

[CASE REPORT]

Nivolumab-induced Vogt-Koyanagi-Harada-like Syndrome and Adrenocortical Insufficiency with Long-term Survival in a Patient with Non-small-cell Lung Cancer

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Abstract:

A 58-year-old man was diagnosed with lung adenocarcinoma with a tumor proportion score of 10%. After six cycles of second-line chemotherapy with nivolumab, he achieved a complete response (CR) but developed uveitis and sensorineural hearing disorder, which were consistent with Vogt-Koyanagi-Harada (VKH)-like syndrome. Simultaneously, pituitary adrenocortical insufficiency was identified. Nivolumab discontinuation and systemic corticosteroid administration resolved these immune-related adverse events (irAEs). The patient has maintained a CR without any chemotherapy for approximately two years. We herein report a patient with a long-term progression-free survival despite chemotherapy discontinuation due to irAEs, including VKH-like syndrome, which were appropriately managed.

Key words: non-small-cell lung cancer, immune-related adverse events, Vogt-Koyanagi-Harada-like syndrome, adrenocortical insufficiency, HLA-DR4

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Introduction

The advent of immune checkpoint inhibitors, such as nivolumab and pembrolizumab [anti-programmed cell death protein 1 (PD-1) antibodies] and ipilimumab [anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody], has revolutionized the treatment of cancers including malignant melanoma, non-small-cell lung cancer, renal cell carcinoma, microsatellite instability-high carcinoma, and Hodgkin lymphoma (1-3). In addition to monotherapy, combination chemotherapy has successfully improved the survival rate of patients with lung cancer. However, immune checkpoint inhibitors have unique side effects, called immune-related adverse

events (irAEs), which can occur in all body organs. IrAEs occur in 70-80% of patients receiving anti-PD-1 antibodies and in up to 90% of patients receiving anti-CTLA-4 antibodies (4-6). IrAEs often lead to treatment discontinuation; therefore, appropriate management of these adverse events is important.

Vogt-Koyanagi-Harada (VKH) disease is a multisystem autoimmune disease with multiple clinical manifestations that can occur in the eyes, inner ear, central nervous system, hair, and skin melanocytes. Immune checkpoint inhibitors have been reported to cause VKH-like syndrome in rare cases.

We herein report a patient with lung cancer who developed various irAEs, including VKH-like syndrome, and

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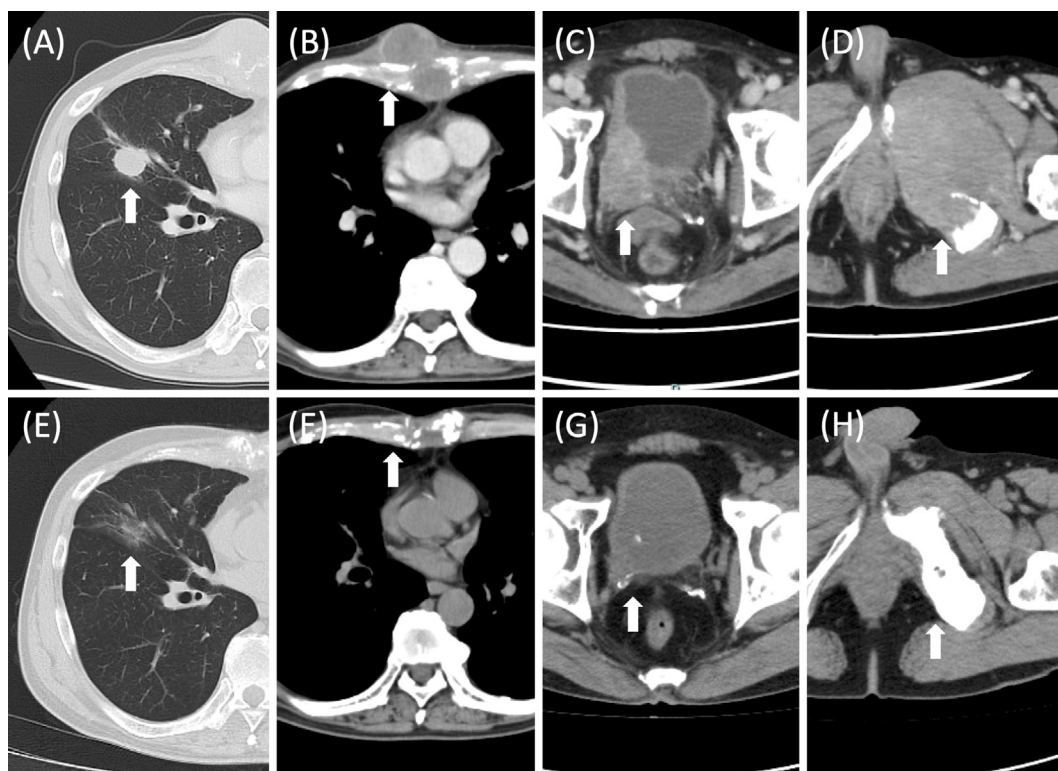


Figure 1. Computed tomography images before nivolumab treatment (A-D) and after six cycles of chemotherapy with nivolumab (E-H). The primary (white arrows in A and D) and metastatic (white arrows in B-D and F-H) lesions showed a complete response according to the Response Evaluation Criteria in Solid Tumors.

maintained a long-term complete response (CR) without chemotherapy, even after drug discontinuation.

Case Report

A 58-year-old man visited our hospital with a right femoral fracture. Computed tomography (CT) showed a 36-mm-diameter mass on the middle lobe of the right lung and multiple bone metastases to the sternum, pelvis, and right femur. The patient underwent open reduction and internal fixation of the right femoral fracture. A histological examination of the femoral bone revealed lung adenocarcinoma. The clinical stage was cT3N2M1c, stage IVB (7), with the patient testing negative for *EGFR*, *ALK*, *ROS-1*, and *BRAF V600E* mutations. His PD-L1 tumor proportion score (TPS) was 10%.

The patient received first-line chemotherapy with carboplatin (area under the curve=6, day 1), pemetrexed (500 mg/m², day 1), and bevacizumab (15 mg/kg, day 1). New metastatic lesions appeared in the bilateral adrenal glands, bladder, and abdominal lymph nodes immediately after four cycles of the first-line chemotherapy. Bleeding from the bladder lesion induced urinary retention and acute kidney injury. After transurethral resection of the bladder tumor, second-line chemotherapy with nivolumab (3 mg/kg, day 1) was administered. After six cycles of the second-line chemotherapy, a marked response was observed on CT, which was consistent with a CR, according to the Response Evaluation Criteria in Solid Tumors (Fig. 1) (8). However, the patient

experienced severe visual impairment and was diagnosed with uveitis approximately four months after the initiation of nivolumab.

His decimal best-corrected visual acuity (BCVA) scores were 0.8 and 0.08 in the right and left eyes, respectively. Furthermore, intraocular pressures were 16 and 17 mmHg in the right and left eyes, respectively. Optical coherence tomography confirmed serous retinal detachment, wavy retinal pigment epithelium, and thickening of the choroid in both eyes (Fig. 2A, B). Fluorescein angiography revealed superfluorescence of the optic disc and granular hyperfluorescence centered on the posterior pole (Fig. 3A, B). Indocyanine green fluorescence angiography showed patchy low fluorescence of the choroid (Fig. 3C, D).

In addition to nivolumab discontinuation, a topical steroid (betamethasone sodium phosphate, 0.1%) was initiated 6 times a day. Two weeks after starting the topical treatment, the patient's decimal BCVA scores recovered to 1.2 and 1.0 in the right and left eyes, respectively. Furthermore, the serous retinal detachment almost disappeared (Fig. 2C, D). However, 3 weeks after starting the topical treatment, the decimal BCVA of his left eye decreased to 0.4, and serous retinal detachment reappeared in the left eye (Fig. 2E, F). During the same period, he developed hearing loss, tinnitus, nausea, vomiting, and diarrhea. An audiometric evaluation revealed bilateral sensorineural hearing loss with a downward slope configuration (Fig. 4A). He had no cutaneous manifestations. Human leukocyte antigen (HLA) serological

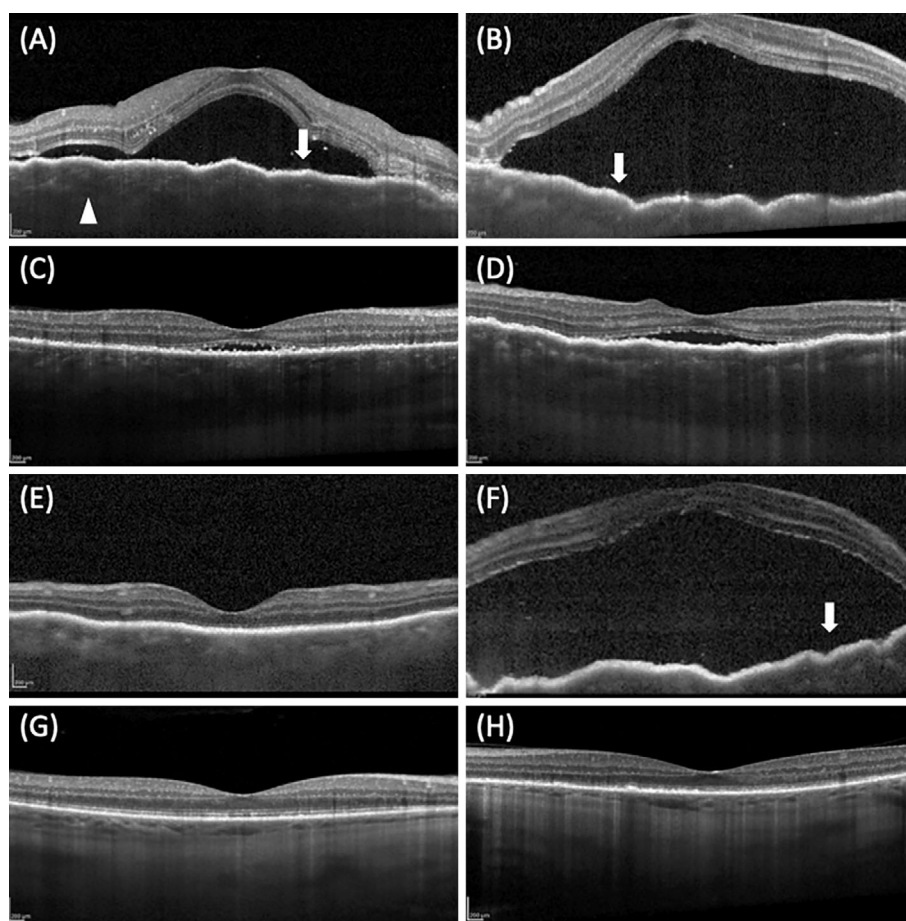


Figure 2. Optical coherence tomography at the onset of visual impairment (A, B), two weeks after starting the topical treatment (C, D), three weeks after starting the topical treatment (E, F), and three months after the initiation of corticosteroid therapy. Serous retinal detachment, wavy retinal pigment epithelium (white arrow), and thickening of the choroid (arrowhead) are shown in both eyes.

DR typing revealed that the patient was DR4-positive (SRL, Tokyo, Japan); his cerebrospinal fluid cell count increased to 16/ μ L. These findings were consistent with VKH-like syndrome. Furthermore, his baseline serum cortisol levels were 0.6 μ g/dL (range, 3.0-19.6 μ g/mL), with no response to adrenocorticotrophic hormone (ACTH) stimulation. Although his prolactin, luteinizing hormone, follicle-stimulating hormone, thyroid-stimulating hormone, triiodothyronine, and thyroxine levels showed normal responses in a triple stimulus test (insulin, thyrotropin-releasing hormone, and luteinizing hormone-releasing hormone), his ACTH and cortisol levels did not show any response. Specifically, the patient's baseline ACTH and cortisol levels were less than 1.0 pg/mL (range, 7.2-63.3 pg/mL) and 0.4 μ g/mL (range, 3.0-19.6 μ g/mL) with peak values of 1.9 pg/mL and 0.3 μ g/mL, respectively. These findings indicated primary and pituitary adrenocortical insufficiency, which was considered to be the cause of nausea, vomiting, and diarrhea.

Systemic corticosteroid therapy was administered (150 mg intravenous hydrocortisone daily for 3 days, followed by 30 and 25 mg oral hydrocortisone daily for 3 days each, and 20 mg daily as a maintenance dose). His nausea and vomiting disappeared rapidly (Fig. 5). After 3 months of systemic

corticosteroid therapy, the patient's decimal BCVA improved to 1.2 in both eyes, and the serous retinal detachment disappeared (Fig. 2G, H). Similarly, the audiometric test findings improved to almost normal (Fig. 4B).

Since nivolumab treatment discontinuation, a CR has been maintained without chemotherapy for approximately two years thus far.

Discussion

Some reports have suggested a correlation between irAEs and efficacy of nivolumab in patients with non-small-cell lung cancer (9-11). Proper management of irAEs is essential for maximizing the therapeutic effect of immune checkpoint inhibitors.

The HLA system is a locus of genes encoding the major histocompatibility complex, a set of cell surface molecules that mediate leukocyte interactions (12). Therefore, HLA plays an important role in not only the functioning of the immune system but also the pathogenesis of autoimmune diseases, including VKH (13). The HLA-DR4 serotype has been reported to be frequently observed in VKH disease patients (14). DR4 has been further classified into several sub-

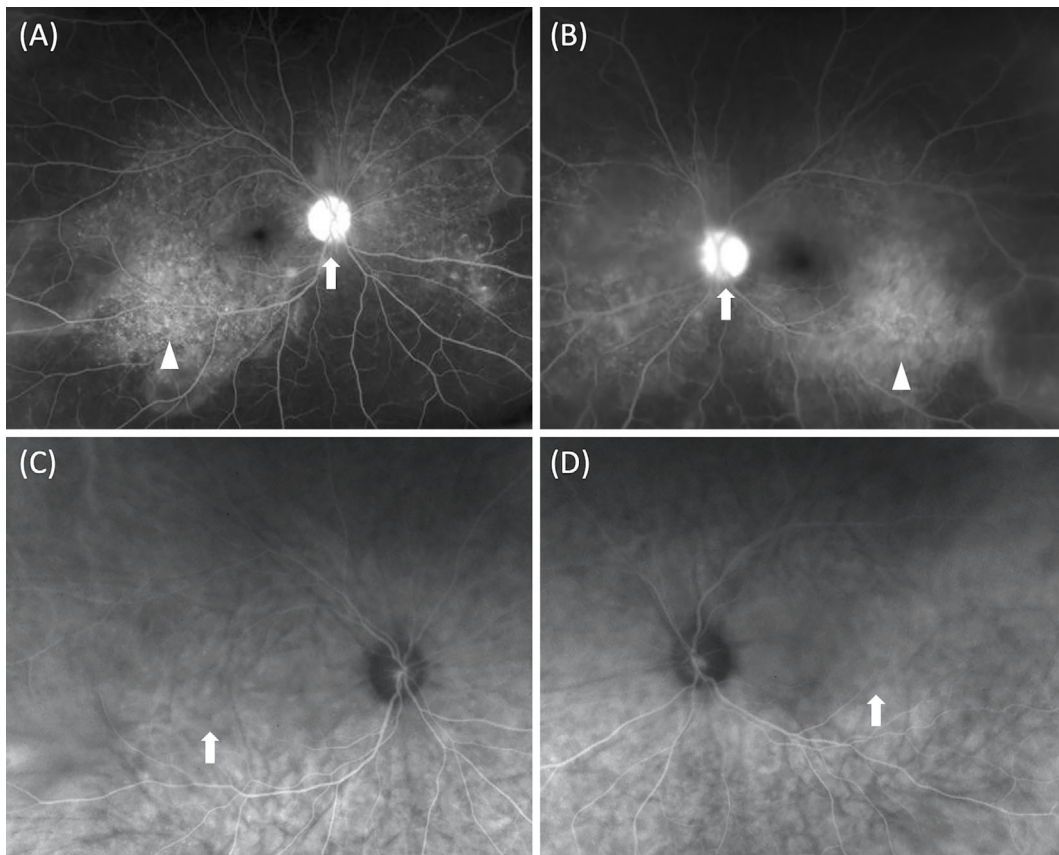


Figure 3. Fluorescein angiography showing superfluorescence of the optic disc (white arrow in A, B) and granular hyperfluorescence centered on the posterior pole (arrowhead in A, B). Indocyanine green fluorescence angiography showing patchy low fluorescence of the choroid (white arrow in C, D) at the onset of visual impairment.

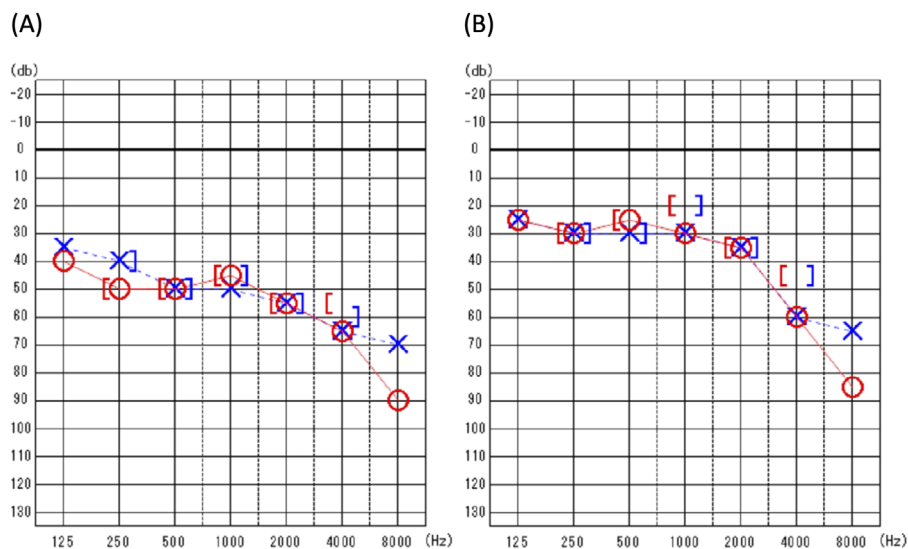


Figure 4. An audiogram revealed bilateral sensorineural hearing loss with a downward slope configuration (A). After systemic corticosteroid treatment, the hearing function was improved (B).

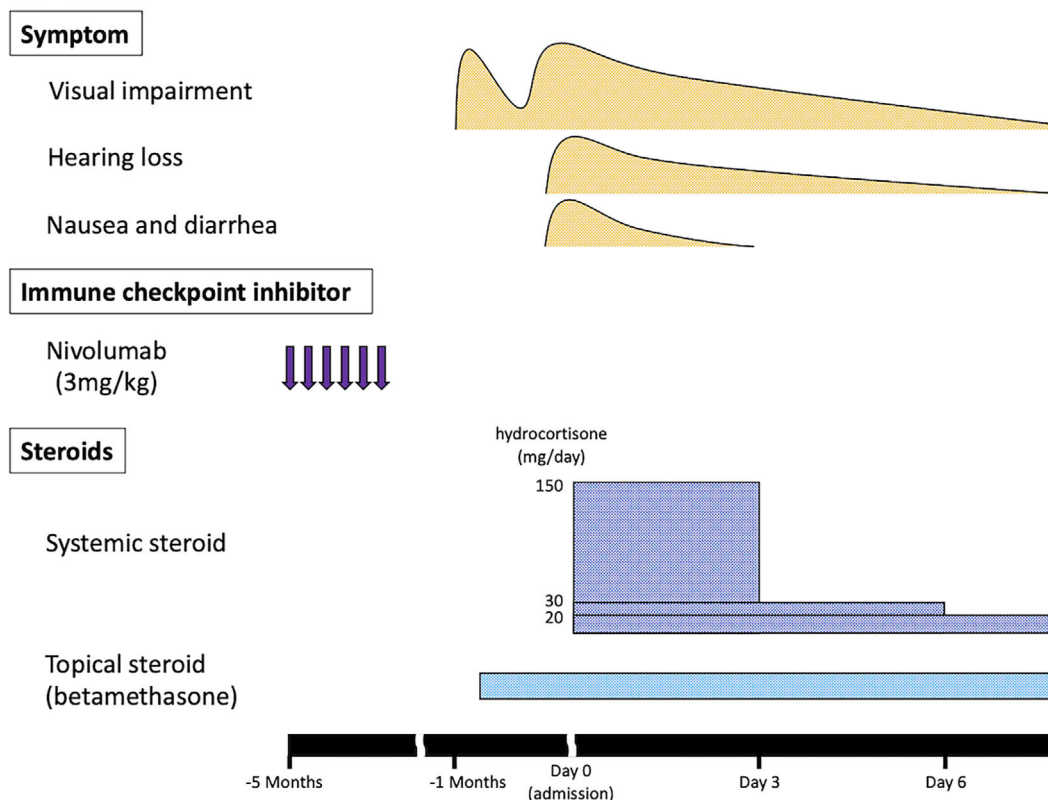
types, and some *HLA-DRB1*04* sub-alleles, including *HLA-DRB1*0404*, *0405*, and *0410*, have been shown to increase the risk of VKH. Certain ethnic groups are known to have a genetic predisposition to develop VKH, especially those with Mongoloid ancestry (15), and among such populations,

very strong correlations have been found with *HLA-DRB1*0405* and *0410* in Japan (16). Although the frequency of *HLA-DRB1*0405* is about 12% in Japan, VKH disease itself is a rare disease. Most Japanese with *HLA-DRB1*0405* are expected to go their entire lives without developing VKH

Table. Previous Reports of Nivolumab-induced Vogt–Koyanagi–Harada (VKH)-like Syndrome.

Reference	Age	Sex	Cycles	Ocular Complication	Neurological and auditory symptom	HLA class II examination	Other irAE	Systemic Corticosteroids
Our case	58	M	6	P	Hearing loss	DR4	Adrenal insufficiency	P (start with 150 mg of hydrocortisone)
18	69	M	2	P	N	DR4 (DRB1*0405) DR9 (DRB1*0901)	-	P (start with 1,000 mg of mPSL)
19	55	M	1	P	N	DR4 (DRB1*0410) DR4 (DRB1*0406)	-	N (only topical treatment)
20	60	F	2	P	Headache	-	-	P (start with 30 mg of PSL)
21	73	M	1	P	Hearing loss	DR4 (DRB1*0405)	-	P (start with 500 mg of mPSL)
	35	F	8	P	Headache Hearing loss	DR4 (DRB1*0405)	Severe erythema exudative multiforme	P (start with 500 mg of mPSL)
22	64	F	6	P	-	-	N	P (start with 500 mg of mPSL)
23	63	F	2	P	-	-	-	N (only topical treatment)

F: Female, M: Male, P: Positive, N: Negative, -: not described, mPSL: Methylprednisolone, PSL: Prednisolone, irAE: Immune-related adverse event

**Figure 5.** The patient's clinical course after nivolumab treatment.

disease (17). Although we were unable to determine the HLA-DR4 subtype in the present case, patients with HLA genotypes at risk for VKH may develop VKH-like syndromes after receiving immune checkpoint inhibitors. Thus far, seven patients with the HLA-DR4 subtype have been reported to have experienced nivolumab-induced VKH-like uveitis, similar to the present patient (Table). However, whether or not there is an association between HLA types

and the effects of immune checkpoint inhibitors - and thus the risk of VKH-like irAEs - remains unclear; therefore, further investigations are required.

In a previous report, one patient with VKH disease-like uveitis as an irAE without symptoms of other organs was treated with only topical steroid. However, the standard treatment for VKH disease is high-dose systemic corticosteroids, which was administered to six other patients (Ta-

ble) (18-23). In the present case, the irAE uveitis appeared initially and was successfully treated with a topical steroid; however, the patient sequentially developed hearing loss and adrenal insufficiency, thus requiring systemic corticosteroid therapy. The treatment had to be interrupted because of various adverse events; however, corticosteroid therapy relieved his irAEs, which led to his long-term disease-free survival.

To our knowledge, this is the first report describing the simultaneous development of VKH-like syndrome and adrenocortical insufficiency in a patient. Furthermore, after immune checkpoint inhibitor discontinuation, the patient has maintained a long-term progression-free survival despite his low TPS and high tumor burden. This case suggests the importance of appropriately managing irAEs and the need for better biomarkers to more accurately predict therapeutic effects.

The authors state that they have no Conflict of Interest (COI).

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