



Anti-PD1 Pembrolizumab Can Induce Exceptional Fulminant Type 1 Diabetes

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A 44-year-old Caucasian woman with no history of diabetes was admitted to the emergency department in 2014 for vomiting and confusion, with polyuria, polydipsia, and a very recent weight loss (15 days). Biological tests revealed severe hyperglycemia and diabetic ketoacidosis (glycemia 50.45 mmol/L, ketones 3+, pH 7.25, HCO₃⁻ 3 mEq/L), with acute renal failure (39 mL/min/1.73 m²) and elevated serum lipase. Pancreatitis was ruled out by an abdominal computed tomography scan. Intravenous insulin resulted in rapid glycemic control. Surprisingly, HbA_{1c} was subnormal (6.85%). Furthermore, anti-GAD and anti-IA2 antibodies were negative and serum C-peptide was undetectable. All these parameters led to the unusual diagnosis of fulminant type 1 diabetes (FD). FD is a rare subtype of type 1 diabetes (T1D) that is especially prevalent in East Asia and differs from the typical T1D in terms of clinical presentation and pathophysiology. FD is characterized by 1) a remarkably abrupt onset of ketoacidosis, 2) a low HbA_{1c} value despite a high plasma glucose level, 3) an absence of insulin secretion capacity after a glucagon test, and 4) an elevated serum pancreatic enzyme level. It is considered a

rapid and violent immune reaction targeted to viro-infected β-cells in genetically predisposed patients that leads to a massive β-cell death (1).

In our patient, we found no evidence of an acute viral infection or of the usual HLA haplotypes of FD found in Japanese patients (1). However, the patient was treated for a metastatic melanoma and FD occurred 2 weeks after a second injection of the anti-programmed cell death-1 (PD1) antibody pembrolizumab. The computed tomography scan evaluation showed an almost complete regression of the metastatic lesions and then pembrolizumab was reintroduced with no further adverse event. To date, the patient's diabetes is controlled with basal-bolus insulin therapy.

Pembrolizumab is a monoclonal antibody against PD1 that has been reported to improve survival in patients with metastatic melanoma with mainly immune-related adverse events (2). In the NOD mice model, PD1 blockade can promote T1D (3). Decreased PD1 expression has also been reported in peripheral CD4⁺ T cells of patients suffering from autoimmune T1D (4). A direct relationship between pembrolizumab therapy and this case of FD is thus plausible. Our patient

received pembrolizumab shortly after she completed a full regimen of ipilimumab. The persistence of the ipilimumab effect may have led to a dual (anti-CTLA4 + PD1) checkpoint blockade, which is known to induce more severe immune-related adverse events.

Recently, Hughes et al. (5) reported five cases of new-onset insulin-dependent diabetes under anti-PD1 antibodies. Two of the five patients described also presented some criteria of FD—low HbA_{1c} value, negative anti-GAD and anti-IA2 antibodies, undetectable serum C-peptide—however, lipase level was not indicated. Interestingly, other parameters are similar between these two cases and our case report: the female sex, the type of cancer (melanoma), and a previous history of autoimmune thyroiditis.

In the context of the increasing indications of anti-PD1 in different cancers, the medical community must be aware of the rare but potentially life-threatening complication of FD.

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