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Noninvasive Estimation of the Lactate Threshold in a Subject With Dissociated Ventilatory and Pulmonary Gas Exchange Indices: A Case Report

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Selected Reports

Noninvasive Estimation of the Lactate Threshold in a Subject With Dissociated Ventilatory and Pulmonary Gas Exchange Indices*

A Case Report

Brian J. Whipp, PhD, DSc; and
Piergiuseppe Agostoni, MD, PhD

This case report describes the responses to incremental work-rate exercise in a healthy subject (with normal pulmonary function), for whom the pulmonary gas exchange (V-slope) and ventilatory-related indexes (*ie*, ventilatory equivalents and end-tidal partial pressures for O_2 and CO_2) uncharacteristically do not occur at the same metabolic rate. Based on the results of additional constant-work-rate exercise tests, we propose that in the (occasional) event of such a dissociation between the V-slope and ventilatory-related responses normally associated with the lactate threshold (θL), then the V-slope index should take priority as the θL estimator.
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Key words: acid base; exercise; ventilation

Abbreviations: θL = lactate threshold; VC = vital capacity; $\dot{V}CO_2$ = carbon dioxide output; $\dot{V}E/\dot{V}CO_2$ = ventilatory equivalent for carbon dioxide; $\dot{V}O_2$ = oxygen uptake; VT = tidal volume

The lactate, or anaerobic, threshold (θL) is the parameter of aerobic function that not only partitions the moderate-to-heavy exercise-intensity domains[1,2] but is currently used for the following reasons: assessing the status of a subject's integrative systemic functioning[2]; optimizing the intensity of training work rates in patients with lung disease[3,4]; judging the appropriateness for a subject to undergo major thoracic or abdominal surgery[5]; triaging a postoperative patient to "the ward" or to an intensive care facility[6]; and indexing the life expectancy of patients with heart disease.[7] Developments in ventilatory, pulmonary gas sensor, and computer technology now make displaying the cluster of ventilatory and pulmonary gas exchange variables necessary for the appropriate noninvasive estimation of θL readily accessible. This is based on the consequences of the increased proton ($[H^+]$) concentration associated with elevated lactate ($[L^-]$) levels in muscle and blood, as follows: (1) the release of CO_2 consequent to the coupled standard [bicarbonate] decrease, yielding a total output in excess of the aerobic component; and (2) the consequent influence on the ventilatory control mechanisms.[2] As shown in Figure 1, this is evidenced, in response to a conventional incremental work-rate test, by a clearly discernible increase in the rates of pulmonary carbon dioxide output ($\dot{V}CO_2$), ventilatory equivalent for O_2, and end-tidal P_{O_2} with respect to oxygen uptake ($\dot{V}O_2$), without a simultaneous decrease in end-tidal P_{CO_2} or an increase in the ventilatory equivalent for carbon dioxide ($\dot{V}E/\dot{V}CO_2$), to rule out nonspecific hyperventilation as the cause of the increased $\dot{V}CO_2$. That is, the pulmonary gas exchange and related ventilatory indexes typically occur at the same metabolic rate.

However, we present here the case of a healthy and physically active young male subject (22 years of age; height, 180 cm; weight, 77 kg) with normal pulmonary function (FEV_1, 4.54 L [100% predicted]; inspiratory capacity, 4.0 L; vital capacity [VC], 5.53 L [98% predicted]) in whom these indexes occur at different metabolic rates (Fig 2). The V-slope index[2,8] of the accelerated pulmonary $\dot{V}CO_2$ (*ie*, $\Delta\dot{V}CO_2/\Delta\dot{V}O_2$) was manifested at a metabolic rate ($\dot{V}O_2$) of approximately 2 L/min, whereas the ventilatory-related indexes occur at a $\dot{V}O_2$ of approximately 3 L/min.

The issue could, of course, be convincingly adjudicated by means of serial arterial (or appropriately arterialized[9]) blood sampling, requiring a sufficient sampling density to span each of the relevant variable-response changes. We chose not to do this, in this case, both with respect to the cost-benefit considerations for the subject but also in the recognition that enough is now known about the determinants (and potential constraints) of pulmonary gas exchange dynamics during exercise (see the studies by Whipp,[1] Wasserman et al,[2] and Whipp et al[10] for discussion) to provide an alternative means of removing any uncertainty as to which of the profiles provides the appropriate estimator (*ie*, without direct measurement of the arterial blood $[L^-]$ profile). This makes use of the

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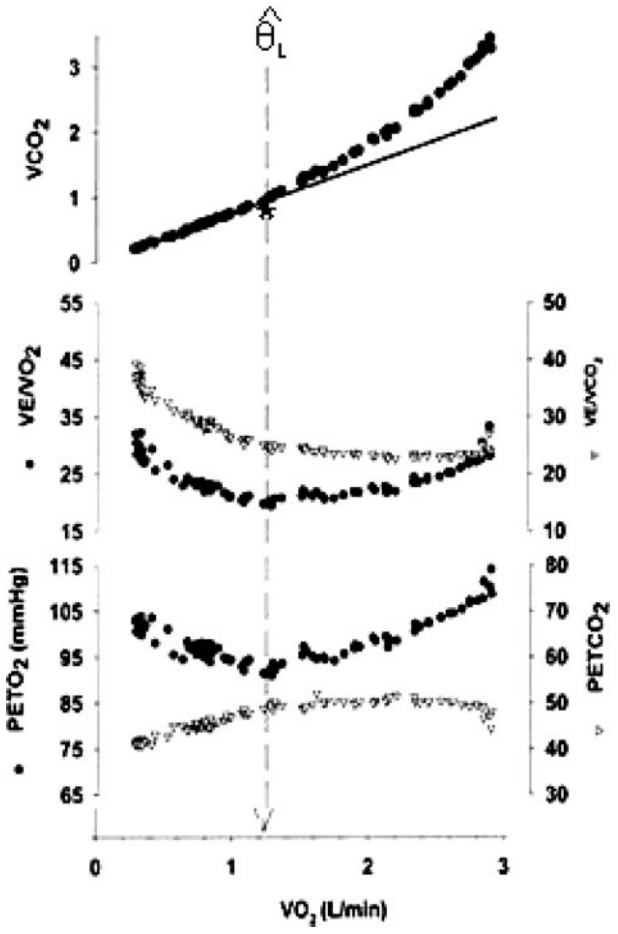

FIGURE 1. Response to an incremental work-rate test in a subject with a conventional ventilatory and pulmonary gas exchange response to the onset of metabolic acidosis. The estimated (-) θL is clearly discernible by the increased rates of pulmonary $\dot{V}CO_2$ (asterisk) and also by the increases in the ventilatory equivalent for O_2 ($\dot{V}E/\dot{V}O_2$) and the end-tidal P_{O_2} (P_{ETO_2}) with respect to $\dot{V}O_2$, but not associated with the $\dot{V}E/\dot{V}CO_2$ increasing and the end-tidal P_{CO_2} (P_{ETCO_2}) decreasing to rule out nonspecific hyperventilation (vertical dashed line).

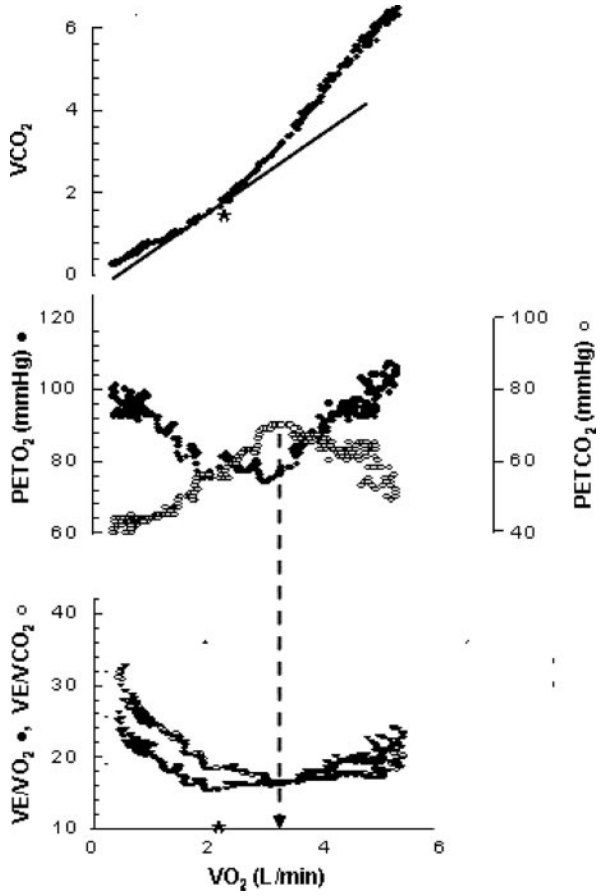

FIGURE 2. Response to a conventional incremental work-rate test in a subject in whom the pulmonary gas exchange index ($\dot{V}CO_2$-$\dot{V}O_2$ slope analysis) [asterisk] precedes the ventilatory-related indexes associated with a lactic acidosis (vertical line with arrowhead).

characteristic change in the kinetics of the $\dot{V}O_2$ response to a constant-work-rate challenge between that of moderate-intensity exercise (*ie*, below θL) and that of heavy-intensity or very heavy-intensity exercise (*ie*, above θL), as shown in Figure 3 (see the studies by Whipp[1] and Jones and Poole[11] for discussion).

Therefore, we subsequently subjected the subject to exercise on the same cycle ergometer (Ergoline 800; SensorMedics; Yorba Linda, CA) and metabolic cart (V-Max; Sensor Medics) as for the prior incremental test, at a constant work rate that was marginally less than that of the V-slope index (Fig 2 [at asterisk]), and also at a second constant work rate that was marginally less than that of the ventilatory-related break point (Fig 2 [at the dashed vertical line]).

The results (Fig 4) clearly indicate that the V-slope index provides the appropriate noninvasive estimation of θL, as the first constant-work-rate test evidenced steady-state ventilatory and V-slope profiles that are manifest only in the moderate-intensity domain,[1,2,11] that is, below θL. The second constant-work-rate test performed slightly below that of the ventilatory-related break point resulting in a continuous

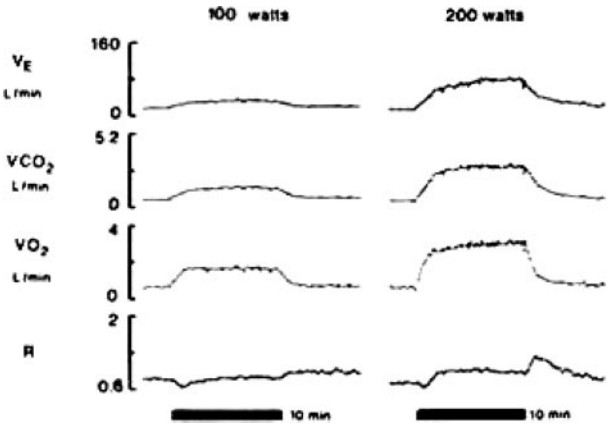

FIGURE 3. Normal ventilatory and pulmonary gas exchange responses to constant-work-rate tests of moderate intensity (below θL) and heavy intensity (above θL).

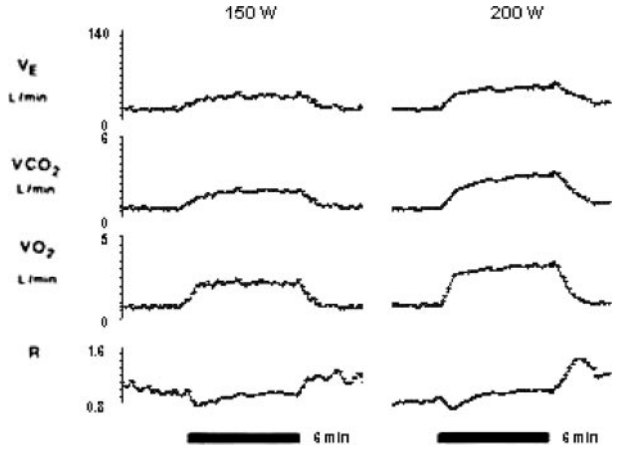

FIGURE 4. Ventilatory and pulmonary gas exchange responses to constant-work-rate tests in the subject shown in Figure 2 (one marginally less than that of the V-slope index [Fig 2, asterisk] and one marginally less than that of the ventilatory-related break point [Fig 2, vertical line with arrowhead]). Note the attainment of steady states in the former and the absence in the latter.

non-steady-state response characteristic of heavier intensity exercise (*ie*, associated with a continuing increase of both blood [L^-] and [H^+]). We therefore propose that in the, admittedly occasional, event of there being a dissociation between the pulmonary gas exchange and ventilatory-related responses normally associated with θL, then the V-slope should take priority as the estimator. If uncertainty persists, then a constant-work-rate test, of the kind utilized in this study can be used for further confirmation.

Finally, of course, it is of interest as to why the V-slope and ventilatory-related indexes do not cohere in this subject. Note that, as shown in Figure 5, ventilation in this subject increases as a virtually unique function of tidal volume (VT) up to a point where further pulmonary distention presumably becomes limiting (*ie*, at this point, the subject's VT attained a value of 100% of the preexercise resting inspiratory capacity and 75% of his VC). This is appreciably higher than the 50 to 60% value reported at maximum exercise in subjects with normal lung function,[2,12–14] such that the unusually slow and deep breathing pattern chosen by the subject is consistent with the progressively increasing and unusually high levels of end-tidal P_{CO_2}.[2,15,16] In fact, thereafter, the ventilatory change is brought about exclusively through breathing frequency; this has previously been demonstrated to "flatten" the end-tidal partial pressure profiles by truncating the duration of the continuing expiratory change in alveolar gas partial pressure (see the study by Whipp et al[15] for discussion). It is not clear why the subject adopted this particular breathing pattern, but, when questioned, he reported that this was how he felt most "comfortable" during the test, despite the progressive hypoventilation resulting in a $\dot{V}E/\dot{V}CO_2$ of approximately 17 at its minimum value rather than the value of approximately 24 that is typical of young healthy men.[2] The associated high peak end-tidal P_{CO_2}, however, developed from a normal eucapnic level at rest and during the unloaded cycling phase

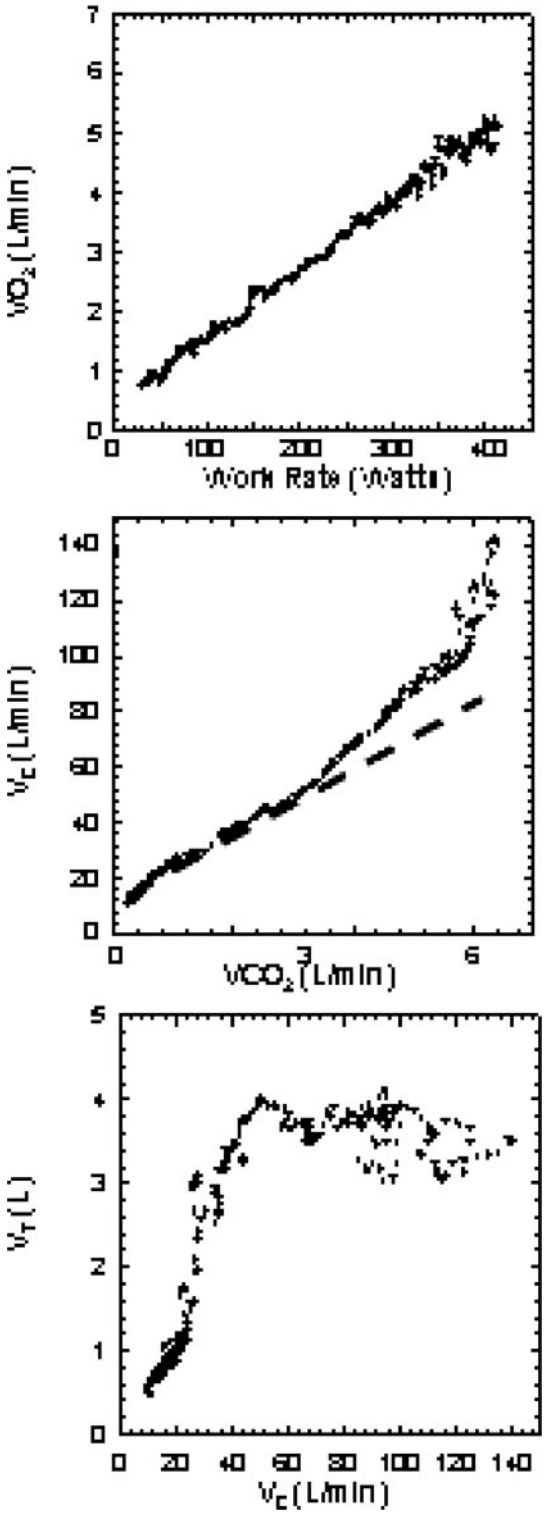

FIGURE 5. The $\dot{V}O_2$ vs work rate, minute ventilation ($\dot{V}E$) vs $\dot{V}CO_2$, and VT vs $\dot{V}E$ relationships during the incremental work-rate test shown in Figure 2. The increase of ventilation is virtually a unique function of tidal volume (at asterisk) up to a point where further pulmonary distention presumably becomes constraining or limiting; thereafter, the ventilatory change is brought about exclusively through breathing frequency, resulting in an immediate hyperventilatory increase in ventilation as a function of $\dot{V}CO_2$ (at asterisk), also evident in Figure 2.

(Fig 2). Subjects who have undergone bilateral carotid body resection[17] and also those, otherwise normal, subjects who exhibit little or no ventilatory response to inhaled CO_2[18] have been shown to have a markedly reduced, or absent, ventilatory response to incremental muscular exercise above θL. In these cases, however, the sub-θL responses were functionally normal (*ie*, there was no pattern of developing hypoventilation in this intensity domain, as shown in the present subject). An additional distinguishing feature in our subject was the brisk frequency-dependent compensatory ventilatory response after VT had attained its maximum and presumably limiting value. We base this on VT attaining 75% of the VC and 100% of the resting inspiratory capacity. The latter value likely provides a close approximation to that of high-intensity exercise, although we did not in this study determine the decrease in end-expiratory lung volume, which is consistently reported in healthy subjects (see the study by Dempsey et al[19] for discussion).

In conclusion, therefore, while a particular breathing pattern, such as the one chosen by this subject, can constrain the additional ventilatory drive that is normally occasioned by lactic acidosis (as, conceivably, might other conditions such as appreciably increased airway resistance), it does not obviate the increased $\dot{V}CO_2$ associated with the lactic acidosis-related increase in mixed venous PCO_2. Hence, the V-slope method provides an appropriate index of θL even when there is no associated ventilatory response.

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Cryptogenic Organizing Pneumonitis During Oxaliplatin Chemotherapy for Colorectal Cancer*

Case Report

Marcelo Garrido, MD; Andrés O'Brien, MD; Sergio González, MD; José Miguel Clavero, MD; and Eric Orellana, MD

The patient presented here is a 30-year-old woman who underwent anterior resection for the initial treatment of rectal cancer. A postoperative study showed a single liver metastasis. The patient received adjuvant pelvic radiotherapy with concomitant 5-fluorouracil (5-FU) treatment followed by liver metastasectomy 6 weeks after the completion of radiation therapy and chemotherapy. Adjuvant therapy with 5-FU, leucovorin, and oxaliplatin (FOLFOX 4 regimen) was continued. The initial five cycles were well tolerated with the occurrence of only paresthesia that did not interfere with function. After the sixth cycle of the treatment, progressive dyspnea and persistent cough developed in the patient, although her clinical history was negative for lung disease. A chest radiograph revealed diffuse bilateral interstitial infiltrates, and a chest CT scan showed bilateral alveolar infiltrates predominant in the right lung. Lung biopsy by video-assisted thoracoscopy was performed, and the histologic report showed cryptogenic organizing pneumonitis (COP). Prednisone therapy (1 mg/kg/d) resulted in a very good clinical

response. In fact, the patient had complete remission of respiratory symptoms including cough and dyspnea after 4 days of treatment, and the chest CT scan showed complete resolution of lung infiltrates after 4 weeks. One month later, the patient continued adjuvant treatment with six cycles of 5-FU, leucovorin, and irinotecan (*ie*, the FOLFIRI regimen) without complications. Thus, oxiplatin was implicated as the likely cause of this drug-induced lung toxicity, which is a very rare complication associated with platins. Diffuse interstitial lung disease, particularly COP, has been described following the administration of the cytotoxic agents bleomycin and busulfan, but a connection to oxaliplatin has not been reported before this case.

(CHEST 2007; 132:1997–1999)

Key words: colorectal cancer; cryptogenic organizing pneumonitis; oxaliplatin

Abbreviations: COP = cryptogenic organizing pneumonia; FOLFOX4 = 5-fluorouracil, leucovorin, and oxaliplatin; 5-FU = 5-fluorouracil

A 30-year-old woman who presented with rectal cancer underwent surgical treatment with anterior resection. Histology indicated moderately undifferentiated tubular adenocarcinoma with perirectal fat invasion and 3 of 15 lymph nodes with tumor invasion. She was referred to our institution to continue adjuvant chemoradiotherapy. An abdominal CT scan, which was performed before treatment onset, showed a single liver metastasis measuring 3.2 × 2.5 cm. A liver MRI confirmed a single liver lesion. The patient completed pelvic radiation therapy with concomitant 5-fluorouracil (5-FU) [200 mg/m^2/d] treatment by continuous infusion. A liver metastasectomy was satisfactorily performed 6 weeks after chemoradiotherapy was completed. The patient continued treatment with an adjuvant 5-FU, leucovorin, and oxaliplatin (FOLFOX 4) regimen every 2 weeks with oxaliplatin (85 mg/m^2 IV) added on day 1, leucovorin (200 mg/m^2 IV) added on days 1 and 2, and 5-FU (400 mg/m^2 IV as a bolus and 600 mg/m^2 in continuous infusion for 22 h) added on days 1 and 2. The initial five cycles were well tolerated with the occurrence of only paresthesias that did not interfere with function (grade 1 sensorial neuropathy).

After the sixth cycle, respiratory symptoms with progressive dyspnea and persistent cough developed in the patient. Her clinical history was negative for lung disease. Concomitant medications used were ondansetron and domperidone. Although the physical examination findings were normal, a chest radiograph revealed diffuse bilateral interstitial infiltrates. Blood cell counts were normal, with leukocyte counts of 4,100 cells/mL and eosinophil counts of 328 cells/mL. The carcinoembryonic antigen concentration was 1.6 U/L, and lactate dehydrogenase concentration was 301 U/L. Arterial blood gas analysis, diffusing capacity of the lung for carbon monoxide measurement, and spirometry findings were normal. A chest CT scan indicated bilateral alveolar infiltrates predominantly in the right lung (Fig 1). Bronchoscopy and BAL were performed. Ziehl-Nielsen stain, direct immunofluorescence, polymerase chain reaction for *Pneumocystis carinii* and *Mycobacterium tuberculosis*, and cultures for common bacteria, acid-fast bacilli, and fungi were all negative. Lung biopsy by video-assisted thoracoscopy was performed, and the histologic report showed peribronchial thickening and numerous intraalveolar fibrous plugs (arrows in Fig 2) and alveolar fibrosis foci, vacuolar macrophages, and granulocytes in some alveolar spaces, thickening alveolar septa by inflammatory cells, and focal hyperplasia of type II pneumocytes with squamous metaplasia consistent with cryptogenic organizing pneumonitis (COP) [Fig 2].

Therapy with prednisone (1 mg/kg/d) was begun with very good clinical response. The patient had complete remission of respiratory symptoms with resolution of dyspnea and cough after 4 days of steroid treatment. A chest CT scan showed complete lung infiltrate resolution 4 weeks later. One month later, the patient resumed adjuvant treatment with six cycles of a 5-FU, leucovorin, and irinotecan (or FOLFIRI) regimen, which included irinotecan (180 mg/m^2 IV) added on day 1, leucovorin (200 mg/m^2 IV) added on days 1 and 2,

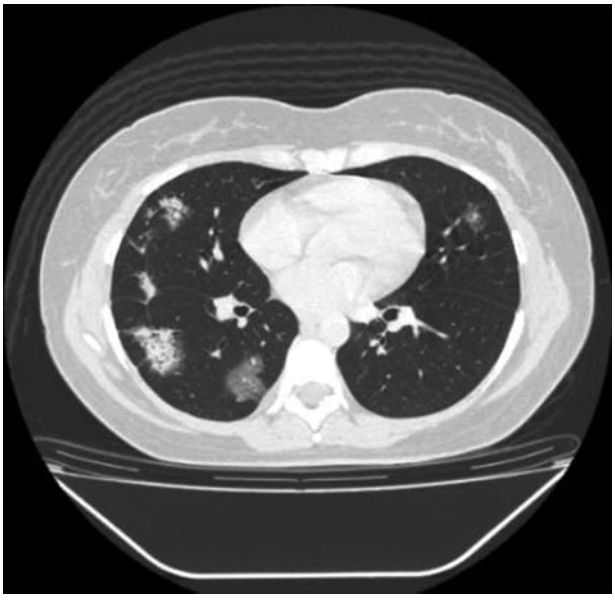

FIGURE 1. A chest CT scan showing bilateral alveolar infiltrates predominantly in the right lung of a patient with progressive dyspnea and persistent cough during chemotherapy with oxaliplatin.

*From the Departamentos de Hematología-Oncología (Drs. Garrido and Orellana), Radiología (Dr. O'Brien), and Anatomía Patológica (Dr. González), and the División de Cirugía Toráxica (Dr. Clavero), Centro de Cáncer, Pontificia Universidad Católica de Chile, Santiago, Chile.

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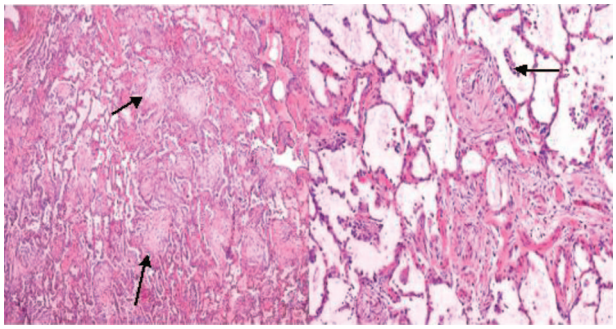

FIGURE 2. Lung biopsy specimen obtained by video-assisted thoracoscopy of a patient with progressive dyspnea and persistent cough during chemotherapy with oxaliplatin. Shown are peribronchial thickening and numerous intraalveolar fibrous plugs (arrows), vacuolar macrophages and granulocytes in some alveolar spaces, thickening of alveolar septa by inflammatory cells, and focal hyperplasia of type II pneumocytes with squamous metaplasia consistent with COP. *Left:* hematoxylin-eosin (original ×40). *Right:* hematoxylin-eosin (original ×100).

and 5-FU (400 mg/m^2 IV bolus and 600 mg/m^2 by continuous infusion for 22 h) added on days 1 and 2, without complications.

DISCUSSION

Different diagnoses of lung infiltrates in cancer patients following chemotherapy include infections, heart failure, neoplasia, lung bleeding, and drug toxicity. Although infections are one of the most common and important causes, an extensive workup of the BAL fluid and biopsy specimens ruled out this diagnosis. In addition, histologic examination findings were negative for neoplasia and lung bleeding. Thus, drug-induced lung toxicity developed in the patient. The most probable cause was determined to be oxaliplatin because of the time-related effects and the lack of response to concomitant treatment with 5-FU.

Third-generation platins like trans-L-1,2-diaminocyclohexane (oxaliplatin) combine with DNA to form DNA repair-resistant adducts.[1] Therapy with oxaliplatin in combination with 5-FU and leucovorin has shown synergistic activity for the treatment of colorectal cancer[2] with a 50% response rate, a 9-month disease-free survival rate, and a 16.2-month overall survival time for patients with metastatic colon cancer.[3] The main secondary reactions related to oxaliplatin are hematologic effects, GI effects, and neurologic toxicity.[4] Hematologic toxicities in response to oxaliplatin therapy include grade 3/4 neutropenia (neutrophil count, $< 1.0 \times 10^9$ cells/L) in 5% of the patients receiving therapy with oxaliplatin alone and in 41.7% of the patients receiving the FOLFOX 4 combination treatment as well as grade 3/4 thrombocytopenia (platelet count, $< 50.0 \times 10^9$ cells/L) in 0.5 to 7.8% of the patients. GI toxicity is frequently exhibited by mild-to-moderate nausea and vomiting. In addition, diarrhea with an increase of less than six stools per day over pretreatment (grade1/2 diarrhea) has been reported with oxaliplatin monotherapy. Neurologic toxicity including paresthesias interfering with function and activities of daily living (grade 2/3 sensorial neuropathy) has been reported following treatment with oxaliplatin, although in most of the cases the effects were reversible.

Common causes of pulmonary injury in patients with cancer are infection, pulmonary hemorrhage, pulmonary lymphangitis carcinomatosa, congestive heart failure, pulmonary embolism, and drug-induced pulmonary toxicity. Anticancer drugs that cause pulmonary toxicity have recently been reviewed by Meadors et al.[5] Lung toxicity is a very rare complication, however, following treatment with platins. Few incidents of acute lung fibrosis have been reported for patients treated with 5-FU and cisplatin.[6] Acute interstitial pneumonitis and acute lung injury culminating in ARDS developed in two patients who were treated with oxaliplatin, and they died after 10 to 20 days.[7,8] Furthermore, eosinophilic lung disease was reported[9] in a patient receiving oxaliplatin for the treatment of colorectal cancer. In a 2001 study,[10] organizing diffuse alveolar damage was reported to develop in a patient treated with a combination of 5-FU and oxaliplatin (*ie*, the FOLFOX 4 regimen). This case study[10] was the only report to date to describe acute lung toxicity associated with this combination of drugs. Diffuse interstitial lung disease, particularly COP, has previously been described as a side effect associated with therapy with cytotoxic agents such as bleomycin and busulfan.[11] Patients with this condition have a high response rate to steroid therapy, but no association of this lung toxicity and oxaliplatin has been reported previously.[12] Thus, the case described in this study is the first report of COP secondary to oxaliplatin treatment.

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