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Cancer Immunology Miniature

Cancer Immunology Research

Clinical Significance of Pancreatic Atrophy Induced by Immune-Checkpoint Inhibitors: A Case–Control Study

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Abstract

Immune-checkpoint inhibitor (ICI)–related diarrhea is attributed to inflammatory colitis, with no other drug-related differential diagnosis. Here, we investigated the occurrence of pancreatic atrophy (PA) in ICI-treated cancer patients and its correlation to exocrine pancreatic insufficiency (EPI). Metastatic melanoma, non–small cell lung carcinoma, and head and neck squamous cell carcinoma patients ($n = 403$) treated with anti–PD-1 ($n = 356$) or anti–CTLA-4 ($n = 47$) were divided into a case group (radiologic evidence of PA); control group matched by age, gender, and previous lines of treatment; and colitis group (ICI-induced colitis). Quantitative pancreatic volumetry was used for calculation of the decrease in pancreatic volume over time (atrophy rate). Thirty-one patients (7.7%) developed PA compared with 41 matched controls ($P = 0.006$). Four patients developed EPI, all from the anti–PD-1–treated group, which resolved with oral enzyme supplementation. The atrophy rate did not correlate with EPI ($P = 0.87$). EPI-related diarrhea presented at a median of 9 months, whereas the diarrhea of anti–PD-1–induced colitis patients ($n = 22$) was presented at a median of 2 months ($P = 0.029$). ICI-induced PA is irreversible and can result in EPI. EPI should be suspected in cases of late-onset steroid-resistant diarrhea with features of steatorrhea and treated with oral enzyme supplements. *Cancer Immunol Res; 6(12); 1453–8. ©2018 AACR.*

Introduction

Immune checkpoints are proteins that control immune cell activation and play an essential role in self-tolerance (1, 2). Commonly, tumors take advantage of these immune breaks as a mean of immune evasion (3). The two most well-known checkpoints are cytotoxic T lymphocyte antigen-4 (CTLA-4) and programmed cell death protein-1 (PD-1), which can be blocked by immune-checkpoint inhibitors (ICI). Anti–CTLA-4 (ipilimumab) has demonstrated superior clinical outcome over chemotherapy in metastatic melanoma patients (4) but is more toxic and less efficient than anti–PD-1 therapy (5). Agents blocking the PD-1 axis (anti–PD-1: nivolumab, pembrolizumab; anti–PD-L1: atezolizumab, avelumab, and durvalumab) have become the therapeutic mainstay in a rapidly growing number of cancer indications (6). To further enhance PD-1 blockade, the combinations of nivolumab with ipilimumab (7) or of pembrolizumab with chemotherapy (8) are approved for the treatment of metastatic melanoma or non–small cell lung cancer, respectively.

ICI toxicity profile is characterized by a wide variety of autoinflammatory reactions called immune-related adverse events (irAE; ref. 9). Diarrhea is a common and important irAE, which is reported in 5% to 35% of ICI-treated patients (10) and is attributed to colitis. This colitis may develop into a life-threatening condition that mandates high-dose corticosteroids, and in resistant cases, treatment with tumor necrosis factor (TNF)-α blockade. High-grade colitis often leads to cessation ICI therapy (11, 12). The only differential diagnosis to colitis suggested by current toxicity guidelines is infectious etiology (12).

In March 2016, a 37-year-old melanoma patient who underwent 9 months of anti–PD-1 therapy presented with grade 4 diarrhea. The patient had no past medical history other than melanoma. After ruling out an infectious etiology, he was clinically diagnosed as having immune-related colitis. His colitis was corticosteroid-resistant, and anti–PD-1 therapy was halted. Colonoscopy, video capsule endoscopy, proctorectography and anal sphincter electromyography, and nerve conduction studies were all concluded as normal. Blood amylase levels were normal. However, blood lipase was mildly increased 1 month after the presentation of symptoms (95 IU/L, normal value 7–60) and subsequently decreased to

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6 IU/L a year later. Revisited intake was suggestive of steatorrhea, and fecal elastase-1 was low (22 μm/g, normal values > 200), thereby confirming the diagnosis of exocrine pancreatic insufficiency (EPI). The patient was treated with oral pancreatic enzymes supplements, which resolved his symptoms. A similar case has been reported in Australia (13). Pancreatic atrophy (PA) that may result in EPI has been reported as an adverse event of tyrosine kinase inhibitors (14, 15). Here, we report on a series of 31 patients who developed PA due to therapy with different ICIs out of 403 patients treated. Four patients developed confirmed symptomatic EPI that was resolved with oral pancreatic enzymes. The clinical characteristics for practical implementation are described and analyzed here.

Materials and Methods

This single-center, retrospective case–control study was approved by the institutional review board of the Sheba Medical Center in accordance with the Declaration of Helsinki. Written informed consent was obtained wherever necessary.

Study population

The study included patients with metastatic cancers who were treated with PD-1 blocking antibodies at the Sheba Medical Center. Specifically, it included melanoma patients who were treated between October 2013 and December 2016, non–small cell lung carcinoma (NSCLC) patients treated between June 2015 and March 2017, and head and neck squamous cell carcinoma (HNSCC) patients treated between September 2015 and January 2016. Patients with metastatic melanoma treated with ipilimumab between May 2010 and December 2011 (before the anti–PD-1 era) were included as an independent group. Medical records of each patient were reviewed. The study population was divided into three groups: case, which includes patients with radiologic evidence of PA; control, which includes patients matched based on age ± 5 years, gender, and previous lines of treatment (ipilimumab, BRAF, and/or MEK inhibitors, chemotherapy) in order to minimize major confounding factors; and colitis, which includes all non-PA patients who had documented anti–PD-1–induced colitis.

Radiologic assessment

All routine follow-up CT scans were reviewed by a senior radiologist (Y. Eshet) using Carestream VuePACS (Carestream Health) software to qualitatively evaluate the pancreas for potential findings of inflammation or atrophy. PA was defined as a decrement in pancreatic width on axial images between a baseline scan (pretreatment) and the last follow-up scan. For each of the study groups, pancreatic volume was quantitated using Multimodality Tumor Tracking software (Intellispace Philips Portal) both on baseline scans and on additionally available follow-up scans. Pancreatic volumes were remeasured by another senior radiologist (S. Apter) and the same senior radiologist (Y. Eshet), both blinded to the initial measurements. Interreader, as well as intrareader, variability did not differ significantly ($P = 0.92$ and 0.99, respectively).

To standardize PA measurements, baseline pancreatic volume and radiologic follow-up time, defined as the time between baseline scan to the last available scan, must be taken into consideration. A parameter called atrophy rate was, thus, generated and defined as the proportion of decrement in pancreatic volume between the baseline and the last available scan, divided by time (number of months of radiologic follow-up):

$$\text{Atrophy rate} = \frac{\Delta\text{Pancreatic volume}/\text{Baselines pancreatic volume}}{\text{Months of radiologic follow-up}}$$

A high atrophy rate indicated a substantial volume decrement during a short time period. Atrophy rate was calculated for each patient and used for statistical analysis. Because it is still unclear what was the best way to calculate atrophy, we emphasize that this parameter was generated and determined only for the purposes of this specific study for hypothesis generation and is, therefore, not validated.

Statistical analysis

Atrophy rate and other continuous variables were compared using two-tailed Student *t* tests. Difference in atrophy rate between the cases and matched controls was assessed using conditional logistic regression. Comparison of atrophy rate, according to therapy type, was conducted using two-tailed parametric *t* tests. Intra- and interobserver agreement was assessed by paired *t* tests. Survival analysis was conducted by the Cox proportional hazard model. All statistical tests were performed with STATA (Version 15.0 for Windows). Significance was defined as a P value of < 0.05.

Results

Included in the study were 292 melanoma patients, 199 NSCLC patients, and 2 HNSCC patients treated with anti–PD-1, and 124 melanoma patients treated with ipilimumab. Of these 617 patients, 403 had consecutive CT scans available for review (356 anti–PD-1 and 47 ipilimumab). Altogether, 31 patients (27/356 anti–PD-1, 4/47 ipilimumab; 7.7%) demonstrated qualitative signs of PA. Table 1 details the clinical characteristics and patient disposition of each group.

The PA was diffuse and included all parts of the pancreas (Fig. 1A and B). Median decrement in pancreatic volume was 43% [interquartile range (IQR), 27–65] over a median of 14.5 months of radiologic follow-up (IQR, 6.5–20). PA was irreversible. The median atrophy rate was 0.043 (IQR, 0.025–0.054). By CT scan, 3 patients exhibited evidence of pancreatitis and a preliminary pancreatic volume rise prior to the atrophy (Fig. 1C). No difference in the atrophy rate between patients with initial pancreatitis to the rest of the PA group was seen (0.035 vs. 0.047, respectively; $P = 0.47$). Blood lipase and amylase are not routinely measured in our institution and were not available for analysis. Atrophy rates were significantly higher among patients treated with ipilimumab or ipilimumab + nivolumab ($n = 6$) compared with anti–PD-1–treated patients ($n = 25$, $P = 0.003$). Atrophy rates for each treatment were 0.036 for pembrolizumab (IQR, 0.025–0.05, $n = 16$), 0.028 for nivolumab (IQR, 0.027–0.045, $n = 9$), 0.058 for ipilimumab (IQR, 0.048–0.077, $n = 4$), and 0.099 for ipilimumab + nivolumab ($n = 2$).

To ascertain that PA is an ICI-related adverse event and is independent of gender, age, or previous therapy, atrophy rates among case and matched control groups were compared. Twenty-five of the PA patients could be appropriately matched

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Table 1. Characteristics of PA patients

	Melanoma (PD-1)	NSCLC	HNSCC	Melanoma (CTLA-4)
Number of patients with available CT scans	195	159	2	47
Number of patients with pancreatic atrophy	17 (8.7%)	8 (5%)	2 (100%)	4 (8.5%)
Age, median (IQR)	62 (50–65)	73 (69–75)	60.5 (60–61)	
Gender, males (%)	10 (58%)	6 (75%)	2 (100%)	2 (50%)
Tumor type	Skin: 14 (82%) Mucosal: 2 (12%) Uveal: 1 (6%)	Adenocarcinoma: 4 (50%) Compatible with adenocarcinoma: 3 (38%) SCC: 1 (12%)	SCC: 2 (100%)	Skin: 4 (100%)
Tumor's unique characteristic	BRAF mutation: Positive: 6 (35%) Negative: 9 (53%) Unknown: 2 (12%)		HPV status: Unknown: 2 (100%)	BRAF mutation: Positive: 1 (25%) Negative: 3 (75%)
Previous lines of treatments	None: 12 (70%) Ipilimumab: 4 (24%) BRAF inhibitor: 1 (6%)	None: 1 (12%) Chemo.: 7 (88%)	Chemo.: 2 (100%)	Chemo.: 4 (100%)
Current therapy				
Pembrolizumab	12 (70%)	2 (25%)	1 (50%)	—
Nivolumab	3 (18%)	6 (75%)	—	—
Nivolumab + ipilimumab	2 (12%)	—	—	—
Pembrolizumab + chemotherapy	—	—	1 (50%)	—
Ipilimumab	—	—	—	4 (100%)
% Decrement of pancreatic volume, median (IQR)	40% (27–66%)	44% (30–54%)	54% (44–65%)	45% (38–50%)
Time of radiologic follow-up, median (IQR)	18 (14–23)	8 (6–14)	9.5 (6.5–12.5)	8 (6.5–14)

Abbreviations: Chemo., chemotherapy; HPV, human papillomavirus; SCC, squamous cell carcinoma.

with a total of 41 control patients (Supplementary Table S1). Although median pretreatment pancreatic volume was similar between the PA and control groups (69.5 mL vs. 75.7 mL, respectively, $P = 0.23$), PA patients had a significantly higher atrophy rate in comparison with matched controls (conditional logistic regression coefficient, 124.5; 95% CI, 34.8–214, $P = 0.006$). Similar analysis conducted with anti–PD-1–treated patients, who had not been exposed to ipilimumab

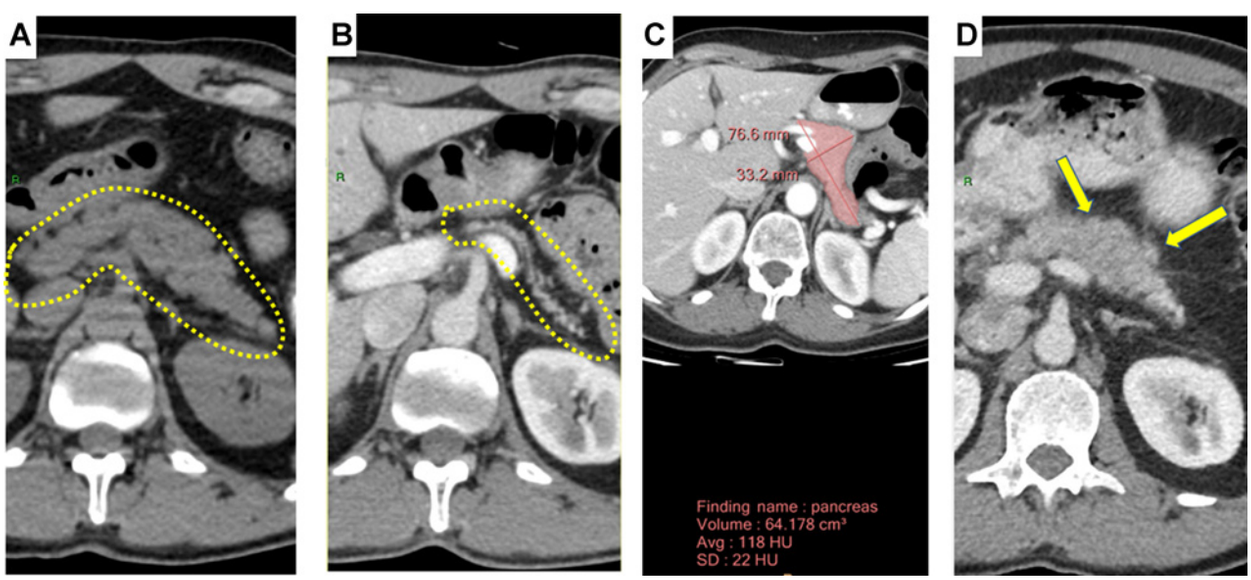

Figure 1.

Pancreatic imaging findings, analyses, and volume dynamics over time. **A,** Baseline CT scan of patient #12. Dashed line surrounds a normal pancreas with a volume of 65 mL. **B,** CT scan of the same patient 18 months after anti–PD-1 treatment initiation. Surrounded by the dashed line is an atrophic pancreas with a volume of 22 mL (volume loss 66%). **C,** Follow-up CT scan of patient #12 9 months after anti–PD-1 treatment initiation. Arrows show edema and haziness of pancreatic borders, suggestive of pancreatitis. **D,** Technique of pancreatic volumetric measurements. The pancreas area is marked on the CT scan.

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Table 2. Characteristics of patients with ICI-induced colitis

	Melanoma (PD-1)	NSCLC	HSCC	Melanoma (CTLA-4)
Number of colitis patients out of cohort	16 of 195 (8.2%)	6 of 159 (3.7%)	0 of 2 (0%)	12 of 47 (25.5%)
Age, median (IQR)	63 (57–65)	70 (63–76)	—	64 (50–67)
Gender, males (%)	6 (38%)		—	7 (58%)
Previous lines of treatments[a]	None: 7 (44%) Ipilimumab: 6 (38%) Pembrolizumab: 2 (12%) BRAF inhibitor: 1 (6%) Chemotherapy: 1 (6%)	None: 2 (33%) Chemotherapy: 7 (44%)	—	HD IL2: 3 (25%) Chemotherapy: 8 (67%) TIL: 1 (8%)
Current therapy				
Pembrolizumab	6 (38%)	2 (33%)	—	—
Nivolumab	3 (19%)	4 (67%)	—	—
Nivolumab + ipilimumab	7 (44%)	—	—	—
Ipilimumab	—	—	—	12 (100%)
Grade of diarrhea				
Grade 1	6 (38%)	0 (0%)	—	3 (25%)
Grade 2	6 (38%)	3 (50%)	—	4 (33%)
Grade 3	4 (25%)	3 (50%)	—	5 (42%)
Grade 4	0 (0%)	0 (0%)	—	0

Abbreviation: HD IL2, high-dose interleukin-2.
[a]Some colitis patients had more than one previous line of therapy.

($n = 21$), still showed a significantly higher atrophy rate in comparison with matched controls (conditional logistic regression coefficient, 127.9; 95% CI, 20.6–234, $P = 0.019$).

Among the 31 PA patients, 4 (12.9%, comprising 1% of the entire cohort) had symptoms of steatorrhea due to EPI, confirmed by low fecal elastase-1. Blood amylase and lipase measurements were available for 3 of these EPI patients. Although blood amylase concentrations remained normal, blood lipase was lower than normal in 2 EPI patients. Atrophy rate among the 4 EPI patients and the rest of the PA patients was similar (0.042 vs. 0.045, respectively, $P = 0.87$).

Because all EPI patients were from the anti–PD-1–treated group, they were compared with 22 non-PA patients who were diagnosed with anti–PD-1–induced colitis (6.2% of all patients; Table 2). Diagnosis of ICI-induced colitis was based on clinical features, CRP elevation, rapid response to steroids, and exclusion of an infectious etiology. Lower GI endoscopies were not performed. Colitis manifested at a median of 2 (IQR, 1–4.7) months from the initiation of anti–PD-1, whereas EPI manifested at a median of 9 (IQR, 8.5–11.7) months ($P = 0.029$; Fig. 2). This difference could not be explained by a time bias because both EPI and colitis patients had a similar follow-up time (17.8 vs. 21.1 months, respectively, $P = 0.62$). Steatorrhea comprised 15% of all cases of anti–PD-1–related diarrhea (4/26 patients) in this study. In line with common practice, ipilimumab induced colitis in 12 of 47 patients (25.5%), with 4 confirmed with colonoscopy.

Potential irAE correlations or clusters with PA could not be identified, probably due to the small sample size. However, it should be noted that 4 PA patients (13%) developed hepatitis, and 2 patients (6.5%) developed pneumonitis and arthritis (Supplementary Table S2). Patient #15 was the only PA patient

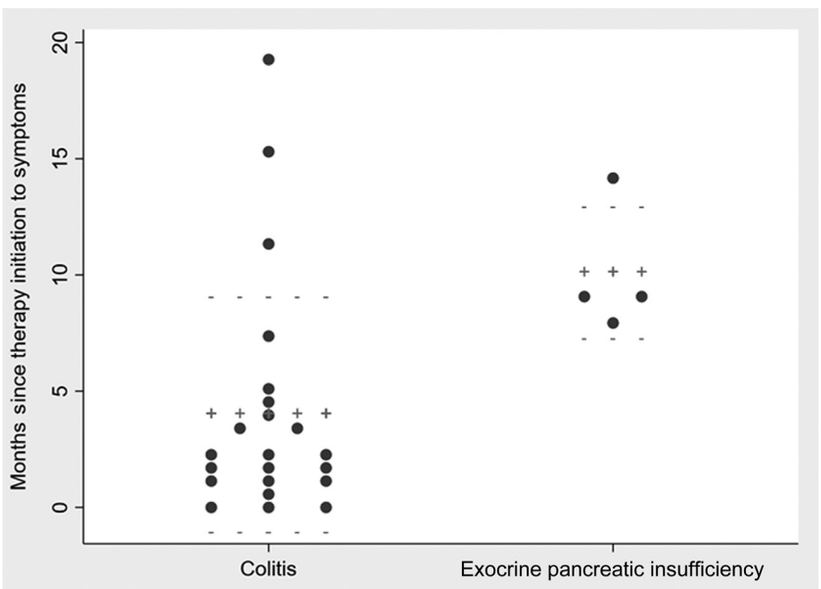

Figure 2.
Onset of diarrhea. Comparison of diarrhea onset between colitis and EPI patients. +, Mean time onset; dashed line, interquartile range.

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with evidence of endocrine pancreatic insult. She had type II diabetes mellitus, which significantly deteriorated 1 month after initiation of anti–PD-1 treatment. A trend toward reduced overall survival of PA patients compared with control patients was observed ($P = 0.056$). Within the PA patients, high atrophy rate correlated with lower overall survival ($P < 0.001$).

Discussion

The main finding of this case–control study is that ICIs, anti–CTLA-4, and –PD-1 can cause PA in 5% to 8.5% of treated patients, independent of disease, age, gender, and previous lines of therapy, suggesting that this is a class effect. It is suggested that ipilimumab could cause more severe PA than PD-1 blockade, which is consistent with its generally higher immune toxicity profile alone (5) or in combination (7). Most of the melanoma control patients also matched their paired cases in BRAF mutation status and LDH. PA may result in a symptomatic, but treatable EPI, which should be regarded as a distinct differential diagnosis for ICI-induced diarrhea. Comprising 15% of all anti–PD-1–related cases of diarrhea, EPI is infrequent, but not rare. The patients who developed the PA-associated EPI exhibited distinct clinical features: late-onset and steroid-resistant diarrhea, with clear characteristics of steatorrhea that completely resolved by supplemental oral pancreatic enzymes. EPI developed and was diagnosed only among anti–PD-1–treated patients, but not in ipilimumab-treated patients. However, this could be masked by the lower survival of this cohort of patients, creating a time bias. Consistent with reports on PA induced by kinase inhibitors (14, 15) and with an independent case report describing anti–PD-1–induced PA (13), normal blood lipase or amylase levels, which were measured for some of our EPI patients, did not exclude the diagnosis. Therefore, ICI-treated patients who develop late-onset steroid-resistant diarrhea, with evidence of PA by imaging, should be tested for fecal elastase-1 to assess the possibility of EPI.

Radiologic PA did not correlate with EPI symptoms. Similarly, a clinical-radiologic discrepancy is well documented in immune-related pneumonitis (16). In another analogy to pneumonitis, half ($n = 14$) of the PA patients presented with an additional irAE, such as hepatitis, arthritis, or pneumonitis. PA might also be a sign of poor outcome due to a trend among PA patients for lower overall survival compared with controls, and the atrophy rate is associated with shorter overall survival. Similar findings were reported in kinase inhibitor–induced PA (15). In anti–PD-1 patients, the only cutaneous irAEs are potentially associated with overall survival (17) but with improved outcome. There are no known associations between irAEs and poor outcome in patients treated with ipilimumab (18) or with ipilimumab + nivolumab (19). Further studies on larger patient cohorts are needed in order to assess the possible association between ICI-induced PA and survival.

The mechanism of ICI-induced PA is unclear. T cells that were regulated by pancreatic cell expression of PD-1 ligand (20) may have lost their inhibition. Such a mechanism was suggested to induce anti–PD-1–related type 1 diabetes mellitus (21). However, the majority of the PA patients did not exert clinical signs of pancreatitis. Among the 4 EPI patients, only one had a minor elevation in blood lipase accompanied by peripancreatic fat stranding on CT. Normal blood enzyme concentration was also described in the anti–PD-1–induced PA case report (13). PA without pancreatitis was reported as a possible toxicity of the antiangiogenic drugs sorafenib (14) and sunitinib (15), explained by potential reduction in the pancreatic endothelia and microvasculature. Endothelial expression of PD-L1 has been demonstrated in the brain (22) and heart (23, 24). In both of these organs, PD-L1 blockade showed increased $CD8^+$ T-cell antiendothelial activity. Inhibition of PD-1 has been reported to increase T-cell activity against endothelial cells in atherosclerotic lesions (25). Thus, it is possible that PA is caused by an indolent antiendothelial T-cell activity. This may explain the slow PA progression over months without signs of pancreatitis. Yet, a pure antiendothelial immune reaction does not explain the signs of pancreatitis seen in 4 PA patients, one of whom eventually developed EPI. Further mechanistic studies in animal models and in clinical samples are needed.

This study had some limitations. One hundred thirty-nine of the 493 identified anti–PD-1-treated patients (28%) and 77 of 124 (62%) ipilimumab-treated patients did not have consecutive or baseline CT scans available for review. This limits the ability to draw accurate conclusions on PA incidence. In the sunitinib-induced PA report, 64 of 168 (38%) patients did not have available scans (15). Serum lipase or amylase concentrations were unavailable for non-EPI patients. These blood tests are not performed routinely for all ICI-treated patients but were performed for the 4 patients with clinical EPI as part of their clinical testing. This, unfortunately, impeded the possibility to compare blood concentrations of pancreatic enzymes and PA progression. Inclusion of patients to the PA group was based on qualitative radiologic assessment of the pancreas in order to simplify the screening radiologic assessment. The quantitative measurements confirmed the qualitative assessment. The simplified qualitative pancreatic assessment is feasible for "real-life" radiologic evaluation of ICI-treated patients. The small cohort of EPI patients described here and the retrospective nature of study design limit accurate reflection of incidence. Four of the 31 PA patients were sequentially exposed to both ICIs. It is impossible to confidently discern exposure to which ICI accounts for the PA, even though their baseline pancreatic volume was similar to the other 27 patients ($P = 068$). Patients treated with ipilimumab + nivolumab were not well represented in this study. These issues can be investigated by revisiting the data from prospective randomized trials (5, 7, 8).

In conclusion, ICIs can induce PA, which may result in EPI. EPI should be suspected in patients with late-onset, steroid-resistant diarrhea that demonstrate PA by imaging tests. Although PA is irreversible, EPI symptoms can be readily treated with oral pancreatic enzyme supplements. It is still unclear whether early intervention with steroids can prevent EPI. Lastly, it remains to be investigated whether ICIs should be discontinued in PA patients due to the possible association with poor survival.

Disclosure of Potential Conflicts of Interest

R. Shapira-Frommer has received speakers bureau honoraria from MSD and Bristol-Myers Squibb. J. Bar reports receiving commercial research funding from AstraZeneca and MSD and is a consultant/advisory board member for MSD, Bristol-Myers Squibb, Roche, and AstraZeneca. G. Markel is Chief Scientific Officer at 4c Biomed; reports receiving commercial research funding from Novartis; has received speakers bureau honoraria from MSD, Bristol-Myers

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Squibb, Novartis, and Roche; has ownership interest in Famewave and 4c Biomed; and is a consultant/advisory board member for MSD, Bristol-Myers Squibb, and Biond Biologics. No potential conflicts of interest were disclosed by the other authors.

Authors' Contributions

Conception and design: Y. Eshet, E.N. Baruch, J. Schachter, G. Markel
Development of methodology: Y. Eshet, E.N. Baruch, B. Boursi, G. Markel
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): Y. Eshet, E.N. Baruch, R. Shapira-Frommer, Y. Steinberg-Silman, T. Kuznetsov, G. Ben-Betzalel, S. Daher, I. Gluck, N. Asher, S. Apter, J. Bar, G. Markel
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): Y. Eshet, T. Kuznetsov, G. Ben-Betzalel, S. Apter, J. Schachter, J. Bar, B. Boursi, G. Markel
Writing, review, and/or revision of the manuscript: Y. Eshet, E.N. Baruch, R. Shapira-Frommer, J. Schachter, J. Bar, B. Boursi, G. Markel
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E.N. Baruch, Y. Steinberg-Silman, T. Kuznetsov, N. Asher, G. Markel
Study supervision: J. Schachter, G. Markel

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