Exocrine and Endocrine Pancreatic Insufficiency Induced by Immune Checkpoint Inhibitors: A Case-Control Study

Deepika Satish MD, I-Hsin Lin PhD, James Flory MD, Hans Gerdes MD, Michael A. Postow, MD, David M. Faleck MD

Memorial Sloan Kettering Cancer Center

Background

- ICI-associated pancreatic adverse events are being recognized with the increased use of immune checkpoint inhibitors (ICI)
- Diarrhea affects up to 35% of ICI-treated patients, and steatorrhea due to exocrine pancreatic insufficiency (EPI) has been suggested in case reports and small studies[1,2,3,4]
- ICI-related diabetes mellitus (ICI-DM) has been recognized primarily presenting with type 1 DM with diabetic ketoacidosis, but other ICI-DM phenotypes, such as the development of hyperglycemia without the need for insulin and the worsening of glycemic control in patients with type 2 DM, has been observed[5]
- To our knowledge, worsening hyperglycemia in association with EPI from ICI therapies has not been described while ICI-related exocrine pancreatic insufficiency (EPI) has been recognized much less

Goal: To describe the first case-control study describing an association between EPI and worsening of glycemic control

Design

Retrospective case-control study of all patients with cancer treated with an ICI at MSKCC 2011 – 2020

N = 13,315 → N = 410 → N = 12,905

Exclusion Criteria:
- Pancreatic cancer
- Pancreatic metastasis
- History of pancreatic surgery

Cases
Inclusion Criteria:
- Pancrelipase use after starting an ICI
- ≥ 1 symptom of EPI: steatorrhea, abdominal pain, weight loss
- Improvement of symptoms with pancrelipase

Total Cases N = 23

Controls
Matching Criteria:
- Age (+/- 5 years)
- Gender
- Race
- Cancer type
- Year of the first dose of ICI

N = 3952 eligible to be matched

Total Controls N = 46

Phenotypes of hyperglycemia defined as decline in glycemic control after the first dose of ICI
- New HgbA1c ≥ 6.5 after the start of ICI
- Initiation of new diabetes medications after ICI use

Results

- 23 patients developed ICI-related EPI and were matched to 46 controls
- Cases and controls had similar proportions of pre-existing diabetes prior to ICI use (2 (8.7%) vs 6 (13.0%), p = 0.92)
- 9 (39.1%) patients with EPI developed new hyperglycemia after ICI use vs 3 (6.5%) controls (p<0.01)
- Median time to onset of EPI: 390 days (IQR 252-578)
- Median time to onset of hyperglycemia: 518 days (IQR 178-595)
- 7 of the 9 patients (77%) developed EPI and hyperglycemia within 10 weeks of the other
- Of the EPI group, 2 patients developed new onset type 1 DM with autoantibodies, 3 patients developed acute hyperglycemia after steroid use, 2 of whom required ongoing antidiabetic agents, and 2 patients had decompensation of their pre-existing DM

Conclusions

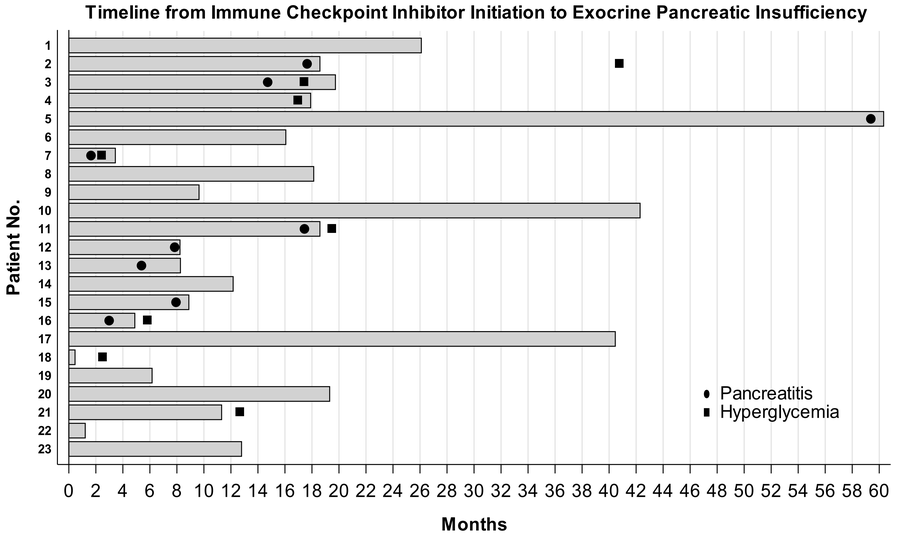
- There are multiple phenotypes of hyperglycemia that can manifest after ICI therapy
- Majority of the patients displayed loss of glycemic control within weeks of exhibiting symptoms of EPI
- Suggestive that there can be concurrent loss of endocrine and exocrine pancreatic function secondary to ICI use

Clinicians should consider exocrine pancreatic insufficiency as a distinct differential diagnosis for delayed ICI-related diarrhea and monitor for concurrent signs of hyperglycemia

Characteristics of Exocrine Pancreatic Insufficiency Patients with Hyperglycemia

Patient	Cancer Type	ICI	DM prior to ICI	Presenting Features				Recent Steroid Use	DM Agent	Type of Hyperglycemia
				Clinical	Presenting Glucose (mmol/L)	Presenting HgbA1c (%)	Autoantibodies			
55M	Melanoma	CTLA-4/PD-1	No	DKA	307	8.9	IA-2	No	Insulin	Type 1 DM
73F	Lymphoma	PD-1	No	Asymptomatic	129	6.5	NR	No	none	Unclear
62M	Genitourinary	PD-1	No	Asymptomatic	172	6.4	NR	No	PO	Type 2 DM
59M	GI/HPB	PD-L1	Yes	NA	NA	NA	NR	No	Insulin	Type 2 DM
67M	Melanoma	CTLA-4/PD-1	No	Acute Hyperglycemia	404	9.3	NR	Yes	PO	Type 2 DM
61F	Melanoma	CTLA-4/PD-1	No	Asymptomatic	NR	NR	NR	No	PO	Type 2 DM
56F	Genitourinary	CTLA-4/PD-1	No	Asymptomatic	123	7.1	NR	No	none	Type 2 DM
50F	Lung	CTLA-4/PD-1	Yes	NA	NA	NA	NR	No	Insulin + PO	Type 2 DM
57M	Lung	PD-1	No	Acute Hyperglycemia	594	9.8	None	Yes	PO	Steroid Induced hyperglycemia
47M	Melanoma	CTLA-4/PD-1	No	Acute Hyperglycemia	470	8	GAD	Yes	Insulin	Type 1 DM
68M	Sarcoma	CTLA-4/PD-1	No	Asymptomatic	131	6.5	NR	No	PO	Type 2 DM

ICI, immune checkpoint inhibitor; EPI, exocrine pancreatic insufficiency; GI, gastrointestinal; HPB, Hepato-Pancreato-Biliary; DM, diabetes; NA, not applicable due to presence of diabetes before ICI administration; NR, not reported; PO, oral; DKA, diabetic ketoacidosis



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