The ROYAL MARSDEN
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Gastrointenstinal Complications of Novel Oncological Therapies

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Learning objectives

1) Overview of immunotherapy agents and their mechanism of action

2) Awareness of the range of adverse effects associated with their use.

3) Review of specific gastrointestinal side effects of immunotherapy including common imaging findings in enterocolitis/colitis, hepatitis & pancreatitis.

4) Outline of GI complications associated with other oncological treatments.

A Targeted Approach

- In recent times cancer treatment has been revolutionised by advances in immunotherapy.
- Immunotherapy seeks to treat cancer by harnessing the body's own immune response, rather than through the administration of previously non-targeted, cytotoxic medication.
- Its use presents radiologists and clinicians with a unique spectrum of side effects with variable timing of onset from the initiation of treatment.

Harnessing the Immune Response

- Immunotherapy regimes can be broadly characterised into active & passive (Figure 1).

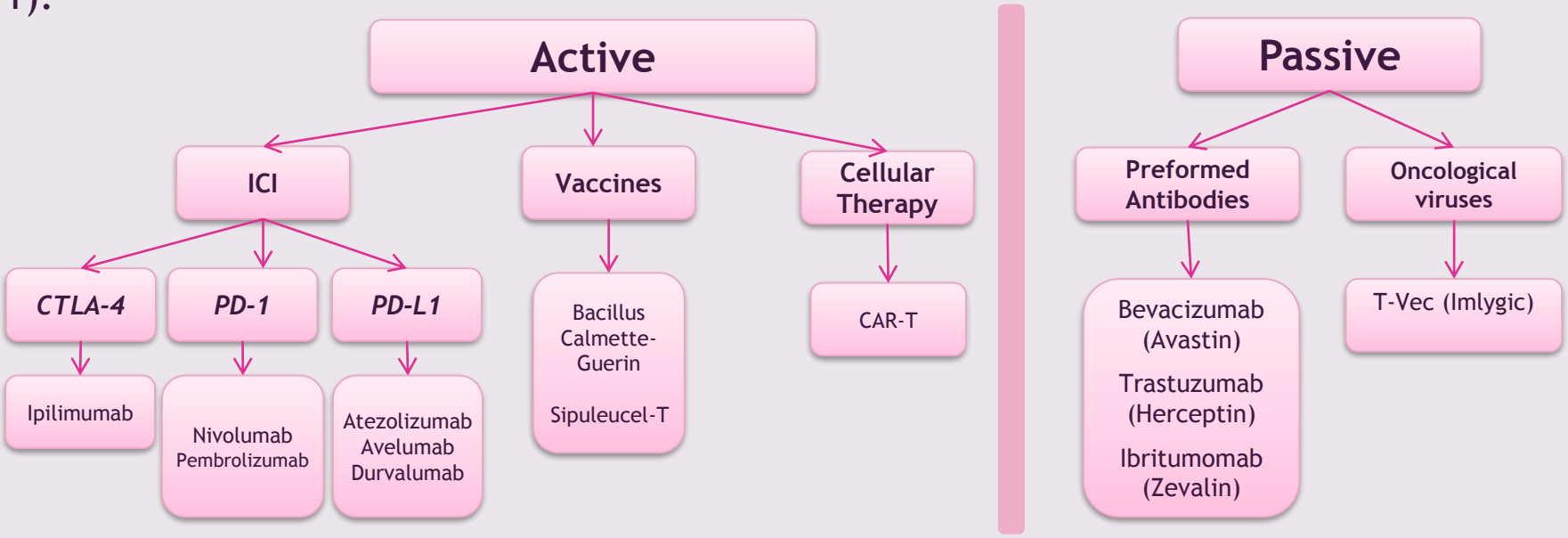


Figure 1: Classification of immunotherapy drugs

- In active immunotherapy, the immune system is empowered (via T-cells) to mount its own anti-tumour response.
- With passive immunotherapy antibodies are directed against antigens on tumour cells.
- The most successful class of immunotherapy agent has been the immune check point inhibitors (ICI).
- The common gastrointestinal side effects & imaging findings associated with this class of therapy will be the focus of this review.

The Immune Checkpoint Inhibitors (ICI)

CTLA-4 and the PD-1/PD-L1 ligand are known as immune checkpoint proteins and are found on the surface of T-cells.

Activation of these proteins leads to down regulation of the immune response; essential in normal physiology to prevent auto-immunity.

Classes of Checkpoint Inhibitors

- CTLA-4 (Cytotoxic T lymphocyte associated Protein 4)
- PD-1 (Programmed Cell Death Protein 1)
- PD-L1 (Programmed Death Ligand 1)

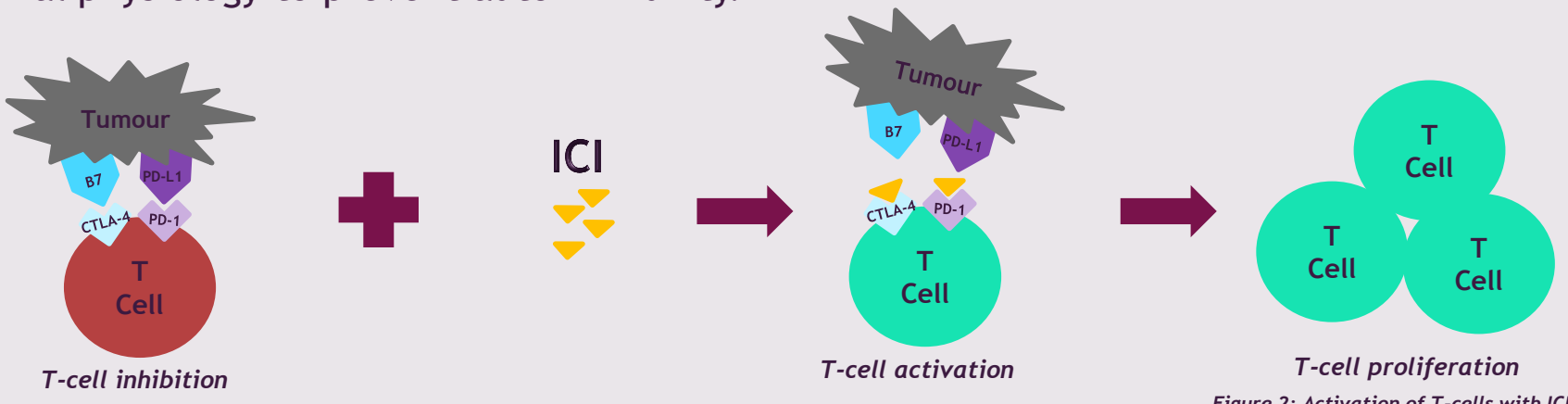


Figure 2: Activation of T-cells with ICIs

Some tumours, however express PD-L1 on their surface allowing them to bind to the PD-1 receptor & activate the inhibition pathway, leading to the inactivation of T-cells (Figure 2).

By binding to these targets, ICI block activation of these inhibitory signals resulting in T-cell stimulation & upregulation of the immune response.

Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med. 2018; 378(2):158-168.

Current ICI Drugs

The ICI are monoclonal antibodies targeted at blocking the check point proteins on the T-cell surface.

Following the approval of the first CTLA-4 inhibitor Ipilimumab for melanoma in 2011, several new ICI drugs have since been developed (Table 1).

These agents have improved outcomes in a wide range of solid tumours & haematological malignancies(1).

Target		FDA approved indication
CTLA-4	Ipilimumab	Melanoma
PD-1	Nivolumab	Melanoma Non-small cell lung cancer Renal cell carcinoma Hepatocellular carcinoma Classic Hodgkin's Squamous cell carcinoma of the head & neck Urothelial carcinoma Colorectal cancer (with high microsatelite instability)
	Pembrolizumab	Melanoma Non-small cell lung cancer Urothelial Gastric cancer Squamous cell carcinoma of the head & neck
PD-L1	Atezolizumab	Non-small cell lung cancer Urothelial carcinoma
	Avelumab	Merkel cell carcinoma Urothelial carcinoma
	Durvalumab	Urothelial carcinoma

Table 1: List of currently approved ICI drugs (1)

(1) Hargadon KM, Johnson CE, Williams CJ. Immune checkpoint blockade therapy for cancer: An overview of FDA-approved immune checkpoint inhibitors. Int Immunopharmacol. 2018;62:29-39.

Immune Related Adverse Effects (IRAE)

- An undesired consequence of the upregulation of the host immune response to tumour cells by ICI drugs is the possible upregulation of T-cell activity towards the host's cells.
- This systemic loss of 'self-tolerance' secondary to ICI results in a multisystem spectrum of side effects (1), defined as immune related adverse effects (IRAE).
- These side effects may mimic autoimmune conditions such as vitiligo or Hasimoto's thyroiditis.
- CTLA-4 blockade is described as resulting in higher frequency and grade of IRAE than checkpoint inhibition of either PD-1 or PD-L1. The degree of toxicity is dose-related with CTLA-4 (2).
- The hypothesis is that CTLA-4 downregulates early T-cell activation and functions centrally, in lymph nodes, whereas the function of PD-L/PD-L1 is more peripheral.

(1) Thallinger C, Füreder T, Preusser M, et al. (2018) Review of cancer treatment with immune checkpoint inhibitors. Wiener klinische Wochenschrift, 130(3-4), 85-91.
(2) Weber JS, Yang JC, Atkins MB, et al. (2015) Toxicities of immunotherapy for the practitioner. Journal of Clinical Oncology, 33(18), 2092.

IRAE

The most frequently occurring IRAE are cutaneous and gastrointestinal (GI). Potential GI IRAE are listed in Figure 3.

- Although the aetiology is not clear, other recognised risk factors for the development of IRAE include:
  - Increasing dose of ICI
    - Particularly with CTLA-4
  - Tumour histology
    - Increased risk of IRAE in melanoma compared with renal cell carcinoma
  - Pre-existing IBD
    - 30% risk of relapse (1)
  - Combined therapy

Diarrhoea

Colitis

Enterocolitis

Gastritis

Hepatitis

Duodenitis

Gastritis

Pancreatitis

Figure 3: GI IRAE

(1) Kähler KC, Eigentler T K, Gesierich A, et al. (2018) Ipilimumab in metastatic melanoma patients with pre-existing autoimmune disorders. Cancer Immunology, Immunotherapy, 67(5), 825-834.

Gastrointestinal IRAE

Diarrhoea is the most common GI side effect of ICI occurring in up to 40% (1) of patients.

A recent systematic review by Tandon et al 2018 (2), confirms it as the most frequently occurring GI IRAE (Table 2), particularly with combined therapy.

	CTLA-4	PD-1/PD-L1
Symptom Onset	1 month	2-4 months
Diarrhoea	30-35%	12-14%
Colitis	6-10%	1-2%

Table 2: Incidence of GI IRAE

The onset of IRAE varies, with colitis tending to occur within 2 months of treatment, although IRAE can occur within 2 years of treatment (3,4). Colitis tends to precede gastritis (5).

(1) Hargadon KM, Johnson CE, Williams, CJ.(2018) Immune checkpoint blockade therapy for cancer: an overview of FDA-approved immune checkpoint inhibitors. International immunopharmacology, 62, 29-39.
(2) Tandon P, Bourassa-Blanchette S, Bishay K, et al. (2018) The risk of diarrhea and colitis in patients with advanced melanoma undergoing immune checkpoint inhibitor therapy: a systematic review and meta-analysis. Journal of Immunotherapy, 41(3), 101-108.
(3) Weber JS, Kähler KC, Hauschild A. (2012) Management of immune-related adverse events and kinetics of response with ipilimumab. Journal of Clinical Oncology, 30(21), 2691-2697.
(4) Boutros C, Tarhini A, Routier E, et al. (2016) Safety profiles of anti-CTLA-4 and anti-PD-1 antibodies alone and in combination. Nature reviews Clinical oncology, 13(8), 473.
(5) Onuki T, Morita E, Sakamoto N, et al. (2018). Severe upper gastrointestinal disorders in pembrolizumab-treated non-small cell lung cancer patient. Respirology case reports, 6(6), e00334.

Gastritis/Duodenitis

Cross-sectional imaging in the evaluation of gastritis is limited, however, gastritis is the most common upper GI side effect associated with ICI.

A study using endoscopy to evaluate patients presenting with diarrhoea found that gastritis and duodenitis were just as prevalent as colitis, with 40% of patients having gastritis at endoscopy & 18% duodenitis (1). Even in cases where visible mucosa appeared normal, histology revealed evidence of inflammation.

Presence of pre-existing Helicobacter Pylori infection has been postulated to be a contributory factor (2).

(1) Fazal MW, Spain, L, Ibraheim H, et al. (2018) PTU-009 Upper gastrointestinal inflammation in patients with immune-checkpoint inhibitor induced diarrhoea.
(2) Nishimura Y, Yasuda M, Ocho K, et al. (2018) Severe Gastritis after Administration of Nivolumab & Ipilimumab. Case reports in oncology, 11(2), 549-556.

Hepatitis

Hepatitis may be detected as an incidental finding on routine bloods.

Imaging is essential to exclude other causes of hepatitis such as portal vein thrombosis or new liver metastases, to avoid unnecessary treatment cessation. Treatment cessation is considered for patients with Grade 3/4 hepatitis (Table 4).

Class	Incidence
CTLA-4	10% (1)
PD-1/PD-L1	1% (1)
CTLA-4 + PD-1/PD-L1	30% (2)

Table 3: Incidence of hepatitis as an IRAE

Pancreatitis

- Literature on the incidence of pancreatitis as an IRAE is limited.
- Treatment with ICI may result in a pancreatic enzyme rise, without clinical signs to fulfil the requirements for a diagnosis of pancreatitis (3).
- More recent case reports have described the occurrence of pancreatic insufficiency, presenting as severe diarrhoea, with no evidence of colitis on imaging or histology (4).

(1) Suzman DL, Pelosof L, Rosenberg A, Avigan MI. Hepatotoxicity of immune checkpoint inhibitors: an evolving picture of risk associated with a vital class of immunotherapy agents. Liver Int. 2018;38 (6):976-987.
(2) Spain, L., Diem, S., & Larkin, J. (2016). Management of toxicities of immune checkpoint inhibitors. Cancer treatment reviews, 44, 51-60.
(3) Weber JS, D'Angelo SP, Minor D, Hodi FS, et al. (2015). Nivolumab versus chemotherapy in patients with advanced melanoma who progressed after anti-CTLA-4 treatment (CheckMate 037): a randomised, controlled, open-label, phase 3 trial. The lancet oncology, 16(4), 375-384.
(4) Prasanna T, McNeil CM, Nielsen T, et al. (2018). Isolated immune-related pancreatic exocrine insufficiency associated with pembrolizumab therapy. Immunotherapy, 10(3), 171-175.

Assessment of IRAE

Consensus recommendations specifically for the assessment & management of IRAE have recently been produced (1) based on previous terminology defined by the National Cancer Institute (2).

	Grade 1	Grade 2	Grade 3	Grade 4
Diarrhoea	Frequency ≤ 4/day	Frequency 4–6/day	Frequency ≥ 7×/day	Life threatening (haemodynamic collapse)
Colitis	Asymptomatic; clinical or diagnostic finding only	Abdominal pain; mucus or blood in stool	Severe abdominal pain; medical intervention indicated; peritoneal signs	Life threatening consequences (e.g bleeding perforation)
Hepatitis Upper limit of normal (ULN)	AST, ALT 3x ULN	AST, ALT 3-5x ULN	>5x ULN ** In patients with prexisting LFT derangement due to hepatic metastases, consider therapy cessation with enzyme rise from baseline >50%	

Table 4: Grading of GI IRAE

Early recognition & grading is essential to guide appropriate management. Diarrhoea and colitis were amongst the most common causes of death in patients treated by ICI in one study (3) & in another systematic review, 31% of toxic deaths were related to GI events (4).

(1) Puzanov I, Diab A, Abdallah K, et al. (2017) Managing toxicities associated with immune checkpoint inhibitors: consensus recommendations from the Society for Immunotherapy of Cancer (SITC) Toxicity Management Working Group. Journal for immunotherapy of cancer, 5(1), 95.
(2) US Department of Health & Human Services; National Institutes of Health; National Cancer Institute. Common terminology criteria for adverse events (CTCAE) V 4.0.
(3) Abdel-Rahman O, ElHalawani H, Fouad, M. (2015) Risk of gastrointestinal complications in cancer patients treated with immune checkpoint inhibitors: a meta-analysis. Immunotherapy, 7(11), 1213-1227.
(4) Khoja L, Day, D, Wei-Wu Chen T, et al. (2017) Tumour-and class-specific patterns of immune-related adverse events of immune checkpoint inhibitors: a systematic review. Annals of Oncology, 28(10), 2377-2385.inhibitors: a systematic review. Annals of Oncology 017;28:2377-85.

Institutional Review

The Royal Marsden is a quaternary referral centre for cancer treatment in central London delivering established and novel oncological treatments. We performed a review of our imaging database for examples of GI IRAE secondary to ICI.

Methods

A review of our Radiological Information System (RIS) and Picture Archiving and Communication System (PACS) between 01/01/2018 - 31/12/2018 was performed using the following key word criteria:

- Acute abdominal pain and diarrhoea
- Deranged liver enzymes
- Colitis
- Hepatitis
- Pancreatitis

Exclusions

- Colitis/pancreatitis/hepatitis secondary to radiotherapy
- Colitis/pancreatitis/hepatitis secondary to chemotherapy agents
- Colitis/pancreatitis/hepatitis not treated with any ICI

Results

- 13 patients were identified as having a GI IRAE on imaging
  - 9 patients had bowel pathology
    - 2 patients had colonic perforation (one with associated colitis)
    - 8 patients had colitis
  - 3 patients had CT evidence of hepatitis
  - 1 patient had pancreatitis

Imaging Protocol

- Single phase CT of the abdomen and pelvis
- Portal venous acquisition following contrast administration or unenhanced CT in patients with a contrast allergy.
- Oral contrast is not routinely given at our institution.
- Predefined imaging features were recorded (Table 5).

Radiological features (Colitis)	
Location	Small bowel (enteritis) Large bowel (colitis) Small & large (enterocolitis)
Pattern	Focal Segmental (10-20 cm) Multisegmental Diffuse (>30cm)
Predominant region involved	Small bowel Ascending colon Transverse colon Descending colon Sigmoid/rectum
Bowel wall thickening	4-8mm 8-12mm >12mm
Oedema	Yes/No
Mesenteric hyperaemia	Yes/No
Presence of bowel dilatation	Yes/No
Perforation	Yes/No
Free fluid	Yes/No

Table 5: Assessing the imaging features of colitis

Summary of Imaging Findings in Colitis

9 patients were identified with a colonic/ small bowel abnormality secondary to ICI:

- 2/9 patients had spontaneous perforations
- 8 patients had evidence of colitis on imaging

- In our cohort of patients, bowel wall thickening was the most commonly identified feature of colitis.
- Free fluid was present in 57% of cases.
- Bowel dilatation was not seen in all cases.

Radiological feature	Number
Location	
- Enteritis	0
- Colitis	7
- Enterocolitis	1
Pattern	
- Focal	1
- Segmental (10-20 cm)	3
- Multisegmental	2
- Diffuse (>30cm)	2
Predominant region	
- Small bowel	1
- Ascending colon	1
- Transverse colon	1
- Descending colon	3
- Sigmoid/rectum	2
Bowel wall thickening	
- 4-8mm	7
- 8-12mm	1
- >12mm	0
Oedema	5
Mesenteric hyperaemia	4
Presence of bowel dilatation	2
Perforation	2
Free fluid	4

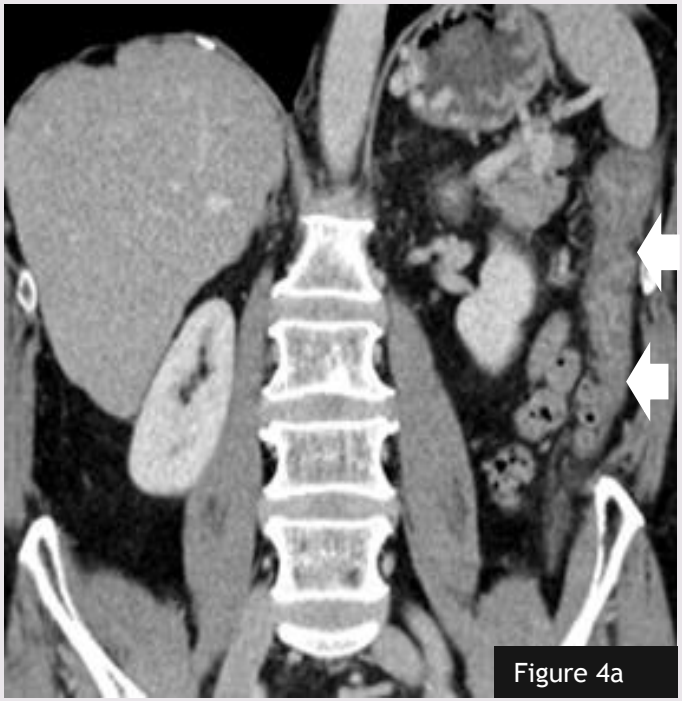
Table 6: Summary of image findings in colitis

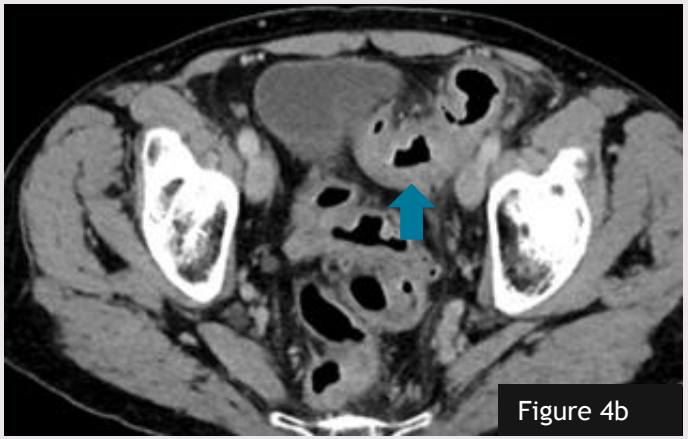
Colitis?

In this patient with extensive diverticular disease (Figure 4), inflammation of the descending (white arrows) & sigmoid colon (blue arrows) may have been attributed to diverticulitis.

The segmental nature of the changes also raises the possibility of an ischaemic aetiology.

Knowledge that the patient was receiving immunotherapy allowed a confident diagnosis of an IRAE.





Figures 4a & 4b: Coronal (a) and axial (b) post contrast CT performed in a patient with raised inflammatory markers and abdominal pain receiving immunotherapy.

Kim KW, Ramaiya NH, Krajewski KM, eta al. (2013) Ipilimumab-associated colitis: CT findings. American Journal of Roentgenology, 200(5), W468-W474.

ICI Colitis Patterns

Two immunotherapy-related colitis patterns have previously been described in the literature:

- Diffuse pattern:
  - Characterised by diffuse bowel wall thickening with mesenteric vessel engorgement and colonic distension engorgement
- Segmental pattern
  - Characterised by wall thickening in the presence of diverticular disease

Segmental distal colitis was the predominant pattern occurring in our cohort even in the absence of underlying diverticular disease.

Barina *et al* (1) observed a similar finding and suggested a third category of immunotherapy-related colitis (segmental without diverticular disease).

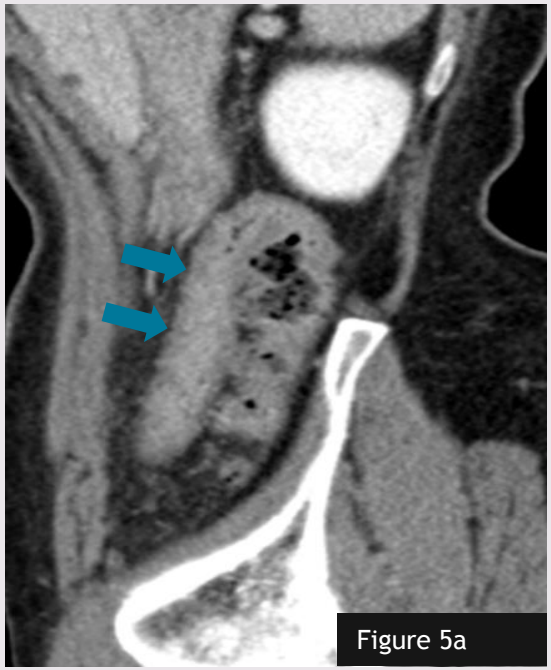


Figure 5a: Post contrast sagittal CT demonstrates segmental thickening of the transverse colon (blue arrows).

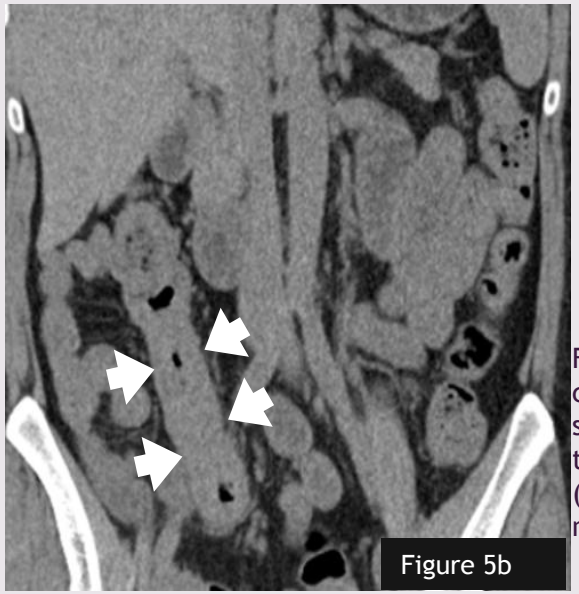
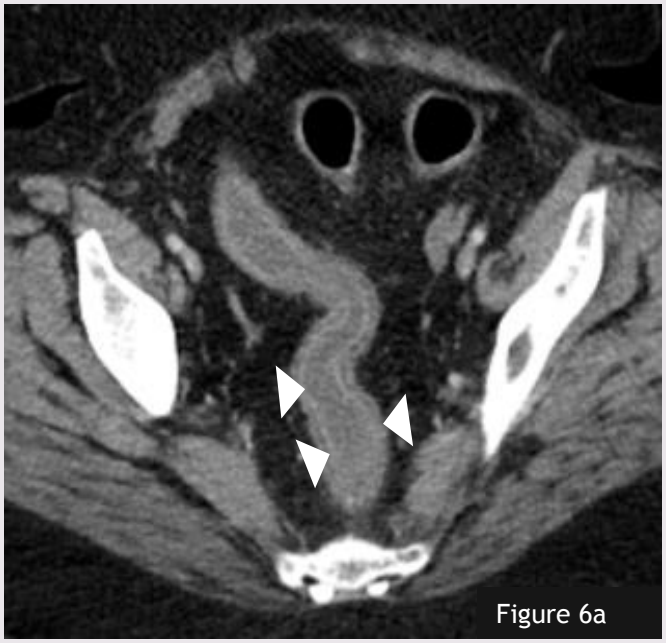


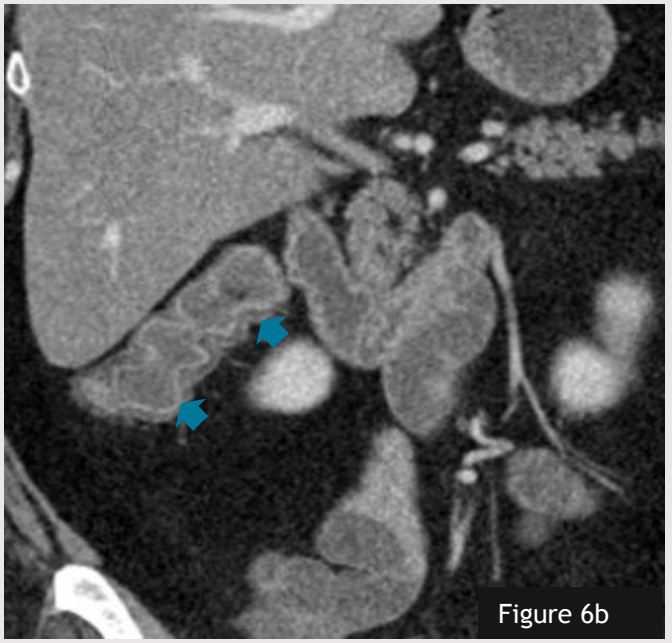
Figure 5b: Unenhanced coronal CT demonstrates segmental thickening of the ascending colon (white arrows). There is no diverticular disease.

(1) Barina AR, Bashir MR, Howard BA, et al. (2016) Isolated recto-sigmoid colitis: a new imaging pattern of ipilimumab-associated colitis. Abdominal Radiology, 41(2), 207-214.

Colitis

Figure 6 demonstrates multifocal, segmental colitis in a melanoma patient on combined Ipilimumab and Nivolumab.

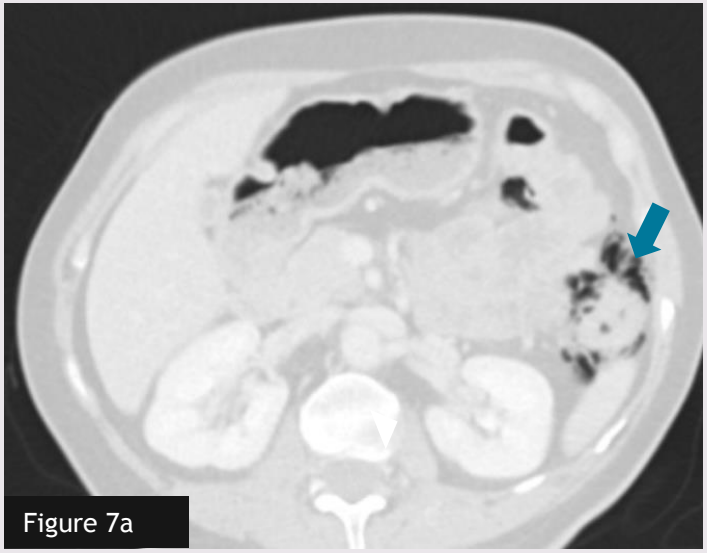


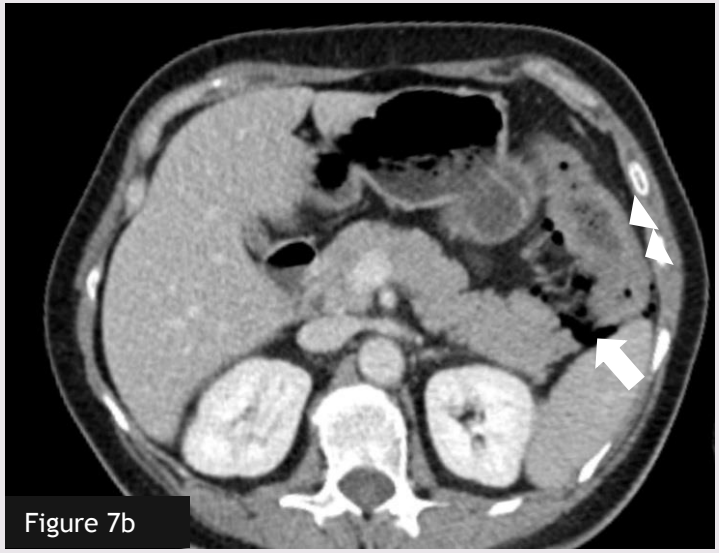


Figures 6a & 6b: Post contrast axial (a) and coronal CT (b). Mucosal hyperenhancement (arrow heads) and mural oedema in the sigmoid colon, with a further similar ‘skip’ area in the hepatic flexure. Block arrows show marked mural oedema.

Perforation

- Spontaneous perforation occurred in two patients with minimal clinical signs.
- This patient received Nivolumab and Placebo as treatment for melanoma.





Figures 7a & 7b: Post contrast axial CT on lung windows (a) and soft tissue windows (b). Bowel wall thickening at the splenic flexure is associated with pneumatosis (a, blue arrow) and perforation (b, white arrow).

- On routine imaging 8 weeks following initiation of therapy, pneumocolon, with mild colonic wall thickening and intraperitoneal free air was detected.
- The patient was managed conservatively with antibiotics as an inpatient.

Perforation

- Spontaneous right colonic perforation occurred in this patient treated with Atezolizumab & Cobimetinib for squamous cell cancer of the larynx.
- The patient reported Grade 1 diarrhoea, with a non peritonitic abdomen & unremarkable inflammatory markers.
- Spontaneous pneumoperitoneum and pneumatosis has previous been described with targeted therapy e.g. Bevacizumab (1).
- Although Cobimetinib, (a Protein Kinase Inhibitor - PKI) is not associated with perforation, other drugs in this class may cause this.

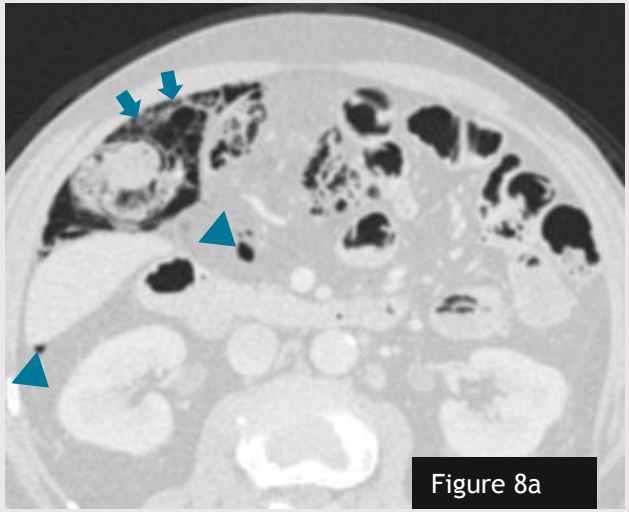


Figure 8a

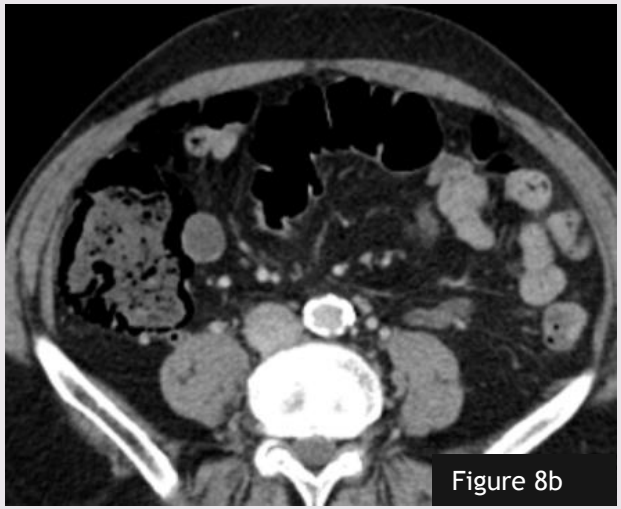


Figure 8b

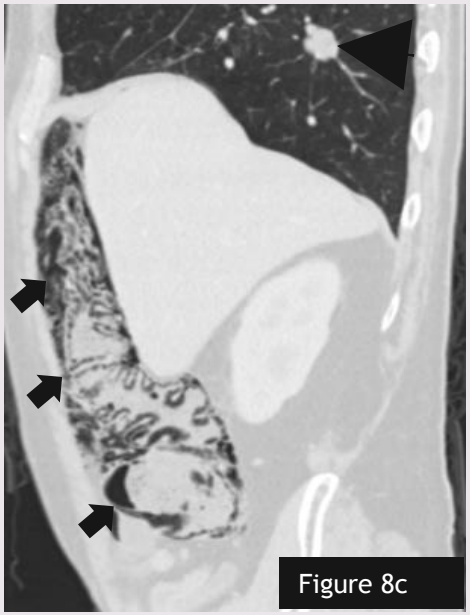


Figure 8c

Figures 8a, 8b & 8c: CT images demonstrate extensive intramural gas involving the ascending (a, black arrows) and proximal transverse colon (b, blue arrows).

Pneumoperitoneum extends along the mesenteric root (a, blue arrowheads). No associated bowel wall thickening. A lung metastasis is demonstrated in the right lower lobe (c, black arrowhead).

(1) Badgwell BD, Camp ER, Feig B, et al. (2007) Management of bevacizumab-associated bowel perforation: a case series and review of the literature. Annals of oncology, 19(3), 577-582.

Hepatitis

Two patients presented with acutely elevated aminotransferase (AST) within one month of commencing Nivolumab.

The imaging features of hepatitis as a side effect of immunotherapy may be indistinguishable from other causes of hepatitis. Treatment of immunotherapy induced hepatitis depends on the degree of liver function derangement. Steroids may be an option, however in certain cases cessation of immunotherapy is required. Hepatotoxicity with immunotherapy may be life-threatening.

The role of imaging in these cases is often to exclude other causes of abnormal AST, such as portal vein thrombosis or new hepatic metastases.

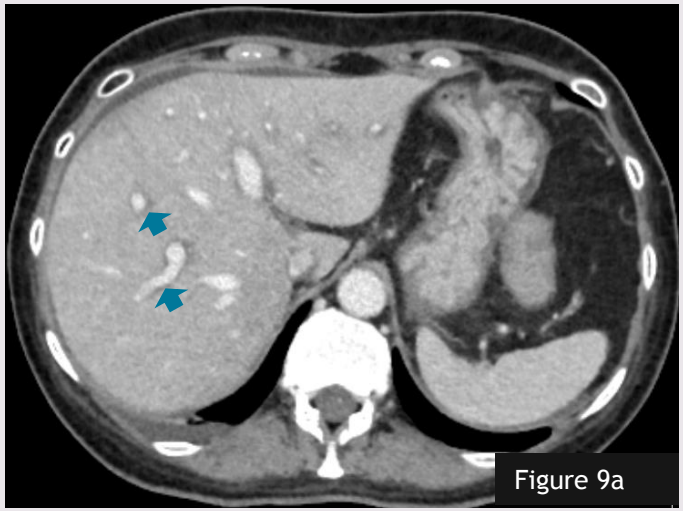


Figure 9a: Axial post contrast CT shows periportal oedema (arrows), supporting a diagnosis of hepatitis in the clinical context.

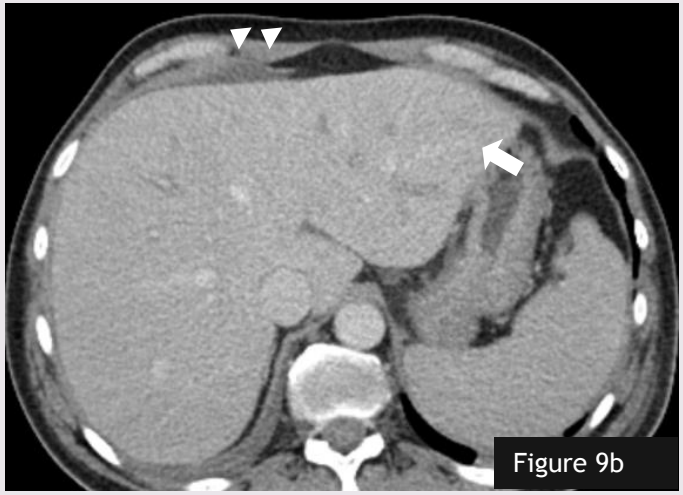


Figure 9b: Axial post contrast CT. There is mild periportal oedema & hepatomegaly (white arrow) with a trace of perihepatic free fluid (arrowhead).

Pancreatitis

This patient presented with abdominal pain and elevated pancreatic enzymes. Peri-pancreatic fat stranding was absent. There was diffuse enlargement of the pancreas (Figure 10b) with no significant change in gland attenuation.

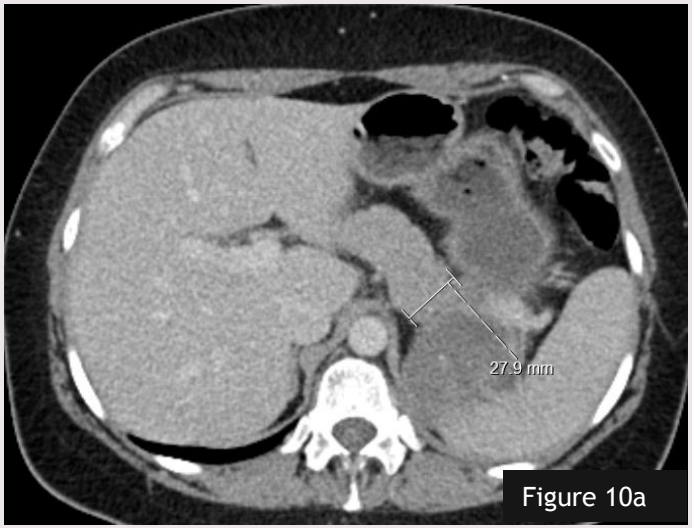


Figure 10a

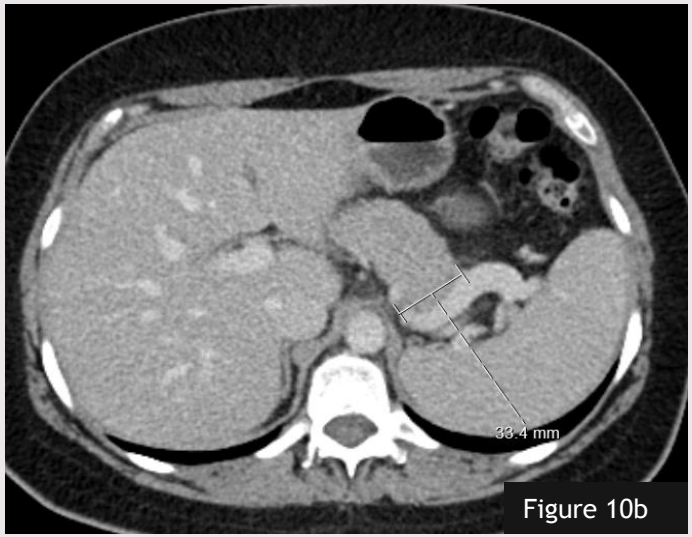


Figure 10b

Figures 10a & 10b: Post contrast axial CT at baseline (a) and 6 months later (b) with onset of symptoms. Interval glandular enlargement is demonstrated. Given the enzyme rise and concurrent ICI treatment, a diagnosis of pancreatitis was made.

Pancreatitis

- Imaging features of pancreatitis as an IRAE may be indistinguishable from pancreatitis due to other causes.
- Appearances mimic autoimmune pancreatitis with mild pancreatic enlargement and a ‘sausage-like’ appearance (1).
- In addition to lack of enzyme rise, ICI induced pancreatitis can be asymptomatic clinically and biochemically (2).
- Imaging can exclude alternative diagnoses (e.g. gallbladder calculi) and assess for complications (e.g. pancreatic necrosis).

(1) Kwak JJ, Tirumani SH, Van den Abbeele, AD, et al. (2015) Cancer immunotherapy: imaging assessment of novel treatment response patterns and immune-related adverse events. Radiographics, 35(2), 424-437.
(2) Tirumani SH, Ramaiya NH, Keraliya A, (2015) Radiographic profiling of immune-related adverse events in advanced melanoma patients treated with ipilimumab. Cancer immunology research, 3(10), 1185-1192.

Future Agents

- Adoptive T-cell therapy (ACT) promises an individualised and specific approach to cancer treatment.
  - T-cells are harvested from the host and genetically altered with addition of a chimeric antigen receptor (CAR).
  - The CAR receptor is designed to recognise specific antigens expressed on the tumour surface.
  - Following lymphocytic depleting chemotherapy, the modified host T-cells-CAR complex is reinfused.

- Tisagenlecleucel-T (Kymriah) and axicabtagene ciloleucel (Yescarta) have already been approved in the UK for use, with more drugs in the pipeline.

MR Parkhurst, JC Yang, RC Langan, ME Dudley, DA Nathan, SA Feldman, et al. T cells targeting carcinoembryonic antigen can mediate regression of metastatic colorectal cancer but induce severe transient colitis Mol Ther, 19 (2011), pp. 620-626.

Conclusion

- ICI are immunomodulatory antibodies which work by upregulating the body's immune response to cancer and are associated with a spectrum of side effects.
- Diarrhoea is the most common GI IRAE and may herald the onset of colitis, prompt recognition of which is essential in order to avoid bowel perforation. Infrequently diarrhoea may also present as a side effect of pancreatic insufficiency following ICI treatment.
- The radiologist should be mindful that the imaging features of IRAE may be subtle.
- Awareness of the radiological manifestations of IRAE in the oncologic patient allows the radiologist to highlight complications of treatment. Timely discontinuation of treatment and initiation of supportive therapy is essential to reduce patient morbidity and mortality.