Pembrolizumab-induced necrotizing myositis in a patient with metastatic non-small-cell lung cancer: a case report

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Practice points

- In cancer patients, about 13% of patients develop immune-mediated adverse effects with pembrolizumab.
- These mostly include dermatitis, colitis, pneumonitis and thyroiditis.
- Necrotizing myositis is a rare complication of pembrolizumab.
- Swelling and muscle weakness of the lower extremities with dyspnea and general deterioration in cancer patients treated with immunotherapy is not always the result of a deep venous thrombosis (DVT) with pulmonary embolism, pneumonitis or heart failure. Although rare, necrotizing myositis must be considered.
- Using another checkpoint inhibitor after a severe immunemediated side effect is possible without any clinical repercussions or worsening of the previous symptoms.

A 57-year-old man presented with swelling and pain in the lower limbs, inability to walk and increasing dyspnea for 2 days. Because of refractory stage IV non-small-cell lung cancer, pembrolizumab was started 21 days before presentation. Since then, he experienced general discomfort, fatigue and bilateral weakness in the legs with exercise limitation. A diagnosis of pembrolizumab-induced grade III myositis was made based on muscle biopsy. Pembrolizumab is a humanized monoclonal antibody against PD-1. It has been approved for the treatment of metastatic melanoma and refractory non-small-cell lung cancer with increased expression of PD-L1 on the cell surface of tumor cells. With such a humanized monoclonal antibody, fewer adverse events are expected than with systemic chemotherapy. However, 13% of patients develop autoimmune side effects which can be severe (grade III, IV or V) in 5–10%. We discuss a case of pembrolizumab-induced myositis, with a brief overview of the literature. Only three cases of pembrolizumab-induced myositis have been reported in literature.

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Presentation of case

A 57-year-old Italian man with recurrence of stage IV non-small-cell lung cancer (NSCLC) was consulted 3 weeks after his first cycle of pembrolizumab. He presented with dyspnea, pain in the right calf muscle, swelling of the lower limbs and was unable to walk for 2 days. Since the first administration of pembrolizumab there had been growing general discomfort, fatigue and bilateral weakness of the legs with exercise limitation.

His personal history was unremarkable. Eight months earlier, following hemianopsy, an oligometastatic adenocarcinoma in the right lung with solitary brain metastasis (cT2aN0M1b), was diagnosed. Next generation sequencing revealed no druggable mutations, only a TP53 mutation. Fluorescence in situ hybridization for ALK was negative, but immunohistochemistry (IHC) for the PD-L1 was 100% positive. First, the cerebral lesion was surgically resected, followed by stereotactic radiotherapy (5 × 7 Gy) at the resection site. The primary tumor was surgically removed by video-assisted thoracoscopic surgery (VATS) with inferior right lobectomy and four cycles of adjuvant chemotherapy (cisplatin–pemetrexed combination) were given. However, already at the end of the adjuvant treatment, disease progression occurred with a new pleural metastasis and a suspect pancreatic lesion.
Figure 1. Biochemical evolution. Evolution after induction of high dose corticosteroids, elevation was seen for more than 6 weeks after start therapy.
CK-MB: CK-cardiac isoenzyme.

Therefore, pembrolizumab (2 mg/kg) in a 3-weekly cycle was started for second-line treatment. There were no specific medical problems in the family history and, at the time of this admission, the patient did not take any other medications. In addition to abdominal obesity and an ex-smoker (45 pack-years) status, no other cardiovascular risk factors were present.

Clinical examination at presentation confirmed a swelling of the lower legs, right more than left, with pain in the right calf. Auscultation of heart and lungs was normal. Vital parameters were normal. Blood tests revealed a sharp increase in muscle and cardiac enzymes: creatine kinase (CK) 11796 U/l (ref. <190 U/l), CK cardiac isoenzyme 112.5 μg/l (ref. <6.2 μg/l), troponin 0.183 μg/l (ref. <0.013 μg/l) (Figure 1). Liver function enzymes and LDH were also disrupted and c-reactive protein was increased to 35 mg/l.
An electrocardiogram (ECG) showed sinus rhythm with new small biphasic T-waves in V2 to V5. Computed tomography (CT) of the chest ruled out pulmonary embolism or other causes of his current dyspnea. Venous duplex scan of the lower limbs did not show venous thrombosis in the pelvis or legs. Transthoracic echocardiography (TTE) showed a normotrophic and normocontractile heart with normal systolic left and right ventricular function, without significant valvular disease. Nuclear magnetic resonance (NMR) of the heart was normal. A cardiogenic origin of the swollen legs and dyspnea was therefore unlikely. Three arguments suggested that a muscular problem with rhabdomyolysis was more likely than an acute coronary syndrome or another primary cardiac disease (e.g., autoimmune myocarditis): the absence of angina pectoris, no noteworthy electrocardiogram abnormalities and the significant discrepancy between strongly augmented CK and only moderately increased troponin levels. The soft tissue ultrasound of his right lower leg revealed a nonspecific distortion of the architecture of the medial gastrocnemius muscle, indicating an area of ischemic muscle. A biopsy of this area was performed and documented a necrotizing myositis. Following specific histological and immunohistochemical analysis, the diagnosis of a grade III autoimmune myositis was confirmed (Figure 2).

High dose intravenous corticosteroids were immediately administered after biopsy taking. A favorable clinical and biochemical evolution was observed within a few days (Figure 1). Corticosteroids were gradually tapered and after 7 days the patient was discharged with oral corticoid therapy. After 6 weeks, an eventual re-challenge with pembrolizumab was planned, but on his computed tomography evaluation a new solitary brain metastasis was detected and the known pancreatic lesion further increased. Because of disease progression and a permanent CK elevation, immunotherapy was stopped. For his brain metastasis, stereotactic radiotherapy was planned and a new combination treatment with docetaxel and nintedanib was started after the radiotherapy. After five cycles, further disease progression was seen with the appearance of a liver metastasis. Atezolizumab, a monoclonal anti-PD-L1
antibody, was administered as fourth-line treatment. The cardiac and muscle enzymes did not increase during this treatment. After three cycles of atezolizumab, a new brain metastasis and an explosively growing liver metastasis were observed, leading to the stopping of atezolizumab treatment.

Discussion

Pembrolizumab is a humanized monoclonal antibody against the PD-1 [1]. It has been approved as single-agent therapy for the treatment of metastatic melanoma and refractory NSCLC [1]. Checkpoint inhibitors, like pembrolizumab, boost the antitumor activity of the immune system. Pembrolizumab is associated with significantly longer progression-free and overall survival in first as in second-line treatment of PD-L1-positive NSCLC in comparison with chemotherapy [1,2]. PD-L1 expression in at least 50% of tumor cells correlated with improved efficacy of pembrolizumab [1–4].

Moreover, pembrolizumab has a favorable benefit-to-risk ratio with fewer adverse events in comparison with systemic chemotherapy [1–3]. Overall, 73.4% of the patients in the pembrolizumab group developed treatment-related adverse events of any grade, in the chemotherapy group this was 90% [1]. Grade III, IV or V treatment-related adverse events occurred in twice as many patients in the chemotherapy group as compared with the pembrolizumab group (53.3 vs 26.6%) [1]. The Common Terminology Criteria for Adverse Events (CTCAE) displays grades I through V with unique clinical descriptions of severity of the adverse events. Patients with grade III adverse events need hospitalization because of severe but not immediately life-threatening events. The most common adverse events are diarrhea, fatigue, fever and general discomfort. About 13% of patients in the pembrolizumab group developed immune-mediated adverse events, which can be severe (grade III, IV or V) in 5–10% [5]. These include dermatitis, colitis, pneumonitis, thyroiditis and inflammation of the hypophysis, but every single organ can be affected.

Our case emphasized that patients treated with pembrolizumab are at risk of developing necrotizing myositis. In this case, the patient had dyspnea but was not in respiratory distress. However, one of the cases discussed in literature resulted in a necrotizing myositis of the diaphragm with respiratory failure and a fatal outcome [6]. Diaphragm involvement cannot be excluded in this case and could be an explanation of dyspnea beside the general deterioration of the patient. The clinical features at presentation are nonspecific, which may result in a delay of diagnosis and treatment. We also want to remark that anti-PD-L1 immunotherapy with atezolizumab did not induce myositis in our patient. Anti-PD-L1 immunotherapy has probably less adverse events than anti-PD-1 immunotherapy; however, as Pillai et al. suggested, the toxicity and efficacy profiles of PD-1 and PD-L1 inhibitors appear to be similar; therefore, further investigations are needed [7].

Patients with grade III autoimmune myositis need to be hospitalized, treated with high-dose corticosteroids and pembrolizumab needs to be interrupted [9]. Our patient clinically responded well to high-dose corticosteroids and the interruption of pembrolizumab. We did not re-challenge because of persisting CK-elevation after 6 weeks and because of his clearly documented disease progression. All three cases of autoimmune myositis related to pembrolizumab, discussed in literature, were treated with plasma-exchange therapy to obtain a full recovery [6,10]. In our case, this was not necessary.

Conclusion

Swelling and muscle weakness of the lower extremities with dyspnea and general deterioration in cancer patients treated with immunotherapy is not always the result of a deep venous thrombosis (DVT) with pulmonary embolism, pneumonitis or heart failure. A rare but severe complication in immunotherapy is an autoimmune myositis which can affect all muscles. Biochemical screening for treatment-induced myositis should be performed regularly in all patients treated with pembrolizumab or other immunotherapies. Prompt recognition and treatment may improve clinical and functional outcome. The myositis treatment consists of high dose corticosteroids, (temporarily) disruption of immunotherapy (pembrolizumab) and, if necessary, plasma-exchange therapy in second line.
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• The authors of this open-label Phase III trial randomly assigned 305 patients who had previously untreated advanced non-small-cell lung cancer (NSCLC) with PD-L1 expression on at least 50% of tumor cells, and no sensitizing mutation of the EGFR gene or translocation of the anaplastic lymphoma kinase gene, to receive either pembrolizumab or a platinum-based chemotherapy. The pembrolizumab group was associated with significantly longer progression-free and overall survival and with fewer adverse events than was platinum-based chemotherapy.

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• The authors of this randomized, open label trial at 202 academic medical centers in 24 countries, studied the effect of pembrolizumab in previously treated NSCLC with PD-L1 expression. They saw that pembrolizumab prolongs overall survival and has a favorable benefit-to-risk profile in patients with previously treated, PD-L1-advanced NSCLC.

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•• The authors, researchers at David Geffen School of Medicine at UCLA, assigned 495 patients receiving pembrolizumab and studied the safety of the product. It has an acceptable side-effect profile.

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• This report presents key information on the US FDA-accelerated approval of pembrolizumab for the treatment of patients with metastatic NSCLC whose tumors express PD-L1 and who have disease progression on or after platinum-derived chemotherapy. Adverse drug reactions were studied, more specifically the immune-mediated adverse reactions.

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• Anti-PD-L1 immunotherapy has probably less adverse events than anti-PD-1 immunotherapy; however, the authors suggested that the toxicity and efficacy profiles of PD-1 and PD-L1 inhibitors appear to be similar. They concluded that further investigations are needed.

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•• The second case report in literature of pembrolizumab-induced necrotic myositis.