Editorial

Post-immunotherapy new onset diabetes (PINOD)—under-recognized etiology, unexplored presentation

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Classifying diabetes

The classification of diabetes has been an enigma for ages. The ancient text of Ayurveda, the Charaka Samhita, classifies urinary disorders (prameha) into twenty types, and madhumeha, or disorders characterized by sweet urine, is classified into two types, obese and non-obese (1). A similar challenge has flummoxed modern diabetes care providers and researchers. The first attempt at a globally accepted framework of diabetes was in 1979, when the National Diabetes Data Group (NDDG) published its recommendations (2). This was followed in 1985 by a document from the World Health Organization (WHO) (3). The authors of these classifications mentioned the limitations of their proposals and the fact that future research would necessitate a relook at their suggestions. Newer developments in our understanding of the etiopathogenesis of diabetes led to changes in the classification of diabetes. These were published by the American Diabetes Association (ADA) and WHO in 1997 and 1999 respectively (4,5). However, these too, are not the final word on this topic.

Various experts have explored the diversity of diabetes through models such as the Ominous Octet and Dirty Dozen (6,7). Others have tried to unify these concepts by creating a beta cell-centric schema of diabetes (8). Proposals from Japan and South Asia delve into the finer details of diabetes by proposing subtypes of type 1 diabetes (9-11). On the other hand, expert opinion considers type 1 and type 2 diabetes as opposite ends of the same spectrum. Irrespective of what taxonomic model is followed, however, all clinicians agree that classification of diabetes is not an easy job.

New onset diabetes post-immunotherapy

It is in this context that a recent paper by Marchand and colleagues (12) gains importance. The authors describe a case series of six patients with developed diabetes during treatment who immunotherapy for malignant conditions. These patients were prescribed the programmed cell death-1 (PD-1) and programmed death-ligand 1 (PD-L1) inhibitors nivolumab, pembrolizumab and durvalumab, for management of a variety of pulmonary and cutaneous tumours. They developed diabetes after a time span ranging from 2 to 13 months. The authors studied the clinical features, phenotype, biochemistry and endocrine and exocrine pancreatic function.

Though there is considerable heterogeneity in the presentation and course of diabetes induced by PD-1 and PD-L1, a prototype of this diabetes is now emerging. Cell immune-mediated structuro-functional beta cell destruction with or without alpha cell involvement, exocrine pancreatic dysfunction, and polyglandular disease, is a succinct description of the phenotype described by Marchand *et al.* (12,13).

Immune etiology

The etiology of PD-1 and PD-L1 induced diabetes is certainly immune in nature, but is not related to the humoral immune dysfunction that characterizes autoimmune type 1 diabetes (12). Rather, it may be due to cell-mediated immune activation that occurs with PD-1 and PD-L1 therapy (14). Though these drugs are expected to focus on tumour-related cell-mediated immunity, their

effects have been noted on various endocrine systems of the body. Autoimmune thyroiditis and hypophysitis have been reported by earlier pharmacovigilant workers (14,15).

In the current case series, this cell-mediated toxicity appears to spare the alpha cell in 4 out of 6, and the exocrine pancreas in 5 out of 6 patients. The beta cell destruction, however, is severe: 4 of 6 patients presented with diabetic ketoacidosis and undetectable C peptide; 5 had severe symptoms including significant weight loss (12). Other endocrine dysfunction, documented in the form of euthyroid and hypothyroid Hashimoto's thyroiditis, or corticotroph insufficiency, is characteristic of associations noted with type 1 diabetes (15).

Marchand's report builds upon a rapidly increasing series of case reports of immunotherapy-related diabetes (13,15). They rightly term this impending epidemic "a diabetic storm ahead".

Unanswered questions

The clinical details shared in this case series do not provide insight into risk factors which can predict onset of PD-1 or PD-L1 induced diabetes. Gender, age body mass index, past history of metabolic dysfunction or current metabolic status do not show any unique characteristics. The type of neoplasia and their spread, or the type of adjuvant chemotherapy does not suggest that there are any specific risk factors for drug induced dysglycemia. The time frame between onset or intensity of immune therapy and diabetes is not clear. Neither is the temporal profile of the disease: PD-1 or PD-L1 induced dysglycemia may be fulminant or gradual in onset, permanent or temporary in nature, and may or may not allow reinstitution of the culprit immunotherapy.

Clinical approach

This editorial began by discussing the classification of diabetes. PD-1 and PD-L1 induced diabetes fits various documented forms of diabetes mellitus. The condition responds to the definition of idiopathic type 1 diabetes, and to that of drug or toxin induced diabetes. Some cases are similar to non-obese type 2 diabetes, while others can be considered a variant of pancreatic diabetes (16). The exact terminology, however, is not as important as the need for prevention and management of diabetes.

As of now, we do not have biomarkers which can predict the onset of this form of diabetes, and assist in primary prevention (15). A thorough search for risk factors of autoimmune dysfunction, including personal, past and family history of vitiligo, skin rash, arthralgia and autoimmune endocrinopathy, may help in rational selection of patients for PD-1 or PD-L1 treatment.

Secondary prevention can be practiced by regular and frequent screening and nature of screening for dysglycemia. Baseline glycemic parameters must be documented prior to starting immunotherapy in oncologic setting. The current case series does not provide guidance regarding the initiation, frequency and nature of screening interventions for diabetes. Patients and their care givers must be counseled about the symptoms suggestive of diabetes and ketoacidosis, and the need to report these immediately to the health care provider.

Early detection will allow early institution of treatment, and help prevent complications associated with poor glycemic control. Current understanding suggests that insulin be the drug of choice in this form of insulinopenic diabetes. However, newer drugs and formulations may find a place in management algorithms of PD-1 and PD-L1 included diabetes. Metformin has been shown to be of value as adjuvant therapy in some cancers (17); it should be used for its insulin-sensitizing and glucose-lowering therapies, provided it is not contraindicated and is well-tolerated.

If ketoacidosis is present, or is anticipated, insulin must be initiated immediately, along with supportive measures. Ideally, the offending immunotherapy should be discontinued. The decision to rechallenge the patient with PD-1 or PD-L1 should be taken on an individualized basis, balancing anticipated oncologic benefit with possibility of metabolic/endocrine dysfunction.

Summary

Marchand *et al.* highlight a new; relatively under-recognized etiology of diabetes, which may be termed 'post-immunotherapy new onset diabetes (PINOD)'. The clinical presentation and course that they describe should help offer preventive and therapeutic interventions, in a timely manner, to persons using PD-1 and PD-L1 drug for management of malignancy.

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None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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