

## Pembrolizumab-Induced Fulminant Type 1 Diabetes Mellitus and Hypothyroidism

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Pembrolizumab, a monoclonal antibody that blocks programmed cell death 1 (PD-1) receptors on T-cells, is a kind of immune checkpoint inhibitors (ICIs) which is used in treatment of metastatic melanoma or non-small-cell lung cancer. ICIs can cause immune-related adverse events (irAEs) to any organ system including endocrinopathies such as hypophysitis, thyroiditis, and rarely diabetes mellitus (DM). A 78-year-old female, who was diagnosed with metastatic melanoma, started pembrolizumab therapy. After three cycles of pembrolizumab therapy, her free T4 level was 0.53 ng/dL and TSH level was 10.57  $\mu$ IU/mL, so her thyroid function test started to show hypothyroidism state. After two more cycles, her free T4 level decreased to 0.36 ng/dL and TSH level increased to 129.10  $\mu$ IU/mL. Also she developed general weakness with weight loss, and blood glucose level increased up to 326 mg/dL and C-peptide level was <0.01 ng/mL. Before pembrolizumab therapy, she didn't have either thyroid dysfunction or DM. She was diagnosed with fulminant type 1 DM and hypothyroidism, and then treated with thyroid hormone replacement and insulin injection. When she was discharged from hospital, treatment regimen was changed from pembrolizumab to imatinib because her response evaluation was confirmed as progressive disease (PD). We present this case because she was the first case in South Korea who developed fulminant type 1 DM and hypothyroidism after pembrolizumab therapy in metastatic melanoma. So, we suggest that clinicians should consider close monitoring of patient's glucose level and thyroid function during pembrolizumab therapy. Also, clinicians should take into account possibilities that a patient who received pembrolizumab therapy might show more than one endocrinopathies belonged to immune-related adverse events.

Table 1. Fulminant Type 1 DM Diagnosis including Glucose tolerance test

	Pre (0hrs)	Post (2hrs)	Reference range
Glucose	309	425	70-110 mg/dL
Insulin	6.50	4.40	1.7-12.5 $\mu$ U/mL
C-peptide	< 0.01	0.01	0.9-4.0 ng/mL
Anti-GAD Antibody	Negative (0.25)		Negative < 1.00 Grey zone 1.00-1.99 Positive $\geq$ 2.00

Table 2. Changes of Glucose level and Thyroid functions tests during pembrolizumab therapy every 3 weeks

	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Admission for Cycle 6	HD 3	Reference range
Serum glucose (mg/dL)	104	100	125	102	168	254	326	70-110 mg/dL
Free T4 (ng/dL)	-	-	-	0.53	0.39	0.36	-	0.6-1.3 ng/dL
TSH ( $\mu$ IU/mL)	-	-	-	10.57	77.51	129.10	-	0.38-5.33 $\mu$ IU/mL
Anti TPO Antibody (IU/mL)	-	-	-	-	-	7.35	-	< 5.61 IU/mL
TSH receptor Antibody (IU/L)	-	-	-	-	-	< 0.80	-	< 1.75 IU/L