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Immune Checkpoint Blockade Anti–PD-L1 as a Trigger for Autoimmune Polyendocrine Syndrome

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Context: The programmed cell death protein 1 (PD-1)/programmed cell death protein ligand 1 (PD-L1) pathway is a key regulator in T-cell activation and tolerance, limiting effector T-cell function in peripheral tissues. Atezolizumab, an anti–PD-L1 monoclonal antibody, is approved for treatment of some types of advanced cancer. Its main treatment-related adverse events are immune related, such as thyroid dysfunction and hypophysitis. Autoimmune endocrinopathy can occur as isolated manifestations; only a few cases of autoimmune polyendocrine syndromes have been reported thus far.

Case: We report a case of polyendocrine syndrome type 2, characterized by Addison disease (AD), type 1 diabetes mellitus (T1DM), accompanied by hypophysitis, in a patient treated with atezolizumab. Testing was positive for 21-hydroxylase and pituitary antibodies and negative for islet cells antibodies. HLA typing revealed DRB1*04 and DQB1*03 haplotypes, which are associated with increased susceptibility to T1DM and AD.

Conclusion: The type and severity of immune-related adverse events in polyendocrine syndrome type 2 are different and depend on the monoclonal antibody used. Although the numerous molecular mechanisms inducing autoimmune endocrine diseases are still unclear, a link exists between HLA haplotypes, gene variants involved in immune checkpoint molecule expression, and increased susceptibility to autoimmune endocrinopathies. Additional studies are needed to identify susceptible patients and adapt therapy to each patient.

Freeform/Key Words: immune checkpoint inhibitors, diabetes mellitus, Addison disease, hypophysitis

Autoimmune polyendocrine syndrome type 2 (APS-2) is a polygenic disease in which HLA alleles and non-HLA genes determine the targeting of specific tissues by autoreactive T cells, leading to organ-specific autoimmunity. Aside from the genetic component, APS-2 is also influenced by environmental and endogenous factors, which act to break immune tolerance and initiate the autoimmune attack [1].

Therapeutic antibodies have been introduced in clinical practice to target key regulators of peripheral immune tolerance (namely, anti–CTLA-4, anti–PD-1, and anti–PD-L1) with the

Abbreviations: AD, Addison disease; irAE, immune-related adverse event; PD-1, programmed cell death protein 1; PD-L1, programmed cell death protein ligand 1; T1DM, type 1 diabetes mellitus.

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objective of activating the immune system against cancer cells. An undesirable but somewhat expected effect of immunotherapy is the triggering of autoimmune diseases. The prevalence of immune-related adverse events (irAEs) is related to the kind of immune checkpoint blockade used: Autoimmune thyroiditis is frequently found after patients are treated with anti–PD-1, whereas hypophysitis, which is considered a very rare condition, has been reported in up to 5% of patients receiving anti–CTLA-4 [2].

Type 1 diabetes mellitus (T1DM) and primary adrenal insufficiency are rare irAEs that can result in life-threatening diabetic ketoacidosis or adrenal crisis, respectively, if not diagnosed timely and managed properly. We describe a case of onset of APS-2 [an association of Addison disease (AD) and diabetes mellitus] accompanied by hypophysitis in a patient treated with the anti–PD-L1 atezolizumab.

1. Case Report

A 60-year-old man was diagnosed with unresectable metastatic lung adenocarcinoma at age 52 years and treated with 37 cycles of chemotherapy with cisplatin and pemetrexed. In April 2018, because of tumor progression, he received a second-line treatment with atezolizumab as part of a phase III/IV, single-arm, multicenter study. He had no comorbidities or a family history of autoimmune or endocrine diseases. Baseline thyroid function assessment, and serum blood glucose and electrolyte levels were unremarkable. Atezolizumab was prescribed at a dosage of 1200-mg every 3 weeks. After the two initial doses, hyperglycemia developed, requiring basal-bolus insulin therapy. After the fourth dose, the patient was admitted to our Endocrinology and Metabolic Diseases Unit because of severe weakness, nausea, abdominal pain, thirst, and dizziness. Laboratory tests revealed severe hyperglycemia with diabetic ketoacidosis, hyperkalemia, and hyponatremia. Pituitary function was tested and found normal (Table 1). After 3 days of insulin infusion and IV fluids, the patient returned to basal-bolus insulin therapy, achieving fair glycemic control. Further assessment showed undetectable serum C-peptide levels and slightly elevated HbA1c. Because of persistence of mild hyperkalemia and hyponatremia, although ketoacidosis was corrected, we assessed the ACTH-adrenal axis, documenting low morning ACTH and cortisol, low urinary free cortisol level, absent response of cortisol to ACTH, and no response of cortisol and ACTH to corticotropin-releasing factor. Serum electrolyte levels normalized after hydrocortisone and fludrocortisone replacement therapy was started. Pituitary function evaluation was suggestive for hypogonadotropic hypogonadism, whereas IGF-1, prolactin, and TSH levels were all normal (Table 1). No adrenal secondary lesions were detected on an abdominal CT scan; sellar MRI with gadolinium contrast showed a normal-sized pituitary gland with regular enhancement and no secondary lesions in the hypothalamic-pituitary region (Fig. 1). After reporting the adverse event to the trial sponsors and competent regulatory body, atezolizumab was withdrawn. Three months after discontinuation of the drug, tumor progression was documented on a CT scan.

A. Organ-Specific Antibodies and HLA Typing

Tests for insulin cell antibodies (tyrosine phosphatase-based islet antigen 2 antibodies and glutamic acid decarboxylase antibody) were negative, whereas tests for 21-hydroxylase antibodies were positive. Pituitary antibodies, tested by immunofluorescence using human pituitary substrate, as previously described [3, 4], were present (Fig. 2). Double immunofluorescence staining showed that these antibodies recognized TSH-secreting cells but not ACTH-, LH/FSH-, or GH-secreting cells.

In our case, detection of pituitary antibodies was done using patient's serum at a 1:10 dilution and an anti-human antibody (Alexa 488, catalog no. 709-546-149; Jackson ImmunoResearch) [5] at a 1:400 dilution to reveal antibody binding. As a second step, for double immunofluorescence, the following antibodies were used: anti-TSH (catalog no. hBeta TSH; A.F. Parlow National Hormone and Peptide Program) [6] at a 1:10 dilution; anti-LH

Table 1. Laboratory and Hormonal Test Results Before (Wk 0) and During Atezolizumab Therapy (Wk 3–11)[a]

	Wk							
Test	**0**	**3**	**6**	**9**	**11**	**12**	**13**	**Reference Range**
Glycemia	96	95	149	189	549	180	220	74–109 mg/dL
C-peptide					0.7		0.0	>1 ng/mL
Sodium	138	141	133	132	121	132	133	135–145 mEq/L
Potassium	3.98	4.26	5.18	5.69	7.91	5.8	4.5	3.5–5.1 mEq/L
Bicarbonate			25	21	15	26		22–30 mmol/L
Calcium					9.2			8.6–10.2 mg/dL
Creatinine					1.1			0.7–1.2 mg/dL
eGFR					95			>90 mL/min
PTH					26			8–40 ng/L
IGF-1					157.2		164.8	49–193 ng/mL
PRL				17.4	11.14			2–25 ng/mL
LH				6.4	1.1		1.2	1.4–12.7 mUI/mL
FSH				21.4	1.3		1.3	1.3–19.5 mUI/mL
Testosterone					1.5		3.2	1.75–7.8 μg/L
SHBG					89.7		90.1	13.0–89.5 nmol/L
ACTH				18	21	4	5	<50 ng/L
Cortisol				8.2	6.1	<0.4	<0.4	6.7–22.6 μg/dL
Cortisol peak after ACTH test							0.4	>18.0 μg/L
Renin							350.6	4.4–46.1 mIU/mL
Aldosterone							1.2 ng/dL	2.2–35.3 ng/dL
TSH	0.98		0.76	0.69	0.72		0.60	0.40–4.00 μU/mL
fT4	1.35		0.96	1.21	1.24		0.83	0.7–1.7 ng/dL
AbTg	<0.1				<1.0		<1.0	<30.0 UI/mL
AbTPO	<0.1				<1.0		<1.0	<10.0 UI/mL
Anti–TSH-R Ab					0.11			< 1.50 UI/L
Anti–21-OH Ab					89.33			<0.40 U/mL
Anti–IA2 Ab					0.0		0.0	<1.0 UI/mL
Anti–GAD Ab					0.0		0.0	<1.0 UI/mL
Anti–pituitary Ab							Positive	Negative

Abbreviations: Ab, antibody; AbTg, Ab anti-thyroglobulin; AbTPO, Ab anti-thyroperoxydase; eGFR, estimated glomerular filtration rate; fT4, free thyroxine; PRL, prolactin.
[a]Examinations were repeated at wk 12 and 13 during insulin and glucocorticoids replacement therapy.

(catalog no. AFP-55881789; A.F. Parlow National Hormone and Peptide Program) [7] at a 1:10 dilution; anti-FSH (catalog no. AFP-891891; A.F. Parlow National Hormone and Peptide Program) [8] at a 1:50 dilution; anti-ACTH (catalog no. 701293; Thermo Fisher Scientific) [9] at a 1:100 dilution; and anti-GH (catalog no. 374266; Santa Cruz Biotechnology) [10]

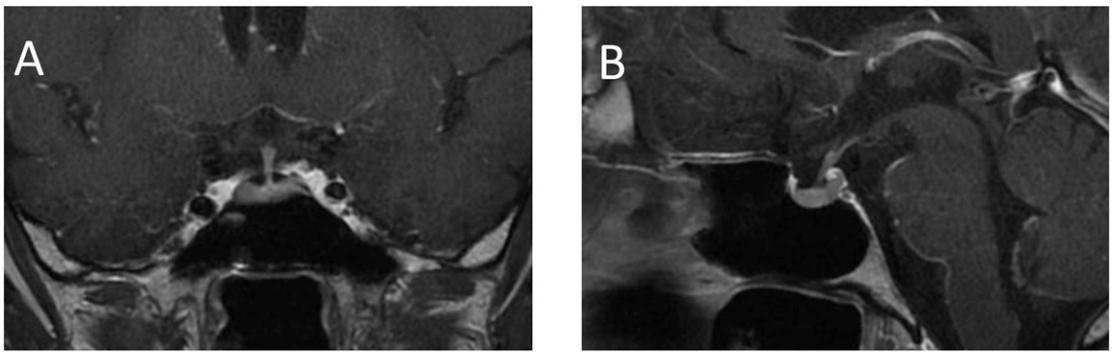

Figure 1. MRI with gadolinium contrast showing a normal-sized pituitary and stalk and normal enhancement. (A) Coronal image; (B) sagittal image.

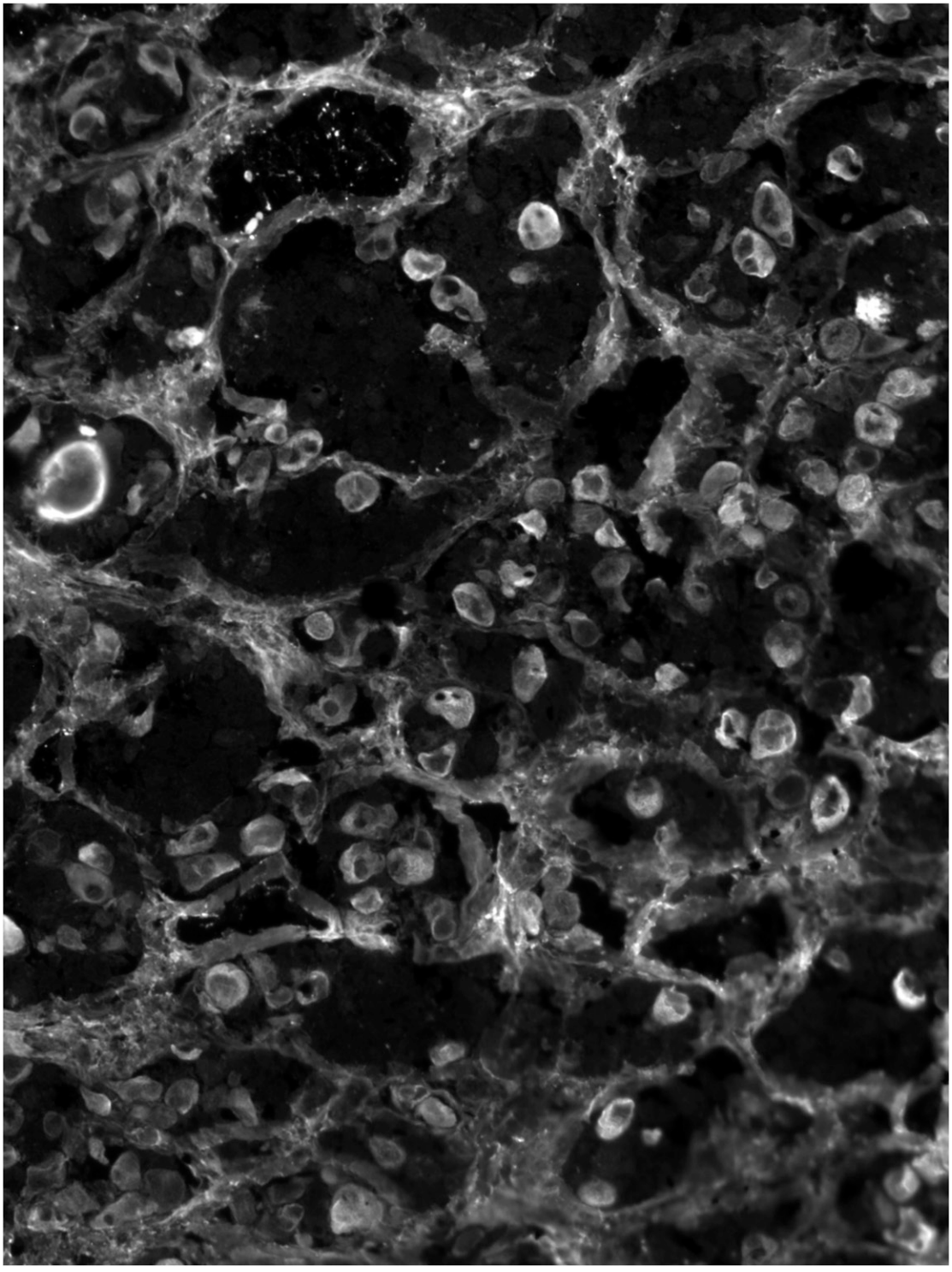

Figure 2. Immunofluorescence cytosolic diffuse staining pattern produced by pituitary antibodies.

at a 1:100 dilution. To reveal antibody binding Alexa 488 (catalog no. 150077; Abcam) [11] or Alexa 594 (catalog no. 115-586-144; Jackson ImmunoResearch) [12] were used at a 1:400 dilution.

HLA typing revealed DRB1*04 and DQB1*03 haplotypes. These were compatible with increased susceptibility to T1DM and AD.

2. Discussion

We report a unique case of an APS characterized by rapid onset of diabetic ketoacidosis, AD, and hypophysitis during anticancer immunotherapy with atezolizumab, an anti–PD-L1 antibody. T1DM is a rare irAE that often manifests a progression through diabetic ketoacidosis. Only 45 cases have been reported so far, to our knowledge: the majority with anti–PD-1 and only six with anti–PD-L1 therapy. In keeping with the current literature, manifestation of diabetes in the patient we report on here was rapid and independent of the dose of anti–PD-L1. Diabetic ketoacidosis was described in 71% of cases so far reported and, remarkably, in almost all (five of six) of patients treated with anti–PD-L1 therapy [2]. Therefore, the term "fulminant diabetes mellitus," used to describe dramatic clinical presentation in patients receiving immunotherapy [13], well applies to this case.

The PD-1/PD-L1 pathway is a key regulator in T-cell activation and tolerance [14], though many other immune effects remain to be elucidated. A mouse model reported in 2003 [15] lends an initial insight into T1DM onset in patients receiving immunotherapy. The study was the first to show that PD-1 and PD-L1 blockade can rapidly precipitate T1DM in NOD mice. PD-L1 was expressed in the inflamed β cells of the mice, suggesting a mechanism of downregulation of lymphocyte function at the site of inflammation by parenchymal cells themselves [15]. In humans, few studies have reported a low expression of PD-1 on activated T cells in patients with T1DM [16, 17]. These observations suggest that an imbalance between activated and resting T cells might promote autoimmunity by a mechanism similar to that of PD-1 blockade therapy [18].

The case we report was characterized by an insidious presentation of hypophysitis with reduced ACTH and gonadotropin secretion. Hypoadrenalism was mixed (*i.e.*, both primary and secondary) and presented with hyponatremia and hyperkalemia that initially went unnoticed due to concomitant ketoacidosis. A strong positivity for pituitary antibodies was evident on immunofluorescence, although MRI did not indicate signs of pituitary inflammation, as described in ~25% of patients who develop hypophysitis secondary to immunotherapy [2].

Table 2. Summary of Cases of Immunotherapy-Related APS Reported During Anti-PD-1[a] and Anti–CTLA-4[b] Therapy[c]

Reference	Tumor Type	Checkpoint Inhibitor	Presentation
Marchand *et al.* [21]	Pulmonary pleomorphic carcinoma	Nivolumab	DM and hypophysitis
Humayun and Poole [22]	Melanoma	Pembrolizumab	DM and hypophysitis
Tsiogka *et al.* [23]	Melanoma	Ipilimumab	DM and hypophysitis
Gauci *et al.* [24]	Melanoma	Nivolumab	DM and thyroid disease
Hofmann *et al.* [25]	Melanoma	Nivolumab	DM and thyroid disease
Li *et al.* [26]	Lung SCC	Nivolumab	DM and thyroid disease
Lowe *et al.* [27]	Melanoma	Nivolumab	DM and thyroid disease
Hughes *et al.* [28]	Melanoma	Nivolumab	DM and thyroid disease
Hansen *et al.* [29]	Melanoma	Pembrolizumab	DM and thyroid disease
Gaudy *et al.* [30]	Melanoma	Pembrolizumab	DM and thyroid disease
Hughes *et al.* [28]	Melanoma	Pembrolizumab	DM and thyroid disease
Kong *et al.* [31]	Lung SCC	Pembrolizumab	DM and thyroid disease
Alhusseini and Samantray [32]	Lung adenocarcinoma	Pembrolizumab	DM and thyroid disease
Min and Ibrahim [33]	Melanoma	Ipilimumab	AD and hypophysitis
Yang *et al.* [34]	RCC	Ipilimumab	AD and hypophysitis
Paepegaey *et al.* [35]	Melanoma	Pembrolizumab	AD and thyroid disease

Abbreviations: DM, diabetes mellitus; RCC, renal cell carcinoma; SCC, squamous cell carcinoma.
[a]Pembrolizumab and nivolumab.
[b]Ipilimumab.
[c]No cases were described during anti-PD-L1 therapy [2].

Hypophysitis secondary to PD-L1 blockade is a very uncommon irAE; it is reported to date in <0.1% of treated patients [2] and is not yet well defined. Hypophysitis secondary to CTLA-4 blockade has higher prevalence (3.2%) and was well characterized in studies showing CTLA-4 antigen expression in pituitary cells [4]. The administration of CTLA-4–blocking antibodies to patients with high levels of CTLA-4 antigen in the pituitary can trigger hypophysitis through type IV (T-cell dependent, typical of autoimmune diseases) and type II (IgG dependent) immune mechanisms [19]. We cannot exclude in this case a similar pathogenesis whereby PD-L1 is expressed on pituitary cells, acts as the target autoantigen, and initiates the immune response. Nonetheless, the latter seems unlikely to account for the effect of atezolizumab, because it contains a modified Fc region designed to limit antibody- and complement-dependent cytotoxicity.

Primary adrenal insufficiency in the patient in this report was confirmed by positivity of 21-hydroxylase and, *ex juvantibus*, by normalization of hyperkalemia with fludrocortisone. AD is an extremely infrequent irAE and, to our knowledge, no cases have been so far reported after anti–PD-L1 [2]. Of note, some reports claim PD-L1 gene variants are associated with risk of AD developing [20].

As in spontaneous APSs, organ-specific autoantibodies often accompany the autoimmune manifestations in patients receiving immunotherapy, although their predictive role and time course is uncertain [2]. The patient we report on showed clear positivity for 21-hydroxylase and for pituitary antibodies, but not for islet cells antibodies. In keeping with other reports, double immunofluorescence staining showed that pituitary antibodies clearly recognized TSH-secreting cells [4] with a not-yet-functional defect of the pituitary-thyroid axis in this patient.

In conclusion, we report the case of a patient with genetic susceptibility(*i.e.*, DRB1*04 and DQB1*03 HLA haplotypes) for T1DM and AD, and in whom the clinical onset of APS was triggered by immunotherapy with anti–PD-L1 blockade at a relatively old age. In patients treated with anti–PD-L1 therapy, blockade onset of APS, although not reported previously, to our knowledge (Table 2), should be kept in mind particularly with respect to the potential sudden development of life-threatening conditions such as diabetic ketoacidosis and adrenal crisis. The distinct functional profiles and antigen targeting of immune checkpoint inhibitors should be taken into account and treatment tailored to the patient to exploit these pathways to enhance immune responses against tumors and minimize irAEs.

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