Clinical characteristics of 21 patients with type 1 diabetes mellitus related to immune checkpoint inhibitors

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Introduction

■ Background

- Type 1 diabetes mellitus (T1DM) is one of the immune-related adverse events (irAEs) associated with immune checkpoint inhibitor (ICI).
- The incidence of T1DM induced by ICI has been reported to be 0.4%.
  Few studies have reported the symptoms and laboratory findings at the onset of T1DM and its clinical features.
- Early detection of T1DM is sometimes difficult, resulting diabetic ketoacidosis (DKA) may lead to serious outcomes.
  Delayed diagnosis and initiation of treatment could be life-threatening.

■ Objectives

- The aims of this study were to summarize the clinical characteristics and treatment course of ICI-associated T1DM and to identify symptoms and laboratory findings for its early detection and diagnosis.

Methods

■ Study design and patient eligibility

- Multi-center (5 cancer centers) , retrospective case series.
- 21 patients who developed T1DM during treatment with ICIs from October 2015 to March 2021.
- Exclusion criteria : treated in clinical trials.

■ Assessment

- The patients' clinical characteristics and laboratory and radiologic findings were collected.

Results

■ Patient characteristics

	n =21	%
Age		
median [range]	63	[32-75]
Gender		
Male	16	76.2
Female	5	23.8
BMI	21.1±2.6	＊(18)
ECOG PS		
0	10	47.6
1	10	47.6
3	1	4.8

＊Data for 18 patients

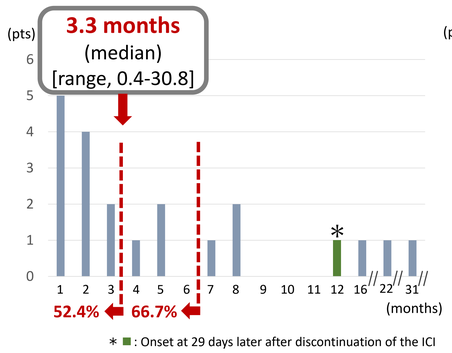
	n =21	%
Tumor types		
Melanoma	8	38.1
Lung	6	28.6
Head and Neck	3	14.3
Gastrointestinal	2	9.5
Kidney	2	9.5
Treatment lines		
1st	6	28.6
2nd	7	33.3
3rd	7	33.3
≧4th	1	4.8
History of diabetes		
Yes (T2DM)	2	9.5
No	19	90.5

■ Treatment regimen

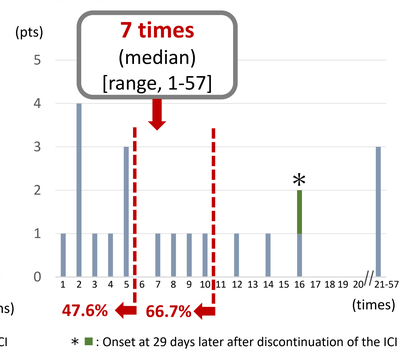
	n =21	%
Monotherapy		
Nivolumab	14	66.7
Combination therapy		
Nivolumab + Ipilimumab	7	33.3

Results

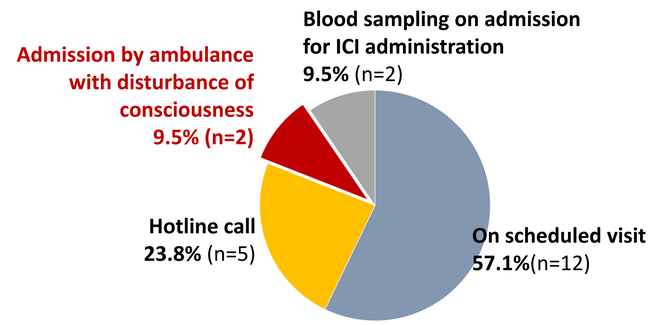
■ Time to clinical diagnosis



■ Number to ICI administrations before onset



■ Occasion when the diagnosis was made



■ Symptoms at diagnosis (overlapping)

	n =21	%
Thirst,polydipsia,polyuria	14	66.7
Abdominal symptoms	11	52.4
Flu-like symptoms	6	28.6
Weight loss	8	38.0
Disturbance of consciousness	**2**	**9.5**

■ Laboratory findings at diagnosis

	n =21	
HbA1c (%)		
median [range]	7.6	[5.6-10.0]
Glucose (mg/dL)		
median [range]	578	[217-1802]
Anti-GAD antibody		%
positive	3	14.2
negative	17	81.0
ND	1	4.8
Plasma C-peptide reactivity (ng/mL)		
median [range]	0.40	[0.03-5.50]

	n =21	%
Diabetic ketoacidosis		
Yes	9	42.9
No	12	57.1
Arterial pH ＊		
median	7.190	＊(9)
[range]	[7.019-7.373]	
Clinical type of T1DM		
fulminant	14	66.7
acute-onset	7	33.3

＊Date for 9 patients with DKA

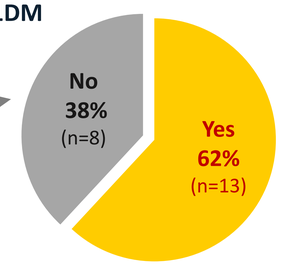
Results

■ Other irAEs

	n=21	%
Number of patients with other irAEs	9	42.9
Endocrinopathy	7	33.3
Thyroid disorder	5	23.8
Pituitary dysfunction	**1**	**4.8**
Thyroid disorder + Pituitary dysfunction	**1**	**4.8**
Colitis	4	19.0
Skin toxicity	2	9.5
Liver toxicity	1	4.8

■ Readmission of ICI after the onset of T1DM

Reason for discontinuation	(n)
PD or cPD	4
Onset of T1DM	**3**
Poor glycemic control	**1**



Summary

- In about 50% of the cases, T1DM occurred within the 3 month and 7th cycles after the initiation of ICIs.
  Meanwhile, T1DM sometimes occurred 1 year after initiation of treatment or after discontinuation.
- Symptoms at the onset of T1DM included hyperglycemic symptoms (thirst, polydipsia, polyuria) in 14 pts (66.7%), abdominal symptoms in 11 pts (52.4%), flu-like symptoms in 6 pts (28.6%), disturbance of consciousness in 2pts (9.5%). Also, diabetic ketoacidosis was present in 9 pts (42.9%) .
- ICIs were restarted in about 60% of the patients.

Conclusion

- Patients with T1DM induced by ICIs showed similar symptoms to those of general T1DM, but those were not always present in each case.
- Of note, in about 60% of the cases the diagnosis of T1DM was made before the development of overt DKA. In some cases, moderate hyperglycemia found incidentally at the scheduled visit led to the diagnosis of T1DM.
- Therefore, routine measurement of plasma glucose levels should be mandatory for early detection of ICI-associated T1DM and if suspected, prompt initiation of insulin treatment should be considered to avoid life-threatening metabolic deteriorations.

【Disclosure Statement of COI】The authors have no financial conflicts of interest disclose concerning the study.