An unusual case report of multiple toxicities in a 50-year-old male receiving Nivolumab and Ipilimumab for metastatic melanoma

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ABSTRACT

An unusual case of a 50-year-old male receiving doublet immunotherapy with Nivolumab/Ipilimumab.

Initially presented with fever and intermittent chest pain, ECG changes and raised cardiac enzymes following cycle 2.

Treated for myocarditis, steroids interrupted for several days after cardiology review, as thought to be non-ST elevation myocardial infarction. Cardiac investigations proved negative for M.I, steroids recommenced.

Presented for a second time with fever, rigors, widespread rash and deranged kidney and liver function.

Diagnosed with Toxic Epidermal Necrolysis related to massive immune response, along with significant hepatitis and nephritis.

Despite high dose steroids, dermatology input and treatment in the intensive care unit, the patient continued to deteriorate and sadly died 11 days later.

INTRODUCTION

This case concerns a 50-year-old male with BRAF positive nodular melanoma, initially diagnosed in June 2021.
Previously treated with wide local excision and twelve cycles of adjuvant Dabrafenib and Trametinib.
Re-staging CT in 2022 revealed a new left axillary metastatic disease and skin nodules. Axillary clearance yielded 2/20 positive lymph nodes.
He opted for doublet immunotherapy and commenced Nivolumab and Ipilimumab in February 2023

Clinical case

First presentation:
Presented with fever on day 15 of cycle 2. On questioning, he mentioned some intermittent chest pain. ECG was abnormal, troponin and creatinine kinase both significantly raised. Initially treated as immunotherapy induced myocarditis. He also had some liver enzyme abnormalities and supressed thyroid stimulating hormone, also thought to be related to immunotherapy. Admitted to hospital and commenced intravenous Methylprednisolone. Cardiologist reviewed - impression was non-ST elevation myocardial infarction, therefore steroids were stopped.
However, angiogram and echocardiogram both normal. Steroids were recommenced. Cardiac enzymes and liver function returned to normal prior to discharge.

Second presentation:
Presented 20 days later with a two-day history of fever, rash, dry cough, and shortness of breath on exertion. He was still taking Prednisolone 60mg OD. On examination, the rash covered 70% of his surface area and was erythematous in nature. Heart sounds were normal, chest was clear on auscultation, and there was no obvious source of infection. ECG was unremarkable, chest x-ray suggestive of inflammatory change. CRP was elevated, and renal and liver function were moderately impaired. A diagnosis of multiple IO toxicity +/- sepsis was made. Intravenous steroids were recommenced along with antihistamines, broad spectrum antibiotics and fluid resuscitation.

There was marked deterioration overnight, necessitating ICU admission the following morning. The rash had started to blister and there was now mucosal involvement. The patient was diagnosed with multiple IO toxicities including Toxic Epidermal Necrolysis (TEN), leading to multiorgan failure, the
He was treated for sepsis with multiple antibiotics throughout the admission, although cultures remained negative throughout. He had a daily dermatology review and further expert advice was sought from a specialist burns unit regarding supportive skin care measures. Despite intensive care, he continued to deteriorate and sadly died 11 days after admission.

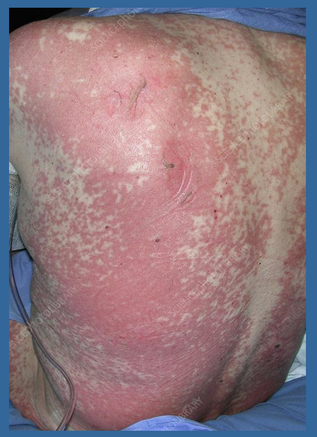

Figure 1. Toxic Epidermal Necrolysis

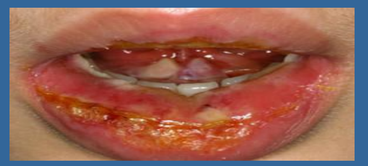

Figure 2. TEN mucosal involvement

	06/04	08/04	12/04	18/04
Creatinine	80	130	321	406
EGFR	> 90	55	18	14
AKI	0	2	3	3
ALT	55	232	-	-
ALP	-	198		308

Table 1. Deterioration in renal and liver function

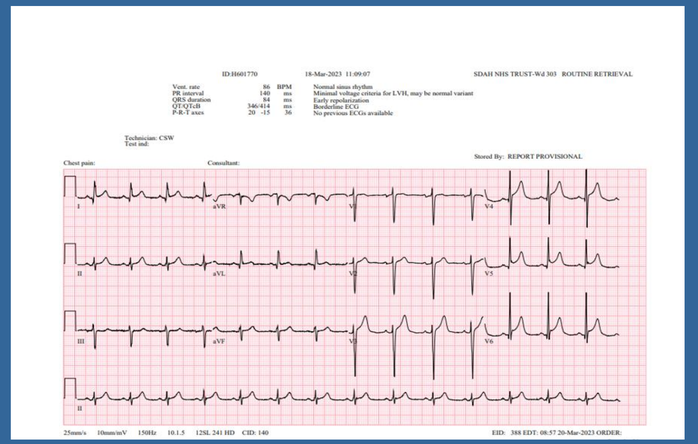

Figure 3: ECG March 2023.

DISCUSSION

Toxic Epidermal Necrolysis is a rare muco-cutaneous reaction; a true dermatologic emergency, associated with life-threatening outcomes and a high incidence of mortality (Kubicki et al, 2020).
The pathophysiology is not fully known, but it is believed to be T-cell mediated, usually in response to a drug, and characterised by acute onset and rapid progression (Frantz et al, 2021).

Cutaneous toxicity is more prevalent in doublet immunotherapy than with Ipilimumab alone (Prostow et al, 2015). High dose, intravenous corticosteroids, and supportive measures such as wound care are the mainstay of treatment, but evidence is lacking and recommendations are unclear (Sommerfelt et al, 2022; Papp et al, 2018).

Immunotherapy toxicities represent a varied challenge in clinical practice and a steep learning curve in diagnosis and management (Conroy and Naidoo, 2022).

CONCLUSIONS

Immunotherapy has rapidly redefined the landscape of cancer treatment; but it also has the potential to unleash a cascade of unpredictable and unintended autoimmune consequences, as demonstrated in this case. It is unknown whether the initial interruption of corticosteroid therapy had any impact on what unfolded over the weeks that followed, but this may have contributed to the subsequent reaction cascade.
Managing IO toxicity presents a unique challenge in clinical practice, with many more patients potentially presenting in an atypical manner, or with multiple toxicities.

This case demonstrates the need to engage with non-oncology specialists to educate and publish on IO toxicity and a move towards more multidisciplinary management

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