Artigo Original

Impact of open lung biopsy on refractory acute respiratory failure*

Impacto de biópsia pulmonar a céu aberto na insuficiência respiratória aguda refratária

CARMEN SILVIA VALENTE BARBAS[1], VERA LUIZA CAPELOZZI[2], CRISTIANE HOELZ[1], RICARDO BORGES MAGALDI[1], ROGÉRIO DE SOUZA[3], MARIA LAURA SANDEVILLE[1], JOSÉ RIBAS MILANEZ DE CAMPOS[1], EDUARDO WEREBE[1], LAERTE O. ANDRADE FILHO[1], ELIAS KNOBEL[1]

ABSTRACT

Objective: To determine the impact that open lung biopsy findings have on decisions regarding changes in the treatment strategies employed for critically ill patients presenting diffuse pulmonary infiltrates and suffering from refractory acute respiratory failure, as well as on their clinical improvement. **Methods:** This study involved 12 mechanically ventilated patients with acute respiratory failure who were subjected to open lung biopsy (by thoracotomy) after not presenting a clinical response to standard treatment. **Results:** The single most common cause of the acute respiratory failure was viral infection, which was identified in 5 patients (40%). The pre-operative evaluation of the cause of respiratory failure was modified in 11 patients (91.6%), and a specific diagnosis was made in 100% of the cases. Regardless of changes in treatment regimen, the mortality rate was 50%. Six patients (50%) survived to be discharged from the hospital. All of the discharged patients survived for at least one year after the open lung biopsy, for an overall one-year survival rate of 50% among the 12 patients studied. For the patients who died in the hospital, the time of survival after open lung biopsy was 14 + 10.8 days. **Conclusion:** We conclude that open lung biopsy is a useful tool in the management of acute respiratory failure when there is no clinical improvement after standard treatment, since it can lead to a specific diagnosis that requires distinct treatment, which probably lowers the mortality rate among such patients.

Keywords: Respiratory distress syndrome, adult; Lung/pathology; Biposy; Acute respiratory syndrome

RESUMO

Objetivo: Verificar o impacto dos resultados da biópsia pulmonar a céu aberto nas decisões que determinem mudanças nas estratégias de tratamento de pacientes críticos, com infiltrados pulmonares difusos e insuficiência respiratória aguda refratária, bem como na melhora de seu quadro clínico. **Métodos:** Foram avaliados 12 pacientes com insuficiência respiratória aguda e sob ventilação mecânica, que foram submetidos à biópsia pulmonar a céu aberto (por toracotomia) após a ausência de resposta clínica ao tratamento padrão. **Resultados:** A maior causa isolada de insuficiência respiratória aguda foi a infecção viral, identificada em 5 pacientes (40%). A avaliação pré-operatória da causa da insuficiência respiratória foi modificada em 11 pacientes (91,6%), e um diagnóstico específico foi feito em 100% dos casos. A taxa de mortalidade foi de 50%, a despeito das mudanças no regime terapêutico. Seis pacientes (50%) sobreviveram e obtiveram alta hospitalar. Todos os pacientes que obtiveram alta sobreviveram por pelo menos um ano após a biópsia pulmonar a céu aberto, totalizando uma taxa de sobrevida em um ano de 50% dentre os 12 pacientes estudados. Quanto aos pacientes que faleceram no hospital, o tempo de sobrevida após a biópsia pulmonar a céu aberto foi de 14 + 10,8 dias. **Conclusão:** Concluímos que a biópsia pulmonar a céu aberto é uma ferramenta útil no controle da insuficiência respiratória aguda quando não se observa melhora clínica após o tratamento padrão, já que pode resultar em um diagnóstico específico que requeira tratamento distinto, provavelmente diminuindo a taxa de mortalidade desses pacientes.

Descritores: Síndrome do desconforto respiratório do adulto; Pulmão/patologia; Biópsia

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*Study carried out in the Intensive Care Unit, Hospital Israelita Albert Einstein, in the Department of Pathology, University of São Paulo School of Medicine and in the Department of Pulmonology, Instituto do Coração (InCor, Heart Institute), Universidade de São Paulo - USP - São Paulo (SP) Brazil.

1. Intensive Care Unit, Hospital Israelita Albert Einstein, São Paulo, Brazil
2. Department of Pathology, Universidade de São Paulo - USP - São Paulo (SP) Brazil.
3. Department of Pulmonology, Instituto do Coração (InCor, Heart Institute), Universidade de São Paulo - USP - São Paulo (SP) Brazil.
Correspondence to: Profa. Vera Luiza Capelozzi, Departamento de Patologia, Faculdade de Medicina da Universidade de São Paulo, Av. Dr. Arnaldo 455 - CEP 01246-903, São Paulo, SP, Brasil. E-mail: vcapelozzi@lim05.fm.usp.br

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INTRODUCTION

Open lung biopsy (OLB) has proven to have a relatively high sensitivity and specificity in the diagnosis of chronic diffuse parenchymal disease. [1-3] However, since it is a surgical procedure typically performed under general anesthesia, physicians can be reluctant to perform OLB in critically ill patients with diffuse pulmonary infiltrates suffering from acute respiratory failure (ARF). Such reluctance creates a paradox in which the patients who most urgently require diagnosis might be denied the benefits of a useful diagnostic method due to fear of peri-operative complications. In addition, some investigators question whether OLB provides any benefit to immunossupressed patients with diffuse infiltrates, many of whom are in ARF.[4-5] However, if OLB does have some benefit in cases of respiratory failure, the maximal benefit might be provided by early biopsy in the acute setting.[6-7] To identify the risks and possible benefits of OLB in patients with diffuse pulmonary infiltrates and ARF (especially refractory ARF), we reviewed our experience over a five-year period.

METHODS

We examined the medical records of all patients who underwent OLB at two different health care facilities between January of 1997 and January of 2002. For inclusion in the study, we selected patients whose chest X-rays revealed diffuse pulmonary infiltrates and who presented acute onset of respiratory failure. Respiratory failure was defined as arterial oxygen tension (PaO_2) of less than 50 mmHg on room air, or a ratio of PaO_2 to inspired oxygen fraction (FiO_2) of less than 200 on supplemental oxygen. To exclude patients presenting the steady deterioration characteristic of a chronic process, ARF was defined as the onset of symptoms of respiratory distress less than ten days prior to the OLB. All OLBs were performed at the discretion of the attending physician, progressive hypoxemia being the most common indication. The details of the OLB procedure and specimen processing at our institution have been described elsewhere.[8] In brief, OLB was performed under general anesthesia. Through a limited thoracotomy, tissue samples were removed with a cutting stapler. We followed a specific protocol for specimen processing. A portion of the surgical specimen was sent to the Electron Microscopy and Surgical Pathology Department of our facility, where the frozen and paraffin sections were examined after appropriate staining. The remaining portion of the specimen was sent to the Microbiology Laboratory, where smears were prepared, and part of the tissue was homogenized. Sections were cultured for aerobic and anaerobic bacteria, as well as for fungi, mycobacteria, Legionella, Nocardia, Chlamydia and viruses. In addition, sections were stained with Gram stain for bacteria and with Grocott's stain for fungi and Pneumocystis carinii (P. Jiroveci), as well as with Ziehl-Neelsen stain for mycobacteria and Nocardia. The results of the stainings were usually available within 3 h after specimen arrival in the laboratory.

RESULTS

Patient characteristics

During the study period, 500 OLBs were performed at our institution, and 12 patients (2.4%) met our study criteria. The mean age was 65 ± 14 years (range, 31-87 years), and 5 of the 12 patients were female. Arterial blood samples for gas analyses revealed a PaO_2/FiO_2 ratio of 157 32 within the first 24 h after the OLB. Prior to surgery, all patients were under invasive mechanical ventilation for 4.5 ± 4.3 days.

Diagnostic results and changes in treatment strategy

The diagnostic results of the OLBs are shown in Table 1, as well as in Figures 1 to 4. All biopsy specimens exhibited abnormalities. At least one specific cause of respiratory failure was found in all cases. The single most common cause was viral infection, which was identified in 5 patients (41.6%). The preoperative diagnosis of the cause of respiratory failure was changed in 11 patients (91.6%). A specific diagnosis was made in 100% of the cases, and treatment strategies were altered based on the OLB results. Change in treatment was defined as the as the addition/subtraction of one or more drugs or the premature discontinuation of advanced life support. Changes in drug treatment regimens typically involved antibiotics or corticosteroids, but also included heparinization and the initiation/discontinuation of antineoplastic

TABLE 1

Open lung biopsy diagnoses and outcomes

Patient	Pre-biopsy diagnosis	Post-biopsy diagnosis	Figure	Outcome
1	Pulmonary ARDS	Viral infection (influenzae/parainfluenzae)	Fig. 1	Death**
2	ALI after chemotherapy	Herpes simplex virus	Fig. 2	Survival
3	ARDS after chemotherapy	Leukemic infiltratio	Fig. 3	Death
4	Pulmonary ARDS	Multiple pulmonary emboli		Survival
5	Pulmonary ARDS	IPF and Klebsiella pneumoniae		Survival
6	ARDS after chemotherapy	Cytomegalovirus pneumonia	Fig. 4	Death**
7	ARDS/abdominal abscess	Sepsis-induced capillaritis/gram-positive infection	Fig. 3	Survival
8	ARDS and malaria	Malaria and Cytomegalovirus pneumonia	Fig. 4	Survival
9	Pulmonary ARDS	Influenza		Death
10	Pulmonary ARDS	Extrinsic allergic alveolitis and tuberculosis		Survival
11	Pulmonary ARDS	IPF/bacterial pneumonia		Death
12	Pulmonary ARDS	Cytomegalovirus pneumonia		Death

**From causes other than acute respiratory failure
ARDS: acute respiratory distress syndrome; ALI: acute lung injury; IPF: idiopathic pulmonary fibrosis

agents for drug-induced toxicity and malignancy, respectively. One patient received antimalarial drugs due to evidence of malaria found at OLB.

Survival

Despite the changes in treatment strategy, the mortality rate was 50%, only 6 patients surviving to be discharged from the hospital. All discharged patients survived for at least 1 year after the OLB, resulting in an overall one-year survival rate of 50% for the 12 patients studied. For those patients dying in the hospital, the time of survival after OLB was 14 + 10.8 days.

Complications

In the post-operative period, two patients presented bronchopleural fistulas. In one of those patients, the fistula was mild and required only prolonged chest tube drainage. The other patient presented a more severe air leak, which impaired alveolar ventilation and required further adjustments in the mechanical ventilation.

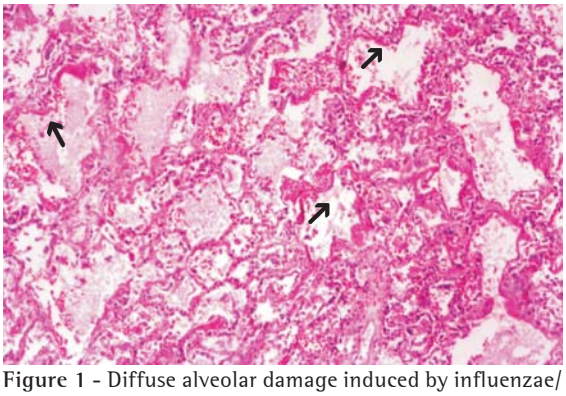

Figure 1 - Diffuse alveolar damage induced by influenzae/parainfluenzae virus: intra-alveolar edema and hyaline membranes (arrows) (H&E X40)

DISCUSSION

Although OLB did provide a specific diagnosis in many patients with diffuse pulmonary infiltrates and ARF, the hospital mortality rate was high in this patient population. Hospital mortality rates from similar but smaller samples of hypoxic immunosuppressed patients undergoing OLB are consistent with our experience, ranging from 57% to 78%.[6, 9-12] In contrast, post-OLB mortality rates reported for immunosuppressed patients on the whole (hypoxic and nonhypoxic) tend to be lower. [13-16] In a study of immunosuppressed patients, Greenman et al.[11] found the mortality rate to be 73% in hypoxic (PaO_2 < 55 mmHg) patients and 39% in nonhypoxic patients. In immunosuppressed patients, Jaffe and Maki[16] found that, in patients undergoing OLB, PaO_2 was significantly higher in those who would survive than in those who would not. Although our study was not designed to evaluate hypoxia as a predictor of mortality in patients undergoing OLB, our hypoxic patients ultimately did not fare well.

Given the high mortality rate, it would be helpful to be able to predict outcome. Poe et al. [12] conducted a retrospective review, attempting to

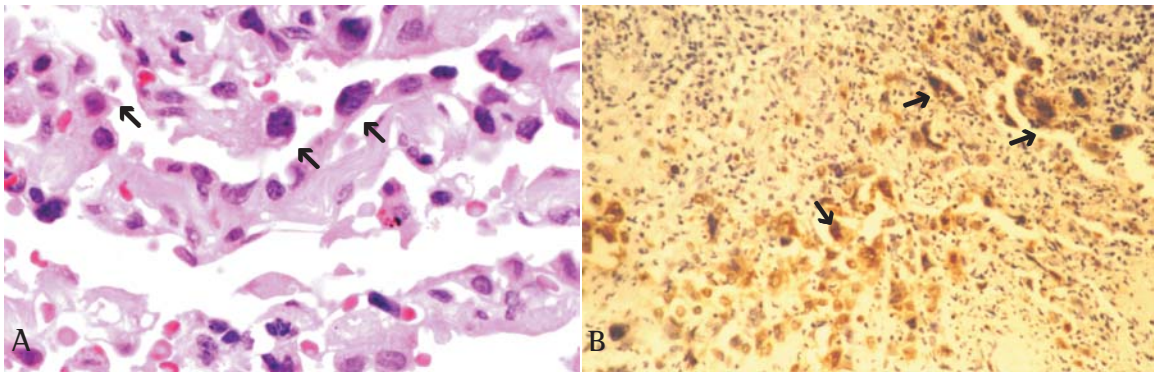

Figure 2 - Diffuse alveolar damage induced by herpes simples vírus. A) Nuclear cytopathic effect in type II pneumocytes (arrows) (H&E, X400). B) Positive immunostaining for antigens of herpes sp (Immunohistochemistry X 200)

predict mortality in immunocompromised patients with pulmonary infiltrates and undergoing either transbronchial biopsy or OLB. The authors found that the need for early mechanical ventilation (within the first 72 h after admission, preoperatively, or for more than 24 h postoperatively), initial room air PaO_2 and corticosteroid therapy at the onset of symptoms were significant predictors of mortality. Of the 8 patients who had a room air PaO_2 of < 50 mmHg, were receiving corticosteroids and required early mechanical ventilation, none survived.

Most investigators feel that mortality in patients undergoing OLB is due to the severity of the underlying disease and is not due to complications related to the surgical procedure.[6-7, 9-10,15] Although this assertion is difficult to prove, none of the complications observed in our study appeared to be the direct cause of death. However, the higher mortality rate in the patients suffering complications, although not statistically significant, suggests that such complications have an impact on patient status. Studies evaluating the impact of OLB complications on outcome should include a unoperated control group. In a prospective, randomized study, OLB was compared to empiric antibiotic therapy for the treatment of acute pneumonitis in 22 non-neutropenic cancer patients, Potter et al.[17] found no significant difference in mortality rates between the two groups. The investigators did feel that the OLB complications experienced by 3 patients (21% of those undergoing OLB) contributed directly to their deaths. Although our patients did not suffer this high rate of catastrophic complications, any complication resulting from a procedure of uncertain benefit is of concern.

Intrathoracic surgery, especially in the hypoxic patient, carries with it the risk of prolonged postoperative mechanical ventilation. Although half of our patients could be extubated postoperatively, 6 patients (50%) were mechanically ventilated until death. It is no known how many of these patients

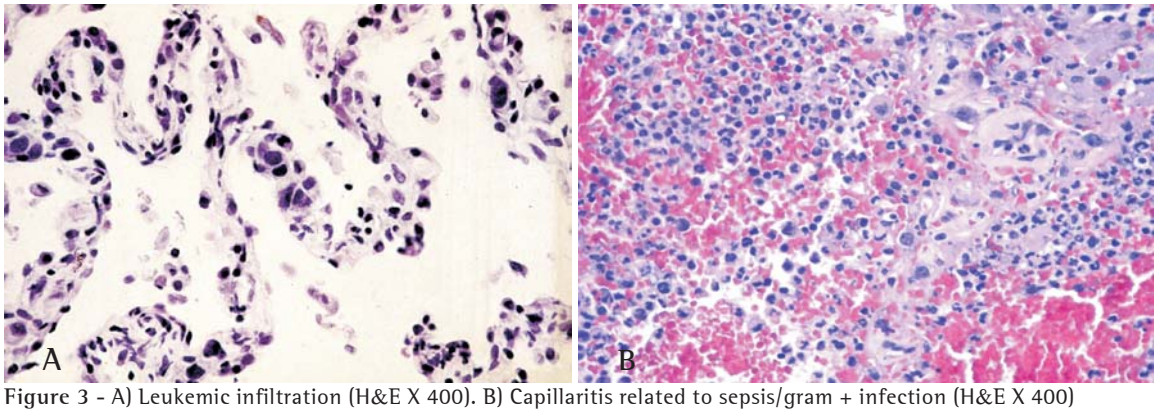

Figure 3 - A) Leukemic infiltration (H&E X 400). B) Capillaritis related to sepsis/gram + infection (H&E X 400)

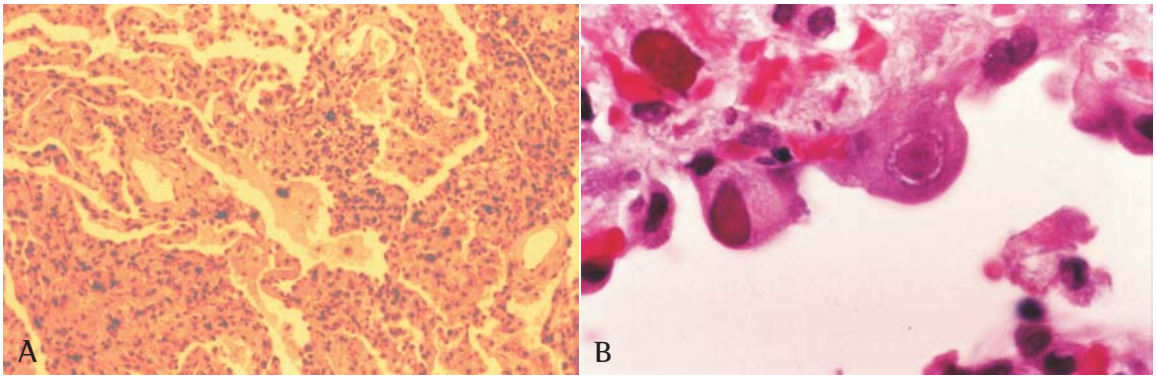

Figure 4 - A) Lung involvement in malaria (H&E X 40). B) Cytomegalovirus pneumonia (H&E X 400)

would have eventually required ventilatory support had OLB not been performed although only one of the patients presented a serious complication (air leak) related to the biopsy.

Our 100% rate of specific diagnoses is higher than those found in studies of OLB involving immunosuppressed patients, which range from 55 to 83%.[6-7, 9-12, 16, 18-20] In many cases, the preoperative diagnosis was erroneous or incomplete. The impact that changes in diagnosis, the making of a specific diagnosis and the subsequent alterations in treatment strategy had on survival is very encouraging, and mirrors the experience of other investigators.[3,17] Delays in diagnosis can account for the fact that the mortality rate for our patients was higher than that presented in the literature, since our study sample included many patients undergoing OLB relatively late in the course of their ARF. Some investigators[16, 21-22] have argued that mortality might have been even greater in the diagnostic group had a diagnosis not been made, a speculation that can be evaluated using our data. In addition, patients without a specific diagnosis might have had less severe diseases and might therefore have been pre-selected for lower mortality.[16] Nevertheless, although OLB is undoubtedly of value in securing or confirming diagnoses, our results suggest that OLB has a positive influence on patient survival rates by informing decisions regarding treatment strategy. Therefore, in cases of ARF, OLB should be performed if, after standard treatment, the minimal invasive diagnosis procedure and evaluation (by pulmonary and intensive care specialists), the patient remains refractory to treatment, requiring invasive mechanical ventilatory support.

When patient benefit is defined by survival, 6 patients (50%), all of whom survived and in whom the OLB findings were judged to be useful in guiding treatment, definitely benefited from the OLB.

In conclusion, OLB can provide a specific, accurate etiologic diagnosis in many patients with diffuse pulmonary infiltrates and ARF when there is no clinical improvement after standard treatment. In addition, OLB can reveal specific diagnoses that require distinct treatment, which could lower the mortality rate for such patients.

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