Successful Treatment of Immune Checkpoint Inhibitor–Induced Diabetes With Infliximab

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We report a case of a 53-year-old male patient with melanoma who was treated with combination immune checkpoint blockade (ICB) with ipilimumab and nivolumab. The patient had advanced disease with metastasis to the liver, lung, and lymph nodes. After two doses of ICB, the patient developed hypocalcemia as a result of an immune-mediated hypoparathyroidism that was treated with calcium and vitamin D substitution. In addition, the patient suffered from immune-related colitis that required treatment with corticosteroids and two doses of infliximab. Combination immunotherapy led to a metabolic complete remission of the melanoma. After tapering corticosteroids, the patient was continued on nivolumab for several weeks. No abnormalities of blood glucose were noted until then in an otherwise lean patient with a BMI of 19.6 kg/m^2. When the patient developed a seronegative oligoarthritis affecting the right knee and both ankles, he was treated with local corticosteroid injections, but no systemic corticosteroids were used. ICB was stopped. Several days later, the patient was seen for progressive fatigue. Laboratory testing showed a mild hyponatremia and a random blood glucose of 22.3 mmol/L. HbA_{1c} was 11.6% (103 mmol/mol), and C-peptide was 933 pmol/L. A mixed meal tolerance test (MMTT) revealed a mixed dysfunction, including impaired insulin secretion and reduced peripheral insulin sensitivity. Autoantibodies against islet cells were positive. Despite peripheral insulin resistance, positive autoantibodies and impaired insulin secretion led to the diagnosis of an immune-mediated diabetes mellitus (DM) similar to a type 1 DM with mixed features of β-cell dysfunction and peripheral insulin resistance. Because CRP levels were low throughout the observation period, systemic inflammation as the main cause of the hyperglycemia was also unlikely. Treatment with insulin injections was begun. Initially, a daily average of 17 units of insulin was required. Because the patient also developed a more active oligoarthritis, we started a therapy with infliximab to block tumor necrosis factor-α (TNF-α). Treatment with infliximab resulted in a reversal of β-cell dysfunction and insulin resistance, and insulin therapy could be stopped. Restaging of the patient 2 months after the last insulin injection and infliximab dose demonstrated an ongoing complete remission of his DM (Fig. 1).

We report the first successful treatment, to our knowledge, of an ICB-induced DM with infliximab. In this lean patient, insulin treatment could be stopped, and MMTT indicated a recovery of pancreatic β-cell function and peripheral insulin sensitivity with consecutive normalization of HbA_{1c}. The role of TNF-α in insulin resistance in rodents is well established, while blockade of TNF-α in patients with type 1 DM has shown clinically meaningful results only in a specific case (1–3). DM as a result of ICB has been reported, and patients have required insulin replacement therapy that could not be interrupted (4), ruling out a spontaneous resolution of ICB-induced DM without anti-inflammatory agents. Our report of a remission following TNF-α blockade suggests that its etiology might be different than in type 1 DM and that TNF-α blockade with infliximab could be used to cure ICB-induced DM. This is of relevance because many patients undergoing ICB treatment for melanoma will have a long-lasting remission, and quality of life is therefore strongly influenced by side effects. It also indicates that some specific patient populations with DM may particularly benefit from anti-inflammatory treatments (5). Certainly, larger cohorts are needed to determine the success rate, but this report advocates for the use of infliximab in patients with ICB-induced DM to restore β-cell function and insulin sensitivity.

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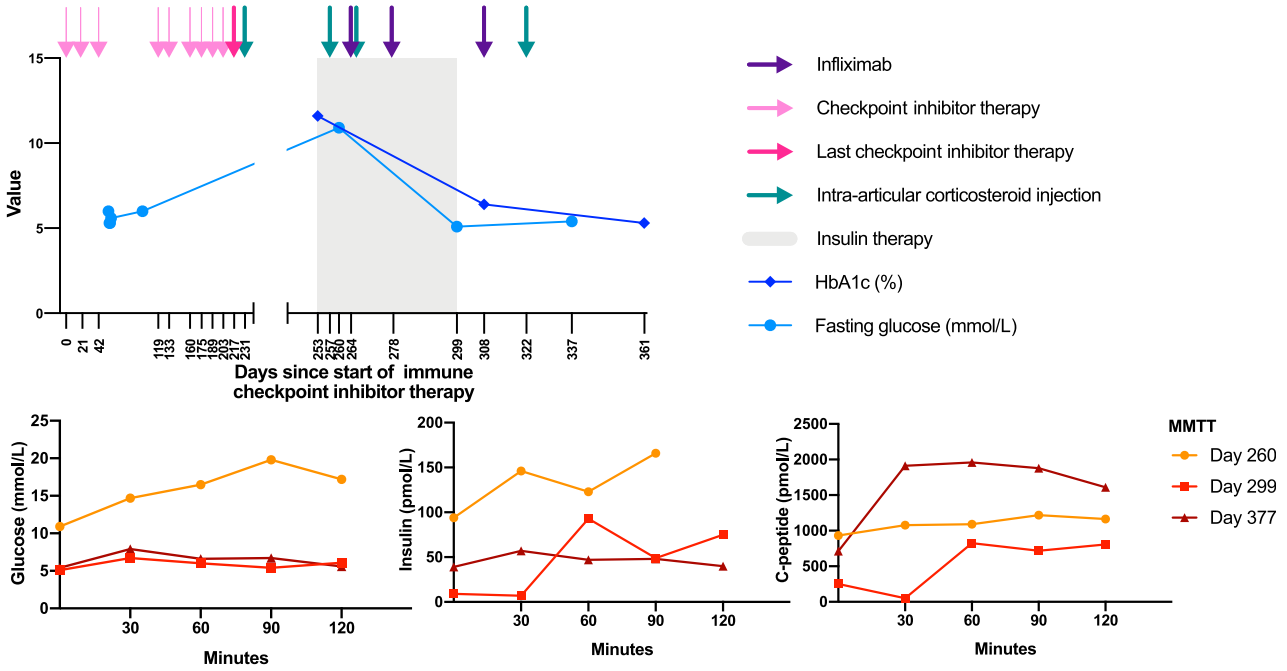

Day	70	253	260	288	299	308	329	337	361
HbA1c (%)		11.6				6.4			5.3
HbA1c (mmol/mol)		103				46			34
Fasting glucose (mmol/L)			10.9		5.1			5.4	
Fasting insulin (pmol/L)			94		9			39	
Fastin c-peptide (pmol/L)			933		252			712	
Whole body insulin sensitivity index			7.6		89.3			40.1	
Insulin secretion index			3.5					2.3	
Anti-islet cell IgG titer			1:100						
Body weight (kg)	67			68	69		68		
CRP (mg/L)		2.9	6.4			2.2	0.3		

Figure 1—Clinical course of ICB-induced DM. Shown are values over the time course after starting the immune checkpoint inhibitor therapy and the MMTT at different time points.

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