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Case Report

Pembrolizumab-induced myasthenia gravis with isolated diaphragmatic involvement in a lung cancer patient: a case report

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***Abstract*:** Immune-related neuromuscular disorders are rare and potentially life-threatening adverse events of immune checkpoint inhibitors (ICIs) used in the treatment of cancer. They tend to have a chronic course that usually leads to the permanent discontinuation of immunotherapy. We present a case of pembrolizumab-induced myasthenia gravis that only involved the diaphragm. The patient is a 71-year-old female with a history of stage IV lung adenocarcinoma under maintenance therapy with pemetrexed and pembrolizumab after a complete response to first-line chemo-immunotherapy. She complained of orthopnea since the previous month and was admitted due to hypoxemic respiratory failure. Radiology showed decreased lung volumes and atelectatic areas in both lower lung fields. A subsequent bronchoscopy ruled out infection and cancer recurrence. Pulmonary function tests revealed a mixed disorder with a severe reduction in maximal inspiratory pressure and a large drop in vital capacity in the supine versus the sited position. Ultrasonography of the diaphragm confirmed bilateral diaphragmatic dysfunction, and the patient was initiated on non-invasive ventilation (NIV) during sleep, which led to symptom relief. A neurological physical examination did not reveal any other muscle involvement. Laboratory tests for myasthenic syndromes showed an elevated titer of the anti-acetylcholine receptor antibody, which confirmed the diagnosis of myasthenia gravis. The patient was subsequently treated with corticosteroids, pyridostigmine, and intravenous immunoglobulin and was gradually able to wean off supplemental oxygen. On follow-up, her chest X-ray and spirometry had improved, but she continued sleeping on NIV. Pembrolizumab was stopped, and she is still free of cancer after 9 months. Clinicians treating cancer patients with immunotherapy should be aware of this rare complication and perform timely investigations in any case of orthopnea in the course of ICI therapy to offer specialized management.

Keywords: case report, diaphragmatic dysfunction, myasthenia gravis, pembrolizumab

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Introduction

The development of immune checkpoint inhibitors (ICIs) has revolutionized cancer treatment in recent years, providing long-lasting tumor responses and significantly extending overall survival (OS) in several malignancies, even in the case of metastatic disease.[1] In non-small-cell lung cancer (NSCLC), continued therapy is superior in terms of OS compared to discontinuation for patients who achieved a response or stable disease after 1 year of treatment with nivolumab.[2] Current practice favors long-term maintenance therapy with ICIs in NSCLC responders, especially in the second-line setting,[3] which increases the probability for immune-related adverse events (irAEs). Furthermore, the observed association between

the incidence of irAEs and the tumor therapeutic response[4] renders this population particularly susceptible to irAEs.

Chronic irAEs, defined as lasting over 12 weeks after discontinuation of an ICI, have not received much attention in clinical trials but seem to occur in over 40% of patients.[5] Two types of inflammation have been implicated in their occurrence: a burnout one causing depletion of relevant cells, as in the case of endocrinopathies and neuropathies, and a smoldering one causing flares and remissions, as in the case of rheumatological toxicities.[6]

Neurological irAEs can affect the central nervous system in the form of acute meningoencephalitis or the peripheral nervous system, manifesting as peripheral neuropathy or myasthenic syndromes with a more chronic course.[7] Immune-related myasthenia gravis (irMG) has been found to occur in 0.24% of ICI-treated cancer patients in a large US cancer center. Co-occurrence with myositis and/or myocarditis may complicate the clinical picture and worsen the prognosis. Ocular symptoms, limb weakness, and dysphagia are common presenting symptoms. Dyspnea may also be prominent, while up to 45% of affected patients may require mechanical ventilation due to respiratory failure in the course of the disease.[8] We report a case of pembrolizumab-induced MG with uncommon isolated diaphragmatic involvement, which highlights the phenotypic diversity of the condition and the challenges in the diagnostic process. This case report was prepared following the CARE Guidelines (Supplemental Material).

Case presentation

The case is a 71-year-old female Caucasian who presented to the emergency department of our tertiary hospital complaining of dyspnea on exertion and orthopnea, gradually worsening over a month. Her medical history was notable for emphysema, arterial hypertension, dyslipidemia, osteoporosis, and a diagnosis of stage IV lung adenocarcinoma 3 years prior to presentation, which was initially treated with six cycles of first-line systemic chemotherapy. Due to a partial response, a right upper lobe posterior segmentectomy was decided and performed 8 months after the diagnosis. Seventeen months later, she developed disease progression and received six cycles of second-line chemoimmunotherapy with carboplatin, pemetrexed, and pembrolizumab every 3 weeks. She achieved a complete response and was thereafter continued on maintenance therapy with pemetrexed and pembrolizumab, having completed three cycles until presentation, the last 18 days before her visit.

On admission, she was afebrile, her blood pressure and heart rate were normal, and she was tachypneic (30 breaths/min). Physical examination revealed diminished breath sounds in the left lower lung field. Arterial blood gases showed type 1 respiratory failure (PaO_2 53.3 mmHg, $PaCO_2$ 35.7 mmHg, pH 7.43 on room air). An initial laboratory investigation revealed elevated creatine phosphokinase (CPK; 416 U/L), while C-reactive protein, high-sensitive troponin I, and N-terminal pro-b-type natriuretic peptide levels were within the normal range. The electrocardiogram and echocardiogram were also both normal. Her chest X-ray (CXR) revealed decreased lung volumes with normal length of the intercostal spaces and a homogeneous left lower lobe shadow obliterating the left hemidiaphragm (Figure 1(a)). The patient was admitted to our pulmonary department for further diagnostic work-up.

A computed tomography pulmonary angiography ruled out pulmonary embolism. Apart from emphysema and post-surgical findings in the right upper lobe, the pulmonary parenchyma showed areas of atelectasis and hypoventilation, more pronounced in the left lower lobe and lingula and less marked in the right lower lobe, with no sign of bronchial obstruction or pleural effusion (Figure 1(b) and (c)). The patient was treated with low-flow oxygen therapy and empiric antibiotic therapy (piperacillin–tazobactam and moxifloxacin). To rule out infection or cancer recurrence, a fiberoptic bronchoscopy with bronchoalveolar lavage was performed, which showed no evidence of mucosal inflammation/infiltration, increased bronchial secretions, or macroscopically visible tumor up to subsegmental bronchi. After the procedure, which involved midazolam administration for sedation, the patient developed acute respiratory acidosis (PaO_2 62.3 mmHg, $PaCO_2$ 62.2 mmHg, pH 7.26 on a 60% Venturi mask) and was subsequently treated with non-invasive ventilation (NIV) for 2 h. Both the culture and the cytological examination of the lavage

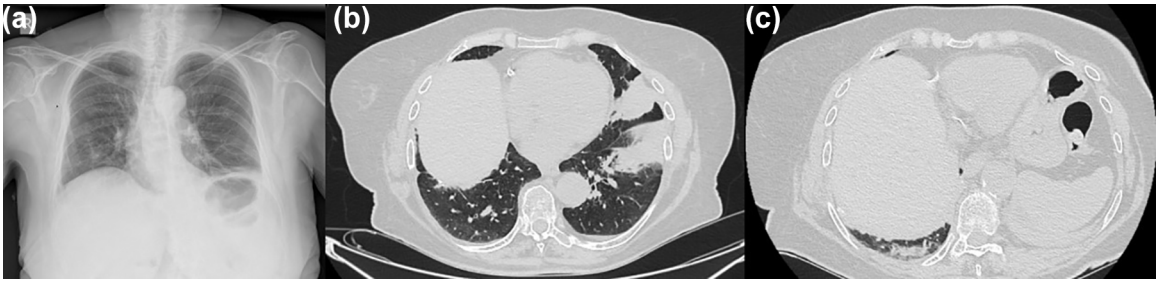

Figure 1. Chest X-ray (a) and computed tomography (b, c) of the case at admission.

were negative for infectious agents and malignant cells, respectively, and antibiotics were promptly stopped.

A disease affecting the respiratory muscles was strongly suspected based on the presenting symptoms, the radiological appearance, and the elevated muscle enzymes. A neurological physical examination revealed normal muscle strength, motor examination, and extraocular movements but diminished tendon reflexes. Pulmonary function tests (PFTs) showed a severe mixed ventilatory disorder (forced expiratory volume in 1 sec (FEV1) 27% and forced vital capacity (FVC) 36% of predicted value, respectively), a severe reduction in diffusion capacity for carbon monoxide (DLCO) (32% of predicted value) with a mild reduction in carbon monoxide transfer coefficient (74% of predicted value), and a drop in FVC of 47% in the supine as compared to the sited position. Maximal inspiratory pressure was severely decreased to 28 cmH_2O (43% of predicted value), while maximal expiratory pressure was within the normal range. Ultrasonography of the diaphragm confirmed minimal excursion of both hemidiaphragms during inspiration, while a computed tomography of the cervical spine showed no pathology. The patient was initiated on NIV with bilevel positive airway pressure in a spontaneous/timed mode during the night, which was well tolerated and resulted in improvement of her symptoms.

Further laboratory tests for myasthenic syndromes, such as N-type and P/Q-type voltage-gated calcium channel, anti-acetylcholine receptor (AChR), anti-muscle-specific kinase, and anti-titin antibodies, were ordered. An elevated titer of the AChR antibody confirmed the diagnosis of MG, which was attributed to the immune dysregulation caused by pembrolizumab. An evaluation of the pituitary hormones also revealed an abnormally high serum thyroid-stimulating hormone level (63.6 mIU/L), strengthening the hypothesis of irAEs caused by the ICI. The patient was commenced on oral prednisolone 75 mg daily, pyridostigmine 120 mg daily, and levothyroxine 88 µg daily. She also received intravenous immunoglobulin (IVIG) for 5 days. She was gradually weaned from supplementary oxygen during the daytime and continued on NIV during sleep. After consulting her oncologist, chemoimmunotherapy was suspended, and she remained on clinical and radiological surveillance. She was also scheduled for 3-day courses of IVIG at 1 and 2 months after the first therapy. At the 2-month follow-up, her CXR showed no signs of consolidation (Figure 2), her CPK levels were normal, and her PFTs had improved (FEV1 49% and DLCO 42% of predictive value, respectively). The steroid dose was then gradually tapered by 5 mg

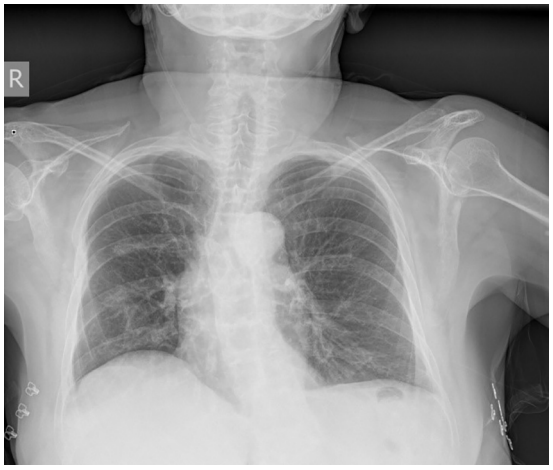

Figure 2. Chest X-ray of the case after 2 months of steroid treatment.

per 15 days. At 9 months, she is still on complete response to her lung cancer, receives prednisolone 5 mg, pyridostigmine 120 mg, and levothyroxine 137 μg daily, and uses NIV at night. Her spirometry and respiratory muscle testing remained unchanged.

Discussion

This case report illustrates an uncommon presentation of pembrolizumab-induced MG as isolated diaphragmatic paralysis that responded well to corticosteroid and IVIG therapy. The diagnostic process that was followed may be limited by the unavailability of electrodiagnostic studies, such as needle electromyography (EMG) or repetitive nerve stimulation studies, which are required for a definite diagnosis of irMG, according to an expert consensus report.[9] Even if this case should be classified as probable irMG by the aforementioned strict criteria, the combination of clinical, imaging, and serological manifestations, as well as the response to immunosuppressive therapy, in our case, as highlighted above, makes an alternative diagnosis highly unlikely. The isolated muscle involvement also precluded the performance of a muscle biopsy to investigate for concurrent myopathy due to the elevated CPK levels, but this could have only prognostic and not therapeutic implications. There is a significant overlap between irMG and immune-related myopathy in terms of disease manifestation, and these two types of ICI-induced neuromuscular disorders may frequently co-occur.[9]

Immune-related myasthenic syndromes represent 14% of all neurological irAEs in the context of ICI treatment and seem to occur more frequently with anti-programmed cell death protein 1/programmed cell death ligand 1 agents.[10] Over 80% of cases constitute new-onset MG, with the rest being relapses of preexisting MG. irMG is diagnosed at an average time of 1 month after ICI initiation.[8] Compared to idiopathic MG, irMG shows a lower prevalence of ocular involvement and a higher prevalence of respiratory compromise, which might explain the high mortality rate (about 30%). Mortality is associated with an earlier onset of MG symptoms in relation to ICI initiation and involvement of multiple organs, especially the myocardium.[11] Permanent ICI suspension and initiation of high-dose corticosteroids (1–2 mg/kg prednisone) are the primary therapeutic measures. In severe cases refractory to steroids or with respiratory involvement, IVIG (2 mg/kg/day over 3–5 days) or plasmapheresis (5–7 sessions) can be considered.[12] The addition of IVIG or plasmapheresis to steroids as first-line therapy for irMG may result in better chances of symptom improvement.[8]

Isolated diaphragmatic dysfunction in the course of ICI treatment without other neurological complications has been previously documented in six cases in the literature.[13–15] In 4 and 1 of the cases, EMG or phrenic nerve conduction studies showed characteristic neuropathic and myopathic changes, respectively, while no case had positive MG-related autoantibodies. All cases were treated with corticosteroids, and three of them with IVIG and/or plasmapheresis. Three cases showed improvement in their respiratory status[14]; one case had no apparent response[13]; and two cases deteriorated and died.[15] Three out of four survivors required long-term ventilatory support during sleep. Timely recognition of the disease and prompt initiation of treatment may be crucial in this setting, even if the serological, electrodiagnostic, or pathology results are pending.

Conclusion

This is the first reported case of seropositive irMG with isolated diaphragmatic involvement and a favorable response to immunosuppressive therapy along with nighttime NIV. Clinicians should be alerted when ICI-treated patients complain about orthopnea and evaluate for the possibility of immune-related neuromuscular disorder even in the absence of limb, ocular, or bulbar muscle involvement. Serological autoantibody testing for MG can be a useful diagnostic aid and should be implemented in such instances. Due to the high mortality rate, appropriate treatment should commence without delay, while chronicity is usual and may require long-term respiratory support.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Informed consent for publication was provided by the patient.

Author contributions

Nefeli Mouratidou: Conceptualization; Data curation; Investigation; Methodology; Writing – original draft.

Dimitrios Papadopoulos: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing – review & editing.

Iro Vrouvaki: Data curation; Investigation; Writing – review & editing.

Vasileios Skouras: Investigation; Resources; Writing – review & editing.

Stamatis Katsenos: Resources; Supervision; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

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Supplemental material

Supplemental material for this article is available online.

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