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DURVALUMAB-INDUCED TRIPLE-M SYNDROME

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ABSTRACT

Background: While the use of immunotherapy has revolutionised the treatment of various cancers, it is often associated with a myriad of immune-related adverse effects.

Case Presentation: In this article, we report a rare case of durvalumab-induced triple-M syndrome in a 69-year-old woman with stage III lung adenocarcinoma. She was admitted with profound generalised muscle weakness, myalgia, and exertional breathlessness, about a week into her second cycle of durvalumab, an immune checkpoint inhibitor. She had clinicopathological features of myositis, myasthenia and myocarditis with acute onset symptomatic tri-fascicular block on electrocardiogram, requiring urgent cardiology intervention. Durvalumab was discontinued and she was treated with a combination of high-dose steroids and intravenous immunoglobulin after which she had clinical and biochemical improvement, albeit with residual muscle weakness.

Conclusion: Myocarditis-myositis-myasthenia complex is a rare side effect of immunotherapy which has been reported in other immune checkpoint inhibitors, but less so with durvalumab. We report this clinical case to raise awareness of this rare and potentially life-threatening adverse effect of this agent.

KEYWORDS

Durvalumab, triple-M syndrome, myositis, myastheniam, myocarditis

LEARNING POINTS

- Triple-M syndrome is a rare immune-related adverse effect, which has been noted in other immune checkpoint inhibitors, but less so with durvalumab specifically.
- Immunotherapy-induced myositis, myocarditis and myasthenia can occur in isolation or, rarely, in association as a syndrome.
- This case demonstrates the potentially life-threatening nature of this entity, the need for early recognition, and multi-specialist teamwork to ensure good outcome.

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INTRODUCTION

Immunotherapy is a well-established systemic anticancer therapy which has vastly improved outcome in various cancer settings. Durvalumab, an immune checkpoint inhibitor (ICI), which inhibits programmed cell death ligand 1 (PD-L1) is licensed for adjuvant treatment of unresectable stage III non-small cell lung cancers (NSCLC) after completing chemoradiotherapy, based on evidence from PACIFIC trial showing its efficacy[1]. We report a rare case of triple-M (myositis-myocarditis-myasthenia) syndrome induced by this monoclonal antibody.

CASE PRESENTATION

The patient was a 69-year-old Caucasian woman and an ex-smoker, with a medical background of chronic bronchitis and presumed giant cell arthritis (GCA) for which she completed 2 years of low dose prednisolone well over 5 years previously. She was functionally independent with ECOG performance status of 1. In August 2023, she was diagnosed with right upper lobe lung adenocarcinoma, T4N2M0 (stage IIIb), with PD-L1 expression score of 20%. She completed concurrent chemoradiotherapy, with four cycles of platinum-based doublet chemotherapy in combination with radiotherapy delivered at a dose of 60 Gy in 30 fractions over six weeks, with no significant toxicities. As shown in *Fig. 1*, her post-treatment computed tomography (CT) scan showed partial response with decrease in the size of the primary lesion and nodal disease. She was subsequently started on adjuvant durvalumab (10 mg/kg given in 2 weekly cycles) as per protocol. One week into the second cycle of durvalumab she developed insidious onset of progressive generalised muscle weakness, exertional dyspnoea, and myalgia. She found herself barely able to walk and was dropping items. At presentation via the Acute Oncology Service, she had difficulty holding her head in an upright position due to neck and truncal muscle weakness. Muscle power on both shoulder and neck flexion and extension were 4/5. There was significant bilateral lower limb weakness. In addition, she had global hyporeflexia, diffuse muscle tenderness, with normal muscle bulk and tone. Eye examination revealed normal visual fields and pupils but diplopia on central and right lateral gaze. The biochemistry profile showed significantly raised serum creatine kinase (CK) 8668 U/l (normal value <200) and troponin-T 870 ng/l (normal value <14) levels with an erythrocyte sedimentation rate (ESR) of 74 mm/hr. Rheumatoid factor was slightly elevated at 17 U/ml (normal range 0-14U/ml). Antinuclear antibody (ANA) was weakly positive, but the rest of the autoantibody tests including anti-anti-muscle-specific kinase (MUSK), antiacetylcholine receptor antibody (aChR), and extractable nuclear antigen (ENA) was negative. She had an isolated raised alanine transaminase (ALT) with normal bilirubin. Initial echocardiography and electrocardiogram (ECG) were normal. Pulmonary function tests showed reduced forced vital capacity (FVC) 51% predicted. Whole spine magnetic resonance imaging (MRI) showed an extensive multi-level paraspinal muscle oedema, in keeping with myositis *(Fig. 2)*. Brain MRI with contrast showed a new 6 mm ring enhancing lesion in the precentral gyrus suspicious of a metastatic deposit. CT pulmonary angiogram showed no evidence of pulmonary embolism, disease progression, effusion, or pneumonic consolidation. There were changes in keeping with myopathy on needle electromyography, but repetitive stimulation showed no decline in amplitude. Her sensory nerve conduction study was normal. In view of her multi-systemic presentation, there was prompt multi-specialist input in her care. She was started on high-dose steroid therapy with methylprednisolone (1 g/day), for the first 72 hours. Steroid therapy was later stepped down to oral prednisolone 1 mg/kg/day. On the fourth day of admission, she developed new onset bradycardia, with a heart rate of 45-50 bpm, and ECG showed sinus bradycardia with tri-fascicular block *(Fig. 3)*. She was urgently transferred to the Cardiac Care Unit for isoprenaline infusion and dual chamber permanent pacemaker insertion. Colchicine and ramipril were also started for myocarditis. In view of ongoing respiratory muscle weakness, she was commenced on intravenous immunoglobulins (IVIG) at a dose of 0.4 g/kg/day for 5 days with regular spirometry. She improved

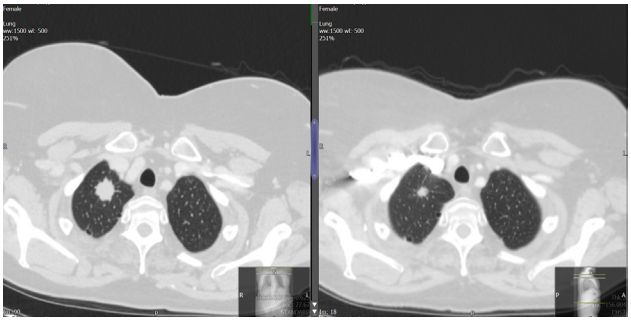

Figure 1. Computed tomography scans before (August) and after chemoradiotherapy (December).

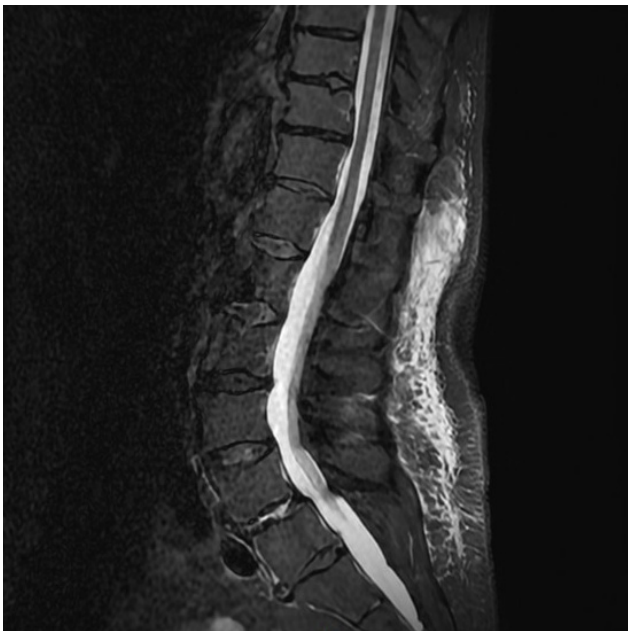

Figure 2. Whole spine magnetic resonance imaging showing paraspinal muscle oedematous changes on STIR sagittal sequence.

with combination of IVIG and high-dose steroids, with biochemical decline in transaminitis, CK and troponin-T levels *(Fig. 4)*. Later in her admission, she also developed atrial fibrillation for which she was anticoagulated with apixaban, a direct oral anticoagulant. She was discharged on a weaning regime of prednisolone after 3 weeks stay in hospital with multi-speciality care, to be followed up by oncology, rheumatology, and cardiology. She was also referred to the Neuro-Oncology team for stereotactic radiosurgery for the intracranial lesion.

DISCUSSION

Durvalumab, a novel, fully humanised, high-affinity monoclonal antibody, blocks the interaction between PD-L1 on cancer cells and its receptor (PD-1) on the T-cell surface, thus enhancing immune recognition and killing of cancer cells. Although durvalumab, like other ICIs, has shown efficacy in a growing number of cancer types, the potential for stochastic immune-related adverse effects (irAEs) remains a clinical challenge. The PACIFIC trial showed both progression-free survival (PFS) and overall survival (OS) benefits from adjuvant durvalumab after chemoradiotherapy[1]. Hence, this agent has been approved in the United Kingdom as a consolidation treatment in NSCLC with PD-L1 expression >1%, provided there is no radiological evidence of disease progression after chemoradiotherapy.

Currently, there is a paucity of data on durvalumab-associated myocarditis-myositis-myasthenia complex due to its rarity. Therefore, diagnosis and management of durvalumab-induced triple-M syndrome can often pose challenges. Firstly, although each component often occurs in isolation, they can also present as an overlap syndrome as observed in this case[2]. The exact reason for this association is not entirely clear, but it has been theorised that molecular mimicry is a possible underlying mechanism. It is therefore crucial to consider investigating patients for the other components of triple-M syndrome when any of these three is observed. ICI-induced neurotoxicity is reported in 1% of patients receiving single agent immunotherapy and in 2-3% in the setting of doublet immunotherapy[3]. ICI-induced myocarditis occurs even less commonly - 0.09% and 0.27% - in single and dual ICI therapy respectively[4]. Secondly, as with other irAEs, the onset time can vary widely. A systematic review of cases showed a trend in favour of early onset with a median time of symptom onset within the first cycle[2]. While most cases of myocarditis tend to present within 12 weeks of initiation of therapy[3], myasthenia has been reported 4 years after the last dose of durvalumab[5]. Furthermore, as seen with other ICIs, triple-M syndrome can present with a wide spectrum of non-specific symptoms. For instance, Golec et al. recently reported a similar case in a 74-year-old male with locally advanced oesophageal cancer, who presented with fatigue and dyspnoea 4 days into second cycle of nivolumab (anti-PD1)[6]. Similarly, Todo et al. reported another case of a 63-year-old patient on pembrolizumab for urothelial cancer, who presented with diarrhoea, rash, and eye symptoms[7].

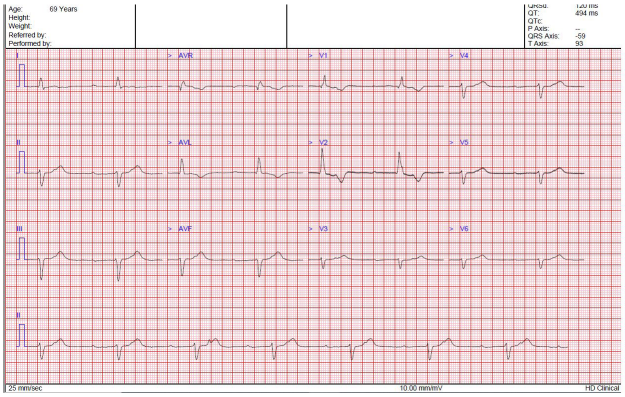

Figure 3. Electrocardiogram showing tri-fascicular block.

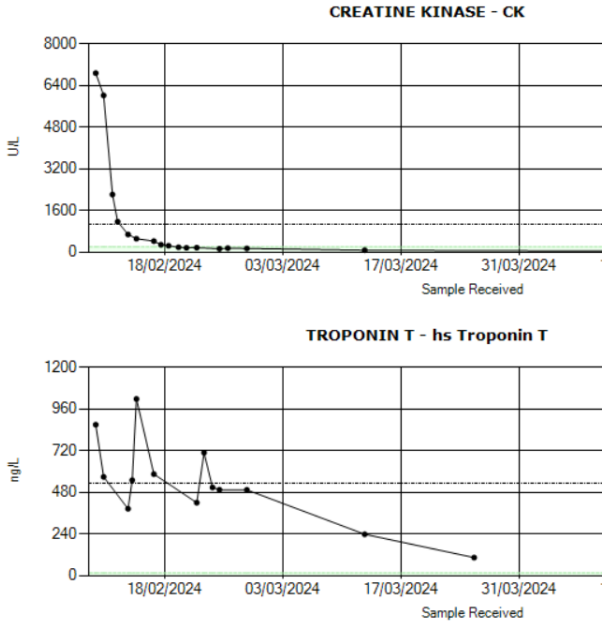

Figure 4. Serum creatinine kinase and troponin-T levels over time.

A thorough clinical assessment, diagnostic work-up, cessation of ICI, and prompt initiation of immunosuppressant and other supportive treatments, as well as multi-disciplinary team efforts played important roles in the management of this patient. Clinical and laboratory evaluation was directed at confirming the diagnosis and excluding other differential diagnoses such as severe anaemia, sepsis, disease progression, paraneoplastic syndromes, metabolic derangements, and cardiopulmonary events. Although, there are no specific biomarkers for immunotherapy-induced triple-M syndrome, a marked elevation in serum CK and troponin-T levels is generally characteristic of myositis and myocarditis respectively. Myositis-autoantibodies are usually negative in majority of patients with ICI-induced myositis, as seen in this case. This patient had extensive paraspinal muscle oedema on whole spine MRI scan, which has been identified as an early radiological feature of myositis[8]. In the later stages of myositis, signs of fatty transformation or muscle atrophic changes may be seen. Obtaining a biopsy of affected muscle(s), where appropriate and available, may show muscle fibre necrosis and atrophy as well as T-lymphocyte and macrophage infiltration, which

have recently been noted to be more characteristic of ICI-induced myositis[9].

Diagnosing myasthenia gravis (MG) relies heavily on clinical assessment, serology, and neurophysiological studies. This typically presents with ocular, bulbar, respiratory, or generalised weakness. In a recent review of 47 cases by Huang et al., anti-ChR and anti-MUSK antibodies serological tests were negative in about 33% and 95% of cases respectively[10]. Also of interest is that autoantibody positivity rates appear to be lower in ICI-induced MG than in non-ICI induced types, with anti-ChR and anti-MUSK antibodies being detected in 85% and 6% of cases respectively[11]. Therefore, given the relatively low sensitivities of these tests, it is important to bear in mind that a negative serology does not exclude ICI-induced MG, as seen in this patient. Electrophysiological studies are useful but, again, the classical decremental response on repetitive stimulation is seen in only about 50% of ICI-related MG cases[10]. Patients with myocarditis may present with asymptomatic elevation in cardiac enzymes, chest pain, palpitations or fatal arrythmias. Our patient had markedly elevated troponin T on admission and subsequently developed trifascicular block *(Fig. 2)*, a few days later, requiring urgent permanent pacemaker insertion. A recent case series of ICI-induced myocarditis, by Aggarwal et al, reported life-threatening arrythmias in two of the patients, requiring urgent pacemaker insertion[12]. It is therefore crucial to have a low threshold for investigating new onset bradycardia and chest pain in these patients. Immunosuppressants form the backbone of management of most irAEs. In the absence of any specific protocol on the use of immunosuppressants in this entity, the European Society of Medical Oncology (ESMO) general guidance for immunosuppression underpinned our decision-making in this case[13]. This entails formulating a diagnosis and grading, exclusion of other differentials, initiation of appropriate immunosuppressants, and ongoing evaluation to adapt treatment strategy after 72 hours. High-dose steroid therapy with intravenous methylprednisolone 1 g once daily for 3 days followed by 1 mg/kg oral prednisolone was initiated, without waiting for the autoantibody results, which can often take days. Other treatment options in combination with steroids such as intravenous immunoglobulins and plasmapheresis have been reported in the literature[2]. It is however important to monitor patients closely when initiating high-dose steroids due to the risk of "steroid dipping" in MG leading to initial paradoxical worsening of muscle weakness. The use of steroid-sparing agents such as mycophenolate mofetil, azathioprine, cyclosporine, and biologics (rituximab or infliximab) has been reported in the literature. However, currently, there are no prospective studies in this area. Therefore, their use in this setting is largely based on anecdotal evidence and extrapolated data from their efficacy in other settings. The rare incidence of this complex may suggest that there are possible inherent factors, genetic and acquired, that increase individual's risk of developing this adverse effect. Our patient had a medical background of presumed GCA, but to our knowledge, there is not enough evidence to suggest a strong association between this arteritis and triple-M syndrome. In the future novel predictive biomarkers of this irAE may emerge and thus guide in individual risk assessment in treatment decision-making process.

CONCLUSION

Although durvalumab-induced triple-M complex is an extremely rare irAE, we anticipate that with increasing use of this ICI for various indications, this potentially life-threatening phenomenon is likely to be seen from time to time, and a high index of suspicion is needed to identify it. Prompt identification and intervention, with multi-disciplinary team approach is crucial in managing this serious irAE.

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