Dear Editor,

While the effectiveness of immune checkpoint inhibitors (ICIs) for advanced malignant tumors is being demonstrated, immune-related adverse effects (irAEs), the adverse effects mediated by immune mechanisms, have become a problem. In hypopituitarism due to ICIs, secondary adrenal insufficiency is most often observed,[1] and hypoglycemia is one of the symptoms of secondary adrenal insufficiency. Although the incidence of hypophysitis was reported to be higher in patients with advanced malignant melanoma following anti-cytotoxic T-lymphocyte antigen 4 (CTLA4) antibody compared with anti-programmed cell death 1 (PD-1) antibody among ICIs,[2] there has been no detailed report of any case of hypopituitarism and hypoglycemia caused by anti-CTLA4 antibody. Here, we report a case with panhypopituitarism induced by ipilimumab (anti-CTLA4 antibody) in a patient presenting with hypoglycemia.

An 82-year-old female was diagnosed with having primary malignant melanoma of the left planter region with left inguinal lymph node metastasis. After 13 courses of treatment with pembrolizumab (2 mg/kg every 3 weeks), she was switched to ipilimumab because of disease progression. Three courses of ipilimumab (3 mg/kg every 3 weeks) were completed without problems. However, she developed malaise and somnolence from 8 weeks after the start of ipilimumab therapy. One week later, her level of consciousness had declined to JCS300, so she was admitted to the emergency division of the hospital. At the time of admission, laboratory tests showed hypoglycemia with a blood glucose level of 26 mg/dL. Her vital sign was stable during transportation and hospitalization, and shock episodes were not seen. Hyponatremia and hypothyroidism were also diagnosed and were suspected to represent irAEs to ipilimumab. The patient also had difficulty in breathing, and chest computed tomography (CT) scans showed ground-glass opacities. The results of endocrine tests suggested panhypopituitarism, including low hormones secreted from the anterior pituitary and each organ. Anti-CTLA4 antibody was negative, and the thyroglobulin level was not increased. Investigation of the cause of hypoglycemia did not show any defect of insulin secretion or increase of insulin resistance. Anti-glutamic acid decarboxylase antibody was negative. Findings suggesting type 1 diabetes mellitus (DM) were not observed [Table 1]. Then, imaging evaluation of the endocrine organs was conducted. Head magnetic resonance imaging showed that the pituitary gland was normal in size [Figure 1a]. Ultrasound of the thyroid gland did not show any degenerative changes, and there were also no significant findings on CT scans of the adrenal gland [Figure 1b and c]. Acute adrenal insufficiency secondary to aspiration pneumonia was suspected, and treatment was started.

### Table 1: Laboratory data of endocrine department

| Parameter   | Value | Reference Range |
|-------------|-------|-----------------|
| ACTH        | <1.0 (7.4–55.7) pg/mL | pg/mL |
| Cortisol    | 1.7 (4.0–23.3) µg/dL | µg/dL |
| 11-OHCS     | 4.5 (7.0–23.0) µg/dL | µg/dL |
| DHEA-S      | 9 (30–201) µg/dL | µg/dL |
| PRA         | <0.2 (0.2–2.3) ng/mL/hr | ng/mL/hr |
| PAC         | 8 (30–159) µg/dL | µg/dL |
| GH          | 0.55 (0.13–9.88) ng/mL | ng/mL |
| IGF-1       | <10 (38–207) ng/mL | ng/mL |
| PRL         | 8.05 (3.12–15.39) ng/mL | ng/mL |
| LH          | 0.62 (11.0–50.0) mIU/mL | mIU/mL |
| FSH         | 4.01 (26.0–120.0) mIU/mL | mIU/mL |
| Estradiol   | 16 (~39) pg/mL | pg/mL |
| ADH         | 5.0 (~2.8) pg/mL | pg/mL |

Underline denotes abnormal values. ACTH: Adrenocorticotropic hormone, 11OHCS: 11hydroxycorticosteroid, DHEAS: Dehydroepiandrosterone sulfate, PRA: Plasma renin activity, PAC: Plasma aldosterone concentration, GH: Growth hormone, IGF1: Insulinlike growth factor1, PRL: Prolactin, LH: Luteinizing hormone, FSH: Folliclestimulating hormone, ADH: Antidiuretic hormone, TSH: Thyrotropin, FT4: Thyroxine, FT3: Triiodothyronine, TRAb: TSH receptor antibody, TgAb: Antithyroglobulin, Tg: Thyroglobulin, FPG: Fasting plasma glucose, CPR: Cpeptide immunoreactivity, IRI: Immunoreactive insulin, IRG: Immunoreactive glucagon, GADAb: Antiglutamyl acid decarboxylase antibody

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Panhypopituitarism induced by ipilimumab

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1d], suggesting that the Hypophysitis secondary to cytotoxic T-lymphocyte-associated

In conclusion, physicians using ICIs should keep in mind that ipilimumab has not been reported before, and the risk is unknown.

As far as we could identify, hypoglycemia due to reaction only occurred in one patient and the details were not up to March 24, 2017, surveillance of 190 patients treated with ipilimumab in Japan antibody.

levels caused by irAEs, type 1 DM by ICIs was reported on only due to type 1 DM have been reported as abnormal glucose insufficiency in patients on ICIs. Cancer patients on treatment is given and the new creations are licensed under the identical terms.

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Figure 1: (a) The pituitary gland was normal in size and swelling was not observed (arrow). (b) The thickness of thyroid isthmus was 3.5 mm (yellow-dotted line). The thyroid gland was slightly enlarged, but degenerative changes were not observed. (c) There was no evidence of adrenal enlargement, necrosis, or calcification (arrow). (d) The eosinophil count was occasionally increased after the start of treatment with pembrolizumab while it showed a persistent increase after the patient was switched to ipilimumab by infusion of hydrocortisone in addition to the administration of antibiotics. The patient’s condition was promptly improved by treatment, so the dose of hydrocortisone was tapered and she was switched to oral steroid therapy. Intake of fluid and food resumed after 5 days of hospitalization together with thyroid hormone supplementation. The subsequent clinical course was favorable, and she was discharged 18 days after admission.

Adrenal insufficiency secondary to panhypopituitarism was developed in this patient. It was previously reported that the eosinophil count can be monitored as a predictor of adrenal insufficiency induced by ICIs.[3-5] In this patient, the eosinophil count was sporadically increased after the start of pembrolizumab administration and was persistently elevated after the patient switched to ipilimumab [Figure 1d], suggesting that the eosinophil count is also a useful index of the risk of adrenal insufficiency in patients on ICIs. Cancer patients on treatment with ICIs are immunocompromised, and the clinical course of our patient suggested that irAEs can become more serious due to concurrent infection. Although some cases of hyperglycemia due to type 1 DM have been reported as abnormal glucose levels caused by irAEs, type 1 DM by ICIs was reported on only those by anti-PD-1 antibody and anti-PD-1 ligand molecules, and there has been no report of type 1 DM by anti-CTLA4 antibody.[1] According to the interim report on the postmarketing surveillance of 190 patients treated with ipilimumab in Japan up to March 24, 2017,[6] hypoglycemia as a serious adverse reaction only occurred in one patient and the details were not published. As far as we could identify, hypoglycemia due to ipilimumab has not been reported before, and the risk is unknown. In conclusion, physicians using ICIs should keep in mind that hypoglycemia may occur as a symptom of adrenal insufficiency by panhypopituitarism among the various irAEs to these agents.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given her consent for her images and other clinical information to be reported in the journal. The patient understands that name and initials will not be published, and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

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