**Short Communication**

**Life Threatening Polymyositis with Spontaneous Haematoma Induced by Nivolumab in a Patient with Previously Resected Melanoma**

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Anti-PD1 antibodies have changed the treatment landscape for a number of cancer entities in the past few years. When given as single agent they are usually very well tolerated, but serious rare toxicity can still occur. We present here a case of polymyositis with associated spontaneous muscular haematoma in a patient treated with single agent nivolumab.

Case report

A 71-year-old gentleman with a completed resected Stage IV (T2a N2b M1a) melanoma was started on adjuvant nivolumab 480mg 4 weekly. He did not have any current significant comorbidities but he had a colorectal cancer treated with curative surgery followed by adjuvant chemotherapy 5 years before. Twenty days post first infusion with nivolumab, he presented with a 7-day history of exertional dyspnea and diplopia. Chest X-ray, echocardiogram and oxygen saturations were normal. Electrocardiography showed a new right bundle branch block and an intermittent 2:1 heart block. The patient could not tolerate CT or MR imaging due to his breathlessness and therefore pulmonary embolism or presence of brain metastases could not be excluded. Therapeutic anticoagulation was not initiated due to the risk of hemorrhagic brain metastases. An initial blood work up revealed possible myositis with associated myocarditis and rhabdomyolysis (creatine kinase level, 2830 u/l [normal range, 40-320] and troponin T level, 840 ng/l, increasing to 1549 ng/l [normal level, 0-14]). Thyroid function tests, cortisol levels and pituitary hormones were normal. Antinuclear antibodies (ANA) and a myositis immunoblot test for OJ, EJ, PL-12, Pl-7, SRP, Jo-1, Pm-Scl75, Pm-Scl100, Ku, SAE, NXP-2, MDA5, TIF-1g, Mi-2 and Ro-52 were negative. A neurological examination was normal and there were no cutaneous signs of paraneoplastic dermatomyositis or polymyositis.

Two days post admission, after a COVID-19 swab resulted negative, the patient was started on intravenous methylprednisolone 1g once a day being nivolumab-induced polymyositis the most likely diagnosis. Methylprednisolone was reduced to 500mg three days after with some marginal improvement of CK and troponin I levels which was however not associated to significant clinical benefit.

On day 9 post admission, he was found to be acutely hypotensive with worsening type two respiratory failure. He was intubated and transferred to critical care. Blood tests showed an acute drop of hemoglobin from 12 – 6g/l in 48 hours and CT imaging confirmed a subacute intramuscular haematoma of the right psoas muscle and right latissimus dorsi muscle (Fig 1 b,e).

A five-day course of intravenous immunoglobulin (IVIG) at 0.4g/kg once a day was initiated. Post IVIG, subcutaneous (SC) weekly methotrexate at an initial dose of 10 mg was started and methylprednisolone was slowly weaned. The patient gradually clinically improved with a falling troponin and normalization of the creatine kinase level but had a prolonged extubation due to respiratory exhaustion. He was eventually stepped down from intensive care after three months. Repeat CT imaging three months post admission showed initial resolution of the hematoma (Fig.1 c,f).

Discussion

To our knowledge this is the first case of autoimmune myositis and spontaneous heamatoma associated with the administration of single agent ICI. Spontaneous hematoma is an extremely rare complication with unclear aetiology of idiopathic myositis (1). Very few cases have been reported in the literature and their outcome has been often fatal. Unlikely the majority of the patients with idiopathic myositis who developed a spontaneous heamatoma, our patient was not on any anti-coagulant treatment because of the risk of haemorragic brain metastases. Disorders of the coagulation-fibrinolysis system have been reported in patients with cancer receiving anti-PD1 antibodies and these may have contributed to the development of the haematoma (2).

Despite the PD-1 pathway seems to be relevant in the pathogenesis of immune-related myositis (3), anti-PD1-related myositis is generally a rare side effect of the treatment (4). However, its frequency is likely to increase as the use of ICIs rises. Recently anti-PD1 antibodies nivolumab (5) and pembrolizumab (6) have been licensed in the adjuvant setting after complete resection of stage III and IV melanoma. Some of these patients may have been surgically cured and it is therefore important to timely recognize rare and potentially life threatening toxicity in order to promptly start adequate treatment.

Declaration of Interest statement

The Authors have declared no conflicts of interest.

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Figure 1: Axial and coronal views of the abdomen at baseline (a & d), day 29 post-infusion of nivolumab (b & e) and day 95 post-infusion (c & f). At baseline normal outline and bulk of the right psoas major muscle is noted (solid arrow). At day 29 post-infusion, a non-contrast (axial figure 1b) and portal venous phase (coronal figure 1e) demonstrates a haematoma within an expanded right psoas major muscle (open arrow) but with no active haemorrhage at time of scan. Subsequently the right psoas major muscle reduces in bulk and density on follow-up imaging at day 95. The left psoas major muscle (asterix) and erector spinae muscles have reduced in bulk with fatty replacement due to resolution of myositis and disuse secondary to hospitalization.