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Learning objectives

The aim of this presentation is to highlight a new class of anti-cancer drug whose function is immune regulation. The side effect profile of these novel treatments will be explained and the radiological appearances of said side-effects will be illustrated. The ultimate goal is to heighten awareness of the potential adverse events that can occur in this cohort of patients.

Background

Ipilimumab is a novel, fully human monoclonal antibody specific for human cytotoxic T lymphocyte associated antigen 4 (CTLA 4). It was approved on 25 March 2011 for use in patients with unresectable or metastatic melanoma.

Traditional systemic therapies have a limited role in the treatment of metastatic melanoma as they are hindered by a poor or short duration of response and a 5 year survival of less than 10%. Other immunotherapies such as interleukin 2 or interferon # showed beneficial effects but these were outweighed by significant systemic toxicity.

The anti CTLA 4 effect of Ipilimumab prolongs the effect of the anti-tumour T cells. In phase 3 trials Ipilimumab has demonstrated various patterns of response such as response in baseline lesions, a reduction in overall tumour burden, response after an initial apparent increase in tumour bulk and a response in index and new lesions. Critically, patients on Ipilimumab may show sustained disease stability or delayed response even after initial disease progression. Therefore clinicians aim to avoid early imaging after the commencement of treatment to avoid early withdrawal of therapy.

Ipilimumab does however have it's own toxicity profile. These side effects are manageable medically but early recognition is crucial to avoid serious consequences. The side effects associated with immune therapies are known as "immune related adverse events".

Potential adverse effects include colitis/diarrhoea, nephritis, uveitis, hypophysitis, dermatitis, endocrinopathies and tumour flair. They are thought to occur as a direct result of breaking immune tolerance upon initiating the CTLA 4 blockade.
Ipilimumab is also undergoing clinical trials for the treatment of non small cell lung cancer, small cell lung cancer and metastatic, hormone refractory prostate cancer as well as other neoplastic conditions.

At the last count there were 5 patients being treated with Ipilimumab in our institution. Four of these patients have presented with "immune related adverse events". A case series will be put forward illustrating the imaging findings of these idioyncratic effects.

**Imaging findings OR Procedure details**

Case 1 (Fig 1-Fig 3) is that of a 67 year old female with metastatic melanoma. Metastatic deposits were present in the lungs, liver, spleen, peritoneum and lymph nodes. Figures 1 and 2 demonstrate how individual index lesions can increase in size on immunotherapy. While there was an appreciable reduction in the size of hepatic deposits on therapy, the splenic lesion demonstrated a paradoxical increase in size.

Figure 3 illustrates the features of colitis affecting the ascending colon which developed on Ipilimumab.

Case 2 (Fig 4-Fig 6) shows selected contrast enhanced CT images of a 38 year old female. She had been on therapy with Ipilimumab for approximately 3 weeks when she presented with right shoulder pain and dyspnœa. CT thorax revealed massive mediastinal lymphadenopathy resulting in significant tracheal deviation and compression. She was subsequently referred for urgent tracheal stenting. The case illustrates the phenomenon of tumour flare that can occur in the early stages of treatment. This inflammatory response can be mistaken for disease progression.

Case 3 (Fig 7-Fig 9) again shows selected CT images of a male patient who had been on Ipilimumab treatment for 2 months. He presented with a history of pyrexia and being generally unwell. As a result the patient was admitted with presumed sepsis and acute renal failure. His blood cultures were however negative and he was referred for a CT for further evaluation. CT showed bilateral renal enlargement with perinephric stranding (Fig 7 & 8) and bilateral pleural effusions (Fig 9).

A diagnosis of nephritis secondary to immunotherapy was made and systemic corticosteroids were commenced. The patient's condition improved on steroids and immunotherapy was continued.
Case 4 (Fig 10-Fig 12) shows images from two CT's of a 48 year old female patient with a 3 month history of Ipilimumab treatment. She presented acutely with abdominal pain and distension and with diarrhoea two weeks post her most recent Ipilimumab dose. Plain film of abdomen was normal however her CT demonstrated a colitis affecting her descending and sigmoid colon with sparing of the rectum. One month post the acute episode of colitis she re-presented with further abdominal symptoms. A repeat CT was performed which revealed a perforated sigmoid colon (Fig 12).

Images for this section:

![Image](image_url)

**Fig. 1:** Pre therapy with Ipilimumab.
Fig. 2: On Ipilimumab.
Fig. 3: On Ipilimumab.
Fig. 4: Tumour flare on Ipilimumab.
Fig. 5: Tumour flare on Ipilimumab.
Fig. 6: Tumour flare on Ipilimumab.
Fig. 7: On Ipilimumab.
Fig. 8: On Ipilimumab.
Fig. 9: On Ipilimumab.
Fig. 10: Colitis of the descending colon.
Fig. 11: Colitis of the descending colon.
Fig. 12: Repeat CT showing a perforated sigmoid colon.
Conclusion

A promising new class of anti-cancer drugs include monoclonal antibodies whose function is immune regulation. Inhibition of CTLA 4 in patients characteristically induces "immune related adverse events". Common reactions include colitis, dermatitis, hepatitis, nephritis, uveitis, hypophysitis, endocrinopathies and tumour flare. Patient-clinician communication and early treatment are emerging as critical issues in the successful management of these side effects thus avoiding major complications. These reactions are inflammatory in nature and may be clearly highlighted by diagnostic imaging.

It appears that as our knowledge of the role that the immune system plays in oncogenesis improves then there will be a greater emphasis on immunotherapies such as Ipilimumab in the treatment of malignancy. As radiologists we will need to be mindful of the potential adverse events which can occur in these patients and look for signs of them on imaging studies.

Personal Information

References