Case study

IMMUNOTHERAPY-INDUCED VOGT KOYANAGI HARADA SYNDROME/CASE REPORT

ABSTRACT

This report describes a case of Vogt Koyanagi Harada Disease (VKH) in a 44-year-old male with metastatic gastric carcinoma who presented with sudden onset headache and decreased vision. The patient was treated with first-line standard therapy for stage IV HER2-positive gastric adenocarcinoma and was on maintenance trastuzumab and pembrolizumab for seven months prior to developing new symptoms. His VKH was diagnosed after multiple imaging and comprehensive ophthalmologic examination. The patient's vision and headaches improved with the initiation of corticosteroid therapy. Although the immunotherapy was discontinued, the trastuzumab was pursued with continued close ophthalmology follow-up. He remains in stable condition despite his cancer. It is critical to consider and recognize immune-related ophthalmologic complications from immunotherapy promptly, even if they are rare, considering its implications. Corticosteroids remain the first line and organ-saving therapy.

Keywords: Blurring vision, Vogt Koyanagi Harada Disease, Pembrolizumab, Herceptin

INTRODUCTION

Therapy for metastatic gastric carcinoma has undergone significant changes in the last few years. Previously, 5-fluoropyrimidine-based cytotoxic chemotherapy was the mainstay of therapy. With the identification of Her2 as a predictive marker, anti-Her2 therapy has been incorporated into

the therapeutic regimen for metastatic gastric carcinoma, as well as gastroesophageal carcinoma. (1) In the last few years' checkpoint inhibitors, both pembrolizumab and nivolumab have also shown survival benefits in metastatic gastric carcinoma. Cytotoxic chemotherapy, combined with trastuzumab and pembrolizumab, is now recommended as the standard of care for the first-line therapy of metastatic gastric carcinoma. (2)

Vogt Koyanagi Harada Syndrome is an autoimmune granulomatous disease that affects all the major 'pigmented' or melanocyte-rich structures, such as the eyes, ears, meninges, skin, and hair. It is a rare disease that is related to and only affects the central nervous system (CNS). Vogt Koyanagi Harada Syndrome has an acute onset, and it is said to occur due to TH1-lymphocyte-mediated aggression to melanocytes. It usually occurs after a viral attack on the body and in the presence of the HLA-DRB1 allele. (3)

This disease was first described by Alfred Vogt in Switzerland, in 1906, when he encountered a patient with the sudden and bilateral onset of iridocyclitis, associated with the premature whitening of the eyelashes. (4) While the declining sight and hearing of the affected person might be the only presenting symptoms, Vogt Koyanagi Harada Syndrome is a multi-system inflammatory disease that is characterized by panuveitis. This may be further associated with various other neurological and cutaneous manifestations, such as headaches, vertigo, poliosis, generalized weakness of the body, and abdominal pain. (5)

This genetic influence seems to vary from ethnicity to ethnicity. Indeed, the DRB1-04*01 allele was found to be prevalent in the East Asian populations, whereas the HLA-DRB1 and HLA-DRB4 alleles were found to be more prevalent in the affected populations as a whole. (6)

People of any age group can be affected. It has been found adult patients are usually affected in the third or fourth decade of their lives, whereas in pediatrics, children up to age three can also be affected. Moreover, females are seen to be affected twice as often as males. (7)

Corticosteroid therapy is the sole mode of treatment for Vogt Koyanagi Harada Syndrome. The mode of administration varies from topical to oral drugs and usually depends on the severity and intensity of the symptoms.

However, the sole focus of the physician should always be to reduce the number of complications and ensure that no irreversible damage occurs to the patient's eyes or any other affected body part.

In this report, we describe a case of VKH syndrome associated with pembrolizumab therapy administered to a patient with metastatic gastric carcinoma. We will also review previous cases published to date. (8)

CASE DESCRIPTION

This case revolves around a 44-year-old male patient diagnosed with metastatic gastric carcinoma. The patient had Stage IV Her2-positive gastric cancer. There were nodal metastases in the retroperitoneum, pelvis, and left supraclavicular region. This was confirmed by the computerized tomography-guided lymph node biopsy [MSS, HER-2 IHC 3+, PD-L1 + (CPS=20)]. The patient completed nine cycles of first-line palliative FOLFOX chemotherapy. Upon completion, Oxaliplatin was dropped (due to side effects), and the patient continued on 5FU, Trastuzumab, and Pembrolizumab for one more cycle. The patient received ten cycles of chemotherapy in total and was then maintained on Trastuzumab and Pertuzumab alone. As a chronic Hepatitis B carrier, he was put on entecavir. He also developed autoimmune hypothyroidism, for which he was treated by levothyroxine oral replacement therapy.

First Scan - October 2021:

- *Little change in the ulcerated lesser curvature gastric mass.*
- *Retroperitoneal and pelvic lymphadenopathy are predominantly not significantly changed.*
- *Some indeterminate thoracic lymph nodes show areas of stability and marginal increase.*

Second Scan - November 2021:

- *Stable gastric wall thickening lesser curvature of the junction between the body and antrum of the stomach. Favor a T3 type lesion.*
- *Stable abdominal and pelvic adenopathy.*
- *Smaller right hilar lymph node.*
- *Stable small left low anterior neck and multi-compartmental mediastinal lymph nodes.*

Third Scan - February 2022

- *Asymmetric wall thickening in the gastric antrum.*
- *Stable lymphadenopathy in the chest, abdomen, and pelvis.*

The patient completed ten cycles of trastuzumab and pembrolizumab maintenance. A few days after cycle n°8, the patient developed sudden onset headaches and decreased vision. He was evaluated in the emergency room and underwent a CT scan of the brain, which turned out normal. As his symptoms persisted, he sought care from an ophthalmologist.

Imaging

The patient's imaging details are as follows:

Fluorescein angiography showed multiple hyper-fluorescent spots that were increasing in size and intensity.

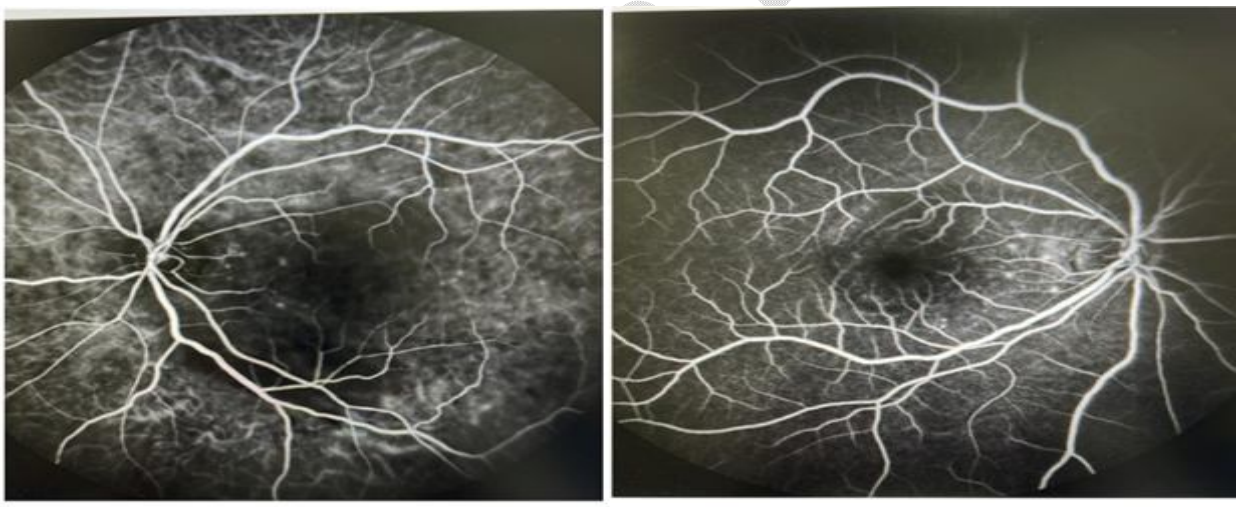

Figure 1

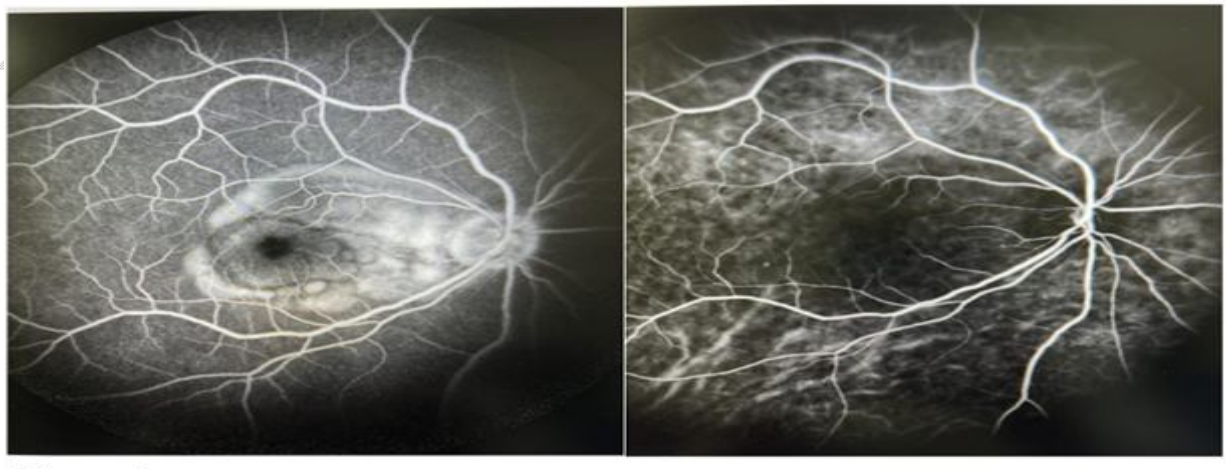

Figure 2

Fig 1: Fluorescein angiography (1st Scan)

Fig.2. Fluorescein angiography (2nd Scan)

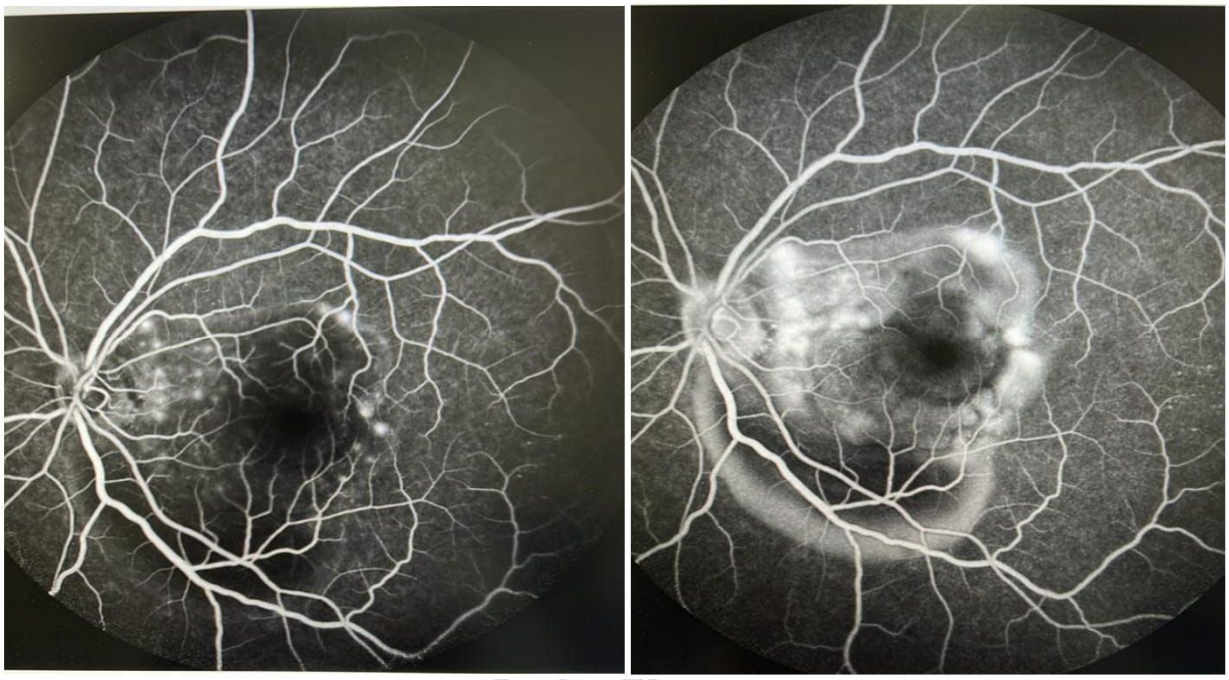

Figure 3: Fluorescein angiography (3rd Scan)

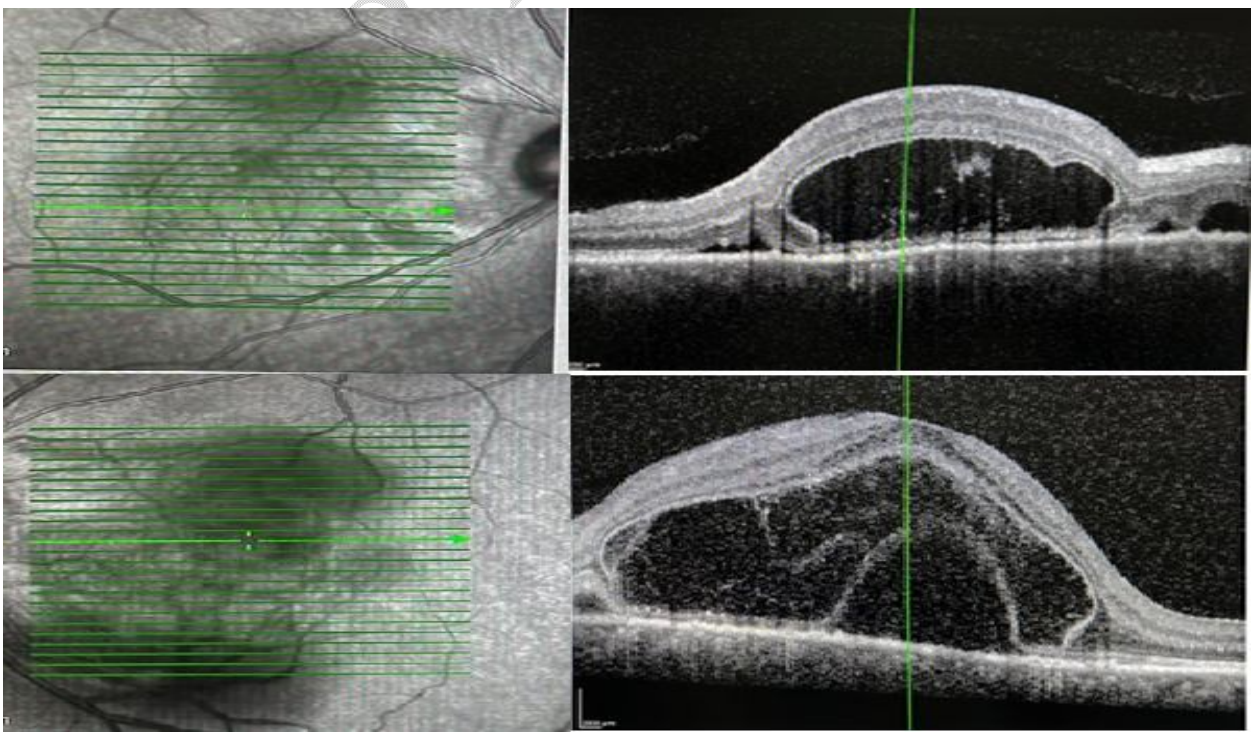

Figure 4: The optical coherence tomography (OCT) of the macula showed a loss of foveal contour and multiple pockets of sub-macular/sub-retinal fluids.

The slit lamp examination demonstrated that the anterior chamber was quiet and that there was a pinguecula in both eyes. The intra-ocular pressure was found to be 16 mm Hg in the right eye and 18 mm Hg in the left one. However, the optical coherence tomography (OCT) of the macula showed a loss of foveal contour and multiple pockets of sub-macular/sub-retinal fluids. Hyper-reflective dots were also found in the sub-retinal fluids in both eyes, suggesing the presence of an underlying inflammatory pathology.

To elaborate on this pathology, an intravenous fluorescein angiogram (IVFA) and indocyanine green angiogram (ICGA) were performed. The IVFA showed multiple hyper-fluorescent spots that were increasing in size and intensity, both of which indicated some sort of active leakage.

The ‘enhanced depth imaging optical coherence tomography’ showed choroidal thickening. It was also confirmed by the ultrasound B-scan. The patient was diagnosed with Vogt Koyanagi Harada Syndrome. For this, he was prescribed a course of methylprednisolone (1g/day for three days). He was also recommended oral prednisone (1-1.5mg/kg per day for at least 4 to 6 months). Pembrolizumab was discontinued, while Trastuzumab was continued as maintenance therapy.

DISCUSSION

Vogt Koyanagi Harada Syndrome is an uncommon or rare type of non-infectious uveitis that occurs in people with pigmented skin. For this reason, it is often found to affect Asians, Hispanics, Middle Easterns, and North Americans more than Africans. (9)

Since the disease is rare, its total prevalence worldwide is less than 10%. In the United States alone, Vogt Koyanagi Harada Syndrome was found to occur in 1.5 to 6 patients per million, which is a significant gap. (10)

It was also found that females (78% approximately) are affected twice as often as males. Mostly middle-aged people are affected by this disease, ranging from the fourth to sixth decade of life. Children and the elderly can also get affected by this condition. (11)

The actual cause of this disease remains unclear. Given its autoimmune and granulomatous etiology, it is obvious that some sort of ongoing insult within the immune system leads to the development of this disease.

The complications in both affected populations vary as well. Indeed, it was seen that the pediatric population is usually affected by subretinal fibrosis, whereas older people are affected by choroidal detachments and optic disc hyperemia. (12)

However, in the majority of the cases, it is the aggressive response of the TH-1 cells to melanocytes that leads to the development of this disorder. Usually, it is a viral trigger that sets off the stimulus for the aggressive response of the TH-1 helper cells. (13)

Microscopically, there is a diffuse thickening of the uveal tract. This manifests in the acute stages as a granulomatous process. In the acute stages of the disease, we also notice the diffuse infiltration of lymphocytes, along with epithelioid cells and multinucleated giant cells taking up most of the space in the uveal tract. (14)

The American Uveitis Society (AUS) has adopted a particular criterion for the diagnosis of VKHD, as follows:

- No history of ocular trauma and/or surgery
- At least three of the following four signs:
    a. Bilateral chronic iridocyclitis;
    b. Posterior uveitis (multifocal exudative retinal or RPE detachments; disc hyperemia or edema; or "sunset glow fundus," which is a yellow-orange appearance of the fundus due to depigmentation of the RPE and choroid);
    c. Neurological signs (tinnitus, neck stiffness, cranial nerve or central nervous system symptoms, or cerebrospinal fluid pleocytosis);
    d. Cutaneous findings (alopecia, poliosis, or vitiligo). (15)

Apart from the ocular manifestations, there are several extraocular manifestations as well. These include CNS symptoms (headaches, neck stiffness, confusion, and CSF pleocytosis), inner ear symptoms (tinnitus, hearing loss, and vertigo), and cutaneous findings (vitiligo, alopecia, and poliosis of the eyelashes, eyebrows, and hair). (16)

The treatment revolves around the patient being given corticosteroids for their condition. The corticosteroids may be topical or oral, depending on the extent of the damage inflicted by the disease. The timing, dosing, and duration of the corticosteroid therapy are important to prevent the recurrence of the disease. (17)

CONCLUSION

Vogt Koyanagi Harada Syndrome is an uncommon disease. Since it is not normally encountered in hospital settings, it is obvious that dealing with it can be difficult. Diagnosing the disease itself can be arduous, let alone starting treatment before the symptoms take a turn for the worse.

However, it can be seen, in this case study, that the early diagnosis through imaging and findings could avoid complications.

Since the patient was already dealing with Stage IV metastatic cancer, it was feared that he might relapse or react to the treatment unfavorably. But the prognosis, so far, has been hopeful and in his favor, and it is thought that it will remain as such in the days to come.

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