Porto, Portugal. E-mail: marianafercoto@gmail.com.

2213-2198/\$36.00

© 2014 American Academy of Allergy, Asthma & Immunology

<http://dx.doi.org/10.1016/j.jaip.2013.12.002>

REFERENCES

1. Damico FM, Bezerra FT, Silva GC, Gasparin F, Yamamoto JH. New insights into Vogt-Koyanagi-Harada disease. *Arq Bras Oftalmol* 2009;72:413-20.
2. Damico FM, Cunha-Neto E, Goldberg AC, Iwai LK, Marin ML, Hammer J, et al. T-cell recognition and cytokine profile induced by melanocyte epitopes in patients with HLA-DRB1*0405-positive and -negative Vogt-Koyanagi-Harada Uveitis. *Invest Ophthalmol Vis Sci* 2005;46:2465-71.
3. Greco A, Fusconi M, Gallo A, Turchetta R, Marinelli C, Macri GF, et al. Vogt-Koyanagi-Harada syndrome. *Autoimmun Rev* 2013;12:1033-8.
4. Sheikh A, Smeeth L, Hubbard R. There is no evidence of an inverse relationship between TH2-mediated atopy and TH1-mediated autoimmune disorders: lack of support for the hygiene hypothesis. *J Allergy Clin Immunol* 2003;111:131-5.
5. Simpson CR, Anderson WJA, Helms PJ, Taylor MW, Watson L, Prescott GJ, et al. Coincidence of immune-mediated diseases driven by Th1 and Th2 subsets suggests a common aetiology. A population-based study using computerized general practice data. *Clin Exp Allergy* 2002;32:37-42.
6. Chi W, Yang P, Li B, Wu C, Jin H, Zhu X, et al. IL-23 promotes CD4+ T cells to produce IL-17 in Vogt-Koyanagi-Harada disease. *J Allergy Clin Immunol* 2007;119:1218-24.
7. Chen L, Yang P, Zhou H, He H, Ren X, Chi W, et al. Diminished frequency and function of CD4+ CD25 high regulatory T cells associated with active uveitis in Vogt-Koyanagi-Harada syndrome. *Invest Ophthalmol Vis Sci* 2008;49:3475-82.
8. Korn T, Bettelli E, Oukka M, Kuchroo VK. IL-17 and Th17 cells. *Annu Rev Immunol* 2009;27:485-517.
9. Agua-Doce A, Graca L. Regulatory T cells and the control of the allergic response. *J Allergy (Cairo)* 2012;2012:948901.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.