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REVIEW ARTICLE

Adverse effects and radiological manifestations of new immunotherapy agents

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ABSTRACT

Immunotherapy has had increasing use in Medical Oncology for a diverse range of primary malignancies. There are various types of immunotherapy which are grouped based on mechanism of action. In recent decades, the immune checkpoint inhibitors (ICI) immunotherapies have been at the forefront of Medical Oncology, sparked by very encouraging results. Some patients with metastatic cancer who were previously deemed palliative were seeing durable response rates and significant increased survival with ICIs. The mechanism of action of ICIs vary wildly compared to the conventional, cytotoxic chemotherapy, upon which traditional radiology response criteria were based and validated upon. Novel responses such as pseudo progression, disease response in the context of new metastases and prolonged stable disease were observed and correlated with improved patient survival with ICI. New radiology response criteria were proposed to better capture disease response to ICI; however, the criteria have been applied heterogeneously and there is continued work in this sector. In addition to the novel responses, ICIs have been linked to numerous, diverse immune-related adverse events (irAE) affecting multiple systems. A large majority of these are mild, but some irAEs are life threatening. Only some of the irAEs have radiological manifestations. It is important that the reporting radiologist recognises potential irAE so clinical teams can be alerted, ICI treatment paused or ceased and steroid treatment initiated. This review will discuss the evolution of the radiology response criteria in ICI and the varied radiological appearances of irAE.

INTRODUCTION

Immunotherapy has been a major advance in cancer treatment and is increasingly used in a diverse range of primary malignancies. Immunotherapy takes advantage of the immune system to improve its anti-tumour response. Immunotherapy is broadly divided into passive and active immunotherapy treatments (Table 1). In passive immunotherapy, preformed antibodies, made *in vitro*, are administered and directed against antigens on the tumour surface. The antibodies bind to the respective target antigen and eliminate tumour cells.

Conversely, active, anti-cancer immunotherapy potentiates the adaptive immune system to stimulate a host anti-tumour response. Tumour cells have created multiple mechanisms to evade destruction by the immune system such as disrupting effective antigen presentation, reducing efficacy of T-cell function and up-regulating pathways that promote tolerance and T-cell anergy.¹ Active immunotherapy attempts to disrupt the aforementioned mechanisms, and are grouped into different subtypes by their mechanisms of action (Table 1). Of these, a type of immunomodulatory

monoclonal antibody, known as immune checkpoint inhibitors (ICI) have caused the most seismic change in medical oncology. Numerous ICIs are now Food and Drug Administration (FDA) approved for a variety of malignancies.²

Checkpoint proteins are receptors expressed on the surface of T lymphocytes and help to down-regulate the immune system, thereby preventing autoimmunity. When checkpoint proteins are bound to certain ligands expressed on the antigen presenting cells of normal and cancerous tissue, T-cell-mediated death is evaded. Using this mechanism, tumours have evaded destruction by the immune system. ICIs are monoclonal antibodies which prevent the checkpoint protein and ligands from binding and thereby permitting T-cell-mediated death of tumour cells.²

The most established ICI is the monoclonal antibody ipilimumab, a cytotoxic T lymphocyte-associated 4 (CTLA-4) inhibitor, which was the first ICI to be approved by the FDA. It is now standard treatment for metastatic malignant melanoma. CTLA-4 is a checkpoint protein expressed on cytotoxic T lymphocytes, which when bound to B7 proteins

Table 1. Examples of active and passive immunotherapy and their common indications in cancer

Subtype of immunotherapy	Example	Common indications
Active immunotherapy <i>Potentiates the adaptive immune system to stimulate a host anti-tumour response</i>		
Recombinant cytokines	Interleukin-2 (IL-2)	Renal cell carcinoma and melanoma
Biochemotherapy	Single-agent or combination chemotherapy and interferon	
Vaccinations	Tumour cell vaccines, Antigen Vaccines Dendritic cell vaccines	GBM= Advanced prostate cancer
Immunomodulatory monoclonal antibodies	Immune checkpoint inhibitors (ICI)	
	Cytotoxic T lymphocyte (CTLA-4) inhibitor e.g. Ipilimumab	Melanoma
	Programmed cell death protein (PD-1) e.g. Pembrolizumab	Non-small cell lung cancer h-n squamous cell carcinoma
	Programmed death ligand (PDL-1) e.g. Atezolizumab	Urothelial carcinoma
Passive immunotherapy <i>Also known as adoptive immunotherapy</i>		
Preformed antibodies	Bevacizumab (Avastin)	Colorectal, non-small cell lung cancers, renal cell carcinoma and glioblastoma multiforme
	Trastuzumab (Herceptin)	HER2 positive metastatic breast cancer and HER2 positive gastric cancer
	britumomab tiuxetan (Zevalin) labelled with ⁹⁰ Y	Follicular B-cell non-Hodgkin's lymphoma

h-n, Head and neck; ICI, immune checkpoint inhibitors; HER2, Human epidermal growth factor receptor 2; GBM, Glioblastoma multiforme;

expressed on normal cells and some malignant cells, prevents T-cell mediated destruction. Ipilimumab binds to the CTLA-4 protein preventing it from binding to the B7 protein, allowing T-cell mediated death.

Another well-exploited checkpoint pathway is the programmed cell death protein 1 (PD-1) and programmed death ligand (PDL-1) axis, which is a critical component of tumour-mediated immunosuppression PD-1, is expressed on the surface of cytotoxic T-cells. When it interacts with PDL-1 on antigen presenting cells, T-cell-mediated death is evaded. Monoclonal antibodies targeting PD-1 and PDL-1 have been approved by the FDA for melanoma, non-small cell lung cancer (NSCLC) and urothelial cancers.

ICIs, and immunotherapy in general, have a very different mode of action compared to conventional, cytotoxic chemotherapy. This contrast has resulted in distinct tumour responses requiring unique response criteria, and adverse event profile which will be the topic of this review.

RADIOLOGY RESPONSE ASSESSMENT

Radiology plays a crucial role as an imaging biomarker in evaluating solid tumours. It informs patient management in routine oncology practice, and imaging is frequently a surrogate end point in clinical trials with serial scans demonstrating change in tumour volume in response to treatment. Guidelines to standardise the reporting of radiology response were formulated to ensure reproducible and uniform reporting across multisite trials. The two initial criteria were the World Health

Organisation, which requires bi-dimensional measurement of target lesions, and response evaluation criteria in solid tumours (RECIST), which requires uni-dimensional measurement of target lesions.^{3,4} RECIST is more widely applied.

The most recent version of RECIST, RECIST 1.1, summates the target lesions' dimensions and non-measurable disease at baseline. The post-treatment sum of disease (SOD) and status of non-measurable lesions are compared to the baseline or nadir scans to determine response (Table 2). Importantly, new disease and early tumour growth denotes progressive disease or treatment failure. Stable disease (SD) may be viewed as treatment success or failure depending on the required oncological response.

The RECIST guidelines were formed on treatment response to conventional, cytotoxic chemotherapy, which blindly targets actively dividing cells. Their intended effect produces tumour shrinkage correlating to improved overall survival. RECIST therefore classifies tumour shrinkage as response and tumour enlargement or new disease as progressive disease (PD).

When RECIST 1.1 was applied to assess immunotherapy response, it demonstrated clear limitations. Reduction of measurable tumour burden with immunotherapy takes longer compared to cytotoxic chemotherapy despite a sufficient immune response. The infiltration of tumour by the body's immune cells or oedema can result in an apparent increase in tumour volume, a phenomenon termed "pseudo progression". Additionally, reduction in tumour burden can occur after RECIST 1.1 defined PD. Studies

Table 2. A summary of the important features of the different response criteria

	RECIST 1.1 (4)	irRC	irRECIST	iRECIST
Target lesion TL minimum size	<ul style="list-style-type: none"> • ≥ 10 mm • ≥ 15 mm if lymph nodes 	$\geq 5 \times 5$ mm	Follows RECIST 1.1	Follows RECIST 1.1
TL measurement	Uni-dimensional	Bi-dimensional	Uni-dimensional	Uni-dimensional
Maximum number of TLs	10 visceral & 5 cutaneous	5 (maximum of 2 per organ)	5 (maximum of 2 per organ)	5 (maximum of 2 per organ)
New lesions	Defines PD	Include in SOD	Include in SOD	iUPD
Response	PD: $\geq 20\%$ $\uparrow$ SOD PR: $\geq 30\%$ $\downarrow$ SOD SD: neither PD or PR CR: resolution of all TL	PD: $\geq 25\%$ $\uparrow$ SOD PR: $\geq 50\%$ $\downarrow$ SOD SD: neither PD or PR CR: resolution of all TL	Follows RECIST 1.1	Follows RECIST 1.1
Year of publication	2009	2009	2013	2017

CR, complete response; irRC, immune-related response criteria; iUPD, unconfirmed progressive disease; PD, progressive disease; PR, partial response; RECIST, response evaluation criteria in solid tumours; SD, stable disease; TL, target lesion;

using cytokines, cancer vaccines and monoclonal antibodies have demonstrated complete response, partial response or stable disease after RECIST 1.1 defined PD.^{5–8} Applying RECIST 1.1 to define PD leads to premature, inappropriate cessation of treatment. Prolonged, stable tumour burden may also be considered as anti-tumour activity and durable response in the context of immunotherapy. In response, various immunotherapy response criteria have been developed in the past decade (Table 2).

irRC

Immune-related response criteria (irRC) was developed in 2009 based on results from a phase II clinical trial treating advanced melanoma patients with ipilimumab.⁵ Four patterns of positive response to treatment were noted in these patients.

- (1) Response in baseline lesions evident by week 12
- (2) Stable disease, which in some patients was followed by a slow steady decline in tumour burden.
- (3) Response after initial increase in tumour burden (pseudo progression).
- (4) Reduction in total tumour burden during or after appearance of new lesions at time points > 12 weeks.

In irRC, a maximum of 10 visceral and 5 cutaneous target lesions are selected at baseline. Bi-dimensional measurements of each target lesion is used, similar to WHO criteria,³ to calculate an SOD. Radically, new lesions were included in the SOD and could be seen in the context of partial response or stable disease. A confirmatory scan ≥ 4 weeks after the first PD scan is needed before PD status can be “confirmed”, helping to exclude possible pseudo progression (see below).

irRECIST

A major limitation of the irRC criteria was the length of time required to assess radiological response due to the large number of target lesions and their bi-dimensional measurements. In 2013, irRECIST or irRECIST 1.1 was proposed using uni-dimensional measurements of target lesions. This was based on a study of 57 advanced melanoma patients treated with ipilimumab in which uni-dimensional measurements correlated equally well with bi-dimensional measurements and were more reproducible.⁹

However, the subsequent application of irRECIST was applied inconsistently in future studies. Additionally, some studies made their own modifications of irRECIST leading to concerns about the accurate interpretation of pooled data.¹⁰

iRECIST

In response to the heterogeneity in the application of immune-related response criteria (irRECIST), a consensus-based, immunotherapy response guidelines, iRECIST, was published in 2017 to define a response criteria to be used prospectively, accumulating a pool of data from which the criteria could be tested and validated. Its primary aim is to provide a consistent framework for the management of clinical trial data and not to influence clinical practice or treatment decisions. iRECIST has not yet been clinically validated and its use is advised for clinical trial protocols only. The response criteria is identical to the RECIST 1.1 until the point of progressive disease. If RECIST 1.1 progressive disease is reached, it is assigned the status of unconfirmed progressive disease (iUPD) under iRECIST. A repeat scan is performed 4–8 weeks after and progressive disease [confirmed progressive disease (iCPD)] is confirmed if the SOD continues to be $\geq 20\%$ compared to the baseline/nadir, the pre-existing new disease is larger, or if there are further new metastases. If iCPD is not confirmed, stable disease, partial response or complete response is assigned based on the SOD compared to baseline/nadir and treatment continues if clinically appropriate. Importantly, if iCPD is not confirmed, the “bar is reset” and the previous iUPD is effectively ignored. iUPD then needs to occur again before iCPD can be assigned in the future [Figure 1].

Pseudo progression

With the use of ICI, the pseudo progression phenomenon has been observed. This has been defined in some studies as a $\geq 25\%$ increase in tumour burden at or earlier than week 12 that was not confirmed as progressive disease (PD) at subsequent assessments.¹¹ Tumour burden can be seen to increase and then subsequently stabilise or regress¹² [Figure 2]. This pattern may be due to continued tumour growth until a sufficient immune response develops, infiltration of the tumour with immune-cell infiltrates and oedema or T-cell infiltration into established, radiologically undetectable tumour

Figure 1. An example of the application of the iRECIST criteria. A patient with metastatic bladder cancer treated with an anti PD-1 ICI. (A) At baseline, there was no lymphadenopathy posterior to the left psoas muscle (arrowed). (B) After the first cycle of treatment, there was new lymphadenopathy posterior to the left psoas muscle (arrowed). Disease elsewhere was stable and the status iUPD was assigned. (C) A repeat CT 4 weeks later demonstrated stable lymphadenopathy posterior to the left psoas muscle (arrowed). There were no new sites of disease and disease elsewhere was stable compared to baseline, therefore progressive disease was not confirmed. The new assigned status became iSD. ICI, immune checkpoint inhibitors; iUPD, unconfirmed progressive disease; RECIST, response evaluation criteria in solid tumours.

deposits. In the large study on which the irRECIST guidelines were based, 9.7% of the patients demonstrated pseudo progression.⁵ A subsequent study showed 7% of patients treated with pembrolizumab for metastatic melanoma had pseudo progressive disease. When RECIST 1.1 and irRC was applied to the same cohort, 15% had RECIST 1.1 progressive disease but non-progressive disease by irRC. These patients had a longer overall survival compared to the patients classified as progressive disease with RECIST 1.1 and

irRC indicating irRC correlated better with disease outcome. This strengthened the argument for continuing treatment beyond radiographic progression.¹¹

Hyper progression

A deleterious response effect has also been observed. A phenomenon, hyper progressive disease (HPD) has been observed.

Figure 2. (a) An example of pseudoproggression. A patient with metastatic lung cancer treated with atezolizumab, an anti PD-L1 ICI. (A) At baseline, the adrenal glands are normal. (B) After the initial cycle of atezolizumab, there are new, bilateral, heterogeneous adrenal masses. The patient was treated past RECIST 1.1 progression. (C) On the subsequent scan, the adrenal masses are smaller. (D) On further imaging with continued atezolizumab, the left adrenal mass is barely perceptible, and the right adrenal mass is significantly smaller. Series of images of the upper abdomen of the same patient (b) (A) No metastatic disease is seen in the left upper quadrant (B) After the initial cycle of atezolizumab, there is a new metastatic peritoneal deposit in the left upper quadrant (C) On subsequent scanning, the left upper quadrant peritoneal deposit is smaller. (D) On further imaging with continued atezolizumab, the left upper quadrant peritoneal deposit has completely resolved. ICI, immune checkpoint inhibitors; RECIST, response evaluation criteria in solid tumours.

Figure 3.(a) Hyperprogressive disease in a patient with metastatic TCC previously treated with a cystectomy and right nephro-ureterectomy. (A) At baseline, there was mild fat stranding in the left iliac fossa with no convincing mass. A urostomy bag and pelvic surgical clips were noted. (B) After treatment with durvalumab, there is a heterogeneous, large, left iliac fossa mass with adjacent peritoneal fat stranding. (C) On the subsequent scan, the mass increased exponentially in size in keeping with HPD. There was also internal hypodensity representing tumour necrosis. Images through the upper abdomen from the same patient as Figure 2 demonstrates HPD in other sites. (b) (A) At baseline, there is a metastatic deposit in the right renal bed. (B) After four months of treatment with durvalumab, the right renal bed mass was significantly larger. (C) A further scan showed further marked increase in size in the metastasis which invaded the right lobe of the liver. HPD was also seen in peritoneal and bone metastases in this patient. HPD, hyper progressive disease. TCC, transitional cell carcinoma.

Champiat et al reported HPD in 9% of patients on anti PD-1/PD-L1 ICI for a range of primary malignancies. In this study, HPD was defined as a RECIST defined progressive disease at first evaluation, and $\geq$ twice tumour burden.¹³ [Figure 3] Older patients appeared to be at greater risk of HPD. There was no association with tumour burden at baseline or a specific tumour type.

A further study, found a HPD incidence of 29% for patients treated with anti PD-1/PD-L1 ICIs in the context of metastatic Head and neck (h-n) squamous cell carcinoma.¹⁴

Kato et al investigated the influence of the tumour genomic profile on the risk of HPD.

They reviewed patients treated with anti PD-1, PD-L1 or CTLA-4 ICIs with stage IV malignancy of various primaries. HPD was defined as time to failure <2 months, a > 50% increase in tumour burden within 2 months of initiation of ICIs and greater than two-fold increase in progression pace. They found all patients with MDM2/MDM4 gene family amplification developed HPD. 20% of the patients with EGFR alterations developed HPD. Based on these results, there was a strong suggestion that certain tumour genomic profiles are at significantly increased risk of HPD and perhaps the profile should influence the use of ICIs.

Immune-related adverse events (irAE)

ICIs have a relatively mild toxicity profile compared to conventional cytotoxic chemotherapy. However, there are recognised adverse events some of which have resulted in deaths. Practice guidelines on toxicities and their management have been published along with grading systems to assess severity.¹⁵ In one study 62% of patients treated with ipilimumab for metastatic melanoma developed a form of immune-related adverse events (irAE).¹⁶ The incidence of irAE may be dose dependent with one study demonstrating an association between the incidence and severity of irAE with increasing ipilimumab dose.¹⁷ irAE have been observed more in ipilimumab compared to anti PD-1/PDL-1 ICIs. This has been attributed to CTLA-4 being part of the early immune response primarily in central, lymphoid tissue, whereas PD-1 limits T-cell responses later in the immune response and primarily in peripheral tissue.¹⁸

Adverse effects are due to induction of autoimmunity or a pro-inflammatory state and increase in T-cell activation. Whilst the ICIs drugs modulate the immune system to reduce tolerance to tumour cells, it also sparks systemic loss of tolerance. In one large cohort of metastatic melanoma patients treated with ipilimumab, the range of irAE was so broad it was suggested "since ipilimumab-induced irAEs can virtually affect any organ system physicians have to consider all symptoms as potentially ipilimumab-associated" and all patients should report all symptoms even if deemed unrelated.¹⁹

Table 3. A table of the more common irAEs in each system

Skin toxicity	Rash
	Pruritis
	Vitiligo
Endocrinopathies	Hypo/hyperthyroidism
	Hypophysitis
	Type 1 diabetes mellitus
Hepatobiliary toxicity	Hepatitis
	Pancreatitis
Gastrointestinal toxicity	Diarrhoea
	Enterocolitis
Lung toxicity	Pneumonitis
Neurological toxicity	Encephalitis
	Transverse myelitis
	Guillain Barré
Rheumatological	Myalgia
	Arthralgia
Renal toxicity	Nephritis
Cardiac toxicity	Pericarditis
	Arrhythmias
	Myocarditis

irAE, immune-related adverse events ;

Many of the irAE do not have radiological manifestations such as immune-related skin toxicity, nephritis, ocular and some endocrinopathies which are diagnosed clinically. IrAE with radiological findings will be discussed further.

Figure 4. A patient with choroidal melanoma with hepatic metastases and retroperitoneal lymphadenopathy treated with anti CTLA-4 ICI. The patient presented with sudden loss of visual fields and visual acuity over days prompting an MRI of the brain. (A) Sagittal reformat of the baseline CT head. The pituitary gland was normal in size. (B) T1 sagittal sequence at acute presentation of neurological symptoms. The pituitary gland was newly enlarged. (C) T1 enhanced coronal sequence shows an enlarged pituitary gland which is enhancing avidly. Hypophysitis was diagnosed. (D and E) T1 sagittal and coronal sequences respectively. After treatment with steroids, the pituitary gland returned to a normal size with normal enhancement. ICI, immune checkpoint inhibitors.

Endocrinopathies

Various endocrine disorders have been known to be induced by ICIs (Table 3).

Hypophysitis is inflammation of the anterior lobe of the pituitary gland which presents with headache, fatigue, dizziness and memory impairment. Most patients have anterior pituitary hormone deficiencies at presentation and hormone replacement should be instituted soon after diagnosis.²⁰ It has been reported in 10% of patients with CTLA-4 ICIs and <1% of patients treated with anti PD-1 or anti PD-L1 ICIs. It is the most common endocrine irAE in patients receiving ipilimumab. It typically presents at 6–12 weeks after initiation of anti CTLA-4 therapy. MRI findings include an enlarged pituitary gland and stalk with variable heterogeneous or homogeneous enhancement.²¹ [Figure 4] Treatment is a form of high-dose glucocorticoids and temporary or complete cessation of ICI treatment.

Pneumonitis

Pneumonitis is a focal or diffuse inflammation of the lung parenchyma. Pneumonitis due to chemotherapy and radiotherapy is well established and documented. Studies have described pneumonitis also in the context of ICI. The largest series reports a 5% (43 patients in a cohort of 915) incidence of pneumonitis of patients on anti PD-1 and anti PD-L1 ICI for a variety of primary malignancies (NSCLC, malignant myeloma, bladder, breast, pancreatic, h-n). Patients taking anti PD-1 or anti PD-L1 ICIs in combination with anti CTLA-4 ICIs had a statistically significant greater incidence of pneumonitis compared to patients taking anti PD-1 or anti PD-L1 ICIs as a monotherapy. The median time to onset was 2.8 months after starting therapy. 56% had additional immune-related toxicity. 86% of patients with pneumonitis improved or resolved. 12% worsened, were treated with

Figure 5. Serial CT chests of a patient with triple negative breast cancer with lymph node metastases treated with pembrolizumab, an anti PD-1 ICI. (A) The lung parenchyma was normal at the baseline scan 15/7/16. (B) After three cycles of pembrolizumab, the patient developed shortness of breath and chest tightness. Discrete, patchy areas of consolidation were seen in a subpleural, peripheral distribution on CT. (C) Symptoms improved with steroids; however, on the subsequent CT performed two months after Figure 6b, the areas of consolidation increased in size. Air bronchograms were seen in an area of consolidation in the left lower lobe (see arrow). This pattern of pneumonitis is in keeping with the cryptogenic organising pneumonia radiological subtype of irAE pneumonitis. ICI, immune checkpoint inhibitors.

immune suppression and corticosteroids and subsequently all died.²²

Five radiological subtypes were described. Cryptogenic organising pneumonia [Figure 5], ground glass opacities, interstitial, hypersensitivity and pneumonitis not otherwise specified. Cryptogenic organising pneumonia, observed in 19% of cases, was described on CT as discrete patchy or confluent consolidation $\pm$ air bronchograms predominantly in a peripheral or subpleural distribution. Ground glass opacities, observed in 37% of cases, were seen as discrete focal areas of increased attenuation with preserved bronchovascular markings. The interstitial subtype CT findings, seen in 22% of cases, were increased interstitial markings with interlobular septal thickening, peribronchovascular infiltration and subpleural reticulation (Figure 6). The hypersensitivity subtype (seen in 7% of cases) described centrilobular nodules and tree-in-bud nodularity on CT. The pneumonitis not otherwise specified subgroup, described in 15% of cases, had a mixture of nodular and other subtype patterns on CT. There are no pathognomonic radiographic features to distinguish ICI-related pneumonitis from pneumonitis of another aetiology. Lung biopsies may help clarify in select cases if the underlying aetiology is unclear.¹⁵ Clinical history of concomitant ICI use, lack of infective symptoms and progressive changes despite antimicrobial is indicative of ICI-induced pneumonitis.

In a meta-analysis of all trials treating NSCLC with anti PD-1 and anti PD-L1 ICI, the overall incidence of pneumonitis was 3.6% with anti PD-1 significantly higher than with anti PD-L1 at 1.3%. Seven deaths were reported in the meta-analysis. There was a significantly higher rate of pneumonitis in treatment of naïve patients.²³ The significance of this is important as Pembrolizumab has been approved for first-line treatment in selected NSCLC patients.²⁴

Figure 6. A patient with metastatic renal cell carcinoma. After six courses of nivolumab, he developed a mild cough and dyspnoea. On CT there was new ground glass opacification, interlobular septal thickening and peribronchovascular infiltration. There was sparing of the subpleural spaces. The clinical symptoms and ICI treatment led to the diagnosis of pneumonitis. The patient was started on steroids. ICI, immune checkpoint inhibitors.

Gastrointestinal

One third of patients who receive anti CTLA-4 therapy have irAEs of the gastrointestinal tract, including aphthous ulcers, oesophagitis, gastritis, diarrhoea and colitis which have all been reported.²⁵ Death and perforation are much less common at <1%.²⁵

Figure 7. (A) Coronal reformat of the baseline scan of a metastatic bladder TCC patient treated with atezolizumab. The colon is normal. (B) 12 weeks after starting atezolizumab, there was marked inflammation of the descending colon. The patient had moderate symptoms of diarrhea, graded by the common terminology criteria for adverse events, as Grade 2. There is thickening of its wall, vascular recruitment and pericolonic fat stranding. (C) After treatment with dexamethasone and a pause in atezolizumab treatment, the colon returned to normal on CT. TCC, transitional cell carcinoma.

Figure 8. A patient on ipilimumab for metastatic melanoma. (A) Fused FDG PET and CT images of the upper abdomen demonstrated normal pancreas with no significant FDG tracer uptake. (B) After continued ipilimumab therapy, the patient developed symptoms and imaging findings of pancreatitis as evidenced by the enlarged distal pancreatic body which was newly metabolically active. FDG PET, ^{18}F -fluorodeoxyglucose positron emission tomography.

Diarrhoea is associated with 27–54% of patients with anti CTLA-4 therapy and can manifest within days to weeks of commencing therapy.²⁶

Colitis

Colitis in anti CTLA-4 ICI has been observed in 8–22% of patients.²⁵ Its incidence is less described for anti PD-1/PDL-1. Typical clinical features are diarrhoea, abdominal pain and fever. Imaging can depict signs of colitis on CT as well as its complications. In the setting of an acute abdomen, it may exclude bowel perforation, obstruction and toxic megacolon. Two distinct forms of ipilimumab-associated colitis have been reported. The more common pattern is diffuse colitis with mild bowel wall thickening, mesenteric vessel engorgement and a fluid-filled colonic distension [Figure 7]. Segmental colitis associated with diverticulosis, is the other pattern, and affects a segment with pre-existing diverticulosis with super-imposed circumferential bowel wall thickening and mesenteric vessel engorgement. None of the patients demonstrate pneumatosis or bowel wall oedema.²⁷ In the same study, all colitis symptoms started within 1–2 weeks of initiating ipilimumab administration.

Figure 9. (A) Baseline CT scan of a metastatic renal cell carcinoma patient. An axial slice through the upper abdomen demonstrates normal liver parenchyma. There has been a right nephrectomy with a post-surgical seroma in the renal bed. (B) Whilst on treatment with pembrolizumab, the liver density became diffusely hypodense in keeping with hepatitis steatosis, which was presumed to be secondary to treatment. The patient had normal liver function tests.

These imaging findings are non-specific and overlap with colitis of other aetiologies. However, clinicians must differentiate between autoimmune from infective colitis as the treatment varies. Auto-immune colitis is treated with steroids whereas infective colitis is treated with antibiotics. Stool tests for enteric pathogens and *Clostridium difficile*, including culture and polymerase chain reaction, must be performed in these patients. Endoscopy with mandatory mucosal biopsies is the diagnostic gold standard for anti CTLA-4-associated colitis; however, a negative endoscopy does not exclude colitis.²⁸

Colitis has also been described in patients on anti-PD-1/PD-L1 ICIs but there is limited data.²⁹ Treatment typically involves discontinuation of ICIs and steroids. If there is no response, infliximab is also used.

Hepatobiliary toxicity

Pancreatitis

Pancreatitis is a rare irAE. In a series of 496 melanoma patients treated with either nivolumab or pembrolizumab, 9 patients developed pancreatitis (1.8%). In 1 case, the CT findings were described as pancreatic swelling and reduced tissue enhancement of the pancreatic body and tail.³⁰ Based on the limited literature on the imaging findings of irAE pancreatitis, it appears the imaging is indistinguishable from pancreatitis of any other aetiology. Similarly, a case at our institute [Figure 8] demonstrated swelling of the pancreatic tail which was also metabolically active on ^{18}F -fluorodeoxyglucose positron emission tomography CT (FDG PET CT). Pancreatitis has also been observed in association with anti CTLA-4-induced enterocolitis.³¹

Hepatitis

Hepatitis has a reported incidence of 5–10% on ICI.¹⁵ Typically asymptomatic, it is typically diagnosed as a transaminitis picked up on the routine blood tests patients have before starting each cycle of ICI. In one study, 2.2% of patients developed hepatitis.³⁰ A further study described the clinicopathological and imaging characteristics of six patients who developed hepatitis whilst on ipilimumab for advanced melanoma. The CT findings described in these patients included new mild hepatomegaly, periportal oedema, periportal lymphadenopathy and diffuse hypoattenuation of the liver [Figure 9]. These imaging findings are indistinguishable from an acute hepatitis of another aetiology.³²

Rheumatological toxicity

Mild or moderate myalgias and arthralgias occur in 2–12% of patients.¹⁵ Non-septic arthritis has also been reported.¹⁹ Treatment with non-steroidal anti-inflammatory drugs are recommended for mild arthralgias and possible low-dose steroids. At our institute, we have observed a case of avascular necrosis in a patient on ipilimumab for metastatic melanoma [Figure 10].

Neurological toxicity

In a review of 59 clinical trials, the incidence of neurological irAE was 3.8% with anti CTLA-4 ICIs, 6.1% with anti PD-1 antibodies and 12% with the combination of both.³³ Less than 1% of the cases were high grade mostly due to severe headaches, encephalopathies [Figure 11], meningitis and Guillan Barré syndrome.

Figure 10. Images of a metastatic melanoma patient with subcutaneous and lymph node metastases. The initial primary melanoma was in the left arm. The patient was treated with pembrolizumab and began to develop intermittent aches in his knees and hips. (A–C) Whilst on continued treatment, serial FDG PET CTs over a period of 2 years, showed ill-defined, increasing sclerosis in the right femoral head and ultimately a comminuted cortical break. Given its indolent course and absence of other bone metastases, this was unlikely to be metastatic. (D) This was also metabolically active. (E) On the maximum intensity projection, the metabolic activity in the right femoral head is visible (see arrow). MIPMaximum intensity projection of the FDG PET also demonstrated metabolically active nodal and skin metastases. FDG PET CT, ^{18}F -fluorodeoxyglucose positron emission tomography CT.

In a review of CNS toxicities of ICI, 13 case reports of irAE encephalitis were identified. Clinical onset was 2.5 months after initiation of treatment and there were a wide range of presenting

symptoms including headache, fever, confusion, disorientation, memory impairment and tremors. Focal abnormalities were seen on MRI in 11 of 15 of these patients with abnormal signal changes

Figure 11. Acute disseminated encephalomyelitis. A patient with a metastatic renal cell carcinoma treated with atezolizumab. Whilst on treatment, the patient developed headaches, peripheral numbness, dizziness, vertigo and expressive dysphasia. The baseline CT head was normal. A CT head and subsequent MRI head were requested. (A) FLAIR sequence from the MRI at acute presentation demonstrated bilateral, white matter hyperintensities in both cerebral hemispheres. These did not enhance, and some had restricted diffusion. A diagnosis of acute disseminated encephalomyelitis was made. (B) After cessation of treatment and steroid treatment, a repeat MRI showed smaller white matter lesions on the FLAIR. No new white matter lesions were seen. (C) 4 months later after treatment with steroids, only tiny signal abnormalities remain in the left frontal lobe. FLAIR, fluid-attenuated inversion-recovery.

Figure 12. Encephalitis may present with signal changes in the limbic system as seen in this patient. with metastatic bladder transitional cell carcinoma. After cystectomy and conventional cytotoxic chemotherapy she developed lung metastases and was initiated on an anti PD-L1 ICI. Baseline CT imaging of the head (not shown) was normal. (A) After 13 cycles, the patient developed dizziness, lethargy, confusion and hypothermia. An MRI head was requested. Coronal T1 post-contrast sequence, demonstrated an enhancing area in the hypothalamus. (B) The axial low dose, unenhanced CT component of an FDG PET CT performed shortly after the acute presentation showed an area of hypodensity in the hypothalamus (see arrow) (C) The FDG component in this image was windowed with an SUV threshold range of 0–10 to assess the brain parenchyma optimally. There was no significant FDG tracer uptake in the hypothalamus abnormality. (D) 1 week after treatment with high-dose steroids, the hyperenhancing area in the hypothalamus significantly decreased in volume with only a thin rim of residual enhancement. FDG PET CT, ^{18}F -fluorodeoxyglucose positron emission tomography CT; ICI, immune checkpoint inhibitors; SUV, standardised uptake value.

in the limbic system [Figure 12], corpus callosum, or posterior reversible encephalopathy. 8 of the 15 patients had complete recovery after initiation of steroid treatment and discontinuation of the immune ICI.³⁴

CONCLUSION

ICIs have dramatically changed the field of medical Oncology in the past decade. With numerous FDA approved ICIs for a plethora of primary malignancies, and even more undergoing Phase 2 and 3 trials, we are potentially in the early stages of its full potential. With increasing use of these therapies, radiologists should be aware of the different response patterns and potential irAE with

their variable appearances on imaging modalities. In the context of trial reporting, radiologists need to be familiar with the de facto response criteria, iRECIST, which awaits clinical validation so that multicentre data captured can be reliably compared.

Clinically, imaging has proven useful in detecting some of the wide ranging irAEs. Some irAEs manifest with subtle symptoms, mimic other conditions or may only be diagnosed reliably on imaging. Thus, radiologists should be aware of the potential irAEs, their radiological manifestations and the importance of alerting this to the clinicians who will invariably cease treatment, at least temporarily.

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