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Immunotherapy-Induced Vogt Koyanagi Harada Syndrome: A Case Report

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Case Study

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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 before developing new symptoms. His VKH was diagnosed after multiple imaging and a comprehensive ophthalmologic examination. The patient's vision and headaches improved with theinitiation of corticosteroid therapy. Although immunotherapy wasdiscontinued,trastuzumab was continuedwith close ophthalmology follow-up. He remains in stable conditiondespitehis cancer. It is critical to consider and recognize immunotherapy-relatedophthalmologic complications immediately, even if they are rare, considering theirimplications. Corticosteroids remain the first-line organ-saving therapy.

Keywords: Blurring vision; vogt koyanagi harada disease; pembrolizumab; herceptin.

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1. INTRODUCTION

Therapy for metastatic gastric carcinoma has undergone significant changes inrecent 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 recent years of 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 forfirst-line therapy formetastatic gastric carcinoma [2].

Vogt Koyanagi Harada syndrome is an autoimmune granulomatous disease that affects all the main 'pigmented' or melanocyte-rich structures, such as the eyes, ears, meninges, skin, and hair.

It is a rare disease that is related to and affectsonly the central nervous system (CNS). Vogt Koyanagi Harada syndrome has an acute onsetand is said to occur due to TH1 lymphocyte-mediated aggression against 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 alsoalsobe associated with various other neurological and skin manifestations, such as headaches, vertigo, poliosis, generalized weakness of the body, and abdominal pain [5].

This genetic influence seemsto 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 alleleswerefound to be more prevalent in the affected populations as a whole [6].

People ofany 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. Furthermore, females are seen to be affected twice as often as males [7].

Corticosteroid therapy is the only 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 toreducethe 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].

2. CASE DESCRIPTION

This case revolves around a 44-year-old male patientdiagnosed 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 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. Uponcompletion, the oxaliplatinwas removed (due to side effects),and the patient continued with 5FU,Trastuzumab and Pembrolizumab for one more cycle. The patient received tencycles of chemotherapy in totaland was then maintained on Trastuzumab and Pertuzumab alone. Asa chronic Hepatitis B carrier, he wasput 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 arepredominantly not significantly changed.
- Some indeterminate thoracic lymph nodes showareas of stability and marginal increase.

Second Scan - November 2021:

- Stable gastric wall thickening that reduces the curvature of the junction between the body and the 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 pembrolizumabmaintenance. A few days after cycle n°8, the patient developed sudden-onsetheadaches 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.

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. Hyperreflective dots were also found in the subretinal fluids in both eyes, suggestingthe presence of an underlying inflammatory pathology.

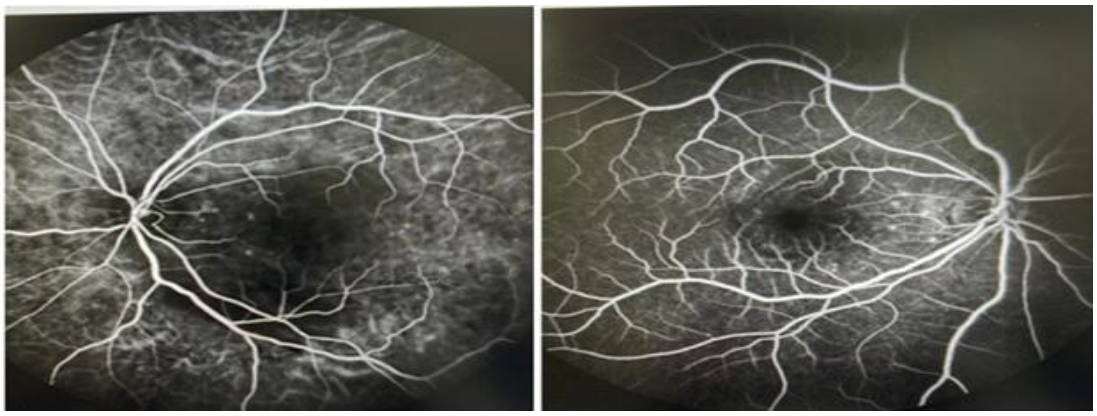

Fig. 1. Flourescein angiography (1st Scan)

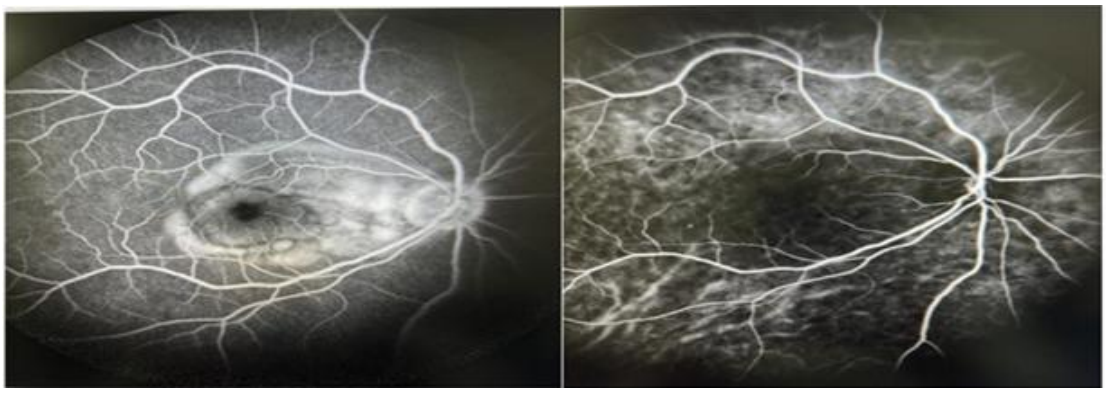

Fig. 2. Flourescein angiography (2nd Scan)

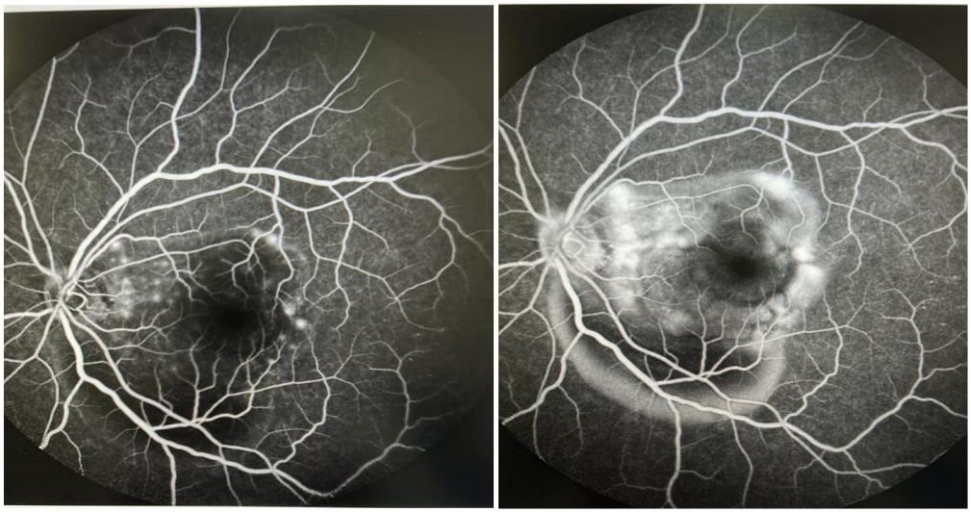

Fig. 3. Fluorescein angiography (3rdScan)

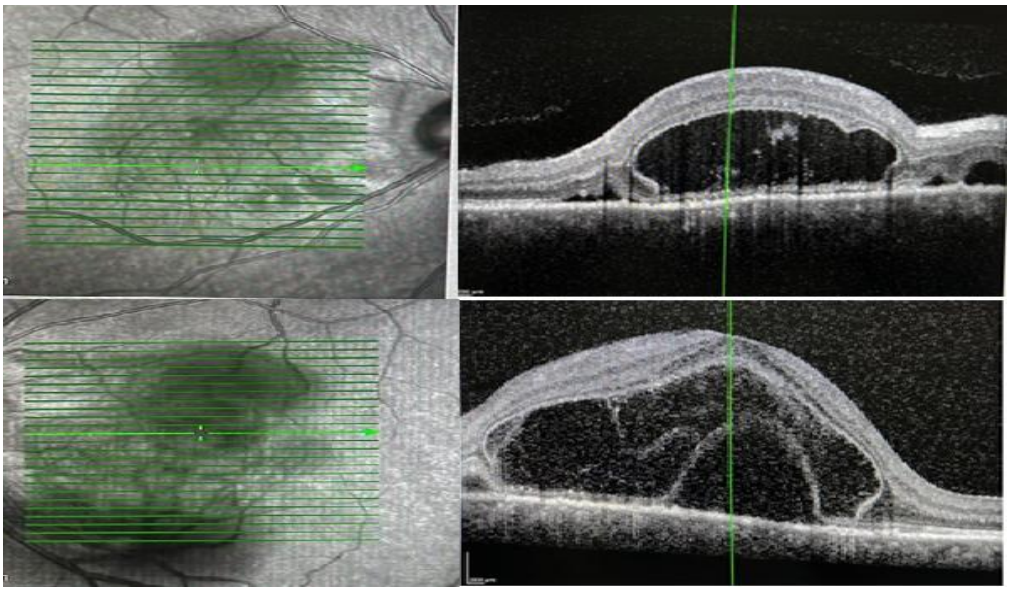

Fig. 4. The optical coherence tomography (OCT) of the macula showed a loss of foveal contour and multiple pockets of submacular / subretinal fluids

To elaborate on this pathology, an intravenous fluorescein angiogram (IVFA) and an 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.

'Enhanced depth imaging optical coherence tomography' showed choroidal thickening. It was also confirmed by the ultrasound B-scan. Thepatient was diagnosed with Vogt Koyanagi Harada syndrome. For this, a course of methylprednisolone (1g/day for three days). He was also recommendedoral prednisone (1-1.5mg/kg per dayfor at least 4 to 6 months). Pembrolizumab was discontinued, while Trastuzumabwas continued as maintenance therapy.

3. 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 the sixth decade of life. Children and the elderly can alsogetaffected by this condition [11].

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

The complications in both affected populations vary as well. Indeed, the pediatric population was found to be usually affected by subretinal fibrosis, while older people are affected by choroidal detachments and hyperemia of the optic disc [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 triggers the stimulus for the aggressive response of 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, symptoms of the cranial nerve or central nervous system, 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 receiving 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 corticosteroid therapy are important to preventrecurrence of the disease [17].

4. CONCLUSION

Vogt Koyanagi Harada syndrome is a rare disease. Since it is not usually encountered in hospital settings, it is obvious that dealing with it can be difficult. Diagnosis of the disease itself can be arduous, let alone starting treatment beforesymptomsturn 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 hopefuland in his favor,andis thought to remainthat way in the days to come.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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