

## Chemotherapy-Induced Late Acute Respiratory Distress Syndrome Following Right Pneumonectomy for Bronchogenic Carcinoma

Mara Tosi MD and Guido Domenighetti MD

**We report 2 patients who suffered late postoperative acute respiratory distress syndrome (ARDS) that was probably chemotherapy-induced. Both patients underwent neoadjuvant combination chemotherapy prior to right pneumonectomy for primary bronchogenic carcinoma, and then suffered ARDS in the remaining lung a few weeks after surgery. No evidence of infection or other specific ARDS etiologies could be found, whereas the bronchoalveolar lavage fluid cell differentiation and protein content suggested the permeability form of lung edema. Both patients had rapid clinical, functional, and radiologic improvement with high-dose corticosteroids. In the first patient the course was complicated by the development of a critical illness polyneuropathy with complete tetraplegia, but the patient recovered. The second patient died from septic shock 4 weeks after starting mechanical ventilation. The incidence of a chemotherapy-related ARDS in the remaining lung, occurring more than 4 weeks after extensive operations or after a pneumonectomy, is unknown. This kind of acute lung injury calls for particularly delicate treatments, the most potentially life-threatening complications being mainly associated with difficulties in ventilatory support and the high doses of corticosteroids required to rescue the remaining lung.** *Key words: neoadjuvant, chemotherapy, pneumonectomy, acute respiratory distress syndrome, ARDS, mechanical ventilation, corticosteroids.* [Respir Care 2003;48(6):606–610. © 2003 Daedalus Enterprises]

### Introduction

Acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) are clinical syndromes characterized by acute and profound pulmonary inflammation, of different origin, with conclusive evidence of increasing permeability of the endothelial and epithelial barriers.<sup>1–3</sup> ALI/ARDS can develop early after resection of primary bronchogenic carcinoma and is associated with a very high mortality rate,<sup>4–6</sup> particularly following right pneumonectomy and extended operations.<sup>6</sup> Several cancer drugs induce pulmonary damage, resulting in a variety of clinical and pathologic responses.<sup>7–9</sup> Chemotherapy-induced pulmonary parenchyma toxicity can include a noncardiogenic pulmonary edema compatible with ALI or ARDS.<sup>9</sup> Late

( $\geq 30$  d) ALI/ARDS after surgery and neoadjuvant therapy is a less well known impending severe complication after extensive resection of non-small-cell lung cancer. We report 2 cases of probable chemotherapy-induced late ARDS following right pneumonectomy for bronchogenic carcinoma. The first occurred in a patient treated with gemcitabine, the second in a patient receiving a combination of vinorelbine and mitomycin.

### Case Report 1

A 72-year-old man underwent right pneumonectomy with mediastinal lymphadenectomy for squamous cell lung cancer initially staged as pT3 pN1 Mx, G2, IIIA in March 2001. He had first undergone neoadjuvant chemotherapy with paclitaxel, carboplatin, and gemcitabine, from October 2000 to February 2001. Four weeks after surgery the patient had a dry cough and worsening of dyspnea. A few days later he developed progressive respiratory failure. On physical examination there was cyanosis, crackles were audible over the left lung, and he was afebrile. Respiratory rate was 35 breaths/min, heart rate was 130 beats/min, and arterial blood pressure was 150/80 mm Hg. The conven-

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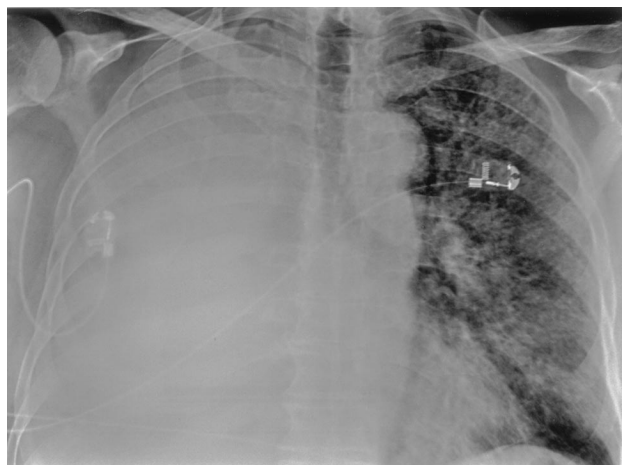


Fig. 1. Admission chest radiograph of patient 1, showing diffuse alveolar-interstitial infiltrates. The chest radiograph of patient 2 had a similar pattern of infiltrates.

tional chest radiograph showed diffuse alveolar-interstitial infiltrates involving the whole left lung. The computed tomography (CT) scan demonstrated reticular opacities, thickened septal lines, and some areas of patchy consolidation (Fig. 1). Laboratory findings showed an inflammatory syndrome, with white blood cell count of 11 cells/ $\mu$ L, normal differential count, and C-reactive protein of 102 mg/L. While receiving 100% oxygen and continuous positive airway pressure of 6 cm H<sub>2</sub>O the patient had P<sub>aO<sub>2</sub></sub> 38 mm Hg, P<sub>aCO<sub>2</sub></sub> 29 mm Hg, pH 7.40, and bicarbonate 20 mEq/L. The ratio of P<sub>aO<sub>2</sub></sub> to fraction of inspired oxygen (P<sub>aO<sub>2</sub></sub>/F<sub>IO<sub>2</sub></sub>) was 38.

The patient was intubated and ventilated in supine position. To avoid ventilator-induced lung injury on the remaining lung we used a pressure-controlled mode (with a maximum plateau pressure titrated at 35 cm H<sub>2</sub>O), high positive end-expiratory pressure (PEEP) (15 cm H<sub>2</sub>O), and very low tidal volume (5 mL/kg of ideal body weight), as suggested by the recent results from the ARDS Network.<sup>10</sup> Inspiration-expiration ratio was 1:2 and respiratory rate was 18 breaths/min. While on those mechanical ventilation settings, arterial blood gas analysis revealed P<sub>aO<sub>2</sub></sub> 46 mm Hg, P<sub>aCO<sub>2</sub></sub> 51 mm Hg, pH 7.31, bicarbonate 23 mEq/L. F<sub>IO<sub>2</sub></sub> was 1.0 and the P<sub>aO<sub>2</sub></sub>/F<sub>IO<sub>2</sub></sub> was 46.

Changes of the patient's position were not useful and even worsened gas exchange. The lung injury score was 3.2.<sup>11</sup> Blood cultures were negative for aerobic and anaerobic bacteria. Serologies for chlamydia, mycoplasma, and respiratory viruses were negative. The urine test for *Legionella* antigen was negative. Cardiac enzymes and the echocardiographically assessed left ventricular function were normal. Bronchoalveolar lavage fluid (BALF) was negative for *Pneumocystis carinii*, *Mycobacterium tuberculosis*, and pyogenic bacteria. No malignant cells were

found. The cell differentiation showed moderately elevated polymorphonuclear leukocytes (10%) with rare lymphocytes (2%) and predominant macrophages (78%). The protein content was 5.1 g/dL and the ratio of edema fluid to plasma total protein was 0.9.

Because of the high associated risks (severely disturbed gas exchange, right pneumonectomy, difficult mechanical ventilation with high PEEP, and unstable hemodynamics) a transbronchial biopsy was not carried out. High-dose corticosteroids were begun on day 3, with methylprednisolone 1 g/d during the first 3 days, followed by 2 mg/kg/d. The antimicrobial spectrum consisted of imipenem and clarithromycin. During the first 3 days of mechanical ventilation, acceptable gas exchange was difficult to obtain, despite high PEEP (16 cm H<sub>2</sub>O), deep sedation, and pharmacologic paralysis (with pancuronium bromide). Turning the patient prone or on the left or right side worsened gas exchange. Acceptable oxygenation was achieved only with inhaled nitric oxide (5–15 ppm).

After the third day the radiologic findings improved. Methylprednisolone was then maintained at 2 mg/kg over 20 days and thereafter progressively reduced to a maintenance dose of 20 mg/d prednisolone. The patient developed a critical illness polyneuropathy with complete tetraplegia. Weaning from mechanical ventilation was impossible, and after 81 days the patient was transferred to a paraplegic center for rehabilitation and long-term weaning. The patient is now living at home with a transtracheal oxygen device, breathing and walking spontaneously, with no evident clinical, bronchoscopic, or radiologic signs of tumor progression.

## Case Report 2

A 58-year-old man underwent right pneumonectomy for a large cell carcinoma of the lung, initially staged as pT3 pNO MO, IIB, in October 2001. He had first undergone neoadjuvant chemotherapy with mitomycin, vinorelbine, and cisplatin, from August 2001 to September 2001, and radiotherapy with a total of 45 gray.

On November 2001 (5 wk after surgery) the patient was readmitted to our hospital because of dyspnea and a dry cough. On physical examination he was subfebrile (37.8° C) and crackles were audible over the left lung. Respiratory rate was 30 breaths/min and heart rate was 114 beats/min. Chest radiography showed left diffuse alveolar-interstitial infiltrates. The CT scan demonstrated reticular opacities, thickened septal lines, and some areas of patchy consolidation (Fig. 2). Laboratory findings showed an inflammatory syndrome, with white blood cell count of 13 cells/ $\mu$ L, with normal differential count, and C-reactive protein of 178 mg/L.

He was first treated with antibiotics (imipenem and clarithromycin), but his condition further deteriorated and he

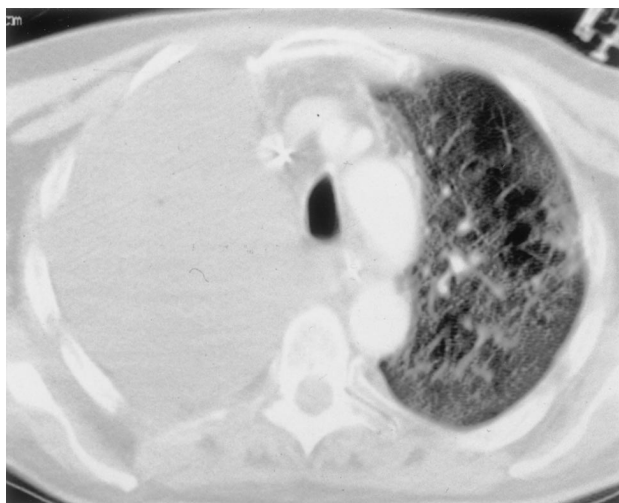


Fig. 2. Computed tomography scan of patient 2 (section above the carina), showing reticular opacities, thickened septal lines, and an area of patchy consolidation. The computed tomography scan of patient 1 had a similar pattern of infiltrates.

developed progressive respiratory failure on the second day after admission. At that time  $P_{aO_2}$  was 50 mm Hg,  $P_{aCO_2}$  was 28 mm Hg, pH was 7.40, and total bicarbonate was 26 mEq/L.  $F_{IO_2}$  was 1.0 and  $P_{aO_2}/F_{IO_2}$  was 50.

After an unsuccessful attempt with noninvasive pressure-support ventilation (inspiratory pressure support of 14 cm  $H_2O$ , PEEP of 6 cm  $H_2O$ ), he was intubated and mechanically ventilated in supine position. To avoid ventilator-induced lung injury to the remaining lung we used a pressure-controlled mode (maximum plateau pressure titrated at 35 cm  $H_2O$ ), high PEEP (12 cm  $H_2O$ ), and very low tidal volume (5 mL/kg of ideal body weight).<sup>10</sup> The inspiration-expiration ratio was 1:2 and the respiratory rate 18 breaths/min. At that time blood gas analysis showed  $P_{aO_2}$  54 mm Hg,  $P_{aCO_2}$  52.5 mm Hg, pH 7.30, and bicarbonate 26 mEq/L.  $F_{IO_2}$  was 1.0 and  $P_{aO_2}/F_{IO_2}$  was 54.

Changes of the patient's position were not useful and even worsened gas exchange. The lung injury score was 3. Blood cultures were negative for aerobic and anaerobic bacteria. Serologies for chlamydia, mycoplasma, and respiratory viruses were negative, as was the urine test for *Legionella* antigen. Cardiac enzymes and echocardiographically assessed left ventricular function were normal. BALF was negative for *Pneumocystis carinii*, *Mycobacterium tuberculosis*, and pyogenic bacteria. BALF cell differentiation showed elevated polymorphonuclear leukocytes (36%), a normal count of lymphocytes (6%), slightly increased eosinophils (4%), and the macrophages were 54%. No malignant cells were found. The protein content of the obtained fluid was 5.3 g/dL and the ratio of edema fluid to plasma total protein was 1:1.

Because of high associated risks (pneumonectomy, high PEEP levels), a transbronchial biopsy was not carried out. Two days after intubation we initiated high doses of corticosteroids, with methylprednisolone 1 g/d over 3 days, followed by 2 mg/kg/d over 10 days. From then on the radiologic findings improved. Corticosteroids were thereafter progressively reduced to a maintenance dose of 20 mg/d prednisolone.

Four weeks after starting mechanical ventilation the patient became highly febrile, gas exchange worsened, and new pulmonary infiltrates appeared on the conventional chest radiograph. Despite a new antimicrobial spectrum the patient developed septic shock and died. The recovered bronchial secretions showed a substantial growth of imipenem-resistant *Pseudomonas aeruginosa*.

## Discussion

ALI and ARDS are considered the most unpredictable and serious early complications following lung resection of primary bronchogenic carcinoma, the highest mortality rate being observed following right pneumonectomy or extended operations.<sup>4-6,12,13</sup> A recent large study found the incidence of these major pulmonary events to be around 4% in a cohort of 1,139 cases undergoing pulmonary resection.<sup>5</sup> The etiology of these early postoperative complications remains mysterious, though animal experiments suggest that increased oxidative stress occurring with one-lung anesthesia might trigger a chain of events leading to ALI/ARDS.<sup>14</sup>

There is little knowledge about the incidence of late ( $\geq 30$  d) ALI/ARDS in postoperative patients who were previously treated with neoadjuvant chemotherapy, including agents known to be associated with the development of noncardiogenic lung edema. The diagnosis of a late chemotherapy-induced ARDS relies first on the documented exclusion of other causes, such as infection, relapse of the underlying disease, and the effects of radiation. The usually observed time proximity to the administration of drugs known to be mainly associated with this syndrome and the early positive response to high doses of corticosteroids may further support the hypothesis that chemotherapy was the cause.<sup>7-9,15</sup> Both patients had CT scan features that suggested ARDS,<sup>16</sup> and these were corroborated by a CT imaging pattern suggestive of gemcitabine pulmonary toxicity in the first patient.<sup>17</sup> The history and diagnostic workup were inconsistent with left heart failure. Also ruled out were infection, a septic syndrome, or other cause such as pancreatitis, aspiration, or progression of the underlying tumoral disease. However, given their reported incidence, other possibilities, such as occult infection or idiopathic ARDS, cannot be excluded.<sup>18-20</sup>

In cases of supposed chemotherapy-induced ALI, in vivo biopsy results have rarely been reported.<sup>21</sup> However, the

autopsy pathology findings in such patients are consistent with a pattern of diffuse alveolar damage.<sup>7,8,21</sup> Transbronchial biopsies were not carried out because significant associated risk factors were apparent on admission and during the acute ARDS stage. Yet the BALF cell differentiation and the protein content suggested the permeability form of lung edema.<sup>22</sup> Taken together, the clinical history, the BALF results, and most importantly, the probable exclusion of other common identifiable causes suggest the chemotherapy as the probable cause of the late ARDS in both patients.

Gemcitabine, with or without paclitaxel, has been associated with ALI/ARDS in about 0.1% of clinical trials,<sup>23</sup> and a few case reports have supported that gemcitabine may be associated with a noncardiogenic pulmonary edema.<sup>8,21,24</sup> Combined vinorelbine-mitomycin treatment has also been considered risky for inducing lung injury, with an estimated 2% incidence of ALI/ARDS.<sup>7,9,25</sup> If started early in the course of the disease, intravenous corticosteroids have been reported to be a rescue therapy in a number of patients with this form of pulmonary injury.<sup>7,8,15,21,26</sup> However, no suggestion is offered concerning the initial dose or the treatment duration. The dramatic clinical presentation in both our patients resulted in the drastic choice of an initial treatment with high doses of methylprednisolone for 3 days, followed by a corticosteroid plan over 20 days (patient 1) or 10 days (patient 2), similar to the protocol proposed by Meduri et al for the unresolving form of ARDS.<sup>27</sup>

### Conclusions

Though in these cases the connection between the chemotherapy and the ARDS could not be verified by biopsy results, these case reports remind us of the possibility of an association between chemotherapy and late ARDS following extended lung resection for primary bronchogenic carcinoma. In the illustrated clinical context prompt identification of new respiratory symptoms in such patients could lead to the early suspicion of ARDS, calling for immediate treatment with corticosteroids, after carefully excluding other more frequent causes of ARDS.

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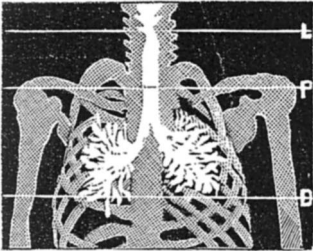
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DR. CHEVALIER JACKSON'S BRONCHOSCOPIC CHART

CASE NO. \_\_\_\_\_  
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RESULT \_\_\_\_\_  
 BRONCHOSCOPIST \_\_\_\_\_

DR. LOUIS H. CLERF  
 BRONCHOSCOPIC CHART

HOSPITAL \_\_\_\_\_ CASE NO. \_\_\_\_\_  
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PILLING-SONIA	MONTH	
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Bronchoscopic Charts  
 of Drs Chevalier Jackson (above) and Louis H Clerf (below).  
 From George P Pilling & Son.  
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 Philadelphia: The Company, 1932.  
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