Original Article

Diagnosis and prognosis of acute respiratory distress syndrome related to diffuse pneumonic-type adenocarcinoma: a single-center case series study

Maxens Decavèle[1,2,3]^, Antoine Parrot[4], Michaël Duruisseaux[5,6], Martine Antoine[7], Anne Fajac[7], Audrey Milon[8], Marie-France Carette[8], Anthony Canellas[4], Aude Gibelin[1], Alexandre Elabbadi[1], Marie Wislez[9,10], Jacques Cadranel[4], Muriel Fartoukh[1]

[1]Groupe Hospitalier Universitaire APHP-Sorbonne Université, Hôpital Tenon, Service de Médecine Intensive Réanimation, Paris, France; [2]Sorbonne Université, INSERM, UMRS1158 Neurophysiologie Respiratoire Expérimentale et Clinique, Paris, France; [3]Groupe Hospitalier Universitaire APHP-Sorbonne Université, site Pitié-Salpêtrière, Service de Médecine Intensive et Réanimation (R3S), Paris, France; [4]Groupe Hospitalier Universitaire APHP-Sorbonne Université, Hôpital Tenon, Service de Pneumologie et Oncologie Thoracique and GRC-04 Theranoscan Sorbonne Université, Paris, France; [5]Department of Respiratory Medicine, Louis Pradel Hospital, Hospices Civils de Lyon Cancer Institute, France; [6]Cancer Research Center of Lyon, Inserm 1052, CNRS 5286, Oncopharmacology Team, Lyon, France; [7]Groupe Hospitalier Universitaire APHP-Sorbonne Université, Hôpital Tenon, Département d'Anatomie et cytologie pathologiques, Plateforme d'oncologie, Pathologie et biologie moléculaire, Paris, France; [8]Groupe Hospitalier Universitaire APHP-Sorbonne Université, Hôpital Tenon Service de Radiologie, Hôpital Tenon, Paris, France; [9]Université de Paris, Centre de Recherche des Cordeliers, Sorbonne Université, INSERM, Team Inflammation, Complement, and Cancer, Paris, France; [10]Oncology Thoracic Unit Pulmonology Department, AP-HP, Hôpital Cochin, Paris, France

Contributions: (I) Conception and design: M Decavèle, A Parrot, M Duruisseaux, MF Carette, M Wislez, J Cadranel, M Fartoukh; (II) Administrative support: M Decavèle, A Parrot, J Cadranel, M Fartoukh; (III) Provision of study materials or patients: M Decavèle, A Parrot, M Antoine, A Fajac, A Milon, MF Carette, A Gibelin, A Elabbadi, M Wislez, J Cadranel, M Fartoukh; (IV) Collection and assembly of data: M Decavèle, A Parrot, M Duruisseaux, A Gibelin, A Elabbadi, M Wislez, J Cadranel, M Fartoukh; (V) Data analysis and interpretation: M Decavèle, A Parrot, M Duruisseaux, M Antoine, A Fajac, A Milon, MF Carette, A Canellas, J Cadranel, M Fartoukh; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Maxens Decavèle, MD. Groupe Hospitalier Universitaire APHP-Sorbonne Université, Service de Médecine Intensive Réanimation, Hôpital Tenon, 4 rue de la Chine 75020 Paris cedex 20, France. Email: maxens.decavele@aphp.fr.

Background: The absence of diagnosis of acute respiratory distress syndrome (ARDS) concerns 20% of cancer patients and is associated with poorer outcomes. Diffuse pneumonic-type adenocarcinoma (P-ADC) is part of these difficult-to-diagnose ARDS, but only limited data are available regarding critically ill patients with diffuse P-ADC. We sought to describe the diagnosis process and the prognosis of P-ADC related ARDS patients admitted to the intensive care unit (ICU).

Methods: Single-center observational case series study. All consecutive patients admitted to the ICU over a two-decade period presenting with (I) histologically or cytologically proven adenocarcinoma of the lung and (II) ARDS according to Berlin definition were included. Clinical, biological, radiological and cytological features of P-ADC were collected to identify diagnostic clues. Multivariate logistic regression analyses were performed to assess factors associated with ICU and hospital mortality.

Results: Among the 24 patients included [70 (61–75) years old, 17 (71%) males], the cancer diagnosis was performed during the ICU stay in 19 (79%), and 17 (71%) required mechanical ventilation. The time between the first symptoms and the diagnosis of P-ADC was 210 days (92–246 days). A non-resolving pneumonia after 2 (2 to 3) antibiotics lines observed in 23 (96%) patients with a 34 mg/L (19 to 75 mg/L) plasma C-reactive protein level at ICU admission. Progressive dyspnea, bronchorrhea, salty expectoration,

^ ORCID: 0000-0003-3552-5053.

fissural bulging and compressed bronchi and vessels were present in 100%, 83%, 69%, 57% and 43% of cases. Cytological examination of sputum or broncho-alveolar lavage provided a 75% diagnostic yield. The ICU and hospital mortality rates were 25% and 63%, respectively. The time (in days) between first symptoms and diagnosis [odds ratio (OR) 1.02, 95% confidence interval (95% CI): 1.00–1.03, P=0.046] and the Simplified Acute Physiology Score II (OR 1.16, 95% CI: 1.01–1.33, P=0.040) were independently associated with ICU mortality.

Conclusions: Non-resolving pneumonia after several antibiotics lines without inflammatory syndrome, associated with progressive dyspnea, salty bronchorrhea, and lobar swelling (i.e., fissural bulging, compressed bronchi and vessels) were suggestive of P-ADC. Delayed diagnosis of diffuse P-ADC seemed an independent prognostic predictor and disease timely recognition may contribute to prognosis improvement.

Keywords: Intensive care unit (ICU); acute respiratory distress syndrome (ARDS); pneumonic-type adenocarcinoma (P-ADC); broncho-alveolar carcinoma; lung cancer

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Introduction

Acute respiratory failure (ARF) is the leading cause of intensive care unit (ICU) admission in cancer patients (1). Despite recent advances in diagnostic investigations, the cause of ARF remains undetermined in up to 20% of cancer patients with ARF (2,3), even in patients meeting acute respiratory distress syndrome (ARDS) criteria (4). In these patients, failure to identify the cause of ARF is independently associated with increased mortality (3,5) and a delayed diagnosis and subsequent delayed treatment may also have unfavorable impact on prognosis (6).

Malignant lung involvement represents recognized causes of ARDS mimickers (7,8), accounting for 20% of ARDS without common risk factors (8) and up to 30% of unexplained pulmonary infiltrates in cancer patients (9). Likely to occur at the time of the malignancy diagnosis (1), the severity of malignant lung infiltration may range from scarce infiltrate to life-threatening ARDS especially in case delayed diagnosis (10).

Pneumonic-type adenocarcinoma (P-ADC) encompasses heterogeneous mechanisms of cancer-related lung injury that may also progress to malignant ARDS, especially in case of tumor spread through air spaces (diffuse P-ADC) (11). Its association with hypoxemia, chest pain, and sometimes fever makes the diagnosis challenging, mimicking infectious pneumonia (12), and may induce delayed diagnosis and management. Moreover, its treatment and prognosis may be substantially different from those of ARDS with common risk factors. Indeed, in comparison with ARDS of common causes, malignant ARDS has been demonstrated with high risk of ICU mortality (up to 96%) (8) and diffuse P-ADC may benefit from early administration of anti-cancer treatments. Thus, a better understanding of the diagnostic features and the determinants of the outcome of P-ADC patients presenting with ARDS are of major clinical importance, since timely diagnosis and appropriate management may improve the prognosis (13). However, no data are available regarding this type of malignant ARDS when ICU admission is required.

Here, we sought to describe the profile and prognosis of patients admitted to the ICU with diffuse P-ADC related ARDS. The primary objective was to provide the diagnostic clues from the clinical suspicion to the pathological confirmation, based on our clinical experience. The secondary objective was to assess the determinants of ICU and in-hospital mortality. We hypothesized that the diagnosis was delayed in most patients, which was associated with a worse prognosis. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-22-12/rc).

Methods

Study design and setting

This observational case series study was conducted from January 1998 to January 2018 in a 20-bed French medical ICU, part of the thoracic oncology department of Tenon

University Hospital, Paris, France, a medical and surgical reference center. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the French Intensive Care Society Institutional Review Board (CE SRLF 21-23) and informed consent was taken from the patients or their relatives.

Patient selection

Patients were included if they met the three following criteria: (I) admission to the ICU during the study period; (II) histologically or cytologically proven adenocarcinoma of the lung according to the 2011 IASLC/ATS/ERS classification of lung adenocarcinoma (14) and the 2015 WHO classification of lung tumors (11); and (III) presenting with ARDS on ICU admission. The ARDS was defined by (I) a new or worsening respiratory symptoms over the last seven days; (II) bilateral pneumonia-like opacities on chest radiograph or computed tomography scan; (III) the absence of suspected cardiogenic pulmonary edema and of common causes of ARDS; and (IV) a PaO_2/FiO_2 ratio ≤300 mmHg (15). A positive end-expiratory pressure level of at least 5 cmH_2O was not necessary for inclusion.

Patients with a previous history of other thoracic or extra thoracic adenocarcinoma, presenting with ARDS of common causes, or under the age of 18 years were excluded. Concomitant bacterial pneumonia was not an exclusion criterion.

Data collection

Characteristics of the patients

Age, gender, performance status (PS) during the week preceding ICU admission, clinically important weight loss, defined by a >5% loss of usual body weight over the last six months, smoking history and main comorbidities using the Charlson Comorbidity Index were collected for each patient. Symptoms and physical signs on respiratory examination (e.g., dyspnea, cough, bronchorrhea, chest pain) were collected. Physiological variables such as body temperature, respiratory rate, heart rate, systolic arterial blood pressure and Glasgow coma scale were also recorded, as well as main laboratory variables (e.g., arterial blood gas, leukocyte count, C-reactive protein, serum creatinine). Severity on admission was assessed by the Simplified Acute Physiology Score (SAPS) II and the Sequential Organ Failure Assessment (SOFA). Advanced life support measures administered during the ICU stay such as mechanical ventilation (MV) either invasive or non-invasive (NIV), High Flow Oxygen Therapy, vasopressors and renal replacement therapy were also collected. Finally, we recorded ICU- and hospital mortality.

Oncological evaluation

All histological (trans-bronchial biopsy, open-lung biopsy and autopsy) and cytological [sputum examination, bronchial aspirate, broncho-alveolar lavage (BAL)] samples were reviewed by experienced lung pathologist (M Antoine) and cytologist (A Fajac) and histological samples of patients admitted before 2011 were re-classified according to current classifications (11,14). For the BAL procedures we used 50 mL of room temperature, sterile 0.9% saline injected via handheld 50 mL syringe, this repeated 4 times to reach a total of 200 mL instilled in the lungs. The cancer diagnosis could be confirmed based on cytological analysis (e.g., BAL), only if at least one agglomerate of neoplastic cells forming typical cytological features of P-ADC was identified. Details on pathological definitions are available in the Appendix 1. Patients were classified as already diagnosed or newly diagnosed P-ADC, depending on whether cancer had been diagnosed before ICU referral or during ICU stay. Molecular testing (i.e., cancer biomarkers) was also collected, when performed. Staging was recorded according to the current TNM Classification System for lung cancer (16). Finally, anticancer treatment (chemotherapy, high doses of corticosteroids) administered during the ICU stay was also collected.

Radiological evaluation

Radiologic characteristics were assessed by an independent radiologist expert (MF Carette). Main CT findings, including (I) normal attenuation, (II) ground-glass attenuation, (III) alveolar consolidation and (IV) crazy paving were quantitatively measured, using a CT-scan extent score (17). Briefly, each lung was divided in three zones, i.e., upper, middle, and lower. Then, the percentage of lung parenchymal surface represented by each pattern was estimated in each six zones (3 right, 3 left). Finally, the average score of the six lung zones was calculated (adding each zone score, divided by 6).

Statistical analysis

Continuous variables are expressed as median (0.25–0.75 interquartile range) and categorical variables are expressed as absolute and relative frequency (%). Each potential

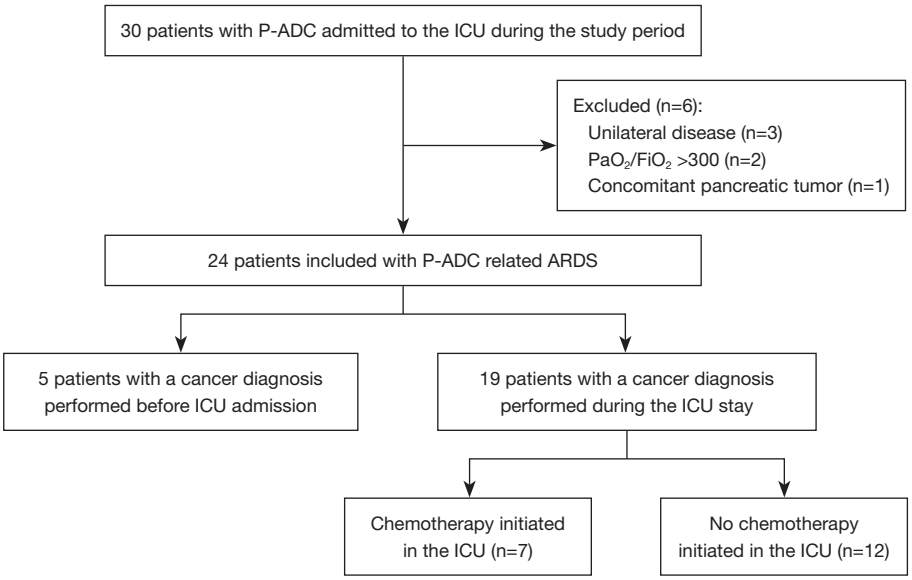

Figure 1 Flowchart. P-ADC, pneumonic-type adenocarcinoma; ICU, intensive care unit; ARDS, acute respiratory distress syndrome.

factor associated with ICU or hospital mortality was evaluated in a univariate model. Variables were compared with Mann-Whitney test for quantitative variables and chi-square test or Fisher exact test for qualitative variables. All tests were two-sided and P values <0.05 were considered statistically significant. Because of the small sample size, a maximum of three variables identified with a P value less than 0.20 in univariate analyses, and/or clinically relevant (including time between first symptoms and diagnosis—the tested hypothesis) were included in a multivariate logistic regression model. The final models were determined using a forward stepwise logistic regression. The Hosmer-Lemeshow Chi-square test was used to check the goodness-of-fit of the final model. Odds ratios (ORs) and their 95% confidence intervals (CI) were calculated for significant factors. Because SAPS II and SOFA scores are highly correlated, SOFA was not entered in the models. Missing data (less than 1%) were not imputed. Statistical analysis was performed with SPSS Base 21.0 statistical software package (SPSS Inc., Chicago, IL, USA).

Results

The flowchart of the study is represented in the *Figure 1*. During the study period, 24 patients with P-ADC related ARDS were referred to our ICU and thus included. These admissions resulted in transfer from the respiratory wards (n=13; 54%), the emergency services (n=6; 25%) or other ICUs (n=5; 21%).

Patient's characteristics

All the patients had a confirmed diagnosis of adenocarcinoma, all TNM staged M1a. The diagnosis was based on the examination of histological samples in 16 (67%) patients (13 trans-bronchial biopsies, 2 open-lung biopsies and 1 lung resection specimen) divided in 9 invasive mucinous adenocarcinoma (IMA) and 7 lepidic predominant adenocarcinoma (LPA). For the eight (33%) remaining patient without histological specimen, the diagnosis of adenocarcinoma was based on cytological analysis of BAL. More details on pathological findings are available in Table S1. The main characteristics of the 24 patients are displayed in *Table 1* and Table S2. The diagnosis of cancer was established during the ICU stay in 19 (79%) patients, 1 (1 to 4) day after ICU admission. For the remaining 5 (21%) patients, the diagnosis was established prior to ICU admission, a median of 2 (0.5–4) months before admission.

Bedside diagnostic reasoning process: from the clinic-radiological suspicion to the quick cytological examination

Main clinical, biological, radiological and cytological diagnostic features of the 24 patients are reported in *Table 2*. Eighteen (75%) had a smoking history (9 active smokers on ICU admission), with a cumulative consumption of 38 (15

Table 1 Univariate analysis: factors associated with ICU mortality

Variables	All (n=24)	ICU mortality		P value
		Non-survivors (n=6)	Survivors (n=18)	
Age (years)	70 (61–75)	71 (67–77)	69 (60–75)	0.42
Gender (male), n (%)	17 (71)	4 (67)	13 (72)	1
Performance status 3–4, n (%)	9 (38)	2 (33)	7 (39)	1
Charlson comorbidity Index	6 (6–7)	6 (6–7)	6 (6–7)	0.99
Time from first symptoms to diagnosis (days)	210 (92–246)	234 (199–413)	155 (88–244)	0.047
Never received anticancer treatment*, n (%)	8 (33)	1 (17)	7 (39)	0.621
Severity assessment on ICU admission				0.04
SAPS II	41 (33–46)	48 (41–56)	36 (31–44)	0.094
SOFA score	3 (2–4)	4 (3–5)	2 (3–4)	–
ARDS severity, n (%)				0.06
Mild	6 (25)	2 (33)	4 (17)	
Moderate	5 (21)	2 (33)	3 (13)	
Severe	13 (54)	2 (33	11 (45)	
Physiological variables on ICU admission				
Systolic blood pressure (mmHg)	129 (105–138)	125 (104–138)	131 (98–140)	0.86
Respiratory rate (cycles/min)	26 (24–30)	44 (34–48)	26 (23–28)	0.004
Heart rate (beats/min)	95 (88–114)	121 (111–129)	93 (85–107)	0.015
Temperature (°C)	37.5 (37.0–38.0)	37.6 (35.0-38.5)	37.5 (37.0–38.0)	0.782
Laboratory variables on ICU admission				
Leukocyte count (10^9/L)	12.3 (8.3–18.9)	12.5 (12.4–21.7)	11.4 (7.7–16.5)	0.121
C-reactive protein (mg/L) (on 21 patients)	34 (14–75)	58 (21–93)	32 (8–77)	0.512
Serum creatinine (µmol/L)	73 (66–93)	83 (63–147)	68 (65–93)	0.613
pH on arterial blood gas	7.43 (7.40–7.44)	7.37 (7.33–7.41)	7.44 (7.41–7.44)	0.01
Total BAL cell count (10^3/mL)	520 (240–900)	630 (160–840)	480 (255–952)	0.864
BAL neutrophil count (10^3/mL)	289 (79–614)	100 (64–563)	300 (54–782)	0.522
Radiological assessment on ICU admission				
Alveolar consolidation extent score	18 (12–43)	45 (13–58)	17 (12–28)	0.321
Normal lung extent score	48 (33–63)	37 (32–58)	52 (34–66)	0.513
Mediastinal lymphadenopathy, n (%)	3 (13)	2 (33)	1 (6)	0.133
Life supporting interventions, n (%)				
Mechanical ventilation	17 (71)	6 (100)	11 (61)	0.134
Non-invasive ventilation only	6 (25)	2 (33)	4 (22)	0.621
Vasopressors	4 (17)	2 (33)	2 (11)	0.257

Data are expressed as number and percentage [n (%)] for categorical variables, and median (interquartile interval) for continuous variables. *, impossibility to dispense anticancer treatment at any time before, during or after ICU discharge. ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; ARDS, acute respiratory distress syndrome; BAL, broncho-alveolar lavage.

Table 2 Specific clinical, biological and radiological features at the time of diagnosis of diffuse P-ADC

Variables	Values
Physical examination features, n (%)	
Dyspnea	24 (100)
Cough	20 (83)
Bronchorrhea	20 (83)
Salty expectoration on 13 patients	9 (69)
Crackles on auscultation	12 (50)
Significant weight loss	10 (42)
Fever	6 (25)
Chest pain	2 (8)
Hemoptysis	1 (4)
Clubbing	1 (4)
Biological features	
Leukocyte count (10^9/L)	12.3 (8.3–18.9)
C-reactive protein (mg/L) on 21 patients	34 (19–75)
Procalcitonin (ng/mL) on 15 patients	0.11 (0.09–0.94)
Serum lactate dehydrogenase (IU/L) on 21 patients	412 (285–645)
Arterial lactate (mmol/L)	1.2 (0.9–1.5)
Serum creatinine (µmol/L)	72 (65–92)
CT-scan radiological features (on 22 patients), n (%)/lung extent score (%)	
Alveolar consolidation	20 (95)/18 (12–43)
Ground-glass attenuation	19 (90)/10 (5–23)
Crazy paving	6 (29)/0 (0–2)
Bronchogram within consolidation	19 (90)
Fissural bulging	12 (57)
Compressed bronchus and vessel	9 (43)
Nodules/micronodules	12 (57)
<10	4 (33)
10–30	5 (42)
>30	3 (2)
Cyst/cavitation	8 (38)
Broncho-alveolar lavage features (on 22 patients), cell count (10^3/mL)/cell proportion (%)	
Total cell count	520 (240–900)
Neutrophil	289 (79–614)/64 (41–85)
Macrophage	141 (35–272)/20 (11–53)
Lymphocyte	11 (2–39)/4 (2–5)
Eosinophil	0 (0–11)/0 (0–2)

Data are expressed as number and percentage (n, %) for categorical variables, and median (interquartile interval) for continuous variables. P-ADC, pneumonic-type adenocarcinoma; CT, computed tomography.

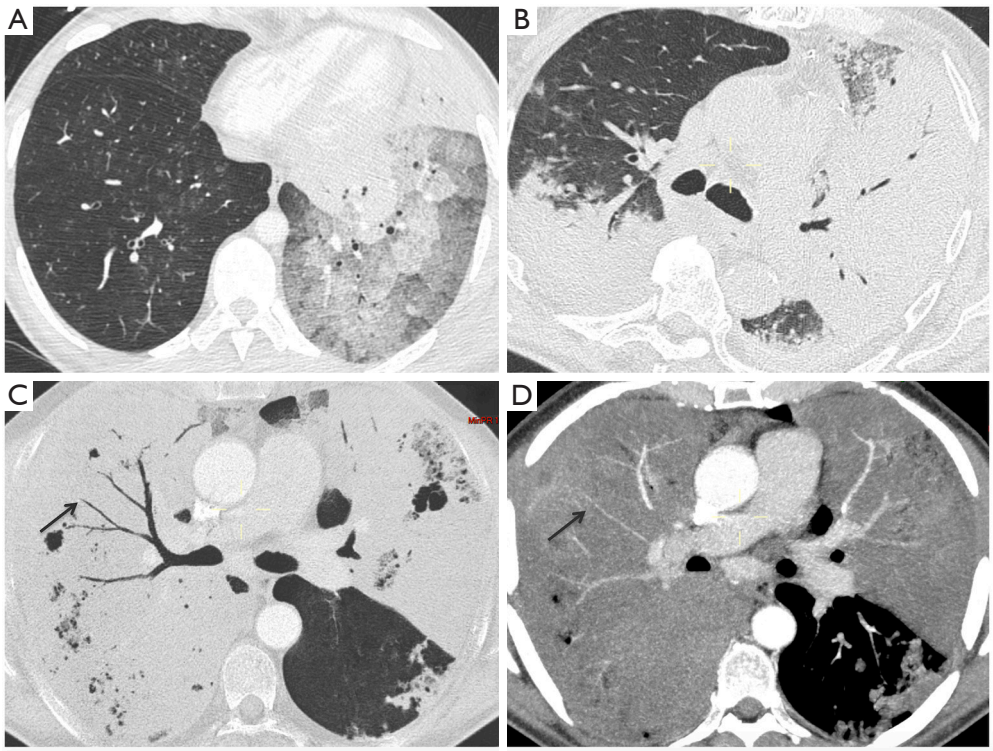

Figure 2 Main radiological features of ARDS related to diffuse P-ADC. (A) Intravenous contrast chest CT-scan shows ground glass attenuation predominant in the left lower lobe. (B) Intravenous contrast chest CT-scan shows bilateral and dense alveolar consolidation predominant in the left lung. (C) Parenchymal window: intravenous contrast chest CT-scan (MipPR: 10.0 mm) and (D) mediastinal window: injected chest CT-scan (MipPR: 10.0 mm) represent respectively the particular pattern of compressed bronchus (black arrow) and compressed pulmonary artery (black arrow) in a same patient, within a dense alveolar consolidation. We also note the presence of cavitation within the consolidation. ARDS, acute respiratory distress syndrome; P-ADC, pneumonic-type adenocarcinoma; CT, computed tomography.

to 48) pack-year.

Clinical and biological features

At the time of diagnosis, all except one patient, presented with a clinical picture of a non-resolving pneumonia for which they had received 3 (2 to 3) antibiotic lines. Most patients presented with isolated respiratory failure. No patients had consciousness disorders. Vasopressors were required in 4 patients (all received also mechanical ventilation). Laboratory tests revealed a mild biological inflammatory syndrome.

Radiological features

Alveolar consolidation and ground glass opacities were the two most frequent and extended radiological patterns (*Figure 2*), with several patterns coexisting in some patients. When present, fissural bulging was associated in 75% of cases (9 of 12 patients) with a particular aspect of compressed bronchi and vessels (*Figure 2*). Mediastinal lymphadenopathy, pleural effusion, atelectasis, pulmonary embolism, interlobular thickening were less frequent and encountered in 3 (13%), 5 (24%), 4 (19%), 2 (10%) and 5 (24%) patients, respectively. Right lower lobe was the most affected lobe in 9 (43%) cases, followed by the left lower lobe in 7 (33%) cases. All these lesions resulted in a remaining lung speared area extent of 48% (33–63%). Repeated CT-scans over time were available in three patients, providing information on natural dynamic expansion of the disease (Figure S1).

Cytological diagnostic challenge and expertise

Fiberoptic bronchoscopy found abundant clear secretions, mucosa inflammation and infiltration in 96%, 36% and 22% of cases, respectively. BAL showed a marked hyper

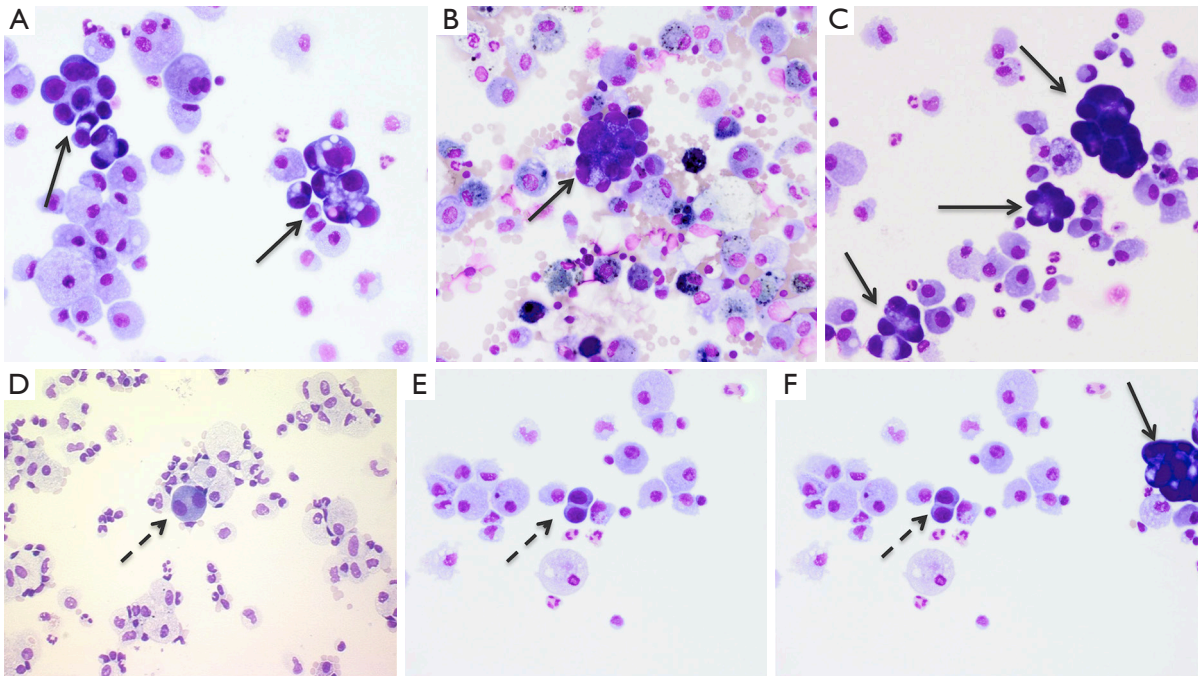

Figure 3 Cytological features of P-ADC and confounding aspects with diffuse alveolar damage (with color): BAL samples (May-Grünwald Giemsa, ×400). (A-C) Different patients with agglomerated (morula) neoplastic cell (full arrows), forming typical cytological features of former broncho-alveolar carcinoma including clean background, absence of 3-dimensional clusters, neoplastic cells in flat sheets, orderly arrangement with round uniform nuclei, absence of nuclear overlap, absence of irregular nuclear membranes, fine granular chromatin, and nuclear grooves (18). (D-F) Cytological pitfall for the diagnosis of broncho-alveolar carcinoma because of its resemblance with cytological alveolar damage. Panel D (A.F courtesy) represents typical agglomerate of (desquamated) type 2 pneumocytes (dotted arrow) in a patient with alveolar damage (ARDS), which could be perceived as similar to the cytological finding in the Panel E (dotted arrow). However, Panel E corresponds to the BAL findings of a patient with P-ADC, as the presence of a typical neoplastic cell agglomerate of broncho-alveolar carcinoma (full arrow) can be observed in an enlarged view of the same picture (Panel F). P-ADC, pneumonic-type adenocarcinoma; BAL, broncho-alveolar lavage; ARDS, acute respiratory distress syndrome.

cellularity with neutrophil predominance, and confirmed the diagnosis in 17 of 23 patients (74% diagnostic yield), exhibiting agglomerated neoplastic cells (*Figure 3A-3C*). Interestingly, among the 3 patients transferred from other ICUs who underwent a BAL before being referred to the ICU, local cytologist reported the presence of desquamated type II pneumocytes in 2 cases, and wrongly concluded to the diagnostic of diffuse alveolar damage (DAD). Mere sputum cytological examination was performed in seven patients with bronchorrhea, and provided the diagnosis in 5 (71%) patients. More details on diagnostic procedure yields are available in Table S3.

ICU and in-hospital mortality

ICU and in-hospital mortality rates were 25% and 63%, respectively. Lengths of ICU and hospital stays were 9 (5 to 15) and 20 (9 to 39) days, respectively. Factors associated with ICU and hospital mortality, identified in univariate analysis, are shown *Table 1* and Table S4 respectively.

Multivariate analysis of factors associated with ICU and hospital mortality are reported in *Table 3*. More details about the variables selected, and the goodness-of-fit of the models are available in Appendix 2. Neither the type of P-ADC (IMA or LPA) nor the mucinous feature was associated with ICU (P=0.68 and P=0.46 respectively) or in-hospital (P=0.68 and P=0.46 respectively) mortality.

Sub-group of newly diagnosed patients

Among the 19 newly diagnosed patients with P-ADC, 7

Table 3 Multivariate analysis of factors associated with ICU and hospital mortality

Variables	Prediction model of ICU mortality		Prediction model of hospital mortality	
	OR (95% CI)	P value	OR (95% CI)	P value
Time between first symptoms and diagnosis (per day)	1.02 (1.00–1.03)	0.046	–	ns
SAPS II (per point)	1.16 (1.01–1.33)	0.040	–	–
Need for mechanical ventilation	–	ns	–	–
Heart rate (per point)	–	–	1.07 (1.00–1.15)	0.041
Impossibility to dispense chemotherapy at any time after diagnosis of the cancer	–	–	17.57 (1.19–254.48)	0.041

Dashes signifies that the variable has been proposed but excluded from the stepwise procedure. ICU, intensive care unit; OR, odds ratio; CI, confidence interval; SAPS, Simplified Acute Physiology Score; ns, no statistical significance.

(37%) received chemotherapy in the ICU in combination with high-dose steroid therapy (Table S2). The patients presenting with fever or biological inflammatory syndrome were more likely to not receive chemotherapy during their ICU stay (*Table 4*). The initiation of chemotherapy in the ICU was not associated with better ICU (P=1.0) or in-hospital (P=0.382) survival.

Discussion

To the best of our knowledge, this is the first series of P-ADC related ARDS patients admitted to the ICU.

Main results can be summarized as follows: in patients admitted to the ICU with an ARDS related to diffuse P-ADC, (I) the clinical diagnosis was suspected by specific clinical, biological and radiological features after several lines of antimicrobial therapies and a prolonged care-pathway, (II) the diagnosis was finally confirmed by mere cytological examination of sputum or BAL in 75% of the cases, (III) the diagnosis was markedly delayed in most of cases, and (IV) this delay was independently associated with ICU mortality.

Clinical suspicion of P-ADC related ARDS: synthesis and comparison with existing data

Faced with a clinical situation of ARDS mimickers or non-resolving pneumonia, the present study provides various elements suggestive of the diagnosis of P-ADC-related ARDS. Firstly, the high incidence of bronchorrhea observed in P-ADC with ARDS, contrasting with the 5–10% incidence observed in P-ADC without ARDS presentation (19), is in line with the fact that bronchorrhea is a late manifestation more likely to be observed in advanced or delayed diagnosed diffuse disease (20). Secondly, the salty taste of the bronchorrhea has been previously reported (21), and is highly specific to P-ADC related bronchorrhea. It is explained by an increased trans-epithelial chloride secretion (22,23), and an excessive transudation of plasma products into the airways (21,23) resulting in a broncho-alveolar mucus osmolality similar to that of plasma (20). Thirdly, nodules, fissural bulging and narrowed bronchus within consolidation at CT-scan were particularly frequent. These three signs have been demonstrated as helpful in differentiating P-ADC from infectious pneumonia (24). The proportion of pseudocavitation observed in our study is also similar to that reported in P-ADC (25). Fourthly, the mild biological inflammatory syndrome observed in our study is in contrast with that expected in patients with infectious pneumonia and should also evoke P-ADC. Finally, the high diagnostic yield of cytological examination (sputum, bronchial aspirate or BAL,) in P-ADC has been reported in different series (26-28), and relies on the identification of agglomerated neoplastic cells (type II pneumocytes or Clara cells) with specific cytological features (18).

However, the identification of such agglomerated neoplastic cells conceals an important diagnostic pitfall. Indeed, diffuse alveolar damage, the pathological hallmark of ARDS, is also characterized by type II pneumocytes proliferation (29), that has been qualified as reactive (30), atypical (31) hyperplasic (32) or desquamated (33) type II pneumocytes. In some cases, and as illustrated in the *Figure 3D-3F*, these cells shed in agglomerates (30-32) with an increased nuclear-cytoplasmic ratio, nuclear membrane irregularities, and prominent nucleoli, thus resembling

Table 4 Characteristics of patients with newly diagnosed P-ADC related ARDS (n=19), receiving or not chemotherapy in the ICU

Variables	Chemotherapy (n=7)	No chemotherapy (n=12)	P value
Gender (male), n (%)	4 (57)	10 (83)	0.352
Age (years)	72 (61–74)	72 (65–76)	0.316
Performance status 3–4, n (%)	1 (14)	6 (50)	0.171
Clinical, laboratory and radiological variables			
Significant weight loss, n (%)	1 (14)	6 (50)	0.174
Temperature (°C)	36.6 (35.9–37.0)	37.5 (37.4–38.4)	0.042
Presence of molecular alterations, n (%)	2 (25)	3 (38)	0.675
Normal lung extent score (%)	52 (37–53)	63 (2–68)	0.492
Serum level of C-reactive protein (mg/L)	8 (6–16)	39 (33–70)	0.007
Presence of bacteria in LRT sample*	1 (14)	4 (33)	0.604
Severity assessment			
SAPS II	36 (34–44)	39 (32–48)	1
SOFA score	4 (2–5)	3 (2–3)	0.445
Severity of the ARDS, n (%)			0.427
Mild	5 (71)	6 (50)	
Moderate	0 (0)	4 (33)	
Severe	2 (29)	2 (17)	
Life supporting interventions, n (%)			
Mechanical ventilation	5 (71)	7 (58)	0.662
Vasopressors	2 (29)	1 (8)	0.526
ICU mortality	1 (14)	2 (17)	1
Hospital mortality	3 (43)	8 (67)	0.381

Data are expressed as number and percentage (n, %) for categorical variables, and median (interquartile interval) for continuous variables. *, at significant threshold: $>10^4$ cfu/mL for broncho-alveolar lavage and $>10^3$ cfu/mL for plugged telescopic catheter. P-ADC, pneumonic-type adenocarcinoma; ARDS, acute respiratory distress syndrome; LRT, lower respiratory tract; ICU, intensive care unit; SAPS, Simplified Acute Physiology Score; SOFA, Sequential Organ Failure Assessment; Cfu, colony forming unit.

the cells of adenocarcinoma (32,34). For instance, several of our diffuse P-ADC patients had been misdiagnosed as "common" ARDS before ICU referral, highlighting the crucial cooperation between clinicians and cytologists in the diagnosis process. The *Figure 4* provides a pictured summary of these main diagnostic features that intensivists should know about diffuse P-ADC mimicking ARDS.

Outcomes: comparison with existing data

The 63% hospital mortality observed in our study seemed substantially higher than the 36% hospital mortality observed in a cohort of 446 lung cancer patients requiring ICU admission for mixed medical and surgical reasons (35). However, this mortality bordered on the 54% hospital mortality of patients with lung cancer admitted for medical reasons (mostly acute respiratory failure) (36) and reached that observed in 1,004 cancer patients with ARDS criteria (64%) (4). In line with previous reports on cancers patients presenting with ARF (3,5,6,10) our results showed that the time between first symptoms and diagnostic was independently associated with ICU mortality even after adjustment on severity. Pragmatically, a subsequent timely initiated chemotherapy may explain this association. This

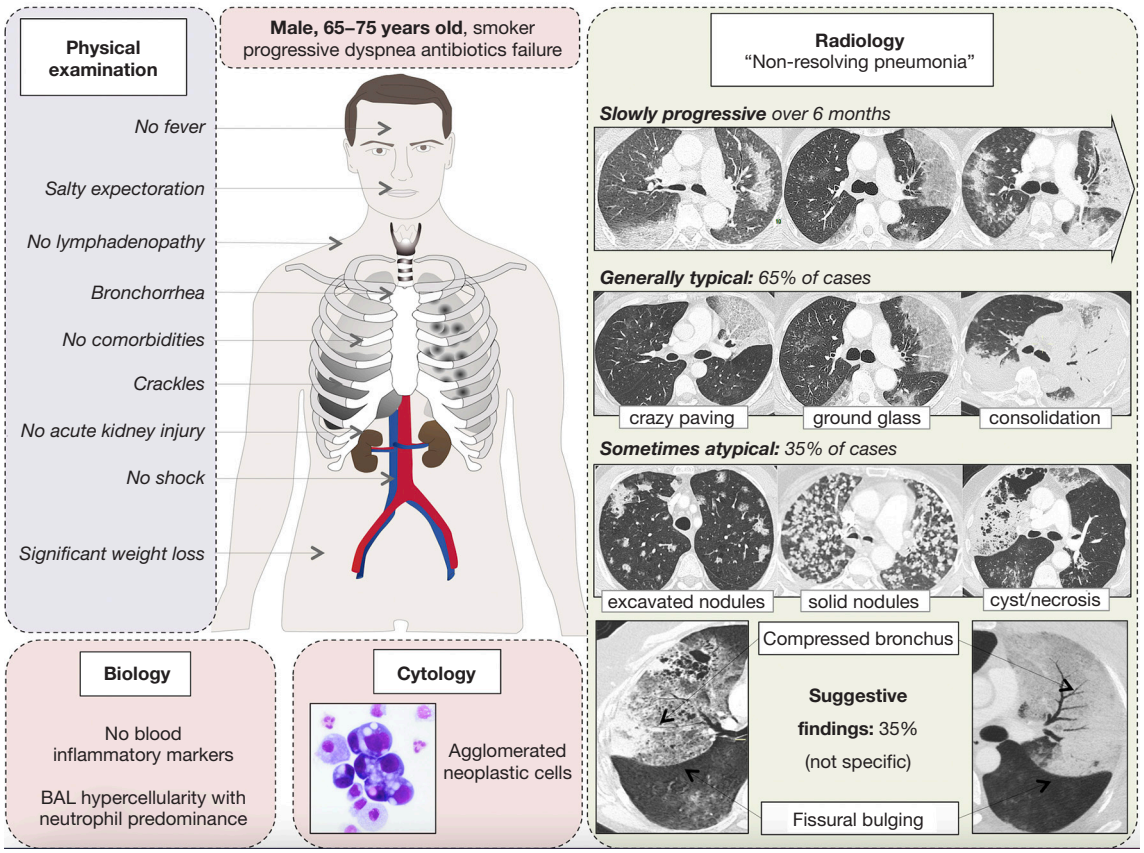

Figure 4 Pictured summary of the study. Delayed diagnosis of diffuse P-ADC is associated with mortality. Timely recognition is crucial but challenging, mimicking infectious ARDS. P-ADC, pneumonic-type adenocarcinoma; BAL, broncho-alveolar lavage; ARDS, acute respiratory distress syndrome.

is striking information for clinical practice regarding the possibility of reducing this delay with a better recognition of the key disease features. The positive influence of chemotherapy maintenance after ICU discharge on survival observed in our study, and reported by others (35,36), may supports a substantial efficacy of chemotherapy in these patients. Thus in the area of promising new therapies (targeted therapy, immunotherapy) (26,37) and the high prevalence of genomic molecular alteration in these patients (26,27,38), especially Kirsten rat sarcoma viral oncogene homolog (KRAS) mutation (39) (33% of KRAS mutation in our study), delay the initiation of chemotherapy seems particularly unsuitable for these patients. Interestingly, the decision to not continue or initiate chemotherapy during the ICU stay was certainly influenced by the suspicion of infection in a patient (higher body temperature and C-reactive protein plasma levels in patients without chemotherapy during the ICU stay).

Limitations

First, this was a retrospective study, which involves a potential bias in patients' selection or data collection, and the small number of subjects limited the performance (discrimination) and thus the interpretation of the multivariate analyses. However, the rarity of the disease remains a major obstacle to prospective or large sample-size studies, even with a multicenter design. Second, we did not compare P-ADC related ARDS patients with other type of ARDS with alveolar consolidation such as community-acquired pneumonia, since clinical, biological and radiological patterns of community acquired pneumonia are well documented. Third, we only considered patients admitted to the ICU. Patients who were not considered for ICU admission for any reason, such as an estimated poor prognosis or a poor performance status, were therefore not included in this analysis.

Conclusions

A rigorous physical, biological, radiological examination should raise a strong suspicion of P-ADC in patients presenting with atypical ARDS. Close collaboration with cytologist is the cornerstone of the diagnosis confirmation. Besides improvement in timely diagnostic recognition, further studies are warranted to test the benefits of high dose corticosteroids and specific anticancer therapy in these patients.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the French Intensive Care Society Institutional Review Board (CE SRLF 21-23). Informed consent was taken from the patients or their relatives.

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Appendix 1

Pathological definitions of P-ADC

P-ADC confirmation based on histological specimen

Former diffuse bronchiolo-alveolar carcinoma (BAC) histologically diagnosed before 2011 were re-classified into either invasive mucinous adenocarcinoma (IMA) or adenocarcinoma with predominant lepidic pattern (LPA), according to the current classification (11,14).

P-ADC confirmation based on cytological specimen

In the absence of histological specimen, the association of a typical former BAC cytological pattern (28) with a highly suggestive clinico-radiological presentation was sufficient to confirm the diagnosis of former diffuse BAC (29,40-45). The typical cytological pattern comprised including clean background, absence of 3-dimensional clusters, neoplastic cells in flat sheets, orderly arrangement of cells with round uniform nuclei, predominance of mucinous cells, absence of nuclear overlap, absence of irregular nuclear membranes, fine granular chromatin, and nuclear grooves (28). When possible, cytological samples were analyzed to distinguish the mucinous and non-mucinous feature (Periodic Acid Schiff/diastase and Blue Alcian).

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Table S1 Pathological findings of the 24 patients

N	Histology	Description	Invasion	Diagnosis	Cytology	PAS+	AB+	Mucinous+
1	–	–			BAL			
2	TBB	Mucinous adenocarcinoma	Yes	IMA		–	–	Yes
3	Autopsy	Mucinous adenocarcinoma	Yes	IMA		–	–	Yes
4	–	–			BAL			
5	TBB	Adenocarcinoma with lepidic growth pattern, non-mucinous predominance	No	ALP		–	–	No
6	TBB	Mucinous adenocarcinoma with inflammatory stroma reaction	Yes	IMA				Yes
7	TBB	Adenocarcinoma	No	ALP		–	–	–
8	TBB	Adenocarcinoma mucinous and non-mucinous with lepidic growth pattern, preserved architecture	No	ALP		–	–	Yes
9	–	–	–	–	BAL	Yes	–	Yes
10	–	–	–	–	BAL	No	No	No
11	TBB	Adenocarcinoma with lepidic growth pattern. Columnar epithelial cells, which line up along the alveolar septa, forming a uni-laminate coating which projects into the alveolar spaces forming fingered papillary structures.	No	ALP				No
12	–	–	–		BAL	No	–	No
13	TBB	Mucinous adenocarcinoma	Yes	IMA	–	–	–	Yes
14	–	–	–		BAL	–	–	ND
15	TBB	Mucinous adenocarcinoma with papillary invasion component	Yes	IMA	–	–	–	Yes
16	TBB	Non-mucinous adenocarcinoma with minimal acinar invasion and lepidic growth pattern	No	ALP	–	–	–	No
17	OLB	Mucinous and non-mucinous adenocarcinoma with micro papillary invasion	Yes	IMA	–	–	–	Yes
18	–	–	–		BAL	–	–	ND
19	TBB	Mucinous adenocarcinoma	Yes	IMA	–	–	–	Yes
20	TBB	Mucinous adenocarcinoma with modified multi–laminate architecture, minimal lepidic growth pattern, papillary invasion	Yes	IMA	–	–	–	
21	TBB	Adenocarcinoma with lepidic growth pattern, non-mucinous predominance	No	ALP	–	–	–	No
22	OLB	Mucinous adenocarcinoma with acinar invasion	Yes	IMA	–	–	–	Yes
23	TBB	Adenocarcinoma, micro–papillary architecture, non-mucinous	No	ALP	–	–	–	No
24	–	–	–		BAL	No	No	No

PAS+, periodic acid Schiff positive; AB+, Alcian blue positive; Mucinous+, mucinous positive; BAL, broncho-alveolar lavage; TBB, trans-bronchial biopsy; OLB, open-lung biopsy; IMA, invasive mucinous adenocarcinoma; LPA, lepidic predominant adenocarcinoma; ND, non-determined.

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Table S2 Additional characteristics of the 24 patients

Variables	Values
Comorbidities, n (%)	
Chronic heart failure	3 (13)
Chronic respiratory disease	2 (8)
Anticancer treatment before ICU referral, n (%)[a]	3 (13)
Physiological variables on admission	
Glasgow Coma Scale	15 (15–15)
Biological variables on admission	
Hemoglobin (g/dL)	12.6 (11.6–14.3)
Blood Gas on admission	
$PaCO_2$ (mmHg)	40 (37–45)
PaO_2/FiO_2	85 (74–122)
Presence of bacteria in lower respiratory tract sample[b], n (%)	6 (25)
Escherichia coli	3 (13)
Enterococcus faecium	1 (4)
Haemophilus influenzae	1 (4)
Proteus mirabilis	1 (4)
Genomic molecular alteration tested, n (%)	
KRAS mutation (among nine patients)	3 (33)
ROS-1 translocation (among four patients)	1 (25)
EGFR mutation (among twelve patients)	1 (8)
ALK gene rearrangement (among eleven patients)	0 (0)
c-MET amplification/mutation (among six patients)	0 (0)
BRAF mutation (among six patients)	0 (0)
PI3K mutation (among six patients)	0 (0)
Anticancer treatment administered in the ICU, n (%)	
Chemotherapy	9 (38)
Carboplatin-Paclitaxel-Bevacizumab	2 (22)
Carboplatin-Paclitaxel	2 (22)
Tyrosine-kinase inhibitors only (3 Erlotinib, 1 Gefitinib)	4 (44)
Carboplatin-Paclitaxel-Erlotinib	1 (11)
High dose corticosteroid therapy	16 (67)
240 mg/day ×3 followed by 1 mg/kg of prednisone equivalent	8 (33)
Life supporting interventions	
Length of mechanical ventilation (days)	9 (4–12)
Nasal high flow oxygen therapy, n (%)	5 (21)
Renal replacement therapy, n (%)	1 (4)
Performance status at hospital discharge (among 9 patients)	2 (2–3)
Survival after ICU admission (days)	41 (12–160)

Results are described as medians and interquartile ranges (IQR) for quantitative variables, and numbers and percentages (%) for qualitative variables. [a], one patient received 1 cure of Etoposide with steroids; the second patient received a first line of Erlotinib, then 2 cures of Carboplatin-Paclitaxel and finally 4 cures of Pemetrexed; the third patient received 4 cures of Carboplatin-Paclitaxel before a second-line of Pemetrexed. [b], at significant threshold: $>10^4$ colony forming unit (cfu)/mL for broncho-alveolar lavage; $>10^3$ cfu/mL for plugged telescopic catheter. ICU, intensive care unit.

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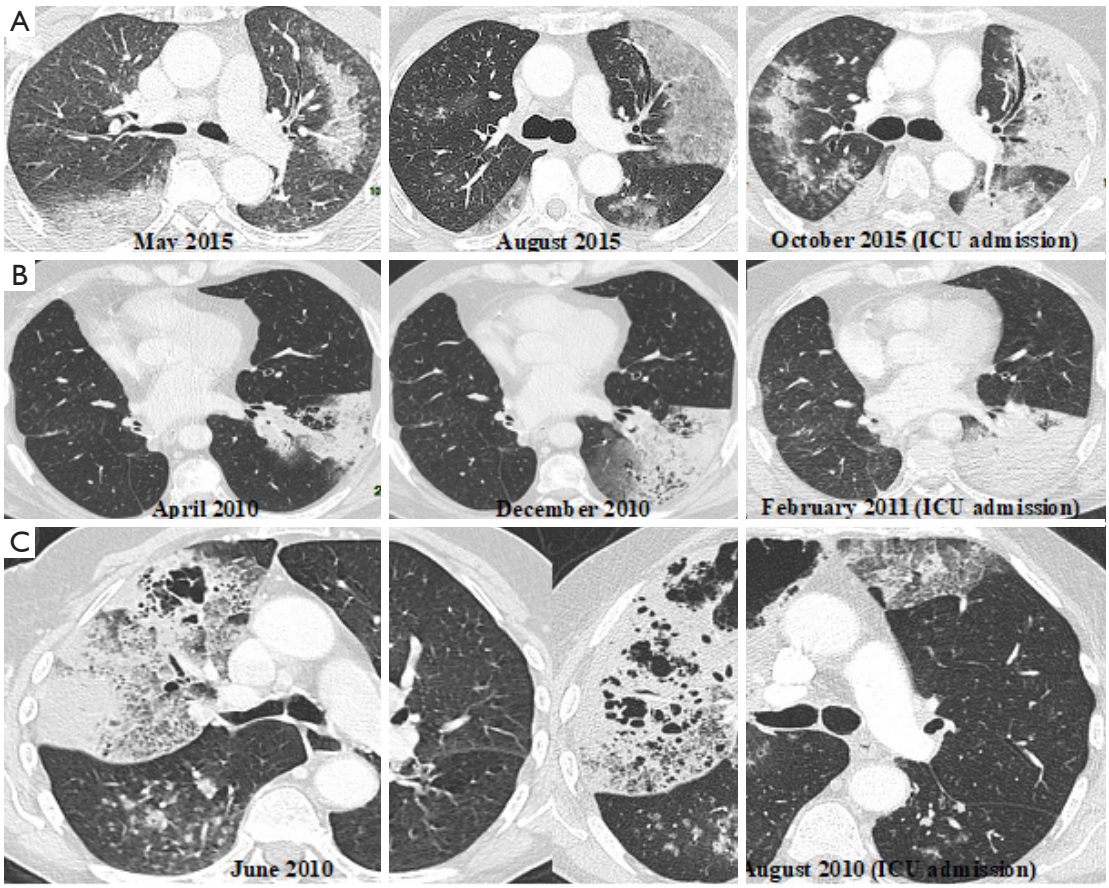

Figure S1 Radiological evolution of diffuse pneumonic-type adenocarcinoma without treatment in three patients (patient A, B and C). Intravenous contrast chest CT-scan in parenchymal windows. Panels A, B and C represent the cancer radiological evolution along time in three distinct patients. Panel A shows a peripheral and bilateral extension of a low-density attenuation, progressing to alveolar consolidation. Panel B shows a peripheral extension of a dense alveolar consolidation. Panel C shows the quick evolution of an excavation process within a 2-month period. Note the presence of a fissural bulging and compressed bronchus in the Panel C. ICU, intensive care unit; CT, computed tomography.

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Table S3 Diagnostic yield of the different respiratory tract samples for the diagnosis of diffuse lepidic adenocarcinoma

Respiratory tract samples	Tenon hospital	Other centers	P value
Sputum examination			
Number of patients concerned by the sample, n	7	0	–
Number of samples, n	15	–	–
Number of positive samples, n (yield in %)	11 (85)	–	–
Number of patients with a positive sputum, n (%)	5 (71)	–	–
Fiberoptic Bronchoscopy (any bronchoscopic sample)			
Number of patients concerned by the procedure, n	22	17	–
Number of bronchoscopy procedures, n	33	25	–
Number of positive procedures, n (yield in %)	22 (69)	3 (12)	<0.001
Number of patients with a positive procedure, n (yield in %)	21 (91)	3 (18)	<0.001
Fiberoptic Bronchial Aspiration			
Number of patients concerned by the sample, n	14	8	–
Number of samples, n	17	12	–
Number of positive samples, n (yield in %)	8 (47)	0 (0)	0.009
Number of patients with positive sample, n (yield in %)	8 (57)	0 (0)	0.017
Fiberoptic Bronchoalveolar Lavage			
Number of patients concerned by the sample, n	22	8	–
Number of samples, n	28	11	–
Number of positive sample, n (yield in %)	18 (64)	1 (9)	0.005
Number of patients with positive sample, n (yield in %)	16 (73)	1 (13)	0.009
Fiberoptic bronchial biopsy			
Number of patients concerned by the sample, n	12	12	–
Number of samples, n	16	15	–
Number of positive samples, n (yield in %)	1 (6)	1 (7)	1.000
Number of patients with positive sample, n (yield in %)	1 (8)	1 (8)	1.000
Fiberoptic trans-bronchial biopsy			
Number of patients concerned by the sample, n	12	2	–
Number of samples, n	14	2	–
Number of positive samples, n (yield in %)	11 (79)	1 (50)	0.450
Number of patients with positive sample, n (yield in %)	11 (79)	1 (50)	0.450
Percutaneous CT-guided lung biopsy			
Number of samples, n	1	0	–
Number of patients with positive sample, n (yield in %)	1 (100)	0 (0)	–
Open lung biopsy			
Number of patients concerned by the sample, n	2	0	–
Numbers of samples, n	2	–	–
Number of positive sample, n (yield in %)	2 (100)	–	–
Number of patients with positive sample, n (yield in %)	2 (100)	–	–
Autopsy (n=1)			
Number of samples, n	1	0	–
Positive, n (%)	1 (100)	0 (0)	–

Results are described as numbers or numbers and percentages (%), contrasting the respiratory tract samples obtained in Tenon Hospital and in other centers prior to the patients' referral. Several samples may be positive in the same patient.

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Table S4 Univariate analysis of factors associated with in-hospital mortality

Variables	Hospital mortality		P value
	Non-survivors (n=15)	Survivors (n=9)	
Age (years)	68 (63–75)	71 (61–75)	0.976
Gender (male), n (%)	10 (67)	7 (78)	1.000
Performance status 3–4, n (%)	7 (47)	2 (22)	0.389
Charlson comorbidity index	7 (7–8)	6 (6–7)	0.604
Time from first symptoms to diagnosis (days)	235 (93–287)	180 (58–237)	0.198
Never received anticancer treatment*, n (%)	8 (53)	0 (0)	0.009
Severity assessment on ICU admission			0.387
SAPS II	42 (36–48))	35 (30–41)	0.466
SOFA score	3 (2–5)	3 (2–4)	
ARDS severity, n (%)			0.476
Mild	7 (48)	6 (67)	
Moderate	4 (26)	1 (11)	
Severe	4 (26)	2 (22)	
Physiological variables on ICU admission			
Systolic blood pressure (mmHg)	131 (107–143)	127 (91–135)	0.232
Respiratory rate (cycle/min)	26 (25-37)	23 (22-28)	0.059
Heart rate (beat/min)	110 (92–117)	89 (83–95)	0.056
Temperature (°C)	37.5 (37.2-38.4)	37.2 (36.5–38.2)	0.548
Laboratory variables on ICU admission			
Leukocyte count (10^9/L)	12.8 (11.0–19.2)	8.4 (7.7–18.5)	0.370
C-reactive protein (mg/L)	58 (33–85)	24 (7–60)	0.104
Serum creatinine (μmol/L)	88 (66–108)	66 (62–84)	0.256
pH on arterial blood gas	7.41 (7.34–7.44)	7.44 (7.42–7.45)	0.203
Total BAL cell count (10^3/mL)	630 (190–245)	425 (255–952)	0.941
BAL neutrophil count (10^3/mL)	344 (63–644)	289 (49–810)	0.958
Radiological assessment on ICU admission			
Alveolar consolidation extent score (%)	22 (12–45)	17 (11–38)	0.724
Normal lung extent score (%)	43 (31–61)	53 (38–68)	0.192
Mediastinal lymphadenopathy, n (%)	2 (13)	1 (11)	1.000
Life supporting interventions, n (%)			
Mechanical ventilation	12 (80)	5 (56)	0.356
Non-invasive ventilation only	4 (27)	2 (22)	0.823
Vasopressors	3 (20)	1 (11)	1.000

Data are expressed as number and percentage (n, %) for categorical variables, and median (interquartile interval) for continuous variables. *, impossibility to dispense anticancer treatment at any time before, during or after ICU discharge. ARDS, acute respiratory distress syndrome; ICU, intensive care unit; BAL, broncho-alveolar lavage.

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Appendix 2

Details about the variables selected, and the goodness-of-fit of the multivariate logistic regression models for intensive care unit and hospital mortality prediction

ICU mortality

(I) Variable proposed in the model (forward stepwise procedure): time between first symptoms and diagnosis/SAPS II/need for mechanical ventilation;
(II) Hosmer-Lemeshow goodness of fit test, P=0.799, indicating good calibration.

Hospital mortality

(I) Variable proposed in the model (forward stepwise procedure): time between first symptoms and diagnosis/heart rate at ICU admission/impossibility to dispense chemotherapy at any time after diagnosis;
(II) Hosmer-Lemeshow goodness of fit test, P=0.706, indicating good calibration.

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