Photo-distributed involvement of DRESS syndrome secondary to BRAF/MEK targeted therapy for metastatic melanoma - learning points from a severe cutaneous adverse event. No. 77

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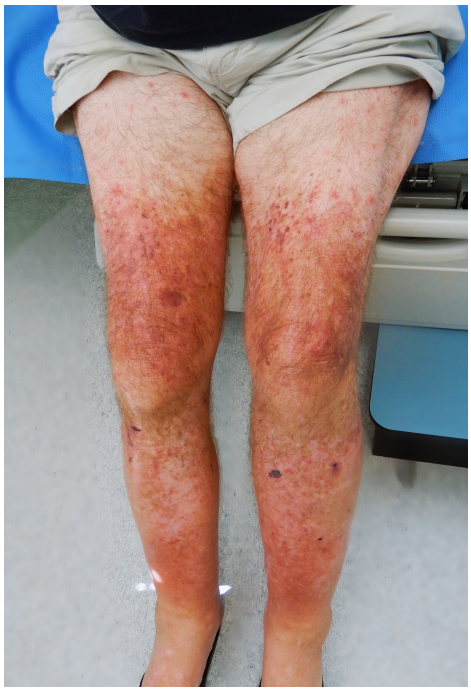
Introduction:
Vemurafenib is a BRAF inhibitor indicated in unresectable or metastatic BRAF V600 mutant melanoma, administered as a targeted therapy combination **(TTC)** with the MEK inhibitor cobimetinib. Cutaneous adverse reactions **(AR)** to combination vemurafenib/cobimetinib **(V/C)** are frequent, though predominantly mild. Photosensitivity is a common cutaneous **AR**, overwhelmingly requiring conservative management only, without **TTC** interruption. Rarely, **V/C** can induce severe cutaneous **AR**.

Case:
A 64-year-old man, was initially diagnosed as T3bN2aMX (AJCC 8th ed) from a BRAF V600E mutant nodular melanoma on the back. Six months later, staging imaging revealed metastases in lymph nodes, lungs and liver.
Initial systemic treatment commenced was **TTC** dabrafenib and trametinib **(D/T)**. After disease progression treatment was changed to the immune checkpoint inhibitors **(ICI)** nivolumab and ipilimumab, which were subsequently ceased due to **ICI** induced myositis**. V/C** was commenced as a third line treatment.
On day 8 of **V/C** he developed a photo-distributed erythematous morbilliform eruption over his face and distal limbs, with sparing under his watch band and post auricular region. There was no mucosal involvement. Over the next 24 hours he reported fevers, general malaise and progression of the eruption to other body sites. He was subsequently admitted. A punch biopsy identified focal basal vacuolar alteration with occasional necrotic keratinocytes, papillary dermal oedema and an inflammatory infiltrate of lymphocytes, histiocytes, neutrophils and eosinophils. A septic screen excluded an infectious precipitant.
Using RegiSCAR criteria[1], DRESS syndrome was diagnosed with a score of 5 {recorded fever >38.5 ° C: -1, enlarged lymph nodes: unknown, eosinophilia: 1 [1.0 × 109/L], atypical lymphocytes: 1, skin rash extent >50%: 1, rash suggesting DRESS: 1, organ involvement: 1 [acute kidney injury (creatinine 237µmol/L)], exclusion of other causes: 1}. **V/C** was immediately ceased and oral steroid therapy 0.5mg/kg and a high potency topical steroid initiated. He steadily improved and recovered fit for discharge 18 days later.
More than 4 weeks later **D/T** was re-commenced, due to concerns re-initiation of **V/C** could re-activate **DRESS** syndrome. After only 3 weeks of **D/T** he was unfortunately readmitted to hospital with vomiting and abdominal pain. Rapidly increased melanoma disease burden lead to bowel obstruction and ultimately death of our patient almost 3 years since his initial melanoma diagnosis.

Learning Points:
*** Photosensitivity is common, whilst DRESS syndrome is not.**
*** Initial presentation of DRESS syndrome can mimic a photosensitive eruption.**
*** Short onset time for DRESS syndrome.**
*** ICI prior to TTC can increase incidence and worsen severity of DRESS syndrome.**



Discussion:
The typical onset of DRESS syndrome is 2 to 6 weeks post drug initiation[2], however, in cases secondary to V/C significantly shorter onset times have been reported, ranging between 6 to 11 days[3]. Clinicians should be mindful of this unusually short onset time, such as the 8 days in our case.
Photosensitivity is a known, common AR in patients receiving V/C, and has been reported in up to 63% of cases, where very few were grade 3 AR, and no grade 4 AR[4]. Concerningly, our case demonstrates that the initial presentation of life-threatening DRESS syndrome can mimic a photosensitive eruption. DRESS syndrome has a mortality rate of 10%[1]. Thankfully, our case had a good response to treatment and was successfully discharged. Our case builds to the current literature speculating that prior ICI can both, increase the incidence[5,6], and worsen the severity[7], of DRESS syndrome secondary to V/C. It is likely the ICI primes the immune system, which is then enhanced by the TTC, and the subsequent immunomodulation may be abnormal[6].
Following multidisciplinary discussion, it was decided not to rechallenge with V/C in our case. There is currently limited and contradictory evidence regarding use of D/T post DRESS syndrome secondary to V/C. There have been reports of successful cases[8], whilst other authors strictly warn against introduction of D/T due to hypersensitivity reactivation[9].

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