

Role of serum vascular endothelial growth factor D in discrimination of patients with polycystic lung diseases

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KEY WORDS

cysts, lymphangioleiomyomatosis, polycystic lung diseases, pulmonary Langerhans cell histiocytosis, vascular endothelial growth factor D

ABSTRACT

INTRODUCTION Polycystic lung diseases (PLDs) include numerous rare diseases including lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), and lymphocytic interstitial pneumonia. In these cases, diagnosis is based on a histological examination of open lung biopsy samples; however, it is not always possible to perform this procedure. Serum markers characteristic for a given entity are still being sought.

OBJECTIVES The aim of the study was to determine the usefulness of assessing serum vascular endothelial growth factor D (VEGF-D) concentration in the differential diagnosis of LAM and other PLDs (OPLDs).

PATIENTS AND METHODS Serum VEGF-D levels were measured by an enzyme-linked immunosorbent assay in 75 patients with PLDs including 29 women with LAM and 46 patients with OPLDs (28 women and 18 men).

RESULTS Serum VEGF-D levels were significantly higher in patients with LAM (median, 1557 pg/ml; interquartile range [IQR], 636–2593 pg/ml) than in all patients with OPLDs (median, 292 pg/ml; IQR, 233–405 pg/ml, $P < 0.0001$) or than in women with OPLDs (median, 344 pg/ml; IQR, 243–452 pg/ml, $P < 0.0001$). The serum VEGF-D level exceeding 468 pg/ml identified LAM patients with the specificity of 90% and sensitivity of 87% (area under the curve of 0.908; 95% confidence interval, 0.820–0.996). In none of the patients with OPLDs serum VEGF-D concentrations exceeded 800 pg/ml.

CONCLUSIONS An increased serum VEGF-D level is a highly specific biomarker useful in a differential diagnosis of LAM and OPLDs.

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INTRODUCTION Polycystic lung diseases (PLDs) constitute a significant proportion of orphan pulmonary disorders. PLDs include such rare diseases as lymphangioleiomyomatosis (LAM), pulmonary Langerhans cell histiocytosis (PLCH), lymphocytic interstitial pneumonia (LIP), and Birt-Hogg-Dubé disease.¹

The estimated incidence of PLD is from 3.4 to 7.8 per 1,000,000 population.¹⁻³ Reliable epidemiological data for the Polish population are still lacking, although several reports from regional respiratory centers have been published in recent years.⁴⁻⁷ LAM is caused by proliferation of

hamartomatous smooth muscle-like cells. The disease affects the lungs but also lymphatic vessels as well as mediastinal and retroperitoneal lymph nodes. LAM cells are prone to produce lymphangiogenic factors, such as vascular endothelial growth factor D (VEGF-D), which induces local angiogenesis and participate in the development of lesions. A sporadic form of LAM (sLAM) occurs with isolated lung involvement or in the course of tuberous sclerosis (TS), which is an autosomal dominant disorder characterized by hamartomas of the skin, kidneys, brain, lungs, retina, and heart. The somatic mutations of the *TSC2* gene

TABLE 1 Characteristics of the study groups

	LAM (n = 29)			OPLDs (n = 46)		
	sLAM (n = 22)	LAM/TSC (n = 7)	PLCH (n = 39)	COPD (n = 5)	LIP (n = 1)	TSC without LAM (n = 1)
men/women, n	0/22	0/7	21/18	0/5	0/1	0/1
mean age, y	41 ± 6	41 ± 4	36 ± 8	48 ± 4	44	18
smoking, mean pack/y	2.0 ± 1.5	3.6 ± 1.6	15 ± 10	5.8 ± 2.5	0	0
disease duration, mo (range)	119 (50–204)	64 (21–100)	56 (4–204)	47 (11–75)	36	226
patients with pneumothoraxes, n	15	2	14	0	1	0
mean number of pneumothoraxes	1.9	0.3	3	0	1	0
VC, % pred.	93 ± 15	97 ± 6	81 ± 10	114 ± 5	98	99
FEV ₁ , % pred.	74 ± 13	69 ± 9	69 ± 15	109 ± 7	99	95
TLC, % pred.	119 ± 28	105 ± 10	99 ± 12	110 ± 8	105	102
RV, % pred.	155 ± 31	115 ± 8	129 ± 44	109 ± 9	102	97
DL _{CO} , % pred.	57 ± 11	59 ± 6	55 ± 9	81 ± 9	89	92
patients with lower distance in 6MWT, n	2	0	3	0	within normal limits	within normal limits
patients with desaturation ≥5% in 6MWT, n	11	3	12	1	no desaturation	no desaturation
PO ₂ , mmHg	77 ± 8	78 ± 5	79 ± 7	81 ± 3	89	95
PCO ₂ , mmHg	33 ± 2	34 ± 1	35 ± 4	33 ± 1	35	36

Data are presented as number, number and range, or mean ± standard deviation.

Abbreviations: COPD – chronic obstructive pulmonary disease with predominant emphysematous component, DL_{CO} – diffusing capacity of the lung for carbon monoxide, FEV₁ – forced expiratory volume in 1 second, LAM – lymphangioleiomyomatosis, LAM/TSC – lymphangioleiomyomatosis in the course of tuberous sclerosis, LIP – lymphocytic interstitial pneumonia, OPLDs – other polycystic lung diseases, PLCH – pulmonary Langerhans cell histiocytosis, PCO₂ – arterial partial pressure of carbon dioxide, PO₂ – arterial partial pressure of oxygen, RV – residual volume, sLAM – sporadic lymphangioleiomyomatosis, TLC – total lung capacity, TSC – tuberous sclerosis, VC – vital capacity, 6MWT – 6-minute walking test

are observed in patients with sLAM, while patients with LAM/TSC typically have germline mutations in the *TSC1* and *TSC2* genes.^{1,8,9}

Likewise, pathological angiogenesis participates in the development of PLCH mainly in LCH lesion formation. Increased VEGF expression was observed in 70% of the patients, particularly with multisystemic manifestations of LCH presentation.¹⁰ PLCH is a disorder caused by polyclonal proliferation of the Langerhans cells, with cancer associated mutation, BRAFV 600E, detected in more than 50% of the cells.¹¹ The lungs can be affected as an isolated organ (frequently in adults) or the involvement of other organs can be observed simultaneously or consequently (typically, the bones, skin, and pituitary gland but also the lymph nodes, liver, spleen, gut, hematopoietic system, or central nervous system).^{1,3,11}

A radiological examination including high-resolution computed tomography (HRCT) plays an important role in the diagnosis of PLD. It shows specific abnormalities and, if compliant with clinical evaluation, they allow a direct diagnosis of LAM or PLCH.^{1–9,11} However, in some patients, the clinical and radiological manifestations are heterogenous. Because this particular group of patients frequently includes smokers, other radiological abnormalities characteristic for tobacco-related diseases, such as chronic obstructive lung disease, desquamative interstitial pneumonia, or respiratory bronchiolitis interstitial lung disease,

are also observed. To ensure reliable diagnosis, open lung biopsy or, less often, transbronchial biopsy has to be performed in such cases.^{1–9,11} Yet, both procedures are hampered by considerably higher risk of side effects in patients with cystic lesions, particularly persistent air leakage, infections, or respiratory failure. Finally, in some patients with a more severe PLD, invasive diagnostic procedures are not applicable owing to respiratory failure, pulmonary hypertension, or even lack of patient consent.^{1–9,11}

Undoubtedly, identification of a disease-specific serum biomarker would be of great clinical use. In recent years, several groups have published promising reports on the potential benefit of VEGF-D as a diagnostic biomarker for LAM.^{12–18} Its higher serum concentration (>800 pg/ml) has been observed in LAM patients but not in subjects with other cystic lung disorders, including PLCH.

In the present paper, we report the data demonstrating the clinical usefulness of serum VEGF-D measurement as part of differential diagnosis in PLD. To our knowledge, this is the first study including such a sizeable group of PLCH patients including both men and women.

PATIENTS AND METHODS The study group consisted of 75 patients with characteristic radiological presentation of cystic abnormalities in chest HRCT, including 29 women with LAM (mean age,

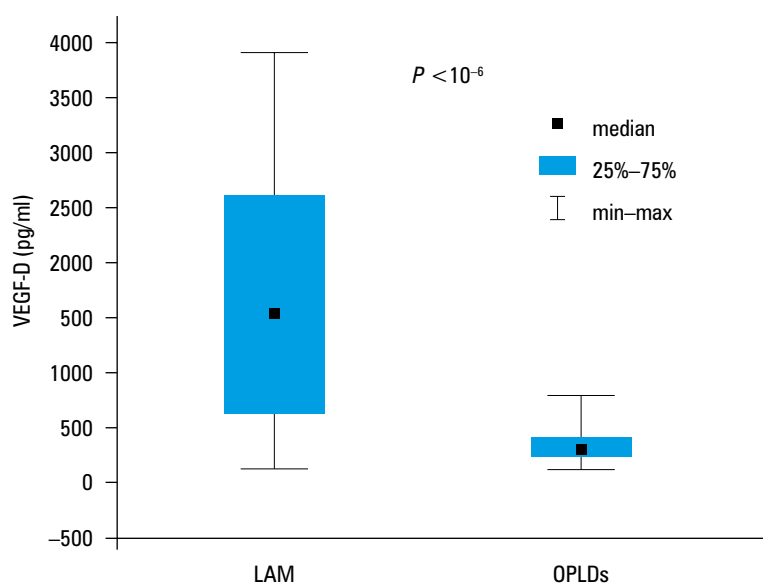


FIGURE 1 Serum vascular endothelial growth factor D (VEGF-D) concentrations in patients with lymphangioleiomyomatosis (LAM) and other polycystic lung diseases (OPLDs)

41 \pm 5.8 years) and 46 patients with other PLDs (OPLDs; mean age, 37.6 \pm 6.5 years). The LAM subgroup included 22 patients with sporadic LAM and 7 patients (women) with LAM in the course of TSC. The group of patients with OPLDs consisted of 39 patients with PLCH (21 women and 18 men), 1 woman with LIP, 1 woman with TSC without LAM, and 5 women with chronic obstructive pulmonary disease, characterized by predominant emphysematous lesions as demonstrated on HRCT. Clinical characteristics of the study group are presented in [TABLE 1](#). The diagnosis of PLD based on the clinical and radiological examination was confirmed by histological assessment of tissue material obtained by open lung biopsy.

Measurement of vascular endothelial growth factor D Blood (5 ml) was collected in serum separator tubes and allowed to clot for 30 min at 4°C and centrifuged at 2500 rpm for 10 min. Serum was aliquoted and stored at -70°C for further analysis. The VEGF-D concentration was determined by a quantitative sandwich enzyme immunoassay technique (R&D Systems, United States). All procedures were performed in accordance with the manufacturer's recommendations. Test sensitivity of 31.3 pg/ml and higher (range, 125 to 4000 pg/ml) allowed for a reliable measurement of serum VEGF-D levels.²⁰ Optical density was assessed at 450 nm using spectrophotometric reader Tecan Infinite M200 (Austria). All measurements were performed in duplicate. The final

results were calculated as the mean value of 2 independent estimations.

A statistical analysis was performed using the Statistica 10, Stat Soft Inc. 1984–2011 software. The receiver operating characteristic (ROC) curve analysis as well as the Mann–Whitney *U* test for the comparative analysis were applied. A *P* value of less than 0.05 was considered statistically significant. The local Bioethics Committee approved the study.

RESULTS Serum VEGF-D concentrations differed significantly between the study groups, with the median level of 1557 pg/ml (range, 468–3897 pg/ml; interquartile range [IQR], 636–2593 pg/ml) in the LAM group vs. 292 pg/ml (range, 126–791 pg/ml; IQR, 233–405 pg/ml) in the OPLD group (*P* < 0.0001) ([FIGURE 1](#), [TABLE 2](#)). Importantly, the median VEGF-D concentration of 344 pg/ml (range, 180–791 pg/ml) in women with OPLDs was significantly lower than in patients with LAM (*P* < 0.0001). In 1 female patient with TSC and no LAM, the VEGF-D level was 387 pg/ml, while in a patient with LIP it was 233 pg/ml. No patients with OPLDs had serum VEGF-D concentrations over 800 pg/ml.

No significant differences within the LAM group were observed, although the median serum VEGF-D concentration in the LAM/TSC group of 1885 pg/ml (IQR, 1621–3821 pg/ml) tended to be higher than in the sporadic LAM group (median, 1053 pg/ml [IQR, 595–2439 pg/ml] ([TABLE 2](#)). However, the difference was not significant.

The cut-off serum VEGF-D level of 468 pg/ml had significant discriminative value for LAM diagnosis (specificity of 90% and sensitivity of 87%; [FIGURE 2](#)).

The ROC curve analysis showed that VEGF-D identified LAM patients with the area under the curve (AUC) of 0.908 (95% confidence interval [CI], 0.820–0.996).

Moreover, serum VEGF-D sustained its diagnostic reliability in the subgroup of women with LAM vs. patients with OPLDs. At the cut-off level of 583 pg/ml, it assured the specificity of 87% and sensitivity of 83% (AUC, 0.889; 95% CI, 0.793–0.985) ([FIGURE 3](#)).

DISCUSSION VEGF-D belongs to a family of growth factors produced both by structural and pathological cells, including LAM and cancer cells.^{19–22} VEGF-D and its receptor

TABLE 2 Serum vascular endothelial growth factor D concentration in the study groups

Study group	n	Median	Lower quartile	Upper quartile	<i>P</i> value
LAM	29	1557	636	2594	<10 ⁻⁶
OPLDs	46	292	233	406	<10 ⁻⁶
women with OPLDs	28	344	243	452	<10 ⁻⁶
sLAM	22	1053	595	2439	0.1
LAM/TSC	7	1855	1621	3821	0.1

Abbreviations: see [TABLE 1](#)

FIGURE 2 Receiver operating characteristic curve for vascular endothelial growth factor D concentrations in patients with lymphangioleiomyomatosis vs. those with other polycystic lung diseases (area under the curve, 0.908; 95% confidence interval, 0.820–0.996)

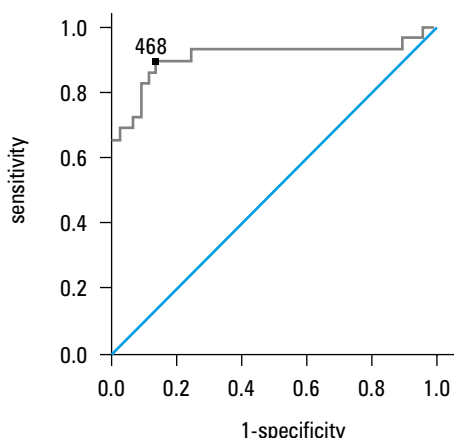
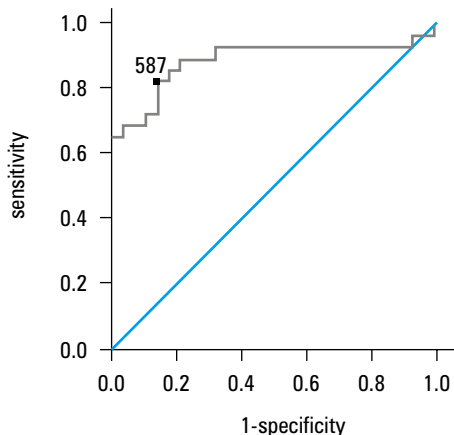


FIGURE 3 Receiver operating characteristic curve for vascular endothelial growth factor D concentrations in women with lymphangioleiomyomatosis vs. those with other polycystic lung diseases (area under the curve, 0.889; 95% confidence interval, 0.793–0.985)



VEGFR-3/Flt-4 are considered the key factors triggering new blood and lymphatic vessel formation and enabling tumor cell to metastasize.¹⁹ It has been well documented that VEGF-D was the only growth factor within the VEGF family significantly related to respiratory pathology in LAM patients. Serum concentrations of other VEGFs, such as VEGF-A or VEGF-C, demonstrated no significant discriminative value between LAM patients and healthy individuals.¹³

From the clinical perspective, it is much more important to be able to differentiate patients within the PLD group than to distinguish between those patients and healthy individuals. The most common lung disorders presenting with polycystic abnormalities in a radiological examination are chronic obstructive pulmonary disease with predominant emphysematous component, PLCH, and LAM. Occasionally, cysts are also observed in the course of Sjögren's syndrome, systemic lupus erythematosus, lymphocytic interstitial pneumonia, light chain disease, congenital cystic malformations, or Birt-Hogg-Dubé disease.¹

In 2008, Young et al.¹⁵ were the first to report significantly lower serum VEGF-D levels in 7 patients with PLCH compared with 38 women with LAM.¹⁵ They later presented data from patients with different PLDs including sporadic LAM (n = 56), LAM/TSC (n = 28), emphysema (n = 10), Birt-Hogg-Dubé disease (n = 12), Sjögren's syndrome accompanied with cystic abnormalities (n = 7), and PLCH (n = 15).¹³ Serum

VEGF-D level in the LAM group was significantly higher than in the other groups, with a diagnostically specific cut-off level of 800 pg/ml. The discriminative value of serum VEGF-D was emphasized by the fact that its high levels were present exclusively in LAM patients. Moreover, it was demonstrated that serum VEGF-D level was as high as 3500 pg/ml in men with TSC (n = 5) and LAM/TSC (n = 2), suggesting the contribution of VEGF-D to LAM cell dissemination and proliferation. Therefore, VEGF-D might be perceived as a promising potential biomarker for monitoring LAM therapy with, for example, mammalian target of rapamycin inhibitors. This has been proved recently in the group of 118 patients with TSC and LAM/TSC treated with everolimus in whom plasma VEGF-D levels correlated with angiomyolipoma lesion and reductions in angiomyolipoma volume.¹⁴

Of particular importance is the possible link between the serum VEGF-D concentration and the extent of lung damage suggested by several authors. Young et al.¹⁵ showed that patients with LAM/TSC had a higher serum VEGF-D concentration than patients with sporadic LAM.¹⁵ Similar findings were shown in our study; however, owing to an insufficient number of patients, the difference was not statistically significant.

Seyama et al.¹³ demonstrated a significant correlation between the VEGF-D level and respiratory function represented by the forced expiratory volume in 1 second percentage of vital capacity (FEV₁%VC) and carbon monoxide transfer factor.¹³ That observation was not confirmed by Glasgow et al.¹⁷ who, in a group of 111 LAM patients, detected no significant association between serum VEGF-D and lung function parameters (FEV₁, forced vital capacity, FEV₁%VC, total lung capacity, residual volume), annual FEV₁ decline or diffusing capacity of the lung for carbon monoxide (DL_{CO}). On the other hand, higher serum VEGF-D in LAM patients with lymphatic system involvement correlated well with the extent of abnormalities displayed by chest computed tomography as well as DL_{CO}.¹⁷ Additionally, in LAM patients treated with sirolimus, reduced serum VEGF-D levels correlated with lung function stabilization, symptom relief, and improvement in the quality of life.¹⁸

We demonstrated substantially higher serum VEGF-D levels in patients with LAM compared with those with OPLDs. Moreover, we confirmed the discriminative significance of VEGF-D cut-off level of 800 pg/ml, thus implying its usefulness in the differential diagnosis of the subjects with cystic abnormalities in a radiological examination. Importantly, the VEGF-D level was low in the patient with TSC without LAM and that with LIP with cystic lesions in the lung as well as in patients with chronic obstructive emphysema and PLCH.

The group of patients with PLCH in our study was considerably larger than in the previous studies, and the measurement of serum VEGF-D

concentrations were preformed both in men and women. However, it should be underlined that not all patients with sLAM had elevated levels of VEGF-D (5 of 22); therefore, values below 500 pg/ml do not exclude LAM. On the other hand, it is a particularly interesting group of patients and further studies on a larger group are needed to analyze the correlation between serum VEGF-D concentrations and the course of the disease.

In conclusion, we believe that serum VEGF-D is a novel promising biomarker that could be successfully used for the differential diagnosis of LAM from OPLDs. Moreover, the use of VEGF-D in everyday clinical practice might result in a considerable reduction in the number of diagnostic open lung biopsies.

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Wartość oznaczania w surowicy stężenia naczyniowego czynnika wzrostowego D w diagnostyce różnicowej chorych na zmiany torbielowate w płucach

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SŁOWA KLUCZOWE

choroby wielotorbielowate płuc, limfangioleiomiomatoza, naczyniowy czynnik wzrostowy D, płucna histiocytoza z komórek Langerhansa, torbiele

STRESZCZENIE

WPROWADZENIE Choroby manifestujące się zmianami torbielowatymi w płucach (*polycystic lung diseases* – PLD) obejmują szereg rzadkich chorób takich jak limfangioleiomiomatoza (LAM), histiocytoza z komórek Langerhansa i limfocytowe śródmiąższowe zapalenie płuc. Podstawą diagnostyki w tych przypadkach jest badanie histologiczne wycinków z płuc, pobranych drogą otwartej biopsji, co nie zawsze jest możliwe. Poszukiwane są markery w surowicy charakterystyczne dla danej jednostki chorobowej.

CELE Celem pracy było zweryfikowanie użyteczności badania stężenia naczyniowego czynnika wzrostowego D (*vascular endothelial growth factor D* – VEGF-D) w diagnostyce różnicowej LAM i innych PLD (*other PLD* – OPLD).

PACJENCI I METODY Stężenia VEGF-D mierzono metodą ELISA u 75 chorych z PLD: 29 kobiet chorych na LAM, 46 chorych na OPLD (28 kobiet i 18 mężczyzn).

WYNIKI U chorych na LAM stwierdzono znamienne wyższe stężenie VEGF-D w surowicy (mediana 1557 pg/ml, *interquartile range* [IQR]: 636–2593 pg/ml) w porównaniu z grupą chorych na OPLD (mediana 292 pg/ml; IQR: 233–405 pg/ml; $p < 0,0001$) oraz z kobietami chorymi na OPLD (mediana 344 pg/ml; IQR: 243–452 pg/ml; $p < 0,0001$). Stężenie VEGF-D w surowicy > 468 pg/ml identyfikowało chorych na LAM z czułością 90% i swoistością 87% (*area under the curve* [AUC]: 0,908; 95% CI: 0,820–0,996). U ani jednego pacjenta chorego na OPLD nie stwierdzono stężenia VEGF-D w surowicy przekraczającego 800 pg/ml.

WNIOSKI Zwiększone stężenie VEGF-D w surowicy jest wysoce swoistym markerem różnicującym chorych na LAM od chorych na OPLD.

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