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AUTOPSY-PROVEN CAUSES OF DEATH IN LUNGS OF PATIENTS IMMUNOCOMPROMISED BY SECONDARY INTERSTITIAL PNEUMONIA

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Terrabuio Junior AA, Parra ER, Farhat C, Capelozzi VL. Autopsy-proven causes of death in lungs of patients immunocompromised by secondary interstitial pneumonia. Clinics. 2007;62(1):69-76.

PURPOSE: To present the more frequent associations found in autopsies of immunocompromised patients who developed secondary interstitial pneumonia as well as the risk of death (odds ratio) in having specific secondary interstitial pneumonia according to the cause of immunocompromise.

METHOD: From January 1994 to March 2004, 17,000 autopsies were performed at Hospital das Clínicas, São Paulo University Medical School. After examining the pathology report review, we selected 558 of these autopsies (3.28%) from patients aged 15 years or more with primary underlying diseases who developed radiologically diffuse infiltrates of the lung during their hospital course and died after secondary interstitial pneumonia (bronchopneumonia, lobar pneumonia, interstitial pneumonia, diffuse alveolar damage, pulmonary recurrence of underlying disease, drug-induced lung disease, cardiogenic pulmonary edema, or pulmonary embolism). Histology slides were reviewed by experienced pathologists to confirm or not the presence of secondary interstitial pneumonia. Statistical analysis included the Fisher exact test to verify any association between histopathology and the cause of immunocompromise; a logistic regression was used to predict the risk of death for specific histological findings for each of the independent variables in the model.

RESULTS: Secondary interstitial pneumonia was histologically represented by diffuse interstitial pneumonitis ranging from mild nonspecific findings (n = 213) to a pattern of diffuse alveolar damage (n = 273). The principal causes of immunocompromise in patients with diffuse alveolar damage were sepsis (136 cases), neoplasia (113 cases), diabetes mellitus (37 cases), and transplantation (48 cases). A high risk of death by pulmonary edema was found for patients with carcinoma of colon. Similarly, in patients with lung cancer or cachexia, A high risk of death by bronchopneumonia (OR = 3.6; OR = 2.6, respectively) was found. Pulmonary thromboembolism was associated with an appreciable risk of death (OR = 2.4) in patients with arterial hypertension. The risk of death was also high in patients presenting hepatic cancer (OR = 2.5) or steroid therapy (OR = 2.4) who developed pulmonary hemorrhage as the histological pattern of secondary interstitial pneumonia . The risk of death by lung metastasis was also elevated (OR = 1.6) for patients that were immunosuppressed after radiotherapy.

CONCLUSION: Patients with secondary immunosuppression who developed secondary interstitial pneumonia during treatment in hospital should be evaluated to avoid death by diffuse alveolar damage**,** pulmonary edema, bronchopneumonia, lung hemorrhage, pulmonary thromboembolism, or lung metastasis. The high-risk patients are those immunosuppressed by hematologic disease; those under steroid treatment; or those with colon or hepatic carcinoma, cachexia, or arterial hypertension.

KEYWORDS: Autopsies. Secondary interstitial pneumonia. Immunocompromised patients. Diffuse alveolar damage.

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INTRODUCTION

Acute pulmonary complications in an immunocompromised host are important causes of death in such pa-

tients. Mortality has been reported to be higher than 40% to 50%, especially in patients who develop diffuse infiltrates.[1,2] Pneumonia of bacterial, viral, or fungal origin is the most frequent complication as a consequence of altered immunological status of the host.[3,4] Nevertheless, an immunocompromised host can develop diffuse radiographic lung infiltrates without evidence of active lower respiratory tract infection,[5–7] a condition that has been named secondary interstitial pneumonia. The differential diagnosis of pulmonary disease in these patients includes infectious pneumonia, recurrence of underlying disease, drug-induced lung disease, diffuse alveolar damage, as well as unrelated processes such as cardiogenic pulmonary edema or pulmonary embolism, or any combination of these.[8–10] Prompt investigation and diagnosis are essential for improving the chances of patient survival.[11,12] Clinical and radiographic findings of acute pulmonary complications in the immunocompromised host are nonspecific,[5-7,13] and computed tomography has been shown to be useful in the assessment of these patients,[5] mainly to assist in guiding biopsy. In this context, the complexity of the clinical presentations turns diagnosis by the clinician into a constant challenge. In spite of recent advances, most types of diagnostic support are still expensive. Not infrequently, the clinician initiates treatment, trying to avoid rapid progression of the disease or more invasive procedures. It is thus important to know the main causes of death in this population to establish correct prophylactic actions, which are the cheaper and more intelligent ways to prevent secondary interstitial pneumonia or the eventual indication for lung biopsy.[14]

The aim of this paper is to present the most frequent associations found in autopsies of immunocompromised patients who developed secondary interstitial pneumonia as well as the risk of death (odds ratio) in having specific secondary interstitial pneumonia according to the cause of immunocompromise.

MATERIALS AND METHODS

Patients and Autopsies: From January 1994 to March 2004, 17,000 autopsies were performed at Hospital das Clínicas, São Paulo University School of Medicine. After examining the pathology report review, we selected 558 of these autopsies (3.28%) from patients aged 15 years or more with primary underlying diseases who developed radiologically diffuse infiltrates of the lung during their hospital course and died after secondary interstitial pneumonia (bronchopneumonia, lobar pneumonia, interstitial pneumonia, diffuse alveolar damage, pulmonary recurrence of underlying disease, drug-induced lung disease, cardiogenic pulmonary edema, or pulmonary embolism). The rapid and fatal clinical course was marked by progressive respiratory failure and did not allow a pathological evaluation of lung biopsies or bronchoalveolar lavage specimens. Complete autopsies were performed in all cases. Tissue samples were taken from all organs, including from each lobe of both lungs. They were immediately fixed in 10% phosphate-buffered formaldehyde solution and embedded in paraffin. Serial sections were cut (3 mm), deparaffinized, and tissues were routinely processed. In all cases, staining with hematoxylin and eosin was done for histological examination, silver stains or mucicarmine for *Pneumocystis* and fungi, Ziehl-Neelsen stain for mycobacterium, and Gram stains for bacteria.

Histopathology: Histology slides from the autopsies were reviewed by experienced pathologists to confirm the presence or not of secondary interstitial pneumonia, according to the following patterns:

- Acute or chronic interstitial pneumonia, defined as a thickened interstitium infiltrated by neutrophils and macrophages (acute) or lymphocytes and plasmocytes (chronic) in uniform temporal appearance;
- Diffuse alveolar damage, defined as interstitial acute inflammation, with edema and neutrophils in uniform temporal appearance and diffuse distribution; alveolar collapse and hyaline membranes are also present.
- Pulmonary recurrence of underlying disease,
- Pulmonary edema, defined as proteinaceous intra-alveolar transudate
- Pulmonary hemorrhage, defined as alveolar spaces containing red cells
- Pulmonary thromboembolism, defined as arterial or venous occlusion by thrombi

Statistical Analysis: First analysis included the verification of association between histopathology and immunocompromise causes and was done using the Fisher exact test. For this purpose, neoplasia cases were stratified according to localization in the pancreas, liver, stomach, esophagus, lung, breast, blood, colon, or nervous system. Transplantation was equally stratified according to the affected organ—in bone marrow, kidney, or liver. We then performed a logistic regression analysis to predict the risk of death for specific histological findings and to estimate the odds ratios for each of the independent variables in the model. We considered results with P values of less than 0.05 to be statistically significant.

RESULTS

Patient gender was 54.3% male and 45.7% female. Patient ages ranged from 15 to 91 years (median 51). The

primary underlying diseases of the 558 patients with diffuse pulmonary infiltrates included cancer (266 cases, 48%), sepsis (266 cases, 48%), transplantation (80 cases, 14%), diabetes mellitus (73 cases, 13%), chemotherapy (46 cases, 8.2%), steroid treatment (40 cases, 7.2%), malnutrition (26 cases, 5%), and radiotherapy (12 cases, 2.2%).

On histological examination, the lungs showed the most evident lesions. Thus, secondary interstitial pneumonia that developed during treatment in the hospital was histologically represented by diffuse alveolar damage**,** primary or metastatic lung cancer, cardiogenic pulmonary edema, and pulmonary thromboembolism. Two hundred and seventy three cases (49%) presented diffuse alveolar damage, 92 (16%) cardiogenic pulmonary edema, 72 (13%) bronchopneumonia, 62 (11%) pulmonary thromboembolism, 40 (7%) pulmonary hemorrhage, and 17 (4%) cases presented primary or metastatic lung cancer (Figure 1).

Among the patients who developed diffuse alveolar damage, we found viral inclusions in 17 cases, all of which were associated with cytomegalovirus; fungi infection in 11 cases, associated with *Aspergillus* sp (n = 9), *Cryptococcus* sp (n = 1), and *Pneumocystis carinii* (n = 1) (Figure 2). Tuberculosis was found in 9 cases of diffuse alveolar damage. The principal causes of immunocompromise in patients with diffuse alveolar damage were sepsis (136 cases), neoplasia (113 cases), diabetes mellitus (37 cases), and transplantation (48 cases). Chemotherapy and radiotherapy were done in 25 and 8 cases, respectively. Twenty-eight patients received steroid treatment, and 24 patients had cachexia. It is important to emphasize that more than 1 type of immunocompromise might be present in the same patient. After comparing all of these associations, we found that the highest risk for dying from diffuse alveolar damage was found in patients with hematological neoplasia or under steroid treatment (Table 1). The same was found for pulmonary edema bronchopneumonia, pulmonary thromboembolism, pulmonary hemorrhage, and primary or metastatic lung cancer. A high risk of death by pulmonary edema was found for patients with carcinoma of colon (Table 1).

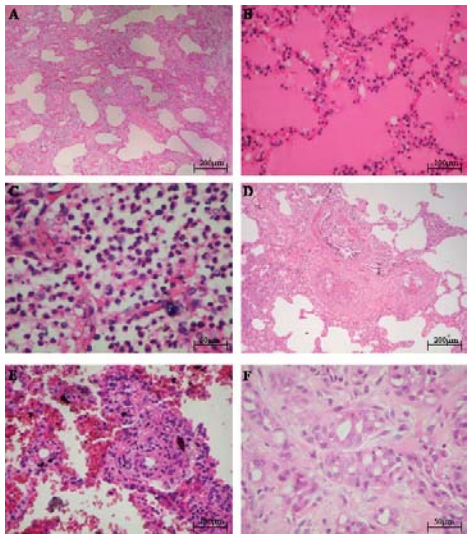

Figure 1 - Secondary interstitial pneumonia / diffuse alveolar damage in immunocompromised patients: (A) diffuse alveolar damage, showing a homogeneous distribution of the inflammatory process and hyaline membranes; (B) cardiogenic pulmonary edema, showing the proteinaceous intra-alveolar transudate; (C) diffuse alveolar damage in patients who developed concomitant bronchopneumonia, showing the numerous neutrophils inside of the alveolar space; (D) pulmonary thromboembolism, showing the significant vascular occlusion; (E) pulmonary hemorrhage, showing alveolar spaces containing red cells; and (F) a case with primary lung cancer. Hematoxylin & eosin X 200 (panels A, D), X 100 (panels B, E), and X 50 (panels C, F).

Table 1 - Results of the logistic regression used to predict the risk of death (odds ratio) in patients with SIP, according to the underlying disease

Variable	B	SE	Wald	Sig	Exp (B)
DAD					
Steroid treatment	1.0229	0.3739	7.4834	0.006	2.7811
Hematological disease	0.6201	0.3014	4.2321	0.03	1.8592
EDEMA					
Colon carcinoma	0.9647	0.5331	3.2755	0.05	2.6241
BCP					
Lung cancer	1.2830	0.5909	4.7139	0.02	3.6075
Caquexia	0.9619	0.4826	3.9724	0.04	2.6167
THROMBOEMBOLISM					
Systemic hypertension	8901	0.4084	4.7516	0.02	2.4355
LUNG HEMORRHAGE					
Hepatic cancer	0.9202	0.5101	3.2540	0.05	2.5098
Steroid therapy	0.8791	0.4025	4.7690	0.02	2.4086
LUNG METASTASIS					
Radiotherapy	0.4934	0.6764	0.5322	0.04	1.6379

SIP = secondary interstitial pneumonia; DAD = diffuse alveolar disease

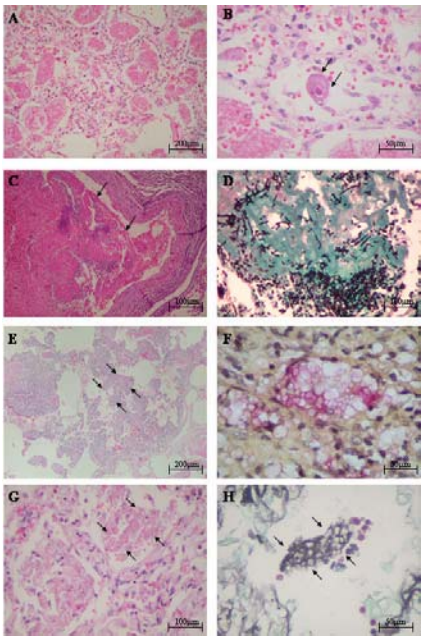

Figure 2 - Histological examination of lungs with diffuse alveolar damage show viral inclusions and fungi infection: (A) diffuse alveolar damage, showing notable amounts of viral inclusions; (B) detail of the cytomegalovirus inclusion (arrows); (C) Fungi infection represented by *Aspergillus* sp. (arrows); (D) detail of numerous *Aspergillus* sp. inside of the alveolar space (stained with silver). (E) diffuse alveolar damage, showing the presences of *Cryptococcus* sp. (arrows); (F) detail of this fungi stained with mucicarmine; (G) Diffuse alveolar damage, showing infection by *Pneumocystis carinii* inside the alveolar space; (F) detail of *Pneumocystis carinii* (arrows) (stained with silver). Hematoxylin & eosin X 200 (panels A, E), X 100 (panels C, G), and X 50 (panel B); Silver stain X 100 (panel D), and X 50 (panel H); Mucicarmine stain X 50 (panel F).

Similarly, in patients with lung cancer or cachexia, the risk of death by bronchopneumonia as determined histologically was high (OR = 3.6; OR=2.6, respectively) . Pulmonary thromboembolism, as determined histologically, was associated with an appreciable risk of death (OR = 2.4) in patients with arterial hypertension. Of interest was the high risk of death for patients with hepatic cancer (OR = 2.5) or steroid therapy (OR = 2.4) who developed pulmonary hemorrhage as the histological pattern of secondary interstitial pneumonia . Equally interesting was the elevated risk of death by lung metastasis (OR = 1.6) for patients that were immunosuppressed after radiotherapy.

DISCUSSION

Conditions that contribute to the requirement for specific histopathological and etiological criteria for definitive diagnosis in patients with immunosuppression are as follows: 1) the nonspecificity of clinical and radiological findings, which are common features for immunosuppressed patients who develop pulmonary involvement during the course of their disease; and 2) co-infections caused by other endemic pathogens in Brazil, such as fungi and tuberculosis.[2,6,16-20] The high cost for special techniques, such as molecular methods, still poses a problem in developing countries.

The above-mentioned considerations prompted us to carry out this study using histopathology of autopsy cases. In doing so, we tried to verify the causes of death in the population of immunocompromised patients who developed secondary interstitial pneumonia .

In this series of adult patients (median age, 51 years), men and women had similar prevalences of secondary interstitial pneumonia . We found that the primary underlying diseases of the 558 patients with diffuse pulmonary infiltrates included cancer (48%), sepsis (48%), transplantation (14%), diabetes mellitus (13%), chemotherapy (8.2%), steroid treatment (7.2%), malnutrition (5%) and radiotherapy (2.2%). A similar distribution was found by Juric et al in 3117 autopsies.[21] They found that the most common causes of death were cardiovascular diseases (40.9%), followed by malignancies (25.2%) and infections (12.9%). Among all cardiovascular diseases, myocardial infarction was the most frequently diagnosed (17.9%) but it should be noted that it was misdiagnosed by clinicians in 16.5% of the cases. Incorrectly diagnosed malignancies were found in only 5.7% of the cases; hematological and lymphoid malignancies (48.8%) were the most common neoplasms and were usually confirmed before death. Infections were found in 46.9% of all autopsies. Bacterial pneumonias and peritonitis were overlooked in 67.5% and 23.5% of the cases, respectively, in which they existed together with another serious condition.

On autopsy, we found that in patients with secondary immunosuppression who developed secondary interstitial pneumonia during treatment in hospital, the lungs were the site with the most evident lesions that were directly responsible by death. These patients died from diffuse alveolar damage**,** primary or metastatic lung cancer, cardiogenic pulmonary edema, or pulmonary thromboembolism.

The most prevalent autopsy finding as cause of secondary interstitial pneumonia in patients with immunosuppression was diffuse alveolar damage, identified in 273 cases. Thus, it is important to emphasize 2 observations made in this study regarding diffuse alveolar damage. The first is the association of this type of damage with patients under mechanical ventilation at the time of death, thus raising the question of whether diffuse alveolar damage could be secondary to mechanical ventilation injury and not related to immunodeficiency. This very important question probably will not be answered by this study because our review was performed on pathologic reports after necropsy, where the information about mechanical ventilation is not is present among the data. With respect to the question of whether dif-

fuse alveolar damage could be secondary to mechanical ventilation injury and not related to immunodeficiency, our answer is yes, because most of the patients undergoing mechanical ventilation already have diffuse alveolar damage. In addition, the morphological pattern of diffuse alveolar damage is different when secondary to barotraumas; in the case of barotrauma, this damage is almost always represented by thin hyaline membranes, while in case of immunodeficiency, all of the diffuse alveolar damage cases presented thicker hyaline membranes and had notable changes in alveolar septae as well as extensive alveolar collapse. Brun-Buisson et al[22] studied the epidemiology and outcome of acute lung injury in European intensive care units (ICUs). They found that acute lung injury occurred in 463 (7.1%) of 6522 admissions and 16.1% of all mechanically ventilated patients; 65.4% cases occurred on ICU admission.

The second important observation about diffuse alveolar damage is the association with infectious etiology represented by fungi, citomegalo, and tuberculosis. Among the fungi, *Aspergillus* sp was the most prevalent. Association between *Aspergillus* and diffuse alveolar damage was similarly found in immunosuppressed patients by other authors.[23–29] Another important association was found between diffuse alveolar damage and citomegalo. In our study, 17 immunosuppressed patients presented diffuse alveolar damage and citomegalo viral inclusions, thus confirming the prevalence of citomegalo in immunosuppressed patients, who are usually very sick patients and are kept in the ICU for long periods; it is possible that in these patients, the diffuse alveolar damage is not secondary to the cytomegalic infection.[30–36]

Diffuse alveolar damage was a prevalent morphological finding in patients immunocompromised by sepsis, neoplasia, diabetes mellitus, or transplantation. As expected, all of these conditions are very prevalent in a series of immunosuppressed patients, probably contributing to their deaths. Diffuse alveolar damage was also a final morphological event in 2 immunosuppressed patients who underwent chemotherapy and radiotherapy but were not undergoing that therapeutic regimen at the time of the death. This finding is very important because if they were under thoracic radiotherapy or under the effects of drugs, the interpretation of the pulmonary findings was completely different, as previously reported by Camus and Rossi.[37,38] Also expected was the prevalence of diffuse alveolar damage as the cause of death in patients with cachexia, which was frequently observed in series of patients with immunodeficiency. However, the highest risk of death by diffuse alveolar damage was found in patients with hematological diseases or under steroid treatment, in agreement with previously reported data.[39-46]

In our study, pulmonary edema was the second most important cause of death, with highest risk for patients with carcinoma of colon. This finding is very similar to that found by Hoelz et al in their study concerning morphometric differences in pulmonary lesions in primary and secondary ARDS.[47]

We found that pulmonary thromboembolism as the morphological pattern for secondary interstitial pneumonia occurred in 11% of patients with arterial hypertension, an appreciable risk of death. Madani et al[48] carried out a retrospective review of all postmortem reports during the period 1991 to 2000 at King's College Hospital, London. They found that during that 10-year period, 16,104 deaths occurred, and 6,833 (42.4%) necropsies were performed. The outcome occurrence, fatal pulmonary embolism, was recorded as cause of death in 265 cases (3.9% of all necropsies; 5.2% of adult cases). No deaths from pulmonary embolism occurred in patients under 18 years of age; 80.0% occurred in patients older than 60 years. Of the fatal emboli, 214 of 265 (80.8%) occurred in patients who had not undergone recent surgery. Of these patients, 110 (51.4%) had suffered an acute medical illness in the 6 weeks before death, most often an acute infectious episode (26 cases).

Of interest in our study was the high prevalence of patients presenting hepatic cancer or steroid therapy who developed fatal pulmonary hemorrhage as the histological pattern of secondary interstitial pneumonia . Parambil et al.[49] studied causes and presenting features of pulmonary infarctions in 43 cases identified by surgical lung biopsy. The underlying cause was identifiable in 31 cases (72%) based on a review of clinical, laboratory, radiologic, and histopathologic data. The 2 most common causes were pulmonary thromboembolism (18 cases, 42%) and pulmonary infections (5 cases, 12%). Thromboembolic pulmonary infarctions typically presented as solitary or multiple nodules located in the subpleural regions. Other causes included diffuse alveolar damage in 2 cases (5%), pulmonary torsion in 2 cases (5%), and 1 case each of lung cancer, amyloidosis, embolotherapy, and catheter embolism. In 12 cases (28%), the underlying cause was not directly identifiable but was probably due to previous pulmonary thromboembolism.

We conclude that patients with secondary immunosuppression who develop secondary interstitial pneumonia during treatment in the hospital should be evaluated to avoid death cause by diffuse alveolar damage**,** pulmonary edema, bronchopneumonia, lung hemorrhage, pulmonary thromboembolism, or lung metastasis. The high-risk patients are those immunosuppressed by hematological disease; who are under steroid treatment; or who have colon or hepatic carcinoma, cachexia, or arterial hypertension.

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RESUMO

Terrabuio Junior AA, Parra ER, Farhat C, Capelozzi VL. Causas de óbito por pneumonia intersticial secundária em autópsias pulmonares de pacientes imunocomprometidos. Clinics. 2007;62(1):69-76.

OBJETIVO: Apresentar as associações mais freqüentes encontradas em autópsias de pacientes imunossuprimidos que desenvolveram pneumonia intersticial secundária bem como o risco de óbito (Odds Ratio) de desenvolver PIS associada à causa da imunossupressão.

MÉTODO: De janeiro de 1994 a março de 2004, 17000 autópsias foram realizadas no Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo. A partir da revisão dos laudos patológicos foram selecionados 558 destas autópsias (3,28%) de pacientes com 15 anos de idade ou mais, com alguma doença de base que desenvolveu um infiltrado pulmonar radiologicamente difuso durante o curso da hospitalização e que depois foi para óbito com pneumonia intersticial secundária (broncopneumonia, pneumonia lobar, pneumonia intersticial, dano alveolar difuso, doença pulmonar recorrente, doença pulmonar induzida por drogas, edema pulmonar cardiogênico e embolismo pulmonar). As lâminas histológicas foram revisadas por patologistas experientes para confirmar ou não a presença de pneumonia intersticial secundária. A análise estatística incluiu o "Teste exato de Fisher" para verificar associação entre a histolopatologia e causa de imunocomprometimento; e regressão logística para predizer o risco de óbito por achados histológicos específicos para cada variável independente do modelo.

RESULTADOS: A pneumonia intersticial secundária foi representada histológicamente por pneumonite intersticial difusa variando de características não especificas leves (n=213) ao padrão histológico de dano alveolar difuso (n=273). A principal causa de imunossupressão nos pacientes com dano alveolar difuso foi sepse (136 casos), neoplasia (113 casos), diabetes melito (37 casos) e transplantados (37 casos). O maior risco de morte por edema pulmonar foi encontrado nos pacientes com carcinoma de cólon. Da mesma forma, nos pacientes com câncer pulmonar ou cachexia ocorreu um alto risco de morte (OR=3.6; OR=2.6, respectivamente) por broncopneumonia. O tromboembolismo pulmonar ofereceu um importante risco de morte (OR=2.4) nos pacientes com hipertensão arterial. Observou-se também risco de morte por câncer hepático (OR=2.5) ou terapia esteroidea (OR=2.4) nos pacientes que desenvolveram hemorragia pulmonar com padrão histológico de pneumonia intersticial secundária. Da mesma forma houve alto risco de morte por metástase pulmonar (OR= 1.6) nos pacientes imunossuprimidos após radioterapia.

CONCLUSÃO: Pacientes com imunossupressão secundária que desenvolveram pneumonia intersticial secundária durante o tratamento dentro do hospital podem ser avaliados para evitar como evento final o dano alveolar difuso, o edema pulmonar, a broncopneumonia, a hemorragia pulmonar, o tromboembolismo pulmonar e a metástase pulmonar. Os pacientes com aumento de risco são aqueles imunossuprimidos por doença hematológica, sob tratamento com esteroides, carcimona hepático, cachexia e hipertensão.

UNITERMOS: Autópsias. Pneumonia intersticial secundária. Pacientes imunocomprometidos. Dano alveolar difuso.

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