Adriell Ramalho Santana[1], Fábio Ferreira Amorim[1,2], Paulo Henrique Alves Soares[3], Edmilson Bastos de Moura[2], Marcelo de Oliveira Maia[2]

Acute respiratory failure caused by organizing pneumonia secondary to antineoplastic therapy for non-Hodgkin's lymphoma

Insuficiência respiratória aguda causada por pneumonia em organização secundária à terapia antineoplásica para linfoma não Hodgkin

1. Escola Superior de Ciências da Saúde - ESCS - Brasília (DF), Brazil.
2. Adult Intensive Care Unit, Hospital Santa Luzia - Brasília (DF), Brazil.
3. Grupo Acreditar - Brasília (DF), Brazil.

ABSTRACT

Interstitial lung diseases belong to a group of diseases that typically exhibit a subacute or chronic progression but that may cause acute respiratory failure. The male patient, who was 37 years of age and undergoing therapy for non-Hodgkin's lymphoma, was admitted with cough, fever, dyspnea and acute hypoxemic respiratory failure. Mechanical ventilation and antibiotic therapy were initiated but were associated with unfavorable progression. Thoracic computed tomography showed bilateral pulmonary "ground glass" opacities. Methylprednisolone pulse therapy was initiated with satisfactory response because the patient had used three drugs related to organizing pneumonia (cyclophosphamide, doxorubicin and rituximab), and the clinical and radiological symptoms were suggestive. Organizing pneumonia may be idiopathic or linked to collagen diseases, drugs and cancer and usually responds to corticosteroid therapy. The diagnosis was anatomopathological, but the patient's clinical condition precluded performing a lung biopsy. Organizing pneumonia should be a differential diagnosis in patients with apparent pneumonia and a progression that is unfavorable to antimicrobial treatment.

Keywords: Cryptogenic organizing pneumonia; Respiratory insufficiency; Drug toxicity; Lung diseases, interstitial; Lymphoma, non-Hodgkin/drug therapy; Tomography, X-ray computed; Case reports

INTRODUCTION

Acute respiratory failure secondary to interstitial lung diseases is a serious condition with high mortality, which requires an early etiological diagnosis and specific treatment. In this respect, this is a significant challenge in clinical practice because there are multiple diagnostic hypotheses, including infectious diseases, pulmonary embolism, organizing pneumonia (OP), acute interstitial pneumonia, alveolar hemorrhage, eosinophilic pneumonia and radiation pneumonitis among others.[1]

Infectious diseases are usually the first cause to come to mind because they represent the most common etiology. However, noninfectious causes are also common and should be evaluated, especially in cases with atypical presentation and progression.[2]

The current article reports a case of acute respiratory failure secondary to OP related to chemotherapy treatment for non-Hodgkin's lymphoma.

CLINICAL CASE

The male patient, who was 37 years old from Brasilia (DF), was admitted to the intensive care unit (ICU) with a condition of dry cough for 4 days with a fever

This study was conducted at the Adult Intensive Care Unit, Hospital Santa Luzia - Brasília (DF), Brazil.

Conflicts of interest: None.

Submitted on November 22, 2012
Accepted on December 19, 2012

Corresponding author:
Fábio Ferreira Amorim
Coordenação de Pesquisa e Comunicação Científica
SMHN Quadra 03, conjunto A, Bloco 1, Edifício FEPECS
Zip Code: 70710-907 - Brasília (DF), Brazil
E-mail: ffamorim@gmail.com

(38.5ºC) and progressive dyspnea. The patient was undergoing antineoplastic therapy for non-Hodgkin's lymphoma with cyclophosphamide, doxorubicin, vincristine, prednisone and rituximab, and the last session was 6 days prior to admission. The patient had no history of tobacco smoking, prior lung disease or occupational or environmental exposure. Upon a physical examination, the patient was tachycardic (115 beats per minute), normotensive (115/68 mmHg) and tachypneic (28 breathing cycles per minute) and had diffuse crackles on pulmonary auscultation. Laboratory tests showed leukopenia (3,100 leucocytes/mm³ with 18% rods and 48% segmented), 273 U/L lactate dehydrogenase and 2.33 mg/dL ultra-sensitive C-reactive protein. The arterial blood gasometry showed 44 mmHg oxygen pressure (PaO_2) and 82% oxygen saturation (SaO_2). The patient showed 62 mmHg PaO_2 and 90% SaO_2 following administration of supplementary oxygen via a Venturi mask with 50% fraction of inspired oxygen (FiO_2). Thoracic computed tomography (CT) indicated extensive pulmonary opacities with a predominantly "ground glass" appearance and bilateral diffuse involvement (Figure 1).

The introduction of noninvasive mechanical ventilation and empiric broad-spectrum antibiotic therapy (piperacillin/tazobactam, clarithromycin, trimethoprim/ sulfamethoxazole and linezolid) was initially chosen.

On the 2nd day of ICU admission, the patient's respiratory mechanics and gas exchange worsened with a drop in SaO_2, and an orotracheal intubation (OTI) and introduction of invasive mechanical ventilation (IMV) with a protective ventilation strategy were chosen. On the 6th day of ICU admission, the patient showed an improvement of gas exchange and respiratory mechanics, and he was extubated after performing the spontaneous breathing test.

However, the patient's breathing worsened on the 15th day of ICU admission; therefore, the patient was subjected to an IVM, and a new OTI was performed. The patient also showed hemodynamic instability when norepinephrine was initiated. The white blood cell count was in the normal range, and the PaO_2/FiO_2 ratio was 69. The blood, urine and bronchoalveolar lavage cultures were negative, as was the analysis of acid-alcohol-resistant bacilli (AARB).

On the 19th day following ICU admission, the patient had an IMV PaO_2/FiO_2 ratio of 74 and 88 mmHg $PaCO_2$ with 15 cmH_2O positive end-expiratory pressure (PEEP) and 6 L/min tracheal gas insufflation. At that time, the OP diagnostic hypothesis was suggested. Pulse therapy with methylprednisolone was initiated (1 g per day for 5 days), and the use of clarithromycin was maintained (500 mg twice daily).

Upon ending the pulse therapy (23rd day), the patient showed a 116 PaO_2/FiO_2 ratio. A thoracic CT showed a large reduction of "ground glass" pulmonary opacities on the 25th hospital day (Figure 2).

A tracheostomy was performed on the 27th day of ICU admission, and on the 31st day, the patient was removed from mechanical ventilation, showing a 402 PaO_2/FiO_2 ratio. The patient was discharged from the ICU on the 42nd day of ICU admission and was discharged from the hospital 8 days later. The patient still showed consolidated "ground glass" pulmonary opacities bilaterally based on the therapeutic monitoring thoracic CT at hospital discharge, which were more pronounced in the posterior and lateral basal segments of the inferior lobes, albeit with significant decrease in the extent of pulmonary opacities (Figure 3). The patient maintained outpatient follow-up and used corticosteroid therapy with 60 mg of prednisone per day for another 6 months.

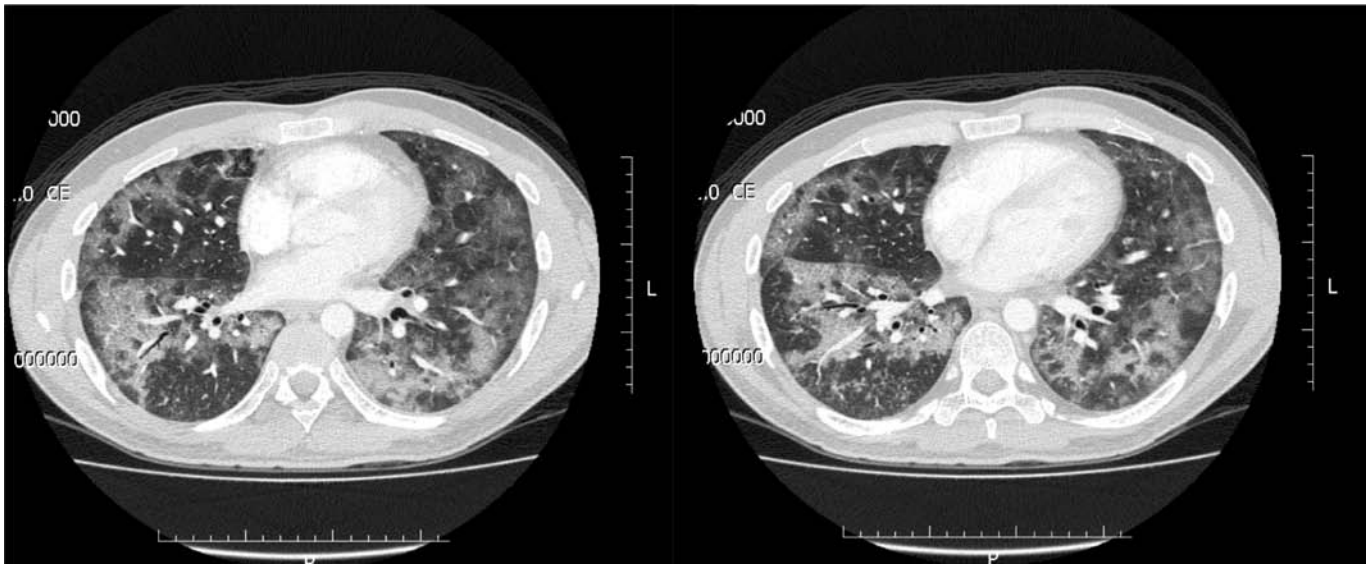

Figure 1 - Thoracic computed tomography at admission. Extensive opacities with a predominantly "ground glass" appearance and bilateral diffuse involvement.

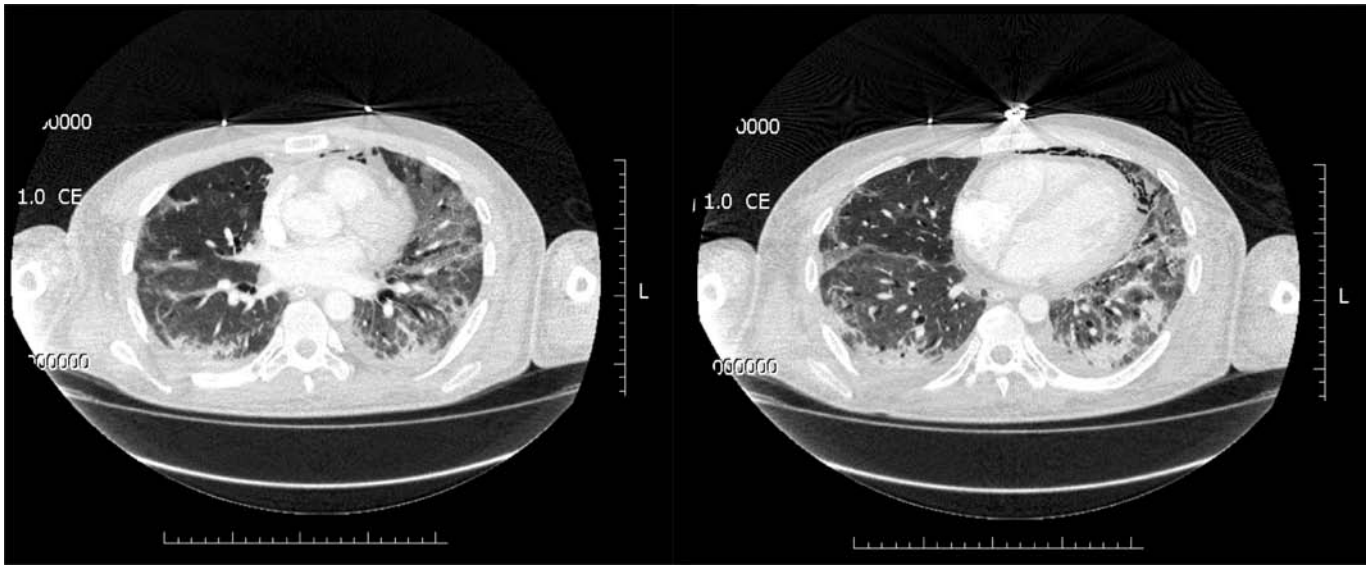

Figure 2 - Thoracic computed tomography following completion of pulse therapy. Bilateral pulmonary "ground glass" opacities predominantly affecting the lingula of the left lung with considerable reduction compared to the previous exam. Consolidated pulmonary opacities in the posterior and lateral basal segments of the lower lobes with pneumomediastinum and bilateral small pleural effusion.

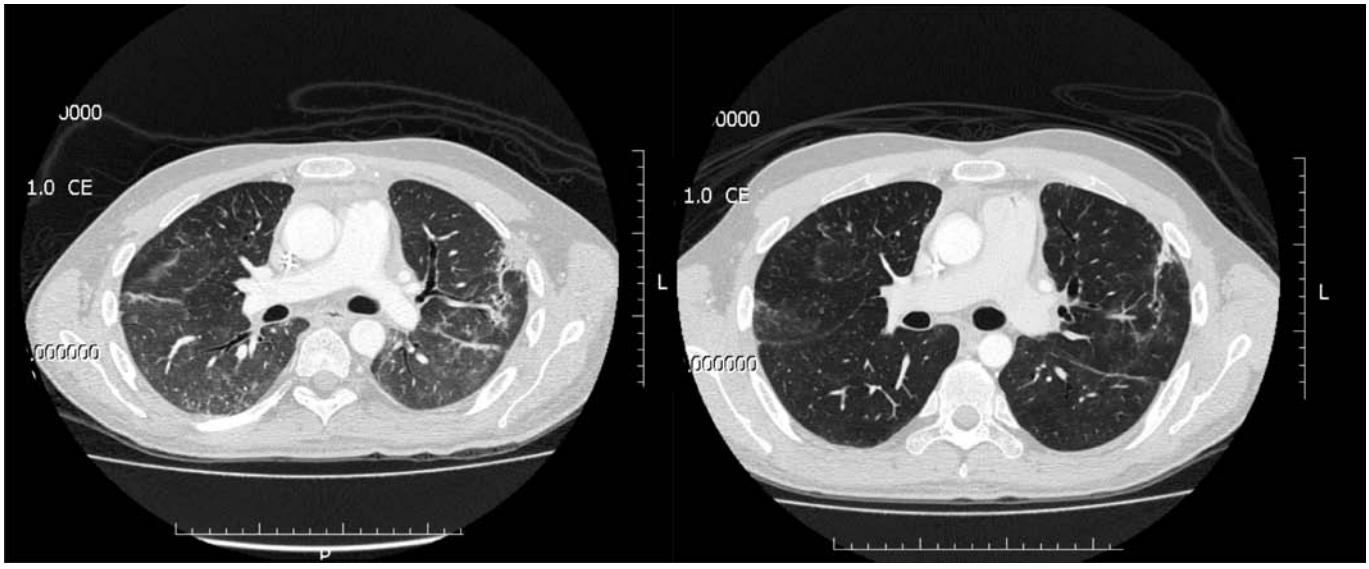

Figure 3 - Thoracic computed tomography at hospital discharge (left) and 1 month later at outpatient monitoring (right). Therapeutic monitoring indicating significant reduction compared to previous exams in the extent of pulmonary opacities, disappearance of pneumomediastinum and pleural effusion at hospital discharge. Computed tomography exhibiting considerable radiological improvement at outpatient monitoring.

DISCUSSION

OP is a clinical entity that may be cryptogenic (formerly known as bronchiolitis obliterans with OP or BOOP (bronchiolitis obliterans organizing pneumonia)) or secondary to connective tissue diseases, infections, radiation therapy, aspiration, drugs and cancer among other causes.[3-7] That classification is essential because treatment of the underlying disease or discontinuation of contact with the aggressive factor is critical for treating secondary OP.

OP is considered a rare disease with an incidence of 1.96/100 thousand, but the number of cases has increased in the last 20 years, primarily affecting adults in the fourth and fifth decades of life with no gender predominance. The mortality ranges from 5 to 27% in studies and is apparently higher in secondary OP.[5-8]

The typical histopathological pattern is identified

by excessive proliferation of granulation tissue in the terminal airways and alveolar ducts, which is characterized by irregular intraluminal filling of the respiratory alveoli and bronchioli with loose plugs of granulation tissue (Masson bodies) and a predominance of alveolar inflammation over the small airways disease (bronchiolitis).[4,6]

The symptoms are nonspecific and usually progress subacutely or chronically with clinical symptoms similar to those of community-acquired pneumonia (CAP), which often delays the diagnosis and treatment. The use of antibiotic therapy for the empirical treatment of infection is ineffective,[3-6] although macrolides are used in the treatment of patients with mild symptoms or as an adjuvant therapy, given their immunomodulatory properties.[9,10] The disease usually develops after a prodrome, wherein the patient shows flu-like symptoms, including fever, fatigue, dry cough and dyspnea. Typically, the diagnosis is not suspected in the first 4 to 10 weeks. The physical examination is nonspecific, and inspiratory crackles occur in two thirds of cases and more commonly in secondary OP.[3-6]

Radiological findings are also nonspecific, thereby leading to an indication for lung biopsy to confirm the diagnosis. In a recent study performed by Drakopanagiotakis et al.,[6] consolidation was noted in 82% of patients on thoracic radiography, which was bilateral in 68.8% of cases with a possible migratory pattern. The density of alveolar infiltrate may vary from "ground glass" to consolidation, which may comprise a few centimeters to a full impairment of a pulmonary lobe or show the appearance of nodules or masses with an air bronchogram in certain instances on high-resolution thoracic CT. This alveolar infiltrate is predominantly peripheral but may have a peribronchovascular location (bronchocentric pattern) less frequently.[7]

Cases of spontaneous regression are rare, and occasionally, OP develops rapidly and progressively, as in the case described in this report, thereby leading to acute respiratory failure. Depending on the extent of injury, certain patients meet the clinical criteria for a diagnosis of acute respiratory distress syndrome (ARDS), albeit with a different histological pattern and without the diffuse alveolar damage typical of ARDS. In those cases, a diagnostic suspicion is crucial because the patients usually respond well to treatment with methylprednisolone pulse therapy (125 to 250 mg every 6 hours), which is administered for 3 to 5 days and is followed by oral corticosteroid therapy with prednisone (1 to 1.5 mg/kg of weight per day) for 4 to 8 weeks.[10] The clinical response is usually fast prior to the radiological improvement, which can require months. Over 80% of patients respond to corticosteroid therapy, but several studies suggest that secondary OP has a worse prognosis. The combination of immunosuppressants can deliver satisfactory results in certain patients who fail to improve with the use of corticosteroids.[6,7,10] Usually, corticosteroid therapy is suspended within 3 to 6 months, but relapses are common (13-58%) and are more frequent in patients with hypoxemia, diffuse alveolar infiltrate, tobacco smoking and secondary OP.[5,6]

Regarding the case reported in this study, it is noteworthy that the lung is an organ that is often affected through injuries resulting from adverse reactions to antineoplastic drugs. These lesions may manifest through a wide variety of clinical syndromes, and OP is one of those entities. Cyclophosphamide, doxorubicin and rituximab have already been reported to cause OP among the drugs used in the antineoplastic treatment of this patient.[11-13]

A limitation of the current report was the failure to perform a histopathological examination to confirm the diagnosis. The severity of clinical symptoms, including unfavorable outcomes following the initial treatment and the high risk of performing surgical procedures, in combination with the pattern of lesions on the thoracic CT and history of exposure to drugs known to be related to the development of secondary OP led to the decision to treat the OP with methylprednisolone pulse therapy. However, that therapy has a high risk of complications that must be stressed. Moreover, a surgical (thoracoscopic or open) lung biopsy remains the gold standard for an OP diagnosis,[3,6] and this procedure is indicated prior to introducing corticosteroid therapy in the absence of contraindications.

OP is a disease that has increased in incidence over recent years and may occasionally progress into acute respiratory failure. The diagnosis of OP is difficult because it shows clinical symptoms similar to CAP, but a thorough medical history evaluation, especially regarding exposure to drugs causing secondary OP, can be helpful when considering this diagnosis.

CONCLUSIONS

The possibility of OP should be considered in patients with apparent pneumonia and an unfavorable response to antimicrobial treatment, especially in cases of acute respiratory failure.

RESUMO

Doenças difusas do parênquima pulmonar pertencem a um grupo de doenças de evolução geralmente subaguda ou crônica, mas que podem determinar insuficiência respiratória aguda. Paciente masculino, 37 anos, em terapia para linfoma não Hodgkin, admitido com tosse seca, febre, dispneia e insuficiência respiratória aguda hipoxêmica. Iniciadas ventilação mecânica e antibioticoterapia, porém houve evolução desfavorável. Tomografia computadorizada de tórax mostrava opacidades pulmonares em "vidro fosco" bilaterais. Devido ao paciente ter feito uso de três drogas relacionadas à pneumonia em organização (ciclofosfamida, doxorrubicina e rituximabe) e quadros clínico e radiológico serem sugestivos, iniciou-se pulsoterapia com metilprednisolona com boa resposta. Pneumonia em organização pode ser idiopática ou associada a colagenoses, drogas e neoplasias, e geralmente responde bem a corticoterapia. O diagnóstico é anatomopatológico, mas condições clínicas do paciente não permitiam a realização de biópsia pulmonar. Pneumonia em organização deve ser diagnóstico diferencial em pacientes com aparente pneumonia de evolução desfavorável ao tratamento antimicrobiano.

Descritores: Pneumonia em organização criptogênica; Insuficiência respiratória; Toxicidade de drogas; Doenças pulmonares intersticiais; Linfoma não Hodgkin/quimioterapia; Tomografia computadorizada por raios X; Relatos de casos

REFERENCES

1. Pinheiro BV. Infiltrado pulmonar no paciente crítico: a importância da biópsia pulmonar. J Bras Pneumol. 2006;32(5):xxiii-xxiv.
2. Monteiro AS, Addor G, Nigri DH, Franco CA. Biópsia pulmonar a céu aberto em pacientes sob ventilação mecânica e com infiltrado pulmonar difuso. J Bras Pneumol. 2005;31(3):212-8.
3. Cottin V, Cordier JF. Cryptogenic organizing pneumonia. Semin Respir Crit Care Med. 2012;33(5):462-75.
4. Epler GR. Bronchiolitis obliterans organizing pneumonia. Arch Intern Med. 2001;161(2):158-64. Review.
5. Drakopanagiotakis F, Polychronopoulos V, Judson MA. Organizing pneumonia. Am J Med Sci. 2008;335(1):34-9. Review.
6. Drakopanagiotakis F, Paschalaki K, Abu-Hijleh M, Aswad B, Karagianidis N, Kastanakis E, et al. Cryptogenic and secondary organizing pneumonia: clinical presentation, radiographic findings, treatment response, and prognosis. Chest. 2011;139(4):893-900.
7. Cordier JF. Cryptogenic organising pneumonia. Eur Respir J. 2006;28(2):422-46. Review.
8. Gudmundsson G, Sveinsson O, Isaksson HJ, Jonsson S, Frodadottir H, Aspelund T. Epidemiology of organising pneumonia in Iceland. Thorax. 2006;61(9):805-8.
9. Stover DE, Mangino D. Macrolides: a treatment alternative for bronchiolitis obliterans organizing pneumonia? Chest. 2005;128(5):3611-7
10. Epler GR. Bronchiolitis obliterans organizing pneumonia, 25 years: a variety of causes, but what are the treatment options? Expert Rev Respir Med. 2011;5(3):353-61.
11. Maldonato F, Limper AH, Jett JR. Pulmonary toxicity associated with systemic antineoplastic therapy: Clinical presentation, diagnosis, and treatment. Uptodate.com [Internet]. 2012 [cited 2012 Nov 16; last updated: Mar 29, 2012]. Available from: http://www.uptodate.com/contents/pulmonary-toxicity-associated-with-systemic-antineoplastic-therapy-clinical-presentation-diagnosis-and-treatment
12. Maldonato F, Limper AH, Jett JR. Pulmonary toxicity associated with antineoplastic therapy: molecularly targeted agents. Uptodate.com [Internet]. 2012 [cited 2012 Nov 16; last updated: Mar 29, 2012]. Available from: http://www.uptodate.com/contents/pulmonary-toxicity-associated-with-antineoplastic-therapy-molecularly-targeted-agents?source=see_link
13. Maldonato F, Limper AH, Jett JR. Pulmonary toxicity associated with antineoplastic therapy: cytotoxic agents. Uptodate.com [Internet]. 2012 [cited 2012 Nov 16; last updated: Mar 29, 2012]. Available from: http://www.uptodate.com/contents/pulmonary-toxicity-associated-with-antineoplastic-therapy-cytotoxic-agents