



# Acute bilateral phrenic nerve neuropathy causing hypercapnic respiratory associated with checkpoint inhibitor immunotherapy

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## ABSTRACT

We present two cases of acute hypercapnic respiratory failure due to diaphragmatic dysfunction secondary to bilateral phrenic nerve paralysis, in patients who were receiving immunotherapy for melanoma. Bilateral diaphragmatic paralysis is an uncommon cause of acute or sub-acute hypercapnic respiratory failure which causes severe breathlessness, orthopnoea and potentially death. Immune checkpoint inhibitors are now standard of care in several solid organ malignancies. However, their use is associated with a risk of developing autoimmune toxicities, which includes mononeuritis. Our two cases demonstrate the potential difficulties in recognising acute hypercapnic respiratory failure and diagnosis of the rare disorder of bilateral diaphragmatic dysfunction, with consequent delays in appropriate management. The occurrence of this rare condition in association with checkpoint inhibitor immunotherapy suggests a possible autoimmune mechanism. Awareness that this rare cause of respiratory failure may occur in patients receiving checkpoint inhibitor therapy might facilitate earlier diagnosis and treatment.

## 1. Introduction

Bilateral diaphragmatic weakness secondary to bilateral phrenic nerve dysfunction is a rare but important cause of acute hypercapnic respiratory failure. Diagnosis may be delayed, particularly in patients with comorbidities since its predominant symptoms are breathlessness and orthopnoea, which are easily misdiagnosed for common disorders such as heart failure. Acute diaphragmatic dysfunction can be due to neurological, myopathic and iatrogenic causes [1].

Immune checkpoint inhibitors have revolutionised the management of a number of solid organ malignancies [2]. As their use becomes more widespread, the recognition and early management of immunotherapy mediated autoimmune toxicities is vital. Neurological toxicities secondary to immunotherapy are rare, but have potentially devastating consequences [3]. We report two cases of bilateral phrenic nerve dysfunction resulting in acute hypercapnic respiratory failure in patients who received immunotherapy for melanoma.

## 2. Case presentation

### 2.1. Case one

A 58-year-old male with stage IIIC melanoma completely resected in January 2018 received 480mg of monthly adjuvant nivolumab. Treatment was ceased after three cycles due to local recurrence requiring further surgery and radiotherapy. He developed immunotherapy mediated hypophysitis six months later causing hypopituitarism for which he was on low-dose prednisone. Three months later, he presented with acute intrascapular pain and progressive right leg weakness and bilateral arm weakness. Examination revealed severely reduced strength of the right leg and distal arms bilaterally, with preserved sensation and hyperreflexia.

MRI revealed high T2 signal and restricted diffusion from C5-T1, consistent with an anterior spinal cord infarction. Extensive vasculitic and thrombophilia screens were negative. A diagnosis of autoimmune vasculitis was made, causing C7 ASIA D incomplete spinal cord injury. He received 1g IV methylprednisolone for 5 consecutive days, however,

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there was minimal functional improvement. On starting spinal rehabilitation, arterial blood gas (ABG) and overnight oximetry to screen for sleep disordered breathing, were unremarkable. Pulmonary function tests demonstrated mild restriction with a total lung capacity (TLC) of 82% predicted and vital capacity (VC) of 79% predicted, in keeping with the patient's spinal cord injury. Upper and lower limb strength improved with rehabilitation.

Two months after his original presentation, he developed dyspnoea with marked orthopnoea and intrascapular pain, which was similar in nature to his original presentation. Clinical examination showed tachypnoea and accessory muscle use. He spoke in short sentences. There were no acute changes in neurological state. Potential diagnoses were hospital acquired pneumonia, pulmonary embolism and immunotherapy induced pneumonitis. However, CT pulmonary angiography demonstrated only basal atelectasis, small pleural effusions but no embolism, tumour recurrence, pneumonia or infiltrate. No tumour was seen on CT of the abdomen or pelvis. An echocardiogram was normal. Comparison with the chest radiograph performed two months prior highlights the interval development of bibasal atelectasis (See Fig. 1).

Although an ABG had shown interval development of a fully compensated hypercapnic respiratory failure with normal A-a gradient, the significance was not recognised until a respiratory review found marked paradoxical respiration. Given the absence of any clinical change in spinal injury, bilateral phrenic neuropathy was diagnosed. Repeat VC decreased by 65% to 28% predicted. Supine VC could not be measured due to orthopnoea. He was commenced on bi-level positive pressure ventilation which improved his symptoms but ultimately required intubation for a repeat MRI, which demonstrated expected evolution of the C5-T1 infarction and confirmed no new changes to account for the bilateral diaphragmatic paralysis. Electromyography demonstrated chronic neurogenic changes of the diaphragm and right trapezius. He was commenced on pulsed methylprednisolone, intravenous immunoglobulin and rituximab but no benefit was seen after three days of treatment. He had previously expressed clear wishes of not wanting long term invasive or non-invasive ventilation and so was extubated and palliated. He passed away peacefully shortly afterwards, with his family present.

### 3. Case two

A 76-year-old male with stage IV melanoma (BRAF V600K mutant) diagnosed in March 2015 had widespread metastases to solid organs, soft tissue and brain. He was commenced on combination checkpoint inhibitor immunotherapy with nivolumab (1mg/kg) and ipilimumab (3mg/kg) every 3 weeks. After two cycles, imaging showed a RECIST partial response to treatment intra- and extra-cranially. His past medical history included severe aortic stenosis, ischaemic heart disease requiring

coronary artery bypass grafting in 2002, heart failure with reduced ejection fraction, atrial fibrillation, hypertension and dyslipidaemia.

Two days prior to his fourth cycle, he presented with acute dyspnoea and orthopnoea. The initial diagnosis was acute pulmonary oedema secondary to severe aortic stenosis, although his chest x-ray did not support this diagnosis. His symptoms improved with bi-level positive pressure ventilation, and he was admitted to Cardiology for aortic balloon valvuloplasty. However, he was still unable to tolerate lying flat despite adequate diuresis. Subsequent ABG showed fully compensated, hypercapnic respiratory failure and pulmonary function tests revealed severe restriction with a TLC of 40% predicted and elevated RV/TLC ratio. Carbon monoxide diffusing capacity (DLCO) was reduced; however, the transfer coefficient (KCO), a measure of diffusion efficiency, was increased at 128% predicted. This was consistent with extrapulmonary restriction accounting for at least part of the diffusion impairment. Chest CT demonstrated marked elevation of the left hemidiaphragm with mild collapse above it, but no tumour or pulmonary infiltrates (See Fig. 2).

On respiratory review, left sided diaphragmatic paralysis and severely impaired function of the right hemi-diaphragm was diagnosed, based on the ABG, CT appearances, pattern of lung function abnormalities and absence of any evidence of heart failure or other causes of severe pulmonary restriction or hypercapnia. MRI brain and cervical spine

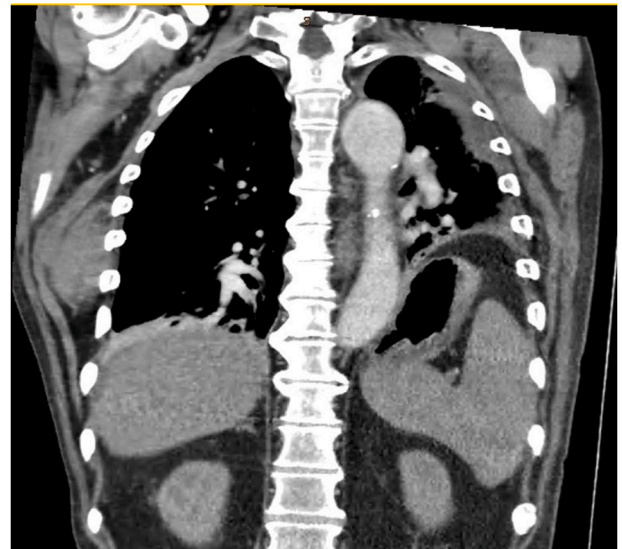


Fig. 2. Section of Computed Tomography from case two demonstrating marked elevation of the left hemidiaphragm.

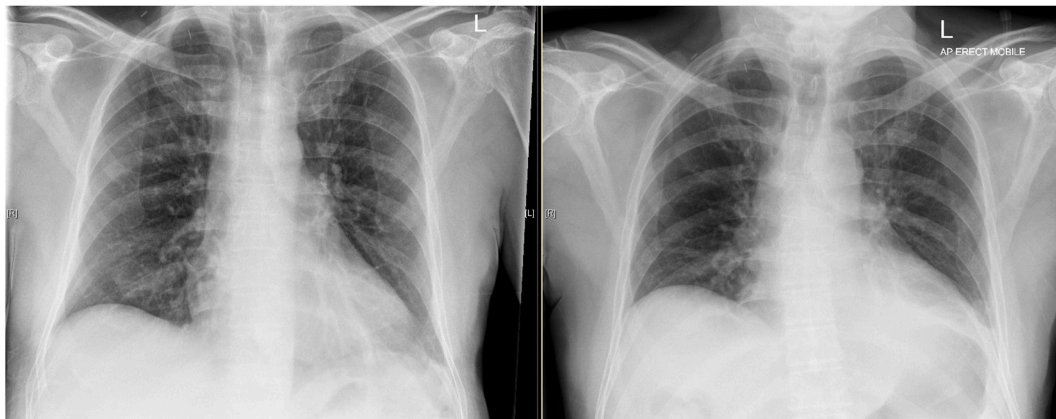


Fig. 1. Chest radiographs of case one taken two months apart, demonstrating the interval development of bi-basal atelectasis.

were performed to exclude immunotherapy mediated neurotoxicity or progression of metastases. It was only partially completed due to severe orthopnoea, but no major cervical spine pathology was demonstrated in the limited sequences performed. Ultrasonography demonstrated minimal excursion of the right hemidiaphragm but no paradoxical movement.

The patient suffered an acute neurological event causing a seizure. He was treated with anticonvulsants, corticosteroids and oxygen but did not regain consciousness. He was not intubated as it was deemed futile in the context of hypercapnic respiratory failure from diaphragmatic weakness. He passed away shortly afterwards.

## 4. Discussion

### 4.1. Clinical discussion

Bilateral diaphragmatic dysfunction is a rare cause of acute hypercapnic respiratory failure and as the two cases demonstrate, the diagnosis may be delayed due to confusion with existing comorbidities. There was strong suspicion of autoimmune mechanisms associated with immunotherapy. Case 1 exhibited an unusual combination of multifocal neurological deficits involving the spinal cord and peripheral nerves, as well as autoimmune hypophysitis, 9 months after cessation of immunotherapy. Case 2 had asymmetrical phrenic nerve disease presenting 2-months after treatment that was confused for heart failure. Both patients had compensated, hypercapnic respiratory failure, which was fatal in Case 1.

In the two cases reported here, profound dyspnoea and orthopnoea were early clinical symptoms that were unexplained by common causes, such as heart failure and without orthodeoxia. Paradoxical respiration was evident in case 1 and is strongly associated with bilateral diaphragmatic dysfunction but often missed during physical examination.

Both patients had hypercapnic respiratory failure which was critical to diagnosis. At that stage of the diagnostic workup, it was unexplained, given the absence of sedation and airways or parenchymal diseases and led to confirmatory investigations. This reinforces the critical importance of ABG measurement when investigating unexplained breathlessness. Normal peripheral oxygen saturations do not exclude hypercapnia and sadly, ABG measurements are currently increasingly omitted even when diagnosis is uncertain.

Although erect and supine VC measurements were not measured in our 2 cases, it typically shows reduction of up to 50% in bilateral diaphragm paralysis, compared to 10% in healthy individuals [4]. Maximal inspiratory and expiratory pressure can be also used to confirm respiratory muscle weakness. Lung volumes should demonstrate restriction while diffusing capacity measurements may show an 'extra-pulmonary' pattern in the absence of underlying lung disease i.e., reduced VA and DLCO but increased KCO.

Checkpoint inhibitor immunotherapy works by interfering with T-cell regulatory pathways to upregulate the body's antitumour response [2] but may result in autoimmune side effects. The risk of these side effects is increased with cytotoxic-T-lymphocyte-associated-antigen-4 (CTLA-4) inhibitors such as ipilimumab compared to programmed-death-1 (PD-1) inhibitors such as nivolumab and is further increased with combination therapy [5]. Overall, the risk of death from autoimmune toxicity is low [5].

Checkpoint inhibitor immunotherapy induced neuropathy is a diagnosis of exclusion, requiring exclusion of other causes of peripheral neuropathy, which occurred in our 2 cases. Awareness of the clinical features of the rare condition of bilateral phrenic nerve dysfunction may allow faster diagnosis.

### 4.2. Imaging discussion

Chest radiograph and CT revealed small lung fields and basal atelectasis which is typical, but also excluded other potential causes of

phrenic nerve injury, including tumour, as well as lung and airways diseases (see Fig. 1). The CT scan performed in case two demonstrated marked elevation of the left hemidiaphragm, consistent with phrenic nerve injury (see Fig. 2).

Fluoroscopic 'sniff tests' assess downward diaphragmatic movement during a forceful sniff. This can appear falsely normal in patients with bilateral diaphragm weakness as the cephalad movement of the ribs may give the impression of caudal displacement of the diaphragm [1]. Fluoroscopic sniff test was not performed in the first case as the patient was too unwell. In the second case, the diagnosis was already confirmed through CT imaging and ultrasound. Combining 'sniff tests' with ultrasonography to evaluate diaphragm movement, as was used in case two, increases diagnostic precision [6]. Diaphragmatic pressure measurements using oesophageal and gastric balloons may more accurately assess diaphragmatic dysfunction [6] but are limited to use in expert centres.

## 5. Review of the literature

Phrenic nerve neuropathy associated with checkpoint inhibitor immunotherapy is rare. There are two previous case reports of bilateral phrenic nerve palsy in four patients [7,8]. Three of these patients received single agent immunotherapy for metastatic melanoma and one received combination ipilimumab and nivolumab for metastatic renal cell carcinoma. The four cases in the literature had similar presenting symptoms to our patients with all reporting profound dyspnoea and orthopnoea and two of the four cases demonstrating marked paradoxical respiration.

One patient also had autoimmune hypophysitis but responded to immunosuppression and did not require ventilation [7]. The other three cases had varying responses to high dose immunosuppression, with one case requiring plasmapheresis. These three patients required long term bi-level positive pressure ventilation for persistent hypercapnic respiratory failure.

## 6. Conclusion

- Bilateral diaphragm weakness is a rare but important cause of hypercapnic respiratory failure manifesting as acute dyspnoea.
- Diagnosis is often delayed due to key clinical symptoms being incorrectly attributed to other, more common pathologies
- Physicians should strongly suspect diaphragmatic dysfunction in patients who present with profound orthopnoea in the absence of heart failure, or who fail to respond to diuresis and have small lung fields on radiology. Paradoxical respiration is a highly specific clinical sign of bilateral diaphragmatic dysfunction.
- Arterial blood gas measurement is a critical test in this condition, since hypercapnia strongly supports the diagnosis in the appropriate clinical setting i.e., orthopnoea and tachypnoea without cardiac or pulmonary disease. They are underused but should be done in unexplained dyspnoea.
- The development of acute neuropathy in patients on checkpoint immunotherapy should raise the possibility of an autoimmune side effect

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