Anti–Programmed Death 1 (PD-1) Antibodies and the Pancreas: A Diabetic Storm Ahead?

Lucien Marchand,[1] Arnaud Thivolet,[2] Pierre Saintigny,[3] Nicole Fabien,[4] Julien Vouillarmet,[1] and Charles Thivolet[1]

CASE SUMMARY

- 55-year-old Caucasian man with advanced pulmonary pleomorphic carcinoma
- Normal BMI: 20.9 kg/m^2
- Developed a fulminant diabetes (revealed by ketoacidosis, HbA$_{1c}$ 8.2% [66.1 mmol/mol]) and hypophysitis after nine courses of nivolumab (anti–programmed death 1 [PD-1]), in parallel with a partial tumor response
- Computed tomography scans showed a dynamic volume change in the pancreas (initial increase after four courses of nivolumab followed by a dramatic decrease at diabetes onset and 3 months later)
- Negative for type 1 diabetes–associated autoantibodies
- Class II HLA haplotypes (DR12-DQ7/DR15-DQ6) not associated with type 1 diabetes
- Bihormonal pancreatic failure: C-peptide undetectable despite the use of ultrasensitive assay, blunted glucagon response after mixed-meal test
- Reduction of exocrine pancreatic function (decrease in fecal elastase-1; 110 μg/g stool, $n > 200$)

CASE NARRATIVE

Nivolumab, a human IgG4 programmed death 1 (PD-1) immune checkpoint–inhibitor antibody, disrupts PD-1–mediated signaling and restores antitumor immunity (1). Many recent studies have emphasized the importance of anti–PD-1 antibodies to improve survival outcomes among patients with advanced melanoma or lung cancer. Several endocrinological side effects have been reported and a few patients developed insulin-requiring diabetes (2). Some cases of fulminant diabetes (extremely acute onset with a near-normal HbA$_{1c}$) have been described with PD-1 inhibitors (3), even though this subtype of diabetes is usually exceptional in Caucasian subjects.

We recently reported the oncological aspects of a 55-year-old lean Caucasian patient (BMI 20.9 kg/m^2) with no familial history of diabetes or autoimmune disease who developed an immediate insulin-requiring diabetes revealed by ketoacidosis (HbA$_{1c}$ 8.2% [66.1 mmol/mol]) after nine courses of nivolumab for a metastatic lung pleomorphic carcinoma (left 70-mm paramediastinal mass, left 50-mm and right 20-mm adrenal masses) with a prolonged tumor response (4). One month later he presented a hypophysitis (secondary adrenal insufficiency revealed by asthenia, hypotension, and hyponatremia; there was still a corticotroph failure 9 months later).

As shown in Fig. 1, while pancreas volume increased initially by 15% after four courses of nivolumab, this patient developed dramatic pancreatic atrophy with a 63% decrease from the initial volume 3 months after diabetes onset. The subject did not have any abdominal pain during nivolumab treatment. Type 1 diabetes (T1D)–related autoantibodies—i.e., islet cell (ICA), glutamic acid decarboxlyase (GADA), insulinoma-associated protein 2 (IA-2A), islet-specific zinc transporter 8 (ZnT8A), and insulin (IAA)—were all negative. HLA class II haplotypes (DR12-DQ7/DR15-DQ6) were not those associated with T1D. The C-peptide response to a mixed-meal test (Delical HP HC; Lactalis, Torcé, France) was completely abolished despite the use of an ultrasensitive assay (Mercodia, Uppsala, Sweden), in contrast to what is generally observed during the first year of classical T1D (5). In addition, glucagon response as measured by a solid-phase two-site enzyme immunoassay (Mercodia) with a detection limit of 1 pmol/L was also blunted, with a reduction of 44% of the peak value and 54%

[1]Department of Endocrinology and Diabetes, Lyon-Sud Hospital, Hospices Civils de Lyon, Pierre-Bénite, France
[2]Department of Radiology, Hospices Civils de Lyon, Lyon, France
[3]Department of Medical Oncology, Léon Bérard Cancer Center, Lyon, France
[4]Department of Immunology, Lyon-Sud Hospital, Hospices Civils de Lyon, Pierre-Bénite, France

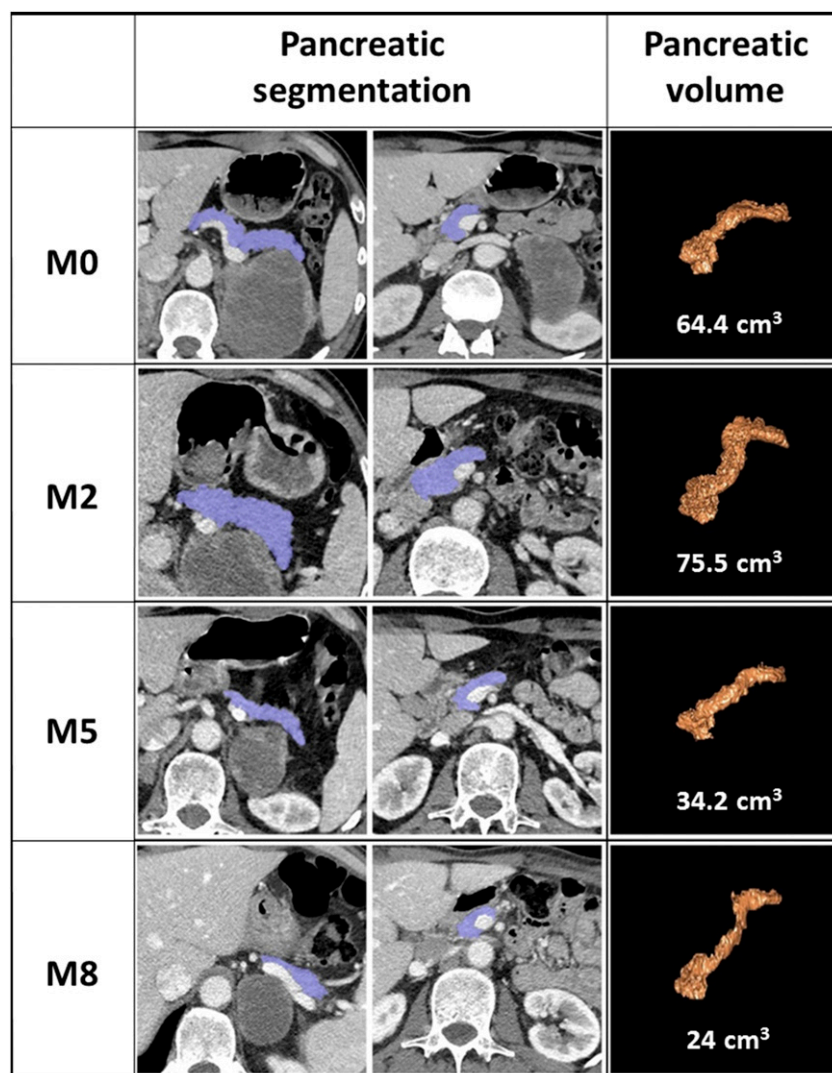Corresponding author: Lucien Marchand, lucien.marchand@chu-lyon.fr.

Figure 1—Evolution of pancreatic volume during nivolumab treatment (in months). Four abdominal computed tomography (CT) scans were performed on a 64-slice multidetector CT scanner (120 kVp; pitch, 1.375; interslice spacing, 1.25 mm; slice thickness, 1.25 mm) before treatment (M0) and during follow-up (M2 to M8; nivolumab was discontinued at diabetes onset [M5]). For volume assessment, manual segmentations and 3-D rendering reconstructions were performed on portal venous phase contrast–enhanced CT images using postprocessing software (IntelliSpace Portal 9.0, Philips Healthcare) with an interactive contour delineation tool (Smart Brush).

of the area under the curve during the mixed-meal test in comparison with the mean $\pm$ SEM value of 14 C-peptide–negative patients with long-standing T1D (31.85 vs. 73.06 $\pm$ 8.1 pmol/L). There was also a decrease in fecal elastase-1 (110 µg/g stool, $n > 200$) without clinical repercussion.

We describe herein for the first time a case of fulminant diabetes induced by a PD-1 inhibitor with a bihormonal pancreatic failure in addition to a reduction of exocrine pancreatic function with acute pancreas atrophy.

In the usual presentation of autoimmune T1D, the exocrine pancreas shows mild immune cell infiltration (6). There is a necessity to further understand the underlying mechanisms of this fulminant form of nivolumab-induced diabetes, in particular the importance of exocrine inflammation that could explain the increase of pancreas volume before diabetes onset. We wondered why this patient developed rapid β-cell loss despite the absence of a high-risk T1D HLA profile and the absence of β-cell autoantibodies. Whether this form of fulminant diabetes was precipitated by the activation of resident immune cells and the development of pancreatitis requires further exploration. A better understanding of these mechanisms should also benefit insight about the classical form of autoimmune T1D.

References

1. Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti–PD-1 antibody in cancer. N Engl J Med 2012;366:2443–2454
2. Barroso-Sousa R, Barry WT, Garrido-Castro AC, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. JAMA Oncol. 28 September 2017 [Epub ahead of print]. https://doi.org/10.1001/jamaoncol.2017.3064
3. Gauci ML, Laly P, Vidal-Trecan T, et al. Autoimmune diabetes induced by PD-1 inhibitor—retrospective analysis and pathogenesis: a case report and literature review. Cancer Immunol Immunother 2017;66:1399–1410
4. Marchand L, Paulus V, Fabien N, et al. Nivolumab-induced acute diabetes mellitus and hypophysitis in a patient with advanced pulmonary pleomorphic carcinoma with a prolonged tumor response. J Thorac Oncol 2017;12:e182–e184
5. Greenbaum CJ, Beam CA, Boulware D, et al.; Type 1 Diabetes TrialNet Study Group. Fall in C-peptide during first 2 years from diagnosis: evidence of at least two distinct phases from composite Type 1 Diabetes TrialNet data. Diabetes 2012;61:2066–2073
6. Rodriguez-Calvo T, Ekwall O, Amirian N, Zapardiel-Gonzalo J, von Herrath MG. Increased immune cell infiltration of the exocrine pancreas: a possible contribution to the pathogenesis of type 1 diabetes. Diabetes 2014;63:3880–3890