Anti-PD1 Pembrolizumab Can Induce Exceptional Fulminant Type 1 Diabetes

A 44-year-old Caucasian woman with no diabetic history 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, HCO$_3^-$ 3 mEq/L) with acute renal failure (39 mL/min/1.73 m$^2$) 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 physiopathology. 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 glucose test, and 4) an elevated serum pancreatic enzyme level. It is considered a rapid and violent immune reaction targeted to vire-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.

Duality of Interest. J.-J.G. has participated in boards organized by Merck Sharp & Dohme. No other potential conflicts of interest relevant to this article were reported.

1Departments of Dermatology and Oncology, La Timone Hospital, Assistance Publique–Hôpitaux de Marseille, Marseille, France
2INSERM, UMR 911, Marseille, France
3Department of Nutrition, Metabolic Diseases and Endocrinology, La Conception Hospital, Assistance Publique–Hôpitaux de Marseille, Marseille, France
4Faculty of Medicine, Aix-Marseille University, Marseille, France
5INSERM, UMR 1062, Marseille, France
6Institut National de la Recherche Agronomique, UMR 1260, Marseille, France

Corresponding author: Sophie Bélia, sophie.beliard@ap-hm.fr.

Received 29 June 2015 and accepted 22 July 2015.

© 2015 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered.
Author Contributions. C.G. wrote and reviewed the manuscript. C.C. wrote the manuscript. S.Mo. reviewed the manuscript and researched data. N.D., Y.P., S.Ma., and M.-A.R. researched the data. J.-J.G. and R.V. reviewed the manuscript. S.B. researched the data and wrote and reviewed the manuscript. S.B. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

References