Multi-system involvement—including purpura fulminans—as an adverse effects of immune checkpoint inhibitor therapy for clear cell renal cell carcinoma

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See Online for appendix

A 61-year-old woman with a 4-day history of asthenia, fever, and a rash was seen by our team in the hospital intensive care unit.

The patient had clear cell renal cell carcinoma with tumoral thrombosis of the right renal vein and inferior vena cava. She was being treated with a checkpoint inhibitor, pembrolizumab—a PD-1 inhibitor—and the endothelial growth factor receptor (VEGF-R) tyrosine kinase inhibitor, axitinib, before re-assessment for surgery, in the oncology day hospital unit. 3 days after the third infusion of pembrolizumab, the patient had been admitted to the intensive care unit because she had become haemodynamically unstable; she had developed heart failure, and purpura fulminans (figure; appendix) over her arms and legs, which had initially appeared as livedo racemose a few hours before. She had also been found to have an ascending sensory motor deficit of her lower limbs.

On examination, we found the patient to be unwell; her blood pressure was 90/60 mm Hg, pulse 30 beats per min, oxygen saturation was 100% on 15 L/min oxygen, and temperature was 32°C. She was confused, with a Glasgow Coma Score of 8 (eye opening response 2, verbal response 2, and motor response 4). She needed both noradrenaline and dobutamine because of her cardiac failure. Additionally, the patient was being treated with meropenem and amikacin; axitinib had been stopped at the point of admission to the intensive care unit.

Laboratory investigations showed high concentrations of N-terminal-pro-B-type natriuretic peptide (10 518 pg/mL; typical level <125 in people younger than 75 years) and troponin (109 ng/L; typical level <14). Concentrations of liver enzymes and thyroid-stimulating hormone were elevated; C-reactive protein concentration was 36 mg/L (typical range 8–10). Analysis of a sample of cerebrospinal fluid (CSF) showed an elevated protein concentration (0·52 g/L; typical level <0·4) and a normal white blood cell count; cultures of blood, CSF, urine, and skin showed no abnormalities.

Figure: **Multi-system involvement as an adverse effect of immune checkpoint inhibitor therapy for clear cell renal cell carcinoma**
Photograph shows extensive bullae and necrotic purpura of the legs.

PCR skin swab testing was negative for *Neisseria meningitidis*, *Streptococcus pneumoniae*, and *Haemophilus influenzae*, resulting in the cessation of antibiotics treatment.

A CT scan of the patient's abdomen showed diffuse thickening of the wall of the colon; echocardiogram showed a left ventricular ejection fraction of 25% (normal range 50–70). MRIs of brain and spinal cord showed no abnormalities. An electromyogram showed severe sensory-motor neurogenic damage compatible with axonal length-dependent processes without demyelination.

Histopathological analysis of a sample of a skin biopsy showed thrombosis with leukocytoclastic vasculitis, which, considering the patient's presentation, investigations, and history in the round, led us to conclude she had developed an immune-induced myocarditis, acute motor and sensory axonal polyneuropathy, colitis, hypothyroidism, hepatitis, and purpura fulminans.

The patient was commenced on pulse methylprednisolone (1 g per day for 5 days) and intravenous immunoglobulin (2 g per kg over 4 days), which resulted in the improvement of her general condition. She had three separate plasma exchanges to clear the pembrolizumab and surgery of the deepest wounds with skin grafts.

The corticosteroids were gradually tapered down over the next 4 months, and at follow-up 6 months later the skin lesions had completely healed. The patient's neoplastic disease was under control—despite discontinuation of the pembrolizumab and axitinib.

Immune checkpoint inhibitors have become established treatments for several cancers including malignant melanoma and renal cell carcinoma. Such developments have, in some patients resulted, in treatment-related adverse effects of variable severity. Immune-related purpura fulminans associated with pembrolizumab has been reported previously in a patient treated for lung carcinoma.

Contributors
We were all involved in the clinical care and management of the patient, collecting the data, and drafting the manuscript. ALB provided supervision. All authors approved the final version of the manuscript. Written consent for publication was obtained from the patient.

Declaration of interests
We declare no competing interests.

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