Monika Szturmowicz[1], Aneta Kacprzak[1], Barbara Burakowska[2], Agnieszka Skoczylas[3], Iwona Bestry[2], Jan Kuś[1], Anna Fijałkowska[4], Adam Torbicki[5], Marcin Kurzyna[5]

[1]I[st] Department of Lung Diseases National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland
[2]Department of Radiology National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland
[3]Freelance statistical analytic
[4]Department of Cardiology National Research Institute for Mother and Child, Warsaw, Poland
[5]Department of Cardiovascular and Pulmonary Thromboembolic Disease CMKP, European Heath Centre, Otwock, Poland

Centrilobular nodules in high resolution computed tomography of the lung in IPAH patients — preliminary data concerning clinico-radiological correlates

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Abstract

Introduction: Inhomogeneity of lung attenuation pattern is observed in high resolution chest computed tomography (HRCT) in some IPAH patients despite lack of interstitial lung disease. Such radiological changes are described either as ill-defined centrilobular nodules (CN) or as focal ground glass opacities (FGGO). There is no consensus in the literature, whether they indicate the distinct type of IPAH, or pulmonary venoocclusive disease (PVOD) with subtle radiological changes. Thus the aim of the present pilot study was to assess the frequency and clinical significance of inhomogenic lung attenuation pattern in IPAH.

Material and methods: 52 IPAH patients (38 females, 14 males, mean age 41 years ± 15 years), entered the study. All available chest CT scans were reviewed retrospectively by the experienced radiologist, not aware about the clinical data of the patients.

Results: CN were found in 10 patients (19%), FGGO — in 12 patients (23%). No lymphadenopathy or interlobular septal thickening suggestive of PVOD were found. The significant differences between CN and the remaining patients included: lower mean age — 31 and 43.5 years, ($p = 0.02$), lack of persistent foramen ovale (PFO) — 0% and 43% ($p = 0.03$), and higher mean right atrial pressure (mRAP) — 12.5 mm Hg and 7.94 mm Hg ($p = 0.01$). No significant survival differences were observed between the groups of CN, FGGO and the remaining patients.

Conclusion: Centrilobular nodules in IPAH were combined with lack of PFO, higher mRAP and younger age of patients.

Key words: idiopathic pulmonary arterial hypertension; centrilobular nodules; high resolution computed tomography of the lung

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Introduction

High resolution computed tomography (HRCT) of the lung is an important tool applied to the differential diagnosis of pulmonary hypertension (PH). The presence of interstitial lung disease or emphysema indicates PH in the course of lung pathology [1]. Moreover, significant interstitial lung disease in HRCT excludes idiopathic pulmonary arterial hypertension (IPAH) [1].

Nevertheless, nonhomogenous lung attenuation is observed in HRCT in some IPAH patients, despite lack of interstitial lung disease [2]. Such pathological changes are described either as ill-defined centrilobular nodules or as focal ground glass opacities. The presence of centrilobular nodules (CN) combined with interlobular septal thickening, enlarged mediastinal lymph nodes and occasionally with the presence of pleural effusion, may be regarded as

Address for correspondence: Monika Szturmowicz, I Department of Lung Diseases, National Institute of Tuberculosis and Lung Diseases, ul. Płocka 26, 01–138 Warszawa, e-mail: monika.szturmowicz@gmail.com
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the radiological signs suggestive of pulmonary venoocclusive disease (PVOD) [3–6]. Some authors found centrilobular nodules both in PVOD and in pulmonary capillary haemangiomatosis (PCH), with a tendency towards larger nodules in PCH patients [7].

In about 5–10% of IPAH patients, CN are described as the only radiological abnormality. There is no consensus in the literature, whether such radiological abnormality indicates the distinct type of IPAH or PVOD with subtle radiological changes [8]. The answer to this question is important, as PVOD is combined with worse prognosis, targeted PAH therapy may be harmful and lung transplantation has to be taken into account in the early course of the disease [9–11].

Thus the aim of the present pilot study was to assess the frequency and clinical significance of nonhomogenous lung attenuation pattern in IPAH patients.

Material and methods

52 IPAH patients (38 females, 14 males, mean age 41 years ± 15 years), diagnosed between 1998 and 2006, entered the study. IPAH was recognized in the patients with precapillary PH confirmed by right heart catheterization, and defined as mean pulmonary artery pressure (mPAP) ≥ 25 mm Hg, pulmonary artery wedge pressure (PAWP) ≤ 15 mm Hg, and pulmonary vascular resistance (PVR) > 3 WU [12].

Chronic thromboembolic pulmonary hypertension (CTEPH) was excluded based on negative results of chest computed tomography with angiography and lung scintigraphy [12]. PH due to the lung diseases was excluded based on: negative anamnesis concerning lung disease, no significant emphysema or fibrosis in HRCT and the results of spirometry and body plethysmography (FEV_1 ≥ 60% pred., FVC ≥ 70% pred., TLC ≥ 70% pred.) [1].

IPAH was diagnosed after exclusion of all known causes of pulmonary arterial hypertension [12].

The standard procedures in IPAH patients consisted of the assessment of functional class (FC) according to WHO, arterialized blood gas analysis, 6-minute walk test (6MWT) performed on the flat ground according to ATS guidelines [13]. Serum N-terminal portion of brain natriuretic propeptide (NT-proBNP) was measured with Elecsys proBNP immunoassay, Roche Diagnostics, Basel, Switzerland. The patients received PAH-specific drugs according to current treatment guidelines and according to drug availability in Poland [14].

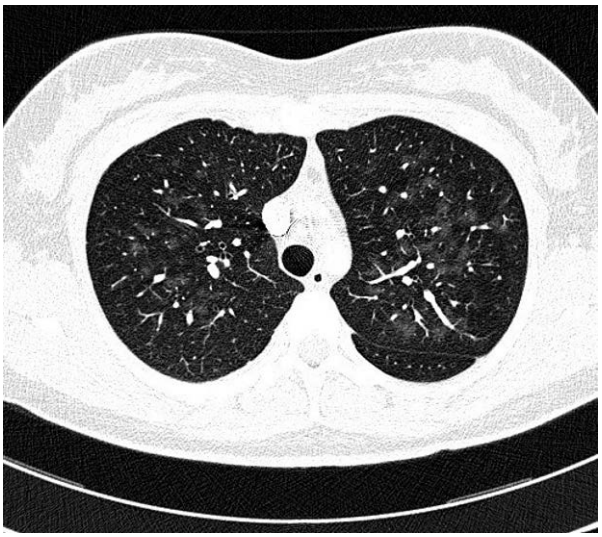

Figure 1. Centrilobular nodules in high resolution computed tomography of the lung of 31-years old female patient with idiopathic pulmonary arterial hypertension

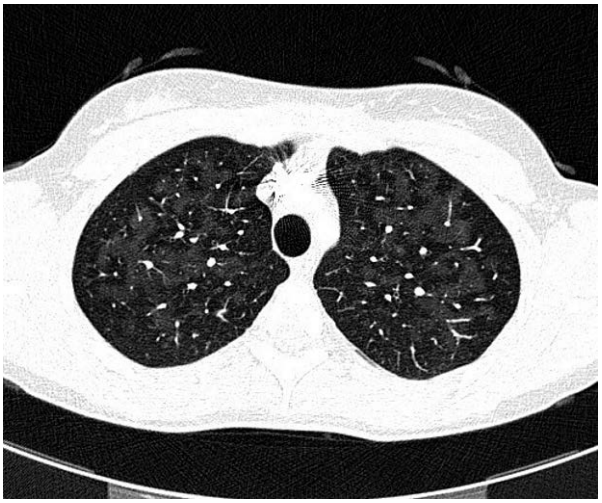

Figure 2. Focal ground glass opacities in high resolution computed tomography of the lung of 19-years old female patient with idiopathic pulmonary arterial hypertension

Transoesophageal echocardiography was applied to diagnose the presence of persistent foramen ovale (PFO).

All available chest CT scans were reviewed retrospectively by the experienced radiologist, not aware about the clinical data of the patients. Nonhomogenous lung attenuation pattern was defined as:

1. Centrilobular nodules (CN) — ill-defined centrilobular ground glass opacities (Fig. 1).
2. Focal ground glass opacities (FGGO) — gauzy areas of ground glass attenuation with central or irregular localization, larger than CN (Fig. 2).

Table 1. Comparison of clinical and laboratory parameters (means ± SD) in IPAH patients with CN, FGGO and NPA

Parameter	CN — 10 pts	FGGO — 12 pts	NPA — 30 pts	p
Age, years	32.1 (13.5)	43.5 (16.3)	43.4 (13.98)	0.06
Gender M:F	4:1	5:1	2:1	0.22
Haemoptysis, no (%)	5 (50%)	3 (25%)	4 (13%)	0.07
PFO, no (%)	0 (0%)	5/9 (56%)	10/26 (38%)	0.03
6MWD, meters	411.2 (82.0)	354.8 (122)	366.9 (131.7)	0.55
WHO FC (I+II/III+IV)	6/4	6/6	19/11	0.52
NT-proBNP pg/ml	3436 (2108)	1568 (1261)	2069 (2165)	0.16
PaO_2, mm Hg	68.1 (16.1)	63.9 (12.8)	65.4 (14.5)	0.77
$PaCO_2$, mm Hg	30.1 (3.8)	32 (5.2)	31.1 (4.0)	0.68

CN — centrilobular nodules; FGGO — focal ground glass opacities; NPA — no parenchymal abnormalities; M — males; F — females; PFO — persistent foramen ovale; 6MWT — six minutes walking test; WHO FC — World Health Organisation functional class; NT-proBNP — N terminal portion of brain natriuretic propeptide; PaO_2 — partial oxygen pressure; $PaCO_2$ — partial carbon dioxide pressure

The remaining patients were classified as the group with no parenchymal abnormalities in HRCT (NPA).

In most patients with CN and FGGO expiratory HRCT was performed to exclude the air-trapping.

The survival time was calculated from the date of HRCT assessment until death or until the end of 8-year observation time (Jan 2016). In transplant recipients the survival time was calculated from HRCT until the day of lung transplantation.

Statistical methods

Statistical analysis was performed in R environment. Normality of the distribution of the selected parameters was assessed with Shapiro-Wilk's test. Homogeneity of variance was assessed with Batlett's test. ANOVA test or Kruskal-Wallis test were used to compare the values of continuous parameters in the groups with CN, FGGO and NPA. For two groups' comparisons, F test and T-Student test or U Mann-Whitney test were used respectively. Pearson's chi-square test or its modifications if appropriate (i.e. Yates correction and Fisher exact test) were applied to compare the categorical variables. Kaplan-Meier survival curves and log-rank test were used for the analysis of prognostic significance of CN and FGGO. $P < 0.05$ was regarded as significant.

Results

CN were found in 10 out of 52 IPAH patients (19%): in 7 of them at diagnosis (13%), in 3 (6%) — in the course of the disease. In all of them CN were described in every subsequent HRCT examination.

FGGO were described in 12 patients (23%). They were also seen in every subsequent HRCT examination, if such was performed.

No overlapping of CN and FGGO was observed. No lymphadenopathy or septal lines suggestive of PVOD were found.

The clinical data of the patients with CN, FGGO and NPA were compared (Table 1).

The CN patients were younger than those with FGGO and NPA. The females predomination was higher in CN and FGGO groups compared to NPA.

Haemoptysis was more frequent in CN patients compared to NPA group (50% and 13% respectively, $p = 0.07$). In none of CN patients PFO was detected, compared to 56% of FGGO patients and 38% of NPA patients ($p = 0.03$).

Haemodynamic evaluation (Table 2) revealed the tendency towards higher mean right atrial pressure (mRAP), lower mixed venous blood oxygen saturation ($satO_2mv$), and lower cardiac index (CI) in CN patients compared to the remaining groups.

Subsequently, the values of selected variables were compared between CN group and all the remaining patients (Table 3).

The significant differences between CN and the remaining patients included: lower mean age (31 and 43.5 years, respectively), lack of PFO (0% and 43% respectively), and higher mRAP (12.5 mm Hg and 7.94 mm Hg respectively). Haemoptysis was found in 50% of CN and 17% of the remaining patients ($p = 0.06$).

Median survival time was 42 (1.5−116) months in CN group, 47.5 (3−120) months in FGGO group and 70.5 (11−210) months in NPA group, the difference was not statistically significant. Nevertheless, only one out of 10 CN patients (10%)

Table 2. Comparison of haemodynamic parameters (means ± SD) in IPAH patients with CN, FGGO and NPA

Parameter	CN — 9 pts	FGGO — 11 pts	NPA — 26 pts	p
mPAP (mm Hg)	59.9 (15)	53.8 (11)	54.6 (14.5)	0.38
CI (l/min/m^2)	2.42 (1.15)	2.54 (0.5)	2.5 (0.54)	0.16
SatO2 mv (%)	51.9 (10.8)	56 (8.01)	57.8 (8.18)	0.099
mRAP, (mm Hg)	12.5 (4.8)	6.9 (3.88)	8.5 (5.97)	0.12
PVRI (WU/m^2)	9.31 (4.14)	6.89 (2.17)	6.4 (2.9)	0.2
Responders, no (%)	3/9 (33)	0/11 (0)	8/26 (31)	0.12

mPAP — mean pulmonary artery pressure; CI — cardiac index; $SatO_2$ mv — mixed venous blood oxygen saturation; mRAP — mean right atrial pressure; PVRI — pulmonary vascular resistance index

Table 3. Comparison of the selected variables (mean ± SD) between CN group and the remaining patients

Parameter	CN — 10 pts	FGGO+NPA — 42 pts	p
Age (years)	31.1 (13.5)	43.5 (14.5)	0.02
mRAP (mm Hg)	12.5 (4.8)	7.94 (5.3)	0.01
mPAP (mm Hg)	59.9 (15)	54.3 (13.2)	0.27
CI (l/min/m^2)	2.42 (1.15)	2.51 (0.52)	0.08
PVRI (WU/m^2)	9.31 (4.14)	6.56 (2.63)	0.12
$satO_2$mv (%)	51.9 (10.8)	57.1 (8.03)	0.11
6MWD (m)	411.2 (82)	363.2 (13.9)	0.29
NT-proBNP (pg/ml)	3436 (2108)	1887 (1869)	0.06
pO_2 (mm Hg)	68.1 (16.1)	64.9 (13.9)	0.56
pCO_2 (mm Hg)	30.5 (3.8)	31.3 (4.33)	0.39
PFO no (%)	0/10 (0)	15/35 (43)	0.03
haemoptysis	5/10 (50)	7/42 (17)	0.06

The abbreviations are explained in Tables 1 and 2

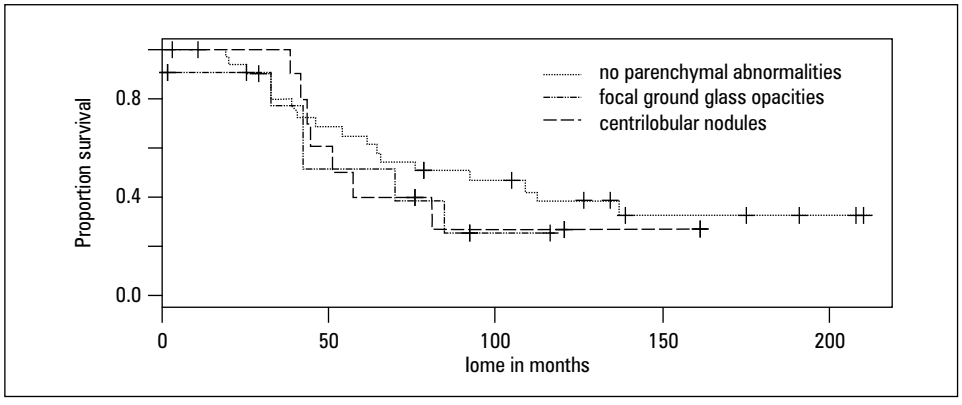

Figure 3. Kaplan-Meier survival curves for IPAH patients according to HRCT result

survived over 8 years, compared to 2/12 (17%) of FGGO and 12/30 (40%) of NPA group.

The survival curves of the three groups are included in Figure 3. No significant differences were observed between the groups (p = 0.662).

Discussion

In the presented group of IPAH patients, the retrospective analysis of HRCT scans revealed the presence of CN in 13% of the patients at the time of

diagnosis, and in 6% of the patients they appeared in the course of the disease. The frequency of CN at diagnosis, reported by our group, was similar to that noticed by Montani et al. and Nolan et al. [9, 15]. Rajaram et al. analysed chest CT scans of IPAH patients from the ASPIRE study, and described various types of ground glass opacities (GGO) in 57% of them, 48% of GGO were classified as centrilobular nodules [2].

The presence of CN in patients with pulmonary arterial hypertension may rise a suspicion of PVOD, especially if they are accompanied by thickened septal lines and enlarged mediastinal lymph nodes. Such constellation of abnormalities at CT scan is often seen in PVOD. In PVOD predominantly small pulmonary veins are affected and that may lead to lung congestion. In Rajaram study thickened septal lines were present in 40% of the patients with ground glass attenuation pattern, and mediastinal lymphadenopathy — in 30% [2]. In the presented group of patients, CN were not combined with any other radiological signs of PVOD.

The appearance of ill-defined CN seen in our group of IPAH patients was quite similar to those observed in bronchiolar disorders or hypersensitivity pneumonitis [16, 17]. Nevertheless, as described in methods, there was no lung disease in anamnesis, no other signs of bronchiolitis, such as tree-in-bud pattern, no air-trapping on expiratory HRCT, no significant reduction of lung volumes in body plethysmography and, thus, the bronchiolar pathology or interstitial lung disease presenting with centrilobular nodules were excluded [18].

In three of our patients, CN were not described on initial HRCT but appeared in the course of IPAH progression. This observation could suggest that CN might be combined with progressive enlargement of small size pulmonary vessels. Nevertheless, CN were not observed in the remaining patients, in whom worsening of PH was found. Thus it is not clear whether CN represent the enlarged pulmonary vessels in IPAH. In the study group, CN described in initial HRCT scans, were also present in every subsequent radiological examination, indicating the possibility of the distinct phenotype of IPAH rather, than the consequence of hemodynamic worsening.

The other explanation of CN in IPAH was given by Nolan et al. who attributed them to the presence of cholesterol granulomas developing as a result of occult pulmonary haemorrhage or the excessive surfactant degradation [15]. Occult pulmonary haemorrhage as the possible cause of centrilobular nodules was also suggested by Rabiller et al. [4], who found significantly higher percentages of haemosiderin-laden macrophages in bronchoalveolar lavage fluid of PVOD patients compared to IPAH patients. This hypothesis may be also taken into account in the presented group of patients as haemoptysis was observed more frequently in CN patients compared to NPA group.

A very interesting finding was the lack of PFO in our group of CN patients. According to our best knowledge, this is the first report concerning PFO status in CN patients. Lack of PFO might be one of the reasons of significantly higher mRAP in CN patients compared to the rest of the group. Moreover, the other hemodynamic indices indicated the tendency for CN patients to be more severely compromised compared to other patients. Such relation may also be depicted by the tendency towards higher NT-proBNP levels in CN patients compared to the remaining population of IPAH patients.

Despite more severe hemodynamic compromise, the CN patients covered longer distance in 6MWT comparing to the others. This might illustrate the influence of age on 6MWT [19], as CN patients were significantly younger than the remaining ones.

Younger age of the patients and females predominance in our group of CN patients indicated that this population differed from classical PVOD population described by Montani et al. [9]. That classical PVOD population included mostly the older patients, with the larger proportion of males than in IPAH.

The prognostic significance of the described various forms of nonhomogenous lung attenuation, was difficult to assess due to small groups of patients analysed in this pilot study. There was, however, a tendency towards better survival in the patients with homogenous attenuation of the lungs in HRCT scans compared to those with CN and with FGGO. The percentage of 8-year survivors was 40% in NPA, comparing to 10% in CN and 17% in FGGO. Thus, the prognostic significance of CN and FGGO in IPAH have to be confirmed on larger group of patients.

Summary

CN were found either at the time of diagnosis or later in the course of the disease in 19% of IPAH patients. They were not accompanied by any other radiological features suggestive of PVOD. The CN patients were significantly younger, with more frequent haemoptysis, lack of PFO and higher mRAP, compared to the remaining IPAH patients. The prognostic significance of CN in IPAH needs further investigations on larger groups of patients.

Conflict of interest

The authors declare no conflict of interest.

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