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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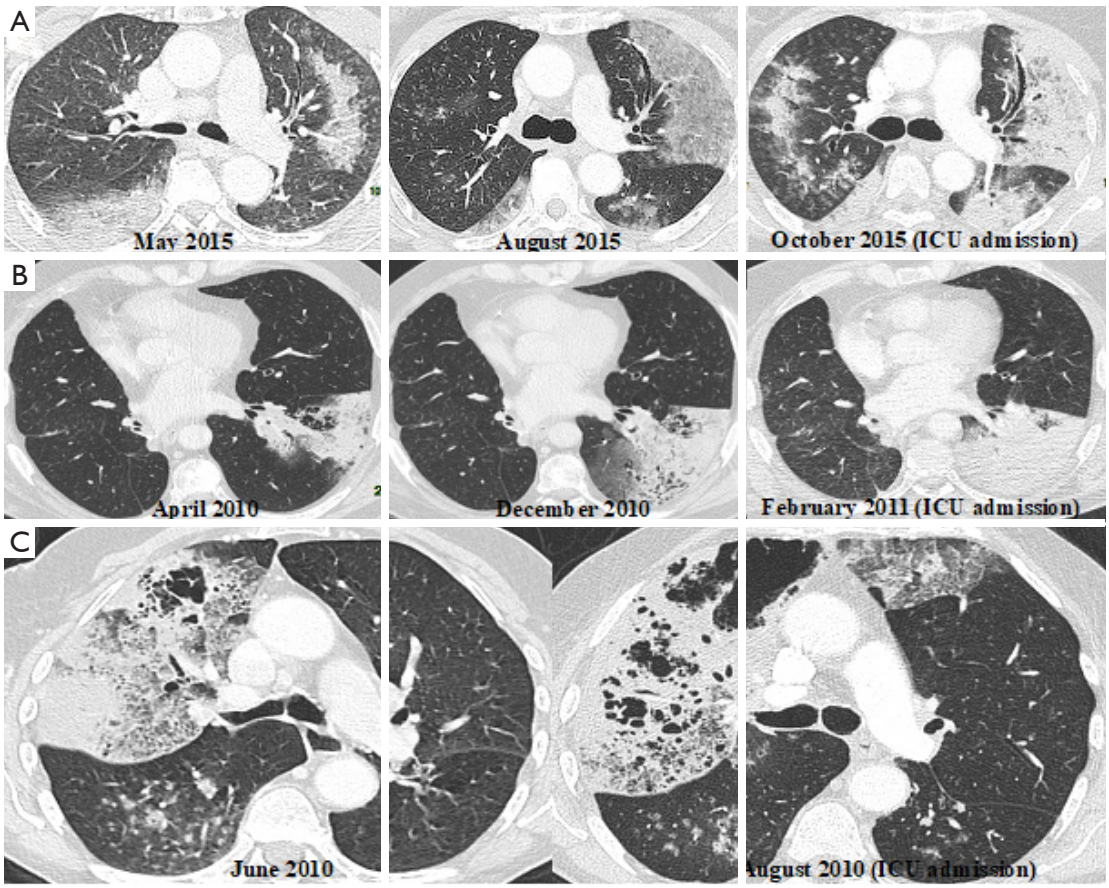

Figure S1 Radiological evolution of diffuse pneumonic-type adenocarcinoma without treatment in three patients (patient A, B and C). Intravenous contrast chest CT-scan in parenchymal windows. Panels A, B and C represent the cancer radiological evolution along time in three distinct patients. Panel A shows 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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