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A new trigger for an old problem-neurogenic pulmonary edema related to intrathecal chemotherapy with pemetrexed

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TO THE EDITOR:

Neurogenic pulmonary edema (NPE) is a noncardiogenic edema defined as acute respiratory distress triggered by a central nervous system (CNS) insult. The most common causes are head trauma, intracranial hemorrhages, and seizures.[1-4] Here, we present the first case of NPE related to intrathecal pemetrexed treatment.

A 34-year-old female undergoing systemic treatment for metastatic EGFR-mutated non-small cell lung cancer (NSCLC) with osimertinib presented to the hospital with symptoms of meningeal progression. In this context, an electively Ommaya catheter was inserted into the third ventricle for intrathecal treatment, and the patient started receiving intravenous infusion of dexamethasone (8 mg/day). After the procedure, SpO_2 on room air, RR, and HR were 97%, 16 breaths/min, and 85 bpm, respectively. The fluid balance remained close to zero, and no blood transfusion was necessary.

Five days later, intrathecal pemetrexed was administered via an Ommaya catheter (pemetrexed 50 mg plus dexamethasone 5 mg dissolved in 0.9% sodium chloride solution to prepare a 5-mL solution). Approximately 16 h after infusion, the patient complained of shortness of breath, cough, and tachycardia. Pulmonary auscultation showed crackles at the lung bases. HR and SpO_2 were 150 bpm and 80% on room air, respectively. Blood pressure was 140/90 mmHg. No sign of intracranial hypertension was observed. Oxygen supplementation was started with a non-rebreathing mask (10 L/min).

Bedside chest X-ray (CXR) showed bilateral lung opacities in the middle and lower fields and possible right pleural effusion (Figure 1A), and a chest CT confirmed extensive bilateral ground-glass opacities, relatively symmetrical, sometimes tending to consolidate, along with septal thickening and small right pleural effusion (Figure 1C). The CT also ruled out thromboembolism. Although there was no previous CXR for comparison, the patient had performed a thoracic spine MRI a few days before (Figure 1D), which revealed that the lungs had no diffuse abnormalities, reinforcing the hyperacute scenario. There were no clinical signs of infection. Serum electrolytes, procalcitonin, renal function, troponin, NT-proBNP (< 125 pg/mL), blood count, and echocardiogram were unremarkable. A bronchoscopy was performed, and the BAL fluid analysis ruled out infection.

The patient was referred to the ICU; non-invasive ventilation (NIV) was initiated in a bilevel ventilation mode (V_T = 6 mL/kg) in 120-min sessions every 8 h, and the patient was weaned from oxygen therapy 5 days later. No antibiotics were used. Control CXR (Figure 1B) and CT after two weeks (Figures 1E and 1F) revealed a significant reduction of lung opacities (Figure 1B). Despite the resolution of respiratory symptoms, the patient was referred to exclusive palliative care and died 60 days later.

The clinical scenario was an acute episode of tachycardia and respiratory distress in a young female after intrathecal pemetrexed for treating metastatic NSCLC. Although diffuse lung disease is not specific in imaging, the CXR findings combined with the quick onset of symptoms and a relatively rapid resolution of the pulmonary impairment favored a diagnosis of acute lung edema with a potential causative factor (intrathecal pemetrexed). The main differential diagnoses were ruled out, including cardiogenic and nephrogenic edema, infection, and aspiration. Pemetrexed pneumonitis is also a differential hypothesis, but the short time interval between drug infusion and onset of symptoms is unfavorable to the usual period of pneumonitis initiation (weeks/months). Low-dose intrathecal pemetrexed also advises against pneumonitis. It was hypothesized, therefore, a neurogenic mechanism for the pulmonary edema as the major cause of the clinical aspects.

Pemetrexed is an anticancer chemotherapy drug used in the treatment of locally advanced or metastatic NSCLC cancer and its intrathecal administration can be performed in patients with meningeal progression. In a clinical trial,[5] intrathecal pemetrexed was administered in 30 patients; the median survival time was 9.0 months (95% CI, 6.6–11.4 months). The most common adverse events were myelosuppression, which occurred in 30% of patients, and neurotoxicity. No pulmonary events were reported.[5]

NPE was first described in 1908 and defined as an increase in pulmonary interstitial and alveolar fluid due to a severe sympathetic discharge after acute CNS involvement.[4] Determining the actual prevalence of NPE is challenging due to the complex diagnosis. Several different CNS triggers have been identified, including infectious diseases (most common), cerebral bleeding, traumatic brain injury, epilepsy, stroke, and others.[6]

The pathogenesis of NPE is poorly understood but is thought to be the consequence of a massive sympathetic discharge secondary to a medulla oblongata injury. This sympathetic storm leads to systemic vasoconstriction,

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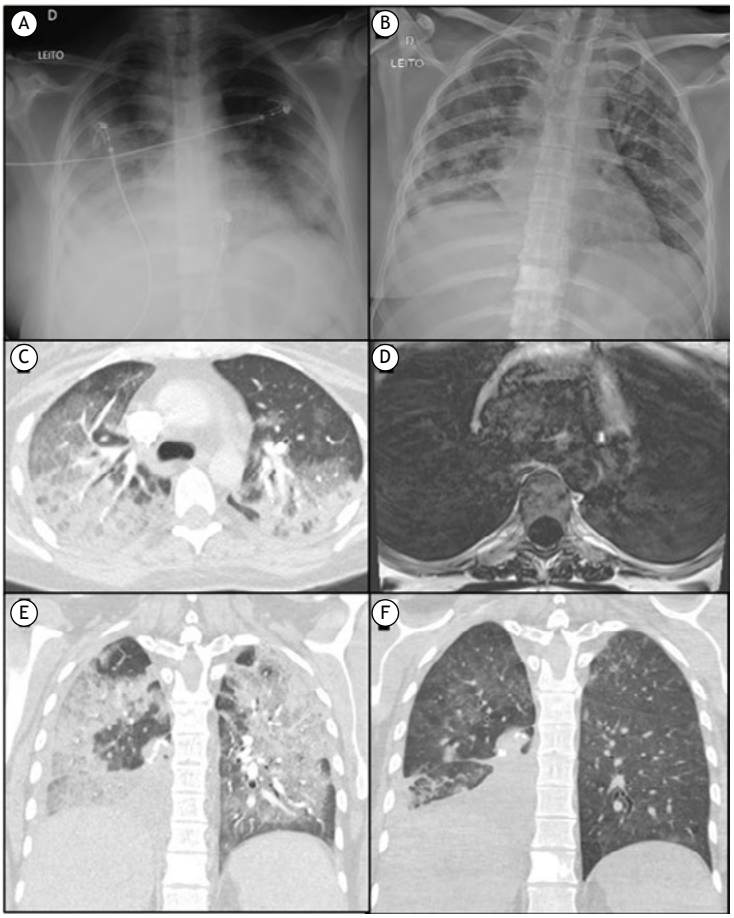

Figure 1. In A, bedside chest X-ray (CXR) demonstrating bilateral lung opacities in the middle and lower fields and possible right pleural effusion. In B, bedside CXR taken two weeks later showed significant improvement of lung opacities. In C, axial CT scan confirming lung involvement and extensive ground-glass opacities, sometimes tending to consolidate, along with septal thickening. In D, a spine MRI performed a few days prior to chest CT reliably ruled out previous lung diffuse abnormalities. Coronal CT scans confirmed significant improvement that were depicted in the control CXR (baseline CT scan in E vs. control CT scan taken two weeks later in F).

an increase in pulmonary blood volume, the rise of pulmonary capillary permeability, and subsequent accumulation of fluid in the alveolar space (pulmonary edema).[7,8]

NPE presents within minutes to hours of a CNS injury. However, more rapid or delayed onset has been described. Dyspnea is the most common symptom. Tachycardia is sometimes seen concomitantly with Takotsubo syndrome, which has a similar mechanism.[9] Physical examination generally reveals tachypnea and basilar crackles. CXRs typically show bilateral alveolar opacities and normal heart size.[6] The diagnosis of NPE include acute CNS involvement, Pao_2/FIO_2 ratio < 200 mmHg, bilateral opacities on chest imaging, no evidence of left atrial hypertension, and absence of other causes (infection, ARDS, aspiration).[10]

The management of NPE consists of addressing the underlying neurological cause and supportive therapy for the pulmonary edema,[5] based on supplemental oxygen therapy and NIV (including CPAP). In extreme cases, intubation with a certain level of PEEP.[6] The role of diuretics is still controversial, and there is no clear recommendation. Although most cases resolve within 48-72 h, the development of NPE is associated with poor long-term outcomes.[6]

This case report highlights the role of intrathecal pemetrexed treatment as a trigger for NPE. To our knowledge, this is the first description in the literature. Medical practitioners should be aware of the importance of early diagnosis and proper management.

Author contributions

FMC, EAF, and AKM: conception, planning, study design, and data collection. EAF, AKM, MAFMF, and FMC: drafting and writing the final version of the manuscript. FMC, MTC, and MAFMF: critical review of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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