CASE REPORT

Nivolumab-induced keratitis and Vogt-Koyanagi-Harada syndrome–like eruptions: a case report

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Abstract

We report a case of simultaneous kerato-uveitis and Vogt-Koyanagi-Harada syndrome–like eruptions associated with nivolumab treatment in a 44-year-old woman with metastatic rectal melanoma. Despite treatment for immune-related adverse events and discontinuation of nivolumab, the patient developed severe vertigo and tinnitus at week 7, as well as progressive depigmentation of her skin and hair and fundal hypopigmentation since month 2. Timely and adequate treatment is needed to improve clinical outcomes and reduce the risk of vision loss. Clinicians should raise their awareness of concurrent immune-related adverse events for any visual or neurological symptoms, especially when immune checkpoint inhibitors are used.

Keywords: Keratitis; Melanoma; Nivolumab; Uveomeningoencephalitic syndrome

Introduction

Nivolumab, a programmed death-1 (PD-1) receptor antibody, is used as targeted immunotherapy against multiple malignancies including melanoma. By upregulating T-cell activity, nivolumab enhances autoimmunity towards cancer cells and hence is termed an immune checkpoint inhibitor. However, it can cause immune-related adverse events (irAEs). We report a case of bilateral kerato-uveitis with Vogt-Koyanagi-Harada (VKH) syndrome–like eruptions following nivolumab treatment for metastatic melanoma.

Case presentation

In August 2020, a 44-year-old woman with stage IV metastatic rectal melanoma was referred to Caritas Medical Centre for bilateral progressive vision blurring after treatment with nivolumab 480 mg/month 2 weeks earlier. She had no known ophthalmic or autoimmune diseases. On presentation, her visual acuity was 0.1 bilaterally. Slit-lamp examination revealed severe superficial keratitis with diffuse punctate corneal erosions (**Figure 1**). The anterior chambers had 2+ cells with posterior synechiae and 2+ to 3+ keratic precipitates. There were mild anterior vitreous cells bilaterally. Posterior uveitis was not evident. The patient was treated with topical cyclosporine 0.1%, lubricants, prednisolone 1%, and atropine 1%. Three days later, the patient's visual acuity improved to 0.2 bilaterally. The kerato-uveitis continued to improve with tapering topical treatment.

At 7 weeks after receiving nivolumab, the patient developed severe vertigo and tinnitus and was diagnosed with vestibular neuritis (an irAE) and was treated with intravenous methylprednisolone 1 mg/kg/day for 5 days. An oncologist attempted a lumbar puncture to evaluate central nervous system involvement but failed. Three weeks later, the patient's visual acuity improved to 0.7 bilaterally, and her neurological symptoms gradually resolved. She was switched to oral prednisolone 1 mg/kg/day with a tapering schedule of 10 mg/week according to her neurological symptoms.

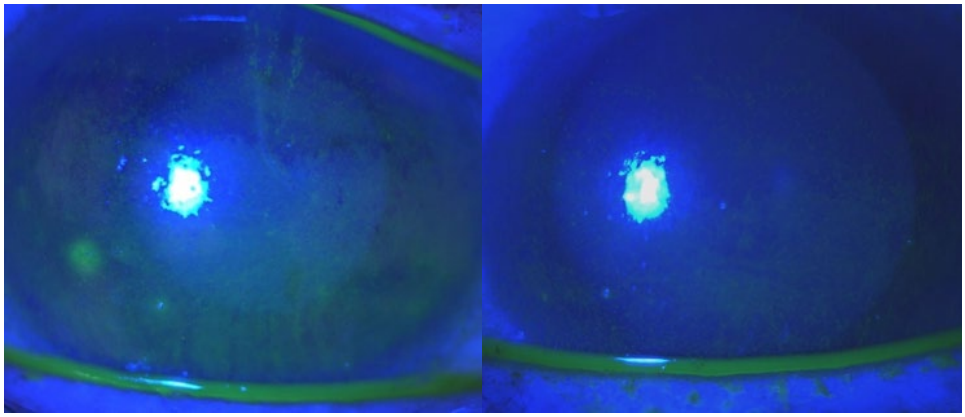

Figure 1. Slit-lamp examination showing diffuse punctate epithelial erosions in both eyes.

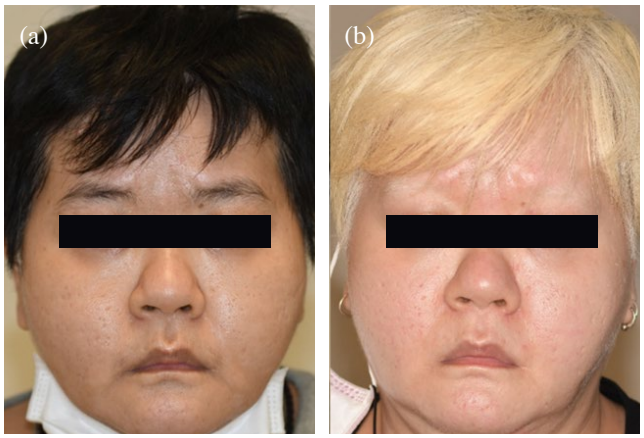

Figure 2. Photographs showing (a) whitening of facial skin and poliosis at 2 months after nivolumab treatment and (b) increased whitening of facial skin, hair of scalp, brows, and eyelashes at 13 months.

At 2 months after receiving nivolumab, the patient developed poliosis and whitening of her facial skin (**Figure 2a**). Unlike in vitiligo, the depigmentation was generalised and did not follow any specific pattern. By 13 months, the poliosis had progressed to the complete whitening of her eyelashes, eyebrows, hair, and scalp (**Figure 2b**).

At 24 months after receiving nivolumab, fundus photographs showed bilateral peripapillary hypopigmentation (**Figure 3**). Optical coherence tomography revealed the absence of subretinal fluid and normal retinal layers in both maculae (**Figure 4**). Fundal fluorescein angiography (**Figure 5a**) and indocyanine green angiography (**Figure 5b**) showed pinpoint hyperfluorescent foci without leakage or signs of active inflammation.

Discussion

In our patient, the only systemic treatment received was nivolumab. Her symptoms resolved after treatment for irAEs and discontinuation of nivolumab. Her uveitis mainly affected the anterior segment; she had generalized depigmentation, rather than vitiligo, followed by fundal hypopigmentation.

Nivolumab inhibits the PD-1 receptor on activated T cells. When PD-1 binds to its ligand, the T cell becomes inactive. Because this ligand is expressed in 40% to 50% of melanomas and far less in other visceral organs,[1] nivolumab blocks T-cell inactivation and thus enhances T-cell proliferation and activity against melanoma cells.

Immune checkpoint inhibitors shift the immune system to a more activated state and may lead to irAEs. Dry eyes and uveitis are known ophthalmic irAEs associated with nivolumab; uveitis is found in 0.24% of patients with melanoma treated with nivolumab.[2] In our literature search, only seven cases of reported VKH syndrome were found. The exact mechanism through which nivolumab causes ophthalmic irAEs is not clear. PD-1+ T cells are heavily involved in anterior uveitis[3] and posterior uveitis.[4] In particular, inhibition of the PD-1 pathway increases the proinflammatory cytokine Th17, which is associated with active scleritis and uveitis.[5] Elevated levels of interleukin-6, granulocyte-colony stimulating factor, and interferon gamma-induced protein 10 in the aqueous and vitreous humors have been found in a patient with nivolumab-induced uveitis.[6] These cytokines are associated with activities of T cells, B cells, macrophages, natural killer cells, and inflammatory dendritic cells. Nivolumab may involve cells other than T cells in the inflammatory process. Analysis of cytokines in the tear fluid of a patient with nivolumab-induced ulcerative keratitis supports the theory of multiple-cell involvement, particularly interleukin-1 and matrix metalloproteinases.[7]

By blocking PD-1, nivolumab may activate T cells specific to melanocytes and lead to nivolumab-associated VKH syndrome, which is associated with human leukocyte antigen DR4.[8-10] This finding suggests that nivolumab induces autoimmune-mediated inflammation of the entire eye, from the ocular surface to the aqueous and vitreous.

Superficial keratitis associated with nivolumab usually responds to topical treatment.[11] In addition to intensive lubrication and topical steroid therapy, topical cyclosporine may provide an additional advantage because it downregulates T-cell activity. A severe case that progressed to corneal perforation was reported.[11] Our patient's response to topical cyclosporine supports the hypothesis that nivolumab-induced

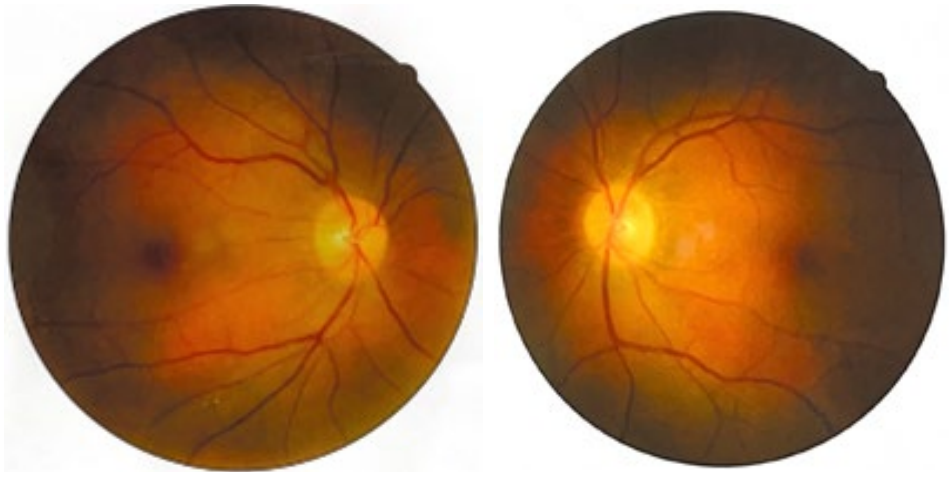

Figure 3. At 2 years after nivolumab treatment, fundus photographs showing bilateral peripapillary hypopigmentation.

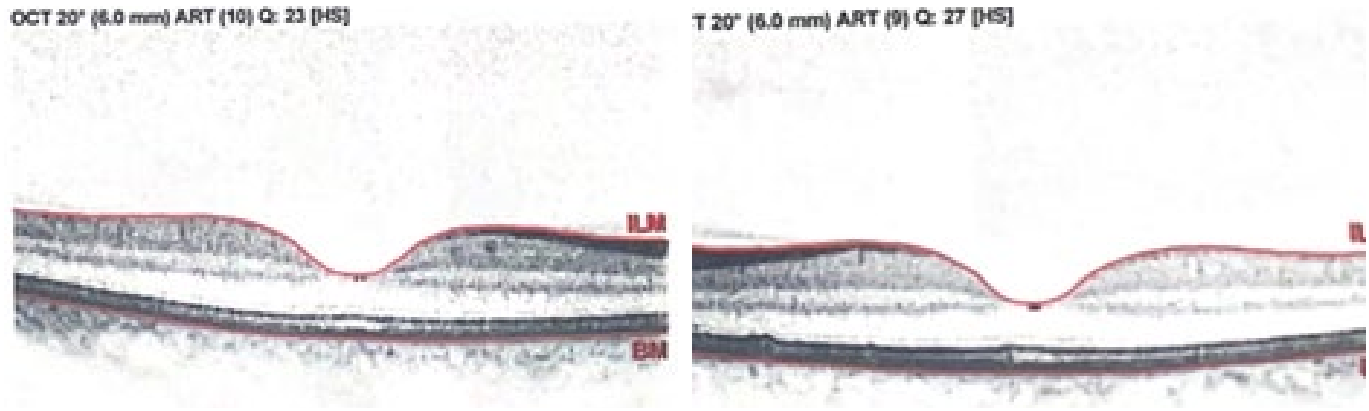

Figure 4. Optical coherence tomography showing the absence of subretinal fluid and normal retinal layers in both maculae.

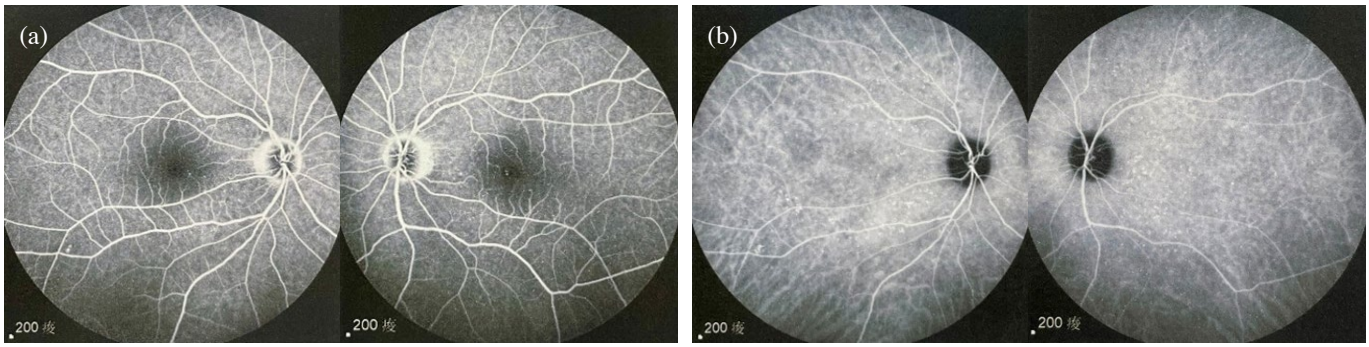

Figure 5. (a) Fundus fluorescein angiography and (b) indocyanine green angiography showing pinpoint hyperfluorescent foci without leakage or signs of active inflammation.

dry eye is mediated by T cells. Keratitis is seldom related to metastatic melanoma alone.

VKH syndrome is believed to be an autoimmune disease involving melanocytes,[12] characterized by granulomatous uveitis, neurological, and auditory symptoms, as well as vitiligo. Most cases of nivolumab-related VKH syndrome present with bilateral posterior uveitis or panuveitis with no neurological or auditory symptoms.[8,9,13,14] In one patient with nivolumab-related VKH syndrome, cerebrospinal fluid pleocytosis was not found after a lumbar puncture.[8] Such differences between VKH syndrome and nivolumab-related VKH syndrome may be explained by the different affinities of activated T cells to the meninges.[14]

Timely and adequate treatment is needed to improve clinical outcomes and reduce the risk of vision loss. Clinicians should raise their awareness of concurrent irAEs for any visual or neurological symptoms, especially when immune checkpoint inhibitors are used.

Contributors

All authors designed the study, acquired the data, analyzed the data, drafted the manuscript, and critically revised the manuscript for important intellectual content. All authors had full access to the data, contributed to the study, approved the final version for publication, and take responsibility for its accuracy and integrity.

Conflicts of interest

All authors have disclosed no conflicts of interest.

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Data availability

All data analyzed in this study are available from the corresponding author upon reasonable request.

Ethics approval

The patient was treated in accordance with the tenets of the Declaration of Helsinki. The patient provided written informed consent for all treatment and procedures and for publication.

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