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BRIEF REPORT

Severe necrotizing myositis associated with long term anti-neoplastic efficacy following nivolumab plus ipilimumab combination therapy

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Abstract

Immune-related adverse events (irAEs), have been reported under immune checkpoint inhibitors. Nivolumab plus ipilimumab (N + I) demonstrated meaningful improvements in key patient-reported outcomes, in patients with pretreated microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC). We report a case of severe necrotizing myositis which occurred in a patient treated with N + I combination for mCRC MSI-H. A 61-year-old woman was diagnosed with mCRC MSI-H and *BRAF*V600E mutated with synchronous liver, pleural, and lymph nodes metastases. After she failed to respond to standard chemotherapy (two lines with 5-fluorouracil, oxaliplatin, and irinotecan + bevacizumab), she received in a clinical trial (CheckMate 142), nivolumab 3 mg/kg, and ipilumumab 1 mg/kg every 3 weeks [4]. One week after the second infusion, she developed rapidly extending proximal muscles weakness associated with diffuse erythematous rash with grade 2/5 strength on abdominal, dorsal, and proximal limb muscles and impressive muscular edema. The creatine kinase level was at 14827 U/L (0–160 U/L), without any detectable autoantibodies. The electromyogram showed a severe myogenic syndrome, and muscular histological analysis demonstrated extensive muscular necrosis, with scarce lymphocytic infiltrates and pathological expression of class I HLA and C5b9 complement deposits with severe endomysial edema. N-I therapy was discontinued. Intravenous methylprednisolone was initiated for 3 days followed by 1 mg/kg/day orally, combined with intravenous immunoglobulins (2 g/kg/day for 2 days). At 3 years of first infusion of N + I, patient is without any new progressive disease, in partial response on the liver, pleural, and nodes metastasis, with only persistent minor psoas weakness.

Keywords Myositis · Check point immune related adverse evens · Immunotherapy

Sir, Immune-related adverse events (irAEs), have been reported under immune checkpoint inhibitors [1–3]. Nivolumab plus ipilimumab (N + I) demonstrated meaningful improvements in key patient-reported outcomes, in patients with pretreated microsatellite instability-high (MSI-H) metastatic colorectal cancer (mCRC) [4]. We report a case of severe necrotizing myositis which occurred in a patient treated with N + I combination for mCRC MSI-H.

A 61-year-old woman was diagnosed with mCRC MSI-H and *BRAF*V600E mutated with synchronous liver, pleural, and lymph nodes metastases. After she failed to respond to standard chemotherapy (two lines with 5-fluorouracil, oxaliplatin, and irinotecan + bevacizumab), she received in a clinical trial (CheckMate 142), nivolumab 3 mg/kg, and ipilumumab 1 mg/kg every 3 weeks [4]. One week after the second infusion, she developed rapidly extending proximal muscles weakness associated with diffuse erythematous rash with grade 2/5 strength on abdominal, dorsal, and proximal limb muscles and impressive muscular edema. The creatine kinase level was at 14827 U/L (0–160 U/L), without any detectable autoantibodies. The electromyogram showed a severe myogenic syndrome, and muscular histological analysis demonstrated extensive muscular necrosis, with scarce lymphocytic infiltrates and pathological expression of class I HLA and C5b9 complement deposits with severe endomysial edema.

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N-I therapy was discontinued. Intravenous methylprednisolone was initiated for 3 days followed by 1 mg/kg/day orally, combined with intravenous immunoglobulins (2 g/kg/day for 2 days). Creatinine kinase levels normalized in 1 month. Prednisone was tapered and stopped after 7 months while the patient's condition slowly improved. She was able to walk unassisted after 2 months. Radiological assessment at 6 weeks of first immunotherapy infusion showed a 50% tumor shrinkage, with a confirmed partial response at 12 weeks. A new lesion on the right adrenal gland was observed at 12 months. Adrenal gland was surgically removed (metastatic localization of CRC). At 3 years of first infusion of N + I, patient is without any new progressive disease, in partial response on the liver, pleural, and nodes metastasis, with only persistent minor psoas weakness.

Anti- PD-1 and or anti CTLA-4 monoclonal antibodies have been associated with grade 3 and 4 irAE in approximately 20% and 10% of patients, respectively [2, 3] and 20 to 50% when combined, depending upon dosing [2, 3]. Frequency of myositis with PD-1 inhibitor is low [5, 6], less than 1%, and may be higher with the combination of anti PD-1 and anti-CTL4 monoclonal antibodies [2]. As described with other irAE, necrotizing myositis occurred quickly after the treatment initiation (within the first 12 weeks) [1, 5]. Two cases of neuromuscular irAE have been reported so far during anti-CTLA-4 therapy among 2.9% of acute neurological complications [5, 7]. Even some cases of autoimmune myositis such as dermatomyositis have been described, usually there are no detectable autoantibodies. Necrotizing severe myositis has been rarely reported. The treatment of this rare adverse effect is challenging, and in severe cases, immunoglobulins or plasmapheresis have been reported, even actually no guidelines can been stated [5, 6]. Our case is provided an example of the potential manifestation of the clinical course, management, and outcome.

Autoimmune adverse reactions can occur with therapeutic approaches that activate anti-tumor immunity by blocking immune checkpoints. However, the overall risk outweighs the durable clinical benefit observed with such therapeutic approach. The use of evidence-based algorithms have been reported to lead to effective management and resolution of most irAEs associated with N + I [4].

Compliance with ethical standards

Disclosures None.

TA was principal investigators in CheckMate 142 and is consultant for BMS and MSD Oncology.

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