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PRACTICE

Frequency and imaging features of abdominal immune-related adverse events in metastatic lung cancer patients treated with PD-1 inhibitor

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Abstract

Purpose To investigate the frequency and imaging features of radiographically evident abdominal immune-related adverse events (irAEs) in patients with metastatic non-small-cell lung cancer (NSCLC) treated with PD-1 inhibitors.

Methods This retrospective study included 137 patients with metastatic NSCLC treated with PD-1 inhibitor nivolumab monotherapy (75 women; median age: 65 years), who had a baseline CT and at least one follow-up abdomen CT during therapy. Baseline and all follow-up abdominal CTs performed for monitoring of nivolumab therapy were reviewed to identify the organ-specific abdominal irAEs including colitis/enteritis, hepatitis, biliary toxicity, pancreatitis, nephritis, sarcoid-like reaction, and pancreatic and adrenal atrophy. Their frequency and imaging features were described.

Results Eighteen (13%) patients had radiologically identified abdominal irAEs (median 2.1 months after starting nivolumab; interquartile range 1.17–5.83 months); 16 patients developed enteritis/colitis (12 pancolitis, two segmental colitis, one enterocolitis, one enteritis), two hepatitis, one adrenalitis. One patient with hepatitis also developed colitis/enteritis. Radiographic abdominal irAE occurred after nivolumab therapy was discontinued in six patients before any subsequent therapy was started. IrAEs prompted nivolumab interruption and treatment with steroids in four patients (three colitis/enteritis, one hepatitis). Most common CT features of colitis/enteritis included mesenteric hyperemia ($n = 15$), bowel wall thickening ($n = 13$), mucosal hyperenhancement ($n = 10$), and fluid-filled colon ($n = 9$).

Conclusion Abdominal irAEs were detected on CT in 13% of NSCLC patients treated with nivolumab, and colitis, in the pancolitis form, was the most common irAE. Given the expanding role of immunotherapy, radiologists should be aware of the frequency and imaging manifestations of abdominal irAEs and the impact on patient management.

Keywords Adverse drug event · Computed tomography · Nivolumab · Carcinoma · Non-small-cell lung · Programmed cell death 1 receptor

Introduction

Programmed death-1 inhibitors (PD-1), a group of immune checkpoint inhibitors, are currently approved by the Food and Drug Administration (FDA) for use in various cancers, including non-small cell lung cancer (NSCLC), melanoma, renal cell carcinoma, and are undergoing clinical trials in several other tumors [1, 2]. Their antitumor activity is based on the inhibition of the PD-1, a receptor expressed on regulatory and effector T cells whose role is to suppress the activation of T cells, when activated by its circulating ligands [3, 4]. When PD-1 receptors are blocked, T cells initiate an inflammatory response against any susceptible tissue, including healthy tissues, leading to a spectrum of potential

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autoimmune-like adverse events, termed immune-related adverse events (irAEs) [5, 6]. Immune-related adverse events occur in more than 70% of patients [7, 8].

Imaging has become an indispensable component in the evaluation of patients treated with immune checkpoint inhibitors, both to assess for treatment response, and to identify irAEs [9, 10]. Timely detection of irAEs on imaging is essential for patient management and adequate therapeutic decisions [10, 11]. Abdominal irAEs represent the most common sites of grade III–IV irAE, with gastrointestinal and liver toxicities, occurring respectively in 4–13% and 4–5% of patients, being the most common irAEs leading to discontinuation of the drug [7, 10]. Since a variety of PD-1/PD-L1 inhibitors are increasingly being used to treat several common malignancies, it is essential for the radiologists to be aware of the radiologically seen abdominal irAEs.

Among the various cancers treated with PD-1 inhibitors, metastatic NSCLC has shown increased progression free and overall survival compared to chemotherapy both as a first-line treatment and in previously treated patients, which has led to FDA approval of nivolumab, a PD-1 inhibitor, for the treatment of NSCLC in 2015 in patients who progressed during or after platinum-based chemotherapy [1, 8].

The purpose of the present study was to investigate the frequency and imaging features of radiographically evident organ-specific irAEs of the abdomen in metastatic NSCLC patients treated with PD-1 inhibitors. We studied this in patients with metastatic NSCLC treated with nivolumab as NSCLC is one of the most common malignancies and at present this subgroup of patients represents a large proportion of patients treated with PD-1 inhibitors in our clinical practice at a large tertiary cancer center. However, the conclusions of this study may also be applicable to other cancers being treated with PD-1 inhibitors.

Materials and methods

Patients

The study population included 137 patients (75 women, 62 men; median age 65 years) with metastatic NSCLC treated with nivolumab as a part of their standard clinical care between January 2015 and May 2017 who had a baseline abdomen/pelvis CT or whole body ^{18}F-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET)/CT, and at least one follow-up abdomen/pelvis CT or FDG-PET/CT performed either during or after nivolumab therapy before starting the subsequent systemic therapy. All imaging studies performed after nivolumab discontinuation before the start of the next therapy were included as PD-1 inhibitors as irAEs can occur months or even years after treatment discontinuation [12, 13].

A total of 448 abdominal imaging studies were evaluated (353 CT and 95 FDG-PET/CT), composed of 137 baseline imaging studies, and 311 follow-up studies (median number of scans per patient: 2, including baseline imaging studies). Of the 353 CT abdomen and pelvis evaluated, 33 (9%) were performed without intravenous contrast media administration. All 95 FDG-PET/CTs were performed without intravenous contrast injection.

The imaging studies and medical records were retrospectively reviewed with the approval from the institutional review board in this Health Insurance Portability and Accountability Act-compliant study. All patients provided written informed consent.

Imaging studies and analysis

Due to the retrospective nature of the study, the imaging parameters and protocols varied among included patients. All cross-sectional imaging studies met the following minimum criteria: CT scans of the abdomen and pelvis were obtained on multidetector scanners (4–128 detectors) with intravenous contrast agent unless medically contraindicated. Axial (≤ 5-mm thickness) and coronal (≤ 4-mm thickness) images were reviewed on Picture Archiving Communication System (PACS; Centricity; GE Healthcare, Chicago, IL), or whole-body ^{18}F-FDG-PET was performed approximately 60 min after i.v. administration of ^{18}F-FDG and noncontrast CT imaging were performed without breath-hold. Axial images (≤ 5 mm thickness) were reviewed on PACS.

All imaging studies were initially reviewed by a cancer imaging-fellowship-trained radiologist (X1.X1.) blinded to all clinical information except diagnosis of NSCLC and treatment with nivolumab. For each patient, the baseline and all follow-up scans after starting nivolumab therapy before initiation of the next systemic therapy were reviewed to identify the development of organ-specific abdominal irAEs. Likelihood of irAE was scored using a 5-point scale: 1, definitely not irAE; 2, probably not irAE; 3, equivocal; 4, probable irAE; and 5, definite irAE [14].

The irAEs evaluated were categorized into one of the following categories if they displayed the imaging features reported in Table 1, in part based on previous papers describing imaging features of irAEs: (1) Colitis/enteritis [10, 14]. Cases of colitis/enteritis were subclassified into: (i) pancolitis, (ii) segmental colitis associated with diverticulosis (SCAD) restricted to a segment of colon with diverticulosis, (iii) enterocolitis, (iv) enteritis [6, 10, 14]; (2) hepatitis [15–18]; (3) pancreatitis [10, 19]; (4) biliary toxicity [20]; (5) nephritis [21, 22]; (6) adrenalitis [23, 24]; (7) sarcoid-like reaction [10, 25]; (8) pancreatic atrophy [26, 27]; (9) adrenal atrophy [26]. We included adrenal atrophy since this may occur as a result of adrenalitis or hypophysitis, and pancreatic atrophy since this may result as a consequence of

Table 1 Immune-related adverse events and imaging findings evaluated

irAE	Imaging findings	References
Colitis/enteritis	Fluid-filled bowel Mesenteric hyperemia Bowel wall thickening (> 4 mm for large bowel, > 3 mm for small bowel) Increased mucosal enhancement on contrast-enhanced CT Increased FDG uptake of the bowel walls	[10, 14]
Hepatitis	Hepatomegaly (hepatic height > 15.5 cm)* Heterogeneous parenchymal enhancement Periportal/pericholecystic edema intense FDG uptake throughout the liver Hepatic attenuation < 40 Hounsfield Units	[15–18]
Pancreatitis	New focal or diffuse pancreatic enlargement Decreased enhancement and/or peripancreatic stranding without a focal lesion suspicious for metastasis Increased FDG uptake throughout the pancreas	[10, 19]
Biliary toxicity	Gallbladder distension, with thickened and edematous walls Mucosal hyperenhancement Pericholecystic fat stranding bile duct dilation FDG uptake of the gallbladder wall	[20]
Nephritis	Focal or diffuse decreased enhancement of the renal parenchyma during portal venous phase if contrast CT Renal pelvic thickening or cortical swelling Diffuse FDG uptake of the bilateral kidneys	[21, 22]
Adrenalitis	Bilateral enlargement of the adrenal glands Mild FDG avidity of the adrenal glands	[23, 24]
Sarcoid-like reaction	New abdominal lymphadenopathy without evidence of infection, occurring in the setting of response at other sites	[10, 25]
Pancreatic atrophy	Reduced size of the pancreas, compared to baseline study on qualitative assessment;	[26, 27]
Adrenal atrophy	Hypotrophic appearance of adrenals, compared to baseline study on qualitative assessment.	[26]

FDG 18F-fluoro-2-deoxy-D-glucose, *irAE* immune-related adverse event

*Measured from mid hepatic line (the half-point distance between the mid-point of the spine and the outermost point on the right liver surface in axial planes) on coronal images

prior immune checkpoint inhibitor-associated pancreatitis [26, 27].

Patients' charts of the cases with an irAE likelihood score of ≥ 3 in the initial review were subsequently screened by a radiologist-in-training (X2.,X2.) for concomitant conditions potentially mimicking irAE, including: infections colitis/enteritis, evaluating the presence of stool cultures positive for bacterial or viral enteropathogens and endoscopy with biopsy showing cytomegalovirus infection, when available; alternative causes of acute kidney injury; biliary cholecystitis; infectious cholangitis; viral, alcoholic or drug induced hepatitis; recurrent pancreatitis; prior use of steroids for pancreatic and adrenal atrophy [28].

The patients with irAE likelihood score ≥ 3 were then reviewed independently by two additional fellowship-trained radiologists (X3.X3.,X6.,X6.) with more than 10 years' experience in reading abdominal CT and PET/CT, blinded to the initial reviewer's scores, how irAE were identified by the first reviewer and all other clinical data. In addition, each of the two radiologists (X3.X3., X6.X6.) was blinded to the other radiologist's score. Cases were considered positive if the irAE score was 4 or 5 by at least two of the three readers.

The date of the first scan demonstrating irAE score 4 or 5 was used to represent the onset of radiographically evident irAEs. Subsequent follow-up scans, if available, were reviewed to assess resolution of the radiographic findings, which was defined as irAE score ≤ 3. For each positive case, specific imaging criteria were described. Cases with radiographically evident abdominal irAEs were subsequently correlated with clinical, laboratory, or histopathologic data, collected by review of medical records and graded according to [29].

Statistical analysis

Descriptive statistics were produced for the demographic and clinical characteristics of cases. Differences in demographics and clinical characteristics were compared between patients with and without radiographically evident irAEs, using the Fisher's exact test for categorical variables and the Wilcoxon test for continuous variables. The time to development of radiographically evident irAEs was calculated using the Kaplan–Meier method, and patients who did not develop radiologically identified irAEs were censored at the

time of last follow-up imaging. All p values were based on a two-sided hypothesis. $P < 0.05$ was considered to be statistically significant. All statistical analyses were conducted using JMP® Software (JMP®, Version 13.0.0 SAS Institute Inc., Cary, NC, 1989–2007).

Results

Frequency and characteristics of abdominal IrAE

Clinical and demographic characteristics of the included patients are reported in Table 2. Of the total of 137 cases, 20 cases with suspected irAE were initially identified after the first imaging review. A case with suspected immune-related nephritis, subsequently diagnosed with acute kidney injury related to dehydration, and a patient with adrenal atrophy with prior 6 months' use of steroids were excluded. After the second imaging analysis, 18 (13%) of 137 patients with radiographically evident abdominal irAEs were identified. These were identified on contrast-enhanced CT in 14 patients, on noncontrast CT in two patients, on PET/CT in two patients. The median time from the initiation of therapy and the development of abdominal irAEs was 2.1 months [interquartile range (IQR): 1.17–5.83]. In 13 of the 18 cases (72%), abdominal irAE occurred within 6 months after the initiation of therapy.

In 12 (67% of patients with irAEs) patients, abdominal irAE occurred during therapy, while in six patients (33% of those who developed irAEs) irAE occurred after nivolumab discontinuation (median time after discontinuation: 3.03 months; IQR 0.98–3.60), before starting the next systemic therapy. In those six cases, nivolumab was discontinued due to disease progression ($n = 2$), and due to clinical irAE ($n = 4$; one myositis, one hepatitis, and diarrhea in two cases).

No significant difference was observed for age, sex, duration of therapy, and Eastern Cooperative Oncology Group performance status between patients with radiographically evident irAE and patients with no imaging evidence of irAE (Table 1). Median time from development of irAE to complete imaging resolution was 2.4 months (IQR 1.17–6.53).

Among the abdominal irAEs evaluated in the study, colitis/enteritis was the most common irAE, seen in 16 patients, followed by hepatitis in two patients, and adrenalitis in one patient (Tables 3 and 4). One patient with hepatitis had also colitis/enteritis. Among the 19 abdominal irAEs (19 irAEs in 18 patients), 17 were detected on CT, two were detected on FDG-PET/CT. No cases of sarcoid-like reaction, pancreatitis, and nephritis were observed. In total, 13 out of 18 patients with imaging irAEs had documented clinical symptoms or had laboratory values suggestive of irAEs. These were 10 patients with colitis/enteritis, two patients with hepatitis, and one patient with adrenalitis. Of the 18 patients with abdominal irAEs, three patients had other IRAEs.

Of the 18 patients with abdominal irAEs, three patients had other IRAEs not identified on abdominal imaging studies. These were pneumonitis in two patients with immune-related colitis, and myositis in the patient with immune-related adrenalitis.

Table 2 Clinical and demographic characteristics of included cases

Demographics	Without irAE (118)	With irAE (19)	Total (137)	*P*-value
Age (median-IQR)	65; 57–72	66; 57-69	65; 57–72	0.5189
Sex				
M	53	9	62	1.00
F	65	10	75	
ECOG performance status baseline				
0	15	1	16	0.2927
1	83	12	95	
2	18	5	23	
≥ 3	2	1	3	
Histology				
Adenocarcinoma	86	13	99	
Squamous cell carcinoma	17	3	20	
Other	15	3	18	0.22
Smoking history				
Current/former smoker	93	14	107	0.56
Never smoker	25	5	30	

IrAE immune-related adverse event, *IQR* interquartile range, *ECOG* Eastern Cooperative Oncology Group

Table 3 Organ-specific immune-related adverse event and onset since therapy initiation

irAE	CT or PET/CT (patients)	Months since therapy initiation, median (range)*	Months from irAE to imaging resolution, median (range)*
Colitis	18 (16)	1.87 (0.07–18.43)	6.93 (1.73–20.63)
SCAD	2 (2)		
Pancolitis	14 (12)		
Enterocolitis	1 (1)		
Enteritis	1 (1)		
Hepatitis**	2 (2)	2.01 (1.63–2.4)	NA
Adrenalitis	1 (1)	5.83	NA

IrAE immune-related adverse event, *SCAD* segmental colitis associated with diverticulosis, *NA* not available

*Median and range among patients who had the events; ** one patient also had colitis

Table 4 Imaging findings in patient with imaging immune-related adverse events

Patient number	IrAE	Imaging findings
1	Diffuse Colitis	Mesenteric hyperemia, fluid-filled bowel loops, bowel wall thickening
2	Diffuse Colitis	Mesenteric hyperemia, fluid-filled bowel loops, increased mucosal enhancement
3	Diffuse Colitis	Mesenteric hyperemia, bowel wall thickening, increased mucosal enhancement
4	SCAD	Mesenteric hyperemia, bowel wall thickening
5	Enterocolitis	Mesenteric hyperemia, fluid-filled bowel loops, bowel wall thickening, increased mucosal enhancement
6	Diffuse Colitis	Mesenteric hyperemia, bowel wall thickening, increased mucosal enhancement
7	Adrenalitis	Bilateral enlargement of the adrenal glands, mild FDG avidity of the adrenal glands
8	Diffuse Colitis	Mesenteric hyperemia, fluid-filled bowel loops, bowel wall thickening
9	Enteritis	Mesenteric hyperemia, bowel wall thickening, increased mucosal enhancement
10	Diffuse Colitis Hepatitis	Mesenteric hyperemia, fluid-filled bowel loops, bowel wall thickening, increased mucosal enhancement Periportal/Pericholecystic edema, heterogeneous parenchymal enhancement
11	Hepatitis	Periportal edema
12	SCAD	Mesenteric hyperemia, bowel wall thickening
13	Diffuse Colitis	Mesenteric hyperemia, fluid-filled bowel loops, bowel wall thickening, increased mucosal enhancement
14	Diffuse Colitis	Mesenteric hyperemia, fluid-filled bowel loops, bowel wall thickening, increased mucosal enhancement
15	Diffuse Colitis	Mesenteric hyperemia, fluid-filled bowel loops, bowel wall thickening, increased mucosal enhancement
16	Diffuse Colitis	Mesenteric hyperemia, bowel wall thickening, increased mucosal enhancement
17	Diffuse Colitis	Fluid-filled bowel loops
18	Diffuse Colitis	Mesenteric hyperemia, increased FDG uptake of the bowel loops

IrAE immune-related adverse event, *SCAD* segmental colitis associated with diverticulosis, *FDG* 18F-fluoro-2-deoxy-D-glucose

Colitis/enteritis

Among the 16 patients with radiographically evident colitis or enteritis, the median interval from the initiation of nivolumab therapy to the development of colitis was 1.87 months (range 0.07–18.43 months). CT features of colitis/enteritis included mesenteric hyperemia ($n = 15$), bowel wall thickening ($n = 13$), increased mucosal enhancement ($n = 10$), fluid-filled colon ($n = 9$), and FDG avidity of the bowel loops ($n = 1$). Twelve patients had a diffuse colitis pattern, two patients had a SCAD pattern, one patient had enterocolitis, and one had enteritis (Figs. 1, 2, 3) (Table 4). Of the 16 patients, diarrhea (4–20 episodes/day) was noted in ten patients, four of which had also abdominal pain. In nine cases, clinical symptoms preceded radiographic irAE, while in one case, imaging irAE was observed 4 days before it was reported clinically. Six patients had no symptoms. Immune-related colitis/enteritis was diagnosed clinically in 10 cases and was diagnosed only on imaging in the remaining six cases.

Colonoscopy and biopsy were performed in two patients, confirming immune-mediated colitis, with histologic evidence of increased intraepithelial lymphocytes, apoptosis, regenerative epithelial changes, and areas of

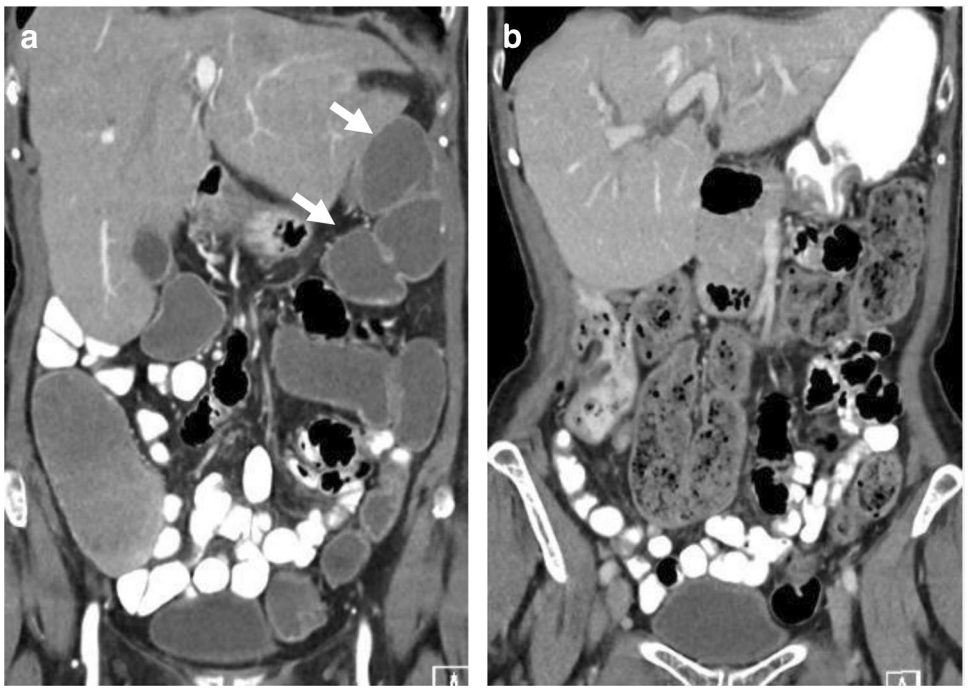

Fig. 1 71-year-old woman with non-small cell lung cancer presenting with diarrhea. **a** Coronal-reconstructed contrast-enhanced CT image performed 8 months after starting treatment with nivolumab shows fluid-filled large bowel (arrows). **b** Coronal-reconstructed contrast-enhanced CT image, performed 8 months after nivolumab was discontinued due to poor performance status, shows resolution of colitis

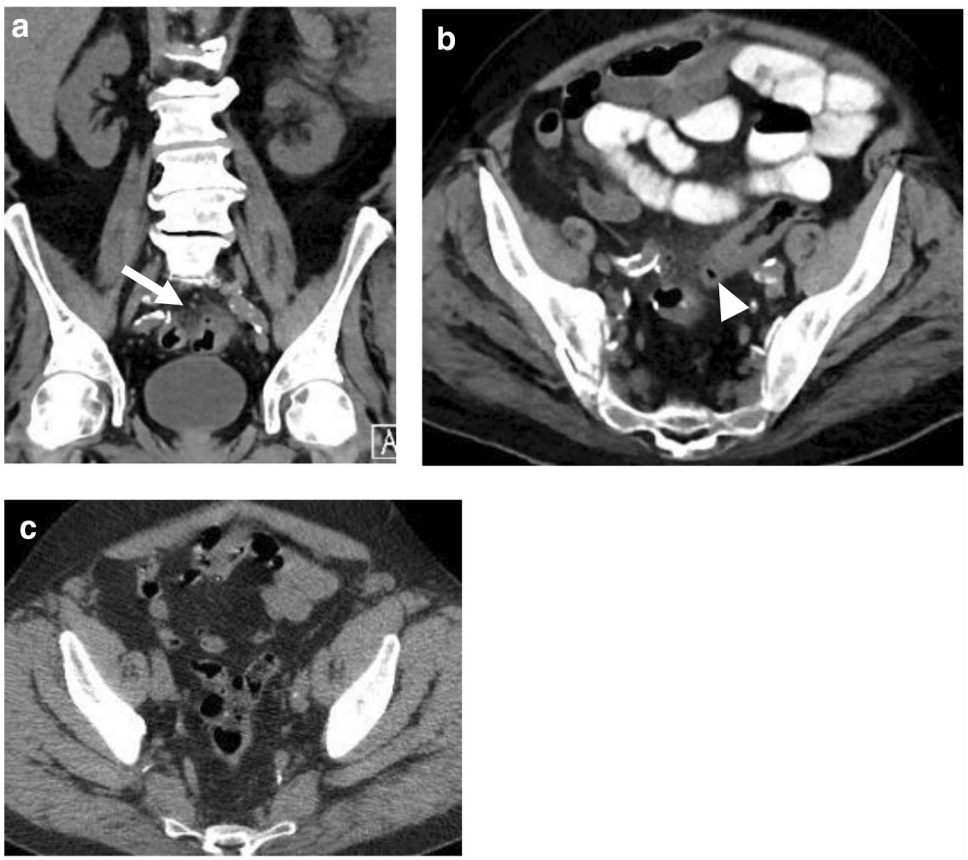

Fig. 2 67-year-old man with non-small cell lung cancer presenting to the emergency department with diarrhea. **a** Axial- and **b** coronal-reconstructed noncontrast CT images, acquired at the time of symptoms acquired 2 days after starting nivolumab, show focal fat stranding (arrow) and sigmoid wall thickening centered around a diverticulum (arrowhead), consistent with segmental colitis associated with diverticulosis. **c** Axial noncontrast CT image acquired before starting therapy shows sigmoid diverticulosis, noncomplicated. A presumptive diagnosis of immune-related colitis was given and nivolumab was interrupted, with resolution of symptoms

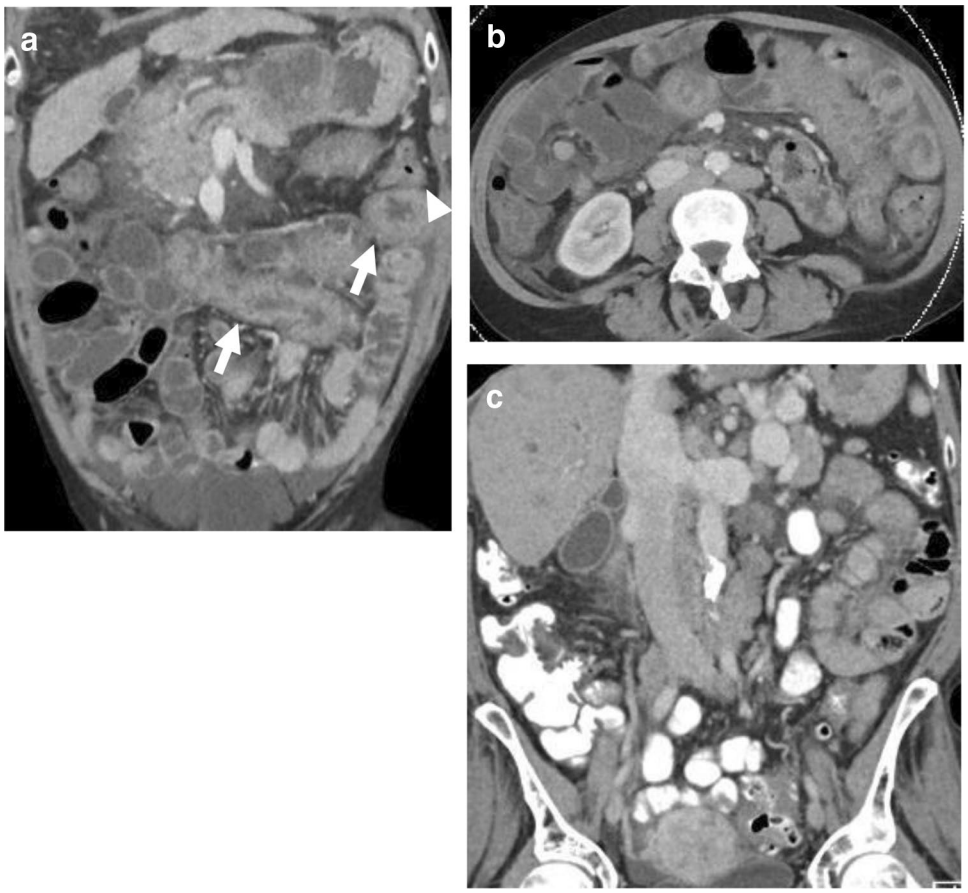

Fig. 3 52-year-old woman with non-small cell lung cancer presenting to the emergency department with diarrhea. **a** Coronal-reconstructed and **b** axial contrast-enhanced CT images performed at the time of symptoms, 1 day after nivolumab was started, show areas of wall thickening of multiple small bowel loops (arrows) and of the large bowel (arrowheads), increased mucosal enhancement, fluid-filled bowel loops, and mesenteric hyperemia. Nivolumab was held for a cycle, with resolution of symptoms. Nivolumab was subsequently interrupted due to progression of disease. **c** Coronal-reconstructed, contrast-enhanced CT image, acquired 2 days before starting nivolumab, shows normal appearing bowel loops

active inflammation, which was thought to be consistent with PD-1-associated colitis.

Oral steroids were given as treatment of presumptive immune-related colitis in three patients (two SCAD, one pancolitis). Nivolumab was held in seven patients with presumptive immune-related colitis, while six cases with imaging evidence of immune-related colitis and no symptoms continued treatment with nivolumab. Two patients with immune-related colitis/enteritis had immune-related pneumonitis: a patient who simultaneously developed SCAD and pneumonitis during nivolumab treatment and a patient who developed diffuse colitis during nivolumab treatment, who subsequently developed immune-related pneumonitis which prompted interruption of the PD-1 inhibitor.

Follow-up scans after radiographic irAEs were available in 11 patients. In 10 patients, the resolution of colitis was noted with a median interval from onset to resolution of 6.93 months (range 1.73–20.63 months). In one patient, the findings of colitis continued at the last follow-up imaging performed 1.67 months after onset.

Hepatitis

Hepatitis was radiologically detected in two patients. One patient developed grade 1 hepatitis [alanine transaminase (ALT) = 143, aspartate transaminase (AST) = 106] 1.63 months after nivolumab was started. Patient showed heterogeneous parenchymal enhancement with low-attenuation areas, periportal, and gallbladder edema. Nivolumab was discontinued and patient was treated with steroids, with subsequent normalization of liver function tests (Fig. 4). This patient had concomitant imaging evidence of pancolitis. The other patient showed periportal edema, grade 2 hepatitis (ALT = 245; AST = 106) which occurred 2.4 months after nivolumab was started, and 1 month after nivolumab was discontinued, due to disease progression (Table 4). No additional clinical follow-up was available. No further follow-up imaging studies were available in both cases.

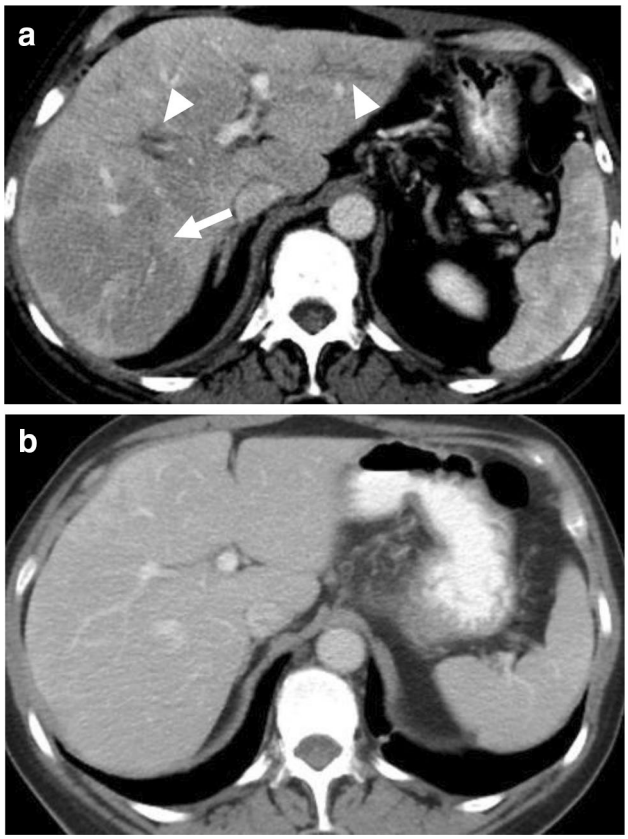

Fig. 4 60-year-old woman with non-small cell lung cancer with elevated transaminases (ALT = 143, AST = 106). **a** Axial contrast-enhanced CT image, acquired two months after nivolumab therapy was started, shows heterogeneous parenchymal enhancement with low-attenuation areas (arrow), and periportal edema (arrowheads). Patient was treated with steroids, and nivolumab was interrupted due to suspected immune-related hepatitis, with resolution of transaminitis. **b** Axial contrast-enhanced CT image acquired 1 month later shows resolution of hepatitis

Adrenalitis

Adrenalitis was radiologically detected in one patient on FDG-PET/CT, with evidence of bilateral FDG-avid mildly enlarged adrenal glands, which occurred 5.83 months after starting nivolumab (Fig. 5) (Table 4). Nivolumab was interrupted due to immune-related myositis. Patient presented with fatigue, hypoglycemia (67 mg/dL) and mild hyponatremia (132 mmol/L). Patient was managed expectantly. No further clinical data or follow-up imaging studies were available.

Discussion

Radiographically evident abdominal irAE were observed in 13% of patients treated with nivolumab in this study. Since there was no difference in the demographics or performance status of patients who did or did not develop irAEs, the radiologists have to rely on imaging features for timely detection of irAEs. Also, in a third of patients who develop irAEs, the toxicity was detected after the treatment was discontinued. Therefore, it is important for the radiologists to be aware of prior history of immunotherapy if possible and specifically look for irAEs in patients who have been treated with immunotherapy.

Our results are consistent with the prevalence of nivolumab-associated irAEs reported in clinical literature: a recent metanalysis analyzing irAE in patients with different cancers treated with nivolumab, showed that abdominal irAE occurred in 14–18%, with colitis/enteritis being the most common, occurring in 10–13% of cases [7]. In a study evaluating the prevalence of radiographic irAE in patients treated with PD-1 inhibitors, abdominal irAE were observed in only 4% of cases treated with nivolumab or pembrolizumab. The relatively lower prevalence of abdominal irAE is likely related to the different inclusion criteria: only patients with clinically confirmed irAE and imaging studies acquired within 15 days from the irAE were included in the study by Mekki et al., whereas we included all patients with imaging evidence of irAE [6, 7].

In our study, radiographic abdominal irAEs occurred at a median time of 2.1 months after the initiation of therapy and resolved after 2.5 months from imaging identification. This is consistent to what reported by the trials on nivolumab in patients with NSCLC, as reported median times to onset and resolution of hepatic and gastrointestinal irAE were less than 3 months [6, 30].

In 33.3% of cases, irAE occurred after therapy was discontinued, before the next systemic therapy was started, with a median time of 3 months between nivolumab discontinuation and imaging evidence of irAE. This phenomenon might be explained by the ability of PD-1 inhibitors to generate powerful memory T cells that may provide durable inflammatory response against any susceptible tissue even in the absence of continued therapy [12]. This finding stresses the importance of appropriate follow-up after discontinuation of therapy, as it irAE can occur months or years after treatment discontinuation [13].

Enteritis/colitis was observed in 16 patients, with median interval from the initiation of nivolumab to the development of colitis of 1.87 months, not significantly different from what reported in various studies [7, 30]. Most commonly observed CT features of colitis/enteritis were mesenteric hyperemia and bowel wall thickening, similar to that reported in a study on radiographic profiling of PD-1 associated irAE [6]. No cases of colonic perforation were observed in our series. In a study on ipilimumab-associated irAE in patients with advanced melanoma, of 28 cases with gastrointestinal irAE, three cases presented with colonic perforation [10]. The absence of colonic perforations in our study,

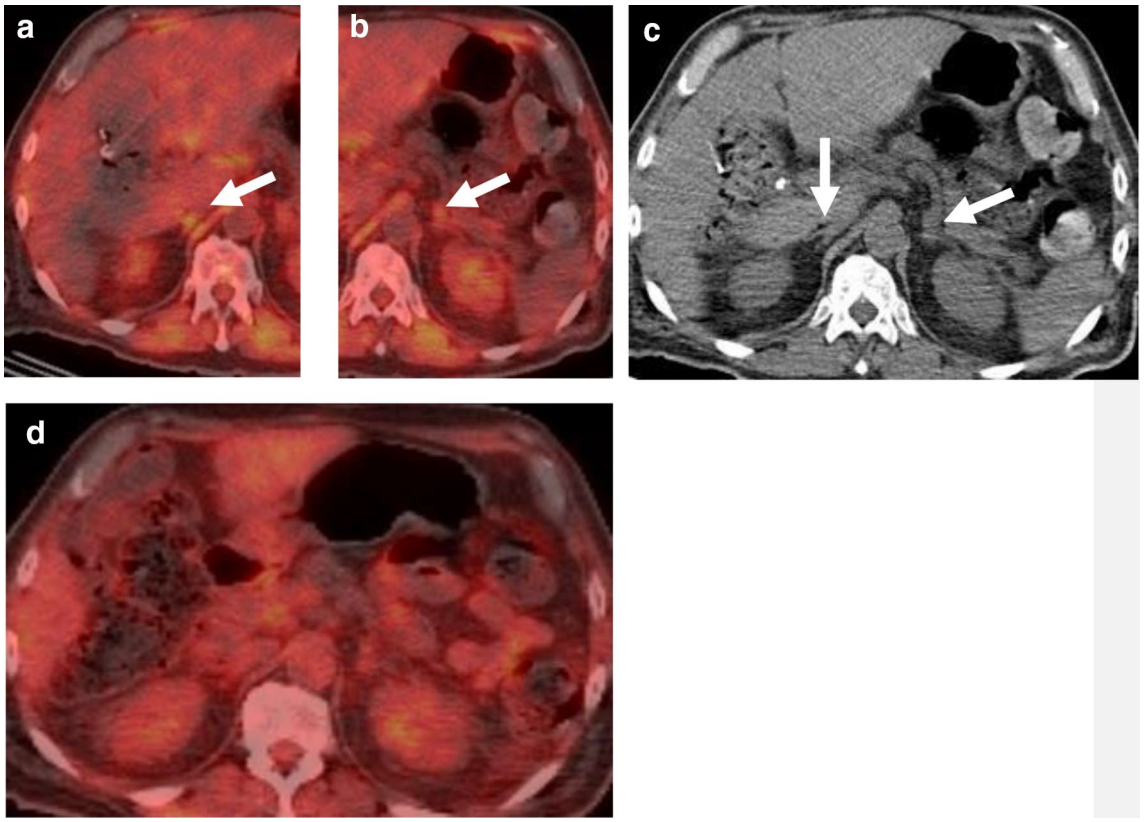

Fig. 5 69-year-old man with non-small cell lung cancer presenting with fatigue, and evidence of hypoglycemia (67 mg/dL) and mild hyponatremia (132 mmol/L). **a**, **b** Axial fused FDG-PET/CT and axial CT images **c**, acquired 3 months after nivolumab was discontinued due to immune-related myositis, show bilateral FDG-avid mildly enlarged adrenal glands (arrows). Patient was managed expectantly. **d** Axial fused FDG-PET/CT acquired before starting nivolumab shows normal appearing adrenal glands, with no FDG uptake

and the lower prevalence of gastrointestinal irAE associated with nivolumab compared to ipilimumab, suggests the possibility of an underlying different inflammatory mechanism of immune-related toxicity for the two immune checkpoint inhibitors [31]. We excluded patients with infectious or inflammatory enteritis/colitis; nonetheless, some cases might have been misdiagnosed as irAE, given differentiation between PD-1-associated colitis/enteritis and other causes of colitis/enteritis on imaging is challenging. However, while pancolitis, mild wall thickening, and fluid-filled colon are commonly observed in PD-1-associated colitis/enteritis, they are less common in inflammatory or infectious enteritis/colitis, which is consistent with our results [6, 32]. In six cases with imaging evidence of immune-related colitis and no clinical symptoms, treatment with nivolumab was continued. This reflects appropriate management of irAE, as continuation of immune checkpoint inhibitor treatment is recommended in asymptomatic (grade 1) irAE [12, 29].

Hepatitis was identified in two patients, both showing periportal edema, and one also showing heterogeneous parenchymal enhancement and gallbladder edema. Both cases had mild hepatitis and showed subsequent normalization of liver function tests [29]. In a study on 39 radiographically evident irAE in patients treated with PD-1 inhibitors, hepatitis was observed in two patients, showing steatosis, lymphadenopathy, hepatomegaly, periportal, and gallbladder edema on ultrasound [6]. In a meta-analysis on PD-1 inhibitors associated irAEs, elevation of AST or ALT levels occurred in 4–5% with nivolumab treatment [7]. Compared to studies which defined hepatitis according to AST and ALT elevation, prevalence of hepatitis in our population was lower, as we defined hepatitis based on the CT findings only.

Adrenalitis was detected in one patient, with evidence of bilateral FDG-avid mildly enlarged adrenal glands. Adrenalitis is reported to occur in up to 3.3% of cases in patients treated with nivolumab [6].

We did not observe any cases of pancreatitis. In a meta-analysis on PD-1 inhibitors associated irAEs, incidence of pancreatitis was < 1% [7]. In addition, in many cases pancreatitis presents only with clinical symptoms and lipase elevation.

Immune-related nephritis has been reported in 1–2% of patients treated with PD-1 inhibitors, whereas we observed none [7]. Nonetheless, cross-sectional imaging is not the

investigation of choice for irAE nephritis, and this condition might have been underreported.

We did not observe any cases of sarcoid-like reaction in the abdomen. Sarcoid-like reactions in the chest are reported in up to 5–7% of cases treated with ipilimumab, whereas incidence in patients treated with PD-1 inhibitors is less frequent, documented in less than 1% of cases [10, 25]. We evaluated sarcoid-like reaction in the abdomen images only, underlying the possibility that this condition might have been underreported in our study. Further investigations on the incidence of sarcoid-like reactions in PD-1 inhibitors are needed.

In total 13 out of 18 patients with imaging irAEs were clinically symptomatic, five were asymptomatic. In our experience, clinical symptoms are often not adequately documented in clinic notes, especially if they don't warrant discontinuation of therapy. Similar findings have been noted with other drug toxicities or complications—such as fat malabsorption in patients treated with sunitinib who had significant pancreatic atrophy and in cancer patients who are diagnosed with incidental pulmonary embolism [33, 34]. Similarly, a systematic review of immune checkpoint inhibitors clinical trials publications has shown that irAE reporting is frequently inconsistent, suggesting that it is possible that irAEs might be underreported even in clinical practice [35]. Therefore, it remains unclear if the remaining five patients were indeed asymptomatic or if it simply indicated lack of documentation.

Our study has few limitations, including its retrospective design in a cohort treated at a single institution. Initial evaluation was performed by a single radiologist. Nonetheless, the initial reviewer was a cancer imaging-fellowship-trained radiologist, aware that the patients were treated with nivolumab and familiar with imaging presentation of irAEs. Also, even equivocal cases with irAE likelihood score of ≥ 3 were included for review by the other radiologists, minimizing the likelihood of missing patients with irAE. Indeed, the prevalence of the irAEs identified in our study was similar to the prevalence of irAE reported in literature, indicating that the majority of cases with imaging findings suspicious for irAEs were identified.

Since we only included the imaging studies until the start of subsequent therapy, we may have underestimated the frequency of delayed occurrence of irAEs, however, we chose the design to exclude the influence of systemic agents other than nivolumab. We evaluated the frequency of abdominal irAE only in patients with cross-sectional imaging of the abdomen. Therefore, many patients who underwent only cross-sectional imaging of the chest have been excluded, with possible underreporting of abdominal irAE seen on images through the upper abdomen routinely obtained during chest CT. The study exclusively focused on organ-specific irAEs in the abdomen and did not include irAEs in other organs such as pneumonitis and hypophysitis. This is because the study was targeted to mainly inform abdominal radiologists interpreting abdominal cross-sectional scans which consist of a major part of oncologic imaging, and non-abdominal irAEs such as pneumonitis have been extensively studied in prior reports [36–39]. Only few CT scans of the abdomen and pelvis were performed without intravenous contrast media administration (9%), likely with negligible effect on identification of irAEs, given that two out of 16 cases in which irAEs were identified on CT (12%) had noncontrast CT. Finally, interval between imaging studies performed during and after treatment varied per clinical care provider's discretion, possibly limiting the identification of radiographic irAE in asymptomatic cases.

In conclusion, abdominal irAEs were detected on CT or FDG-PET/CT in 14% NSCLC patients treated with nivolumab monotherapy, and colitis, in the pancolitis form, was the most common irAE. In a third of patients who develop irAEs, the toxicity was detected after the treatment was discontinued. Given the expanding role of immunotherapy in clinical practice, radiologists should be aware of the frequency and imaging features of abdominal irAEs. The radiologists should also recognize the impact of abdominal irAE in the subsequent management of cancer patients, because a significant proportion of abdominal irAEs occur after treatment is discontinued.

Compliance with ethical standards

Conflict of interest Francesco Alessandrino, MD: no conflict of interests. Sonia Sahu, MD: no conflict of interests. Mizuki Nishino MD, MPH Consultant to Bristol-Myers Squibb, Toshiba Medical Systems, WorldCare Clinical, Daiichi Sankyo; Research grant from Merck Investigator Studies Program, Toshiba Medical Systems, AstraZeneca; Honorarium from Bayer and Roche. The investigator, M.N., was supported by 1R01CA203636 (NCI). Anika E. Adeni: no conflict of interests. Sree Harsha Tirumani, MD: no conflict of interests. Atul B. Shinagare, MD: Consultant, Arog Pharmaceuticals. Mark Awad, MD, PhD: Consultant Bristol-Myers Squibb, Merck, Genentech, AstraZeneca. Research funding from Bristol-Myers Squibb.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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