An unusual immune checkpoint toxicity

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Mr. TP

- April 2011 - 64 yo male presented with nasal congestion and rhinorrhoea. Found to have a nasal polyp anterior to the inferior turbinate, which was biopsied and revealed mucosal melanoma.

- Baseline staging CT/PET scan showed local disease only;
- Treated with radical surgery with wide-local excision including resection of cartilage, mucosa and the surrounding bone.

- Histopathology demonstrated a T3N0 right nasal cavity mucosal melanoma.
- Molecular pathology: BRAF, KIT and NRAS WT.

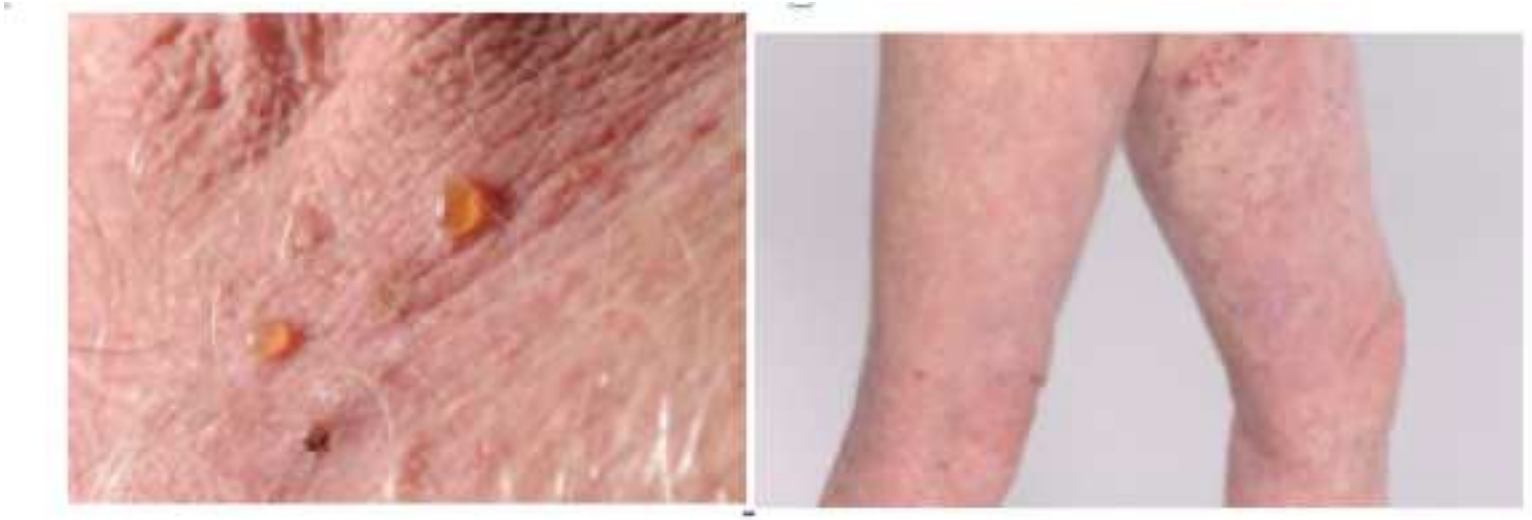
- July 2013 - Restaging PET showed aggressive local disease recurrence and widespread metastases involving the liver and lung.

- Commenced palliative chemotherapy with DTIC - completed 6 cycles with PR for 2 months

- Jan 2014 - PD in lungs/liver - treated with 4 cycles of ipilimumab - marked PR lasting 6 months.

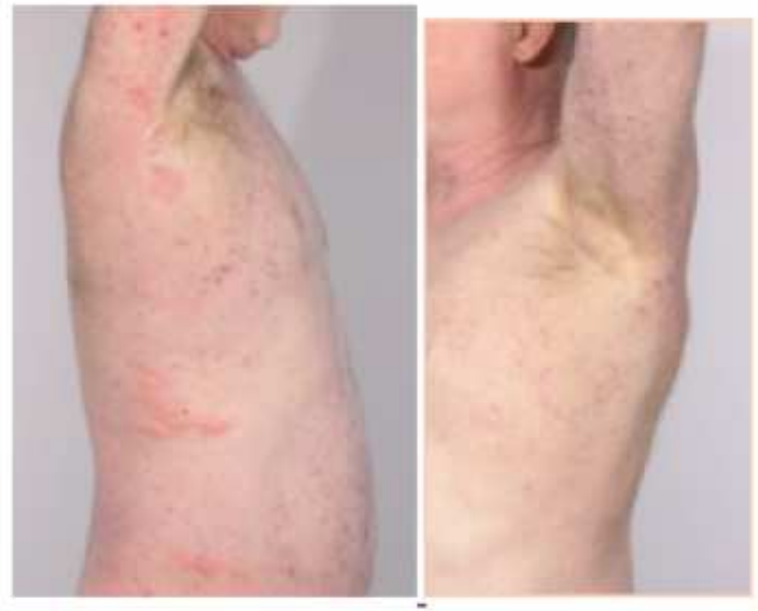
- November 2014 – further PD, commenced on pembrolizumab.
- While on Pembrolizumab, developed local recurrence requiring further surgery and post-op RT
- May 2016 – further PD 18 months into treatment with pembrolizumab, thus rechallenged with 4 x ipilimumab.
- Four weeks after the completion of treatment, he developed a pruritic bullous eruption involving the hands, feet and groin.

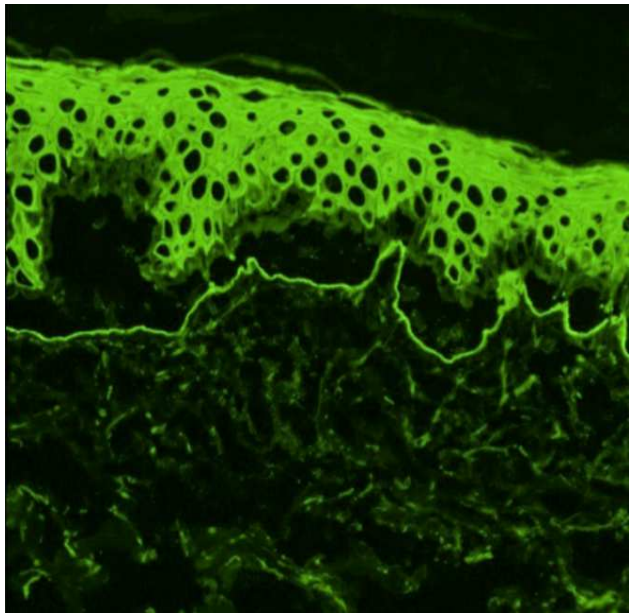
DDx?



- Direct immunofluorescence was performed on a right thigh skin biopsy, which showed immunofluorescence at the basement membrane zone with antibodies to IgG and C3c consistent with **Bullous Pemphigoid.**

- He was managed with a short course of high dose prednisolone 50mg daily and topical diprosone with subsequent rapid resolution of the bullae within 3 weeks.





- January 2017, scans show significant PD – with large burden of life-threatening visceral disease.

What to do now?

- Pt was rechallenged with combination Ipilimumab + Nivolumab after discussion of risks vs benefits.
- Three weeks after commencing treatment, he developed severe widespread bullous pemphigoid (BP) involving more than 80% of his body surface area.
- High-dose oral prednisolone was re-initiated at 50 mg daily. Only partial improvement was seen over 4 weeks, and prednisolone was unable to be weaned below 25mg daily despite the addition of doxycycline 100mg bd, nicotinamide 500mg bd and potent topical corticosteroids.
- The eruption became increasingly morbid, with the patient requiring hospitalisation for dressings and supportive care.
- Subsequently he was given intravenous immunoglobulin (IVIg) at a loading dose of 2g/kg over 3 days. This was followed by monthly infusions at 1g/kg thereafter, with substantial improvement in the BP over 6 weeks, allowing prednisolone to be weaned.
- His BP remained in remission following 4 months of IVIg and he continues to receive monthly infusions of 1g/kg.
- June 2017 – started on carboplatin/paclitaxel for metastatic melanoma.

Not for further immunotherapy!