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Original Research

Lipase elevation and type 1 diabetes mellitus related to immune checkpoint inhibitor therapy – A multicentre study of 90 patients from the German Dermatooncology Group

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Abstract ***Aim:*** Immune checkpoint inhibition (ICI) triggers immune-related adverse events (irAEs). The relevance of lipase elevation remains unclear.
Patients and methods: Skin cancer patients with newly detected serum lipase elevation (at least twofold upper normal limit) or newly diagnosed type I diabetes mellitus upon ICI therapy were retrospectively collected at 14 German skin cancer centres.
Results: We identified 68 patients with lipase elevation occurring after a median time of 19 (range 1–181) weeks on ICI, 15 (22%) thereof had symptoms consistent with pancreatitis. Forty-seven patients (73%) had other irAE, mainly colitis. Discontinuation (n = 24, 35%) or interruption (n = 26, 38%) of ICI resulted in decrease of lipase after reinduction of ICI lipase levels increased again in 12 of 24 patients. In 18 patients (27%), ICI was continued unchanged, and in 12 (67%) of them, lipase levels normalised. Twenty-two patients were identified with newly diagnosed type I diabetes mellitus related to ICI, and 12 (55%) thereof had also lipase elevation mainly shortly before or after the diagnosis of diabetes. Fourteen (64%) patients had other irAE, mainly thyroiditis. Irrespective of lipase elevation, patients frequently showed a rapid onset with ketoacidosis, decreased c-peptide, and strongly increased blood glucose levels.
Conclusion: Increased serum lipase during ICI is often not associated with pancreatitis but with other irAE as possible cause. Therefore, it might be sufficient to regularly monitor blood glucose levels and perform further workup only in case of signs or symptoms of pancreatitis and/or exocrine pancreas insufficiency.

1. Introduction

Lipase elevation and newly diagnosed type I diabetes mellitus are regularly observed during immune checkpoint inhibition (ICI). In a recent meta-analysis by Wang et al. [1], the incidence of grade ≥3 lipase elevation was 0.73%, which represented the fourth most common grade ≥3 adverse event after fatigue, anaemia, and aspartate transaminase (AST) elevation. The incidence of (all grade) diabetes mellitus was 0.43%. This meta-analysis focused on the adverse events (AEs) during single-agent PD-1 or PD-L1 CPI. Another meta-analysis revealed an increased relative risk (RR) for lipase elevation [2]. These data were obtained from the study from Su et al. (2018). Here, compared with ipilimumab/nivolumab alone, the RR for all-grade and high-grade lipase elevation under combination treatment of nivolumab and ipilimumab was 6.43 (95% confidence interval: 1.43–28.99, p = 0.015) and 6.44 (95% CI: 1.39–29.79, p = 0.017), respectively. The frequency appears to be related to the type of ICI used. Lipase elevations were detected in 9% of patients receiving nivolumab plus ipilimumab and 2% of patients receiving ipilimumab monotherapy [3,4]. Also, the incidence of diabetes mellitus appears to be higher in patients receiving nivolumab plus ipilimumab (0.5%) compared with monotherapy with PD-1 inhibitors (0.3%) [5].

Although type I diabetes mellitus related to ICI is diagnosed and treated as type I diabetes occurring in patients without ICI, the clinical and therapeutic relevance of lipase elevation is unclear. Current guidelines either do not mention lipase elevation [6,7] or do not recommend lipase monitoring unless pancreatitis is clinically suspected [8,9] or do recommend regular lipase monitoring [5,10].

To get more insight into the relevance of lipase elevations during ICI, we conducted a case series in our German Dermatologic Cooperative Oncology Group (DeCOG) network of patients with at least >2.0× upper limit normal (ULN) lipase elevation or with newly diagnosed type I diabetes mellitus.

2. Methods

2.1. Study design

We performed a retrospective multicentre study within the DeCOG. The ethics committee of Hannover Medical

School granted approval for the retrospective collection of data from melanoma patients (vote number 1612). The patients were selected according to the following criteria: checkpoint inhibitor therapy for advanced skin cancer (with PD-1, CTLA4, or PD-L1 inhibitors alone or in combination) and development of lipase elevation (at least 2× ULN) or newly diagnosed type I diabetes mellitus related to ICI.

2.2. Data collection

Eligible patients were localised retrospectively by the participating centres, and the centres were asked to provide patient data meeting the inclusion and exclusion criteria mentioned previously. The period was not fixed. Anonymised data were collected in a standardised way, including demographics (age, sex), tumour characteristics (such as type and stage of tumour, ECOG performance status), the checkpoint inhibitor therapy given type of inhibitor, date of therapy start and best response according to RECIST 1.1 criteria [11] (graded into complete response [CR], partial response, stable disease, and progressive disease). The details on the lipase elevation and diabetes (onset, amylase, treatment, detection of glutamic acid decarboxylase 65 autoantibodies, insulinoma antigen 2 autoantibodies, insulin autoantibodies, and islet cell autoantibodies, C-peptide and haemoglobin A1c levels) were collected. Evidence of pancreatitis, which was defined as characteristic symptoms of severe epigastric pain and/or radiographic signs (such as oedematous swelling of the pancreas) in addition to the lipase elevation, was recorded [14]. Moreover, the occurrence of other irAE was also recorded. The lipase and amylase elevation was graded according to Common Terminology Criteria for Adverse Events Version 4.03 graded lipase elevations as grade 1 if >ULN to 1.5× ULN, grade 2 > 1.5–2× ULN, grade 3 >2–5× ULN, and grade 4 >5× ULN [12].

Statistical analyses were performed by applying the chi-square test, Fisher's exact test, and two-tailed t test. Mann–Whitney *U* and Kruskal–Wallis tests were used

Table 1
Comparison of patients with lipase elevation with and without signs and symptoms of pancreatitis.

		Symptomatic lipase elevation (n = 15)	Asymptomatic lipase elevation (n = 53)	p value
Age (years)	Median (range)	60.5 (33–79)	57.3 (20–90)	0.468
Sex	Male (%)	9 (60%)	24 (45%)	0.314
	Female (%)	6 (40%)	29 (55%)	
ICI	PD1 inhibitor (%)	5 (33%)	24 (45%)	0.582
	Ipilimumab (%)	0	1 (2%)	
	PD1 + ipilimumab (%)	10 (67%)	19 (36%)	
	Other (%)	0	9 (17%)	
Tumour	Melanoma (%)	14 (93%)	49 (92%)	0.176
	Uveal melanoma (%)	1 (7%)	3 (6%)	
	Merkel cell carcinoma (%)	0	1 (2%)	
Best response	CR (%)	3 (20%)	8 (15%)	0.404
	PR (%)	5 (33%)	17 (32%)	
	SD (%)	3 (20%)	6 (11%)	
	PD (%)	4 (27%)	9 (17%)	
	Adjuvant	0	3 (6%)	
	Unknown	0	10 (19%)	
Interval from start of ICI to lipase elevation	Median (range), weeks	30.9 (2–181)	16.3 (1–130)	0.163
Extent lipase elevation	Median (X-fold ULN)	16.8	7.8	**0.003**
	Minimum to maximum (X-fold ULN)	2.2–48.3	2.0–55.0	
Amylase elevated	Yes (%)	14 (93%)	40 (75%)	0.315
	No (%)	1 (7%)	12 (23%)	
	Unknown (%)	0	1 (2%)	
Other irAE	Yes (%)	11 (73%)	38 (72%)	0.889
	No (%)	4 (27%)	15 (28%)	
Treatment lipase elevation	Steroids (%)	13 (87%)	23 (43%)	**0.008**
	Other (%)	1 (6.5%)	3 (6%)	
	None (%)	1 (6.5%)	27 (51%)	
Change of ICI because of lipase	None (%)	1 (7%)	17 (32%)	**0.004**
	Interruption (%)	3 (20%)	23 (44%)	
	Discontinuation (%)	11 (73%)	13 (24%)	

CR, complete response; ICI, Immune checkpoint inhibition; irAE, immune-related adverse event; PD, progressive disease; PR, partial response; SD, stable disease.
Significant p-values are indicated in bold (significance considered $p < 0.05$).

as non-parametric tests where appropriate using SPSS (IBM, version 26). A p value <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics

A total of 68 patients were identified with lipase elevation at least 2× ULN. They received ICI mainly for cutaneous melanoma, one patient for Merkel cell carcinoma, and five patients for uveal melanoma. The median follow-up for these patients from the start of ICI was 52 weeks (the interquartile range [IQR] 32.5–91 weeks). The ICI regimen was mainly PD-1 inhibitor based (in 29/68 patients either nivolumab or pembrolizumab monotherapy, in 29/68 patients plus ipilimumab). One patient received ipilimumab monotherapy, nine patients received other therapies, either within blinded clinical studies (where either PD-1 inhibitor plus placebo or another drug was given) or avelumab for Merkel cell carcinoma in one patient.

Table 2
Comparison of patients with elevated lipase versus patients with elevated lipase plus newly diagnosed type I diabetes mellitus.

		Lipase elevated (n = 68)	Lipase elevated plus diabetes (n = 12)	p value
Age (years)	Median (range)	58.1 (20–90)	61.4 (32–77)	0.500
Sex	Male (%)	33 (48.5%)	6 (50%)	0.925
	Female (%)	35 (51.5%)	6 (50%)	
ICI	PD1 inhibitor (%)	29 (42.5%)	5 (42%)	0.844
	Ipilimumab (%)	1 (2%)	1 (8%)	
	PD1 + ipilimumab (%)	29 (42.5%)	4 (33%)	
	Other/unknown (%)	9 (13%)	2 (17%)	
Tumour	Melanoma (%)	62 (91%)	11 (92%)	0.564
	Uveal melanoma (%)	5 (7%)	1 (8%)	
	Merkel cell ca. (%)	1 (2%)		
Best response	CR (%)	11 (16%)	2 (17%)	0.451
	PR (%)	22 (32%)	2 (17%)	
	SD (%)	9 (13%)	2 (17%)	
	PD (%)	13 (19%)	1 (8%)	
	Adjuvant	3 (4%)	3 (25%)	
	Unknown	10 (14%)	2 (16%)	
Interval from start of ICI to lipase elevation	Median (range) weeks	19.6 (1–181)	19,3 (1–67)	0.737
Extent lipase elevation	Mean (X-fold ULN)	9.8	6.8	0.369
	Median (X-fold ULN)	6.4	4.6	
	Minimum to maximum (X-fold ULN)	2.0–55.0	1.1–30.0	
Amylase elevated	Yes (%)	54 (79%)	6 (50%)	0.067
	No (%)	13 (19%)	5 (42%)	
	Unknown (%)	1 (2%)	1 (8%)	
Other irAE	Yes	49 (72%)	8 (67%)	0.726
	No	19 (28%)	4 (33%)	
Type other irAE	Thyroiditis	6 (9%)	4 (33%)	
	Transaminases elevated	10 (15%)	4 (33%)	
	Nephritis	8 (12%)	1 (8%)	
	Rash/vitiligo	6 (9%)	1 (8%)	
	Hypophysitis	19 (28%)	1 (8%)	
	Colitis/gastrointestinal	1 (2%)		
	CK elevation	2 (3%)		
	Sjögren syndrome	1 (2%)		
	Pneumonitis	1 (2%)		
	Sarcoidosis	1 (2%)		
	Arthritis			
Treatment lipase elevation	Steroids (%)	36 (53%)	4 (33%)	0.227
	Other (%)	4 (6%)	0	
	None (%)	28 (41%)	8 (67%)	
Change of ICI due to lipase	None (%)	18 (26%)	1 (8%)	0.101
	Interruption (%)	26 (38%)	4 (33%)	
	Discontinuation (%)	24 (36%)	6 (50%)	
	Unknown (%)		1 (8%)	

CR, complete response; ICI, Immune checkpoint inhibition; irAE, immune-related adverse event; PD, progressive disease; PR, partial response; SD, stable disease.

Lipase elevation was in median 6.4× ULN (range 2.0–55.0) and developed after a median of 19 weeks on ICI (range 1–181 weeks). In 15 patients (22%), signs and symptoms consistent with pancreatitis were reported, and 53 patients (78%) were asymptomatic.

Because of lipase elevation, ICI was discontinued in 24 patients (35%; in two patients also because of PD and in one patient also because of CR), and lipase elevation declined to grade 0/1 after discontinuation. In 26 patients (38%), ICI was interrupted until lipase dropped to grade 0/1, and after reinduction of ICI, lipase elevation recurred again in 12 of 26 patients. In 18 patients (27%), ICI was continued without change; in 12 of these patients (67%), lipase levels normalised without intervention; and in six patients (33%), the lipase levels continued to be increased. Of these six patients, three had lipase elevations grade 2 (2.0-fold ULN), three had lipase elevations grade 3 (2.1–2.5-fold ULN). Thus, the elevation was only moderate. Twenty-two patients with newly diagnosed type I diabetes mellitus were registered. Those patients received ICI for cutaneous melanoma (21 patients) or uveal melanoma (one patient).

The median follow-up in these patients from the start of ICI was 73.5 weeks (IQR 49–116 weeks). The

Table 3
Comparison of patients with newly diagnosed type I diabetes mellitus with and without elevated lipase.

		Diabetes plus lipase elevated (n = 12)	Diabetes without lipase elevated (n = 10)	p value
Age (years)	Median (range)	61.4 (32–77)	55.1 (31–75)	0.336
Sex	Male (%)	6 (50%)	4 (40%)	0.639
	Female (%)	6 (50%)	6 (60%)	
ICI	PD1 inhibitor (%)	5 (42%)	9 (90%)	0.163
	Ipilimumab (%)	1 (8%)	0	
	PD1 + ipilimumab (%)	4 (33%)	0	
	Other	2 (17%)	1 (10%)	
Tumour	Melanoma (%)	11 (92%)	10 (100%)	
	Uveal melanoma (%)	1 (8%)		
Best response	CR (%)	2 (17%)	2 (20%)	0.872
	PR (%)	2 (17%)	2 (20%)	
	SD (%)	2 (17%)	1 (10%)	
	PD (%)	1 (8%)	3 (30%)	
	Adjuvant	3 (25%)	2 (20%)	
	Unknown	2 (17%)		
Interval from start of ICI to lipase elevation	Median (range) weeks	19.3 (1–67)		
Interval form start of ICI to diabetes	Median (range) weeks	20.3 (3–53)	36.8 (1–83)	0.159
Amylase elevated	Yes (%)	6 (50%)	1 (10%)	0.073
	No (%)	5 (42%)	5 (50%)	
	Unknown (%)	1 (8%)	4 (40%)	
C-peptide reduced	Yes (%)	6 (50%)	4 (40%)	0.421
	No (%)	3 (25%)	1 (10%)	
	Unknown (%)	3 (25%)	5 (50%)	
HbA1c elevated	Yes (%)	9 (75%)	7 (70%)	0.528
	No (%)	1 (8%)	3 (30%)	
	Unknown (%)	2 (17%)		
Autoantibodies detectable	Yes (%)	3 (25%)	5 (50%)	0.179
	No (%)	3 (25%)	5 (50%)	
	Unknown (%)	6 (50%)		
Ketoacidosis	Yes (%)	3 (25%)	8 (80%)	**0.030**
	No (%)	7 (58%)	1 (10%)	
	Unknown (%)	2 (17%)	1 (10%)	
Other irAE	Yes	8 (67%)	6 (60%)	0.346
	No	4 (33%)	4 (40%)	
Type other irAE	Thyroiditis	4 (33%)	4 (40%)	
	Transaminases elevated	4 (33%)	1 (10%)	
	Nephritis	1 (8%)	1 (10%)	
	Rash/vitiligo	1 (8%)		
	Hypophysitis	1 (8%)		
Change of ICI because of lipase	None (%)	1 (8%)	3 (30%)	0.337
	Interruption (%)	4 (33%)	1 (10%)	
	Discontinuation (%)	6 (50%)	4 (40%)	
	Unknown (%)	1 (8%)	2 (20%)	

CR, complete response; ICI, Immune checkpoint inhibition; irAE, immune-related adverse event; PD, progressive disease; PR, partial response; SD, stable disease.
Significant p-values are indicated in bold (significance considered $p < 0.05$).

patients received mainly PD-1 inhibitor–based ICI (14/22 patients nivolumab or pembrolizumab monotherapy and 4/22 patients plus ipilimumab); 1 of 22 patients received ipilimumab monotherapy; and in 3 of 22 patients, the exact schedule was unknown because of a blinded clinical study combining a PD-1 inhibitor with placebo or another substance.

Type I diabetes mellitus was diagnosed after a median of 22 (range 1–83) weeks on ICI. All patients were treated with insulin.

Blood amylase levels were also recorded and, in majority of our patients, increased, but later and not as strong as the lipase levels (Table 2). There was only one diabetes patient (1%) with an isolated amylase elevation without lipase elevation, whereas 18 of 78 patients (23%) with increased lipase levels did not show increased amylase (Table 2).

3.2. Patients with lipase elevation with and without clinical symptoms of pancreatitis

Fifteen patients (22%) with clinical signs and symptoms consistent with pancreatitis were compared with 53 asymptomatic patients (78%; Table 1). In symptomatic patients, the extent of lipase elevation was significantly higher (16.8× ULN versus 7.8× ULN; $p = 0.003$), corticosteroids were used significantly more often ($p = 0.008$), and ICI was significantly more often interrupted or discontinued in symptomatic patients ($p = 0.004$). In all patients, symptoms normalised with adequate treatment, and there was no case of chronic pancreatitis reported.

3.3. Patients with lipase elevation with and without diabetes

Sixty-eight patients with increased lipase only were compared with 12 patients with increased lipase and type I diabetes (Table 2). No significant differences were detected between both groups; in particular, the interval from the start of ICI to the detection of lipase elevation was very similar with about 19 weeks. In patients with diabetes and lipase elevation, the most common additional irAE (33%) was thyroiditis; in patients with lipase elevation without diabetes, it was colitis and other gastrointestinal irAE (28%). The diagnosis of diabetes

Table 4
Comparison of patients with elevated lipase with and without other irAE.

		Other irAE (n = 47)	No other irAE (n = 21)	p value
Age (years)	Median (range)	56 (20–86)	62 (37–90)	0.547
Sex	Male (%)	20 (43%)	13 (62%)	0.140
	Female (%)	27 (57%)	8 (38%)	
ICI	PD1 inhibitor (%)	16 (34%)	13 (62%)	0.148
	Ipilimumab (%)	1 (2%)		
	PD1 + ipilimumab (%)	22 (47%)	7 (33%)	
	Other/unknown	8 (17%)	1 (5%)	
Tumour	Melanoma (%)	43 (92%)	19 (90%)	0.725
	Uveal melanoma (%)	3 (6%)	2 (10%)	
	Merkel cell carcinoma	1 (2%)	0	
Best response	CR (%)	7 (15%)	4 (19%)	0.157
	PR (%)	11 (23%)	11 (52%)	
	SD (%)	8 (17%)	1 (5%)	
	PD (%)	10 (21%)	3 (14%)	
	Adjuvant	2 (4%)	1 (5%)	
	Unknown	9 (19%)	1 (5%)	
Interval from start of ICI to lipase elevation (weeks)	Mean	16.8	21.1	0.248
	Median	9	22	
	Range	1–181	1–91	
Extent lipase elevation	Mean (X-fold ULN)	9.9	9.5	0.889
	Median (X-fold ULN)	6.8	6.1	
	Min-Max (X-fold ULN)	2–55	2–43.1	
Amylase elevated	Yes (%)	38 (81%)	16 (76%)	0.32
	No (%)	9 (19%)	4 (19%)	
	Unknown (%)		1 (5%)	
Treatment lipase elevation	Steroids (%)	25 (53%)	11 (52%)	0.129
	Other (%)	1 (2%)	3 (14%)	
	None (%)	21 (45%)	7 (33%)	
Change of ICI because of lipase	None (%)	14 (30%)	4 (19%)	0.647
	Interruption (%)	17 (36%)	9 (43%)	
	Discontinuation (%)	16 (34%)	8 (38%)	

CR, complete response; ICI, Immune checkpoint inhibition; irAE, immune-related adverse event; PD, progressive disease; PR, partial response; SD, stable disease.

more often resulted in interruption or discontinuation of ICI (p = 0.101).

3.4. Patients with diabetes with and without lipase elevation

Twelve patients with diabetes and lipase elevation were compared with ten patients with diabetes without lipase elevation (Table 3). Lipase elevation occurred in median only 1 week before diagnosis of diabetes; in one patient, lipase elevation was noted after the diagnosis of diabetes. As compared with diabetes patients without lipase elevation, diabetes patients with lipase elevation had significantly less frequently ketoacidosis (p = 0.03). In addition, there were trends that in patients with lipase elevation, the diabetes mellitus occurred earlier during ICI (p = 0.159), amylase was also elevated (p = 0.073), and ipilimumab-containing regimens were used more often (p = 0.163).

3.5. Patients with other irAE

Patients with elevated lipase (Table 4) and diabetes (Table 5) developed other irAE in approximately 70%. Patients with type I diabetes mellitus with other irAE were significantly older than those without other irAE (Table 5). In both groups, there was a trend that patients receiving an ipilimumab-containing regimen had more often other irAE than patients with PD1 inhibitor monotherapy (Tables 4 and 5).

The spectrum of other irAE was quite different between patients with elevated lipase and diabetes patients.

Table 5
Comparison of patients with diabetes with and without other irAE.

		Other irAE (n = 14)	No other irAE (n = 8)	p value
Age (years)	Median (range)	68 (50–77)	54.5 (31–70)	**0.028**
Sex	Male (%)	6 (43%)	6 (75%)	0.145
	Female	8 (57%)	2 (25%)	
ICI	PD1 inhibitor (%)	7 (50%)	7 (87.5%)	0.057
	Ipilimumab (%)		1 (12.5%)	
	PD1 + ipilimumab (%)	4 (29%)		
	Other/unknown	3 (21%)		
Best response	CR (%)	2 (14%)	2 (25%)	0.446
	PR (%)	3 (21%)	1 (12.5%)	
	SD (%)	1 (7%)	1 (12.5%)	
	PD (%)	0	2 (25%)	
	Adjuvant	5 (38%)	1 (12.5%)	
	Unknown	3 (21%)	1 (12.5%)	
Interval from start of ICI to lipase elevation (weeks)	Mean	18.1	22.3	0.781
	Median	10	17	
	Range	1–67	10–40	
Interval from start of ICI to diabetes (weeks)	Mean	24.6	35.2	0.364
	Median	16.5	36.5	
	Range	3–38	1–66	
Amylase elevated	Yes (%)	5 (36%)	2 (25%)	1
	No (%)	5 (43%)	4 (50%)	
	Unknown (%)	3 (21%)	2 (25%)	
C-peptide reduced	Yes (%)	7 (50%)	3 (37.5%)	0.616
	No (%)	3 (21%)	1 (12.5%)	
	Unknown (%)	4 (29%)	4 (50%)	
HbA1c elevated	Yes (%)	11 (79%)	5 (62.5%)	0.571
	No (%)		1 (12.5%)	
	Unknown (%)	3 (21%)	2 (25%)	
Autoantibodies detectable	Yes (%)	2 (14%)	1 (12.5%)	0.705
	No (%)	4 (29%)	4 (50%)	
	Unknown (%)	8 (57%)	5 (37.5%)	
Ketoacidosis	Yes (%)	7 (50%)	4 (50%)	0.597
	No (%)	6 (43%)	2 (25%)	
	Unknown (%)	1 (7%)	2 (25%)	
Treatment lipase elevation	Steroids (%)	3 (21%)	1 (12.5%)	0.601
	None (%)	11 (79%)	7 (87.5%)	
Change of ICI because of lipase	None (%)	2 (14%)	2 (25%)	0.389
	Interruption (%)	2 (14%)	3 (37.5%)	
	Discontinuation (%)	7 (50%)	3 (37.5%)	
	Unknown (%)	3 (22%)		

CR, complete response; ICI, Immune checkpoint inhibition; irAE, immune-related adverse event; PD, progressive disease; PR, partial response; SD, stable disease.
Significant p-values are indicated in bold (significance considered p < 0.05).

Although 28% of patients with elevated lipase had colitis and other gastrointestinal irAE, followed by elevated transaminases (15%), rash/vitiligo (12%), thyroiditis (9%), and hypophysitis (9%), diabetes patients had more often thyroiditis (36%), followed by increased transaminases (23%), nephritis (9%), rash/vitiligo (4.5%), and hypophysitis (4.5%), but no gastrointestinal irAE (Tables 2 and 5, Fig. 1).

4. Discussion

The relevance of lipase elevation during ICI is unclear. Thus, we retrospectively collected and analysed cases from our DeCOG network. Moreover, we also collected patients with newly diagnosed type I diabetes mellitus related to ICI.

We show that in most patients with elevated lipase, amylase also is increased, but the onset is later and less frequent. There was only one case of type I diabetes mellitus with solely increased amylase but normal lipase levels. This confirms a previous observation in 119 patients receiving nivolumab plus ipilimumab, who showed elevation of lipase in 26.9% (grade ≥3) and of amylase in 8.4% (grade ≥3) [13]. Thus, the monitoring of both lipase and amylase is not necessary; in fact, lipase only is sufficient.

However, the main question is if regular monitoring of lipase is necessary during ICI therapy at all. This would be useful if pancreatitis or diabetes mellitus could be detected early or prevented.

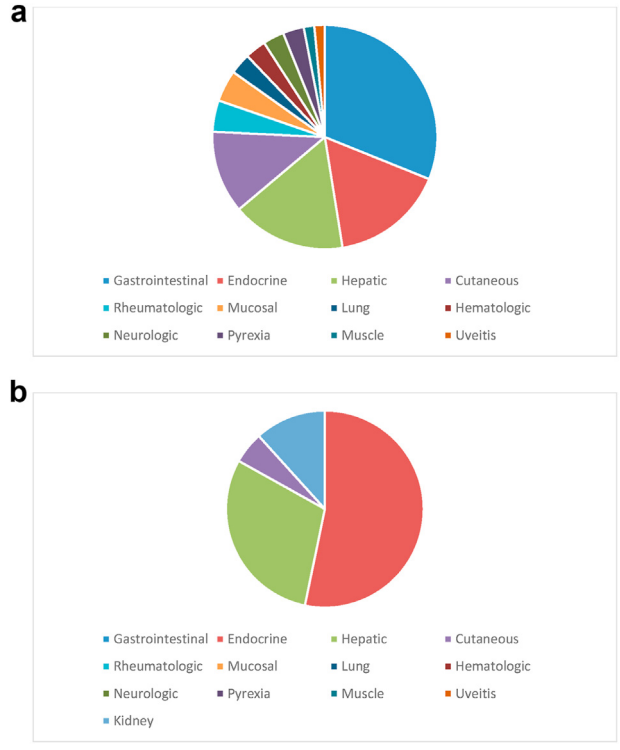

Fig. 1. Other irAE in patients with elevated lipase (A) or diabetes (B). Percentage of patients with involvement of the respective organ system depicted.

In 22% of patients with lipase elevation, this elevation was accompanied by signs and symptoms of pancreatitis. In other patients, no signs and symptoms of pancreatitis were detected by clinical and/or radiological investigations. One explanation could be that lipase can also be elevated because of extrapancreatic causes such as inflammation of the gastrointestinal tract like inflammatory bowel disease or infectious colitis, liver injury, renal impairment, and sarcoidosis [14,15] or even in the absence of pathologic findings [16]. In 72% of our patients with increased lipase, other irAE occurred, mainly of the gastrointestinal tract. Therefore, it is possible that the increased lipase is not because of pancreatitis but because of inflammation of other organs. In this case, lipase increase could be even misleading by directing the attention to the pancreas. Moreover, after interruption of ICI, lipase levels dropped in most cases and also in some patients where ICI was continued because the lipase elevation was asymptomatic.

Also, exocrine pancreatic insufficiency was described in association with checkpoint inhibitor therapy. A case–control study found four patients with exocrine pancreatic insufficiency in 403 patients treated with CPI [17]. The lipase and amylase levels were normal in these patients; there was only a minor lipase elevation in one patient. Two more case reports with exocrine pancreatic insufficiency occurring during CPI also described normal lipase and amylase levels [18,19].

Type I diabetes mellitus was diagnosed in 11 of 12 patients within 1 week after increased lipase was noted; in 1 of 12 patients, lipase increased after diagnosis of diabetes mellitus. On the other hand, type I diabetes mellitus also occurred without increase in lipase. A recent review of published patients with diabetes associated with ICI revealed similar results compared with our series [20]: 52% (13/25 patients) had elevated lipase (in our study 55%, 12/22 patients), and thyroiditis was the most common additional irAE.

We found that type I diabetes mellitus related to ICI frequently showed a rapid onset. Although diabetes patients without lipase elevation commonly presented with ketoacidosis, at later time points after initiation of ICI and without autoantibodies, diabetes patients with lipase elevation showed rarely ketoacidosis, occurred at an earlier time point, developed more often autoantibodies and amylase elevation, and had been more often treated with ipilimumab.

In our lipase group, 44.5% of patients received an ipilimumab-including regimen; in the diabetes group, 23% of patients received an ipilimumab-including regimen.

The mean duration of ICI until the onset of type I diabetes was 22.1 weeks (1.9–72.0 weeks) in a study of 22 Japanese patients [21], which is very similar to our

data (median 22 weeks, range 1–83 weeks). This study also showed similarities between fulminant onset type I diabetes in some patients and with acute onset in others. They suggested the term 'anti-PD-1 antibody-related (type 1) diabetes'. In our view, more data are necessary to investigate if different subtypes of diabetes are triggered by ICI.

Taken together, our study provides evidence that regular lipase monitoring during ICI is not helpful for early detection of pancreatitis and diabetes mellitus and that lipase elevation is probably often because of extrapancreatic causes. Therefore, it might be sufficient to regularly monitor blood glucose levels and perform further workup only in case of signs or symptoms of pancreatitis and/or exocrine pancreas insufficiency. As our study has the limitations of a retrospective study, such as a possible selection bias, as well as limited information on the individual course of clinics and lipase elevation, further ideally prospective studies with higher numbers of patients are needed to improve standard recommendations.

Authors' contributions

R.G. and I.G. contributed to study concepts and design. R.G., I.G., and C.K. contributed to Data acquisition: All authors.

quality control of data and algorithms. R.G. and I.G. prepared the article. All authors contributed to data acquisition, data analysis and interpretation, editing and reviewing the article, and final approval of article.

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