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

Ryota Ushio¹, Masaki Yamamoto¹, Atsushi Miyasaka¹, Muraoka Tatshuya¹, Hiromi Kanaoka¹, Hironori Tamura¹, Ayami Kaneko¹, Ami Izawa¹, Nobuyuki Hirama¹, Shuhei Teranishi¹, Saki Manabe¹, Tatsuya Inoue², Kunihiko Shibata³, Yasuyuki Sugiura⁴, Makoto Kudo¹ and Takeshi Kaneko⁵

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

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.

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 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/m$^2$, 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 corticosteroid (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 DR typing revealed that the patient was DR4-
positive (SRL, Tokyo, Japan); his cerebrospinal fluid cell count increased to 16/μL. These findings were consistent with Vogt-Koyanagi-Harada (VKH)-like syndrome. Furthermore, his baseline serum cortisol levels were 0.6 μg/dL (range, 3.0-19.6 μg/mL), with no response to adrenocorticotropic 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 μg/mL (range, 3.0-19.6 μg/mL) with peak values of 1.9 pg/mL and 0.3 μg/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. 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. 2H, I). 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 nivolmab 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-
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.

**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).
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 corticosteroids. However, the standard treatment for VKH disease is high-dose systemic corticosteroids, which was administered to six other patients (Ta-
ble). In the present case, the irAE uveitis appeared initially and was successfully treated with a topical corticosteroid; 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).

Acknowledgement
We thank Mark Abramovitz, PhD, from Edanz Group (https://en-author-services.edanz.com/ac) for editing a draft of this manuscript.

References
1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. Nat Rev Cancer 12 (4): 252-264, 2012 (in eng).
2. Topalian SL, Drake CG, Pardoll DM. Immune checkpoint blockade: a common denominator approach to cancer therapy. Cancer Cell 27 (4): 450-461, 2015 (in eng).
3. Sharma P, Hu-Lieskovan S, Wargo JA, Ribas A. Primary, Adaptive, and Acquired Resistance to Cancer Immunotherapy. Cell 168 (4): 707-723, 2017 (in eng).
4. Hodi FS, O’Day SJ, McDermott DF, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med 363 (8): 711-723, 2010 (in eng).
5. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med 366 (26): 2443-2454, 2012 (in eng).
6. Brahmer JR, Tykodi SS, Chow LQ, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med 366 (26): 2455-2465, 2012 (in eng).
7. Schwartz LH, Liitère S, de Vries E, et al. RECIST 1.1-Update and clarification: From the RECIST committee. Eur J Cancer 62: 132-137, 2016 (in eng).
8. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer 45 (2): 228-247, 2009.
9. Sato K, Akamatsu H, Murakami E, et al. Correlation between immune-related adverse events and efficacy in non-small-cell lung cancer treated with nivolumab. Lung Cancer 115: 71-74, 2018 (in eng).
10. Haratani K, Hayashi H, Chiba Y, et al. Association of immune-related adverse events with nivolumab efficacy in non-small-cell lung cancer. JAMA oncology 4 (3): 374-378, 2018.
11. Teraoka S, Fujimoto D, Morimoto T, et al. Early Immune-Related Adverse Events and Association with Outcome in Advanced Non-Small-cell Lung Cancer Patients Treated with Nivolumab: A Prospective Cohort Study. J Thorac Oncol 12 (12): 1798-1805, 2017 (in eng).
12. Caillat-Zucman S. Molecular mechanisms of HLA association with autoimmune diseases. Tissue Antigens 73 (1): 1-8, 2009 (in eng).
13. Davis JL, Mittal KK, Freidlin V, et al. HLA associations and ancestry in Vogt-Koyanagi-Harada disease and sympathetic ophthalmitis. Ophthalmology 97 (9): 1137-1142, 1990.
14. Islam S, Numaga J, Fujino Y, et al. HLA class II genes in Vogt-Koyanagi-Harada disease. Investigative ophthalmology & visual science 35 (11): 3890-3896, 1994.
15. Concha del Río LE, Arellanes-García L. Vogt-Koyanagi-Harada Disease in the Developing World. International Ophthalmology Clinics 50 (2): 189-199, 2010.
16. Shindo Y, Inoko H, Yamamoto T, Ohno S. HLA-DRB1 typing of Vogt-Koyanagi-Harada’s disease by PCR-RFLP and the strong association with DRB1* 0405 and DRB1* 0410. British journal of ophthalmology 78 (3): 223-226, 1994.
17. Saito S, Ota S, Yamada E, Inoko H, Ota M. Allele frequencies and haplotypic associations defined by allelic DNA typing at HLA class I and class II loci in the Japanese population. Tissue antigens 56 (6): 522-529, 2000.
18. Kikuchi R, Kawagoe T, Hotta K. Vogt-Koyanagi-Harada disease-like uveitis following nivolumab administration treated with steroid pulse therapy: a case report. BMC ophthalmology 20 (1): 1-6, 2020.
19. Arai T, Harada K, Usui Y, Irisawa R, Tsuboi R. Case of acute anterior uveitis and Vogt-Koyanagi-Harada syndrome-like eruptions induced by nivolumab in a melanoma patient. The Journal of dermatology 44 (8): 975-976, 2017.
20. Matsuo T, Yamasaki O. Vogt-Koyanagi-Harada disease-like posterior uveitis in the course of nivolumab (anti-PD-1 antibody), interposed by vemurafenib (BRAF inhibitor), for metastatic cutaneous malignant melanoma. Clin Case Rep 5 (5): 694-700, 2017 (in eng).
21. Fujimura T, Kambayashi Y, Tanaka K, et al. HLA-DRB 1* 04: 05 in two cases of Vogt-Koyanagi-Harada disease-like uveitis developing from an advanced melanoma patient treated by sequential administration of nivolumab and dabrafenib/trametinib therapy. The Journal of Dermatology 45 (6): 735-737, 2018.
22. Wang W, Lam W-C, Chen L. Recurrent grade 4 panuveitis with serous retinal detachment related to nivolumab treatment in a patient with metastatic renal cell carcinoma. Cancer Immunology, Immunotherapy 68 (1): 85-95, 2019.
23. Obata S, Saishin Y, Teramura K, Ohji M. Vogt-Koyanagi-Harada disease-like uveitis during nivolumab (anti-PD-1 antibody) treatment for metastatic cutaneous malignant melanoma. Case reports in ophthalmology 10 (1): 67-74, 2019.