


# <sup>18</sup>F-FDG PET/CT features of immune-related adverse events and pitfalls following immunotherapy

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## Introduction

The introduction of Immunotherapy as a viable treatment option for many malignancies such as melanoma, non-small cell lung cancer and renal cell carcinoma has revolutionized cancer management and continues to grow rapidly.

Immunotherapy relies on activation of the patient's own immune system to recognize and kill cancer cells and is generally facilitated *via* modulation of the programmed cell death protein 1 (PD1) or PD1/programmed cell death protein ligand 1 (PD1/PDL1) axis or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) pathway.<sup>1</sup>

Both the PD1/PDL1 and CTLA-4 pathways are normally negative regulators of T-cell immune function. Immune check point inhibitors (ICIs), which include CTLA-4 inhibitors (ipilimumab) and PD1 inhibitors (pembrolizumab and nivolumab) allow activation and proliferation of more T-cell clones resulting in immune system activation.

The CheckMate 066 trial randomized 418 treatment naïve metastatic melanoma patients without BRAF mutation to nivolumab immunotherapy or Dacarbazine chemotherapy. Overall survival at 1 year was 72.9% in

## Summary

<sup>18</sup>F-FDG PET/CT scanning is routinely performed to stage and evaluate the treatment response in many malignancies. Immunotherapy is a rapidly growing treatment option for many cancers, and both clinicians and imaging specialists need to be familiar with <sup>18</sup>F-FDG PET/CT imaging characteristics unique to patients on this type of treatment. In particular, many immune-related adverse events (irAEs) can be detected on <sup>18</sup>F-FDG PET/CT and early accurate identification is critical to reduce treatment related morbidity and incorrect interpretation of malignant disease status. This pictorial essay reviews frequently encountered irAEs in clinical practice and their appearances on <sup>18</sup>F-FDG PET/CT along with a brief discussion on pseudoprogression and hyperprogression.

**Key words:** nuclear imaging; nuclear medicine; oncologic imaging; <sup>18</sup>F-FDG PET.

the nivolumab cohort compared to 42.1% in the Dacarbazine cohort. Median progression free survival was 5.1 and 2.2 months respectively.<sup>2</sup>

The Keynote-024 trial randomized 305 patients with advanced non-small cell lung cancer to either pembrolizumab immunotherapy or standard chemotherapy with immunotherapy again having a significantly improved progression-free survival compared to standard chemotherapy (10.3 *versus* 6.0 months respectively).<sup>3</sup>

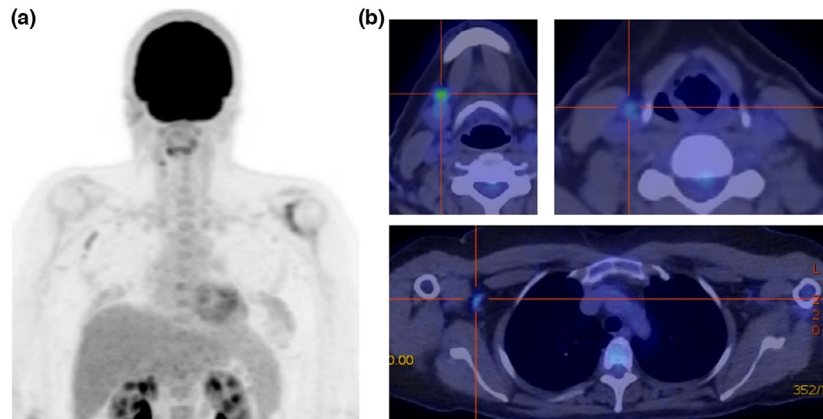
With the rapid growth of immunotherapy as a treatment option, immune-related adverse events (irAEs) are increasingly being encountered in clinical practice, which can be potentially serious or life-threatening.

<sup>18</sup>F-FDG PET/CT scanning is frequently routinely performed for staging and re-staging of cancer patients and in addition to detecting cancer can also detect tissue inflammation, one of the hallmarks of irAEs. This unique capability sets <sup>18</sup>F-FDG PET apart from conventional imaging with CT and MRI and potentially enables early identification of irAEs and an opportunity to intervene prior to the development of clinical symptoms. Alternatively, it may be used to confirm a particular irAE when clinically suspected.

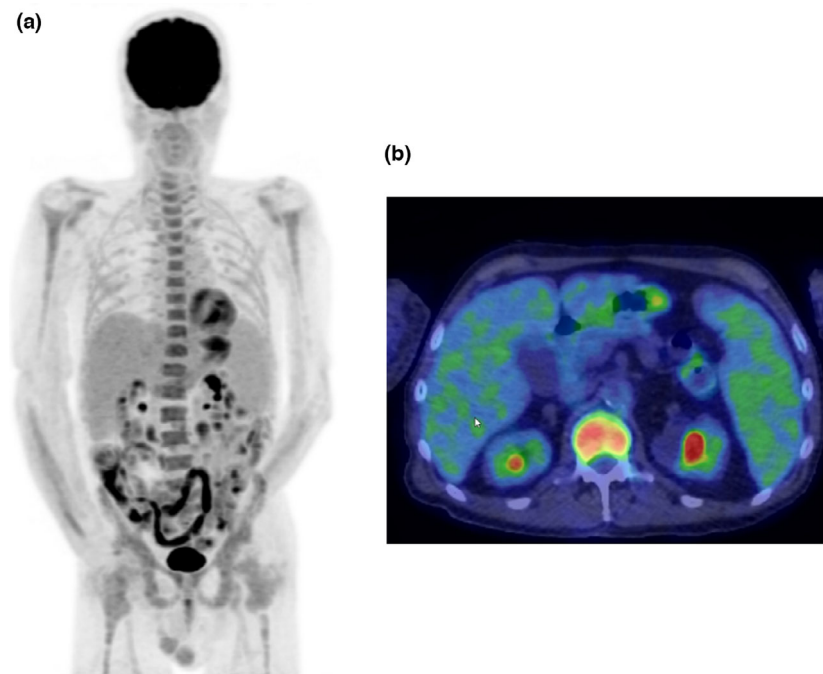
**Table 1.** Examples of CTLA-4 and PD1/PDL1 checkpoint inhibitors

CTLA-4	PD1	PDL1 inhibitor
Ipilimumab	Pembrolizumab	Atezolizumab
Tremilimumab	Nivolumab	Avelumab
	Cemiplimab	Durvalumab
	Dostarlimab	

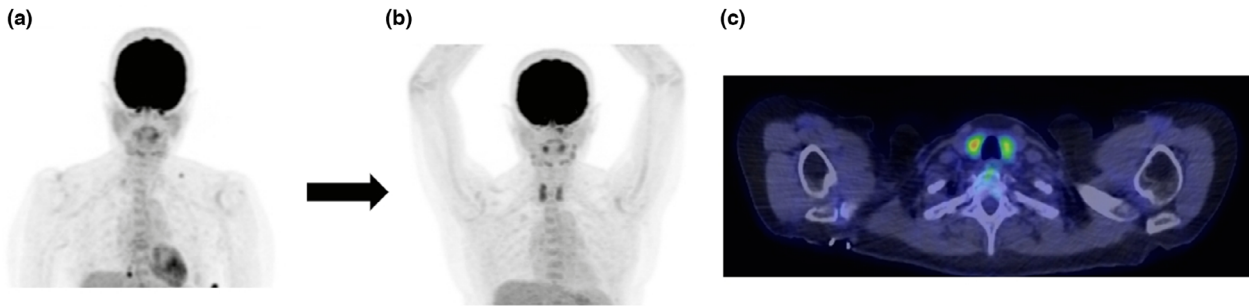
Immune-mediated inflammatory changes on  $^{18}\text{F}$ -FDG PET/CT may also result in interpretative errors, and hence, it is important for clinicians and PET reporting specialists to be familiar with the broad spectrum of potential non-malignant inflammatory change that may be seen on  $^{18}\text{F}$ -FDG PET/CT in patients undergoing immunotherapy.



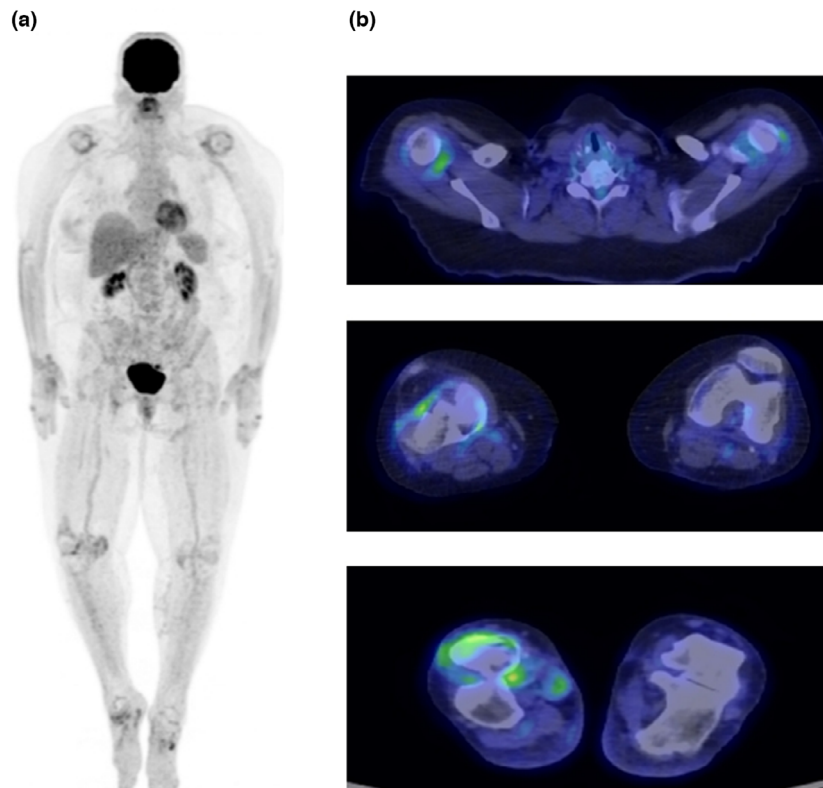
**Fig. 1.** Reactive nodes. Fifty-year-old woman with metastatic melanoma treated with surgery and four cycles pembrolizumab. (a) PET MIP demonstrates mildly increased  $^{18}\text{F}$ -FDG uptake in right axillary, right level IB and right level III cervical nodes. (b) Axial Fused PET/CT images of the same nodes. As the nodes are not in the drainage basin of the primary site of malignancy (lower limb) and are only mildly  $^{18}\text{F}$ -FDG-avid, they are more consistent with immunotherapy related nodal activation/reactive change rather than metastatic disease.



**Fig. 2.** Reactive marrow and spleen. Seventy-three-year-old man with surgically resected metastatic melanoma treated with adjuvant pembrolizumab. (a) PET MIP demonstrates diffuse moderately increased  $^{18}\text{F}$ -FDG uptake throughout the marrow of the axial and proximal appendicular skeleton in keeping with immune mediated marrow activation. (b) Axial Fused PET/CT images of the spleen demonstrate splenomegaly and diffuse mildly increased  $^{18}\text{F}$ -FDG uptake throughout and subtle reversal of normal liver to spleen  $^{18}\text{F}$ -FDG ratio.



**Fig. 3.** Thyroiditis. Sixty-three-year-old woman with metastatic melanoma to nodes and subcutaneous tissues treated with pembrolizumab. (a) Baseline PET MIP demonstrating nodal and soft tissue metastases. (b) Post four cycles pembrolizumab PET MIP demonstrating complete resolution of metastatic disease but diffusely increased <sup>18</sup>F-FDG uptake in both lobes of thyroid gland in keeping with thyroiditis. (c) Axial Fused PET/CT images of the thyroid gland confirms increased <sup>18</sup>F-FDG uptake in both lobes.



**Fig. 4.** Synovitis/arthritis medium and large joints. Seventy-four-year-old woman with metastatic melanoma treated with pembrolizumab. (a) PET MIP post six cycles pembrolizumab demonstrating diffuse mild to moderately increased <sup>18</sup>F-FDG uptake in the shoulders, knees, ankles and wrists consistent with immune mediated synovitis/reactive arthropathy. (b) Axial Fused PET/CT images of shoulders, knees and ankles demonstrating corresponding sites of increased <sup>18</sup>F-FDG uptake.

### Immune-related adverse events

Immune-related adverse event can affect almost any organ in the body, with more common sites of involvement being skin, colon, liver, lungs, endocrine organs, synovium and joints.<sup>4</sup> IrAEs often mimic de-novo autoimmune diseases clinically but differ at the level of tissue pathology.<sup>5</sup> A systematic review of patterns of irAEs

suggests Grade 3–4 irAEs are more common with CTLA-4 inhibitors compared to PD1 inhibitors.<sup>6</sup>

Pneumonitis, hypothyroidism, arthralgias and cutaneous reactions are more frequently seen with PD1 inhibitors compared to CTLA-4 inhibitors, whilst colitis and hypophysitis are more frequently seen with CTLA-4 inhibitors. It should be noted; however, there is significant overlap in potential irAEs regardless of the type of

immunotherapy and for all intents and purposes, any irAE is possible with all check point inhibitors.

The use of combination CTLA-4 and PD1/PDL1 check-point inhibitor therapy is often used in higher risk or more advanced disease and this is associated with higher rates of irAEs compared with single agent immunotherapy. In the Checkmate 067 trial, which evaluated 945 Stage 3/4 Melanoma patients randomized to either ipilimumab alone, nivolumab alone or in combination, Grade 3–4 irAEs were significantly higher with combination therapy (59%) *versus* ipilimumab alone (28%) or nivolumab alone (23%)<sup>7</sup> (Table 1).

### Nodal activation

Immune checkpoint inhibitors frequently result in increased metabolic activity in lymph nodes related to immune activation. <sup>18</sup>F-FDG nodal uptake is usually only mild to moderately increased; however, on occasions can be extremely intense.

It can be difficult at times to differentiate reactive nodal increase in <sup>18</sup>F-FDG uptake from metastatic disease particularly if the nodes are located in a similar draining basin to the primary site of malignancy. Reviewing the CT component of the PET/CT scan to determine the size of nodes and whether nodal fatty hilar structures are preserved (suggesting benign rather than malignant change) is often

useful. Immune activated 'reactive' nodes are most frequently seen in mediastinal, pulmonary hilar, upper abdominal, axillary and inguinal nodal regions, however, can occur in any location (Fig. 1).

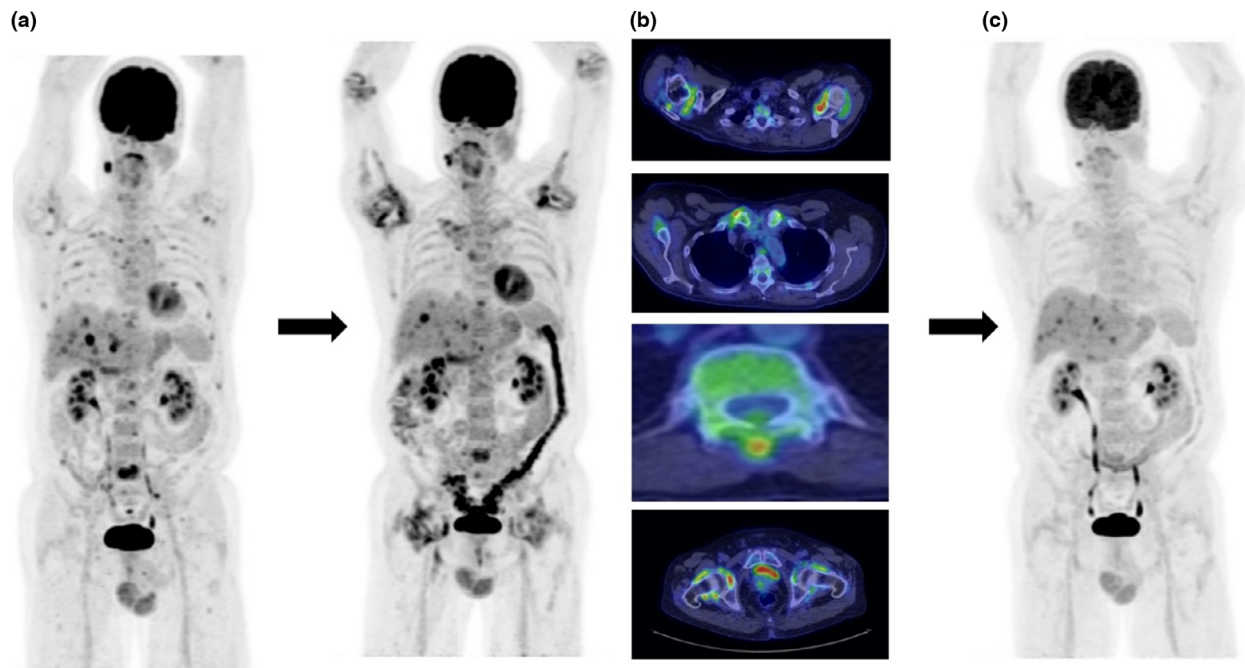
Further, along with the spectrum of immune nodal activation is the development of granulomatous/sarcoid like reactions. Similar to de-novo granulomatous disease, this most frequently presents as relatively symmetrical mild to intensely increased <sup>18</sup>F-FDG uptake in bilateral pulmonary hilar and mediastinal nodes. The relatively symmetrical nature of nodal <sup>18</sup>F-FDG uptake is highly suggestive of benign granulomatous disease (Fig. 12).

### Reactive bone marrow/splenic activity

Diffuse mild to moderately increased <sup>18</sup>F-FDG uptake is frequently seen in bone marrow of the axial and proximal appendicular skeleton and within the spleen, reflecting an immune activated reticuloendothelial system. Increased splenic uptake is reflected by inversion of the normal liver to spleen uptake ratio with or without splenomegaly (Fig. 2).

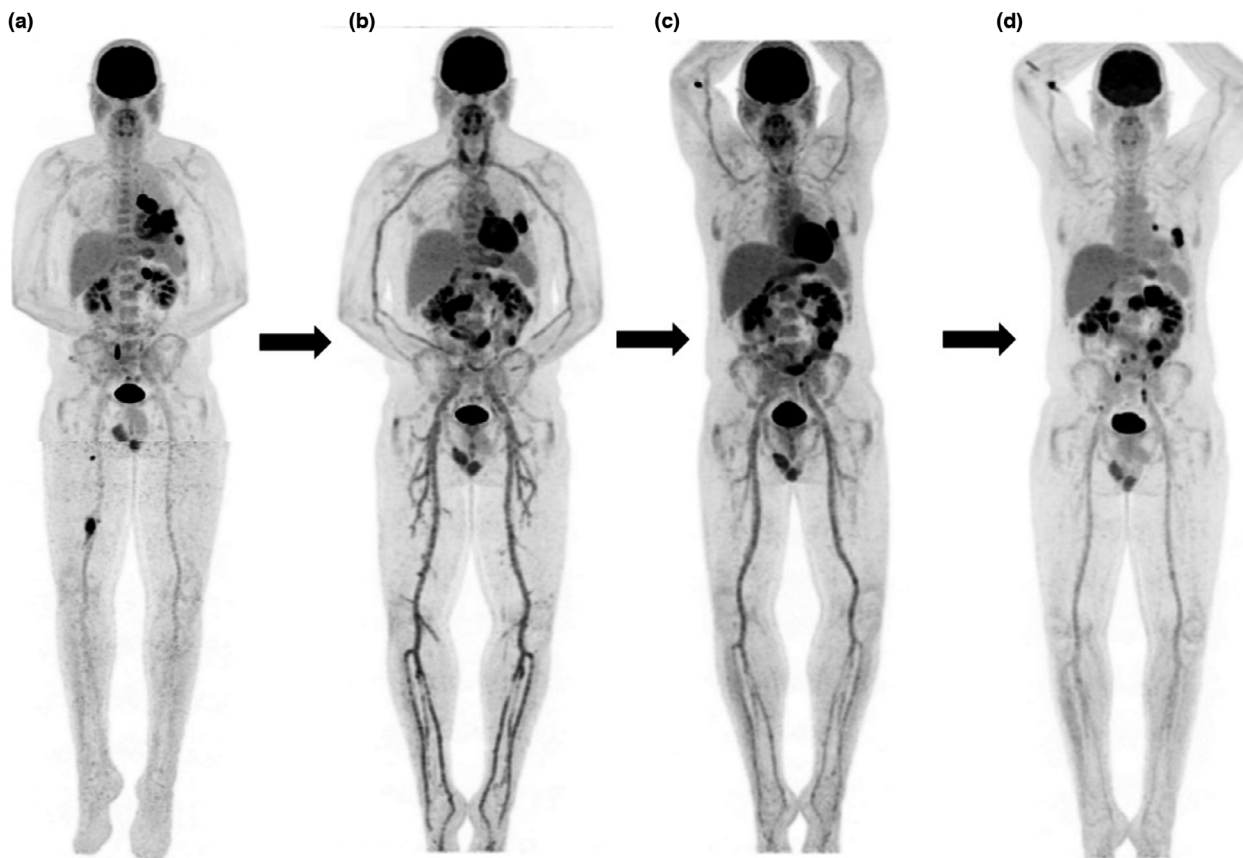
### Thyroiditis

Clinically may manifest as either hypothyroidism or hyperthyroidism, which can be differentiated with



**Fig. 5.** Polymyalgia rheumatica and colitis. Fifty-eight-year-old man with metastatic melanoma treated with combination ipilimumab and nivolumab followed by maintenance nivolumab. (a) Baseline PET MIP demonstrates widespread skeletal, liver and right submandibular nodal metastatic disease. (b) PET MIP and Axial fused PET/CT images post four cycles ipilimumab and nivolumab demonstrate severe relatively symmetrical synovitis/inflammation of the shoulders, sternoclavicular joints, hip joints and interspinous regions in a pattern typical for Polymyalgia Rheumatica. Colitis is also present in the descending colon. (c) PET MIP images following 100 mg weaning Prednisolone dose daily for 3 weeks and maintenance nivolumab demonstrates complete resolution of Synovitis/Polymyalgia Rheumatica and colitis and reduction in metastatic disease.





**Fig. 6.** Vasculitis and thyroiditis. Fifty-two-year-old man with metastatic melanoma treated with combination ipilimumab and nivolumab. (a) Baseline PET MIP demonstrates widespread left pulmonary and pleural, left adrenal, small bowel and right thigh muscle metastases. (b) PET MIP Post three cycles ipilimumab and nivolumab demonstrates partial response at sites of metastatic disease, autoimmune thyroiditis (biochemically hypothyroid) and widespread severe medium and large vessel vasculitis of the upper and lower limbs. (c) PET MIP 3 weeks post 50 mg Prednisolone daily demonstrates reduction in medium and to a lesser extent large vessel vasculitis in the upper and lower limbs. (d) PET MIP 3 months post completion of ipilimumab and nivolumab demonstrates resolution of vasculitis and persistent low volume metastatic disease.

biochemical thyroid function testing. More frequently seen with PD1/PDL1 checkpoint inhibitor therapy.<sup>8</sup> PET/CT scan demonstrates diffuse mild to moderately increased <sup>18</sup>F-FDG uptake throughout both lobes of the thyroid gland (Figs 3, 6).

### Arthritis/synovitis

Clinically manifests as small and large joint pain and reduced mobility. PET/CT scan demonstrates diffuse mild to moderately increased synovial <sup>18</sup>F-FDG uptake compatible with synovitis, which is often relatively symmetrical in nature (Fig. 4).

### Polymyalgia rheumatica

Clinically manifests frequently as neck, shoulder, hip and lower back pain. PET/CT scan demonstrates increased <sup>18</sup>F-FDG uptake most commonly around the shoulders, sternoclavicular and hip joints. Also, in extra-articular

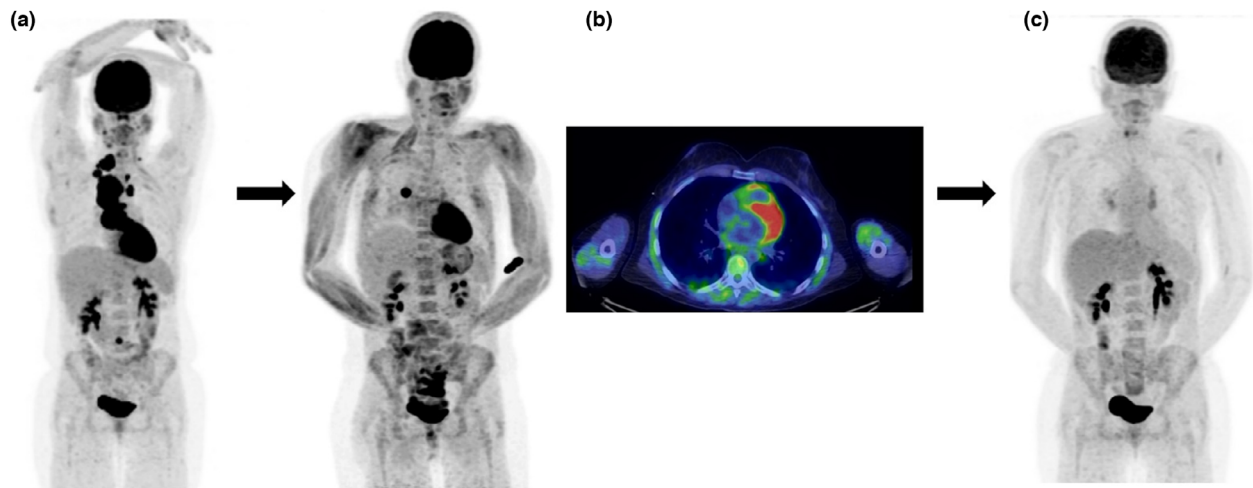
regions between columnal spinal processes, ischial tuberosities and pre-pubic area<sup>9</sup> (Fig. 5).

### Vasculitis

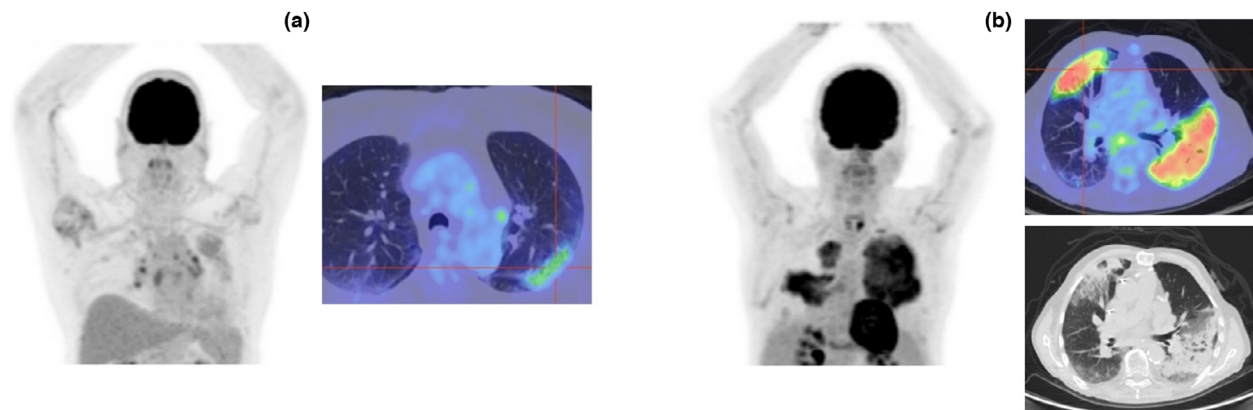
Usually medium and large vessel vasculitis and vasculitis of the central and peripheral nervous system.<sup>10</sup> Only medium and large vessel vasculitis is usually detected on PET/CT scan, with diffusely increased <sup>18</sup>F-FDG uptake most commonly demonstrated in medium and large vessels of the upper and lower limbs (Fig. 6).

### Myositis/myocarditis

Immune mediated myositis may affect limb girdle, axial or oculomotor muscles with an estimated incidence of 0.3% for CTLA-4 or PD1 monotherapy and 1% for combination therapy.<sup>11</sup> Myositis involving limb girdle or axial muscles is manifest on PET scan by diffuse mild to



**Fig. 7.** Myositis. Thirty-nine-year-old woman with metastatic melanoma treated with combination ipilimumab and nivolumab followed by maintenance nivolumab. (a) Baseline PET MIP demonstrates extensive intra-thoracic and to a lesser extent cervical and mesenteric nodal metastatic disease. (b) PET MIP and Axial fused PET/CT images post four cycles ipilimumab and nivolumab demonstrate diffuse mild to moderately increased  $^{18}\text{F}$ -FDG uptake throughout skeletal muscles of the upper and lower arms and chest wall consistent with myositis. Marked reduction in metastatic disease also noted. (c) PET MIP images 4 months later on maintenance nivolumab demonstrates complete resolution of myositis and metastatic disease.



**Fig. 8.** Pneumonitis. (a) Seventy-five-year-old man with metastatic melanoma on pembrolizumab. PET MIP and Axial fused PET/CT images demonstrate mildly  $^{18}\text{F}$ -FDG-avid ground glass change on CT in the left upper lobe typical of early immune mediated pneumonitis. (b) Eighty-five-year-old man with metastatic melanoma on pembrolizumab. PET MIP, Axial Fused PET/CT and CT images demonstrate intensely  $^{18}\text{F}$ -FDG-avid organizing pneumonia pattern left lower lobe, right upper and middle lobes consistent with advanced pneumonitis. This completely resolved subsequently with a 75 mg weaning dose of prednisolone over 3 weeks.

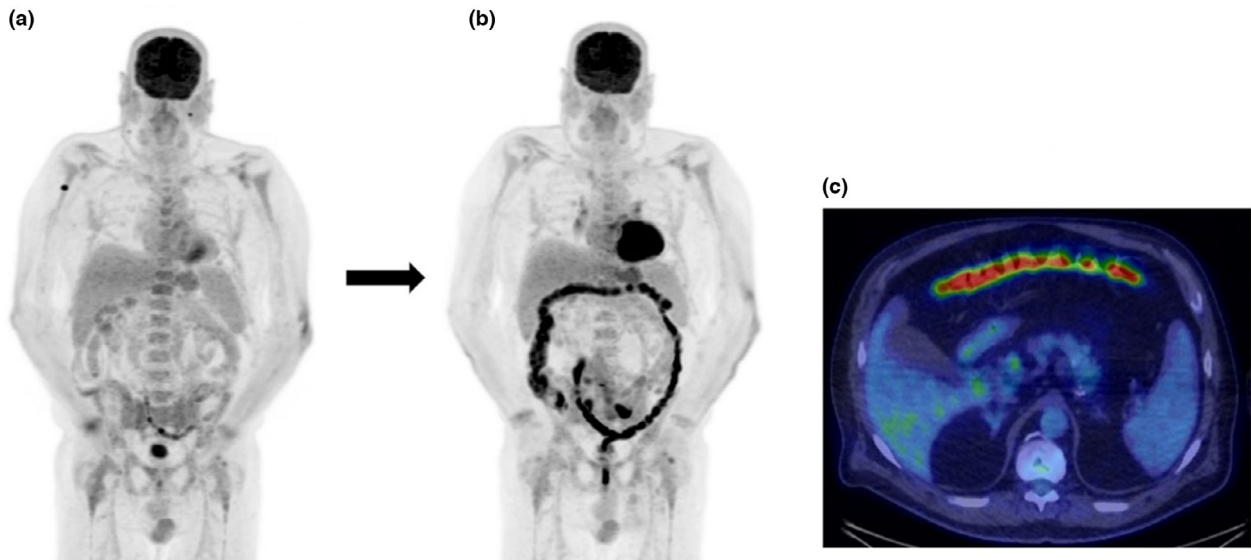
moderately increased  $^{18}\text{F}$ -FDG uptake in involved muscle groups (Fig. 7).

In approximately 32% of cases, myositis is complicated by concomitant myocarditis.<sup>12</sup> Myocarditis can be detected on PET/CT scanning and is best characterized by heterogenous moderate to markedly increased  $^{18}\text{F}$ -FDG uptake in the left ventricular myocardium. If myocarditis is clinically suspected, patients are best prepared prior to PET/CT scanning with a high fat very low carbohydrate diet and prolonged fasting protocol optimized for suppression of physiological  $^{18}\text{F}$ -FDG

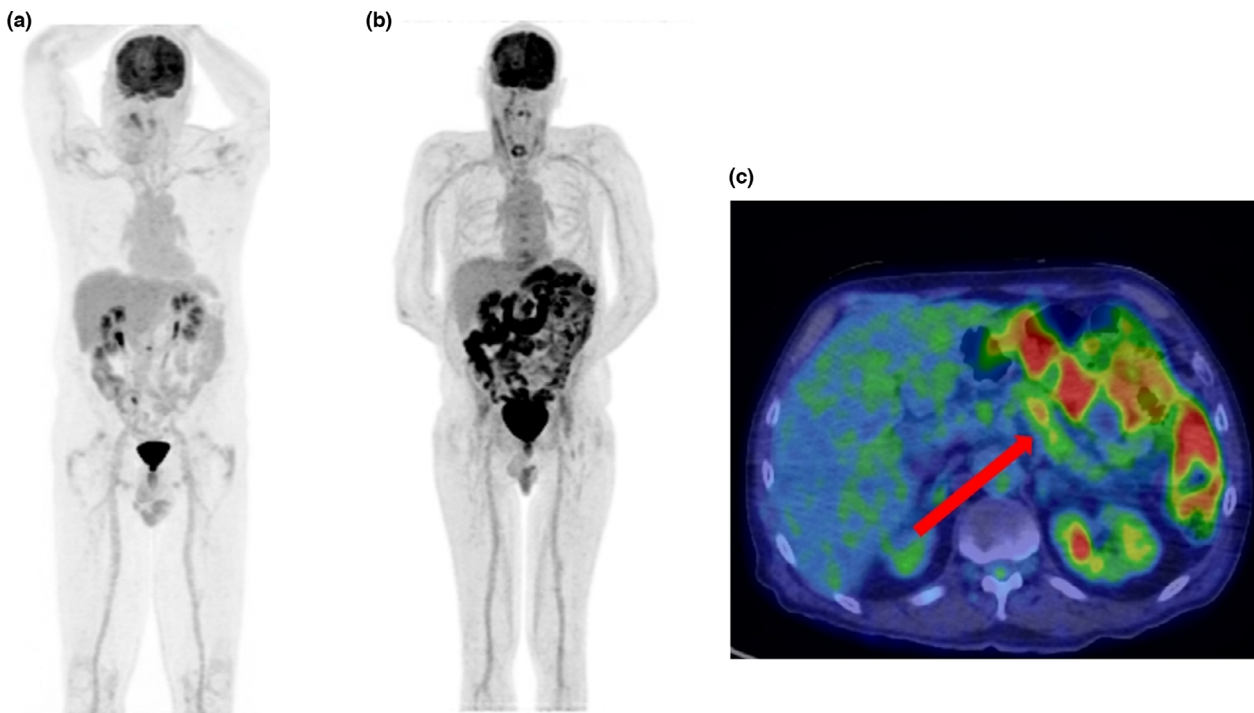
myocardial uptake similar to that recommended for Cardiac Sarcoidosis work up.<sup>13</sup>

## Pneumonitis

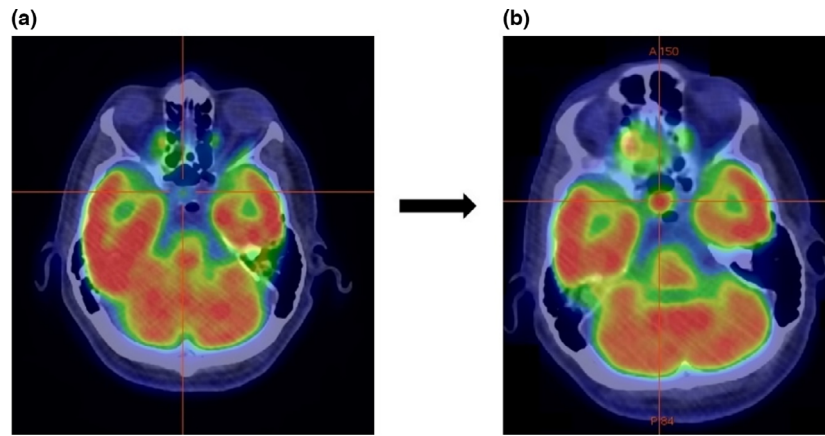
The incidence of pneumonitis with PD1/PDL1 Inhibitors ranges from 0% to 10%<sup>14</sup> and is defined as focal or diffuse inflammation of the lung parenchyma. Pneumonitis can also occur with chemotherapy (docetaxel,<sup>15</sup> gemcitabine,<sup>16</sup> bleomycin<sup>17</sup>) or prior radiotherapy<sup>18</sup> hence the clinician must be extra vigilant for this complication



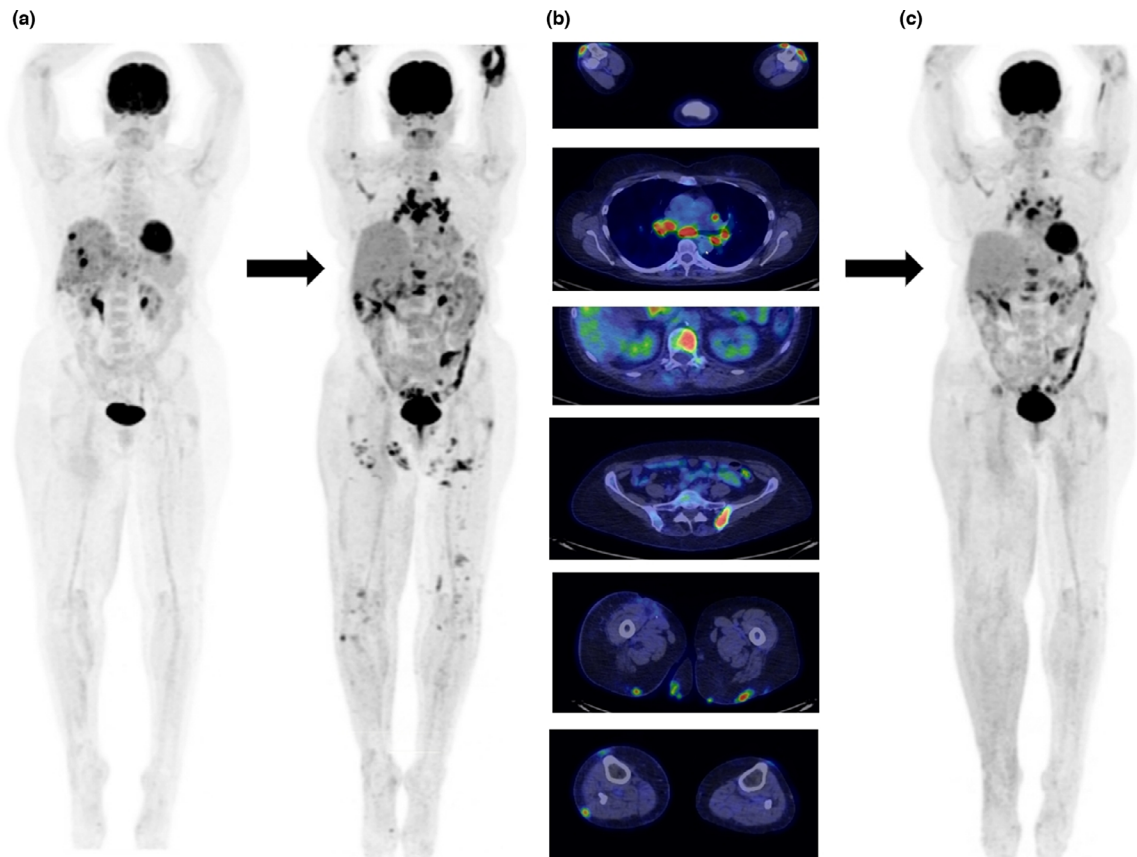
**Fig. 9.** Colitis. Seventy-year-old man with metastatic melanoma treated with four cycles pembrolizumab. (a) Baseline PET MIP demonstrates low volume metastatic disease right cervical nodes, subcutaneous tissues left upper neck and right upper back. (b) Post four cycles pembrolizumab PET MIP demonstrating complete resolution of metastatic disease but diffuse markedly increased <sup>18</sup>F-FDG uptake throughout the colon in keeping with Colitis. (c) Axial fused PET/CT images demonstrate corresponding diffuse intense <sup>18</sup>F-FDG uptake throughout the transverse colon.



**Fig. 10.** Pancreatitis. Sixty-five-year-old man with metastatic melanoma treated with pembrolizumab. (a) Baseline PET MIP demonstrates complete metabolic tumour remission post four cycles pembrolizumab. Small focus intense <sup>18</sup>F-FDG uptake L2/3 spinous process in keeping with benign arthritic change. Further small focus intense <sup>18</sup>F-FDG uptake right pelvis in keeping with physiological urinary activity right ureter. (b) Post eight cycles pembrolizumab PET MIP demonstrates intense <sup>18</sup>F-FDG uptake in colon (colitis), small bowel (enteritis) and moderate uptake in pancreas (pancreatitis). (c) Axial Fused PET/CT images demonstrating intense <sup>18</sup>F-FDG uptake colon and small bowel loops and mild-to-moderate uptake in pancreas (arrow) in keeping with pancreatitis.



**Fig. 11.** Hypophysitis. Sixty-one-year-old man with metastatic melanoma treated with combination ipilimumab and nivolumab. (a) Baseline Axial Fused PET/CT images of pituitary gland. (b) Post four cycles immunotherapy Axial Fused PET/CT images demonstrating focal intense  $^{18}\text{F}$ -FDG uptake in the pituitary gland consistent with hypophysitis.



**Fig. 12.** Panniculitis/granulomatous disease. Sixty-year-old woman with metastatic melanoma treated with combination ipilimumab and nivolumab. (a) Baseline PET MIP demonstrates multiple liver metastases. (b) PET MIP and Axial fused PET/CT images post two cycles ipilimumab and nivolumab demonstrate relatively symmetrical intensely  $^{18}\text{F}$ -FDG-avid bilateral pulmonary hilar and mediastinal nodes in keeping with immune mediated granulomatous disease/sarcoidosis. Multiple intensely  $^{18}\text{F}$ -FDG-avid subcutaneous nodules bilateral elbow, gluteal, thigh and knee regions confirmed on biopsy as non-necrotizing granulomata (panniculitis). Multiple new  $^{18}\text{F}$ -FDG-avid bony lesions in T10, T11, T12 and the left ilium in keeping with new metastatic disease or further bone granulomata. (c) PET MIP images following 75 mg weaning Prednisolone dose daily for 3 weeks demonstrating complete resolution of subcutaneous panniculitis and reduction of pulmonary hilar and mediastinal granulomatous disease.



**Table 2.** Incidence of organ specific autoimmune side effects from checkpoint inhibitors (adapted with permission)<sup>22</sup>

Adverse effect	PD1/PDL1 inhibitor	CTLA-4 inhibitor	Combination
Hyperthyroidism			
All grade	5% (4–6)	4% (2–7)	NA
Grade 3–4	0% (0–0)	NA	NA
Hypothyroidism			
All grade	8% (7–9)	3% (2–5)	15% (12–19)
Grade 3–4	0% (0–0)	0% (0–0)	0% (0–2)
Arthralgia			
All grade	8% (7–11)	5% (3–9)	11% (8–14)
Grade 3–4	0% (0–0)	0% (0–1)	0% (0–2)
Myositis			
All grade	0% (0–1)	NA	NA
Grade 3–4	0% (0–0)	NA	NA
Pneumonitis			
All grade	4% (2–6)	1% (0–2)	NA
Grade 3–4	1% (1–2)	1% (0–1)	NA
Colitis			
All grade	1% (1–2)	8% (6–10)	16% (10–25)
Grade 3–4	1% (0–1)	5% (4–6)	11% (6–19)
AST or ALT elevation			
All grade	5% (4–7)	5% (2–9)	19% (15–23)
Grade 3–4	1% (1–2)	2% (1–4)	9% (6–12)
Hypophysitis			
All grade	1% (0–1)	4% (2–7)	NA
Grade 3–4	0% (0–0)	2% (1–3)	NA
Rash			
All grade	10% (8–13)	23% (19–27)	41% (36–45)
Grade 3–4	0% (0–1)	1% (1–2)	5% (3–7)
Pruritis			
All grade	15% (12–17)	25% (21–29)	34% (29–38)
Grade 3–4	0% (0–2)	1% (0–1)	2% (1–4)

Values in parenthesis are 95% CI. NA, not available.

should immunotherapy be combined with these treatments due to significant cumulative risk. The most common CT findings of pneumonitis are organizing pneumonia pattern and ground glass opacities.<sup>19</sup> On PET/CT scan, these changes can vary from mild to intensely FDG-avid depending on the severity of pneumonitis (Fig. 8).

## Colitis

The incidence of Colitis is up to 15% for combination PD1/CTLA-4 checkpoint inhibitor therapy,<sup>20</sup> up to 8% for CTLA-4 and 2% for PD1/PDL1 therapy alone respectively.<sup>4</sup> PET/CT scanning usually demonstrates heterogeneous moderate to markedly increased <sup>18</sup>F-FDG uptake in the colon. It should be noted, there can be quite significant variable physiological <sup>18</sup>F-FDG uptake in the colon. The use of metformin in particular results in markedly increased non-pathological uptake of <sup>18</sup>F-FDG in the colon and should be ceased at least 48 h prior to scanning.<sup>21</sup> Colonoscopy and biopsy remain the gold standard for diagnosis (Figs 5, 9).

## Oesophagitis/gastritis

Both oesophagitis and gastritis are relatively common and not always immunotherapy related. Nonetheless, mild-to-moderate increases in <sup>18</sup>F-FDG uptake are frequently demonstrated in patients undergoing immunotherapy.

## Hepatitis/pancreatitis

The incidence of hepatitis is ~5% for single agent CTLA-4 or PD1/PDL1 inhibitors and rises to 19% for combination therapy. Hepatitis is generally not visualized on <sup>18</sup>F-FDG PET/CT scanning. The incidence of clinically significant pancreatitis with either CTLA-4 or PD1/PDL1 inhibitors is approximately 1–2%.<sup>4</sup> This is manifest on PET/CT scanning by increased <sup>18</sup>F-FDG uptake within the pancreas, with a correlation between the degree of uptake and severity of pancreatitis (Fig. 10).

## Hypophysitis

Hypophysitis is predominantly a complication of CTLA-4 inhibitors with an incidence of ~4%.<sup>4</sup> It occurs in ~1% of PD1/PDL1 therapy. The anterior pituitary gland is generally affected and is manifest on PET/CT scan by new focal moderate to markedly increased <sup>18</sup>F-FDG uptake in the pituitary gland post immunotherapy commencement (Fig. 11).

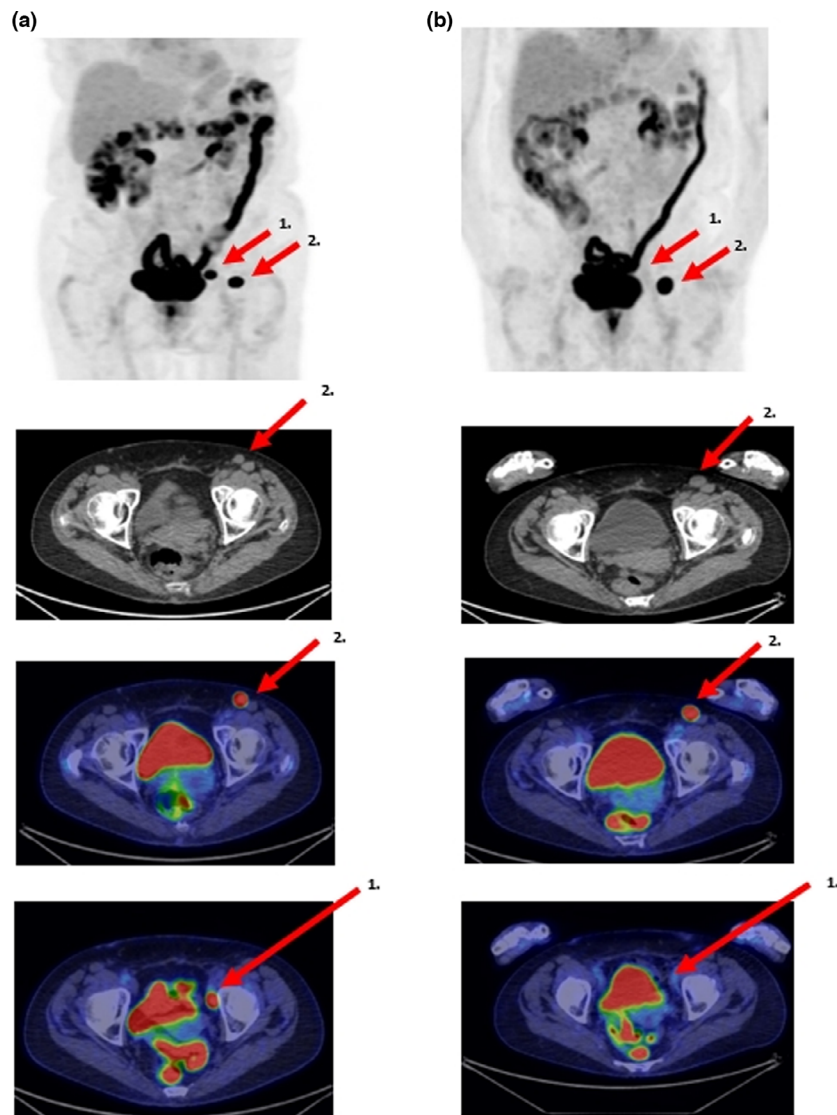
## Cutaneous conditions/panniculitis

Autoimmune rash and pruritis are common with immune checkpoint inhibitors, up to 25% with CTLA-4, 15% with PD1/PDL1 and 41% with combination therapy.<sup>22</sup> Cutaneous manifestations are generally not visualized on <sup>18</sup>F-FDG PET/CT scanning.

Immune mediated inflammation of subcutaneous tissue/fat (panniculitis) can be visualized on PET/CT and is manifest by mild to moderately <sup>18</sup>F-FDG-avid nodules within areas of subcutaneous fat, most frequently in the buttock and anterior abdominal regions and extensor and flexor surfaces of the arms and legs (Fig. 12, Table 2).

## Pseudoprogression

Pseudoprogression describes the phenomenon of apparent disease progression (increase in size and FDG-avidity of pre-existing lesions or increase in number FDG-avid lesions) on an <sup>18</sup>F-FDG PET scan within 12 weeks of commencement of immunotherapy. This is subsequently followed by a decrease in tumour burden if immunotherapy is continued. Immunotherapy related pseudoprogression is seen in up to 10% of Melanoma patients (especially those on CTLA-4 inhibitor therapy), 8% of renal cell carcinoma, 7% Urothelial cell, 6% Non-Small Cell lung cancer and 2% Head and Neck Squamous cell carcinoma patients.<sup>23</sup>



**Fig. 13.** Melanoma pseudoprogression. Eighty-six-year-old woman with metastatic melanoma treated with pembrolizumab. (a) Baseline PET MIP, Axial CT and fused PET/CT demonstrates metastatic left external iliac (Arrow 1) and left inguinal (Arrow 2) nodal metastases. (b) PET MIP, Axial CT, Axial fused PET/CT 12 weeks post pembrolizumab treatment demonstrates resolution of left external iliac node (Arrow 1) but significant increase in size and FDG-avidity of left inguinal node (Arrow 2) suggestive of disease progression. Left inguinal node surgically excised 4 weeks later, with histopathology demonstrating fibrosis and chronic inflammatory change only with no evidence of melanoma (pseudoprogression).

There is no consensus as to the exact molecular mechanism of pseudoprogression; however, it is generally associated with a presumed immune mediated inflammatory infiltrate around and within the tumour on histology. Metabolically active inflammatory cells exhibit increased  $^{18}\text{F}$ -FDG uptake on PET scans, which likely accounts for the apparent increase in size and FDG-avidity of malignant lesions and possible new lesions, which likely reflect inflammatory granulomas rather than malignant disease.<sup>24</sup>

It is important for clinicians and PET/CT reporting specialists to be aware of this phenomenon in order to

prevent the premature discontinuation of treatments, which otherwise may be effective.

To take into account pseudoprogression, a modified RECIST 1.1 for immune-based therapeutics Response Evaluation Criteria in Solid Tumours (termed iRECIST) has been developed by the RECIST working group.<sup>25</sup> The main difference between iRECIST and standard RECIST 1.1 is the concept of resetting the bar if progression is followed by tumour shrinkage at the next assessment.

A new category of unconfirmed progression (iUPD) has been created in iRECIST, which requires confirmation of

progression (increase in size or number of lesions) on follow up imaging. This is generally recommended at 4–8 weeks following an initial study demonstrating apparent disease progression.<sup>26</sup>

An example of Melanoma pseudoprogression is provided in Fig. 13.

## Hyperprogression

Hyperprogression describes unexpected true rapid disease progression following the commencement of immunotherapy and is reported to occur in up to 4–29% of cases.<sup>27</sup> This is usually reflected on <sup>18</sup>F-FDG PET/CT as a rapid increase in size, number and intensity of FDG-avid lesions, which are confirmed as disease on histology. As expected, progression free and overall survival is significantly worse in this cohort of patients.

The phenomenon of hyperprogression is somewhat controversial with ongoing debate as to whether immunotherapy is truly driving accelerated tumour growth or whether the tumour intrinsically has a more aggressive phenotype and would progress in this accelerated manner regardless of treatment type.<sup>28</sup> Nonetheless, clinicians need to be aware of this potential phenomenon as if rapid disease progression is confirmed, change in treatment is warranted.

## Summary

The use of immunotherapy for a wide variety of malignancies continues to grow and both clinicians and PET/CT specialists need to be familiar with the imaging characteristics and potential pitfalls unique to this type of therapy in order to deliver optimal and appropriate patient care. The upregulation of immune pathways by immune checkpoint inhibitors can result in a broad range of adverse effects that can affect any organ system many of which have characteristic appearances on <sup>18</sup>F-FDG PET/CT.

Further complicating immunotherapy response evaluation with <sup>18</sup>F-FDG PET/CT is the phenomenon of pseudoprogression where a small proportion of patients exhibit apparent disease progression on <sup>18</sup>F-FDG PET/CT despite actually having a true underlying, sometimes complete response to treatment.

Conversely, hyperprogression describes rapid unexpected true disease progression on <sup>18</sup>F-FDG PET/CT following commencement of immunotherapy and portends a poor prognosis.

Being familiar with the broad range of possible immunotherapy induced <sup>18</sup>F-FDG PET/CT changes, reviewing prior imaging and all PET/CT components along with correlation with the patient's clinical history are all essential in the accurate interpretation of <sup>18</sup>F-FDG PET/CT in this era of Immunotherapy. If there are incongruent features, there should be a low threshold for biopsy and histological correlation.

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## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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