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A Severe and Rare Immune-related Toxicity Associated with a Complete Response to Combination Immunotherapy for Metastatic Melanoma – A Case Report of Acral Vascular Syndrome

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Abstract

Combination immune check point inhibitor (ICI) therapy has dramatically transformed the outlook for patients with metastatic melanoma. However, there is a significant risk of immune-related adverse events, which can be life threatening. We report a rare case of severe acral vascular syndrome and pneumonitis after one dose of combination ICI therapy. The patient was promptly commenced on high dose corticosteroid therapy and supportive medications, with complete resolution of the vasculitis and pneumonitis by six months. Importantly, after three years of follow up, he continues to achieve a sustained response to ICI therapy.

Keywords: Immunotherapy, Immune-related Adverse Events, Vasculitis, Pneumonitis, Melanoma

Introduction

Systemic therapies for metastatic melanoma have undergone a revolution in the past decade. The outlook for patients has dramatically transformed with the use of combination targeted therapy and immune checkpoint inhibitors (ICIs) [1]. The main ICIs current used for metastatic melanoma are the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) blocker ipilimumab and the programmed cell-death protein 1 (PD-1) blockers nivolumab and pembrolizumab.

Although these therapies are associated with a potential durable survival benefit, a new class of adverse events has emerged, named immune-related adverse events (irAEs). These include endocrinopathies, pneumonitis, liver toxicity, colitis and skin toxicity, and rarely nephritis and neurological toxicities. Combination ICI therapy with ipilimumab and nivolumab carries an increased risk of irAEs compared to single agent therapy [2]. In addition, an association between irAEs and improved survival outcomes has been reported for patients treated with ICIs [3,4].

Immune-related vasculitis secondary to ICIs is relatively uncommon in clinical trial results [5]. We report a case of acral vascular syndrome and pneumonitis in a patient with metastatic melanoma treated with combination ICI therapy. Importantly, after three years of follow up, this patient has achieved a sustained complete response to ICI therapy.

Case presentation

We report a 72- year old Caucasian gentleman with a history of invasive lentigo melanoma, Clark level IV, which was completely resected in 2012. He had no other significant medical history.

He presented with cough to his local doctor in early 2017. A CT chest and abdomen revealed multiple lung lesions, mediastinal lymphadenopathy and an isolated liver lesion. Biopsy of the largest lung mass (6cm diameter) confirmed BRAF-mutation positive metastatic melanoma. His blood tests showed normal organ function and a lactate dehydrogenase (LDH) within normal limits. He had no intracranial metastases.

He was commenced on combination targeted therapy with BRAF and MEK inhibitors, achieving good disease control for six months. His disease then progressed, with new lung nodules seen on staging CT (asymptomatic) (see Figure 1). Given his excellent performance status, he was commenced on combination ICI therapy with ipilimumab and nivolumab in December 2017.

He developed immune related pneumonitis two weeks after commencing immunotherapy, with new shortness of breath, dry cough and fine bilateral crepitations on chest examination. CT chest showed bilateral parenchymal changes consistent with pneumonitis (see figure 2), and his CRP was 170. His septic screen was negative, ruling out infection. He was commenced on oral prednisolone 1.5mg/kg with proton pump inhibitor cover for gastric protection. His symptoms significantly improved within 48 hours of commencing prednisolone.

Simultaneously while starting treatment for pneumonitis, he developed Raynaud's phenomenon-like symptoms in both hands. This was not associated with pain, arthralgia or neuropathy. After one week, these symptoms progressed with peri-ungual blue discoloration of the fingertips bilaterally, punctateulcers and nocturnal pain (see figure 2). On examination, his vital signs were within normal limits and his capillary refill time was five seconds.

He was admitted to a tertiary hospital, and underwent extensive radiological, serological and rheumatologically work up. Doppler ultrasound showed normal blood flow in the forearm blood vessels. An autoimmune panel revealed an anti-nuclear antibody (ANA) titre of 1:2000 with a homogenous pattern. Other vasculitis testing including anti-neutrophilic cytoplasmic autoantibody (ANCA), extractable nuclear antigen (ENA), and anti-double stranded DNA antibodies and cryoglobulins were negative. Complement levels were within normal limits. There was no infective source, hyperviscosity syndrome or systemic embolic events found to explain the clinical symptoms. Arterial Doppler and CT angiogram of the upper extremities and brain did not reveal any evidence of systemic vasculitis.

A diagnosis of immune-related acral vascular syndrome was thought most likely, with the potential differential diagnosis of paraneoplastic acral vascular syndrome considered. In addition to high-dose

prednisolone, he was commenced on the calcium channel blocker nifedipine CR 30mg daily, aspirin 100mg daily and trimethoprim/sulfamethoxazole for pneumocystis jirovecii (PJP) prophylaxis. He also followed supportive measures including avoiding cold, wearing cotton gloves and regular gentle exercise.

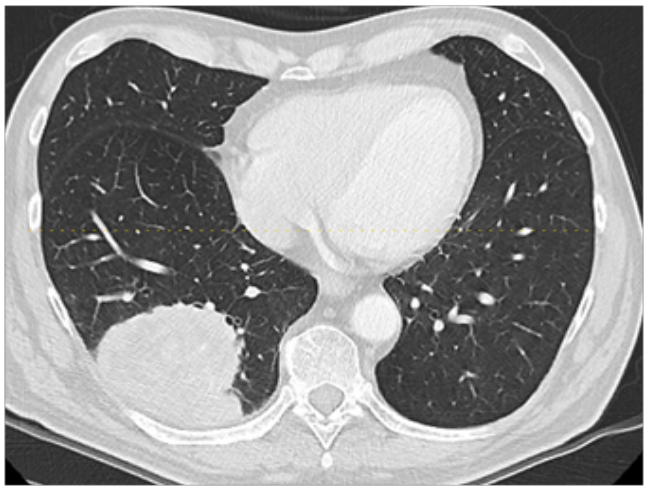
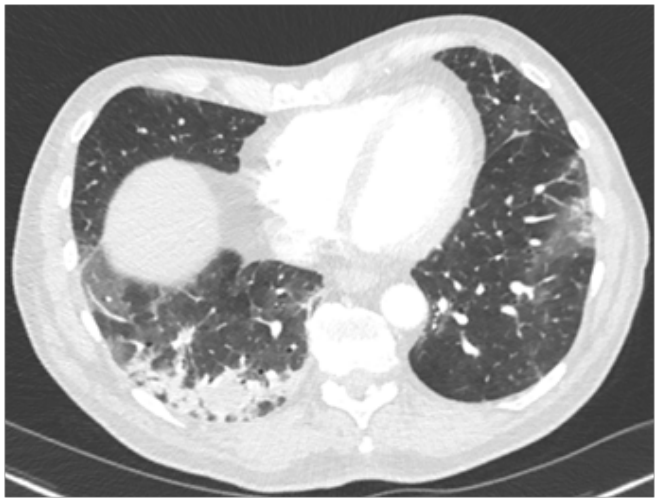
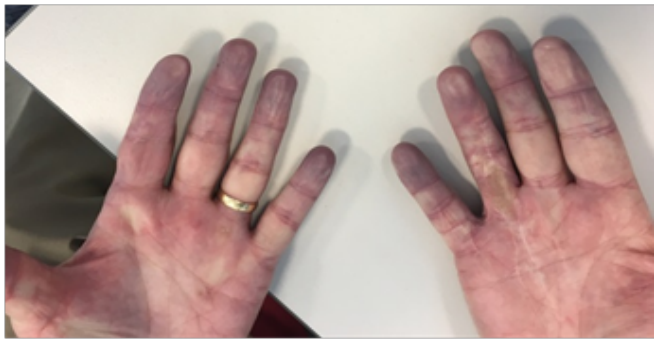


Figure 1: Initial CT November 2017 prior to commencing immunotherapy





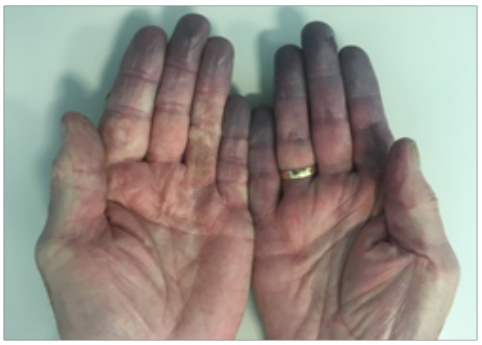


Figure 2: December2017 post 1 cycle immunotherapy(pneumonitis). Simultaneously developed Raynaud's phenomenon-like symptoms in both hands (picture 1) with worsened after 1 week (picture 2)

After one month, he developed dry gangrene on three fingertips (see figure 3), for which no surgical intervention was recommended. He experienced local infections in the affected fingers, managed with topical antiseptic and systemic antibiotics. He remained on 70mg of prednisolone for the next three weeks and this was then tapered slowly over four months. He did not have any long-term sequelae of high-dose corticosteroid use. The clinical features of acral vasculitis gradually improved, and he regained his normal finger function after nine months from initial presentation (see figure 4 and 5).

Of particular note, despite receiving only one cycle of combination immunotherapy, his repeat staging CT showed a good partial response, and a FDG PET scan after 6 months showed a complete metabolic response (see figure 4). Furthermore, after three years of follow up, his most recent CT shows an ongoing response (see figure 5), and he has remained clinically well and free of any residual complications.

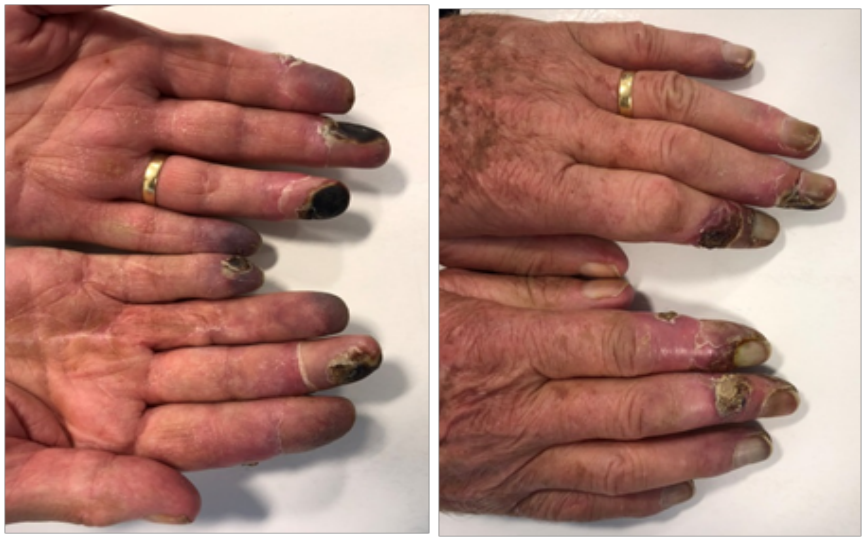


Figure 3: March 2018, 3 months after commencing high-dose prednisolone (dry gangrene)

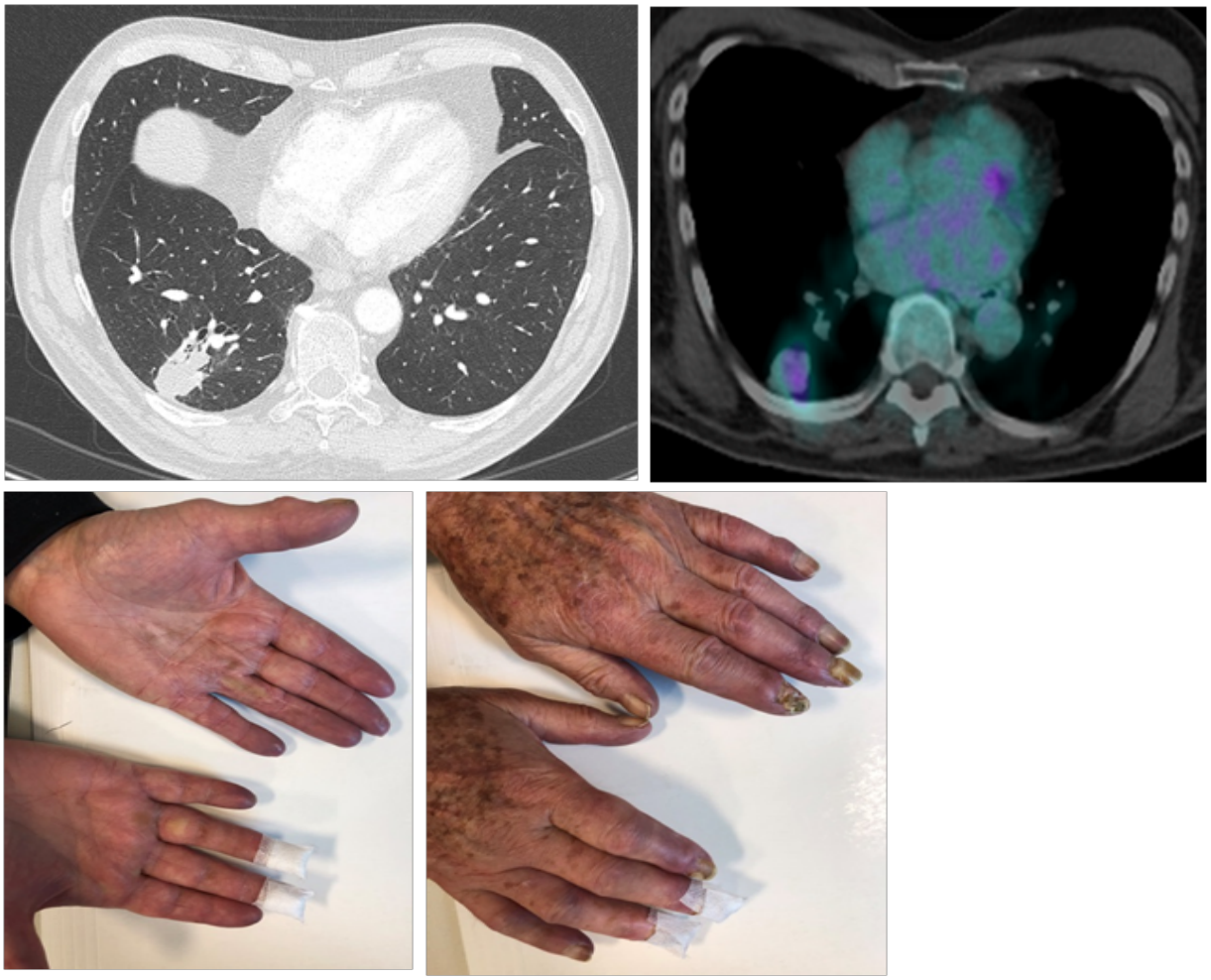


Figure 4: CT June 2018 (6 months after immunotherapy) showing partial response, and FDG PET scan August 2018 showing complete metabolic response. Improving vasculitis clinically.

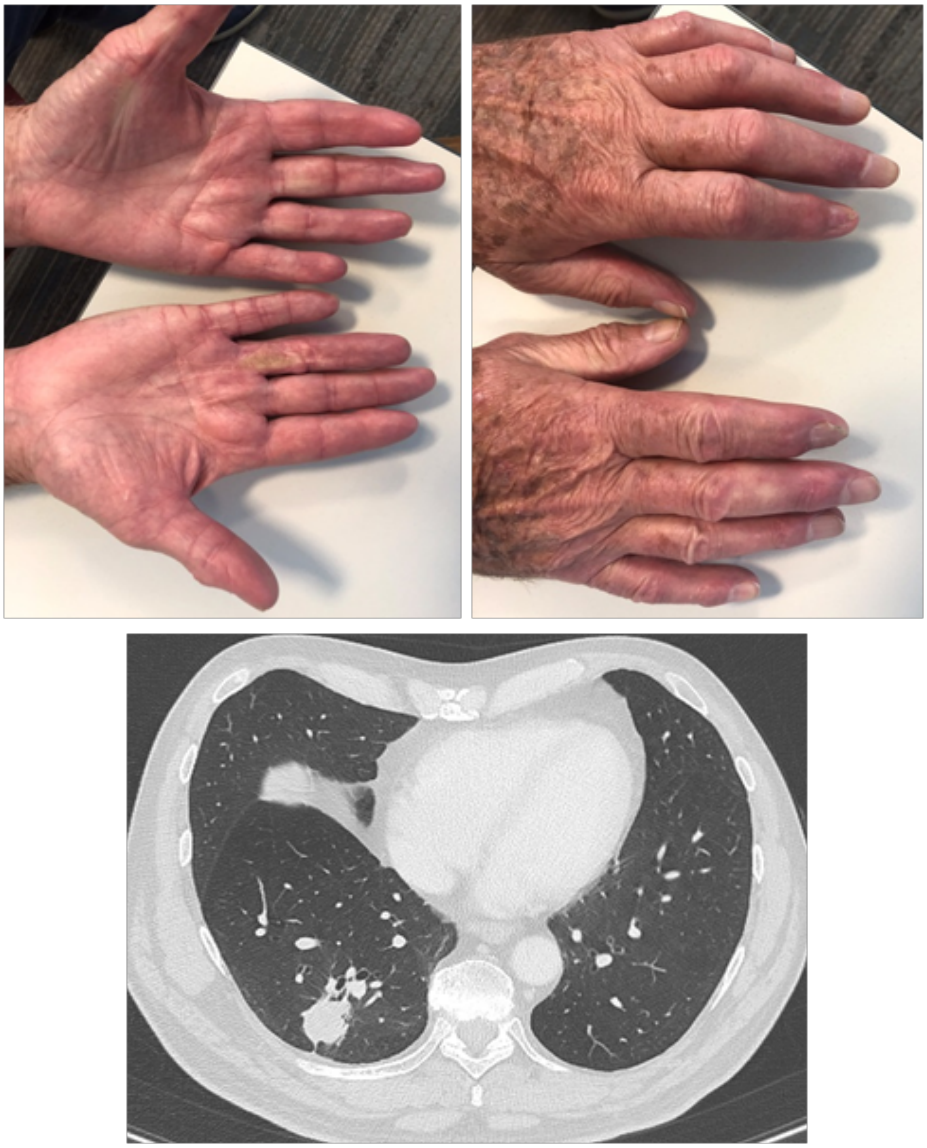


Figure 5: February 2019 (recovery from vasculitis). Most recent CT August 2020 (almost 3 years after immunotherapy):

Discussion

Our case highlights the rare irAE of acral vascular syndrome, which is unique toxicity of immunotherapy requiring a multidisciplinary approach for investigation and management. We considered the possible differential diagnosis of paraneoplastic vasculitis for our patient. However, given that the patient had another irAE (pneumonitis), had resolution of symptoms with ICI discontinuation and steroid treatment, and had a CT showing a partial response to immunotherapy, this was thought less likely [6].

Acral vascular syndrome is a rare clinical entity characterised by ischaemia and necrosis predominantly affecting the hands. This includes Raynaud's phenomenon (the sequence of initial pallor, subsequent cyanosis followed by rubor and dolor) and digital necrosis [7]. Given that ICIs are now approved for use in multiple different cancer types, physicians should have a high level of suspicion for an irAE when Raynaud's phenomenon-like symptoms develop during treatment with ICIs. This requires prompt identification and close monitoring for the development of complications such as digital ischaemia, which may have severe implications for quality of life and function.

Vasculitis induced by ICIs is rare, and predominantly involves large vessels. One review of the literature found that of 20 confirmed cases of vasculitis secondary to ICIs, there were only three cases of small vessel vasculitis seen [8]. The onset and symptoms of acral vasculitis can also vary, with one case report showing an onset six months after commencing combination immunotherapy and being associated predominantly with sensory polyneuropathy [9]. Similar to our case, there was complete clinical improvement seen with corticosteroid treatment.

Our case illustrates the complexities and challenges of managing rare side effects of ICIs. A comprehensive work up in consultation with the appropriate other medical and surgical subspecialties is recommended to achieve a rapid diagnosis and response for the patient. Due to rarity of the issue, an optimal treatment pathway has not yet been defined. Glucocorticoids remain a key treatment for severe acral vascular syndrome. For our patient, calcium channel blockers provided symptomatic relief. In the literature, various other treatments have been used, including prostaglandins, sildenafil, heparin, sympathectomy and amputation, with varying outcomes [10-14].

Patients who experience severe irAEs requiring cessation of therapy may not have detrimental consequences for their cancer. In fact, many achieve on going disease control after the ICI is stopped [3, 4, 15, 16]. It is not clear if this is related to the irAE being an indicator of drug activity or a general upregulation of the immune system. These associations require validation in prospective studies,

and biomarkers for identifying patients at higher risk of severe toxicity and those more likely to achieve disease responses are needed.

To our knowledge, this case demonstrates the longest follow up for a patient with resolved acral vascular syndrome who achieved a sustained complete response off immunotherapy. Acral vasculitis is a known rare irAE that can occur with any ICI therapy. With prompt initiation of corticosteroids and supportive medications, resolution of symptoms and return of function can be achieved for these patients.

Competing interests: The authors declare that they have no competing interests.

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