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ORIGINAL RESEARCH

Cardiovascular risk in pulmonary alveolar proteinosis

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ABSTRACT

We hypothesized that cardiovascular events and/or indices of cardiac dysfunction may be increased in pulmonary alveolar proteinosis (PAP). Systemic and pulmonary arterial hypertension, arrhythmias, pulmonary embolism, stroke and ischemic heart attack were reported. Patients underwent serum anti-GM-CSF antibodies, disease severity score (DSS), Doppler transthoracic echocardiograph, glucose, thyroid hormones, lipids, troponin and pro-Brain natriuretic peptide (BNP) examination. Thirteen patients (8 female) were studied, median age of 47. Pro-BNP inversely related to DLCO% and TLC%; troponin directly related to DSS, age, $P(A\text{-}a)O_2$, left atrium-, left ventricle-end-diastole diameter and BMI. On multiple regression analysis DSS was the only parameter significantly and strongly related with troponin ($R^2 = 0.776$, $p = 0.007$). No cardiovascular event was reported during follow-up. In PAP cardiovascular risk indices relate to lung disease severity. Therefore, PAP patients could be at increased risk for cardiovascular events. Quantitation of its magnitude and potential links to lungs' physiologic derangement will be addressed in future studies.

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Introduction

Pulmonary alveolar proteinosis (PAP), an ultra-rare chronic alveolar filling pulmonary disease, is characterized by the inappropriate accumulation of surfactant phospholipoproteins in alveolar macrophages and/or diffusely in the airspaces.[1,2] Its most common form, autoimmune PAP (aPAP), is related to autoantibodies against granulocyte macrophage colony stimulating factor (GM-CSF) severely affecting lung macrophages' ability to process catabolized lipoid material.[1,2] Chronic hypoxemia and progressive dyspnea are the main clinical manifestations in most patients.[3] In smokers with chronic hypoxemic respiratory disorders such as chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis, cardiovascular comorbidities occur more frequently and may affect both severity and prognosis.[4,5] In patients with PAP several factors of cardiovascular risk are constantly present during the natural history of the disease. Such risk factors include progressive hypoxemia due to a gradual decline of the respiratory reserve,[3,6,7] smoking history (reported in up to two-thirds of patients),[8,9] and higher serum levels of triglycerides and cholesterol.[10–17] However, despite rare reports of death associated with myocardial infarction,[9] to our knowledge there are no studies examining cardiovascular risk and events in patients with PAP. Based on the aforementioned information, the aim of the present study was to examine cardiovascular risk and indices of cardiac dysfunction in PAP patients and their possible association with markers of disease severity.

Materials and methods

All consecutive patients with PAP referred to a Tertiary University Hospital Pulmonary Medicine Department from 2008 to 2015 were included in the study and epidemiological, clinical and laboratory data were prospectively collected. The mean follow-up period was 35.8 ± 18.1 months. Diagnosis was documented by cytological examination of bronchoalveolar lavage (8 patients) or by histopathologic examination of lung biopsy (5 patients). The autoimmune nature of the disease was documented by the presence of neutralizing anti-GM-CSF antibodies measured in serum as already described in the literature.[9,18] The cutoff

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value for anti-GM-CSF antibodies was set at 10 μg/ml, whereas 4–9 μg/ml was considered as intermediate value. In all patients, disease severity score (DSS) was calculated for each patient as already described in the literature: DSS 1 – no symptoms and partial pressure of oxygen in arterial blood (PaO_2) ≥70 mmHg; DSS 2 – symptomatic and PaO_2 ≥ 70 mmHg; DSS 3 – 60 ≥ PaO_2 < 70 mmHg; DSS 4 – 50 ≥ PaO_2 < 60 mmHg; and DSS 5 – PaO_2 < 50 mmHg.[19,20] All documented infection events were systematically reported. Cardiovascular manifestations such as systemic arterial hypertension, echocardiographic signs indicative of pulmonary arterial hypertension,[21] arrhythmias, pulmonary embolism, stroke and ischemic heart attack were reported. Patients underwent arterial blood gases measurement, pulmonary function tests and measurement of their exercise capacity using the 6-minute walking test (6MWT), Doppler transthoracic echocardiography and computed tomography pulmonary angiography (CTPA) if indicated, within a time span of 1–2 weeks. Biochemical parameters associated with cardiovascular risk/dysfunction such as glucose, thyroid hormones, lipids, troponin [Elecsys® Troponin T high sensitive, Cobas Roche] and pro-Brain natriuretic peptide (BNP) [Elecsys® proBNPII, Cobas Roche] were also measured. Troponin values over 14 pg/ml and pro-BNP values above 125 pg/ml were considered as abnormal. Based on treatment status patients were divided into: (1) treated either with inhaled GM-CSF (iGM-CSF) alone and/or whole lung lavage (WLL), (2) in no treatment demanding, and in (3) treatment demanding-not treated yet. Treatment with iGM-CSF (Leukine ®Sargramostim; licensed to Genzyme Corporation, Sanofi-Aventis U.S. LLC, Cambridge, MA, USA) is already described in detail in the literature.[22] The study protocol was approved by the ethics committee of the hospital and informed consent was provided by all participants.

Statistical analysis

Data are expressed as median (interquartile ranges). Comparisons of biomarkers between treated and untreated patients were performed with Mann–Whitney U test and Kruskal–Wallis test for the comparison of two or three or more groups, respectively. Subgroups were compared using the Dunn's multiple comparison tests. Correlations were assessed using Spearman's rank correlation coefficient. In the multivariate analysis, a multiple linear regression model was created using troponin as the dependent variable and left atrium diameter, left ventricle end-diastole diameter and DSS as independent variables; p-values <0.05 were considered statistically significant. Analysis was performed with SPSS 17 (SPSS, Chicago, IL USA).

Results

Thirteen patients (8 female), with median [interquartile range (IQR)] age: 47 years (37.5–57) and body mass index 24.7 (20.65–32.3), were studied. Autoimmune PAP was documented in 10 patients (77%). Three patients were current smokers, three ex-smokers and seven never smokers. Six patients were already treated with iGM-CSF and/or WLL and five patients were not yet treated. Demographic and functional characteristics of the study subjects are provided in Tables 1 and 2. No significant difference was detected between treated and untreated patients. A history of diabetes mellitus, hypothyroidism, coronary artery disease, arterial hypertension and dyslipidemia were encountered in 2/13, 3/13, 1/13, 1/13 and 1/13 patients, respectively. Opportunistic infections were reported in two patients (15.3%), one due to MAC *non-tuberculosis mycobacterium* and one due to *Nocardia* spp. One patient of the untreated group died due to severe respiratory failure related to septic shock without, however, the specific pathogen being identified. Only one patient had echocardiographic indices of left heart dysfunction with an ejection fraction (EF) of 45%, all the rest having an EF >65%. No significant valvular or pericardial disease was documented and no echocardiographic signs indicative of pulmonary hypertension were detected (Table 2). Three patients presented abnormal pro-BNP values. Pro-BNP was inversely related to diffusing capacity for carbon monoxide (DLCO%) pred ($r = -0.745$, $p = 0.01$) and total lung capacity (TLC%) pred ($r = -0.552$, $p = 0.01$). Troponin was directly related with DSS ($r = 0.755$, $p = 0.007$), age ($r = 0.575$, $p = 0.04$), BMI ($r = 0.599$,

Table 1. Demographic and clinical characteristics of the patients (n = 13).

Parameter	All patients (n = 13)
Treated with iGM-CSF and/or WLL/ no need for treatment/ untreated	6/ 2/ 5
Age at diagnosis (years)	43.0 (31.2–54.0)
Age (years)	47.0 (37.5–57.0)
Gender (M/F)	5/8
Smoking habit (ex/no/yes)	3/7/3
BMI (kg/m^2)	24.7 (20.6–32.3)
Anti GM-CSF Ab (μg/ml)	15.2 (7.9–99.0)
$P(A\text{-}a)O_2$ (mmHg)	35.5 (0.7–55)
History of infection (%)	2 (15.3)
DSS	2.0 (1.0–3.0)
Years from diagnosis	5.0 (2.0–10.5)

Ab: antibody; BMI: body mass index; DSS: Disease severity score; F: Female; iGM-CSF: Inhaled granulocyte macrophage colony stimulating factor; M: Male; $P(A\text{-}a)O_2$: Arterial alveolar oxygen difference; WLL: Whole lung lavage.

Table 2. Pulmonary function testing (n = 12) and Doppler transthoracic echocardiography characteristics of the patients (n = 13).

Parameter	All patients (n = 13)
FEV_1 (% predicted)	76.5 (58.7–91.2)
FVC (% predicted)	72.6 (55.3–90.9)
FEV_1 /FVC (%)	83.4 (82.7–91.3)
TLC (% predicted)	67.4 (55.7–81.9)
DLCO (% predicted)	49.4 (37.7–71.7)
EF	0.65 (0.65–0.65)
Left atrium (mm)	37 (30.5–41.0)
End diastole LV (mm)	44 (41.5–48.5)
End systole LV (mm)	27 (24.0–31.5)
Diameter RV (mm)	32 (27.5–37.5)
RVSP (mmHg)	22.0 (18.5–29.2)
TAPSE (mm)	22.0 (20.2–25.8)
TRV (m/s)	2.25 (2.0–2.57)

DLCO: Diffusing capacity for carbon monoxide; EF: Ejection fraction; FEV_1: Forced expiratory volume in 1 second; FVC: Forced vital capacity; LV: Left ventricle; RV: Right ventricle; RVSP: Right ventricular systolic pressure; TAPSE: Tricuspid annular plane systolic excursion; TLC: Total lung capacity; TRV: Tricuspid regurgitation velocity.
Normal values: EF = 60–80%; Left atrium = 10–39 mm; end diastole LV = 36–56 mm; End systole LV = 24–40 mm; diameter RV < 40 mm.

p = 0.03) and parameters of left heart function such as left atrium diameter (r = 0.687, p = 0.01) and left ventricle end-diastole diameter (r = 0.637, p = 0.019) (Figures 1 and 2). Since troponin is a biomarker which represents cardiac dysfunction in order to test the possible effect of disease severity on cardiac dysfunction (and thus troponin levels), we performed a multiple linear regression model using troponin as the dependent variable and left atrium diameter, left ventricle end-diastole diameter, DSS and BMI as independent variables. This multiple regression analysis showed that DSS was the only parameter that was

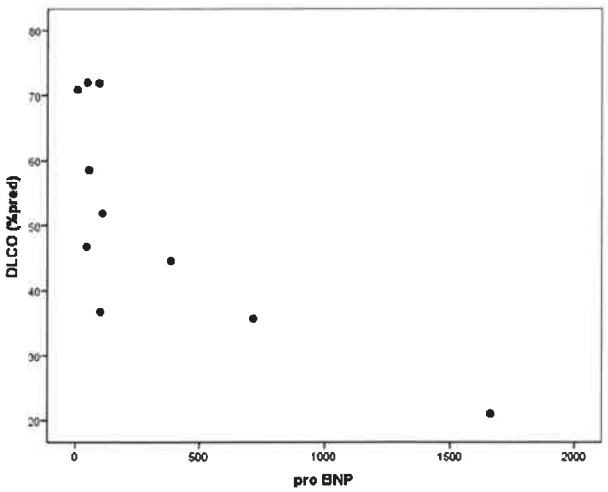

Figure 1. Spearman's correlation between Pro-BNP and DLCO% in PAP patients (n = 10). Pro-BNP is inversely correlated with DLCO% (r = –0.745, p = 0.01).
DLCO: diffusing capacity for carbon monoxide; PAP: pulmonary alveolar proteinosis pro-BNP: pro-brain natriuretic peptide.

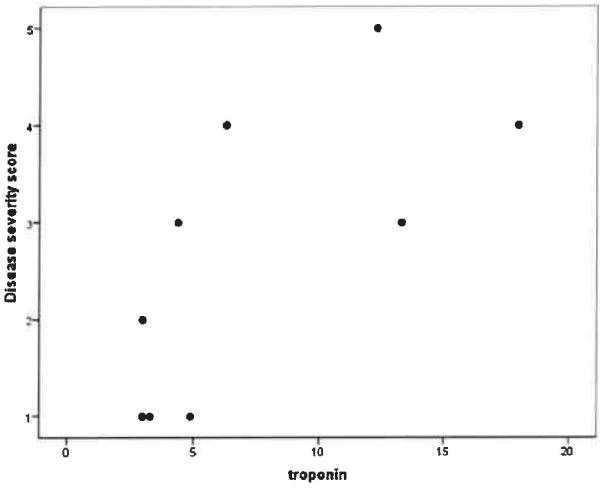

Figure 2. Spearman's correlation between troponin and disease severity score (DSS) in PAP patients (n = 11). Troponin is directly correlated with DSS (r = 0.755, p = 0.007).
PAP: pulmonary alveolar proteinosis.

Table 3. Multivariate analysis for determinants of troponin levels.

	Unstandardized coefficient B	Standard error	Standardized coefficient beta	Significance p
Left atrium	0.127	0.278	0.139	0.659
End diastole LV	0.627	0.280	0.454	0.055
DSS	3.182	0.887	0.838	**0.007**
BMI	–0.4	0.195	–0.575	0.075

BMI: body mass index; DSS: disease severity score; LV: left ventricle.

Table 4. Laboratory characteristics of the patients (n = 13).

Parameter	All patients (n = 13)
LDH (mg/dl)	223.0 (200.0–341.0)
CRP (mg/l)	3.44 (3.44–4.28)
Pro-BNP (pg/ml)	97.6 (47.0–386.7)
Troponin (pg/ml)	4.4 (3.0–12.3)
TSH (µU/ml)	2.04 (1.36–3.25)
Uric acid (mg/dl)	4.6 (2.9–5.8)
Cholesterol (mg/dl)	211.0 (179.0–265.0)
Triglyceride (mg/dl)	100.0 (66.0–226.0)
LDL (mg/dl)	130.0 (94.5–167.0)
HDL (mg/dl)	52.0 (40.5–61.5)

CRP: C-reactive protein; DSS: Disease severity score; HDL: high density lipoprotein; LDH: lactate dehydrogenase; LDL: low density lipoprotein; LV: Left ventricle; pro-BNP: Pro-brain natriuretic peptide; TSH: thyroid stimulating hormone.
Normal values: LDH (135–225 mg/dl), CRP (0–6 mg/l), pro-BNP (<125 pg/ml), Troponin (<14pg/ml), TSH (0.27–4.20 µU/ml), Uric acid (2.4–5.7 mg/dl), Cholesterol (140–220 mg/dl), Triglyceride (<200 mg/dl), LDH (<159 mg/dl), HDL (45–65 mg/dl).

significantly and strongly related with troponin when adjusted for the effect of BMI, and the left atrium and left ventricle end-diastole diameter (R^2 = 0.776) (p = 0.007, beta = 0.83) (Table 3). No hospitalization for severe

arrhythmia, ischemic heart attack, pulmonary embolism or stroke was registered through the follow-up period of 35.8 ± 18.1 months. One reported death was attributed to sepsis as already mentioned. Serum levels of triglyceride and cholesterol were found normal. (Table 4). No statistically significant differences were detected for troponin, pro-BNP, lactate dehydrogenase, cholesterol, low density lipoprotein, high density lipoprotein, uric acid, thyroid stimulating hormone and C-reactive protein levels between treated and untreated patients (data not shown).

Discussion

In the present study it is shown that significant associations were detected between cardiovascular risk indices (such as troponin and pro-BNP) and PAP disease severity indices (such as DSS, TLC% and DLCO%), despite the absence of a noteworthy increase in the overt cardiovascular complications in PAP patients. Both troponin and pro-BNP are highly sensitive biomarkers of cardiac dysfunction and bear significant prognostic value in respiratory diseases such as COPD, sleep apnea syndrome and pulmonary embolism. [23–25] Previous studies have shown that pro-BNP has an excellent negative predictive value for left ventricular dysfunction and heart failure and is a reliable discriminator of right ventricular impairment and mortality, whereas elevation of troponin was related to all-cause mortality in COPD. [26,27] In the present study PAP severity indexes were found to relate to both cardiac dysfunction biomarkers, which could suggest chronic subclinical or occult cardiac dysfunction mainly attributed to hypoxemia [20,28,29] that might constitute a risk in the future to overt clinical cardiovascular events. The fact that DSS was found to represent disease severity and not hypoxemia alone could be attributed to the composite nature of the index evaluating symptoms of the patient as well, which could better capture potential links with the lung's physiologic derangement.

Previous studies have shown that in aPAP more than up to 70% of patients have comorbidities and that although the incidence of PAP-related death is very low, most deaths are attributed to other conditions including myocardial infarction.[9,30] Very few cases of pulmonary embolism and pulmonary hypertension are reported.[9,31] Systemic arterial hypertension (8.5–14%), diabetes mellitus (3.8–6%), hyperlipidemia (4.2%), hypothyroidism (<1%) and infections (5.7–11%) are encountered less frequently compared with our study group.[8,9] Rates could vary between different studies due to the fact that populations are not age and gender matched as well as to epidemiological discrepancies between countries and continents.

Based on the existing evidence, lung mechanic derangement associated with hypoxia and/or autoimmunity and/or dysregulation of lipid metabolism could lead to the development of pulmonary hypertension and be associated with cardiovascular disease.[4,5,10,14,15,32] The fact that the patients of this study did not develop any overt cardiovascular event could be attributed to the limited number, relatively young age and preponderant female gender of patients, the short duration of follow-up, the fact that the majority of patients were never smokers or ex-smokers and that no severe dyslipidemia was documented. Treatment could have also played a role since WLL or iGM-CSF significantly improves both gas exchange and lipid metabolism.[10,19] The absence of echocardiographic signs indicative of pulmonary hypertension could be explained by the lack of alveolar interstitial wall inflammation and/or significant fibrosis characterizing PAP patients in contrast to other chronic respiratory diseases which present with significant parenchymal remodeling processes predisposing to PH. [3,32–35]

Our study has several limitations. First, pulmonary arterial pressure was measured through transthoracic echocardiography and not through right heart catheterization. Second, the small number of patients might weaken the interpretation of the correlations found. Due to the small number of patients and the real life design of the study, diabetes mellitus and coronary artery disease patients were not excluded from the analysis and this should be kept in mind at the data interpretation. Studies with larger number of patients and longer follow-up are needed to further quantify the increased cardiovascular risk in PAP patients

Conclusion

In conclusion, indices of cardiovascular risk are related to markers of disease severity in a small cohort of PAP patients. Thus, PAP patients might be at increased risk for cardiovascular events. The magnitude and the potential links with the lungs' physiologic derangement need to be addressed in future studies including a greater number of patients.

Financial & competing interests disclosure

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Key issues

- In patients with PAP several factors of cardiovascular risk are constantly present. Such risk factors include progressive hypoxemia, smoking history (reported in up to two-thirds of patients) and higher serum levels of triglycerides and cholesterol.
- However, there are no studies examining cardiovascular risk and events in patients with PAP. We hypothesized that cardiovascular events and indices of cardiac dysfunction may be increased in PAP patients.
- In the present study it is shown that significant associations exist between cardiovascular risk indices such as troponin and pro-BNP and disease severity indices such as DSS, TLC% and DLCO%, despite the absence of a noteworthy increase in the overt cardiovascular complications in PAP patients.
- In PAP patients indices of cardiovascular risk correlate to markers of disease severity.
- PAP patients might be at increased risk of cardiovascular events. The magnitude and the potential links with the lungs' physiologic derangement need to be addressed in future studies.

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