Acta Diabetologica (2019) 56:489–490
https://doi.org/10.1007/s00592-018-1246-4

LETTER TO THE EDITOR

Nivolumab-induced fulminant type 1 diabetes (T1D): the first Italian case report with long follow-up and flash glucose monitoring

Francesco Tassone[1] · Ida Colantonio[2] · Elena Gamarra[1] · Laura Gianotti[1] · Claudia Baffoni[1] · Giampaolo Magro[1] · Giorgio Borretta[1]

Received: 15 October 2018 / Accepted: 19 October 2018 / Published online: 25 October 2018

Nivolumab, an Immune Checkpoint Inhibitor (ICI) against programmed death-1 receptors expressed on T-lymphocytes, has been approved by the Food and Drug Administration (FDA) for the treatment of multiple cancers such as Non-squamous Cell Lung Cancer [1]. There are some concerns on this class of ICIs about immune-related adverse events, including thyroid dysfunction, hypophysitis, adrenal insufficiency and autoimmune diabetes mellitus (DM) [1].

Fulminant DM is a clinical entity firstly described in Japan, mainly characterized by markedly rapid onset of hyperglycemia with ketoacidosis, near normal glycated hemoglobin (HbA1c) levels despite remarkable hyperglycemia. Peculiar genetic factors, including human leukocyte antigen genes, are associated with the development of this subtype of diabetes and this could be the reason of the more frequent presentation of these cases in Asian populations. The Japanese Diabetes association has provided criteria for the diagnosis of this form of DM [2].

Nivolumab-induced DM resembles fulminant DM as the severe acute onset with extremely acute hyperglycemia and DKA could lead, if not recognized and properly treated, to patient exitus.

Several nivolumab-induced diabetic cases are reported in literature but mainly in Asia or other continents, also recently reviewed [3]. Here, we present, to our knowledge, the first Italian nivolumab-induced fulminant type 1 DM case report.

The patient is a 42-year-old man affected by a pulmonary adenocarcinoma at stage IV.

Despite his positive family history for T1DM (his father died at 55 years for cardiac diabetic complications), the patient had neither a history of diabetes mellitus himself nor evidence of pancreatic metastases. He had been started on nivolumab (3 mg/kg) once every 2 weeks on the 21st of July 2016 for four cycles (last cycle the 2nd of September). Fasting plasma glucose (FPG) was 87 mg/dL before starting nivolumab, still 84 mg/dL in August and 103 mg/dL on the 12th of September 2016. On 20th of September FPG rose to 147 mg/dL. Preoperative checks required by thoracic surgeon few days later revealed an FBG of 335 mg/dl and HbA1c 6% (42 mmol/mol).

He was admitted in our Division on the 5th of October 2016 with mild diabetic ketoacidosis (arterial pH 7.29, highly positive urine ketones), random PG of 632 mg/dL with fructosamine 183.7 umol/l (vn < 285), 33 days after the last administration of nivolumab. Basal serum C-peptide was 0.2 ng/dL with no response to the glucagon stimulation test (0.2 ng/mL in all the four determinations of the test). Serum amylase and lipase were normal on admission. No history of flu-like symptoms in the last 3 months before admission was reported. The patient was diagnosed as having nivolumab-induced fulminant T1DM with severe insulin deficiency. Antibodies against glutamic acid decarboxylase were positive (22.9 U/ml), whereas anti-IA2 (insulinoma-associated antigen-2) antibodies and Islet Cell Autoantibodies (ICA) were negative. Human leukocyte antigen class II haplotypes were DRB1*03:15-DQB1*02:06. He was treated with intravenous hydration, insulin drip, and electrolyte replacement. Thereafter, he continued to require insulin therapy and was subsequently discharged on subcutaneous multiple daily insulin (MDI) treatment. Serum C-peptide was still low at 0.1 ng/mL 3 months after the discharge, with a poor metabolic control persistent until nowadays (about 2 years from

Managed by Massimo Porta.

✉ Francesco Tassone
francesco.tassone@gmail.com

[1] Division of Endocrinology, Diabetes & Metabolism, Santa Croce e Carle Hospital, Cuneo, Italy

[2] Division of Oncology, Santa Croce e Carle Hospital, Cuneo, Italy

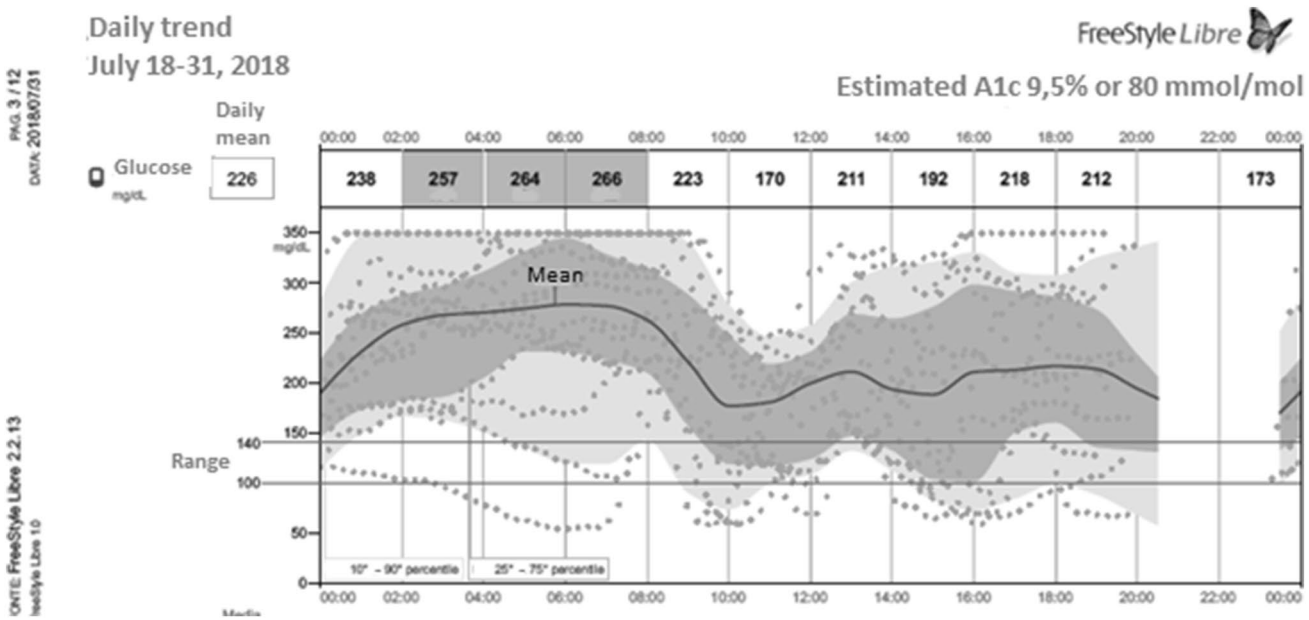

Fig. 1 Flash glucose monitoring report of the patient

the diagnosis, C-peptide still 0.1 ng/ml), despite intensive treatment with MDI.

We recently we have started using flash glucose monitoring (FGM) to improve his glucose control (Fig. 1).

Despite the MDI therapy scheme with increasing insulin requirement (rising recently to 0.74 U/kg, basal 34%, bolus 66%), the glycemic control of the patient is still characterized by mean hyperglycemia (more evident during night), marked glycemic variability and high risk of hypoglycemia after meals.

Compared to other case reports in literature (followed-up for few months), our novel findings are the relatively long follow-up of 2 years with the observation of a persistently reduced insulin secretion over time.

The temporal coincidence with nivolumab treatment makes it unlikely to be a sporadic case of T1DM, moreover, the rapid onset of the this clinical picture, fulfilling diagnostic criteria of fulminant T1DM, should alert also the Italian clinician to recognize and diagnose this severe clinical condition even at our latitudes.

Lastly, our findings are in line with those recently reported by Marchand and coworkers in this journal [4].

In summary, we present a case of a patient developing nivolumab-induced fulminant type 1 DM about 10 weeks after starting nivolumab, with long lasting severe impairment of insulin secretion and difficulty in achieving a good metabolic control as pointed out in the FGM graph.

This report might provide some further clinical insight into the pathophysiology of T1DM caused by nivolumab and proves how this type of diabetes represents a challenge for the clinician who may need to resort to technology for its proper treatment.

Compliance with ethical standards

Conflict of interest All authors declare that they have no conflict of interest.

Human and animal rights disclosure All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from the patient.

References

1. Postow MA, Sidlow R, Hellmann MD (2018) Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med 378(2):158–168 **(PubMed PMID: 29320654)**
2. Imagawa A, Hanafusa T, Awata T et al (2012) Report of the Committee of the Japan Diabetes Society on the Research of Fulminant and Acute-onset Type 1 diabetes mellitus: new diagnostic criteria of fulminant type 1 diabetes mellitus. J Diabetes Investig 3(6):536–539 **(PubMed PMID: 24843620)**
3. Clotman K, Janssens K, Specenier P, Weets I, De Block CEM (2018) Programmed cell death-1 (PD-1) inhibitor induced type 1 diabetes mellitus: mini-review. J Clin Endocrinol Metab. https://doi.org/10.1210/jc.2018-00728. **(PubMed PMID: 29955867)**
4. Marchand L, Thivolet A, Dalle S et al. (2018) Diabetes mellitus induced by PD-1 and PD-L1 inhibitors: description of pancreatic endocrine and exocrine phenotype. Acta Diabetol https://doi.org/10.1007/s00592-018-1234-8 **(PubMed PMID: 30284618)**