Original Article

Leucine-rich a-2 glycoprotein as a potential biomarker of idiopathic multicentric Castleman disease with pulmonary involvement: a single-center case-control study from Japan

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Background: There are no known biomarkers for monitoring disease activity in idiopathic multicentric Castleman disease (MCD) with pulmonary involvement. We investigated the utility of serum leucine-rich α2-glycoprotein levels, which reflects interleukin 6 independent inflammatory change, for monitoring disease activity in patients with idiopathic MCD with pulmonary involvement.

Methods: We retrospectively examined cases of idiopathic MCD diagnosed at Osaka University Hospital. The serum levels of leucine-rich α2-glycoprotein were compared between patients with idiopathic MCD and healthy controls. The difference in leucine-rich α2-glycoprotein levels before and after treatment (Δleucine-rich α2-glycoprotein) was evaluated with respect to the relationship with pulmonary function. In addition, the relationship between cytokine and chemokine profiles and the leucine-rich α2-glycoprotein concentration was investigated. The results were analyzed using pathway analysis.

Results: The leucine-rich α2-glycoprotein concentrations were significantly higher in treatment-naïve patients (n=5) than in healthy controls (n=3) (P=0.035). Further, the Δleucine-rich α2-glycoprotein concentration was significantly correlated with Δ percent diffusing capacity of the lung for carbon monoxide (r=–0.88, P=0.049) and tended to correlate with Δ percent vital capacity (r=–0.68, P=0.21) although the difference was not significant for the latter association. The concentrations of chemokines and cytokines, such as CXCL9, CXCL11, CXCL1, and a proliferation-inducing ligand, were higher in the patient group than in the healthy control group. Enrichment analysis indicated that leucine-rich α2-glycoprotein could be elevated via the upregulation of chemokines in patients with idiopathic MCD using these parameters.

Conclusions: Leucine-rich a2-glycoprotein may be useful for monitoring disease activity in patients with idiopathic MCD with pulmonary involvement.

Keywords: Multicentric Castleman disease (MCD); leucine-rich α2-glycoprotein; chemokine; disease activity

Submitted Dec 28, 2021. Accepted for publication Apr 07, 2022.
doi: 10.21037/jtd-21-1973
View this article at: https://dx.doi.org/10.21037/jtd-21-1973

Introduction

Multicentric Castleman disease (MCD) is a multiclonal lymphoproliferative disease characterized by aggregation of plasmacytes with hyperplastic germinal center of the lymphatic node, resulting in systemic inflammation and potentially fatal multiple organ failure, involving pulmonary manifestation. The incidence per million persons is 5.1–5.7 in the United States and 2.4–5.8 in Japan (1,2). Patients with idiopathic MCD (iMCD) account for approximately 30% of patients with MCD (3). Although the etiology of iMCD remains unclear, interleukin-6 (IL-6) plays a key role in the pathogenesis and symptomatology of the disease (4). In this context, monoclonal antibodies directed against the IL-6 receptor (tocilizumab) and IL-6 (siltuximab) have been developed as treatment options for iMCD. However, IL-6 levels are not elevated in all patients with iMCD, and approximately 50% of patients do not benefit from IL-6 inhibition (5). In addition, some patients have low serum IL-6 levels even during disease flare-ups (6,7), suggesting that IL-6-independent pathways may drive disease pathogenesis in a subset of patients with iMCD. In addition to IL-6, several other mediators, such as CXCL13, IL-1, and tumor necrosis factor α (TNF-α), have been reported as candidate pathogenic factors (8). Currently, there are no validated biomarkers for monitoring the disease activity in iMCD. Particularly, it is difficult to evaluate disease activity of pulmonary manifestation with iMCD, which respirologists occasionally treat.

Leucine-rich α2-glycoprotein (LRG) is an approximately 50-kDa glycoprotein, including eight leucine-rich repeat domains (9). LRG is induced by IL-6 and other cytokines such as IL-22 by induction of STAT3 and TNF-α, IL-1β by induction of NFκB (10). Previous studies have demonstrated that LRG may serve as a potential biomarker for inflammation-related diseases such as Crohn's disease, infection, asthma, and various types of cancer (11-17). In particular, in patients with ulcerative colitis, LRG levels are more strongly correlated with disease activity than C-reactive protein (CRP) levels (18). Additionally, LRG could detect inflammation in patients with rheumatoid arthritis during IL-6 blockade treatment (19). These findings indicate that LRG could reflect both IL-6-dependent and -independent inflammatory changes and thus may have the potential to monitor disease activity in iMCD, which cannot be detected only by CRP. However, data on the role of serum LRG levels in patients with iMCD are lacking.

We hypothesized that LRG could be a biomarker of pulmonary manifestation of iMCD, which has no indicator of disease progression. The present study aimed to evaluate the utility of serum LRG levels for monitoring disease activity in patients with iMCD with pulmonary involvement. We present the following article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1973/rc).

Methods

Study design

We conducted a retrospective study of 165 patients diagnosed with Castleman Disease at Osaka University Hospital between January 2008 and July 2018 identified via a computer search. Of these, 68 patients had iMCD and 20 patients had iMCD with abnormal shadow in the lung. Finally, five patients with histologically confirmed iMCD diagnosis with pulmonary involvement were examined, whereas 15 patients were excluded because they only had imaging findings but their diagnoses were not histologically confirmed. Longitudinal data of pulmonary function tests such as percent diffusing capacity of the lung for carbon monoxide (%DLco), percent vital capacity of the predicted normal value (%VC) and percent forced expiratory volume in 1 s (FEV1.0%) were collected. In addition, the parameters obtained in clinical practice, such as CRP, hemoglobin, platelets, neutrophil counts, and KL-6 were estimated. Sera from three healthy volunteers without any diagnosed disease were used as samples of healthy controls. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients provided informed consent, and this study was approved by the ethical review board of Osaka University Hospital (#20019).

Evaluation of the serum LRG concentration

LRG was quantified in the sera of the five iMCD patients with pulmonary involvement by latex-enhanced immunoturbidimetric assay in the laboratory of SEKISUI CHEMICAL, Tokyo, Japan. LRG measurements were performed before and during remission (defined as a CRP level of <10 mg/L and fewer than two minor diagnostic criteria (20) after treatment with tocilizumab and/or steroid in the same patients with iMCD). The difference in LRG

Table 1 Patient characteristics

No.	Sex	Age (years)	PS	Trigger for consultation	Biopsy site	Extra pulmonary symptoms	Treatment	Outcome
1	M	60	2	Dyspnea on exertion	Mediastinal lymph node left upper and lower pulmonary lobe	Moderate anemia, mild hypoalbuminemia	Tocilizumab	Alive (6.6 years)
2	M	36	1	Hyperproteinemia	Right upper and inguinal pulmonary lobe and skin	Moderate anemia, severe hypoalbuminemia, renal dysfunction (nephrotic syndrome), skin lesion	Steroid	Alive (2.9 years)
3	M	67	2	Abnormal shadow	Mediastinal lymph node	Renal dysfunction (elevated creatinine level)	Tocilizumab	Alive (2.0 years)
4	F	43	2	Proteinuria, Hematuria	Right upper and lower pulmonary lobe	Renal dysfunction (mesangial proliferative glomerulonephritis)	Steroid	Alive (3.1 years)
5	M	54	1	Rash	Left upper and lower pulmonary lobe	Skin lesion, renal dysfunction	Steroid	Alive (3.0 years)

PS, performance status; M, male; F, female.

levels before and after treatment was examined.

Measurement of cytokines and chemokines

We investigated the cytokine and chemokine profiles of patients with iMCD and the relationship between these mediators and the LRG concentration. The serum cytokines TNF-α, IL-13, IL-4, IL-10, IL-6, IL-2, TNF-β, interferon-γ, IL-17A, IL-12p70, a proliferation-inducing ligand (APRIL), B-cell activating factor, and CD40L and serum chemokines monocyte chemoattractant protein-1, CXCL10, eotaxin, CCL17, macrophage inflammatory protein (MIP)-1α, MIP-1β, CXCL9, MIP-3α, CXCL5, CXCL1, CXCL11, and IL-8 were analyzed using a LEGEND plex™ Human B Cell Panel and a LEGEND plex™ Human Proinflammatory Chemokine Panel (BioLegend Inc., San Diego, CA, USA) according to the manufacturer's instructions. The concentrations of cytokines and chemokines were evaluated using a FACS Canto II Flow Cytometer (BD Bioscience, San Jose, CA, USA). In addition, pathway analysis was performed using selected factors that significantly differed between naïve patients with iMCD and healthy controls.

Statistical analysis

A permutation test was used to compare the serum LRG concentration between patients with iMCD and healthy controls. Pearson's rank correlation coefficient was estimated to analyze the relationships of parameters of pulmonary faction test and LRG and other serum proteins. Complete case analysis was used for handling missing data. All statistical analyses were performed using R ver. 4.0.2 software (available at http://www.R-project.org; R Foundation for Statistical Computing, Vienna, Austria). Pathway analysis was performed using Cytoscape software with ClueGo plug-in based on the Reactome pathway database. Statistical significance was set at $P<0.05$.

Results

Patient characteristics

The characteristics of the five patients with iMCD are shown in *Table 1*. The median age at blood sampling before treatment was 54 years (interquartile range, 43–60 years). One patient was female (20.0%). These characteristics were not different from healthy controls (42 years old, male; 49 years old, female; 78 years old, male). Three patients with iMCD received steroids, while two received tocilizumab. The details of histological findings, baseline chest imaging, and comprehensive pulmonary function test are shown in the Appendix 1.

Evaluation of LRG concentrations

The LRG concentrations were significantly higher in treatment-naïve patients before treatment induction than in the healthy controls ($P=0.035$). Although the other factors

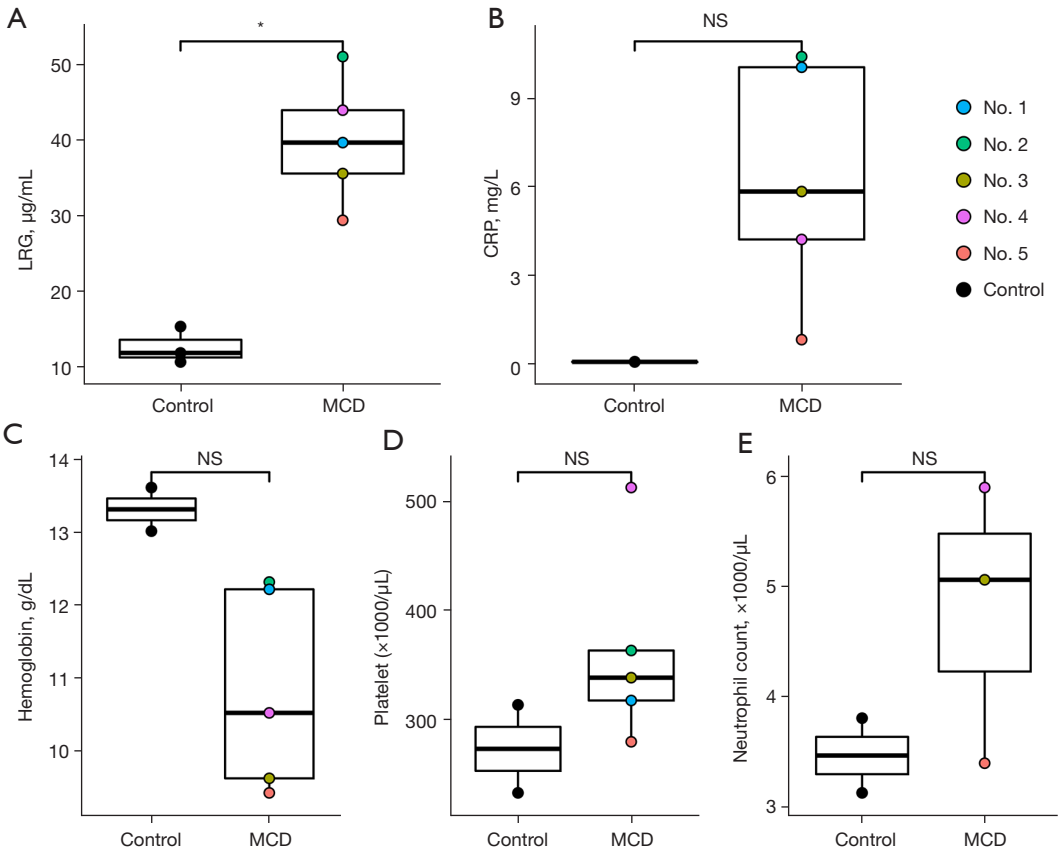

Figure 1 Comparison of the serum LRG level between patients and healthy controls. The serum LRG levels were significantly higher in treatment-naïve patients than in healthy controls. (P=0.035). A permutation test was used. An asterisk means that the P value is less than 0.05. LRG, leucine-rich α2-glycoprotein; CRP, C-reactive protein; NS, means no significant difference.

such as CRP level, hemoglobin level, platelet count, and neutrophil count differed between iMCD patients and healthy controls, especially IL-6 dependent factors such as CRP level, hemoglobin level, and platelet count were higher in iMCD patients (*Figure 1*). Concerning the delta difference (referred to as Δ below) before treatment and during remission, the ΔLRG concentration was significantly correlated with Δ%DLco (r=–0.88, P=0.049). Additionally, the ΔLRG concentration tended to correlate with Δ%VC (r=–0.68, P=0.21), although not significantly. However, although the ΔCRP concentration was significantly correlated with Δ%DLco (r=–0.94, P=0.016), a relationship between ΔCRP and Δ%VC was not detected. The ΔKL-6 concentration tended to be correlated with Δ%VC and Δ%DLco; however, these relationships were not significant. Further, the ΔIL-6 concentration was not correlated with respiratory function (*Figure 2*). These results implied that LRG concentration could be a biomarker of MCD-associated pulmonary lesions.

Subsequently, we focused on whether LRG and CRP behaved differently with respect to the clinical course regarding respiratory function. In patient No. 3, both the LRG and CRP levels decreased below the threshold after the induction of tocilizumab, while in patient No. 5, the LRG level did not decrease below the threshold, although the CRP level decreased below the threshold after steroid use. Further, in patient No. 3, the %VC remained steady and the %DLco increased. However, the %VC and %DLco worsened in patient No. 5 (*Figure 3*). This result suggested that LRG has the potential to detect smoldering inflammation or progressive disease under anti-inflammatory treatment, which could not be detected by CRP estimation due to masking.

Changes were evaluated for biochemical, symptoms, and radiographic findings to evaluate the correlation of LRG and other factors before and after treatment such as steroid and

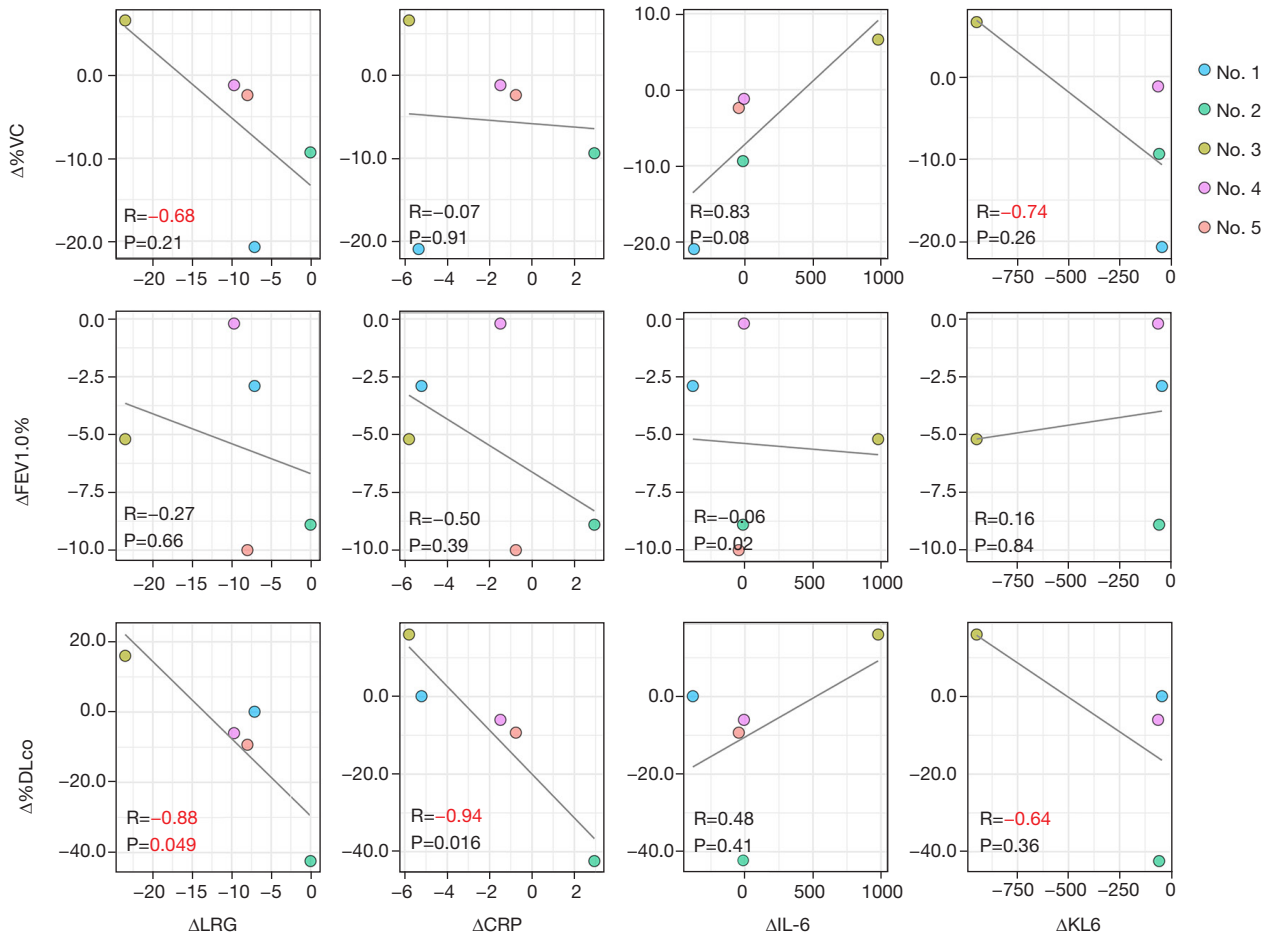

Figure 2 The relationship between the change in inflammatory markers and the change in respiratory function. The change in the LRG concentration was significantly correlated with the change in %DLco (r=–0.88, P=0.049) and tended to correlate with the change in %VC (r=–0.68, P=0.21), although not significantly. Pearson's rank correlation coefficient was estimated to analyze the relationships of parameters. %VC, percent vital capacity of the predicted normal value; FEV1, forced expiratory volume in 1 second; %DLco, percent diffusing capacity of the lung for carbon monoxide; LRG, leucine-rich α2-glycoprotein; CRP, C-reactive protein; IL, interleukin; KL6, Krebs von den Lungen-6.

tocilizumab (Table S1, Figure S1). LRG tended to correlate with biochemical values such as hemoglobin, albumin, and CRP, although not with radiological findings and symptoms changes as observed in CRP. Subsequently, we scrutinized the relationships with ΔLRG and ΔCHAP scores, proposed as the scoring system for disease activity (21). The ΔLRG tended to correlate with Δthe CHAP score, although not statistically significant due to the small sample size (Figure S2).

The correlation between LRG levels and iMCD severity based on Castleman's Disease Collaborative Network Criteria was evaluated (22). Only patient No. 5 was classified as severe iMCD because of renal dysfunction and pulmonary involvement. However, the LRG levels of this patient were not the highest. This may imply that LRG can be a useful individual biomarker but cannot reflect disease severity across individuals.

Cytokine and chemokine quantification

Cytokine and chemokine levels were evaluated in treatment-naïve patients compared to healthy controls. The concentrations of chemokines such as CXCL9, CXCL11, and CXCL1 (all P<0.05) were higher in the patient group than in the healthy control group. In addition, the concentration of APRIL, which is known to be associated with the proliferation of plasma cells, was significantly higher in patients with iMCD than in healthy controls

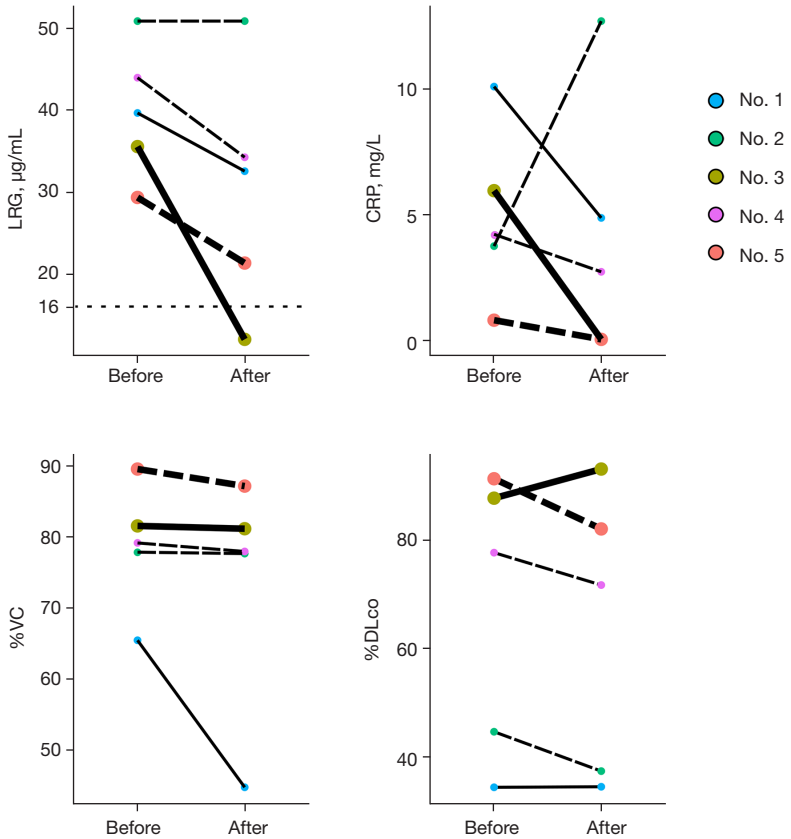

Figure 3 Changes in inflammatory marker levels and pulmonary function. The solid and long dashed lines represent patients treated with tocilizumab and steroids, respectively. A permutation test was used. LRG, leucine-rich α2-glycoprotein; CRP, C-reactive protein; %VC, percent vital capacity of the predicted normal value; %DLco, percent diffusing capacity of the lung for carbon monoxide.

(P<0.05). The IL-6 levels also tended to be higher in patients with iMCD than in the controls, but the difference was not significant (P=0.25) (*Figure 4*). No other cytokines or chemokines significantly differed between the two groups (Table S2).

Enrichment analysis

The pathway analysis indicated that LRG and chemokines were linked via neutrophil degranulation (*Figure 5*).

Discussion

The present study aimed to evaluate the utility of serum LRG levels for monitoring disease activity in patients with iMCD with pulmonary involvement. The results indicated that serum LRG levels could reflect disease activity with respect to respiratory function and have the potential to detect smoldering inflammation under anti-inflammatory treatment. In addition, pathway analysis implied that the pathway of LRG upregulation in patients with iMCD differed from that of CRP upregulation. Enrichment analysis showed a higher LRG level was induced via CXCL1 associated with the neutrophil degranulation pathway. In this study, other chemokines, such as CXCL11 and CXCL9, were significantly increased in patients with iMCD. Previous studies have noted the greater importance of chemokines relative to cytokines for monitoring the disease activity of patients with iMCD. In particular, CXCL13 was identified as a representative of iMCD flares using proteomics. Elevated CXCL13 can trigger B cells to mature into plasma cells, frequently observed in histological samples (23). One interesting finding of the current study was that APRIL levels were significantly higher in patients with iMCD than in controls. This implied that increased plasma cells in patients with iMCD were introduced via

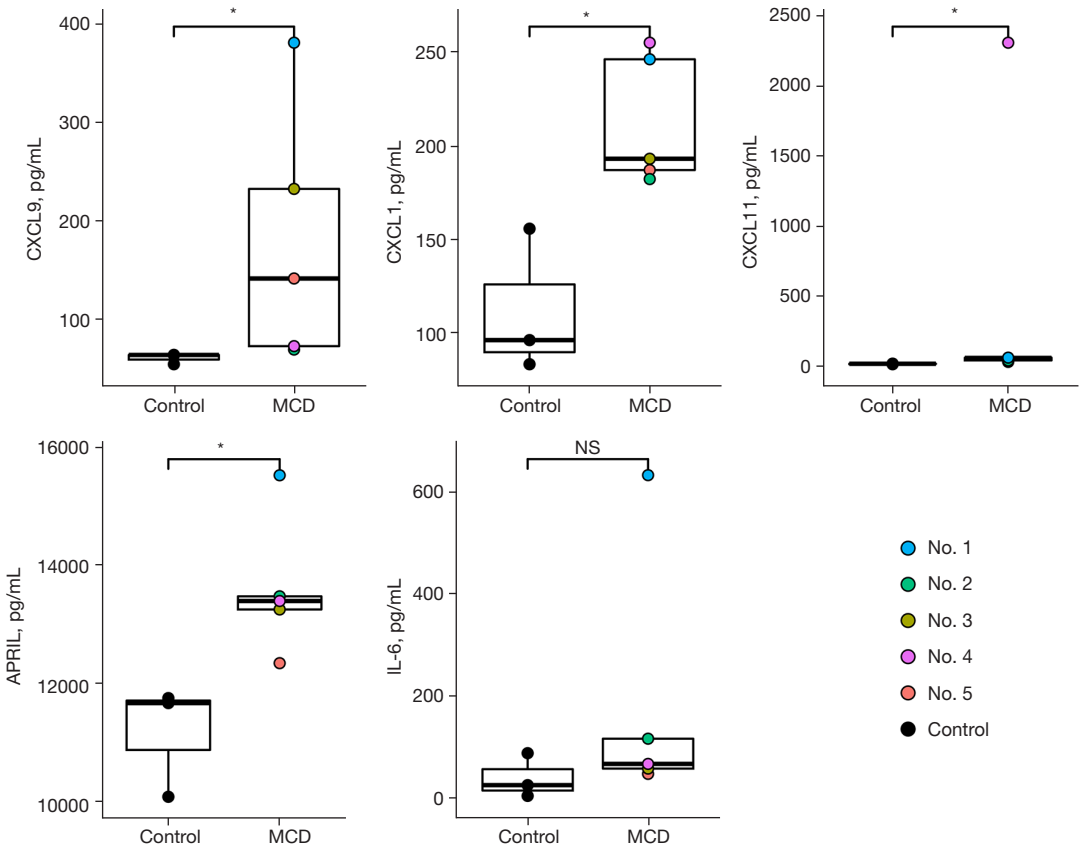

Figure 4 Cytokine and chemokine quantification. Cytokine and chemokine levels were compared between treatment-naïve idiopathic MCD patients and healthy controls. The CXCL9, CXCL11, CXCL1 concentrations and APRIL were higher in the patient group than in the healthy control group. A permutation test was used. An asterisk means that the P value is less than 0.05. MCD, multicentric Castleman disease; APRIL, proliferation-inducing ligand; NS, means no significant difference.

CXCL13 and APRIL.

The delta difference in serum LRG levels before and after treatment reflected respiratory function changes, such as % forced vital capacity and %DLco. Regarding ventilatory impairment in iMCD, a previous report demonstrated that iMCD patients with pulmonary involvement presented with obstructive ventilatory impairment (4/13) and impaired gas exchange (12/13) (24). In this study, over 50% (3/5) of the patients presented with the same type of ventilatory impairment. The serum CRP level did not reflect both factors but was correlated with %DLco. Thus, LRG may be a better biomarker of iMCD with pulmonary involvement.

This study has a few limitations. First, in this observational study, bias may have been present in patient selection. Because we could not distinguish pulmonary manifestation of iMCD and lung abnormal shadow of other comorbidities by image findings, we focused on histologically-confirmed iMCD patients with thoracic lesions. However, pulmonary manifestation is not a common manifestation of iMCD. The patients with thoracic lesions who needed biopsy were rare, resulting in selection bias caused by small sample size. Additionally, we could not evaluate patients who were not histologically examined. Patients with subtle pulmonary lesions were also excluded from the study.

Second, because we used serum collected in the biobank, the data of hemoglobin, platelet, and neutrophil count of one of three healthy control patients were missing. These could underestimate the difference between the five iMCD patients and healthy controls. Third, we could not evaluate whether LRG levels can be used to follow patients longitudinally because none of the five patients developed progressive disease based on CDCN response

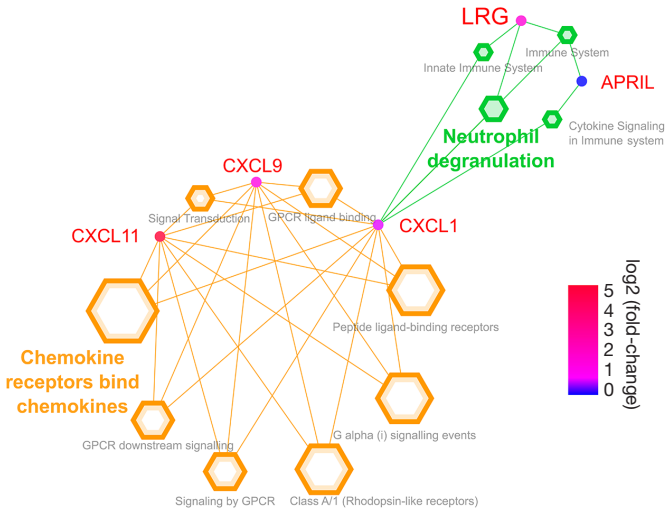

Figure 5 Enrichment analysis findings. Using Reactome pathway analysis via R, we found that LRG and chemokines were linked via neutrophil degranulation. LRG, leucine-rich α2-glycoprotein. APRIL, proliferation-inducing ligand.

criteria. Fourth, the specificity of LRG for monitoring of pulmonary manifestation of iMCD was not confirmed because iMCD with and without pulmonary involvement or other mimickers such as HHV8 positive MCD and POEMS syndromes were not compared. Fifth, this study was a single-center cohort study conducted in Japan; thus, the results may not completely represent the entire population of patients with iMCD with pulmonary involvement. A multicenter, international prospective study will be needed in future research to resolve these limitations.

Conclusions

LRG could detect inflammation, such as deterioration of pulmonary function, during anti-inflammatory treatment and may be more useful than CRP for monitoring disease activity in patients with iMCD with pulmonary involvement.

Acknowledgments

We thank Mana Nakayama for collecting the samples.
Funding: This work was supported by the Japan Society for the Promotion of Science KAKENHI [JP19K08650 to YT; JP18H05282 to AK]; Center of Innovation program from the Ministry of Education, Culture, Sports, Science and Technology of Japan [to AK]; Japan Agency for Medical Research and Development [J200705023, J200705710, J200705049, JP18cm016335, and JP18cm059042 to AK]; Kansai Economic Federation grant [to AK]; and Mitsubishi Zaidan grants [to AK]. This study was supported in part by SEKISUI CHEMICAL (Tokyo, Japan), which estimated serum LRG levels.

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1973/rc

Data Sharing Statement: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1973/dss

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1973/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1973/coif). AK reports grants from the Japan Society for the Promotion of Science KAKENHI [JP19K08650 to YT; JP18H05282]; Center of Innovation program from the Ministry of Education, Culture, Sports, Science and Technology of Japan; Japan Agency for Medical Research and Development [J200705023, J200705710, J200705049, JP18cm016335, and JP18cm059042]; Kansai Economic Federation grant;

and Mitsubishi Zaidan. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All patients provided informed consent, and this study was approved by the ethical review board of Osaka University Hospital (#20019).

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Cite this article as: Takata S, Takeda Y, Hirata H, Shirai Y, Morita T, Futami Y, Naito Y, Masuhiro K, Shiroyama T, Miyake K, Naka T, Kumanogoh A. Leucine-rich a-2 glycoprotein as a potential biomarker of idiopathic multicentric Castleman disease with pulmonary involvement: a single-center case-control study from Japan. J Thorac Dis 2022;14(5):1332-1341. doi: 10.21037/jtd-21-1973

Supplementary

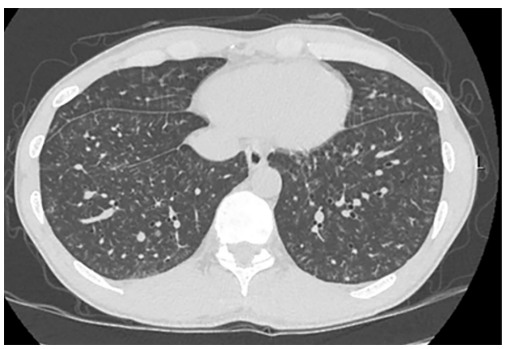
The detail of histological findings, baseline chest imaging, and comprehensive pulmonary function test of each patient

No. 1

Histological findings:

A biopsy specimen of the upper and lower lobe of the left lung presented lymph follicle formation and infiltration of lymphoplasmacytic cells in the alveolar interstitium and bronchovascular bundle. A mediastinal lymph node sample presented plasmacytosis in the interfollicular space, and the infiltrated plasma cells did not present deviation of κ / λ ratio by light chain in situ hybridization (ISH).

Chest imaging at baseline:



Diffuse ground-glass opacity and interlobular septal thickening were found.

Pulmonary function test. (at baseline)	
VC (L)	3.97
VC % predicted (%)	87
FEV1.0 (L)	8.46
FEV1.0% (%)	89.9
DLco % predicted (%)	79.6

VC, Vital capacity; FEV, Forced expiratory volume in one second; DLco, diffusing capacity of lung for carbon monoxide.

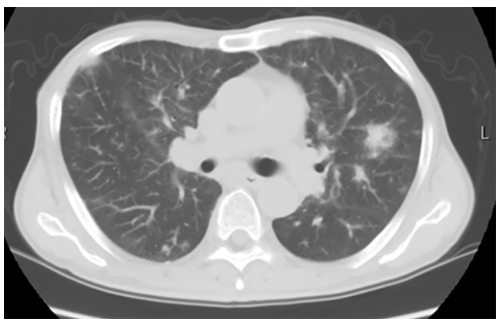
https://dx.doi.org/10.21037/jtd-21-1973

No. 2

Histological findings:

A biopsy specimen of the middle and lower lobe of the right lung revealed infiltration of lymphocytes and plasma cells. Fibrotic interstitial change and developing germinal center were partly shown. $IgG4^+/IgG^+$ ratio was not too high, although dying was weak.

Chest imaging at baseline:



Patchy shadow and diffuse ground-glass opacity were shown.

Pulmonary function test. (at baseline)	
VC (L)	2.55
VC % predicted (%)	74.5
FEV1.0 (L)	2.08
FEV1.0% (%)	76.4
DLco % predicted (%)	77.2

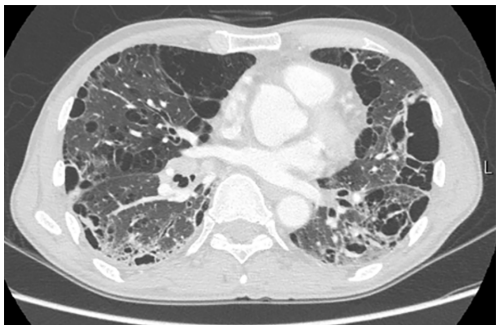
https://dx.doi.org/10.21037/jtd-21-1973

No. 3

Histological findings:

A mediastinal lymph node biopsy specimen revealed plasmacytosis in the interfollicular space. $IgG4^+/IgG^+$ ratio was approximately 20%.

Chest imaging at baseline:



Multiple cystic changes and reticular and ground-glass opacities were shown in the predominantly bilateral lower lobes of the lungs.

Pulmonary function test. (at baseline)

VC (L)	2.76
VC % predicted (%)	65.4
FEV1.0 (L)	1.90
FEV1.0% (%)	69.6
DLco % predicted (%)	34.2

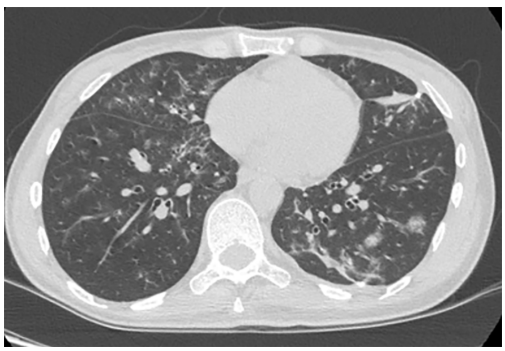
https://dx.doi.org/10.21037/jtd-21-1973

No. 4

Histological findings:

A biopsy specimen of the upper and lower lobe of the right lung revealed aggregation of small lymphoid cells around the bronchiole. The infiltration of plasma cells was shown. $IgG4^{+}/IgG^{+}$ ratio was approximately 10%.

Chest imaging at baseline:



Diffuse ground-glass opacities were shown.

Pulmonary function test. (at baseline)	
VC (L)	2.54
VC % predicted (%)	79.1
FEV1.0 (L)	1.56
FEV1.0% (%)	64.5
DLco % predicted (%)	77.7

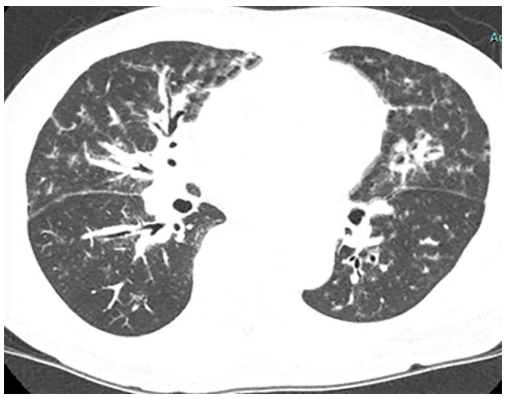
https://dx.doi.org/10.21037/jtd-21-1973

No. 5

Histological findings:

A biopsy specimen of the upper and lower lobe of the left lung revealed the infiltration of plasma cells in the alveolar interstitium. $IgG4^+/IgG^+$ ratio was approximately 20% and 50% in lung and mediastinal lymph node specimens, respectively.

Chest imaging at baseline:



Diffuse ground-glass opacities and thickened bronchovascular bundles were shown.

Pulmonary function test. (at baseline)	
VC (L)	3.61
VC % predicted (%)	89.5
FEV1.0 (L)	2.75
FEV1.0% (%)	76.8
DLco % predicted (%)	91.4

https://dx.doi.org/10.21037/jtd-21-1973

Table S1 Changes of imaging findings of the lung and symptoms before and after treatment

Patient No	Change of image findings of lung	Change of symptom
No. 1	Multi cystic change appeared. Ground grass opacity improved.	Fever and dyspnea on exertion improved.
No. 2	Ground glass opacity partially improved and partially progressed.	No symptom at first visit and no change.
No. 3	Multi cystic change progressed.	Dyspnea on exertion and cough were not changed.
No. 4	Ground glass opacity partially improved.	Fever and fatigue improved.
No. 5	Ground glass opacity were not changed.	Dyspnea on exertion was not changed.

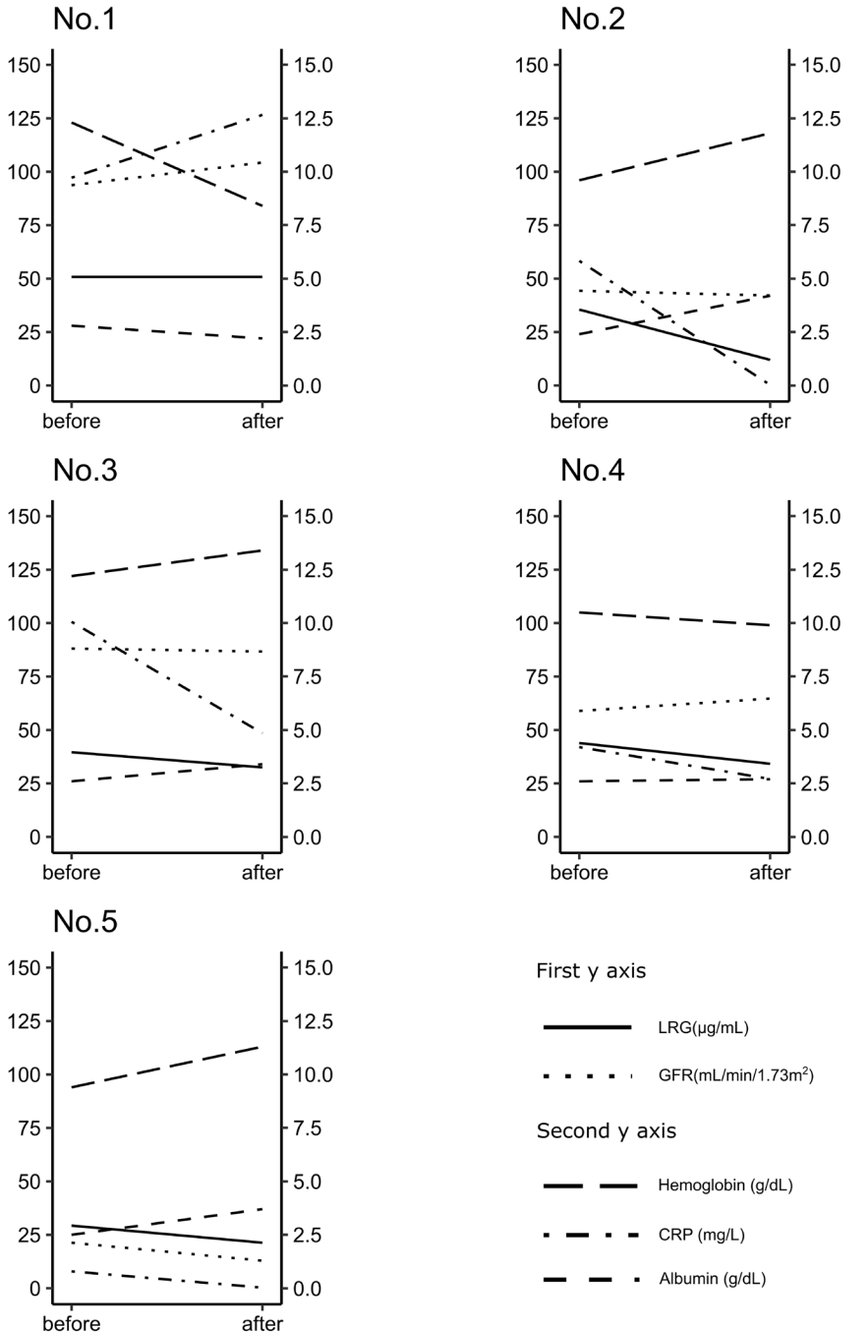


Figure S1 Biochemical findings before and after treatment. LRG tended to correlate with biochemical values such as hemoglobin, albumin, and CRP.

https://dx.doi.org/10.21037/jtd-21-1973

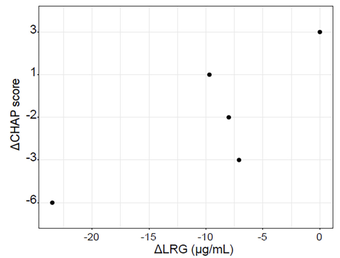


Figure S2 Correlation of ΔLRG and ΔCHAP score. The ΔLRG tended to correlate with ΔCHAP score, although not statistically significant due to the small sample size. (Polyserial correlation coefficient = 0.8795, P value =0.7818).

Table S2 Cytokine and chemokine quantification

	CXCL1	CXCL9	CXCL11	IL-10	MIP-1α	ENA-78	MIP-1β	MIP-3α	Eotaxin	IL-8	CXCL10	MCP-1	TARC	APRIL	BAFF	IL-6	IL-17A	IFN-γ	IL-2	IL-4	IL-12p70	IL-13	sCD40L	TNF-α	TNF-β
MCD	193.2	142	60.3	15.5	343.1	423.5	35.3	38.5	153.6	219.5	64.4	316.6	251.3	13401.5	2849.6	67.2	19.1	2.5	68.3	38.8	49	10.9	10556.3	66.4	52.7
(n=5)	(182.3–255)	(70–380.6)	(32.3–2305)	(2–24.3)	(153.6–536.6)	(202.8–542.8)	(21–83.8)	(19.3–86.1)	(65.4–12000)	(94.3–1409.4)	(55.3–178)	(166.6–1542.3)	(115–287.3)	(12353.6–15520.3)	(1562.2–3812.5)	(47.7–633)	(3.6–34.9)	(2.5–26.1)	(22.5–249.9)	(6.4–77.9)	(45.1–56.3)	(4.8–43.9)	(3499.3–16400.3)	(3.4–235.4)	(21.9–319.9)
Control	96.6	64.6	18.9	2	112.5	227.3	86.5	35.9	75.2	1035	93.8	229.6	196.6	11681.1	1838.8	25.6	3.6	2.5	22.5	10.5	35.7	13.4	12959.4	16.7	106.9
(n=3)	(83.8–155.9)	(55.2–64.7)	(15.6–19.6)	(2–4.1)	(60.5–287.7)	(178.2–355.1)	(18.5–115.7)	(33.9–47.8)	(25.4–85.5)	(174.9–1109.6)	(91–94.3)	(189.6–379.3)	(147.7–536.5)	(10101.9–11765.2)	(1552.1–2878.6)	(4.5–88.2)	(3.6–14.9)	(2.5–15.9)	(22.5–22.5)	(3.6–34.1)	(26.1–60)	(4.8–20.6)	(9708–17445.1)	(15.8–78.4)	(95.4–315.4)
p-value (permutation test)	0.03571	0.03571	0.03571	0.1429	0.07143	0.25	0.5714	0.5714	0.3929	1	0.7857	1	0.7857	0.03571	0.3929	0.25	0.2321	0.6429	0.2857	0.1429	0.5714	0.7857	0.5714	0.5714	0.5714

MCD, multicentric Castleman disease; IL, interleukin; MIP, macrophage inflammatory protein; MCP, monocyte chemoattractant protein; APRIL, a proliferation-inducing ligand; IFN, interferon; TNF, tumor necrosis factor

https://dx.doi.org/10.21037/jtd-21-1973