

TGF- β_1 in bronchoalveolar lavage fluid in diffuse parenchymal lung diseases and high-resolution computed tomography score

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KEY WORDS

diffuse parenchymal lung diseases, high-resolution computed tomography score, interstitial pulmonary fibrosis, TGF- β_1

ABSTRACT

INTRODUCTION In the pathogenesis of diffuse parenchymal lung diseases (DPLDs), growth factors, including transforming growth factor β_1 (TGF- β_1), are responsible for cell proliferation, apoptosis, chemotaxis, and angiogenesis, and also for the production and secretion of some components of the extracellular matrix.

OBJECTIVES The aim of the study was to evaluate correlations in DPLDs between TGF- β_1 levels in bronchoalveolar lavage (BAL) fluid and high-resolution computed tomography (HRCT) score.

PATIENTS AND METHODS The study was performed in 31 DPLD patients in whom a selection of lung segments with high and low intensity of abnormalities was estimated by HRCT score. All patients underwent BAL with TGF- β_1 measured by an enzyme immunoassay in BAL fluid and video-assisted thoracic surgery lung biopsy from both selected segments.

RESULTS All 31 patients were diagnosed, and based on histopathology, they were classified into 2 groups: idiopathic interstitial pneumonia (usual interstitial pneumonia – 12, nonspecific interstitial pneumonia – 2, cryptogenic organizing pneumonia – 2, and desquamative interstitial pneumonia – 1) and granulomatous disease (sarcoidosis – 7, extrinsic allergic alveolitis – 5, and histiocytosis X – 2). The final analysis was performed in 28 patients who showed nonhomogenous distribution on HRCT. TGF- β_1 levels in BAL fluid were significantly higher in the areas with high intensity of abnormalities assessed by HRCT score ($P = 0.018$, analysis of variance). These levels were not different between the groups, but a trend towards higher levels in idiopathic interstitial pneumonia was observed.

CONCLUSIONS The results confirm that TGF- β_1 may be a good but not specific marker of fibrosis in DPLDs. A significant positive correlation between TGF- β_1 levels in BAL fluid and the HRCT score was observed.

INTRODUCTION Diffuse parenchymal lung diseases (DPLDs) are a heterogeneous group characterized by progressive dyspnea, the presence of diffuse reticular markings on the chest X-ray, and restrictive impairment in pulmonary function tests. DPLDs include not only diseases of known etiology, such as collagenosis or occupational

exposure, but also idiopathic interstitial pneumonias (IIP) and a large group of granulomatous diseases (GD), such as sarcoidosis, extrinsic allergic alveolitis (EAA), and rare histiocytosis X or lymphangioleiomyomatosis.

In the pathogenesis of DPLDs, especially of interstitial pulmonary fibrosis (IPF), growth

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TABLE 1 Clinical characteristics of patients

	IIP (n = 15)	GD (n = 13)	P	All patients (n = 28)
F/M	10/5	5/8	0.289	15/13
age, yrs	48 ± 14.2 47 (35.5–59)	46.9 ± 9.6 46 (40–55)	0.807	47.5 ± 12.0 47 (40–57)
smokers	6	2		8
comorbidities				
ischemic heart disease	2	2		
arterial hypertension	2	2		
diabetes	0	1		
pulmonary function tests				
VC, %	63.6 ± 15.0 61.5 (52.9–71.2)	86.8 ± 23.4 92.6 (79–97)	0.003	74.8 ± 22.5 75.4 (55–93.1)
FEV ₁ , %	68.7 ± 19.4 66.9 (56.2–78.2)	87.0 ± 20.3 87.9 (72–101.7)	0.016	77.6 ± 21.6 78 (58–94.6)
FEV ₁ /VC, %	100.6 ± 15.0 103.3 (88.6–112.2)	100.5 ± 12.5 100.6 (96–106)	0.992	100.5 ± 13.6 102 (90.5–108.1)
single-breath DLCO, %	66.5 ± 21.5 62.9 (53.4–81.8)			
TLC, %	69.8 ± 8.3 69.4 (63.1–75.4)			

Abbreviations: DLCO – diffusing capacity of the lung for carbon monoxide, F – female, FEV₁ – forced expiratory volume in 1 second, GD – granulomatous disease, IIP – idiopathic interstitial pneumonias, M – male, TLC – total lung capacity, VC – vital capacity

factors play a key role. They include transforming growth factor β (TGF- β), platelet-derived growth factor, insulin-like growth factor, and tumor necrosis factor, which are responsible for cell proliferation, apoptosis, chemotaxis, and angiogenesis, and also for the production and secretion of some components of the extracellular matrix. The most important is TGF- β produced by a variety of cells, including platelets, neutrophils, eosinophils, fibroblasts, and endothelial cells. In the study conducted by Smith et al.¹ TGF- β protein level was 11-fold higher in IPF patients compared with normal control lungs. A substantial body of evidence suggests that TGF- β is a critical cytokine that promotes pulmonary fibrosis. In IPF patients, TGF- β levels correlate with mortality.² A predominant isoform of TGF- β in IPF is TGF- β_1 .

In the diagnosis of IPF, high-resolution computed tomography (HRCT) plays an important role. HRCT sensitivity in the diagnosis of IPF is estimated at 86%,³ but the final diagnosis of a DPLD should be based on clinical features, radiological findings, and pathological evaluation of the biopsy specimen.^{4–6}

The distribution of diffuse parenchymal opacities in DPLDs is usually nonhomogenous – the areas of active inflammation and fibrosis may be adjacent to normal lung parenchyma. The HRCT score is a semiquantitative method of the overall assessment of distribution and type of diffuse opacities. It enables to determine the areas of the highest and lowest intensity of abnormalities and possible correlations with the levels of growth factors.

The aim of the study was to assess correlations between TGF- β_1 levels in bronchoalveolar lavage (BAL) fluid in DPLD patients and the activity of changes assessed by HRCT score.

PATIENTS AND METHODS A group of consecutive patients with suspected DPLD were included in the study. The final diagnosis had not been established prior to inclusion despite the clinical and radiological findings (especially HRCT) and the use of minimally invasive methods (e.g., trans-bronchial lung biopsy). In all patients, antinuclear and antineutrophil cytoplasmic antibodies were negative. Patients' general condition allowed to perform video-assisted thoracic surgery (VATS) lung biopsy under general anesthesia (American Society of Anesthesiologists, 1–3).

Only 1 patient with sarcoidosis had diabetes, and 2 patients from the IIP and GD groups had arterial hypertension and ischemic heart disease (TABLE 1).

Exclusion criteria were as follows: a radiological pattern of opacities typical for sarcoidosis or IIP, diagnosis of connective tissue disease, general status that excluded VATS, and lack of informed consent.

HRCT of the lungs was performed using the spiral HeliCAT Twin Flash (Elsint, Israel) with the Indy workstation (Silicon-Graphics, United States) and the software (OmniPro, United States). The HRCT score was calculated according to the Bergin and Remy-Jardin criteria.^{7,8} For each slice, as well as for the whole lung and individual

TABLE 2 High-resolution computed tomography score criteria for determining the intensity of abnormalities

Type and intensity of opacities	Horizontal distribution	Lobular distribution	Intensity of diffused opacities	Activity of diffuse opacities
1/nodular	0 – universal	0 – none	0 – none	0 – none
2/linear	1 – subpleural	1 – subpleural	1 – low	1 – low
3/ground glass	2 – peripheral	2 – peripheral	2 – middle	2 – middle
4/consolidations	3 – axial	3 – axial	3 – high	3 – high
score for each criterion		4 – centroalveolar		
0 – none		5 – panlobular		
1 – (0–25%)				
2 – <25–50%)				
3 – (>50%)				

lung segments, the semiquantitative assessment for the following types of opacities was performed: 1) nodular, 2) linear, 3) ground-glass, and 4) consolidations. The HRCT score was complemented by semiquantitative assessment of additional categories: 5) horizontal distribution pattern, 6) lobular distribution, 7) grade of intensity of diffuse opacities, and 8) activity of diffuse opacities (TABLE 2). The HRCT score for the whole lungs was calculated as the sum of all scores of 22 to 26 slices divided by the maximal possible score; the result was expressed as a percentage. The HRCT score for individual segments was calculated in the same way. The most involved (high; sA) and the least involved (low; sB) segments on the same side were determined. The HRCT score was independently calculated by 2 radiologists.

BAL was performed according to the American Thoracic Society guidelines,⁹ under mild intravenous sedation with midazolam (1–5 mg i.v.) and fentanyl (0.05–0.1 mg i.v.), using the IT160 videobronchoscopes (Olympus Medical Systems Corporation, Tokyo, Japan). All patients received oxygen through a nose catheter, and saturation and heart rate were monitored using a pulseoximeter during bronchoscopy.

In patients with nonhomogenous distribution of changes in HRCT score, BAL was performed from segments sA and sB. The tip of the bronchofiberscope was wedged in the chosen segment, and 4 portions of saline (50 ml each) were instilled. After instillation, the saline was gently sucked and collected in silicone container. Supernatant obtained after centrifugation was stored in –70°C.

TGF- β_1 levels in BAL fluid were measured by an enzyme immunoassay using commercial kits (“sandwich” ELISA, R&D Systems, Quntikine®, Human TGF- β_1 , United States).

VATS lung biopsy was taken from the segments chosen using the above-mentioned criteria and was performed under general anesthesia with double-lumen intubation. The standard video equipment was used (light source Quantum 3000 and video-camera 784, Stryker, United States with monitor PVM 204 3MD, Sony, Japan) and rigid 9 mm thoracoscope 30°, (Storz, Germany). The biopsies were performed using the EndoGia universal staplers (Tyco, United States).

For pathological examination, the standard hematoxylin-eosin stained, paraffin-embedded tissue blocks were used. The analysis was performed independently by 2 pathologists; neither of them was informed about the radiological findings nor the results of HRCT score.

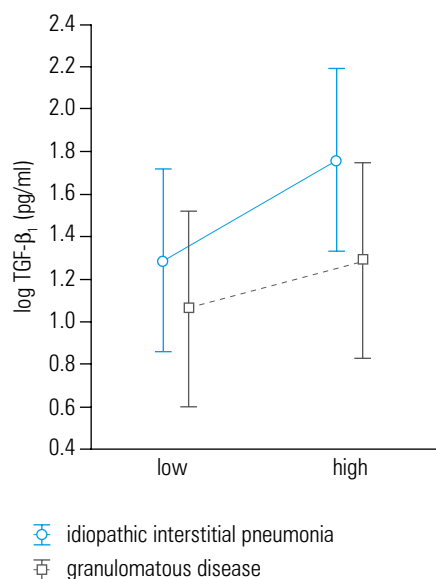
The study was approved by the Bioethical Committee of the Jagiellonian University, Kraków, Poland. All patients received detailed information regarding the procedures; also, their potential risks and benefits were discussed. Informed consent was obtained from all patients.

Statistical analysis Statistical analysis was performed using the Statistica™ software (Statsoft Inc., United States). Summary statistics were expressed as mean, standard deviation, median, as well as 25% and 75% percentiles. The Student’s t-test with separate estimation of variances was used for preliminary group comparison. The general linear model for response variables, including qualitative and quantitative variables and their interactions, was also used. The Tukey’s test was used for multiple comparisons. The level of significance was set at $P \leq 0.05$.

RESULTS Based on clinical and radiological findings and histological results of VATS lung biopsy, the diagnosis was established in all 31 patients. Histological examination of lung specimens alone enabled to establish a definitive diagnosis in 83.9% of patients. Based on histopathology, the patients were classified into 2 groups: IIP and GD. The IIP group included 17 patients: usual interstitial pneumonia (UIP) – 12, nonspecific interstitial pneumonia (NSIP) – 2, cryptogenic organizing pneumonia (COP) – 2, and desquamative interstitial pneumonia (DIP) – 1. The GD group included 14 patients: sarcoidosis – 7, EAA – 5, and histiocytosis X – 2. In 3 patients with homogenous distribution on HRCT, histiocytosis X – 1, UIP – 1, and COP – 1 were diagnosed.

Comorbidities did not affect TGF- β_1 levels in the studied patients. A smoking history correlated with higher TGF- β_1 levels ($P = 0.042$, analysis of variance [ANOVA]). There was no association between TGF- β_1 and age ($P = 0.630$, ANOVA) or sex ($P = 0.936$, ANOVA) (TABLE 1).

FIGURE Transforming growth factor β_1 (TGF- β_1) levels in bronchoalveolar lavage fluid were significantly higher in the areas with high activity of changes estimated by high-resolution computed tomography score ($P = 0.018$, analysis of variance)



The final analysis was performed in 28 patients who showed nonhomogenous distribution of changes on HRCT.

In the GD group, TGF- β_1 levels in sA were 4.4 ± 3.6 pg/ml, while in sB 3.4 ± 2.3 pg/ml. In the IIP group, TGF- β_1 levels were 9.0 ± 8.6 pg/ml and 4.7 ± 3.3 pg/ml in sA and sB, respectively. The TGF- β_1 levels in BAL fluid were significantly higher in the areas with high activity of changes estimated by HRCT score ($P = 0.018$, ANOVA). TGF- β_1 levels in BAL fluid were not different between the groups, but a trend towards higher levels in the IIP group was observed (FIGURE 1).

DISCUSSION The diagnosis of DPLDs is usually based on radiological findings, but even such a reliable method as HRCT has some limitations. Its accuracy in the diagnosis of IPF varies from 50% to 90%¹⁰⁻¹³ and largely depends on the experience of a radiologist.

However, in some cases, histological confirmation is necessary and VATS lung biopsy might be required. Open lung biopsy can determine the diagnosis in patients with DPLD in 70% to 93% of cases.¹⁴ In our study, histological examination of VATS lung specimen allowed to establish a definitive diagnosis in 83.9% of patients, but the final diagnosis of DPLD, based on clinical features, radiological findings, and histopathologic results, was established in all patients.

A technique that is suggested to increase the diagnostic yield of HRCT is the semiquantitative HRCT score. Its advantage is the quantitative assessment of the types of opacities and their activity. The use of HRCT score gives a unique opportunity to assess correlations between TGF- β_1 levels in BAL fluid in DPLD patients and the radiological activity of changes. Until now, there have been no data assessing the association between HRCT score and profibrotic TGF- β_1 .

Based on the HRCT score, our data have shown that TGF- β_1 levels in all patients were significantly higher in the areas with high disease activity

($P = 0.018$). Our results confirm the previous observations of Khalil et al.,¹⁵ who also reported higher levels of TGF- β_1 in active sites in IPF patients.

We also found that TGF- β_1 levels in BAL fluid were similar between the groups, although there was a trend towards higher levels in the IIP group. Similarly, Meloni et al.¹⁶ showed no differences in TGF- β levels in patients with scleroderma-associated interstitial lung disease, IPF, and sarcoidosis compared with healthy subjects. Also Salez et al.¹⁷ showed normal TGF- β_1 levels in sarcoidosis and healthy volunteers. Limper et al.¹⁸ observed that TGF- β_1 may play an important role in the synthesis of some compounds of the extracellular matrix, especially fibronectin and fibronectin receptor $\alpha 5 \beta 1$, and not only in IPF, but also in noncaseating granulomas, which implies that TGF- β_1 might modulate the mechanisms of repair and fibrosis in patients with sarcoidosis. These reports suggest that TGF- β_1 may not be a specific marker for any interstitial lung disease.^{15-17,19} Higher levels of TGF- β in IPF patients were found not only in lung biopsies, but also in BAL fluid.²⁰ Continuous mRNA expression of TGF- β_1 in alveolar macrophages may be responsible for higher TGF- β_1 levels in IPF patients.²¹ Some authors attempted to assess the factors that may activate TGF- β , such as thrombospondin 1 (TSP-1). Ide et al.²² reported increased levels of TSP-1 in serum and BAL fluid in IIP patients.²² However, the role of TSP-1 in the pathogenesis of IIP requires further investigation.

A number of studies assessed the role of genetic factors in the pathogenesis of IPF. Xaubet et al.²³ showed that TGF- β_1 polymorphism does not predispose to the development of IPF, but may play an important role in the progression of the disease. TGF- β may also influence the prognosis of interstitial lung diseases. Hiwatari et al.²⁴ demonstrated that the elevated levels of TGF- β in IPF patients might cause the progression of fibrosis and shorter survival.²⁴

Results of the present study confirm that TGF- β_1 in BAL fluid may be a good but not specific marker of fibrosis in DPLDs. A significant positive correlation between TGF- β_1 levels in BAL fluid and the activity assessed by HRCT score was observed.

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TGF- β_1 w popłuczynach oskrzelowo-pęcherzykowych u chorych na śródmiąższowe choroby płuc a aktywność zmian w tomografii komputerowej o wysokiej rozdzielczości

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SŁOWA KLUCZOWE

rozlane
śródmiąższowe
choroby płuc,
samoistne
włóknienie płuc,
TGF- β_1 , tomografia
komputerowa
o wysokiej
rozdzielczości

STRESZCZENIE

WPROWADZENIE W patogenezie rozlanych śródmiąższowych chorób płuc (*diffuse parenchymal lung diseases* – DPLD) czynniki wzrostu, w tym transformujący czynnik wzrostu β_1 (*transforming growth factor* β_1 – TGF- β_1), są odpowiedzialne za proliferację, apoptozę, chemotaksję i angiogenezę, a także produkcję i wydzielanie niektórych składników macierzy zewnątrzkomórkowej.

CELE Celem pracy była ocena zależności między stężeniami TGF- β_1 w popłuczynach oskrzelowo-pęcherzykowych u chorych na DPLD, a aktywnością zmian w tomografii komputerowej o wysokiej rozdzielczości (*high-resolution computed tomography* – HRCT) opartą na HRCT score.

PACJENCI I METODY Badanie przeprowadzono u 31 chorych na DPLD, u których na podstawie HRCT score wyznaczono segmenty płuca o największym i najmniejszym nasileniu zmian. U wszystkich chorych wykonywano płukanie oskrzelowo-pęcherzykowe, oznaczano stężenia TGF- β_1 w popłuczynach oskrzelowo-pęcherzykowych metodą immunoenzymatyczną, a następnie wideotorakoskopową biopsję płuca z dwóch wyznaczonych segmentów.

WYNIKI Rozpoznanie ustalono u wszystkich 31 badanych, a na podstawie wyniku badania histopatologicznego wyróżniono 2 grupy chorych na: samoistne włóknienie płuc (zwykłe śródmiąższowe zapalenie płuc – 12, nieswoiste śródmiąższowe zapalenie płuc – 2, kryptogenne organizujące się zapalenie płuc – 2 i złączające śródmiąższowe zapalenie płuc – 1) oraz choroby ziarniniakowe (sarkoidoza – 7, alergiczne zapalenie pęcherzyków płucnych – 5 i histiocytoza X – 2). Ostateczną analizę przeprowadzono u 28 chorych z nierównomierną dystrybucją zmian w HRCT. Stężenia TGF- β_1 w popłuczynach oskrzelowo-pęcherzykowych były istotnie większe w miejscach o dużej aktywności zmian, wyznaczonych na podstawie HRCT score ($P = 0,018$; analiza wariancji). Stężenia te nie różniły się między grupami, jakkolwiek obserwowano trend w kierunku większych stężeń u chorych na samoistne włóknienie płuc.

WNIOSKI Wyniki badań potwierdzają, że TGF- β_1 może być dobrym, jednak niespecyficznym markerem procesu włóknienia w DPLD. Zaobserwowano dodatnią, istotną statystycznie korelację pomiędzy stężeniem TGF- β_1 w popłuczynach oskrzelowo-pęcherzykowych i aktywnością zmian w HRCT score.

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