DOI: 10.1002/cia2.12052

LETTER TO THE EDITOR

WILEY Journal of Cutaneous Immunology and Allergy

Panhypopituitarism in metastatic melanoma patient treated with ipilimumab and pembrolizumab

Dear Editor,

Immune checkpoint inhibitors (ICI) are now main strategies for metastatic melanoma. However, these therapies trigger immune-related adverse events (irAE). The endocrine organs of irAEs include pituitary, thyroid, and adrenal glands, as well as other downstream target organs.[1] Here, we report a case of panhypopituitarism induced by ipilimumab and pembrolizumab in an advanced melanoma patient.

An 82-year-old woman had a primary nodular melanoma on the left heel and underwent a wide local excision and sentinel lymph node biopsy 2 years before she was referred to us. She was diagnosed as having melanoma, stage IIIA (pT3b, N1a, M0; Breslow tumor thickness, 4 mm; Clark's level IV, with ulceration). She received an inguinal lymph node dissection and followed by weekly PEG-interferon-α injection. However, we discontinued PEG-interferon-α therapy because of occurrence of interferon-induced retinopathy. One year after the operation, positron emission tomography-computed tomography (PET-CT) showed multiple metastases in the left femur subcutis and recurrence of primary tumor. Biopsy specimens obtained from the recurrent tumor area confirmed the diagnosis of melanoma without a *BRAF* mutation. Thus, we administered pembrolizumab at 3 mg/kg every 3 weeks. After total five courses of pembrolizumab, she developed multiple skin metastases in the left femur. The treatment was switched to ipilimumab at 3 mg/kg every 3 weeks, which was repeated four times. She had general fatigue and appetite loss at 14 weeks after the initiation of ipilimumab. At 16 weeks, she had disturbance of consciousness and was conveyed to our emergency room.

Laboratory tests indicated 35 mg/dL of fasting plasma glucose, indicating marked hypoglycemia. Endocrinologically, adrenocorticotropic

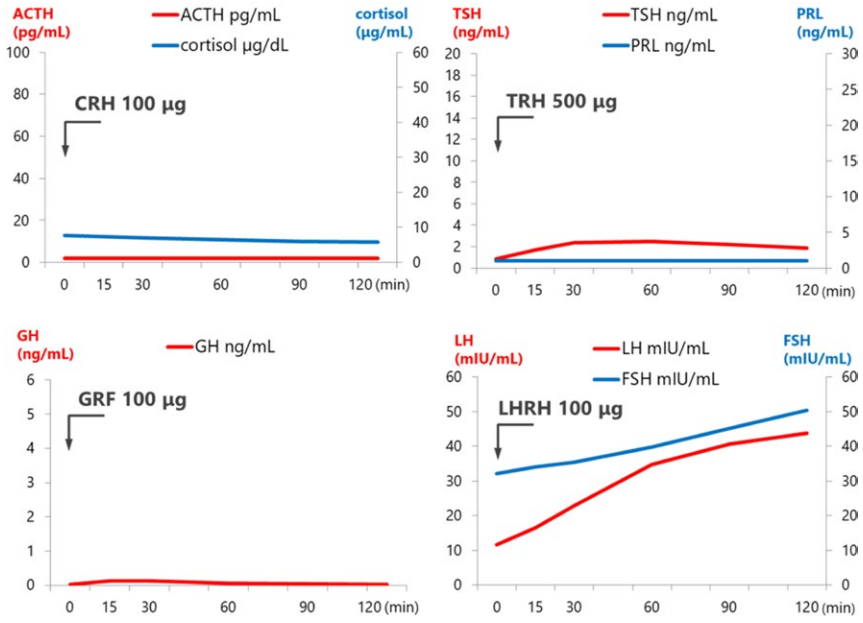

FIGURE 1 Pituitary stimulation tests with hypothalamic hormone. Six anterior pituitary hormones, including ACTH, thyroid stimulating hormone (TSH), growth hormone (GH), prolactin (PRL), luteinizing hormone (LH), follicle stimulating hormone (FSH), and cortisol, were measured after stimulation of the hypothalamic hormones. Stimulation test with corticotrophin-releasing hormone (CRH) shows disturbance in the secretion of ACTH. TSH response to thyrotropin-releasing hormone (TRH) and GH response to GH-releasing peptide-2 (GHRP-2) are also abrogated. LH-releasing hormone (LH-RH) stimulation test demonstrates the delayed response of LH and FSH

hormone (ACTH; 2.0 pg/mL; normal, 7-56 pg/mL) and cortisol (5.8 μg/L; normal, 7.1-19.6 μg/L) were decreased. Magnetic resonance imaging (MRI) findings of her pituitary gland were normal. Hypothalamic hormone challenges showed a disturbance in the secretion of ACTH, growth hormone (GH), thyroid stimulating hormone (TSH), and prolactin (PRL) (Figure 1). Luteinizing hormone-releasing hormone (LH-RH) tests revealed a delayed response to LH and follicle stimulating hormone (FSH) (Figure 1). Thus, we diagnosed her condition as ipilimumab-induced panhypopituitarism. She was treated with 1 mg/day of betamethasone, which markedly improved her hypoglycemia, appetite loss, and general fatigue.

Panhypopituitarism is a rare condition, but its frequency has recently been increased by the use of ICI. The phase 3 CheckMate 067 trial showed that the incidence of hypophysitis was 7% in patients receiving the combination therapy of ipilimumab and nivolumab, which was higher than 1% in those treated with nivolumab and 4% in those with ipilimumab monotherapy.[2] Symptoms of hypophysitis were reported to become overt at a median time of 11 weeks after initiation of ipilimumab monotherapy.[3,4] In the mechanism underlying hypophysitis, it is proposed that anti-CTLA-4 antibody binds to CTLA-4-expressing pituitary cells, leading to type II and type IV hypersensitivity.[5,6] Alternatively, the antibody therapy might promote sensitization of pituitary cell-specific cytotoxic T cells.

Hypophysitis-induced symptoms, such as fatigue and anorexia, are nonspecific in cancer-bearing patients.[7] It is kept in mind that hypophysitis is one of the important irAEs, and careful attention should be paid to the patients treated with ICI.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Haruka Goto https://orcid.org/0000-0003-2213-5830

Haruka Goto MD[1]
Akira Kasuya MD, PhD[1]
Kie Imura MD[1]
Hidehiko Miyazawa MD[1]
Toshiharu Fujiyama MD, PhD[1]
Keisuke Kakizawa MD[2]
Yoshiki Tokura MD, PhD[1]
[1]*Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu, Japan*
[2]*Division of Endocrinology, Department of Internal Medicine 2, Hamamatsu University School of Medicine, Hamamatsu, Japan*

Correspondence
Haruka Goto, MD, Department of Dermatology, Hamamatsu University School of Medicine, Hamamatsu, Japan.
Email: haruka0905@gmail.com

REFERENCES

1. Villa NM, Farahmand A, Du L, et al. Endocrinopathies with use of cancer immunotherapies. Clin Endocrinol. 2018;88:327–32.
2. Wolchok JD, Chiarion-Sileni V, Gonzalez R, et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. N Engl J Med. 2017;377:1345–56.
3. Joshi MN, Whitelaw BC, Palomar MT, Wu Y, Caroll PV. Immune checkpoint inhibitor-related hypophysitis and endocrine dysfunction: clinical review. Clin Endocrinol. 2016;85:331–9.
4. Torino F, Barnabei A, Paragliola RM, Marchetti P, Salvatori R, Corsello SM. Endocrine side-effects of anti-cancer drugs: mAbs and pituitary dysfunction: clinical evidence and pathogenic hypotheses. Eur J Endocrinol. 2013;169:R153–64.
5. Iwama S, De Remigis A, Callahan MK, Slovin SF, Wolchok JD, Caturegli P. Pituitary expression of CTLA-4 mediates hypophysitis secondary to administration of CTLA-4 blocking antibody. Sci Transl Med. 2014;6:230ra245.
6. Caturegli P, Di Dalmazi G, Lombardi M, et al. Hypophysitis secondary to cytotoxic T-lymphocyte-associated protein 4 blockade: insights into pathogenesis from an autopsy series. Am J Pathol. 2016;186:3225–35.
7. Faje A. Immunotherapy and hypophysitis: clinical presentation, treatment, and biologic insights. Pituitary. 2016;19:82–92.